Essentials of Anatomic Pathology

SECOND EDITION

Edited by

Liang Cheng, MD

David G. Bostwick, MD



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Edited by

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Preface

We are delighted to bring our readers this second edition of *Essentials of Anatomic Pathology*, which we have developed to cover the curriculum of anatomic pathology for a pathology residency training program. This second edition provides the readers with comprehensive, evidence-based practice information in an outline format that is clear and easy to follow. Although designed mainly for residents embarking on an exciting career, the presentation and level of detail are also ideal for the practicing pathologist who may wish to review a specific topic, as well as for medical students, cytotechnologists, pathologist assistants, and other medical professionals who have an active interest in anatomic pathology.

The successful organization of *Essentials of Anatomic Pathology* remains unchanged in this new edition. The book is divided into two main parts. Part I, General Pathology, covers general anatomic pathology, including Diagnostic Molecular Pathology, Human Genetic Disorders, Forensic Pathology, Diagnostic Electron Microscopy, Microbiology for the Surgical Pathologist, Transplantation Pathology, and Cytopathology. Part II, Organ Systems, considers the various organ systems and the multitude of diseases encountered in each. We have added seven new chapters to expand coverage to include such topics as Transplantation Pathology, Spleen, Non-Neoplastic Skin Diseases, Head and Neck, Eye and Ocular Adnexa, Vulva and Vagina, and Penis and Scrotum. Best of all, over 2000 images have been added to the text and color versions are easily accessible on the accompanying CD-ROM. The chapters have been revised extensively to incorporate both newly discovered diagnostic biomarkers and new tumor classification and staging information. Several chapters have been completely rewritten by new contributors. As before, each chapter is preceded by a detailed list of contents for easy reference.

It is our hope that this vastly expanded second edition of *Essentials of Anatomic Pathology* will serve as a frontline resource for pathology residents and practicing pathologists in this era of information and technology explosion. Our sincere thanks and gratitude go to each of the contributors who made this project possible. We would like to thank Ryan P. Christy from the Multimedia Education Division of the Department of Pathology at Indiana University, who has edited the digital images for this book. In addition, we are deeply grateful to the capable staff at Humana Press for their suggestions, help, patience, and encouragement during the preparation of this edition.

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Preface to the First Edition

The past decade has witnessed remarkable progress in surgical pathology. The ability of contemporary surgical pathologists to reach a definite diagnosis has been enhanced greatly by innovative immunohistochemical techniques and markers. The information that is useful for pathology practice may not be readily accessible in the daily signout. An up-to-date handbook that contains relevant information to establish an accurate diagnosis would be of great practical value. Therefore, we have concentrated on diagnostic criteria and differential diagnosis to ensure an accurate diagnosis.

The purpose of *Essentials of Anatomic Pathology* is to provide a concise review of anatomic pathology for pathologists in training and practicing pathologists, integrating recent advances in diagnostic surgical pathology. This book is organized to allow easy reference for daily practice. It will be a useful resource for medical students, as well as for anyone actively interested in pathology.

Part I covers general anatomic pathology, including diagnostic molecular pathology, medical cytogenetics, human genetic disorders, microbiology for surgical pathologists, forensic pathology, and cytopathology. Part II is classified by organ system and covers important diagnostic features of common diseases and tumors. The pertinent clinical information, salient diagnostic features, relevant ancillary data (for example, immunohistochemical profiles), main differential diagnoses of each disease, and most recent tumor-staging information are presented in a consistently user-friendly format. We believe that this format will provide easy access to essential information necessary for signout. It is not meant as a substitute for lavishly illustrated, comprehensive textbooks, but to complement them as a practical aid. We hope that this text will materially aid in continuing efforts to recognize, understand, and accurately interpret the gross and light microscopic findings in anatomic pathology specimens.

We earnestly solicit constructive criticism from colleagues so that the utility of this text can be expanded and improved to its maximum potential.

Liang Cheng, *MD*
David G. Bostwick, *MD*

Contents

Preface ..... *v*

Preface to the First Edition ..... *vii*

Contributors ..... *xi*

Companion CD ..... *xv*

Part I General Pathology

1 Diagnostic Molecular Pathology
James Huang, Sharie B. Parks, and Richard D. Press *3*

2 Human Genetic Disorders
Teresa M. Kruisselbrink, Noralane M. Lindor, and John F. O'Brien *37*

3 Forensic Pathology
Jeffrey J. Barnard and Frank P. Miller, III *87*

4 Diagnostic Electron Microscopy
Moo-Nahm Yum and Michael P. Goheen *135*

5 Microbiology for the Surgical Pathologist
Deborah E. Blue-Hnidy and Stephen D. Allen *155*

6 Transplantation Pathology
Oscar W. Cummings *231*

7 Cytopathology
Fadi W. Abdul-Karim and Claire W. Michael *261*

Part II Organ Systems

8 Neuropathology
Arie Perry and Bernd W. Scheithauer *359*

9 Lymph Node
Ellen D. Remstein and Paul J. Kurtin *423*

10 Spleen
Dennis P. O'Malley and Attilio Orazi *467*

11 Bone Marrow
Dennis P. O'Malley *493*

12 Neoplasms of the Skin and Immunodermatology
Daniel P. Vandersteen and Melanie K. Triffet-Treviño *533*

13 Non-Neoplastic Skin Diseases
Steven D. Billings and Antoinette F. Hood *611*

14 Endocrine Pathology
J. Aidan Carney *633*

15 Bone and Joints
Jasvir S. Khurana and Madalina Tuluc *677*

16 Soft Tissue Tumors
Alessandra F. Nascimento, David Schembri-Wismayer, and Antonio G. Nascimento *711*

17 Tumors of the Salivary Glands
Adel K. El-Naggar and John G. Batsakis *761*

18 Head and Neck
John D. Henley and Don-John Summerlin 795

19 Eye and Ocular Adnexa
Jose M. Bonin 833

20 Mediastinum and Thymus
Chung-Che (Jeff) Chang, Gordon G. Zeng, and Joseph F. Tomashefski, Jr. 867

21 Cardiovascular Pathology
Eric A. Pfeifer and Liang Cheng 895

22 Lung
Carol F. Farver, Andrea V. Arrossi, and Henry D. Tazelaar 915

23 Breast
Eoghan E. Mooney and Fattaneh A. Tavassoli 965

24 Vulva and Vagina
Wenxin Zheng 1001

25 Uterus and Fallopian Tube
Maritza Martel and Fattaneh A. Tavassoli 1019

26 Ovary and Peritoneum
Kevin J. Wu and Gary L. Keeney 1069

27 Placenta and Gestational Trophoblastic Disease
Raymond W. Redline 1097

28 Non-Neoplastic Renal Diseases
Donna J. Lager 1117

29 Tumors of the Kidney
Gregory T. MacLennan, Liang Cheng, and David G. Bostwick 1147

30 Urinary Bladder
Liang Cheng, Antonio Lopez-Beltran, and David G. Bostwick 1175

31 Prostate
David G. Bostwick and Liang Cheng 1219

32 Testis and Testicular Adnexa
Kenneth A. Iczkowski 1247

33 Penis
Gustavo Ayala and Antonio L. Cubilla 1273

34 Esophagus and Stomach
Elias A. Castilla and John R. Goldblum ... 1287

35 Small Intestine, Appendix, Colorectum, and Anus
Shuan C. Li 1317

36 Pancreas
N. Volkan Adsay and Olca Basturk 1347

37 Non-Neoplastic Hepatobiliary Disease
Romil Saxena, Hagen Blaszyk, and Kenneth P. Batts 1369

38 Neoplasms of the Liver and Biliary System
Romil Saxena, Hagen Blaszyk, and Kenneth P. Batts 1413

Index 1437

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Companion CD

Color versions of the illustrations appearing in the book and the photomicrographs appearing in Chapter 4 may be found on the Companion CD attached to the inside back cover. The image files are organized into folders by chapter number and title and are viewable in most Web browsers. The CD is compatible with both Mac and PC operating systems.

Part I

General Pathology

1

Diagnostic Molecular Pathology

James Huang, MD, Sharie B. Parks, PhD
and Richard D. Press, MD, PhD

CONTENTS

I. DNA Diagnostic Methodologies 1-3
Southern Blot Assay 1-3
Polymerase Chain Reaction Assay 1-3
PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) Assay 1-4
PCR-Fluorescence Resonance Energy Transfer (PCR-FRET) 1-5
PCR-Denaturing High Pressure Liquid Chromatography (HPLC) Screening Assay 1-6
Real-time Quantitative Reverse Transcription PCR 1-6
DNA Sequencing 1-6

II. Molecular Diagnosis in Hematology 1-8
Hereditary Hemochromatosis 1-8
Factor V Leiden 1-9
Prothrombin G20210A Mutation 1-10

III. Molecular Diagnosis of Hematopoietic Neoplasms.....1-10
Introduction and Methods 1-10
Molecular Assessment of Clonality 1-13
General Guidelines for the Rational Use of Specific Molecular Pathology Assays....1-16
Genetic Lesions Associated with Specific Diseases 1-17
Chronic Myeloproliferative Diseases (CMPD) 1-17
Myelodysplastic/Myeloid Proliferative Diseases 1-18
Myeloid Dysplastic Syndrome (MDS) 1-18
Acute Myeloid (non-lymphoblastic) Leukemia (AML) 1-18
Acute Lymphoblastic Leukemia/ Lymphoma (ALL/LBL) 1-20
Mature B-cell Neoplasms 1-21
Chronic Lymphocytic Leukemia/ Small Lymphocytic Leukemia 1-21
B-cell Prolymphocytic Leukemia 1-22
Lymphoplasmacytic Lymphoma 1-22
Hairy Cell Leukemia 1-22
Marginal Zone Lymphoma (MZL) 1-22
Follicular Lymphoma 1-22
Mantle Cell Lymphoma 1-23
Diffuse Large Cell Lymphoma 1-23
Mediastinal (thymic) Large B-cell Lymphoma 1-23
Intravascular Large B-cell Lymphoma 1-24
Primary Effusion Lymphoma 1-24
Burkitt's Lymphoma/Leukemia (BL) 1-24
Plasma Cell Neoplasms 1-24
Mature Peripheral T-cell Lymphoma/ Leukemia 1-24
Anaplastic Large Cell Lymphoma 1-25
NK Cell Neoplasms 1-25
Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL) 1-25

Classical Hodgkin Lymphoma (CHL).....1-25
Histiocytic and Dendritic Cells Neoplasms 1-25
Mastocytosis 1-25

IV. Molecular Diagnostics of Solid Tumors 1-26
Sarcomas 1-26
Gastrointestinal Stromal Tumor (GIST) 1-26
Multistep Carcinogenesis: The Colorectal Cancer (CRC) Paradigm 1-26
HER-2 / Neu Overexpression in Breast Cancer: Predicting Response to Molecularly Targeted Therapy 1-28

V. Molecular Diagnosis in Microbiology 1-28
Introduction and Methods 1-28
Hepatitis C Virus (HCV) 1-29
Cytomegalovirus (CMV) 1-30

VI. Suggested Reading.....1-33

DNA DIAGNOSTIC METHODOLOGIES

Southern Blot Assay (Figure 1)

General

- Requires microgram (μg) quantities of high quality, high molecular weight genomic DNA
- Genomic DNA is digested with one or more specific restriction enzymes which cut the DNA into various sized fragments
- Digested DNA fragments are separated in a size dependent manner via agarose gel electrophoresis, yielding a smear of DNA when visualized by ethidium bromide and UV light
- DNA is transferred from the gel to a nylon or nitrocellulose membrane, which is then hybridized to a labeled probe specific to the gene of interest
- When the membrane is exposed to film, only the DNA fragments which hybridize to the labeled probe are visualized
- Differences in size between the patient's band(s) and those of a normal control yield important information regarding the patient's gene alteration

Benefits

- Useful for detecting large scale deletions, insertions, or duplications in a gene or several genes in a region
- In the hands of very skilled technologists, can be quantitative

Limitations

- Unable to accurately detect point mutations, small deletions/insertions/duplications unless they disrupt a restriction enzyme site
- Requires large amounts of high quality DNA
- Entire process takes several days to complete

Examples

- Detecting deletions in the dystrophin gene, causing Duchene and Becker muscular dystrophies
- Detecting deletions or duplications within the mitochondrial genome, which cause a variety of disorders

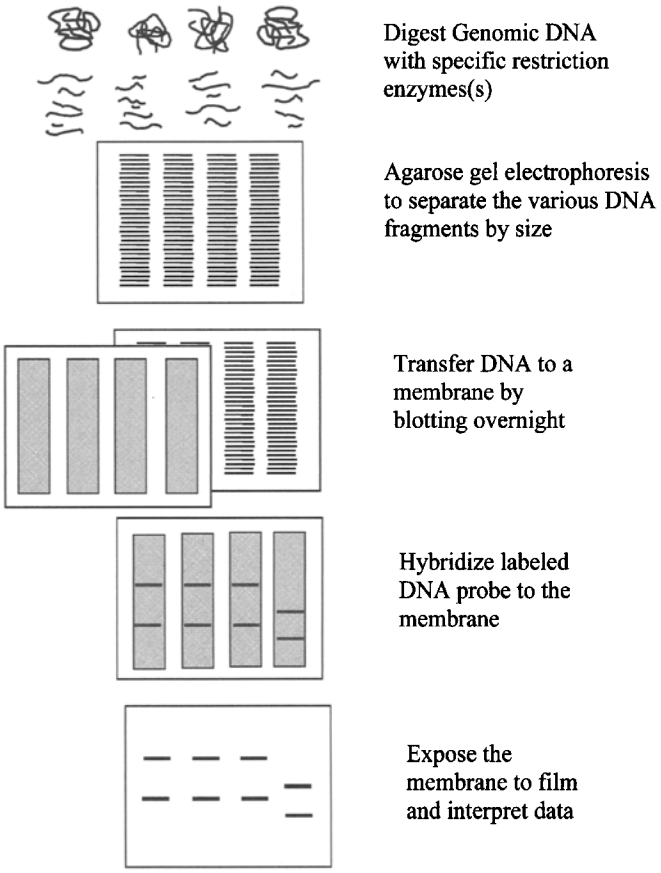


Fig. 1. Southern blot analysis. Fragmented genomic DNA is separated by size on an agarose gel. DNA fragments are transferred to a membrane that is then hybridized to a probe from the gene of interest. Band sizes are compared to those of a normal control.

Polymerase Chain Reaction (PCR) Assay (Figure 2)

General

- Requires only nanogram (ng) quantities of intact or partially degraded genomic DNA (or RNA) derived from blood, fresh frozen tissue, or fixed tissue
- The gene of interest is enzymatically amplified $>10^8$-fold over background using short target-specific oligonucleotide primers, the four deoxynucleotides (dNTPs), and a thermostable DNA polymerase
- The reaction mixture is exposed to multiple rounds of amplification via a three-temperature cycle:
  - 95°C Denatures the two DNA strands
  - 55–65°C Allows primers to anneal to template
  - 72°C Allows the polymerase to extend the primers into full length product
- Polymerase chain reaction (PCR) products are separated in a size-specific manner by agarose gel electrophoresis, stained with ethidium bromide and visualized under UV light
- Alternatively, PCR products can be visualized by capillary gel electrophoresis or by fluorescence (in real-time PCR)
- The size of the PCR products yields information about the region of the gene between the two primers

Benefits

- Useful for detecting small insertions or deletions
- Differences in size between patient and control samples can be accurately measured
- Requires a small amount of DNA (or RNA), which may be of poor quality
- Entire process can be completed in several hours

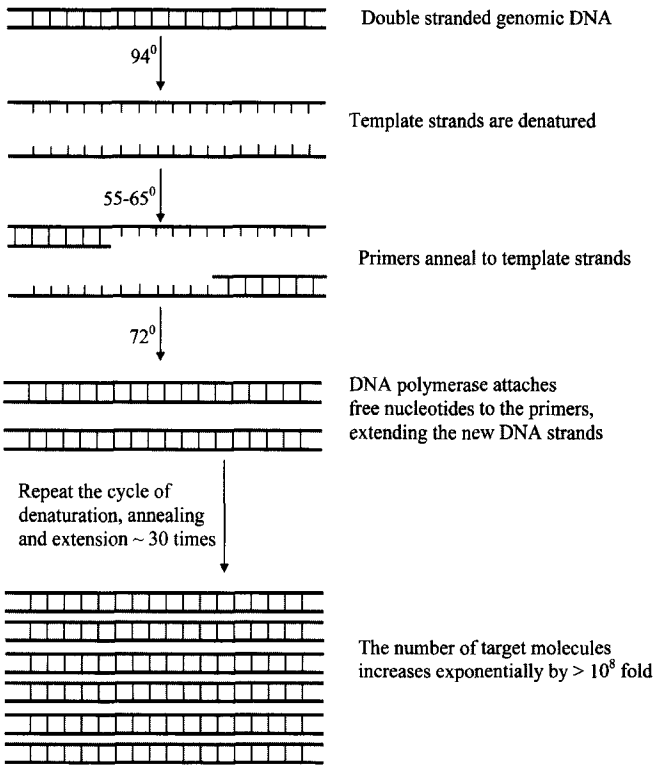


Fig. 2. Schematic representation of the polymerase chain reaction (PCR). Through repeated cycles of heating and cooling, DNA polymerase makes multiple copies of a specific target sequence, using gene specific primers and free nucleotides (dNTPs).

Limitations

- Cannot detect large deletions or insertions within the gene region
- Is not usually quantitative, unless special measures are taken (as in real-time PCR)

Example

- Detection of 3 bp deletion (ΔF508) in the CFTR gene causing cystic fibrosis
- PCR is used in conjunction with several other methodologies, such as restriction fragment length polymorphism (RFLP), fluorescence resonance energy transfer (FRET), denaturing high pressure liquid chromatography (dHPLC), and sequencing (*see* following)
- Almost every molecular diagnostic approach (except Southern blot) utilizes PCR in some way

PCR-Restriction Fragment Length Polymorphism (PCR-RFLP) Assay

General

- PCR products are digested with a specific restriction enzyme that detects a known single nucleotide change (or mutation) within the gene of interest. The mutation must create or destroy a restriction enzyme site

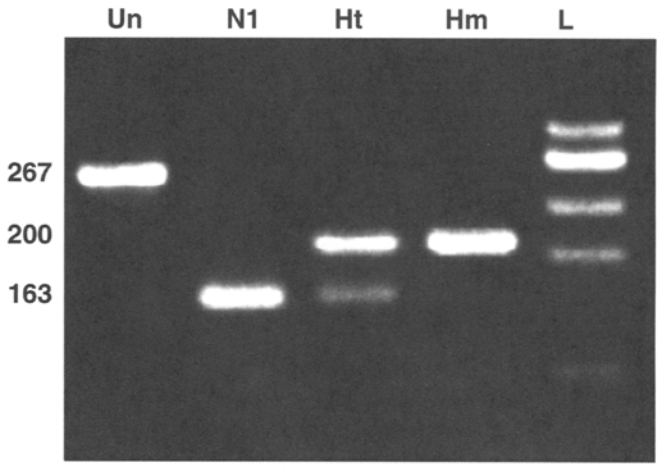


Fig. 3. Representative Factor V Leiden PCR-RFLP gel. Samples were PCR amplified and digested with the restriction enzyme MnlI. Fragments were separated by size via agarose gel electrophoresis. *Un*, undigested PCR product; *Nl*, homozygous normal; *Ht*, heterozygous; *Hm*, Leiden homozygous; *L*, DNA ladder used for size comparison. Numbers on the left indicate fragment sizes in basepair.

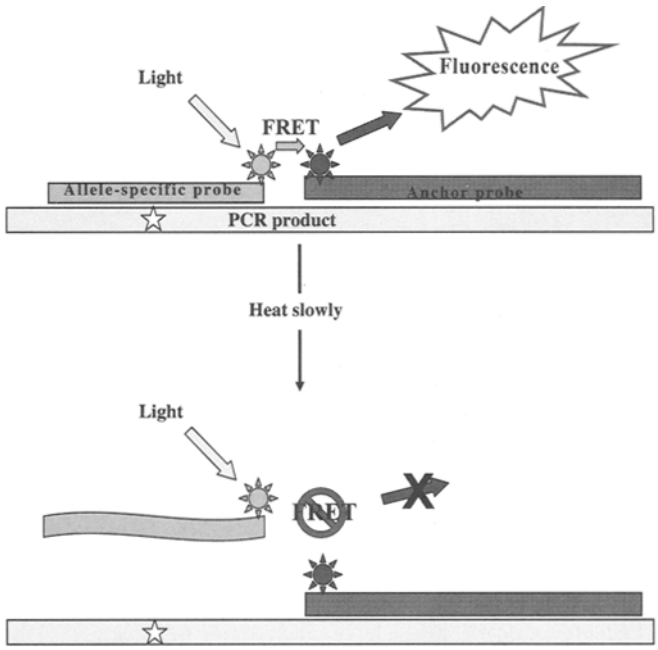


Fig. 4. PCR-FRET (Fluorescence resonance energy transfer). After PCR amplification, a fluorescent signal is only detected when the allele-specific probe and anchor probe are both annealed to the PCR product. As samples are slowly heated, the shorter allele-specific probe denatures, and signal is lost. The temperature at which this happens (the melting temperature) indicates either a perfect match between the probe and the target (wildtype) or a single mismatch (mutation). The star represents the nucleotide of interest.

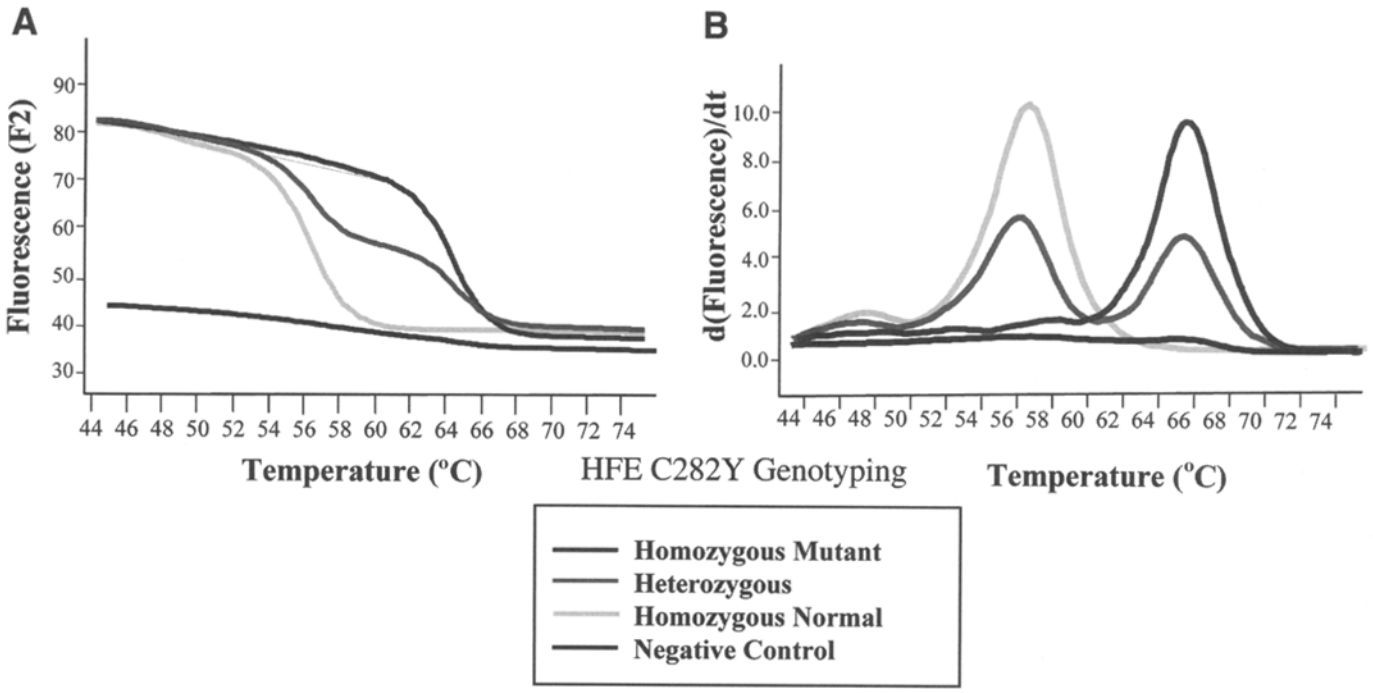


Fig. 5. Hemochromatosis (HFE gene) FRET data for three genotypes and a negative control. Melting curves **(A)** indicate that different genotypes lose fluorescent signal at different temperatures. The first derivative data yields melting peaks **(B)**, which are more straightforward to interpret.

- Digested PCR fragments are visualized by agarose gel electrophoresis, ethidium bromide staining and UV light. The pattern of fragment sizes indicates the presence or absence of the specific nucleotide change

Benefits

- Works well for detecting previously characterized single nucleotide changes
- Is technically simple to perform
- Requires common laboratory equipment

Limitations

- Does not detect novel, uncharacterized alterations
- It is possible for a nonpathologic nucleotide change near the one of interest to similarly affect enzyme digestion patterns and result in a false positive

Example

- Detection of the Factor V Leiden R506Q mutation causing thrombophilia **(Figure 3)**

PCR-Fluorescence Resonance Energy Transfer (PCR-FRET) (Figure 4)

General

- PCR is performed in the presence of two fluorescently labeled oligonucleotide probes, one of which is specific for a well-characterized single nucleotide polymorphism (SNP) of interest
- When PCR amplification is complete, the two labeled probes hybridize to the site of the SNP and emit a fluorescent signal that is only possible when both probes are bound to the same DNA template
- The samples are slowly heated and the temperature at which the allele-specific probe denatures from the target (and fluorescent signal is lost) indicates the presence or absence of the SNP of interest. The allele discrimination is based on the principle that mis-matched hybrids will disassociate (melt) at a lower temperature than perfectly matched hybrids

Benefits

- The entire assay (PCR and mutation detection) can be completed in less than 2 hours
- The assay can be designed such that a neighboring nonpathologic alteration will not be confused with the SNP of interest

Limitations

- Fluorescently labeled probes are expensive
- Requires nonstandard, somewhat expensive equipment

Example

- Detection of the HFE C282Y and H63D mutations resulting in hereditary hemochromatosis (HH) **(Figure 5)**

PCR-Denaturing High Pressure Liquid Chromatography (dHPLC) Screening Assay (Figure 6)

General

- PCR products are heated to denature complimentary strands, and allowed to slowly reanneal. If the sample is heterozygous for the presence of a small nucleotide substitution/ insertion/ deletion, four populations of double stranded DNA molecules will result (two homoduplexes and two heteroduplexes)
- Samples are analyzed on an HPLC instrument that efficiently separates homoduplexes and heteroduplexes. Any pattern of peaks that is different from the normal control (homoduplexes only) is indicative of a possible mutation. Follow-up DNA sequencing is used to confirm or discount the presence of an alteration

Benefits

- Will detect various single nucleotide changes, small deletions, small insertions
- Saves time and money by indicating which samples should be sequenced

Limitations

- Is only a screening technique, suspicious samples must be sequenced
- Lots of optimization is often necessary for each target
- Requires expensive, nonstandard laboratory equipment

Example

- Screening for c-kit mutations predictive of a Gleevec response in gastrointestinol (GI) stromal tumors

Real-time Quantitative Reverse Transcription PCR

General

- Highly sensitive for detecting and quantitating very low levels of RNA
- cDNA is generated from RNA by traditional reverse transcription methods
- Enzymatic reaction uses PCR reagents plus two fluorescently labeled DNA probes (similar to Fig. 4.)
- With each cycle of annealing, the probes hybridize to newly synthesized PCR products and a measurable fluorescent signal is generated in a product-dependent manner
- The PCR cycle number at which the PCR product is first detectable (the "crossing point" or "cycle threshold") is directly proportional to the concentration (log) of the input DNA target
- An internal control gene (i.e., *GAPDH*) is often used to normalize values

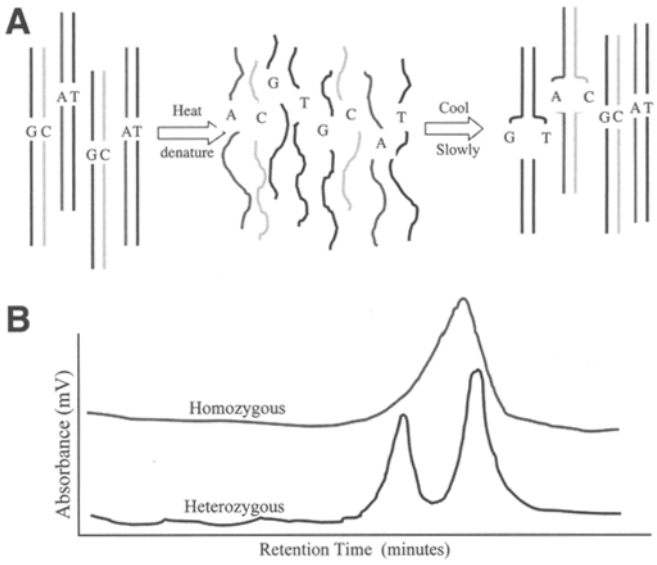


Fig. 6. Schematic representation of dHPLC. PCR products are heated to denature sense and antisense strands, and allowed to cool. If the sample is heterozygous, four populations of double stranded molecules will result, including a normal sense strand coupled with a mutant antisense strand, a mutant sense strand coupled with a normal antisense strand (heteroduplexes), and the two original homoduplex molecules (**A**). Samples are then analyzed on an HPLC instrument, which retains DNA molecules based upon size and composition. A homozygous sample has only one population of double stranded molecules and will demonstrate a single peak. Heterozygous samples yield multiple peaks indicating the presence of heteroduplexes (**B**). The sample can then be sequenced to determine the exact nature and location of the mutation.

Benefits

- Highly sensitive for detecting and quantitating low levels of transcript
- Results are generated in a single day

Limitations

- Optimization can be tedious and difficult
- It can be difficult to work with RNA, which is highly susceptible to degradation
- Requires expensive, nonstandard laboratory equipment

Example

- Quantitating bcr-abl fusion transcripts in patients with chronic myelogenous leukemia undergoing Gleevec therapy **(Figure 7)**

DNA Sequencing

General

- Uses DNA from the gene of interest which has been amplified by PCR

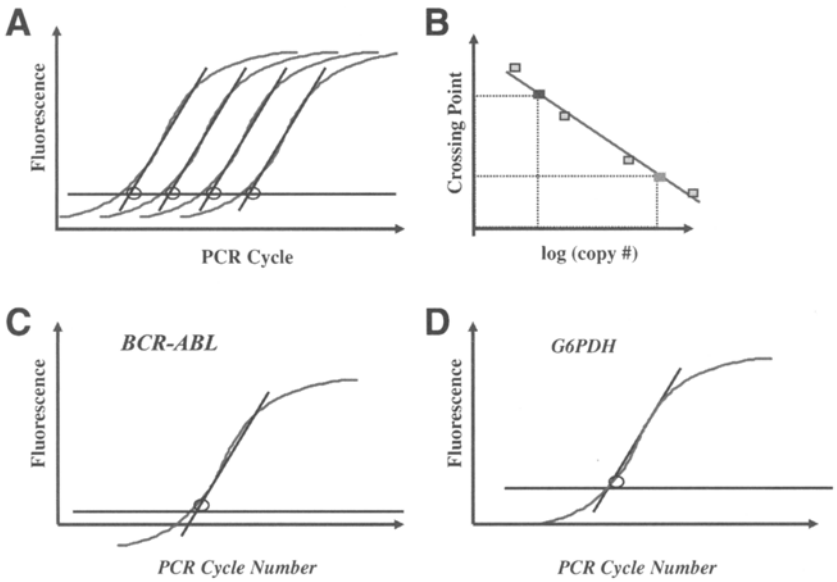


Fig. 7. Real-time RT-PCR for quantification of *BCR-ABL* transcripts for monitoring the molecular response of CML to Gleevec therapy. The standard curve resulting from amplifying calibration controls with known amounts of transcripts are shown as raw amplification curves (**panel A**) and a resultant calibration curve (**panel B**). There is a linear relationship between the crossing point (PCR cycle at which the amplification curve rises above baseline) and the input copy number of original transcripts. For BCR-ABL, the specific fluorescent signal results from the presence of 2 fluor-labeled hybridization probes to *ABL* exon a3. **Panels C** (*BCR-ABL* primers and probes) and **D** (*G6PDH* housekeeping gene primers and probes) show the amplification curves from a patient that is not responding to Gleevec therapy—as assessed by the approximately equal crossing point (concentration) of *BCR-ABL* RNA compared to *G6PDH* RNA. A good Gleevec response would be indicated by a significant right-shift of the *BCR-ABL* curve—indicative of a lower BCR-ABL transcript burden.

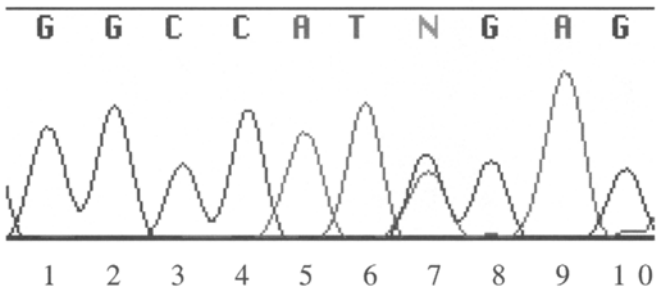


Fig. 8. Results of fluorescent dideoxynucleotide sequencing and capillary electrophoresis. This patient is heterozygous at nucleotide 7; one allele has a G (black) at this location and the other has an A (green).

- Two types: Maxam and Gilbert method and Sanger dideoxynucleotide method
- Sanger method is most commonly used
- Enzymatic reaction using a single primer, DNA polymerase, the four deoxynucleotides (dNTPs) and one isotopic or fluorescently labeled dideoxynucleotide at a much lower concentration
- One strand of the DNA is replicated. When a dideoxynucleotide is added to the growing strand, elongation stops
- The reaction yields molecules of various sizes, each ending where a dideoxynucleotide has been added. Four reactions are performed, each with a different dideoxynucleotide. Collectively, the results yield the sequence of nucleotides within the region of interest
- If the dideoxynucleotides are fluorescently labeled, four reactions can be performed in a single tube, with each nucleotide represented by a different color
- Samples are separated by capillary electrophoresis; each peak represents a single nucleotide
- Heterozygous samples are indicated by two different colored peaks at the same location **(Figure 8)**

Benefits

- Visualization of each nucleotide makes sequencing the gold standard for mutation detection
- Reactions can be completed in a single day

Limitations

- Reagents can be expensive
- Sequencing an entire gene can be labor intensive

Example

- Sequencing the BRCA-1 gene in patients with hereditary breast cancer

MOLECULAR DIAGNOSIS IN HEMATOLOGY

Hereditary Hemochromatosis (HH)

- HH is a common autosomal recessive disorder of iron overload, often caused by a mutation in the HFE gene. The HFE protein normally binds to the transferrin receptor. In HH, the GI mucosa absorbs excessive amounts of iron. Consequently, excessive toxic iron is stored in the organs, especially the liver, heart, pancreas, and skin

Clinical

- Disease onset in males between 40 and 60 yr
- Onset in females after menopause
- Damage from the excess iron accumulation can include:
  - Cirrhosis of the liver and eventual liver failure
  - Arrhythmias and eventual heart failure
  - Diabetes (from pancreatic iron)
  - Skin discoloration (bronzing)
  - Arthritis
  - Hypothyroidism
  - Hypogonadism, impotence, sterility
  - Fatigue, weakness

Differential Diagnosis

It is critical to exclude:

- Secondary iron overload caused by:
  - Transfusions
  - Hemolytic anemia
  - Hemodialysis
  - Ingested iron sources (foods, cookware, medicines)
- Primary iron overload caused by:
  - African iron overload
  - Neonatal hemochromatosis
  - The TFR2 gene—an autosomal recessive disorder resulting in severe iron overload in teen years

Prevalence

In the Caucasian population, approx 1/200–1/500 individuals has two mutant HFE alleles. The carrier rate is approx 1/8–1/10

Diagnosis

- Clinical symptoms (nonspecific)
- Family history
- Increased transferrin-iron saturation (>60% for men, >50% for women)
- Serum ferritin concentration—increases over time for affected individuals, but is not specific to HH
- Liver biopsy showing increased hepatic iron (by iron stain or quantitative analysis)
- Quantitative phlebotomy
- Direct DNA testing for the C282Y (major) and H63D (minor) HFE mutations

Therapy

- Routine phlebotomy is effective for most patients
- Patient should be bled until iron deficient (ferritin <50 ng/mL)
- Early treatment (before symptoms arise) prevents essentially all sequelae of HH

Inheritance

- Autosomal recessive disorder with incomplete penetrance
- Penetrance higher in males than females
- Primarily affects Northern European Caucasians

The Hemochromatosis Gene

- HFE
- Homologous to major histocompatibility complex (MHC) class I proteins
- Normal HFE forms heterodimer with β2 microglobulin
- On the cell surface, the HFE-β2 microglobulin complex binds to the transferrin receptor, reducing its affinity for iron bound transferrin

Hemochromatosis-Specific Mutations in HFE

- *C282Y (Major Mutation)*:
  - Homozygosity for the C282Y point mutation accounts for 80–90% of symptomatic HH patients
  - Approx 0.3% of the unaffected population is homozygous for the C282Y mutation (reduced penetrance)
  - Approx 10–13% of Caucasians are heterozygous for the C282Y mutation. Carriers may experience mildly increased iron levels, but are usually not symptomatic
  - C282Y mutation prevents HFE protein from binding the transferrin receptor
  - Detectable by PCR-RFLP, PCR-FRET, and other methods
- *H63D (Minor Mutation)*:
  - Compound heterozygosity for C282Y/H63D accounts for 3–8% of HH patients
  - Penetrance of the C282Y/H63D genotype is very low—less than 2% develop symptoms
  - H63D homozygotes may account for ~1% of HH patients, although the clinical significance of this allele alone is not clear
  - Homozygosity for H63D is quite common in the normal population, and penetrance is extremely low
  - Detectable by PCR-RFLP, PCR-FRET and other methods

Clinical Utility of HFE C282Y DNA Test

- Can confirm HH diagnosis in patients with elevated iron
- Obviates need for liver biopsy as the 'gold standard' diagnostic test
- Clinical sensitivity is 80–90% in iron overloaded subjects

- Specificity is limited by penetrance
- C282Y homozygosity is highly penetrant for laboratory iron overload, but only a minority of homozygotes develop clinical symptoms

Factor V Leiden

Factor V Leiden thrombophilia is a common hereditary hypercoagulable syndrome resulting from a single point mutation (R506Q) in the factor V gene. This mutation renders the factor V protein resistant to cleavage by activated protein C (APC), resulting in a condition referred to as APC resistance

Clinical

- Deep vein thrombosis (DVT)
- Pulmonary embolism
- Indications of an inherited hypercoagulable syndrome:
  - Recurrent thrombotic episodes
  - Thrombosis at a young age (<50)
  - Thrombosis at unusual anatomic sites (cerebral, mesenteric, portal, or hepatic veins)
  - Pregnancy related venous thrombosis (or in association with oral contraceptives or hormone replacement therapy)
  - Family history

Acquired Risk Factors for Venous Thrombosis

The following conditions work synergistically to increase the risk of thrombosis in a patient with the factor V Leiden mutation

- Pregnancy
- Long periods of immobility
- Post surgical state
- Use of oral contraceptives
- Use of hormone replacement therapy
- Trauma
- Cancer

Prevalence

- The most common cause of inherited thrombophilia in Caucasians
- Heterozygosity for the R506Q mutation is found in 3–8% of the US population; incidence varies by ethnicity
- R506Q homozygosity is found in 1/5000 Caucasians
- R506Q is found in 15–20% of patients experiencing their first episode of DVT
- R506Q is found in 50–60% of patients with recurrent or estrogen-related thrombosis

Differential Diagnosis

- Of patients with APC resistance, 5% do not have the factor V Leiden mutation
- Acquired APC resistance (pregnancy or lupus anticoagulant)
- Venous thromboembolism can be caused by the prothrombin G20210A mutation, inherited deficiencies in protein C, protein S, and antithrombin

Genetics and Biochemistry

- Factor V Leiden is caused by a well conserved point mutation in the gene for coagulation factor V
  - G to A transition at nucleotide 1691 replaces an arginine (R) with glutamine (Q) at residue 506 (R506Q)
  - Normal factor V protein is cleaved by APC at arginine 506
  - Mutant glutamine (Q) 506 is cleaved much less efficiently by APC
  - Cleavage resistant factor V has longer half life, resulting in a hypercoagulable state

Relative Risk

- Leiden heterozygotes have a 4–10-fold increased risk of venous thrombosis
- The Leiden mutation predisposes the carrier to increased thrombosis, however most heterozygotes remain asymptomatic
- Leiden homozygotes have an ~80 fold increased risk of inappropriate venous thrombosis

Diagnosis

Traditional Laboratory Diagnosis

- Functional APC resistance test is used as a screening test:
  - Ratio of partial thromboplastin times (PTTs) measured both in the presence and absence of exogenous APC (+APC/–APC)
  - Failure of added APC to significantly increase the PTT suggests APC resistance
  - Ratio of (+APC/–APC) determines APC resistance
  - Leiden homozygotes may have APC ratio as low as 1.0–1.5
  - Of patients with functional APC resistance, 90–95% will have the Leiden mutation (heterozygous or homozygous)
  - Factors which interfere with APC resistance test include heparin, lupus anticoagulant

DNA Diagnosis

- Direct DNA testing for factor V Leiden mutation is now the gold standard
- May be performed by PCR-RFLP, PCR-FRET or other methods
- Correlates very well with APC resistance test
- Indications for Leiden DNA test:
  - Confirm diagnosis in thrombophilic patients
  - Screen presymptomatic family members of patients with the Leiden mutation

Benefits and Limitations of APC Resistance Testing and DNA Testing

- APC resistance test is less costly and is currently more widely available (low tech)
- Functional test can be inaccurate in cases of prolonged baseline PTT
- DNA test is more definitive and results are unambiguous. Specificity is 100%, sensitivity is 90%
- DNA test may miss 5–10% of APC resistance (those owing to other causes)

Management of Homozygotes

- Acute thrombotic episode—treat with heparin, followed by warfarin
- Recommended long term treatment and prophylaxis with warfarin to prevent recurrent thrombosis

Management of Heterozygotes

- Those with first DVT event and presence of another reversible risk factor (pregnancy, oral contraceptives, immobility) may not need long term warfarin
- First DVT and no obvious risk factor—consider undetermined genetic risk factor and consider long term warfarin
- Patients with recurrent thrombotic events usually require long term anticoagulation therapy and prophylaxis
- Family members should be screened
- Patients should be counseled to avoid high risk thrombotic situations and to get prophylactic anticoagulants before exposure to oral contraceptives, immobility, surgery, or pregnancy

Thrombosis Likely Requires "Two Hits": A Single Factor V Leiden mutation and one of the following:

- Deficiency of protein C, protein S or antithrombin III
- An acquired risk factor (pregnancy, surgery, immobilization, trauma, cancer)
- Lupus anticoagulant
- Hyperhomocysteinemia
- Prothrombin G20210A mutation
- A second factor V Leiden mutation (homozygosity)

Prothrombin G20210A Mutation

- Single point mutation at nucleotide 20210 in the 3′ untranslated region of the factor II (prothrombin) gene
- 1–2% of normal control individuals are heterozygous for G20210A
- 18% of patients with personal and family histories of venous thrombosis are heterozygous
- 6–8% of patients with confirmed DVT/ pulmonary embolism are heterozygotes
- Carriers have a 3–5 fold increased risk of inappropriate thrombosis
- Mutation stabilizes mRNA transcript resulting in higher levels of prothrombin (factor II)
- Seems to be synergistic with factor V Leiden
- Diagnosed by direct DNA testing (PCR-RFLP, PCR-FRET, etc)
- Relatively high incidence suggests hypercoagulable patients should be evaluated
- 2nd most common cause of hereditary thrombophilia

MOLECULAR DIAGNOSIS OF HEMATOPOIETIC NEOPLASMS

Introduction and Methods

- Consistent nonrandom genetic alterations are the hallmark of the majority of hematopoietic neoplasms
- Morphological and immunophenotypic studies are not always sufficient for disease classification and prognostic stratification
- Molecular studies are sometimes necessary for:
  - Clonality assessment: monoclonal *vs* polyclonal
  - Lineage determination: B- *vs* T-cell
  - Diagnostic/prognostic classification: Some molecular lesions are associated with specific types of lymphoma/ leukemia with prognostic and therapeutic implications
  - Detection of minimal residual disease: Unique molecular markers are often useful for therapeutic response monitoring, early detection of relapse, and evaluation of effectiveness of the "purging" of therapeutic bone marrow prior to transplanation
- Comparison of current routine cytogenetic and molecular diagnostic techniques:
  - Standard cytogenetic karyotyping:
    - Study the numerical and gross abnormalities of whole chromosomes of the tumor using nonspecific "banding" stains of metaphase chromosome spreads
    - Low sensitivity detection method (5–10%)
    - Nonspecific: target genes determining biologic behavior not analyzed
    - Tumor cell metaphase spreads typically of poor quality
    - Slow turnaround time: at least 1 wk (for cell growth and analysis)
  - Fluorescence *in situ* hybridization (FISH) **(Figure 9)**:
    - Study the specific region of an individual chromosome of the tumor using a specific fluor-labeled probe hybridized to interphase or metaphase cell spreads

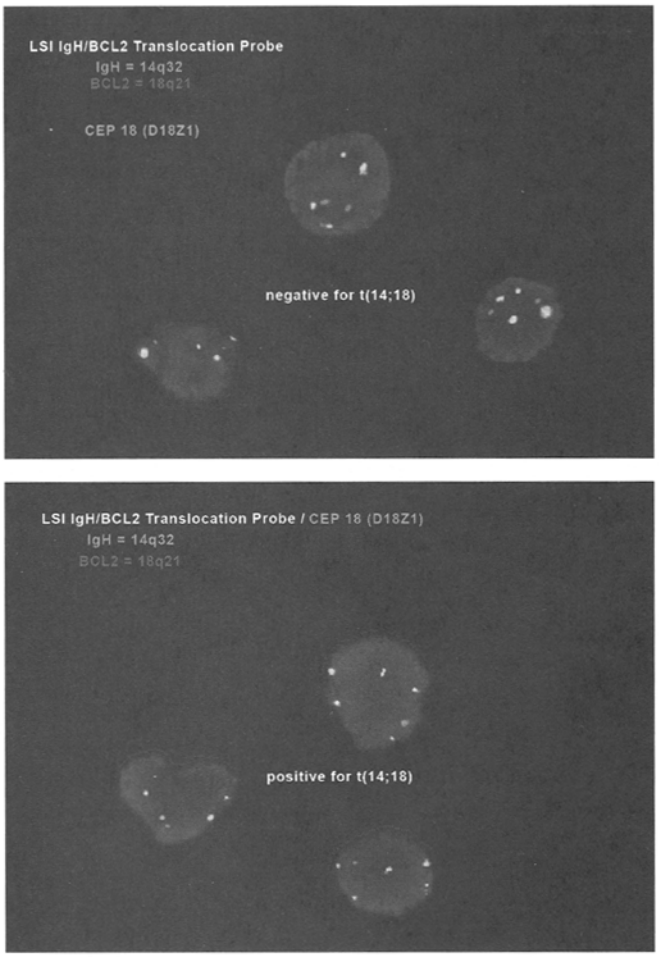


Fig. 9. Detection of the translocation t(14;18) by fluorescence *in situ* hybridization (FISH). Fluorescent probes specific for *BCL2* (red), IgH (green), and the chromosome 18 centromere (aqua = control) were hybridized to tumor cell spreads. **(Panel A)** depicts a "negative" sample, each cell showing 2 distinct signals of each color. **Panel B** is a follicular lymphoma sample with each cell showing two abnormal yellow (*BCL2/IgH*) fusion signals. The yellow signal is the result of the juxtapositioning of the red (*BCL2*), and green (IgH) signals as the result of the t(14;18).

- Both fresh and paraffin tissue (either tissue sections or air dried cytological preparations) are suitable
- Can be applied to both dividing (metaphase) and nondividing (interphase) cells
- Detect numeric abnormalities (gains or losses), a major advantage over PCR
- Sensitivity of detection: high (but not as high as PCR)
- Only specific genes or chromosomes analyzed
- Quick turnaround time: average 24 to 48 hours

– Southern blot analysis:
  - Study the DNA extracted from the tumor
  - Novel rearranged bands imply tumor clone
  - Intensity of rearranged band estimates tumor cell burden
  - Not as sensitive as PCR: requires more DNA
  - Slow turnaround time: 2–5 days
– PCR: using either DNA or RNA reverse transcriptase-PCR (RT-PCR):
  - Use one primer from each "partner" gene (for assessing translocation breakpoints)
  - Unrearranged (nontumor) cells give no product
  - "Novel" bands indicate gene-specific translocation events
  - "Novel" bands serve as sensitive genetic markers for tumor cell clones
  - Useful in monitoring disease course after therapy
  - More sensitive method: need only small amounts of DNA/RNA
  - Often applicable to fixed tissue (i.e., paraffin blocks)
  - Cost effective
  - Can be automated (to some degree)
  - Usually nonquantitative with routine PCR
  - Can be quantitative, especially with real-time PCR
– Mutational analysis:
  - Restriction endonucleases or allele-specific primers or probes can be used to detect specific point mutations
  - Denaturing HPLC can be used to screen for sequence abnormalities in the specific gene segments
  - Examples of mutations in genes with clinical significance in hematopoietic malignancy: *FLT3*, *TP53*, *ATM*, *IgH* somatic mutation, C-KIT
  - Labor intensive if multiple variable mutation sites exist
  - Can be semiautomated

♦ New molecular protocols are being used for routine diagnostic testing:
– Quantitative RT-PCR:
  - Has become a routine diagnostic procedure in some clinical laboratories
  - Quantitation of leukemic fusion transcripts helps to evaulate response to therapy and detection of early molecular relapse
  - Standardized protocols available for several types of leukemias such as childhood acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and acute promyeloid leukemia
– Spectral karyotyping (SKY):
  - Uses 24 color assay for visualization of all chromosomes in one experiment

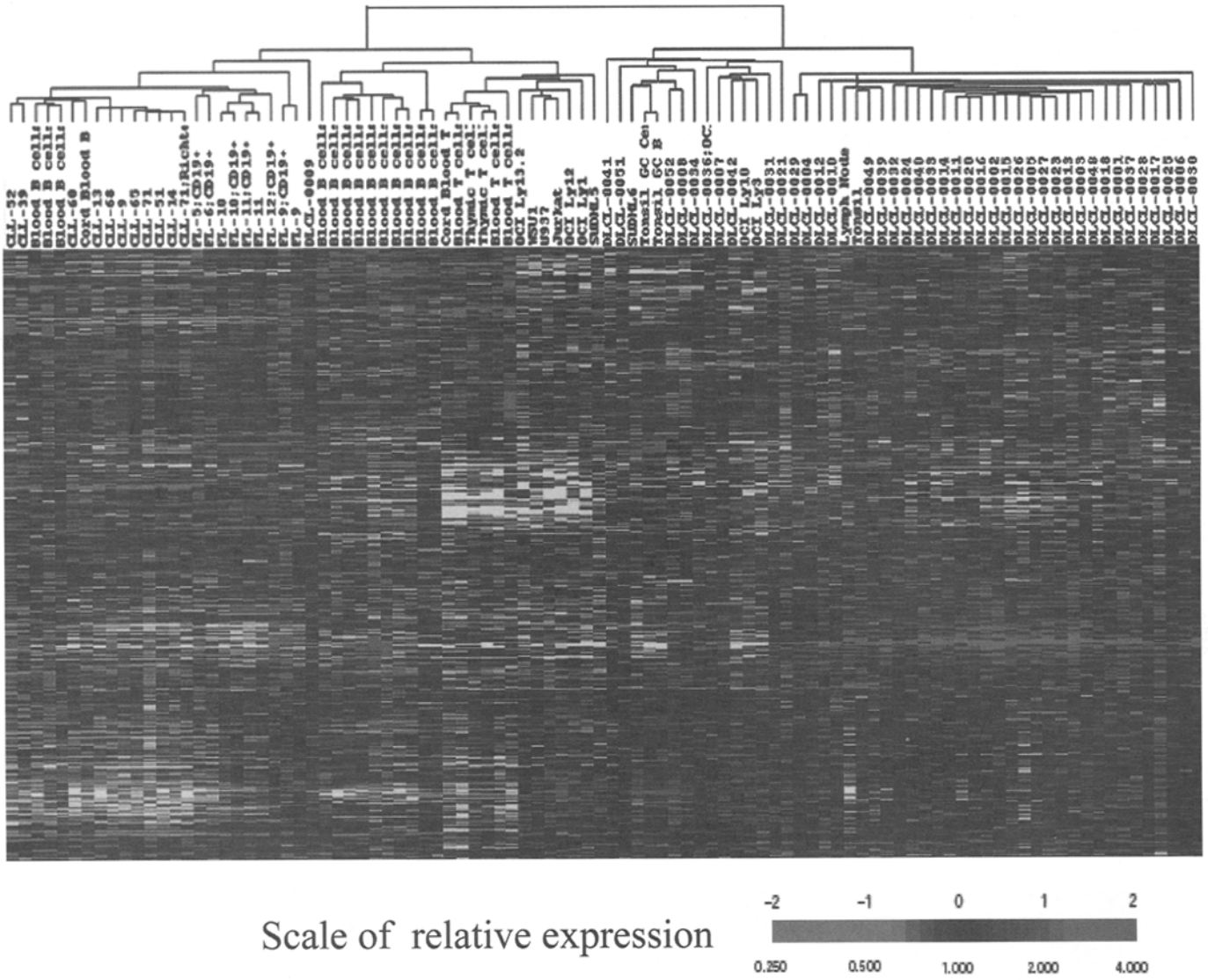


Fig. 10. Hierarchical clustering of 96 samples of normal and malignant lymphocytes; clustered based on the expression of 2000 known genes- as analyzed by microarray analysis. Each row represents a separate gene and each column a separate lymphocyte cell sample. Fluorescent cDNA probes prepared from each experimental RNA sample are hybridized to the array chip, each containing thousands of immobilized cDNA or oligonucleotide sequences. Shown are the relative ratios of hybridization of each lymphocyte sample to each reference gene. These ratios are a measure of relative gene expression in each experimental sample and are depicted according to the color scale shown at the bottom. As indicated, the scale extends from fluorescence ratios of 0.25 to 4(–2 to +2 in log base 2 units). Red indicates overexpression. Green indicates underexpression. Grey indicates missing or excluded data. In this manner, the experimental lymphocyte samples can be classified into "clusters" (or groups), each with a similar pattern of global gene expression. For some tumors, this type of gene expression "clustering" analysis can sub-classify morphologically indistinguishable tumors into biologically distinct prognostic categories.

- More sensitive than traditional karyotyping
- Subtle karyotypic rearrangments or structural aberrations can be detected

– Comparative genomic hybridization (CGH):
  - Assess the genomic gains or losses by evaluating the relative binding of different fluorescently labeled normal and tumor DNA's to normal chromosomes

– Gene expression profiling with microarray (**Figure 10**):
  - Assess the global gene expression profile or focused gene expression signatures by simultaneous hybridization of fluorescently labeled tumor RNA (or cDNA or cRNA) to thousands of "probes" immobilized as an array onto a miniaturized solid support

Table 1. Number of Variable Region Domains

	IG				*TCR*		
Gene Segments	H	κ	λ	α	β	γ	δ
V (variable regions)	50	25	30	60	46	8	10
D (diversity regions)	24	0	0	0	2	0	3
J (joining regions)	6	5	4	50	12	5	3

- Two platforms available: cDNA and oligonucleotide microarrays
- High throughput
- Requires fresh tissue or cells
- Genes expressed at low levels or genes with unstable mRNA may not be detected
- Interpretation is technically challenging , especially when the tissue samples contain admixed benign and malignant cells
- Requires further validation and standardization for clinical use

Molecular Assessment of Clonality

Immunoglobulin and T-Cell Receptor Gene Rearrangements

- Genetic rearrangements in the immunoglobulin and T-cell receptor genes determine the diversity of immune responses
- Cell-specific gene rearrangements can be used as a molecular "signature" of a clone of B- or T-cells
- Molecular methods to detect these gene rearrangements can determine the presence of a "clone" of identical lymphocytes—a hallmark of neoplasia
- Useful for both primary diagnosis and posttherapy disease monitoring

Immunoglobin and T-Cell Receptor Gene Rearrangements in Normal Lymphocyte Development

In the germline (unrearranged state), the Ig and TCR genes are composed of discontinuous coding regions **(Table 1)**

Immunoglobulin Heavy (IgH) Chain (Figure 11) and Light Chain Gene Rearrangements

- Unique V, D, and J region DNA rearrangements in each B-cell generate the variable regions (antigen-binding domains) of the Ig light and heavy chains

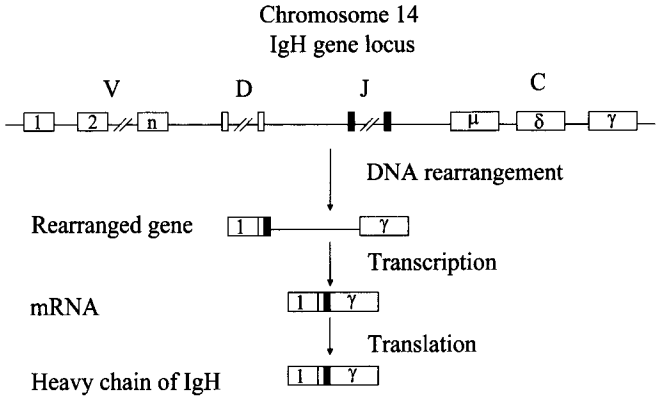


Fig. 11. The process of B-cell receptor immunoglobulin heavy (IgH) chain gene rearrangement during the differentiation of the B cell. The DNA in the IgH chain gene locus is cut and recombined to make a rearranged gene that is able to produce one of millions of functionally active immunoglobulin heavy chains. This gene can then be transcribed into mRNA, which is, in turn, translated into the specific heavy polypeptide chain.

- 1st rearrangement: D_H to J_H with insertion of random number of nucleotides (N) between D_H and J_H
- The V_H gene then joins to the D_HNJ_H segment with insertion of random number of nucleotides (N) between V_H and D_H
- The $V_HND_HNJ_H$ segment then joins with a C_H constant region gene and its switch region to generate $V_HND_HNJ_HC_H$
- VDJC is transcribed and translated into an Ig heavy chain
- Failed rearrangements are followed by attempts at rearranging the second IgH allele
- κ and λ undergo VJC gene rearrangements similar to heavy chain genes (except no D regions for light chain genes)
- κ light chain genes rearrange after successful Ig heavy chain gene rearrangement
- λ light chain genes rearrange only after both κ alleles fail to successfully rearrange
- Approx 10^{14} different variable region configurations exist (for immune diversity)

T-cell Receptor Gene Rearrangements

- Mechanism of TCR gene rearrangement very similar to IgH (above)
- TCR genes undergo VDJ or VJ rearrangments in the order: TCRδ, TCRγ, TCRβ, and TCRα
- A majority of circulating T-cells express TCRα/β and they undergo the entire spectrum of rearrangements
- A small population of T-cells express TCRγ/δ and do not undergo TCRβ and TCRα rearrangements
- TCR rearrangements do not occur in natural killer (NK) cells

Antigen Receptor Gene Rearrangements as Markers of Clonality

- Principle: Each individual lymphocyte contains a uniquely rearranged DNA pattern within the IgH or TCR genes
- Routine molecular methods (Southern blot and/or PCR) are not sufficiently sensitive to detect VDJ genetic rearrangements in a single cell
- Molecular analysis of polyclonal lymphocyte populations (reactive lymph nodes) will then show a heterogeneous mixture of unique (each individually invisible) "single-cell" signals
- The gel electrophoresis pattern will reveal a very faint "smear"—consisting of many hundreds of heterogeneously-sized DNA fragments
- The size heterogeneity in the VDJ DNA fragments of nonclonal lymphocytes results from:
  - Many differently sized V, D, J, or C genes being represented
  - Insertion of a random number of N nucleotides between VD and DJ
  - Imprecise exonuclease-mediated gene recombination
- Clonal lymphocyte populations (i.e., lymphoma) contain, by definition, thousands of cells with the identical IgH (B-cell) or TCR (T-cell) gene rearrangement:
  - Molecular analysis (Southern or PCR) will then show a single detectable nongermline VDJ rearrangement (from the predominant clone of cells)
  - The gel electrophoresis pattern will reveal a distinct BAND (reflecting the predominant clone) often together with a faint "smear" (the background polyclonal lymphocyte population)

Southern Blot Detection of IgH (Figure 12) and TCR Gene Rearrangements

- Requires fresh or frozen tissue (not fixed)
- Tissues should be trimmed of "nontumor" tissue to increase diagnostic sensitivity
- Requires $>10^7$ cells (>1 mg tissue)
- Tissue DNA digested with restriction enzyme, and electrophoresed
- Typically use 2–3 enzymes simultaneously to increase diagnostic sensitivity
- Southern blot probed with IgH probe (for suspected B-cell lesions) and/or TCRβ probe (for suspected T-cell lesion)
- Distinct nongermline rearranged bands (not smears) imply a monoclonal lymphocyte population suggesting malignancy
- Sensitivity: Southern blot will detect rearranged band if lymphocyte clone represents >1–5% of the cells analyzed
- Tumor cell load of <1% of total cells will yield false negative signal

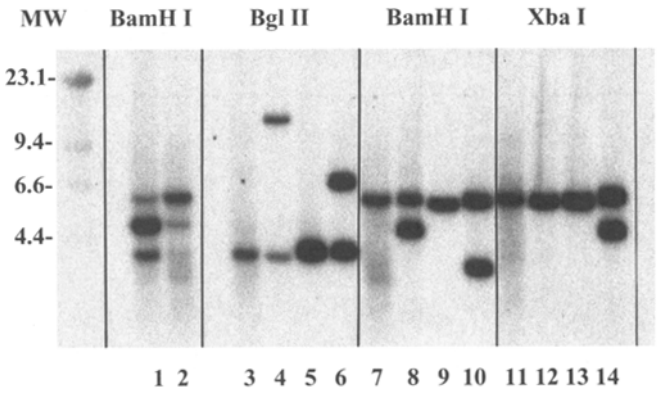


Fig. 12. Southern blot hybridization for IgH gene rearrangements. A positive (lymphoma) B-cell line control is shown in lanes 1 and 2, both showing clonally rearranged DNA bands in addition to the germline (unrearranged) band at ~4 kb. A negative control (polyclonal tonsil) in lanes 3, 7, and 11, shows only the germline (unrearranged) band and no additional clonally rearranged bands. Patient sample 1 (lanes 4 and 8) and patient sample 3 (lanes 6, 10, and 14) show clonally rearranged bands. Patient sample 2 (lanes 5, 9, and 13) shows no clonal rearrangement. Each DNA sample was digested with the restriction enzymes BamHI, Bal II or Xbal I as indicated. The digested IgH locus fragments are detected by hybridization with a radiolabeled probe from the joining region of the Immunoglobulin heavy chain gene.

- Rearrangement with IgH or TCRβ probe usually (not always) suggests tumor cell lineage (B- or T-cell origin)
- Intensity of rearranged band reflects quantity of tumor cells
- May be useful for estimating tumor burden
- Southerns can also be probed with immunoglobulin light chain gene (κ or λ probes)

Limitations of Southern Blot Gene Rearrangement Studies

- Low sensitivity: tumor cell burden below 1–5% may not be detected
- Long turnaround time: 2–5 days
- Requires significant amounts of DNA (can be problematic for skin and other small lesions)
- Southern blots of the TCRβ chain are not able to detect gene rearrangements in malignancies of γ/δ T-cells or NK-cells
- Some of these limitations can be overcome with PCR methods

PCR-based Detection of IgH and TCR Gene Rearrangements

- Requires fresh, frozen, or fixed tissue
- Tissues should be trimmed of "nontumor" tissue to increase diagnostic sensitivity
- Requires only $>10^4$–10^5 cells

IgH PCR for B-cell clonality determinations

- Sense PCR primers: from conserved sequences within V_H region (frameworks I, II, or III)
- Antisense PCR primers: from conserved sequences within J_H region
- Depending on primer pairs chosen, PCR product band from a clone of rearranged B-cells will be 70–380 bp in length
- V_H and J_H regions in germline (unrearranged) cells are too distant for successful PCR amplification and yield no PCR product
- So only rearranged cells (clones) yield detectable PCR bands
- Gel interpretation: detectable PCR band between 70–380 bp suggests clonal B-cell population
- Analytical sensitivity: clones of B-cells representing >0.1–10% of all cells will yield detectable PCR band (dependant on primers, tissue source, PCR conditions)
- Diagnostic sensitivity: only ~70–90% of known lymphomas will yield detectable IgH PCR products (dependant on primers, tissue source, PCR conditions, tumor type)
- Sequence heterogeneity in V_H and J_H regions may prevent primer binding in some clones

T cell receptor PCR for cell clonality determinations

- Sense PCR primers: from conserved sequences within V or D regions
- Antisense PCR primers: from conserved sequences within J region
- Depending on primer pairs chosen, PCR product band from a clone of rearranged T-cells will be 55 and 100 bp in length
- V and J regions in germline (unrearranged) cells are too distant for successful PCR amplification and yield no PCR product
- Typically, a panel of multiple primer pairs is used, as any one primer pair will fail to bind to a significant minority of TCR genes
- So only rearranged cells (clones) yield detectable PCR bands
- Gel interpretation: detectable PCR band between 55 and 100 bp suggests clonal T-cell population
- Analytical sensitivity: clones of T-cells representing >0.1–5% of all cells will yield detectable PCR band (dependant on primers, tissue source, PCR conditions)
- Diagnostic sensitivity: only ~70–90% of known T-cell lymphomas will yield detectable TCR PCR products (dependant on primers, tissue source, PCR conditions, tumor type)
- TCRβ PCR requires a large number of primers (>30) owing to the complexity of TCRβ locus
- TCRγ PCR is preferred for diagnostic purposes:
  - TCRγ region is less complex: the typical diagnostic PCR contains 4 primers against different V regions and a multiplex of J region primers and detects >90% of clonal T- cell neoplasms
  - TCRγ locus is consistently rearranged prior to TCRβ locus
  - γ/δ T-cell neoplasms show evidence of clonality by PCR for TCRγ but not by Southern blotting for TCRβ

Advantages of PCR-based methods for gene rearrangements

- Rapid result—often same day as biopsy
- Increased diagnostic sensitivity (afforded by amplification technology)
- Can be used on small amounts of DNA (from smaller biopsies)
- DNA integrity can be somewhat compromised (fixed or archival tissue acceptable)

Disadvantages of PCR-based methods for gene rearrangements

- Consensus primers may fail to amplify some VDJ clones
- Oligoclonal cells of questionable clinical significance may generate specific bands
- No quantitative information

Clinical Utility of IgH and T-Cell Receptor Gene Rearrangement Studies

Diagnosis of lymphoma and leukemia

- B-cell lymphoma and leukemia: Most have clonal IgH gene rearrangements and some may have TCRgene rearrangements
- T-cell lymphoma and leukemia: Most have TCR gene rearrangements, some may have clonal IgH gene rearrangements
- Presence of a TCR gene rearrangement is not necessarily diagnostic for T-cell linage
- Presence of a IgH gene rearrangement is not necessarily diagnostic for B-cell lineage
- Hodgkin lymphomas: They have IgH gene rearrangement but often not detectable unless tumor cells are enriched by microdissection
- NK-cell neoplasm: No detectable TCR gene rearrangement
- AML: ~20% have clonal IgH or TCRβ gene rearrangements (typically TdT positive cases)

Monitoring disease progress

- Once a clone of lymphocytes has been discovered, PCR and/or Southern blotting can be used to continually track the tumor cell clone to evaluate response to therapy (minimal residual disease)

- Disappearance of the "tumor-specific" gel band may correlate with successful therapy
- Reappearance of the "tumor-specific" gel band may correlate with disease relapse
- PCR clearly more sensitive than Southern blotting for minimal residual disease determinations

Molecular Determination of Clonality of Nonlymphoid Maligancies

- One of the two X-chromosomes is randomly inactivated in the early embryonic development of all females
- In neoplasms, nonrandom inactivation of X chromosome genes indicates monoclonality
- The human androgen receptor (HUMARA) locus (X-linked) has highly polymorphic trinucleotide (CAG) repeats. It is used to detect monoclonal nonrandom X-inactivation in nonlymphoid malignancies
- Evaluation of methylation sensitive restriction endonuclease sites or methylation-specific PCR primers can also be used because methylation is a marker for inactivated regions of the X-chromosome
- Can only be applied to female patients

General Guidelines for the Rational Use of Specific Molecular Pathology Assays

- The diagnosis of hematopoeitic malignancy can be made for a majority of cases without molecular studies
- A diagnosis of lymphoma should NEVER be made using only the gene rearrangement data
- Gene rearrangement data should always be interpreted along with the accompanying clinical, histologic, and immunophenotypic data
- Molecular studies can best be utilized to address the specific questions raised after morphological and immunological evaluations are performed
- It is always recommended that representitive fresh tissue or cells be archived whenever possible for possible molecular studies since fresh tissue or cells is always better than fixed paraffin tissue for molecular studies
- Clonal gene rearrangement usually (not always) indicates malignancy and benign (reactive lesions) are usually (not always) nonclonal:
  - Antigen receptor gene rearrangement PCR may give false positives owing to a few clonal lymphocytes in the study samples
  - Clonality of antigen receptor gene rearrangements, especially a pattern of oligoclones, is some times seen in:
    - Autoimmune diseases (i.e., Sjogren's syndrome and rheumatoid arthritis)
    - Infections (i.e., *Helicobacter pylori* gastritis, viral infections)
    - Dermatitis
    - Immune response to tumors
    - Immune reconsititution post-bone marrow transplant
- Ultrasensitive qualitative PCR methods may detect leukemia/lymphoma associated translocations in normal individuals: i.e., t(14;18), t(9;22), t(2;5), t(12;21), and 11q23. Single time point MRD detection is not necessarily predictive
- A negative PCR for Ig gene rearrangement does not entirely rule out a clonal lymphoid population due to sample problems such as:
  - A small clonal B-cell population in a background of polyclonal B-cells
  - DNA degradation or inadequate DNA extraction
  - Using limited or inappropriate primers for DNA amplification
  - Somatic hypermutation in mature B-cells, especially in folliclar lymphoma
  - Ig H gene deletion (10%)
  - Oligoclonal rearrangements and ongoing rearrangement in precursor B-cells
- Translocation detection by PCR may be negative owing to the heterogeneity of the breakpoints (i.e., DNA PCR for t(11;14) has a high false negative rate). FISH may then be a better alternative method
- Selection of methods for antigen receptor gene rearragements:
  - PCR for IgH and TCRγ is usually the first choice for evaluation of B- or T- cell clonality
  - If they are negative and a suspicion for lymphoma remains, Southern blot for IgH or TCRβ can be considered if fresh tissue is available
  - PCR for Igκ may help when PCR for IgH is negative and suspicion for lymphoma remains
- Disease-specific considerations:
  - If follicular lymphoma or mantle cell lymphoma are suspected, molecular studies for t(14;18) or t(11;14) may be considered if morphological and immunological features are not diagnostic. FISH is usually better than PCR
  - Differential diagnosis between Burkitt lymphoma/leukemia and large cell lymphoma can be difficult in some cases, Molecular studies for *c-MYC* translocations are helpful. FISH is usually better than PCR
  - For leukemia and myelodysplastic syndrome, peripheral blood or bone marrow are routinely studied by conventional karyotyping. Molecular studies for specific molecular lesions are sometimes indicated in the following conditions:
    - Confirm the diagnsosis: i. e., acute promyelocytic leukemia, chronic myelogenous leukemia
    - Prognostic stratifications: i.e., acute leukemia and chronic lymphocytic leukemia
    - Posttherapeutic evaluation for presence of minimal residual disease when leukemic molecular markers are available

Genetic Lesions Associated with Specific Diseases

Chronic Myeloproliferative Diseases (CMPD)

Seven disease entities are included under current WHO classification

- Chronic myelogenous leukemia (CML)
- Chronic neutrophilic leukemia (CNL)
- Chronic eosinophilic leukemia (CEL)/hypereosinophilic syndrome
- Polycythemia vera (PV)
- Chronic idiopathic myelofibrosis(CIMF)
- Essential thrombocythemia (ET)
- CMPD, unclassifiable

Genetic and molecular features

- CML: chromosomal translocation t(9;22) with or without additional genetic abnormalities.
- CNL, CEL, PV, ET, and CIMF: negative for t(9;22) but may have nonspecific recurrent abnormalities

Translocation t(9;22)(q34;q11) (Philadelphia chromosome) (Ph)

- Most CML cases are cytogenetically positive for t(9;22)(q34;q11)
- About 2.5% of CML cases are only positive at the molecular level
- Cases with clinical and morphological features of CML without detectable t(9;22)(q34;q11) are classified as atypical CML under the current WHO category of myelodysplastic/myeloproliferative diseases that often show dysplastic features
- Also present in ~25% of adult B lineage ALL and 5% of childhood ALL. The presence of t(9;22) in ALL predicts poor prognosis
- The translocation involves the ABL tyrosine kinase proto-oncogene on 9q34 and the BCR gene (breakpoint cluster region) on 22q11
- It results in aberrant expression of a BCR-ABL fusion protein with enhanced tyrosine kinase (and transforming) activity
- 2 predominant breakpoint regions within bcr:
  - Major breakpoint cluster region (M-BCR) in most CML cases and ~ half of ALL cases; resulting synthesis of a 210 kD BCR-ABL kinase
  - Minor breakpoint cluster region (m-bcr) (further upstream in BCR) in most pediatric ALL cases and ~ half of adult ALL cases; resulting synthesis of shorter 190 kD BCR-ABL kinase
- The breakpoint occurs rarely in the BCR mu region, resulting in a large fusion protein, p230. Patients with this fusion may have prominent neutrophilic maturation

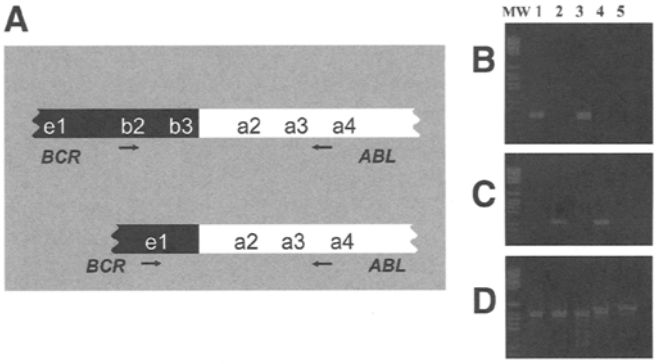


Fig. 13. Qualitative RT-PCR analysis for the detection of BCR-ABL fusion transcripts in CML. **(Panel A)** depicts the locations of the two sense PCR primers (in bcr exon b2 or e1) and the common anti-sense primer (in abl exon a4). **(Panel B)** shows RT-PCR for *BCR-ABL* with exon e1 BCR primer. **(Panel C)** shows RT-PCR for *BCR-ABL* with exon b2 BCR primer. **(Panel D)** shows RT-PCR for Beta 2 microglobulin as a house keeping gene control. Lane 1 depicts a patient sample (and lane 3 a positive control sample) with an e1a2 fusion gene. Lane 2 depicts a patient sample (and lane 4 a positive control sample) with a b3a2 fusion gene. Lane 5 shows a negative control. MW, Molecular weight ladder.

- Detection methods:
  - Routine cytogenetics:
    - Insensitive, slow, nonspecific, technically difficult
    - Necessary to perform at diagnosis and during the course of the disease for monitoring clonal evolution or emergence of Ph-negative clones
  - FISH:
    - Sensitive, quick, and specific
    - Faster turnaround time than routine cytogenetic karyotyping
  - Southern blot analysis with bcr probes:
    - *BCR-ABL* translocation creates novel tumor-specific Southern blot bands
    - Useful for primary diagnosis in "difficult" cases (cytogenetically negative)
    - Slow, relatively insensitive (1–5% tumor cell load) and requires abundant DNA
  - RT-PCR **(Figure 13)**:
    - Requires only small amounts of tissue RNA. RT-PCR with an ABL primer and a BCR primer (M-BCR and/or m-BCR)
    - Only tumor cells (with juxtaposed *BCR* and *ABL*) yield PCR signal
    - Fast turnaround
    - Extremely sensitive tumor cell detection; quantitative with real-time PCR technology

- Useful for monitoring minimal residual disease, particularly after targeted imatinib therapy
- *BCR-ABL* reappearance (or increased amount) after therapy predicts clinical relapse
- Greater than 3 log reduction of *BCR-ABL* RNA levels is predictive of sustained remission
- Unable to detect clonal evolution
- There is a high concordance between peripheral blood and bone marrow testing
- RT-PCR positivity 6 months after stem cell transplantation predicts a high risk of relapse
- RT-PCR positivity precedes cytogenetic and hematologic relapse by several months

Myelodysplastic/Myeloid Proliferative Diseases

Four disease entities are included under current WHO classification

- Chronic myelomonocytic leukemia (CMML)
- Atypical chronic myeloid leukemia (aCML)
- Juvenile myelomonocytic leukemia (JMML)
- Myelodysplastic/myeloid proliferative disease, unclassifiable

Genetic and molecular features

- All negative for t(9;22)(q34;q11) (Philadelphia chromosome): BCR-ABL
- Cytogenetic and molecular studies are often necessary to rule out CML
- Nonspecific and recurrent genetic abnormalities are frequently detected: +8, +13, –7/del(7q), del(20q), i(17q), del (12p), or structural abnormalities of 12p
- t(5;12) (q31;p12), resulting in formation of an abnormal fusion gene, TEL-PDGFRβ, occurring in fewer than 1–2% of CMML, and usually associated with eosinophilia
- Ras mutation in about 40% of patients with CMML, and 20% of JMML
- Cytogenetic studies are helpful for establishing the diagnosis in the right clinicopathological setting
- FISH is helpful for monitoring disease status
- Absence of genetic abnormalities does not rule out myeloproliferative/myelodysplastic syndrome

Myeloid Dysplastic Syndrome (MDS)

Five disease entities are included under current WHO classification

- Refractory anemia (RA)
- Refractory anemia with ringed sideroblasts (RARS)
- Refractory cytopenia with multilineage dysplasia (RCMD)
- Refractory anemia with excess blasts (RAEB)
- 5q-syndrome

Genetic and molecular features

- Nonspecific, recurrent cytogenetic abnormalities include +8, –5, del(5q), –7, del (7q), and del(20q) as well as complex karyotypes
- Present in about 25% of cases with RA, less than 10% of RARS, Up to 50% of cases with RCMD, 30 to 50% of cases with RAEB
- Deletion between bands q31 and 33 of chromsome 5 is the sole cytogenetic abnormality in 5q-syndrome, associated with a long survival
- Although most changes are not specific, the presence of cytogenetic abnormalities helps to establish the diagnosis and to define the prognosis
- Three major risk categories are based on cytogenetic findings:
  - Good risk: Normal cytogenetics, isolated (5q), isolated del(20), and –Y
  - Poor risk: complex abnormalities, i.e., >3 recurring abnormalities, or abnormalities of chromosome 7
  - Intermediate risk: all other abnormalities

Acute Myeloid (non-lymphoblastic) Leukemia (AML)

Many disease entities are included under current WHO classification

Four different AML's with recurrent genetic abnormalities defined in current WHO classification

- AML with t(8;21)(q22;q22) (*AML1-ETO*):
  - Constitute about 5–12% of AML, and about one third of AML with maturation
  - Bone marrow may have less than 20% of blasts. Do not classify them as RAEB
  - t(8;21) fuses AML1 (chromosome 21) with ETO (chromosome 8) to create AML1-ETO fusion protein, an aberrant transcription factor
  - It is most characterically associated with AML with maturation, FAB M2 subtype, however, seen in only about 40% of AML-FAB M2
  - Greater than 90% of t(8;21) positive cases have M2 morphology
  - AML with t(8;21) have a particular sensitivity to therapeutic regimens containing high dose cytosine arabinoside
  - A good prognostic association is well established in adult AML. Predicts good response to therapy
  - Detectable by cytogenetics, Southern blot, or RT-PCR
- AML with inv(16)(p13;q22) or t(16;16)(p13;q22) (*CBFβ-MYH11*):
  - Constitute about 10–12% of AML
  - Usually show monocytic and granulocytic differentiation and abnormal eosinophils (FAB, M4Eo)
  - High rate of complete remission and favorable prognosis

- Inv(16) fuses CBFβ gene (q22) (a transcription factor) with MYH11 (p13) (smooth muscle myosin heavy chain)
- Detected by cytogenetics or RT-PCR
- The inv(16) can sometimes be quite subtle and may be missed occasionally if the metaphase preparations are suboptimal
- The break points in the two genes are quite heterogeneous with at least 10 different fusion transcripts generated

♦ AML with t(15;17)(q22;q11-22) (*PML-RARα*) and variants:
- t(15;17) is the hallmark of acute promyelocytic leukemia (APL or AML FAB M3) including both classic hypergranular form and microgranular variant
- Constitute about 5–8% of AML
- Abnormal promyelocytes predominate including both typical and microgranular types
- Frequently associated with disseminated intravascular coagulation
- Timely confirmation with FISH or RT-PCR very important so the patient can be effectively treated with all trans-retinoic acid
- High rate of complete remission and favorable prognosis
- About 99% of APL have t(15;17)(q22;q21), resulting in a fusion between the retinoic acid receptor alpha (*RARα*) (chromosome 17q12) (a retinoid regulated transcription factor) with the promyelocytic leukemia (PML or MYL) gene (chromosome 15q22)
- The remaining 1% of APLs have variant translocations with disruption of *RARα* gene at 17q21: t(11;17)(q23;q21) resulting in a fusion gene PLZF-*RARα* t(11;17)(q13;q21) resulting in a fusion gene NuMA-*RARα* t(5;17)(q35;q21) resulting in a fusion gene NPM-*RARα* der(17) resulting in a fusion gene STAT5-*RARα*
- The *RARα* fusion transcription factors have altered activity and promote leukemogenesis
- All APL except the t(11;17)(q23;q21) variant can be effectively treated with retinoic acid. Treatment with histone deacetylase (HDAC) inhibitors is required to induce differentiation in APL with t(11;17)(q23;q21)
- Cytogenetics (typically) and FISH are often the primary choice. About 15% have been reported to be cytogenetically negative owing to cryptic lesions and technical failures
- In the common t(15;17) translocation, the breakpoints in *RARα* are well conserved in intron 2, while there are two major breakpoints in the PML gene. A single downstream RARα primer and two upstream PML primers are required for the detection of most (greater than 90%) PML-*RARα* fusion transcripts
- Molecular methods are available for detection, but false negative studies may occur
- RT-PCR is useful for detecting minimal residual disease after all-trans retinoic acid therapy
- Persistent PCR positivity after treatment predicts relapse
- Persistent PCR negativity predicts continued remission

♦ AML with 11q23 (MLL) abnormalities:
- The MLL (stands for mixed lineage leukemia, or myeloid lymphoid leukemia) gene on chromosome 11q23
- The gene has also been named ALL1, HTRX1, or HRX
- The most common translocations include t(9;11)(q21;q23); t(11;19)(q23;p13.1); t(11;19)(q23;p13.3)
- Partial tandem duplication is also reported
- Intermediate survival
- Seen in AML and MDS
- Found in ~80% of ALL cases in infants
- AML with 11q23 translocations often show monocytic differentiation (M4 or M5), or prior therapy with topoisomerase II inhibitors
- MLL translocations involve at least 80 different translocation partner genes including FEL (AF4) on 4q21 in the t(4;11), AF9 on 9q21 in the t (9;11) and one of three different genes ENL, ELL and EEN on 19p13 in the different t(11;19) translocations
- MLL regulates the expression of genes via chromatin remodeling. Many of the fusion partners are putative transcription factors
- Predicts poor response to standard therapies
- Commercial FISH probes are available to detect the break apart of the MLL gene
- Molecular studies are confounded by the many different partner genes involved in the translocations
- Breakpoints in MLL cluster in an 8.3 kb region may be detected by Southern blot or RT-PCR analysis

♦ Genetic abnormalities are common but nonspecific in other types of AML:
- AML with multilineage dysplasia:
  - Chromsome abnormalities similar to those seen in MDS
  - Often show gain or loss of major segments of certain chromoses: –7/del(7q), –5/del(5q), +8, +9, +11, del(11q), del(12p), –18, +19, del(20q), +21
  - Less often t(2;11), t(1;7) and translocations involving 3q21 and 3q26 regions
- AML, therapy related:
  - The predominant cytogenetic abnormality is a balanced translocation involving 11q23
  - Other abnormalities include t(8;21), t(3;21), inv(16), t(8;16) and t(6;9)
- Acute leukemia of ambiguous lineage:
  - About one third of them have the Philadelphia chromosome
  - Some associated with 11q23 abnormalities

  - Substantial cases show rearrangement or deletion of the Ig-heavy chain gene or TCR chain genes
- AML not otherwise categorized, mainly based on morphological features and lineage differentiation:
  - No unique chromosomal abnormalities have been identified
  - Nonspecific and recurrent cytogenetic lesions often observed

♦ Prognostic stratification of AML based on genetic abnormalities:
- Favorable prognosis with higher rate of complete remission (70% to 85%) and better 5-year survival (35% to 60%):
  - t(8;21), t(15;17), inv (16), or t(16;16)
- Unfavorable prognosis with lower rate complete remission (25% to 60%) and worse 5-year survival (2% to 15%):
  - –5, –7, 3q abnormality or complex
- Intermediate prognosis:
  - Normal, +8, +21, or 11q23 abnormality

FLT3 abnormalities

♦ FLT3 is a receptor tyrosine kinase expressed by hematopoietic progenitor cells and downregulated during differentiation

♦ Abnormalities of *FLT3* have been described as an internal tandem duplication (ITD) of the juxtamembraneous domain and missense mutation at Asp835

♦ The ITD occurs in about 23% of AML cases with the point mutation in about 7% of cases

♦ *FLT3* abnormalities result in the constitutive activation of the the tyrosine kinase domains via autophosphorylation, leading to a persistent "on" signal in the leukemic cells

♦ Molecularly targeted therapy with FLT3 inhibitors are under active investigation

♦ Detection of FLT3 abnormalities is helpful to select a subset of AML patients for clinical trials with these new agents

♦ FLT3 abnromalities are associated with poor prognosis in AML less than 60 years old, independent of karyotype

♦ PCR (both DNA and RT) assays targeting the ITD or Asp 835 regions are available for diagnosis

Acute Lymphoblastic Leukemia/Lymphoma (ALL/LBL)

Two disease entities are included under current WHO classification

♦ Precursor B acute lymphoblastic leukemia/lymphoma (B-ALL/LBL)

♦ Precursor T acute lymphoblastic leukemia/lymphoma (T-ALL/LBL)

Genetic and molecular associations

♦ Classification is mainly based on morphological and immunological features

♦ B-ALL/LBL:
- The genetic findings are prognostically important and used to modify the treatment in pediatric disease
- Favorable prognosis with higher rate of complete remission (70–85%) and better 5-year survival (35–60%): t(12;21)(p13;q22) or hyperdiploid (51–65)
- Unfavorable prognosis with lower rate of complete remission (25–60%) and worse 5-year survival (2–15%): t(9;22)(q34;q11.2), t(4;11)(q21;q23), t(1;19)(q23;p13.3) or hypodiploidy
- Intermediate prognosis: del(6q), del(9p), del(12p), hyperdiploidy (less than 51), near triploidy or near tetraploidy
- Specific association with morphological and immunological features:
  - *MLL* rearranged: often CD10–, CD24– and CD15+
  - B-ALL with t(1;19): often CD10+,CD34–, and CD20– or dim, cytoplasmic mu+
  - B-ALL with t(12;21): often show high density of CD10 and HLA-DR but no expression of CD9 or CD20

♦ T-ALL/LBL:
- Translocations often involving TCR loci at 14q11.2 (α and δ), 7q35 (β) and 7p14-15 (γ) are present in about one third of the cases
- Partner chromosomes including 8q24.1 (*MYC*), 1p32(*TAL1*), 11p15(*RBTN1*), 11p13(*RBTN2*), 10q24(*HOX11*), and 1p34.3-35 (*LCK*)
- Microdeletion of 5' regulatory region of TAL1 locus in about 25% of cases
- Deletion del(9p) (loss of *CDKN2A*) in about 30% of cases
- Specific clinical significance is not evident

t(1;19)(q23;p13): E2A -PBX1

♦ t(1;19) occurs in ~25% of ALL with pre-B (cytoplasmic Ig) immunophenotype

♦ Predicts poor prognosis and need for more aggressive treatment

♦ t(1;19) fuses the *E2A* transcription factor (chromosome19) with the *PBX1* transcription factor (chromosome 1)

♦ Creates E2A-PBX1 fusion protein, a transcription factor with direct transforming activity

♦ Detected by cytogenetics (less sensitive) or RT-PCR

♦ Some cases have t(1;19) by cytogenetics but no *E2A-PBX1* (by RT-PCR)

♦ These cytogenetic false positives (unlike those with detectable *E2A-PBX1*) have a good response to standard therapies

t(9:22)(q34;q11)

♦ It is the most common translocation in adult ALL (25–35% of cases)

♦ 5% of children with ALL, 1% of AML-M1 (without maturation)

- It occurs almost exclusively in the precursor B-cell ALLs (CD10+) with frequent aberrant coexpression of myeloid antigen CD13 and CD33
- Associated with uniform poor prognosis
- The breakpoints in the ABL gene are usually consistent in both CML and ALL, but they vary in the *BCR* gene
- RT-PCR detects a BCR-ABL fusion in up to 10% of ALL cases with normal karyotypes
- Commercial FISH probes are available

t(12;21)(p13;q22)

- Results in a fusion between *AML1* (*CBFα2* chromosome 21) and *TEL* (*ETV6*, chromosome 12)
- The normal *TEL* allele is deleted in most cases
- The most common translocation in pediatric ALL
- About 20% of pediatric ALL, 3% of adult ALL
- Precursor B-lymphoblasts with t(12;21) often express myeloid antigen
- Associated with good prognosis, but increased risk for late relapse
- Only rarely detectable by conventional cytogenetics (submicroscopic)
- Requires FISH or molecular methods (PCR and/or Southern) for detection

t(4;11)(q11;q23)

- Present in about 70% of infantile ALL and about 5% of adult and pediatric ALL
- Results in a fusion between *MLL* (chromosome 11) and *AF4* (*FEL*, chromosome 4)
- Leukemic blasts are often early precursor B-cells, negative for CD10, but with aberrant expression of CD15 and CD65
- Associated with an adverse prognosis in both infants and adults
- Detectable by conventional cytogenetics
- Commercial FISH probes are avaiable
- RT-PCR with a single exon 8 *MLL* primer and a single exon 7 *AF4* primer is sufficient in detection of all known fusion transcripts

t(8;14)(q24;q32)

- Brings the *c-MYC* protooncogene (chromosome 8) under the regulation of the IgH enhancer (chromosome 14)
- Typically associated with Burkitt lymphoma/leukemia, one of the most rapidly dividing neoplasms, requiring intensive therapy in order to achieve better outcomes
- 75% of cases of Burkitt lymphoma/leukemia are positive for t(8;14), the remainder positive for t(2;8) or t(8;22) (with light chain partner genes)
- For t(8;14), long-distance PCR assays are required because the breakpoints in and around the *c-MYC* and IgH genes are widely dispersed
- FISH and Southern blot analysis with *c-MYC* probes are often the methods of choice
- Clinical, morphological and immunological features are quite well characterized. Ki-67 is positive in almost 100% of tumor cells, serving as a surrogate marker
- Commercial *c-MYC* FISH probes are available. A FISH study for the *c-MYC* translocation is the method of choice for quick confirmation of the diagnosis

Mature B-cell Neoplasms

The following clinicopathological entities are included under current WHO classification

- Small lymphocytic lymphoma (SLL)/chronic lymphocytic leuekemia (CLL)
- Prolymphocytic leukemia
- Mantle cell lymphoma (MCL)
- Follicular lymphoma (FL)
- Hairy cell leukemia (HCL)
- Marginal zone lymphoma (MZL)
- Diffuse large B-cell lymphoma (DLBCL)
- Burkitt lymphoma/leukemia (BL)

Overview

- Morphological and immunological features are adequate for the diagnosis and classification of the majority of mature B-cell lymphomas
- Some lesions show features overlapping with reactive lymphoid hyperplasia; molecular characterization then often indicated
- Residual disease could be submicroscopic, requiring sensitive techniques for detection
- Molecular assays are frequently performed in appropriate clinical settings for determining clonality (to establish the diagnosis of lymphoma), the presence of specific genetic lesions (to clarify the classification), and detection of minimal residual disease
- Specific translocations are present in FL, MCL, and a subset of MZL. These translocations are defining genetic lesions with great diagnostic significance

Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma

- Ig H and L chain genes are clonally rearranged
- Two distinct types based on Ig VH gene mutation status:
  - Pregerminal center type (40–50%): Germline IgH, naive B-cells, often CD38+, increased ZAP-70 expression and poor prognosis (median survival: 3 yrs)
  - Postgerminal center type (50–60%) : Mutated IgH, memory B-cells, often CD38-, decreased ZAP-70 expression (median survival: 7 years)
- CLL/SLL has a variety of nonspecific, recurrent genetic lesions of prognostic significance

- About 80% of the cases have abnormal karyotypes:
  - Trisomy 12 (20%), predominatly in pregerminal center type
  - Deletions at 13q14 (~50%), more often in postgerminal center type
  - Deletions at 11q22–23 (20%), often in pregerminal center group, associated with poor prognosis
  - Deletions at 17p13 (10%), associated with loss of *TP53* and poor prognosis
  - Deletions at 6q21 (5%)
- Routine cytogenetic or FISH studies are the method of choice for evaluation of genetic lesions
- Molecular assays for IgH mutational status are not routinely performed

B-cell Prolymphocytic Leukemia

- Rare disease
- Ig H and L chain genes are clonally rearranged
- Abnormalities of TP53 gene occur in about 53% of cases
- Deletions at 11q23 and 13q14 are reported

Lymphoplasmacytic Lymphoma

- Rare disease
- Ig H and L chain genes are clonally rearranged
- There is somatic mutation in VH genes
- ~50% of cases show t(9;14)(p13;q32) involving PAX-5 gene:
  - *PAX-5* encodes a B-cell specific activator protein (BSAP)
  - Expression of BSAP is independent of the translocation

Hairy Cell Leukemia

- Ig H and L chain genes are clonally rearranged
- VH genes show somatic mutation
- No specific cytogenetic abnormalities identified
- Cyclin D1 is overexpressed in about 50–75% of the cases
- No detectable t(11;14) or *BCL-1* rearrangements

Marginal Zone Lymphoma (MZL)

The category includes the following entities under current WHO classification

- Splenic MZL
- Extranodal MZL of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal MZL

Genetic and molecular associations

Splenic MZL

- Ig H and L chain genes are clonally rearranged
- Most have somatic mutation with intraclonal variation in IgH gene
- 40% of cases show allelic loss of chromosome 7q21-32
- Trisomy 3 is uncommon
- No t(14;18) or t(11;18) detected

MALT lymphomas

- Ig H and L chain genes are clonally rearranged
- About 60% of them have trisomy 3
- About 25–50% of them have t(11;18)
- No association with t(14;18) or t(11;14)
- Gastric MALT lymphoma and t(11;18) (q21;q21):
  - Partner genes are *API2* (chromosome 11) and *MLT* (chromosome 18)
  - Produce a *API2-MLT* chimera
  - Both involved in apoptosis regulation
  - Associated nuclear BCL-10 positive staining by IHC
  - Independent of H. Pylori infection
  - Do not respond to antibiotic treatment
  - Detection methods: IHC for BCL10 protein, RT-PCR for fusion transcript, or FISH for translocation

Nodal MZL

- A rare disease
- Not well genetically characterized

Follicular Lymphoma

- Ig H and L chain genes are clonally rearranged
- Variable region genes show somatic mutations with intraclonal heterogeneity
- 100% of the cases show cytogenetic abnormalities
- 70–95% of them have t(14;18) involving BCL2 gene:
  - Not specific for follicular lymphoma, also present in ~20% of diffuse B-cell lymphomas
  - Juxtaposes IgH gene with the *BCL2* gene on chromosome 18
  - Lymphomas show 2 predominant breakpoint regions within *BCL2*
  - Major breakpoint region (MBR) utilized in ~60–70% of tumors
  - Minor cluster region (MCR) breakpoints in most of the other tumors
  - *BCL2* coding regions left intact by translocations
  - IgH regulatory controls stimulate inappropriate overproduction of BCL2 protein
  - *BCL2* normal function is suppression of apoptosis (programmed cell death)
  - B-cell *BCL2* over-production suppresses cell death, promotes inappropriate cell survival, and thus increases the chances for secondary oncogenic genetic aberrations
  - Southern blot with MBR and/or MCR *BCL2* probe will show "novel" rearranged bands, but insensitive for low tumor cell burdens

- PCR with primer for *BCL2* (MBR and/or MCR) and primer for J_h (IgH):
  - Only cells with rearrangements (i.e., tumor cells) will show a PCR product
  - Highly sensitive: typical detection limit is 1 lymphoma cell in 10^4–10^5 background cells
  - Useful for monitoring for minimal residual disease after therapy
  - Useful for checking "purged" bone marrow prior to transplantation
  - May be overly sensitive
  - Some benign lymphoid tissue (tonsils, nodes) may contain rare cells with t(14:18), below the sensitivity limit of most PCR assays

♦ Other genetic and molecular abnormalities:
- t(14;18) as a sole abnormality in only 10%
- Rare cases with t(2;18) (p12;q21)
- +7 (20%)
- +18 (20%)
- 3q27-28 (15%)
- 6q23-26 (15%), suggesting deletion of tumor supressor genes
- 17p (15%), alteration in TP53 gene, associated with a worse prognosis
- *BCL6* rearranged (15%)
- *BCL6* mutations (40%)
- Additional abnormalities may involve chromosomes 1, 2, 4, 5, 12, 13, or X

Mantle Cell Lymphoma

♦ Ig H and L chain genes are clonally rearranged
♦ Variable region genes are unmutated in the majority of the cases
♦ Small proportion of cases show somatic mutation
♦ Virtually all cases carry characteristic t(11;14)(q13;q32):
- Partner genes are IgH (chromosome 14) and *CYCLIN D1* (chromosome 11)
- CYCLIN D1 gene is also known as CCND1, BCL-1, PRAD1
- Juxtapositioning near IgH causes inappropriate overexpression of BCL-1
- BCL-1 normally functions to inactivate (phosphorylate) the tumor-suppressing retinoblastoma protein RB, thus preventing its suppression of cell cycle progression
- Overexpressed CYCLIN D1 thus promotes inappropriate cell growth
- Immunohistochemistry for CYCLIN D1 protein is adequate in most cases
- When immunostains are equivocal , FISH, Southern Blot or PCR can be considered
- FISH is more sensitive (~100%) than conventional cytogenetics (70–75%)

♦ Other genetic and molecular abnromalities:
- *ATM* mutation or deletion
- Total or partial trisomy 12
- Deletions at 13q14 or 17p can be seen

♦ No BCL2 or c-MYC rearrangement

Diffuse Large Cell Lymphoma

♦ A diverse group with different morphological subtypes: centroblastic, immunoblastic, T-cell/histiocyte-rich, anaplastic, plasmablastic, lymphomatoid granulomatosis type
♦ Clinicopathological variants: primary mediastinal large B-cell lymphoma, primary CNS lymphoma, primary effusion lymphoma, primary cutaneous large cell lymphoma of the leg, intravascular large cell lymphoma
♦ Epstium Bavr virus (EBV) infection of the neoplastic cells may be seen, more commonly associated with underlying immune deficiency
♦ Gene expression profiling shows three different subtypes with different gene expression signatures: germinal center B-cell (GCB) like, activated B-cell (ABC) like, type III with overlapping features:
- GCB-DLBCL: ~50%, CD10+, median survival of ~10 years
- ABC-DLBCL: ~35%, CD10–, median survival of ~2 years

♦ Ig H and L chain genes are clonally rearranged
♦ Variable region genes show somatic mutations
♦ 20–30% of cases show t(14;18) with translocation of *BCL2* gene
♦ ~30% of cases show 3q27 abnormalities involving BCL6 gene:
- *BCL6* gene on chromosome 3q27 is often translocated to a partner chromosome including IgH (chromosome 14); light chain gene (chromosome 22q11), and others
- BCL6 encodes a likely transcription factor which may regulate B-cell growth when inappropriately overexpressed
- *BCL6* abnormalities are not specific for DLBCL

♦ MYC rearrangement is uncommon
♦ Morphological/immunostains are sufficient for routine diagnosis
♦ Genetic and molecular studies typically not indicated

Mediastinal (thymic) Large B-cell Lymphoma

♦ Ig H and L chain genes are clonally rearranged
♦ Hyperdiploid karyotypes with gains of 9p and amplification of *REL* gene are often seen
♦ *NAL* gene overexpression is identified in a high proportion of the cases
♦ *BCL2*, *BCL6* and *c-MYC* rearrangements are absent

Intravascular Large B-cell Lymphoma

- The majority of cases have Ig gene rearrangements
- Rare cases have *TCR* gene rearrangement
- No characteristic chromosomal abnormalities have been identified

Primary Effusion Lymphoma

- Ig H and L chain genes are clonally rearranged
- Some cases have *TCR* gene rearrangement
- HHV-8/KSHV viral genomes are present in all cases
- EBV is found in most cases
- No characteristic chromosomal abnormalities have been identified

Burkitt's Lymphoma/Leukemia (BL)

- Ig H and L chain genes are clonally rearranged
- Variable region genes show somatic mutations
- All cases have a translocation of *c-MYC* (on chromosome 8):
  - Most commonly as t(8;14) involving IgH gene (chromosome 14)
  - Less commonly as t(2;8) or t(8;22) involving either of the light chain genes
  - Deregulation of *c-MYC* promotes lymphomagenesis
  - Diagnosis usually apparent by histology and immunophenotype
  - Molecular methods typically not required for clinical practice
  - However, *c-MYC* translocation detection by cytogenetic or molecular methods denotes an aggressive high-grade B-cell lymphoma with a high proliferative rate
  - The *c-MYC* translocations are not entirely specific for BL. Secondary B-acute lymphoblastic leukemia/lymphoma following follicular lymphoma is reported to also be positive
- EBV genomes in tumor cells are detectable in:
  - Almost all endemic cases
  - Less than 30% of sporadic cases
  - 25–40% of immunodeficiency cases
- Other genetic lesions include inactivation of *TP53* in ~30% of cases

Plasma Cell Neoplasms

WHO Classification

The category includes the following entities under current WHO classification

- Plamsa cell myeloma
- Plasmacytoma
- Immunoglobulin deposition diseases
- Osteosclerotic myeloma (POEMS syndrome)
- Heavy chain disease

Genetic and molecular association

- Clonal rearrangement of Ig genes commonly detected:
  - Most cases (~about 95%) show a single, monoclonal rearranged Ig band
  - Some cases (~about 5%) show multiple rearranged Ig bands
  - JH segments and/or parts or all of the chromosome 14 (where IgH gene is located) may be lost in light chain only disease
- About 20–60% of plasma cell myelomas have structural and numerical chromosomal abnormalities:
  - More chromosomal aberrations are seen in cases with progressive disease than in newly diagnosed cases
  - Most frequent changes are complex karyotypic abnormalities with multiple chromosomal gains or losses
- Translocations, deletions, and mutations are also present:
  - About 10% of cases have t(11;14)(q13;q32) involving *CYCLIN D1*
  - About 25% of cases have deletion of 17p13 associated with allelic loss of *TP53*
  - Expression of *PAX-5* gene (chromosome 9) is altered, resulting in loss of CD19
  - Normal plasma cells are CD19 positive while myeloma cells are CD19 negative
  - Deletion of 7q is also seen, associated with multidrug resistance

Mature Peripheral T-cell Lymphoma/Leukemia

WHO Classification

The category includes the following entities under current WHO classification

- T-cell prolymphocytic leukemia
- T-cell large granular lymphocytic leuekemia
- Adult T-cell leukemia/lymphoma
- Enteropathy T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis like T-cell lymphoma
- Mycosis fungoides and Sezary syndrome
- Primary cutaneous CD30 positive lymphoproliferative disorder
- Angioimmunoblastic T-cell lymphoma
- Periperal T-cell lymphoma, unspecified
- Anaplastic large cell lymphoma

Overview

- Less common and more aggressive than B-cell lymphomas
- A variety of translocations involving one of the T-cell receptors: α or δ on chromosome 14 and β or γ on chromosome 7. Partner genes are typically transcription factors whose expression is dysregulated due to translocation

- The t(2;5) is the most common cytogenetic abnormality in systemic anaplastic large cell lymphoma
- Clonal TCR gene rearrangement supports the diagnosis of T-cell lymphoma
- Detection of the t(2;5) helps to confirm the diagnosis of CD30+ anaplastic large cell lymphoma associated with a better prognosis
- Clinical and pathological correlation is always necessary for definitive diagnosis
- Monoclonality does not equal lymphoma
- Presence of t(2;5) does not equal CD30+ anaplastic large cell lymphoma

Anaplastic Large Cell Lymphoma

- About 90% of the cases show clonal TCR gene rearrangements
- Some cases show no Ig or TCR gene rearrangements
- EBV is negative
- The majority of cases express ALK protein, owing to *ALK* translocation:
  - t(2;5)(p23;q35) (70–80%), resulting in the *NPM-ALK* fusion gene on 5q35
  - Variants (20–30%): *TPM3* gene at 1p21, *TFG* at 3p21, *ATIC* at 2p35, *CLTC* at 17p23 and other genes
  - Translocations result in expression of ALK protein which is not normally expressed in lymphocytes
  - Patients with ALK positive ALCL have better survival than ones with ALK negative ALCL
  - Rarely B-cell lymphomas have *ALK* translocations with ALK protein expression
  - Translocations are detectable by cytogentics, FISH and Southern blot
  - Fusion transcripts are detectable by RT-PCR
  - Abnormal expression of ALK proteins is detectable by immunohistochemistry
  - For routine diagnosis, ALK immunohistochemistry is preferred test
  - FISH is more sensitive than RT-PCR
  - Not all *ALK* gene abnormalities are detectable by RT-PCR
  - RT-PCR may be used in monitoring minimal residual disease. It can detect much lower levels (1 in 10,000) of the disease than the standard PCR test for TCR gene rearrangement (1 in 100–1000)
- ALK negative cases: genetic lesions not studied

NK Cell Neoplasms

- TCR genes are in germline configuration
- Pattern of X chromosome inactivation can be used for clonality evaluation (in females)
- A variety of nonspecific but recurrent and clonal cytogenetic abnormalities are reported with del(6)(q21q25) as the commonest one
- EBV genomes are present in the majority of cases

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

- L&H cells have clonally rearranged Ig genes
- Rearrangements not detectable in whole tissue but detectable in enriched single L&H cells
- VH genes have a high load of somatic mutation with ongoing mutation
- EBV infection is consistently absent in the L&H cells

Classical Hodgkin Lymphoma (CHL)

- Ig gene rearrangements are present in Hodgkin Reed–Sternberg (HRS) cells in >98% of cases
- Rare cases show clonal TCR rearrangements
- Rearrangements not detectable in whole tissue but detectable in enriched single HRS cells
- VH genes have a high load of somatic mutation without ongoing mutation
- No detectable Ig mRNA and protein due to a lack of the octamer dependent transcription factor Oct2 and or its coactivator BOB.1:
  - Other B-cell lymphomas and NLPHL have detectable Oct2 and/or BOB.1
- There is persistent activation of NFκB, preventing apoptosis in HRS cells. This may be caused by:
  - Defects of the natural inhibitors of NFκB
  - Aberrant activation of IκB kinase (IKK)
  - Overexpression of TNF receptor associated factor (TRAF) 1 molecule
  - EBV infection, producing LMP1
- EBV infection in HRS cells is common:
  - Characterized as latency type II EBV infection, producing LMP1 and EBNA-1 but not EBNA-2
  - About 75% of mixed cellularity HL
  - 10–40% of nodular sclerosis HL
  - Almost 100% in patients in developing regions and those with HIV infection
- Aneuploid and hypertetraploid karyotypes are common in HRS cells
- Recurrent gains of the chromosomal subregions of chromosomal arms 2p, 9p, and 12q and amplifications on chromosomal bands 4p16, 4q23-q24, and 9p23-p24 are revealed by CGH
- No t(14;18) and t(2;5) detected

Histiocytic and Dendritic Cells Neoplasms

- Ig or TCR genes are in a germline state

Mastocytosis

- Recurring genetic abnormalities including somatic point mutations of *c-KIT*, a tyrosine kinase receptor for stem cell factor (or mast cell growth factor)

MOLECULAR DIAGNOSTICS OF SOLID TUMORS

Sarcomas

- Specific chromosomal translocations are the predominant genetic alteration in a variety of sarcomas
- 11 different sarcomas (*see* **Table 2**) have had specific chromosomal translocation breakpoints molecularly characterized:
  - The resulting fusion gene (or transcript) is present in the majority of cases of each of these categories of sarcomas i.e., the presence of these genetic alterations is a sensitive diagnostic test
  - The specific fusion gene (or transcript) for each tumor type is typically not associated with any other type of tumor i.e., the presence of these genetic alterations is a specific diagnostic test
- The detection of these chromosomal translocations is often very helpful for primary diagnosis, particularly given the similar morphology of many of these tumors
- PCR-based diagnostic methods are becoming routine—with one primer directed at each specific fusion partner:
  - Only tumor cells with the specific translocation will yield a PCR-positive signal
  - Nontumor cells (or tumor cells of a different "type") will be PCR negative
  - RNA (not DNA) used as the typical PCR-based diagnostic target owing to the heterogeneity of translocation breakpoints within introns
  - RT-PCR also a powerful tool for minimal residual disease detection and monitoring the efficacy of therapy
- In most of these sarcomas, the fusion genes created by these specific chromosomal translocations encode transcription factors aberrantly regulating gene expression:
  - The novel chimeric fusion proteins formed by the translocation often obtain novel biochemical functions—typically as a "new" transcription factor with altered activity
  - The novel biochemical activities of these chimeric fusion proteins include enhanced proliferative capability, inhibition of apoptosis, inhibition of differentiation, and facilitation of lineage commitment—all specific properties of tumor cells

Gastrointestinal Stromal Tumors (GIST)

- Mesenchymal gut neoplasms—old nomenclature was intestinal leimyosarcoma
- GIST's express the cell-surface receptor c-kit (CD117), a transmembrane tyrosine kinase that is the receptor for steel factor:
  - Most GIST's have detectable gain of function mutations in the c-kit kinase
  - Mutated c-kit has constitutively activated kinase activity that drives cell proliferation and inhibits apoptosis
- GIST's are insensitive to standard chemotherapy but are sensitive to targeted therapy with imatinib (Gleevec), a small molecule inhibitor of activated tyrosine kinases (perhaps better known as the new best therapy for CML):
  - Imatinib is now considered the consensus best therapy for GIST
- The spectrum of activating mutations in c-kit is heterogeneous
- Identifying the type and location of c-kit mutations has significant clinical relevance:
  - GIST patients with exon 11 c-kit mutations (75% of all GIST's) are more sensitive to imatinib and carry a better prognosis than tumors with other (or no) c-kit mutations
  - Determining the c-kit mutation status is becoming routine to predict responses to imatinib

Multistep Carcinogenesis: The Colorectal Cancer (CRC) Paradigm

- All CRC's (and their adenomatous precursor lesions) contain discrete genetic alterations:
  - The sequence and timing of these mutations is predictable during the usual progression from hyperplasia to adenoma to carcinoma
  - The specific gene alterations found in specific stages of CRC confirms the "multi-hit" model of carcinogenesis:
    - Carcinogenesis requires the sequential accumulation of multiple genetic alterations in a single target cell, the sum total of which create the full cancer cell phenotype
  - "early" CRC lesions (hyperplasia and adenoma) include loss or mutation of either:
    - "gatekeeper" genes that normally function to regulate cell growth and differentiation:
      - "gatekeeper" genes are often "tumor suppressor" genes, such as APC—commonly lost or mutated in early precancerous lesions (hyperplasia and early adenoma)
      - APC mutation is the earliest observable genetic alteration in cells destined to become CRC
    - "caretaker" genes that normally function to maintain genomic stability:
      - "caretaker" gene mutations in early colonic precursor lesions include mismatch repair genes such as MSH2, MLH1, PMS1, and PMS2
  - Later stages of CRC multistage tumorigenesis associated with:
    - Methylation abnormalities (typically hypomethylation)—as another mechanism to inactivate tumor suppressor genes. Often first apparent in early adenomas

Table 2. Chromosomal Translocations and Fusion Genes in Sarcomas

Tumor	*Cytogenetic translocation*	*Fusion genes*
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	PAX3–FKHR
Alveolar rhabdomyosarcoma	t(1;13)(p36;q14)	PAX7–FKHR
Alveolar soft-part sarcoma	t(X;17)(p11;q25)	TFE3–ASPL
Clear-cell sarcoma	t(12;22)(q13;q12)	EWS–ATF1
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	COL1A1–PDGFB
Desmoplastic small-round cell tumor	t(11;22)(p13;q12)	EWS–WT1
Ewing's sarcoma / primitive neuroectodermal tumor	t(11;22)(q24;q12)	EWS–FLI1
Ewing's sarcoma / primitive neuroectodermal tumor	t(21;22)(q22;q12)	EWS–ERG
Ewing's sarcoma / primitive neuroectodermal tumor	t(7;22)(p22;q12)	EWS–ETV1 (rare)
Ewing's sarcoma / primitive neuroectodermal tumor	t(2;22)(q33;q12)	EWS–E1AF (rare)
Ewing's sarcoma / primitive neuroectodermal tumor	t(17;22)(q12;q12)	EWS–FEV (rare)
Infantile (congenital) fibrosarcoma	t(12;15)(p13;q25)	ETV6–NTRK3
Inflammatory myofibroblastic tumor	t(1;2)(q22;p23)	TPM3–ALK
Inflammatory myofibroblastic tumor	t(2;19)(p23;p13)	TPM4–ALK
Myxoid chondrosarcoma	t(9;22)(q22;q12)	EWS–CHN
Myxoid chondrosarcoma	t(9;17)(q22;q11)	TAF2N–CHN (rare)
Myxoid liposarcoma	t(12;16)(q13;p11)	TLS–CHOP
Myxoid liposarcoma	t(12;22)(q13;q12)	EWS–CHOP (rare)
Synovial sarcoma	t(X;18)(p11;q11)	SYT–SSX1
Synovial sarcoma	t(X;18)(p11;q11)	SYT–SSX2
Synovial sarcoma	t(X;18)(p11;q11)	SYT–SSX4 (rare)

  - Proto-oncogene activation: typically a ras family member in CRC. Often first apparent in intermediate adenomas
  - Loss of other tumor suppressor genes: typically p53 or loss of chromosome segment 18q (the DCC gene) in CRC. Often first apparent in late adenomas or early carcinomas

- Inherited alterations in the same "gatekeeper" or "caretaker" genes (often mutated in "sporadic" cancers) are often found in patients with familial cancer syndromes:
  - Familial adenomatous polyposis (FAP)—with APC "gatekeeper" gene mutations
  - hereditary nonpolyposis colon carcinoma (HNPCC)—with "caretaker" mismatch repair gene mutations
  - retinoblastoma—with "gatekeeper" Rb gene mutations
  - breast cancer—with "caretaker" BRCA-1 or BRCA-2 mutations
  - Von Hippel–Lindau syndrome (renal cell carcinomas and others)—with "gatekeeper" VHL gene mutations
  - Li-Fraumeni syndrome (multiple tumor types)—with "gatekeeper" p53 gene mutations
- Altered mismatch repair genes confer the phenotype of "microsatellite instability" (MSI) that is often measured in the lab by a PCR based assay:
  - microsatellites are short DNA stretches (typically 1–5 nucleotides), repeated several times in tandem. Most common example is repeats of the dinucleotide CA (for example 11 or 15 or 20 sequential CA repeats)
  - gain or loss of repeat units (in tumor DNA *vs* normal DNA), as assessed by the size of PCR products, is designated as "microsatellite instability"
  - microsatellite instability (indicative of deficient mismatch repair genes) is seen in ~15% of all colorectal cancers and confers a relatively good prognosis compared to tumors without MSI

HER-2/Neu Overexpression in Breast Cancer: Predicting Response to Molecularly Targeted Therapy

- Human epidermal growth factor receptor 2 (HER-2) (also known as neu or c-erbB-2) is an oncogene that is overexpressed in ~30% of invasive breast cancers:
  - Encodes a tyrosine kinase receptor that transduces intracellular growth-promoting (oncogenic) signals
  - Mechanism of overexpression is typically gene amplification
- Her-2 overexpression is an important predictive and prognostic biomarker:
  - HER-2 overexpression predicts tumor aggressiveness and adverse prognosis for breast cancer patients
  - HER-2 overexpression predicts benefit from anthracycline (doxorubicin)-based adjuvant chemotherapy
  - For metastatic breast cancer, HER-2 overexpression predicts benefit from treatment with targeted anti-HER-2 monoclonal antibody therapy (trastuzumab)
  - Determining HER-2 oncogene status is now an integral part of the routine clinical-pathologic evaluation of breast cancer
- Common lab methods for determining HER-2 overexpression include semi-quantitative immunohistochemistry (protein target) and/or FISH (DNA target):
  - Both routinely performed on usual formalin fixed paraffin-embedded tissue section
  - When performed with appropriate quality assurance measures, HER2 FISH and immunohistochemistry methods almost always yield concordant results
  - As compared to immunohistochemistry, FISH has a higher failure, higher reagent cost, and longer turnaround time
  - FISH methods, however, may be better predictors of clinical outcomes, particularly in cases with indeterminate immunohistochemistry

MOLECULAR DIAGNOSIS IN MICROBIOLOGY

Introduction and Methods

Molecular microbiology utilizes the technology of molecular genetics for the clinical diagnosis and prognosis of infectious diseases

Uses

- the primary detection of infectious organisms—qualitative and quantitative
- monitoring responses to antiinfective therapy
- Epidemiologic Typing: comparing "clonality" between epidemiologically related isolates
- Epidemiologic surveillance: screening high-risk patients for nosocomial organisms
- Determining virulence: i.e., antibiotic/ antiviral resistance

Nucleic acid isolation and purification

- DNA and RNA can be made from blood, tissue, body fluids, paraffin blocks
- Classic DNA extraction method: organic extraction
- New, quick DNA preparation methods:
  - salt precipitation
  - quick-spin affinity columns
  - automated robotic extractors are becoming more routine

Major diagnostic methods

- Direct Probe Hybridization (without amplification)
- Nucleic Acid Amplification:
  - Polymerase chain reaction (PCR)
  - Other amplification technologies

Advantages of PCR as a microbiologic detection tool

- Target amplification provides extreme sensitivity:
  - 1–100 molecules of target nucleic acid can be detected
- Excellent Specificity:
  - Only targets homologous to both primers will be amplified
- Applicable to detection of any infectious organism: particularly useful for those that can not be easily cultured
- Can also be a quantitative method (with real-time PCR)

Disadvantages of PCR

- Requires specialized equipment and personnel
- Not presently well-standardized
- Risk of false positives from PCR product contamination carry-over
- Commercial reagents not widely available (except the most common pathogens)

Detection of PCR products

Ethidium Bromide (EtBr) Staining of Gels

- Intercalates specifically into duplex DNA
- Fluoresceses under UV Light to yield visible DNA "band" of a particular size
- Low Sensitivity: Requires ~10 ng PCR product DNA
- Will detect specific and nonspecific PCR products
- Useful for detecting "abundant" organisms after PCR

Southern blotting

- Electrophorese PCR products to separate by size
- Denature to make single stranded DNA
- Transfer to solid support (membrane)
- Hybridize to labeled viral-specific probe DNA: radioactive or chemiluminescent
- Probe binds to complementary sequences to generate specific bands, observable on X-ray film
- approx 10,000 times more sensitive than ethidium bromide and also highly specific

Semi-automated PCR product detection

- Routine clinical utility of diagnostic PCR will require rapid, nonradioactive, semiautomated detection methodologies
- Faster, more precise, more economical than tedious manual gel-based detections
- Can be as sensitive and specific (or moreso) as manual gel-based detections
- Several competing technologies exist; popular formats include:
  - solid-phase capture of PCR products and microplate colorimetric readout (PCR-ELISA)
  - fluorescent real-time PCR

Other amplification methodologies: non-PCR

- Ligase chain reaction
- transcription-mediated amplification (TMA)
- NASBA
- branched chain DNA (bDNA)
- a variety of others

Clinical microbiologic applications of amplification technologies

- Rapid detection of organisms not optimally identifiable by routine methods—culture and serology
- Applicable to virtual any organism for which some DNA sequence information is available
- Tests available now for a multitude of organisms

Pathogen detection: PCR vs culture and/or serology

- Culture often impossible: Hepatitis C, Pneumocystis, toxoplasma
- Culture often slow and insensitive: HIV, Mycobacterium, enterovirus, B. pertussis
- Sensitivity may be crucial: Herpes simplex or mycobacterium in the CNS

Infectious agents for which PCR-based tests have clear clinical utility

- Viruses:
  - hepatitis C virus
  - Herpes family viruses (CMV, HSV, EBV)
  - HIV
  - many others: enterovirus, rotavirus, adenovirus
- Mycobacteria:
  - rapid ID of Mycobacteria from clinical sample
  - rapid speciation of mycobacterial culture: TB vs non-TB
- Spirochetes: borrelia burgdorferi (Lyme disease) and T. pallidum (syphilis)
- Sexually transmitted disease agents:
  - chlamydia, N. gonorrhoeae, treponema pallidum
- Immunodefiency-associated pathogens:
  - fungi: dimorphic fungi, aspergillus, pneumocystis
  - parasitic: toxoplasma
- respiratory pathogens:
  - mycoplasma
  - legionella
  - influenza, parainfluenza
- Novel organisms:
  - universal amplification of 16s rDNA

Hepatitis C Virus (HCV)

- Primary Etiologic Agent of what used to be called "Non-A, Non-B Hepatitis"
- Member of the Flavivirus family: RNA genome of 9.4 kb
- Transmitted parenterally, perinatally, sexually
- Very high frequency of chronic hepatitis in infected pts
- Increased risk of cirrhosis and hepatocellular carcinoma
- PCR-based diagnostic tests are a model for analogous tests of many other organisms

HCV laboratory diagnosis

- HCV Serologic Tests: Tests to detect antibodies to HCV:
  - ELISA immunoassay is primary screening test:
    - detects serum antibodies to viral proteins (c22-3, c100-3, c33c)
    - ~90% sensitive
    - Specificity: 70–100% in high-risk groups; ~50% in low risk groups (blood donors)
  - Recombinant immunoblot assay (RIBA, Western blot):
    - Primarily a supplemental, confirmatory test
    - Serum reacted with 4 recombinant HCV antigens immobilized on a strip
    - c22-3, c33c, c100-3, c100-3 (5-1-1)
    - Positivity defined as reactivity with at least 2 different HCV antigens
    - Reactivity with only one HCV antigen defined as indeterminate
  - Seroconversion ~11 weeks after exposure

- Symptoms (and increased transaminases) often present after 6–8 weeks
- Window of seronegativity: 6–11 weeks after infection
- Tests to detect HCV antigens - NONE
  - The viral RNA can be considered the "antigen" target for PCR-based assays
- Weaknesses of antibody tests:
  - Acute disease may precede seroconversion by 3–5 weeks
  - Low specificity in low-risk populations
  - False negative test in immunocompromised pts
  - False positive test in pts with autoimmune disease (many have hepatitis)
  - Antibody test remains positive indefinitely—irrespective of hepatitis

♦ Direct Detection of HCV by RNA-PCR:
- The only available method for directly measuring virus (rather than an antibody response)
- Methodology:
  - Extract RNA from serum or plasma
  - Copy RNA into cDNA with reverse transcriptase
  - PCR amplify the cDNA with oligonucleotide primers to a conserved region of the HCV genome (such as the 5′ nontranslated region)
- Qualitatively or quantitatively detect the amplified HCV DNA:
  - Southern blot analysis with an HCV-specific probe
  - PCR-ELISA (colorimetric detection)
  - Fluorescent real-time PCR

♦ Controls for the HCV RNA PCR Assay:
- Strict physical containment of PCR products to avoid contamination
- RNA mixed with HCV-positive RNA ("spiked" control RNA such as Δ68 in **Figure 14**) to detect potential PCR inhibitors in clinical specimens
- Water controls to detect reagent contaminations
- Positive and negative "RNA extraction" controls

♦ Clinical Utility of HCV RNA PCR (Qualitative) (**Figure 14**):
- Primary diagnosis of acute hepatitis C before seroconversion (~11 weeks)
- HCV hepatitis in patients with no antibody response (immune-compromised)
- Patients with indeterminate or ambiguous serologic assays
- To monitor efficacy of antiviral therapy (typically with interferon and ribavirin):
  - Loss of HCV RNA after therapy confirms effective anti-viral response and defines treatment success

♦ Clinical Utility of Quantitative HCV RNA PCR Tests (**Figure 15**):
- To predict efficacy of antiviral therapy:
  - Pretreatment HCV RNA level is a significant predictor of sustained interferon responsiveness
  - Initial low level viremia correlates with sustained antiviral response:
    - cutoff viral load approx. 800,000 copies per mL for stratifying high/low risk of response
  - High pretherapy viral load predicts poor response to IFN therapy
- To serially monitor anti-viral therapy (typically with interferon and/or ribavirin):
  - Successful therapy correlates with sequentially falling or undetectable HCV RNA
- To determine disease severity:
  - High viral titers correlate with advanced disease stage

♦ Other semiautomated quantitative HCV RNA methods:
- bDNA (branched chain): signal (not target) amplification
- Quantitative competitive PCR-ELISA
- NASBA (nucleic acid sequence based amplification)
- Fluorescent real-time PCR

Cytomegalovirus (CMV)

A complex DNA virus of the Herpes family

♦ Produces latent infections (often asymptomatic in immunocompetent hosts)

♦ Common cause of life- or sight-threatening systemic disease in immunocompromised patients:
- transplant recipients: pneumonitis, enteritis
- AIDS/HIV: retinitis, CNS infection, polyradiculitis
- neonates - congenital CMV

Prevalence

♦ 30–70% of US population is infected (seropositive): immuno-competent are not typically symptomatic

CMV diagnostic tests

♦ Serology:
- IgG antibody indicates past exposure
- IgM antibody indicates recent exposure or reactivation
- serologic tests have limited utility for diagnosis of clinically active disease

♦ Histopathologic changes:
- characteristic basophilic intranuclear inclusions (owl's eye) in infected cells

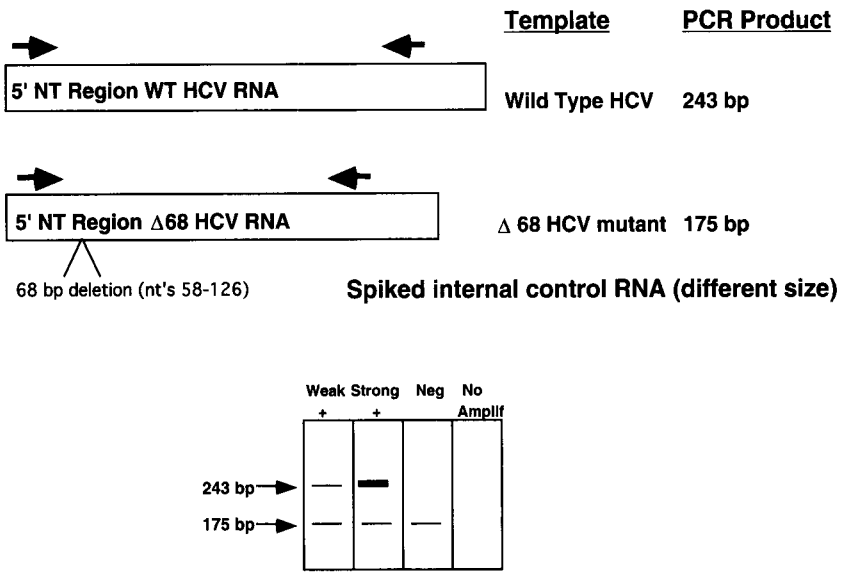


Fig. 14. HCV RNA detection by qualitative RT-PCR. RNA prepared from serum is reverse transcribed and PCR amplified with primers from the conserved 5′ non-translated region of the hepatitis C virus. To control for the absence of inhibitors and insure successful PCR , each sample is spiked with a small quantity of a synthetic RNA (Δ68) containing the identical primer-binding sites but with a 68 base pair internal deletion. After PCR, electrophoresis reveals a 175 bp PCR product in all "amplifiable" samples (the result of successful PCR of the spiked Δ68 RNA), but a 243 bp product only in those samples containing HCV RNA. The absence of the Δ68 signal at 175 bp indicates either a failed PCR reaction or a PCR inhibitor and suggests the need for a repeat analysis.

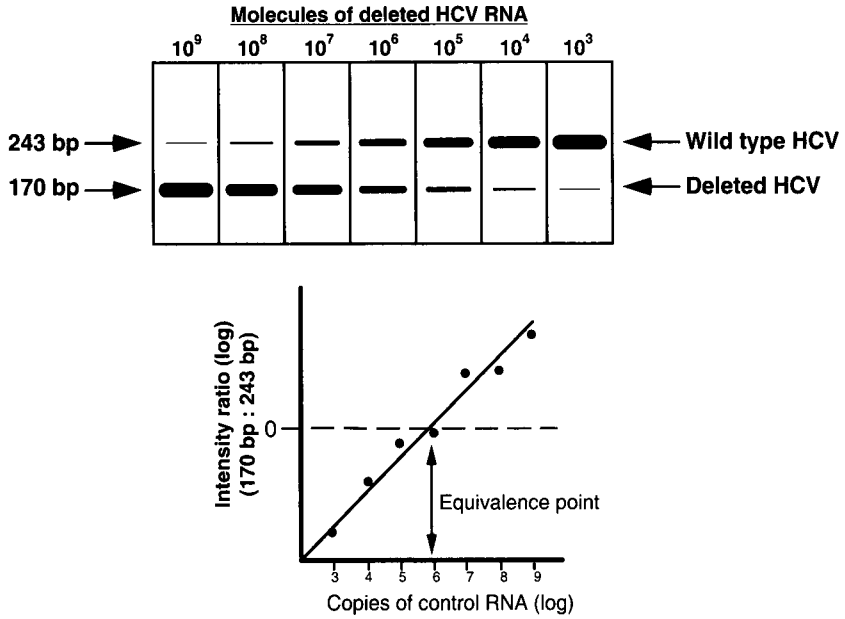


Fig. 15. Quantitative competitive RT-PCR for determining Hepatitis C RNA viral loads.
Each serum-derived patient RNA sample is PCR amplified in the presence of variable quantities of Δ68 "deleted" synthetic HCV RNA (from 1 thousand to 1 billion molecules). The intensity of the wild type/deleted signal is then plotted (log scale), and the amount of "known" deleted HCV RNA at the equivalence point (defined as equal wild type and deleted signals) then indicates the amount of "unknown" wild type HCV template. Because this method is so technically laborious, it has now largely been replaced by fluorescent real-time PCR methods.

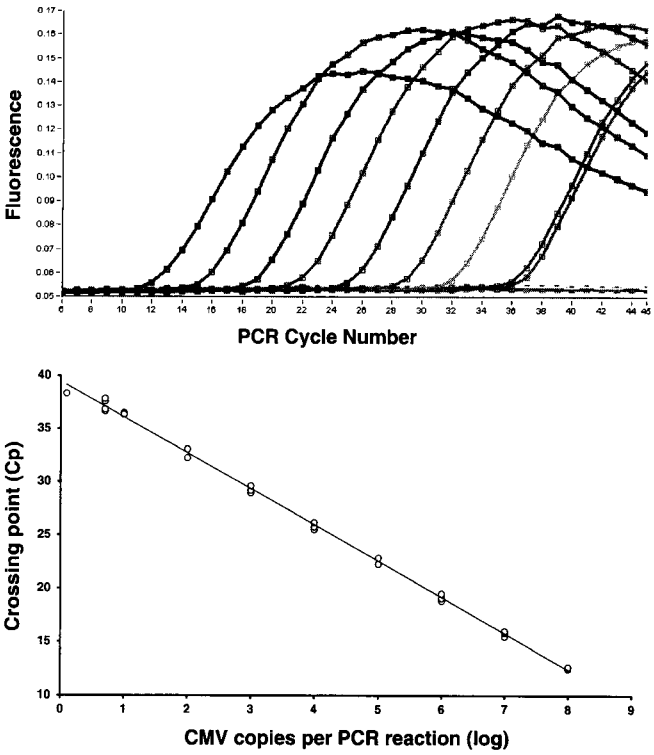


Fig. 16. CMV real-time PCR A well-quantitated stock of CMV DNA was serially diluted and subjected to real-time quantitative PCR with primers and probes to the CMV glycoprotein B gene. **(Panel A)** shows the raw amplification curves from one such experiment, and panel B shows a composite graphical representation of 3 such combined serial dilution experiments. The panel A tracings represent input CMV copy numbers of (from left to right) 10^8, 10^7, 10^6, 10^5, 10^4, 10^3, 10^2, 10, 5, 2.5, 1.25, and 0.625 molecules per PCR reaction. The lowest detectable dilution was 5 copies per PCR reaction. The PCR cycle number at which the amplification curve first rises above background levels (the "crossing point") is then plotted against the known template quantity **(Panel B)**. The resulting standard curve can then be used to determine the CMV viral load from the crossing point of any unknown sample.

- specific for CMV, but not very sensitive
- requires biopsy specimen

♦ CMV Antigenemia assay:
- direct immunostain of peripheral blood WBC's with CMV-specific antibodies
- specific and rapid, but less sensitive than culture or PCR

CMV viral culture

♦ Traditional diagnostic "gold standard" (before PCR)

♦ sensitive and specific, but may require 1–2 weeks of culture

♦ Rapid shell vial (centrifuge-assisted) viral culture: more rapid but less sensitive
- Culture followed by CMV-specific immuno-stain after 1–2 culture days

CMV detection: PCR vs culture

♦ PCR is more sensitive, more rapid, more expensive than viral culture:
- results typically available within 1–3 days

♦ PCR may be better predictor of active CMV disease in some patient groups, particularly bone marrow transplant recipients

♦ Earlier, more sensitive detection of CMV may lead to earlier, more effective therapy in transplant and AIDS patients

♦ Quantitative CMV viral loads useful for monitoring responses to antiviral therapy

CMV PCR test

♦ Specimen: whole blood (or plasma or white cells), body fluid, tissue

♦ Extract DNA

♦ PCR with CMV-specific primers:
- internal control: coamplify patient DNA with primers to an endogenous human gene to ensure presence of "amplifiable" DNA and detect potential PCR inhibitors
- usual positive, negative, sensitivity controls

♦ Detect by fluorescent real-time PCR **(Figure 16)** or gel electrophoresis or other methods

♦ Sensitivity: typically 200–400 molecules/mL

♦ Clinical Utility of CMV PCR (in bone marrow transplant patients)
- screen all posttransplant patients with weekly PCR's (culture not necessary)
- give preemptive ganciclovir therapy when PCR is positive; do not treat if PCR is negative
- spares most patients ganciclovir-mediated bone marrow toxicity
- most BMT centers use similar protocols
- in BMT, PCR is consensus best test for CMV—detects active disease earlier and with higher sensitivity than either viral culture or antigenemia assays
- monitor viral load posttherapy to ensure adequate antiviral responses

♦ CMV PCR for solid organ transplants and HIV:
- PCR is clearly the most sensitive test for presymptomatic disease detection
- Perhaps too sensitive?
  - may detect "asymptomatic" viremia
  - conflicting reports: highly method and lab dependent
- Lesson: know your lab's capabilities

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2

Human Genetic Disorders

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CONTENTS

I. Chromosomal Disorders 2-3
Chromosomal Aneusomy 2-3
Trisomy 21 (Down Syndrome) 2-3
Trisomy 13 (Patau Syndrome) 2-4
Trisomy 18 (Edward Syndrome) 2-4
Klinefelter Syndrome (XXY) 2-5
Turner Syndrome (45,X) 2-5
Microdeletion Syndromes 2-6
Angelman Syndrome 2-6
Prader-Willi Syndrome 2-7
Cri du Chat Syndrome 2-7
22q Deletion Syndrome (DiGeorge [DGS]/Velo-Cardio-Facial Syndrome [VCF]) 2-7
Smith-Magenis Syndrome 2-8
Beckwith-Wiedemann Syndrome 2-8
Miller-Dieker Syndrome 2-8
William Syndrome 2-9
Chromosome Breakage Syndromes 2-9
Fanconi Anemia 2-9
Bloom Syndrome 2-9
Ataxia Telangiectasia 2-10
Xeroderma Pigmentosum 2-10

II. Single Gene Disorders 2-10
Trinucleotide Repeat Disorders 2-10
Fragile X Syndrome 2-11
Myotonic Dystrophy 2-12
Friedreich Ataxia 2-12
Huntington Disease 2-12
Spinal Cerebellar Ataxia (SCA) (Types I–VIII) 2-13
Spinal and Bulbar Muscular Atrophy (SBMA, Kennedy Disease) 2-13
Duchenne/Becker Muscular Dystrophy (DMD/BMD) 2-13
Spinal Muscular Atrophy (SMA), Types I, II, and III 2-14
Charcot-Marie-Tooth Disease 2-14
Hereditary Neuropathy with Liability to Pressure Palsies 2-14
Skeletal Disorders 2-14
Achondroplasia 2-14
Osteogenesis Imperfecta (Types I–IV) 2-15
Connective Tissue Disorders 2-15
Fibrillin-Related 2-15
Marfan Syndrome 2-15
Collagen-Related 2-16
Ehlers-Danlos Syndrome 2-16
Stickler Syndrome 2-17
Alport Syndrome 2-17
Hematologic Disorders 2-18
α Thalassemia 2-18
β Thalassemia 2-18
Sickle Cell Anemia 2-19
Hemophilia A 2-19
Hemophilia B 2-19
von Willibrand Disease 2-20
Other Genetic Disorders 2-20
Cystic Fibrosis 2-20
Albinism (Ocutocutaneous Albinism type I [OCA1]) 2-21
Neurofibromatosis Type I (von Recklinghausen) 2-21

Neurofibromatosis Type II 2-22
Tuberous Sclerosis 2-22

III. Metabolic Disorders 2-22
Amino Acid Disorders 2-22
Phenylketonuria 2-22
Tyrosinemia Type 1 (most prevalent) 2-23
Maple Syrup Urine Disease 2-24
Homocystinuria 2-24
Urea Cycle Disorders 2-25
Organic Acidemias 2-25
Isovaleric Acidemia 2-25
Propionic Acidemia 2-26
Methylmalonic Acidemia 2-27
Carbohydrate Metabolism Disorders 2-27
Glycogen Storage Disease (Type I) 2-27
Galactosemia 2-28
Galatokinase Deficiency 2-28
Transport Disorders 2-28
Familial Hypophosphatemic Rickets 2-28
Cystinuria 2-29
Hartnup's Disease 2-29
Cystinosis 2-29
Metal Metabolism Disorders 2-30
Wilson Disease 2-30
Acrodermatitis Enteropathica 2-30
Menkes Disease 2-31
Hemochromatosis 2-31
Purine Metabolism Disorders 2-32
Lesch-Nyhan 2-32
Adenosine Deaminase 2-32
Peroxisomal Disease 2-33
Zellweger Syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease 2-33
Adrenoleukodystrophy (X-linked) 2-33

IV. Lysosomal Storage Diseases 2-33
Mucopolysaccharidoses 2-33
Mucolipidoses 2-34
I-Cell Disease 2-34
Pseudo-Hurler Polydystrophy 2-34
Sphingolipidoses 2-35
GM1 Gangliosidosis 2-35
GM2 Gangliosidosis (Tay-Sachs) 2-36
Sandhoff Disease 2-36
Niemann-Pick, Types A and B 2-37
Niemann-Pick, Type C (NP-C) 2-37
Gaucher Disease 2-37
Krabbe Disease 2-38
Metachromatic Leukodystrophy 2-39
Fabry Disease 2-39

V. Familial Cancer Syndromes 2-40
Familial Adenomatous Polyposis 2-40
MYH-associated Polyposis 2-40
Basal Cell Nevus Syndrome (Gorlin Syndrome) 2-41
Breast/Ovarian Cancer 2-41
Colon Cancer (Hereditary Nonpolyposis) 2-42
Cowden's Syndrome (Multiple Hamartoma Syndrome) 2-43
Li-Fraumeni Syndrome 2-43
Multiple Endocrine Neoplasia Type 1 2-44
Multiple Endocrine Neoplasia Types 2A, 2B, and Familial Medullary Thyroid Carcinoma (FMTC) 2-44
Peutz-Jeghers Syndrome 2-45
Retinoblastoma (RB) 2-45
von Hippel-Lindau (VHL) 2-46
Wilms' Tumor 2-46

VI. Mitochondrial Disorders 2-47

VII. Suggested Reading 2-48

CHROMOSOMAL DISORDERS

Chromosomal Aneusomy

Trisomy 21 (Down Syndrome)

Chromosome and Gene Location

- Additional chromosome 21
- Trisomy of the bottom 1/3 of chromosome 21 is sufficient for the clinical phenotype (21q22 is the critical region)

Inheritance

- 95% meiotic nondisjunction (47 chromosomes present):
  - 80–90% maternal, increases with maternal age
  - 10–20% paternal
  - 1% risk of recurrence or maternal age related risk (whichever is greater)
- 3–4% unbalanced translocation (46 chromosomes with an extra chromosome 21 fused to another chromosome):
  - 50% sporadic (not inherited)
  - 50% balanced translocation in one parent, often translocation of acrocentric chromosomes (13,14,15,21,22)
- 1–2% mosaicism (at least two different cell lines):
  - Results from postzygotic nondisjunction or loss of the extra 21 in one cell line

Incidence

- 1/800 live births

Clinical

- Phenotype:
  - Flat facial profile, thick nuchal fold, upward slanting palpebral fissures, depressed nasal bridge, epicanthal folds, Brushfield spots of iris **(Figure 1A)**, single transverse palmar crease **(Figure 1B)**, gap between 1st and 2nd toe **(Figure 1C)**, low set c-shaped ears
- Neurologic:
  - Learning disabled (IQ=40–80), poor Moro reflex, infantile hypotonia, developmental delay, joint hyperflexibility, increased risk for Alzheimer disease
- Others:
  - 40% congenital heart defects (endocardial cushion defects including atrioventricular canal defect, and ventricular septal defects), increased risk for childhood acute leukemia, hypothyroidism, obesity, short stature, increased incidence of pulmonary hypoplasia, duodenal atresia
- Life expectancy:
  - 75% spontaneously abort in first trimester. If live born, 80% survival at age 30

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies extra chromosome 21

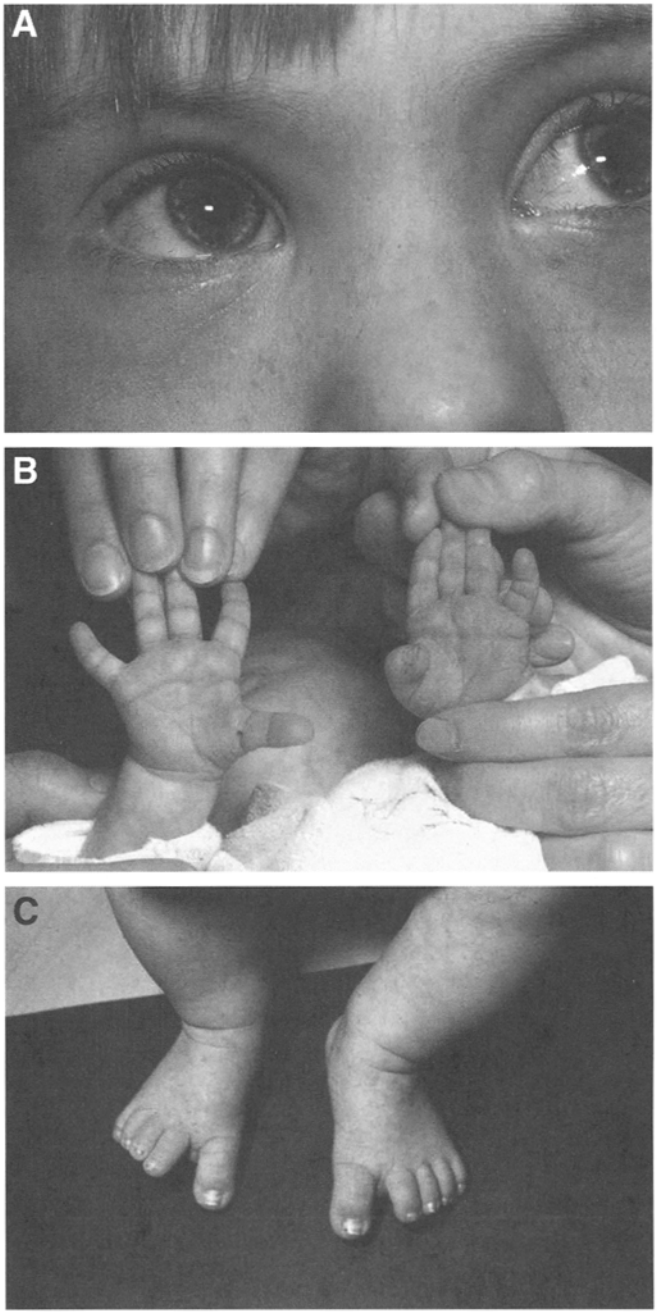


Fig. 1. Down syndrome—Brushfield spots on irides **(A)**. Single transverse palmar creases and fifth finger clinodactyly **(B)**. Gap between first and second toes **(C)**.

- Prenatal:
  - Altered maternal serum markers in the first trimester (increased human chorionic gonadotrophin (hCG), decreased pregnancy associated plasma protein A [PAPPA]) and second trimester (decreased α-fetoprotein and unconjugated estriol, increased hCG and inhibin A)

- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis

♦ Ultrasound:
- Thickened nuchal fold, congenital heart defects, duodenal atresia ("double bubble" sign), short humerus and femur, short middle phalanx of the fifth finger

Treatment

♦ Not curable, supportive/symptomatic

Trisomy 13 (Patau syndrome)

Chromosome and Gene Location

♦ Additional chromosome 13

Inheritance

♦ 80% meiotic nondisjunction:
- 80–90% maternal, increases with maternal age
- 10–20% paternal

♦ 20% unbalanced translocations (derived from parental carrier of balanced chromosomal translocation involving chromosome 13)

Incidence

♦ 1/10,000 births

Clinical

♦ Phenotype:
- Spectrum of midline abnormalities ranging from simple ocular hypotelorism to cyclopia to complete absence of eyes. Other features include prominent occiput, microcephaly, malformed low set ears, cleft lip and palate, polydactyly of hands and feet, clenched hands, rocker bottom feet, transverse palmar crease **(Figure 2)**

♦ Neurologic:
- Complete or incomplete holoprosencephaly, severe mental retardation, seizures, deafness, hypotonia, apneic spells

♦ Others:
- Congenital heart defects (hypoplastic left heart and ventricular septal defects), urogenital defects, cryptorchidism (males), bicornuate uterus and hypoplastic ovaries (females), polycystic kidneys, umbilical hernia, omphalocele

♦ Life expectancy:
- 90% die in first year of life (2/3 by 6 months)

Laboratory

♦ Cytogenetics:
- Chromosome analysis identifies extra chromosome 13

♦ Prenatal:
- Maternal serum markers are not useful
- Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis

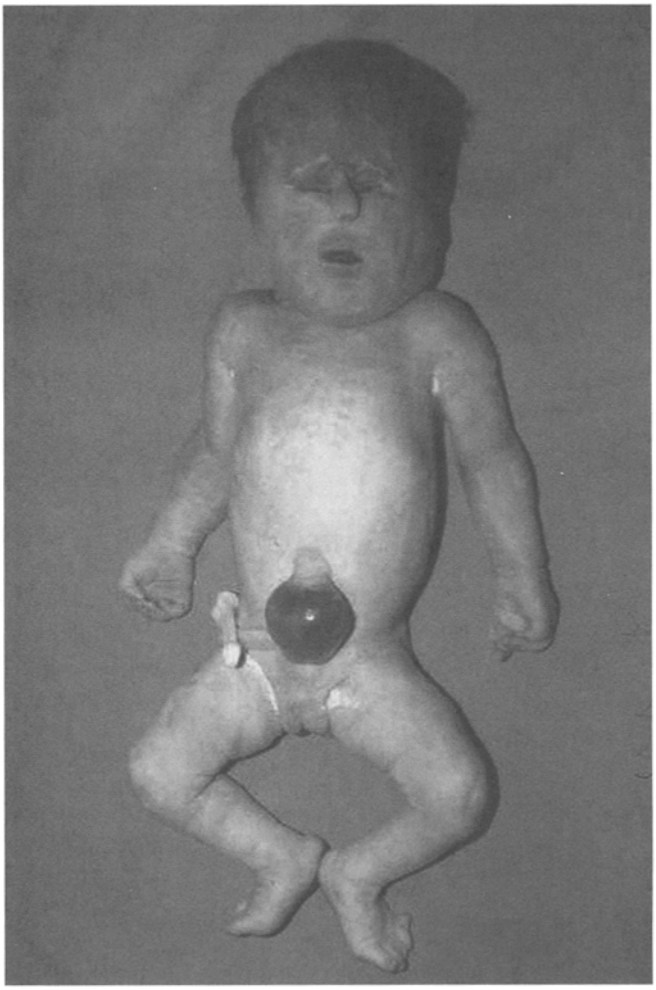


Fig. 2. Trisomy 13—showing hypotelorism and tube-like nasal structure. Polydactyly on foot.

♦ Ultrasound:
- Holoprosencephaly, cleft lip and palate, cystic hygroma, polydactyly, congenital heart defects, cystic kidneys, omphalocele

Treatment

♦ Not curable, supportive/symptomatic

Trisomy 18 (Edward Syndrome)

Chromosome and Gene Location

♦ Additional chromosome 18

Inheritance

♦ Meiotic nondisjunction:
- 95% maternal, increases with maternal age
- 5% paternal

Incidence

♦ 1/5000–1/10,000 births

Clinical

- Phenotype:
  - Microcephaly with prominent occiput, micrognathia, malformed ears, cleft lip and palate, clenched hands, second and fifth digits overlapping third and fourth (**Figure 3**), rocker-bottom feet, single transverse palmar crease, hypoplastic nails
- Neurologic:
  - Severe mental retardation, seizures, hypertonia
- Others:
  - Severe intrauterine growth retardation, congenital heart defects (ventricular septal defects), urogenital defects, cryptorchidism, horseshoe kidney, diaphragmatic hernia, omphalocele
- Life expectancy:
  - 95% spontaneously abort. Of those live born, 90% die within first year of life

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies extra chromosome 18
- Prenatal:
  - Altered maternal serum markers (decreased α-fetoprotein, unconjugated estriol, and human chorionic gonadotrophin) may detect 80% of cases
  - Prenatal diagnosis through chromosome analysis of chorionic villi or amniocentesis
- Ultrasound:
  - Clenched hands, club and rocker-bottom feet, micrognathia, cleft lip and/or palate, congenital heart defects, omphalocele, diaphragmatic hernia, neural tube defects, choroid plexus cysts, cystic hygroma

Treatment

- Not curable, supportive/symptomatic

Klinefelter Syndrome (XXY)

Chromosome and Gene Location

- Extra X chromosome

Inheritance

- 55% Maternal nondisjunction
- 45% Paternal nondisjunction
- Also may be mosaic XY/XXY

Incidence

- 1/800 males

Clinical

- Phenotype:
  - Tall habitus, undervirilized, small testes in men, gynecomastia, poor musculature



Fig. 3. Trisomy 18—clenched hand and overlapping fingers.

- Neurologic:
  - Mild delay, behavioral immaturity, shyness, learning disabilities (reading), speech delay
- Others:
  - Infertile
- Life expectancy:
  - Normal

Laboratory

- Cytogenetics:
  - Chromosome analysis identifies XXY
  - Leydig cell hyperplasia, absence of spermatogenesis, increased follicular stimulating hormone and estradiol, and decreased testosterone

Treatment

- Testosterone supplementation for development of secondary sexual characteristics

Turner Syndrome (45,X)

Inheritance

- 55% 45,X:
  - 80% loss of paternal X chromosome
  - 20% loss of maternal X (no maternal age effect)
- 25% 46,XX:
  - Structural alteration in one X chromosome
- 15% mosaic:
  - 45X with 46XX, 46XY, or others

Chromosome and Gene Location

- X chromosome

Incidence

- 1/2000–1/5000 female births: most common single-chromosome finding in spontaneous abortions

Clinical

- Phenotype:
  - Short stature, webbed neck (**Figure 4**), lymphedema of hands and feet, high arched palate, cystic hygroma, low posterior hairline, hypoplastic widely spaced nipples
- Neurologic:
  - Normal or near-normal intelligence; may have delay in speech, neuromotor skills, and learning abilities
- Other:
  - Gonadal dysgenesis (infertility, primary amenorrhea), renal malformations (horseshoe kidney), cardiovascular malformations (coarctation of aorta, hypoplastic left heart), increased risk for gonadoblastoma if mosaic for some Y chromatin
- Life expectancy:
  - 99% spontaneously abort prior to 28 weeks, those who survive infancy usually reach adulthood

Laboratory

- Cytogenetics:
  - Chromosome analysis indicates monosomy X or other variant
- Prenatal:
  - Elevated α-fetoprotein (only in cases of cystic hygroma and hydrops)
- Ultrasound:
  - Cystic hygroma (detectable after 10 weeks), lymph collections (ascites, pleural effusion), congenital heart disease, renal anomalies

Treatment

- Estrogen and thyroid hormone replacement therapy for secondary sexual characteristics and growth

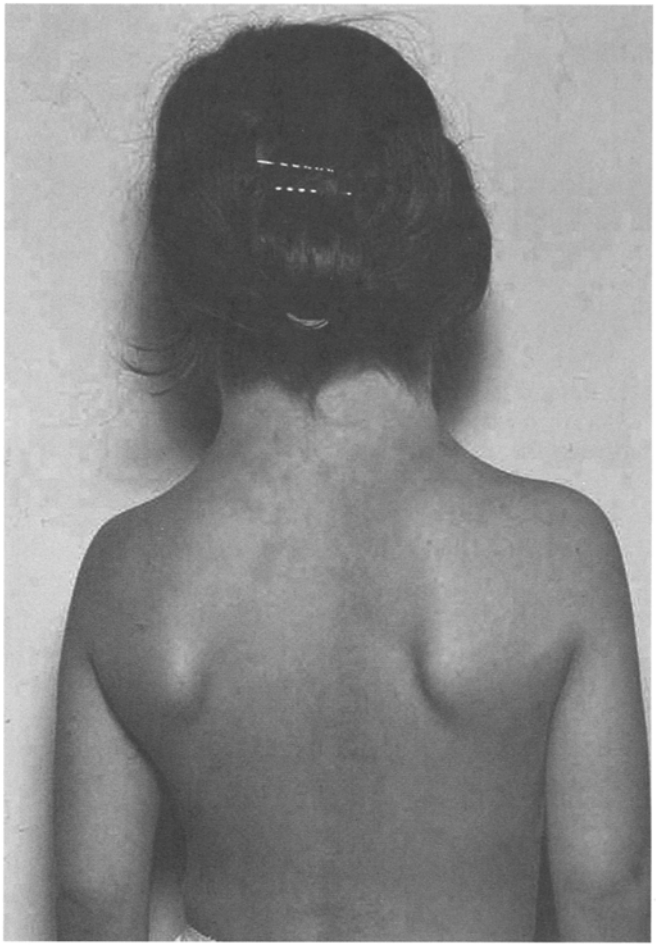


Fig. 4. Turner syndrome—webbing of the neck and low posterior hairline.

Microdeletion Syndromes

Angelman Syndrome

Chromosome and Gene Location

- 15q11.2

Inheritance

- Angelman syndrome results from the loss of the maternally imprinted region at chromosome 15q11.2; loss can occur via numerous mechanisms. Recurrence is dependent on the mechanism of loss
- 60–70% deletion of maternal 15q11.2
- 5% paternal uniparental disomy (two copies of the paternal chromosome)
- 1% imprinting defect
- 11% Ubiquitinprotein-ligase E3A (UBE3A) mutation
- 11% unknown

Incidence

- 1/20,000

Clinical

- Phenotype:
  - Prominent mandible, open-mouthed expression, hypereflexia, microcephaly, brachycephaly, optic atrophy
- Neurologic:
  - Ataxia, severe mental retardation, seizures, gross motor developmental delay
- Others:
  - Absent speech, inappropriate laughter, arm flapping, feeding difficulties
- Life expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic analysis and/or fluorescent *in situ* Hybridization (FISH) detects deletion
- Molecular methylation analysis identifies missing maternal allele

- Molecular uniparental disomy studies identify two copies of paternal allele
- Sequence analysis identifies mutations in UBE3A gene

Treatment

- Not curable, supportive/symptomatic

Prader-Willi Syndrome

Chromosome and Gene Location

- 15q11.2

Inheritance

- Prader-Willi syndrome results from the loss of the paternally imprinted region at chromosome 15q11.2, loss can occur via numerous mechanisms. Recurrence is dependent on the mechanism of loss
- 70–75% deletion of paternal 15q11.2
- 20–25% maternal uniparental disomy (two copies of maternal chromosome 15)
- Remainder are thought to be imprinting defects

Incidence

- 1/10,000–1/25,000

Clinical

- Phenotype:
  - Hypotonia, hypogonadism, obesity, small hands and feet, almond-shaped eyes, short stature
- Neurologic:
  - Mild-to-moderate mental retardation
- Others:
  - Failure to thrive, hyperphagia
- Life expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic analysis and/or FISH detects deletion
- Molecular methylation analysis identifies missing paternal allele
- Molecular uniparental disomy studies identify two copies of maternal allele
- Mutation analysis of imprinting center

Treatment

- Not curable, supportive/symptomatic

Cri du Chat Syndrome

Chromosome and Gene Location

- 5p15

Inheritance

- 85% sporadic (85% deletion, 4% mosaics, 3% ring chromosomes, 4% translocations)
- 12% familial translocations, inversions & parental mosaicism

Incidence

- 1/50,000

Clinical

- Phenotype:
  - "Catlike" cry, microcephaly, hypertelorism, micrognathia, transverse palmar crease, hypotonia
- Neurologic:
  - Mental retardation
- Others:
  - 50% no speech, growth failure
- Life expectancy:
  - Most survive into adulthood

Laboratory

- Cytogenetic and/or FISH identifies abnormality of 5p15

Treatment

- Not curable, supportive/symptomatic

22q Deletion Syndrome (DiGeorge [DGS]/ Velo-Cardio-Facial Syndrome [VCF])

Chromosome and Gene Location

- 22q11.2

Inheritance

- 90% are deletions involving multiple genes, most cases are sporadic
- Approximately 10–15% are familial (autosomal dominant)

Incidence

- 1/4000

Clinical

- The disturbance of neural crest migration of pharyngeal pouches is thought to cause clinical features
- Interpatient variability is dependent on extent of deletion
- Phenotype:
  - Short palpebral fissures, high arched palate, micrognathia, low set ears, bulbous nose, square nasal tip, cleft palate (VCF), small open mouth, retrognathia, microcephaly, slender hands and digits
- Cardiac manifestations:
  - Tetralogy of Fallot, outflow tract defect, right sided aortic arch, interrupted aortic arch, ventricular septal defect
- Neurologic:
  - Mild-moderate learning difficulties, seizures, tetany, emotional and behavioral problems
- Others:
  - Hypoparathyroidism, neonatal hypocalcemia (DGS), immune/T-cell deficit (DGS), hypernasal speech, hypospadius, short stature

♦ Life expectancy:
– Most reach adulthood if cardiac lesion is not life threatening

Laboratory

♦ Biochemical:
– Hypocalcemia, decreased T-cells
♦ Cytogenetics:
– Deletion 22q11 usually not visible on routine chromosome studies. FISH studies demonstrate deletion

Treatment

♦ Cardiac surgery, calcium supplements, supportive care

Smith-Magenis Syndrome

Chromosome and Gene Location

♦ 17p11.2

Inheritance

♦ Most are sporadic interstitial deletions, a few cases of pericentric inversions with breakpoints in 17p11

Incidence

♦ 1/50,000

Clinical

♦ Phenotype:
– Brachycephaly, flat, broad mid-face, prominent forehead
♦ Neurologic:
– Seizures, mental retardation
♦ Others:
– Hyperactivity behavioral problems including screaming outburst, speech delay, self-mutilation
♦ Life expectancy:
– Most survive into adulthood

Laboratory

♦ Cytogenetic analysis and/or FISH detects deletion

Treatment

♦ Not curable, supportive/symptomatic

Beckwith-Wiedemann Syndrome

Chromosome and Gene Location

♦ 11p15, multiple genes are located within this region including IGF2, KCNQ1OT1, H19, and CDKN1C

Inheritance

♦ 85% sporadic (20% of these have paternal uniparental disomy [two copies of the paternal allele], 50–60% have hypomethylation of KCNQ1OT1, 5–10% have mutation in CDKN1C, up to 35% have no identifiable etiology.)
♦ 10–15% have positive family history, autosomal dominant with incomplete penetrance and variable expressivity, 40% have mutation in CDKN1C
♦ <1% have cytogenetic abnormality
♦ Recurrence is dependant on mechanism of genetic abnormality

Incidence

♦ 1/14,000

Clinical

♦ Phenotype:
– Macroglossia, macrosomia, nephromegaly, splenomegaly, midface hypoplasia, cryptorchidism
♦ Neurologic:
– Seizures, developmental delay
♦ Others:
– Omphalocele, increased risk for embryonal tumors (Wilms's tumor, adrenal cortical carcinoma, hepatoblastoma, rhabdomysosarcoma, neuroblastoma)
♦ Life expectancy:
– Most survive into adulthood

Laboratory

♦ Cytogenetic analysis identifies paternal duplications, translocations, or inversions of 11p15 (fewer than 1% of cases)
♦ Molecular UPD analysis identifies two copies of paternal 11p15
♦ Methylation studies indicate hypomethylation of KCNQ1OT1 or H19
♦ Direct DNA analysis identifies mutations in CDKN1C in some sporadic and familial cases

Treatment

♦ Not curable, supportive/symptomatic

Miller-Dieker Syndrome

Chromosome and Gene Location

♦ 17p13.3

Inheritance

♦ 90% are sporadic deletions of 17p13.3

Incidence

♦ 1/100,000

Clinical

♦ Phenotype:
– Lissencephaly (smooth brain), microcephaly, anteverted nostrils, carp mouth, agenesis of corpus callosum
♦ Neurologic:
– Seizures, mental retardation
♦ Others:
– Failure to thrive, absent speech
♦ Life expectancy:
– Variable, but most die in childhood

Laboratory

- Cytogenetic analysis and/or FISH detects deletion of 17p13.3

Treatment

- Not curable, supportive/symptomatic

William Syndrome

Chromosome and Gene Location

- 7q11.23

Inheritance

- Mostly sporadic, a few cases of autosomal dominant inheritance have been reported

Incidence

- 1/20,000 live births

Clinical

- Phenotype:
  - Elfin facies, broad forehead, bitemporal narrowness, periorbital fullness, wide mouth, broad nasal tip, long philtrum, micrognathia, supravalvular aortic stenosis, peripheral pulmonary stenosis, growth retardation, small widely spaced teeth
- Neurologic:
  - Mental retardation
- Others:
  - Gregarious personality, joint limitations, hypercalcemia
- Life expectancy:
  - Most survive into adulthood

Molecular Genetics

- Contiguous gene syndrome with deletion of 7q11.23. Elastin gene locus is deleted in approx 99%, which most likely accounts for widespread abnormal connective tissue vasculature

Laboratory

- Deletion usually not visible by routine chromosome analysis, FISH analysis is usually necessary to identify deletion. Molecular dosage and heterozygosity analysis also available
- Elevated serum calcium

Treatment

- Not curable, supportive/symptomatic
- Monitoring of vitamin D and calcium in the diet

Chromosome Breakage Syndromes

Fanconi Anemia

Chromosome and Gene Location

- Genetically heterogeneous (multiple gene loci involved)

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical

- Short stature
- Absent or hypoplastic radii and thumbs
- Brown skin pigmentation
- Pancytopenia
- Anemia
- Increased incidence of leukemia
- Kidney defects:
  - Absent
  - Duplication of kidney or collecting system
  - Horseshoe kidney
- Cryptorchidism
- Developmental delay

Molecular Genetics

- Multiple complementation groups have been identified and appear to be involved in the formation of a protein complex that participates in a DNA-damage response pathway. The exact molecular mechanism that leads to impaired genomic stability has not been elucidated

Laboratory

- Increased chromosomal breakage, gaps, and rearrangements after exposure to diepoxybutane or mitomycin C (DNA alkylating agents)
- Mutation analysis available on limited basis for specific mutations

Treatment

- Supportive
- Transfusions
- Steroid therapy
- Bone marrow transplantation for anemia and leukemia

Bloom Syndrome

Chromosome and Gene Location

- 15q26.1

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Short stature
- Facial erythema
- Increased susceptibility to infections
- Increase incidence of leukemia

- High pitched voice
- Normal intelligence
- Most frequent in Ashkenazi Jewish population

Molecular Genetics

- Decreased activity of DNA ligase I leads to genomic instability and multisystem anomalies

Laboratory

- Increased chromosomal sister chromatid exchange (12X normal)
- Quadrilateral formation is increased, as are random breaks and translocations between nonhomologous chromosomes

Treatment

- Not curable, supportive/symptomatic
- Minimized exposure to radiation/mutagenic agents

Ataxia Telangiectasia

Chromosome and Gene Location

- 11q22–q23, ATM gene

Inheritance

- Autosomal recessive

Incidence

- 1/40,000–1/100,000

Clinical

- Cerebellar ataxia, conjunctival telangiectasia, IgA deficiency
- Predisposition to malignancy
- Increased infections
- Growth failure, onset in first two years of life
- Death usually occurs in the second or third decade

Molecular Genetics

- Defect in DNA repair mechanisms leading to chromosomal breakage, increased intrachromosomal recombination, sensitivity to ionizing radiation, and abnormal resistance to inhibition of DNA synthesis by ionizing radiation

Laboratory

- Elevated serum alpha-fetoprotein
- Immunoblotting identifies absence or significant reduction in ATM protein
- Absent or markedly reduced ATM kinase activity
- Increased chromosomal breakage and X-radiation sensitivity; especially with breakpoints at sites of immunoglobin genes or receptors,7;14 chromosomal translocation is identified in 5–15% of cells
- Molecular analysis of ATM gene identifies mutation in approx 95% of patients

Treatment

- Not curable, supportive/symptomatic
- Treatment of infections and neoplasms, avoidance of radiation

Xeroderma Pigmentosum

Chromosome and Gene Location

- Multiple loci

Inheritance

- Autosomal recessive

Incidence

- 1/1,000,000 in United States

Clinical

- Sensitivity to sunlight (blistering and freckling with little exposure, beginning in childhood)
- Predisposition to malignancy (especially skin cancer)
- Mental deterioration in some
- Death usually occurs before adulthood

Molecular Genetics

- Defective in ultraviolet-induced DNA repair mechanisms
- Skin cells unable to repair sunlight-induced DNA damage

Laboratory

- Diagnosis is based on clinical criteria, no routine clinical laboratory abnormality is observed in patients with XP
- Cytogenetic analysis can identify clones of cells with chromosome abnormalities, increased ultraviolet-induced chromosome breaks and sister chromatin exchanges
- Fibroblasts show ultraviolet hypersensitivity and abnormal unscheduled DNA synthesis

Treatment

- Not curable, supportive/symptomatic
- Avoidance of ultraviolet light

SINGLE-GENE DISORDERS

Trinucelotide Repeat Disorders

A growing number of inherited disease syndromes (primarily neurologic) are known to be caused by the abnormal presence of an expanded tract of trinucleotide repeats within disease-specific genes **(Table 1)**

The clinical hallmark of these trinucleotide repeat diseases is anticipation. Anticipation may be defined as an amplification in the number of expanded repeats in successive generations and the clinical observance of an earlier age of onset and increased rate of disease progression.

Table 1. Common Trinucleotide Repeat Disease

Disease	*Gene*	*Repeat sequence*	*Repeat location, type of region*	*Normal allele size (# repeats)*	*Expanded mutant allele (fully penetrant)*
Fragile X Syndrome	FMR1	CGG	exon 1, 5′ untranslated region	5–44	>230
Myotonic Dystrophy	DMPK	CTG	exon 15, 3′ untranslated region	5–35	50–>2000
Friedreich Ataxia	X25	GAA	intron 1	5–33	≥66
Huntington's Disease	IT15	CAG	exon 1, polyglutamine coding	9–26	≥40
Spinocerebellar Ataxia Type 1	SCA1	CAG	exon 8, polyglutamine coding	6–44	39–91
Spinocerebellar Ataxia Type 2	SCA2	CAG	exon 1, polyglutamine coding	14–30	36–64
Spinocerebellar Ataxia Type 3	SCA3/MJD1	CAG	exon ?, polyglutamine coding	12–47	53–86
Spinocerebellar Ataxia Type 6	CACNA1A	CAG	3′ end of gene, polyglutamine coding	4–18	20–33
Spinocerebellar Ataxia Type 7	SCA7	CAG	exon 1, polyglutamine coding	4–19	36–≥200
Spinal and Bulbar Muscular Atrophy	AR	CAG	exon 1, polyglutamine coding	11–34	>38

Diagnosis is made by determining the number of trinucleotide repeats within a specific disease-causing expandable allele (within the proper clinical context). The normal allele will have a "normal range" of trinucleotide repeats, whereas the disease-associated (expanded) allele will contain an increased number of repeats (in the hundreds, for some diseases). Premutation and reduced penetrance alleles can exist in between the normal and fully expanded ranges.

Fragile X Syndrome

Chromosome and Gene Location

- Xq27.3

Inheritance

- X-linked dominant

Incidence

- 1/1500 males (accounts for up to 5% of male mental retardation)
- 1/2500 females

Clinical

- Mental retardation (IQ 50–60)
- Large narrow face with moderately increased head circumference
- Macroorchidism (80%)
- Large ears

Molecular Genetics

- Expanded CGG repetitive element within FMR-1 gene
- 5–44 repeats: normal
- 45–58 repeats: intermediate, may increase in number but does not expand to full mutation
- 59–200 repeats: premutation (meiotic instability), no associated phenotype
- 201–4000 repeats: full mutation, leads to abnormal methylation and transcriptional suppression of FMR-1 gene and absence of FMRP (RNA binding protein)
- CGG repeat expansion is through female germline (males transmit premutation repeat without much change)
- Sherman's Paradox:
  - Describes apparent deviation from traditional Mendelian inheritance and varies according to whether the causative gene is transmitted through a male or female
  - In Fragile X, this is the result of expansion from premutation to full mutation through the male germline – "Normal" transmitting male

Laboratory

- Molecular analysis detects expanded CGG repeat and is now the test of choice
- Chromosomal fragile site is apparent when cultured in folate-deficient/thymidine-inhibiting

Treatment

- Not curable
- Supportive/symptomatic

Myotonic Dystrophy

Chromosome and Gene Location

- 19p13.3

Inheritance

- Autosomal dominant

Incidence

- 1/8000

Clinical

- Myotonia (impaired muscle relaxation)
- Muscle wasting
- Cataracts
- Frontal balding
- Cardiac conduction disturbances
- Swallowing and speech disability
- Facial weakness
- Neonatal hypotonia
- Delayed motor development
- Wide phenotypic range from severely affected infants to minimally symptomatic elderly

Molecular Genetics

- Expansion of a trinucleotide CTG repeat in the myotonic dystrophy protein kinase gene:
  - 5–35—normal allele size
  - 50–100—minimally affected
  - 2000+—severely affected (congenital form)
- Expansion occurs preferentially through maternal transmission

Laboratory

- Molecular analysis identifies expanded repeat
- Electromyogram shows slow nerve conduction velocities

Treatment

- Not curable, supportive/symptomatic
- Monitor for cataracts, cardiac conduction disturbances, diabetes, sleep apnea, and other endocrine problems

Friedreich Ataxia

Chromosome and Gene Location

- 9q13

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical

- Age of onset is approx 10–16 years
- Ataxia, muscle weakness, dysarthria, absent deep tendon reflexes, scoliosis, hypertrophic cardiomyopathy, hammer toes, pes cavus, diabetes (10–20%)
- Normal intelligence

Life Expectancy

- 30–60 years

Molecular Genetics

- Expansion in a trinucleotide GAA repeat in the Frataxin gene, some individuals carry an inactivatng gene mutant
- Normal alleles range from 5–33 repeats, affected individuals have >66 repeats

Laboratory

- Molecular analysis identifies expanded repeat
- Electromyogram shows slow nerve conduction velocities

Treatment

- Not curable, supportive/symptomatic

Huntington Disease

Chromosome and Gene Location

- 4p16.3

Inheritance

- Autosomal dominant

Incidence

- 3/100,000–7/100,000

Clinical

- Slowly progressive disorder with onset usually in midlife
- Manifestations include any combination of mental impairment, restlessness, choreiform movements, psychiatric changes, and dysarthria
- Life expectancy is approx 50–60 years

Molecular Genetics

- Disease results from an expansion of a trinucleotide CAG repeat in the Huntington gene
- Normal alleles range from 10 to 26 repeats
- Individuals with Huntington disease have more than 36 repeats
- Allele sizes of 27–35 are intermediate, not associated with symptoms, but may have risk of expansion in the next generation

Laboratory

- Molecular analysis identifies expanded repeat
- Computed tomography and magnetic resonance imaging identifies atrophy of the caudate nucleus and putamen

Treatment

- Not curable, supportive/symptomatic

Spinal Cerebellar Ataxia (SCA) (Types I–VII)

Chromosome and Gene Location

Inheritance

- Autosomal dominant

Incidence

- Varies by subtype and ethnicity

Clinical Findings

- Adult onset gait ataxia, dysarthria, dysphagia, ophthalmoplegia
- Decreased vibrations sense and sphincter disturbances
- Death usually occurs 10–20 years following age of onset

Molecular Genetics

- Expansion of trinucleotide repeat. *See* Table 1

Laboratory

- Molecular analysis identifies expanded trinucleotide repeat
- Molecular genetic testing available for many subtypes

Treatment

- Not curable, supportive/symptomatic

Spinal and Bulbar Muscular Atrophy (SBMA, Kennedy Disease)

Chromosome and Gene Location

- Xq11–q12

Inheritance

- X-linked recessive

Incidence

- 1/50,000 males

Clinical

- Teen to adult onset of muscle weakness, atrophy, and fasciculations with bulbar involvement
- Androgen insensitivity (gynecomastia, reduced fertility, testicular atrophy)

Molecular Genetics

- Expansion of trinucleotide CAG repeat in the human androgen receptor gene
- Normal allele size ranges from 11 to 34 repeats, affected individuals have repeat sizes of 36–62

Laboratory

- Molecular analysis identifies expanded repeat

Treatment

- Not curable, supportive/symptomatic
- Hormone replacement as needed

Duchenne/Becker Muscular Dystrophy (DMD/BMD)

Chromosome and Gene Location

- Xp21

Inheritance

- X-linked recessive

Incidence

- 1/3500 (male), 1/1500 (female carriers)
- 30% of cases are new mutations
- 5–15% of sporadic cases are a result of mother being gonadal mosaic (carries a subpopulation of oocytes with the mutation)

Clinical

- DMD:
  - Difficulties involving gait, jumping, and climbing stairs
  - Gower sign (use of arms to push themselves into standing position by moving their hands up their thighs, indicative of hip weakness)
  - Pseudohypertrophy of the calf muscles, muscle weakness
  - Dilated cardiomyopathy
  - Gastrointestinal dilation
  - 25–35% with mental retardation
  - Loss of ability to walk by age 10–15 years
  - Death usually occurs in the second decade
- BMD:
  - Milder course with onset in first or second decade
  - Slower progression
  - Survival into 30's and 40's
  - Cardiac and mental problems are rare

Molecular Genetics

- Dystrophin is a protein found in the sarcolemma of normal muscle. It is thought to be involved in the anchoring of the cytoskeleton of the muscle cell to extracellular proteins
- DMD and BMD result from alterations within the dystrophin gene (deletions [60%], duplications [5%] point mutations [35%])
- Deletions which disrupt the reading frame of the triplet code (frameshift mutations) lead to DMD
- Deletions which do not disrupt the reading frame (in-frame mutations) most often lead to BMD

Laboratory

- Pathology:
  - Variability in size of muscle fibers, degeneration, atrophy of individual fibers, and proliferation of endomysial and perimysial connective tissue. Antidystrophin antibodies detect <3% of normal dystrophin in DMD, 3–10% in mild DMD or severe BMD, >20% normal dystrophin correlates with BMD

- Creatine kinase (CK):
  - 50–100X the normal range, 2/3 of carriers have elevated CK. Caution must be used as CK levels vary with age, pregnancy, and activity
- Genetics:
  - Deletions and duplications detected directly by molecular analysis, linkage analysis available when deletion/ duplication negative

Treatment

- Not curable, supportive/symptomatic

Spinal Muscular Atrophy (SMA), Types I, II, and III

Chromosome and Gene Location

- 5q

Inheritance

- Autosomal recessive

Incidence

- 1/25,000

Clinical

- *See* **Table 2**

Molecular Genetics

- Survival motor neuron (SMN) is homozyously deleted in nearly all of types I and II and about 80% of type III SMA

Laboratory

- Atrophy of anterior horn cells
- Molecular analysis for deletions in exon 7 and/or exon 8 of SMN gene

Treatment

- Not curable, supportive/symptomatic

Charcot-Marie-Tooth Disease

Chromosome and Gene Location

- Numerous loci have been identified

Inheritance

- Autosomal dominant
- Autosomal recessive
- X-linked

Incidence

- 1/2500

Clinical

- Progressive muscular atrophy and weakness of feet and legs (during first two decades), pes cavus, central nervous system involvement includes optic and cochlear nerve
- CMT1 is differentiated on the basis of being a demyelinating neuropathy, with decreased nerve conduction velocities and absent deep tendon reflexes
- CMT2 is an axonal neuropathy with normal or slightly decreased conduction velocities, deep tendon reflexes are preserved

Molecular genetics

- Multiple genes at different loci are involved in each type. Some subtypes are clinically indistinguishable and are designated solely on molecular findings

Laboratory

- Molecular testing is available for many of the CMT subtypes

Treatment

- Not curable, supportive/symptomatic

Hereditary Neuropathy with Liability to Pressure Palsies

Chromosome and Gene Location

- 17p11.2

Inheritance

- Autosomal dominant

Incidence

- Unknown

Clinical

- Recurrent transient palsies
- Sensory dysfunction (result of compression to peripheral nerve)
- Pes cavus
- Scoliosis

Molecular Genetics

- Deletion of peripheral myelin protein 22 gene at 17p11.2. Repetitive elements surround this region
- Unequal crossing over between misaligned repetitive elements leads to the HNPP deletion and the CMT1A duplication
- *De novo* mutations are most often paternally derived

Laboratory

- Sausage-shaped swellings of myelin sheath (tomacula)
- Reduced motor and sensory conduction velocity
- Cytogenetics using FISH or molecular genetics analysis identifies deletion of 17p11.2

Treatment

- Not curable, supportive/symptomatic

Skeletal Disorders

Achondroplasia

Chromosome and Gene Location

- 4p16.3

Table 2. Spinal Muscular Atrophy

Type I (Werdnig-Hoffmann)	*Type II (Intermediate Type)*	*Type III (Kugelberg-Welander)*
Reduced fetal movements	Mild/arrested type 1	Waddling gait
General muscle weakness	Non-ambulatory	Muscle weakness
Respiratory muscle weakness	Increased life span when respiratory function preserved	Fasciculations
Arthrogryposis		Contractures
Tongue fasciculations		Ambulation feasible
Contractures		
Death often by 1 year		

Inheritance

- Autosomal dominant; 80% result from a new mutation

Incidence

- 1/25,000

Clinical

- Short stature, due to shortened limbs
- Genu varum
- Large head
- Frontal bossing
- Hypoplasia of midface
- Infantile hypotonia
- Gross motor developmental delay
- Normal intelligence
- Normal life expectancy
- Also at risk for cord compression due to odontoid hypoplasia

Molecular Genetics

- Mutation in transmembrane domain of fibroblast growth factor transmembrane receptor (FGFR-3)

Laboratory

- X-ray implicates skeletal involvement
- Molecular testing for FGFR-3 mutation is available

Treatment

- Not curable, supportive/symptomatic

Osteogenesis Imperfecta (Types I–IV)

Chromosome and Gene Location

- COL1A1 gene (Chromosome 17)
- COL1A2 gene (Chromosome 7)

Inheritance

- Autosomal dominant, often due to new mutation

Incidence

- 1/5000–1/10,000

Clinical

- *See* **Table 3**

Molecular Genetics

- Collagen is the major protein of the white fibers of connective tissue, cartilage, and bone
- There have been numerous types of collagens identified
- Mutations in the procollagen genes, whose products make up the triple helix of type 1 collagen, lead to the various types of Osteogenesis Imperfecta
- Clinical presentation is dependent on the extent to which the mutation alters the protein product

Laboratory

- X-ray implicates skeletal involvement
- Direct molecular analysis of procollagen genes available

Treatment

- Not curable, supportive/symptomatic
- Surgical intervention when indicated

Connective Tissue Disorders

Fibrillin Related

Marfan Syndrome

Chromosome and Gene Location

- 15q

Inheritance

- Autosomal dominant
- 15–30% result from a new mutation

Incidence

- 1/10,000

Table 3. Clinical Findings of Osteogenesis Imperfecta

	Inheritance	*Clinical Findings*	*Abnormal Collagen Chains*
Type I	Autosomal Dominant	Bone fragility, blue sclera, hearing loss	Pro-α2(I) Pro-αI(I)
Type II	Autosomal dominant, but usually new germline mutation.	Perinatal lethal, calvarial under-mineralization, beaded ribs, compressed femurs, 6-7% recurrence risk due to parental gonadal mosaicism	Pro-α2(I) Pro-αI(I)
Type III	Autosomal Dominant/Recessive	Multiple prenatal bone fractures, limb shortening, limb deformities, deafness, blue sclera	Pro-α2(I)
Type IV	Autosomal Dominant	Mild, short stature, mild deformity, dentinogenesis imperfecta, white sclera	Pro-α2(I)

Clinical

- Diagnosis based on clinical criteria
- Tall, thin habitus
- Long extremities
- Arachnodactyly **(Figure 5A)**
- Pectus deformity **(Figure 5B)**
- Scoliosis
- Ectopia lentis
- Retinal detachment
- Mitral valve prolapse
- Aortic dilation **(Figure 5C)**
- Aortic aneurysm
- Life expectancy is reduced to about 2/3 of normal life span

Molecular Genetics

- Mutations in gene for fibrillin, a structural protein which is the major constituent of microfibrils

Laboratory

- Mutation analysis and molecular linkage analysis to 15q for familial cases is available

Treatment

- Surgical intervention when indicated
- Close monitoring of heart defects as they can lead to sudden death
- Use of β adrenergic blockade

Collagen Related

Ehlers-Danlos Syndrome

Chromosome and Gene Location

- Multiple loci for collagen genes (1q, 2q, 7q, 9q)

Inheritance

- Most are autosomal dominant
- Some autosomal recessive and X-linked recessive

Incidence

- 1/5000–1/10000

Clinical

- Dependent on which type of Ehlers-Danlos is present. Features common to most types include:
  - Joint hypermobility
  - Skin fragility
  - Skin hyperextensibility
  - Blue sclera
  - Papyraceous scars
  - Kyphoscoliosis
  - Hernias
  - Short stature
  - Joint dislocation
  - Ocular fragility
- Type IV (the arterial form) is the most serious subtype, with a predisposition to arterial rupture and perforation of a hollow viscus

Molecular Genetics

- Collagen is the major protein of the white fibers of connective tissue, cartilage, and bone
- Mutations in collagen genes leads to decreased synthesis, altered secretion, and instability of collagen
- The defect for some types is unknown

Laboratory

- Direct analysis available for some subtypes
- Histological features are nondiagnostic

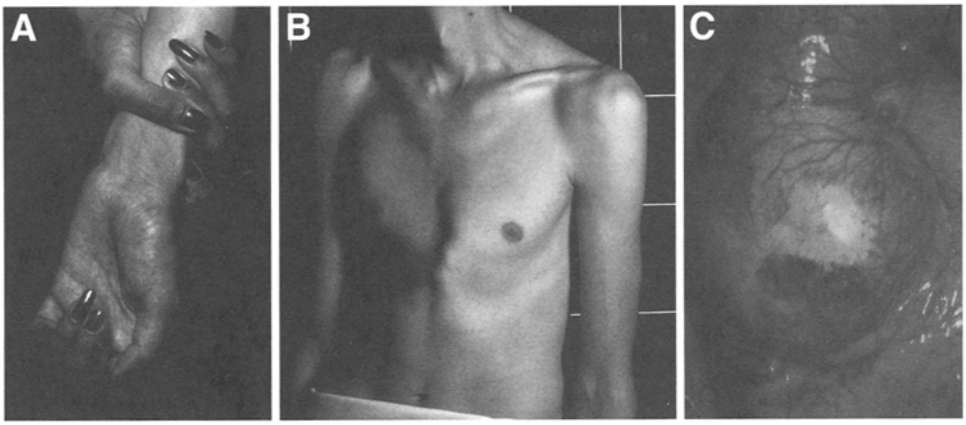


Fig. 5. Marfan syndrome—Arachnodactyly, wrist sign **(A)**. Pectus deformity and striae on shoulders **(B)**. Intraoperative view of dilated aortic root **(C)**.

Treatment

- Not curable, supportive/symptomatic

Stickler Syndrome

Chromosome and Gene Location

- 12q13, 6p21.3, 1p21

Inheritance

- Autosomal dominant

Incidence

- Unknown

Clinical

- Progressive myopia, retinal detachment, blindness
- Pierre-Robin syndrome (micrognathia and abnormal smallness of the tongue, often with cleft palate)
- Severe myopia, congenital glaucoma, and retinal detachment
- Premature degenerative changes in various joints with abnormal epiphyseal development
- Mitral valve prolapse
- Cataracts

Molecular Genetics

- Genetic heterogeneity
- Mutations in three genes; COL2A1, COL11A1, and COL11A2, have been associated with Stickler syndrome

Laboratory

- Skeletal X-rays show changes of a skeletal dysplasia
- Direct molecular analysis available

Treatment

- Not curable, supportive/symptomatic

Alport Syndrome

Chromosome and Gene Location

- Xq22.3 (COL4A5), 2q36-q37 (COL4A3 and COL4A4)

Inheritance

- X-linked (80%)
- Autosomal recessive (15%)
- Autosomal dominant (5%)

Incidence

- 1/50,000

Clinical

- Renal failure
- Sensorineural deafness
- Lenticonus
- Macular changes

Molecular Genetics

- Mutations in the type IV collagen genes result in abnormalities in expression of the collagen chains and absent or defective structure and function in the collagen networks of the basement membranes
- Molecular testing on clinical basis

Laboratory

- Microscopic hematuria
- Urinary red cell casts
- Proteinuria
- Leukocyturia
- Abnormal glomerular basement membrane on electron microscopy

Treatment

- Not curable, supportive/symptomatic
- Kidney transplant as indicated

Hematologic Disorders

α-*Thalassemia*

- The normal adult hemoglobin is a tetramer of two α and two β chains
- The α-thalassemias are a group of inherited conditions characterized by decreased synthesis of α-globin chains resulting in an imbalance of chains for the formation of the hemoglobin tetramer

Chromosome and Gene Location

- 16p13.1-pter (there are two α-globin genes present on each chromosome at this locus)

Inheritance

- Complex: individuals with α-thalassemia may have alterations in two, three, or four α-globin genes

Incidence

- Varies by population, being most common in African-American, Southeast Asian, Mediterranean, and Indian populations
- Severe forms occur almost exclusively among Asians

Clinical

- An individual with one altered gene is a silent carrier and does not have any clinical symptoms
- Individuals with two altered genes are referred as having "α-thalassemia trait," which is manifested by mild anemia with microcytosis, hyperplasia of marrow red cells, increased iron, and modest splenomegaly
- Hemoglobin H disease results when three α-globin genes are altered. This is characterized by moderate to marked anemia, enlarged liver and spleen, and marrow expansion
- Hydrops fetalis results when all four α genes are not functional. The hemoglobin is formed without α chains and is called Hemoglobin Barts. The oxygen affinity of Hemoglobin Barts is so high that it cannot release oxygen to the tissues. Death occurs from anoxia *in utero*

Molecular Genetics

- Numerous mutations have been found
- The most common type of mutation is a deletion that results from the misalignment and subsequent recombination of the α-thalassemia genes

Laboratory

- Abnormal cell morphology
- Hemoglobin electrophoresis shows abnormal proportion of alternate hemoglobins
- Reticulocytes are used to evaluate globin chain synthesis
- Molecular genetic analysis available

Treatment

- Transfusion
- Splenectomy
- Iron chelation therapy
- Bone marrow transplantation

β-*Thalassemia*

Chromosome and Gene Location

- 11p15.5

Inheritance

- Autosomal recessive

Incidence

- Most common in Mediterranean, Middle East, South, and Southeast Asia

Clinical

- β-thalassemia becomes clinically evident as the fetal hemoglobin production decreases and adult hemoglobin is supposed to replace it (around 6 months of age)
- Normally, both α- and β-globin chains are produced in roughly equal amounts. When β-globin synthesis is decreased, α-globin synthesis increases
- Free α chains are very unstable and precipitate in the red cell
- Erythropoiesis is ineffective and results in anemia
- There is a phenomenal increase in erythropoiesis with marrow expansion and persistence of erythropoiesis in the liver and spleen
- There are numerous classes of β-thalassemia based on the extent to which β chain production is decreased
- β-Thalassemia Major results from the homozygous or compound heterozygous state and is characterized by anemia, failure to thrive, fever, diarrhea, stunted growth if untreated
  - Features secondary to extramedullary hematopoiesis, result in chipmunk face, skeletal deformities, liver and spleen enlargement
  - Another feature is increased pigmentation
  - Death often occurs in second or third decade due to cardiac complications
- β-Thalassemia intermedia has milder phenotype and results from homozygosity or compound heterozygosity of alleles with a reduced β-chain production
  - May result from coinheritance of α- and β-thalassemia
  - Variable presentation

Molecular Genetics

- Numerous alterations have been described, including
  - Deletions
  - Transcriptional mutations
  - RNA processing mutations
  - Nonsense and frameshift mutations

Laboratory

- Abnormal cell morphology
- Elevated iron

- Hyperplastic marrow with hyperplasia of red cell precursors
- Hemoglobin electrophoreses shows increases in minor hemoglobins
- Molecular analysis available

Treatment

- Frequent transfusions
- Splenectomy
- Chelation therapy
- Bone marrow transplantation

Sickle Cell Anemia

Chromosome and Gene Location

- 11p15.5

Inheritance

- Autosomal recessive

Incidence

- 1/500 African American births

Clinical

- Failure to thrive
- Repeated infections
- Pallor
- Palpable spleen
- Painful swelling
- Splenomegaly
- Painful crisis due to vasoocclusive episodes usually affecting the limbs, back, abdomen and chest
- Chronic organ damage (renal, hepatic, retinopathy, leg ulcerations)

Molecular Genetics

- Glutamic acid to valine substitution in β-chain alters the configuration of the hemoglobin molecule:
  - This causes the cells to sickle and obstruct blood flow in small vessels leading to ischemia of tissues and organs

Laboratory

- Sickling and reduced oxygen tension of red cells
- Hemoglobin electrophoresis and/or isoelectric focusing identifies abnormal hemoglobin (part of many state's newborn screening programs)
- Direct molecular testing for nucleotide substitution

Treatment

- Prophylactic penicillin in infants and children
- Transfusion during splenic or hepatic sequestration crises

Hemophilia A

Chromosome and Gene Location

- Xq28

Inheritance

- X-linked recessive

Incidence

- 1/5000 to 1/10,000

Clinical

- The clinical severity is related to the level of Factor VIII coagulant activity in the plasma. If level is <1% of normal the disease is severe and is characterized by spontaneous recurrent bleeds into the hip, shoulder, knee, ankle, and elbow
- If untreated, severe pain and loss of cartilage may result
- Bleeding into muscles may result in nerve compression
- Intracranial bleeding may occur and may be fatal
- In moderate hemophilia (1–5% of normal Factor VIII activity), bleeding usually occurs following mild trauma, excessive bruising and some arthrosis may also be present
- In mild hemophilia (>6% Factor VIII activity) bleeding usually follows severe trauma, dental work, or surgery

Molecular Genetics

- Numerous mutations have been identified:
  - Approximately 45% of severe hemophiliacs have an inversion within the gene
  - Point mutations are also common (32% of all hemophilia A)
  - Mutations result in decreased Factor VIII coagulant activity

Laboratory

- Prolonged partial thromboplastin time (PTT)
- Normal prothrombin time (PT)
- Normal thrombin clotting time (TCT)
- Normal von Willebrand factor and ristocetin cofactor
- Decreased Factor VIII clotting activity
- Molecular genetic analysis for mutation detection and linkage analysis

Treatment

- Avoid trauma and anitcoagulants
- Factor VIII replacement therapy to raise Factor VIII activity (approx 10–15% of patients develop inhibitors against Factor VIII)

Hemophilia B

Chromosome and Gene Location

- Xq27.1-q27.2

Inheritance

- X-linked recessive

Incidence

- 1/40,000

Clinical

- The clinical severity is related to the level of Factor IX coagulant activity in the plasma and is very similar to classical Hemophilia A
- If level is <1% of normal, the disease is severe and is characterized by spontaneous recurrent bleeds
- Intracranial bleeding may occur and may be fatal
- In moderate hemophilia (1–5% of normal Factor IX activity), bleeding usually occurs following mild trauma, excessive bruising and some arthrosis may also be present
- In mild hemophilia (>6% Factor IX activity) bleeding usually follows only severe trauma, dental work, or surgery

Molecular Genetics

- Almost 500 unique mutations have been described, including many deletions and point mutations, however no common recurrent mutation
- Mutations result in decreased Factor IX activity

Laboratory

- Prolonged PTT
- Normal PT
- Normal TCT
- Normal von Willebrand factor and ristocetin cofactor
- Decreased Factor IX clotting activity
- Molecular genetic analysis for mutation detection and linkage analysis

Treatment

- Avoid trauma and anticoagulants
- Apply pressure and cold compresses to bleeding sites
- Factor replacement therapy to raise Factor IX

von Willebrand Disease

Chromosome and Gene Location

- 12p

Inheritance

- Autosomal dominant (70%) and autosomal recessive

Incidence

- 1/8000 for autosomal dominant type
- Autosomal recessive inheritance:
  - 1/2,000,000–1/300,000 in Western Europeans and Scandinavians
  - 1/200,000 in Middle Eastern Arabs

Clinical

- Bleeding from mucous membranes (nose, gums)
- Menorrhagia
- Prolonged bleeding after injury

Molecular Genetics

- Numerous mutations characterized including deletions, missense and nonsense mutations, leading to decreased activity of von Willebrand factor

Laboratory

- Prolonged bleeding time
- Decreased factor activity (von Willebrand and Factor VIII)
- Reduced ristocetin cofactor, normal or prolonged PTT
- Normal PT, thrombin time, and platelet count

Treatment

- Avoid trauma and anticoagulants
- Apply pressure and cold compresses to bleeding sites
- Replacement therapy for von Willebrand factor

Other Genetic Disorders

Cystic Fibrosis

Chromosome and Gene Location

- 7q31

Inheritance

- Autosomal recessive

Incidence

- 1/2500 in the Caucasian population, lower in other ethnic groups

Clinical

- Chronic pulmonary disease
- Pancreatic insufficiency
- Elevated sweat electrolytes
- Males generally infertile due to absence of the vas deferens
- Meconium ileus in neonate (10–16% of patients)
- 50% survival at age 30

Molecular Genetics

- Defect in the cystic fibrosis transmembrane conductance regulator gene results in:
  - Abnormal electrolyte transport
  - Excessive sodium absorption
  - Decreased chloride secretion
- Over 600 mutations described are associated with a wide range of clinical severity:
  - δ F508 most common in Caucasians (75% of carriers)
  - W1282X most common in Ashkenazi Jews (60% of carriers)

Laboratory

- Molecular analysis identifies approx 90% of CF mutations
- Elevated sweat chloride (>60mmol/L)

Treatment

- Antibiotics for control of respiratory infections
- Postural drainage and inhalation therapy
- Pancreatic enzyme replacement therapy

Albinism (Oculocutaneous Albinism type 1 [OCA1])

Chromosome and Gene Location

- 11q14–21 (OCA1)
- There are numerous other types of Albinism

Inheritance

- Autosomal recessive

Incidence

- 1/30,000

Clinical

- Hypopigmented skin and hair
- Nystagmus
- Reduced iris and retinal pigment
- Foveal hypoplasia

Molecular Genetics

- Melanin is the dark brown to black pigment that is normally produced in the skin, hair, pigmented coat of the retina, and in the medulla and zona reticularis of the adrenal gland
- Tyrosinase is an enzyme critical to melanin production
- Mutations in the tyrosinase gene therefore alter melanin production and lead to hypopigmentation and ocular changes
- Mutations in other genes involved in melanocyte production, transportation, or proliferation lead to various other types of Albinism

Laboratory

- Deficient tyrosinase activity on hairbulb
- Molecular genetic analysis available

Treatment

- Not correctable, supportive/symptomatic
- Avoidance of direct sunlight

Neurofibromatosis Type I (von Recklinghausen)

Chromosome and Gene Location

- 17q11.2

Inheritance

- Autosomal dominant. 50% are due to new mutation and 50% are inherited from a parent

Incidence

- 1/4000

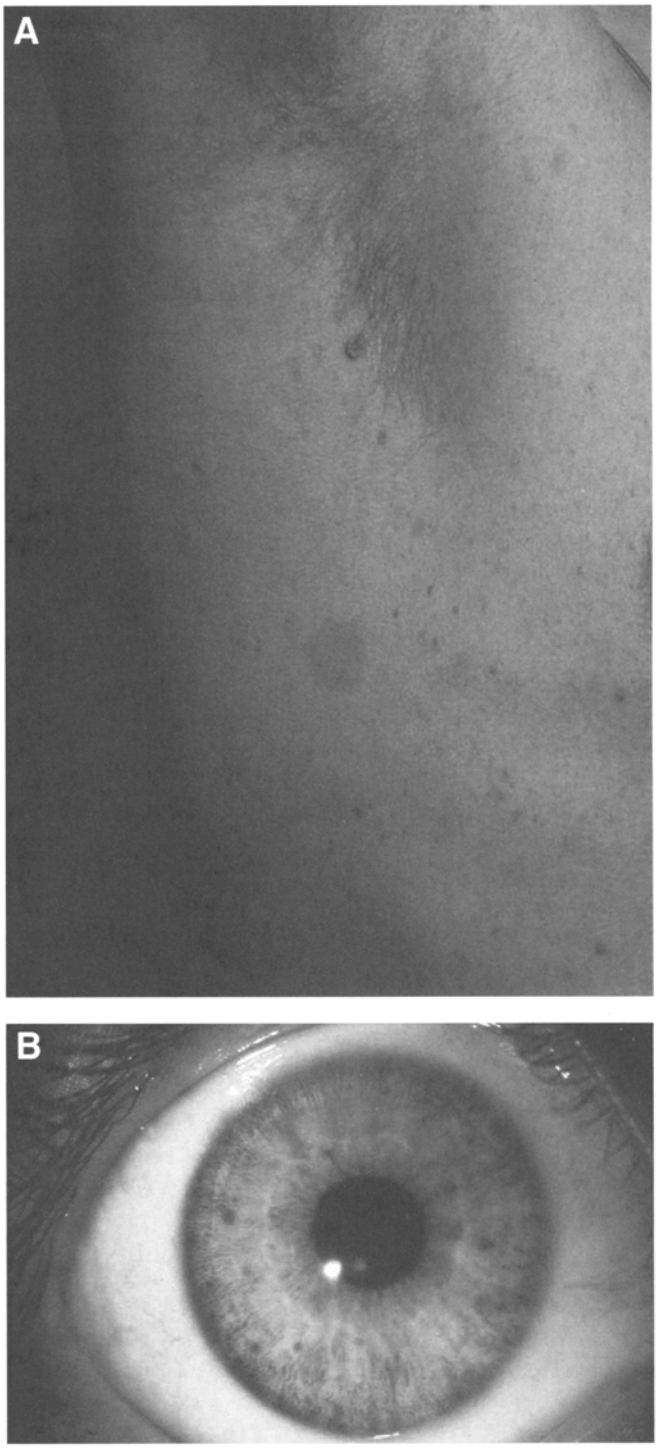


Fig. 6. Neurofibromatosis Type 1–Café au lait macule and axillary freckling (**A**). Lisch nodules (**B**).

Clinical

- Diagnosis based on established clinical criteria
- Neurofibromas
- Café au lait spots (**Figure 6A**)

- Axillary freckling **(Figure 6A)**
- Lisch nodules **(Figure 6B)**
- Optic gliomas
- Intellectual handicap (40%)

Molecular Genetics

- The NF1 gene appears to be a tumor-suppressor gene. Its product, called neurofibromin, is a GTPase activating protein–like polypeptide that appears to down regulate the RAS oncogene
- Protein truncating mutations have been found in approx 70% of affected patients

Laboratory

- Molecular testing identifies mutation in approx 70% of individuals

Treatment

- Surgical intervention when indicated

Neurofibromatosis Type II

Chromosome and Gene Location

- 22q

Inheritance

- Autosomal dominant
- 50% are new mutations

Incidence

- 1/50,000

Clinical

- Diagnosis based on established clinical criteria
- Vestibular schwannomas (bilateral acoustic neuromas)
- Loss of hearing, presenile lens opacities
- Subcapsular cataracts

Molecular Genetics

- The NF2 gene appears to be a tumor-suppressor gene
- Numerous mutations have been identified

Laboratory

- Molecular analysis available
- Bilateral eighth-nerve masses on computerized tomography or magnetic resonance imaging

Treatment

- Surgical intervention when indicated

Tuberous Sclerosis

Chromosome and Gene Location

- 9q33–34
- 16p13.3

Inheritance

- Autosomal dominant, with reduced penetrance
- 60–75% are new mutations in the family

Incidence

- 1/30,000

Clinical

- Diagnosis based on established clinical criteria
- Highly variable
- Facial angiofibromas **(Figure 7A)**
- Hypopigmented or leaf shape spots (by Woodslamp) **(Figure 7B)**
- Shagreen patches
- Seizures
- Mental retardation
- Subependymal giant-cell astrocytomas
- Renal cell cancer or renal cysts
- Angiomyolipomas
- Cardiac rhabdomyomas
- Cortical tubers
- Subependymal nodules
- Retinal hamartomas
- Dental enamel pits

Molecular Genetics

- Approximately half of the families are linked to TSC1 on chromosome 9 and half are linked to TSC2 on chromosome 16
- Numerous mutations have been reported in both genes

Laboratory

- Linkage analysis is available, but may not be informative for some families
- Molecular analysis clinically available

Treatment

- Not curable, supportive/symptomatic
- Surgical removal of tumors

METABOLIC DISORDERS

Amino Acid Disorders

Phenylketonuria (PKU)

Chromosome and Gene Location

- 12q24

Inheritance

- Autosomal recessive

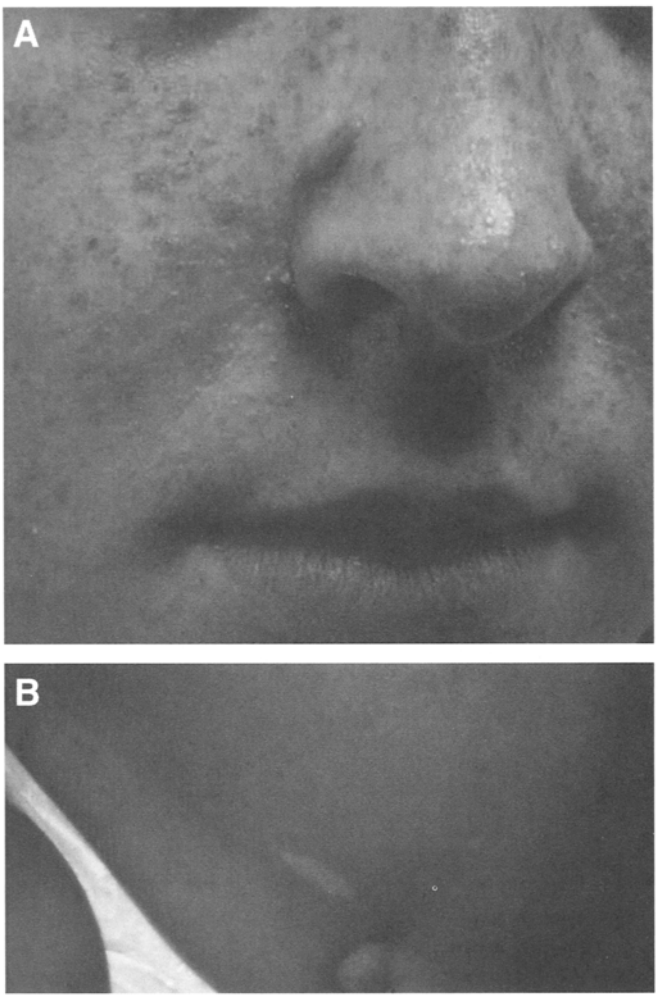


Fig. 7. Tuberous sclerosis—Facial angiofibromas (**A**). Hypopigmented macule (**B**).

Incidence

- 1/10,000 to 1/25,000 (lower in African-Americans and Ashkenazi Jews)

Clinical

- Mental retardation
- Seizures
- Hyperactivity
- Eczema
- Hypopigmentation
- "Mousey" odor
- Maternal PKU—Children born to mothers with PKU have a high risk (90%) of having mental retardation, microcephaly, impaired growth, and cardiac malformations if mothers have not received dietary restriction of phenylalanine during pregnancy

Molecular Genetics

- Mutations in phenylalanine hydroxylase gene cause:
  - Inactivation of enzyme (more than 100 described)
  - Disrupting the conversion of phenylalanine to tyrosine with subsequent hyperphenylalaninemia

Laboratory

- Newborn screening detects elevated blood phenylalanine using tandem mass spectrometry, fluorometric, or Guthrie bacterial inhibition assay
- Molecular genetic analysis available for carrier status and prenatal testing

Treatment

- Low phenylalanine diet supplemented with tyrosine throughout life

Tyrosinemia Type 1–fumarylacetoacetic acid hydrolase (FAH)

Chromosome and Gene Location

- 15q23–q25

Inheritance

- Autosomal recessive

Incidence

- Varies by population, highest incidence along the St. Laurence waterway in Canada (1/1846)

Clinical

- Vomiting, acidosis
- Diarrhea
- Failure to thrive
- Rickets
- Hepatic cirrhosis
- Fanconi renotubular syndrome
- Urine odor of rotten cabbage (caused from methionine metabolites)
- Increased risk for hepatocellular carcinoma

Molecular Genetics

- Mutations in the gene for Tyrosinemia inactivate the enzyme fumarylacetoacetate hydrolase which results in the accumulation of tyrosine and its metabolites (succinylacetoacetate, succinylacetone, and fumarylacetone) in the liver and kidney
- Numerous mutations have been found and are generally population specific

Laboratory

- Often confused with transient neonatal tyrosinemia or liver disease
- Increased urine tyrosine and metabolites and especially succinyl acetone
- Decreased fumarylacetoacetate hydrolase activity in liver biopsy specimens or cultured fibroblasts
- Molecular analysis also available

Treatment

- Low phenylalanine, tyrosine, and methionine diet delays but does not stop progression of disease

- 2-(2-nitro-4-trifluoro-methylbenzoyl)-1,3-cyclohexanedione (NTBC) treatment reduces the accumulation of toxic metabolites and ameliorates the severe clinical manifestations

Maple Syrup Urine Disease

Chromosome and Gene Location

- 19q13.1–q13.2 (type 1—E1a subunit)
- 1p31 (type 2—E2 subunit)
- 6p22-p21 (type 3—E1b subunit)

Inheritance

- Autosomal recessive

Incidence

- 1/125,000–1/300,000

Clinical

- Variable based on type, level of enzyme deficiency, and management of acute episodes
- Features include:
  - Apnea
  - Hypoglycemia
  - Poor feeding
  - Maple syrup odor of urine and sweat
  - Vomiting
  - Lethargy
  - Hypertonicity
  - Muscle rigidity
  - Seizures
  - Bilateral ptosis

Molecular Genetics

- The branched chain α-ketoacid dehydrogenase is a mitochrondrial enzyme consisting of four subunits; E1a, E1b, E2, and E3 (each subunit is located on a different chromosome)
- The enzyme system is responsible for the decarboxylation of the branched-chain amino acids; leucine, isoleucine, and valine
- Mutations in the genes encoding the various subunits result in defective expression and buildup of the branched chain amino acids and their metabolites in the blood, urine, and cerebral spinal fluid

Laboratory

- Deficiency of branched chain a-ketoacid dehydrogenase activity in leukocytes and cultured skin fibroblasts (prenatal diagnosis also available)
- Elevation of leucine, isoleucine, valine, allo-isoleucine, depressed alanine in serum and urine
- Elevated branched chain amino acids can be detected in blood spots by tandem mass spectrometry

Treatment

- Thiamine for B1 responsive form
- Not curable, supportive/symptomatic
- Manage acute episodes
- Reduce intake of branched chain amino acids by using special formulas and reducing protein intake

Homocystinuria

Chromosome and Gene Location

- 21q22.3

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical

- Dislocation of ocular lens
- Myopia
- Strabismus
- Cataract
- Glaucoma
- Thinning and lengthening of the long bones
- Osteoporosis
- Scoliosis
- High arched palate
- Pes cavus
- Genu valgum
- Biconcave vertebrae
- Thromboembolism
- Bluish mottling of the skin on legs and hands
- Mental retardation and seizures

Molecular Genetics

- The enzyme cystathionine-B-synthase (CBS) converts homocysteine to serine and cystathionine
- Mutations in the gene encoding of the enzyme result in an inactivation of this enzyme, which leads to elevated methionine and homocysteine levels, and low cysteine levels

Laboratory

- Homocysteine in urine
- Hyperhomocystinemia with reduced cysteine and increased methionine in plasma or serum. Decreased enzyme activity in fibroblasts, liver biopsy specimens, or PHA-stimulated lymphocytes (prenatal diagnosis available)
- Molecular analysis available for mutation detection

Treatment

- High doses of pyridoxine (vitamin B6), which is a cofactor of CBS, are given to decrease homocysteine levels (increases conversion of homocysteine to cysteine)
- Folic acid permits response to pyridoxine and optimizes conversion of homocysteine to methionine

Table 4. Urea Cycle Disorders

	Chromosome	*Enzyme*	*Inheritance*	*Incidence*
Carbamyl Phosphate Synthetase Deficiency	2q35	Carbamyl phosphate synthetase	Autosomal recessive	1/60,000
Ornithine Transcarbamylase Deficiency	Xp21.1	Ornithine transcarbamylase	X-linked recessive	1/30,000
Citrullinemia	9q34	Argininosuccinate synthase	Autosomal recessive	Rare
Arginosuccinic Aciduria	7cen-q11.2	Argininosuccinate lyase	Autosomal recessive	1/70,000
Argininemia	6q23	Arginase	Autosomal recessive	Rare

- Betaine is used in pyroxidine-unresponsive patients to lower plasma homocysteine levels by allowing conversion to methionine
- Low methionine diets reduce accumulation of methionine and homocysteine and their metabolites
- Patients treated from newborn period have had fewer complications than those treated late or untreated

Urea Cycle Disorders

- The urea cycle functions to prevent the accumulation of toxic nitrogenous compounds and also contains several reactions required for the synthesis of arginine
- The urea cycle consists of five biochemical reactions. Defects in the biosynthesis of any of the five expressed enzymes in this pathway lead to disease

Chromosome and Gene Location

- *See* **Table 4**

Inheritance

- *See* **Table 4**

Incidence

- *See* **Table 4**

Clinical

- All defects with the exception of arginase deficiency result in a similar clinical phenotype which includes:
  - Lethargy
  - Coma
  - Hypotonia
  - Seizures
  - Persistent vomiting
  - Poor feeding
  - Hepatomegaly
- The onset usually occurs after feeding in newborn period or after infections or protein overload
- In arginase deficiency, children are often asymptomatic for the first few months to years of life:
  - Clinical features include:
    - Loss of developmental milestones
    - Increased clumsiness
    - Spastic quadriplegia with loss of ambulation
    - Loss of speech
    - Seizures
    - Progressive mental retardation

Molecular Genetics

- *See* table for enzyme involved. Enzyme defects lead to the accumulation of ammonia and alters levels of other amino acids
- Ammonia is a neurotoxin that adversely affects the central nervous system (CNS)

Laboratory

- Hyperammonia, altered amino acid levels specific to each reaction
- Deficient enzyme activity
- Prenatal diagnosis is also available

Treatment

- Not curable, supportive/symptomatic
- Control of and avoidance of acute episodes
- Restrict protein, high caloric diet to minimize breakdown of protein
- Prognosis is better if disorder is treated promptly

Organic Acidemias

Isovaleric Acidemia

Chromosome and Gene Location

- 15q14-q15

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Usually presents within the first few days of life, symptoms include:
  - Acute attacks of vomiting
  - Acidosis
  - Ataxia
  - Lethargy
  - Coma
  - Seizures
  - Mental retardation
- Attacks are usually triggered by stresses such as infections or surgery

Molecular Genetics

- Isovaleryl CoA dehydrogenase catalyzes the conversion of isovaleric acid to 3-methylcrotonic acid in the branched chain amino acid leucine degradation pathway
- Deficient isovaleryl CoA dehydrogenase results in the accumulation of isovaleric acid and its metabolites, which are toxic to the body

Laboratory

- Elevated isovaleric acid
- Hyperammonemia
- Hypocalcemia
- Pancytopenia and neutropenia
- Thrombocytopenia
- Anemia
- Elevated urine isovalerylglycine in acute attack
- Deficiency of isovaleryl CoA dehydrogenase in leukocytes or cultured skin fibroblasts
- Prenatal diagnosis available

Treatment

- Not curable, supportive/symptomatic
- Avoidance of and symptomatic control of acute episodes
- Correct dehydration, electrolyte disturbances, and metabolic acidosis
- Reduction protein intake
- Removal of excess isovaleric acid by use of glycine and carnitine (allows for urinary excretion)

Propionic Acidemia

Chromosome and Gene Location

- 13q32

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Onset occurs within the first few weeks of life
- Symptoms include:
  - Apnea
  - Hypoglycemia
  - Poor feeding
  - Vomiting
  - Lethargy
  - Coma
  - Hypotonia
  - Seizures
  - Frequent infections
  - Osteoporosis
  - Mental retardation
- Symptoms may be triggered by infections, constipation, and protein overload

Molecular Genetics

- Propionyl-CoA-carboxylase (PCCA) is a mitochondrial enzyme consisting of 12 subunits (six α-subunits and six β-subunits)
- The gene for each subunit is located on different chromosomes: Chromosome 13(α) and chromosome 3q(β)
- Propionic Acidemia can arise from mutations in either the α or β subunit
- PCCA is involved in the catabolic pathway for the odd chain length fatty acids; threonine, methionine, isoleucine, and valine
- Deficiencies of PCCA lead to the accumulation of propionic acid, which results in the inhibition of citric acid cycle enzymes, acetylglutamate synthetase, granulocytes, and T- and B-cell development
- Numerous mutations have been described in the β- and α-subunits

Laboratory

- Metabolic acidosis
- Hypoglycemia
- Hyperammonemia
- Carnitine deficiency
- Elevated glycine
- Elevated propionic and methylcitric acids
- Neutropenia
- Thrombocytopenia
- Deficiency of PCCA activity in leukocytes or cultured skin fibroblasts
- Prenatal diagnosis available

Treatment

- Not curative. Avoidance of and symptomatic control of acute episodes

- Correct dehydration, electrolytes disturbances, and metabolic acidosis (bicarbonate)
- Decreased protein intake
- Antibiotics prevent production of propionic acid by intestinal bacteria
- Some individuals respond to biotin treatment, as it is a cofactor for PCCA

Methylmalonic Acidemia

Chromosome and Gene Location

- 6p21

Inheritance

- Autosomal recessive

Incidence

- 1/50,000

Clinical

- Lethargy
- Failure to thrive
- Recurrent vomiting
- Dehydration
- Respiratory distress
- Muscular hypotonia
- Growth retardation
- Psychomotor retardation
- Impairment of renal function
- Neurological abnormalities

Molecular Genetics

- Methylmalonic acid is derived from propionic acid as part of the catabolic pathway of isoleucine, valine, threonine, methionine, cholesterol, and odd-chain fatty acids
- Methylmalonic acid is converted to succinic acid by methylmalonyl-CoA mutase and a cobalamine cofactor
- Defects in the mutase or its cofactor result in the accumulation of methylmalonic acid and its precursors
- Six complementation groups have been identified indicating multiple alleles
- Numerous mutations within the mutase gene on chromosome 6 have been reported

Laboratory

- Ketosis, acidosis, anemia, elevated urinary and serum methylmalonic acid
- Decreased or absent mutase activity in cultured fibroblasts
- Prenatal diagnosis available

Treatment

- Restricted protein
- Vitamin B12 supplements to lower methylmalonic acid levels

Carbohydrate Metabolism Disorders

Glycogen Storage Disease (Type I)

Chromosome and Gene Location

- 17q21

Inheritance

- Autosomal recessive

Incidence

- 1/120,000

Clinical

- Hypoglycemia
- Hypertension
- Excessive perspiration
- Bruising
- Nose bleeds
- Short stature
- Delayed puberty
- Protuberant abdomen
- Liver adenomas
- Hepatomegaly
- Hepatoblastoma
- Hepatocellular carcinoma
- Chronic pancreatitis
- Renal insufficiency

Molecular Genetics

- The enzyme glucose-6-phosphatase catalyzes the conversion of glucose-6-phosphate to glucose
- Mutations in the gene encoding glucose-6-phosphatase result in a deficiency of this enzyme and the subsequent inability to free glucose for use in the body
- Mutations have been found in about 75% of patients studied
- There are various other types of glycogen storage diseases which result from deficiencies of other enzymes involved in the glycogen metabolism pathway

Laboratory

- Deficiency of glucose-6-phosphatase in liver biopsy (enzyme not present in skin fibroblasts)
- Lipidemia
- Hyperuricemia
- Hyperlacticacidemia
- Ketonemia
- Lactic acidosis
- Molecular analysis available

Treatment

- Steps to eliminate glycogen as a glucose source
- Maintenance of normal blood glucose concentration, by supplementation of glucose, pancreatic enzymes, and cornstarch

- Limited intake of fructose and galactose
- Low-fat diet
- Liver transplantation if necessary

Galactosemia

Chromosome and Gene Location

- 9p13

Inheritance

- Autosomal recessive

Incidence

- 1/30,000

Clinical

- Babies with galactosemia may appear normal at birth. Symptoms begin soon after milk feedings have begun. Symptoms include:
  - Lethargy
  - Irritability
  - Vomiting
  - Seizures
  - Feeding difficulties
  - Poor weight gain
  - Failure to thrive
  - Jaundice
  - Hepatomegaly
  - Hypoglycemia
  - Ascites
  - Splenomegaly
  - Hepatic cirrhosis
  - Lens opacities
  - Increased susceptibility to infections
- Long term complications include:
  - Speech deficits
  - Ataxia
  - Dysmetria
  - Diminished bone density
  - Premature ovarian failure

Molecular Genetics

- Galactose-1-P uridyl transferase (GALT) catalyzes the conversion of galactose-1-phosphate, to glucose-1-phosphate
- Deficiency of GALT results in the accumulation of galactose-1-phosphate, which causes injury to the parenchymal cells of the kidney, liver, brain, ovaries, and eyes
- One mutation (Q188R) accounts for about 60% of galactosemia alleles
- 12% of Caucasian population carry Duarte variant which decreases enzyme activity, but does not result in phenotypic consequence

Laboratory

- Newborn screening uses dot enzyme fluorescent assay and/or measurement of galactose-1-phosphate in red blood cells
- Classic and variant alleles can be detected with isoelectric focusing or molecular analysis
- Molecular analysis is used in conjunction with biochemical testing for prognostication, heterozygote detection, and prenatal diagnosis
- Serum in affected individual shows elevated transaminase, hyperbilirubinemia, follicular stimulating hormone, leutenizing hormone, decreased estrogen, and anemia
- *E. coli* septicemia occurs frequently

Treatment

- Eliminate lactose and galactose from the diet, special formula is necessary
- Even with good dietary control there may be poor intellectual function, speech problems, and ovarian dysfunction

Galatokinase Deficiency

Chromosome and Gene Location

- 17q24

Inheritance

- Autosomal recessive

Incidence

- 1/40,000

Clinical

- Cataracts
- Neonatal jaundice
- Normal intelligence

Molecular Genetics

- Galactokinase catalyzes the conversion of galactose to galactose-1-phosphate
- Galactokinase deficiency results in the accumulation of galactose
- Some galactose is converted to galacticol, which may be responsible for the cataract formation

Laboratory

- Deficiency of galactokinase activity in red blood cells

Treatment

- Elimination of lactose and galactose from the diet

Transport Disorders

Familial Hypophosphatemic Rickets

Chromosome and Gene Location

- Xp22.2-p22.1

Inheritance

- X-linked dominant (also autosomal recessive and sporadic forms)

Incidence

- 1/1,000,000

Clinical

- Bowing of lower extremities
- Waddling gait
- Short stature
- Decreased femur/shaft angle
- Dolichocephaly
- Tooth deformities

Molecular Genetics

- Deficiency interferes with phosphate reabsorption in kidney and conversion of 25-hydroxy-d to 1,25-hydroxy-2d

Laboratory

- Hyperphosphaturia
- Normal amino acids
- X-rays show metaphyseal widening and fraying, cupping of metaphyses at tibia, femur, radius, and ulna
- Molecular mutation analysis available

Treatment

- Phosphate supplements, surgery for limb deformities

Cystinuria

Chromosome and Gene Location

- 2p16.3

Inheritance

- Complex autosomal recessive with genetic compounds of multiple alleles producing three clinical types

Incidence

- 1/2000 in England to 1/100,000 in Sweden
- Overall, approx 1/7000

Clinical

- Urinary tract calculus
- Cystine stones are formed and crystals appear in the urine
- Increased risk for impaired cerebral function

Molecular Genetics

- Mutations in the SLC3A1 gene on chromosome 2p are responsible for type I; mutations in SLC7A9 are responsible fore types II and III
- The relationship between the genetic compounds has not been elucidated

Laboratory

- Dibasic aminoaciduria (excess excretion of cystine) and increased urinary lysine, arginine, and ornathine
- Molecular mutation analysis available

Treatment

- Dietary therapy to reduce cystine excretion and increase solubility
- Decreased methionine
- Low-sodium diets
- High fluid intake
- Alkanization of urine by sodium bicarbonate or sodium citrate to increase solubility of cystine
- Drugs which increase solubility
- Surgery to remove stones
- Penicillamine treatment for stone dissolving

Hartnup Disease

Chromosome and Gene Location

- 5p15

Inheritance

- Autosomal recessive

Incidence

- 1/30,000

Clinical

- Cerebellar ataxia
- Emotional instability, psychosis
- Delayed development
- Severe retardation
- Photosensitive skin rash

Molecular Genetics

- Thought to be caused by a genetic defect in neutral amino acid transport across the brush-border membrane of the renal and intestinal epithelium

Laboratory

- Characteristic pattern of increased secretion of the monoaminomonocarboxylic acids (alanine, serine, threonine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, histidine, glutamine, and asparagine)

Treatment

- Nicotinic acid or nicotinamide for deficiency of this vitamin, reduces rash, ataxia, and psychotic behavior
- High protein diet or supplementation

Cystinosis

Chromosome and Gene Location

- 17p

Inheritance

- Autosomal recessive

Incidence

- 1/100,000 and 1/200,000

Clinical

- There appears to be three types of cystinosis with varying degrees of involvement
- Nephrotic-classic, renal, and systemic disease in which children develop dehydration, acidosis, vomiting, electrolyte imbalances, hypophosphatemic rickets, failure to grow, photophobia, corneal crystals, hypothyroidism, myopathy, decreased ability to sweat, and renal failure by age 9–10
- Intermediate late onset of nephrotic cystinosis
- Nonnephrotic, clinically affecting only the corneas

Molecular Genetics

- Defective carrier mediated transport of cystine causes accumulation of cystine and formation of crystals in the lysosomes of most tissues
- Mutations in the CTNS gene are responsible for all three types of cystinosis

Laboratory

- Elevated leukocyte cystine
- Cystine crystals in tissue biopsy of bone marrow, conjunctiva, kidney, liver, intestine, and other tissues (not present in skin biopsy) cystine storage in pancreatic islet cells, aorta, atrophic ovaries, and brain
- Molecular mutation analysis available
- Prenatal diagnosis available

Treatment

- Management of electrolyte imbalance
- Renal allografts
- Growth hormones
- Therapy with cysteamine averts the otherwise inevitable renal failure, but systemic therapy does not improve the corneal keratopathy, cysteamine eye drops may prevent photophobia

Metal Metabolism Disorders

Wilson Disease

Chromosome and Gene Location

- 13q14

Inheritance

- Autosomal recessive

Incidence

- 1/30,000 live births

Clinical

- Liver disease
- Neurologic disturbance
- Acute jaundice
- Hemolysis
- Dysarthria
- Involuntary movement
- Renal tubular acidosis
- Osteoarthropathy
- Cardiomyopathy
- Golden-brown granular pigmentation is seen in the outer crescent of the iris ("Kayser-Fleischer" rings)

Molecular Genetics

- The gene encodes a Copper-binding P-type ATPase
- Expression occurs primarily in the liver, kidney, and placenta
- Defects in the gene lead to defective liver-specific copper transport and defective copper excretion into the bile
- Copper accumulates in the liver and other tissues and inhibits various enzymatic reactions
- Numerous mutations have been identified

Laboratory

- Reduced serum copper level and ceruloplasmin, increased urinary copper excretion
- Elevated copper in liver biopsy

Treatment

- Zinc acetate, which inhibits intestinal absorption of copper
- Penicillamine, tetrathiomolybdate, or trientine (which may have fewer side effects) increase urinary copper excretion
- Liver transplantation when necessary

Acrodermatitis Enteropathica

Chromosome and Gene Location

- 8q24.3

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Symptoms most often occur early in infancy after transition from breast milk to cow's milk
- Features include:
  - Dry, scaly, reddish skin lesions on face, knees, elbows, and perineal areas
  - Reddish hair
  - Hair loss
  - Photophobia
  - Conjunctivitis
  - Corneal dystrophy

- Chronic diarrhea
- Growth retardation
- Delayed wound healing
- Immune defects

Molecular Genetics

- Impaired zinc absorption due to an absent or defective ligand in the gut, which facilitates zinc absorption
- The variety of clinical features is likely due to the fact that zinc plays a role in numerous metabolic pathways

Laboratory

- Without therapy, plasma zinc concentration and serum alkaline phosphatase, as well as urinary excretion of zinc, are very low

Treatment

- Oral zinc compounds abolish the manifestations of the disease

Menkes Disease

Chromosome and Gene Location

- Xq13

Inheritance

- X-linked recessive

Incidence

- 1/100,000–1/250,000

Clinical

- Hypothermia
- Hypotonia
- Myoclonic seizures
- Chubby, rosy cheeks
- Kinky, colorless friable hair **(Figure 8)**
- Failure to thrive
- Severe mental retardation
- Optic atrophy
- Osteopenia with pathologic fractures (may be mistaken for child abuse)

Molecular Genetics

- The gene product is a copper transporting ATPase
- Mutations in this gene result in defective copper absorption and transport
- A wide spectrum of mutations has been identified

Laboratory

- Low serum copper and ceruloplasmin levels
- Intracellular accumulation of copper in cultured cells. Molecular mutation analysis available, prenatal diagnosis also available

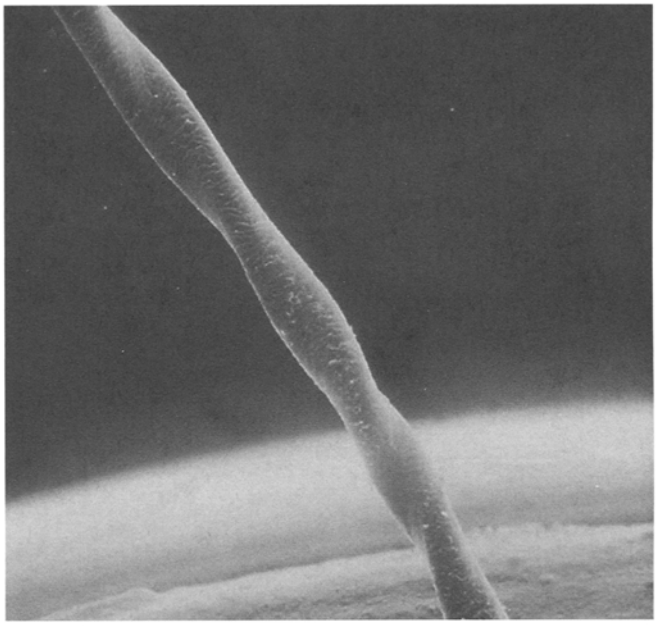


Fig. 8. Menkes disease—Magnified image of pili torte of hair.

Treatment

- Copper histidine treatment has had limited success. Many patients deteriorate and die of complications from seizures before 2 years of age

Hemochromatosis

Chromosome and Gene Location

- 6p21.3

Inheritance

- Autosomal recessive

Incidence

- Varies by population
- 1/200–1/300 in Northern European populations
- Lower in others

Clinical

- Fatigue
- Palpitations
- Premature arthritis
- Impotence in males
- Amenorrhea in females
- Cardiac arrhythmias
- Congestive heart failure due to cardiomyopathy
- Cirrhosis with hepatosplenomegaly
- Ascites
- Hyperpigmentation
- Onset is generally between ages 40–60
- Females have later onset due to menses/child birthing

Molecular Genetics

- A gene called HLA-H or HFE has been shown to be altered in a majority of hemochromatosis patients
- The most common mutation causes an amino acid substitution at codon 282 (C282Y)
- Approximately 85% of hemochromatosis patients of Northern European descent are homozygous, 5–10% are heterozygous, and an additional 5–10% do not carry the C282Y mutation
- A second less frequent alteration is an amino acid substitution at codon 63 (H63D), its role in this disease is controversial, but may increase one's risk for developing hemochromatosis
- It has been hypothesized that the C282Y mutation results in an abnormal protein trafficking or cell surface expression of the HFE gene

Laboratory

- Elevated serum transferrin saturation and concentration
- Elevated hepatic iron concentration on liver biopsy
- Molecular mutation analysis available

Treatment

- Phlebotomy reduces iron stores to normal
- Chelating agents remove smaller amounts of iron but are not as effective as phlebotomy

Purine Metabolism Disorders

Lesch-Nyhan

Chromosome and Gene Location

- Xq26-q27

Inheritance

- X-linked recessive

Incidence

- 1/300,000

Clinical

- Hypotonia
- Delayed motor development
- Choreoathetosis
- Spastic movements
- Hyperreflexia
- Self-injurious behavior
- Gouty arthritis
- Kidney stones composed of uric acid
- Carrier females develop gout in later years

Molecular Genetics

- The enzyme hypoxanthine guanine phosphoribosyl-transferase converts hypoxanthine and xanthine to nucleotides, inosinic acid, and guanylic acid
- Deficiency in enzyme activity results in accelerated purine production *de novo* and increased uric acid:
  - Deficiencies may also result in decreased synthesis of nucleotides

Laboratory

- Elevated serum uric acid concentration
- Elevated urate to creatinine ratio in urine
- Marked increases in the production and excretion of uric acid
- Absence of hypoxanthine guanine phosphoribosyl-transferase activity in erythrocytes and fibroblasts (prenatal diagnosis available)
- Molecular mutation analysis available, including prenatal diagnosis

Treatment

- Avoidance of dehydration
- Adequate nutrition
- Behavior control and modification
- Allopurinol to prevent damage to kidneys
- Experimental gene therapy

Adenosine Deaminase

Chromosome and Gene Location

- 20q13

Inheritance

- Autosomal recessive

Incidence

- 1/200,000–1,000,000

Clinical

- Severe immunodeficiency
- Complete impairment of T-cell function
- Rib cage abnormalities
- Chondroosseous dysplasia

Molecular Genetics

- Mutations in the gene encoding the enzyme adenosine deaminase result in the accumulation of adenosine, 2′ deoxyadenosine and 2′-O-methyladenosine, which leads to lymphocyte toxicity and subsequent immunodeficiency

Laboratory

- Absence of adenosine deaminase in red cell, or cultured fibroblasts
- Prenatal diagnosis available

Treatment

- Enzyme replacement therapy has resulted in clinical and immunologic improvement in some patients
- Bone marrow transplantation to replace enzyme

Peroxisomal Disease

Zellweger Syndrome, neonatal adrenoleukodystrophy, and infantile Refsum disease

Chromosome and Gene Location

- 7q11.23 (also chromosomes 1, 2, 6, 8, 11, 12, and 17)

Inheritance

- Autosomal recessive

Incidence

- 1/25,000–1/50,000

Clinical

- Clinical spectrum with Zellweger syndrome representing the most severe presentation, infantile Refsum disease is the least severe phenotype
- High forehead
- Unslanting palpebral fissures
- Hypoplastic supraorbital ridges
- Epicanthal folds
- Severe weakness
- Hypotonia
- Seizures
- Eye abnormalities
- Profound mental retardation
- Early lethality
- Liver cysts
- Chondrodysplasia punctata
- Hearing loss and visual impairment

Molecular Genetics

- Peroxisome biogenesis disorders are caused by mutations in several different genes involved in peroxisome biogenesis
- Mutations have been identified in a variety of these genes

Laboratory

- Reduced or absent peroxisomes
- Catalase in cytosol
- Reduced plasmalogens
- Accumulation of very long chain fatty acids
- Increased phytanic acid
- Bile acid intermediates
- Increased L-pipecolic acid
- Increased urinary excretion of dicarboxylic acids
- Molecular mutation analysis available

Treatment

- Not curable, supportive/symptomatic

Adrenoleukodystrophy (X-linked)

Chromosome and Gene Location

- Xq28

Inheritance

- X-linked recessive

Incidence

- 1/20,000–1/50,000

Clinical

- Learning deficits (attention deficit disorder, hyperactivity), followed by regression of academic performance
- Leg weakness, loss of sphincter control, and sexual dysfunction
- Progressive spastic paresis
- Loss of hearing and vision
- Dementia
- Demyelination of cerebral hemispheres

Molecular Genetics

- Mutations in the ALD-gene are thought to result in defective peroxisomal B-oxidation of very long chain fatty acids (VLCFAs), the protein is an ATP binding cassette (ABC) protein transporter
- Deficiency results in the accumulation of VLCFAs in the adrenal cortex and brain gangliosides, plasma, blood cells, and cultured fibroblasts
- Numerous mutations have been identified in the ABCD1 gene, testing currently being done by linkage

Laboratory

- Accumulation of unbranched saturated fatty acids with a chain length of 24–30 carbons in plasma, cultured skin fibroblasts
- Molecular mutation analysis is available
- Prenatal diagnosis available

Treatment

- Not curable, supportive/symptomatic
- VLCFA-restricted diet, bone marrow transplantation
- Corticosteroid replacement therapy for adrenal insufficiency

LYSOSOMAL STORAGE DISEASES

Mucopolysaccharidoses

- The mucopolysaccharidoses are a group of lysosomal storage disorders caused by the deficiency of any of the enzymes involved in the stepwise degradation of dermatan sulfate, heparan sulfate, keratan sulfate, or chondroitin sulfate (glycosaminoglycans)

- Glycosaminoglycans are constituents of extracellular matrix of connective tissue and are also present in mitochondria, and nuclear and cell membranes
- The GAGS are also implicated as important ligands on endothelial cells (heparan)
- Accumulation of glycosaminoglycans interferes with the normal functioning of cells, tissues, and organs

Chromosome and Gene Location

- *See* **Table 5**

Inheritance

- *See* **Table 5**

Incidence

- *See* **Table 5**

Clinical

- **Table 5:** Clinical manifestations of glycosaminoglycan storage includes:
  - Coarse facial features
  - Thick skin
  - Corneal clouding
  - Organomegaly
- Features characteristic of defective cell function include:
  - Skeletal dysplasia (dysostosis multiplex)
  - Mental retardation
  - Growth deficiency and hearing loss
- Joint contractures, heart valve abnormalities, and hernias result from abnormal connective tissue formation

Laboratory

- Decreased enzyme activity in cultured fibroblasts, leukocytes, serum, or plasma; prenatal diagnosis available
- Urinary glycosaminoglycans (heparan, dermatan, and keratan sulphate)
- Radiographs show skeletal abnormalities
- Direct molecular genetic analysis available for most subtypes

Treatment

- Not curable, supportive/symptomatic
- Bone marrow transplantation and enzyme replacement have been reported to arrest clinical regression features in Types I and VI, though the efficacy is dependent on early treatment
- Prophylaxis for patients with cardiac abnormalities
- Orthopedic surgery for skeletal complications

Mucolipidoses

- Mucolipidoses are a group of disorders which result from abnormal lysosomal enzyme transport, in which lysosomal enzymes are inappropriately secreted into the extracellular medium instead of being targeted to the lysosomes

I-Cell Disease

Chromosome and Gene Location

- 4q21-q23

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Low birth weight
- Plump swollen face
- Hernias
- Clubfoot
- Dislocation of hips
- Kyphosis
- Hypotonia
- Severe growth failure
- Stiffening of all joints
- Protuberant abdomen
- Coarse facial features
- Psychomotor retardation

Molecular Genetics

- The primary deficiency is in the enzyme GlcNac-1 phosphotransferase, which catalyzes the first step in the synthesis of the mannose-6-phosphtase recognition marker on lysosomal hydrolases. Mannose-6-phosphate serves as a specific recognition marker for targeting these enzyme to lysosomes
- Mutations within the gene disrupt interactions and recognition of a mannose-6-phosphate uptake ligand, resulting in disproportionally high extracellular partitioning of nearly all lysosomal enzymes

Laboratory

- Cytoplasmic granular inclusions in skin fibroblasts (swollen lysosomes), prenatal diagnosis available
- Decreased activity of lysosomal acid hydrolases in I-cells with increased activity in culture media and which translates in vivo to increased serum levels of most lysosomal enzymes
- Numerous membrane bound vacuoles in connective tissue cells
- Molecular genetic testing available only for select subtypes

Treatment

- Not curable, supportive/symptomatic

Pseudo-Hurler Polydystrophy

Chromosome and Gene Location

- 4q21-q23

Table 5. Mucopolysaccharidoses

Name	Inheritance	Chromosome	Enzyme Deficiency	Excess Excretion	Clinical Features	Incidence
Hurler's Syndrome (MPS I H)	Autosomal Recessive	4pl6.3	α-L-iduronidase	dermatan and heparan sulfate	Corneal clouding, dysostosis multiplex, organomegaly, heart disease, mental retardation, death in childhood	1/100,000
Scheie (MPS I S)	Autosomal Recessive	4pl6.3	α-L-iduronidase	dermatan and heparan sulfate	Corneal clouding, stiff joints, normal intelligence normal life span	Unknown
Hunter Syndrome (MPS II)	X-linked Recessive	Xq28	iduronate 2-sulfatase	dermatan and heparan sulfate	Dysostosis multiplex, organomegaly, mental retardation, death before 15 years	1/100,00 male births
Sanfilippo Syndrome (MPS III)	Autosomal Recessive	17q25.3	1. Sulfamidase 2. Alpha-N-acetyl-glucosaminidase 3. Acetyl-CoA α-glucosaminide N-acetyltransferase 4. N-acetylglucosamine-6-sulfate sulfatase	heparan sulfate	Profound mental deterioration, hyperactivity	Unknown
Morquio Syndrome (MPS IV)	Autosomal Recessive	16q24.3 (Type IV-A), 3(type IV-B)	1. N-acetyl-galactosamine-6-sulfate sulfatase (Type IV-A) 2. B-galactosidase (Type IV B)	keratan sulfate	Skeletal abnormalities, corneal clouding, odontoid hypoplasia	1/300,000
Maroteaux-Lamy Syndrome (MPS VI)	Autosomal Recessive	5ql3.3	N-acetylgalactosamine-4-sulfate sulfatase	dermatan sulfate	Dysostosis multiplex, corneal clouding, (normal intelligence)	1/200,000

Inheritance

- Autosomal recessive

Incidence

- Rare

Clinical

- Joint stiffness
- Decreased mental development
- Plump face
- Reduced growth rate
- Mild mental deficiency
- Osteoporosis
- Dysostosis multiplex

Molecular Genetics

- The same enzyme defect as in I-cell disease, except a milder allelic variant

Laboratory

- Cytoplasmic granular inclusions in skin fibroblasts (swollen lysosomes), prenatal diagnosis available
- Decreased activity of lysosomal acid hydrolases in I-cells with increased activity in culture media serum
- Numerous membrane bound vacuoles in connective tissue cells

Treatment

- Not curable, supportive/symptomatic

Sphingolipidoses

GM1 Gangliosidosis

Chromosome and Gene Location

- 3p21.33

Inheritance

- Autosomal recessive

Incidence

- Unknown

Clinical

- Onset is generally in childhood
- Psychomotor retardation
- Hepatosplenomegaly
- Bony abnormalities (widening of the long bones and ribs; broad, short, stubby fingers; contractures)
- Failure to thrive
- Gum hypertrophy
- Macroglossia
- Macrocephaly
- Protuberant abdomen
- Coarse facies
- Frontal bossing
- Depressed nasal bridge
- Hypertelorism
- Cherry red spot on macula
- Exaggerated startle response
- Also other forms with onset between ages 3–50

Molecular Genetics

- β-galactosidase cleaves the terminal galactose from a number of compounds including GM1 ganglioside, galactose oligosaccharides, and derivatives of keratan sulfate
- Mutations lead to deficiency of the enzyme and result in the accumulation of GM1-gangliosides, oligosaccharides, and keratan sulfate derivatives

Laboratory

- Empty appearing vacuoles on electron microscopy
- Large foam cells in bone marrow
- Skeletal change on X-ray
- Deficient B-galactosidase in cultured fibroblasts and leukocytes

Treatment

- Not curable, supportive/symptomatic

GM2 Gangliosidosis (Tay-Sachs)

Chromosome and Gene Location

- 15q

Inheritance

- Autosomal recessive

Incidence

- 1/3600 (Ashkenazi Jewish)

Clinical

- Hypotonia
- Exaggerated startle response
- Inability to hold head up or sit
- Cherry red spot on macula
- Convulsions
- Optic atrophy
- Blindness
- Mental retardation
- Macrocephaly
- Fatal by 4 years of age

Molecular Genetics

- The enzyme hexosaminidase A catalyzes the degradation of gangliosides (constituents of neuronal cell membranes)
- Deficiency results in the accumulation of GM2-gangliosides in the brain, nervous system, liver, spleen, and heart, leading to the disruption of cell function and death
- Hexosaminidase A is made up of an α and a β chain
- The α chain is encoded on chromosome 15, mutations lead to a deficiency of hexosaminidase A (mutations in the β chain lead to Sandhoff disease, *see* below)
- Four disease causing mutations are common in the Ashkenazi Jewish population, and account for 92% of the mutations in this group

Laboratory

- Decreased hexosaminidase A in serum, leukocytes and cultured fibroblasts, prenatal diagnosis available:
  - Very effective for carrier screening as well
- Direct mutation analysis also available
- Pseudodeficiency alleles (more common in non-Jewish population) may falsely indicate carrier status

Treatment

- Not curable, supportive/symptomatic

Sandhoff Disease

Chromosome and Gene Location

- 5q13

Inheritance

- Autosomal recessive

Incidence

- 1/75,000 (non-Jewish)
- 1/250,000 (Jewish)

Clinical

- Hypotonia
- Exaggerated startle response
- Inability to hold head up or sit
- Cherry red spot on macula
- Convulsions
- Hepatosplenomegaly

- Blindness
- Mental retardation
- Macrocephaly
- Fatal by 4 years of age

Molecular Genetics

- The enzymes hexosaminidase A and hexosaminidase B catalyze the degradation of gangliosides and other glycoproteins/GAGS
- Hexosaminidase A is made up of an α and a β chain, hexosaminidase B is made of two β chains
- The β chain is encoded from a gene on chromosome 5, mutations in this gene therefore result in a deficiency of both hexosaminidase A and hexosaminidase B
- Deficiency results in the accumulation of GM2-gangliosides in the brain, nervous system, liver, spleen, and heart, leading to the disruption of cell function and death

Laboratory

- Deficient hexosaminidase A and hexosaminidase B in serum, leukocytes and cultured fibroblasts, prenatal diagnosis available

Treatment

- Not curable, supportive/symptomatic

Niemann-Pick, Types A and B

Chromosome and Gene Location

- 11p15.1-p15.4

Inheritance

- Autosomal recessive

Incidence

- Type A—1/40,000 (Ashkenazi Jewish)

Clinical

- Type A—failure to thrive, hepatosplenomegaly, progressive neurodegeneration, death by age 3
- Type B—Hepatosplenomegaly, respiratory insufficiency, little or no neurologic involvement, may survive into adolescence or adulthood

Molecular Genetics

- Deficiency of the lysosomal hydrolase acid sphingomyelinase, causes accumulation of sphingomyelin in cells and tissues
- Three common mutations have been found in Ashkenazi Jewish population (L302P, R496L, and fsP330) and account for >95% of the mutations in this population; other more rare mutations have been found in other ethnic groups

Laboratory

- Deficiency of acid sphingomyelinase, increased tissue cholesterol levels
- Enzyme assays and direct mutation analysis available

Treatment

- Not curable, supportive/symptomatic

Niemann-Pick, Type C (NP-C)

Chromosome and Gene Location

- 8q11 (NPC1), 14q24 (NPC2)

Inheritance

- Autosomal recessive

Incidence

- 1/150,000

Clinical

- Neonatal jaundice
- Histiocytosis in marrow
- Neurological evidence depends on variant (infantile-adult)
- Progressive neurological deterioration. Ataxia, dyarthria, dystonia, dementia
- Vertical supranuclear gaze impairment

Molecular Genetics

- Mutation causes impaired homeostatic regulation of cholesterol levels within cells
- Mutation prevents egress of free cholesterol from the lysosomal compartment

Laboratory

- Delayed induction of cholesterol esterification following low density lipoprotein (LDL) uptake
- Filipin staining of accumulated cholesterol in fibroblasts
- Molecular mutation analysis available on limited basis

Treatment

- No current treatment to change natural progression
- Supportive pharmacological care for CNS symptoms

Gaucher Disease

Chromosome and Gene Location

- 1q21

Inheritance

- Autosomal recessive

Incidence

- Type 1: 1/600 (Ashkenazi Jewish), 1/60,000–1/360,000 non-Jewish
- Type 2: <1/500,000 live births
- Type 3: 1/100,000

Clinical

- Type 1—Age of onset varies widely, from children to adults. Disease severity is also variable. Symptoms include:
  - Enlarged liver and spleen (causes abdominal protuberance)
  - Fatigue
  - Anemia

- Excessive bleeding
- Pain in lower extremities
- Fractures
- Growth failure
- Infiltrative bony lesions

♦ Type 2—Onset is within first few months of life:
- Inattentiveness
- Loss of head control
- Poor sucking and swallowing
- Failure to thrive
- Spasticity
- Tonic arching of back
- Strabismus
- Seizures
- Enlargement of liver and spleen
- Progression of disease is rapid, death from respiratory complications usually occurs within several months

♦ Type 3—Clinically heterogeneous:
- Presentation in mid to late childhood
- Myoclonus
- Dementia
- Ataxia
- Horizontal supranuclear gaze palsy
- Seizures
- Spasticity
- Enlarged spleen and liver
- Death from neurologic degeneration in second or third decade

Molecular Genetics

♦ Glucocerebrosidase hydrolyzes glucosylceramide to glucose and ceramide

♦ Mutations in the gene encoding glucocerebrosidase result in the accumulation of glucosylceramide in the lysosomes

♦ There are four common mutations, N370S, L444P, 84GG, IVS2(+1), which account for >90% of the mutations in the Ashkenazi Jewish population

♦ N370S is not found in Type 2 or 3 and is thought to confer a less severe phenotype when compounded with other mutations

Laboratory

♦ Deficiency of glucocerebrosidase activity (not accurate for carrier determination) in cultured fibroblasts

♦ Prenatal diagnosis available

♦ Anemia

♦ Leukopenia

♦ Thrombocytopenia

♦ Increase in iron stores

♦ Prolonged bleeding time

♦ Deficiency of factors IX, XI and von Willebrand

♦ Presence of Gaucher storage cells in bone marrow

♦ Molecular genetic analysis is available for the above mutations

Treatment

♦ Enzyme replacement therapy (most effective on patients with Type 1 disease)

♦ Transfusions may be required for hypersplenism or bone marrow failure

♦ Skeletal problems are treated with limitation of activity, prostheses, analgesics, and surgical intervention

Krabbe Disease

Chromosome and Gene Location

♦ 14q

Inheritance

♦ Autosomal recessive

Incidence

♦ 1/100,000–1/200,000

Clinical

♦ Onset within first six months:
- Feeding difficulty
- Irritability
- Fever
- Failure of development
- Spasticity
- Cortical blindness
- Optic atrophy
- Deafness
- Death by age 2

♦ Also late onset variants

Molecular Genetics

♦ Galactosylceramide B-galactosidase is a lysosomal enzyme which degrades galactocerebroside to ceramide and galactose

♦ Mutations in the gene cause deficient activity and result in the accumulation of enzyme substrates which lead to the early destruction of oligodendroglia (type of glial cell that forms the myelin sheath of nerve fibers in the central nervous system)

♦ Mutations in gene have been identified

Laboratory

♦ Deficient galactosylceramide B-galactosidase activity.

♦ Prenatal diagnosis available

♦ Elevated protein in cerebral spinal fluid, decreased nerve conduction velocity

- Accumulation of globoid cells and calcium on magnetic resonance, white matter abnormalities, small brain, glial cell proliferation
- Peripheral nerves show segmental demyelination
- Molecular testing available

Treatment

- Not curable, supportive/symptomatic
- Hematopoietic stem cell transplantation has slowed course of disease in patients diagnosed before onset of infantile and later onset forms

Metachromatic Leukodystrophy

Chromosome and Gene Location

- 22q13.31-qter

Inheritance

- Autosomal recessive

Incidence

- 1/100,000

Clinical

- Loss of developmental milestones
- Gait difficulty
- Hypotonia
- Decline in speech and mentation
- Spasticity
- Death by age 6
- Juvenile and adult onset also seen

Molecular Genetics

- Arylsulfatase A with sphingolipid activator protein (SAP1) metabolize cerbroside sulfate
- Mutations lead to enzyme deficiency which results in accumulation of galactosyl-3-sulfate cerebroside, and metachromatic material in neural and nonneural tissues
- A few common mutations have been found
- A psuedomutation which decreases enzyme activity but does not cause disease a confounding factor in diagnosis

Laboratory

- Arylsulfatase A deficiency in cultured fibroblasts in leukocytes, fibroblasts, prenatal diagnosis available (pseudodeficient alleles complicate assay)
- Increased protein in the cerebrospinal fluid and decrease in nerve conduction velocity
- Demyelination and deposits of metachromatic granules in central and peripheral nervous system
- Increase in sulfatides in white matter
- Decrease in other myelin lipids (cholesterol and sphingomyelin)
- Molecular genetic studies are also available

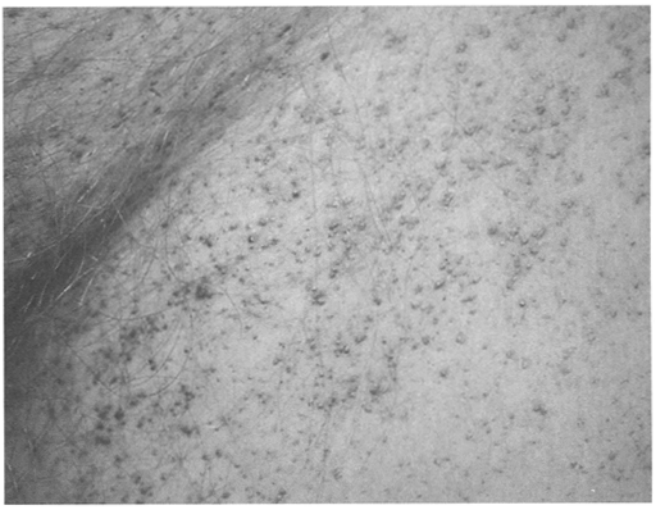


Fig. 9. Fabry disease—Angiokeratomas.

Treatment

- Not curable, supportive/symptomatic
- Bone marrow transplantation slows progression of symptoms

Fabry Disease

Chromosome and Gene Location

- Xq22.1

Inheritance

- X-linked recessive

Incidence

- 1/40,000 males

Clinical

- Childhood or adolescent onset
- Pain in distal extremities
- Fever
- Elevation of erythrocyte sedimentation
- Vascular lesions
- Cardiomyopathy
- Central nervous system usually spared
- Peripheral edema
- Corneal opacities
- Skin lesions (angiokeratomas, **Figure 9**)
- Reduced motor nerve conduction velocities
- Renal failure later as disease progresses
- Carrier females are usually asymptomatic some may have an attenuated form of the disease

Molecular Genetics

- α-galactosidase is an enzyme involved in the degradation of glycosphingolipids

- Mutations in the gene result in the accumulation and deposition of glycosphingolipids with terminal α-galactosyl moieties in body fluids and nonneuronal tissues of the body

Laboratory

- Deficient α-galactosidase A activity in plasma or serum, tears, and fibroblasts, prenatal diagnosis available
- Tissue deposition of crystalline glycosphingolipids
- Molecular genetic testing is available

Treatment

- Peripheral neuropathy may respond to carbamazepin, phenytoin, or neurotropin
- Dialysis and renal transplantation
- Enzyme replacement therapy

FAMILIAL CANCER SYNDROMES

Familial Adenomatous Polyposis

Chromosome and Gene Location

- 5q21-q22

Inheritance

- Autosomal dominant
- 20–25% are the result of new mutations

Incidence

- 3/100,000

Clinical

- Multiple (>100) polyps early in life (by age 20 over 90% of gene carriers will develop polyps)
- Polyps progress to colonic carcinoma by age 40
- Additional features include congenital hypertrophy of the retinal pigment epithelium (CHRPE) and supernumerary teeth
- Other tumors may occur [duodenal, thyroid, brain, liver, desmoid tumors **(Figure 10)**, childhood hepatoblastomas]
- "Gardner syndrome" refers to individuals with FAP who have extracolonic manifestations such as tumors of the jaw, lipomas, and fibromas

Molecular Genetics

- Numerous mutations have been identified in the adenomatous Polyposis coli (APC) gene, most mutations lead to truncated protein product
- The protein is thought to be involved in maintaining normal apoptosis and decreasing cell proliferation. The APC protein may also be involved in maintaining chromosomal stability

Laboratory

- Direct mutation analysis via full gene sequencing, various mutation scanning methods, protein truncation are all currently available. Linkage testing is also available for families without an identifiable mutation

Treatment/Surveillance

- Genetic consultation is necessary to determine the utility of genetic testing in these families
- For individuals with a diagnosis of FAP, colectomy is advised when polyps become too numerous to remove or watch
- For individuals who have a positive gene test or who have not had genetic testing and are at risk, flexible sigmoidoscopy every 1–2 years beginning at age 10–12 years through age 35, colonoscopy when polyps are detected. Regular endoscopy of duodenum
- Annual thyroid palpation
- Ophthalmologic examination for CHRPE
- For children at risk, α-fetoprotein testing and abdominal palpation is recommended for hepatoblastoma annually until age 6

MYH-associated Polyposis

Chromosome and Gene Location

- 1p34.3-p32.1

Inheritance

- Autosomal recessive

Incidence

- ~1–2% of the general population are carriers of one MYH mutation

Clinical

- Multiple (>15–100) polyps early in life, similar to the presentation of attenuated FAP
- Polyps are likely to progress to carcinoma if left untreated
- Additional features may include similar extracolonic manifestations exhibited with FAP

Molecular Genetics

- Two mutations account for ~85% of mutations within the European Caucasian population (Y165C, G382D)
- Other founder mutations exist in certain ethnic groups (i.e. Indian, Pakistani)
- The MYH protein repairs DNA by removing adenine residues that are mispaired with 8-oxoguanine during replication of oxidized DNA

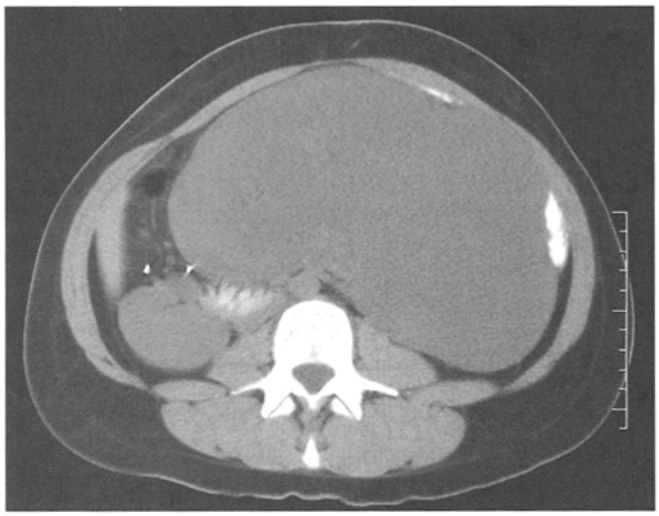


Fig. 10. Familial adenomatous polyposis—Desmoid tumor.

♦ Biallelic MYH mutations are identified in upto 20% of individuals with 15–100 polyps and up to 7% with greater than 100 polyps

Laboratory

♦ Direct mutation analysis for the two common mutations is clinical available. Full gene sequencing will soon be available. Carrier screening can also be performed once a mutation has been identified within a family

Treatment/Surveillance

♦ Genetic consultation is necessary to determine the utility of genetic testing in these families

♦ For individuals with a diagnosis of attenuated FAP without clear evidence of dominant inheritance, testing for MYH should be considered

♦ Treatment/surveillance of families with bi-allelic MYH mutations should be modeled after patients with classical or attenuated FAP

Basal Cell Nevus Syndrome (Gorlin Syndrome)

Chromosome and Gene Location

♦ 9q22.3

Inheritance

♦ Autosomal dominant

Incidence

♦ 1/55,000 (in United Kingdom)

Clinical

♦ The following criteria have been proposed for a making a diagnosis. (The sensitivity and specificity are not known.) A diagnosis is made when two major or two minor and one major criteria are fulfilled:

- Major criteria:
  - Multiple basal cell carcinomas
  - Basal cell nevi
  - Odontogenic keratocyst
  - Polyostotic bone cyst
  - Palmar or plantar pits
  - Ectopic calcification
  - Family history of basal cell nevus syndrome
- Minor criteria:
  - Congenital skeletal anomaly:
    - Bifid, fused, splayed or missing rib
    - Bifid wedged or fused vertebra
    - Head circumference in the 97th %
    - Cardiac or ovarian fibroma
    - Medulloblastoma
    - Lymphomesenteric cysts
  - Congenital malformation:
    - Cleft lip and/or palate
    - Polydactyly
    - Eye anomaly
- Others:
  - Tall stature
  - Frontal bossing with large head
  - Ocular hypertelorism
  - Broad nasal root
  - Enlarged jaw

Molecular Genetics

♦ Mutations in PTCH gene leads to premature stop or frameshift

♦ The protein is thought to be involved in controlling cell fates, patterning, and growth in numerous tissues

Laboratory

♦ Molecular genetic testing available by direct DNA or linkage

Treatment/Surveillance

♦ Early excision of basal cell tumors

♦ Annual screening by dermatologist in puberty and more frequently as needed

♦ Gynecologic examination, annually in adulthood

Breast/Ovarian Cancer

Chromosome and Gene Location

♦ 17q12 (BRCA1)

♦ 13q12 (BRCA2)

Inheritance

♦ Autosomal dominant

Incidence

♦ Varies by population:

- 1/1000 BRCA1 mutation in general Caucasian population

- 1/100 carrier frequency of 185delAG mutation in Ashkenazi Jewish women
- 8/100 carrier frequency for 6174delT in Ashkenazi Jewish women diagnosed with breast cancer < age 42
- Overall carrier frequency for either BRCA1 or BRCA2, estimated to be 1/100–1/2500 across different populations

Clinical

- Early onset (premenopausal) adenocarcinoma of the breast, often bilateral disease
- Additionally, ovarian cancer is a prominent feature of BRCA1 families, but less so for BRCA2
- Breast cancer in males is more common in BRCA2 families but also present in BRCA1 families
- Males carrying a mutated BRCA1 gene are at an increased risk (3.3 relative risk) of developing prostate cancer
- Increased risk for for pancreatic cancer with BRCA2 carrier
- BRCA1 is thought to account for 50% of all familial early onset cases (2.5–5% of all breast cancers) and about 80% of inherited breast and ovarian cancer
- BRCA2 is estimated to account for 17–35% of hereditary breast cancer
- It is estimated that individuals who carry a BRCA1 or BRCA2 gene mutation may have as high as 56–87% risk of developing breast cancer and 27–63% risk of developing ovarian cancer by age 70, compared to the lifetime general population risk of 1/8 for breast cancer and 1/70 for ovarian cancer

Molecular Genetics

- Various mutations (deletions, insertion, point mutations) have been identified, most result in truncation or absence of BRCA1 and BRCA2 proteins
- Both are thought to be tumor-suppressor genes

Laboratory

- Molecular testing available for BRCA1 and BRCA2

Treatment/Surveillance

- Chemoprophylaxis with tamoxifen or related compounds
- Screening recommendations include monthly breast self examination ages 18–21, annual or semiannual clinical breast examination for ages 25–35
- Annual mammography suggested beginning by ages 25–35
- Annual or semiannual screening using transvaginal ultrasound and serum CA-125 ages 25–35 (caution: less than half of early stage ovarian tumors produce elevated levels of CA-125)
- For prostate cancer surveillance in BRCA1 and BRCA2 carriers, rectal examination and PSA level should be offered annually
- Prophylactic mastectomy and/or oophorectomy have been undertaken to reduce risk

Hereditary Nonpolyposis Colon Cancer (HNPCC)

Chromosome and Gene Location

- 3p21.3 (hMLH1)
- 2p22-p21 (hMSH2)
- 7p22 (hPMS2)
- 2p16 (hMSH6)

Inheritance

- Autosomal dominant

Incidence

- May account for 1–3% of all colon cancers

Clinical

- Colorectal cancer:
  - 2/3 in right colon
  - Average age at diagnosis is 45
  - 80% lifetime risk for colon cancer
- Endometrial adenocarcinoma
- Increased risk for ovarian, transitional cell renal collecting system, ureter, stomach, small bowel, hepatobiliary tract, and pancreatic cancers. Also at an increased risk for sebaceous carcinomas, and basal and squamous cell carcinomas of the skin
- Muir-Torre syndrome is a variant form of HNPCC characterized by a combination of benign or malignant sebaceous skin tumors and internal malignancy due to mutations in hMSH2 or hMLH1
- Turcot syndrome is characterized by brain tumor (glioblastoma multiforme) and colorectal tumors and is also associated with HNPCC
- The following Amsterdam criterion were developed to assist in the definition of HNPCC. All four conditions need to be fulfilled to meet the Amsterdam criterion. However, the criterion have been found to be overrestrictive for clinical use:
  - Three cases of colon cancer of which two people are first degree relatives of the third person
  - Colon cancer occurs in two generations
  - One colon cancer diagnosed before age 50
  - The family does not have Familial Adenomatous Polyposis (FAP)

Molecular Genetics

- The products of the genes hMLH1, hMSH2, hMSH6 and PMS2 participate in a DNA mismatch repair complex
- The hMLH1 and hMSH2 account for most of the mutations found in HNPCC families to date
- Most mutations are thought to result in a truncated protein
- Colon cancer is a multistep process, meaning that a number of mutations in different genes need to occur before the onset of colon cancer

- When a mutation occurs in a mismatch repair complex, the ability to repair other random mutations is compromised, thus leading to an accumulation of mutations (microsatellite instability)
- The mutations may inactivate tumor suppresser genes and lead to the subsequent penetrance of colon cancer

Laboratory

- Nearly all tumors show widespread microsatellite instability (MSI). MSI in combination with immunostaining is a useful tool to identify which gene may be involved
- Immunohistochemistry (IHC) can be utilized on the tumor tissue to identify the presence or absence of protein expression for hMLH1, hMSH2, hMSH6, and hPMS2 proteins. IHC helps to determine the gene of interest for a given family
- Mutational analysis for point mutations and large genomic rearrangements (duplications and deletions) is available
- Histological appearance of tumors is nondiagnostic, but increase in tumor infiltrating lymphocytes and mucinous histology is characteristic of tumors with MSI

Treatment/Surveillance

- For asymptomatic, suspected or known gene carriers, a full colonoscopy every 1–3 years beginning at ages 20–25
- Annual screening for endometrial cancer beginning ages 25–35
- Endometrial biopsy and urinalysis with cytology every 2 years beginning age 35
- Annual urinalysis and cytology beginning at age 25
- Annual skin surveillance
- Periodic upper gastrointestinal endoscopy beginning age 35 for families in which gastric cancer has occurred
- Prophylactic subtotal colectomy has been used to reduce risk
- Prophylactic hysterectomy and oophorectomy after childbearing may reduce risk

Cowden's Syndrome (Multiple Hamartoma Syndrome)

Chromosome and Gene Location

- 10q23 (PTEN)

Inheritance

- Autosomal dominant

Incidence

- Unknown

Clinical

- Multiple hamartomas including:
  - Cobblestone-like hyperkeratotic papules of gingiva and buccal mucosa
  - Fibroadenomatous breast enlargement
  - Hamartomatous polyps of the stomach, small bowel, and colon
  - Cerebellar gangliocytomatosis
  - Breast cancer in 25–50% of female gene carriers
  - May also be increased risk for endometrial cancer and thyroid adenoma and carcinomas
- In children:
  - Mucocutaneous lesions
  - Lipomas
  - Fibromas
  - Hemangiomas and progressive macrocephaly
  - Mild-to-moderate delay may be present at an early age

Molecular Genetics

- Mutations in PTEN gene thought to disrupt the tyrosine/dual-specificity phosphatase domain of this gene

Laboratory

- Molecular mutation analysis available

Treatment/Surveillance

- Surveillance for thyroid masses, breast cancer beginning at age 20
- May consider prophylactic mastectomy for women at risk
- Endometrial cancer screening beginning around age 35 years
- Annual urinalysis to help detect renal carcinoma
- Annual physical examination starting at 18 years of age for skin changes and baseline thyroid ultrasound examination

Li-Fraumeni Syndrome

Chromosome and Gene Location

- 17p13.1 (TP53)
- 22q12.1 (CHEK2)

Inheritance

- Autosomal dominant

Incidence

- Rare—fewer than 400 families worldwide

Clinical

- Soft tissue sarcomas
- Early onset breast cancer
- Adrenocortical and brain tumors
- Osteosarcomas
- Leukemia
- Risk of developing invasive cancer is approx 50% by age 30 and 90% by age 70
- Classical definition requires one patient with sarcoma under age 45; a first degree relative under age 45 with any cancer, and a third affected first or second degree

relative with either sarcoma at any age or any cancer under age 45

Molecular Genetics

- Approximately 50% of Li-Fraumeni families have mutations in the p53 tumor-suppressor gene
- Mutation types include nonsense mutations, and splice site mutations generate truncated protein products

Laboratory

- Mutation analysis available for TP53, otherwise no other specific laboratory findings

Treatment/Surveillance

- Screening includes annual mammogram
- Physical exam of breasts every 6 months
- Monthly self-breast exam beginning in adulthood
- Annual blood count and review of peripheral smear for leukemia
- Annual exam beginning in infancy for all related findings

Multiple Endocrine Neoplasia Type 1

Chromosome and Gene Location

- 11q13

Inheritance

- Autosomal dominant

Incidence

- 1/5000–1/50,000 live births

Clinical (also see Chapter 11)

- Hyperparathyroidism
- Peptic ulcer disease
- Parathyroid adenomas
- Pancreatic islet cell tumors (most commonly gastrinomas)
- Insulinoma
- Pituitary adenoma (prolactinoma)
- Features are relatively consistent within families

Molecular Genetics

- MEN1 gene encodes a transcript called menin
- Numerous frameshift, nonsense, missense, and in-frame deletions have been reported
- Function of protein is not known

Laboratory

- Elevated ACTH
- Abnormal secretin test
- Hypoglycemia
- Hypergastrinism
- Hyperparathyroidism
- Glucose intolerance
- Molecular analysis is available

Treatment/Surveillance

- Screening recommendations include an annual evaluation for prolactin, cortisol, glucose, calcium, and phosphorus
- Physical exam with endocrinologic review of systems

Multiple Endocrine Neoplasia Types 2A, 2B (MEN2A and MEN2B) and Familial Medullary Thyroid Carcinoma (FMTC)

Chromosome and Gene Location

- 10q11.2

Inheritance

- Autosomal dominant

Incidence

- 1/30,000
- 5–10% of thyroid cancers are of the medullary type, of these, 20% are due to germline mutations in the RET protooncogene

Clinical (also see Chapter 14)

- MEN2A:
  - Medullary thyroid carcinoma (>95%)
  - Pheochromocytoma (>50%)
  - Hyperparathyroidism (parathyroid hyperplasia or adenoma) (15–30%)
- MEN2B:
  - Same features as MEN2A, but earlier onset (10 years)
  - Parathyroid disease is rare
  - Additional findings include:
    - Mucosal neuromas **(Figure 11)**
    - Thickened corneal nerves
    - Marfanoid habitus
    - Gastrointestinal involvement
- FMTC:
  - Medullary thyroid carcinoma only
  - More benign than MEN2A or 2B

Molecular Genetics

- Mutations in cystiene residues of extracellular binding domain in exons 10, 11, 13, 14, and 15 of the RET protooncogene account for most of the cases of MEN2A and FMTC
- A single point mutation in exon 16 (M918T) is the most common cause for MEN2B
- Mutations within these exons of the RET protooncogene account for approx 95% of MEN2A families, 85% of FMTC, and 95% of MEN2B families

Laboratory

- Mutations in RET protooncogene
- Elevated calcitonin after pentagastrin stimulation



Fig. 11. Multiple endocrine neoplasia type 2B—mucosal ganglioneuroma.



Fig. 12. Peutz-Jegher syndrome with freckles on lips.

- Metanephrines may be elevated if pheochromocytoma is present
- Parathyroid hormone and calcium elevation may also be present

Treatment/Surveillance

- Screening recommendations include genetic testing for at risk individuals
- For positive individuals, prophylactic thyroidectomy and screening for pheochromocytoma and hyperparathyroidism is indicated

Peutz-Jeghers Syndrome

Chromosome and Gene Location

- 19p13.3

Inheritance

- Autosomal dominant

Incidence

- 1/25,000–1/50,000 births

Clinical

- Numerous pigmented spots on lips and buccal mucosa (more rarely on face, forearms hands, feet, and perianal area). **(Figure 12)**
- Multiple gastrointestinal hamartomatous polyps in the jejunum (malignant transformation not common)
- Risk of any malignancy estimated is 50%
- Most reported cancers are in stomach or duodenum in patients under 40 years
- Also associated with cancers of the breast, cervix, ovaries, testis, and pancreas

Molecular Genetics

- Disorder is due to mutations in the serine threonine kinase STK11 gene
- 50% are due to a new mutation

Laboratory

- Polyps can have a unique cellular morphology imparting branching-tree-like appearance of mucosa with interdigiting smooth muscle
- Molecular testing available

Treatment/Surveillance

- Removal of polyps if feasible
- Screening includes upper and lower gastrointestinal (GI) endoscopy and small bowel X-rays when GI symptoms are present (repeated every 2–3 years for those with a diagnosis)
- Regular breast and gynecologic screening after age 20
- Mammography between age 20 and 30 repeated every 2–3 years
- Regular testicular exam for at-risk males
- Periodic colon cancer screening after age 35
- Annual pelvic examination and ultrasound
- Abdominal (or endoscopic) ultrasound of pancreas every 1–2 years beginning age 30

Retinoblastoma (RB)

Chromosome and Gene Location

- 13q14

Inheritance

- Approximately 60% are unilateral and sporadic
- 15% are unilateral and hereditary
- 25% are bilateral and hereditary and autosomal dominant with 90% penetrance
- In inherited cases, an affected individual will have a 50% risk of passing the gene on the their offspring
- One altered gene is *not* sufficient to cause RB
- Another sporadic event needs to occur in this gene to cause RB (thus incomplete penetrance)
- Individuals who carry the gene and do not have RB still have a 50% risk of passing the gene on to their offspring

Incidence

- 1/15,000–1/20,000 live births

Clinical

- Strabismus and/or leukocoria, multifocal, and bilateral tumors of the retina
- Other secondary cancers include:
  - Osteosarcomas
  - Fibrosarcomas
  - Melanomas
- May also be at an increased risk for lung, prostate, and breast cancer

Molecular Genetics

- Numerous large and small deletions as well as point mutations have been found in the RB1 gene
- The protein is involved in cell cycle and cell growth regulation

Laboratory

- Deletions and point mutations in RB gene (molecular mutation analysis and FISH analysis are available)

Treatment/Surveillance

- Surgery options include:
  - Enucleation (removal of entire eye)
  - Cryosurgery (kills cancer by freezing it)
  - Photocoagulation (uses narrow beam of strong light to kill blood vessels that feed the tumor)
- Chemotherapy and radiation are also options
- Screening includes ophthalmologic examination at birth and every 8–12 weeks to age 2, every 6 months from age 2 to 12, annually thereafter

von Hippel–Lindau (VHL)

Chromosome and Gene Location

- 3p25–26

Inheritance

- Autosomal dominant
- 100% penetrant by age 65

Incidence

- 1/36,000

Clinical

- Diagnosis of VHL is made if patient has one symptom from Section A plus one symptom from Section B, two symptoms from Section A, or a family history of VHL, and one symptom from either section:
  - Section A:
    - Retinal hemangioblastomas (45–59%)
    - Cerebellar hemangioblastoma (44–72%)
    - Spinal hemangiobiastoma (13–59%)
  - Section B:
    - Pheochromocytoma (15%)
    - Pancreatic cystic disease
    - Cystadenoma of the epididymis (10–26%)
    - Renal cysts (60%)
    - Renal carcinoma

Molecular Genetics

- Numerous deletion, insertion, nonsense and missense mutations in the VHL gene
- VHL gene is a tumor-suppressor gene
- The gene product functions to negatively regulate transcription

Laboratory

- Mutation analysis of the VHL gene
- Linkage analysis also available for suitable pedigrees

Treatment/Surveillance

- Laser therapy
- Cryotherapy
- Photocoagulation
- Radiation
- Surgery
- Screening recommendations include:
  - Annual physical exam with neurologic evaluation for signs of cerebellar or cord lesions
  - Annual ophthalmologic examination
  - Red blood cell count for polycythemia
  - Annual urinalysis
  - Urine cytology and urinary metanephrines
  - MRI imaging of CNS and cord at age 11
  - Annual imaging no later than age 18 for kidneys and pancreas by CT and/or ultrasound

Wilms' Tumor

Chromosome and Gene Location

- 11p13 (WT1)
- 11p15.5 (WT2)
- Plus an additional unidentified locus

Inheritance

- Mostly sporadic, autosomal dominant with reduced penetrance (60%) and variable expressivity

Incidence

- 1/10,000
- 10–30% have germline mutation in WT1

Clinical

- Wilms' tumor is a tumor affecting the kidney

- Tumor development requires two hits to the WT1 gene, one germline mutation and another somatic mutation
- Deletions which lead to hemizygosity (one copy) of the gene WT1 are associated with Wilms's tumor, aniridia, genitourinary malformations, and mental retardation syndrome
- Missense mutations in WT1 zinc finger region lead to Denys-Drash syndrome which includes male pseudohermaphrodism and nephropathy progressing to renal failure
- WT2 gene is subject to genomic imprinting (promoter on paternal allele, suppressor on maternal allele)
- Paternal uniparental disomy of chromosome 11p15 (two copies of the gene from the father) leads to Beckwith-Weidemann syndrome (overgrowth condition with hemihypertrophy, macroglossia, omphalocele, abdominal organomegaly, ear pits and creases and predisposition to Wilms' tumor)

Molecular Genetics

- The WT1 gene product is a developmentally regulated transcription factor of the zinc finger family which is expressed primarily in the gonads and kidneys; it is thought to be a tumor suppressor gene which binds to p53 gene and suppresses expression
- The WT2 locus is thought to be an imprinted growth promoter on paternal allele and an imprinted growth suppressor on maternal allele

Laboratory

- Molecular testing available–60% sensitivity

Treatment/Surveillance

- Surgery, chemotherapy, and radiation therapy
- Screening includes abdominal exams every 1–2 months and ultrasound every 4–6 months through age 6

MITOCHONDRIAL DISORDERS

- Mitochondria are the cellular organelles which generate energy for cellular processes by producing ATP through oxidative phosphorylation
- The mitochondria contain their own DNA, separate from genomic DNA
- Mitochondrial DNA is a double stranded circular molecule, which encodes 13 protein subunits of four biochemical complexes and 24 structural RNA's required within the mitochondria for translation of the protein-coding units
- Although the mitochondria can replicate, transcribe and translate their DNA independent of nuclear DNA, the mitochondria are dependent on imported proteins coded by nuclear DNA for their structure and function
- Each mitochondria contains 2–10 molecules of DNA, and each cell contains numerous mitochondria

Chromosome and Gene Location

- Mitochondrial DNA (mtDNA) (37 genes)
- Numerous nuclear genes

Inheritance

- Mitochondrial DNA (and therefore alterations within the mtDNA) is inherited through the maternal germline (transmitted in the ovum, not in sperm). Therefore mitochondrial diseases due to defects in mitochondrial encoded DNA will show only maternal inheritance; both males and females can be affected. However, most mitochondrial dysfunction is due to alterations in nuclear genes and is inherited in an autosomal recessive pattern
- Mitochondria replicate and segregate into daughter cells randomly
- During this process, the proportion of normal and mutant cells in a given cell may shift
- The term heteroplasmy refers to the coexistence of normal and mutant mitochondrial DNA in the same cell
- Homoplamsy refers to the presence of all normal or all mutant mitochondrial DNA
- Whether a person is affected by mitochondrial disease and to what extent is dependent on the proportion of mitochondria which contain mutant mitochondrial DNA
- The proportion of mutant mitochondrial DNA required for a particular disease varies among individuals, organ systems, and tissues, and in general is based upon the balance between oxidative supply and demand

Incidence

- Unknown

Clinical

- Nearly all tissues depend on oxidative metabolism
- Therefore, mitochondrial diseases are complex multisystem disorders that include a variety of neurologic, ophthalmologic, cardiac, endocrine, gastrointestinal, and pulmonary manifestations
- Below are examples of some of the mitochondrial diseases which exhibit maternal inheritance:
  - Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS):
    - Seizures
    - Stroke-like episodes
    - Brain dysfunction
    - Cerebral structural changes

  - Short stature
- Myoclonic epilepsy with ragged-red fibers (MERRF):
  - Myoclonus
  - Seizures
  - Cerebellar ataxia
  - Mitochondrial myopathy
- Leber's hereditary optic neuropathy (LHON):
  - Bilateral visual loss
  - Central scotomas
  - Abnormal color vision
- Kearns-Sayre syndrome:
  - Chronic progressive external ophthalmoplegia
  - Retinal degeneration
  - Heart block

Molecular Genetics

- Numerous deletions and point mutations have been identified
- Mitochondrial DNA is thought to mutate more than 10 times as frequently as nuclear DNA
- Additionally, mtDNA does not have the protective effect of introns, histones, or repair systems
- Sequencing of the entire mtDNA is available

Laboratory

- Ragged-red fibers in skeletal muscle
- Elevated serum and cerebrospinal fluid lactate
- Myopathic potentials
- Axonal and demyelinating peripheral neuropathy on conduction studies
- Cardiac conduction defects
- Defective oxidative phosphorylation
- Mitochondrial DNA mutations

Treatment

- Not curable, supportive/symptomatic, variety of vitamins and cofactors often used

SUGGESTED READING

Online resources

GeneReviews—www.geneclinics.org

Online Mendelian Inheritance in Man (OMIM)—www.ncbi.nlm.nih.gov

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3

Forensic Pathology

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CONTENTS

I. General Concepts 3-3
Cause of Death 3-3
Manner of Death 3-3
Mechanism of Death 3-3

II. Identification 3-3
Positive Identification 3-3
Circumstantial Identification 3-3
Anthropological Identification 3-3

III. Time of Death and Postmortem Changes 3-3
General 3-3
Livor Mortis (Lividity) 3-3
Rigor Mortis (Rigidity) 3-4
Algor Mortis (Body Cooling) 3-5
Decomposition 3-5
Gastric Emptying 3-5
Forensic Entomology 3-5
Postmortem Chemistry 3-6

IV. Sudden Death from Natural Disease 3-6
Classification 3-6
Cardiovascular Causes of Death 3-7
Hypertensive Cardiovascular Disease.....3-7
Aortic Stenosis 3-7
Long QT Syndrome (LQTS) 3-7
Hypertrophic Cardiomyopathy 3-8
Dilated Cardiomyopathy 3-8
Restrictive Cardiomyopathy 3-8
Myocarditis 3-8
Mitral Valve Prolapse 3-8
Aortic Dissection 3-9
Pulmonary Thromboembolism 3-9
Cerebrovascular Disease 3-10
Intracerebral Hemorrhage (Apoplexy)....3-10
Ruptured Berry Aneurysm 3-10
NonVascular Causes of Death 3-10
Chronic Alcoholism 3-10
Epilepsy 3-11
Bronchial Asthma 3-11
Waterhouse-Friederichsen Syndrome....3-12
Colloid Cyst of Third Ventricle 3-12
Diabetic Ketoacidosis 3-12
Anaphylaxis 3-12
Sudden Infant Death Syndrome (SIDS).....3-13

V. Physical Injuries.....3-15
Mechanical Trauma 3-15
Blunt Force Injuries 3-17
Abrasion 3-17
Contusion 3-17
Laceration 3-18
Fractures 3-18
Head Injuries.....3-19
Intracranial Hemorrhages 3-20
Cerebral Contusions 3-21
Fat Embolism 3-23
Shaken Baby Syndrome (SBS).....3-23
Firearms Injuries 3-24
General Principles.....3-24
Handguns 3-24
Rifles.....3-28
Sharp Force Injuries 3-28
Asphyxia.....3-29
Compression of Neck 3-30

Obstruction of Airway 3-32
Mechanical Asphyxia 3-34
Drowning 3-36
Atmospheric Pressure Changes 3-36
Decreased Atmospheric Pressure 3-36
Increased Atmospheric Pressure....3-37
Barotrauma 3-37
Thermal Injuries Related to Temperature Changes 3-37
Local Hypothermia....3-37
Systemic Hypothermia 3-38
Immersion Hypothermia....3-38
Wind Hypothermia 3-38
Paradoxical Undressing 3-38
Hide and Die Syndrome 3-38
Local Hyperthermia (BURNS) 3-38
Smoke Inhalation 3-38
Systemic Hyperthermia 3-39
Electrical Injuries 3-40

VI. Toxicology 3-41

Alcohols and Acetones 3-41
Methanol (Wood Alcohol) 3-41
Isopropyl (Rubbing Alcohol) 3-41
Acetone....3-41
Ethylene Glycol 3-42
Cocaine and Cocaethylene 3-42
Cocaine 3-42
Cocaethylene....3-43
Opiates 3-43
Amphetamines 3-43
Barbiturates 3-44
Psychoactive Drugs 3-44
Lysergic Acid Diethylamide (LSD) 3-44
Phencyclidine (PCP)....3-44
Marihuana....3-44
γ-hydroxybutyrate (GHB)....3-44
Antidepressants 3-45
Tricyclic Antidepressants 3-45
Antipsychotics 3-45
Analgesics 3-45
Metals....3-46
Arsenic 3-46
Lead 3-46
Mercury....3-46
Cobalt 3-46
Thallium 3-47
Other Chemicals....3-47
Organophosphates....3-47
Strychnine....3-47
Freons 3-47

VII. Suggested Reading 3-47

GENERAL CONCEPTS

Cause of Death

- Injury, disease, or a combination of the two responsible for initiating the events leading to death; may be brief or prolonged:
  - If prolonged with survival, sequelae may develop from the initiating or proximate cause, which leads to intermediate causes of death such as pneumonia, pulmonary embolism, or bronchopneumonia
- Examples of causes of death:
  - Coronary artery atherosclerosis
  - Blunt force injury of head
  - Gunshot wound of head
  - Hanging
  - Mixed drug intoxication

Manner of Death

- Circumstances in which the cause of death arose
- Separated into two categories:
  - Natural
  - Unnatural:
    - If unnatural, then further subdivided into accident, suicide, homicide, or undetermined (undetermined could be natural)

Mechanism of Death

- Physiologic derangement or biochemical disturbance that is incompatible with life and is initiated by the cause of death; does not appear on death certificate
- Examples of mechanism of death:
  - Ventricular fibrillation
  - Respiratory arrest
  - Exsanguination

IDENTIFICATION

Positive Identification

- Visual identification:
  - Family and friends
  - Personal identification (driver's license, social security card)
  - Tattoos, scars, congenital defects, finger-prints, dental examination (comparison of pre and postmortem dental X-rays and charting), X-ray (pre and postmortem X-ray comparison: frontal sinus, vertebral column, ribs, unique bony or therapeutic identifying features), foreign objects (orthopedic hardware)
  - DNA (blood, tissue, bone)

Circumstantial Identification

- For use on significantly altered decedents such as burned and decomposed bodies:
  - Secured residence or motor vehicle associated with suspected decedent
  - Personal effects on body or at scene (wallet, clothing, credit cards, unique jewelry, etc.)

Anthropological Identification

- Age (range)
- Race (more complicated with interracial procreation)
- Sex (most consistent)
- Stature
- Hair examination (may help identify race as well as hair color)

TIME OF DEATH AND POSTMORTEM CHANGES

General

- No time of death test exists
- Eyewitness is best determination of time of death
- Generally give estimates and ranges for time of death:
  - Sepsis and heat accelerate decomposition
  - Cold delays decomposition

Livor Mortis (Lividity)

- Blue–purple discoloration in dependent areas of body **(Figure 1A,1B)**
- Minimal with blood loss and dark pigmentation
- Usually visible within 24 hours following death, maximum usually 8–12 hours postmortem:
  - After 8–12 hours postmortem, lividity may become fixed and will no longer blanch

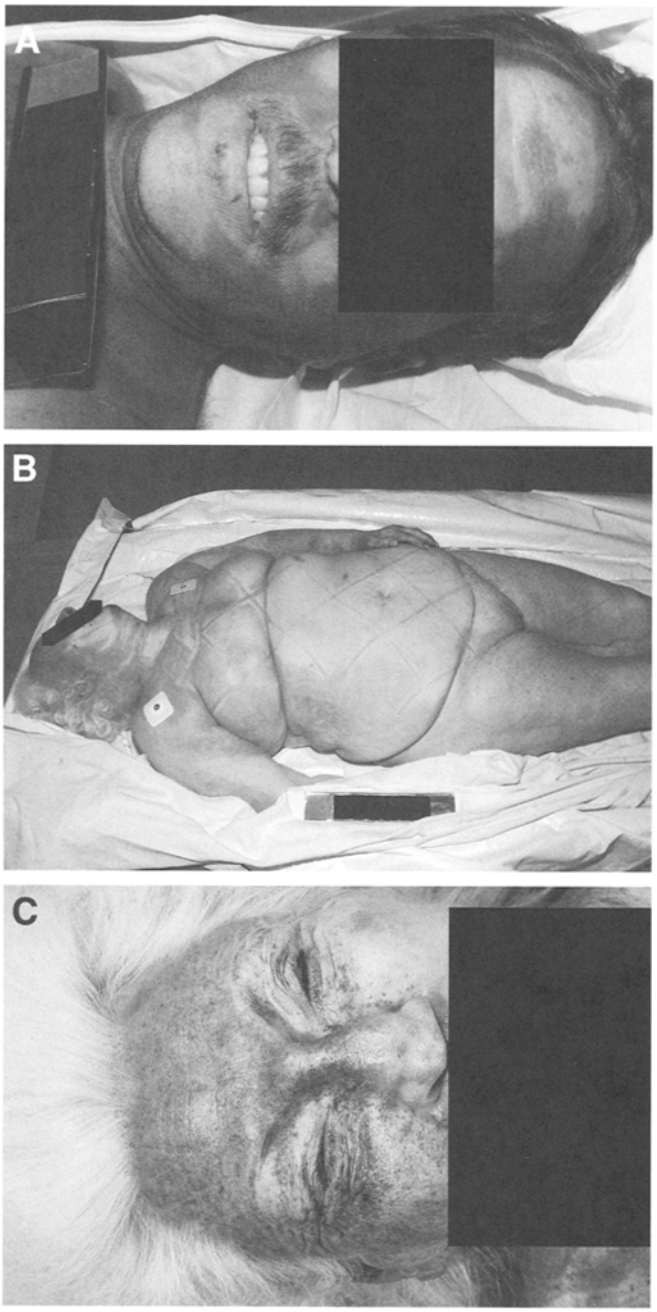


Fig. 1. Pressure pallor of anterior livor over weight-bearing points (**A**). Patterned anterior livor (**B**). Tardieu spots and anterior livor (**C**).

- May form antemortem with prolonged hypotension
- Accelerated rate of fixation with increased temperature and decomposition
- Delayed with cool temperature
- Lividity may appear different from:
  - Refrigeration: pink to cherry red (retained oxygen in cutaneous vessels)



Fig. 2. Rigor fixed opposite gravity, indicating subsequent movement of deceased from original position.

  - Carbon monoxide: cherry red (carboxyhemoglobin)
  - Cyanide: pink to cherry red (excessive oxygen retention from inhibition of cytochrome oxidase)
  - Fluoroacetate: cherry red (excessive oxygen retention from inhibition of cytochrome oxidase)
  - Hydrogen sulfide: green (sulfhemoglobin)
- Advanced livor mortis in which dependent capillaries and venules become over-extended, rupture, and coalesce, forming pinpoint hemorrhages called Tardieu spots **(Figure 1C)**

Rigor Mortis (Rigidity)

- Begins at death
- Due to cellular loss of ATP and accumulation of lactic acid with lowering of pH
- Occurs in all cells, but is externally manifested most prominently in the musculature
- Usually visible within 2–4 hours following death
- May be fully developed 6–12 hours following death **(Figure 2)**
- Accelerated in infants, febrile illnesses, sepsis, increased environmental temperatures, electrocution, seizures, and any excessive muscular activity prior to death
- Reduced or delayed in emaciated, elderly, and cold
- Disappears with decomposition
- Loss of ATP prevents detachment of cross-bridges between actin and myosin and increased free calcium ions
- Can affect involuntary muscles (pupil disparity postmortem)
- Cutis anserina: rigor mortis of arrector pili muscles (goose flesh)
- Cadaveric spasm: rigor mortis in agonal contraction (e.g., clenched fist, articles still held in hand)

Algor Mortis (Body Cooling)

- Postmortem cooling:
  - Conduction: heat transferred by direct contact to another object
  - Radiation: heat transferred to adjacent air by infrared rays
  - Convection: heat transferred through moving air currents adjacent to body
  - Heat loss decreased by an insulator such as clothing and increased body fat
  - Heat loss increased in cold water
  - Body temperature will approach environmental temperature
  - Body temperature before death may be increased by sepsis, hyperthyroidism, exercise, heat stroke, seizures, drugs (cocaine, amphetamines, anticholinergics, phencyclidine), and head injuries
  - Body temperature may decrease prior to death due to shock, cold environment, and drugs (alcohol, sedatives, opiates, and phenothiazines)
  - No exact formula to calculate the time of death from body temperature:
    - Ideally, body temperature decreases 2–2.5°F per hour for the first few hours
    - Decreases at an average of 1.5–2°F per hour in first 12 hours
    - In the following 12–18 hours, decreases an average of 1°F per hour

Decomposition

- Involves two processes:
  - Autolysis: breakdown of cells and organs by intracellular enzymes; accelerated by heat and slowed by cold
  - Putrefaction: process due to bacteria and fermentation; accelerated in patients with sepsis and increased temperature
- Decomposition is accelerated with higher environmental temperatures, obesity, heavy clothing, and sepsis
- Delayed by cold environment
- Generalized sequence of decomposition:
  - Decrease of rigor mortis and fixation of livor mortis
  - Green discoloration in the right lower quadrant of the abdomen
  - Green discoloration of the head, neck, and shoulders
  - Swelling of face (bacterial gas formation)
  - "Marbling" (hemolysis of blood with hemoglobin and hydrogen sulfide reaction, creating green–black discoloration along blood vessels)
  - Generalized bloating and skin slippage (body discoloration: green to black)
- Additional terminology:
  - Mummification: dehydration of body, most prominently seen in dry, hot climates in which skin develops a dry, leathery appearance
  - Miliaria: white–gray pinpoint discoloration seen below capsule of liver, kidney, and spleen, and below endocardium due to precipitation of calcium and other salts
  - Adipocere: gray–white, waxy material seen in bodies immersed in water or in damp warm environments in which neutral fats are converted to oleic, palmitic, and stearic acids
  - Tache noir: brown to black band of discoloration of the bulbar conjunctivae and sclerae from drying, in which eyes are open
  - Embalming: delays decomposition
  - Intrauterine maceration is a result of autolysis, not putrefaction

Gastric Emptying

- In general, there is variation from day to day in gastric emptying, even in healthy subjects
- Larger meals associated with longer emptying time than smaller meals
- Liquids empty faster than solids
- Mean emptying half-time for liquids is ~$1^1/_2$ hours
- Mean emptying half-time for solids is ~$4^1/_2$ hours
- Gastric emptying is delayed in diabetes mellitus, anorexia nervosa, illness, emotional stress, exercise, severe injury, and drugs (alcohols, narcotics, phenothiazines, atropine, and β-adrenergic drugs)
- Gastric emptying times are increased in certain medications (e.g., Valium) and certain types of exercise

Forensic Entomology

- Different insects are attracted at different stages of decomposition and may aid in the determination of how long a body has been dead
- Temperature and humidity are major factors controlling the deposition of eggs and the rate of development of necrophagous insects
- Flies are the most common insects:
  - Eggs are deposited soon after death in the daytime and take 24–48 hours to hatch into maggots
  - Maggots grow larger to pupa stage (6–10 days); adult flies emerge in 12–18 days
- As body decomposes, insects settle on body
- The following factors determine how soon and how many insects appear:
  - Rate of decomposition
  - Burial
  - Immersion in water
  - Mummification
  - Geography

- Must differentiate injury from postmortem artifacts created most commonly by:
  - Roaches
  - Ants
  - Mice and rats
- Scene markers, unscientific, but helpful:
  - Date of uncollected mail
  - Newspapers in front of house
  - Television guide open to specific date
  - Clothing attire
  - Sales receipts
  - Interviews with neighbors
- Vitreous humor:
  - Vitreous potassium not reliable for estimation of time of death
  - Intracellular potassium released after death, but not a reliable mathematical rate
  - Anything that accelerates decomposition increases the release of potassium

Postmortem Chemistry

- Vitreous humor:
  - Hypertonic dehydration pattern:
    - Increased sodium (> 155 mEq/L)
    - Increased chloride (> 135 mEq/L)
    - Increased urea nitrogen (VUN) (40–100 mg/dL)
  - Uremia pattern:
    - Normal to minimal increase in sodium and chloride
    - VUN > 150 mg/dL
  - Low salt pattern (alcoholic, pyloric obstruction, diuretic treatment):
    - Sodium < 130 mEq/L
    - Chloride < 105 mEq/L
    - Potassium < 15 mEq/L (low relative to decomposition pattern)
  - Decomposition pattern:
    - Sodium < 130 mEq/L
    - Chloride < 105 mEq/L
    - Potassium > 20 mEq/L
  - Diabetic pattern:
    - Glucose > 200
    - In ketoacidosis, may get acetone
    - Cannot diagnose hypoglycemia because glucose decreases postmortem
- Blood, postmortem stable:
  - Creatinine stable
  - Total cholinesterase stable (can rule out organophosphate poisoning)
  - Cortisol stable
  - TSH stable
  - Calcium stable
- Blood, postmortem increase:
  - Alkaline phosphatase, increase
  - Creatine phosphokinase (CPK), increase
  - Amylase, increase
  - Catecholamines, increase
  - Insulin, increase
  - Magnesium, increase
  - Potassium, increase
- Blood, postmortem decrease:
  - T4, decrease
  - Glucose, decrease
  - Sodium, decrease
  - Chloride, decrease

SUDDEN DEATH FROM NATURAL DISEASE

Classification

- Classification in which an autopsy discloses the cause of death from disease with regard to certainty
- Class 1:
  - Autopsy discloses cause of death with 100% certainty
  - Accounts for ~5% of natural deaths in medicolegal population
  - Examples:
    - Myocardial infarct with rupture
    - Dissecting aortic aneurysm with rupture
    - Intracerebral hemorrhage
- Class 2:
  - Does not have structural changes inconsistent with life, but advanced disease is present, sufficient for death
  - Accounts for 90% of natural deaths in medicolegal population
  - Examples:
    - Advanced heart disease
    - Chronic lung disease
    - Metastatic malignancy
    - Complications of chronic alcoholism

- Class 3:
  - A disease with lethal potential present, but not sufficiently advanced that under ordinary circumstances would be a competent cause of death:
    - Requires a compelling history and exclusion of other causes to allow for marginal pathologic findings to be determined to be responsible for the fatality
  - Infrequent in medicolegal population
  - Example: witnessed collapse with moderate coronary artery disease present at autopsy and negative toxicology, with no other significant pathologic findings:
    - Despite marginal findings at autopsy, one must conclude that death was because of heart disease
    - Conduction disorders should be considered
- Class 4:
  - Disease in which lethal structural findings are not readily demonstrable at autopsy
  - Autopsy fails to disclose alternative explanation
  - Example: epilepsy
- Class 5:
  - Cause of death is undetermined after autopsy and toxicologic studies
  - There is no evidence that death is due to unnatural causes

Cardiovascular Causes of Death

Atherosclerotic Heart Disease

Clinical

- Most common cause of unexpected natural death in the western world

Autopsy

- Marked narrowing of coronary arteries, typically >75% of lumen, in which a thrombus may or may not be present

Microscopic

- Recent or remote myocardial infarct may be present:
  - May see perivascular and interstitial fibrosis only
  - In some cases, no significant microscopic findings are present
  - Contraction band necrosis may be present in cases of ischemia, but may also be an artifact of resuscitation

Mechanism

- Pump failure
- Sudden arrhythmia

Hypertensive Cardiovascular Disease

Clinical

- May or may not have a history of hypertension
- No other symptoms, other than sudden cardiac arrest, may exist

Autopsy

- Concentric left ventricular hypertrophy
- Granular kidneys

Microscopic

- Myocardial fiber hypertrophy
- Sclerosis of mural cardiac arteries
- Arteriolar nephrosclerosis

Mechanism

- Sudden arrhythmia with an increased oxygen demand of hypertrophied muscle mass:
  - Hypertensive cardiovascular disease may coexist with atherosclerotic heart disease and lead to the acceleration of coronary atherogenesis

Aortic Stenosis

Clinical

- Bicuspid aortic valve (males, 50–70 age group)
- Rheumatic valvular disease (women, 35–55; mitral involvement also)
- Degenerative (Monckeberg's calcification) changes (>age 60, involving all three cusps)

Autopsy

- Calcification and obstruction of aortic valve
- Left ventricular hypertrophy

Microscopic

- Calcification of valve
- Myocardial fiber hypertrophy

Mechanism

- No findings distinctive for aortic stenosis mechanism
- Sudden arrhythmia because of instability from obstructive blood flow to coronary arteries

Long QT Syndrome (LQTS)

Clinical

- May be etiology of some cases of Sudden Infant Death Syndrome (SIDS)
- Affects approx 1 in 5000 individuals
- QT interval prolongation greater than 460 ms
- 60% of affected individuals present with syncope, seizures, or sudden death
- 40% of affected individuals are asymptomatic throughout life
- Six variants LQT_1–LQT_6:
  - LQT_1 ($KVLQT_1$, potassium channel gene, chromosome 11)—25% of cases
  - LQT_2 (HERG, potassium channel gene, chromosome 7)—20–25% of cases

- LQT_3 (SCN5A, sodium channel gene, chromosome 3) –5% of cases

♦ May suffer drowning or near drowning (LQTS1 most commonly)

Autopsy

♦ Rule out cardiomyopathy

♦ Must do molecular workup to rule out channelopathy

Mechanism

♦ Cardiac ion channelopathy leading to lethal dysrhythmia

Hypertrophic Cardiomyopathy

Clinical

♦ Most common cause of sudden death in athletes <35 years of age

♦ Male: female = 2:1

♦ Autosomal dominant

♦ Affects one of every 500 people

Autopsy

♦ May be symmetrical or asymmetrical thickening of interventricular septum at distal outflow tract

♦ Wide range of phenotypes

Microscopic

♦ Myofiber disarray most prominent in septum

♦ Plexiform interstitial fibrosis mechanism of action

♦ Thickened intramural coronary arteries

Genetics

♦ Autosomal dominant with variable penetrance

♦ Mutations in genes that encode sarcomere proteins

♦ Gene defect for cardiac myosin-binding protein C may be late onset (middle age and favorable prognosis)

Dilated Cardiomyopathy

Clinical

♦ May be associated with progressive congestive heart failure with early death

♦ May be associated with sudden death

♦ May develop secondarily in viral myocarditis, chronic alcoholism, peri or postpartum, or secondary to Duchenne's or myotonic dystrophy

Autopsy

♦ Enlarged dilated heart

♦ Flabby heart with all four chambers dilated

♦ Frequent endocardial thickening; may have mural thrombi

Microscopic

♦ Interstitial fibrosis

♦ Hypertrophied and attenuated myocytes

Restrictive Cardiomyopathy

Clinical

♦ Associated with systemic diseases such as amyloidosis, hemochromatosis, and glycogen storage diseases

♦ Clinically less common than hypertrophic and dilated cardiomyopathy; affects both sexes and all ages

♦ Decreased diastolic relaxation and elevated ventricular filling pressure

Autopsy

♦ Myocardium is stiff because of either infiltration from benign or malignant process, scarring, or intracellular accumulations

Microscopic

♦ Dependent on etiology of cardiomyopathy

Myocarditis

Clinical History

♦ May be associated with sudden death or progressive heart failure

♦ May be associated with virus, bacteria, fungus, protozoa, or autoimmune reaction

♦ Most common in forensic field is viral related

♦ May have history of recent viral-like symptoms

Autopsy

♦ Heart may be slightly dilated and flabby

♦ May have focal areas of mottling or may be grossly normal

Microscopic

♦ Diffuse or patchy cellular infiltration, mainly lymphocytes

♦ In some cases, accompanied by marked myocardial fiber necrosis

Mechanism

♦ Ectopic focal cardiac irritability leading to ventricular dysrhythmias

Mitral Valve Prolapse

Clinical

♦ Occurs in ~5–10% of general population

♦ Primary form may be inherited as autosomal dominant

♦ Mid systolic click

♦ Most common presenting symptom = palpitations (Premature ventricular contractions [PVCs]):

- PVCs associated with Marfan's syndrome, Ehlers–Danlos syndrome, pseudoxanthoma elasticum, osteogenesis imperfecta, straight thoracic spine syndrome, and pectus excavatum

♦ Predisposed to infectious endocarditis and mitral regurgitation

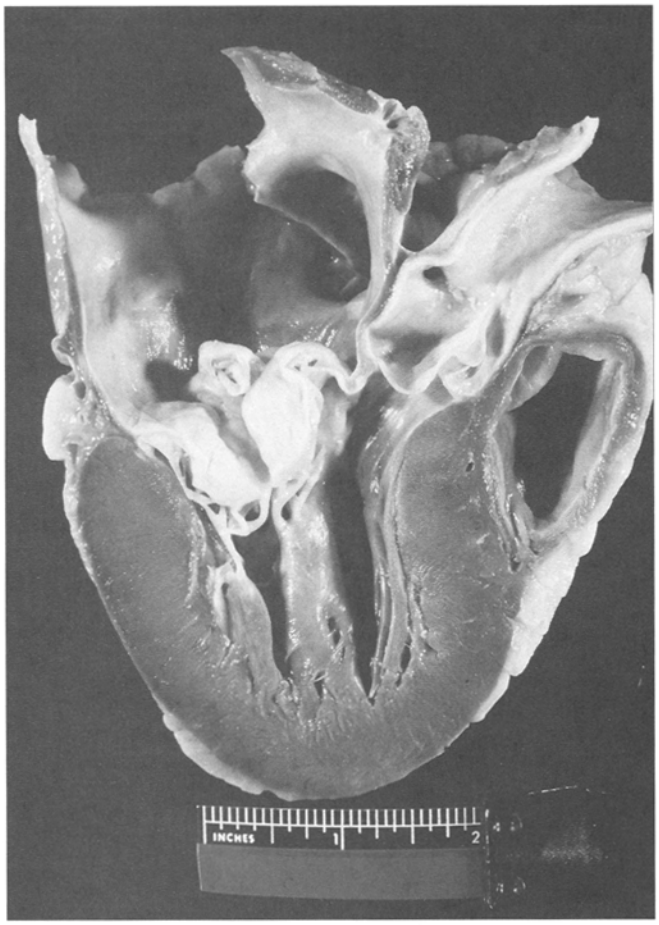


Fig. 3. Redundant mitral valve and left ventricular hypertrophy.

Autopsy

- Redundancy of leaflets with prolapse into left atrium **(Figure 3)** eventually get secondary fibrosis of leaflets
- Elongation of chordae tendineae
- Ventricular friction lesion

Microscopic

- Myxomatous degeneration with acid mucopolysaccharides and thickening and mucinous infiltration of zona fibrosa of mitral valve

Mechanism

- Frequent PVCs from impact of anterior mitral leaflet on atrial septum
- Rare progression to lethal dysrhythmia **(Figure 4)**

Aortic Dissection

Clinical

- Hypertension (coexists in 70–90% of patients) and weakness of aortic wall (e.g., Marfan's syndrome)
- Male predominant (3:1)

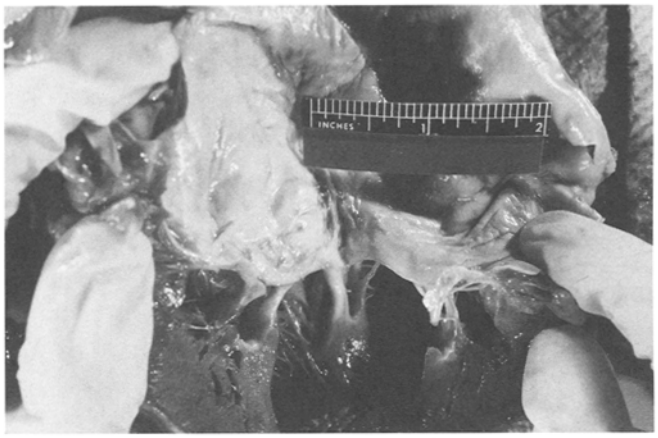


Fig. 4. Mitral valve stenosis.

- Increased incidence in pregnancy
- Dissection usually heralded by onset of severe chest pain or back pain

Autopsy

- Initiating event is a tear in the aortic intima in which blood dissects into the media
- Dissection propagates distally and proximally
- Most common cause of death is rupture of aortic dissection either in the pericardial space or into the left chest cavity

Microscopic

- Variation from medial necrosis to no specific pathologic changes

Mechanism of Action

- Exsanguination

Pulmonary Thromboembolism

Clinical

- Predisposing factors:
  - Cardiovascular disease (CVD)
  - Malignant tumors
  - Pregnancy
  - Morbid obesity
  - Immobility
  - Postoperative bed rest
  - Trauma
- Hereditary predispositions:
  - Congenital deficiencies of antithrombin III, Protein C, Protein S, and plasminogen
  - Activated Protein C resistance (Factor V Leiden)
  - Hyperhomocysteinemia
  - Elevated levels of antiphospholipid antibody

- Prevalence of venous thromboembolism in antithrombin III, Protein C, or Protein S deficiency is >50%
- Clinical symptoms:
  - Sudden death
  - Chest pain
  - Shortness of breath

Autopsy

- Coiled thrombi, not conforming to the shape of the pulmonary arterial tree
- >95% arise in the large deep veins of lower legs, including popliteal, femoral, and iliac vein
- Occasionally, thrombi are also recovered in pelvic veins, especially in pregnancy and periprostatic veins
- Rarely, thromboembolus may cross through interatrial or interventricular defect to systemic circulation (paradoxical embolus)

Microscopic

- Platelet–fibrin–red blood cell mass with lines of Zahn
- Thrombi within lower extremity
- Veins may demonstrate organization
- May see organizational changes in pulmonary arterial wall if survival for several days postembolism

Mechanisms

- Occlusion of pulmonary trunk and right ventricle
- Minimal flow to left ventricle, leading to sudden death or cardiovascular collapse
- Occlusion of smaller arteries may lead to sudden death by vasospasm, sudden increase in blood pressure and right heart failure, or bradycardia due to vasovagal reflex

Cerebrovascular Disease

Intracerebral Hemorrhage (Apoplexy)

Clinical

- Associated with hypertension
- Most common in middle-aged and elderly
- May present with headaches and seizures

Autopsy

- Common sites of hemorrhage:
  - External capsule with hemorrhage into basal ganglia
  - Cerebellum
  - Thalamus
  - Pons

Microscopic

- Sharp demarcation of hematoma from surrounding brain with death of neurons and glia in adjacent tissue
- If survival >24 hours, cerebral edema present with early organizational changes consisting of monocytes and macrophages invading into edges of hematoma
- If preexisting hemorrhage has occurred, hemosiderin may be present, and if small hematoma occurs with survival after several years, residual cysts with brown-orange discolored walls may be present with hemosiderin and gliosis (so-called apoplectic cyst)

Ruptured Berry Aneurysm

Clinical

- Accounts for 4–5% of sudden, rapid natural death; occurs at bifurcations of intracranial arteries
- Exists in 1–2% of population
- Median age of rupture = 50 years
- Increased incidence of saccular aneurysms in certain disorders:
  - Fibromuscular dysplasia
  - Polycystic kidney disease
  - Moyamoya disease
  - Coarctation of the aorta

Autopsy

- Large saccular aneurysm at branch points may be easily identified (**Figure 5A–C**); however, in other cases, aneurysms may be small and destroyed when they rupture and may be difficult to detect at autopsy
- Aneurysms may rupture into and dissect into brain parenchyma

Preferential Locations

- 40% related to intracranial portion of internal carotid artery, usually at juncture of internal carotid and posterior communicating artery
- 30% anterior communicating artery
- 20% middle cerebral artery
- 5–10% associated with posterior cerebral arteries and basilar and vertebral artery

Microscopic

- Typically thin-walled pouch in which endothelium may be incomplete with adjacent blood clot
- Muscle coat and elastic lamina typically stop abruptly at neck of aneurysm, and wall of aneurysm is fibrotic

Mechanism of Action

- Cerebral ischemia with cerebral infarction

NonVascular Causes of Death

Chronic Alcoholism

Clinical

- May see in binge drinkers where alcohol can be a cardiac irritant and lead to sudden arrhythmia
- Long-term alcohol abuse with well-known complications
- Alcohol withdrawal with delirium tremens and Wernicke's disease

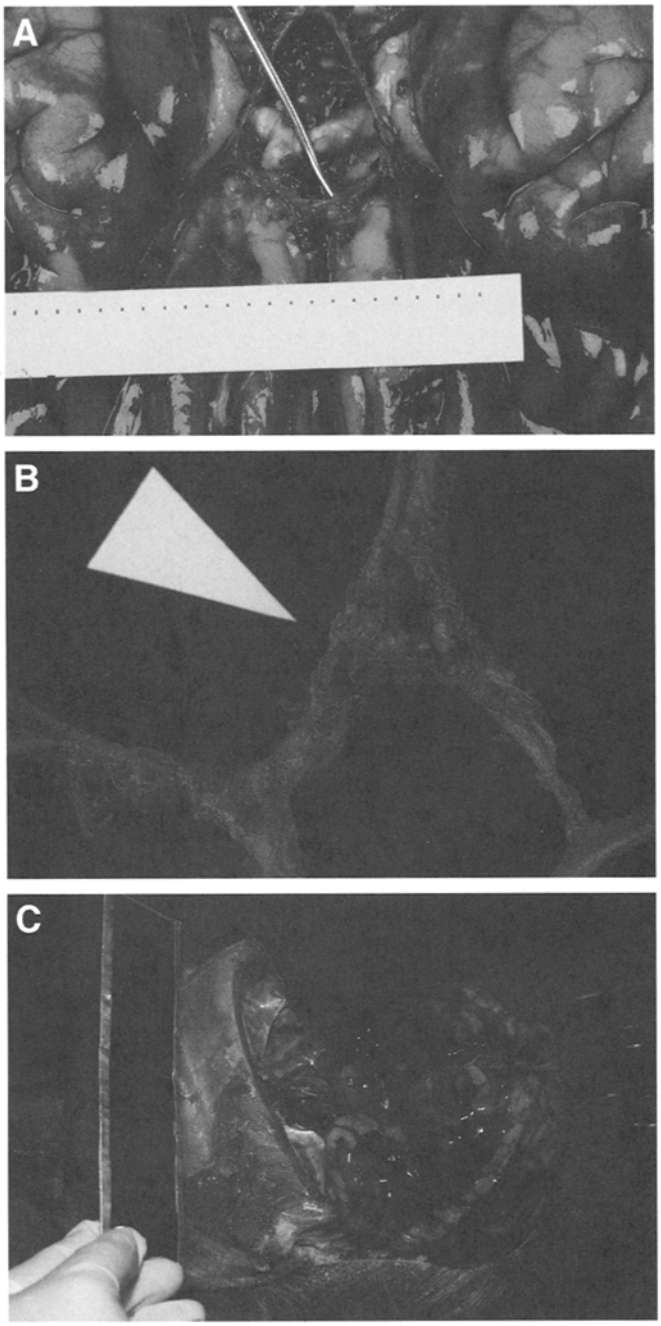


Fig. 5. Berry aneurysm (**A**). Circle of Willis with ruptured berry aneurysm (**B**). Subarachnoid hemorrhage due to intracranial carotid artery aneurysm (**C**).

Autopsy

- May include a variety of findings:
  - Alcoholic cardiomyopathy
  - Acute pancreatitis
  - Cirrhosis of the liver (**Figure 6**)
  - Wernicke's encephalopathy

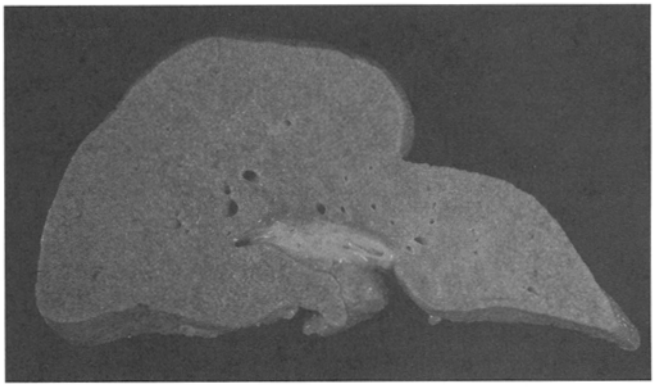


Fig. 6. Cirrhosis and hepatic steatosis.

  - Fatty metamorphosis of the liver
  - Central pontine myelinolysis (seen with rapid correction of hyponatremia)

Microscopic

- Specific to particular disease processes

Mechanism

- Alcohol may function as a cardiac irritant or may cause electrolyte abnormalities (e.g., magnesium deficiency)

Epilepsy

Clinical

- Must have antemortem diagnosis of epilepsy
- Agonal convulsive episode is not adequate for diagnosis of epilepsy

Autopsy Findings

- May be normal anatomic brain
- May have mesiotemporal sclerosis within Sommer's sector
- May find contusion of tongue
- May have nonspecific pulmonary edema

Microscopic Findings

- When present, cell loss may be seen in CA1 and CA4 sectors of hippocampus

Mechanism

- May have prolonged tonic–clonic seizures with cardiac and respiratory exhaustion
- May have non-visible seizure with paroxysmal autonomic dysfunction

Bronchial Asthma

Clinical

- History of asthmatic bronchitis; death typically occurs during acute asthmatic paroxysm
- Death may not correlate with the severity of the autopsy findings

- Death more common at night or in early morning
- Higher incidence of death in African Americans than Caucasians (rule out concomitant sickle cell disease trait)

Autopsy

- Mucoid plugging of bronchi
- Edema of mucosa
- Voluminous hyperexpanded lungs with indentation by ribs

Microscopic

- Prominent mucus in bronchus
- Goblet cells and eosinophils in mucus (Charcot–Leyden crystals)
- Hyaline thickening of basement membrane in bronchial mucosa
- Bronchiolar and bronchial smooth muscle hyperplasia
- Goblet cell hyperplasia
- Peribronchial neutrophilic lymphocytic and eosinophilic inflammation

Mechanism

- Decreased oxygenation
- Elevated carbon dioxide retention
- Increased pulmonary vascular resistance, metabolic acidosis
- Eventual exhaustion and death

Waterhouse–Friederichsen Syndrome

Clinical

- Toxic febrile illness of acute onset with rapid deterioration classically seen associated with *Neisseria meningitidis*

Autopsy

- Bilateral adrenal hemorrhages
- Petechiae to purpura on skin surface
- Cerebral hemispheres may or may not be visibly suppurative **(Figure 7A–D)**

Microscopic

- Adrenal glands with varying degrees of hemorrhage
- Affected skin and adrenal glands may show acute neutrophilic infiltrate

Mechanism

- Bacterial toxemia and adrenal insufficiency, catastrophic rapid onset of shock

Colloid Cyst of Third Ventricle

Clinical

- Sudden episodes of headache associated with position of head
- Appearance in adult life

Autopsy

- Sudden acute hydrocephalus due to obstruction of foramen of Monroe
- 1–4 cm in diameter
- Cerebral edema
- Mass originates from anterior part of third ventricle
- Cross section of cyst reveals gelatinous hyaline material

Microscopic

- Epithelial layer of collagenous capsule
- Mucus goblet cells present
- + stain for mucin with mucicarmine and PAS

Mechanism

- Acute hydrocephalus with herniation and compression of brainstem

Diabetic Ketoacidosis

Clinical

- History of diabetes mellitus in most cases; however, onset may precede formal diagnosis of disease

Autopsy

- May be unremarkable
- Large amounts of glucose and acetone, often detected in vitreous humor
- Blood may contain acetone

Microscopic

- Hyperosmolar nephrosis of proximal tubules
- Kimmelstiel-Wilson glomerulopathy
- Pancreatic islet cell changes (rare)
- Armanni-Ebstein lesion

Mechanism

- Metabolic acidosis
- Dehydration
- Cerebral edema (rarely)

Anaphylaxis

Clinical

- Sudden onset of shortness of breath and edema of face, hives, and vascular collapse
- May develop from insect bites, medication, or food

Autopsy

- Edema of epiglottis and airway obstruction

Microscopic

- Edema and eosinophilic infiltration in airway occasionally:
  - Hypereosinophilia within vasculature of liver and heart

Mechanism

- Cardiovascular collapse with sudden onset of shock from systemic vasodilatation that includes pulmonary edema and obstructive angioedema of upper airway

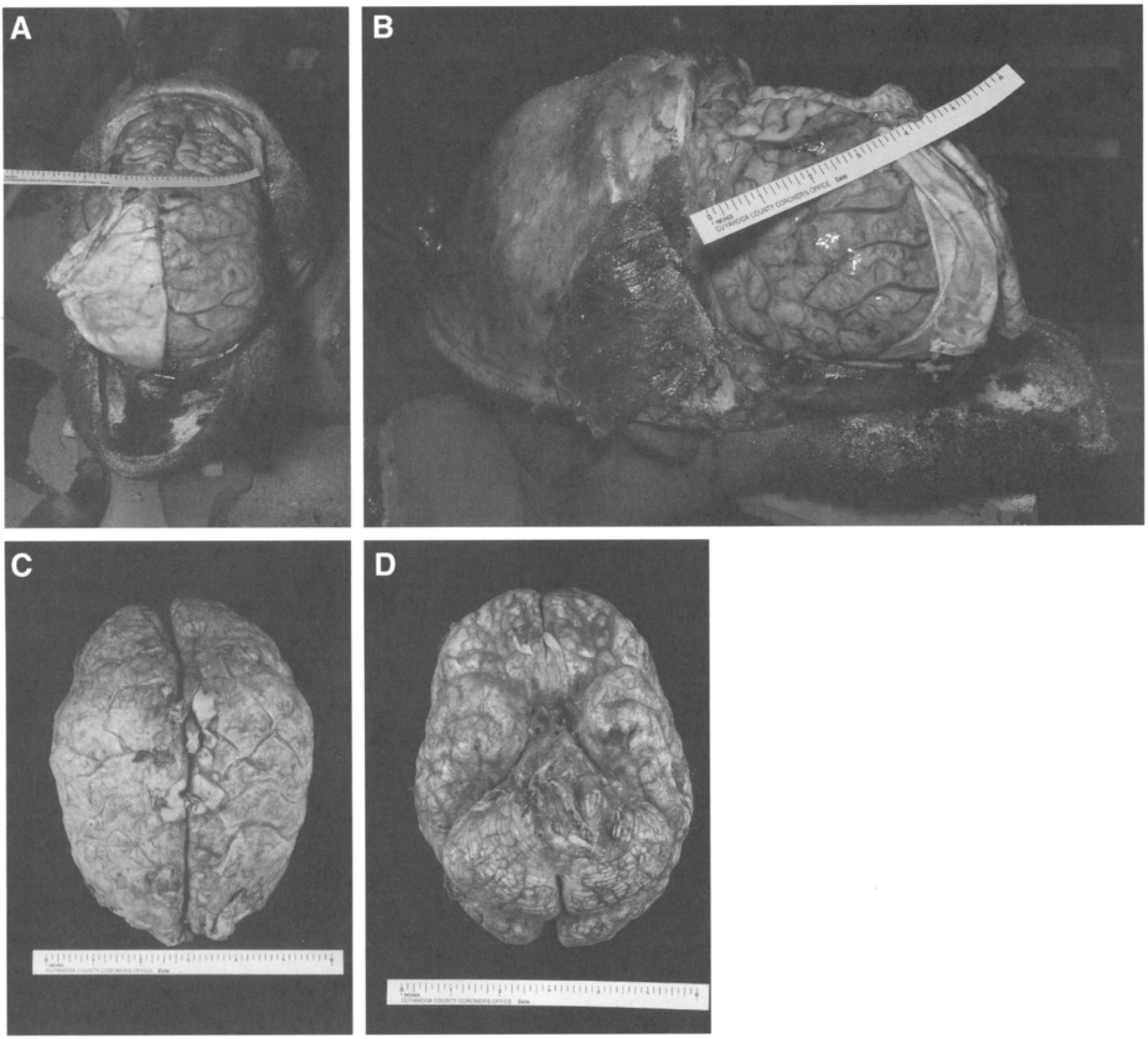


Fig. 7. Purulent bacterial meningitis **(A)**. Bacterial meningitis **(B)**. Bacterial meningitis, fixed brain, superior view **(C)**. Bacterial meningitis, fixed brain, inferior view **(D)**.

Toxicology

- Elevated total tryptase level with beta tryptase level >1 ng/mL, indicating mast cell degranulation

Manner of Death

- Manner of death determined to be natural or accidental dependent on local convention

Sudden Infant Death Syndrome (SIDS)

- Sudden death of infant < 1 year of age, which remains unexplained after performance of a complete postmortem investigation
- Investigation includes:
  - Review of the case history
  - Examination of the scene of death
  - Complete autopsy with toxicologic studies and metabolic screening

Clinical

- SIDS represents 10–12% of deaths in the first year of life
- Majority of deaths occur between 2–4 months of age
- Incidence is 1–2 per 1000 infants
- Recurrence rate in a family is ~1–2%

Risk Factors Associated with SIDS

- Maternal risk factors:
  - Poor prenatal care
  - Multiparity at a young age
  - Unmarried mother
  - Low education level
  - Tobacco use
  - Drug use
  - Lack of breast-feeding
  - Maternal anemia
  - Low weight gain in pregnancy
- Neonatal risk factors:
  - Male gender
  - Prematurity
  - Small for gestational age infant
  - Low birth weight
  - Low Apgar scores (<7)
  - Respiratory distress
  - Tachycardia
  - Tachypnea
  - Cyanosis
  - Fever
  - Hypothermia
  - Irritability
  - Poor feeding
  - Prone sleeping position
  - Infant of twin birth
  - African American
  - Native American

Pathogenesis

- Theories proposed include:
  - Congenital apneic spells or abnormal respiratory control
  - Brainstem dysfunction
  - Abnormal sleep and arousal patterns
  - Upper airway or small airway disease
  - Cardiovascular abnormalities
  - Undetected metabolic defects
  - Abnormal temperature regulation
  - Infections that are undetected, especially botulism
  - "Developmental vulnerability"
- Preventative measure suggested is putting an infant to sleep on its side or back instead of on its stomach
- SIDS very likely represents a group of disorders that have not yet been delineated as causes of sudden death in infants
- Metabolic disorders and inapparent viral syndromes may comprise a significant part of this group of deaths
- A very small number of infant deaths diagnosed as due to SIDS are undoubtedly concealed homicides, particularly smotherings

Autopsy

- Petechiae of the thymus, pleura, or epicardium
- Gliosis of the brainstem and central nuclei
- Pulmonary edema or intraalveolar hemorrhage
- Pulmonary hemosiderosis has been described
- Histologic evidence of recent viral illness
- Extramedullary hematopoesis
- Increased amounts of brown fat in periadrenal adipose tissues

Manner

- SIDS is a death due to natural causes
- A second death in the same family can be ruled "manner undetermined"
- A third death in the same family is extremely suspect, and one or more of the infants' deaths are probably homicides

Inborn Errors of Metabolism Resulting in Sudden Death

- Disorders of β-oxidation of fatty acids
- Glycogen storage disorders
- Other disorders

Disorders of β-oxidation of Fatty Acids

- Fatty acids are an important source of energy for neonates
- Enzymes necessary to carry out β-oxidation can be developmentally immature and inadequate in the perinatal period
- Infants usually present with sudden death or hypoketotic hypoglycemia
- Collapse of metabolic pathways owing to concurrent illness or physiologic stress can precipitate symptoms after depletion of hepatic glycogen stores
- Myopathy, cardiomyopathy, and liver dysfunction result from the accumulation of fatty acids in the mitochondria and microsomes
- Fatty changes of the liver are indistinguishable from Reye's syndrome

Specific Disorders

- Medium-chain acyl-CoA dehydrogenase deficiency (MCAD):
  - MCAD is the first step in fatty acid oxidation:
    - MCAD deficiency may represent 1–10% of SIDS deaths
    - Autosomal recessive disorder
    - Carrier rate may be as high as one in 50 people, resulting in an incidence of 1 in 2500 to 1 in 7000 individuals

- Two known DNA point mutations at positions 985 (A to G) and 583 (S to A)

– Diagnosis:
- Elevated levels of cis-4-decanoic acid and dodecanoic acid in postmortem fluids
- Organic acid analysis in urine or vitreous fluid
- Fatty acid oxidation assay in fibroblasts, liver homogenate, or cells obtained at amniocentesis

♦ Long-chain acyl-CoA dehydrogenase deficiency (LCAD):
– Inability to metabolize fatty acids longer than 12–14 carbons

♦ Short-chain acyl-CoA dehydrogenase deficiency (SCAD):
– Inability to metabolize fatty acids smaller than six carbons

♦ Multiple acyl-CoA dehydrogenase deficiency (MADD):
– Inability to metabolize fatty acids regardless of length

♦ Disorders of carnitine metabolism:
– Carnitine is a required co-factor of fatty acid oxidation
– Low maternal carnitine can result in deficiency in the neonate
– Sudden death has been reported in infants with carnitine deficiency in the plasma membrane
– Carnitine palmitoyl transferase type I deficiency
– Carnitine palmitoyl transferase type 11 deficiency
– Carnitine palmitoyl translocase deficiency

♦ Diagnosis:
– Carnitine levels in blood
– Bile acylcarnitine levels
– Palmitoyl-carnitine oxidation assay using cultured fibroblasts
– Therapy for carnitine-related disorders

♦ Therapy for carnitine-related disorders:
– Carnitine supplementation
– Diet modification

♦ Glycogen storage disorders:
– Myophosphorylase deficiency (McArdle's disease)
– Glycogen storage disease 1a (Glucose-6phosphatase deficiency)
– Glycogen storage disease 1b (Transport protein T1 deficiency)
– Glycogen storage disease 1c (Transport protein T2 deficiency)

♦ Other disorders:
– Lactic acidemias
– Aminoacidopathies
– Disorders of carbohydrate metabolism
– Hyperglycinemia
– Urea cycle defects

PHYSICAL INJURIES

Mechanical Trauma

♦ When force applied to any part of the body results in harmful disturbance of function or structure

Principles and Effects

Amount of Force

♦ Wound-producing capacity for kinetic energy is determined by weight and velocity:
– Formula: KE = $MV^2/2g$:
- M = weight (mass)
- V = velocity
- g = acceleration of gravity

♦ Kinetic energy of a moving object increases arithmetically with weight, but geometrically with velocity (example: doubling the weight of a bullet doubles the kinetic energy, but doubling the velocity quadruples the kinetic energy)

♦ Further energy may be present if a rotational component exists, again best demonstrated in bullets:
– Formula: RE = $Mr^2/2g$:
- M = weight (mass)
- r = cross-section radius
- g = acceleration of gravity

– Or RE = $IW^2/2g$:
- I = rotational inertia
- W = angular velocity in radians/second
  Or W = 2 × number of rotations/second
- g = acceleration of gravity

Rate of Energy Transfer

♦ The shorter the duration of impact, the greater energy transfer and the greater the potential for injury

Surface Area

♦ The larger the area through which force is transmitted, the less the intensity and potential for injury

Target Area

♦ Some tissues are more fragile than other tissues and a fixed amount of force applied to one tissue may cause no injury vs the same force applied to another tissue

Local Effects of Mechanical Injury

- Hemorrhage:
  - Once bleeding begins, it will continue until thrombosis, vasoconstriction, or equalization of intravascular and extravascular pressure occurs
  - Rate of hemorrhage is important. A slower rate of blood loss may allow the body to adapt and tolerate greater accumulations prior to symptom development. A rapid rate of accumulation in similar locations may be lethal (example: rapid accumulation of 150 mL of blood in the pericardium or 50 mL of blood in the intracranial cavity may be lethal)
- Aseptic inflammation: noninfected inflammatory response to injury
- Local infection when protective layer of tissue is injured; infectious agent may be carried into wound during traumatic event

Systemic Effects of Mechanical Injury

- Primary shock:
  - Reflex vasodilatation
  - Decreased blood pressure and loss of consciousness (examples: dilatation of rectum, puncture of pleura, pressure to carotid sinuses)
- Secondary shock:
  - Excessive reduction of blood volume (hypovolemic shock)
  - Hemorrhage necessary to produce circulatory collapse governed by rate of loss
  - 1/3 blood volume lost rapidly leads to hemorrhagic shock
  - 1/2 blood volume lost rapidly leads to death
- Shock injuries to organs:
  - Shock kidney: ischemic damage (shunting of blood from cortex to medulla)
  - Shock lung: hyaline membranes, alveolar and interstitial edema, and interstitial inflammation
- Embolism:
  - Thromboembolism
  - Thrombus may occur as a result of direct venous injury or stasis of blood flow from edema or inactivity
  - Thrombus may detach, resulting in fatal pulmonary thromboembolism
- Fat embolism:
  - Occurs with fracture of long bones and injury to adipose tissue
- Fat embolism syndrome:
  - Progressive pulmonary insufficiency
  - Petechial rash
  - Mental deterioration 1–3 days following injury
  - May have fever, tachycardia, and renal failure
  - Occurs in 90–100% of cases with major fractures, especially in motor vehicle collisions

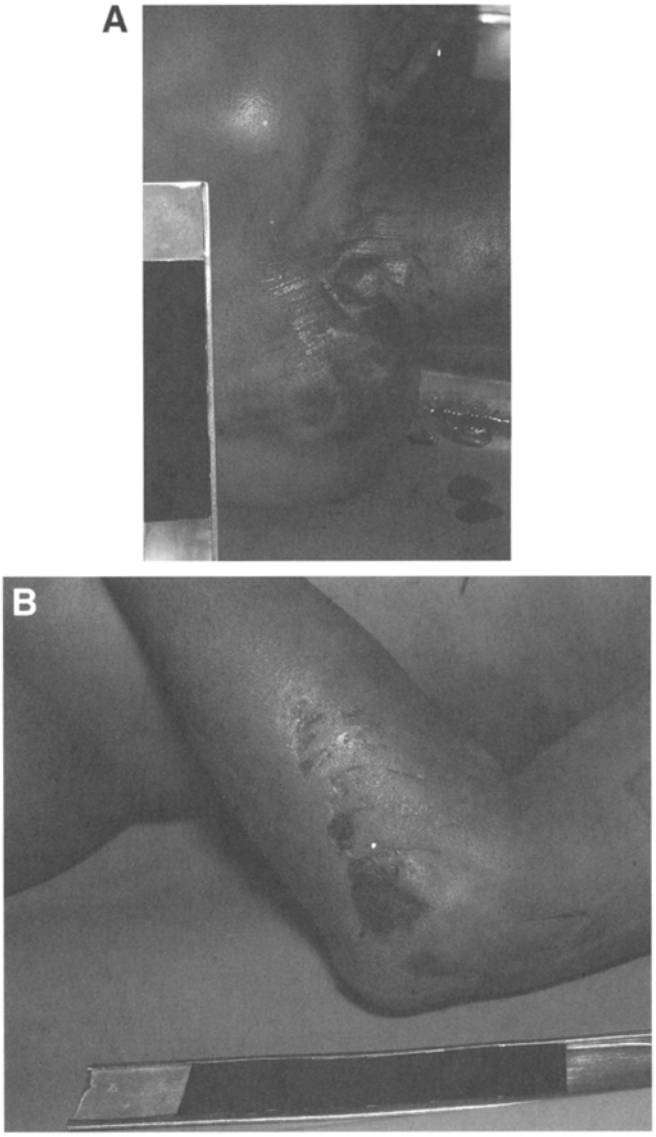


Fig. 8. Brush-burn abrasion **(A)**. Brush-burn and linear abrasions **(B)**.

  - Usually lethal when brain involved and with massive fat embolism to lung, AV anastomoses in lung, tearing of lung parenchyma, or interatrial or interventricular defect
- Air embolism:
  - Air entrance into dilated veins of gravid uterus during oro-genital intercourse or instrumentation, through incision or laceration of veins (especially neck region), disconnection of catheters, and intraoperative procedures of posterior cranial fossa
  - Air enters right side of heart, forming air lock; X-ray of chest may reveal right heart filled with air
  - Air may enter left side of heart with injury to lung in which air may then embolize to cerebral or coronary artery



Fig. 9. Abrasions with skin margin rolled to distal end.

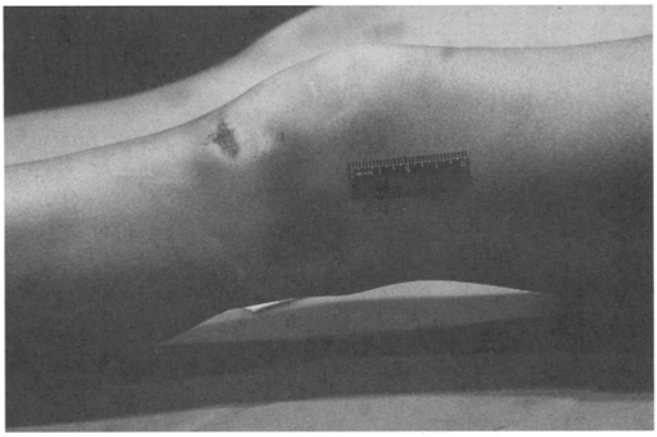


Fig. 10. Abrasions and contusions.

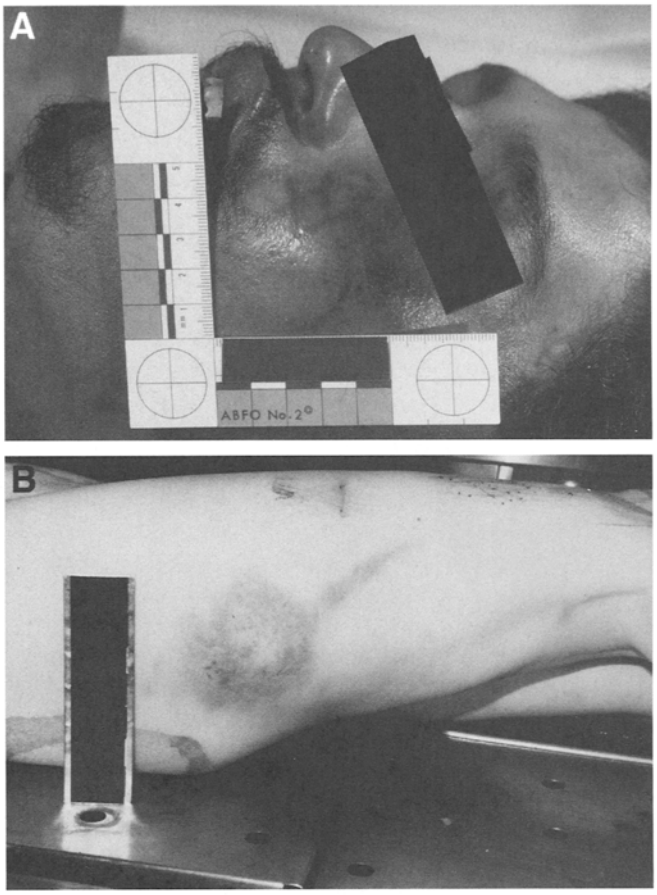


Fig. 11. Patterned contusion with ABFO ruler for future pattern comparison **(A)**. Patterned contusion **(B)**.

Blunt Force Injuries

Abrasion

- A superficial scrape or scratch injuring the upper layers of skin:
  - Types of abrasions:
    - Linear abrasion: a scratch
    - Friction abrasion: a brush burn, such as from dragging on a road surface **(Figure 8A,B)**
    - Graze: superficial skin injury from a projectile such as a bullet
    - Impact abrasion: can result in a patterned injury that provides information about the object that caused the injury
  - Abrasions can occur antemortem or postmortem:
    - Postmortem abrasions:
      - Lack the vital reactions such as hemorrhage, hyperemia, and edema that occur antemortem
      - Postmortem loss of epithelium will result in a dried, parchment-like, yellow-tan lesion **(Figure 9)**
      - Postmortem abrasions in areas involved by dependent lividity must be carefully examined

Contusion

- An area of hemorrhage into the tissues causes tearing of blood vessels by blunt trauma:
  - May be larger or smaller than the impacting object
  - May be difficult to see in dark-skinned persons
  - A deep bruise may not appear on the body surface if death follows a short time after the injury
  - A contusion may appear at a location other than a point of impact
  - Contusions due to accidents usually involve protuberant or prominent parts of the body, especially areas overlying bone **(Figure 10)**
  - Patterned contusions can provide information about the object that caused the injury **(Figure 11A,B)**
- Dating of contusions:
  - Contusions resolve from the center outward and from the periphery inward

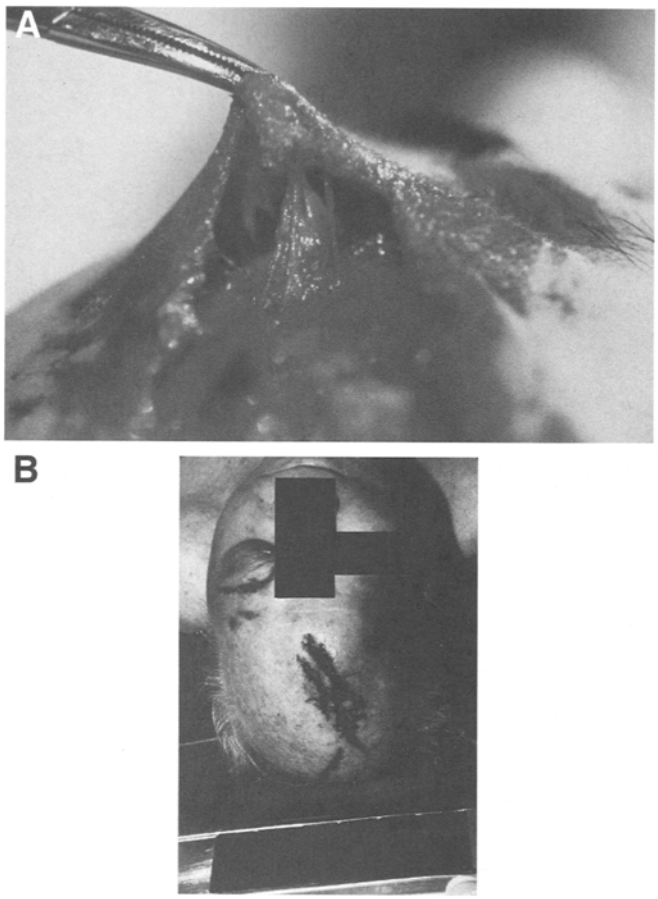


Fig. 12. Laceration with prominent tissue bridging **(A)**. Laceration with marginal abrasion **(B)**.

- Contusions are often of different ages due to separate episodes of trauma
- The coloration of contusions can provide a crude approximation of their age, but contusions of the same age can vary in their degree of resolution in a single individual:
  - Colors and their approximate ages are as follows:
    - Red: immediate
    - Blue–purple: 1–4 hours
    - Green: 4–7 days
    - Yellow: 7–10 days
    - Return to normal coloration: 14–21 days
- Microscopy can be used to identify hemosiderin in an injury that is 24-hours-old
- Iron stains are helpful in identifying hemosiderin in an injury
- Hematoidin requires several days to be detected

Laceration

♦ A tear produced by a blunt instrument:
- The edges of the tear have:
  - Abraded margins
  - Ragged edges
  - Tissue bridging of the defect by vessels, nerves, and connective tissue **(Figure 12A,B)**
- The tear is produced by stretching the tissues beyond their elastic tensile strength or crushing and forcible separation of the tissues during compression between two hard surfaces, such as a weapon and the bone underlying the skin

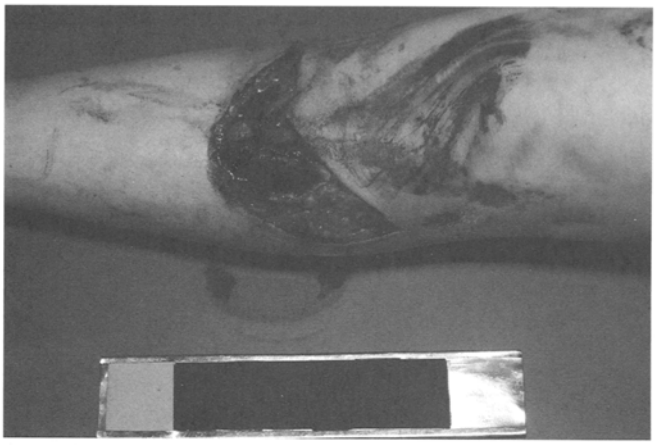


Fig. 13. Open tibial fracture with laceration and grease-stained abrasions.



Fig. 14. Dicing abrasions of left face—MVA driver.

Fractures

♦ Broken bones as a result of blunt force injury: **(Figure 13)**
- Fractures are produced by a combination of compressive, tensile, and shearing forces acting on the bone
- Special types of fractures:
  - Spiral fractures are due to a twisting motion applied to a long bone of an extremity, usually the legs
  - Bucket handle fractures result from pulling on an extremity and fracturing the bone through a growth plate or pulling off the bone attached to a tendon or ligament that supports a joint

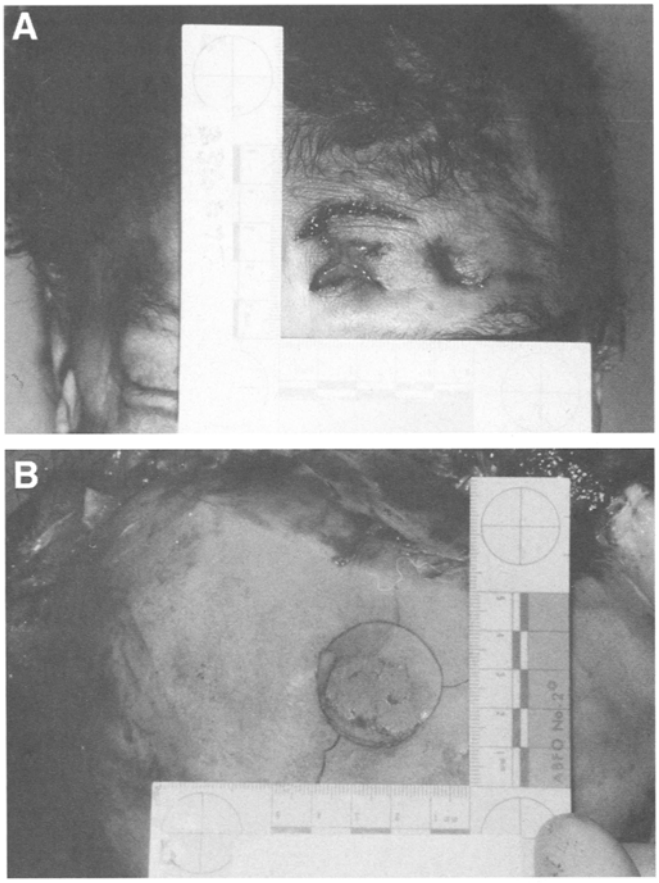


Fig. 15. Patterned laceration **(A)**. Patterned depressed skull fracture underlying laceration in Fig. 15**A** **(B)**.

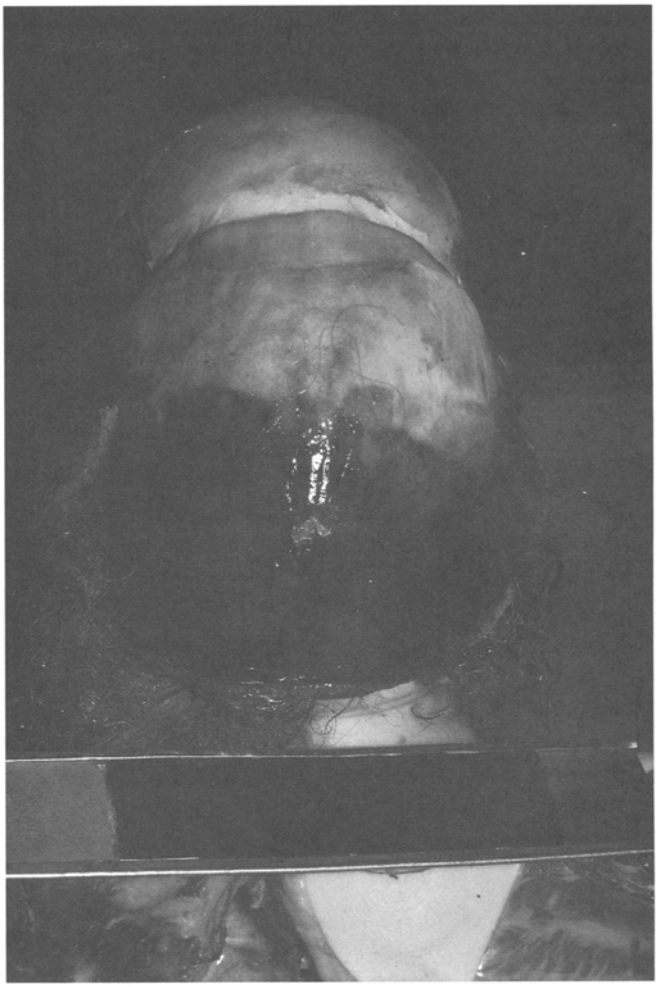


Fig. 16. Subgaleal hemorrhage.

- Spiral fractures and bucket handle fractures in children are highly suggestive of child abuse

Road Traffic Injuries

- Motor vehicle accidents can cause massive blunt force injuries:
  - The most common cause of death is head injury
- The tempered side window glass of an automobile produces a special type of injury known as a "dicing" abrasion:
  - The tempered glass shatters into small cubes as it breaks and can cause a patterned injury on the side of the face that is nearest the tempered window **(Figure 14)**
  - The safety glass of the front windshield of an automobile is laminated between two layers of plastic:
    - Windshields do not cause dicing abrasions

Head Injuries

- Blunt force injuries of the head result in several interrelated traumatic lesions

External Scalp Injuries

- Lacerations **(Figure 15A,B)**
- Contusions
- Abrasions
- Thermal injuries

Subscalpular Hemorrhage

- Occurs directly beneath the area of impact **(Figure 16)**
- May be larger or smaller than the impacting object
- Can result in hematoma formation
- Can occur in the setting of consumptive coagulopathy

Skull Fractures

- Fracture seen in 80% of fatal head injuries
- Bone is more susceptible to tensile than compressive stress
- Skull fractures may occur without significant brain injury

Types of Skull Fractures

- Linear Fractures: **(Figure 17)**
  - Local deformation by an intermediate-sized (>5 cm^2) object
  - Originate in the inner table of the skull after tensile failure

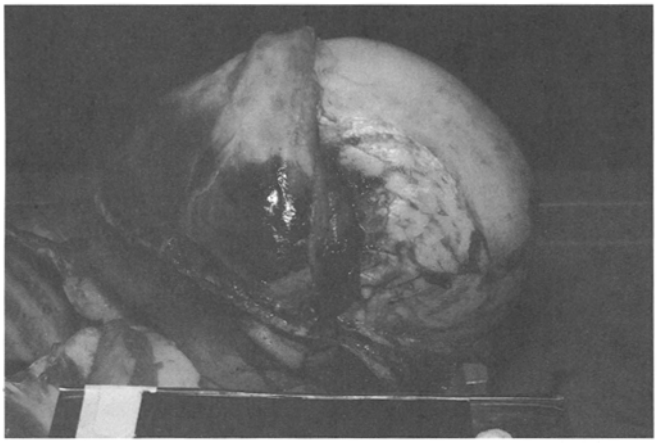


Fig. 17. Temporoparietal skull fracture with temporalis muscle and subgaleal hemorrhages.

- Depressed Fractures:
  - Result from impacts with small objects that have areas of impact <5 cm^2
  - Cerebral injuries often occur due to intrusion of bone into the cranial cavity
- Comminuted Fractures:
  - Multiple fragments result from high-energy impacts
  - Fractures radiate from the site of impact
- Diastatic Fractures:
  - Separation of cranial sutures > 2 mm
  - Primarily seen in children
- Contrecoup Fractures:
  - Fracture of bone away from the blow due to forces transmitted from the site of impact to the thin bones of the skull
  - Can occur with large impact areas or impacts of a fixed skull
- Basilar Fractures: **(Figure 18)**
  - Fractures of the floor of the skull involving the anterior, middle, or posterior cranial fossa
  - Lateral impacts produce side-to-side fractures
  - Frontal or occipital impacts cause sagittal fractures
  - Result from significant impact injury
- Ring Fractures:
  - Basilar fractures that circumscribe the foramen magnum:
    - Can be caused by a vertex impact or a fall onto the buttocks, resulting in axial loading of the floor of the skull
    - Implies significant impact injury

Intracranial Hemorrhages

Epidural Hemorrhage

- Usually underlies the temporal bone
- 85% of patients with epidural hemorrhage have skull fracture

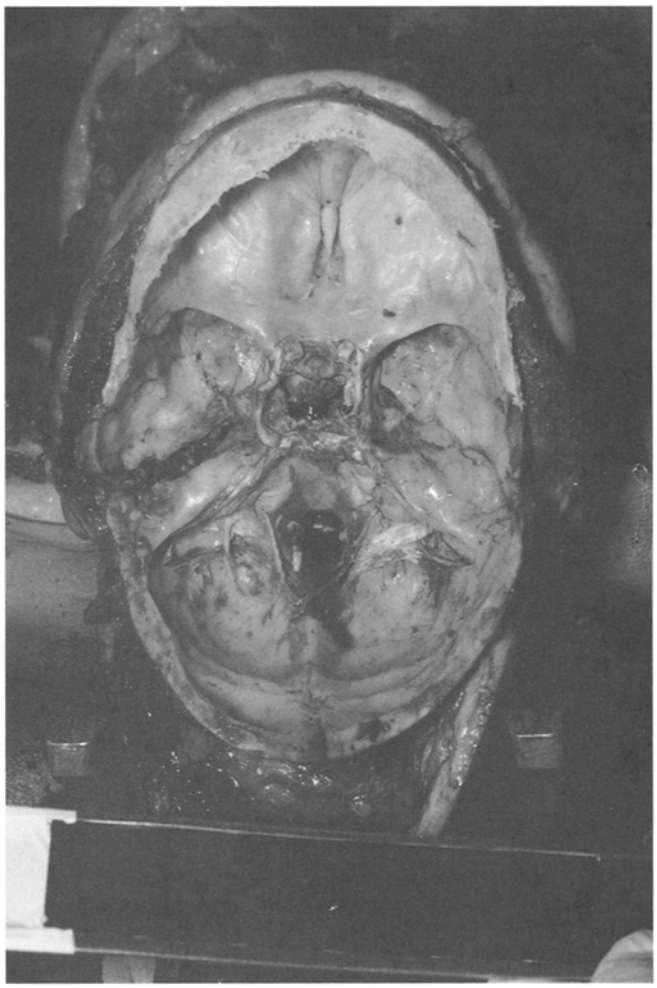


Fig. 18. Basilar skull fracture, hinge type.

- Caused by laceration of vessels on the inner table of the skull, most commonly the middle meningeal artery and its branches
- Hemorrhage dissects the dura away from the inner table
- Hematoma compresses the underlying brain
- Fatal cases have >75 mL of blood clot
- Death occurs due to increased intracranial pressure and herniation

Subdural Hematoma

- Caused by disruption of bridging veins between the cortical surface and dural sinuses
- Usually caused by rotational injury
- Atrophy of the cerebrum increases the distance spanned by bridging veins and promotes the occurrence of subdural hematoma
- Blood spreads freely in the subdural space and often covers the entire hemisphere

- Slow accumulation of blood clot is tolerated much better than rapid accumulation with sudden increases in intracranial contents:
  - The volumes of subdural hematoma that accumulate slowly can be quite large
- Clinically significant acute hemorrhage is >50 mL in an adult and >30 mL in children
- 100 mL of blood clot is often fatal in normal adults
- In contrast to flattening produced by epidural hemorrhage, subdural hemorrhage preserves the outline of the gyri because the blood is distributed over the hemisphere
- Older patients and chronic alcoholics, both of whom develop cerebral atrophy, can tolerate larger amounts of subdural blood clot

Classification of Subdural Hematomas

- Acute subdural hematoma: blood and clot present for the first 48 hours
- Subacute subdural hematoma: a mixture of clotted and fluid blood is present for 2–14 days
- Chronic subdural hematoma: only fluid blood is present after 14 days:
  - Chronic subdural hematomas can be a cause of dementia

Autopsy

- Liquid clot for the first 1–3 days
- At 4 days, there is non-uniform adherence of the clot to the dura
- Neomembrane is visible at 7–10 days and well developed in 2–4 weeks

Microscopic

- Dating of subdural hematomas is inaccurate after 1 month of age
- Healing is a continuum and the healing times must be generalized
- Neutrophils are present in the clot at approx 24–48 hours
- Edematous nuclei are present at the dural edge in about 2–3 days
- Macrophage infiltration occurs in approx 2–5 days
- Erythrocytolysis occurs at about 4–5 days
- Two to five fibroblast layers are present at approx 2–5 days
- Angiogenesis is usually visible by 1 week
- Giant capillaries are present at about 2 weeks
- Arachnoid neomembrane develops at approx 2 weeks
- The inner and outer neomembranes are usually well developed at 4 weeks
- Hyalinization occurs at 1–3 months
- Secondary hemorrhages into a subdural hematoma occur from the thin-walled giant capillaries ~1 month after the original injury

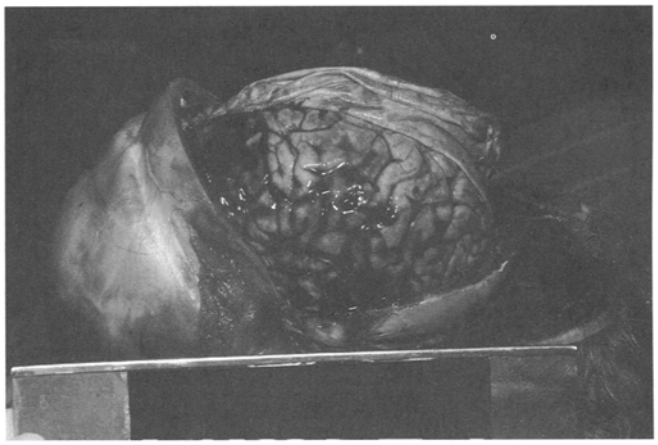


Fig. 19. Frontal and temporal subarachnoid hemorrhage.

- Growth of chronic subdural hematomas is secondary to repeat episodes of bleeding from the giant capillaries

Subarachnoid Hemorrhage

- Blood is present in the subarachnoid space following localized trauma **(Figure 19)**
- Often accompanies cerebral contusions
- May be because of rotation of the brain in the subarachnoid space
- Death can occur from pure subarachnoid hemorrhage due to vasospasm or acute hydrocephalus
- Posterior fossa subarachnoid hemorrhage can result from vertebral artery laceration following relatively minor injuries
- Examination of the vascular system for aneurysm, vascular malformation, or vessel lacerations should be performed at time of autopsy
- Small lesions can be obscured by adherent clot following fixation

Cerebral Contusions

Coup Contusions

- Result from temporary deformation of the skull at the site of impact
- Occur in a head that is at rest relative to a moving object
- The skull impacts the tips of the gyri with destruction of the molecular layer
- An alternative theory proposes that there is a local suction effect following temporary deformation of the skull
- The term should only be used when skull fractures are absent at the site of impact

Contrecoup Contusions

- Contusions occurring distant from the site of impact
- Occur in a moving head, often as it strikes a fixed object

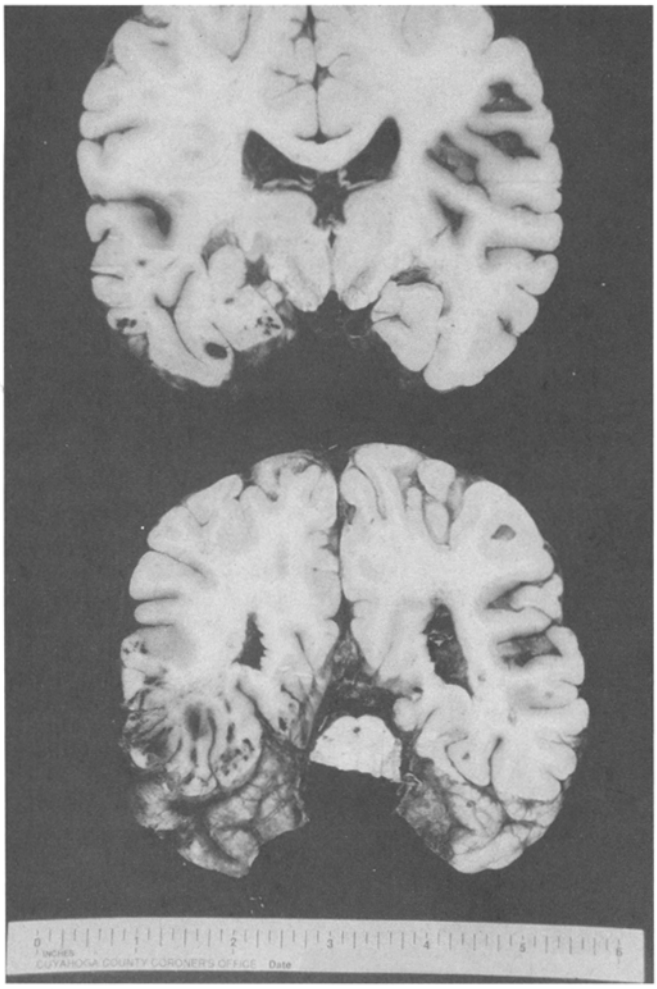


Fig. 20. Contusions of cerebral cortex.

- Typically involves the inferior frontal and temporal lobes and the anterior tips of the frontal and temporal poles
- Often accompanies falls with occipital impacts
- Proposed mechanisms include:
  - Cushioning of the brain by cerebrospinal fluid accumulation as the inertia of the brain causes it to lag behind the moving skull as the skull impacts
  - The CSF cushion minimizes coup injury and the lack of CSF in the contrecoup areas opposite the impact maximizes the contact of the brain with irregular bony surfaces of the floor of the skull and the skull opposite the impact
  - The development of cavitation and negative pressure opposite the site of impact
  - Tensile strain of the contrecoup areas as the brain moves toward the site of impact

Fracture Contusions

- Injuries of the brain surface underlying skull fracture **(Figure 20)**
- Can be remote from the site of impact if skull fracture is present

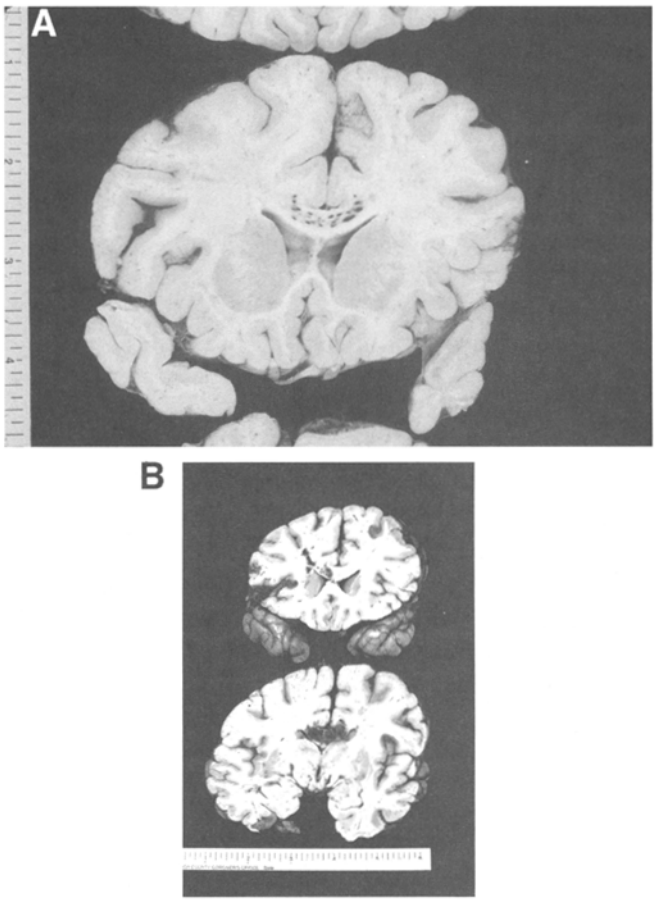


Fig. 21. Diffuse axonal injury-Hemorrhages in corpus callosum **(A)**. Diffuse axonal injury with petechiae of corpus callosum **(B)**.

Herniation

- Produced by subfalcial, transtentorial, or cerebellar tonsillar herniation
- Can result from herniation related to cerebral swelling or transitory motion of brain structures

Diffuse Axonal Injury

Clinical

- Symptoms can vary from transitory loss of consciousness with concussion to irreversible coma
- The white matter, especially the corpus callosum, is most involved
- Ethanol intoxication increases the clinical severity of the head injury

Autopsy

- Hemorrhages of corpus callosum **(Figure 21A,B)**
- Can involve the interventricular septum and fornix

- Hemorrhage of the superior cerebellar peduncle
- Cerebral edema
- Hemorrhage of the basal ganglia

Microscopic

- Axonal retraction balls are visible in the white matter using routine Hematoxylin and Eosin (H&E) and silver stains within 24 hours of injury
- Groups of retraction balls of similarly oriented axons may be seen
- Immunohistochemical stains can detect axonal injury within 1–2 hours (GFAP, β-amyloid precursor protein, ubiquitin)
- Astrocytes or microglia proliferate after a period of weeks

Pathophysiology

- Caused by rotational acceleration or deceleration resulting in sheer strain characterized by the change in acceleration over time (dA/dt)
- Transection of the axon at the time of injury is not necessary
- Mild injury may be limited to transmembrane ionic disturbances in the axon, which will spontaneously recover
- More severe injury produces reactive changes that result in delayed axotomy (Wallerian degeneration)
- Damage to structural elements of cytoskeleton
- Swelling of mitochondria occurs followed by increases in axonal diameter
- Microtubules become misaligned and are damaged, halting antegrade or retrograde axonal flow of organelles
- Cytoskeleton can also disintegrate at the point of damage
- The axolemma separates from the myelin sheath
- Proteins continue to be transported from the cell body to the site of injury
- Axonal bulb or swelling develops and axotomy occurs (Wallerian degeneration)
- Calcium influx into leaking axolemma may be responsible for cytoskeletal collapse

Brainstem Avulsion

- Laceration of the brainstem or avulsion related to severe hyperextension of the head as a result of facial impact
- Most common is a pontomedullary tear
- Often accompanied by atlanto-occipital dislocation, ring fracture, or high-cervical fracture
- Most commonly produced by motor vehicle accidents

Complications of Head Injuries

Hypoxic Ischemic Encephalopathy

- Occurs in 90% of head injury deaths
- The brain is particularly sensitive to hypotension and inadequate perfusion
- Hypoxia and hypotension combine to cause particularly severe ischemic injury
- Trauma may sensitize the brain to ischemia mediated by increased glycolysis, increased extracellular glutamate, and potassium flux
- Other organ injuries such as acute lung injury, systemic hypotension, and anemia related to trauma contribute to the cerebral insult

Cerebral Swelling

- Localized swelling can occur because of hemorrhage or contusion
- Diffuse swelling can occur related to hypoxic ischemic insults
- Vasogenic edema with increased hydrostatic pressure and damage to the blood–brain barrier can occur
- A cytotoxic component due to membrane pump failure and glutamate accumulation following ischemia is present
- Cerebral swelling may be increased by reperfusion injury following the restoration of blood pressure

Fat Embolism

Clinical Symptoms

- Occur 1–4 days following injury:
  - Petechial rash
  - Respiratory distress
  - Neurologic deterioration

Autopsy Findings

- Petechial hemorrhages of white matter
- Necrosis of foci in cortex, cerebellum, and brainstem
- Atrophy of white matter with long-term survival

Microscopic Findings

- Intravascular fat present in tissues stained with fat stains (ORO)
- Perivascular hemorrhages and/or infarcts of white matter
- Perivascular infarcts of gray matter

Shaken Baby Syndrome (SBS)

- Major cause of fatal child abuse deaths as a result of head injury
- Mortality rate = 20–25%
- Most children < 1 year of age and almost all cases < 2 years
- The major problem is diffuse axonal injury following stretching and tearing of axons during vigorous shaking
- Vigorous shaking is shaking that occurs 2–3 cycles per second

Clinical

- Unconsciousness
- Coma
- Seizures



Fig. 22. Retinal hemorrhages, as seen with rear illumination.

- Respiratory depression
- Bradycardia
- Xanthochromic spinal fluid
- Intracranial hemorrhage
- Other injuries of child abuse are often present

Autopsy

- Cerebral edema
- Subdural and/or subarachnoid hemorrhages
- Retinal hemorrhages are seen in 75–90% of cases **(Figure 22)**
- Evidence of head impact or skull fractures need not be present
- Detachment of the retina may occur
- Neck injuries can be present

Microscopic

- Diffuse axonal injury
- Cerebral edema

Associated Injuries

- Rib fractures can be present laterally or posteriorly just lateral to the spine, caused by squeezing the child's chest during shaking
- Victims of shaken baby syndrome with a prolonged survival interval develop:
  - Cerebral fluid collections
  - Cerebral atrophy
  - Cystic encephalomalacia
  - Cerebral infarcts because of hypoxic ischemic damage related to cerebral edema and intracranial hemorrhage

Firearms Injuries

General Principles

- Firing progression:
  - Trigger pull: firing pin strikes cartridge case
  - Primer detonates: ignites gunpowder
  - Gunpowder combustion: gas production
  - Pressure formation: expulsion of bullet
- Handguns and rifle barrels have spiral grooves in interior with elevated area between grooves called "lands":
  - Lands impart spin to projectile
- Typical primer material includes lead styphnate, barium nitrate, and antimony sulfide

Handguns

Revolvers and Pistols

Bullet Caliber

- Bullet diameter measured in hundredths of an inch or millimeters
- May be small caliber: 0.22 and 0.25; medium caliber: 0.32, 0.38, 0.357, 9 mm; or large caliber: 0.40, 0.41, 0.44, and 0.45

Cutaneous Entrance Wound

- Diameter of defect not directly comparable to caliber of bullet
- Abraded margin, occurs when bullet impacts skin
- If impact to skin is perpendicular, abrasion will be symmetrical and uniform
- When skin impact is at an acute angle, asymmetrical abrasion is widest on the side from which the bullet approached

Range of Fire

Terminology

- Soot: black carbonaceous particles of residue consisting of completely burned gun powder and vaporized metals from primer, bullet, and cartridge case, which has a black disk-like appearance
- Powder tattooing or stippling: larger particles, mainly consisting of burning, partially burned, and unburned gunpowder, but also metal shavings and other debris from barrel and cartridge case:
  - Numerous red–brown to orange–red punctate lesions

Contact Range of Fire

- Barrel tip in contact with skin surface **(Figure 23A,B)**
- Soot on skin and in wound track
- If tight contact, then the majority of soot in depth of the wound with cherry red discoloration of surrounding skin where carbon monoxide from combustion of gases binds to muscle to form carboxymyoglobin
- If loose contact, then prominent soot on skin surface **(Figure 23C)**

Close Range of Fire

- Soot and gunpowder stippling surrounding wound **(Figure 24A,B)**
- Soot generally travels no more than 6–8 inches

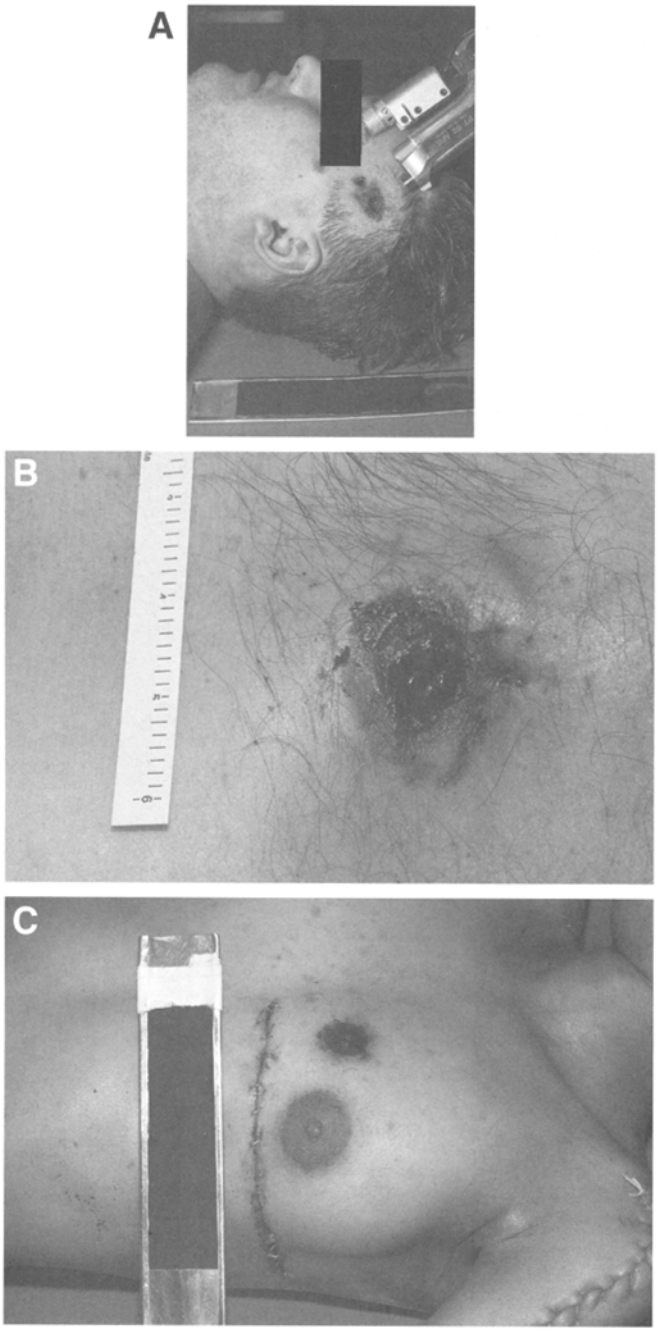


Fig. 23. Contact-Muzzle stamp abrasion and laser sight abrasion compared with suspected gun **(A)**. Contact gunshot wound with muzzle stamp **(B)**. Near contact gunshot wound **(C)**.

Medium or Intermediate Range of Fire

- Gunpowder stippling only, no soot
- Gunpowder stipples routinely 3–3$^1/_2$ feet, but certain gunpowder may travel farther

Distant Range of Fire

- No residue on skin
- Indicates barrel tip to skin distance of at least 3–3$^1/_2$ feet

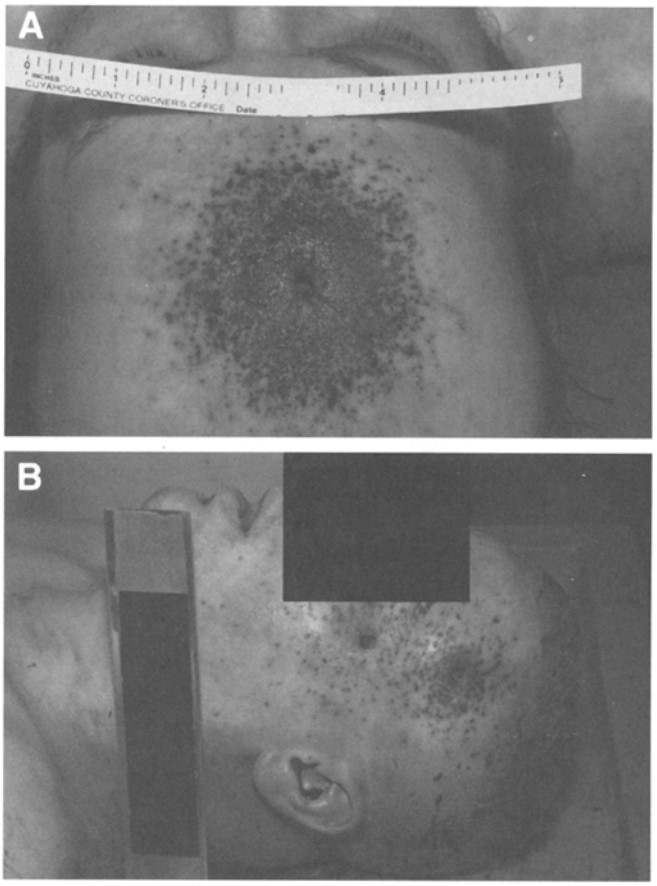


Fig. 24. Close gunshot wound with soot and dense stippling **(A)**. Close and intermediate gunshot wounds with dense and loose stippling **(B)**.

Indeterminate Range of Fire

- Cannot determine range of fire because of interposed target between barrel tip and skin
- Example of interposed target: doors, windows, metallic wall

Cutaneous Exit Wounds

- Typically larger than entrance wound, but may be slit-like
- Rarely has abrasions, but if skin is supported by elastic bands of undergarments or firm external surface, then may have a "shored" abrasion **(Figures 25 and 26)**

Gunshot Wounds of Head

- Entrance wound in skull has internal beveling (larger on internal table than outer table) **(Figures 27A–C, 28–32)**
- Exit wound has external beveling (defect larger on outer table than inner table)
- With gunshot wound through skull, there is energy propagation through bone with orbital plate fracture and subsequent spectacle hemorrhage from dissection of blood, which spares the supraorbital ridge, differentiating it from a blunt force injury **(Figure 33)**

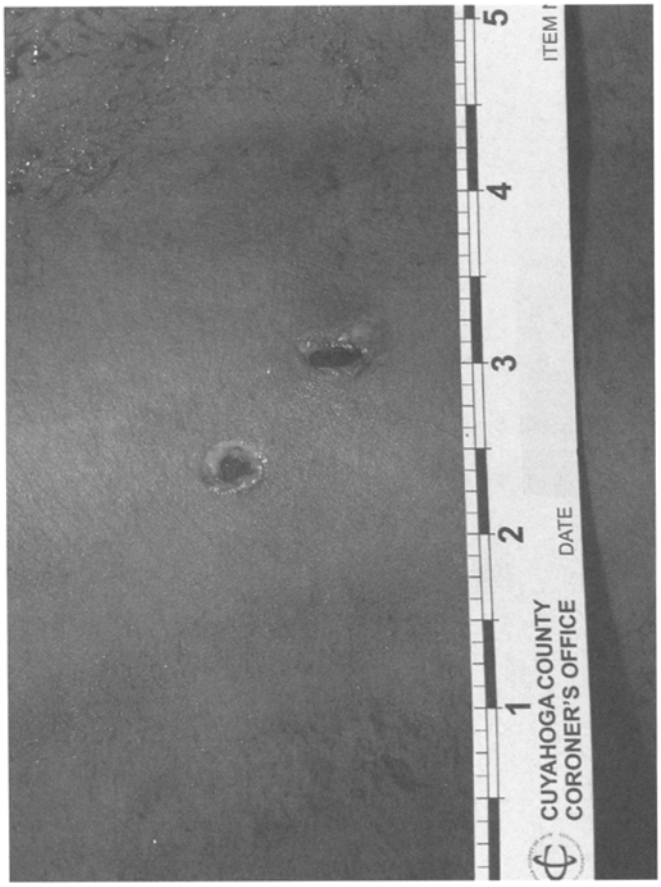


Fig. 25. Shored gunshot exit wounds.

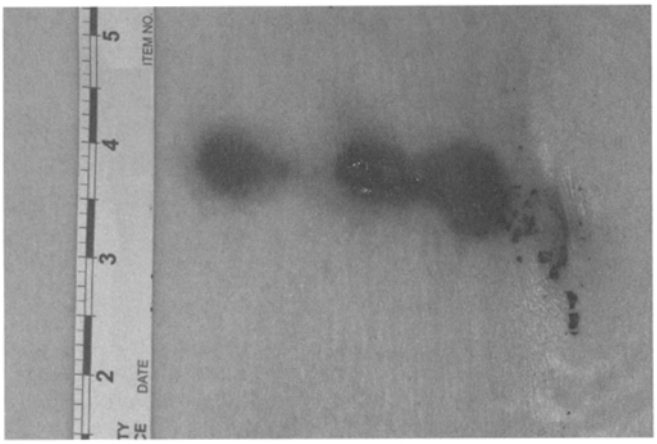


Fig. 26. Gunshot wound with exit and re-entry. Soot around initial entrance.

Shotguns

- Smooth bore weapon; no lands and grooves
- May fire more than one projectile: single projectile, slug, multiple projectiles, buckshot, or birdshot
- "Gauge": number of lead balls of a given diameter equal to one pound:
  - Example: 12 gauge = 12 spherical lead balls of a bore diameter of 0.729 inch equal to one pound
- Shotgun bore diameter can also be described in thousandths of an inch:
  - Example: 0.410 = "4–10"
- Choke describes constriction of muzzle end of barrel used to reduce pellet dispersion:

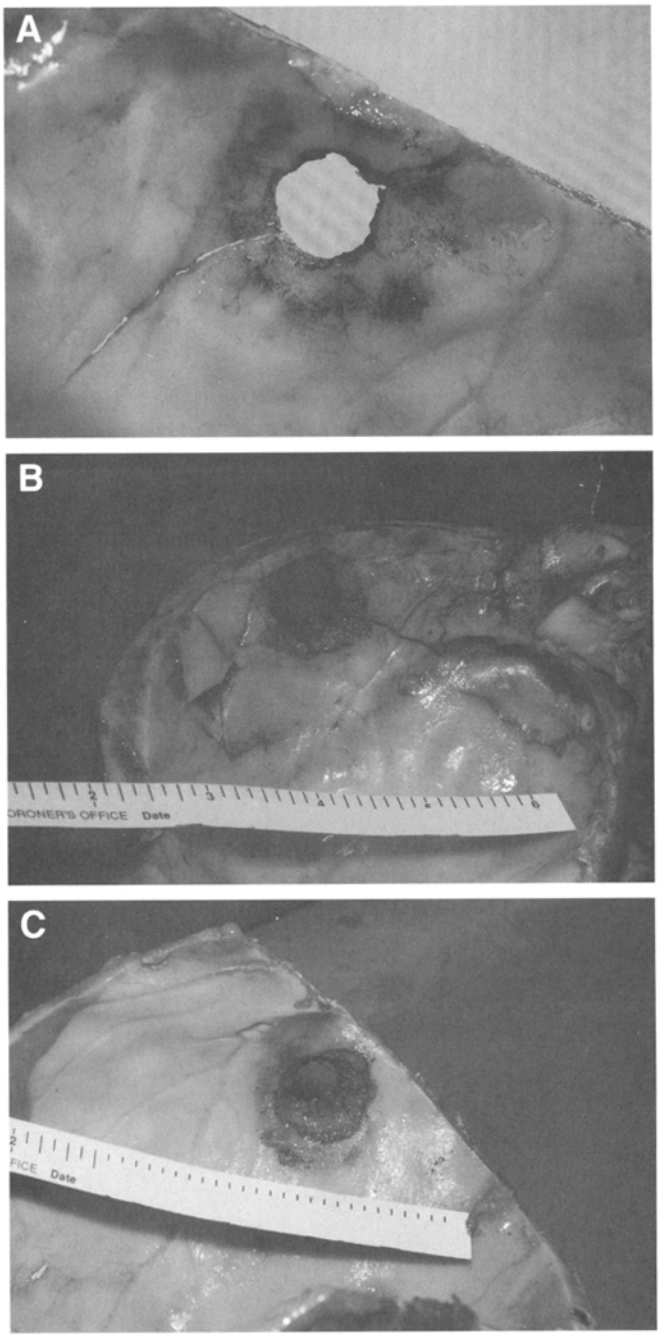


Fig. 27. Contact entrance wound. Dura stripped by gases. Soot deposit between skull and dura **(A)**. Inward beveling of gunshot entrance wound with soot and fractures **(B)**. Inward beveling of skull entrance wound–soot present **(C)**.

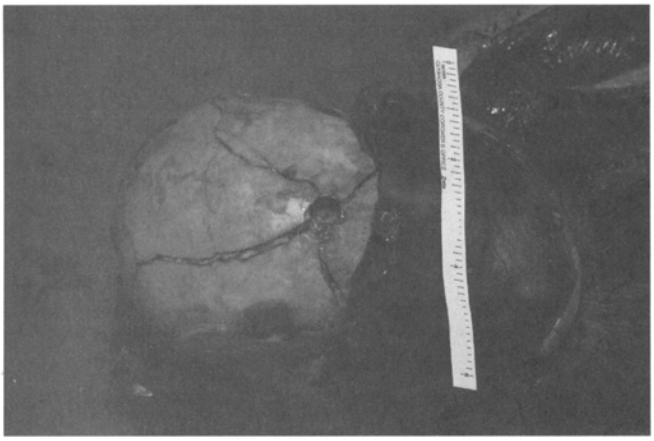


Fig. 28. Fractures radiating from gunshot wound.

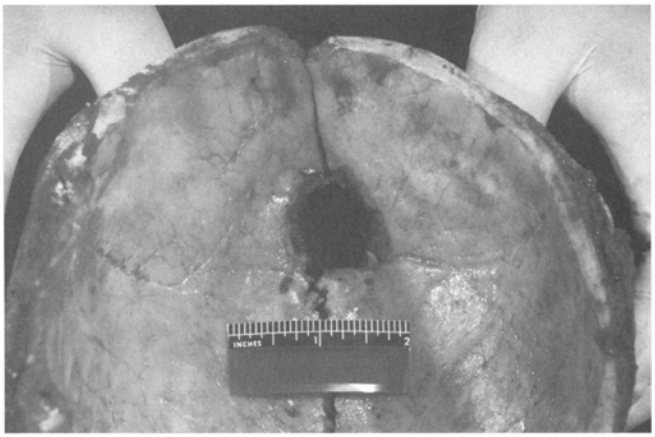


Fig. 29. Keyhole entrance wound of skull with loosening of sagittal suture.

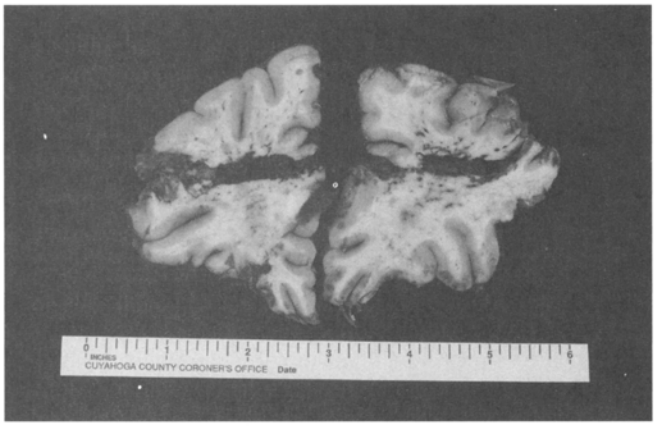


Fig. 30. Gunshot wound track through frontal lobes.

- Ranges from full to none
- Is determined as percentage of shot falling, in 30 inch circle when weapon fired at distance of 40 yards:
  - Full choke: 60–75%
  - No choke (cylinder): 25–35%

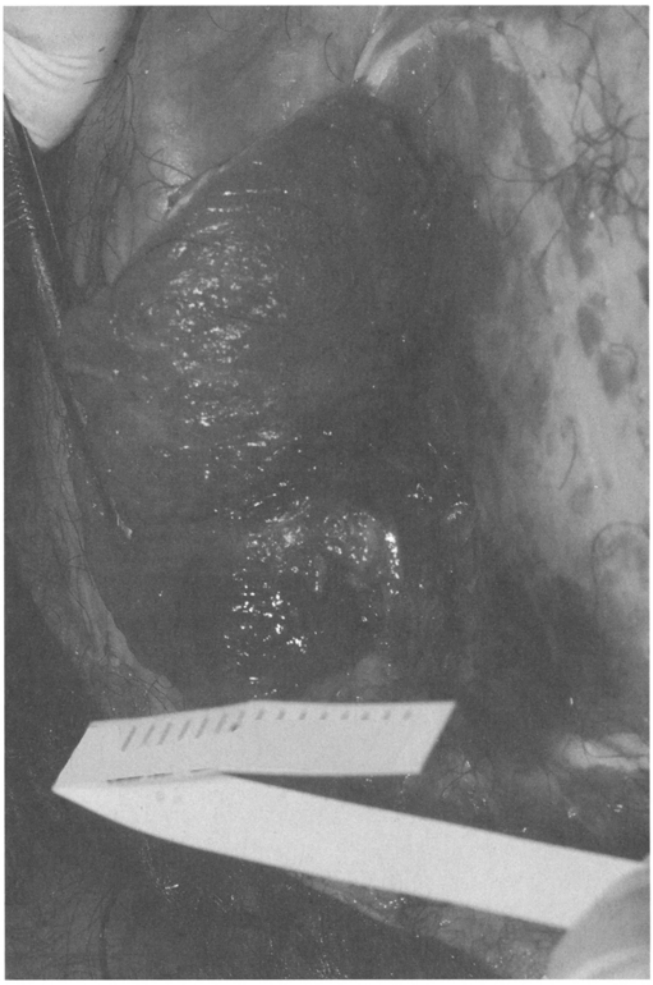


Fig. 31. Bullet in temporalis muscle. No exit in scalp.

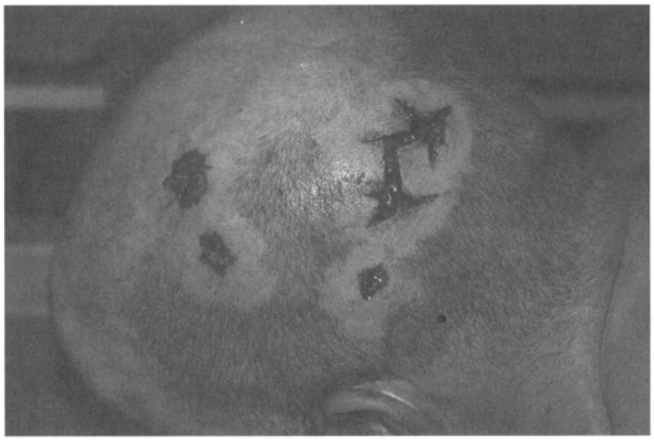


Fig. 32. Gunshot wounds with stellate splits resembling lacerations.

Range of Fire

- Contact: round defect with soot on skin and in depths of wound
- Barrel tip $1^1/_2$–2 feet from skin surface: single defect

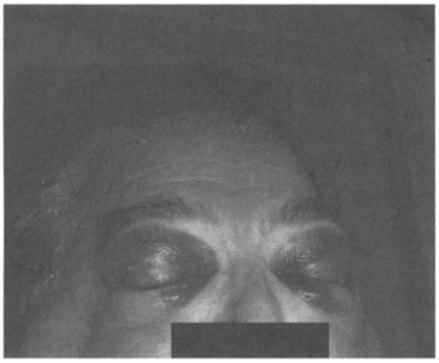


Fig. 33. Bilateral periorbital ecchymoses-Spectacle hemorrhages.

- Barrel tip 3 feet from skin surface: single defect with slight discontinuous irregular margin **(Figure 34)**
- Approx $3^1/_2$–4 feet, barrel tip to skin: central defect with individual satellite perforations
- As barrel tip is farther withdrawn, get more individual perforations until only separate perforations and no single central defect
- Broad rule of thumb is for every 1 inch of pattern, you have up to 3 feet of distance from barrel tip to skin
- Wadding enters central defect up to 5–10 feet, then drifts laterally, striking the skin and creating an abrasion
- Wadding marks the skin up to 15–20 feet
- Soot will travel out to 1 foot
- Gunpowder will travel up to 2–3 feet

Ammunition

- Shotgun shells consist of a plastic or paper body (the tube), a brass head, cardboard or composite wads, and lead shot
- Wadding in birdshot loads: small
- Winchester: cupwad with plastic shot cup
- Remington: power piston
- Federal: plastic wad column
- Buckshot: have white filler material that surrounds shot, can impact skin, and must be differentiated from gunpowder stippling

Rifles

- Rimfire rifles can fire projectiles at relatively low velocity, as seen in handguns (650–1400 feet/s)
- Center fire rifles can fire projectiles at high velocity (2400–4000 feet/s)
- By increasing velocity, the kinetic energy and wounding potential is markedly increased

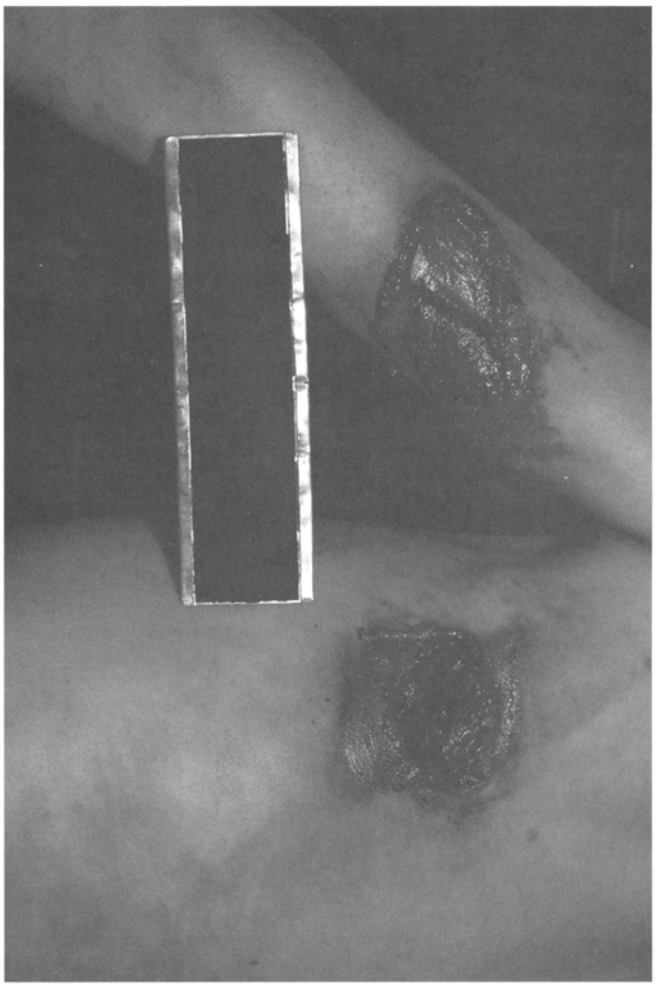


Fig. 34. Shotgun wound of arm and chest.

- Center fire rifle ammunition may be subdivided into hunting type ammunition and full metal jacketed ammunition
- The goal of hunting ammunition is to expend all of its energy so that it frequently does not exit body, but fragments inside; has a characteristic "lead snowstorm" X-ray pattern
- Full metal jacketed ammunition usually exits body without fragmenting and its goal is to injure the victim, but not expend all of its energy
- Temporary cavity may be large and organs not directly perforated may still be injured
- Entrance wound is typically small and round, similar to a handgun entrance wound
- Exit wounds are often large and irregular

Sharp Force Injuries

- Sharp vs blunt:
  - Sharp: mechanically cuts and divides tissue to depth of object inserted
  - Blunt: crushes and tears tissue with bridging in wound depth

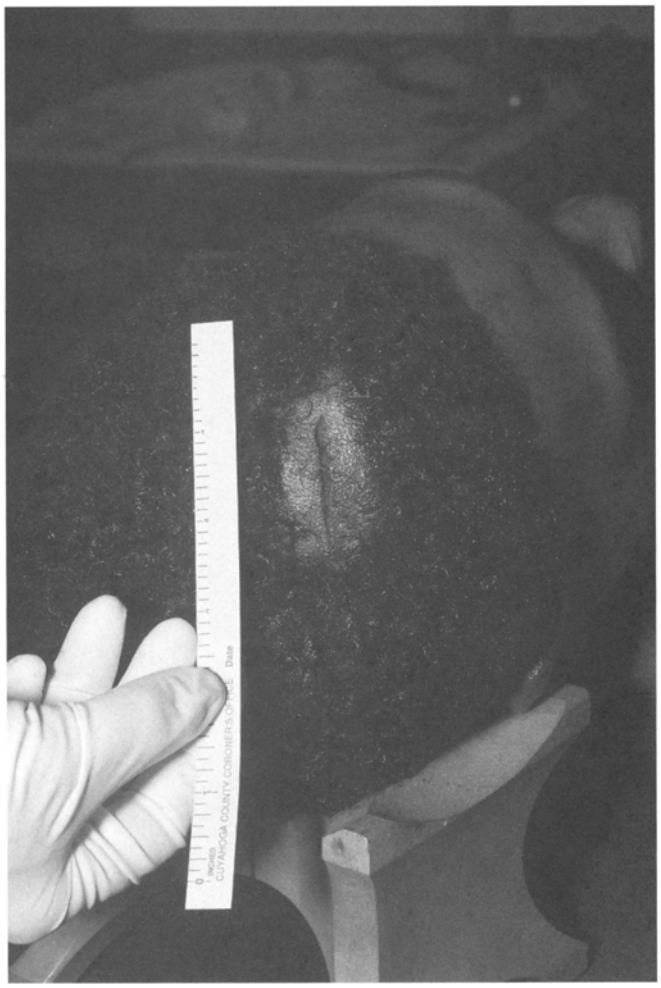


Fig. 35. Linear incised wound.

Incised Wound

- Caused by a sharp-edged object drawn over tissue **(Figure 35)**
- Wound defect is longer on skin than it is deep
- Edges may be straight or jagged
- No marginal abrasion
- No tissue bridging
- Bleeding may be extensive
- Typically seen on head, neck, and extremities **(Figure 36)**
- If the wound is on the neck or through visible large vein, then X-ray for embolism
- On margin of wounds, may see superficial parallel incisions, consistent with serrated knife

Stab Wound

- Caused by pointed or sharp object being forced into tissue in a thrusting manner **(Figure 37A–D)**
- Wound track is deeper than the surface defect is long
- No tissue bridging and no marginal abrasions, with the exception of possible hilt mark

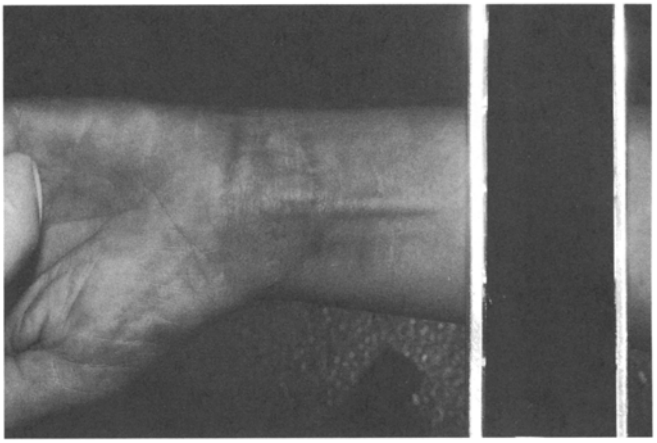


Fig. 36. Healed superficial incised wounds-suicidal hesitation mark scars.

- Skin surface may reflect characteristics of weapon: single or double edged, Phillips screwdriver, serrated knife
- Skin defect appearance variable due to orientation with respect to Langer's lines
- Exsanguination, infection, or air embolism may cause death
- X-ray for knife tip fragments
- Depth of wound not equal to length of blade: wound may be shorter due to partial insertion or longer due to compressibility of body, especially in the abdominal area

Chop Wound

- Caused by sharp heavy instruments: ax, hatchet, cleaver; intermediate between sharp and blunt force injuries
- Deep gaping wounds that may have deep bruising and fracture
- May have marginal abrasion and contusion

Defense Wound

- Occurs when one is defending one's self from assailant
- Usually seen on upper extremities **(Figure 38A–C)**
- Appearance of wound varies with weapon
- May be seen in both stab and incised wounds

Asphyxia

- A condition in which there is an absence or reduction of oxygen in body tissues and increased carbon dioxide tension

Autopsy

- Tends to be fairly classical and nonspecific (may be seen in other causes of death as well):
  - Visceral congestion
  - Cyanosis
  - Petechiae **(Figure 39A,B)**
  - Fluidity of blood

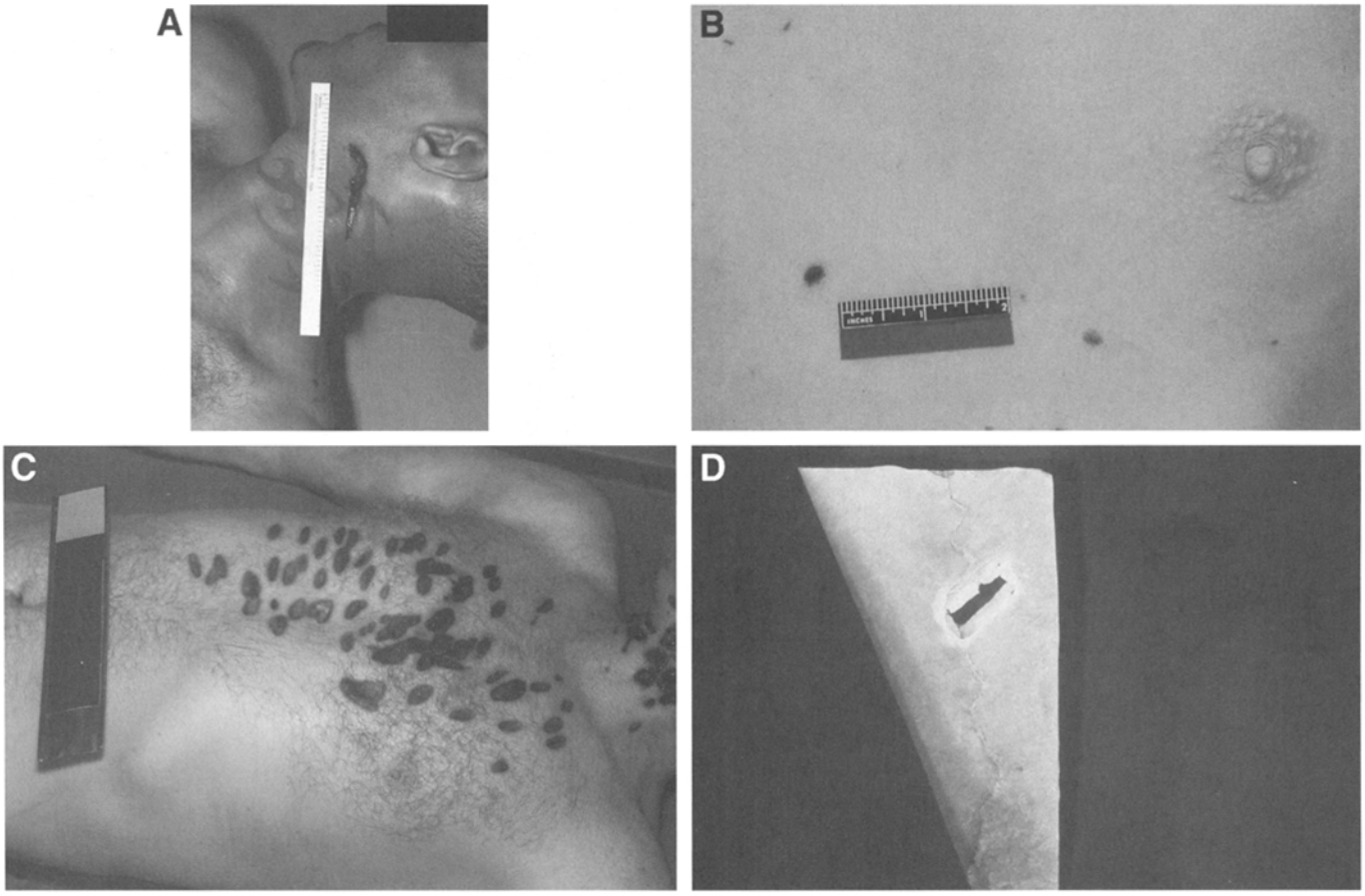


Fig. 37. Stab wound of neck with anterior incised component **(A)**. Stab wounds-ice pick **(B)**. Multiple stab wounds, some with a yellow–brown drying perimortem appearance **(C)**. Inward beveling of rectangular stab wound in bone **(D)**.

Types: Compression of Neck

Hanging

- Compression of neck by noose, with compression of arterial and venous blood supply to and from brain
- Suspension may be complete or incomplete **(Figure 40)**
- Hanging is almost always suicidal and very rarely accidental or homicidal
- Consciousness lost rapidly

Autopsy

- Fractures uncommon, but increased in elderly with calcification of cartilage
- "Hangman's fracture": fracture of odontoid process of C2 with fragments of bone driven into medulla oblongata
- Hangman's noose: classic hangman's noose with knot on left side to throw head backward to fracture neck
- Crease or groove in neck where ligature is located is called a "furrow" **(Figure 41A–C)**
- Soft material may leave no furrow
- In dependent areas of body with gravitational effect, get lividity, punctate hemorrhages, and Tardieu spots

Strangulation

Ligature Strangulation

- Most common in females
- Vascular occlusion with loss of consciousness in ~10–15 s
- Ligatures include electrical cords, telephone cords, sheets, and neckties

Autopsy

- Marked congestion above ligature; confluent scleral hemorrhages with conjunctival petechiae; furrow when present is usually horizontal and below the thyroid cartilage **(Figure 42)**
- May get fracture of thyroid and hyoid cartilage

Manual Strangulation

- Compression of internal structures of neck by hands or forearms
- Compression of blood vessels with rapid loss of consciousness
- All manual strangulations are homicides

Autopsy

- Petechiae of sclerae, conjunctivae, and face, with cyanosis above level of compression

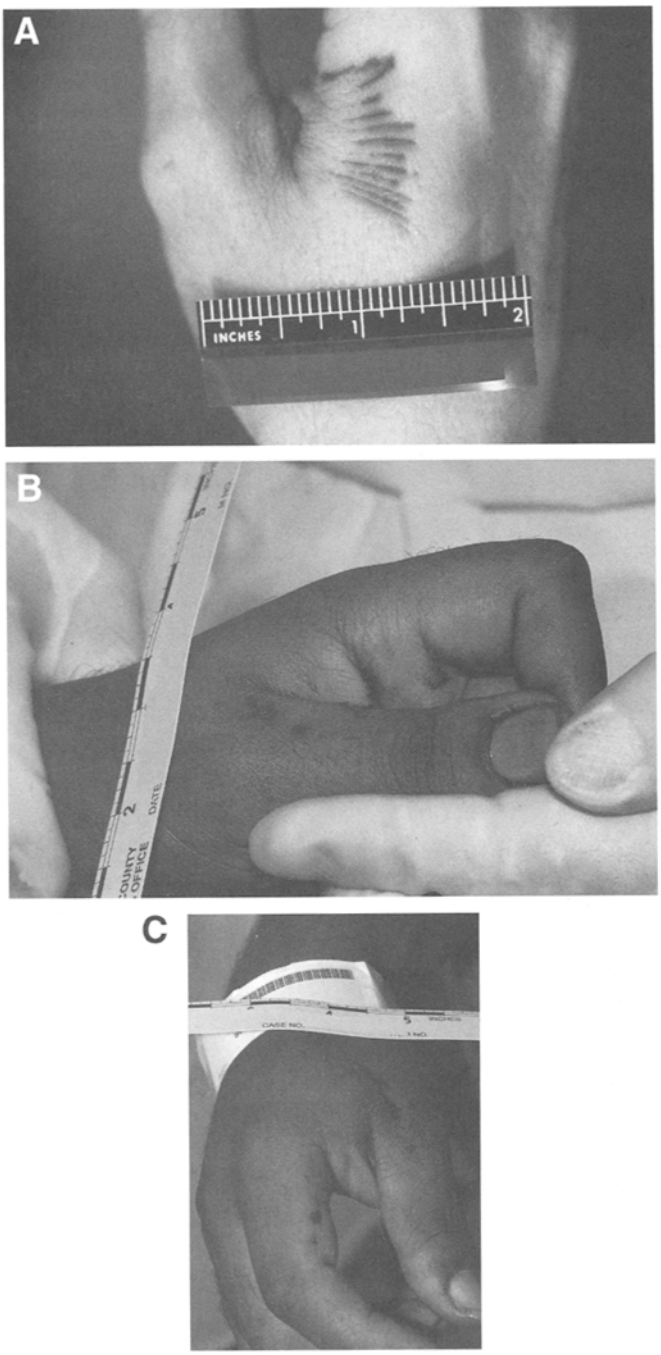


Fig. 38. Defense wound with parallel abrasions from serrated knife **(A)**. Defense wounds-incised wounds and abrasions **(B)**. Defense wounds-abrasions **(C)**.

- Usually, hemorrhage is located in neck musculature **(Figure 43A,B)** and sometimes there are fractures of hyoid bone and thyroid cartilage (usually over the age of 30)
- Frequently see abrasions and fingernail marks on skin
- Victim is usually female
- Sexual assault should always be considered in manual strangulation

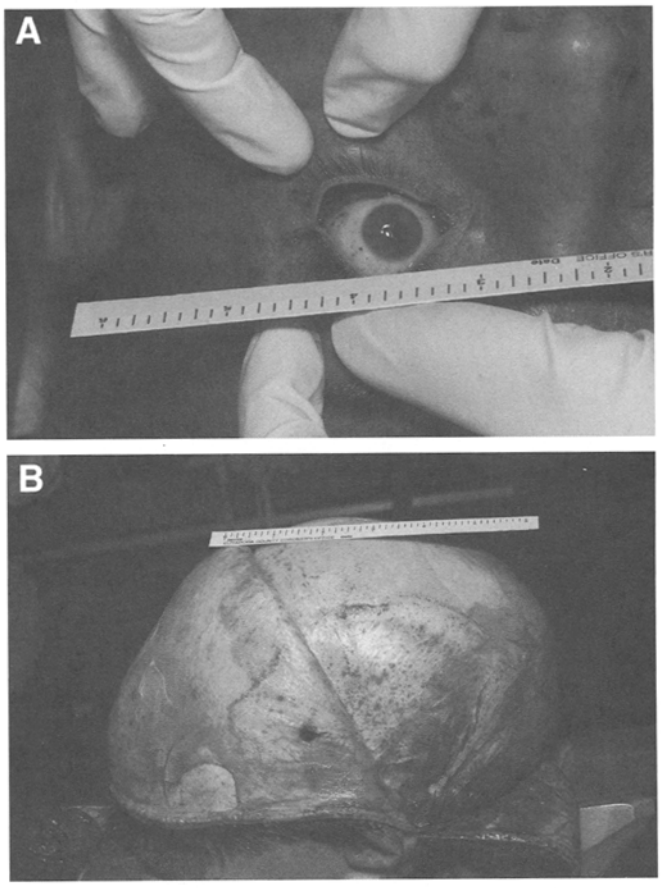


Fig. 39. Conjunctival petechiae **(A)**. Cephalic congestion and petechiae **(B)**.

- Note: Petechiae are not confined to strangulation and may be seen in asphyxial deaths, heart failure, vomiting or coughing, and postmortem lividity in prone position

Choke Hold (Shime-Waza)

- Also called bar arm control
- Forearm is placed against the front of the neck with force applied in a front to back direction, causing compression of the neck
- This is used to occlude the upper airway and carotid artery
- Excessive force can distort the larynx, leading to fractures of the larynx and, in some cases, the hyoid bone
- Carotid sinus stimulation may occur, leading to arrhythmia and death

Carotid Sleeper Hold (Lateral Vascular Neck Restraint)

- Symmetrical force is applied by the forearm and the upper arm to the side of the neck, such that the compression is on carotid arteries and jugular veins and not the larynx

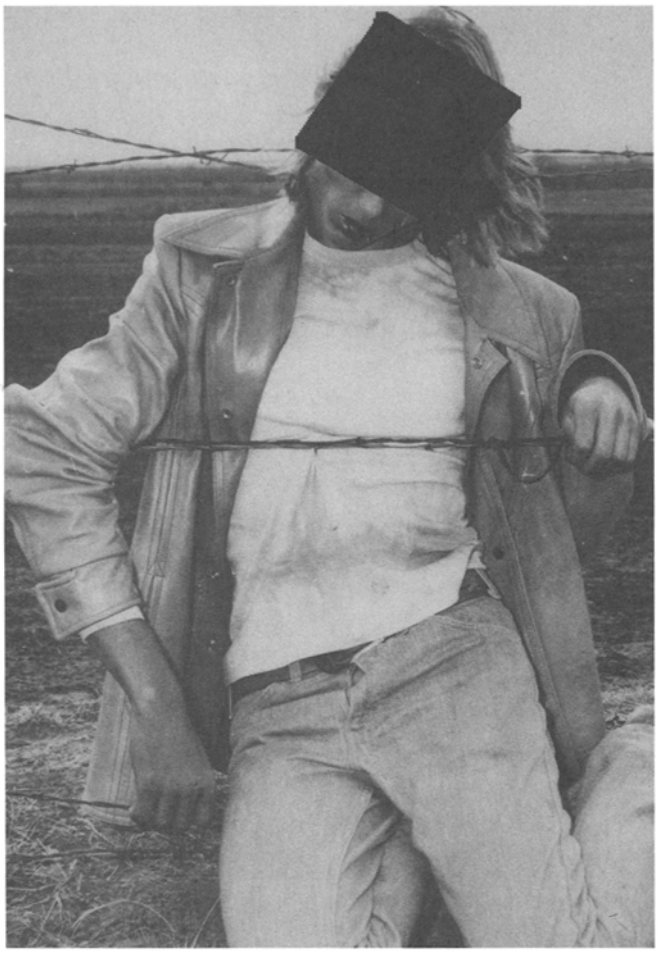


Fig. 40. Suicidal hanging.

- Consciousness is lost in 10–15 s
- Blood flow to the brain is decreased 85%
- May cause stimulation of carotid bradycardia and there may be increased catecholamines and arrhythmia that can lead to death if compression of arteries and veins is prolonged

Autoerotic Asphyxia

- Asphyxia by compression of the neck induced to enhance sexual enjoyment, usually during masturbation
- Almost always male
- Scene investigation: typically, the male is found nude or wearing female clothing, in a private area, and bound with a rope around the neck
- Virtually always has an escape mechanism in place
- Frequently, pornographic literature surrounds the scene
- Death typically occurs when there is a miscalculation of timing during the act of sexual gratification in which consciousness is lost and death occurs

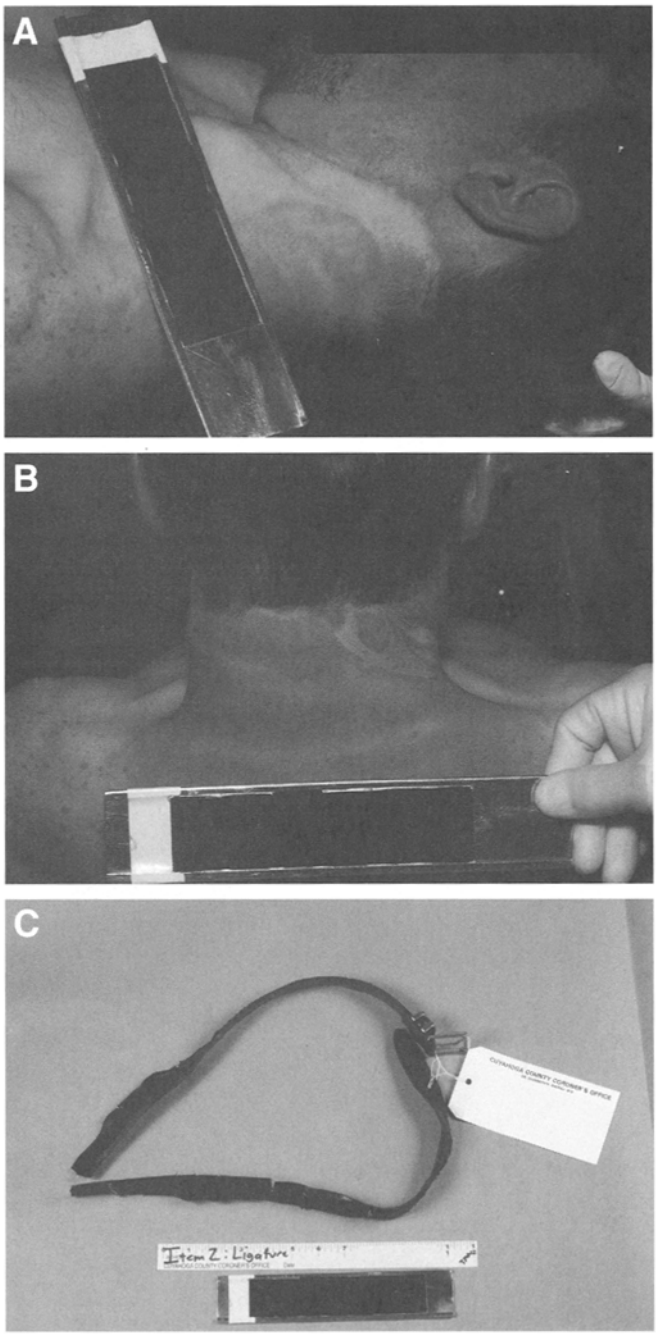


Fig. 41. Pale wide ligature furrow **(A)**. Posterior view of furrow in Fig. 41A. Note pattern on right neck **(B)**. Belt used as ligature in Fig. 41A, B **(C)**.

- Investigation is important to ensure that these cases are not certified as suicide

Types: Obstruction of Airway

Smothering

- A mechanical obstruction or occlusion of external airway (nose and mouth)

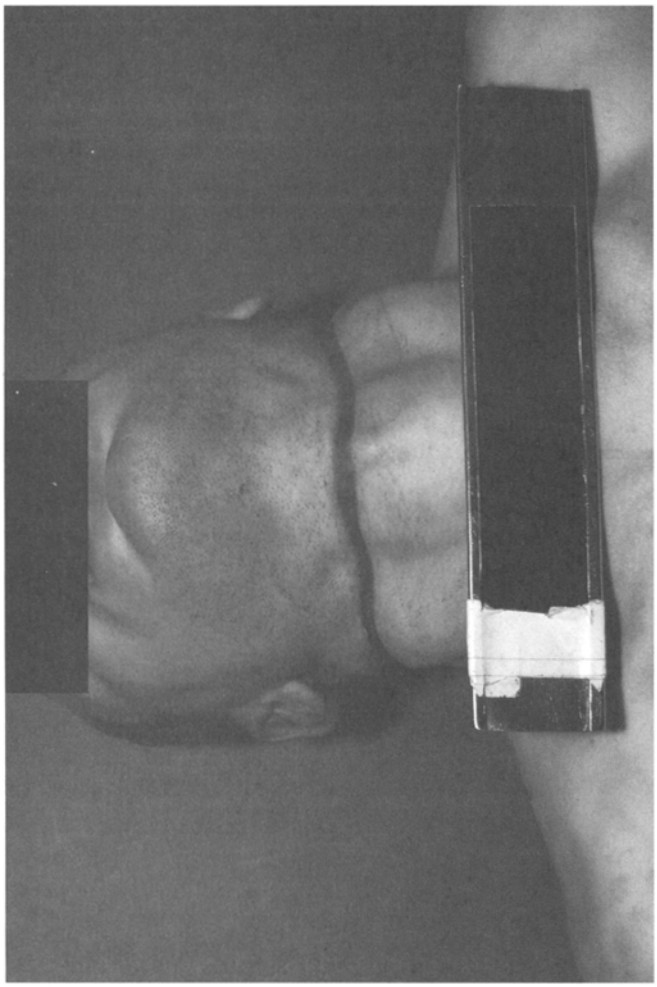


Fig. 42. Dried ligature furrow above larynx.

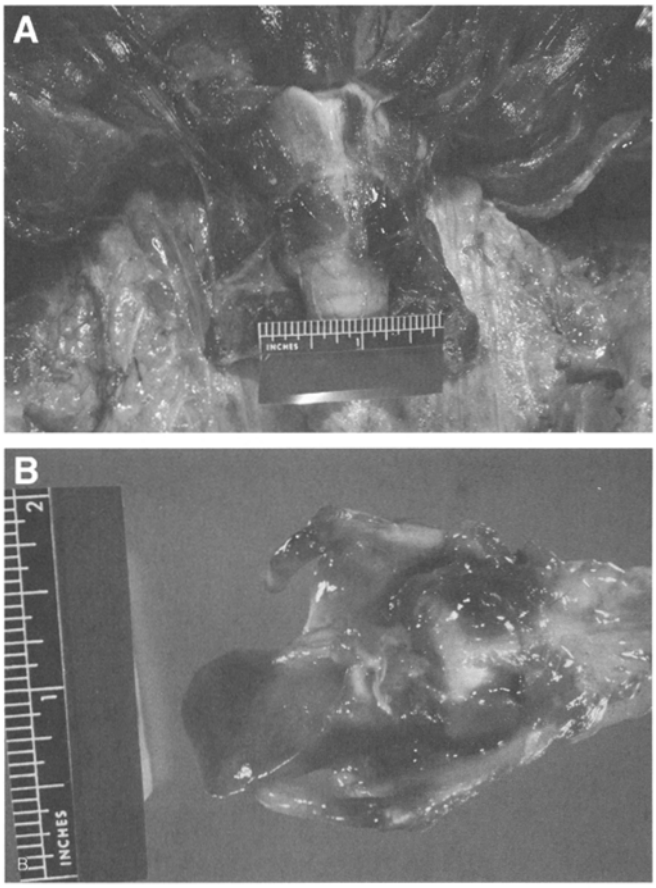


Fig. 43. Nuchal strap muscle hemorrhages over larynx **(A).** Larynx with posterior soft tissue hemorrhages **(B).**

- Usually homicide or suicide
- Most common suicidal smothering is a plastic bag over the head

Autopsy

- Non-specific, often without petechiae
- Accidental smothering occurs when an infant is trapped between a small mattress and railing, with face against mattress
- Gags can cause smothering, obstructing airway and swelling by saliva, creating a greater obstruction (even though unintentional, this is homicide)
- Most homicidal smotherings occur in the very young, very old, debilitated, or incapacitated by disease or drugs

Entrapment (Environmental Suffocation)

- Smothering in which individual is located in a confined space and uses all of oxygen:
  - Example: child in refrigerator
- May also occur when an individual enters an area with a deficiency of oxygen (example: excessive carbon dioxide in underground wells produced by plants that produce CO_2 and deplete oxygen)

Autopsy

- Nonspecific

Obstruction Of Airway By Foreign Material (Choking)

- Caused by obstruction of air passages
- Most are accidents that occur in children aspirating foreign bodies (e.g., balloons, buttons, pen tops, peanut butter, and hot dogs)
- May occur homicidally with gags in oral airway
- In adults, airway obstruction frequently involves food **(Figures 44 and 45)**
- In neurologically impaired or acute intoxication (with alcohol or drugs), food lodges in larynx and the individual cannot breathe
- Cafe coronary: individual eating in restaurant suddenly stands up and collapses:
  - CPR performed with the idea that this is of cardiac origin
- Small amount of food in airway at autopsy is not indicative of choking; individuals aspirate food agonally in cardiac arrest (20–25%)

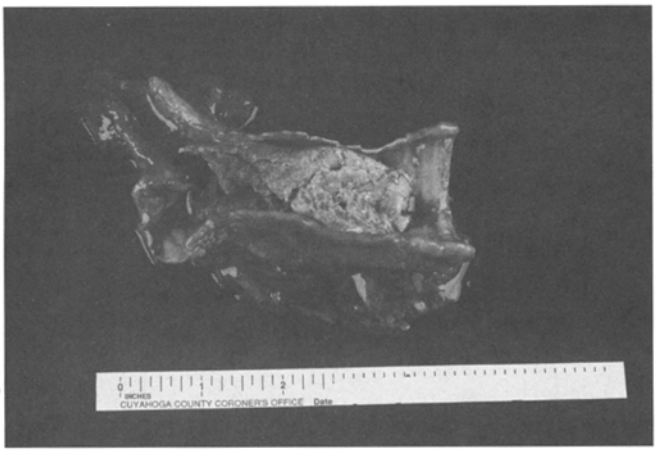


Fig. 44. Bolus of food in distal trachea.

- Food must be bolus in larynx, or, if aspiration of food, must extend from larynx to main bronchi, with complete obstruction by food
- Aspiration of food seen in neurologically impaired, intoxicated, and schizophrenics

Swelling of Airway

- Occurs in acute inflammatory processes with subsequent swelling and obstruction of airway
- Acute epiglottitis
- Clinically have sore throat and hoarseness, with difficulty swallowing
- Can get rapid airway obstruction and need a tracheal tube or tracheostomy
- Haemophilus influenzae most common cause in both children and adults

Autopsy

- Large edematous epiglottis with soft tissue obstructing airway
- Neoplasms of larynx (polyps or cancer)
- Diphtheria
- Asthma (see previous description)

Types: Mechanical Asphyxia

Traumatic Asphyxia

- Almost always accidental
- Occurs when a large weight falls or compresses the chest or upper abdomen, making respiration impossible
- Most common when a car jack slips on an individual repairing a car, causing the vehicle to fall on top of the victim

Autopsy

- Purple to blue-black congestion of head, neck, and upper chest, with numerous petechiae of sclerae, conjunctivae, and periorbital skin **(Figure 46)**

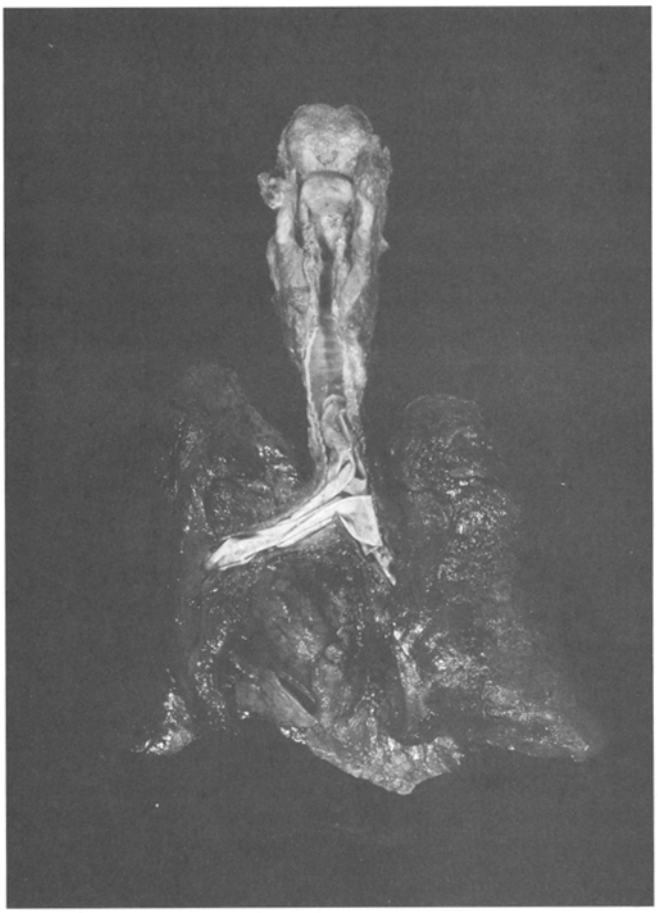


Fig. 45. Foreign body (latex glove) in airway.

- Retinal hemorrhages may occur
- Also seen with constricting snakes

Positional Asphyxia

- Associated with intoxication by alcohol or drugs
- Individual falls into a confined area and, because of intoxication, is unable to extricate him or herself
- By virtue of body position, is unable to breathe and, therefore, dies

Autopsy

- Congestion
- Cyanosis
- Petechiae

Types: Chemical Asphyxia

- Death not because of toxicity of gas, but to displacement of or inability to use oxygen

Carbon Dioxide

- Nontoxic and odorless
- Located in sewers, mines, and underground wells
- Death due to hypoxic environment and lack of oxygen

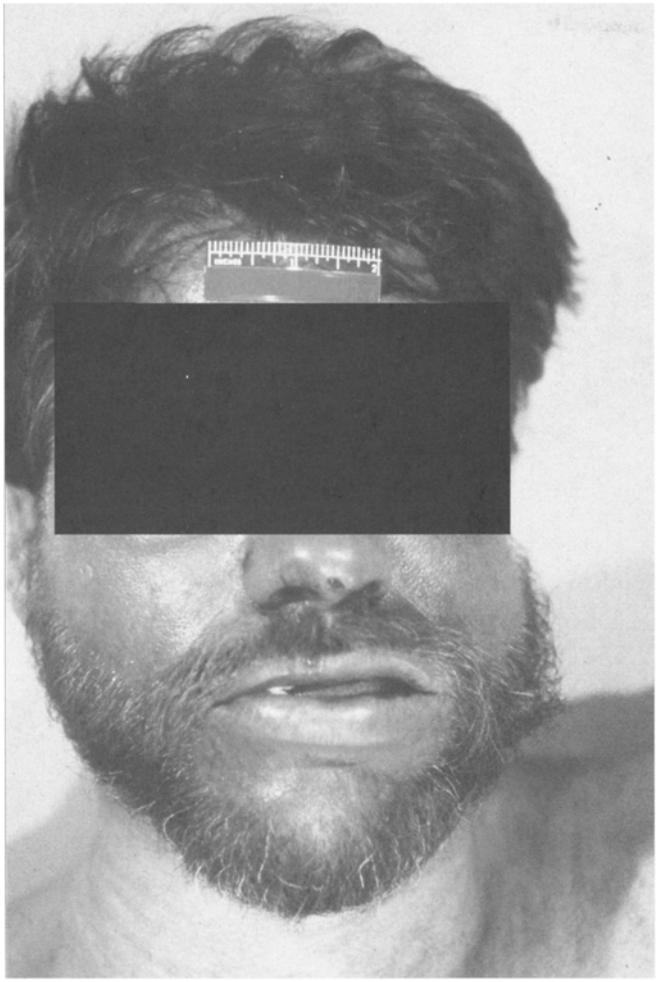


Fig. 46. Marked facial livor from mechanical compression.

Methane

- A component of natural gas
- Sewers and mines:
  - Toxicology is negative
  - Rarely does autopsy reveal cyanosis
  - Environment must be analyzed to determine what gases are present

Hydrogen Cyanide

- Prevents utilization of oxygen at cellular level
- May be either potassium or sodium cyanide
- Rapid-acting poison
- Cyanide binds to the ferric ion atom of the intracellular cytochrome oxidase
- Cyanide deaths are usually suicide and usually by persons who have availability of cyanide at place of employment (chemists, photographers, and engravers)
- Hydrogen cyanide used for execution in gas chamber for judicial executions

Autopsy

- If taken orally, the body and stomach contents may smell like bitter almonds
- Ability to smell cyanide is genetic; most persons cannot smell it
- Gastric mucosa and livor mortis are bright red due to excessive oxyhemoglobin
- If inhalation of hydrogen cyanide, the livor mortis and blood are bright red
- If cyanide is present, it will decrease postmortem
- In decomposition, bacteria can produce cyanide

Hydrogen Sulfide

- Produced by fermentation of organic matter
- Found in sewers, sewage plants, cesspools, and oil and chemical industries
- "Sewer gas": hydrogen sulfide, carbon dioxide, and methane
- Deaths from hydrogen sulfide are usually accidents
- Smell of rotten eggs

Autopsy

- May get formation of methemoglobin
- Dark colored blood
- Organs may have green to blue–green appearance

Carbon Monoxide

- Colorless, odorless, and tasteless
- Sources: fires, automobile exhaust, defective heaters, incomplete combustion of burning product
- Produced whenever materials are burned with inadequate oxygen to produce complete combustion
- Get tissue hypoxia and competes with oxygen for binding sites on oxygen carrying heme proteins (hemoglobin, myoglobin, cytochrome *C* oxidase, cytochrome P-450)
- Carbon monoxide has 250–300 times greater affinity for hemoglobin than oxygen
- Smokers have regular levels of carboxyhemoglobin of ~3–6%
- Number one source of carbon monoxide in fatalities is fire
- Number two source of carbon monoxide in fatalities is inhalation of exhaust fumes
- Symptoms of carbon monoxide poisoning:
  - 0–10%: generally no symptoms
  - 10–20%: headache and weakness
  - 30–40%: severe headache, dizziness, nausea, and vomiting
  - 40–50%: slurred speech, blurred vision, stupor, difficulty breathing
  - >50%: comatose, respiratory failure, and death in preexisting disease or elderly; carbon monoxide as low as 20–30% may be fatal
  - House fire carbon monoxide averages 50–60%
  - Car exhaust fatalities average 70%

Autopsy

- Cherry red livor mortis
- Common lesion, if survival, is bilateral necrosis of globus pallidus (nonspecific)
- Brain is sensitive to effects of carbon monoxide
- Half-life elimination of carbon monoxide with 100% oxygen is 90 min
- Flash fire: can see rapid combustion of fire, such as from gasoline in which motor vehicle explodes and incinerates
- Individuals may not have significantly elevated carbon monoxide levels

Types: Drowning

- Submersion in liquid and irreversible cerebral hypoxia
- Volume of water inhaled can range from small to large

Dry Drowning

- 10–15% of all drownings get:
  - Small volume of water inhaled
  - Laryngospasm prevents further water from entering airway
  - Nondemonstrable at autopsy
- Most cases get inhalation of large volume of water in process of drowning
- Type of water inhaled has little to do with drowning:
  - Fresh water alters or denatures surfactant
  - Salt water dilutes or washes surfactant away

Near Drowning

- Submersion victim is transported to hospital and survives for ~24 hours
- Rare instances get prolonged survival in cold water, especially in children

Autopsy

- No specific findings
- Diagnosis of exclusion
- Submersion wrinkling (washerwoman's hands, 1–2 hours in water)
- Edema fluid in mouth and airways
- Heavy lungs with edema fluid and foam cone in trachea and bronchi **(Figure 47)**
- May have hemorrhage in petrous temporal ridge or mastoid bone
- Occasionally have right ventricular dilation
- No drowning test exists

Drowning in Bathtubs

- Seen in children
- Seizure disorders
- Cardiac arrhythmia



Fig. 47. Drowning—Froth cone in nose and mouth.

- Drug overdose
- Must rule out natural death with subsequent submersion and body dumped into water after death

Scuba Diving

- Most common cause of death is drowning
- May get carbon monoxide in tanks that is mixed with air from gasoline-driven compressors
- With rapid ascent to surface, may develop air embolism, pneumothorax, or interstitial emphysema

Atmospheric Pressure Changes

- Gas volume increases with decreased barometric pressure
- Solubility of gas in liquid (e.g., blood) is proportional to partial pressure of gas in ambient atmosphere
- Injurious effects are dependent on three characteristics when atmospheric pressure is abnormal:
  - Direction and magnitude of change
  - Rate of change
  - Duration of change

Decreased Atmospheric Pressure

- Lowering of pressure by as little as 50% can result in significant systemic hypoxia leading to death
- Increase in atmospheric pressure is tolerated better than decrease
- Hypoxia from decreased pressure results in significant shifting of blood volume to pulmonary system from peripheral vasoconstriction
- Develop pulmonary arterial hypertension and damage to capillary endothelium and alveolar pneumocytes

Acute Mountain Sickness

- Majority occurs when there is ascension rapidly to elevations > 2500 meters (8200 feet)
- Symptoms include headache, nausea, vomiting, and insomnia

- ♦ May become life-threatening when develop acute high-altitude pulmonary edema and cerebral edema
- ♦ Usually develops first 8–24 hours at high altitude
- ♦ In addition to lower oxygen tension, also have lower environmental temperatures, increased ultraviolet radiation, and decreased humidity and get hyperventilation, dehydration, and hypokalemic alkalosis
- ♦ Hypobaric dysbarism (Aviator's Bend's)

Autopsy

- ♦ Congested lungs and interstitium with prominent alveolar edema and hyaline membranes
- ♦ Retinal hemorrhage and cerebral edema may also occur
- ♦ May also develop sickle cell crisis in persons with hemoglobin SC and sickle thalassemia
- ♦ Symptoms have been seen in pilots, especially early on with the advent of flight to heights capable of creating hypobarism

Increased Atmospheric Pressure

- ♦ Injuries occur on return from elevated to normal barometric pressure
- ♦ Rate of change of atmospheric pressure important in injury production
- ♦ Unless pressure is lowered slowly to normal, decompression sickness (dysbarism, Caisson disease, the bends, staggers, or chokes) can occur
- ♦ With increase in atmospheric pressure, get net flow of nitrogen (4/5 of air) from alveoli through blood in which gas dissolves into tissue
- ♦ Upon return to normal pressure, rapid gas bubble formation develops in tissue and blood because nitrogen forms faster than can be transported to lungs for expiration
- ♦ Ocean surface under pressure of 1 atmosphere
- ♦ Every 33 feet descended adds 1 additional atmosphere of pressure

Acute Decompression Sickness

- ♦ Associated with Henry's law in which rapid ascension with inability to exhale rapidly leads to accumulation of gas bubbles with mediastinal interstitial emphysema, subcutaneous emphysema, pneumothorax, and, in some cases, air embolism
- ♦ May get arterial gas embolism from ruptured alveoli, which may lodge in cerebral vessels with symptoms ranging from focal neurologic deficits developing hours after dive to rapid collapse and unconsciousness immediately after surfacing
- ♦ Females and obese predisposed
- ♦ Fatalities most associated with pulmonary and central nervous system (CNS) involvement
- ♦ Chronic complications of decompression sickness characterized by demyelination of dorsal and lateral columns of thoracic spinal cord

Barotrauma

- ♦ Associated with Boyle's law and because of failure of a gas-filled space to equalize its internal pressure to that of the outside environment
- ♦ Effects are most severe in cavities within bone that cannot expand or contract
- ♦ Barotrauma of middle ear is most common disorder in divers; may lead to pain and conduction hearing loss due to rupture of the tympanic membrane
- ♦ Barotrauma of inner ear may lead to sensorineural hearing loss and tinnitus
- ♦ Barotrauma of paranasal sinus is the second most common disease of divers, especially in frontal sinus:
  - May be associated with chronic dysfunction of sinuses with either anatomic abnormalities or chronic allergies

Thermal Injuries Related to Temperature Changes

- ♦ General principles:
  - Narrow range of internal temperature must be maintained:
    - Increase in tissue temperature more likely to cause injury than decrease
    - Cellular injury or death occurs if tissue temperature is maintained at a level >5°C above or >15°C below that which is normal for blood
    - Skin is principal site of heat loss or heat gain
  - Heat load = heat generated from oxidation of metabolic products + heat acquired from environment:
    - Normal body temperature = 98.6°F (37°C) orally
    - 1°F (0.6°C) higher rectal
    - Temperature variations by age, time of day, physical exertion (exercise may increase temperature 3–4°)
  - Newborn and elderly have temperatures 1°C higher
  - Heat loss occurs from four mechanisms:
    - Conduction
    - Radiation
    - Evaporation
    - Convection

Local Hypothermia

- ♦ Localized injury from cold classified as immersion foot or frostbite:
  - Immersion (or trench) foot occurs with prolonged exposure to wet and cold, nonfreezing conditions:
    - Primary injury is neuromuscular, resulting from ischemic tissue injury
  - Frostbite: exposure to freezing conditions involving damage to the skin and vasculature:
    - Get vasomotor alterations, aggregation, and stasis of erythrocytes leading to vascular obstruction

- Typically involves exposed body surfaces, most prominently those farthest away from central circulation (ears, nose, and extremities)
- May be superficial, involving the skin, or may cause gangrene of deep tissues

Systemic Hypothermia

- Results when heat loss exceeds heat production and allows body temperature to fall below 95°F:
  - Heat loss expedited by decreased humidity, wetness or immersion, or wet clothing
- Three stages of hypothermia:
  - Sensation of cold and shivering: body approx 90°F
  - Stage of depression with developing bradycardia, hypotension, and bradypnea: body temperature 75–90°F
  - Cessation of thermal regulatory control: body temperature <75°F
- Unconsciousness develops at ~86°F
- Cardiac dysrhythmias common with ventricular fibrillation developing at core temperature of 77–82°F

Immersion Hypothermia

- More rapid loss of heat in water than in air:
  - Water temperature 4–9°C = death in 70–90 min
  - 0°C = fatalities in $^1/_2$ hour
  - In water temperatures >70°F, survival time depends solely on the fatigue factor of the individual
  - When individuals die within 10–15 min after entry into frigid water, death is, apparently, not related to reduced body temperature, but to shock of rapid entry into cold water

Wind Hypothermia

- Body will lose heat more rapidly with increasing wind velocity
- Infants are more susceptible to hypothermia than adults (greater surface area to body mass)

Paradoxical Undressing

- Term employed when individual is found undressed in cold environment, believed to be caused by hallucination of warmth as a result of paralysis of thermal regulatory system

Hide and Die Syndrome

- Seen in elderly, paradoxical undressing: hidden in closets, cupboards, etc.
- Most cases of hypothermia involve elderly or people under the influence of alcohol:
  - Other predisposing conditions: infancy, exhaustion, or debilitating disease or injury
  - May also be associated with disease processes such as myxedema and sepsis

Autopsy

- No pathognomonic findings of hypothermia
- If rapid death, usually no findings except cherry-red discoloration from retained oxyhemoglobin
- If prolonged survival, then may develop thromboses; pancreatitis; ulceration and hemorrhage of stomach, ileum, and colon; and bronchopneumonia

Local Hyperthermia (Burns)

- Inverse relationship between intensity of thermal exposure and amount of time required to produce burn (e.g., higher the temperature, the shorter duration of exposure necessary to create injury)
- Earliest evidence of hyperthermal injury is capillary dilation with increased capillary permeability and eventual capillary leakage
- Cutaneous burns may be identified as first, second, or third degree or as partial thickness or full thickness:
  - First-degree burn (e.g., sunburn)
  - Second-degree burn involves vesication or blister
  - Third-degree burn: scar formation in repair
  - Fourth-degree burn: charring
  - Partial thickness: no permanent damage to dermis; includes both first- and second-degree burns; regeneration of epithelium (second-degree burn) from margins of burned area and underlying hair follicle
  - Full thickness burns: damage to dermis and adnexal structure including hair follicles (third degree); form scar
- Get secondary shock with extensive burns due to loss of plasma at injury site
- Get bacterial infection where tissue sloughed
- Other complications include phlebothromboses, ulcers of stomach and small intestine (Curling's ulcer), renal failure, and inhalation damage (when associated with fire)
- Estimation of total body surface area: "Rule of 9s":
  - Head: 9%
  - Upper extremities: 9% each
  - Front of torso: 18%
  - Back: 18%
  - Each lower extremity: 18% (front and back)
  - Neck: 1%
- Household fires rarely exceed 1600°F:
  - Cremation at 1800–2000°F for $1^1/_2$–$2^1/_2$ hours

Smoke Inhalation

- Get cherry red lividity
- Soot in nares and oral cavity and may coat larynx, trachea, and bronchi **(Figure 48)**
- Absence of soot does not preclude carbon monoxide inhalation



Fig. 48. Soot in airway of fire victim. Note extent of soot beyond carina into bronchi.

- Cyanide produced in burns from synthetic substances only rarely contributes to death
- In fourth-degree charring, may see "pugilistic attitude" with boxer appearance of arms secondary to contraction of muscles of upper extremity
- "Fire epidural hematoma": postmortem artifact with fairly large aggregate of chocolate-brown dried blood overlying frontal, parietal, and temporal areas

Systemic Hyperthermia

- Failure of thermal regulation and may occur if exposed to significant heat from environment or inability of body to eliminate heat from metabolic processes

Mechanism Of Heat Loss

Radiation

- Heat loss via energy emission from skin surface (65% of body heat loss)

Convection

- Cooling by air current (12–15% body heat loss)

Conduction

- Direct contact with cooler surfaces (very little heat loss)

Evaporation (Perspiration)

- Only heat loss mechanism that works when ambient temperature exceeds 92°F
- Amount of sweat vaporized is limited by ambient humidity
- Transpiration heat loss through exhaled water vapor (dissipates 5% of body heat)
- Important mechanism of heat loss in animals
- Functionally elevated temperatures lead to generalized vasodilatation, rapid pulse, and stimulation of respiratory centers

Heat Stroke

- Uncontrolled overproduction of body heat or impairment of body's ability to lose heat
- Commonly occurs in spell of hot (>90°F) humid weather
- Predisposing conditions include old age; cardiovascular disease and other debilitating conditions; skin disorder; medications including neuroleptic, diuretic, and anticholinergic or anesthetic agent; alcoholism; disorders with impaired heat loss; and failure to curtail physical activity
- Also increased risk in healthy young people, especially military recruits, laborers, and athletes who overexert themselves in hot, humid weather:
  - Especially prominent in individuals with sickle cell trait
- Environmental factors contributing to heat stroke include poor ventilation, residence of upper floors of buildings, and closed automobiles in direct sunlight
- Individuals > 65 have 10–12 times risk of heatstroke as compared to younger adults

Autopsy Findings

- Nonspecific
- If survive following hyperthermia, may get complications, including pneumonia, renal failure, hepatic failure, and sepsis

Malignant Hyperthermia

- Drug-induced syndrome occurring during and after administration of general anesthesia
- Characterized by increased oxygen consumption and rapid rise in temperature
- Genetic predisposition that allows release of calcium from smooth endoplasmic reticulum with overload of calcium in mitochondria
- Previously associated with halothane and succinylcholine
- Symptoms include tachycardia, hyperthermia, rhabdomyolysis, and skeletal muscle rigidity

Neuroleptic Malignant Syndrome

- Seen in individuals on antipsychotic medication, most notoriously phenothiazine therapy
- Estimated between 0.5–1% of patients exposed to neuroleptic
- Young men predominate
- Predisposing factors include physical exhaustion, dehydration, organic brain disease, and long-acting depo neuroleptic drugs
- Clinical symptoms include hyperthermia, hypertonicity of skeletal muscles, and fluctuating consciousness with instability of autonomic nervous system
- Mortality ranges from 20–30%
- Causes of death include respiratory failure, cardiovascular collapse, renal failure, arrhythmias, and thromboembolism (if prolonged survival)

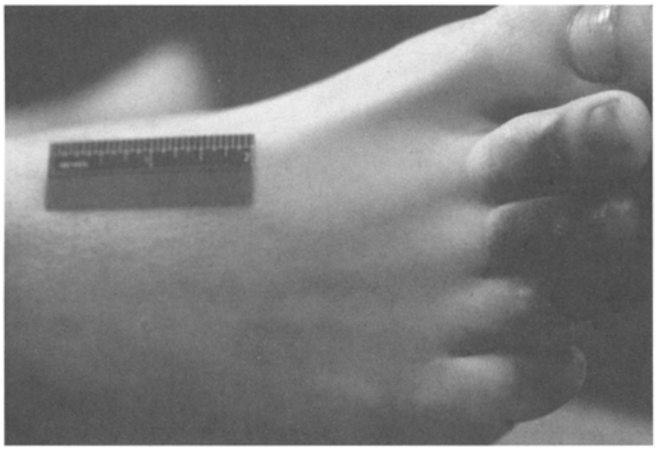


Fig. 49. Electrical burns.

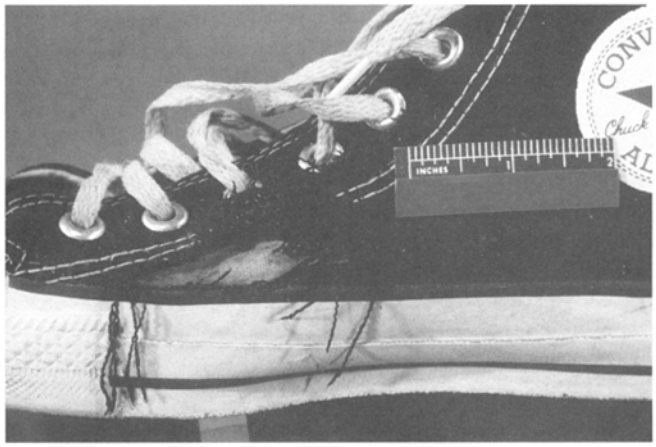


Fig. 50. Exit path of lightning strike.

- Respiratory failure may result from aspiration pneumonia
- May see in Parkinson's patients with sudden discontinuation of medication

Electrical Injuries

General Concepts

- Degree of injury dependent on:
  - Voltage of current
  - Type of current
  - Resistance at point of contact
  - Location of current path, critical
  - Duration of current
  - Body must complete a circuit between two conductors
  - Death may be produced with low voltage from alternating current (46 and 60 volt)
  - Any voltage > 25 should be considered potentially lethal
  - Alternating current is more dangerous than direct current
  - Voltages < 220 tend to fibrillate heart without affecting respiratory center
  - Voltages > 1000 tend to produce paralysis of respiratory center without affecting heart
- Amount of current: $C = V/R$:
  - C = Current in amperes
  - V = Potential in volts
  - R = Resistance in ohms (body's opposition to flow of current)
- Effective current dependent on resistance of tissues involved:
  - Callused, thick skin may reach resistances of 1 million ohms or more
  - Wet or moist skin may have resistance of 1000 ohm
- More prolonged contact, more serious effect
- $^2/_3$ of electrical injuries occur at work (usually linemen or construction workers in contact with high voltage power line):
  - Remaining $^1/_3$ occur in residences with low-voltage current
- 5% of all admissions to burn hospitals are related to electrical injury

Electrical Injury

- Greatest resistance to flow of current is skin
- Electrothermal injury limited to skin **(Figure 49)**
- Death occurs from primary fibrillation of the heart
- Failure of respiratory center from fibrillation with paralysis of respiratory center or prolonged fibrillation of respiratory muscle

Autopsy

- Small, circumscribed, indurated lesion, central necrosis, and "nuclear streaming" of dermal nuclei
- High-voltage burns: large area of contact with deep charring injuries, even amputation of extremities
- May get coagulative necrosis of muscle nerve and skin, with thrombosis of blood vessel and eventual renal failure
- Heart and central nervous system: arm to arm conduction involves heart; head to foot conduction involves nervous system and heart
- Small current through chest can be fatal; large current through extremity alone may have limited effect

Lightning

- Typical lightning discharge occurs during storms, but may occur with clear skies; most commonly occurs in afternoon
- Highest conductor of electricity preferentially struck includes trees, poles, antennae, pylons, and unprotected buildings

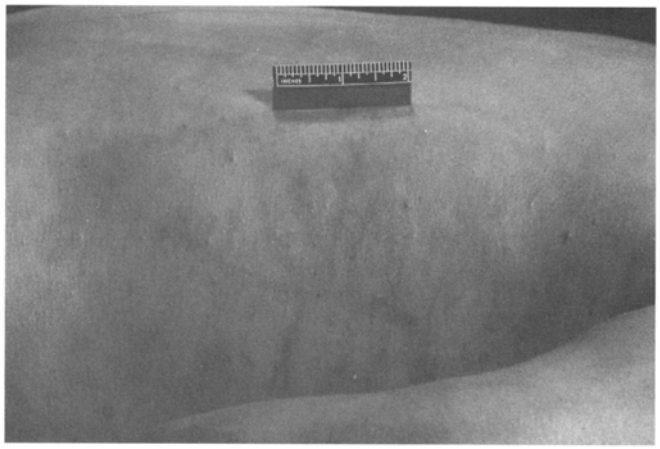


Fig. 51. Lightning print (ferning).

- Geographic features predisposing to strikes include caves, fissures, faults, metallic ores, and natural radioactivity
- Humans most exposed live on mountain or work outdoors (e.g., farmers or herders)
- Lightning may strike directly (entering through head or arm) **(Figure 50)** or indirectly:
  - Direct strikes also occur in the open when carrying something metallic, such as umbrella, golf clubs, jewelry, or hearing aids
  - Indirectly as victim is secondarily struck following primary strike of tree or another person
- Effects of lightning depend on nature of strike (direct or indirect), intensity of current, time spent through body, pathway taken, and activity of person at time of strike
- Lightning may depolarize the entire myocardium or cause fracture or rupture of blood vessels and viscera
- If survive strike, victims may develop complications, including cardiac arrhythmias, infarction, cataracts, and renal failure
- Skin may show arborescent cutaneous hyperemia known as ferning or lightning print **(Figure 51)**

TOXICOLOGY

Alcohols and Acetones

Ethanol (Drinking Alcohol)

- Source:
  - Beer: 3–6% ethanol content
  - Wine: 6–12% ethanol content
  - Distilled liquor: 20–85% ethanol content
  - Trace endogenous production
  - Cough syrup, mouthwash, and solvents contain ethanol
- Metabolism:
  - Absorbed from stomach and small intestine
  - Metabolized in liver to acetaldehyde and acetic acid
  - Elimination of alcohol: 0.015 g/dL per hour –0.02 g/dL per hour
- Toxic effects:
  - Central nervous system: respiratory depression (lethal concentration ~0.4 g/dL, some survivors have had levels above this), Wernicke-Korsakoff syndrome, delirium tremens
  - Liver: steatosis, cirrhosis, and hepatitis
  - Heart: cardiac arrhythmia and cardiomyopathy

Methanol (Wood Alcohol)

- Source:
  - Solvents, fuel, antifreeze, trace endogenous production
- Metabolism:
  - Methanol metabolized to formaldehyde, which is metabolized to formic acid
- Toxic effects:
  - Central nervous system depressant, blindness, acidosis
- Lethal dose = 100–200 mL

Isopropyl (Rubbing Alcohol)

- Source:
  - Solvents, rubbing alcohol
- Metabolism:
  - May be absorbed through skin or orally ingested:
    - Isopropanol is metabolized to acetate and formate
    - Acetone may be present in blood and urine (glucose will not be elevated)

Acetone

- Source:
  - Fingernail polish remover, solvent, small amount of endogenous production
- Metabolism:
  - Ingested and absorbed, acetone metabolized to acetate, formate, and isopropanol
- Toxic effects:
  - Acidosis, endogenous level may also be associated with ketoacidosis

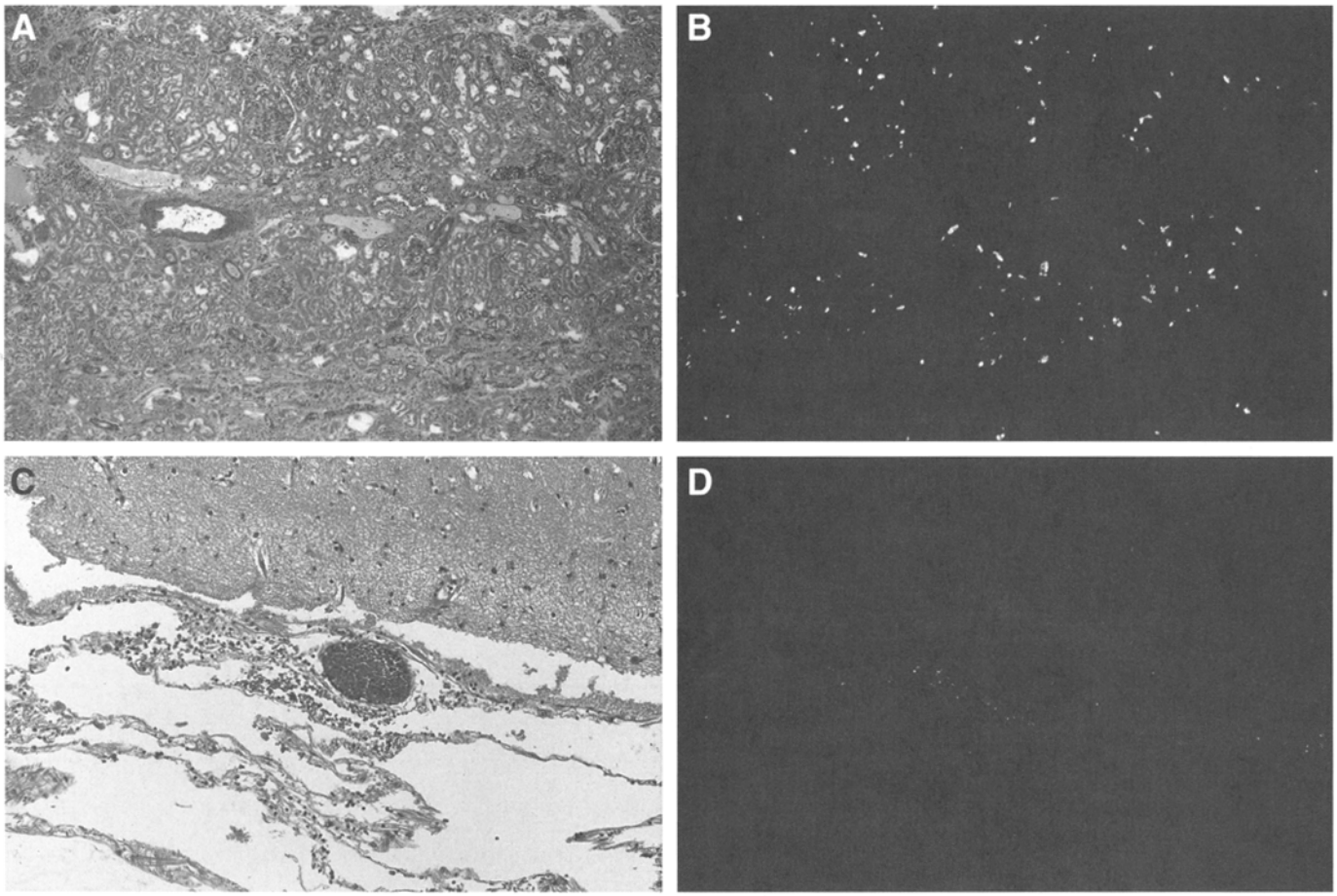


Fig. 52. Kidney with oxalate crystals following ethylene glycol poisoning **(A)**. Kidney with oxalate crystals following ethylene glycol poisoning-polarized light **(B)**. Leptomeninges with oxalate crystals **(C)**. Leptomeninges with oxalate crystals—polarized light **(D)**.

Ethylene Glycol

- Source:
  - Antifreeze
- Route:
  - Ingestion
- Metabolism:
  - Many compounds including oxalate
- Toxic effects:
  - Central nervous system depressant, acidosis, and renal failure
- Unique pathologic findings:
  - Calcium oxalate crystals (kidneys and central nervous system) **(Figures 52A–D)**
- Lethal dose = 100 mL

Cocaine and Cocaethylene

Cocaine

- Source:
  - Erythroxylon coca plant
- Route:
  - Injection, snorting, sniffing, and ingestion
- Metabolism:
  - Metabolizes to three different compounds
  - Benzoylecgonine, norcocaine, and ecgonine methyl ester
  - Benzoylecgonine and ecgonine methyl ester will metabolize to ecgonine
  - When alcohol is present, cocaine combines with ethanol to form by-product cocaethylene
- Active metabolites:
  - Norcocaine and cocaethylene
- Half-life:
  - Cocaine: $^1/_2$–$1^1/_2$ hours
  - Benzoylecgonine: 5–10 hours
  - Cocaethylene: 1–2 hours
- Mechanism:
  - Blocks re-uptake of sympathomimetic neurotransmitters into nerve terminal

- Biological effects of cocaine:
  - Increased blood pressure, heart rate, body temperature, and respiration
  - Dilated pupils
  - Anxiety, talkativeness, agitation, hyperactivity, and mood swings
  - Central nervous stimulation followed by central nervous depression
  - Addiction, tolerance, and withdrawal
- Toxicity:
  - Cardiovascular: arrhythmia, hypertension, myocardial infarction
  - CNS: seizures, strokes, psychosis
- Autopsy:
  - Hypertrophic heart, scarred injection sites, intravenous "drug tracks"
- Microscopic:
  - Myocardial fibrosis, pulmonary hemorrhage, and giant cell reaction in skin
- Lethal dose: variable
- Blood should be placed in sodium fluoride tubes to inhibit plasma esterases

Cocaethylene

- Source:
  - Only metabolite formed from a combination of cocaine and ethanol
- Metabolism:
  - In vitro studies found that conversion occurs in liver by nonspecific carboxylesterase, which catalyzes the transesterification of cocaine to cocaethylene
- Effects:
  - Increase of blood pressure and pulse
  - Improvement in psychomotor performance
  - More pleasant euphoria
  - Increases in plasma norcocaine concentration
  - Longer half-life
- Toxicity:
  - Greater cardio-toxicity than cocaine

Opiates

- Source:
  - Oriental poppy (Papaver Somniforum)
- Drug of abuse:
  - Heroin
- Prescription drugs:
  - Morphine, hydrocodone, methadone, and codeine
- Route:
  - Injection, ingestion, and smoking

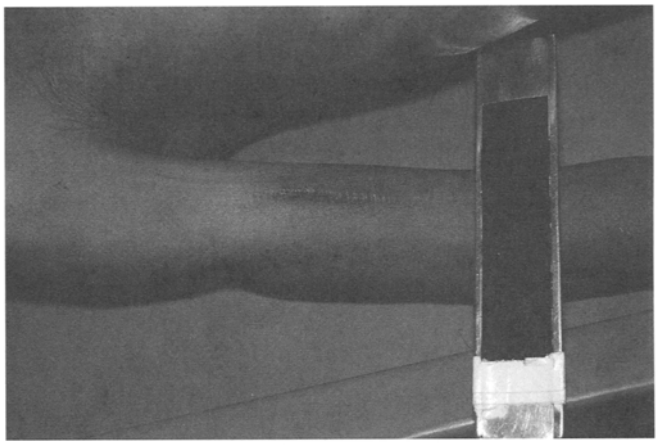


Fig. 53. Healed injection site scars—track marks.

- Metabolism:
  - Heroin metabolized rapidly to 6-monoacetyl-morphine, which is metabolized to morphine
- Half-life:
  - Heroin: 5 min
  - 6-monoacetylmorphine: 15–45 min
  - Morphine: 1–7 hours
- Physiologic effects:
  - Analgesia, euphoria, drowsiness, respiratory depression, pinpoint pupils, antitussive, hypotension, and lower seizure threshold
- Toxicity:
  - Central nervous system depressant and respiratory depressant
- Autopsy:
  - Needle tracks (**Figure 53**), skin popping, foam cone in airway
- Microscopic:
  - Foreign body granulomata in both skin and lungs
- Lethal levels: variable
- Mechanism of action:
  - Bind to opiate receptors in thalamus, limbic system, substantia gelatinosa, periaqueductal gray, blocks nociceptive (pain) reflexes

Amphetamines

- Source:
  - Drugs of abuse including designer drugs, amphetamine, methamphetamine, MDA, and MDMA
- Route:
  - Ingestion, injection, and smoking
- Physiologic effects:
  - Stimulation, sympathomimetic, and anorectic
- Metabolism:
  - Methamphetamine metabolizes to amphetamine, which metabolizes to norephedrine

- Toxicity:
  - CNS and behavior changes
  - Cardiovascular system, arrhythmias, and hypertension
- Lethal level: variable
- Mechanism:
  - Sympathomimetic
- CNS effect through antiserotonin action

Barbiturates

- Source:
  - Abusive use of medication (e.g., phenobarbital, secobarbital, and amobarbital)
- Route:
  - Ingestion, injection, drug rarely abused nowadays
- Physiologic effects:
  - Sedative-hypnotic, anticonvulsant
- Metabolism:
  - P-hydroxylation and conjugation in liver
- Toxicity:
  - Central nervous system: hypersensitivity
- Autopsy:
  - Barbiturate "blisters" (6–9% of acute barbiturate intoxication)
  - Globus pallidus necrosis (nonspecific)
- Lethal level:
  - Long-acting, barbiturates 8 mg/dL
  - Short-acting, 3.5 mg/dL
- Mechanism of action:
  - CNS depressant

Psychoactive Drugs

Lysergic Acid Diethylamide (LSD)

- Source:
  - Drug of abuse
- Route:
  - Ingestion
- Physiologic effects:
  - Hallucination, flashbacks, recurrent episodes of acute intoxication after days or weeks of abstinence, psychosis, and hyperthermia
- Metabolism:
  - Biotransformation by N-demethylation, N-deethylation, and hydroxylation
- Toxicity:
  - CNS behavioral effects
- Mechanism of action:
  - CNS effect through antiserotonin action

Phencyclidine (PCP)

- Source:
  - Drug of abuse
- Route:
  - Ingestion, injection, smoking, and snorting
- Physiologic effects:
  - Hallucinations, lethargy, hypertension, and decreased respiratory rate
- Toxicity:
  - CNS behavioral effects, respiratory depression, sudden death
- Metabolism:
  - Oxidative metabolism to two inactive metabolites
- Mechanism of action:
  - Blocks dopamine uptake and release of stored catecholamines

Marihuana

- Source:
  - *Cannabis sativa* plant
- Route:
  - Smoking and ingestion
- Active component:
  - Tetrahydrocannabinol (THC), stored in adipose tissue
- Metabolism:
  - THC (active) is metabolized to 11-hydroxy-THC (active) and 8-hydroxy-THC (active):
    - 11-hydroxy-TH metabolized to 11-carboxy-THC (inactive)
    - 8-hydroxy-THC metabolized to 8,11-dihydroxy-THC (inactive)
- Physiologic effects:
  - Euphoria, lethargy, drowsiness, anxiety, paranoia, and psychosis
- Toxicity:
  - Rarely lethal, but may have hallucinations
- Analysis:
  - THC in blood indicates recent use (within 24–48 hours)
  - Carboxy-THC in urine indicates use in past 3–4 weeks

γ-hydroxybutyrate (GHB)

- Source:
  - Metabolite of gamma aminobutyric acid
- Route:
  - Ingestion and injection
- Physiologic effects:
  - None until combined with alcohol, then drowsiness, euphoria, amnesia, and loss of consciousness

- Toxicity:
  - Respiratory depression, seizures, coma, hypotension, and death

Antidepressants

Tricyclic Antidepressants

Amitriptyline

- Source:
  - Prescription medication
- Route:
  - Ingestion and injection
- Physiologic effects:
  - Mood elevation
- Toxicity:
  - Hyperthermia, cardiac arrhythmia, coma, and convulsions
- Mechanism:
  - Not well known, but inhibits pump mechanism responsible for uptake of epinephrine and serotonin in adrenergic and serotonergic neurons
- Metabolism:
  - Amitriptyline metabolizes to nortriptyline (active)

Fluoxetine (Prozac)

- Source:
  - Medication
- Route:
  - Oral
- Physiologic effects:
  - Antidepressant, can have side effects of insomnia, anxiety, manic behavior, and suicidal ideation
- Toxicity:
  - Hypertension, tachycardia, and lethargy
- Mechanism:
  - Blockade of serotonin re-uptake

Antipsychotics

Phenothiazine

- Source:
  - Prescription drug
- Route:
  - Ingestion and injection
- Physiologic effects:
  - Psychotropic and antiemetic
- Toxicity:
  - Central nervous system: behavioral effects
  - Cardiovascular effects: sudden death, tardive dyskinesia, neuroleptic malignant syndrome
- Mechanism:
  - Strong anti-adrenergic and weaker peripheral anticholinergic activity
- Metabolism:
  - Elimination, slow
  - Conversion to sulfoxide
  - Demethylation

Haloperidol (Haldol)

- Source:
  - Prescription medication
- Route:
  - Oral, injection
- Physiologic activity:
  - Antipsychotic
- Toxicity:
  - Tardive dyskinesia, neuroleptic malignant syndrome, extrapyramidal symptoms, tachycardia, muscular rigidity, hypotension, sudden death
- Metabolism:
  - Extensively biotransformed to inactive metabolites
- Mechanism of action:
  - Unknown

Analgesics

Acetaminophen

- Source:
  - Over-the-counter medication
- Route:
  - Oral ingestion
- Physiologic effects:
  - Analgesic and antipyretic
- Toxicity:
  - Hepatotoxicity (24–48 hours after overdose)
- Lethal dose:
  - 20 g
- Toxic concentration:
  - >160 mg/L
- Autopsy:
  - Centrilobular hepatic necrosis
- Metabolism:
  - Conjugated with glucuronide (45%), sulfate (20%), and cysteine (15–55%)

Acetylsalicylic Acid (Aspirin)

- Source:
  - Over-the-counter medication
- Route:
  - Ingestion
- Physiologic effects:
  - Analgesic, antipyretic, antiinflammatory, and anticlotting effects

- Metabolism:
  - Hydrolyzed by liver and blood esterases; to salicylic acid (analgesic that accounts for most pharmacological activity of parent drug)
- Toxicity:
  - Sudden death by hypersensitivity, Reye syndrome, respiratory alkalosis, metabolic acidosis, hemorrhage, or chronic interstitial nephritis
- Lethal dose:
  - 2–5 g
- Toxic concentration:
  - 500 mg/L

Metals

Arsenic

- Source:
  - Pesticides, ceramics, wood preservatives
- Route:
  - Ingestion, inhalation
- Mechanism:
  - Inhibition of enzymes by binding to sulfhydryl groups, including respiratory enzymes
- Predilection for vascular endothelium, increasing permeability
- Toxicity:
  - Gastrointestinal: nausea and vomiting, abdominal pain, "rice water diarrhea"
  - Cardiovascular: dysrhythmia
  - CNS: peripheral motor and sensory neuropathy
  - Cutaneous: Bowen's disease, "Mees lines," hyperkeratosis of palms and soles, garlic odor
- Autopsy:
  - Multiple keratoses, generalized visceral hyperemia, cerebral edema, many have fatty metamorphosis of liver
  - In chronic poisoning, may have hyperkeratosis of hands and soles of feet
- Microscopic:
  - Hepatocellular necrosis, interstitial myocarditis, subendocardial hemorrhage, renal tubular degeneration, hemorrhagic arsenical encephalitis
- Lethal dose:
  - 200–300 mg (normally present in tissues in low concentrations)

Lead

- Source:
  - Paints, battery, glazing putty, moonshine whiskey
- Route:
  - Ingestion and inhalation
- Toxicity:
  - Convulsions, intestinal cramps, hemorrhage, vomiting, anemia, peripheral motor neuropathy, Fanconi's syndrome (aminoaciduria, glycosuria, hyperphosphaturia)
- Autopsy:
  - Lead line in gums at base of teeth, cerebral edema, eosinophilic intranuclear inclusions in proximal convoluted tubules, perivascular PAS + droplets in CNS, basophilic stippling, and increased red blood cell fragility
- Mechanism:
  - Inhibits aminolevulinic acid dehydrase, ferrochelatase, and nucleotidase, which leads to blocked synthesis of hemoglobin

Mercury

- Source:
  - Paint industry, dentistry
- Route:
  - Inhalation, ingestion, transdermal absorption
- Toxicity:
  - CNS: emotional lability, depression, outbursts of anger, insomnia
  - Kidney: acute renal failure
- Autopsy:
  - Swollen kidney with dark pyramids, atrophy of cerebral cortex and cerebellum
- Microscopic:
  - Neuronal loss and gliosis
- Mechanism:
  - Precipitation of proteins and inhibition of multiple enzyme systems, such as oxidative mitochondrial phosphorylation, and cytochrome *C* oxidase

Cobalt

- Source:
  - Industry, medication, beer, radioactive cancer therapy
- Route:
  - Ingestion, inhalation, radiation
- Toxicity:
  - Nausea, vomiting, paralysis, hypotension
- Autopsy:
  - Hemorrhage in liver and adrenal glands, renal and pancreatic degeneration, pericardial effusions, cardiac dilatation and hypertrophy (beer drinker's heart disease)
- Microscopic:
  - Sudanophilic droplets in myocardium
- Mechanism:
  - Inhibition of enzymes, alpha-ketoglutarate dehydrogenase, and pyruvate dehydrogenase

Thallium

- Source:
  - Medication, over-the-counter preparation, pesticides
- Route:
  - Ingestion
- Toxicity:
  - Alopecia with sparing of axillary, facial hair, and inner $^1/_3$ of eyebrows, abdominal pain, vomiting, and ataxia
- Autopsy:
  - Alopecia
- Microscopic:
  - Degenerative changes in the neurons and nerve fibers

Other Chemicals

Organophosphates

- Source:
  - Insecticides
- Route:
  - Inhalation, ingestion, and absorption
- Toxicity:
  - Muscular paralysis, respiratory failure, blurred vision, salivation, sweating, and convulsions
- Autopsy:
  - Nonspecific
- Mechanism:
  - Cholinesterase inhibition with accumulation of acetylcholine (look for decreased cholinesterase in blood)

Strychnine

- Source:
  - Rodenticides
- Route:
  - Ingestion, injection, inhalation
- Toxicity:
  - Stimulant, seizures (sardonic rigor), muscular paralysis
- Autopsy:
  - No specific finding
- Mechanism:
  - Blockade of post synaptic neuronal inhibition
- Lethal dose:
  - 60–100 mg

Freons

- Source:
  - Air conditioners, refrigerators, aerosol cans
- Route:
  - Inhalation
- Toxicity:
  - Arrhythmias, central nervous depression, simple asphyxia
- Autopsy:
  - No specific findings

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4

Diagnostic Electron Microscopy

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CONTENTS

I. Introduction....4-2
II. The Nucleus....4-2
III. The Cytoplasm....4-2
IV. The Cell Surface (Plasmalemma)....4-10
V. The Extracellular Constituents....4-12
VI. Diagnostically Useful Ultrastructural Features of Neoplasms....4-12
VII. The Glomerulopathies....4-18
Glomerulonephritides Characterized by Immune-Type Dense Deposits....4-18
Glomerulopathies in which Immune-Type Dense Deposits Are Absent or Scant....4-19
Glomerulopathies Characterized by Distinctive Ultrastructural Deposits....4-19
Glomerulopathies with Structural Abnormalities of the Basement Membrane....4-20
Glomerulopathies Associated with Vascular Endothelial Injury....4-20
VII. Suggested Reading....4-20

INTRODUCTION

- In 1986 Ernst Ruska was awarded with the Nobel Prize in Physics for his pioneering work in the development of the electron microscope. The electron microscope, with its power of resolution, opened up the smaller new world of biology. Its diagnostic utility in anatomic pathology was contested by advanced immunohistochemical and molecular genetic techniques in recent years. The electron microscope still remains a useful tool in selected instances of tumor diagnosis and renal biopsy interpretation. The main contribution of the electron microscopy has been and will continue to be to the understanding of the structure–function relationships at the subcellular level
- In analyzing tumors, we must be always reminded of the fact that most of the diagnostically useful ultrastructures are phenotypic differentiation markers of a cell lineage, not tumor-specific, and that they are subject to interobserver discordance, sample bias and technical artifact

THE NUCLEUS

- Chromatin pattern:
  - Euchromatin (finely and evenly dispersed):
    - Actively dividing immature cells
    - Examples: seminoma, Ewing's sarcoma, undifferentiated (lymphoepithelioma-like) carcinoma
  - Heterochromatin (condensed, clustering):
    - Resting, inactive cells
    - An increased number and size of condensed chromatin clumps in an enlarged nucleus and an enlarged nucleolus are a fairly common finding of various malignant neoplasms
- Nuclear configuration:
  - Extreme cerebriform irregularity:
    - Examples: Sézary syndrome and mycosis fungoides, dermatofibrosarcoma protuberans, fibroadenoma of the breast
  - Elongated and corrugated contour:
    - Examples: smooth muscle neoplasms
  - Numerous nuclear pockets:
    - Examples: lymphoma and lymphocytic leukemia
  - Cleaved or cleft nuclear envelope:
    - Examples: lymphoma and lymphocytic leukemia, thyroid papillary carcinoma, Brenner tumor, granulosa cell tumor **(Figure 1)**, urothelial (transitional cell) neoplasm
- Nuclear inclusions:
  - Viral particles (virions):
    - Round, elliptical or strand-like structures having a central dense core (nucleoid) and an outer shell (capsid)
    - Examples: Papovavirus (45–53 nm), Adenovirus (70–90 nm), Herpes (100–150 nm; simplex, Varicella-zoster, Cytomegalovirus **(Figure 2)**, Epstein-Barr virus), Poxvirus (220–450 nm), hepatitis B virus (42 nm), human immunodeficiency virus (HIV, 100–130 nm)
    - For identification of a specific virus, an immunohistochemical or molecular genetic study (such as in situ hybridization) is needed
  - Intranuclear glycogen:
    - Examples: liver cells in diabetes, glycogen storage disease, Wilson's disease, and hepatocellular tumor
  - Intranuclear tubular inclusions:
    - Examples: hyperplastic or neoplastic type II pulmonary alveolar cells
- Nucleolus:
  - Multiple pleomorphic enlarged nucleoli:
    - A common finding in various malignant tumors
  - Inconspicuous nucleoli:
    - A common finding in resting, inactive cells
    - Examples of tumor: small cell carcinoma, neuroblastoma, Ewing's sarcoma
  - Anastomosing rope-like nucleolus:
    - An example: seminoma (dysgerminoma)

THE CYTOPLASM

- Mitochondria:
  - Tubulo-vesicular cristae:
    - Typically seen in steroid producing cells, such as adrenal cortical adenoma **(Figure 3)**, Leydig cell tumor, ovarian hilus cell tumor, luteoma of pregnancy, thecoma, sex-cord stromal tumor and granulosa cell tumor
  - Giant mitochondria (megamitochondria):

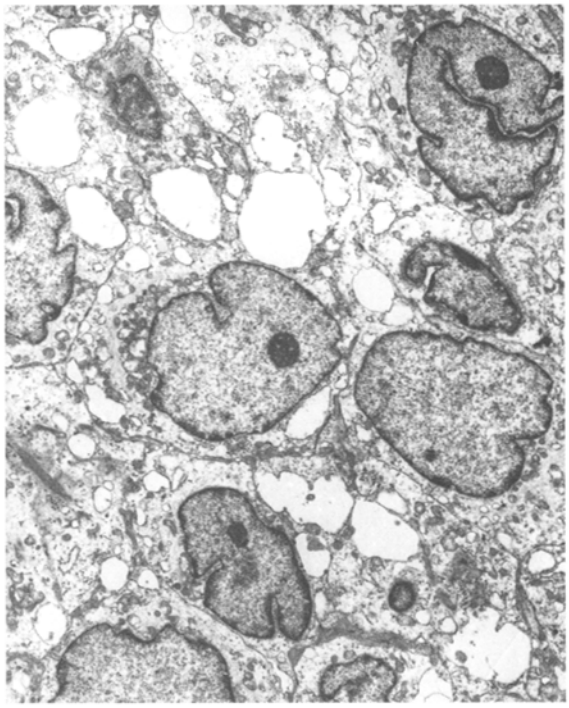


Fig. 1. Granulosa cell tumor.

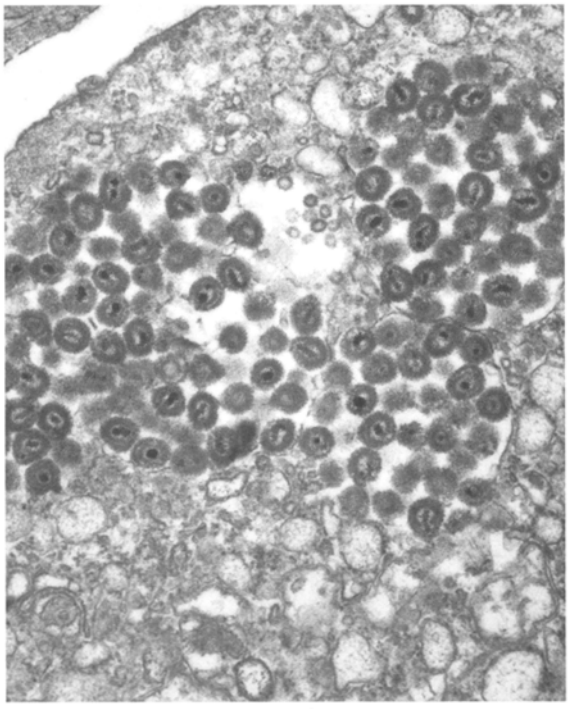


Fig. 2. CMV virus particles.

- Certain adenomas of the pituitary, thyroid, salivary glands
- Secretory endometrial glands
- Alcoholic liver cells

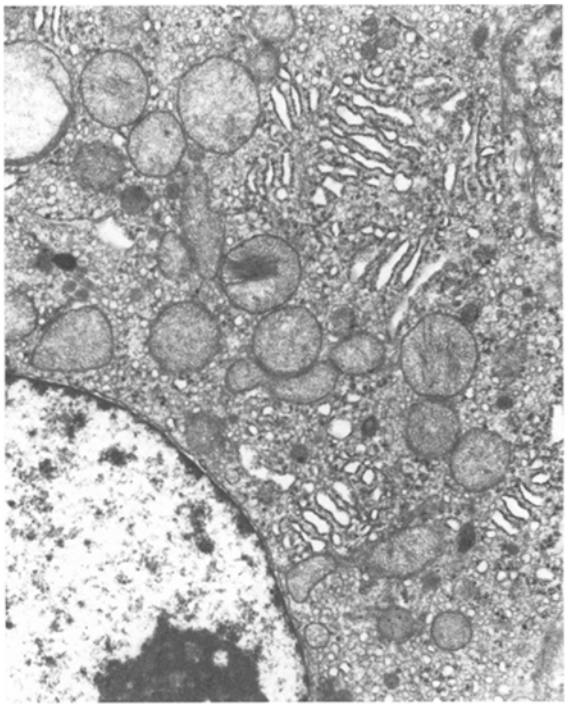


Fig. 3. Aldosteronoma (aldosterone secreting adrenal cortical adenoma).

- Abundant mitochondria:
  - Cells with excess mitochondria are called oncocytes
  - Oncocytoma of thyroid gland (also called Hürthle cell neoplasm), salivary gland, parathyroid, kidney **(Figure 4)** and bronchial gland
  - Warthin's tumor
- Mitochondrial myopathies:
  - Increased numbers of mitochondria that are often unusually large and abnormally-shaped, having abnormal cristae and crystalloid inclusion bodies
  - A heterogeneous group of myopathies with mitochondrial abnormalities being a common denominator; a clinical correlation is always needed to reach a clinically relevant diagnosis

♦ Increased free ribosome and polyribosome:
- Immature blastic or undifferentiated tumor cells; e.g. Ewing's sarcoma, seminoma, lymphoblastic lymphoma, undifferentiated (lymphoepithelioma-like) carcinoma, Burkitt's lymphoma

♦ Increased granular endoplasmic reticulum:
- Cells synthesizing proteins for export; e.g. plasma cells, multiple myeloma, immunoblastic lymphoma, acinic or acinar cell carcinoma (salivary gland and pancreas), hepatocellular adenoma and carcinoma, fibroma, fibrosarcoma, malignant fibrous histiocytoma, chondroid tumors and osteoblastic tumors

♦ Tubulo-reticular structures (inclusions) **(Figure 5)**:



Fig. 4. Oncocytoma.



Fig. 5. Tubulo-reticular inclusion.

- Modified endoplasmic reticulum system, present often with cylindrical confronting cisternae
- Seen in vascular endothelial cells, lymphocytes, monocytes of patients with increased α and β interferon; e.g., acquired immunodeficiency syndrome (AIDS), systemic lupus erythematosus and scleroderma
- Increased smooth endoplasmic reticulum:
  - Steroid secreting cells; e.g., sex cord stromal tumors, granulosa cell tumor, thecoma, Sertoli–Leydig cell tumor, hilus cell tumor of the ovary, Leydig cell tumor of the testis and adrenal cortical tumors
  - Hepatocellular adenoma and carcinoma
  - Liver cells of patients with protracted use of barbiturate
- Lysosomes:
  - Primary lysosomes (0.25–0.5 μm)—Membrane-limited dense bodies, sometimes mistaken as neurosecretory dense core granules
  - Secondary lysosomes (autophagosome, heterophagic vacuoles, residual bodies, or lipofuscin pigment)
    - Lysosomes containing intracellular metabolic products or phagocytosed extracellular material
  - Abundant lysosomes:
    - Granular cell tumor (**Figure 6**), granular cell ameloblastoma, congenital epulis, thyroid follicular neoplasm, prostatic adenocarcinoma, myelocytic or monocytic leukemia
  - Michaelis–Guttmann bodies:
    - Multilaminated, calcified spherules formed in secondary lysosomes, often containing calcium apatite crystals
    - Found in macrophages of malakoplakia
  - Lamellar lysosomal inclusions or myelinosomes:
    - *See* below (lamellar inclusions)
  - Lysosomal storage diseases:
    - Accumulation of secondary lysosomes containing various types of dense materials including myelinosomes, in parenchymal cells and/or macrophages, genetically transmitted as autosomal recessive disease; e.g., Tay–Sachs disease, Fabry's disease (**Figure 7**)
- Ribosome-lamella complex:
  - Several layers of parallel cylindrical lamellae, separated by ribosome like granules
  - Most commonly seen in patients with hairy cell leukemia
  - Also described in various other neoplasms and disorders; e.g., chronic lymphocytic leukemia, various lymphomas, reactive lymph node, adrenal cortical adenoma, insulinoma, Sertoli cell tumor, meningioma and glioma
- Mucus granules (0.7–1.8 μm):
  - Membrane-limited granular, reticulated, or flocculent material of various density
  - Electron microscopy does not differentiate various types of mucins; for this purpose, histochemical and immunohistochemical studies are needed

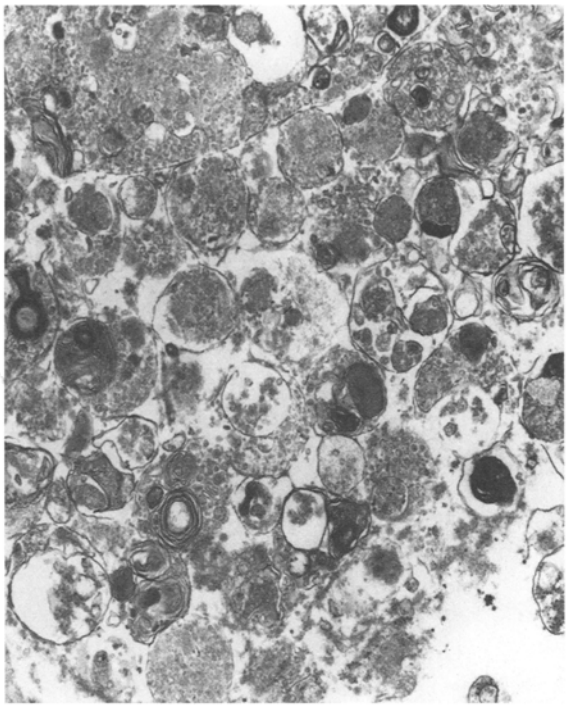


Fig. 6. Granular cell tumor.

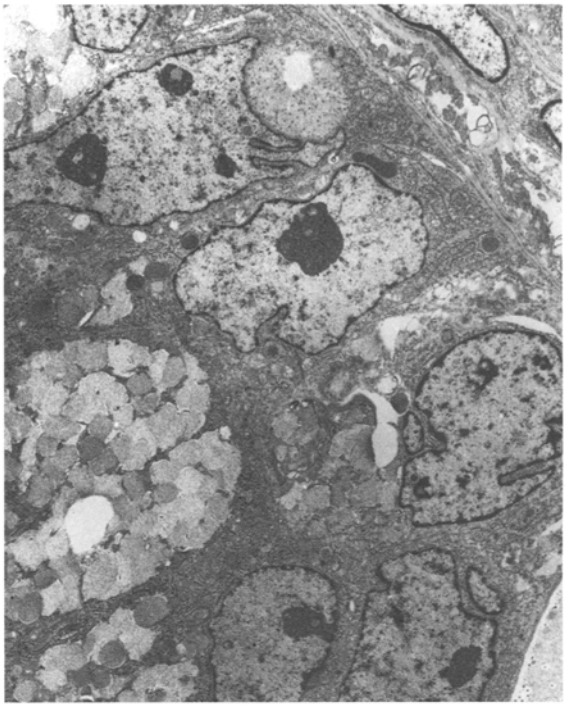


Fig. 8. Adenocarcinoma of lungs, mucin cell type.

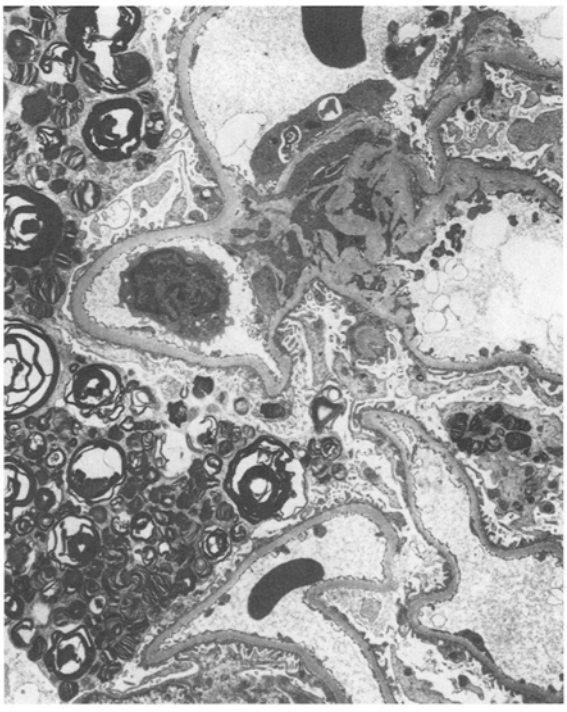


Fig. 7. Fabry's disease affecting glomerular podocyte.

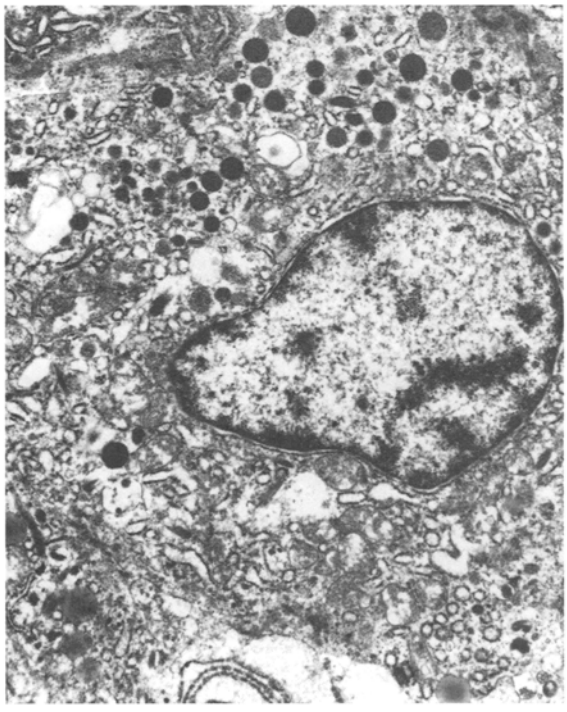


Fig. 9. Acinic cell carcinoma.

- Seen in mucin-producing acinar or ductal epithelial cells of normal and neoplastic exocrine glands **(Figure 8)**

♦ Serous or zymogen granules (0.5–1.5 μm):

- Membrane-limited, dense granular matrix, may or may not contain enzymes
- Exocrine gland (pancreatic acinar cells, serous acinic cells of salivary gland **(Figure 9)**, serous glands of the

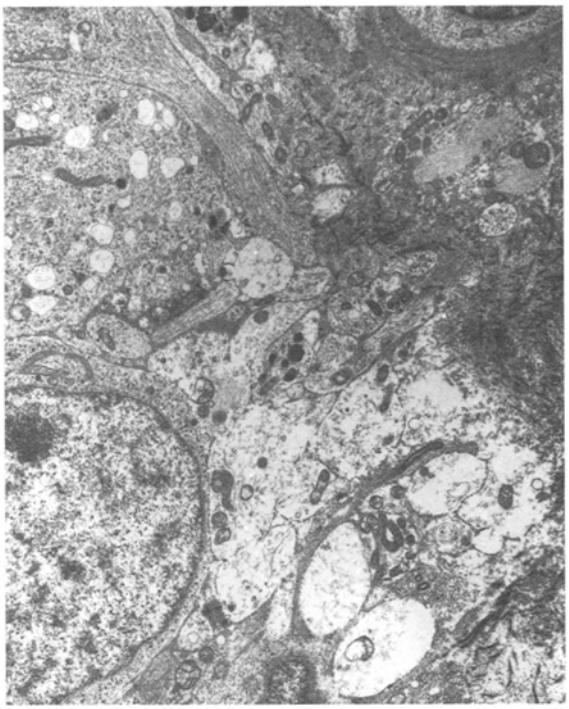


Fig. 10. Neuroblastoma.

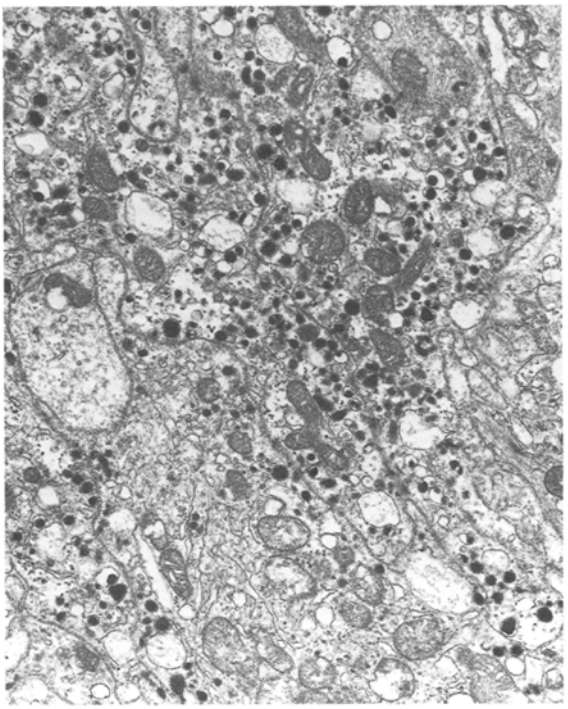


Fig. 11. Pheochromocytoma.

upper respiratory tract) tumors, gastric chief cells, Paneth cells:

- Caveat—A histological designation of serous tumor does not necessarily mean that the cells have serous or zymogen granules. Ovarian serous tumors occasionally contain a few small mucus, rather than serous granules. Serous cystadenoma (microcystic) of the pancreas has abundant glycogen and rare apical seretory granules

♦ Neurosecretory, dense core (or neuroendocrine) granules:

- Membrane-limited dense core granules vary in size, shape and density (50–400 nm)
- In neuroblastoma **(Figure 10)**, esthesioneuroblastoma, ganglioneuroblastoma, 100 nm round dense core granules are more concentrated in cell processes than in cell bodies
- Pheochromocytoma **(Figure 11)**—two cell types, one with eccentric dense cores (norepinephrine) and the other (epinephrine) with centrally located spherical cores, resembling granules of neuroblastoma
- Paraganglioma **(Figure 12)**—spherical granules (100–200 nm)
- Carcinoid tumor **(Figure 13)**—serotonin-secreting pleomorphic granules
- Medullary thyroid carcinoma—two types of calcitonin-containing granules, type I—large, medium-dense and with no halo, and type II—small, very dense and with halo
- Merkel cell tumor (cutaneous neuroendocrine carcinoma)—small spherical granules (115–200 nm)

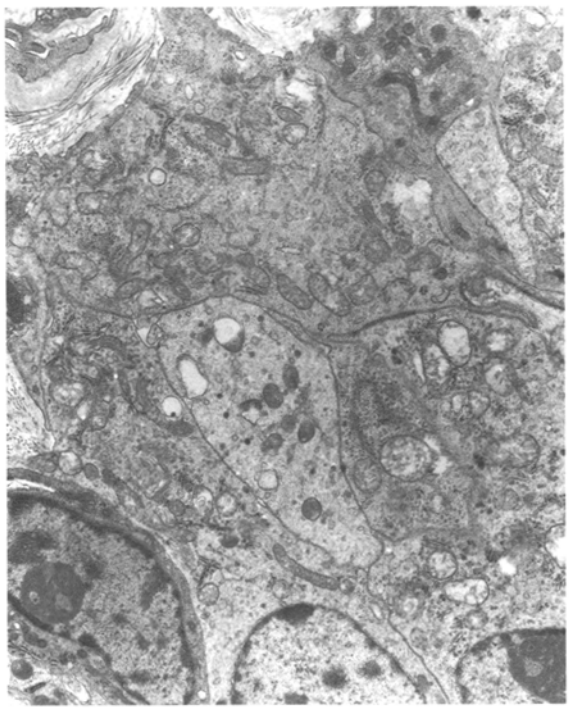


Fig. 12. Middle ear paraganglioma.

- Pulmonary tumorlet—Dense core granules similar to those of carcinoid tumor
- Small **(Figure 14)** and large cell neuroendocrine carcinoma—sparse dense core granules

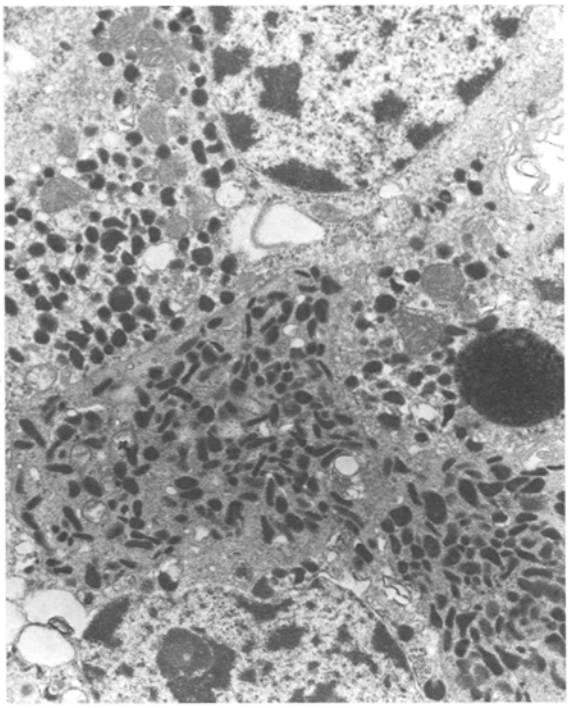


Fig. 13. Carcinoid tumor.

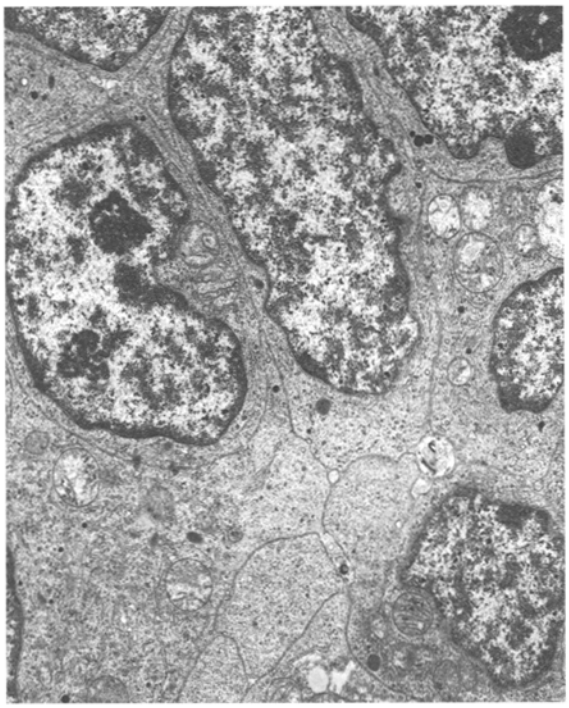


Fig. 14. Small cell neuroendocrine carcinoma.

- Renal juxtaglomerular cell tumor—spherical or rhomboid granules

♦ Glycogen:
- Often washed away in routine preparation

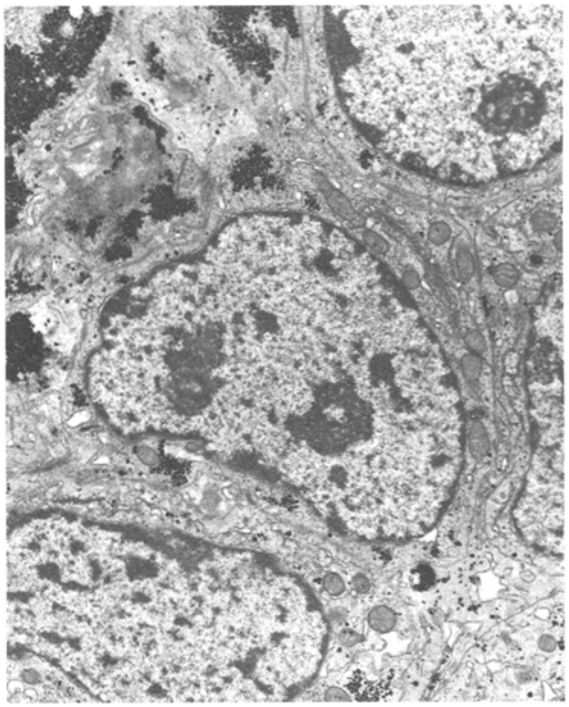


Fig. 15. Ewing's sarcoma.

- Two-forms:
  - β glycogen; irregular shaped 15–30 nm particles
  - α glycogen; rosette-like aggregates (prominent in the liver)
- Abundant in Ewing's sarcoma (**Figure 15**), seminoma, rhabdomyosarcoma, yolk sac tumor, clear cell adenocarcinoma of the breast, vagina, endometrium, ovary (**Figure 16**), salivary gland and kidney; clear cell sarcoma, sugar tumor of the lung, some hepatocellular adenoma and carcinoma:
  - Caveat—Water-clear cells of a parathyroid adenoma contain numerous small vesicles, not glycogen

♦ Lipids:
- Lipid droplets are not limited by a membrane
- In adipose tissue, normal and neoplastic
- Hibernoma contains abundant lipid droplets and mitochondria
- Steroid-secreting tumors—thecoma, ovarian hilus cell tumor, Leydig cell tumor (**Figure 17**), adrenal cortical tumors—contain numerous lipid droplets
- Also present in sebaceous gland tumor, renal clear cell carcinoma, xanthoma, fibrohistiocytoma

♦ Crystals of Reinke (**Figure 17**):
- Hexagonal prism-like, highly ordered 10 nm thick filaments, not limited by a membrane
- Seen in Leydig cells, ovarian hilus cells
- Crystals found in 35% of Leydig cell tumors

♦ Charcot–Böttcher "crystalloids":

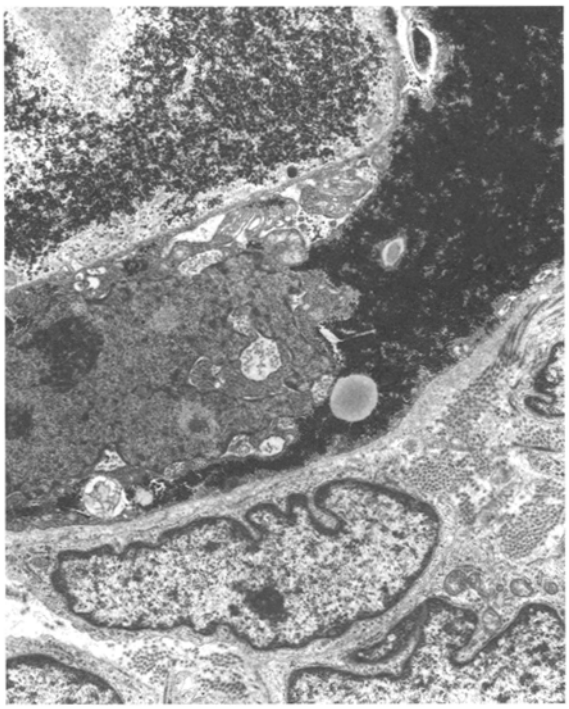


Fig. 16. Clear cell adenocarcinoma of ovary.

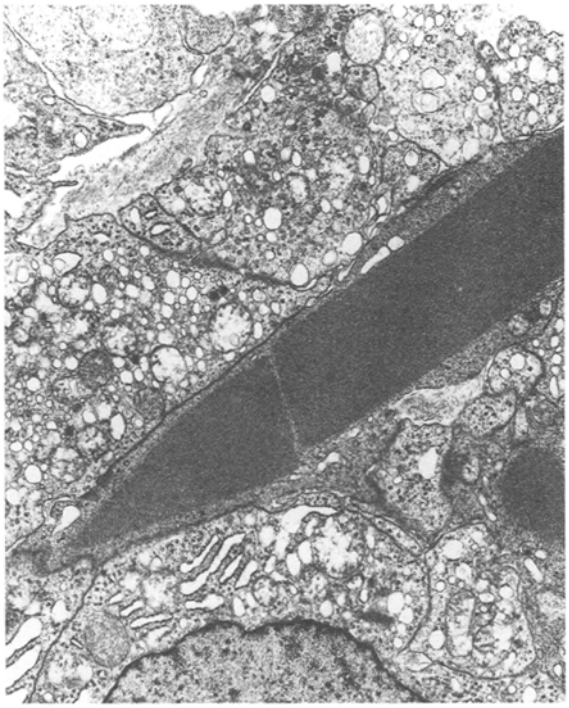


Fig. 17. Leydig cell tumor Reinke crystal.

- Closely packed electron-dense, longitudinal arrays of fibrils or tubules lacking a geometric crystalline lattice in postpuberty Sertoli cells
- Described in an occasional case of Sertoli cell tumor

♦ Lamellar inclusion body (myelinosome) (**Figure 18**):

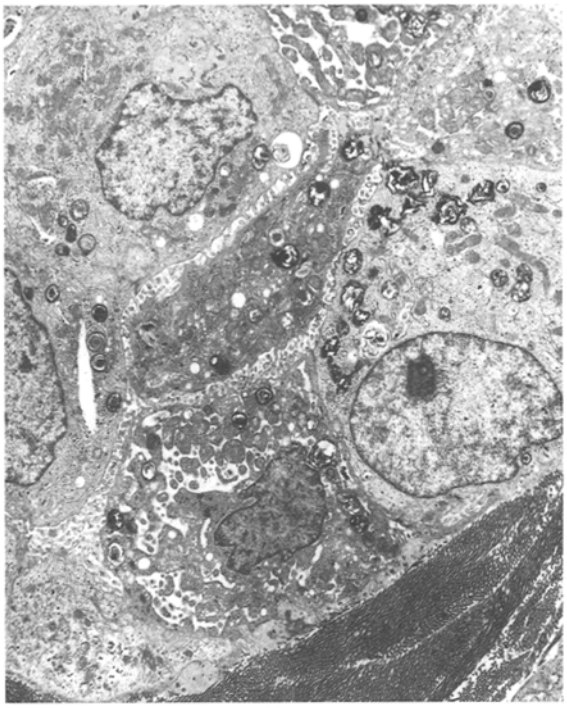


Fig. 18. Lamellar inclusion bodies in bronchiolo-alveolar carcinoma.

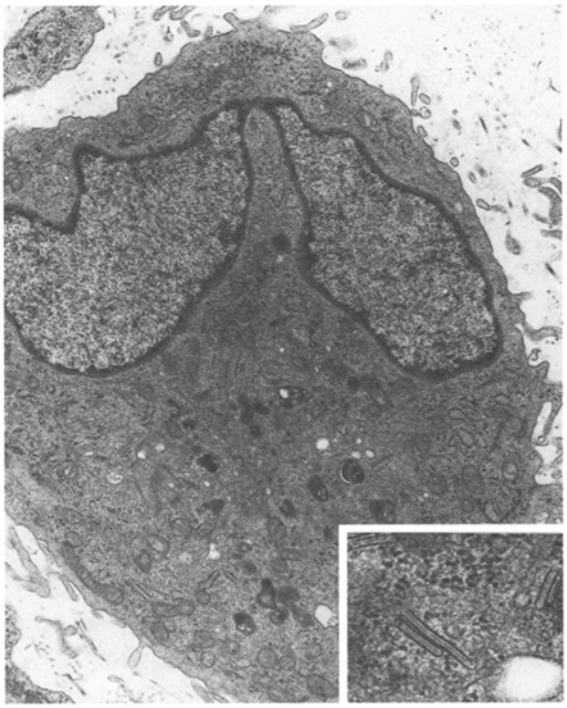


Fig. 19. Langerhans or Birbeck granules (Inset) in Langerhans histiocyte.

- Concentrically arranged, stacked electron-dense membrane
- Source of surfactant in type II alveolar cells

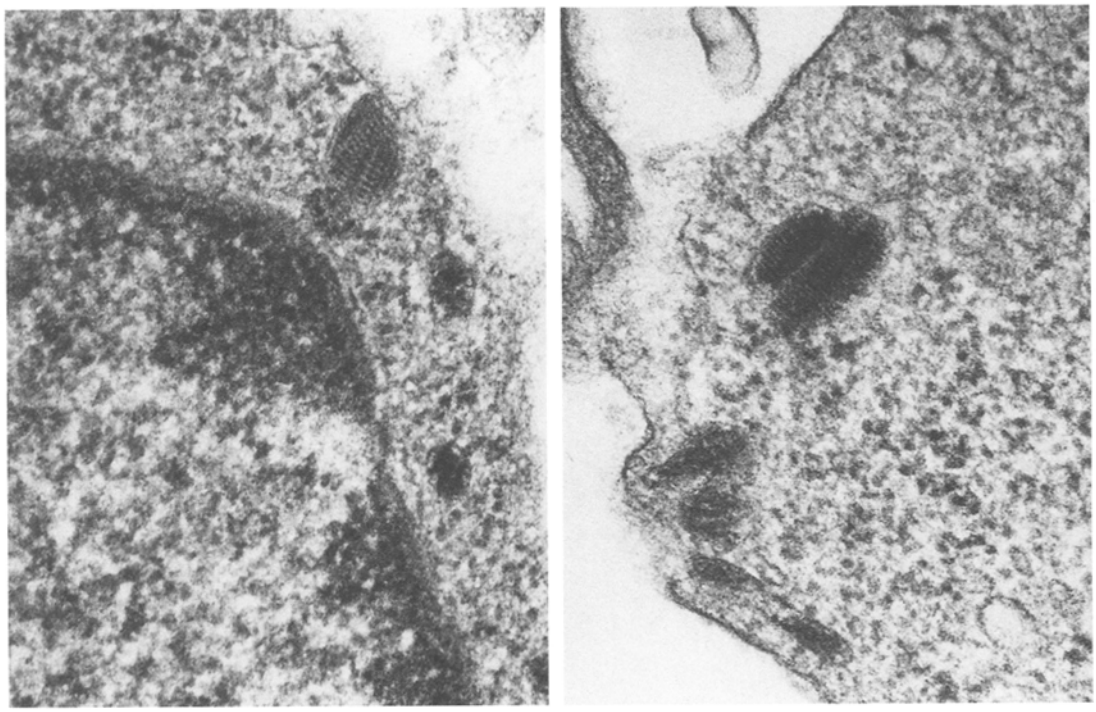


Fig. 20. Melanosomes.

- A metabolic (not necessarily toxic, as claimed initially) product of many drugs including amiodarone and gentamycin
- Seen in bronchiolo-alveolar carcinoma and lysosomal storage diseases

♦ Langerhans cell granule (Birbeck granule) **(Figure 19)**:
- A 34 nm wide rod-shaped structure of variable length with a periodic or striated zipper-like core
- The limiting membrane is often dilated at one end giving the granule a tennis racket-like appearance
- Positive for CD1 antigens and S-100 protein
- Seen in Langerhans cell histiocytosis (eosinophilic granuloma, Letterer–Siwe disease, Hand–Schüller–Christian disease)
- Absent in follicular dendritic and interdigitating dendritic cells

♦ Melanosome **(Figure 20)**:
- Matures stepwise from Stage I to IV
- Stage II–III melanosomes are most characteristic, consisting of ovoid or ellipsoidal vesicles with striated internal structures
- As melanin pigment deposits, the internal structure turns invisible
- Seen in melanocytic neoplasms

♦ Weibel–Palade body **(Figure 21)**:
- A rod-shaped body with microtubular internal structures embedded in dense matrix
- Seen in blood vessel endothelial cells but not in lymphatic endothelial cells
- Seen in benign vasoformative tumors, and epithelioid hemangioendothelioma
- Not usually found in malignant vasoformative tumors, such as angiosarcoma, Kaposi's sarcoma

♦ Cytoplasmic fibrils/filaments:
- Microtubules; 25 nm wide:
  - Axonemes of cilia
  - Neurotubules in neuronal cell tumors (neuroblastoma, ganglioneuroma, primitive neuroectodermal tumor), schwannoma
  - Intracisternal microtubules—described in melanoma and myxoid chondrosarcoma
- Thick filaments (muscle myosin); 15 nm wide:
  - In striated muscle cells, thick and thin myofilaments are set side by side
- Intermediate filaments; 10 nm wide:
  - Cytokeratin, vimentin, desmin, glial filaments, and neurofilaments; with the exception of tonofibrils (cytokeratin forming characteristic dense curvilinear bundles **[Figure 22]**), they are not distinguishable by electron microscopy
- Actin microfilaments; 6 nm wide:
  - Found in smooth and striated muscle cells, myofibroblast, myoepithelial cell
- Nemaline rod:



Fig. 21. Weibel-Palade bodies of endothelial cells.

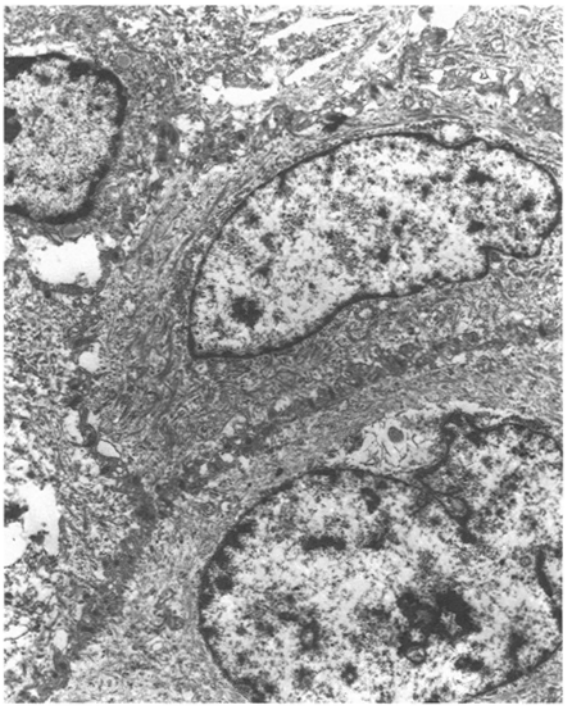


Fig. 22. Squamous cell carcinoma.

- First described in nemaline myopathy; it has been seen in muscular dystrophy and polymyositis
- Thread-like or oblong structures having a lattice-like appearance, found beneath the sarcolemma

– Mallory's hyalin or body:

- An irregularly shaped accumulation of cytokeratin intermediate filaments in liver cells
- Seen in alcoholic and nonalcoholic steato-hepatitis, Wilson's disease, various cholestatic conditions
- Also described in hepatocellular carcinoma

THE CELL SURFACE (PLASMALEMMA)

♦ Interdigitating complex cell membranes:

– Common in glandular epithelial tumors (gastrointestinal adenocarcinomas, parathyroid adenomas and sweat gland tumors), epithelioid sarcoma, meningothelial meningioma and schwannoma

♦ Cilia:

– Respiratory epithelial cilia on cross section show a pair of centrally located microtubules and nine pairs of doublets at the periphery (9+2 pattern). Outer and inner dynein arms extend from each doublet

– In primary ciliary dyskinesia (or immotile cilia syndrome), outer and/or inner dynein arms are completely or almost completely absent. Those males with this defect are infertile, and other patients may have Kartagener's syndrome

– Cilia are lost in malignant tumors. Various abnormalities of the cilia are described in benign epithelial tumors. They are not useful in differential diagnosis

♦ Pinocytotic vesicles:

– Seen in well-differentiated smooth muscle, vascular endothelial and perineurial tumors

♦ Microvilli:

– Closely packed rigid microvilli (brush border), characteristic anchoring rootlets and glycocalyx; seen in adenocarcinoma of gastrointestinal tract and intestinal-type adenocarcinoma of other sites

– Long, branching, shaggy microvilli—in mesothelial cell and mesothelioma **(Figure 23)** (epithelial type)

– Microvillus inclusion disease

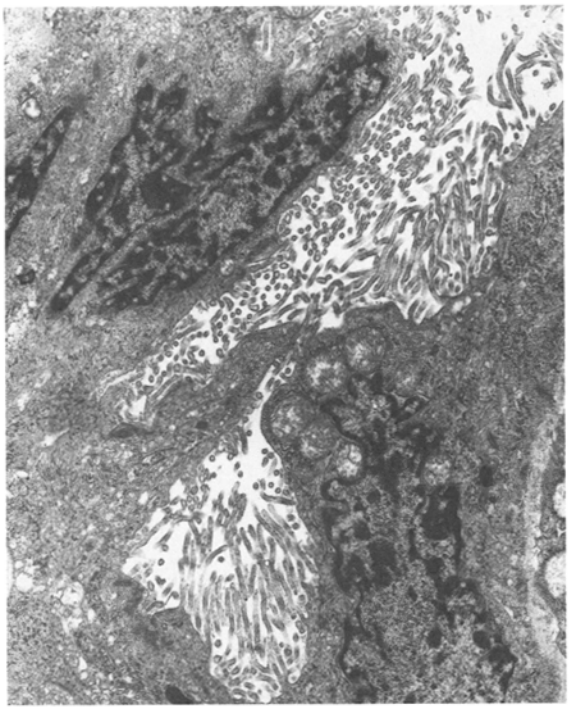


Fig. 23. Mesothelioma.

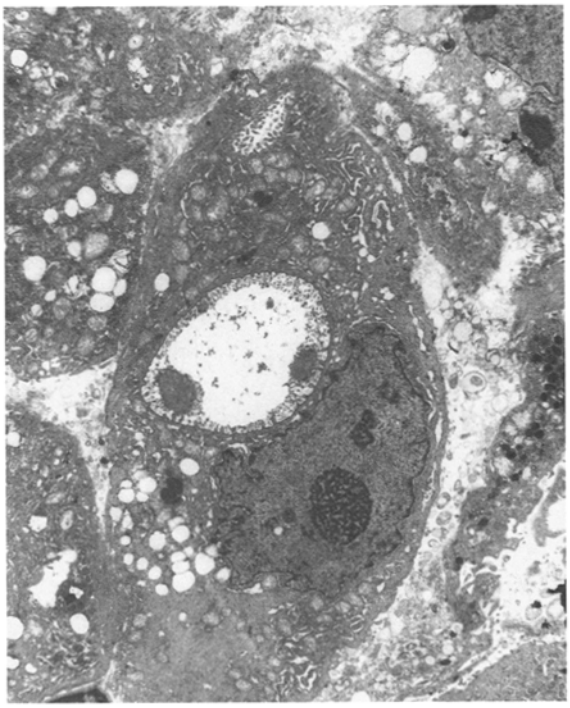


Fig. 24. Ductal breast carcinoma.

- An inherited, autosomal recessive condition, presenting with intractable diarrhea and steatorrhea
- Usually fatal in 2 years

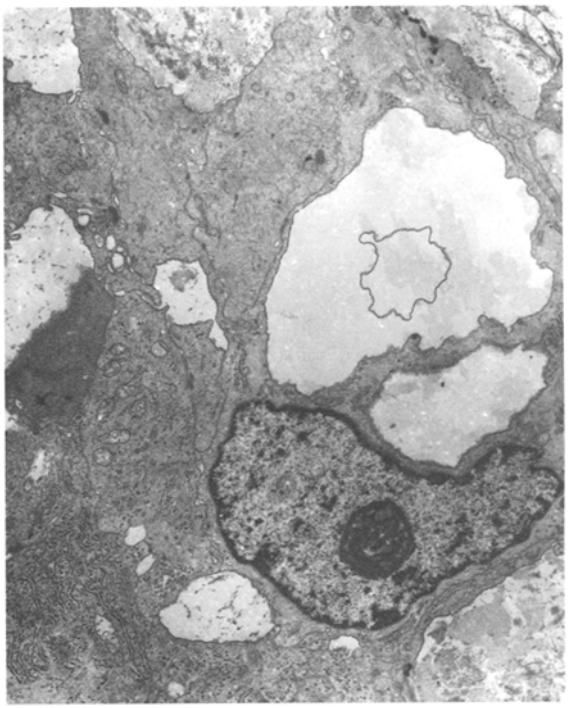


Fig. 25. Epithelioid hemangioendothelioma.

- Histologically may resemble celiac sprue
- Electron microscopy is diagnostic; (1) Abnormal microvilli at the luminal aspect of the enterocyte; (2) apical intracytoplasmic inclusions lined by microvilli

♦ Intracytoplasmic lumens:
- Their presence associated with microvilli is a useful marker for adenocarcinoma
- Prominent in breast carcinoma (**Figure 24**) (both ductal and lobular)
- However, they are also found in adenocarcinomas of the lung, mesotheliomas, meningiomas and neuroendocrine tumors

♦ Cell Junctions:
- In general, the number of intercellular junctions are reduced in tumor cells compared with the normal counterpart; they tend to be rudimentary
- Cell junctions of various types are found in all benign and malignant epithelial tumors, meingothelial meningiomas, thymomas, mesotheliomas, endocrine gland tumors, neuroendocrine tumors, germ cell tumors, sex cord stromal tumors, epithelioid sarcoma, epithelial component of synovial sarcoma, and vascular endothelial cell and its tumors (**Figure 25**)
- In most other mesenchymal tumors, cell junctions are poorly developed, primitive or inconspicuous
- In leukemia, granulocytic sarcoma and lymphoma, cell junctions are absent (one exception being follicular dendritic cell tumor)

THE EXTRACELLULAR CONSTITUENTS

- Luse bodies:
  - Fusiform long-spacing collagen fibers with a periodicity of 100–150 nm
  - Seen most characteristically in schwannoma
- Amianthoid fibers:
  - Giant collagen fibers with diameter up to 10 times of normal collagen fibrils (60 nm)
  - Detected in chondrosarcoma, synovial sarcoma, neurogenic sarcoma and meningioma
- Skeinoid fibers:
  - Tangles of curvilinear fibrils with a periodicity of 41–48 nm
  - Described in neurogenic spindle cell tumors and gastro-intestinal autonomic nerve tumors
- Amyloidosis and amyloidoma:
  - A β-pleated sheet configuration
  - Congo-red positive, birefringent under polarized light
  - Haphazardly arranged, nonbranching fibrils with a diameter of 7 to 10 nm
- Differential diagnosis between bullous pemphigoid and acquired epidermolysis bullosa:
  - The bulla in bullous pemphigoid lies in the lamina lucida, and the anchoring fibrils are normal; while the bulla in acquired epidermolysis bullosa occurs below the lamina densa, and the anchoring fibrils are totally absent or markedly reduced

DIAGNOSTICALLY USEFUL ULTRASTRUCTURAL FEATURES OF NEOPLASMS

- *See* **Tables 1** and **2**
- Acinic cell carcinoma of the salivary gland and acinar cell carcinoma of the pancreas (**Figure 9**):
  - Membrane-limited electron-dense round zymogen granules (0.3–1.5 μm)
  - Stacked rough endoplasmic reticulum
  - Well developed Golgi apparatus
  - Occasional small lumens lined by microvilli and juxtaluminal junction complexes
- Adenoid cystic carcinoma (salivary gland, breast, upper airway, skin):
  - Clusters of polygonal cells forming microcystic spaces containing multi-layered basal lamina, flocculent matrix and microfibrils
  - Three type of cells are identified:
    - Undifferentiated, with a high nucleus/cytoplasm ratio and organelle-poor cytoplasm
    - Myoepithelial cells, with thin (actin) filaments condensed against cell membrane, facing the microcystic space that is lined by basal lamina
    - Ductular cells, forming true lumens lined by microvilli and held by junctional complexes
- Adenoma and adenocarcinoma (tumors of exocrine glandular epithelium in general):
  - True glandular lumen or intracytoplasmic lumen lined by microvilli (not specific; also seen in epithelial mesothelioma, choroid plexus papilloma, glandular component of synovial sarcoma, and neuroendocrine neoplasms)
  - Various cell junctions
  - A distinct basement membrane along the stromal interface (**Figure 4**)
  - A well-developed Golgi apparatus and exocrine secretory granules (mucus, serous, or zymogen)
  - Intermediate filaments (cytokeratin)
  - Interdigitation of cell membrane
  - In clear cell type, pools of glycogen particles
  - Characteristic features of intestinal type adenocarcinoma; rigid microvilli with prominent core rootlets, glycocalyx, junctional complex, and mucus granules
- Adipose neoplasms (lipomas and liposarcomas):
  - Lipid droplets
  - Pinocytotic vesicles
  - Basal lamina
  - Varying amounts of rough endoplasmic reticulum, intermediate filaments, mitochondria, and glycogen particles
- Adrenal cortical neoplasms (**Figure 3**):
  - Abundant smooth endoplasmic reticulum
  - Lipid droplets
  - Mitochondria with lamellar cristae (aldosteronoma), or with tubulovesicular cristae (cortisol-secreting tumor)
- Spironolactone bodies:
  - Spherical laminated whorls of smooth membrane resembling surfactant myelinosomes
  - Seen in zona granulosa cells of patients treated with the aldosterone antagonist, spironolactone
- Black adenoma of the adrenal cortex

Table 1. Small Round Cell Tumors

	Neuroblastoma	*Neuroendocrine tumor*	*Ewing's sarcoma*	*PNET*	*Rhadomyo-Sarcoma*	*Lymphoma*	*DRCTDD*
Glycogen	±	±	+	+	+	±	±
Dense core Granules	+	+	–	±	–	–	±
Cell junctions	+	+	+	+	+	–	+
Cytoplasmic filaments	+	+	±	+	+ thick and thin	±	+
Microtubules	+	–	–	±	–	–	–
Basal lamina	–	±	–	–	+	–	+
Others	Neuropil				Z-band		

+ present; - absent; ± occasionally present; PNET = primitive neuroectodermal tumor; DRCTDD = desmoplastic round cell tumor of divergent differentiation

Table 2. Large Cell Tumors

	Squamous Cell carcinoma	*Transitional Cell carcinoma*	*Adeno-carcinoma*	*Neuro-endocrine tumor*	*Melanoma*	*Lymphoma*	*Sarcoma*
Cell Junctions	+	+	+	+	–	–	±
Microvilli with Lumen	–	–	+	±	–	–	±
Filaments	+ tonofibrils	+	+	+	+	±	+
Secretory Granules	–	–	+	+	–	–	–
Golgi RER	+	+	+	+	+	–	+
Basal Lamina	+	+	+	+	–	–	±

RER=Rough Endoplasmic Reticulum + present; - absent; ± occasionally present

- Abundant lipofuscin inclusions in zona reticularis type cells of a usually nonfunctioning adenoma

♦ Alveolar soft part sarcoma:

- Golgi associated small dense granules (90 nm) and larger secretory granules (300 nm)
- Rhomboid crystals in the larger granules in about 50% of the cases
- Stacked rough endoplasmic reticulum, clusters of mitochondria, variable glycogen particles, lipid droplets and rare rudimentary cell junctions
- Basal lamina around groups of tumor cells

♦ Brenner tumor:

- Epithelial cells having the following features are present in the fibroma–thecoma-like background:

- Cleaved nuclei
- Varying numbers of glycogen particles, lipid droplets, lysosomes, and vesicles
- Intercellular spaces containing prominent microvilli
- Interdigitating cell membranes
- Numerous small desmosomes
- Basement membrane (basal lamina) enclosing the epithelial clusters
- The borderline tumors have secretory (mucus) cells and ciliated cells along the cystic cavities

♦ Bronchiolo-alveolar carcinoma:
- A pure or a mixture of type II pneumocytes, Clara cells and mucus-secreting cells:
  - Type II pneumocytes have surfactant myelinosomes and intranuclear microtubular inclusions **(Figure 18)**
  - Clara cells are nonciliated secretory cells of the terminal bronchioles, having electron-dense, apical granules (350–1200 nm). Many of them contain fingerprint-like internal structures
  - Mucus cells with abundant apical mucus granules and intestinal type microvilli

♦ Carcinoid **(Figure 13)**/islet cell tumors:
- Nests of oval or spindle cells, surrounded by basal lamina
- Occasionally the nests have a lumen with microvilli
- Desmosomes and intermediate filaments
- Numerous cytoplasmic neurosecretory dense-core granules

♦ Chondroid tumors (chondroma and chondrosarcoma):
- Scalloped cell surface
- Abundant rough endoplasmic reticulum
- Occasional clusters of glycogen, lipid and intermediate filaments
- No basal lamina

♦ Cholangiocarcinoma:
- Intestinal type microvilli on the luminal surface
- Mucus granules, abundant free ribosomes, scanty rough endoplasmic reticulum
- No glycogen
- A continuous basement membrane, often surrounded by a densely collagenous stroma

♦ Clear cell adenocarcinomas of the vagina, cervix, endometrium and ovary **(Figure 16)**:
- Abundant cytoplasmic glycogen
- Short and blunt microvilli
- Junction complexes
- Stacks of rough endoplasmic reticulum
- Microcysts, tubules and papillae lined by hobnail, cuboidal cells or solid areas of polygonal cells

♦ Clear cell renal carcinoma:
- Rich in both cytoplasmic glycogen and lipid droplets
- In contrast, chromophobe cell renal carcinoma contains numerous cytoplasmic vesicles of unknown origin
- Microlumen formation, sparse microvilli, primitive cell junctions, and basal lamina around groups of cells

♦ Clear cell sarcoma of tendons and aponeurosis:
- Large pools of glycogen particles
- In the majority, melanosomes **(Figure 20)** are found

♦ Desmoplastic small cell tumor with divergent differentiation:
- Small groups of epithelial cells joined by primitive desmosome-like junctions
- Irregularly-shaped nuclei, heterochromatin, inconspicuous nucleoli
- Abundant ribosomes, a prominent Golgi apparatus and bundles of intermediate filaments in the paranuclear region
- Occasional cells with glycogen and neurosecretory granules
- Basal lamina
- Collagenous stroma containing fibroblasts and myofibroblasts

♦ Embryonal carcinoma:
- A high nucleus/cytoplasm ratio, with large elongated or irregularly-shaped nuclei having clumped chromatin and large, often multiple nucleoli
- Abundant free ribosomes
- Mitochondria, aggregates of glycogen particles and intermediate filaments readily found
- In better differentiated areas, smooth and rough endoplasmic reticulum, desmosomes, gland lumens, junction complexes, microvilli, and basal lamina are seen

♦ Epithelioid sarcoma:
- Clusters of large polygonal cells having round or indented nuclei with coarse chromatin, multiple nucleoli and abundant cytoplasm
- Numerous intermediate filaments and occasional tonofibrils
- A moderate amount of mitochondria, ribosomes, and endoplasmic reticulum
- Cell junctions including desmosomes
- Rare discontinuous basal lamina around groups of tumor cells

♦ Ewing's sarcoma **(Figure 16)**:
- Sheets of uniform cells with large oval nuclei with smooth nuclear contour and finely dispersed chromatin
- Nucleoli are small or inconspicuous
- Numerous free ribosomes and aggregates of glycogen particles
- An occasional cell showing cytoplasmic filaments
- Primitive cell junctions

- Fibromas and fibrosarcoma:
  - Consisting of fibroblastic cells with abundant rough endoplasmic reticulum, a small number of mitochondria and a few bundles of intermediate filaments, and surrounded by collagen fibers
- Fibrous histiocytoma, benign and malignant:
  - Tumors of fibroblastic cells and modified fibroblasts having histiocytic features, giant or multinucleate fibroblastic cells and histiocytic cells
- Follicular dendritic cell neoplasm:
  - Oval or elongated nuclei with small amount of peripheral heterochromatin
  - Scant cytoplasmic organelles
  - Long cytoplasmic processes held together by desmosomes
  - No Birbeck granules found
- Gastrointestinal autonomic nerve (GAN) tumor:
  - A recently described, still controversial entity
  - Presented as a subgroup of gastrointestinal stromal tumors (GIST)
  - Consisting of spindle and epithelioid cells, often tightly arranged
  - Long, interdigitating cytoplasmic processes resembling axons
  - Intermediate filaments, microtubules and dense core granules
  - Bulbous synaptic vesicle-like structures
  - Small primitive cell junctions between the axonic processes
  - Aggregates of curvilinear collagen fibrils ("skeinoid fibrils") in the intercellular space
- Gastrointestinal stromal tumor (GIST):
  - A tumor consisting of spindle and epithelioid cells, tightly packed together, displaying ultrastructural features of muscle cell, Schwann cell, fibroblast, autonomic nerve cell or primitive mesenchymal cell
  - A subgroup with features of autonomic nerve cell, described under the name of GAN tumor (*see* above)
  - Skeinoid fibers may be seen between the cells
  - The majority of the cases having features of smooth muscle
- Granular cell tumor **(Figure 6)**:
  - Clusters of polygonal cells having abundant cytoplasm
  - Numerous pleomorphic phagolysosomes
  - Slender cytoplasmic processes joined by rare rudimentary junctions
  - Basal lamina around groups of tumor cells
- Granulosa cell tumor **(Figure 1)**:
  - Nests of oval cells in part surrounded by basal lamina, and joined by primitive desmosome-like junctions
  - In adult form, nuclei tend to be deeply indented and the nucleus/cytoplasm ratio is high
  - In juvenile form, the nucleus/cytoplasm ratio is low and the nucleus is not indented
  - In both types, cytoplasm is rich in lipid droplets and smooth endoplasmic reticulum; mitochondria have tubular or tubulovesicular cristae
- Hemangiopericytoma:
  - Spindle or polygonal cells arranged in a palisade around blood vessels
  - Basal lamina around tumor cells
  - Primitive cell junctions
  - Pinocytotic vesicles
  - Intermediate filaments in the cytoplasm
- Hepatocellular adenoma and carcinoma:
  - Intercellular canaliculi and intraluminal or cytoplasmic bile (homogeneous dense bodies, varying sized vesicles or membranous whorls)
  - Well-developed smooth endoplasmic reticulum and abundant mitochondria
  - Aggregates of intermediate filaments (Mallory bodies) or cytoplasmic dense, solid inclusions of α-1 antitrypsin in some cases
  - Glycogen particles and lipid droplets may be conspicuous
- Hilus cell tumor (of the ovary):
  - Ultrastructures are identical to those of testicular Leydig cells **(Figure 17)**
- Interdigitating dendritic cell neoplasm:
  - Large indented or pleomorphic nuclei with peripheral heterochromatin
  - Sparse cytoplasmic organelles
  - Interdigitating cytoplasmic processes with no desmosomes
  - No Birbeck (or Langerhans) granules
- Langerhans cell histiocytosis **(Figure 19)**:
  - Large mononuclear cells with filopodia
  - Birbeck or Langerhans granules (rod-shaped structures with striated core, sometimes with bulbous end giving a tennis racket-like appearance)
  - Primary lysosomes present but secondary lysosomes (phagolysosomes) usually absent
- Leukemia, myelocytic (granulocytic sarcoma) and myelomonocytic:
  - Primary cytoplasmic (azurophil) granules
  - Myeloperoxidase activity in the cytoplasmic granules
  - Auer rods (rod-shaped, membrane-limited structures with dense lamellar internal substructure, resulting from coalescence of azurophilic granules)
  - Absence of cell junctions

- Leukemia, lymphocytic:
  - Peripherally condensed heterochromatin
  - Rare, myeloperoxidase-negative primary lysosomes, but no secretory granules in the cytoplasm
  - No cell junctions
- Leukemia, hairy cell:
  - Small lymphoid cells with villus-like (hairy) cytoplasmic projections, best seen in blood sample
  - In spleen and lymph node, filopodia or cell processes are interdigitating
  - Ribosome-lamellar complexes, usually in the paranuclear location, found in 50% of the cases
- Leydig cell tumor of testis (and hilus cell tumor of ovary) **(Figure17)**:
  - Round nucleus, dispersed chromatin and medium-sized nucleolus
  - Abundant vesicles of smooth endoplasmic reticulum
  - Many lipid droplets
  - Mitochondria with tubulovesicular cristae
  - Microvilli covering the cell surface, basal lamina covering nonvillous surface
  - Reinke crystals are diagnostic but present in a minority of cases (35%)
- Lymphoepithelial (lymphoepithelioma-like) carcinoma or undifferentiated carcinoma of nasopharynx:
  - Clusters of polygonal cells with small primitive desmosomes
  - Tonofibrils
  - Prominent free ribosomes
- Lymphomas:
  - Nucleus with peripheral heterochromatin
  - Abundant free ribosomes
  - Absence of intercellular junctions
  - Stacks of rough endoplasmic reticulum in plasmacytoid and immunoblastic cells
  - Various nuclear configurations, round to indented, multilobated, cleaved, or cerebriform
  - In special types, the cell surface is covered with microvilli (filliform or anemone cell)
  - The cytoplasm may contain numerous vesicles (signet ring cell)
  - Nuclear pockets may be seen
- Malignant melanoma **(Figure 20)**:
  - Stage II and III melanosomes (elliptical membrane-limited structures with striated lamellar core, without or with dense melanin deposition)
  - Stage I (vesicles) and stage IV (heavily pigmented) melanosomes, and atypical melanosomes are not as specific as stage II and III melanosomes for diagnosis
  - Unusual findings rarely described, include basal lamina, microvilli, primitive cell junctions and intracisternal microtubules
- Meningioma:
  - Long, interdigitating cell processes with desmosomes and other forms of cell junctions
  - Numerous intermediate filaments
- Merkel cell carcinoma (cutaneous neuroendocrine carcinoma):
  - Dense core granules
  - Intercellular junctions
  - Aggregates of paranuclear intermediate filaments or tonofibrils
- Mesothelioma, epithelial cell type **(Figure 23)**:
  - Numerous, long slender microvilli with a height/width ratio of 10/1 or higher
  - No anchoring actin rootlets and no glycocalyx
  - Prominent intercellular junctions including desmosomes
  - Abundant intermediate filaments and tonofibrils
  - Basal lamina
  - Glycogen particles and intracytoplasmic lumens may be seen
- In spindle cell type or sarcomatous mesothelioma, a spectrum of cells; fibroblastic, myofibroblastic, mesothelial and other hybrid cells are seen
- Neuroblastoma **(Figure 10)**:
  - Oval cells with crowded cytoplasmic processes (neuropil)
  - Dense-core neurosecretory granules
  - Microtubules and intermediate filaments in cell processes
  - Primitive intercellular junctions and rare synaptic vesicles
- Neuroendocrine neoplasm, low grade (carcinoid, well differentiated neuroendocrine tumor)
- Neuroendocrine neoplasm, intermediate grade (atypical carcinoid, well-differentiated neuroendocrine carcinoma)
- Neuroendocrine neoplasm, high grade (small cell or oat cell carcinoma, large cell neuroendocrine carcinoma, Merkel cell carcinoma):
  - Oval or spindle cells often with polar processes
  - Dense core neurosecretory granules
  - Intercellular junctions
  - Intermediate filaments
- Oncocytomas, oncocytic neoplasms. *See* Mitochondria
- Osteoblastic neoplasms (osteoma, osteoblastoma, osteosarcoma):
  - Polygonal cells with scalloped cell surface
  - Abundant dilated rough endoplasmic reticulum

- Hydroxy-apatite deposits in the matrix containing woven type I collagen fibers (osteoid)
- Variable numbers of intermediate filaments, glycogen particles, lipid droplets and mitochondria

♦ Ovarian surface epithelial neoplasms:
- Serous tumors (benign, borderline, and malignant):
  - Glandular lumens and papillae
  - Microvilli and cilia
  - Junctional complexes
  - Basal lamina
  - Glycogen and rare secretory granules may be present
- Mucinous tumors:
  - Glandular lumens
  - Occasional papillae
  - Microvilli
  - Junctional complexes
  - Basal lamina
  - Mucus granules
- Endocervical type (uniform small secretory granules, fibrillogranular bodies and basal nuclei)
- Intestinal type (absorptive, goblet and neuroendocrine cells)
- Endometrioid tumors:
  - Tubular glandular lumens
  - Microvilli
  - Junctional complexes
  - Basal lamina
  - Paranuclear filaments
  - Abundant glycogen
  - Desmosomes and tonofibrils in the squamous morules
- Clear cell tumors (see clear cell adenocarcinoma above)
- Transitional cell tumors (Brenner tumors):
  - Cystic structures or solid sheets of large polygonal cells
  - Basal lamina
  - Intercelluar spaces lined by numerous microvillus-like projections without desmosomal junctions
  - Numerous pinocytotic vesicles
  - Short microvilli on the luminal surface
  - Junctional complexes
  - Nuclear membrane occasionally invaginated

♦ Paraganglioma and pheochromocytoma **(Figure 11, 12)**:
- Nests of polygonal cells surrounded by basal lamina
- Round (in paraganglioma) and pleomorphic (in pheochromocytoma) dense core granules
- Prominent Golgi apparatus
- Sustentacular (supporting Schwann-like) cells seen in paraganglioma but not in pheochromocytoma

♦ Primitive neuroectodermal tumor:
- Oval cells with polar processes
- Cytoplasm mostly with free ribosomes, focal intermediate filaments, occasional microtubules and rare dense cored granules
- Small intercellular junctions
- Irregularly shaped nuclei with heterochromatin and varying-sized nucleoli
- Glycogen may be found in the cytoplasm

♦ Rhabdoid tumor (renal and extrarenal):
- Loosely arranged collection of oval cells with irregularly-shaped nuclei and large nucleoli
- Large paranuclear whorls of intermediate filaments and occasional tonofibrils
- Rudimentary cell junctions

♦ Rhabdomyosarcoma (alveolar and embryonal):
- Thick (15 nm) myosin filaments with or without thin (6 nm) actin filaments
- Thick filament-ribosomal complexes
- Z-band formation
- Basal lamina (in alveolar but not embryonal type)
- Glycogen in the cytoplasm

♦ Schwannoma and malignant peripheral nerve sheath tumor:
- Spindle nuclei with heterochromatin and numerous interwoven cell processes surrounded by basal lamina
- No unique cytoplasmic organelles
- Secondary lysosomes may be seen
- Primitive cell junctions
- Luse bodies (long-spacing type I collagen fibers) may be found in the matrix

♦ Seminoma and dysgerminoma:
- Closely apposed large polygonal cells, held by various cell junctions, most often desmosome-like
- Large euchromatic nuclei and large rope-like nucleoli
- Abundant glycogen particles and scant organelles

♦ Sertoli cell tumor:
- Tubules lined by basal lamina
- Junctional complexes
- Well-developed Golgi
- Charcot–Böttcher filaments may be found
- Lipid droplets common

♦ Small cell carcinoma, pulmonary type—*see* neuroendocrine cell neoplasms above

♦ Small cell carcinoma, ovarian hypercalcemic type

- No dense core granules and no glycogen found
- Nests, cords, follicle-like groups of polygonal cells with intermediate junctions and desmosomes
- Dilated rough endoplasmic reticulum and numerous free ribosomes

♦ Squamous cell carcinoma (**Figure 22**):
- Desmosomes
- Tonofibrils
- Keratohyalin granules in well differentiated carcinoma
- Filopodia between cells, occasionally joined by desmosomes
- Basal lamina

♦ Synovial sarcoma:
- In a biphasic tumor, the epithelial components are surrounded by basal lamina
- Luminal side has microvilli and junctional complexes
- Spindle cells are closely apposed and rudimentary junctions present between them
- Sparse collagen fibrils and dense stromal matrix in the background

♦ Thymoma:
- Epithelial components are of squamous cell in ultrastructure
- Lymphocytes of various quantity in the background

♦ Transitional cell carcinoma:
- Desmosomes
- Interdigitating, microvillus-like filopodia on lateral cell borders
- Small invaginations of luminal cell membrane, and the presence of apical vesicles and filaments are characteristic of normal urothelium, and are seen rarely in tumors
- Basal lamina

* The readers are further referred to Chapter 28, Non-Neoplastic Renal Diseases, by Donna L. Lager, M.D., for the section following

THE GLOMERULOPATHIES*

Glomerulonephritides Characterized by Immune-type Dense Deposits

♦ Dense deposits are predominantly localized in the subepithelial space:
- Membranous glomerulonephritis:
  - Subepithelial dense deposits tend to be numerous and to affect every capillary loop
  - Deposits show early cupping, or appear sunken in the basement membrane
  - Extension of basal lamina material around the deposits gives the appearance of "spikes" on Jones' silver methenamine stain
  - Deposits become rarefied and buried in the basement membrane to be incorporated in it at the late stage
  - Epithelial foot processes are extensively effaced and the podocytes exhibit numerous microvillus-like projections
  - Dense deposits in the mesangium may coexist occasionally in idiopathic membranous glomerulonephritis, but almost always in membranous lupus nephritis (WHO Class V)
- Acute postinfectious proliferative glomerulonephritis:
  - Subepithelial dense deposits tend to be fewer, larger (hump-like) and more variable in size than those of membranous glomerulonephritis
  - Small dense deposits are almost always present in the mesangium and in the subendothelial space of the capillary basement membrane
  - Effacement of epithelial foot processes is patchy
  - Granulocytes and monocytes are increased in the capillary lumen

♦ Dense deposits are primarily in the mesangium:
- IgA nephropathy:
  - Large confluent deposits are found in the paramesangial space (at the base of capillary loops)
- Henoch-Schönlein nephritis with purpura (HSP):
  - Morphologically the glomerular lesions are almost identical to those of IgA nephropathy
  - Patients with HSP have, in addition, leukocytoclastic vasculitis affecting skin, joints and intestine
  - Mesangial dense deposits may extend into the adjacent subendothelial space
  - Subepithelial deposits (sometimes hump-like) are also encountered but infrequently
- Mesangial proliferative lupus nephritis (WHO Class II):
  - Mesangial deposits are positive for IgG and/or IgM and C3
- Idiopathic mesangial proliferative glomerulonephritis:
  - EM findings are similar to mesangial proliferative lupus nephritis
  - It is most often seen in children presenting with the nephrotic syndrome or with nonnephrotic range proteinuria and hematuria
- Mesangial IgM nephropathy:

- Mesangial dense deposits are usually small and inconspicuous
- Patients present with proteinuria with or without edema

♦ Dense deposits are present predominantly in the subendothelial space of the capillary loops but also in the mesangium:
  – Membranoproliferative glomerulonephritis, Type1
  – Focal proliferative (WHO Class III) and diffuse proliferative (WHO Class IV) lupus nephritis

Glomerulopathies in which Immune-Type Dense Deposits Are Absent or Scant

♦ Minimal change glomerulopathy:
  – Extensive effacement of epithelial foot processes, associated with no demonstrable dense deposits

♦ Focal segmental glomerulosclerosis:
  – Sclerotic segments represent collapsed capillaries with wrinkled basement membrane, increased mesangial matrix, and sometimes deposition of collagen fibers
  – Electron dense deposits may be seen in the subendothelial or mesangial location of the sclerotic or hyalinized segments
  – The focus of hyalinosis corresponds to a capillary loop where the endothelial fenestrated membrane is denuded and the lumen is filled with amorphous dense material often containing lipid vacuoles
  – Detachment of a podocyte with the gap replaced by laminated, newly formed basement membrane-like material is a characteristic change in focal segmental glomerulosclerosis
  – An additional finding in HIV (human immunodeficiency virus)-associated nephropathy is the presence of tubuloreticular structures in the cytoplasm of capillary endothelial cells

♦ AntiGBM (glomerular basement membrane) crescetic glomerulonephritis:
  – No discernable immune-type dense deposits are demonstrable, despite the fact that there exists characteristic smooth linear staining of immunoglobulins on the glomerular basement membrane
  – Disruption of the basement membrane is associated with proliferating parietal epithelial cells, accumulation of white blood cells and deposition of fibrin (active crescent)
  – Plasma proteins resembling immune-type dense deposits may be located in the area of capillary destruction

♦ ANCA (antineutrophil cytoplasm antibody)-positive or pauci-immune, crescentic glomerulonephritis, including Wegener's granulomatosis:
  – EM findings are similar to anti-GBM nephritis

♦ Diabetic glomerulopathy (intercapillary and nodular glomerulosclerosis):
  – It is characterized by widening of the lamina densa of the glomerular basement membrane, and an increase in mesangial cells and matrix A segmental lesion similar to that of focal segmental glomerulosclerosis may occur in diabetic glomerulopathy

Glomerulopathies Characterized by Distinctive Ultrastructural Deposits

♦ Dense deposit disease (type 2 membranoproliferative glomerulonephritis):
  – Dense deposit (this one is not immune-type) lies on the lamina densa of the glomerular basement membrane but is much denser than the lamina densa itself
  – It is discontinuous, varying in width and length
  – It has a water color quality; it is homogeneous in density and finer than the granularity of the immune-type dense deposits
  – Round deposits of same quality occur in the mesangium as well

♦ Light chain deposition disease:
  – The deposits are denser and coarser than immune-type deposits
  – They precipitate on the basement membrane as a continuous band. The darkest zone corresponds to the lamina rara interna (subendothelial side of the basement membrane)
  – In tubules, the deposits are located on the outer part of the basement membrane

♦ Amyloidosis:
  – Regardless of their chemical nature, all amyloids consist of non-branching randomly oriented fibrils, 7–10 nm thick
  – The fibrils deposit in the mesangial matrix first, and later on the basement membrane. The amyloid fibrils also appear on the outer part of the tubular basement membrane as well as in the vascular wall

♦ Fibrillary (immunotactoid) glomerulopathy:
  – Some include fibrillary and immunotactoid glomerulopathies in the spectrum of an entity, while others consider them as separate entities
  – Both are Congo red negative, and appear to be immune-type deposits in which organized fibrils or microtubules are formed
  – In fibrillary glomerulopathy, the fibrils are about 15–25 nm and in immunotactoid glomerulopathy, about 30–50 nm in diameter
  – As in amyloidosis, the fibrils accumulate in the mesangium first and then on the capillary basement membrane later

- In lupus nephritis and cryoglobulinemia-associated glomerulopathy, immune-type dense deposits may contain finger-print like or curvilinear microtubular substructures

Glomerulopathies with Structural Abnormalities of the Basement Membrane

- Alport's hereditary nephritis:
  - Widespread, irregular thinning and widening of the basement membrane with trabeculation or lamellation of the glomerular capillary basement membrane
- Thin glomerular basement membrane disease:
  - In benign familial recurrent hematuria, the sole abnormality found may be diffuse, extensive thinning of the glomerular capillary basement membrane (less than 130 nm in children and less than 200 nm in adults)

Glomerulopathies Associated with Vascular Endothelial Injury

- Detachment of endothelial cells from the glomerular capillary basement membrane, resulting in formation of micro-pseudoaneurysm, mesangiolysis and thrombosis (thrombotic microangiopathy):
  - Hemolytic uremic syndrome
  - Thrombotic thrombocytopenic purpura
  - Antiphospholipid syndrome
  - Scleroderma (systemic sclerosis)
  - Acute renal failure in pregnancy (eclampsia and postpartum acute renal failure)
  - Radiation nephritis
  - Cyclosporine and tacrolimus (FK506) associated nephropathy
  - Acute and chronic allograft glomerulopathy
  - Malignant hypertension

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5

Microbiology for the Surgical Pathologist

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CONTENTS

I. Bacteria 5-4
Aerobic, Facultatively Anaerobic (or Microaerophilic) Bacteria 5-4
Gram-Positive Cocci 5-4
Staphylococcus aureus 5-4
Staphylococcus epidermidis and other Coagulase-Negative Staphylococci (CNS) 5-5
Streptococcus pneumoniae (The Pneumococcus) 5-6
Streptococcus pyogenes (Group A *Streptococcus*) 5-7
Streptococcus agalactiae (Group B *Streptococcus*) 5-8
Enterococcus species 5-8
Alpha-hemolytic streptococci (viridans streptococci) 5-9
Gram-Positive Bacilli 5-9
Bacillus anthracis (Etiologic Agent of Anthrax) 5-9
Bacillus cereus 5-10
Corynebacterium diphtheriae 5-10
Corynebacterium jeikeium (Formerly Group "JK" Bacilli) 5-11
Listeria monocytogenes 5-11
Nocardia Species (Nocardiosis) 5-11
Rhodococcus equi 5-12
Gram-Negative Bacilli: Enterobacteriaceae 5-14
Escherichia coli 5-14
Shigella species (Cause Bacillary Dysentery) 5-15
Nontyphoidal Salmonella infections 5-15
Salmonella typhi (Typhoid Fever) 5-15
Yersinia enterocolitica 5-16
Yersinia pestis 5-16
Klebsiella pneumoniae 5-17
Other Gram-Negative Bacilli 5-17
Campylobacter jejuni 5-17
Helicobacter pylori (See Chapter 34) 5-18
Vibrio vulnificus 5-18
Pseudomonas and Related Genera 5-19
Legionella pneumophila 5-19
Haemophilus influenzae 5-20
Bordetella pertussis 5-20
Brucella species 5-20
Gram-Negative Cocci 5-22
Neisseria gonorrhoeae 5-22
Neisseria meningitidis 5-22
Anaerobic Bacteria and Diseases 5-23
Anaerobic Sporeforming Bacilli: The Clostridia 5-23
Clostridium perfringens 5-23
Clostridium septicum and Bacteremia 5-25
Clostridium difficile 5-26
Clostridium botulinum and Botulism 5-26

Clostridium tetani and Tetanus 5-27
Anaerobic, Nonsporeforming Gram-Negative Bacilli: the *Bacteroides fragilis* Group, *Prevotella* and *Porphyromonas* species, and the Genus *Fusobacterium* 5-28
Anaerobic Gram-Positive Cocci: the "Peptostreptococci" 5-29
Anaerobic Nonsporeforming Gram-Positive Bacilli.....5-29
Actinomyces species and Actinomycosis 5-29
Mycobacterium Species 5-30
Miscellaneous Other Bacteria.....5-30
Bartonella henselae.....5-30
Bartonella quintana 5-31
Bartonella bacilliformis 5-32
Rickettsia rickettsii and Rocky Mountain Spotted Fever.....5-32
Calymmatobacterium granulomatis.....5-33

II. Fungi 5-34
Hyaline Fungi.....5-34
Aspergillus species 5-34
Fusarium species.....5-35
Mucor, Absidia, and *Rhizopus* species.....5-35
Penicillium marneffei 5-35
Pseudallescheria/Scedosporium....5-37
Dimorphic Fungi 5-37
Blastomyces dermatitidis 5-37
Coccidioides immitis.....5-37
Histoplasma capsulatum.....5-39
Paracoccidioides brasiliensis 5-39
Sporothrix schenckii 5-42
Superficial Mycoses 5-42
Malassezia furfur 5-42
Hortaea werneckii.....5-42
Piedraia hortae 5-42
Trichosporon beigelii 5-43
Dermatophytes (Cutaneous mycoses) 5-43
Subcutaneous Mycoses 5-44
Dematiaceous (darkly pigmented) Fungi 5-44
Alternaria species 5-44
Chromoblastomycosis.....5-45
Phaeohyphomycosis 5-45
Yeasts 5-45
Candida albicans and Other *Candida* species 5-45
Cryptococcus neoformans.....5-46
Candida (Torulopsis) glabrata 5-46
Other Fungi 5-47
Pneumocystis jiroveci 5-47
Prototheca wickerhamii 5-49
Rhinosporidium seeberi 5-49

III. Viruses 5-50
Adenovirus 5-50
Cytomegalovirus (CMV) 5-50
Epstein-Barr Virus (EBV).....5-50
Hantavirus 5-52
Hepatitis viruses 5-53
Herpes Simplex Virus 1 & 2 (HSV) 5-53
Human Immunodeficiency Virus (HIV) 5-53
Human Papillomavirus (HPV) 5-54
Human T-Cell Lymphotropic (Leukemia/Lymphoma) Virus 1 & 2 (HTLV) 5-54
Measles 5-54
Molluscum contagiosum.....5-54
Parvovirus B19 5-55
Polyomavirus.....5-55
Rabies Virus 5-55
Respiratory Syncytial Virus 5-56
Varicella-Zoster Virus (VZV) 5-56
Variola Major (Smallpox) 5-56

IV. Parasites.....5-57
Protozoa 5-57
Acanthamoeba species 5-57
Babesia microti 5-57
Balantidium coli 5-57
Cryptosporidium parvum 5-57
Cyclospora cayetanensis.....5-59
Entamoeba histolytica.....5-59
Giardia lamblia.....5-59
Isospora belli.....5-59
Leishmania species 5-60
Microsporidia 5-61
Naegleria fowleri 5-62
Plasmodium species 5-62
Sarcocystis hominis.....5-63
Toxoplasma gondii 5-63
Trichomonas vaginalis 5-63
Trypanosoma species 5-65
Helminths 5-66
Cestodes (Tapeworms) 5-66
Diphyllobothrium latum 5-66
Echinococcus species 5-66
Hymenolepis species 5-66
Spirometra (sparganosis).....5-66
Taenia species 5-66
Nematodes (Roundworms).....5-67
Intestinal 5-67
Ancylostoma duodenale and *Necator americanus* 5-67

Ascaris lumbricoides 5-67
Dracunculus medinensis 5-68
Enterobius vermicularis (Pinworm) 5-68
Strongyloides stercoralis 5-68
Trichinella spiralis.....5-68
Trichuris trichiura (Whipworm) 5-69
Microfilaria (Tissue Roundworms) 5-69
Brugia malayi 5-70
Loa loa.....5-70
Mansonella perstans 5-70
Onchocerca volvulus 5-70
Wuchereria bancrofti 5-71
Zoonotic Roundworms 5-71
Angiostrongylus species 5-71
Anisakis species.....5-71
Capillaria philippinensis....5-71
Dirofilaria immitus 5-72
Gnathostoma species.....5-72
Toxocara canis (Visceral larva migrans) 5-72
Trematodes (Flukes) 5-73
Clonorchis sinensis 5-73
Fasciola hepatica 5-73
Fasciolopsis buski 5-73
Paragonimus westermani 5-73
Schistosoma species 5-74

V. Other.....5-74
Myiasis 5-74
Sarcoptes scabiei.....5-74
Tunga penetrans 5-74

VI. References/Suggested Reading 5-75

BACTERIA

Aerobic, Facultatively Anaerobic (or Microaerophilic) Bacteria

GRAM-POSITIVE COCCI

Staphylococcus aureus

Catalase positive and coagulase positive species; gram-positive cocci which tend to occur in clusters and packets, but also may occur singly or in pairs. *Staphylococcus aureus* is one of the most important bacterial pathogens of humans.

Clinical

- Skin and soft tissue infections:
  - Pyoderma, folliculitis, furuncle [boil], carbuncle, staphylococcal scalded skin syndrome (SSSS)
  - Hidradenitis suppurativa – involving apocrine sweat glands in axillae, perineal or genital areas
  - Mastitis – occurs in 1% to 3% of nursing mothers
  - A leading cause of nosocomial infections including surgical wound infections
  - Erysipelas, cellulitis, and fasciitis–more often caused by *Streptococcus* spp
- Botryomycotic abscesses:
  - Most common location – subcutaneous tissue
  - Other locations – liver, kidney, lung, prostate, and lymph nodes
  - Predisposing factors – trauma or foreign bodies; cystic fibrosis
  - Other causes (e.g., *Pseudomonas aeruginosa*)
- Organ infections and disseminated infections:
  - Bacteremia or septicemia – increased incidence in past 2 decades:
    - Nosocomial – often in patients with infected vascular or urinary catheters
    - Community acquired
    - Methicillin resistant *S. aureus* (MRSA) – common in both of above
  - *S. aureus* endocarditis:
    - ~ 30% of cases in patients with previously normal valves, ~ 20% in patients with prosthetic valves;
    - Most endocarditis involving intravenous drug users due to *S. aureus* (69%)
    - Bulky vegetations – very destructive to valve tissue
    - Left sided valves most frequently involved; but often right-sided in IV drug abusers
    - A source of bacteremia and septic emboli to distant organs
  - Deep abscesses (often metastatic); various organs – or cellulitis
  - Pulmonary infections:
    - ~ 10% of community acquired pneumonia and
    - ~ 20–30% of nosocomial pneumonia due to *S. aureus*
    - Recent emergence of necrotizing pneumonia due to Panton–Valentine–Leucocidin + *S. aureus*; preceded by influenza-like syndrome; frequently lethal
  - Osteomyelitis:
    - Due to *S. aureus* in 50% to 70% of cases
    - Bones infected hematogenously or by contiguous contamination
    - *S. aureus* is second in osteosynthetic prosthesis infections after coagulase negative staphylococci
  - Septic arthritis:
    - Children – *S. aureus* is most frequent cause
    - Adults – *S. aureus* is most frequent cause of nongonococcal septic arthritis; major underlying risk factors are:
      - Rheumatoid arthritis
      - Diabetes mellitus
- *S. aureus* toxin-related diseases:
  - Staphylococcal scalded skin syndrome (also called Ritter disease):
    - Caused by exfoliative A and B toxins
    - Most frequent in children
    - *S. aureus* infection of nasopharynx or skin
    - Characteristic sunburn-like rash over entire body & fragile bullae
    - Intraepithelial split in granulosa layer
  - Staphylococcal superantigens cause:
    - Food poisoning:
      - Est. 6 to 8 million US cases per year
      - Occurs 2 to 6 hours after ingesting preformed heat stable enterotoxin in contaminated food
      - *S. aureus* harbors up to 15 enterotoxins – defined as superantigens (able to produce vomiting and diarrhea in primate models)
    - Toxic shock syndrome (TSS):
      - Originally associated with use of hyperabsorbent tampons
      - Now known to be caused by growth of *S. aureus* in surgical wounds (as well as vaginas)
      - Patients develop shock, renal failure, coagulopathy, liver disease, respiratory distress, generalized erythematous rash, and necrosis at infected site

Macroscopic

- Varying size abscesses (white, gray, yellow, pink, tan, or brown pus surrounded by viable tissue)

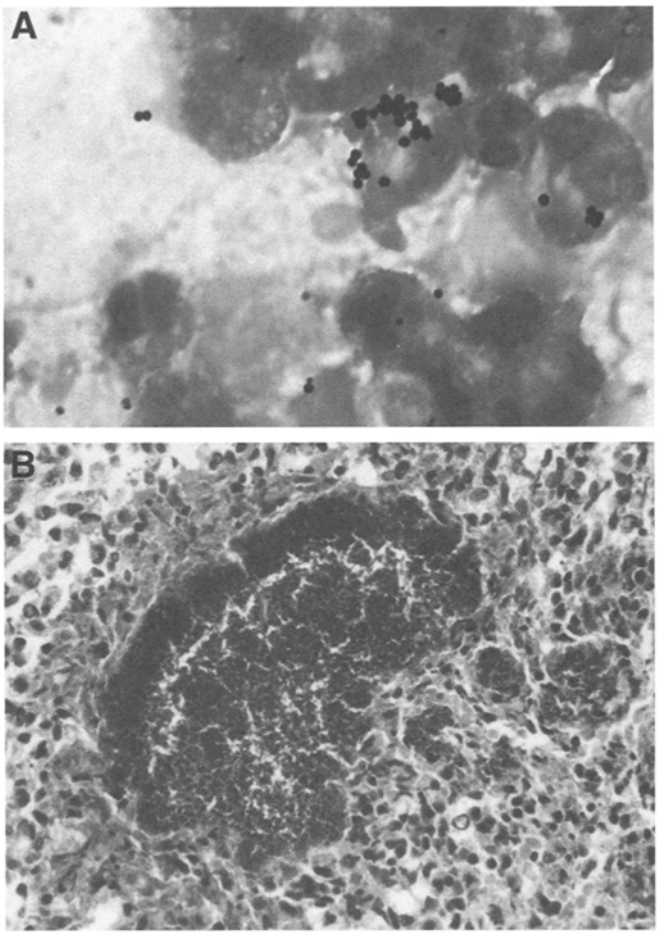


Fig. 1. **(A)** *Staphylococcus aureus* in Gram stained smear of purulent exudate, **(B)** Botryomycotic abscess (H&E).

Microscopic ***(Figure 1A,B)***

- Acute pyogenic inflammation which is particularly destructive (no matter if lesion involves skin, subcutaneous tissue, heart valves, lungs, bones, brain or other deep organ)
- Polymorphonuclear leukocyte is major cellular component
- Abscess formation – characterized by a localized area of acute inflammation surrounding a focus of necrosis
- In H&E stains, dead, dying or viable cocci often appear as amphophilic granular material
- In botryomycosis, abscesses contain basophilic granules in an acellular eosinophilic coagulum (Splendore-Höppli material)

Special Stains

- Staphylococci – 0.7 to 1.2 μm gram-positive cocci; tendency to form clusters
- Brown and Brenn (B&B) is best tissue Gram's stain for gram-positive bacteria
- Brown-Hopps (B-H) is best tissue Gram's stain for gram-negative bacteria
- MacCallum-Goodpasture, another modified tissue Gram's stain, can also be used to determine the gram reaction of bacteria

Differential Diagnosis

- Impetigo – includes Herpes simplex or Varicella zoster
- Abscess – includes other nonanaerobic bacteria and various anaerobic bacteria
- Cellulitis and fasciitis – differential includes *Streptococcus pyogenes*, anaerobes and other bacteria
- *Streptococcus pyogenes* is an additional cause of Toxic Shock Syndrome
- Botryomycosis – differential includes:
  - Actinomycotic granules and
  - Deep mycotic infections

Diagnostic Techniques

- Culture or other means of demonstrating microorganism may be required for definitive diagnosis
- Antimicrobial susceptibility testing aids in selecting antibiotics for treatment

Staphylococcus epidermidis **and Other Coagulase-Negative Staphylococci (CNS)**

Catalase positive, but coagulase negative *Staphylococcus* species; gram-positive cocci which tend to occur in clusters and packets, but also may occur singly or in pairs.

Clinical

- Inhabit normal human skin and mucosal surfaces
- Often contaminate clinical specimens, but may be true pathogens.
- In general, *S. epidermidis* is the most prevalent of the CNS in infections
- Nosocomial bacteremia – CNS are the most common cause – However:
  - Typically, 1% to 3% of blood cultures are contaminated with CNS and
  - ~25% to ~75% of CNS isolated from blood cultures are contaminants
- Endocarditis of native and prosthetic valves:
  - CNS cause ~5% to 8% of all cases of bacterial endocarditis; CNS are not common causes of native valve endocarditis
  - In contrast, CNS are the most common cause of prosthetic valve endocarditis (~40% of cases)
- Intravenous catheter infections— *S. epidermidis* is the single most common cause
- Cerebrospinal fluid (CSF) shunt infections – *S. epidermidis* is the most common microorganism
- Prosthetic joint infections (e.g., of the hip and knee) can involve CNS

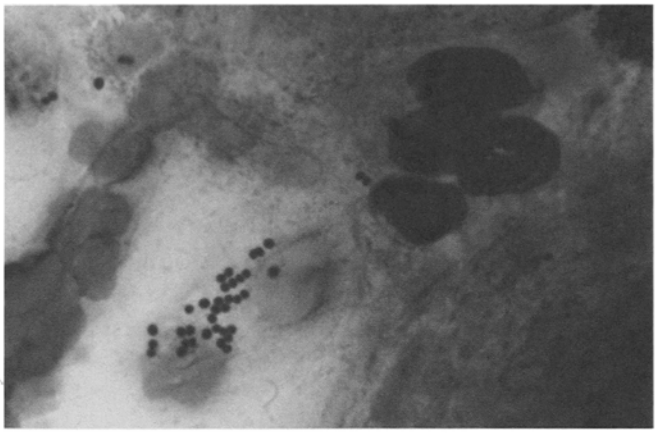


Fig. 2. Coagulase negative *Staphylococcus* species in sputum specimen (Diff-Quik).

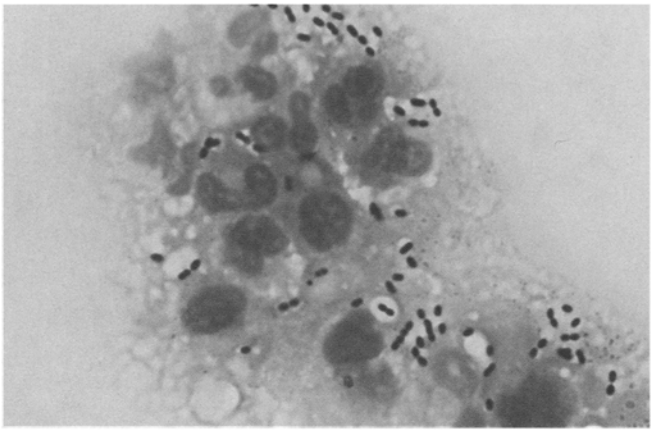


Fig. 3. *Streptococcus pneumoniae* in sputum (Gram).

- Urinary tract infections in young, sexually active women – *S. saprophyticus* is a common cause

Diagnostic Techniques ***(Figure 2)***

- Microscopic and special stain features indistinguishable from those of *S. aureus*
- Identification of isolates in microbiology laboratory based on relatively simple biochemical tests

Streptococcus pneumoniae (The Pneumococcus)

Clinical

- Colonizes nasopharynx:
  - 5% to 10% of healthy adults and
  - 20% to 40% of healthy children
- Common cause of community-acquired pneumonia in adults
- The most common cause of meningitis in adults, except during a *Neisseria meningitidis* outbreak
- The most common cause of meningitis in children in countries where children are vaccinated for *Haemophilus influenzae* type B
- The most prevalent pathogen in otitis media in children (40% to 50% of cases), or second only to nontypable *H. influenzae*
- The most common cause of otitis media in adults
- The most common cause of acute paranasal sinusitis, or second only to nontypeable *H. influenzae;* often preceded by viral infection (e.g., common cold)

Macroscopic

- Lobar pneumonia – most cases caused by *S. pneumoniae*; less frequent causes include *Klebsiella pneumoniae*, staphylococci, streptococci, *H. influenzae* and *Legionella* sp. The classic stages follow:
  - Congestion – seen in first 24 hours
  - Red hepatization – red, firm, liver-like consolidation (abundant neutrophils and erythrocytes)
  - Gray hepatization – lytic destruction of erythrocytes with persistent fibrinosuppurative exudate
  - Resolution – exudate destroyed and cleared; lung restored to normal
  - Complications – empyema, lung abscess, pericarditis
- Meningitis:
  - CSF cloudy or purulent (abundant neutrophils and bacteria)
  - Leptomeningeal exudate often thickest over cerebral convexities near sagittal sinus
  - Meningeal vessels engorged and prominent
  - Underlying brain swollen

Microscopic ***(Figure 3)***

- Acute neutrophilic host response
- Polysaccharide capsule (90 antigenic serotypes) – prevents pneumococci from being phagocytosed

Special Stains

- Gram's stain – Slightly elongated, "lancet", or "football" shaped gram-positive cocci, usually in pairs in clinical materials
- Halo-like appearance of capsule against background is often prominent

Differential Diagnosis

- *Enterococcus* spp. although not common in respiratory infections or meningitis, can be morphologically similar
- Other genera and species may form pairs of cocci (including staphylococci and other streptococci), but most are not "Lancet" or "football" shaped
- May be confused with *Klebsiella pneumoniae* in overdecolorized Gram's stain
- *K. pneumoniae* in underdecolorized Gram's stain may resemble pneumococci

Diagnostic Techniques

- Good quality sputum for culture (microbiology laboratories reject poor quality "sputa" based on established criteria)

- Blood cultures indicated: ~25% of patients with pneumococcal pneumonia have + blood cultures)
- Urine assay for pneumococcal polysaccharide: + in 2/3 of patients with pneumococcal pneumonia, but also + in up to 15% of patients with non-pneumococcal pneumonia, and + in healthy children with nasopharyngeal colonization

Streptococcus pyogenes (Group A Streptococcus)

Catalase negative, gram-positive, spherical to ovoid cocci that occur in pairs or chains. Also one of the most important bacterial pathogens of humans. Colonizes throats of 15% to 20% of asymptomatic school children; carriage rate in adults is lower.

Clinical

- Pharyngitis and tonsillitis:
  - *S. pyogenes* is the most common bacterial cause
  - Major antecedent of post-streptococcal glomerulonephritis
- Scarlet fever:
  - Caused by *S. pyogenes* strain that produces erythrogenic toxins
  - Usually associated with pharyngitis and tonsillitis
  - Most common between ages of 3 and 15 years
  - Punctate, erythematous rash that is most abundant over trunk and inner aspects of arms or legs
  - Face involved but an area around mouth is unaffected (circumoral pallor)
- Erysipelas:
  - Acute inflammation of skin due to *S. pyogenes* (group C strep occasionally)
  - Mostly occurs in infants and in adults over 30
  - Characterized by rapidly spreading, cutaneous swelling and rash involving face ("butterfly" distribution)
- Impetigo:
  - Caused by staphylococcus or streptococcus infection involving superficial layer of epidermis
- Streptococcal cellulitis:
  - Acute, spreading inflammation of skin and subcutaneous tissues
  - Results from infection of burns, wounds or surgical incisions
  - Predisposing factors: intravenous drug injection; impaired lymphatic drainage from upper (e.g., post-mastectomy) or lower extremities
- Necrotizing fasciitis (streptococcal gangrene, or "hospital gangrene"):
  - Described in 1924 by Meleney
  - Predisposing factors:
    - Trauma or appendicitis in young people
    - Diabetes, congestive heart failure, or surgical trauma in older people

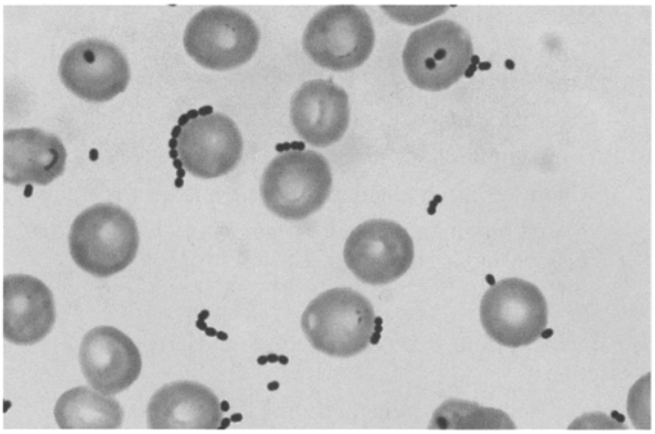


Fig. 4. *Streptococcus* species in positive blood culture (Gram).

  - Infection involves deeper subcutaneous tissue and fascia
  - Extensive/rapidly spreading necrosis, and gangrene of the skin and underlying structures
  - Mortality high: 20% to 70%
  - Virulent *S. pyogenes* sometimes called "flesh-eating bacteria"
- Nonsuppurative post-streptococcal sequelae (described in other chapters):
  - Acute rheumatic fever:
    - Nonsuppurative inflammatory lesions involve primarily the heart , joints, subcutaneous tissues
    - Follows group A streptococcal upper respiratory infections
  - Post-streptococcal glomerulonephritis:
    - An acute inflammatory disorder of the renal glomerulus characterized by edema, hypertension, hematuria, and proteinuria.
    - A delayed sequela of pharyngeal or cutaneous infection with certain "nephritogenic" strains

Microscopic (***Figure 4***)

- Scarlet fever:
  - Dermis edematous and hyperemic; scant perivascular lymphocytes and other mononuclear cells
  - Inflammation of epidermis; hyperkeratosis and desquamation of skin
- Erysipelas:
  - Epidermis shows spongiosis
  - Acute edematous, neutrophilic inflammation in dermis; prominent around vessels and adnexa, extends into subcutaneous tissue
- Impetigo and pyoderma due to *S. pyogenes*:
  - Resembles that caused by *S. aureus*
  - Abscess formation less common than with *S. aureus*

- Streptococcal cellulitis:
  - Diffuse interstitial, neutrophilic infiltrates of cellular connective tissue
  - Minimal damage to host tissue
- Necrotizing fasciitis (streptococcal gangrene):
  - Characterized by hemorrhage, edema, necrosis plus
  - Mixed inflammatory cell inflammatory infiltrate that dissects along fascial planes

Special Stains

- Streptococci may be difficult to see in H&E stained sections
- Brown and Brenn is the preferred tissue Gram-stain
- Spherical or ovoid Gram-positive cocci, often in short chains in histologic sections; the finding of >10 cocci per chain aids in recognizing streptococci in stained smears of body fluids, exudates, and cultures

Differential Diagnosis

- Staphylococci cause similar infections, but tend to form clusters and almost never form long chains
- Other bacteria including Clostridia, anaerobic cocci (with similar microscopic features) and other anaerobes cause similar infections

Streptococcus agalactiae (Group B *Streptococcus)*

Catalase negative, gram-positive cocci that occur in pairs or chains. An important bacterial pathogen of neonates and infants under 3 months, pregnant women, and also older adults. Asymptomatic colonizer of lower gastrointestinal tract and genitourinary tract (20% to 40% of adult women). ~60% of infants born to colonized mothers become colonized with mother's *S. agalactiae.*

Clinical

- Early-onset neonatal disease:
  - Acquired in utero or at birth (1st week of life)
  - Characterized by sepsis, pneumonia and meningitis
- Late-onset neonatal disease (older infants):
  - Occurs between 1 week and 3 months of life
  - Acquired from mother or another infant
  - Predominant manifestations: pneumonia with meningitis
- In pregnant and post-partum women, causes urinary tract infections, endometritis
- In addition; an emerging cause of morbidity and mortality (15% to >30%) in men and nonpregnant women:
  - Generally older individuals; diabetes mellitus or underlying liver disease (e.g., 2° to alcohol) are commonest predisposing factors
  - Most common manifestations: bacteremia, pneumonia, bone and soft tissue infections

Microscopic

- Congenital pneumonia (due to contamination of amniotic fluid after premature rupture of membranes or prolonged labor) often has lobar distribution:
  - Neutrophilic inflammation; lacks fibrin (amniotic fluid is fibrinolytic)
  - Squamous debris and other elements of meconium increased
- Perinatally acquired pneumonia due to *S. agalactiae:*
  - Hyaline membranes and neutrophilic infiltrates often present
  - Presence of large numbers of gram-positive cocci in hyaline membranes
- Purulent meningitis:
  - Resembles meningitis caused by other bacteria
  - Meningitis due to *S. agalactiae* is rare beyond newborn period in infants or in older children

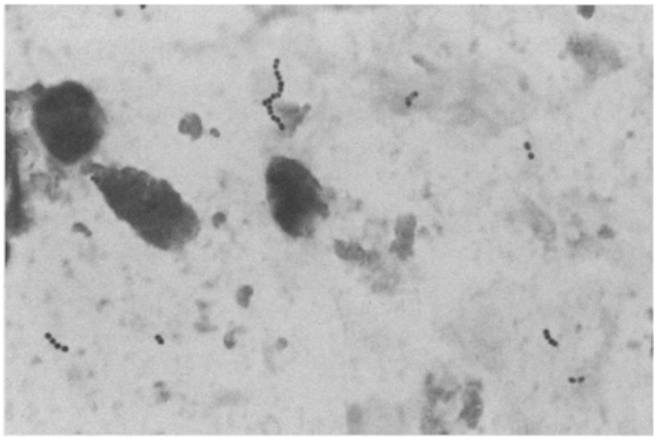


Fig. 5. *Enterococcus faecium* pneumonia (bronchoalveolar lavage specimen [Gram]).

Special Stains

- Brown-Brenn (the preferred tissue Gram's stain)
- Presence of gram-positive cocci in chains aids in diagnosis **(Figure 5)**

Differential Diagnosis

- Distinction from noninfectious hyaline membrane disease can be made by demonstrating bacteria in the hyaline membranes plus a more pronounced neutrophilic inflammation
- *S. agalactiae* and *Escherichia coli* tied for 1st place as the most common bacterial causes of neonatal meningitis. Their microscopic features differ.

Enterococcus Species

Previously included with the group D streptococci, these catalase negative, gram-positive cocci normally inhabit the gastrointestinal tracts of humans and other animals. The most commonly encountered *Enterococcus* species in infections are *E. faecalis* (~80% to 90%) and *E. faecium* (~10% to 15% or more of enterococcal isolates)

Clinical

- Patients at increased risk of infection: those hospitalized for long periods of time and those being treated with broad-spectrum antibiotics:
  - Inherently resistant to many commonly used antibiotics (e.g., oxacillin, cephalosporins, and other β-lactam agents) or have
  - Acquired resistance genes (e.g., aminoglycosides, vancomycin)
- Cause ~10% of nosocomial infections
- Urinary tract infections (common in patients with urinary catheters)
- Wound infections (e.g., intraabdominal); many are polymicrobial and the significance of *Enterococcus* spp. is not always clear
- Bacteremia (especially in patients with intravascular catheters)
- Bacterial endocarditis; *Enterococcus* spp. cause ~15% of cases
- Pneumonia (well-documented but unusual)
- Meningitis (a rare cause)

Microscopic ***(Figure 5)***

- Usually acute inflammation
- Gram-positive cocci that occur in singles, pairs and chains of varying lengths

Differential Diagnosis

- Frequently indistinguishable from *Streptococcus pneumoniae* on direct microscopic examination

Alpha-hemolytic Streptococci (Viridans Streptococci)

"Viridans" is a descriptive name, not a taxonomic name, for *Streptococcus* spp. other than *S. pneumoniae* that produce partial hemolysis of erythrocytes in blood agar

Clinical

- Certain oral species, particularly *Streptococcus mutans*, play a significant role in dental plaque formation and dental caries
- Other types of clinical settings from which alpha-hemolytic streptococci (e.g., *S. sanguis, S. constellatus, S. intermedius* and/or others) are isolated include bacteremia, infective endocarditis, aspiration pneumonia, and abscesses in multiple organs

Gram-Positive Bacilli

Bacillus anthracis (Etiologic Agent of Anthrax)

Sporeforming, gram-positive rod which grows aerobically, and produces catalase; differs from other *Bacillus* spp. encountered in clinical microbiology laboratories by its lack of hemolysis on blood agar, inability to hydrolyze gelatin or ferment salicin and its absence of motility. Bioterrorist (BT) events in 2001 resulted in heightened awareness of its potential use as a lethal bioweapon (BW).

Clinical

- Cutaneous:
  - About 95% of naturally occurring cases are cutaneous
  - Lesions usually occur on abraded skin
- Inhalational (wool sorter's disease):
  - Develops 1–5 days after inhaling spores
  - "Flu-like" onset with fever, myalgia, nonproductive cough
  - Left shifted neutrophilia
  - Sudden onset of severe respiratory distress
  - Widened mediastinum on chest X-ray
  - Shock, then death within 24–48 hours
- Gastrointestinal:
  - Rare; most reported cases from Africa and Southeast Asia
  - Acquired through ingestion of *B. anthracis* spores (e.g., in contaminated undercooked meat)
  - Nausea, vomiting, anorexia, fever, abdominal pain, severe bloody diarrhea

Macroscopic – Hallmark is hemorrhage and edema

- Cutaneous:
  - Macular then papular lesion in 48 hours
  - Pruritic vesicle subsequently develops with surrounding blue-black tissue
  - Vesicle ruptures producing classic black eschar that is painless and usually self-limiting
- Inhalational:
  - Hemorrhagic lymphadenitis and mediastinitis
  - Manifestations of hematogenous spread: especially hemorrhagic meningitis (i.e., "cardinals cap")
- Gastrointestinal:
  - Localized oropharyngeal lesion or
  - Severe systemic disease with localized lesion in terminal ileum or cecum

Microscopic

- Hemorrhage, edema, necrosis, fibrin deposition, neutrophils, profound bacillemia
- Lymphoid necrosis (with sinus histiocytosis and hemorrhage in lymph nodes)
- Necrotizing vasculitis in small cerebral vessels

Special Stains

- Gram-positive, large "boxcar" shaped bacillus
- Spores not seen in histologic sections or in smears of fresh clinical specimens

Differential Diagnosis

- Staphylococcal cellulitis, tularemia, plague, cat scratch disease, rat bite fever, sporotrichosis

Diagnostic Techniques

- If anthrax is suspected, local and state public health authorities must be notified immediately

- CDC phone numbers for questions and consultation 24/7 are (770) 488-7100 or (770) 488-4819 (website: www.cdc.gov/ncidod/hip or www.bt.cdc.gov)
- Biosafety level 2 microbiology laboratory practices in a CDC Level A or Level B laboratory are required
- Level A laboratories must have at least a class II certified biological safety cabinet and level A protocols, and algorithms for ruling out suspicious microorganisms (available from CDC website)
- Microbiologic culture of organisms from blood culture, sputum, tissue, aspirates, or CS

Bacillus cereus

Sporeforming, gram-positive rod which grows aerobically, produces catalase, produces hemolysis on blood agar and is motile. Ubiquitous in nature and hospital environment. Other *Bacillus* spp. such as *B. subtilis* and *B. sphaericus* are common laboratory contaminants.

Clinical

- Gastrointestinal (GI):
  - Toxin-induced emetic form (fried rice); short incubation period of 1 to 6 hours similar to staphylococcal food poisoning
  - Diarrheagenic food poisoning; incubation period of 10 to 12 hours similar to *Clostridium perfringens* food-borne illness
- Non-GI Infections:
  - Local (ocular, trauma, burn, and wound infections)
  - Bacteremia/septicemia (intravenous drug use, indwelling catheters, hemodialysis)
  - Central nervous system (shunt or trauma associated)
  - Respiratory
  - Endocarditis

Macroscopic

- Cutaneous infections may begin as single necrotic bulla
- Reports of bacillus central nervous system infections: brain abscess, subarachnoid hemorrhage, necrotic lesions at gray-white junction

Microscopic ***(Figure 6)***

- Vasculitis, coagulative necrosis, and hemorrhage
- Large clusters of large bacilli in necrotic areas
- Little to no inflammatory response in neutropenic patients

Special Stains

- Brown and Brenn: sporeforming gram-positive or gram-variable bacillus
- PAS+ after diastase digestion

Differential Diagnosis

- *Clostridium* species
- *Bacillus anthracis*

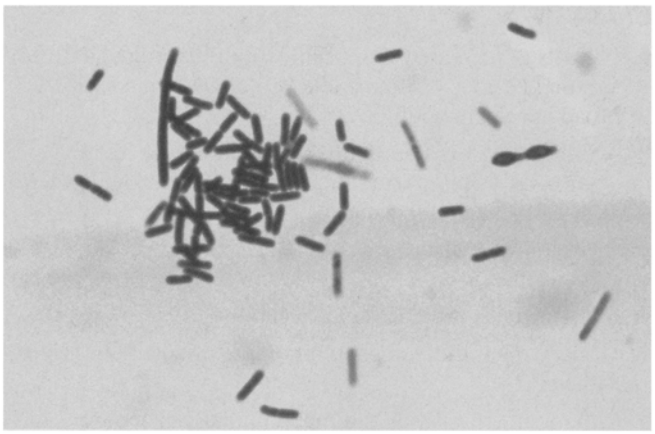


Fig. 6. *Bacillus* species (microbiologic culture [Gram]).

Diagnostic Techniques

- Culture for definitive diagnosis

Corynebacterium diphtheriae

Clinical

- Diphtheria: caused by *C. diphtheriae*, a pleomorphic gram-positive rod with swollen ends that forms "picket fence" arrangements or "palisades", "Chinese letters" and other interesting appearances
- Respiratory spread; *C. diphtheriae* proliferates at site of attachment (e.g., oropharyngeal pseudomembrane)
- Ulcerative cutaneous lesions are also primary sites of infection
- Phage-encoded exotoxin damages heart and peripheral nerves

Macroscopic

- Diphtheritic pseudomembrane: thick, gray or black, tenacious exudate; adheres to submucosa; may cause bleeding and asphyxiation if sloughed away
- Skin ulcers also may be covered with gray pseudomembrane

Microscopic

- Pseudomembrane contains fibrin, neutrophils, necrotic debris
- Exotoxin damage to heart: fatty myocardial change with isolated myofiber necrosis
- Exotoxin induced neuritis: degeneration of myelin sheaths

Special stains

- Loeffler's methylene blue stain showing diphtheroid forms with metachromatic granules
- Immunofluorescent staining of 4-hour cultures

Differential Diagnosis

- Includes infectious mononucleosis, streptococcal or viral pharyngitis and tonsillitis, Vincent's angina, and acute epiglottitis

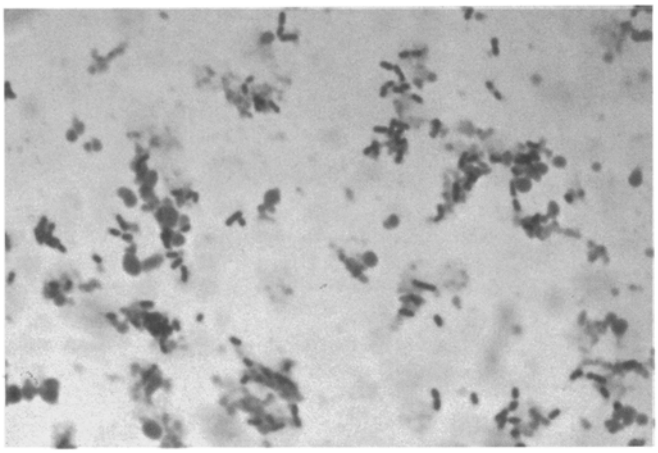


Fig. 7. *Corynebacterium jeikeium*, in positive blood culture (Gram).

- Definitive diagnosis requires microbiologic culture

Corynebacterium jeikeium (Formerly Group "JK" Bacilli)

Clinically important resistance to most antibiotics except vancomycin. Most infections are nosocomial.

Clinical: infections caused by *C. jeikeium* and other *Corynebacterium* species include:

- Intravenous catheter-related blood stream infections
- Skin and soft tissue infections
- Pneumonia
- Prosthetic valve and native valve endocarditis
- Cerebral spinal fluid shunt infections and meningitis
- CAPD-related peritonitis

Microscopic ***(Figure 7)***

- Gram-positive pleomorphic rods; "Chinese letters"

Differential Diagnosis

- Definitive diagnosis requires microbiologic culture

Listeria monocytogenes

Small, pleomorphic, Gram-positive, non-sporeforming, rods with diphtheroid features.

Motile at room temperature. Ubiquitous in nature.

Clinical

- Food-borne illness
- Severe infection in pregnant women
- Granulomatosus infantiseptica (stillborns)
- Placentitis
- Neonatal sepsis and meningitis
- Infections of immunocompromised hosts (e.g., organ transplant recipients; patients with AIDS)

Microscopic and Special Stains

- Acute meningitis: findings are non-specific: similar to pyogenic meningitis caused by *Neisseria meningitidis* or *Haemophilus influenzae*
- The presence of small Gram-positive rods in cerebrospinal fluid can be diagnostic, but *L. monocytogenes* may be confused with *H. influenzae* if underdecolorized.
- Placentitis: characterized by acute inflammation and abscess formation

Nocardia species (Nocardiosis)

- Nocardiosis: disseminated or localized infection caused by obligately aerobic, gram-positive, branching, filamentous rods of the genus *Nocardia*
- Classification: within the "aerobic nocardioform actinomycetes" subgroup of the "aerobic actinomycetes,":
  - Large and diverse group of bacteria, many of which are only distantly related phylogenetically
  - Genera included in this subgroup: *Mycobacterium, Corynebacterium, Nocardia, Rhodococcus, Gordona,* and *Tsukamurella.*
  - *Tropheryma whippelii*, the cause of Whipple's disease, is also a member of this subgroup.

Epidemiology and Clinical Manifestations

- *Nocardia* spp. ubiquitous in soil, organic materials, and water; nocardiosis occurs worldwide
- Infections arise exogenously (unlike Actinomycosis) from inhalation or direct inoculation
- *Nocardia asteroides* complex causes most (about 80–90%) respiratory and disseminated infections
- *N. brasiliensis*, and *N. otitidis-caviarium* cause most cutaneous infections
- Predisposing factors:
  - Leukemia/lymphoma
  - Immunosuppressive therapy
  - AIDS
  - Chronic pulmonary disorders (e.g., pulmonary alveolar proteinosis)
  - Chronic granulomatous disease of childhood
- Pulmonary disease (the predominant clinical manifestation):
  - Lung lesions: cavitating abscesses (sometimes large) or
  - Fibrinosuppurative pneumonia; usually minimal fibrosis
  - Tendency for hematogenous spread from lungs as primary site to other body sites, particularly CNS (usually with brain abscess)
- Cutaneous or subcutaneous lesions:
  - Result either from traumatic inoculation or from systemic dissemination from the lungs
- Treatment of choice for nocardiosis is trimethoprim/sulfamethoxazole (Rx of choice for Actinomycosis is ampicillin, amoxicillin or penicillin G or penicillin V)

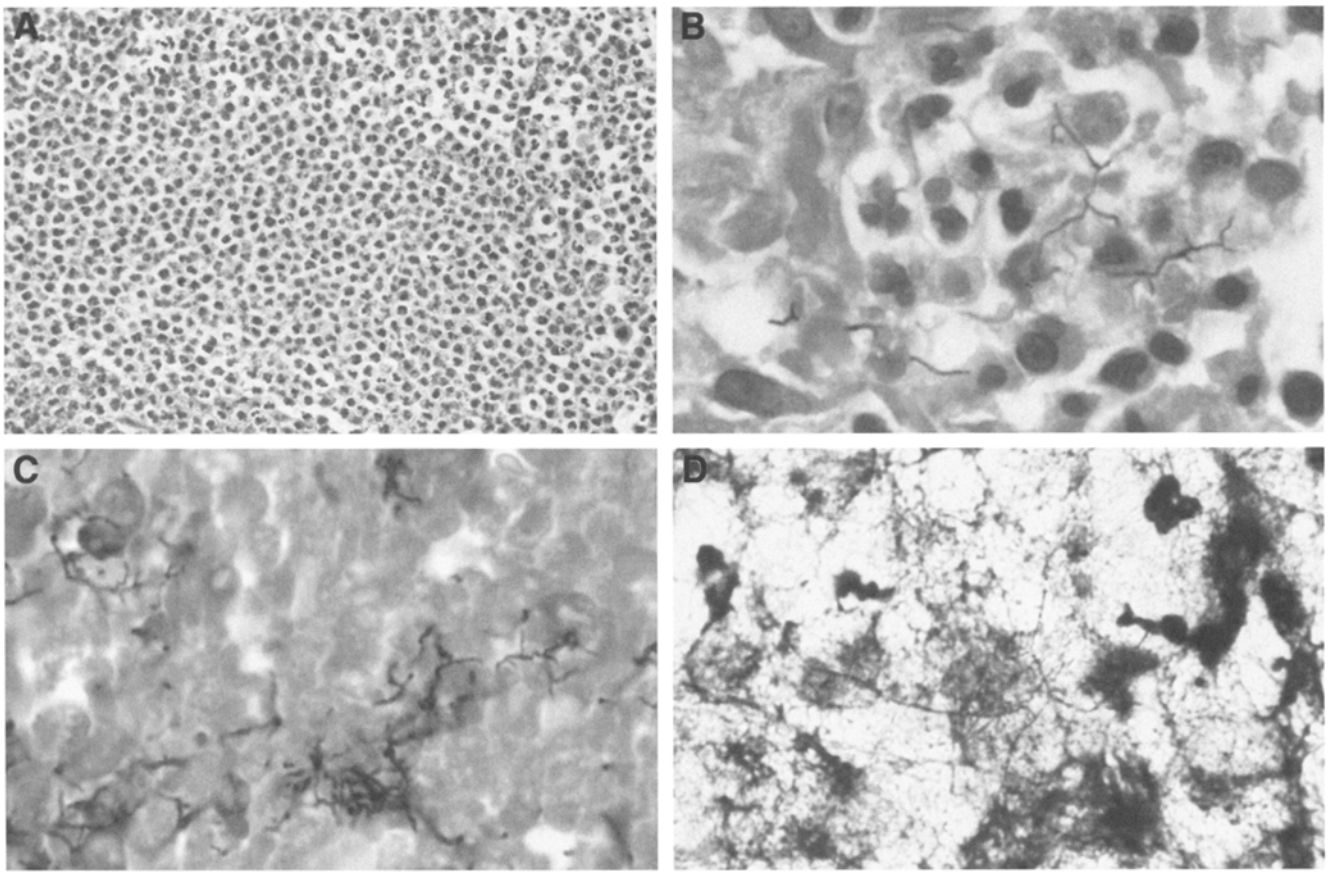


Fig. 8. Pneumonia due to *Nocardia* species; **(A)** H&E, **(B)** Brown & Brenn, **(C)** GMS, **(D)** modified acid fast stain.

Pathology and Stains ***(Figure 8A-D)***

- Host response in nocardiosis is usually suppurative necrosis with abscesses, or there may be diffuse fibrinosuppurative pneumonia
- In chronic infections, multiloculated abscesses and sinus tracts filled with purulent exudates occur
- Fibrinosuppurative pleuritis with empyema; a common complication
- In pulmonary and systemic infections, *Nocardia* species almost never form sulfur granules (unlike *Actinomyces israelii*); their thin, branching filaments are not stained with H&E or PAS.
- In cutaneous mycetomas, *Nocardia* species form granules
- *Nocardia* filaments stain with Gomori methenamine silver or Grocott's stain and with tissue Gram's stains (particularly Brown and Brenn)
- *Nocardia* forms gram-positive, beaded filamentous rods, usually ≤1 μm in diameter, with more or less right angle branching
- Fite's (modified acid fast) stain of tissue sections: *Nocardia* stains partially acid-fast or positive
- *Nocardia* also stains partially acid fast using a modified Kinyoun stain for fresh tissue imprints or smears of exudates
- Note: *Nocardia* spp. will not stain acid-fast using Ziehl-Neelsen or auramine-rhodamine stains
- *Actinomyces israelii* and the other species that cause Actinomycosis are not acid-fast

Other Diagnostic Techniques

- Microbiologic culture required for definitive identification and susceptibility testing

Rhodococcus equi

Clinical

- Cavitary pneumonia in immunocompromised patients
- Subcutaneous abscesses
- Brain abscesses
- Osteomyelitis
- Lymphadenitis,
- Endophthalmitis

Macroscopic

- Lung tissue removed as lobectomy specimens reveal cavitary lesions surrounded by consolidated lung
- Extrapulmonary lesions: abscesses surrounded by nodular and firm tissue

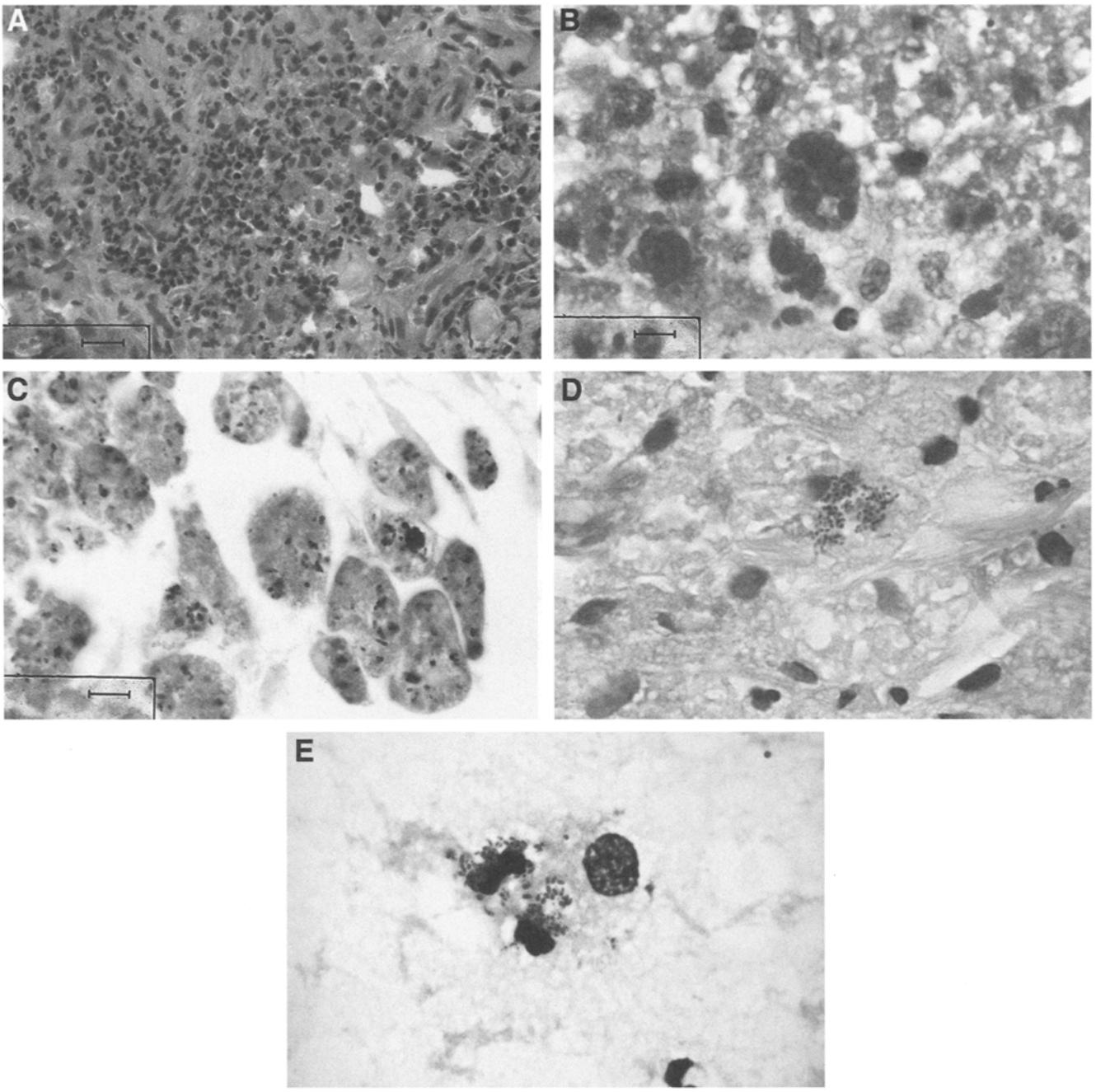


Fig. 9. *Rhodococcus equi* infection; wall of soft-tissue abscess; **(A)** H&E, **(B)** PAS-positive inclusions, **(C)** pleomorphic coccobacilli in macrophages (GMS), **(D)** gram-positive coccobacilli (Brown & Brenn), **(E)** partially acid-fast coccobacilli (modified Kinyoun).

*Microscopic **(Figure 9A-E)***

- Acute suppurative inflammation or granulomatous inflammation
- Granulation tissue may be prominent
- Malakoplakia

Special Stains

- PAS stain: PAS-positive inclusions in macrophages; called Michaelis-Gutmann bodies when they become calcified
- Brown and Brenn: gram-positive coccobacillus
- Fite stain of paraffin sections or modified Kinyoun stain of fresh touch preparations or tissue imprints: partially acid-fast coccobacilli; Note: *R. equi* will not stain acid-fast using Ziehl-Neelsen or auramine-rhodamine stains
- Other useful stains include: Gomori methenamine silver, Grocott, Giemsa, and Alizarin-red

Differential Diagnosis

- Differentiated from *Histoplasma capsulatum* and other fungi by morphology and microbiologic culture
- Differentiated from *Mycobacterium* species by morphology and microbiologic culture
- Pulmonary Whipple's disease caused by *Tropheryma whippelii*: macrophages more likely to be foamy and not eosinophilic; more likely to be found in pulmonary interstitium and peribronchial smooth muscle
- Non-infectious processes (eg., suppurative bronchiolitis, lipid storage disorders and exogenous lipid pneumonia); differentiated by special stains and microbiologic culture

Gram-Negative Bacilli: Enterobacteriaceae

Escherichia coli

Gram-negative, facultatively anaerobic ("aerobic") rod; fermenter; oxidase negative. The most common gram-negative bacillus in the GI tract that grows aerobically; most infections are endogenous (organism originates from patient's own microbiota ["normal flora"]). *E. coli* accounts for about 50% of the bacterial isolates in clinical microbiology laboratories.

Clinical

- Extraintestinal infections: both community acquired and nosocomial:
  - Bacteremia: the most common cause of gram-negative rod blood-stream infections
  - Urinary tract infections (UTIs): the most common cause of UTIs; usually limited to cystitis, but also causes pyelonephritis or prostatitis.
  - Neonatal meningitis
  - Pneumonia
  - Peritonitis: usually polymicrobial
  - Wound and soft tissue infections (e.g., cellulitis)
  - Osteomyelitis; joint infections
- Intestinal illness:
  - Travelers' diarrhea due to enterotoxigenic *E. coli* (ETEC)
  - Bloody diarrhea, hemorrhagic colitis, and hemolytic uremic syndrome due to enterohemorrhagic *E. coli* (EHEC) and other Shiga toxin-producing *E. coli* (STEC) strains
  - Diarrhea caused by enteropathogenic *E. coli* (EPEC); a leading cause of infant diarrhea in developing countries
  - Enteroinvasive *E. coli* (EIEC); foodborne outbreaks in developing countries

Macroscopic

- Extraintestinal infections:
  - Apart from clinical settings, there are no distinguishing features

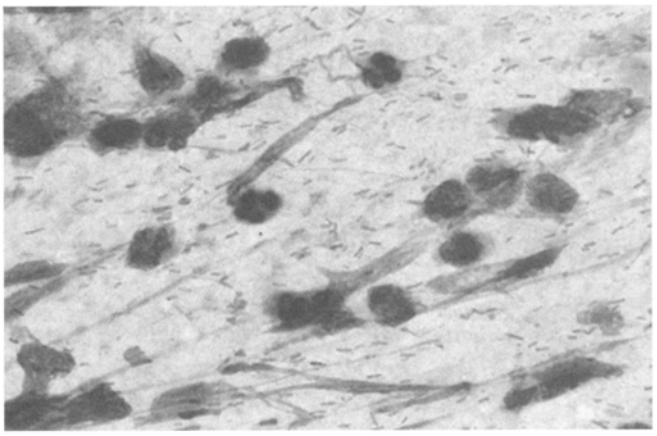


Fig. 10. *Escherichia coli* in Gram stained smear of sputum.

- Intestinal infections: gross findings depend upon pathogenic mechanisms:
  - Traveler's diarrhea due to ETEC: abundant watery diarrhea but no gross pathologic lesions (similar to cholera)
  - EHEC diarrhea: spectrum of findings varies from grossly unremarkable to patchy mucosal ulceration and hemorrhage, usually more prominent in right colon; pseudomembranes may be present
  - Gross findings in EPEC and EIEC unremarkable as in ETEC diarrhea

Microscopic ***(Figure 10)***

- Extraintestinal infections characterized by acute neutrophilic inflammation; findings are similar to those in infections involving pyogenic cocci
- Intestinal infections:
  - ETEC: microscopically unremarkable as in cholera
  - EHEC diarrhea: findings vary from mild non-specific inflammation to severe hemorrhagic colitis

Special Stains

- Medium size gram-negative rods; Brown-Hopps better than Brown and Brenn tissue Gram's stain for gram-negative rods in tissue sections
- PAS is also useful for observing *E. coli* and other gram-negative bacteria in tissue sections
- Diff-Quik and Giemsa stains aid in visualizing *E. coli* and other gram-negative bacteria in direct smears of body fluids, exudates and touch preparations of fresh clinical materials

Differential Diagnosis

- Extraintestinal *E. coli* infections are morphologically similar to infections caused by a wide variety of other bacteria
- EHEC diarrhea findings are similar to those seen in GI infections caused by *Shigella, Salmonella* or *Campylobacter* species; if pseudomembranes are present, other causes of pseudomembranous colitis (e.g., *Clostridium difficile*) should be considered

Diagnostic Techniques

- Microbiologic culture for *E. coli* extraintestinal infections
- Sorbitol-MacConkey agar for EHEC and other STEC
- PCR or DNA probes for enterotoxin genes or other virulence genes

Shigella species (Cause Bacillary Dysentery)

Gram-negative, non-motile rods; differentiated to species on basis of antigenic characteristics and fermentation test results; principal virulence factors include invasiveness (Sereny test+) and Shiga-toxin production

Clinical

- Most US cases caused by *Shigella sonnei* (60% to 80%); the next most common species is *S. flexneri*; *S. dysenteriae*, the most virulent species is far less common
- Most patients are children (<5 years old)
- Range of clinical manifestations includes:
  - Asymptomatic intestinal carriage,
  - Watery diarrhea, or
  - Severe dysentery with abdominal cramping, bloody mucoid stools
- Shigella is very unusual in infections outside the GI tract
- Seldom found in blood cultures; Shigella bacteremia more likely in AIDS or other immunocompromised patients
- Reactive arthritis with urethritis and conjunctivitis (e.g., Reiter's syndrome) is a known complication of shigellosis (associated with HLA-B27 haplotype)

Macroscopic

- Involvement of colon much more pronounced than in small intestine
- Extent of colon involvement varies from subtotal to total; continuous initially but patchy during recovery phase
- The most common gross findings are erythema, edema and superficial ulceration in 40%, and pseudomembranes in 20%

Microscopic

- Edema, congestion, focal hemorrhages, crypt hyperplasia, depletion of goblet cells, neutrophilic infiltration and ulcers common
- Crypt abscesses and capillary thrombi also common

Special Stains

- Gram-negative rods in mucosa, and crypts; also may be in lamina propria
- Invasion beyond lamina propria rare

Differential Diagnosis

- *Escherichia coli*
- *Salmonella* species
- *Campylobacter* species
- *Clostridium difficile* (pseudomembrane formation)

Diagnostic Techniques

- Microbiologic culture

Nontyphoidal Salmonella infections

Salmonellae are Gram-negative rods, motile (with rare exception), ferment glucose but not lactose; identified based on antigenic characteristics (O and H agglutinins) and biochemical test results. Taxonomic classification remains complex; >2400 "O" serotypes (referred to as "species"); of these, *Salmonella typhimurium* and *S. enteritidis* are among the most common.

Clinical

- Incubation period: usually 6–48 hours
- Occurs primarily in children
- A range of clinical syndromes
- Manifestations include diarrhea, often with fever and abdominal cramps
- Typically, the diarrhea lasts 3–7 days
- Outbreaks most often foodborne (e.g., contaminated eggs, ice cream, turkey, chicken, beef)
- Also waterborne spread

Pathology (of food poisoning)

- Acute ileocolitis; mucosa eroded
- Mixed inflammation in lamina propria
- Microscopic examination of stools reveals neutrophils and red blood cells
- Mucosa returns to normal in ~ two weeks
- Other Salmonella infections include:
  - Localized infections (e.g., osteomyelitis associated with sickle cell disease)
  - Bacteremia (most commonly due to *S. typhi, S. paratyphi, S. choleraesuis, S. enteritidis*)

Diagnostic Techniques

- Isolation and identification of *Salmonella* species from stool
- Requires selective media

Salmonella typhi (Typhoid Fever)

Clinical

- Severe systemic infection referred to as "enteric fever" – characterized by fever and abdominal symptoms
- Incubation period typically is 7–14 days
- Headache, malaise, abdominal pain and tenderness, constipation, myalgias, mental status changes
- Fever a classic sign of typhoid fever, but does not always develop
- "Rose spots" (maculopapular rash on trunk develops in 30% to 50% of patients)
- Cervical lymphadenopathy
- About half of patients develop hepatosplenomegaly

Macroscopic

- Enlarged lymphatic submucosal nodules of small intestine and colon; especially Peyer's patches of terminal ileum (may ulcerate with long axes in direction of bowel flow)

Microscopic

- Typhoid nodules: focal collections of macrophages (macrophages with erythrophagocytosis, debris and bacteria)
- Salmonellae may localize in conjunctivae, meninges, joints, kidneys, gallbladder (3% carriers)
- Pneumonia a frequent complication (superinfection)

Diagnostic Techniques

- Microbiologic cultures of blood, urine, and stool
- Other specimens cultured may include Rose spots, and/or bone marrow

Yersinia enterocolitica

Clinical

- In the US, *Y. enterocolitica* is an infrequent cause of diarrhea and right lower quadrant abdominal pain (frequently thought to be due to an attack of acute appendicitis clinically)
- More common in Northern Europe, South America, Africa, and Asia
- Incubation period: usually 4–6 days.
- Foodborne outbreaks (e.g., associated with chocolate milk in New York, pasteurized milk in Tennessee, raw pork intestines [chitterlings] in Atlanta and Baltimore)

*Pathology (**Figure 11**)*

- May involve terminal ileum and colon (i.e., acute self-limited enterocolitis) or acute terminal ileitis (i.e., with the terminal ileum as the main focus)
- Intestinal lesions may be similar to those seen in typhoid (with ulceration involving Peyer's patches), but intestinal perforation is rare
- Enlarged mesenteric lymph nodes with "stellate abscesses" (findings similar to those in lymphogranuloma venereum or lymph nodes in cat-scratch disease)
- Implicated as an uncommon cause of acute appendicitis

Special Stains

- Gram-negative coccobacilli, Brown-Hopps stain
- Silver stains (e.g., Warthin-Starry) may be useful for demonstrating bacteria
- Immunohistochemical stains have sometimes been used

Differential Diagnosis

- Typhoid
- Tuberculosis
- Pseudotuberculosis
- Brucellosis
- Intestinal tularemia

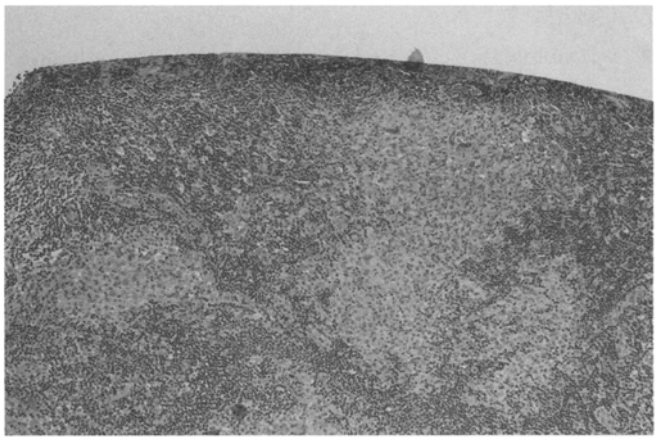


Fig. 11. *Yersinia enterocolitica*; mesenteric lymph node (H&E).

- Lymhogranuloma venereum
- Crohn's disease

Microbiologic culture

- Cold enrichment technique (enrichment buffer at 4°C)
- Bacteria grow well at low temperatures; motile at 25°C but not at 35°C

Yersinia pestis

Clinical Features

- Natural reservoir includes rats and ground squirrels
- Spread of organism: flea bites, direct contact with infected materials or by inhalation of aerosols from individuals with pneumonia
- Human plague (mortality is high):
  - Bubonic:
    - Patients have high fever
    - Painful, swollen lymph node with hemorrhagic lymphadenitis – (usually groin or axilla)
  - Primary and secondary pneumonic
  - Primary and secondary septicemic
- As for *B. anthracis, Y. pestis* another potential BT agent

Special Stains

- Gram-negative coccobacillus with characteristic bipolar ("safety pin") staining can be helpful, but not diagnostic

Diagnostic Techniques

- If plague is suspected, local and state public health authorities must be notified immediately.
- CDC phone numbers for questions and consultation 24/7 are (770) 488-7100 or (770) 488-4819 (website: www.cdc.gov/ncidod/hip or www.bt.cdc.gov)
- Biosafety level 2 microbiology laboratory practices in a CDC Level A or Level B laboratory are required
- Level A laboratories must have a least a class II certified biological safety cabinet and level A protocols, and

algorithms for ruling out suspicious microorganisms (available from CDC website)

- Microbiologic culture of organisms from aspirates, tissue, sputum, blood culture or CSF

Klebsiella pneumoniae

Encapsulated gram-negative rods that inhabit the gastrointestinal tract. They also colonize upper respiratory tracts of ~5% to 10% of healthy individuals.

Clinical

- Important cause of community-acquired and nosocomial infections
- Predisposing factors: diabetes mellitus, alcoholism, chronic obstructive pulmonary disease, and other underlying illnesses
- Common infections:
  - Pneumonia (sputum sometimes resembles "currant jelly")
  - Urinary tract infections
  - Bacteremia
  - Surgical wound infections

Pathology

- Pyogenic pneumonia may be patchy, lobular or lobar
- An entire lobe may be consolidated as in lobar pneumonia due to *S. pneumoniae*
- Pneumonia due to *K. pneumoniae* is similar to that caused by *S. pneumoniae,* but tends to be more destructive (abscess formation and empyema more common than for pneumococcal pneumonia)

Special Stains ***(Figure 12)***

- Gram-negative bacilli demonstrated best in Brown-Hopps tissue Gram's stain
- Can be confused with *S. pneumoniae* in overdecolorized Gram's stains

Diagnostic Techniques

- Pathologic features of *K. pneumoniae* infections not specific
- Microbiologic culture required for definitive diagnosis

Other Gram-Negative Bacilli

Campylobacter jejuni

- Small, motile, comma-shaped gram-negative bacterium
- Microaerophilic, grows optimally in an atmosphere of 5% to 10% oxygen plus increased carbon dioxide
- Inhabits intestines of many fowl, domestic and wild animals; both food and waterborne outbreaks common

Clinical

- Most common bacterial cause of gastroenteritis in the US
- Spectrum of illness ranges from mild diarrhea to moderately severe enteritis, or sometimes fatal colitis with bloody and/or purulent stools

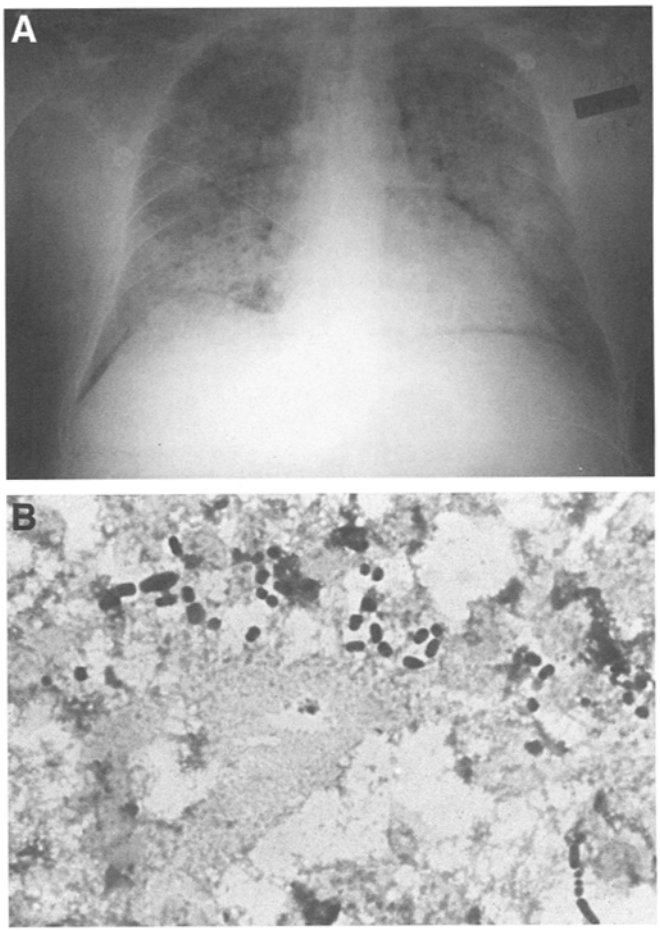


Fig. 12. *Klebsiella pneumoniae*; **(A)** chest X-ray, **(B)** positive blood culture (Gram).

- Abdominal pain frequently the predominant symptom.
- Bacteremia (in ≤1% of patients with *C. jejuni* infection; *C. fetus* is the *Campylobacter* species most commonly implicated in bacteremia)

Macroscopic

- Erythema and friability of colon
- May resemble idiopathic ulcerative colitis or Crohn's

Microscopic

- Cryptitis (neutrophil infiltration), crypt abscesses, preservation of crypt architecture, capillary congestion, edema of lamina propria
- Other nonspecific findings have included "unremarkable" or mild inflammation, terminal ileitis, or pseudomembranous colitis

Special Stains

- Curved gram-negative rods, "s" or "gull-wing" shaped (in blood or other microbiologic cultures)
- Morphologic forms of organisms seldom documented in histologic sections

Differential Diagnosis

- Idiopathic inflammatory bowel disease
- Other infectious colitides, eg. *Salmonella* or *Shigella*

Diagnostic Techniques

- Microbiologic culture

Helicobacter pylori (See Chapter 34)

Vibrio vulnificus

A motile, gram-negative, rod-shaped and curved, oxidase positive, lactose positive, free-living marine bacterium. Occurs in coastal waters of the Gulf of Mexico, the Atlantic and Pacific oceans, and also in the Great Salt Lake in Utah as well as other lakes (e.g., in New Mexico and Oklahoma). *V. vulnificus*: the most virulent non-cholera *Vibrio* species.

Clinical

- Primary septicemia:
  - Most frequent occurrence: patients with known liver disease (75% in one study) who eat raw oysters or other shellfish containing the organism
  - Secondary skin lesions in 90% (usually ecchymoses, bullae, and necrotizing cutaneous and soft tissue lesions)
  - Mortality high (~50%)
- Wound infections:
  - Follow sea water exposure to open wounds or injury (e.g., while fishing, swimming, shucking oysters and other activities)
  - Findings include erythema, swelling, intense pain, cellulitis, fasciitis, myositis or gas gangrene, particularly involving lower or upper extremities
  - Bacteremia: occurs in ~30% who have *V. vulnificus* primary wound infection (mortality lower than that of patients with primary septicemia)
  - Mortality for those with *V. vulnificus* primary wound infections and underlying liver disease (e.g., cirrhosis) is about 25%; prognosis better if patients do not have liver disease
- Gastroenteritis (by itself):
  - Vomiting, diarrhea and abdominal pain occur in approximately 10%
  - Prognosis excellent (no mortality associated)

Pathology ***(Figure 13A,B)***

- Skin lesions of patients with primary septicemia and skin lesions resulting from seawater – related wound infections similar; findings include
- Intense neutrophilic infiltration of subcutaneous tissue
- Abundant bacteria within the inflammatory cell infiltrate
- Acute vasculitis and thrombosis with a haze of many bacteria in vessel walls
- Acute necrotizing inflammation involving dermis

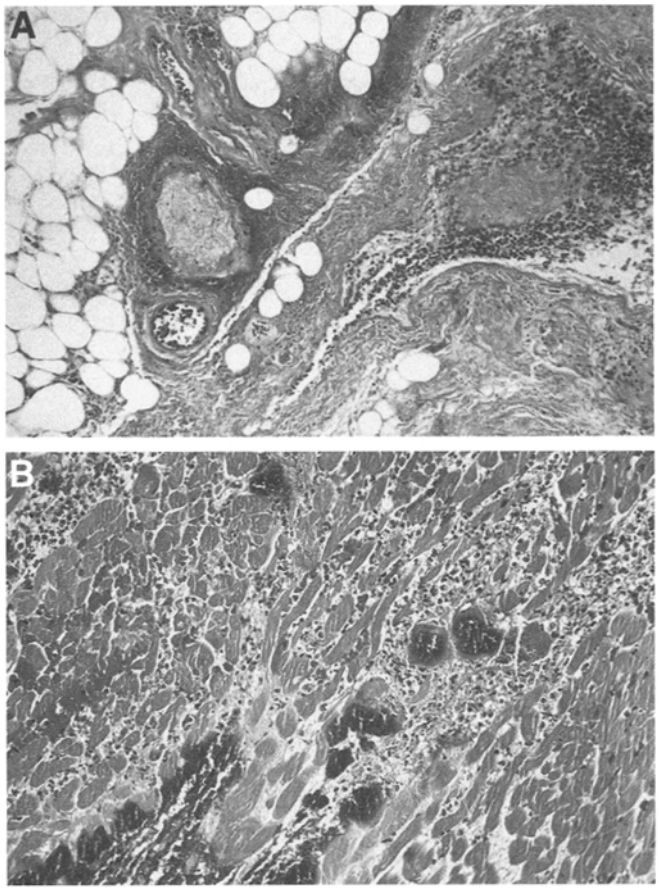


Fig. 13. *Vibrio vulnificus* wound infection with **(A)** vascular necrosis and cellulitis (H&E), **(B)** skeletal muscle necrosis, and neutrophilic infiltrate (H&E).

- In addition, there may be areas of intense fasciitis, myositis, necrotizing vasculitis and myonecrosis

Special Stains

- Gram-negative comma shaped bacilli
- Brown-Hopps tissue Gram's stain is particularly useful

Differential Diagnosis

- The necrotizing skin, and soft tissue lesions are similar to those produced by *Clostridium* species, *Aeromonas* species, and *Streptococcus* species, as well as polymicrobial infections involving *Bacteroides* species, the anaerobic and microaerophilic cocci, as well as other anaerobic and non-anaerobic microorganisms.
- The "cloud-like" appearance of bacteria in vessel walls and similar vascular lesions can be seen in necrotizing infections caused by *Pseudomonas aeruginosa.*

Diagnostic Techniques

- Microbiology laboratories should be notified if *V. vulnificus* or another Vibrio is suspected.
- Thiosulfate citrate bile salts sucrose (TCBS) agar is the primary isolation medium of choice, but is not available

in all laboratories, particularly those that are geographically far from coastal areas

- Even though *V. vulnificus* is a halophilic, oxidase positive, and lactose positive Vibrio, it grows on many if not most non-selective blood agar media, and on routinely used enteric selective plating media (e.g., MacConkey, xylose-lysine, and Hektoen-enteric agar), as well as in most blood culture media. It can be confused with lactose-positive *Enterobacteriaceae*

Pseudomonas and Related Genera

General characteristics

- Ubiquitous in environment (e.g., in/on flowers, sinks, toilets, and respiratory therapy equipment in hospitals) and in upper respiratory and intestinal microbiota of hospitalized patients; can contaminate disinfectant solutions, distilled water and stain solutions
- Small, thin, gram-negative rods; motile by means of polar flagella
- Non-fermenters; utilize glucose oxidatively
- Most produce cytochrome oxidase (*Enterobacteriaceae* are oxidase negative)

Pseudomonas aeruginosa

- Bacteremia/septicemia:
  - Most common in patients with neutropenia, diabetes mellitus, severe burns or hematologic neoplasms
  - Most common infection sites leading to bacteremia: pulmonary, urinary tract and skin
  - Ecthyma gangrenosum – well demarcated, hemorrhagic and necrotic skin lesion with vascular necrosis and large numbers of bacteria in bacteremic patient with neutropenia
- Skin infections:
  - Burns – Colonization followed by localized necrotizing vasculitis and bacteremia
  - Folliculitis – exposure to *P. aeruginosa* in hot tubs, whirl pools, swimming pools
- Chronic, suppurative, external otitis (swimmer's ear)
- Pulmonary infections:
  - *P. aeruginosa* common in cystic fibrosis patients
  - Findings vary from asymptomatic colonization to life-threatening, necrotizing bronchopneumonia
  - Microscopic: necrotizing inflammation with large numbers of neutrophils, and masses of bacteria in and around walls of thrombosed vessels
  - Chronic infection may lead to bronchiectasis and pulmonary fibrosis
- Urinary tract infections – mostly in catheterized patients
- Other infections:
  - Keratitis in wearers of contact lenses or after corneal trauma
  - Endocarditis or osteomyelitis – primarily in intravenous drug abusers

Burkholderia (Pseudomonas) cepacia

- Several characteristics shared with *P. aeruginosa:*
  - Causes bacteremia/septicemia (often catheter related and polymicrobial)
  - Pulmonary infections
    - Frequently in patients with cystic fibrosis or chronic granulomatous disease
    - Findings range from simple colonization to necrotizing pneumonia
  - Skin and soft tissue infections associated with burns or surgical wounds

Burkholderia mallei – Glanders in Livestock

Burkholderia pseudomallei – Human Melioidosis

- Acquired in humans primarily in wounds or following non-traumatic exposure to water or soil
- Very rare in Western hemisphere
- Endemic areas include Vietnam, Indonesia, Thailand, Malaysia, Singapore, China (especially Hong Kong), Taiwan, Cambodia, Laos, the Phillipines, India, Pakistan, Papua, New Guinea, Fiji, tropical Australia and parts of Africa
- Person-to-person spread unusual; laboratory infection documented but rare
- Clinical findings range from asymptomatic infection to localized cutaneous ulcers or abscesses, chronic pneumonia with features similar to tuberculosis, or septicemia with metastatic abscesses in multiple organs
- Histopathologic findings: (1) abscesses and (2) necrotizing and non-necrotizing granulomas

Stenotrophomonas maltophilia

- Pneumonia
- Central venous catheter-related bacteremia
- Other less frequent infections include endocarditis, sinusitis, cellulitis, liver abscess, and meningitis
- Like *Pseudomonas aeruginosa*, *S. maltophilia* is resistant to many antibiotics.

Acinetobacter baumannii

- Gram-negative coccobacilli that may be in the form of cocci that are easily confused with *Neisseria* species
- *Acinetobacter* species cause septicemia, wound infections, pulmonary and urinary tract infections.
- They are often resistant to multiple antibiotics and treatment can be problematic.

Legionella pneumophila

Clinical

- Legionnaire's disease – severe confluent lobar pneumonia
- Pontiac fever less severe
- Extrapulmonary involvement possible
- High fever 40°C, diarrhea, hyponatremia

Microscopic and Special Stains

- Gram-negative bacillus
- Dieterle, Warthin-Starry, Giemsa

Diagnostic Techniques

- Direct Fluorescent Antibody (DFA)
- Urinary antigen
- Culture

Haemophilus influenzae

Small, non-motile, pleomorphic gram-negative rods. Nonencapsulated (or) "nontypeable" strains colonize upper respiratory tracts of 30%-80% of healthy individuals; *H. influenzae* type B colonization has decreased substantially (now in < 1%) since vaccine was introduced.

Clinical Illnesses Caused by Nonencapsulated ("nontypeable") *Haemophilus influenzae*

- Otitis media (causes about 25% of the 25 million episodes per year in the US)
- The most common bacterial cause of exacerbations of chronic obstructive pulmonary disease
- Community acquired pneumonia in adults; particularly common in adults
- Pneumonia in children; a major cause in developing countries
- Acute maxillary sinusitis (sinus aspirates required for diagnosis)
- Neonatal sepsis (increasing frequency since 1980's; associated with significant morbidity and mortality)
- Purulent conjunctivitis (occurs sporadically and in outbreaks)

Clinical Illnesses Caused by *Haemophilus influenzae* Type B

- Pyogenic meningitis:
  - Most serious form of illness caused by *H. influenzae*
  - Now far less frequent than before vaccine was introduced; occurs most often in incompletely immunized persons
  - No clinical feature distinguishes it from purulent meningitis caused by other microorganisms
  - At autopsy, the exudate is usually basal; in pneumococcal meningitis exudate is usually more prominent over the cerebral convexities near sagittal sinus
- Acute epiglottitis
- Pneumonia and empyema
- Cellulitis
- Bacteremia
- Septic arthritis

Diagnostic Techniques

- Microbiologic laboratory studies required

Bordetella pertussis

Clinical

- Whooping cough, infects glottis
- Infants 1–2 months of age at greatest risk, as well as unimmunized/incompletely immunized children
- 6–20 day incubation; 3 stage illness:
  - 1 – catarrhal (1–2 weeks) nonspecific upper respiratory symptoms, highly communicable
  - 2 – paroxysmal (2–4 weeks or more) increased severity and frequency of cough with whoop, marked lymphocytosis
  - 3 – convalescent (1–2 weeks) decreased coughing; complete recovery in weeks to months

Pathology

- Bronchitis, bronchiolitis with slight extension of interstitial inflammatory infiltrate into alveoli
- Acute inflammatory exudate with sloughed, degenerated epithelial cells in airway lumen
- Segments of denuded bronchial wall

Special Stains

- Gram-negative coccobacillus

Diagnostic Techniques

- Direct fluorescent antibody test in conjunction with culture of posterior nasopharynx increases sensitivity and specificity
- "Mercury droplet" colonies on Bordet-Gengou agar

Brucella species

Prevalent in Mediterranean basin, Arabian peninsula, India, Mexico, parts of Central and South America and Africa

Clinical

- Zoonosis derived from:
  - Untreated goat's milk or cheese (*B. melitensis*)
  - Cow's milk (*B. abortus*)
  - Exposure to infected cattle (*B. abortus*),
  - Swine (*B. suis*)
  - Dogs (*B. canis*)
- Incubation 2–8 weeks
- Brucellosis:
  - Nonspecific fever, chills, headache, malaise, +/– hepatosplenomegaly
  - Lymphadenopathy, anorexia, nausea, vomiting, abdominal pain, diarrhea, constipation
  - Sudden death (rare) may occur within days or weeks of delirium and coma
  - Recurrent "undulant" fever – periodic nocturnal fevers; most common form; most likely to have skeletal involvement

- Chronic intermittent – rare with vague symptoms, mild fever, profound weakness
- Complications include meningitis, endocarditis (most common fatal complication), pericarditis, hepatic and splenic abscesses, osteomyelitis, arthritis, sacroiliitis

♦ As for *B. anthracis* and *Y. pestis,* another potential BT agent

Microscopic

♦ Sequestered in reticuloendothelial cells; granulomas
♦ Bone marrow:
- Granulomas in 75%, small with indistinct borders
- May have increased histiocytes and erythrophagocytosis

Special Stains

♦ Gram-negative coccobacillus
♦ Difficult to stain and identify in tissue sections

Diagnostic Techniques

♦ Serologic agglutination tests or ELISA
♦ If brucellosis is suspected, local and state public health authorities must be notified immediately
♦ CDC phone numbers for questions and consultation 24/7 are (770) 488-7100 or (770) 488-4819 (website: www.cdc.gov/ncidod/hip or www.bt.cdc.gov)
♦ Biosafety level 2 microbiology laboratory practices in a CDC Level A or Level B laboratory are required
♦ Level A laboratories must have at least a class II certified biological safety cabinet and level A protocols, and algorithms for ruling out suspicious microorganisms (available from CDC website)
♦ Microbiologic culture of organisms from blood, bone marrow and infected tissues

Francisella Tularensis and Tularemia

Small, non-motile, strictly aerobic, catalase positive, non-fermentative, gram-negative coccobacilli

♦ *F. tularensis*, along with *Yersinia pestis*, *Brucella* species (see above), and *Clostridium botulinum* (along with certain additional microorganisms), included in the list of Select Biological Agents of Human Disease:
- Transfer of these bacteria regulated by US Federal Code 42 CFR Part 72.6
- Except for CLIA-regulated diagnostic work, laboratories that work with, send or receive these bacteria must be registered with the CDC
- More information available from the CDC Office of Health and Safety (http://www.cdc.gov/od/ohs/lrsat)

Epidemiology

♦ Causes tularemia (also sometimes called rabbit fever, deer fly fever, or glandular fever)
♦ Naturally occurring tularemia is a zoonosis; worldwide (primarily northern hemisphere) in distribution
♦ An estimated 100–200 human cases of tularemia in US per year
♦ *F. tularensis* infects rabbits, various rodents, squirrels, raccoons, cats, deer and many other kinds of animals (humans considered accidental hosts)
♦ Naturally Transmitted by:
- Bite of infected tick, particularly including the dog tick (*Dermacentor variabilis*), wood tick (*D. andersoni*) and Lone Star tick (*Amblyomma americanum*) in North America
- Contact with infected wild animal (e.g., rabbit hunter, muskrat trapper) or domestic animal [e.g., pet cat that caught infected mouse]) or
- Inhalation of aerosol (e.g., by a squirrel hunter on a windy fall day)
- Waterborne outbreaks (water contaminated by beavers or other animals)

♦ Hazardous for laboratory personnel; infectious dose very small for *F. tularensis* (infectious dose very small also for *Y. pestis*)

Clinical

♦ Headache, malaise, fever chills usually begin abruptly 3–5 days after tick bite or exposure to infected animal
♦ Ulceroglandular tularemia:
- Skin lesion at site of tick bite (in area of enlarged lymph node)
- Reddish papule that ulcerates
- Bacteremia and lymphadenopathy – also usually present

♦ Glandular tularemia:
- Less common form
- Enlarged, painful lymphadenopathy
- No ulcerated skin lesion

♦ Typhoidal tularemia:
- Also a less common form
- Patient has sepsis clinically, but no lymphadenopathy or ulcerated skin lesion
- Patient may have pneumonia or evidence of other organ involvement
- Diagnosed usually by blood cultures

♦ Oculoglandular tularemia:
- Rare; through direct contamination of conjunctiva (e.g., fingers; exposure to aerosols)
- Ulcer on palpebral conjunctiva; enlargement of nearby lymph nodes

♦ Oropharyngeal:
- From ingestion of contaminated, poorly cooked meat; water
- Manifestations include pharyngitis, tonsillitis, and cervical lymphadenopathy

♦ Pneumonic tularemia:
- From inhalation of aerosolized *F. tularensis*
- Those at risk: hunters, farmers, sheap shearers, landscapers, and laboratory workers

- Radiographic findings: bronchopneumonia (may be bilateral), or lobar infiltrates, hilar adenopathy, pleural effusions; or focal infiltrates, or apical infiltrates.

Microscopic

- Inflammatory response:
  - Acute: fibrin, neutrophils, macrophages, and T lymphocytes involved; often with liquefactive necrosis
  - Later: characterized by lymphocytes, macrophages, and giant cells
  - Also may be caseation, calcification and fibrosis in chronic lesions
- Lymph nodes: subcapsular or geographic areas of necrosis that may resemble infarcts
- Lungs: findings may include extensive necrosis and cavitation

Special Stains

- *F. tularensis* not visualized by use of any of the tissue Gram's stains
- Silver impregnation stains (e.g., Warthin-Starry, Steiner or Dieterle) may reveal tiny coccobacilli in macrophages
- Specific direct fluorescent antibody stains or immunohistochemical stains (formalin-fixed tissue) used at CDC

Diagnostic Techniques

- Biosafety Hazard: collection and processing of specimens extremely hazardous for all involved
- *F. tularensis*: not readily isolated and not readily identified in microbiology laboratory
- If tularemia is suspected, local and state public health authorities must be notified immediately.
- CDC phone numbers for questions and consultation 24/7 are (770) 488-7100 or (770) 488-4819 (website: www.cdc.gov/ncidod/hip or www.bt.cdc.gov)
- Biosafety level 2 microbiology laboratory practices in a CDC Level A or Level B laboratory are required
- Level A laboratories must have at least a class II certified biological safety cabinet and level A protocols, and algorithms for ruling out suspicious microorganisms (available from CDC website)

Gram-Negative Cocci

Neisseria gonorrhoeae

Gram-negative, oxidase and catalase positive coccus that occurs as diplococci (pairs) with adjacent sides flattened.

Clinical Manifestations and Pathology

- Acute gonococcal urethritis: with dysuria, pyuria and frequency
- Cervicitis: neutrophilic, lymphocytic and plasmacytic inflammation; focal epithelial necrosis and reactive cellular atypia
- Pelvic inflammatory disease; manifestations include endometritis, salpingitis, tuboovarian abscess (frequently involves mixed anaerobic and aerobic vaginal flora), pelvic peritonitis, and perihepatitis (Fitz-Hugh-Curtis syndrome) in varying combinations
- Rectal gonococcal infection: ~ 40% of women with uncomplicated gonorrhea (also men who have sex with men)
- Bacteremia: occurs in ~ 0.5% to 3% of patients with gonorrhea
- Arthritis: in young adults; caused by *N. gonorrhoeae* relatively frequently
- Ophthalmia neonatorum (purulent conjunctivitis): the most common clinical manifestation in infants
- Pharyngitis

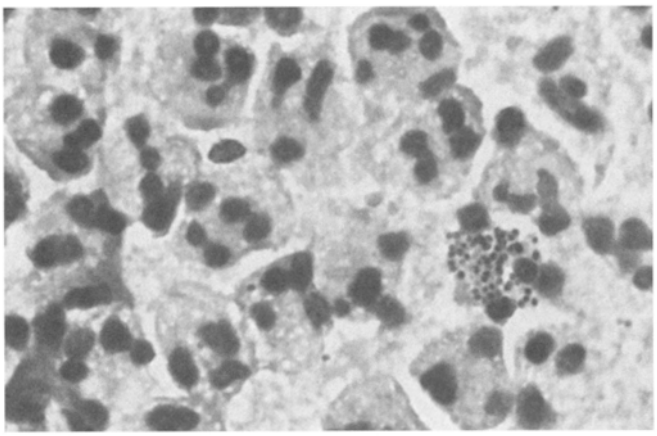


Fig. 14. *Neisseria gonorrhoeae*; smear of exudate from male urethra (Gram).

Microscopic ***(Figure 14)***

- Gram's stain is a sensitive and specific way to diagnosis gonococcal urethritis in symptomatic (but not asymptomatic) males only.
- The finding of neutrophils and intracellular gram-negative cocci in a direct smear of urethral exudate from males is considered diagnostic of gonorrhea.
- For females, Gram's stain is not recommended (sensitivity and specificity are lacking)
- Gram's stain appearance of *Acinetobacter* species in female genitourinary tract microbiota can be morphologically indistinguishable from that of *N. gonorrhoeae.*

Diagnostic Techniques

- Culture, the historic "gold standard" diagnostic method, is sensitive and specific but has largely been replaced by DNA probe tests in clinical microbiology laboratories.
- For testing children or persons who have been sexually assaulted for gonorrhoeae, culture is still considered the only appropriate means of diagnosis.

Neisseria meningitidis

Gram-negative, oxidase and catalase positive, encapsulated coccus that occurs as diplococci (pairs) with adjacent sides flattened. Commonly carried in nasopharyngeal flora of healthy individuals. Currently 13 antigenic serogroups: A, B, C, D, X, Y, Z, E, W-135, H, I, K, and L.

Clinical Manifestations and Pathology

- Meningitis: the second most common cause of community acquired meningitis in adults; majority of cases due to groups B and C; occurs with or without sepsis
- Meningococcemia: with sepsis; with or without meningitis (**Figure 15A**):
  - Purpura fulminans (widespread hemorrhage)
  - Disseminated intravascular coagulation (DIC)
  - Waterhouse-Friedrickson syndrome (bilateral hemorrhagic necrosis of adrenals); not unique to *N. meningitidis*, caused also by *H. influenzae*

*Microscopic (**Figure 15B, C**)*

- Purulent inflammation
- Gram-negative diplococcus

Diagnostic Techniques

- Gram-stain of CSF both sensitive and specific for *N. meningitidis*; however, other bacteria including *Acinetobacter* species are morphologically similar
- Microbiologic culture required for definitive diagnosis

Anaerobic Bacteria and Diseases

Anaerobic Sporeforming Bacilli: The Clostridia

- Genus *Clostridium*: composed of anaerobic, gram-positive, sporeforming rods:
  - But a few (e.g., *C. tertium* and *C. histolyticum*) are aerotolerant
- Unlike the genus *Bacillus*:
  - *Clostridium* species typically form spores anaerobically but not aerobically
  - *Clostridium* species do not produce catalase
- Although there are ≥ 150 validly published species (at this writing), only 30 or so are involved in diseases. Of these species, about half are toxigenic, capable of causing a number of important diseases (e.g., tetanus; pseudomembranous colitis)
- Principal habitats are soil and intestinal tracts of humans and other animals
- Most of the time clostridia coexist peacefully within and around us, but circumstances may change leading to dire consequences (e.g., gas gangrene)
- Endogenous diseases involving clostridia from the hosts own microbiota are more common than exogenous diseases (e.g., foodborne botulism)
- Both toxin mediated diseases (some with no or limited morphologic changes) and suppurative/necrotizing infections (with profound tissue damage) are produced

Clostridium perfringens

Clostridial myonecrosis (Gas Gangrene)

- *C. perfringens* type A – the most common cause
- Pathogenesis involves:

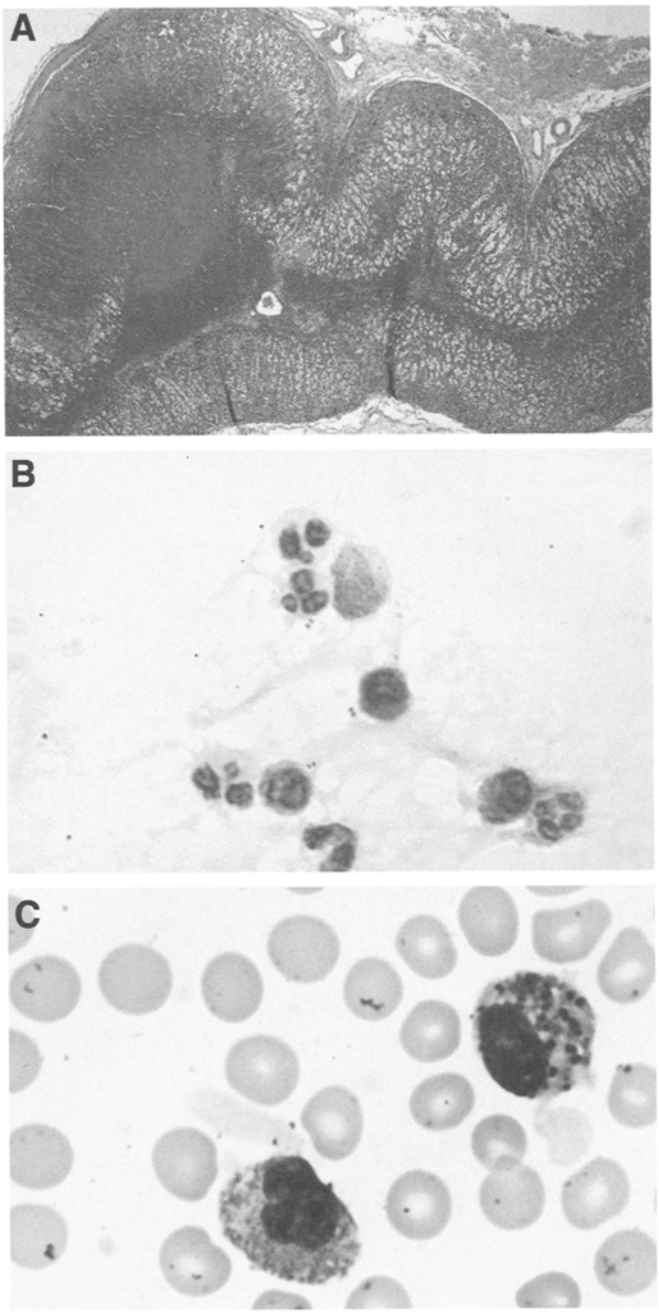


Fig. 15. Adrenal hemorrhage and necrosis; **(A)** patient with meningococcal sepsis (Waterhouse-Friedrickson syndrome), **(B)** peripheral blood buffy coat smear (Wright), **(C)** cerebrospinal fluid (Gram).

  - Traumatic injuries, both major and minor
  - Spontaneous myonecrosis in absence of trauma; associated with colon cancer, other forms of bowel disease, leukemia, and neutropenia
  - α-toxin (lecithinase; also called phospholipase C) plays major role in disseminated infection and hemolysis (may be massive)

- θ-toxin (also has hemolytic and cytolytic properties)
- Rapid multiplication and metabolic activity of organism with gas production

♦ Other causative agents include *C. septicum* (especially in patients with spontaneous myonecrosis and/or underlying malignancy), *C. novyi, C. histolyticum, C. sordellii*

Clinical Features

♦ Rapidly progressive, life-threatening condition with necrosis of muscle and soft tissues, gas (mostly hydrogen and nitrogen), and prominent systemic signs of toxemia and hypotension.

♦ Patient experiences increasingly severe pain in a traumatic or surgical wound

♦ Skin: intensely edematous, red or bronze, often with large hemorrhagic bullae

♦ Crepitance (gas) aids in making a diagnosis but:
- Not always present, particularly early in the course of the disease
- Not specific: occurs also in infections involving other toxigenic as well as nontoxigenic species of *Clostridium*, *Streptococcus*, *E. coli* and other enterics, and in polymicrobial infections involving non-clostridial anaerobes plus other microorganisms

♦ Thin, watery, sanguinolent or brownish discharge with foul-sweet odor

♦ Shock and renal failure may develop rapidly

Pathology and Microbiologic Diagnosis ***(Figure 16)***

♦ Early diagnosis needed to stop rapid progression of devastating disease; drastic surgical measures usually required.

♦ Involved muscle has poor blood supply and fails to respond to stimuli, indicating it is dead (undergoes liquefactive necrosis; may appear gelatinous)

♦ Direct microscopic examination of discharge material, aspirated fluid, or frozen section reveals a necrotic background with no inflammatory cells and abundant, relatively large, box-car shaped gram-positive rods. (However, neutrophilic infiltrates will be present in the advancing edges of the lesion.)

♦ Spores almost never seen microscopically in clinical materials when myonecrosis is due to *C. perfringens*

♦ Spores usually evident microscopically in myonecrosis caused by other species of *Clostridium* (e.g., *C. septicum*)

♦ Other bacteria can cause infections with gas and severe muscle involvement similar to clostridial myonecrosis (e.g., "streptococcal myonecrosis," or "anaerobic streptococcal myositis"), but these can be differentiated by direct microscopic examination and microbiologic cultures.

♦ Cultures:
- Aspirates, fresh tissue
- Blood cultures (positive in about 15% of patients)
- *C. perfringens* grows rapidly (12–18 hours of incubation) in various laboratory media; produces abundant gas

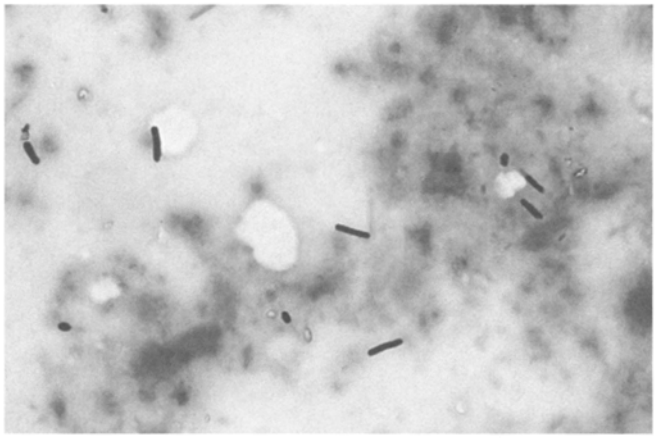


Fig. 16. *Clostridium perfringens* myonecrosis, direct smear of aspirated material from upper extremity lesion (Gram).

- Other characteristics:
  - Medium to large gram-positive rods (spores not seen initially)
  - Double zone of hemolysis on anaerobe blood agar
  - Lecithinase activity on egg yolk agar
  - Proteolytic

Clostridial Suppurative Myositis

♦ A more benign infection with far less muscle destruction than gas gangrene, which lacks systemic toxemia findings.

♦ Localized pain, tenderness and fluctuant swelling, usually in a thigh or forearm; management includes surgical drainage (not amputation)

♦ Seen mostly in intravenous drug abusers, or associated with injections of therapeutic drugs (e.g., in diabetic patients)

♦ Pathologic findings: abscess formation in skeletal muscle and acute inflammation in adjacent soft tissue and fascia

Clostridial Cellulitis

♦ Cellulitis without myonecrosis can be caused by *C. perfringens*, other clostridia or a variety of other bacteria

♦ Localized or extensive suppurative, gas forming infection involving soft tissue, but without the systemic toxemia that is characteristic of clostridial myonecrosis.

♦ Neither the cellulitis nor the gas extends into skeletal muscle.

Uterine Gas Gangrene

♦ Dramatic, fulminating, life-threatening illness due to toxigenic clostridial invasion of myometrium

♦ In the US:
- Now rare; it once occurred relatively frequently as a consequence of self-induced or illegal abortions
- Also occurs as a complication of spontaneous abortion, vaginal delivery, cesarean section, amniocentesis and uterine tumors in nonpregnant women

- Clinical features dominated by severe toxemia and septic shock, with massive intravascular hemolysis (mostly caused by α-toxin), hemoglobinuria ("port wine" urine), acute renal failure (acute tubular necrosis)
- Uterus undergoes necrosis; pathology similar to findings in skeletal muscle (above)

Intestinal illnesses caused by Clostridium perfringens

- Food poisoning:
  - Caused by *C. perfringens* type A strains which produce enterotoxin
  - One of the commonest causes of food-borne disease in the US
  - Incubation period 7–15 hours; typically after eating meat or meat products contaminated with about 10^8 vegetative cells
  - In small intestine, *C. perfringens* undergoes sporulation, producing the enterotoxin
  - Profuse diarrhea and abdominal pain (nausea and vomiting infrequent)
  - Pathologic features of *C. perfringens* food poisoning in humans not clear
- Pseudomembranous colitis:
  - While *Clostridium difficile* (discussed elsewhere) is the major cause of pseudomembranous colitis and antibiotic associated diarrhea,
  - *C. perfringens* has also been reported to cause these conditions (incidence unknown)
- Enteritis necroticans (Pig Bel):
  - Caused by β-toxin producing strains of *C. perfringens* type C
  - Life-threatening infectious disease characterized by ischemic necrosis of small intestine
  - Cases most frequently reported from Papua, New Guinea: occurs in other developing countries of the world, and in developed countries including the United Kingdom and the US
  - Factors involved:
    - Consumption of pork or other contaminated meat
    - Poor nutrition
    - A diet rich in trypsin inhibitors (e.g., sweet potatoes, peanuts or soy beans)
    - Other trypsin inhibitors (e.g., *Ascaris lumbricoides*)
  - Pathology:
    - Although jejunum is the usual primary site, the entire small bowel may be involved
    - Acute, patchy, hemorrhagic, necrotizing, ulcerative, and inflammatory disease
    - Pseudomembranes may be present
    - Some have gas cysts but most do not
    - Prominent mucosal inflammation and ulceration
    - Submucosa edematous with neutrophilic infiltrates
    - Small vessel thrombosis often prominent
    - Full thickness necrosis occurs in advanced disease
    - Tissue Gram's stains may reveal mixed bacteria but not permit differentiation between pathogenic clostridia and the normal microbiota
  - Differential diagnosis:
    - Ischemic bowel disease and infections due to other bacteria
- Diagnostic Techniques:
  - PCR methods in research settings, but not commercially available
  - Feces, blood, bowel wall and peritoneal fluid should be collected for microbiologic studies to include isolation, identification and typing of *C. perfringens*

Clostridium septicum and Bacteremia

Microaerotolerant, histotoxic species with potential of causing severe life-threatening disease

- *C. septicum:* rarely recovered from feces of healthy humans:
  - More commonly present in feces of patients with colon cancer and
  - In normal appendices.
- Ranked as second or third most frequent cause of gas gangrene during wartime
- Currently recognized increasingly as a major cause of spontaneous (nontraumatic) myonecrosis
- *C. septicum* bacteremia occurs frequently in patients with:
  - Occult colon cancer
  - Leukemia/lymphoma
  - Diabetes mellitus
- Patients present clinically with:
  - Signs of sepsis
  - Abdominal pain, tenderness, vomiting and diarrhea
  - Rapid metastatic spread of infection and myonecrosis to distant locations
- Another important association with *C. septicum* bacteremia is necrotizing enterocolitis in neutropenic patients
- Pathology: **(Figure 17A,B)**:
  - Macroscopically in neutropenic colitis, there is thickening, ulceration and hemorrhagic necrosis of the cecum (with or without involvement of the ascending colon and/or terminal ileum)
  - Microscopic examination of involved cecum reveals hemorrhagic necrosis of the mucosa, ulceration, marked edema and thickening of the submucosa, but with few inflammatory cells
  - Gas cysts are sometimes present, particularly in the submucosa
  - Macroscopic and microscopic findings in myonecrosis and other soft tissue infections due to *C. septicum* are

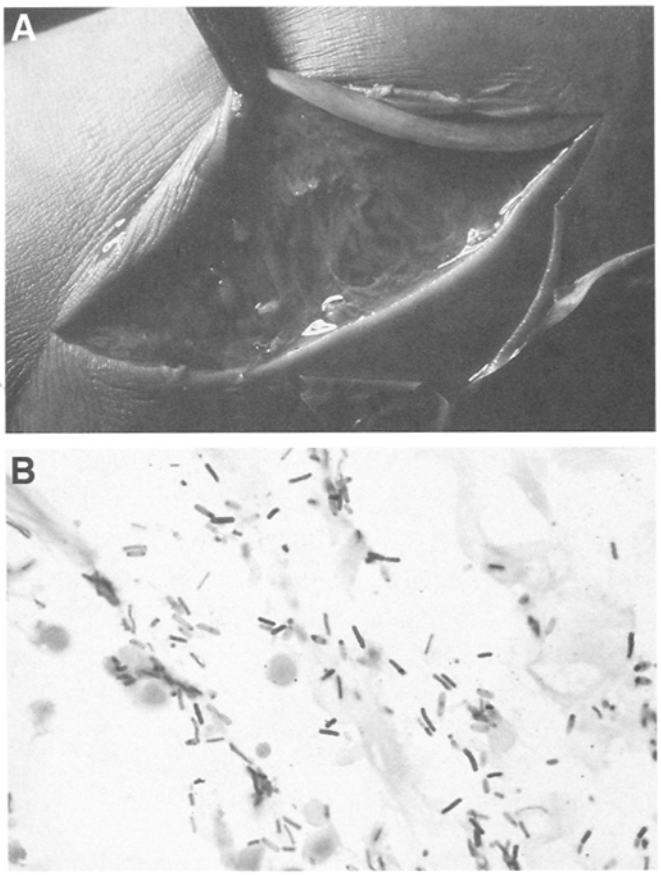


Fig. 17. *Clostridium septicum* myonecrosis involving lower extremity (**[A]** gross photo), **(B)** gram-positive rods with subterminal spores in a necrotic background (Brown & Brenn).

similar to those observed in myonecrosis caused by *C. perfringens*

- Tissue Gram's stains (i.e., Brown and Brenn) may reveal large numbers of gram-positive, sporeforming rods in the involved tissue

♦ Microbiology:

- Commercially available immunofluorescent antibody stains can aid in identifying the organism in fresh clinical materials or in tissue sections
- Blood, fresh tissue (e.g., bowel wall), peritoneal fluid, intestinal contents or feces can be cultured for *C. septicum*

Clostridium difficile

Obligately anaerobic gram-positive rods that produce subterminal spores

Epidemiology and Pathogenesis

♦ *C. difficile* and its toxins commonly present in feces of healthy neonates

♦ Carriage rate in feces of children older than 2 years and in healthy adults is 2–3%

♦ *C. difficile* can be isolated from ≥20% of adults who have recently received antibiotics, though toxin is not frequently detected in their stools

♦ *C. difficile* intestinal illness almost always associated with antibiotic exposure

♦ Virulence: most virulent strains produce toxins A&B; some produce only toxin B:

- Enterotoxin (toxin A): induces positive fluid response in rabbit ileal loop model
- Cytotoxin (toxin B): induces cytopathic effects in many tissue culture cell lines
- Until recently, all toxigenic strains capable of causing disease were believed to produce both toxins, but now it is known that some toxigenic strains produce only toxin B (but not toxin A), and that these strains also cause antibiotic associated diarrhea and pseudomembranous colitis
- Strains producing neither toxin considered nonpathogenic

Clinical Features and Pathology ***(Figure 18A,B)***

♦ *C. difficile* produces spectrum of findings:

- Asymptomatic colonization with unremarkable mucosa
- Antibiotic-associated diarrhea without or with nonspecific inflammation of colon (colitis)
- Pseudomembranous colitis (pathologic findings not diagnostic for *C. difficile*):
  - Grossly: yellow plaques (usually patchy) overlying an ulcerated mucosa
  - Microscopically: marked mucosal and submucosal edema with intense neutrophilic inflammation. The most characteristic finding is that of a Pseudomembrane – particularly a "summit lesion" (sometimes reminiscent of a "volcanic eruption" or a "mushroom cloud") contains abundant fibrin, mucin, neutrophils, and sloughed mucosa

♦ The major cause of nosocomial diarrhea, and a potentially serious threat to immunocompromised patients:

- Spread by spores on hands
- Spores on bed sheets, bedpans, various surfaces in hospital environment

Diagnostic Techniques

♦ Isolation of toxigenic *C. difficile* that produces toxin B or both toxins A&B (non-toxigenic *C. difficile* represents colonization not related to disease)

♦ Direct detection of toxin B (e.g., by cytotoxin neutralization assay) or toxins A&B (e.g., by a commercial EIA kit) in patient's feces

C. botulinum and Botulism

♦ Botulism: rare, life-threatening neuroparalytic disease caused by action of one of the most potent toxins known

♦ Seven known antigenic types of botulinal toxin (A-G); types A, B and E cause most human disease

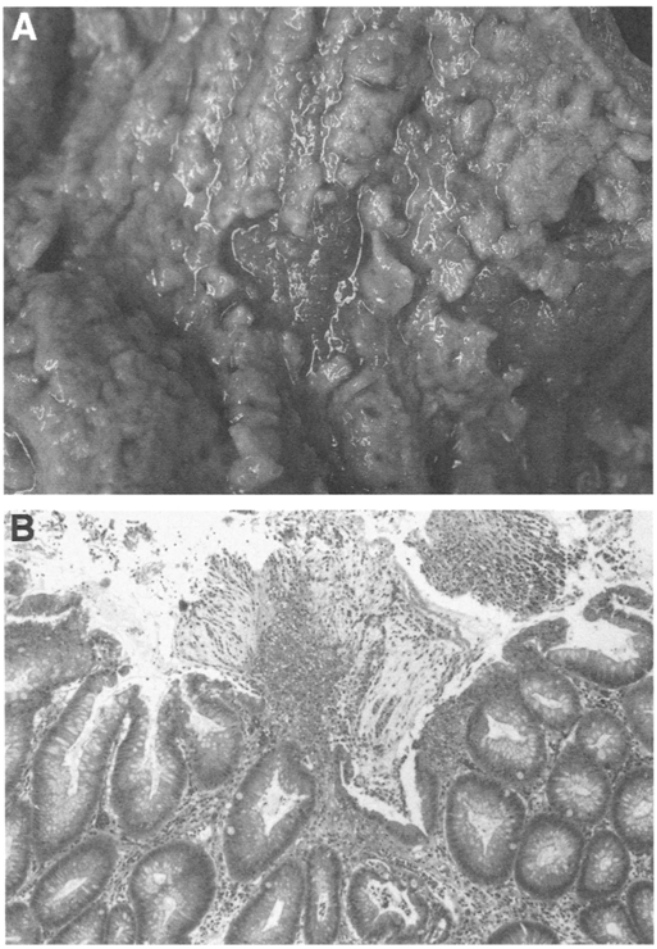


Fig. 18. *Clostridium difficile* - pseudomembranous colitis ([**A**] gross photo), (**B**) pseudomembranous colitis (H&E).

- Spores of most strains of *C. botulinum* survive at 100° C for several hours

Clinical Features

- Toxin enters blood stream from site where it was absorbed or produced
- Then carried to peripheral nerve endings, particularly neuromuscular junctions of motor neurons, where
- It binds irreversibly to presynaptic membranes, and prevents release of acetylcholine
- Clinical hallmark of botulism is acute flaccid paralysis:
  - Begins with bilateral cranial nerve impairment involving muscles of face, head, pharynx
  - Then descends symmetrically to involve muscles of thorax and extremities
  - Death may result from respiratory failure due to:
    - Paralysis of tongue or muscles of pharynx with occlusion of upper airway, or
    - Paralysis of diaphragm and intercostal muscles
- Five categories of botulism:
  - Classical food-borne botulism: caused by ingesting preformed botulinal toxin in contaminated food
  - Wound botulism: results from growth of *C. botulinum* and production of toxin *in vivo* in an infected wound
  - Infant botulism (the form encountered most frequently in the US): caused by growth and production of toxin within the intestinal tract of an infant colonized by *C. botulinum*
  - Botulism due to intestinal colonization in children and adults (with production of toxin within the intestine)
  - Inhalational botulism: results from aerosolization of botulinum toxin (e.g., as a bioterrorist weapon)
  - Pathology – No histopathologic findings attributed to neurophysiologic dysfunction that occurs in botulism, regardless of category

Diagnostic Techniques

- Most hospital microbiology laboratories not equipped to process specimens from patients suspected of having botulism
- Physicians should notify State Health Department or the CDC immediately if botulism is suspected
- CDC phone numbers for questions and consultation 24/7 are (770) 488-7100 or (770) 488-4819 (website: www.cdc.gov/ncidod/hip or www.bt.cdc.gov)

C. tetani and Tetanus

- *C. tetani*, the only major pathogen among the Clostridia that produce terminal spores
- Organism and its spores: soil and intestinal contents of animals (including humans, occasionally)
- Tetanus: extremely dramatic neurologic illness caused by action of potent toxin elaborated by *C. tetani*, "tetanospasmin."
- Tetanospasmin blocks release of neurotransmitter (gamma-aminobutyric acid) at synapses in CNS:
  - Inhibitory impulses to motor neurons blocked
  - Uninhibited firing of motor nerve transmissions results in prolonged muscle spasms (hallmark of the disease)
- Tetanus rare in the US
- Often associated with puncture wounds that do not appear serious
- Injecting drug-user associated infections:
  - Recent reports of *C. tetani* infections in injecting drug-users ("skin popping") in California
  - Also *C. novyi* infections in injecting drug-users (recently in the UK, particularly Wales)
- Neonatal tetanus:
  - Babies born to inadequately immunized mothers
  - Has followed application of non-sterile materials (e.g., soil) to umbilicus

- Pathology and Microbiology: no characteristic histopathologic findings of *C. tetani* wound infections
- Diagnosis: based on clinical features (particularly):
  - Trismus or "lockjaw" with difficulty opening mouth (painful, contracted masseter muscles)
  - Risus sardonicus (involving orbicularis oris contraction)
  - Opisthotonic posturing
  - Neither biopsies nor microbiology cultures aid in making diagnosis

Anaerobic, Nonsporeforming Gram-Negative Bacilli: the *Bacteroides fragilis* Group, *Prevotella* and *Porphyromonas* Species, and the Genus *Fusobacterium*

Current frequency of medically important anaerobes isolated from properly collected clinical specimens

- About 35% of all anaerobe isolates are the medically important anaerobic gram-negative rods
- Anaerobic cocci account for 25% of the isolates
- The non-sporeforming gram-positive rods account for about 25% of the isolates
- Clostridia now account for < 15% of the anaerobe isolates

Among the most important inhabitants of the human microbiota in the:

- Oral cavity
- Gastrointestinal tract
- Vagina

Most infections caused by these bacteria are "endogenous" (sources of the organisms are the hosts' own microbiota)

- Many of the infections caused by these bacteria are polymicrobial
  - Involving gram-negative anaerobes: mixed with other anaerobes (e.g., anaerobic cocci or non-sporeforming gram-positive rods) or
  - Gram-negative anaerobes mixed with facultative anaerobes

Infections in which anaerobic, nonsporeforming gram-negative rods are involved and important include:

- Blood stream infections
- Brain abscess; subdural empyema
- Dental/oral infections (e.g., periodontal disease, root canal infections)
- Chronic sinusitis
- Chronic otitis media; mastoiditis
- Peritonsillar abscess
- Neck space infections
- Aspiration pneumonia
- Lung abscess
- Thoracic empyema
- Pyogenic liver abscess
- Peritonitis; intraabdominal abscess
- Appendicitis and its complications
- Post-operative wound infections following intraabdominal/pelvic surgery
- Endometritis, salpingitis, tuboovarian abscess
- Necrotizing skin and soft tissue infections including:
  - Necrotizing fasciitis (although originally associated with group A *Streptococcus*, it commonly involves *Bacteroides* species mixed with other bacteria)
  - Synergistic necrotizing cellulitis:
    - High mortality (about 50%); patients often die of septic shock
    - Most common site is the perineum
    - Major antecedents:
      - Perirectal abscess or ischiorectal abscess; lesions may spread to pelvis or abdomen, the buttocks, the thighs
      - Lower leg vascular disease or diabetic foot ulcers
    - About 75% of patients have diabetes; about 50% have cardiovascular and renal disease; about 50% are obese
    - This is a polymicrobial infection in which *Bacteroides* species and various other anaerobes are common (e.g., anaerobic cocci), particularly *E. coli* and other enterics
    - Surgical management involves radical debridement
  - Nonclostridial crepitant cellulitis:
    - Most often seen in diabetic patients
    - Lower extremities, the most common sites of involvement; the infectious process tracks along fascial planes
    - Bacteria most commonly involved: *Bacteroides* species, anaerobic cocci, *E. coli, Klebsiella* or other enteric bacteria
    - Infections not as serious as those described above for *C. perfringens* and other histotoxic clostridia
    - Skeletal muscle remains viable
    - Presence of gas in soft tissue does not mean that the patient has myonecrosis
    - Surgical management should not be nearly so aggressive as that required for gas gangrene; should be tailored to the correct diagnosis

Pathology ***(Figure 19)***

- Gross examination of specimens can provide important clues suggesting the presence of anaerobes (particularly a putrid odor, pus, or necrotic tissue)
- Direct gram-stained smears of aspirates, exudates, touch preparations of specimens or frozen sections can aid in

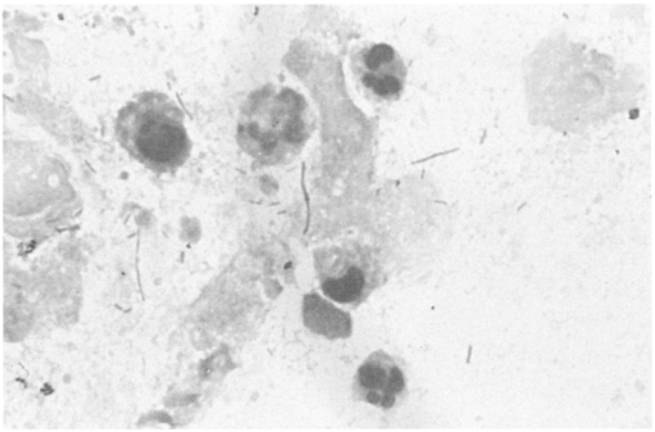


Fig. 19. *Fusobacterium nucleatum* (& mixed anaerobes) head & neck infection (Gram).

presumptive diagnosis long before results of microbiologic cultures or permanent sections are available

- Infections involving the anaerobic gram-negative bacteria are characterized by acute suppurative, necrotizing inflammation
- Abscess formation is considered the hallmark of infections caused by the *Bacteroides fragilis* group
- The anaerobic gram-negative bacteria in this group include rod shaped bacilli, some with vacuoles (e.g., *Bacteroides* species):
  - Sizes vary from medium (*Bacteroides* spp.) to small (many *Prevotella* and *Porphyromonas* species)
  - *Fusobacterium nucleatum* forms thin, needle shaped rods; *F. necrophorum* and other species of *Fusobacterium* tend to be pleomorphic

Anaerobic Microbiology

- Anaerobic cultures are indicated in the kinds of serious infections listed above
- Good anaerobic microbiology depends upon proper selection, collection and transport of the specimens:
  - In the selection of specimens, sites contaminated by normal flora should be avoided
  - Prior to collection of specimens, skin or mucosal surfaces should be decontaminated
  - Specimens to collect are tissue samples (e.g., biopsy or tissue removed at surgery) or exudates aspirated by needle and syringe
  - Tissue should be placed in sterile, screw-capped containers which then can be sealed in anaerobic gas-impermeable bags for transport to the lab
  - Pus should be injected into an anaerobic transport container
  - Swabs are not desirable for anaerobic specimens as they tend to dry out and carry only a small volume of material

Anaerobic Gram-Positive Cocci: the "Peptostreptococci"

As a group, the anaerobic cocci share similar habitats, but are isolated somewhat less frequently than the anaerobic nonsporeforming gram-negative bacilli in the microbiology laboratory

Recent Taxonomic Changes

- Until recently most clinically important species of anaerobic cocci were classified in the genus *Peptostreptococcus*
- Recently, major taxonomic revisions have taken place; now, *Peptostreptococcus anaerobius* is the only remaining species in this genus
- Those formerly called *P. magnus* and *P. micros*: now called *Finegoldia magna* and *Micromonas micros*
- *Peptostreptococcus asaccharolyticus*: now called *Peptoniphilus asaccharolyticus*
- *Peptostreptococcus parvulus,* also commonly isolated from clinical specimens, is now *Atopobium parvulum*
- While additional taxonomic changes have been made within the anaerobic cocci, many clinicians and microbiologists are still not aware of them. Thus, the terms "Peptostreptococci" or anaerobic gram-positive cocci are still used in discussions about these bacteria

Infections in which the "Peptostreptococci" are Commonly Encountered

- Many of the types of polymicrobial infections listed for the anaerobic nonsporeforming bacilli (above) are mixed with anaerobic cocci
- Anaerobic pleuropulmonary infections, deep wound infections following surgical procedures, anaerobic osteomyelitis (due to *Finegoldia magna*) and a number of skin and soft tissue infections (e.g., diabetic foot infections) are examples of infections that more commonly involve this group of bacteria

Pathology and Anaerobic Microbiology

- Gross and microscopic findings indistinguishable from those described for the anaerobic nonsporeforming gram-negative bacilli
- Direct smears and tissue Gram's stains reveal varying size gram-positive cocci ranging from relatively large diameter (e.g., *Finegoldia magna*) to tiny (e.g., *Micromonas micros*); arrangements can not be distinguished from those of the nonanaerobic cocci
- Anaerobic culture – complicated by strict oxygen sensitivity and relatively slow growth of the anaerobic cocci

Anaerobic Nonsporeforming Gram-Positive Bacilli

Actinomyces species and Actinomycosis

- Actinomycosis is an endogenous infection caused by anaerobic or aerotolerant filamentous bacteria, mostly of the genus *Actinomyces*

- Bacteria that have been reported to cause actinomycosis in humans include *A. israelii, A. naeslundii, A. odontolyticus, A. gerencseriae, A. viscosus, A. meyeri, A. georgiae, A. neuii* subsp. *neuii, Propionibacterium propionicum* (formerly *Arachnia propionica, Bifidobacterium dentium* (formerly *B. eriksonii*), *Rothia dentocariosa*, and *Eubacterium nodatum*:
  - In humans the major cause of actinomycosis is *A. israelii*
  - In animals, the principal cause is *A. bovis*
- Species of *Actinomyces* inhabit the oropharynx, gastrointestinal tract and vagina of healthy individuals

Clinical – four forms of actinomycosis based on anatomic regions of the body

- Cervicofacial ("lumpy jaw"):
  - Most common form of actinomycosis
  - May develop without prior injury to the oropharyngeal mucosa, or
  - May complicate periodontal disease, dental extractions or other dental/oral trauma
  - Characteristic swelling and firmness of local tissues, abscess formation, and sinus tracts which may extend from the oral cavity through the mandible or other bone as well as soft tissue and skin
  - Material from draining sinus tracts may contain "sulfur granules," (i.e., yellow or brown-yellow colonies of bacteria surrounded by adherent leucocytes, usually a few to several mm in diameter)
  - Cervicofacial actinomycosis may extend into maxillary sinus or other sinuses, invade the orbit, or cranial bones; or may extend to thorax, involve other bones, joints, the skin or the CNS
- Thoracic:
  - Develops most often following aspiration of oropharyngeal contents
  - But sometimes from direct extention from cervicofacial infection
  - All tissues/organs of thoracic cavity potentially susceptible
- Abdominal:
  - Usually arises from intestine following trauma or perforation (e.g., appendicitis)
  - Infection may extend directly within abdomen to involve any tissue or organ (or could spread hematogenously)
- Pelvic:
  - Mostly associated with use of intrauterine devices
  - Also may arise from an intestinal/colonic focus

Macroscopic

- Yellow (sometimes green) granules in a background of sanguineous material
- Sinus tracts with purulent exudates
- Gray bands of fibrous connective tissue

Microscopic ***(Figure 20A-C)***

- H&E stained sections: solitary or multiple abscesses; sinus tracts; granulation tissue and fibrosis
- Sulfur granules with Splendore-Hoeppli material (amphophilic or eosinophilic center with peripherally radiating serrate margins)
- Actinomycotic filaments not readily seen in H&E or PAS stains

Special Stains

- GMS-positive: thin, delicate filaments with right angle branching
- Brown and Brenn tissue Gram's stain: Gram-positive, 1μm diameter, beaded, branching filaments
- Fite modified acid-fast stained section: negative (not acid-fast, and not partially acid-fast)
- Modified Kinyoun acid-fast stain of smears or tissue touch preparations: negative as well

Differential Diagnosis

- Hematoidin crystals, dense clumps of spermatozoa, mucin or fibrin threads in cytologic preparations
- *Nocardia*; septate hyphae (eumycotic mycetoma); nonbranching bacilli or cocci (botryomycosis) may form sulfur granules. Differentiate with GMS, Brown and Brenn Gram's stain, and acid-fast stains

Diagnostic Techniques

- Anaerobic culture
- Enrichment broth culture (Thiol) with extended, prolonged (2–4 week) incubation often necessary
- Immunofluorescence

Mycobacterium species

Mycobacterium tuberculosis and the non-tuberculous Mycobacteria produce necrotizing and non-necrotizing granulomatous inflammation in the lungs and other organs and tissues. A detailed discussion is provided in Chapter 22, and they are considered in additional chapters including Chapters 9 and 37

Miscellaneous Other Bacteria

Bartonella henselae

Reservoirs include domestic cats, cat fleas (*Ctenocephalides felis*), ticks

Clinical Features

- Bacillary angiomatosis (BA):
  - Widespread unusual vascular proliferation, mostly in HIV patients
  - May affect any organ system but skin lesions most common, especially mucocutaneous junctions
  - Number/distribution of skin lesions reflects level of immunosuppression and infection route; if subcutaneous, can erode bone causing osteolytic bone lesions
  - Splenic or hepatic peliosis

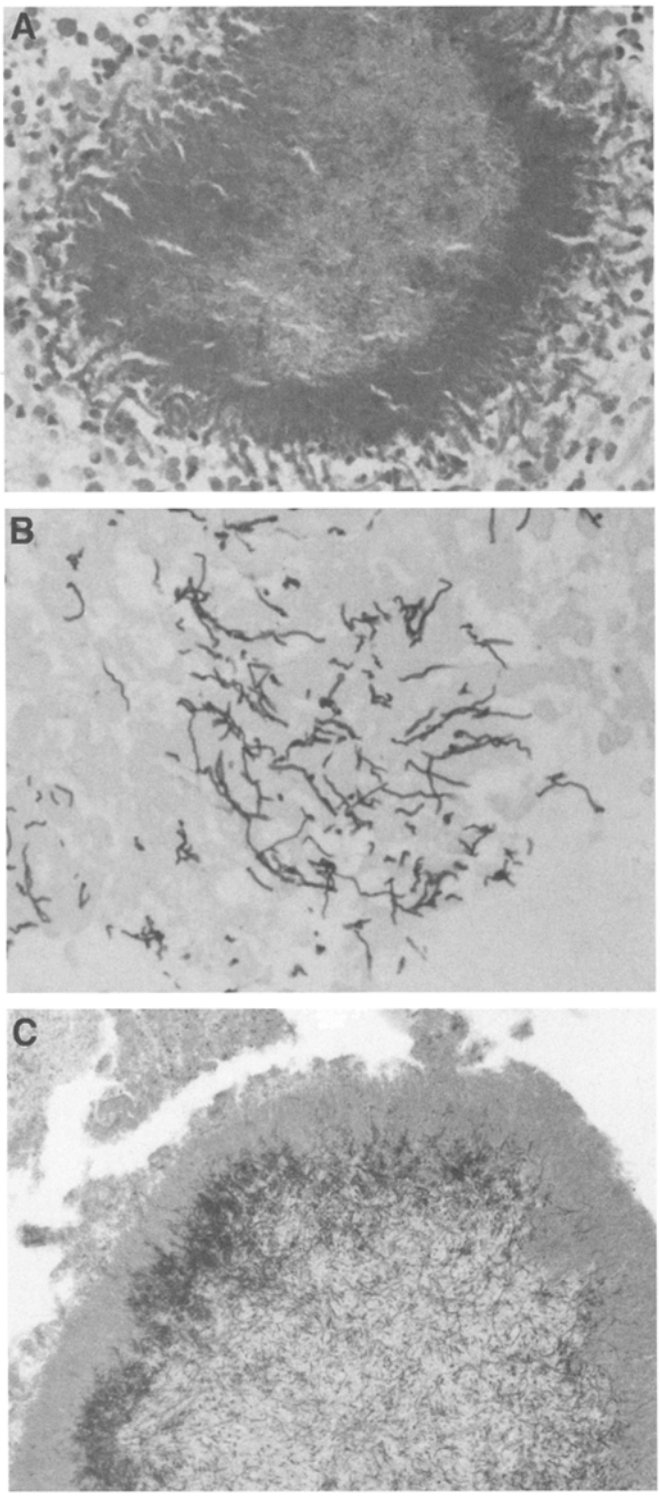


Fig. 20. *Actinomyces israelii*; pulmonary actinomycosis; sulfur granule; **(A)** H&E, **(B)** GMS, **(C)** Brown & Brenn.

- Central nervous system and respiratory tract lesions documented

♦ Cat-scratch disease (CSD) and oculoglandular syndrome of Parinaud:

- Chronic regional lymphadenopathy in children and adolescents; mostly September-March (July and August in warm climates); develops ~2 weeks after exposure
- 90% of patients have cat exposure (bite, scratch or lick usually from cat less than 1 year old)
- Tender head and neck nodes, other sites; single node in half of cases; regresses after 2–4 months

♦ Primary papule or pustule persists 2–3 weeks

♦ Fever, malaise, headache, muscle aches, sore throat, and rash may occur

Macroscopic

♦ Bacillary angiomatosis:
- Papules and nodules ranging from tan to pink-red-purple with intact, smooth or ulcerated surfaces
- Enlarged lymph nodes with punctate red areas
- Hepatosplenomegaly with blood filled spaces

♦ Cat-scratch disease
- Enlarged lymph node

Microscopic ***(Figure 21A, B)***

♦ Bacillary anigiomatosis:
- Well-circumscribed lobular vascular proliferation with extracellular purple granular clusters of bacilli and surrounding neutrophils and leukocytoclastic debris
- Large cuboidal endothelial cells with vesicular nuclei and prominent nucleoli line vessels and may protrude into lumen
- Macrophages may predominate if partially treated
- Lymph node effacement; organisms more abundant than in cutaneous lesions

♦ Cat-scratch disease:
- Stellate microabscesses, granulomas and follicular hyperplasia of lymph nodes

Special Stains

♦ Weakly Gram-negative bacillus but modified Gram's stains, Gomori's methenamine silver, periodic acid-Schiff, acid-fast will not show organism well

♦ Warthin-Starry (silver impregnation, also Steiner, Dieterle); Giemsa+

Differential Diagnosis

♦ Clinically skin lesions identical to Kaposi's sarcoma and pyogenic granuloma

Diagnostic Techniques

♦ Culture; antibodies to *B. henselae* more prevalent in patients with AIDS and neurologic symptoms

Bartonella quintana

Reservoir includes louse (*Pediculus humanus*)

Clinical Features

♦ Endocarditis in homeless, trench fever, fastidious cutaneous bacillary angiomatosis

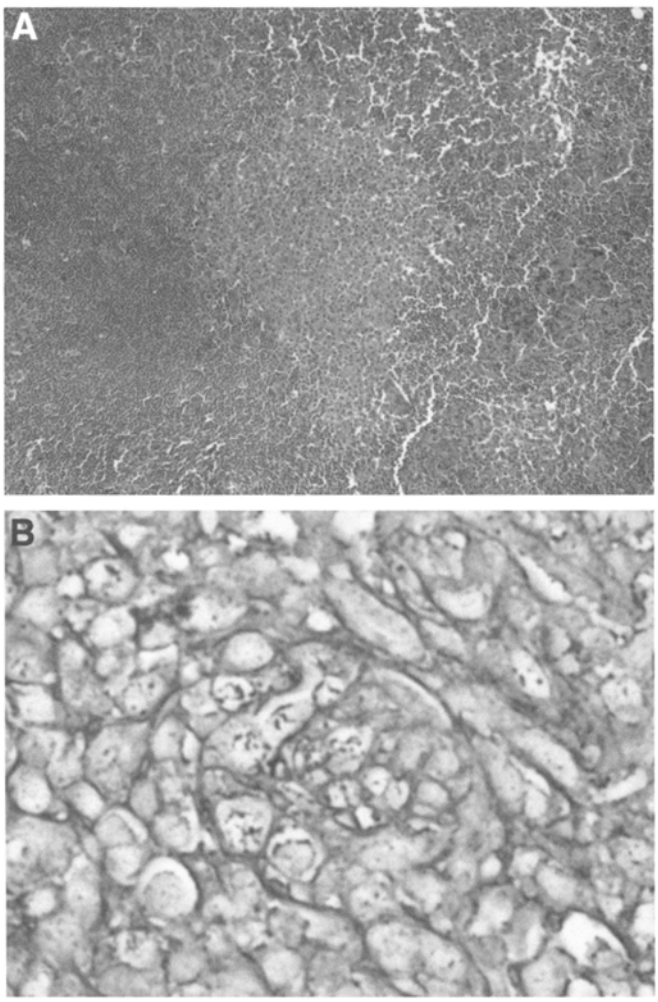


Fig. 21. Cat scratch disease; **(A)** lymph node (H&E), **(B)** Warthin-Starry.

Macroscopic

♦ See *B. henselae*

Microscopic

♦ See *B. henselae*

Special Stains

♦ Weakly Gram-negative bacillus but modified Gram's stains, Gomori's methenamine silver, periodic acid-Schiff, and acid-fast stains are not adequate for demonstrating Bartonellae in tissue section

♦ As for *B. henselae, B. quintana* is a small, aerobic, curved bacillus (≤0.5 μm × 1 to 2 μm), best seen in silver impregnation stains (e.g., Warthin-Starry, Steiner, or Dieterle), also, but not commonly visualized using Giemsa in US labs

Differential Diagnosis

♦ See *B. henselae*

Diagnostic Techniques

♦ Culture, serology

Bartonella bacilliformis

Geographically restricted to Peru, Ecuador, Columbia

Sandfly Vector (Phlebotomus)

Clinical Features

♦ Oroya fever (Carrion's disease):
- Abrupt or insidious onset 3 weeks to 3 months post bite of infected vector
- Anorexia, headache, malaise, slight fever for 2–7 days
- Severe anemia, muscle and joint pain, dyspnea, angina, delirium, coma possible
- Organisms may be isolated from blood in this stage

♦ Verruga peruana:
- Muscle, bone and joint pain may persist after resolution of Oroya fever
- Characterized by nodular lesions on exposed body parts, mucous membranes, or internal organs, developing over 1–2 months and lasting months to years
- Organisms may be isolated from cutaneous lesions, occasionally blood and bone marrow during this stage

Macroscopic

♦ Red-purple nodular nontender skin lesions

Microscopic

♦ As with bacillary angiomatosis (see *B. henselae*) but lymphocytes and plasma cells predominate

♦ Colonies of organisms fewer (Rocha-Lima bodies)

♦ Verruga peruana can have spindled form

Special Stains

♦ Weakly Gram negative bacillus but modified Gram's stains, Gomori's methenamine silver, periodic acid-Schiff, acid-fast will not show organism well

♦ Warthin-Starry, Steiner, Dieterle, Giemsa+

Differential Diagnosis

♦ Clinically skin lesions identical to Kaposi's sarcoma and pyogenic granuloma

Diagnostic Techniques

♦ Culture, serology

Rickettsia rickettsii and Rocky Mountain Spotted Fever (RMSF)

♦ Small, obligately intracellular bacteria

♦ Replicate in endothelial cells, causing vasculitis

♦ Tick vectors determine geographic distribution of the disease:
- *Dermacentor variabilis* (American dog tick); eastern United States (most common in southeast and south central US)
- *Dermacentor andersoni* (Rocky Mountain wood tick); Rocky Mountains
- *Rhipicephalus sanguineus*; Mexico
- *Amblyomma cajennense*; Mexico, and Central and South America

Clinical

- Incubation period (2 days to 2 weeks)
- Usually starts with fever, myalgia, and severe headache (often nausea, vomiting, or abdominal pain as well)
- Rash: generally maculopapular, but may be petechial
  - Usually begins around wrists and ankles 2–5 days after onset, rash may also begin on trunk; rash spreads over body
  - Involvement of hands and soles is considered the "hallmark" (but is not seen in all patients who develop RMSF rash)
  - Rash may be delayed, or absent, particularly in elderly or in blacks (Rocky Mountain Spotless Fever)
- Focal neurologic deficits may be prominent
- Other manifestations may include signs of meningoencephalitis, pulmonary edema, acute renal failure, coagulopathy, shock, and necrosis of skin
- RMSF mortality in untreated persons during preantibiotic era was about 20%; in fatal cases, death usually occurs ~7 to 15 days after onset

Pathology ***(Figures 21A,B)***

- *R. rickettsii* infection injures endothelial cells and vascular smooth muscle cells
- Vascular lesions may be present in any organ
- Characterized by focal hemorrhages, intramural and perivascular lymphocytes and macrophages. Neutrophils not prominent in these lesions
- Thromboses present in only a small portion of the involved vessels

Diagnostic Techniques

- Rickettsia stain poorly in Gram's stains of tissue sections; best in Giemsa, but histologic findings not specific and not reliable
- Microbiologic cultures not helpful
- Diagnosis primarily by serologic testing (i.e., 4-fold or greater rise in antibody titer -immunofluorescent antibody testing of patient's sera)
- Specific immunohistologic methods on frozen sections or on formalin-fixed, paraffin-embedded sections

Calymmatobacterium granulomatis

Endemic foci in all continents

Clinical Features

- Sexually transmitted disease; granuloma inguinale/Donovanosis/granuloma venereum
- Acute or chronic progressive inflammatory disease of genital and anal skin and subcutaneous tissue with ulcerating, necrotizing lesions
- After 7–30 day incubation, small papule erodes skin becoming progressively enlarging ulcers
- Old lesions are hypertrophic, red, indurated granulation tissue
- Lesion painless unless secondarily infected
- Pseudobuboes represent subcutaneous granulation tissue

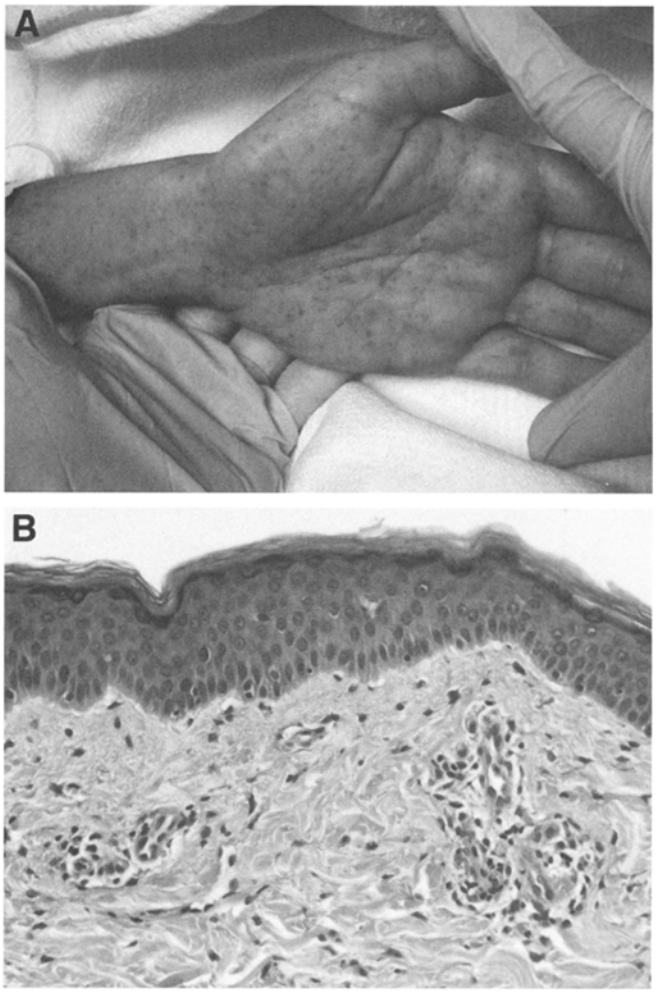


Fig. 22. Rocky mountain spotted fever; **(A)** skin, **(B)** cutaneous biopsy (H&E).

Microscopic

- Donovan bodies (20–90 μm histiocytes with eccentric nucleus and clusters of bacilli in compartments in cytoplasm) in cytologic smears or tissue sections – variable numbers in upper half of granulation tissue near ulcer margins
- Dense mixed dermal infiltrate with predominantly macrophages, occasional neutrophils, granulation tissue, fibrous tissue later
- Acanthotic epithelial border, intraepidermal abscess, elongated rete ridges and pseudoepitheliomatous hyperplasia

Special Stains

- Minute Gram-negative coccobacillus

Differential Diagnosis

- Syphilis and chancroid clinically

Diagnostic Techniques

- Biopsy and cytologic smears

FUNGI

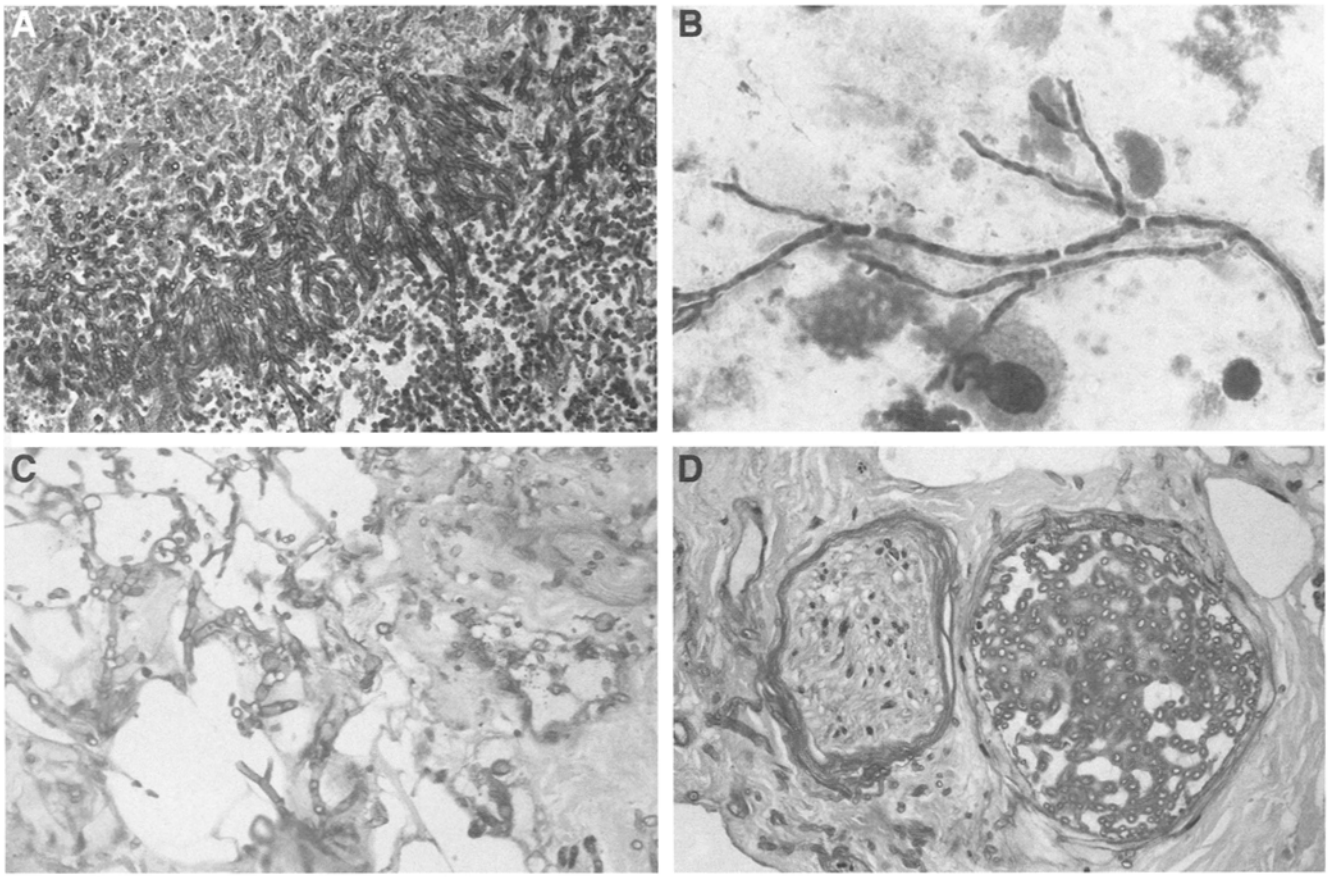


Fig. 23. **(A)** Arborizing radial growth of *Aspergillus* spp. in lung, H&E, **(B)** Cytologic preparation of bronchoalveolar lavage fluid demonstrating septate hyphae with acute angle branching, consistent with *Aspergillus* spp. (and many other septate hyaline fungi), DQ, **(C)** Pulmonary aspergillosis demonstrating fragments of septate hyphae with acute angle branching, PAS, **(D)** Perineural and vascular invasion by *Aspergillus* spp., PAS.

Hyaline Fungi

Many genera of septate hyaline fungi exist and are indistinguishable from one another based on histology alone.

These include, but are not limited to *Aspergillus*, *Fusarium*, *Pseudallescheria*, *Penicillium*, *Paecilomyces*, *Acremonium* and *Scopulariopsis*.

Aspergillus species

Found widely in environment; common contaminants in cultures

Clinical

- Disseminated opportunistic infections in immunocompromised patients
- Predisposing factors: neutropenia, malignancy (especially hematologic), AIDS, transplant patients, long-term steroid use
- Primary pulmonary infection may disseminate hematogenously to skin, or skin may be primary

Macroscopic

- Colonies begin white then become shades of yellow, green, brown, or black, depending on species

Microscopic ***(Figure 23A-D)***

- 2–5 μm septate hyphae with acute angle branching and progressive arborizing branches
- Often see vascular invasion with thrombosis and infarction
- Neutrophilic to granulomatous
- Conidiophores (fruiting bodies) allow identification to species but are rarely seen in tissue

Special Stains

- Gomori's methenamine silver (GMS), periodic acid-Schiff (PAS)

Differential Diagnosis

- Many genera of septate fungi exist and are indistinguishable from one another based on histology alone

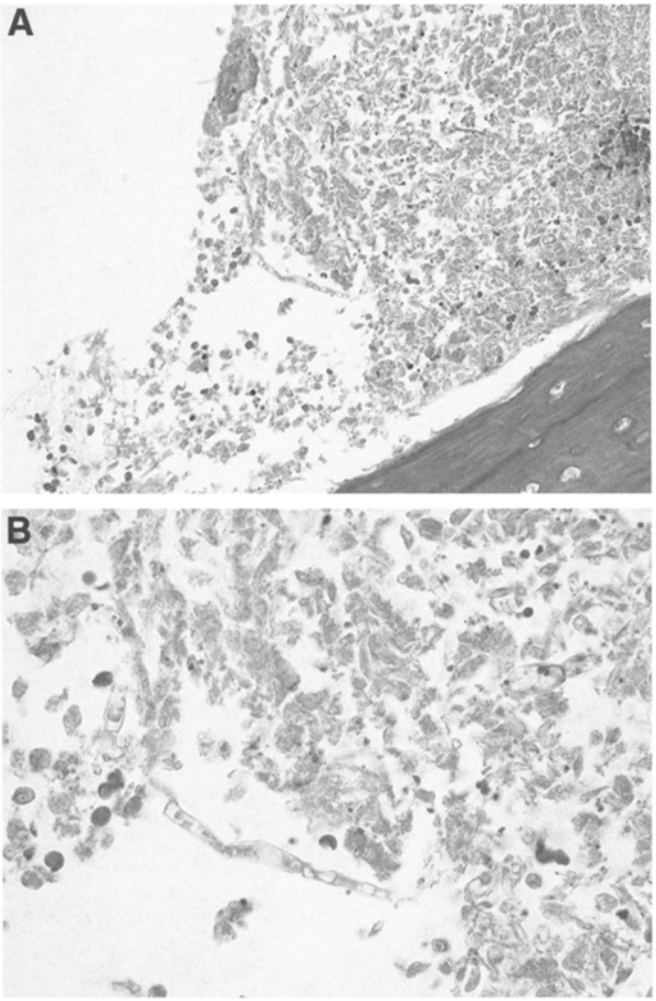


Fig. 24. *Fusarium* osteomyelitis; (**A** & **B**) pale/nonstaining septate hyphal fragments (photo center) within necrotic debris, H&E.

Diagnostic Techniques

- Speciation based on conidial arrangement
- Culture is required for definitive identification

Fusarium species

Clinical

- Commonly a contaminant
- Eye infections, mycetoma, sinusitis, skin and nail infections
- Disseminated opportunistic infections in immunocompromised patients

Macroscopic

- Abscess, infarct or granuloma
- White colony with pink-violet center over time

*Microscopic **(Figure 24A,B)***

- Abscess or nodular infarct due to septic thrombosis
- Septate hyphae with acute angle branching
- Sickle or canoe shaped conidia on lactophenol cotton blue preparation from colony

Special Stains

- Gomori's methenamine silver (GMS), periodic acid-Schiff (PAS)

Differential Diagnosis

- Many genera of septate fungi exist and are indistinguishable from one another based on histology alone

Diagnostic Techniques

- Culture is required for definitive identification

Mucor, Absidia, and *Rhizopus* species

Though not typically grouped with hyaline fungi, they are presented here for purposes of comparison

Ubiquitous; present in soil, compost, decaying vegetable matter, and water

Clinical

- Risk factors: uncontrolled diabetes, burns, surgery, severe illness, leukopenia, AIDS, intravenous drug use
- Affinity for myelin: rhinocerebral infection begins in sinuses with rapid spread along optic nerve into brain
- Pulmonary, cutaneous and disseminated disease
- Death can be rapid, in <24 hours

Macroscopic

- Fast growing "lid lifter" (Petri dish lid rises because of rapid growth and colony filling plate)

*Microscopic **(Figure 25A-F)***

- Broad, ribbon-like, aseptate hyphae with right angle branching
- Often will fold back on themselves
- Rare septation possible
- Neutrophilic infiltrate
- Vascular invasion, infarcts and perineural invasion may be present

Special Stains

- Gomori's methenamine silver (GMS), periodic acid-Schiff (PAS)

Differential Diagnosis

- Differentiation based on presence/absence/location of rhizoids

Diagnostic Techniques

- Culture is required for definitive identification

Penicillium marneffei

- Found in soil of Asia, Far East, Thailand
- Reservoir in bamboo rat
- Truly is dimorphic

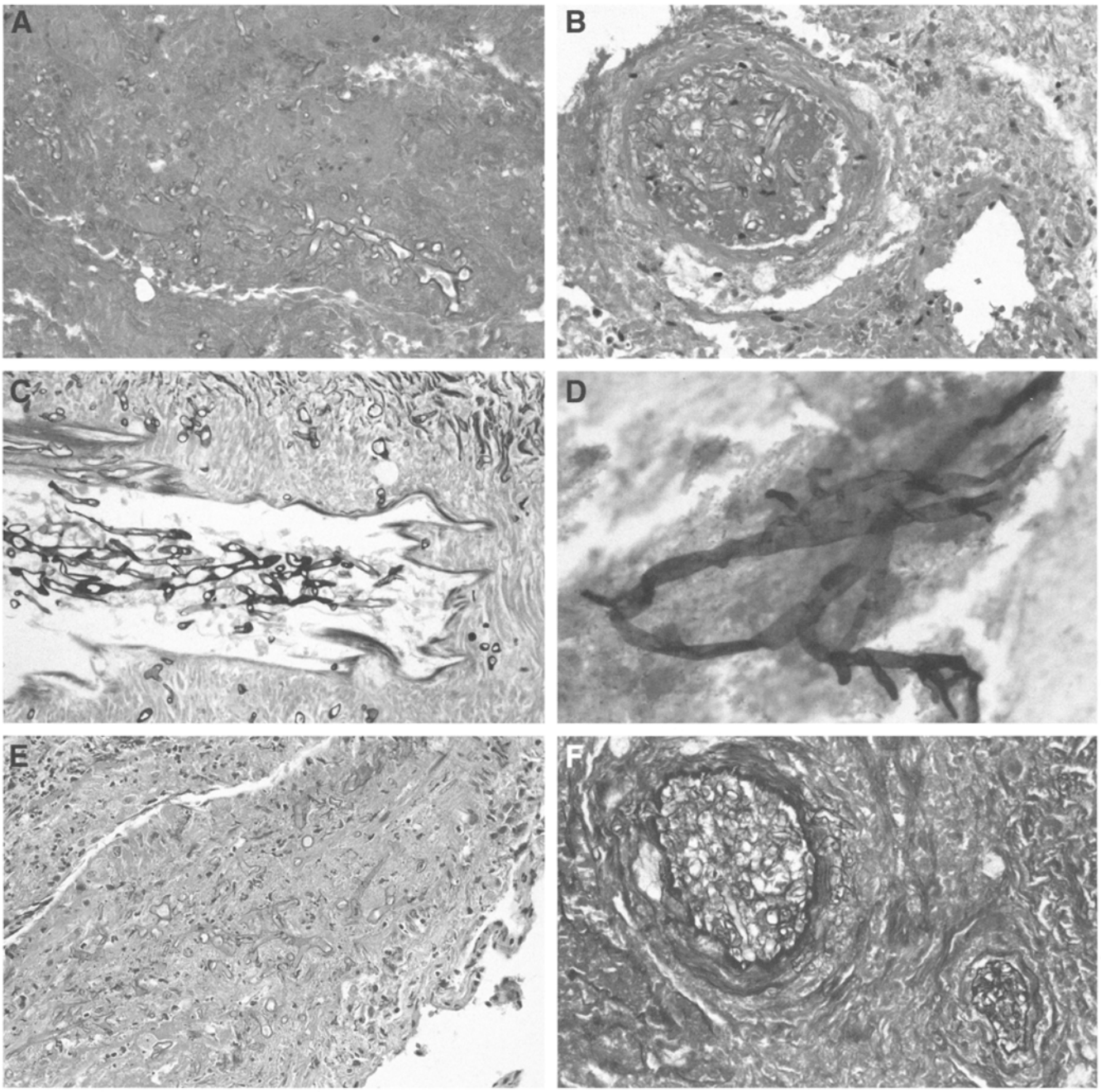


Fig. 25. **(A)** Broad, aseptate hyphae of zygomycosis, H&E, **(B)** Zygomycosis with vascular invasion similar to that seen with *Aspergillus* spp., nasal/sinus biopsy, H&E, **(C)** Pulmonary zygomycosis, GMS, **(D)** Cytologic preparation of bronchoalveolar lavage fluid. Broad, ribbony hyphae commonly fold back on themselves, GMS, **(E)** PAS, **(F)** Zygomycosis demonstrating vascular invasion, LG-PAS (light green-PAS).

Clinical

- Disseminated opportunistic infections in immunocompromised patients
- Keratitis, external ear, respiratory and urinary tract infections
- Endocarditis post valve prosthesis placement
- Mycetoma

Macroscopic

- Colonies begin white and become blue-green with age
- Red reverse may indicate *P. marneffei*

Microscopic

- Granulomatous, suppurative or necrotizing inflammatory patterns
- 2.5–5 μm intracellular yeasts

- 8 µm extracellular yeasts with rounded ends and a central septum (no budding)

Special Stains

- Gomori's methenamine silver (GMS), periodic acid-Schiff (PAS)

Differential Diagnosis

- Many genera of septate fungi exist and are indistinguishable from one another based on histology alone
- Yeast form may mimic *Histoplasma capsulatum*, but does not bud

Diagnostic Techniques

- Histopathology is rapid and reliable

Pseudallescheria/Scedosporium

Clinical

- Disseminated opportunistic infections in immunocompromised patients
- Mycetoma with draining sinus tracts at site of inoculation
- Pulmonary fungus balls, ocular infections
- Important to distinguish from other septate fungi because it is not sensitive to amphotericin B

Macroscopic

- Infarct, abscess, fungus ball – spherical and spongy, usually loose in a cavity
- Mycetoma: granules in exudate are fungal colonies
- White cottony colony turns gray-brown

Microscopic

- Vascular invasion, necrotizing pneumonitis, pulmonary abscesses and nodular infarcts
- Random haphazard branching of hyphae
- Fungus ball is composed of necrotic lung in center:
  - Loose, randomly branching hyphae and well-organized periphery
  - Alternating zones of mycelial hyper- and hypocellularity
  - Diagnostic conidia may be found superficially

Special Stains

- Gomori's methenamine silver (GMS), periodic acid-Schiff (PAS)

Differential Diagnosis

- Many genera of septate fungi exist and are indistinguishable from one another based on histology alone

Diagnostic Techniques

- Culture is required for definitive identification

Dimorphic Fungi

Blastomyces dermatitidis

Dimorphic mold

Natural inhabitant of warm moist soil around Great Lakes and upper Mississippi River, its tributaries and the southeast

Clinical

- Primary pulmonary with inapparent, self-limiting illness or with severe symptoms
- Chronic cutaneous disease with or without occult osseous lesions
- Single-organ system involvement, occult for many years
- Generalized, systemic multiorgan disease with rapid course
- Almost always begins in lungs via inhalation
- Occasionally progressive and severe, especially if immunocompromised, but most commonly spontaneously resolves following flu-like illness
- Skin or mucous membrane involvement usually indicates systemic disease; may be initial lesion

Macroscopic

- Skin and mucous membrane lesions (including larynx) may resemble squamous cell carcinoma
- Eccentric, well-circumscribed lytic lesions in metaphyses of long and small bones
- White to gray-brown delicate silky mold at 25–30°C after 7–30 days of incubation

Microscopic ***(Figure 26A-E)***

- 6–15 µm broad based budding yeasts with refractile double walls at 35-37°C
- Hyaline septate hyphae with 2–4 µm oval single-celled conidia "lollipops" borne singly at tips of long or short conidiophores on lactophenol cotton blue prep of colony
- Florid pseudoepitheliomatous hyperplasia in skin and mucous membranes, a major clue for presumptive diagnosis
- Inflammatory reaction to *B. dermatitidis* both suppurative and granulomatous

Special Stains

- Gomori's methenamine silver (GMS), periodic acid-Schiff (PAS)

Differential Diagnosis

- *Coccidioides immitis* immature spherules
- *Histoplasma capsulatum*, *Scedosporium apiospermum*, and *Chrysosporium* (all produce "lollipops" in mold form as seen on lactophenol cotton blue prep of colony)
- Mold to yeast conversion may be difficult
- *Paracoccidioides brasiliensis* has multiple buds

Coccidioides immitis

- Diphasic and multimorphic: hyphal/arthroconidial "saprobic" phase in nature and routine culture, and spherule/ endospores "parasitic" phase in human tissue
- Endemic in hot dry alkaline soil in Southwestern United States including San Joaquin Valley, northern Mexico and Central America
- Arthroconidia develop from mycelial form in subsurface desert sand and easily become windborne

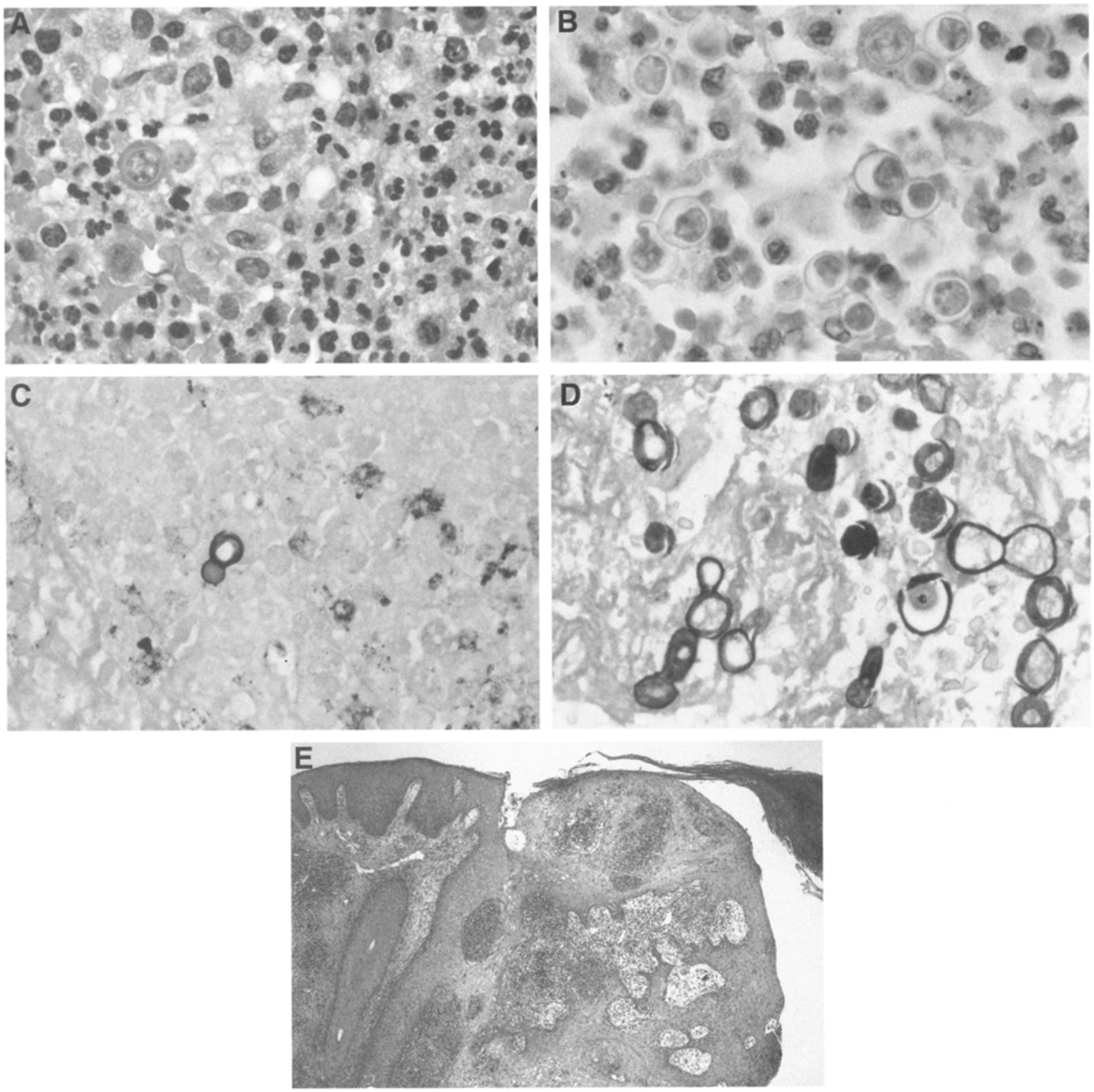


Fig. 26. **(A)** Broad-based bud of *Blastomyces dermatitidis* (left of center) with neutrophilic infiltrate in systemic soft tissue infection, H&E, **(B)** Multiple broad-based budding yeasts of *Blastomyces dermatitidis* with scattered neutrophils in soft tissue infection, H&E, **(C)** bronchoalveolar lavage, GMS, **(D)** Broad-based buds of *Blastomyces dermatitidis* mimicking empty spherules of *Coccidioides immitis*, GMS, **(E)** *Blastomyces dermatitidis* infection demonstrating pseudoepitheliomatous hyperplasia of skin, H&E.

Clinical

- Primary pulmonary disease:
  - Results from inhalation of highly infectious arthroconidia
  - May be acute, flu-like and self-limited
  - 60% are asymptomatic; only 2% develop chronic pulmonary disease with sequelae
- Cutaneous disease:
  - Usually a complication of disseminated disease

  - Primary cutaneous disease from inoculation of open skin lesions possible but rare
  - Erythema nodosum, erythema multiforme, granulomatous iridocyclitis
- Only 0.5% disseminate
- Most commonly Filipino, native African, Mexican and Asian ancestry
- Muscles, tendons, bone, joints, skin more common; CNS and genital less common
- HIV infection is a risk factor for coccidioidomycosis in endemic areas
- Third most frequently reported opportunistic infection in HIV positive patients

Macroscopic

- Solitary peripheral "coin lesions" or granulomas that may cavitate in lung
- White to gray-tan cobweb colonies with light orange to yellow pigment after 1–2 weeks at 25–35°C; more powdery with age as arthroconidia form
- Highly infectious: do not work with fungal culture suspected of being *Coccidioides* in the open air; BSL-2 precautions required

Microscopic ***(Figure 27A-F)***

- 10–60 µm thick-walled spherules containing 2–4 µm endospores in tissue
- Delicate hyphae break into alternately staining thick-walled barrel-shaped arthroconidia
- Granulomatous inflammation and necrosis +/– eosinophils

Special Stains

- Gomori's methenamine silver stains endospores only; periodic acid-Schiff

Differential Diagnosis

- Endospores released from spherules may resemble yeast forms
- *Blastomyces* yeasts may mimic spherules
- *Trichosporon*, *Geotrichum*, *Malbranchia*, *Gymnoascus* and *Oospora* species also produce arthroconidia
- Yeast forms of *Histoplasma capsulatum* and *Cryptococcus neoformans* may mimic free endospores

Diagnostic Techniques

- Mold to spherule conversion may be difficult
- Histopathology and culture most reliable for diagnosis in patients with AIDS

Histoplasma capsulatum

Dimorphic mold; endemic in drainage basins of the Ohio, Mississippi, and Missouri River valleys, Central America

Mycelial form present in warm, moist soil rich in organic content, especially soil fertilized with bird or bat excreta (bird roosts, chicken coops, old buildings frequented by bats)

Spores produced by mycelia are disseminated by wind then inhaled; mature into yeast form at body temperature

Clinical

- Most common systemic fungal disease in United States
- Acute or chronic histoplasmosis:
  - Cough, fever, night sweats, malaise, weight loss
- Disseminated histoplasmosis primarily in immunocompromised (AIDS and lymphoid malignancy):
  - Central nervous system (CNS) histoplasmosis
  - Mediastinal fibrosis (sclerosing mediastinitis)
- Most commonly asymptomatic infection with hilar and mediastinal lymphadenopathy
- Chest X-ray: diffuse/patchy interstitial infiltrates +/– nodules

Macroscopic

- Silky or hair like, white to gray-tan mold with tuberculate macroconidia after 10–30 days of incubation at 25–30°C
- Spectrum of findings: ranges from acute to chronic; similar to tuberculosis; chronic pulmonary histoplasmosis gross findings may include cavitary lesions (most often in upper lobes), fibrosis with emphysema, a residual solitary nodule (histoplasmoma) with onion-skin layered appearance, enlarged necrotic and calcified hilar lymph nodes and varying degrees of fibrosis

Microscopic ***(Figure 28A-E)***

- 2–4 µm oval yeasts with single eccentric nucleus and perinuclear clearing at 37°C
- Narrow-necked single buds, clustered within reticuloendothelial cells (histiocytes/macrophages) in tissue sections
- Surrounded by a halo giving false impression of a capsule
- 5–15 µm rough-walled (spiked/tuberculate) macroconidia on lactophenol cotton blue prep of colony

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff, Giemsa

Differential Diagnosis

- *Trichophyton rubrum* colony has red diffusible pigment; *Sporothrix schenckii; Leishmania donovani* has kinetoplast

Diagnostic Techniques

- May be difficult to convert to yeast form in culture; however, culture is gold standard
- Hematoxylin and eosin (H&E) and fungal (silver) stains
- Serology, eg. immunodiffusion and complement fixation, urinary *Histoplasma* antigen test, exoantigen test, nucleic acid probe

Paracoccidioides brasiliensis

Dimorphic mold; endemic in soil in Brazil (most commonly), South and Central America; Mexico

Clinical

- Inhalation leads to pulmonary disease (chronic granulomatous disease)

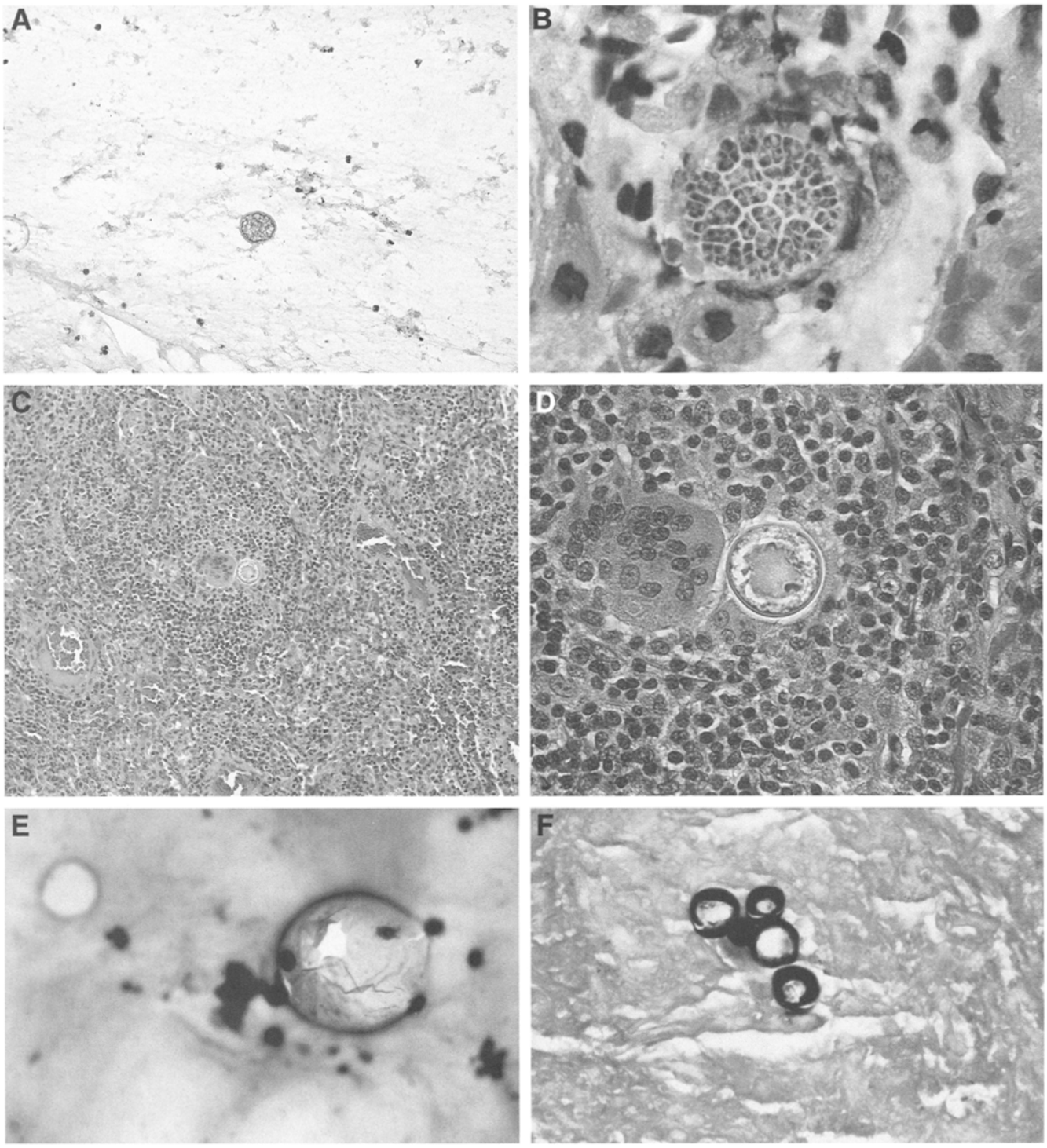


Fig. 27. (**A** & **B**) *Coccidioides immitis,* cytologic smear showing single spherule containing endospores, H&E, (**C** & **D**) Spherule of *Coccidioides immitis* with adjacent giant cell in lung, H&E, **(E)** Empty spherule of *Coccidioides immitis* in a cytologic preparation, DQ, **(F)** Empty spherules of *Coccidioides immitis* mimicking *Blastomyces dermatitidis*, GMS.

- Spreads to mucous membranes of nose, mouth, occasionally gastrointestinal tract, skin, lymph nodes

Macroscopic

- Acute disseminated form:
  - Mucocutaneous and intestinal ulcers, lymphadenopathy, osteolytic bone lesions or osteomyelitis
- Chronic disseminated form:
  - Pulmonary cavitation, ulceration of mucous membranes, necrotic/granulomatous adrenal lesions

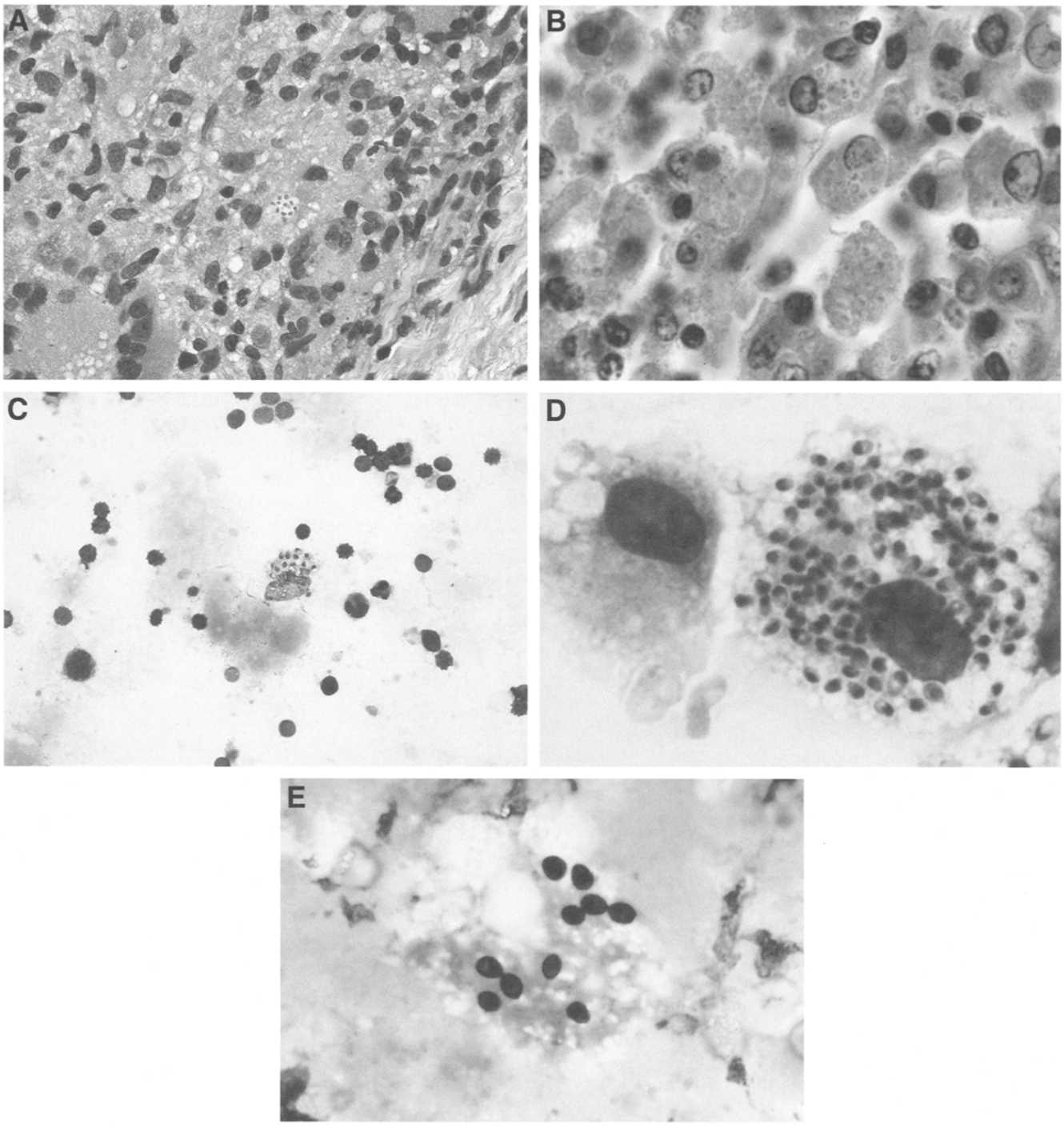


Fig. 28. Intracellular *Histoplasma capsulatum*; **(A)** in a lymph node (photo center), H&E, **(B)** in tissue, H&E, **(C)** Predominantly intracellular *Histoplasma capsulatum* with scattered neutrophils, macrophages and rbcs in a bronchoalveolar lavage, Giemsa, **(D)** 2–4 μm yeasts of *Histoplasma capsulatum* within a macrophage in a bronchoalveolar lavage, Giemsa, **(E)** Oval 2–4 μm narrow-necked budding yeasts of *Histoplasma capsulatum*, GMS.

Microscopic

- Pseudoepitheliomatous hyperplasia in epidermis and mucosa, suppurative and granulomatous inflammation – mimics tuberculosis or sarcoid
- "Mariner's wheel", multiple narrow-necked buds arise from mother cell

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff

Differential Diagnosis

- *Histoplasma capsulatum, Blastomyces dermatitidis,* capsule-deficient *Cryptococcus neoformans, Coccidioides immitis*

Diagnostic Techniques

- May be difficult to convert to yeast form in culture; however, culture is gold standard

Sporothrix schenckii

- Found worldwide in soil, rose thorns, shrubs, trees, bark, mulch, and moss

Clinical

- Skin, subcutis and systemic infections transmitted by inoculation injury associated with rose bushes
- Nodules and ulcers along lymphatics and at site of inoculation
- Pneumonia in alcoholics

Macroscopic

- Cutaneous ulcers and verrucous lesions
- Colony: wrinkled to leathery cream-tan-black or "dark and greasy"

Microscopic

- Florid pseudoepitheliomatous hyperplasia
- Neutrophilic abscesses surrounded by granulomatous inflammation
- Asteroid bodies may be present in microabscesses or suppurative center of granuloma:
  - yeast cell(s) surrounded by 20–40 μm stellate Splendore-Hoeppli intensely eosinophilic refractile material
- Cigar bodies – fusiform budding yeast cells at 37°C
- Many daisy-like conidia resetting around a bulbous ended conidiophore at 25°C

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff

Differential Diagnosis

- Squamous cell carcinoma, Hamazaki-Wesenberg bodies, sarcoidosis, *Coccidioides immitis, Blastomyces dermatitidis, Histoplasma capsulatum,* capsule-deficient *Cryptococcus neoformans*

Diagnostic Techniques

- Culture or direct immunofluorescence for definitive diagnosis

Superficial Mycoses

Malassezia furfur

Clinical

- Tinea versicolor (hypo- and hyperpigmented macules)
- Vascular catheter and hyperalimentation associated infections

Macroscopic

- Rarely biopsied because organisms easily seen in skin scrapings

Microscopic

- Mild hyperkeratosis, follicular plugging, acanthosis, neutrophilic infiltrate
- Yeasts shaped like old-fashioned Coke bottle; spaghetti and meatballs appearance of hyphae and yeasts

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff

Diagnostic Techniques

- Lipophilic – requires olive oil (oleic acid/long chain fatty acids) dropped onto plate for growth to occur; growth occurs only in areas where oil contacts agar

Hortaea werneckii

Clinical

- Tinea nigra palmeris – asymptomatic, minimally scaly macules on palms or soles
- Seen mainly in tropical and subtropical areas

Macroscopic

- Dark/black macules on palm of hand
- Colonies initially yeast-like then become hyphal and olive-black with black reverse (dematiaceous)

Microscopic

- Nonspecific hyperkeratosis, mild mononuclear perivascular infiltrate in dermis
- Black two-celled oval yeast (annellides with central septum) in skin scrapings; brown-black hyphae in tissue sections (younger hyphae may not be well pigmented)

Special Stains

- Not necessary for dematiaceous fungi

Differential Diagnosis

- Acral melanoma, clinically

Diagnostic Techniques

- Direct microscopic examination of skin scrapings

Piedraia hortae

Clinical

- Black piedra; occurs in tropical areas

Macroscopic

- Stony hard black nodule on hair shaft
- Hyphal colonies dark green-black with black reverse (dematiaceous)

Microscopic

- Black nodule on hair shaft composed of spore sacs and spores

Special Stains

- Not necessary for dematiaceous fungi

Diagnostic Techniques

- Direct microscopic examination of hair

Trichosporon beigelii

Clinical

- Superficial mycoses, white piedra (hair shaft infection) of beard, scalp or pubic hair
- Opportunist, pneumonia, localized or systemic deep infections especially in immunodeficient patients

Macroscopic

- Infarcts and abscesses
- Soft, cream-colored nodules on hair shaft

Microscopic

- White nodule on hair shaft composed of mycelia that fragment into brick-like arthroconidia; true and pseudohyphae; blastoconidia along hyphae
- Nodular infarcts and angioinvasion; radial sunburst growth pattern similar to aspergillosis; abscesses and granulomas may be seen

Special Stains

- Gomori's methenamine silver

Differential Diagnosis

- Candidiasis, aspergillosis, pseudallescheriasis, other opportunistic mycoses

Diagnostic Techniques

- Culture and demonstration of fungal elements in biopsy specimens
- Cross-reactivity with anticryptococcal antibody latex agglutination

Dermatophytes

- Disease restricted to keratinized layers of skin, hair and nails (keratin metabolized as nitrogen source)
- Dissemination reported in immunocompromised patients
- Most common of all fungal infections
- Contagious
- Three different Genera:
  - *Trichophyton*
    - Numerous species
    - Microconidia important for identification, macroconidia rarely helpful, biochemical tests helpful
  - *Epidermophyton:*
    - Single species: *E. floccosum*
    - Macroconidia important for identification, microconidia not produced
    - Killed by refrigeration
  - *Microsporum:*
    - Numerous species
    - Macroconidia important for identification, microconidia produced but not useful in identification, biochemical tests not useful

Clinical

- Ringworm or tinea: inner pale ring-like healing area surrounded by red expanding infection
- *Trichophyton* spp. – most commonly cause foot (*T. mentagrophytes*) and nail infections
- *Trichophyton tonsurans* – most common cause of tinea capitis
- *Trichophyton schoenleinii* – causes favus with scarring and permanent hair loss
- *Epidermophyton* – infects groin and feet
- *Microsporum audouinii* commonly causes tinea capitis in children

Macroscopic

- Red, scaly skin lesions
- Colonies generally white and fluffy or granular with light tan reverse:
  - Notable notes and exceptions:
    - *Trichophyton rubrum* has cherry red reverse after about 3 weeks' growth
    - *Trichophyton mentagrophytes* may have red-brown reverse
    - *Trichophyton tonsurans* colonies are buff-brown
    - *Epidermophyton* colonies are olive green/khaki
    - *Microsporum canis* colonies have bright yellow reverse
    - *Microsporum gypseum* colonies are cinnamon with orange-brown reverse
    - *Microsporum audouinii* colonies are light gray with pink reverse

Microscopic ***(Figure 29A-C)***

- Hyaline septate hyphae confined to stratum corneum in histologic skin sections
- KOH mount:
  - *Trichophyton rubrum* – "birds on a wire" microconidia
  - *Trichophyton mentagrophytes* – grape clusters and spiral microconidia
  - *Trichophyton tonsurans* – elongated balloons or stretched teardrop microconidia
  - *Trichophyton schoenleinii* – antler hyphae and "favic chandeliers"

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff

Diagnostic Techniques

- KOH mount of skin scrapings, hair or nails; calcofluor white fluorescent stain

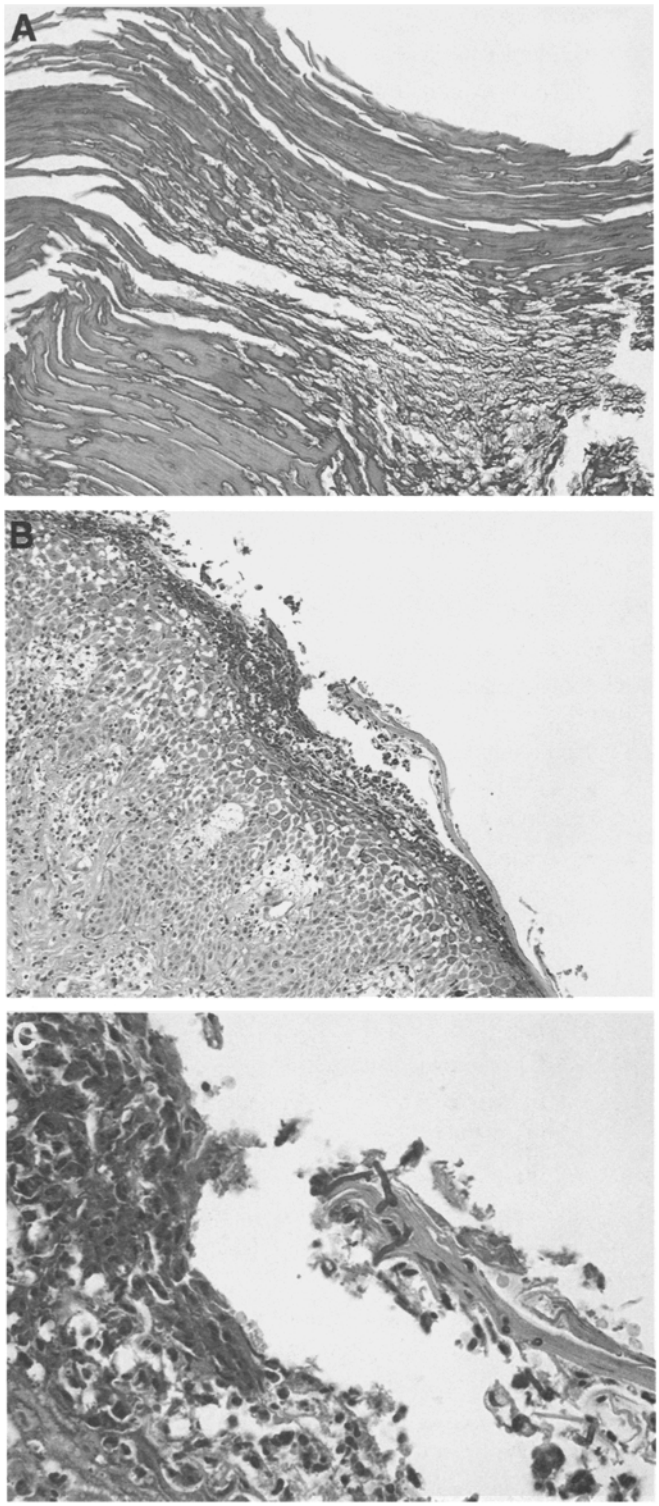


Fig. 29. Onychomycosis; **(A)** abundant branching hyphae in keratin stain poorly and appear as negative images, H&E, (**B** & **C**) Dermatophytosis demonstrating hyphal fragments in epidermis, skin, PAS.

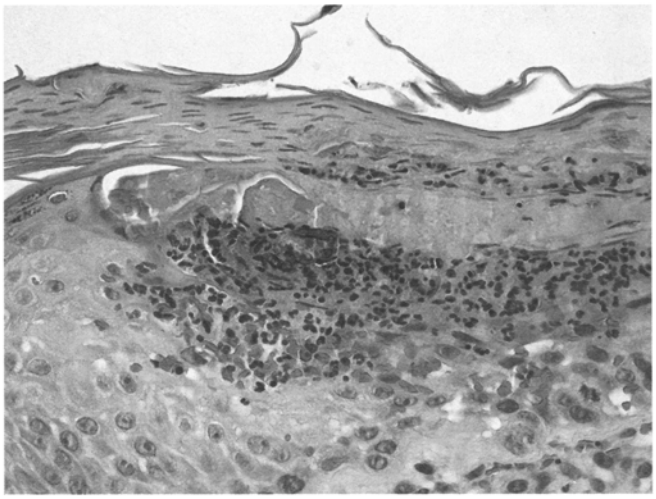


Fig. 30. Neutrophilic abscess in skin contains fragments of septate dematiaceous hyphae, H&E.

- Growth on cornmeal or potato dextrose agar to enhance production of conidia for identification

Subcutaneous Mycoses

Dematiaceous Fungi

Black/dark pigmented fungi that produce melanin – protective against phagocytosis and oxidative burst **(Figure 30)**

Exist worldwide as saprophytes and plant pathogens; man is accidental host

Many Genera including, but not limited to *Alternaria* (see below), *Exophiala*, *Curvularia* (boomerang shaped conidia), *Stachybotrys*

Implicated in chromoblastomycosis and phaeohyphomycosis

If pigmentation equivocal, Fontana-Masson stain helpful for confirming presence of melanoid pigments

Alternaria species

Clinical

- Commonly colonizes human skin but rarely causes disease
- Risk factors include immunosuppression and severe illness, traumatic inoculation
- Secondary cutaneous disease by hematogenous spread from pulmonary source

Macroscopic

- Colonies darkly pigmented with jet black reverse

Microscopic

- Pigmented brown septate hyphae with "snowshoe" or "drumstick" shaped muriform conidia (longitudinal and transverse septae)

Special Stains

- Periodic acid-Schiff or Fontana-Masson, but not necessary for dematiaceous fungi

Diagnostic Techniques

- Direct examination of specimen or histopathology

Chromoblastomycosis

Worldwide distribution, mostly tropics and subtropics; present in soil and decaying organic material

Many agents including, but not limited to *Fonsecaea pedrosoi*, *Phialophora* (phialides and conidia look like flowers in a vase), *Cladosporium*, *Cladophialophora*, *Rhinocladiella* which are also dematiaceous fungi

Most common cause of chromoblastomycosis in Americas = *Fonsecaea pedrosoi*

Clinical

- Chronic infections of skin and subcutaneous tissue
- Dissemination to deep organs rare
- Acquired by traumatic implantation of dematiaceous fungi (barefoot agricultural workers)
- Slow-growing (evolving over years) warty nodules progress to cauliflower-like appearance at inoculation site, generally dorsal surfaces of feet and lower legs
- Progression without treatment = lymphangitis to elephantiasis to amputation
- No evidence it is contagious

Macroscopic

- Colonies darkly pigmented with jet black reverse

Microscopic

- Chronic suppurative process with neutrophils and fungi, pseudoepitheliomatous hyperplasia, granulomatous infiltrate and abscess
- 5–7 μm muriform cells a.k.a. copper pennies a.k.a. sclerotic or Medlar bodies: copper-colored thick-walled spherical bodies that divide by septation in two planes
- Wooden sliver or splinter not found in tissue section

Special Stains

- Periodic acid-Schiff or Fontana-Masson but not necessary for dematiaceous fungi

Differential Diagnosis

- Squamous cell carcinoma, phaeohyphomycosis, keratoacanthoma, leishmaniasis, Kaposi's sarcoma, paracoccidioidomycosis, cutaneous tuberculosis, sarcoidosis, blastomycosis

Diagnostic Techniques

- Clinical presentation and direct examination of specimen or histopathology for muriform cells
- >70% culture positive; identification based on predominating type of sporulation

Phaeohyphomycosis

Worldwide saprophyte present in soil, wood and decaying vegetable matter

Many agents including, but not limited to *Alternaria*, *Exophiala jeanselmei*, *Bipolaris*, *Wangiella*, *Curvularia*, *Cladophialophora bantiana* (neurotropic)

Clinical

- Acquired by traumatic implantation of dematiaceous fungi
- Subcutaneous and systemic infection via pulmonary route; lymphadenopathy rare
- Immunosuppression predisposes to infection

Macroscopic

- Single or multiple firm to fluctuant painless subcutaneous abscesses

Microscopic

- Pigmented moniliform fungal elements within giant cells in cyst walls and extracellularly in central necrotic debris
- Cystic or granulomatous
- Dense connective tissue with stellate suppurative necrosis and unaffected overlying epidermis
- Terminal and intercalated vesicular swellings in hyphae resemble chlamydoconidia
- Wooden sliver or splinter found in tissue section

Special Stains

- Periodic acid-Schiff or Fontana-Masson but not necessary for dematiaceous fungi

Differential Diagnosis

- Chromoblastomycosis

Diagnostic Techniques

- Clinical presentation and direct examination of specimen or histopathology

Yeasts

Candida albicans and Other *Candida* Species

Clinical

- Normal flora of gastrointestinal tract
- Intertrigo (skin fold) infections, paronychia, diaper rash, thrush, esophagitis, balanitis, vaginitis, urinary tract infections, pneumonia
- Immunosuppression, steroids, antibacterials, obesity increase risk of infection
- May disseminate via hematogenous spread from urinary or gastrointestinal tract

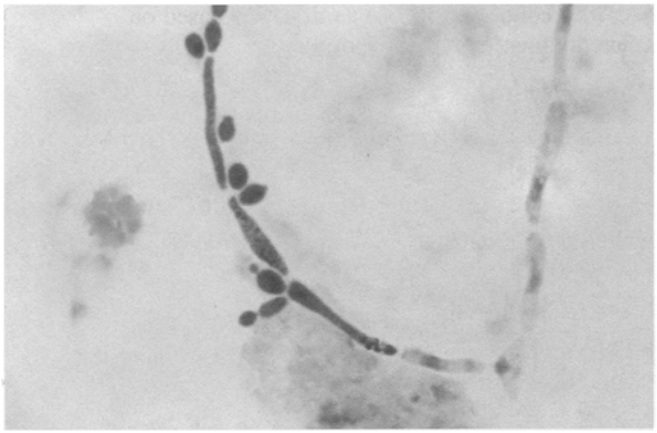


Fig. 31. Yeast forms of *Candida* spp., Diff-Quik.

- High mortality; *C. tropicalis* and *C. krusei* most common agents

Macroscopic

- Superficial infection appears white-tan and velvety with dark red adjacent tissue
- Locally invasive lesions (ulcers) have sharp margins with granular base and tan-yellow friable exudate
- Disseminated candidiasis is invasive infection involving parenchyma of at least two organs, excluding mucosa of gastrointestinal, respiratory or genitourinary tracts

Microscopic ***(Figure 31A,B)***

- Yeast with narrow-necked budding and "sausage-link" pseudohyphae; blastoconidia
- Dense neutrophilic infiltrate in the epidermis and superficial dermis
- May see a spongiform subcorneal pustule indistinguishable from psoriasis
- Chronic inflammatory infiltrate in deeper levels
- Disseminated forms may have leukocytoclastic vasculitis (especially with *Candida tropicalis*)

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff

Differential Diagnosis

- *Cryptococcus neoformans* varies more in size

Diagnostic Techniques

- Germ tube test:
  - 95% positive in *C. albicans*
  - Occasional positive in *C. tropicalis*
  - All other *Candida* spp. negative

Cryptococcus neoformans

- Found in soil and pigeon droppings (attics, belfries, cornices)
- Can remain viable for years

Clinical

- Inhalation leads to mild pulmonary disease
- Meningitis, cutaneous, mucocutaneous, osseous and visceral infection also may occur

Macroscopic

- Slimy, glistening white meninges
- Cutaneous lesions: papules and pustules to solitary, well-circumscribed ulcerated nodule

Microscopic ***(Figure 32A-D)***

- 2–15 µm variably sized encapsulated yeasts with single bud and narrow attachment
- Often neutrophilic infiltrate, but may be granulomatous, especially in immunocompetent patients

Special Stains

- India Ink direct exam of cerebrospinal fluid (see diagnostic techniques below)
- Gomori's methenamine silver, periodic acid-Schiff; mucicarmine or alcian blue to detect capsule
- Fontana-Masson stains cell wall

Differential Diagnosis

- Blastoconidia of *Candida* spp. are more uniform in size, *Sporothrix schenckii*, *Torulopsis glabrata*, immature spherules of *Coccidioides immitis*
- Capsule-deficient forms may mimic *Histoplasma* and *Blastomyces*

Diagnostic Techniques

- Direct antigen testing has higher sensitivity than India Ink
- Yields dark brown colonies on birdseed (niger seed) agar
- Urease+

Torulopsis

Ubiquitous fungus; widely distributed saprophyte

Normal flora of skin, oropharynx, gastrointestinal tract, urethra, vagina

Low virulence

Clinical

- Infections range from asymptomatic to life-threatening; nosocomial fungemia and funguria
- Predisposing factors:
  - Intravenous and urethral catheters, intravenous drug use, prolonged antibiotic therapy, diabetes mellitus, immunosuppression, corticosteroid therapy

Macroscopic

- Nonspecific; abscess and necrosis possible

Microscopic

- No pseudohyphae produced in tissue, blastoconidia only

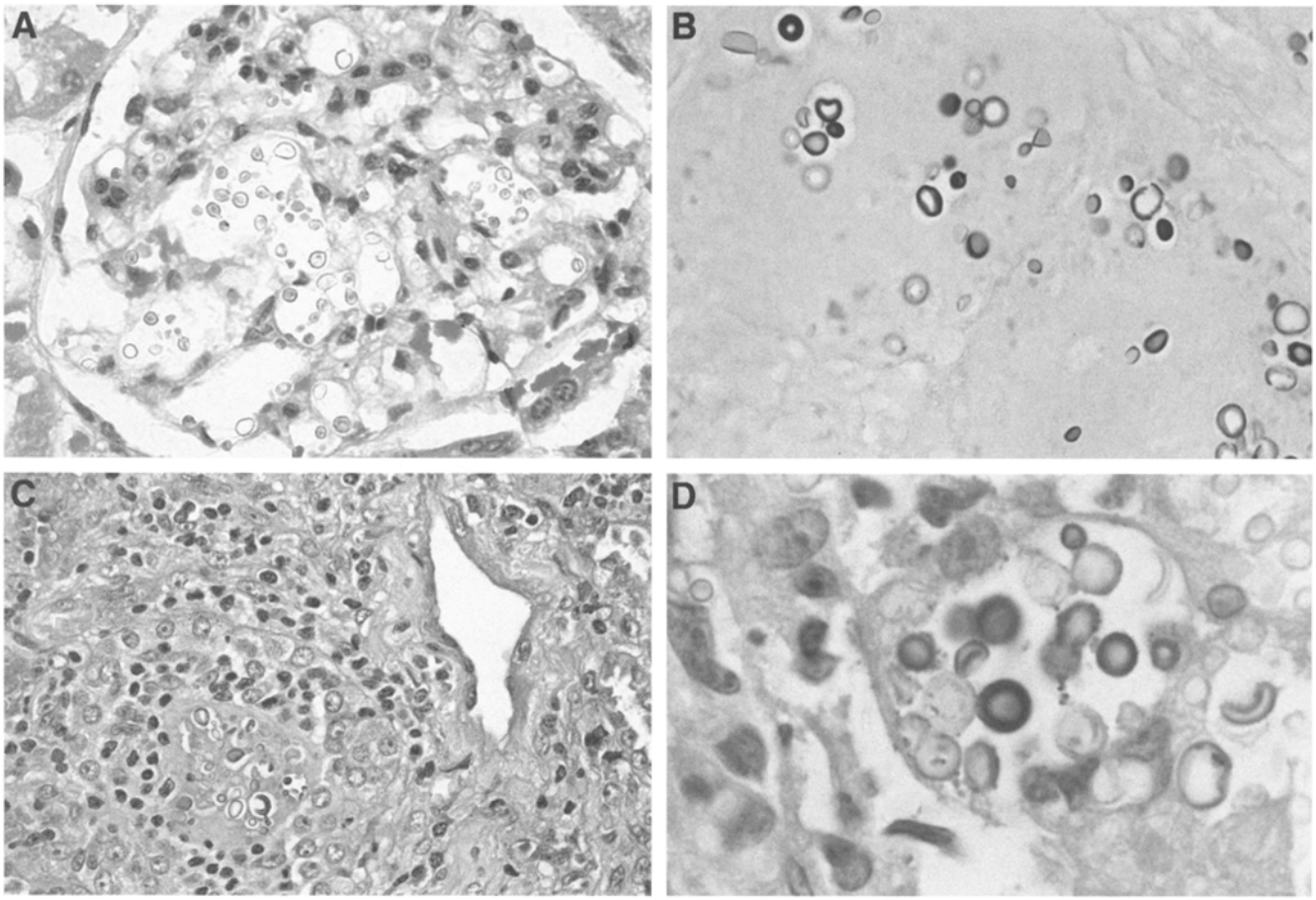


Fig. 32. **(A)** Refractile, poorly-staining yeasts with halos in kidney glomerulus, *Cryptococcus neoformans*, H&E, **(B)** Variably sized yeasts of *Cryptococcus neoformans* with narrow-necked buds and halos, GMS, **(C)** PAS, **(D)** mucin.

- Yeasts typically smaller than *Candida* spp. (2–5 μm) and extracellular or intracellular with narrow-necked budding
- Range of no inflammation to suppuration, necrosis and abscess formation as with *Candida* spp.

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff

Differential Diagnosis

- *Histoplasma capsulatum* has halo effect and is intracellular
- More budding and pleomorphism with *Candida* (*Torulopsis*) *glabrata*

Diagnostic Techniques

- Differentiated from *Candida* spp. based on fermentation and assimilation reactions from colonial growth

Other Fungi

Pneumocystis jiroveci (Formerly *carinii*)

Worldwide distribution

Truly a fungus; most closely resembles *Saccharomyces cerevisiae* by 16S ribosomal RNA sequencing

Clinical

- Nonspecific findings mimic other opportunistic infections
- Pneumonia in immunocompromised patients
- Bilateral ground glass infiltrates on radiologic imaging
- AIDS defining illness

Macroscopic

- Firm, granular, consolidated pulmonary parenchyma with occasional nodules and cavities

Microscopic ***(Figure 33A-G)***

- Variety of reaction patterns, excluding pure acute suppurative response possible; pink foamy/bubbly intra-alveolar material on hematoxylin-eosin stain
- Gomori's methenamine silver stain:
  - Extracellular cysts appear as black 4–7 μm spherules with two comma-like internal thickenings of cell wall
  - Cup or crescent shaped when collapsed
- Giemsa or Diff-Quik stain:
  - 2–8 μm trophozoites (ameboid; clusters appear as bubble like spaces with dotlike nuclei)

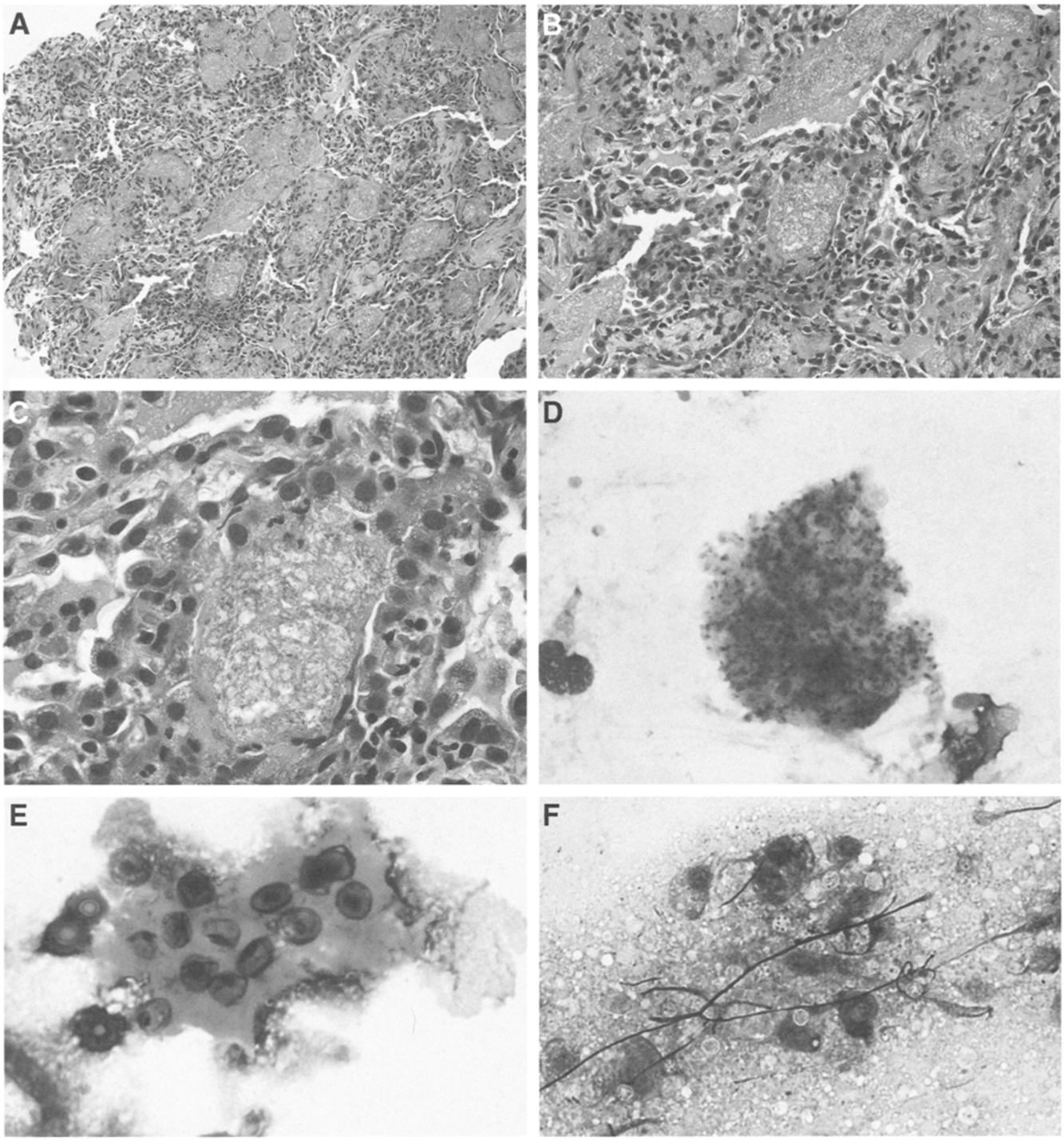


Fig. 33. **(A)** Foamy intra-alveolar "exudate" of *Pneumocystis* pneumonia, lung, H&E, **(B & C)** cyst outlines become obvious on higher power, H&E, **(D)** Trophozoites of *Pneumocystis jiroveci* in a bronchoalveolar lavage. Cyst outlines become evident if one focuses up and down with the microscope. Giemsa, **(E)** Cysts with intracytoplasmic thickenings, GMS, **(F & G)** Sporozoites, trophozoites and negative image outlines of cysts in cytologic preparation of bronchoalveolar lavage fluid, Giemsa.

  - 1–2 μm sporozoites (clusters of dotlike purple nuclei surrounded by an unstained cyst wall)

Special Stains

- Gomori's methenamine silver (GMS) demonstrates cysts
- Giemsa or Diff-Quik stain demonstrates trophozoites, sporozoites and negatively stained cyst walls

Differential Diagnosis

- *Histoplasma capsulatum, Candida (Torulopsis) glabrata, Cryptococcus neoformans*

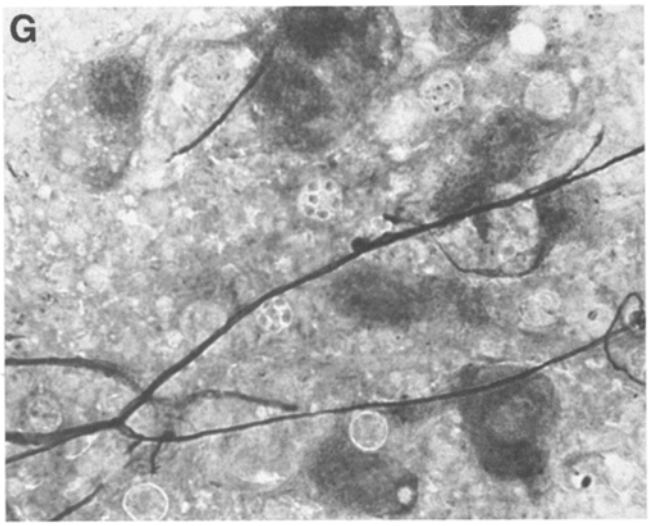


Fig. 33. *(Continued)*

Diagnostic Techniques

- Cannot be cultivated on cell-free media; therefore, diagnosis depends on demonstration of organisms in biopsy or cytology specimens

Prototheca wickerhamii

Clinical

- Ubiquitous saprobe
- Local cutaneous or rarely systemic disease, especially patients who are immunocompromised or have nonintact skin
- 50% of infections are cutaneous and mostly due to traumatic inoculation
- Indolent centrifugal spread of papulonodular, eczematoid, herpetiform dermatitis, verrucous nodules or wound infection on limb or face; olecranon bursitis

Microscopic ***(Figure 34A, B)***

- Unicellular, achlorophyllic, aerobic alga
- Distinctive 3–30 μm morula or soccer ball-like sporangia on wet mount preparations have symmetric endospores
- Mixed inflammatory infiltrate (predominantly granulomatous) in epidermis and dermis
- May be ulcerated, have intraepidermal microabscesses with hyperkeratosis, parakeratosis and acanthosis
- Organisms single or clustered but most numerous in areas of inflammation
- May be within macrophages or giant cells (foreign body and Langhans' types)

Special Stains

- Periodic acid-Schiff and methenamine silver stains on histologic sections highlight sporangia
- Gram positive
- Lactophenol cotton blue demonstrates characteristic wedge shaped radially arranged sporangiospores within sporangia

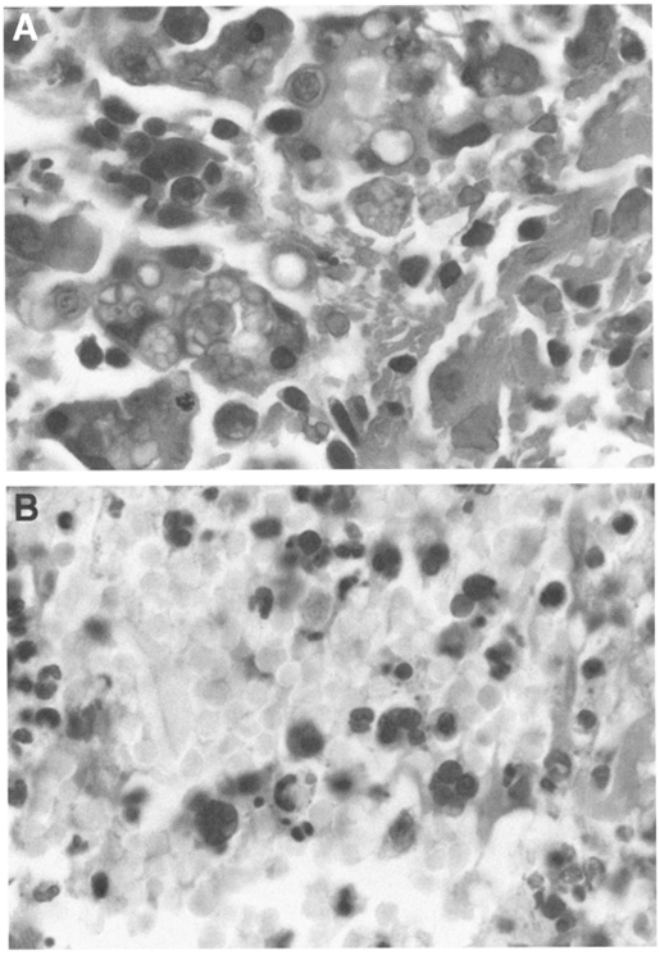


Fig. 34. *Prototheca* in skin with clusters of sporangia containing radially arranged sporangiospores, (A) H&E, (B) PAS.

Diagnostic Techniques

- Cultured on conventional fungal media
- Characteristic morphology of organism on hematoxylin-eosin stain

Rhinosporidium seeberi

Found in soil and stagnant water; reported in East Asia, Ceylon, India, and rural Georgia

Clinical

- Presumably acquired by inoculation
- Nasal, nasopharyngeal or oral polyps appear pink-red with "salt dots"
- Conjunctival, paranasal sinus, and external genital lesions

Macroscopic

- Friable, pink-red, warty mucosal polyps or papillomas with "salt dots"

Microscopic

- 6–350 μm round sporangia with 5 μm thick wall containing 7–9 μm lobulated endospores with globular

bodies in stroma of polyp with granulation tissue and chronic inflammatory infiltrate

- Granulomatous response if rupture of sporangia occurs

Special Stains

- Gomori's methenamine silver, periodic acid-Schiff, Mayer's mucicarmine

Differential Diagnosis

- *Coccidioides immitis, Prototheca*

Diagnostic Techniques

- Cannot be cultured; diagnosis depends on direct examination (histopathologic or cytologic)

VIRUSES

Adenovirus

- Nonenveloped dsDNA

Clinical

- Upper and lower respiratory infections, conjunctivitis, hemorrhagic cystitis, colitis in AIDS, gastroenteritis in children; may be asymptomatic

*Microscopic **(Figure 35A-C)***

- Bronchiolar necrosis, coagulative necrosis, hyaline membranes, diffuse alveolar damage
- Infected nuclei of bronchial epithelium and alveoli appear smudged or may have a round, eosinophilic nuclear inclusion with surrounding halo and marginated chromatin

Diagnostic Techniques

- Immunohistochemistry, cell culture, immunofluorescence, PCR and DNA probes available

Creutzfeldt-Jakob Disease

- Agent of transmissible spongiform encephalopathy

Clinical

- Sporadic, iatrogenic and new variant CJD
- Insidious onset sensory of disturbance, progressive dementia, myoclonic jerking, rigidity
  - New variant CJD:
    - Abnormal behavior, dementia, ataxia and myoclonus
    - Young adult at death with illness duration about 12 months
  - Sporadic CJD:
    - Dementia, ataxia and myclonus with periodic complexes on EEG
    - Older adult at death with illness duration about 4 months

*Microscopic **(Figure 36)***

- Spongiform change of gray matter with some involvement of white matter
- Variable degree of cerebellar involvement; greater with vCJD
- Variably-sized cytoplasmic vacuoles indent nuclei and decrease over time
- Gliosis increases over time
- Lack of inflammatory response

Differential Diagnosis

- Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, kuru

Diagnostic Techniques

- Clinical and histopathologic findings
- 100% of vCJD have PRNP codon 129 Met/Met (only 83% of sCJD)

Cytomegalovirus (CMV)

Enveloped dsDNA herpesvirus

Clinical

- Ubiquitous – can infect almost any body site
- Serious disease in immunocompromised patients, especially in HIV
- Pneumonitis

*Microscopic **(Figure 37A,B)***

- Enlarged cells with owl's eye eosinophilic nuclear inclusion and marginated chromatin
- Granular cytoplasmic inclusions
- Interstitial pneumonia, diffuse alveolar damage

Differential Diagnosis

- Malignancy

Diagnostic Techniques

- Immunohistochemistry, in situ hybridization, molecular techniques available

Epstein-Barr Virus (EBV)

- Nonenveloped ssRNA (+) sense picornavirus

Clinical

- Infectious mononucleosis in young adults – may be asymptomatic; fever, sore throat, cervical lymphadenopathy, elevated liver function studies, splenomegaly
- Burkitt's lymphoma, nasopharyngeal carcinoma

Microscopic

- Mild acute hepatitis with predominately portal and sinusoidal lymphocytic infiltrate

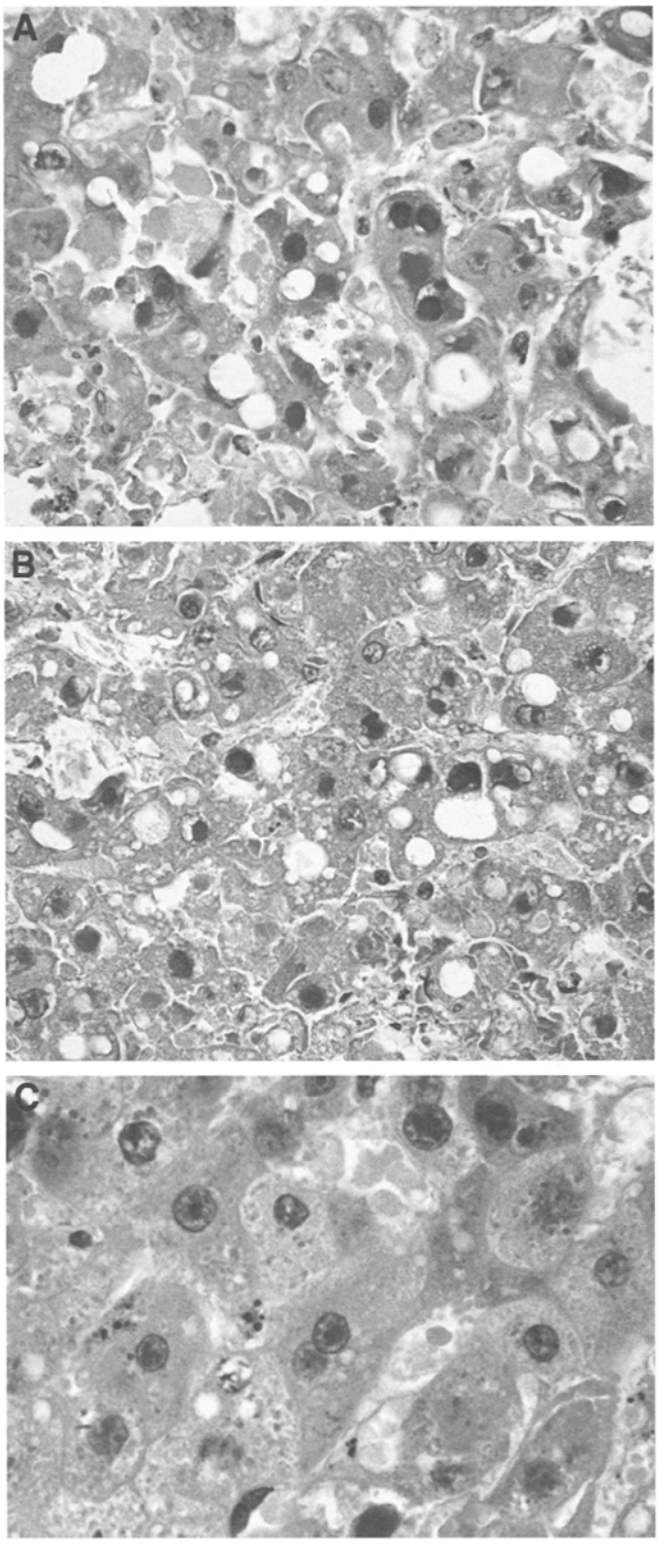


Fig. 35. **(A,B,C)** Ground-glass nuclear inclusions of adenovirus in liver, H&E.

- Little necrosis or cholestasis
- Mitoses and epithelioid granulomas may be seen
- Viral inclusions not seen

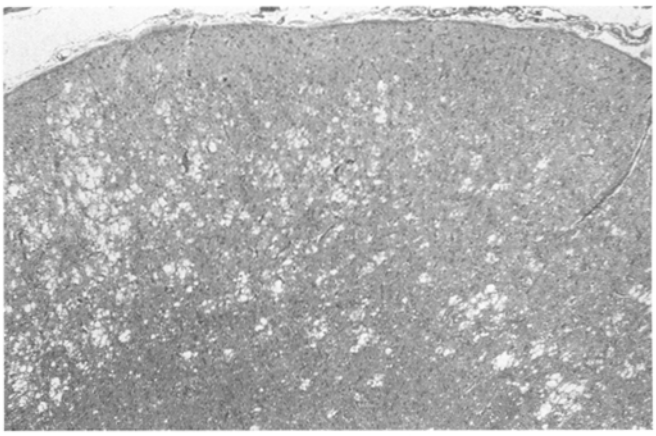


Fig. 36. Creutzfeldt-Jakob Disease in brain, H&E.

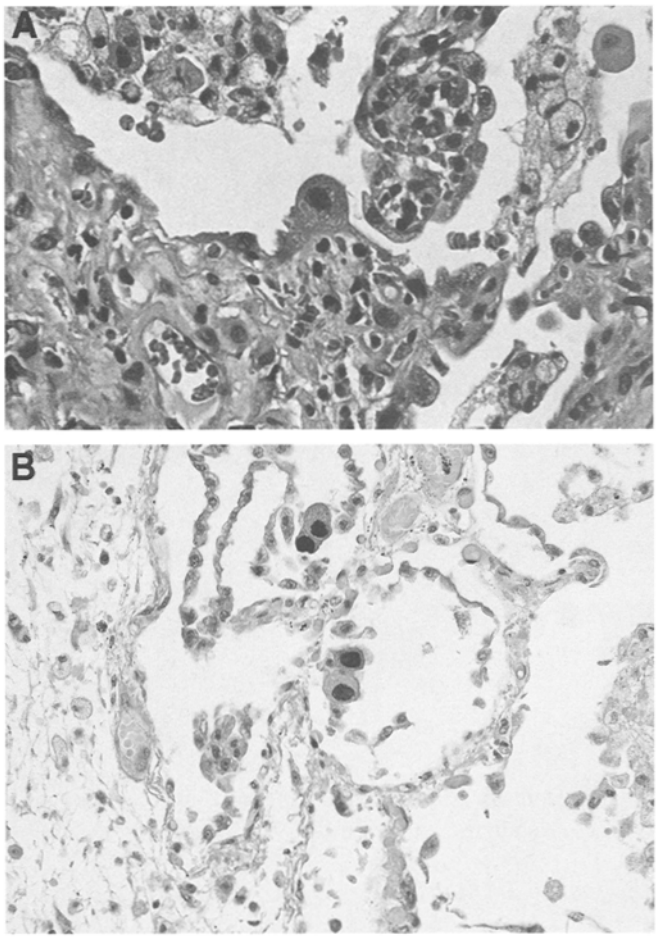


Fig. 37. **(A)** Centrally located, enlarged cell with abundant cytoplasm, consistent with cytomegalovirus infection in lung, H&E, **(B)** immunoperoxidase stain.

Differential Diagnosis

- Cytomegalovirus has characteristic inclusions

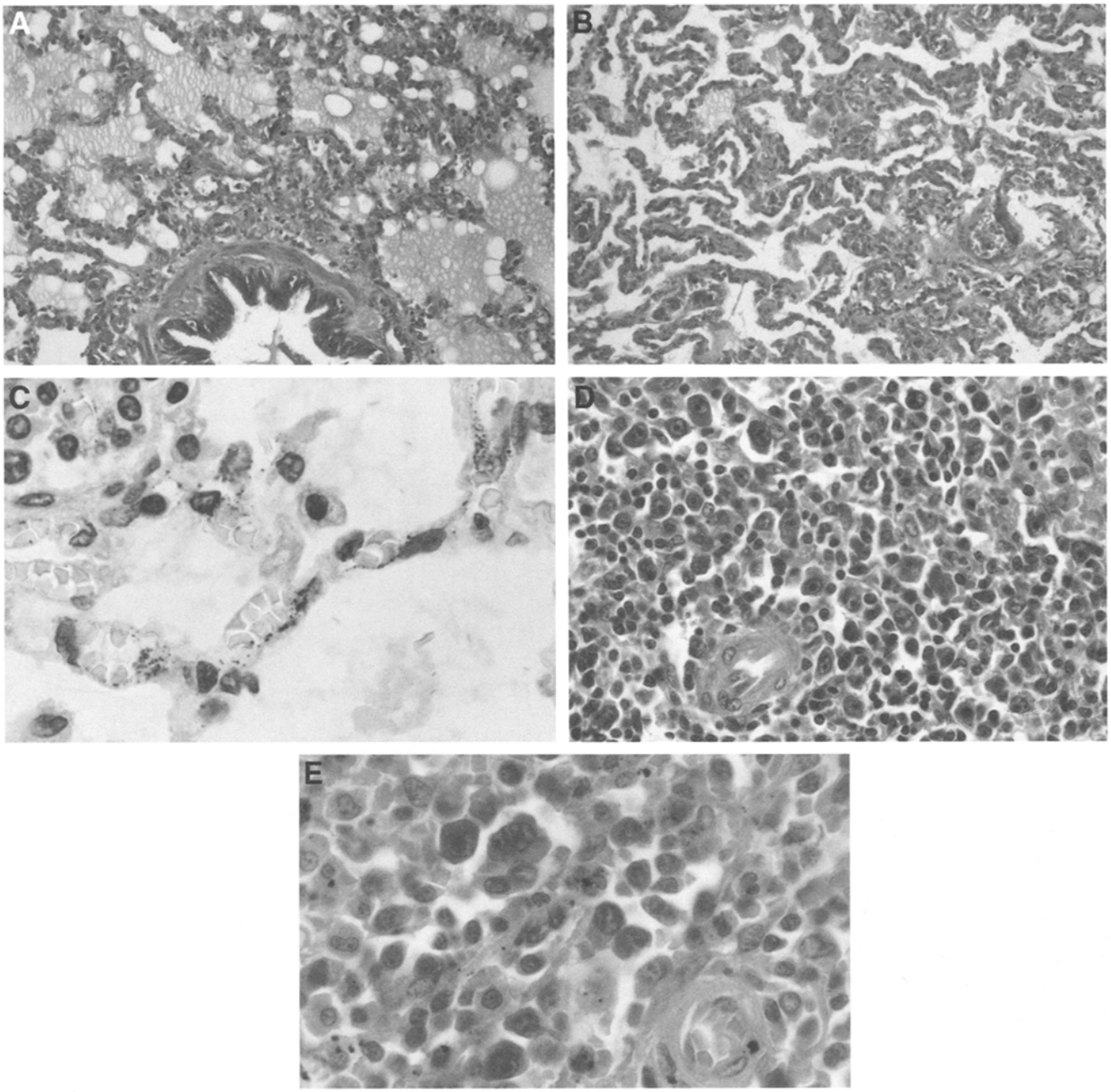


Fig. 38. Hantavirus infection of lung; **(A)** alveolar edema, H&E, **(B)** Interstitial pneumonia, H&E, **(C)** immunoperoxidase stain, **(D & E)** Hantavirus infection of spleen, H&E.

Diagnostic Techniques

- Immunohistochemistry available, serology, nucleic acid amplification techniques (NAAT)

Hantavirus

Enveloped ssRNA (-) sense bunyavirus

Clinical

- Fever, cough, myalgia, gastrointestinal complaints
- Rapid development of bilateral chest infiltrates and respiratory failure – death in three days
- Thrombocytopenia, left shift

Macroscopic

- Pulmonary edema and pleural effusion

*Microscopic **(Figure 38A-E)***

- Mild interstitial pneumonia with delicate hyaline membranes
- No viral inclusions are seen

Differential Diagnosis

- Early diffuse alveolar damage

Diagnostic Techniques

- Immunohistochemistry available

Hepatitis Viruses

- See Chapter 37 Non-Neoplastic Hepatobiliary Disease for further detailed discussion and images of hepatitis A, B, C, D, E, F, G

Herpes Simplex Virus I and 2 (HSV)

Enveloped dsDNA herpesvirus

Clinical

- Generally HSV1 is associated with orofacial infections and HSV2 with genital infections; however, either may occur "above or below the belt":
  - HSV1:
    - Primary infection usually asymptomatic
    - Rare keratoconjunctivitis, respiratory infection, infection of any part of skin or mucosa
    - Recurrence triggered by sunlight, fever, illness
  - HSV2:
    - Acquired via sexual contact or by neonates during vaginal delivery to mom with active genital lesions
- Herpetic whitlow: painful paronychial HSV1 or HSV2 infection of distal finger; usually in medical or dental personnel
- Widespread disseminated systemic disease in immunocompromised patients

*Microscopic **(Figure 39A-C)***

- The 3 M's: Multinucleation, Molding of nuclei and Margination of chromatin
- Ground-glass nuclei or with eosinophilic nuclear inclusion
- Necrosis, diffuse alveolar damage

Differential Diagnosis

- Varicella-zoster virus

Diagnostic Techniques

- Immunohistochemistry available, direct immunofluorecence for viral antigen on infected cells, cell culture

Human Immunodeficiency Virus (HIV 1 & 2)

Enveloped ssRNA (+) sense retrovirus

Infects helper T cells

Clinical

- Causative agent of acquired immunodeficiency syndrome (AIDS)

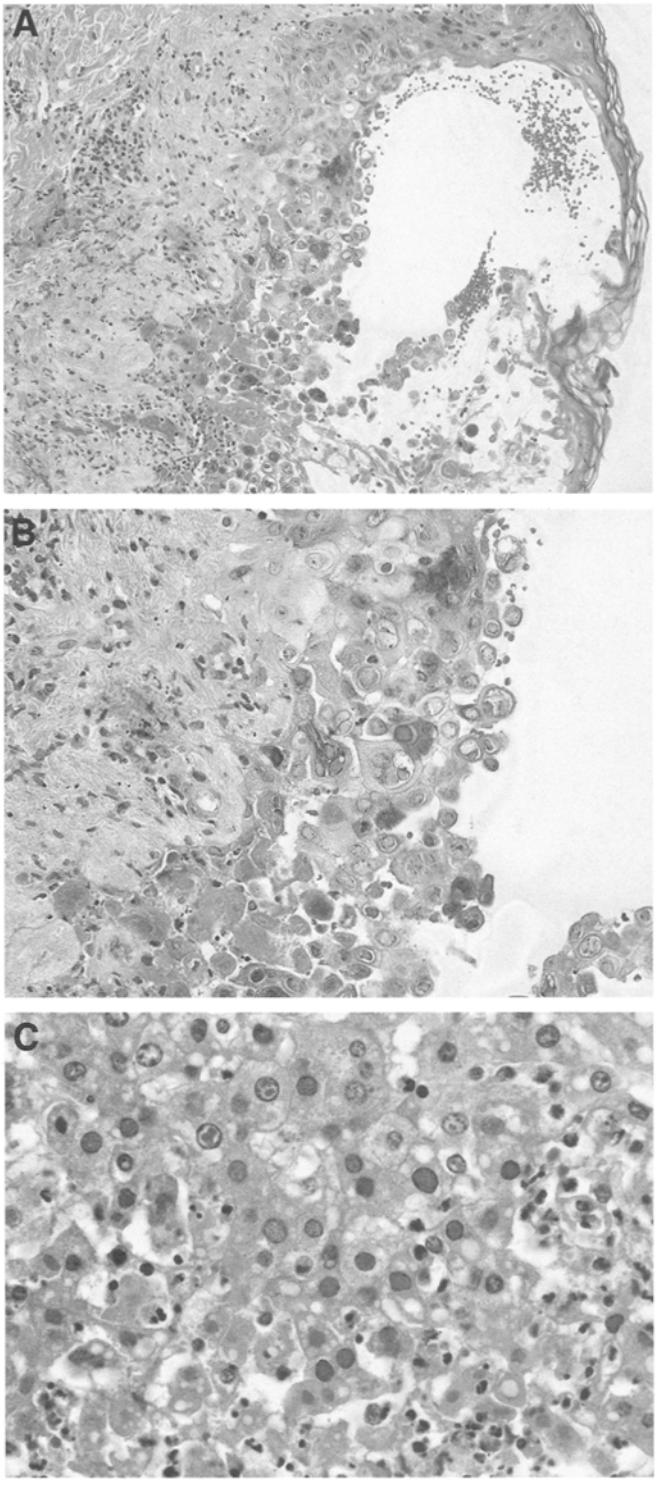


Fig. 39. Herpes simplex virus infection; **(A)** skin, H&E, **(B)** Multinucleated cells with nuclear molding and margination of chromatin, **(C)** Ground-glass nuclei with margination of chromatin in liver infected by herpes simplex virus, H&E.

- Many AIDS indicator diseases
- Transmission via blood, semen, transplacentally
- Death due to opportunistic infection (many possible agents) or malignancy (Kaposi's sarcoma, body cavity lymphomas, nonmelanomatous skin cancer
- Persistent generalized lymphadenopathy

Microscopic

- Hyperplasia of follicular centers, tingible-body macrophages, plasma cells
- Scant/absent mantle zones
- Interfollicular vascular proliferation
- Hyperplasia of parafollicular B lymphocytes
- Decreased CD4 to CD8 ratio with infiltration of CD8 cells into follicular centers
- With progression: loss of follicular centers with intrafollicular hyalinized vessels, lymphocyte depletion

Diagnostic Techniques

- Western blotting, serology, HIV RNA detection, viral load and HIV drug resistance testing available

Human Papillomavirus (HPV)

Nonenveloped dsDNA papovavirus

> 67 types identified to date

Clinical

- Verruca vulgaris (common wart):
  - HPV types 2, 4, 7
- Condyloma acuminatum with low cancer risk:
  - HPV types 6 and 11
- Condyloma acuminatum with high cancer risk:
  - HPV types 16, 18, 31, 33, and 51
- Bowenoid papulosis:
  - HPV types 16, 18, 31, 33, and 51
- Laryngeal carcinoma:
  - HPV type 30
- Verrucous carcinoma:
  - HPV types 2 and 6

Microscopic ***(Figure 40)***

- Raisinoid shrunken nuclei with irregular outline and perinuclear halo (koilocytes), bi- or multinucleation

Differential Diagnosis

- Fungal, protozoal, bacterial infections causing "inflammatory" halos

Diagnostic Techniques

- Immunohistochemistry, in situ hybridization, PCR available

Human T-Cell Lymphotropic (Leukemia/ Lymphoma) Virus 1 and 2 (HTLV)

- Enveloped ssRNA (+) sense retrovirus

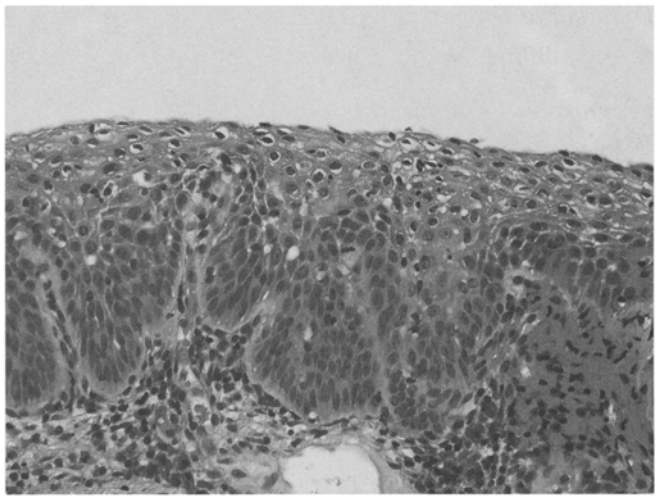


Fig. 40. Human papillomavirus infection and moderate dysplasia of cervix, H&E.

Clinical

- Endemic in Caribbean and Japan
- Aggressive and widespread at diagnosis
- Hepatosplenomegaly, skin involvement, hypercalcemia

Microscopic

- Pleomorphic multilobated lymphoid cells in peripheral blood
- Polymorphous infiltrate with multilobated cells in lymph node
- Mature helper T-phenotype

Diagnostic Techniques

- Serology

Measles

Enveloped ssRNA (-) sense paramyxovirus

Clinical

- Rubeola, pneumonia, encephalitis, subacute sclerosing panencephalitis

Microscopic ***(Figure 41)***

- Warthin-Finkeldey giant cells with smudged nuclei
- Nuclear and cytoplasmic inclusions may be seen
- Interstitial pneumonia and diffuse alveolar damage

Diagnostic Techniques

- Cell culture, RT-PCR (reverse transcription), immunofluorescence, serology

Molluscum Contagiosum

- Enveloped dsDNA poxvirus

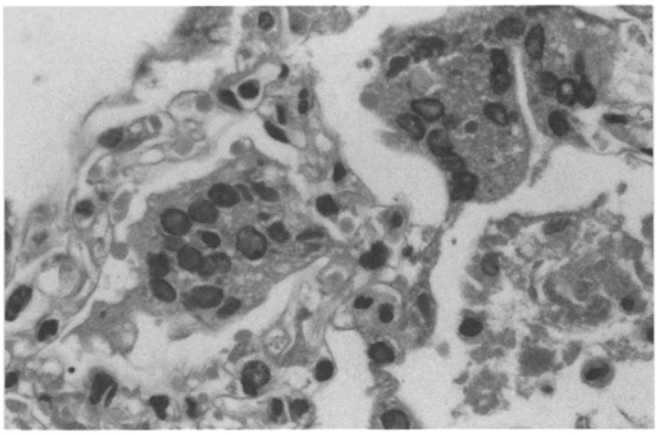


Fig. 41. Multinucleated cells with ground-glass nuclei in measles pneumonia, H&E.

Clinical

- 1–3 mm skin-colored umbilicated papules
- Can be sexually transmitted
- May spontaneously disappear

Microscopic ***(Figure 42A,B)***

- Lobular acanthosis and inverted (cup-shaped) epidermal proliferation
- Characteristic basophilic homogenous cytoplasmic inclusions (molluscum or Henderson-Paterson bodies)

Parvovirus B19

Nonenveloped ssDNA

Clinical

- Fifth disease or erythema infectiosum in children
- Bone marrow aplasia (especially in immunocompromised)
- Hydrops fetalis with placentomegaly, fetal pleural effusion and pulmonary hypoplasia
- Acute self-limiting disease to chronic illness

Microscopic

- Pulmonary hypoplasia, numerous erythroblasts and iron deposits in fetal liver (extramedullary hematopoiesis)

Diagnostic Techniques

- Immunohistochemistry available, serology, in situ hybridization

Polyomavirus

Nonenveloped dsDNA papovavirus

Clinical

- Infects immunocompetent and immunocompromised patients
- Many asymptomatic, some with hematuria
- Most resolve spontaneously

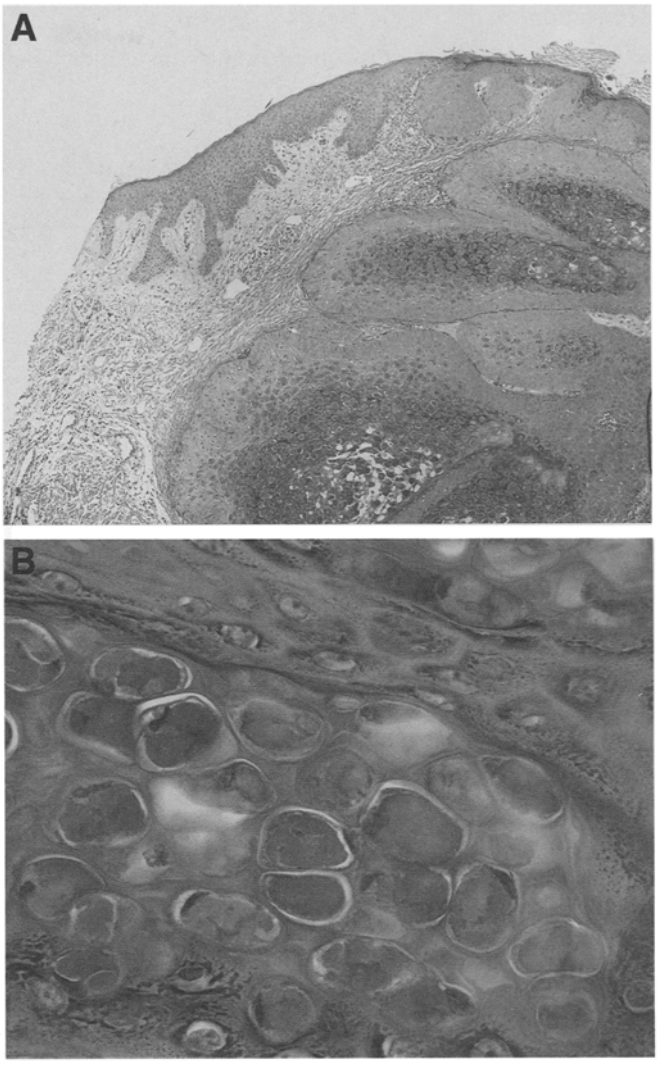


Fig. 42. (**A** & **B**) Molluscum contagiosum, skin, H&E.

Microscopic

- Solitary cells ("decoy cells") in urine with enlarged smudged nuclear inclusion and surrounding thin halo

Differential Diagnosis

- Carcinoma, cytomegalovirus has larger cells and may have cytoplasmic inclusions

Diagnostic Techniques

- Immunocytochemistry available

Rabies Virus

Enveloped ssRNA (-) sense rhabdovirus

Clinical

- Rabies; attacks posterior horns; encephalitis
- Fatal infection of central nervous system acquired via saliva from bite of infected animal

Microscopic

- Negri bodies – oval, eosinophilic intracytoplasmic inclusions

Diagnostic Techniques

- Direct fluorescent antibody detection of viral antigen, immunoenzymatic tests, molecular and serologic testing available

Respiratory Syncytial Virus

Enveloped ssRNA (-) sense paramyxovirus

Clinical

- Croup, respiratory infections (bronchiolitis and pneumonia)

Microscopic

- Multinucleated giant cells
- Small, round eosinophilic intracytoplasmic inclusions may be seen
- Necrotizing bronchiolitis, interstitial pneumonia

Diagnostic Techniques

- Cell culture, immunofluorescence, enzyme immunoassay, PCR

Varicella-Zoster Virus (VZV)

Enveloped dsDNA herpesvirus

Clinical

- Varicella (chicken pox):
  - Primary infection – vesicles with erosion, ulceration, then crust formation
  - Virus dormant in spinal or cranial sensory ganglion post-infection
- Herpes zoster (shingles) in dermatomal distributions:
  - Reactivated infection in adults
- Widespread generalized infection or pneumonia in immunocompromised patients

Microscopic ***(Figure 43A,B)***

- Necrosis and eosinophilic inclusions (lungs, kidney, liver, adrenal if disseminated), diffuse alveolar damage
- The 3 M's: Multinucleation, Molding of nuclei and Margination of chromatin
- Ground-glass nuclei or with eosinophilic nuclear inclusion

Differential Diagnosis

- Herpes simplex virus

Diagnostic Techniques

- Cell culture, immunofluorescence, PCR

Variola Major (Smallpox)

- Enveloped dsDNA poxvirus
- Strict human host range
- Transmitted via large respiratory droplet or less commonly by aerosol or direct contact with rash
- Re-emergence as agent of bioterrorism

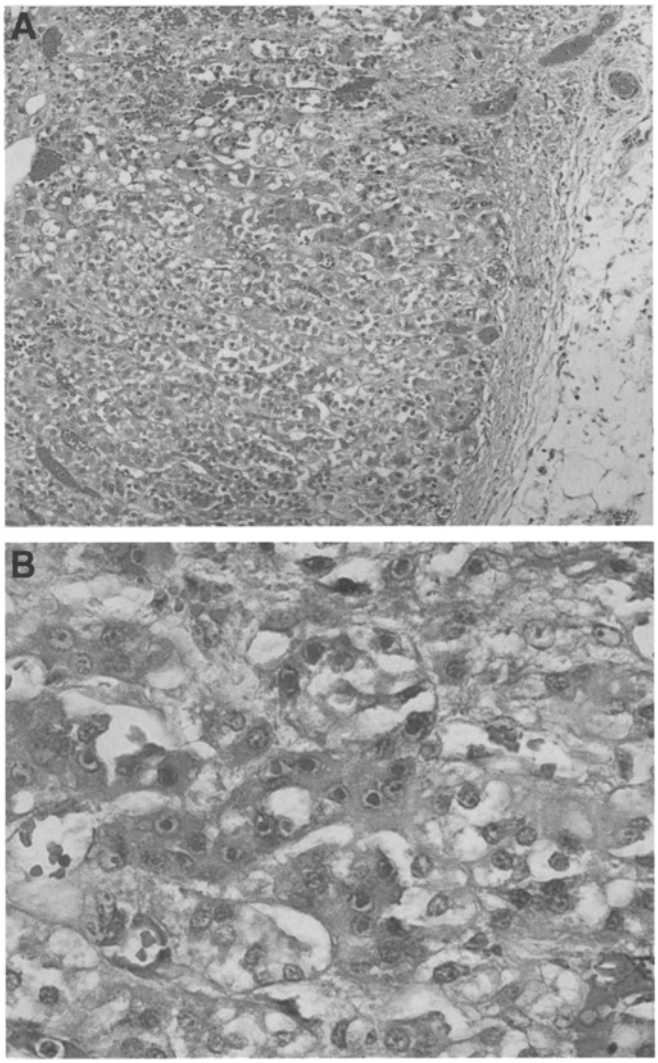


Fig. 43. (**A** & **B**) Varicella infection of adrenal, H&E.

Clinical

- 10–14 day asymptomatic incubation followed by quick-rising fever to 103°F. with dermal petechiae, headache, backache, vomiting
- Centrifugal rash with greater numbers of lesions on oral mucosa, face and extremities than on trunk:
  - Initially macular, then popular, then vesicular by day 4–5 and pustular by day 7
  - Encrusted and sloughed by day 14
  - All lesions deep-seated and same stage of development

Microscopic

- Requires biosafety level 4 laboratory handling (see Diagnostic Techniques)

Differential Diagnosis

- Chicken pox (Varicella-zoster virus) has centripetal rash with superficial lesions in crops, disseminated

herpes simplex, drug reactions, molluscum contagiosum

Diagnostic Techniques

- Suspected cases should immediately be reported to the appropriate local and state public health departments
- CDC phone numbers for questions and consultation 24 hours, seven days per week are (770)488-7100 or (770)488-4819 (website:www.cdc.gov/ncidod/hip or www.bt.cdc.gov)
- Electron microscopy, cell culture, serology, PCR, RFLP (restriction fragment length polymorphism)

PARASITES

Protozoa

Acanthamoeba species

Obligate aerobes containing mitochondria; inhibited by bile; trophozoites do not survive in intestinal tract

Ubiquitous in water and soil

Human exposure:

- Swimming in warm lakes, rivers, swimming pools
- Nonsterile contact lens cleaning solutions

Clinical

- Keratitis in contact lens wearers or history of eye trauma and exposure to contaminated water, corneal ulceration with marked ocular pain
- Chronic granulomatous amebic encephalitis
- Elderly, immunocompromised, or debilitated patients
- Can be fatal but spontaneous recovery is not uncommon; relatively slow course
- May disseminate to skin and elsewhere, especially with AIDS

Macroscopic

- *Acanthamoeba culbertsoni* causes hemorrhagic necrosis and infarcts in brain
- Other less virulent *Acanthamoeba* spp. cause more chronic CNS lesions

Microscopic ***(Figure 44A,B)***

- Necrotizing granulomas containing trophozoite and cyst forms

Differential Diagnosis

- Has double layered outer membrane on electron microscopy (*Balamuthia mandrillaris* has 3)
- Herpes keratitis clinically

Diagnostic Techniques

- CSF, corneal scrapings, tissue biopsy; direct microscopic examination
- Culture on water agar seeded on surface with live enteric gram-negative bacilli

Babesia microti

Great Lakes and northeast U.S.

Transmitted by *Ixodes dammini* tick (same as *Borrelia burgdorferi*)

Normosplenic patients (in contrast to severe/fatal infections in splenectomized patients in Europe)

Clinical

- Spectrum from asymptomatic in young, normosplenic, immunocomptetent persons to potentially life-threatening hemolytic disease in elderly, asplenic or immunosuppressed persons
- Nonspecific presentation with fever, chills, malaise, nausea, vomiting, weight loss, icterus depending on extent of hemolysis, hepatosplenomegaly

Microscopic

- Tetrads of tiny ring forms within normal sized rbc

Special Stains

- Giemsa of peripheral blood smear

Differential Diagnosis

- *Plasmodium falciparum*

Diagnostic Techniques

- Fluorescent Maltese cross formation; buffy coat preparation improves detection

Balantidium coli

Zoonotic parasitic infection

Ciliate transmitted by fecal-oral route (infective oocysts passed in feces are ingested by new host)

Clinical

- Gastrointestinal infection: bloody dysentery
- Infection generally mild and self-limited unless immunocompromised

Macroscopic

- Colonic ulceration and transmural necrosis
- Early lesion flask-shaped like that due to *E. histolytica*

Microscopic

- Large ciliate (50–100 × 40–70 μm) with kidney-shaped macronucleus and a micronucleus
- Trophozoite and cyst forms
- Ulcer covered by purulent necrotic material with underlying edema and lymphoplasmacytic infiltrate

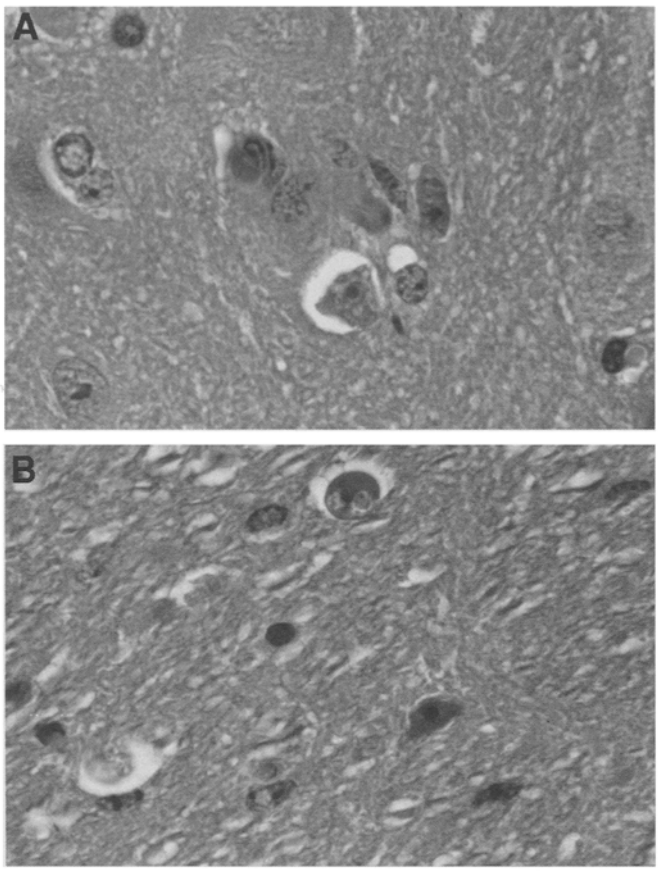


Fig. 44. Granulomatous amebic encephalitis due to *Acanthamoeba;* **(A)** trophozoite with retraction artifact just below center field, H&E, **(B)** cyst in upper center field, H&E.

- Trophozoites single or in groups in inflamed mucosa, submucosa or necrotic material overlying ulcer crater
- Secondary bacterial infection

Special Stains

- Not necessary

Diagnostic Techniques

- Identification of cysts or trophozoites in stool or trophozoites in colonic mucosal biopsies
- Rotary boring motility

Cryptosporidium parvum

- Coccidian; fecal-oral spread
- Oocysts survive chlorination

Clinical

- Gastrointestinal infection: diarrhea in immunocompromised or high volume infection, especially in AIDS patients
- Self-limited in immunocompetent patients

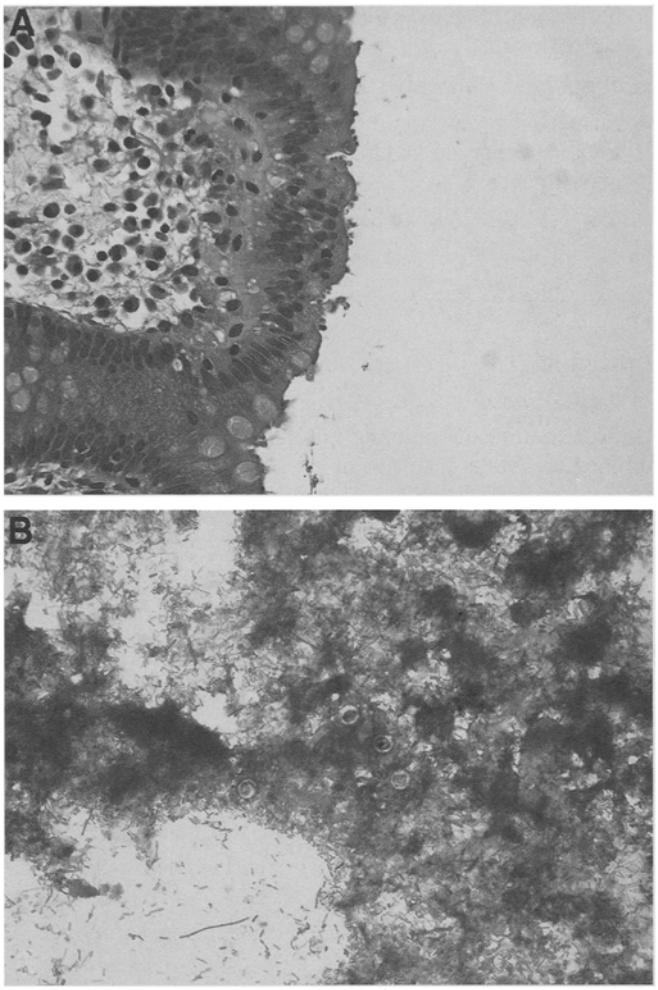


Fig. 45. **(A)** Small bowel biopsy demonstrating intracellular, extracytoplasmic blue "beads" in the brush border, consistent with *Cryptosporidium* spp., H&E, **(B)** Stool smear demonstrating 4-5 µm *Cryptosporidium* oocysts, MAF.

Microscopic ***(Figure 45A,B)***

- Intracellular but extracytoplasmic organism in parasitophorous vacuole
- 4–5 µm oocyst with 4 naked sporozoites inside (no sporocyst)
- Mild to moderate villous atrophy, crypt dilation and lymphoplasmacytic infiltrate in lamina propria
- Jejunum usually most heavily involved

Special Stains

- Modified Kinyoun acid-fast stain on stool smear; look like crinkled tissue paper

Differential Diagnosis

- *Cyclospora cayetanensis* is twice the size

Diagnostic Techniques

- Small intestinal biopsy diagnostic
- Immunofluorescence, EIA and ELISA for antigen in stools

Cyclospora cayetanensis

Coccidian found worldwide; large U.S. outbreak associated with Guatemalan raspberries

Clinical

- A cause of traveler's diarrhea
- Prolonged self-limited diarrhea may last weeks
- Diarrhea in immunocompromised patients

Microscopic

- 8–10 μm oocyst with two sporocysts inside
- Blunting of jejunal villi (villous atrophy), crypt hyperplasia

Special Stains

- Modified Kinyoun acid-fast on stool smear; look like crinkled tissue paper

Differential Diagnosis

- *Cryptosporidium parvum* is half the size

Diagnostic Techniques

- Autofluoresces under ultraviolet light

Entamoeba histolytica

- Worldwide but more prevalent in tropics
- Gastrointestinal amoeba transmitted via cysts (infective form) and fecal-oral route
- Obligate anaerobe lacking mitochondria and is resistant to bile
- More common in lower socioeconomic status, immigrants, institutional living, male homosexuals

Clinical

- Amebic dysentery, crampy abdominal pain, flatulence, diarrhea (watery stool with mucus and blood); liver abscess (occasionally lung, brain)

Microscopic

- Flask-shaped ulcers with neutrophilic inflammatory response in colon; may perforate
- Trophozoite (12–60 μm and asymmetrical) and cyst forms (10–20 μm and spherical)
- Targetoid nucleus with tiny central karyosome and scant peripheral chromatin (troph has single nucleus, cyst has 4 or fewer nuclei)
- Clean, finely granular cytoplasm; ingests rbcs (diagnostic); 10% of cysts have chromatoid bars with smooth, rounded ends

Special Stains

- Trichrome of stool smear

Differential Diagnosis

- *Entamoeba hartmanni*, *E. dispar* (harmless commensal)

Diagnostic Techniques

- Identification of trophozoites in colon biopsy, feces or aspirate
- Antigen detection

Giardia lamblia

Gastrointestinal flagellate found worldwide; associated with overcrowding and poor sanitation (fecal-oral transmission)

The most frequently identified intestinal parasite in the United States

Mature cyst is the infective form and is resistant to chlorine concentrations typically used in city water systems

Clinical

- Diarrhea, day care infections, campers and hikers, B12 malabsorption
- Abdominal distension due to intestinal gas, lactose intolerance, flatulence, abdominal cramping
- Less commonly low-grade fever, nausea, vomiting
- Infection usually resolves in 1–4 weeks but may persist for months, especially in children

Microscopic ***(Figure 46A,B)***

- Trophozoite (looks like a face with glasses and whiskers; has 6 flagellae) and cyst forms (4 nuclei)
- Found free-floating or attached to surface of gastrointestinal epithelial cells with a ventral sucker – crescent shaped on profile but pear-shaped en face
- Minimal to no inflammatory response
- Cysts are found in formed stools; the trophozoite is found in diarrheal stools (transit time too short for cyst formation

Special Stains

- None needed; routine hematoxylin and eosin sufficient

Diagnostic Techniques

- "Falling leaf" motility on wet mount; direct immunofluorescence and ELISA for *Giardia* antigens in stool

Isospora belli

Worldwide gastrointestinal coccidian; endemic in some tropical and subtropical areas (Chile, Brazil, Colombia, Africa, Southwest Asia)

Fecal-oral transmission of sporocysts

Clinical

- Acute, mild to profuse, nonbloody, watery diarrhea resolves in two weeks in immunocompetent
- Diarrhea and malabsorption in immunocompromised may last weeks, months or years and can ultimately lead to death
- Low-grade peripheral eosinophilia

Microscopic

- 25–30 μm ellipsoid oocyst with two internal spherical sporocysts and 4 banana-shaped sporozoites within each sporocyst

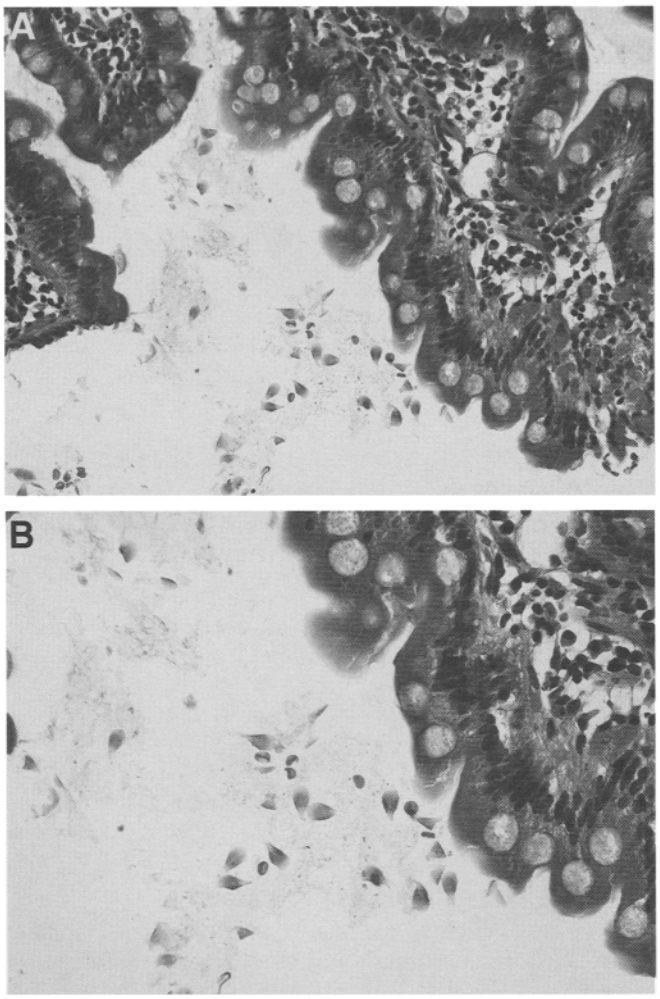


Fig. 46. (**A** & **B**) Small bowel biopsy demonstrating many free-floating binucleated *Giardia* trophozoites, H&E.

- Small bowel villous atrophy, crypt hyperplasia, intraepithelial lymphocytes; subnuclear, loose-fitting parasitophorous vacuoles

Special Stains

- Modified Kinyoun acid-fast stain of stool smear
- Alcian blue added to hematoxylin-eosin of biopsies; tissue Giemsa gives best contrast

Differential Diagnosis

- *Cryptosporidium* oocysts are much smaller

Diagnostic Techniques

- Intermittent shedding requires several stool specimens

Leishmania species

Found worldwide except Australia and Antarctica

Old World = tropical and subtropical Asia, India, Africa, Mediterranean

New World = the Americas

Clinical

- Infection acquired via bite of *Phlebotomous* sand fly which is smaller than a mosquito and penetrates standard mosquito nets
- Ranges in severity from self-limited cutaneous disease to potentially fatal disseminated disease
- Old World cutaneous leishmaniasis most often caused by *L. tropica* complex
- New World cutaneous leishmaniasis is caused by *L braziliensis* complex and *L. mexicana* complex; *L braziliensis* can produce destructive mucocutaneous form called espundia
- Three types of disease: cutaneous, mucocutaneous and visceral:
  - Cutaneous:
    - (localized, disseminated, recidivans (recurrent) and post-kala azar/postvisceral dermal)
    - Usually restricted to exposed areas of skin
    - 60% due to *L. mexicana*; Chiclero ulcers on earlobes
    - Disseminated when immune system fails to respond to invading parasites
    - Recidivans may occur 1–15 years after primary infection
    - Post-kala azar dermal rare and years after recovering from visceral disease
  - Mucocutaneous:
    - Predominantly rural and jungle regions of New World
    - Occurs when primary cutaneous infection with *L. brasiliensis* subspecies *brasiliensis* or *panamensis* disseminates to upper respiratory tract
    - Frequency variable: rare in Yucatan and Guatemala but occurs in 80% of cases in Brazil
    - Progression from chronic cutaneous ulcer with hematogenous and lymphatic dissemination producing lesions in oral, pharyngeal and nasal mucosa to invasion of nasal septum and paranasal fossae with severe mutilation of midface to death
  - Visceral (kala azar):
    - Most serious
    - Occurs in New and Old World infections
    - Parasites found throughout reticuloendothelial system
    - Patients present with fever, malaise, hepatosplenomegaly, anorexia, wasting, pancytopenia, hypergammaglobulinemia; skin has irregular areas of dark pigmentation
- Blood-borne transmission and transfusion-associated leishmaniasis possible

Macroscopic

- Cutaneous centrally ulcerated plaque

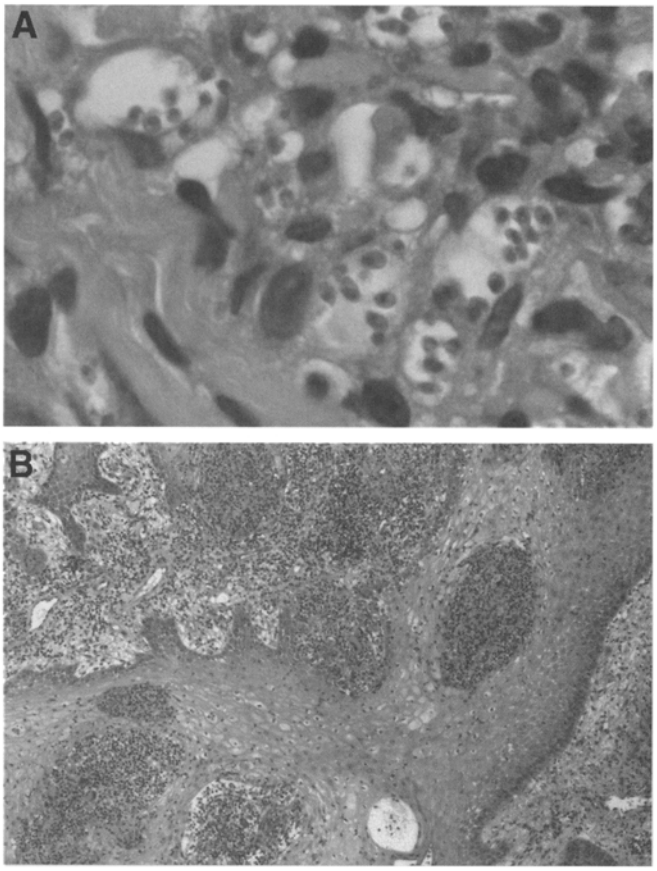


Fig. 47. Leishmaniasis. **(A)** Kinetoplasts are difficult to see here, H&E, **(B)** Pseudoepitheliomatous hyperplasia of skin, H&E.

*Microscopic **(Figure 47A,B)***

- 2–4 μm organisms contain a bar-shaped paranuclear kinetoplast (specialized mitochondrial structure containing extranuclear DNA)
- Irregular acanthosis with or without epidermal ulceration and dense dermal infiltrated of mixed inflammatory cells, pseudoepitheliomatous hyperplasia; many organisms early but decrease as immune response mounts
- In disseminated lesions, dermis contains sheets of macrophages; organisms disappear in healing phase leaving only a granulomatous reaction
- Nonspecific inflammatory infiltrate with rare organisms in macrophages and few or no tuberculoid formations seen in espundia

Special Stains

- Histologic sections or smears stained with hematoxylin and eosin, Giemsa or reticulin stains

Differential Diagnosis

- *Histoplasma capsulatum* lacks a kinetoplast

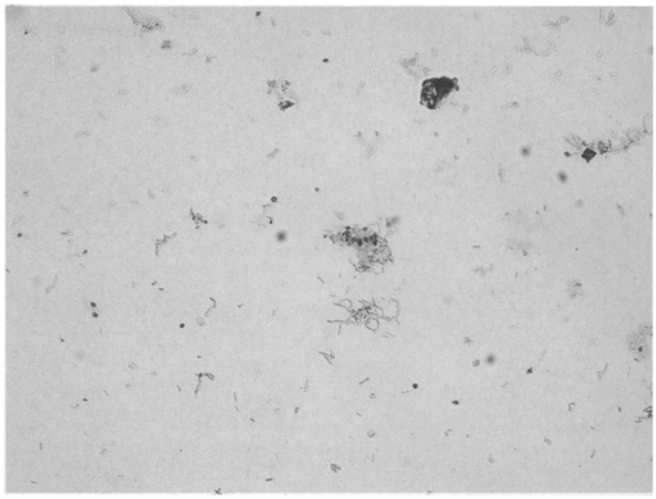


Fig. 48. Stool smear demonstrating microsporidial spores in center of field. Modified Weber trichrome stain.

Diagnostic Techniques

- Cutaneous leishmaniasis: amastigotes may be demonstrated in lesion biopsy, skin scrapings, or aspirates by hematoxylin and eosin, Giemsa, or Brown-Hopps; PCR
- Visceral leishmaniasis: serology (anti-rK39) qualitative; quantitative to follow course of infection; hematoxylin and eosin or Giemsa stain of bone marrow, liver, spleen or lymph node biopsy; PCR
- Cultural growth in Novy-Nicolle-McNeal (NNN) media

Microsporidia

Coccidia; multiple Genera

Obligately intracellular true eukaryotes that produce spores via unique, coiled polar tubule packaged within spore, acting as a "hypodermic needle" to inject infectious sporoplasm into host cell

Clinical

- Opportunistic infections in AIDS, infections of gastrointestinal tract (diarrhea), urinary tract, lungs, cholangitis, myositis, encephalitis
- *Enterocytozoon bieneusi* infects enterocytes in AIDS patients, causing severe protracted diarrhea, weight loss and malabsorption; cholangitis and cholecystitis; most common microsporidian
- *Encephalitozoon* diarrhea, keratitis, brain lesions, disseminated infections

*Microscopic **(Figure 48)***

- Intracytoplasmic in superficial small intestinal mucosal cells; oval with transverse band

Special Stains

- Modified Weber trichrome, acid-fast, periodic acid-Schiff, Gram

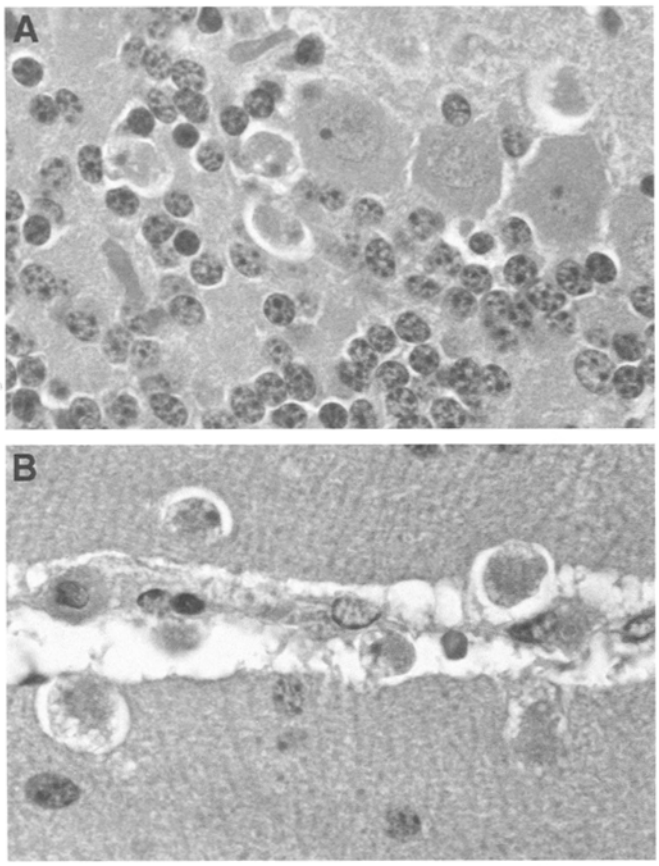


Fig. 49. Primary amebic meningoencephalitis; **(A)** with three *Naegleria fowleri* trophozoites left of center field, H&E, and **(B)** a single trophozoite in center of field, H&E.

Diagnostic Techniques

- Electron microscopy to diagnose to species level

Naegleria fowleri

Free-living amoeba

Clinical

- Diffuse and fulminant primary amebic meningoencephalitis acquired from swimming in fresh water
- Typically affects children and young adults
- Usually fatal; gains access to the CNS by migration across the cribriform plate from nasal mucosa via olfactory nerve; amoebic rhinitis

Macroscopic

- Purulent meningoencephalitis with necrotizing abscesses of brain

*Microscopic **(Figure 49A,B)***

- Trophozoites, especially perivascular; no cysts

Differential Diagnosis

- *Acanthamoeba* spp. have cyst form as well as trophozoites

Diagnostic Techniques

- Purulent CSF may contain trophozoites

Plasmodium species

Many species exist, but four infect humans: *P. falciparum*, *P. ovale*, *P. malariae* and *P. vivax*; sexual phase (sporogony) occurs in gut of mosquito; asexual phase (schizogony) takes place in human rbcs

Life cycle:

- rbc invaded by single parasite (merozoite), transforms to ring form (trophozoite), dark "malarial pigment" forms as troph grows and hemoglobin it needs for growth is converted to insoluble iron porphyrin and hematin
- Mature troph divides into a segmented form (schizont) which mature to be recognized as individual merozoites with nucleus and cytoplasm
- Some merozoites do not develop into schizonts, but mature into sexual forms (gametocytes) instead

Clinical

- Malaria – anemia, thrombocytopenia, splenomegaly; blackwater fever = fever and dark urine produced with massive intravascular hemolysis and subsequent hemoglobinuria (due to *P. falciparum*); delirium, seizure, coma, death:
  - *P. falciparum* produces the most severe disease (malignant tertian malaria) and is most commonly associated with death; therefore, most important to recognize
  - *P. malariae* – quartan malaria (72 hour cycle); associated with M antigen
  - *P. vivax* – benign tertian malaria (48 hour cycle); most common
  - *P. ovale* – common in West Africa, rare elsewhere

Microscopic

- *P. falciparum*
  - Peripheral blood findings:
    - Characterized mainly by very small ring forms; may have multiple ring forms per small or normal-sized rbc; appliqué forms (rings look like they are plastered to side of rbc)
    - Banana-shaped gametocytes seen in <20%
    - Intermediate forms not often seen; schizonts seen mainly in overwhelming infections and moribund patients
  - Tissue findings (e.g., CNS malaria)
    - Other stages of *P. falciparum* usually are not found in the peripheral blood smear owing to adherence to capillary/venule endothelial cells within organs, eg., brain
    - 24 or more merozites per schizont; malarial pigment present looks like nuclear dust; Maurer's dots look like cleft-shaped granules

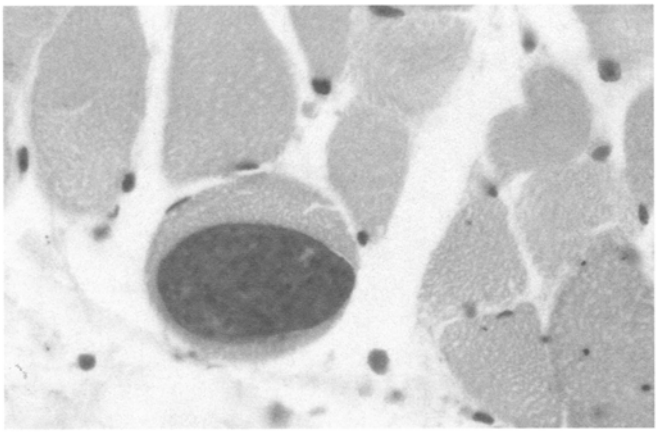


Fig. 50. Sarcocyst containing bradyzoites in skeletal muscle, H&E.

- *P. malariae* has rare rings; mature band forms in normal sized rbc, ~6–12 merozoites/schizont (fewest) arranged in rosettes; large round-oval gametocytes
- *P. vivax* has Schuffner's dots (looks similar to basophilic stippling); infects immature rbcs (enlarged); large rings with ameboid mature forms; schizonts have 12–24 segments; large round-oval gametocytes
- *P. ovale* has rare Schuffner's dots, coarse stippling, 10–14 merozoites/schizont; rbcs appear to have feathered edges and are enlarged

Special Stains

- Giemsa stains of thick and thin peripheral blood smears

Differential Diagnosis

- *Babesia*; *Leishmania donovani* is extracellular

Diagnostic Techniques

- Parasitemia highest during febrile paroxysm, may require several specimens over time for diagnosis
- Thick smear more concentrated with lysed rbcs allows detection of parasites; Morphology assessed and species differentiated based on thin smear findings

Sarcocystis

Gastrointestinal coccidian; obtained from poorly cooked beef or pork; humans are intermediate or definitive host; sexual cycle develops in subepithelium of small bowel mucosa

Clinical

- Often asymptomatic or self-limited; polymyositis and eosinophilia rare; nausea, vomiting, diarrhea

*Microscopic (**Figure 50**)*

- 25–33 μm oocyst with "collapsed" wall around 2 sporocysts; may contain up to 4 sporozoites; encysted sporozoites in skeletal or cardiac muscle in intermediate host

Differential Diagnosis

- *Toxoplasma gondii* and *Trypanosoma cruzi* are both smaller

Diagnostic Techniques

- Identification of sporulated oocysts or sporocysts in stool; muscle biopsy

Toxoplasma gondii

- Obligate intracellular sporozoan; definitive host is domestic cat; both the asexual and sexual phases take place in the GI tract of the cat; asexual stage takes place in other animals and humans
- Transmitted via ingestion of oocysts on food or ingestion of meat of infected animals (pork, lamb); transplacentally

Clinical

- Three forms:
  - Self-limited febrile (cervical) lymphadenopathy; fever, rash, sore throat
  - Severe lethal infection in immunocompromised host; necrotizing encephalitis, pneumonitis, myocarditis
  - Congenital infection in infants (microcephaly, hydrocephaly, chorioretinitis, cerebral calcifications, seizures, and psychomotor retardation; it may also lead to abortion or stillbirth):
    - Congenital toxoplasmosis is in the differential of the "blueberry muffin baby" that has generalized blue-red papules and nodules due to dermal erythropoiesis
- Asymptomatic in most patients with normal immunity

*Microscopic (**Figure 51A-F**)*

- 3–4 × 6–7 μm crescent-shaped tachyzoites (trophozoites) invade nucleated host cells
- 200 μm tissue cyst in brain, heart, skeletal muscle surrounded by protective membrane contains several hundred bradyzoites and is seen in chronic disease

Special Stains

- Giemsa stain of lymph node reveals trophozoites during lymphadenopathy stage, periodic acid-Schiff

Differential Diagnosis

- *Isospora*, Microsporidia, *Leishmania*, *Trypanosoma cruzi*, *Pneumocystis jiroveci*

Diagnostic Techniques

- By adulthood, ~50% of Americans have antibodies to *T. gondii*
- Serologic testing: indirect immunofluorescent antibody, indirect hemagglutination, ELISA

Trichomonas vaginalis

- Vaginal protozoan flagellate with worldwide distribution
- Most prevalent nonviral, sexually transmitted disease with 4–28 day incubation

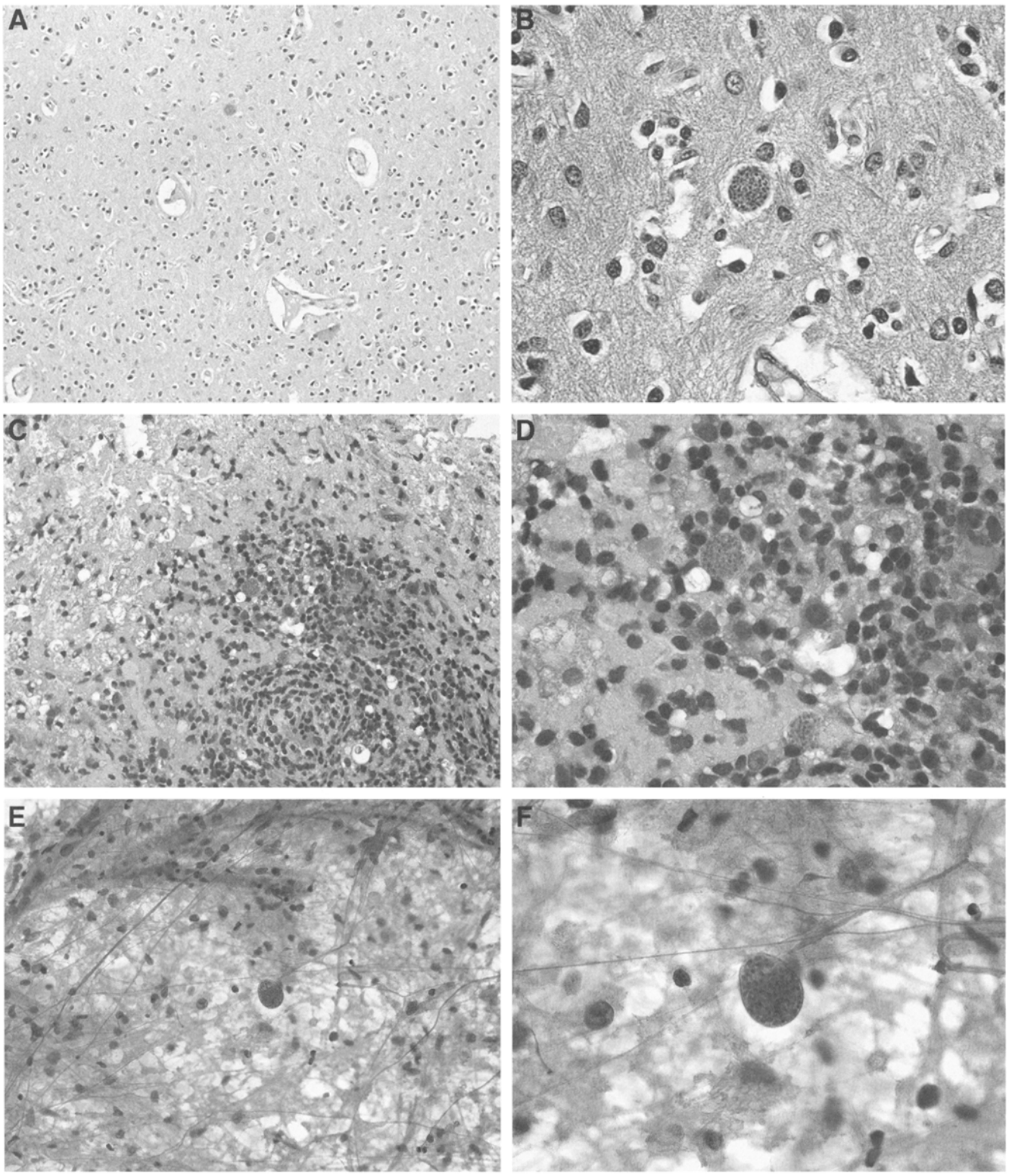


Fig. 51. Three *Toxoplasma* cysts (**[A]** two in center field and one above center), **(B)** single cyst, (**C** & **D**) *Toxoplasma* cyst and chronic inflammatory infiltrate in brain, (**E** & **F**) *Toxoplasma* cyst in squash preparation of brain tissue, H&E.

Clinical

- Sexually transmitted infection, urinary tract infection, chronic vaginitis, intermittent but persistent foul-smelling, yellow-green, frothy discharge, dyspareunia, vaginal pruritus, and dysuria; erythema of vaginal and cervical mucosa, friable granular cervix (strawberry cervix)
- Urethritis and prostatitis in men but most are asymptomatic

Microscopic

- Trophozoite only (oval and 7–23 μm); no cyst form; can exist off the host for 1–2 hours, and in secretions, urine, and water for up to 24 hours
- Four apical flagella, one flagellum in association with an undulating membrane that extends half the length of the organism, and a single nucleus

Special Stains

- Papanicolaou, Giemsa, acridine-orange

Diagnostic Techniques

- Identification of motile organism ("jerky" motility) in wet mount of vaginal or urethral discharge
- Papanicolaou smear; generally not identified on biopsy
- Can be cultured under anaerobic conditions on Diamond's medium

Trypanosoma species

Trypanosoma cruzi: Mexico and S. America; transmitted by triatomid, reduviid or kissing bug that defecates while biting and host scratches bite, inoculating infected feces into skin

Trypanosoma brucei gambiense: West Africa; transmitted by tsetse fly

Trypanosoma brucei rhodesiense: East Africa; transmitted by tsetse fly

Clinical

- *Trypanosoma cruzi*:
  - Chaga's disease (South American trypanosomiasis) affects visceral, especially heart
  - Acute form with fever, lymphadenopathy, anorexia, hepatosplenomegaly, edema, Romaña's sign (bites around eyes)
  - Chronic form with cardiomyopathy, interstitial myocarditis, megaesophagus, megacolon and CNS (central nervous system) involvement
- *Trypanosoma brucei gambiense*:
  - African sleeping sickness, lymph node and CNS involvement; more chronic form; Winterbottom's sign (enlarged posterior cervical lymph nodes)
- *Trypanosoma brucei rhodesiense*:
  - African sleeping sickness more acute and fulminant (rapid onset and rapidly progressive), CNS involvement

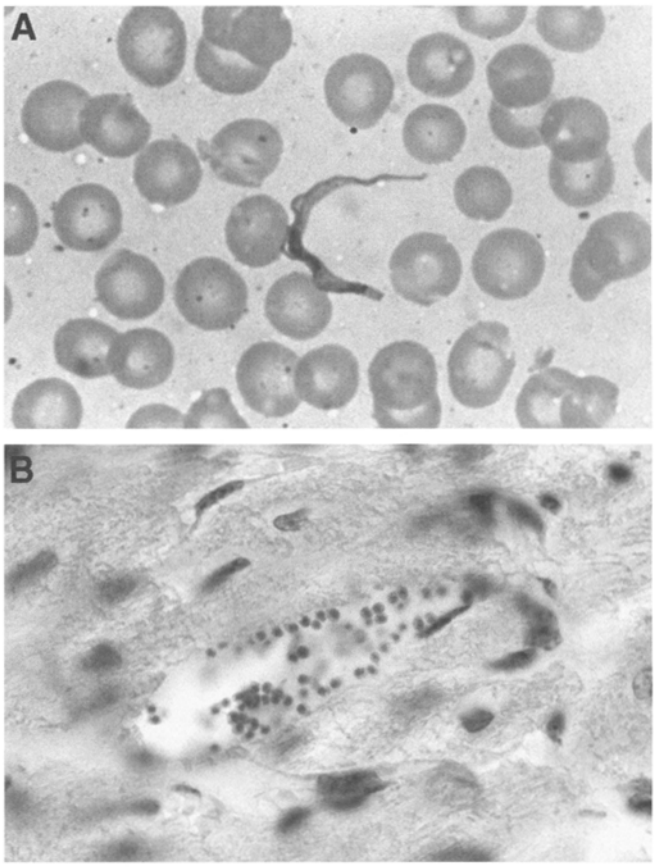


Fig. 52. *Trypanosoma cruzi*; **(A)** trypomastigotes with prominent terminal kinetoplast in peripheral blood smear, Giemsa, **(B)** amastigotes in myofiber in acute chagasic myocarditis, H&E.

Microscopic ***(Figure 52A,B)***

- 15–30 μm trypanosomes with whip-like polar flagellum originating from dotlike kinetoplast located posterior to the central nucleus; undulating membrane running length of body projects beyond anterior point of organism
- *Trypanosoma cruzi* – C shaped trypomastigotes on peripheral blood smear are characteristic but not diagnostic, amastigotes in reticuloendothelial cells or cardiac muscle do not circulate in peripheral blood
- *Trypanosoma brucei gambiense* – S shaped trypomastigote on peripheral blood smear; amastigotes in lymph nodes
- *Trypanosoma brucei rhodesiense* – S shaped trypomastigote on peripheral blood smear; amastigotes in lymph nodes

Special Stains

- Giemsa

Differential Diagnosis

- *Leishmania donovani* amastigotes

Diagnostic Techniques

- Peripheral blood smear; antigen identification by ELISA

Helminths

Cestodes (Tapeworms)

Diphyllobothrium latum

- Broad fish tapeworm; temperate climates; transmitted via ingestion of undercooked fish

Clinical

- B12 deficiency (worms live in small intestine)

Macroscopic

- Worms are 3–10 m long with >3000 proglottids

Microscopic

- Proglottids of adult worms are broader than long with central rosette appearance of uterine branches
- Suctorial groove on "head" (scolex) formed by two (di-) longitudinal folds (bothria)
- Operculated approximately 60X 75 μm egg with terminal knob (only operculated tapeworm found in man)

Differential Diagnosis

- *Paragonimus westermani* eggs are bigger (80–100 μm)

Diagnostic Techniques

- Identification of eggs in stool

Echinococcus species

Dog or hydatid tapeworm; humans are accidental hosts

Clinical

- Rupture of cyst may lead to death from anaphylactic shock

Macroscopic

- Hydatid cysts in liver, lungs, brain have inner lining with germinal membrane from which protoscolices develop
- 3–6 mm worm with 3 proglottids and scolex with double row of hooklets; few uterine components in segments

Microscopic

- Hydatid sand (scolices and free hooklets) present in cyst

Diagnostic Techniques

- Ultrasound; needle biopsy not recommended

Hymenolepis species

- Live in small intestine; *H. nana* is most common tapeworm in U.S.; may have flea or beetle intermediate host; acquired via fecal-oral route
- *H. diminuta* is rat tapeworm (rat as definitive host), meal beetle intermediate

Clinical

- Usually asymptomatic

Macroscopic

- *H. nana*: tiny scolex with spiny rostellum, 4 suckers and ring of spines; wider than long proglottids
- *H. diminuta*: small, spherical scolex with 4 deep suckers and rounded rostellum with no hooklets; nondescript proglottids

Microscopic

- *H. nana*: 40–60 μm round-oval egg with large clear space between embryo and shell, polar filaments and thickenings
- *H. diminuta*: 70–85 μm round-oval egg with large clear space between embryo and shell, no polar filaments; thicker shelled than *H. nana*
- Ova have internal lateral polar thickenings, three hooklets in central embryo, no radial striations

Differential Diagnosis

- *Hymenolepis* ova differentiated based on size and presence/absence of polar filaments

Diagnostic Techniques

- Identification of ova in stool

Spirometra species (Sparganosis)

Southeast Asia and Africa, eastern and southern U.S.; dogs and cats are definitive hosts, crustaceans are 1st intermediate hosts and fish, snakes and frogs are 2nd intermediate hosts

Infection acquired by ingesting water containing infected copepods (*Cyclops*) or uncooked snake

Clinical

- Painful subcutaneous lesions, Romaña's sign, elephantiasis-like swelling or frontoparietal cerebral abscesses
- Sparganosis = invasion of extraintestinal tissue by plerocercoid stage (sparganum)
- Allergic edematous/urticarial response due to subcutaneous migration

Macroscopic

- Subcutaneous, visceral and skeletal muscle nodules; rarely migrates to brain
- Worm similar to *Diphyllobothrium latum*

Microscopic

- Similar to *Diphyllobothrium latum*

Differential Diagnosis

- *Diphyllobothrium*

Diagnostic Techniques

- Tissue examination

Taenia species

- *Taenia solium* – pork tapeworm:
  - Humans as definitive hosts after ingesting undercooked pork containing encysted larvae

- Disease rarely occurs in the United States but is quite common in parts of Asia, Africa, Europe, and Central and South America

♦ *Taenia saginata* – beef tapeworm:
- Humans as definitive hosts after ingesting undercooked beef containing encysted larvae
- Disease is fairly common in regions with overcrowding and poor sanitation, such as parts of Africa, South America, and Russia; rare in United States but occasionally occurs in southwestern states

Clinical

♦ *Taenia solium:*
- Larvae in intestines, eggs (cysticercosis) anywhere, especially eyes and brain

♦ *Taenia saginata:*
- Larvae mature in intestines and attach to jejunal mucosa to produce eggs
- No cysticercosis; patients usually asymptomatic and recognize disease only when passing proglottids in stool; may have weight loss, nausea, abdominal pain

Macroscopic

♦ *Taenia solium*: 2–4 m, hooks on scolex; 800–1000 proglottids that are longer than wide

♦ *Taenia saginata*: 4–10 m, no hooks on scolex; up to 2000 proglottids that are longer than wide; adult worm may live 20 years

Microscopic

♦ *Taenia solium* and *Taenia saginata* eggs indistinguishable from one another: round with thick shells and radial striations, 3 pair internal hooklets

♦ *Taenia solium* gravid segments have central uterine stem and <13 lateral branches

♦ *Taenia saginata* gravid segments have central uterine stem and >13 lateral branches

Differential Diagnosis

♦ *Taenia solium* and *Taenia saginata* eggs have identical appearance

Diagnostic Techniques

♦ Identification of proglottids or eggs in stool

Nematodes (Roundworms)

INTESTINAL

Ancylostoma duodenale and *Necator americanus*

Infection occurs worldwide but is limited to warm climates with heavy rainfall

Life cycle:

♦ An infected individual defecates depositing feces containing eggs in soil

♦ Eggs develop into rhabditiform larvae, which migrate through the soil and become filariform larvae (infective form)

♦ Disease transmitted when unprotected skin comes into contact with filariform larvae that penetrate skin, most commonly between toes ("ground itch"), and migrate to lymphatics, heart, lungs

♦ Coughed up by host, swallowed, carried to gut where they mature into adult worms, produce eggs and can live up to 15 years

♦ *Ancylostoma duodenale* – Old World hookworm, occurs in India, the Middle East, Asia, and the Mediterranean

♦ *Necator americanus* – New World hookworm, occurs in southern United States and tropical areas of Americas

Clinical

♦ Majority asymptomatic due to low worm burden

♦ Gastrointestinal blood loss, peripheral eosinophilia, cough, wheezing, fever, abdominal pain, cramping and impaired peristalsis

♦ Microcytic anemia due to chronic blood loss caused by attachment and feeding of the worm in the gut; *Ancylostoma* extracts ~0.2 ml of blood each day, *Necator* ~0.02 ml

Macroscopic

♦ 10 mm adult worm with hooked tail; *Ancylostoma* has 2 pair of chitinous teeth and *Necator* has 2 cutting plates

Microscopic

♦ 50 μm, oval, thin-shelled ovum with 4–8 lobed embryo

♦ Rhabditiform larvae have long buccal cavity (as long as body is wide) and inconspicuous genital primordium

Differential Diagnosis

♦ Eggs of the two genera are identical in appearance; *Strongyloides* eggs and larvae

Diagnostic Techniques

♦ Identification of eggs or rhabditiform larvae (rare) in stool

Ascaris lumbricoides

Worldwide but most common in warm climates

Most commonly affects children, especially in areas of poor sanitation/crowded living conditions

Eggs deposited in soil when infected person defecates and require 3 weeks to embryonate and become infectious (may remain infectious x5 years or more)

Transmitted by ingestion of eggs: foodborne, fomite, airborne

Clinical

♦ Sometimes asymptomatic appendicitis, biliary obstruction, hepatic abscess, pancreatitis, abdominal pain and malabsorption, intestinal obstruction, peripheral eosinophilia (hypersensitivity response to parasite), pneumonia resembling asthma (allergic reaction to larval

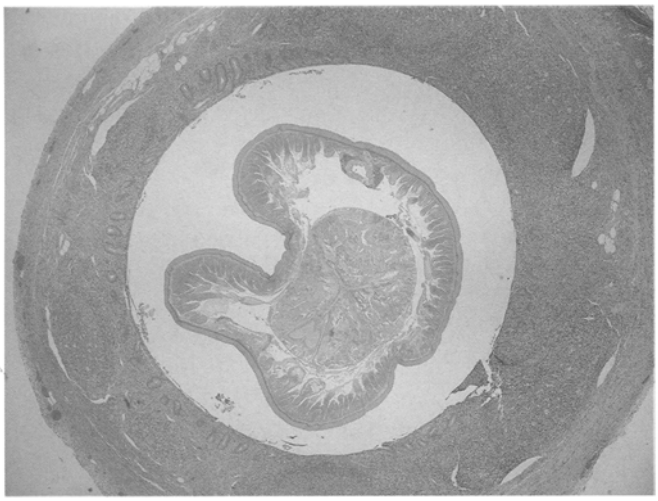


Fig. 53. Ascariasis. Appendix containing cross-section of worm with thick outer cuticle, prominent musculature and centrally located digestive tract, H&E.

worm migration); adults may migrate outside bowel (e.g., bile ducts/gall bladder, nose/mouth, anus)

Macroscopic

- 25–35 cm; male smaller with curved tail

*Microscopic **(Figure 53)***

- Fertile eggs: 60 µm round-ovoid, thick shell and albuminous coat (mammillated), various states of cleavage give lobulated internal appearance
- Decorticate eggs: lack albuminous coat leaving smooth surface resembling vegetable cells
- Infertile eggs: 90 µm elongated shell often lacking albuminous coat and having nondescript globules internally

Diagnostic Techniques

- Worm cross-sections identified in appendix; eggs identified in stool

Dracunculus medinensis

Guinea worm; Pakistan, India, west coast Africa

Ingest cyclops (copepod) from water, worm migrates to feet and may cause skin blisters and soft tissue calcifications; larvae develop into adult worms in serous cavities and gravid females migrate to subcutaneous tissue; ~one year to complete

Clinical

- Emergence of female gravid worm through skin ulcer; burning sensation and ulceration of skin at site of infection; surgical removal from subcutaneous tissue by slowly winding them on a stick

Macroscopic

- Adult worm up to 100 cm (longest nematode that infects humans)

Microscopic

- Subcutaneous abscess, central necrosis surrounded by granulomatous reaction, soft tissue erosion, epithelioid cells, histiocytes, neutrophils, plasma cells, eosinophils, giant cells
- Larvae have smooth annulated cuticle, prominent musculature and digestive tube

Diagnostic Techniques

- Diagnosis usually made clinically

Enterobius vermicularis (Pinworm)

Worldwide; one of the most common parasitic infections; most common in children and poor with crowded living conditions

Life cycle:

- Adult worms live in cecum; female migrates through colon to anus during night and deposits eggs on perianal skin and sheets; eggs transferred to host fingers by scratching
- May also be airborne off sheets or clothing; remain viable and infectious for several days
- Infection transmitted when eggs are ingested or inhaled and swallowed

Clinical

- Gastrointestinal disturbance possible, perianal pruritis prominent and worse at night, secondary bacterial infection due to excoriation
- Vaginitis, endometritis, salpingitis
- Usually no peripheral eosinophilia

Macroscopic

- 8–13 mm adult female worm with pointed tail sometimes seen on perianal skin; male smaller and usually not seen

*Microscopic **(Figure 54)***

- Ovoid egg with one flattened side; worm has lateral alae at head and contains diagnostic eggs
- Worm cross-sections in appendix common

Diagnostic Techniques

- Cellophane tape prep

Strongyloides stercoralis

- The smallest of intestinal nematodes
- Geographic distribution similar to hookworm
- Filariform larvae penetrate skin and follow transpulmonary route; autoinfection possible

Clinical

- Intestinal infection only symptomatic with large worm loads – peptic ulcer-like pain aggravated by eating; peripheral eosinophilia, malabsorption; fever, dyspnea, cough, wheezing with pulmonary phase
- Dissemination in immunosuppressed patients

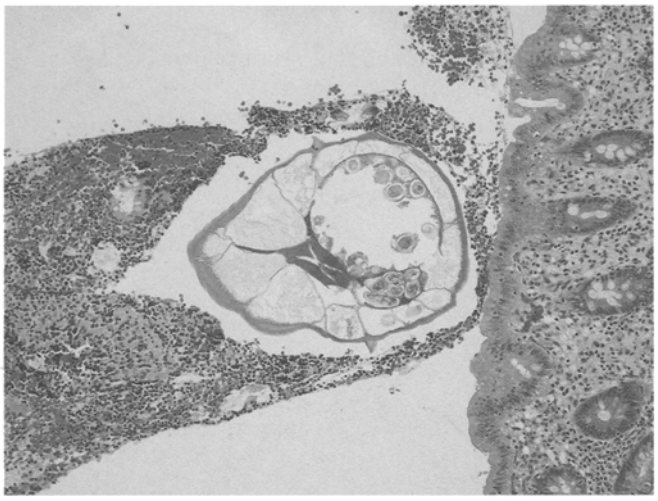


Fig. 54. Enterobiasis. Appendix containing cross-section of worm with prominent lateral spines and numerous eggs diagnostic of *Enterobius vermicularis*, H&E.

Microscopic ***(Figure 55A-C)***

- Larva has curved tail and is very similar to hookworms, but has a shorter buccal cavity and longer primitive genitalia
- May see calcified worm fragments in histologic sections of colon

Differential Diagnosis

- Hookworm larvae

Diagnostic Techniques

- Identification of 0.75–1 mm rhabditiform larvae with short buccal cavity and prominent genital primordium in stool, duodenal aspirates, jejunal biopsy or sputum; eggs usually not seen

Trichinella spiralis

- Worldwide excluding Asia and Australia (rare cases)
- Infection acquired by eating undercooked meat containing encysted larvae (pork, bear); freezing for 20 days destroys cysts; salting and drying does not

Clinical

- Most infections asymptomatic due to low worm load; abdominal pain, diarrhea, fever, myalgia, weakness
- Marked peripheral eosinophilia

Macroscopic

- Adult male and female (2–4 mm) live in intestine for 4 months producing >1000 larvae that will become encysted in skeletal muscle
- Larvae that enter skeletal muscle survive, grow, encapsulate, calcify and may live for up to 10 years

Microscopic

- Spiral larvae encysted in skeletal muscle
- Most often infected muscles include the diaphragm, extraocular muscles, tongue, deltoid and intercostal muscles

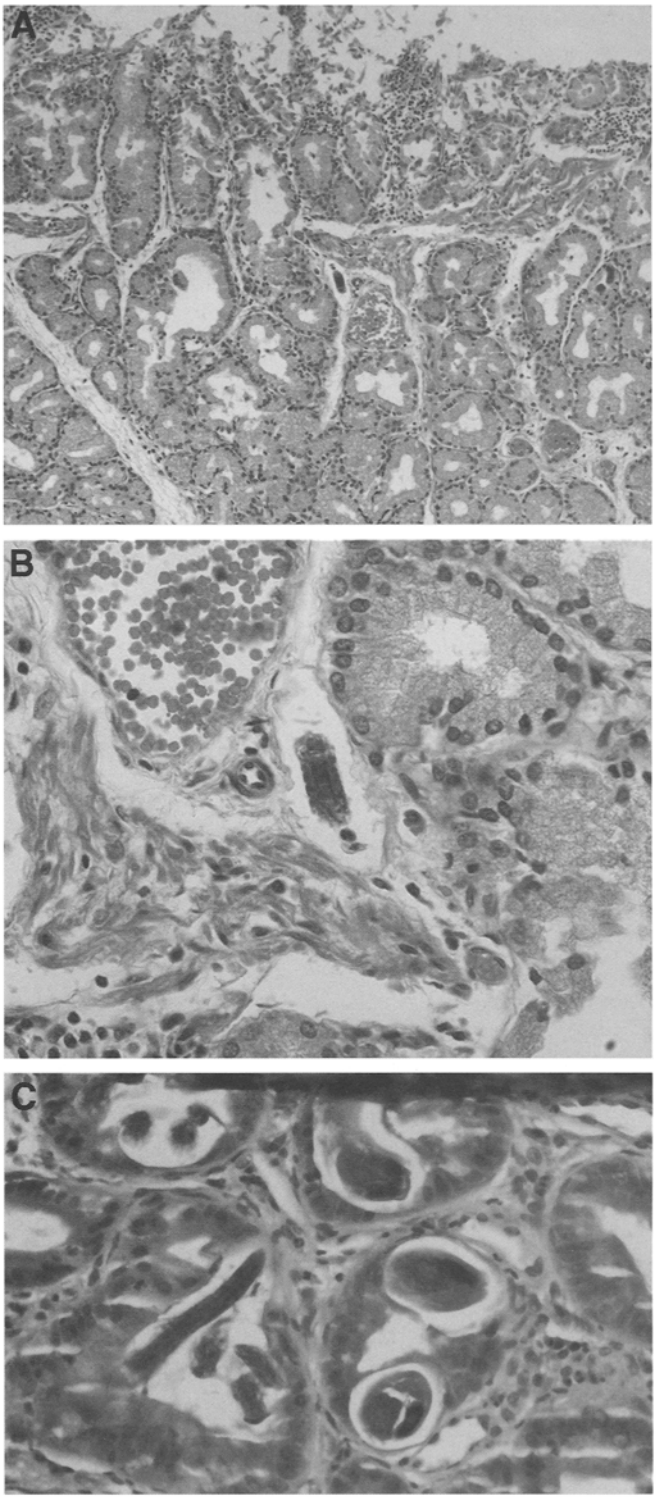


Fig. 55. Fragments of *Strongyloides* worm deep in intestinal mucosa (**[A]** center and left, **[B]** center, **[C]** multiple partially calcified worm fragments), H&E.

Diagnostic Techniques

- Detection of spiral larvae in trypsin-digested tease mounts of deltoid or gastrocnemius muscle; ELISA

Trichuris trichiura (Whipworm)

- Worldwide but more common in warm, humid areas where defecation in soil is standard practice, in institutions or crowded communities with poor sanitation
- Eggs require 21 days in external environment for maturation
- Fecal-oral transmission; fertile eggs infective; eggs hatch and mature in duodenum then move to cecum

Clinical

- Asymptomatic if low worm burden
- Diarrhea, rectal itching, abdominal pain, nausea, anemia
- Colonic or rectal prolapse with high worm load

Macroscopic

- Adult worms 35–45 mm with whip-like anterior and thick handle-like posterior

Microscopic

- Barrel-shaped 54 μm egg with bipolar hyaline plugs (5000–10,000 produced/day)

Diagnostic Techniques

- Identification of eggs in stool

Microfilaria (Tissue Roundworms)

- Generally, filiariae (adults) living in various tissues produce microfilariae that circulate in peripheral blood (excluding *Onchocerca*) and can survive 1–2 years
- Microfilariae are not infective and require intermediate host; reintroduced to humans during blood feedings by vector; may take months or years to develop symptoms

Brugia malayi

- Mosquito vector (*Anopheles*, *Aedes*); 3rd stage larva is infective form

Clinical

- Lymphatic and lymph node involvement; elephantiasis

Macroscopic

- Adult worm reaches 10 cm

Microscopic

- 245–295 × 7.5–10 μm sheathed microfilariae; long cephalic space with two discrete nuclei at tail end

Special Stains

- Giemsa thick and thin smears of peripheral blood; sheath stains pale pink

Differential Diagnosis

- Other microfilariae

Diagnostic Techniques

- Nocturnal periodicity

Loa loa

- Eye worm; *Chrysops* deer fly vector; African rainforest

Clinical

- Calabar swellings (painful or pruritic subcutaneous nodules), fever, urticaria, pruritis
- May migrate across eye below conjunctiva causing tearing and pain; peripheral eosinophilia
- Adult worm lives in subcutaneous tissue and migrates ~1cm per hour under conjunctiva or skin

Microscopic

- Sheathed microfilariae with column of nuclei that extends completely to tail tip

Special Stains

- Giemsa thick and thin smears of peripheral blood

Differential Diagnosis

- Other microfilariae

Diagnostic Techniques

- Identify microfilariae in peripheral blood smear or direct mount of blood or adult in eye or calabar swelling; released on diurnal schedule – draw blood sample during day

Mansonella perstans

- Transmitted by midges or blackfly

Clinical

- Rash, fever, nonserious infection

Microscopic

- Unsheathed; no nuclei to tail

Special Stains

- Giemsa thick and thin smears of peripheral blood

Differential Diagnosis

- Other microfilariae (differentiate from *Onchocerca* by position of nuclei)

Diagnostic Techniques

- Identify microfilariae in peripheral blood smear

Onchocerca volvulus

Transmitted by Simulian black flies, which breed in and around fast-flowing rivers in Africa and Central and South America

Clinical

- Dermatitis with dense fibrous subcutaneous nodules (up to 25 mm) containing adult worms at site of bite (onchocercoma)
- Iritis may lead to blindness ("river blindness" is most serious complication)
- Lymphatic obstruction and elephantiasis; wrinkling of skin "leopard skin"; nonfatal

Macroscopic

- Female worm up to 50 cm in length; male 5 cm

Microscopic

- Granulomatous inflammatory reaction induced by worms

Diagnostic Techniques

- Identification of microfilariae in teased snips of skin (saline) since they do not circulate in blood; enzyme immunoassay for river blindness

Wuchereria bancrofti

Mosquito vector (*Culex*); 3rd stage larva is infective form

Clinical

- Filariasis, elephantiasis of genitalia and lower extremities, fever, chills, headache, local redness

Macroscopic

- Adult worm reaches 10 cm

Microscopic

- 245–295 × 7.5–10 μm sheathed microfilariae with short cephalic space; column of nuclei terminates 15–20 μm proximal to tail tip
- Worm embedded in fibrous stroma surrounded by chronic inflammatory infiltrate; may be found in distended lymphatic vessels or nodes

Special Stains

- Giemsa thick and thin smears of peripheral blood

Differential Diagnosis

- Other microfilariae

Diagnostic Techniques

- Nocturnal or subperiodic depending on region of world – important for timing of blood collection

Zoonotic Roundworms

Angiostrongylus species

Rat lung worm; China, Hawaii, tropics, Central America; ingestion of infected snail, prawn or unwashed vegetables with secretions of infected slug

Clinical

- Meningitis, blood and CSF eosinophilia, gastrointestinal disturbance

Macroscopic

- Often no gross lesions of brain and spinal cord; distal small intestine and ascending colon inflammation and tumor-like masses
- 21–35 mm female filariform worm (males 16–19 mm); bursa copulatrix at posterior end with bursal rays and spicules, configuration and length of which, respectively, are of taxonomic importance

Microscopic

- One of most common causes of eosinophilic meningitis
- Worm fragments, granulomas of mesentery, brain, or spinal cord
- Glial scars containing hemosiderin, microscopic hemorrhages, eosinophils and Charcot-Leyden crystals

Differential Diagnosis

- Schistosomiasis, echinococcosis, gnathostomiasis, paragonimiasis, cysticercosis, ascariasis

Diagnostic Techniques

- Histologic sections of brain, spinal cord

Anisakis species

- Source: herring, marine animals and fish; Japan, Netherlands; ingestion of undercooked fish

Clinical

- Asymptomatic
- Acute infection (abdominal pain, nausea, vomiting, diarrhea occurring 1–12 hours after eating infected fish)
- Chronic infection (intermittent abdominal pain, nausea, vomiting lasting weeks to years)
- Peritonitis; peripheral leukocytosis and eosinophilia; penetration of gastric mucosa

Macroscopic

- Cuticle, lateral chords and esophagus evident on worm cross-section (10–29 mm larvae)

Microscopic

- Abscess, eosinophilic granulomas of stomach; larvae cause deep tunnels surrounded by granulomatous inflammation in stomach and also migrate into omentum, liver, pancreas, lungs

Differential Diagnosis

- *Ascaris*

Diagnostic Techniques

- Whole worm (from vomitus, stool, surgery or endoscopy) preserved in 70% ethanol and cleared in phenol to facilitate visualization of morphologic features

Capillaria philippinensis

- Far East (Phillipines and Thailand)
- Source: ingestion of undercooked fish; worm develops and multiplies in intestine but predominates in jejunum

Clinical

- Malabsorption syndrome, diarrhea, abdominal pain, borborygmi ("gurgling stomach"), Pudoc's mystery disease, protein-losing enteropathy, death

Macroscopic

- 2.3–5.3 mm female and 1.5–4 mm male worms with anterior end narrower than posterior end

Microscopic

- Worm fragments in small intestinal crypts; crypt atrophy, infiltration of lamina propria with lymphocytes, plasma cells, neutrophils, macrophages, and a few eosinophils

- Villi blunted, flattened or destroyed with sloughed mucosa
- Peanut or barrel shaped egg with flattened bipolar plugs and radially striated thin shell

Differential Diagnosis

- *Trichiuris* eggs, strongyloidiasis, hookworm infection, giardiasis, tropical sprue

Diagnostic Techniques

- Eggs, larvae and adults all may be seen in stool

Dirofilaria species

Dog heartworm – adult worms develop in heart, microfilariae circulate in blood

Mosquito (*Culex, Aedes, Anopheles*) is vector and intermediate host; human is accidental host

Temperate and tropical regions including U.S., former Soviet Union, Canada, Australia, Japan, Sri Lanka, Malaysia, many Mediterranean countries

Clinical

- Larval migrans (serpiginous red rash); coin lesion on chest X-ray (intraparenchymal lung nodule); human infection rare, spurious and benign

Macroscopic

- 25–30 cm female worm; 12–16 cm male worm
- Gray fibrous 2–3 cm pulmonary nodule +/– coiled worm inside

Microscopic ***(Figure 56)***

- Worm cross-section with smooth multilayered cuticle projects inward to form internal diametrically opposed ridges that look like inverted lateral spines; prominent muscles and two uterine tubes may be evident
- Worms may be faintly eosinophilic and easily overlooked
- Larvae lodge in pulmonary arterioles and form granulomatous nodules
- Nodule consists of central coagulation necrosis with surrounding histiocytes, monocytes, lymphocytes, eosinophils and Langhans' giant cells

Special Stains

- Movat pentachrome stain helps distinguish vessel wall, worm's cuticle, muscle and internal organs

Differential Diagnosis

- Etiologies of other coin lesions: carcinoma, tuberculosis, fungal infections, hamartomas

Diagnostic Techniques

- ELISA, indirect immunofluorescence

Gnathostoma species

Far East (predominantly Japan and Thailand); cats and dogs are definitive hosts

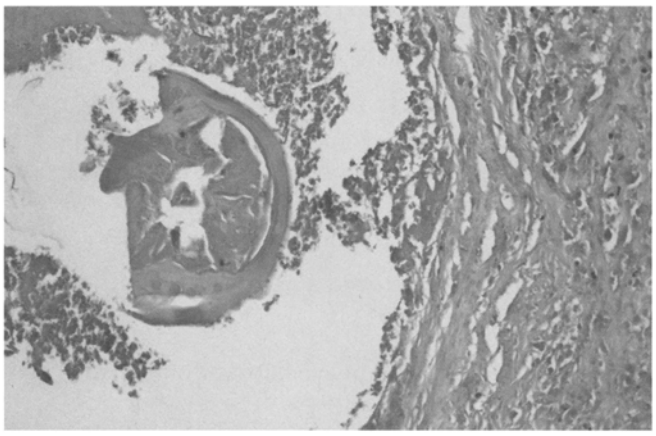


Fig. 56. Pulmonary dirofilariasis demonstrating fragment of worm with smooth cuticle and prominent musculature, H&E.

Humans are accidental hosts infected through ingestion of undercooked fish, chicken or pork; larvae do not mature but penetrate gastric wall and migrate to tissues

Clinical

- Acute visceral larval migrans, nausea, swelling; meningitis, encephalitis, uveitis, retinal detachment and blindness possible
- CNS invasion may be life-threatening

Macroscopic

- 10–45 mm female and 10–25 mm male worms; immature form causes human disease and has four rows of hooklets on head bulb instead of 8

Microscopic

- 70 × 40 μm transparent egg has unipolar cap and thick wall
- Necrotizing inflammatory tracts in soft tissue; edema, necrosis, hemorrhage, eosinophils, plasma cells, neutrophils; acute inflammatory reaction becomes fibrogranulomatous

Differential Diagnosis

- Sparganosis, cutaneous paragonimiasis, cutaneous larva migrans, trichinosis (eye swelling) and myiasis clinically

Diagnostic Techniques

- Tissue biopsy and identification of third stage larva

Toxocara canis (Visceral Larva Migrans)

Large intestinal roundworm of cats and dogs

Worldwide; common in southeastern U.S.; thrives in warm humid climates

Humans are incidental host by ingesting embryonated eggs in soil deposited by infected animal (embryonation requires 2 weeks before they become infectious, then remain infectious for months to years)

Eggs hatch in intestine, penetrate mucosa and travel via portal circulation into the lung and pulmonary capillaries until their growth limits vascular travel and they migrate into tissue

Clinical

- Visceral larva migrans, granulomatous endophthalmitis, blindness; larvae deposit in various organs, usually liver; manifestations related to tissues invaded by larvae, most commonly skeletal muscle, heart, brain, liver, lung, eye
- Most cases self-limited and asymptomatic; symptomatic cases often associated with asthma due to high IgE levels; fever, hepatosplenomegaly, focal neurologic deficits, seizure, pulmonary infiltrates, cardiac arrhythmias, decreased visual acuity; peripheral eosinophilia
- Disease more severe in young children and with high number of invading larvae

Microscopic

- Necrosis, hemorrhage, abscess and granuloma formation with numerous eosinophils

Diagnostic Techniques

- Tissue biopsy; no eggs or worms in stool because organism does not mature in human

Trematodes (Flukes)

Clonorchis sinensis

Chinese liver fluke; Far East

Egg from human feces (or sputum) deposited in water, ingested by snail (miracidium infects snail), cercariae from snail ingested by fish and encyst

Human acquires by eating undercooked fish

Clinical

- Bile duct obstruction; increased risk of cholangiocarcinoma

Macroscopic

- 1.5 cm worms in biliary tree

Microscopic

- 27–35 μm operculated, urn-shaped egg with shoulders and abopercular boss/knob

Diagnostic Techniques

- Identification of eggs in stool

Fasciola hepatica

Sheep liver fluke; contaminated watercress

Egg from human feces (or sputum) deposited in water, ingested by snail (miracidium infects snail), cercariae from snail attach to water plants and encyst

Human acquires by eating uncooked water plants

Clinical

- Bile duct obstruction, cholangiocarcinoma

Macroscopic

- Worms in biliary tree; 3 cm adult with cone-shaped anterior

Microscopic

- 150 μm operculated egg

Differential Diagnosis

- Fasciolopsis buski eggs appear identical

Diagnostic Techniques

- Identification of eggs in stool; adult worms seen only on surgical removal

Fasciolopsis buski

Acquired by eating contaminated aquatic plants; Far East

Egg from human feces (or sputum) deposited in water, ingested by snail (miracidium infects snail), cercariae from snail attach to water plants and encyst

Human acquires by eating uncooked water plants

Clinical

- Small intestine is site of infection

Macroscopic

- 2–7.5 cm adult worm with rounded anterior

Microscopic

- 150 μm operculated egg

Differential Diagnosis

- *Fasciola hepatica* eggs appear identical

Diagnostic Techniques

- Identification of eggs in stool; adult worms seen only on surgical removal

Paragonimus westermani

Oriental lung fluke; acquired by eating contaminated raw/undercooked crab

Egg from human feces (or sputum) deposited in water, ingested by snail (miracidium infects snail), cercariae from snail infect crabs and crayfish

Human ingestion releases larvae that migrate through bowel to lung and eggs are coughed up and swallowed to be released in feces

Clinical

- Chronic pulmonary fibrosis

Macroscopic

- Cystic cavities in lung
- 8–16 mm spoon-shaped adult worm

Microscopic

- 80–120 μm operculated egg with shoulders and abopercular thickening

Differential Diagnosis

- Differentiate from other operculated eggs based on size (*D. latum*, *F. buski*, *F. hepatica*)

Diagnostic Techniques

- Identification of ova in stool or sputum

Schistosoma species

Three species of Schistosoma cause disease in humans:

- *S. hematobium* (India, Africa); bladder fluke; snail host
- *S. japonicum* (Asia, Philippines); blood fluke
- *S. mansoni* (Africa, Asia, South America, Caribbean islands); blood fluke

Life cycle: eggs hatch in freshwater to form miracidia which infest snail, divide to form hundreds of cercariae which are released; these free-swimming forms penetrate human skin and enter circulation, mature to adult form in portal venous system

Clinical

- *S. hematobium* – squamous cell carcinoma of bladder; veins of pelvic area and urinary bladder; releases eggs in urine; hematuria, hydronephrosis; eggs also found in stool
- *S. japonicum* – veins of small intestine, liver, brain; portal hypertension and esophageal varices
- *S. mansoni* – veins of colon; releases eggs in stool; portal hypertension and esophageal varices
- Venous obstruction and tissue damage due to egg deposition
- Swimmer's itch due to penetration of nonpathogenic species of schistosome cercariae

Macroscopic

- Adult worms 2.5–3 cm; female resides in gynocophoral canal of male

Microscopic

- Look for calcified eggs and foreign-body type granulomas in target organs:
  - *S. hematobium* – 110–170 μm eggs have terminal spine
  - *S. japonicum* – 70–100 μm eggs have small, delicate lateral hook-like spine
  - *S. mansoni* – 115–180 μm eggs have lateral spine

Differential Diagnosis

- Easily differentiated from other roundworms based on comparatively large size

Diagnostic Techniques

- Modified Ziehl-Neelsen acid-fast stains spines and shells of *S. japonicum* and *S. mansoni*, only the spine of *S. hematobium*

OTHER

Myiasis

Clinical

- Invasion of skin or soft tissue by fly larvae (maggots); extremely painful
- Wound myiasis: swarming maggots on surface, *Chrysomia* spp.
- Furuncular myiasis: papule/nodule with central opening, *Dermatobia hominis* (bot fly)

Microscopic

- Tunnel from epidermis to lower dermis with larva inside surrounded by mixed inflammatory infiltrate, focal collagen degeneration, foreign body reaction
- Larva has abundant striated muscle, respiratory tubules, thick cuticle with pigmented spines

Differential Diagnosis

- *Tunga penetrans* (flea) invades as adult, not larva, contains eggs and has no tunnel; wood splinter, ticks, scabies mite

Sarcoptes scabiei

Scabies – allergic dermatitis caused by burrowing of mite *Sarcoptes scabiei* in epidermis

Found worldwide; highest incidence in people <20 years old; acquired via close contact

Female mite may live up to 19 days without human host

Clinical

- Intense pruritis especially at night; axillary folds, buttocks and interdigital folds common sites; thin elevated serpiginous tracts; pustules may form with secondary infection

Microscopic

- Burrows confined to stratum corneum except blind end where mite may be found in upper stratum malpighii
- Mild parakeratosis surrounding burrow; spongiosis and vesicles at burrow head
- Nonspecific inflammatory infiltrate with lymphocytes and eosinophils in dermis

Special Stains

- Excrement, eggs and mites PAS+

Diagnostic Techniques

- Biopsy or mineral oil skin scrapings may contain adult mites

Tunga penetrans

Invasion of skin by adult gravid female flea *Tunga penetrans* (jigger or chigger flea)

Clinical

- Mostly affects feet but may be any area of body, singly or in crops

- Tiny black spot after invading (opening of flea's posterior end through which it breathes and discharges eggs)
- Becomes pruritic as enlarges (painful if adjacent to nailbed); overlying keratin white with erythematous edge
- Flea matures in 10–14 days, discharges eggs and collapsed carcass sloughs

Microscopic

- Flea within epidermis surrounded by elongated rete ridges with head penetrating into upper dermis
- Flea contains dilated loops of gut, developing eggs, branching tracheae, bands of hypertrophied striated muscle
- Host dermis hyperemic with mixed inflammation consisting of eosinophils, lymphocytes, plasma cells
- Host-flea interface hold-fast apparatus (jigsaw interlocking) adheres flea tegument tightly to patient's keratin

Differential Diagnosis

- Tick, fly larvae

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6

Transplantation Pathology

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CONTENTS

I. Introduction 6-3
- General Considerations 6-3
  - Transplant Recipient Criteria and Workup 6-3
  - Donor Criteria and Workup 6-3
- Transplantation Immunology 6-3
- Immunosuppression 6-4
- Complications Common to All Transplants 6-4
  - Infection 6-4
    - Nonopportunistic 6-4
    - Opportunistic 6-4
  - Neoplasia 6-5
    - Condyloma 6-5
    - *De Novo* Carcinogenesis 6-5
    - Posttransplant Lymphoproliferative Disorder 6-6
    - Polymorphous Variant 6-6
    - Monoclonal Variant 6-6
  - Rejection—General Patterns 6-7
    - Hyperacute Rejection 6-7
    - Acute Cellular Rejection 6-7
    - Chronic Cellular Rejection 6-7
    - Acute Vascular Rejection 6-7
    - Chronic Vascular Rejection (transplant vasculopathy) 6-7
  - Disease Recurrence 6-7
  - Drug Toxicity 6-7

II. Kidney Transplantation 6-7
- Indication for Transplantation 6-7
- Clinical Considerations 6-7
- Rejection 6-7
  - Hyperacute Rejection 6-7
  - Delayed Hyperacute Rejection 6-7
  - Evaluation of the Kidney Biopsy for Rejection 6-7
  - Banff Criteria: Consensus diagnostic criteria for renal allograft rejection 6-8
  - Antibody-Mediated Rejection 6-8
  - Borderline Changes, "suspicious for acute rejection" 6-8
  - Acute Rejection 6-8
  - Chronic/Sclerosing allograft Nephropathy 6-9
  - Other Changes Not Considered Rejection 6-9
- Transplant Nephropathy/Glomerulopathy 6-9
- Recurrent Disease 6-9
  - Glomerulonephritis 6-9
  - *De Novo* Glomerulonephritis 6-10
  - Drug Toxicity 6-11
- Virus Infection 6-11
  - BK Virus 6-11
  - Cytomegalovirus (CMV) 6-12
- Acute Tubular Necrosis 6-12
- Ureter Obstruction/Pyelonephritis 6-12
- Posttransplant Lymphoproliferative Disorder 6-12

III. Heart Transplantation 6-12
- Indication for Transplantation 6-12
- Clinical Considerations 6-12
- Rejection 6-12
  - Hyperacute Rejection 6-12
  - Acute Cellular Rejection 6-13
- Transplant Coronary Artery Disease (Cardiac Transplant Vasculopathy/ Chronic Rejection) 6-13
- Other Biopsy Findings 6-14

IV. Lung Transplantation 6-15
Indication for Transplantation 6-15
Clinical Considerations 6-15
Rejection 6-16
Acute Cellular Rejection 6-16
Chronic Rejection 6-16
Early Posttransplant Changes.....6-16
Diffuse Alveolar Damage 6-16
Cryptogenic Organizing Pneumonia (Bronchiolitis obliterans—organzing pneumonia, BOOP).....6-16
Infection 6-17
Nonhealing Bronchial Margin 6-17
Recurrent Disease.....6-17

V. Liver Transplantation 6-17
Indication for Transplantation 6-17
Clinical Considerations 6-18
Rejection.....6-19
Acute Rejection 6-19
Consensus Banff Criteria 6-19
Chronic Rejection.....6-19
Mechanical Bile Duct Obstruction.....6-20
CMV Infection 6-20
Preservation Effect 6-21
Recurrent Disease.....6-21
Drug Effect.....6-22
Posttransplant Lymphoproliferative Disorder 6-22

VI. Pancreas/Islet Cell Transplantation 6-23
Indication for Transplantation 6-23
Clinical Considerations 6-23
Rejection.....6-23
Nakhleh Grading System for pancreatic allograft rejection 6-23
Drachenberg Grading System for paricreatic allogoaft rejection 6-23
CMV Infection 6-24
Posttransplant Lymphoproliferative Disorder 6-24

VII. Bone Marrow Transplantation (BMT)..6-24
Indication for Transplantation 6-24
Clinical Considerations 6-24
Graft vs Host Disease (GVHD) 6-24
Skin.....6-24
Gut 6-25
Liver 6-25
Veno-Occlusive Disease (VOD) 6-26
Lung 6-26
Posttransplant Lymphoproliferative Disorder 6-26

VIII. Small Bowel Transplantation 6-27
Indication for Transplantation 6-27
Clinical Considerations 6-27
Preservation Injury 6-27
Rejection.....6-27
Pittsburgh Criteria.....6-27
Chronic Rejection 6-27
CMV Infection 6-27
Posttransplant Lymphoproliferative Disorder 6-27

IX. Cornea Transplantation 6-28

X. Other Transplants 6-28
Hand 6-28
Xenotransplantation 6-28

XI. Suggested Reading.....6-28

INTRODUCTION

- Organ failure is a common cause of death
- Donor organs were quickly destroyed by the recipient unless donor and recipient are identical twins
- With the advent of modern immunosuppression, organ transplantation became feasible (one no longer needed to be an identical twin) **(Table 1)**

Table 1. Worldwide Transplants as of 2001

Organ	*Centers*	*No. Performed*
Kidney	588	535,075
Stem Cell/BMT	249	117,984
Liver	235	100,179
Heart	236	61,195
Pancreas	163	17,002
Lung	120	16,432
Intestine	10	279

General Considerations

- Transplant Recipient Criteria and Workup
  - Waiting list for most organs is long and many patients die awaiting a suitable organ
  - Good health except for the failed organ. Rarely multiple organs can be transplanted together, i.e., heart and lung for congenital heart disease; pancreas and kidney for type I diabetes
  - Age not a definite excluding factor however:
    - Premature infants may be too small to technically perform the transplant.
    - Older patients (>70 years old) often have multiple diseased organs
  - Cardiac, pulmonary, liver, renal function assessed for adequacy
  - High-grade malignancy, i.e., metastatic colon cancer, a general contraindication to transplantation because of recurrence and death
  - HIV infection is considered on a case by case basis—more feasible now with better HIV therapy
  - Primary amyloidosis is a general contraindication to transplant
  - Must be psychosocially appropriate
  - Suitable transplant candidates are placed on waiting list
  - Factors affecting ranking may include tissue match, blood type, length of time on the waiting list, immune status and the distance between the potential recipient and the donor
  - Heart, liver, and intestine patients—sickest transplanted first
- Donor Criteria and Workup
  - Donor suitability—healthy (no viral infections, no rapid onset dementia, no high-grade malignancy), "normal" organs
  - Donations monitored by United Network for Organ Sharing (UNOS) www.unos.org—transplant survival data by organ and transplantation site
  - Harvested organs distributed in region
  - If no suitable recipient, offered nation wide
  - Organs are harvested from brain dead donors and perfused with Wisconsin solution (proprietary) to prolong extracorporeal usefulness
  - Heart and lung have short "shelf life" 8–10 hours; liver and kidney up to 24 hours
    - Organ and donor matched for ABO, HLA, and screened for antibody incompatibility (serology crossmatch), CMV, EBV, and often toxoplasmosis
    - Other criteria may also be important, i.e., size and weight depending on the organ

Transplantation Immunology

- The Major Histocompatibility Complex (MHC) of the immune system that governs "self vs other" resides in three loci on chromosome 6—the human leukocyte antigens (HLA)
- The HLA antigens are inherited in a Mendelian dominant fashion each person with two haplotypes
- Class I MHC antigens are present on the surface of all nucleated cells
- The class I antigen is composed of three α chains (coded by genes HLA-A, HLA-B and HLA-C) noncovalently bound to β_2-microglobulin
- Class II antigens are found on activated T-cells, monocytes, macrophages, Langerhans cells, dendritic cells, endothelium—antigen presenting cells (APC) and certain other cells
- Class II antigens are a heterodimer composed of a α and a β chain coded by the HLA-D region
- Both Class I and II molecules contain peptide binding sites
- The allograft activates recipient T-cells via direct and indirect allo-recognition
- Direct allo-recognition—donor APC cells migrate to recipient lymphoid organs and interact with recipient T-cells
- Indirect allo-recognition—recipient APC cells bind donor antigen and interact with the T-cells

- T-cell activation:
  - APC cell binds to the T-cell receptor on the T-cell (step 1)
  - "Costimulation" by other cells surface antigens (CD28, CD40, CD40L, B71, B72) required for activation (step 2):
    - Lack of costimulation results in anergy
  - Binding with costimulation increases intracellular calcium via tyrosine kinase pathways (step 3)
  - Increased cytoplasmic calcium levels activate calcineurin (step 4)
  - Activated calcineurin dephosphorylates Nuclear Factor for Activated T-cells (NFAT) which is then transported into the nucleus (step 5)
  - NFAT binds to the Introlukin-2 (IL-2) promoter increasing the synthesis of IL-2 (step 6)
  - Increased IL-2 causes increased DNA synthesis by binding to IL-2 receptors and recruits additional T-cells (step 7)
- Activated T-cells destroy the allograft (cellular rejection)

Immunosuppression

- Immunosuppressive agents interfere with T-cell activation and thereby induce temporary tolerance of the graft
  - Common agents include:
    - OKT3, antilymphocyte globulin (ALG) and antithymocyte globulin (ATG):
      - Interferes with step 1 (*see* above)
      - Can induce serum sickness; induce antibodies
    - Corticosteroids:
      - Block step 6
      - Numerous side effects (glucose intolerance, osteoporosis etc.)
    - Cyclosporin A, Tacrolimus (FK506):
      - Blocks step 4; nephrotoxic
    - Azathioprine:
      - Blocks step 7 (adenosine synthesis)
      - Causes bone marrow suppression
    - Mycophenolate mofetil:
      - Blocks step 7 (guanine synthesis)
      - Causes bone marrow suppression
    - Rapamycin (Sirolimus):
      - Blocks step 7 (IL-2 driven cell cycle progression)
      - Causes bone marrow suppression
    - Basiliximab, daclizumab (anti-IL2 receptor antibodies):
      - Block late step 7
  - A combination of immunosuppressive agents is usually employed, idiosyncratic to the institution and the organ
  - Immunosuppression is a careful balancing act:
    - Too little immunosuppression leads to graft destruction
    - Too much immunosuppression leads to uncontrollable opportunistic infection or viral activation (Cytomegalovirus [CMV], Human papilloma virus [HPV], Epstein-Barr Virus [EBV], Hepatitis B Virus [HBV], Hepatitis C Virus [HCV]) in infected individuals
  - Contact with allo-antigens (transfusion, pregnancy, transplantation) may produce anti-HLA allo-antibodies via B and T-cell interactions—humoral rejection
  - Allo-antibodies may injury graft capillaries (hyper-acute rejection) or arteries (chronic rejection)
  - There may a component of low grade humoral rejection in many transplant patients but its recognition is difficult
  - No effective therapy for humoral rejection

Complications Common to All Transplants

INFECTION

Nonopportunistic

- Identical in clinical and histologic findings to those seen in the nontransplant patient; common sites and agents include:
  - Pneumonia: *Pseudomonas, Staphylococcus, Streptococcus, Enterobacteriacea*
  - Sepsis: *Staphylococcus, Enterobacteriacea, Pseudomonas, Enterococcus,* Anerobes
  - Wound Infection: *Staphylococcus, Pseudomonas, Enterococcus, Enterobacteriacea,* Anerobes, Mixed flora
  - Urinary tract: *Enterococcus, Enterobacteriacea, Pseudomonas*

Opportunistic

Virus

- CMV—most common infection after transplantation:
  - ~80% adult population exposed to and harbor latent virus
  - Typically noted 30+ days after the transplant
  - Classic nuclear enlargement with intranuclear and cytoplasmic inclusions **(Figure 1)**
  - Present with graft dysfunction, possibly fever
  - Culture, immunohistochemistry or molecular methods may aide diagnosis
  - Occurs in the graft itself or nontransplanted organs
  - Treated with gancyclovir and lowered immunosuppression
- Adenovirus:
  - Most common in children
  - Classic intranuclear inclusions
  - Usually seen in gut, liver, or lung
- Herpes viruses:
  - Classic intranuclear inclusions **(Figures 2,3)**
  - Brain, skin, liver most commonly affected
- EBV:
  - Common virus >50% of the adult population exposed and harbor latent virus
  - EBV negative donor organ matched to negative recipient to prevent Posttransplant lymphoproliferative disorder

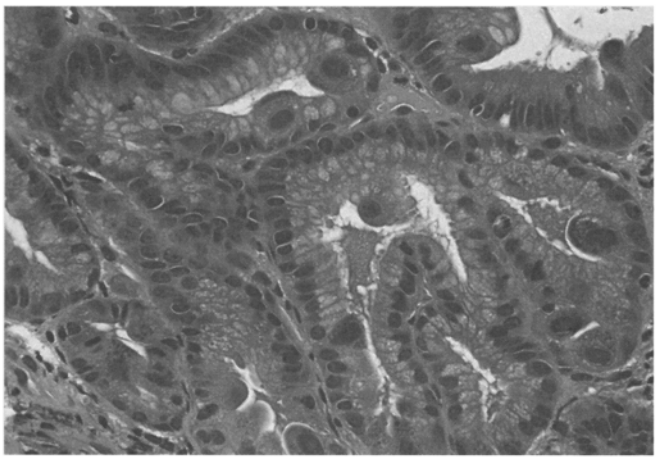


Fig.1. Cell with nuclear enlargement and classic CMV nuclear and cytoplasmic inclusions in gastric mucosa. Inflammatory reaction to the virus is variable with little inflammation seen here. Levels into the block are helpful. If only the nuclear inclusions are noted, it might be confused for Herpes or adenovirus. If only the cytoplasmic inclusions are found, may be confused with toxoplasma.

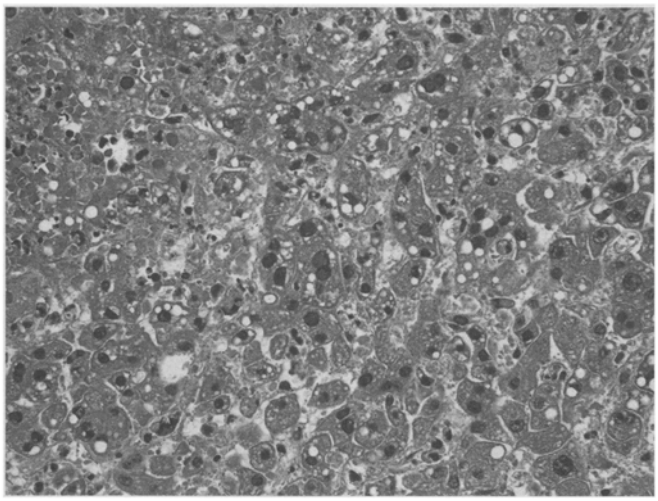


Fig. 2. Liver with classic Herpes hepatitis. Only ground-glass nuclear inclusions with little or no nuclear enlargement are seen with this virus.

Protozoan

- *Pneumocystis:*
  - Classic pulmonary histology (**Figures 4, 5**) treated in the usual fashion
- *Toxoplasmosis:*
  - Inflammatory infiltrates may be seen in heart, lung, brain associated with classic cytoplasmic inclusions (**Figure 6**)

Fungi

- *Candida:*
  - Can involve any site

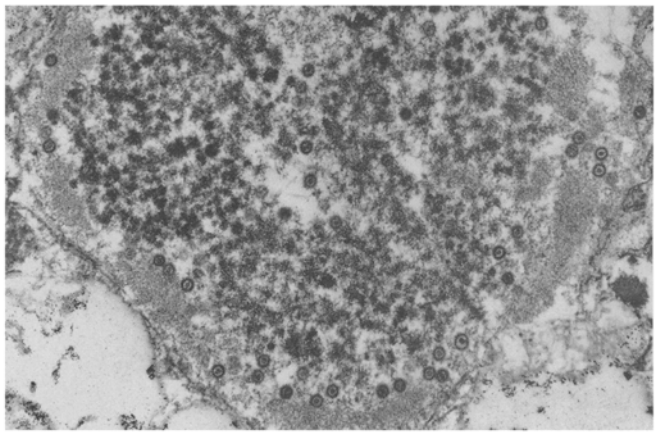


Fig. 3. Ultrastructural examination of the liver from Fig. 3 shows classic targetoid particles of Herpes virus. This technique is useful is distinguishing Herpes inclusions from adenovirus inclusions.

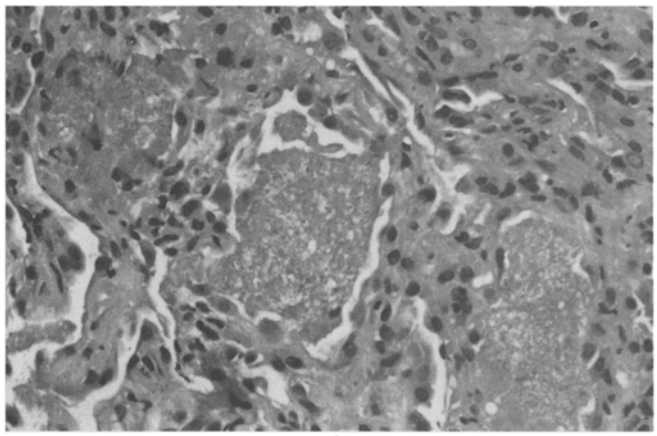


Fig. 4. Lung with classic foamy alveolar exudates and slight chronic inflammation of the interstitium consistent with Pneumocystis.

  - Classic pseudohyphae well visualized with silver stain/ Gomori methenamine silver (GMS) or periodic acid Schiff (PAS)
- *Aspergillus:*
  - Angioinvasive hyphae often presents with infarction of involved organ

Neoplasia

Condyloma

- Immunosuppression causes increased viral proliferation
- Condylomas very common, secondary to HPV

De novo carcinogenesis

- Also common
- Cutaneous squamous cell carcinoma most common
- Kaposi sarcoma

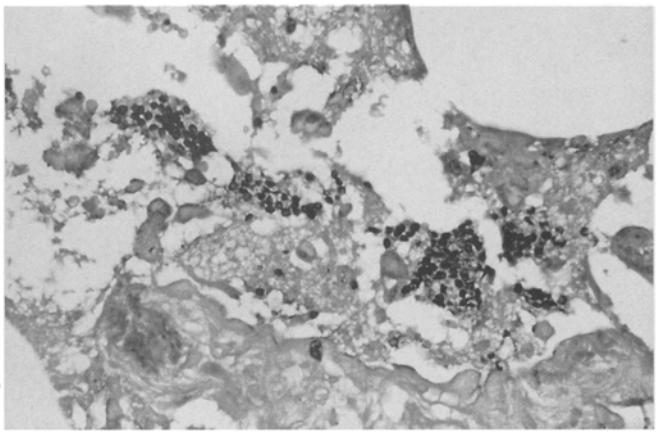


Fig. 5. Gomori Methamine Silver stain of Fig. 4 showing classic Pneumocystis cysts.

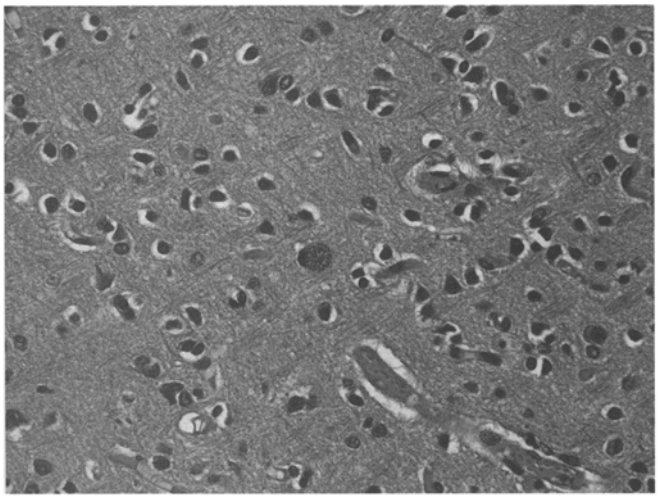


Fig. 6. Toxoplasma cyst from the brain from a 7-year-old status post bone marrow transplant for ALL.

Posttransplant lymphoproliferative disorder

- Seen in 2% of all organ transplant patients
- Higher incidence in children ~ 20%, because of higher rate of EBV negativity before transplant
- More common with intense immunosuppression
- Polymorphous variant:
  - Presents with fever, pharyngitis, lymphadenopathy
  - May occur in the graft itself or in nongrafted sites, i.e., lymph nodes
  - Histology is the dense polymorphous mononuclear infiltrate with prominent immunoblasts, plasma cells and easily found mitotic figures **(Figure 7)** EBV in almost all cases, can be demonstrated by culture, immunohistochemistry, or molecular techniques
  - Flow cytometry shows polyclonal B-cell proliferation
  - Often responds to lowered immunosuppression 20–40 % mortality

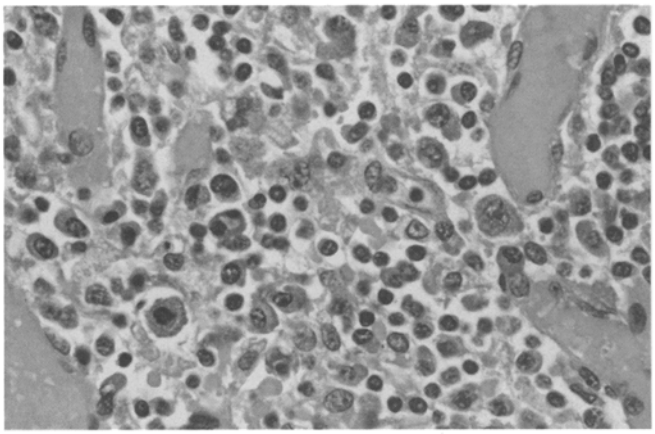


Fig. 7. Enlarged lymph node showing a pleomorphic infiltrate including numerous plasma cells and large plasmacytoid cells with scattered immunoblasts consistent with polymorphous Post-transplant Lymphoproliferative Disorder. Immunostaining for EBV was positive (not shown).

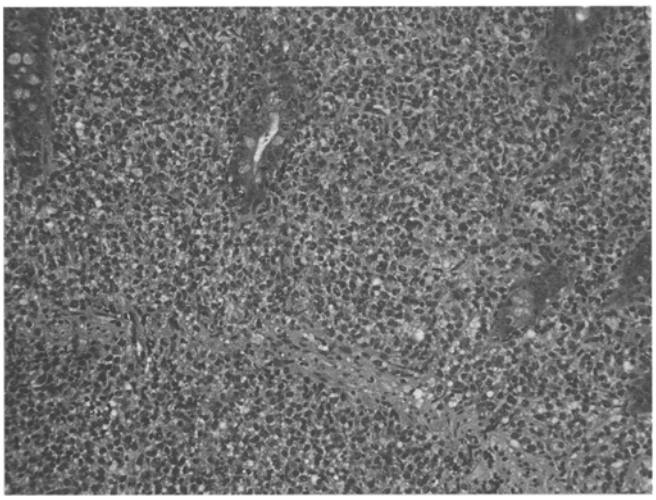


Fig. 8. Colon mass showing a diffuse, relatively monotonous infiltrate of large atypical lymphocytes of Post-Transplant Lymphoproliferative Disorder lymphoma. Immunostaining for EBV was negative (not shown).

- Monoclonal variant:
  - Often presents as a mass
  - May occur in the graft itself or in nongrafted site
  - Histology is the dense monotonous mononuclear infiltrate of immunoblasts type cells with easily found mitotic figures **(Figure 8)**
  - EBV less easily demonstrated by culture, immunohistochemistry, can be shown by molecular techniques
  - Flow cytometry shows monoclonal B-cell proliferation
  - Lowered immunosuppresion required for possible response to chemotherapy 70–80 % mortality
- NonEBV driven lymphoma can also develop

Rejection - General Patterns

Hyperacute rejection

- Immediate graft failure secondary to preformed antibodies
- Marked congestion—may see fibrin platelet thrombi in capillaries

Acute cellular rejection

- Seen first 7–10 days after transplant
- Organ dysfunction often clinically evident
- Mixed mononuclear infiltrate of lymphocytes, lymphoblasts, eosinophils attaching epithelial structures
- Endotheliitis—lymphocytes associated with and disrupting endothelium (usually with enlarged chromatic nuclei) of small veins may be seen
- Usually responds to increased immunosuppression
- Precursor to chronic rejection

Chronic cellular rejection

- Later occurrence but can be seen as early as two months posttransplant but usually one or more years later
- Severe organ dysfunction
- Mononuclear infiltrate associated with marked destruction, loss, or fibrosis of epithelial structures
- Usually associated with transplant arteriopathy
- Untreatable resulting in graft failure

Acute vascular rejection

- Necrotizing or cellular vasculitis
- Usually associated with severe cellular rejection
- Responds poorly to therapy

Chronic vascular rejection (transplant vasculopathy)

- Diffusely involves moderately sized arterioles
- Foamy intimal change
- Concentric fibromuscular proliferation with an intact internal elastica
- Usually associated with chronic cellular rejection
- Untreatable at present

Disease Recurrence

- Organ dependent—*see* below

Drug Toxicity

- Probable common cause of morbidity in the transplant patient
- Poorly recognized, often a diagnosis of exclusion
- Osteoporosis, hypertension and glucose intolerance common side effects of immunosuppressive drugs

KIDNEY TRANSPLANTATION

Indication for Transplantation

- Chronic renal failure second to hypertension, diabetes, glomerulonephritis, and others

Clinical Considerations

- Cadaveric and living related donors used
- Living related organs fair slightly better (95% 1 year graft survival compared with 88% graft survival for cadaveric grafts)
- Allograft usually placed ectopically in the pelvic fossa
- Renal artery and vein anastomosed to iliac vessels; ureter tunneled into urinary bladder
- Native kidneys are usually left in situ except in Adult Polycystic Kidney Disease (infection and neoplasia risk—may develop renal cell carcinoma)
- Donor organ sometimes biopsied for evaluation of arteriolonephrosclerosis **(Figure 9)**
- We report number of sclerotic glomeruli vs the total number of glomeruli

Rejection

- Hyperacute (immediate) rejection:
  - When revascularized, graft becomes dusky and fails to make urine
  - No useful therapy available—results in graft loss
  - As a result of preformed antibodies producing microvascular injury
  - Sections show marked congestion
  - Immunofluorescence shows capillary immunoglobulin deposition
- Delayed hyperacute (accelerated acute) rejection:
  - Occurs several to 48 hours after the transplant
  - Creatinine increases; antibody mediated damage to small and large vessels
  - Often results in graft failure
- Evaluation of the Kidney Biopsy for Rejection:
  - Presents with elevation of creatinine 7–10 days or longer after transplantation
  - Diagnoses by cutting needle biopsy obtained often with ultrasound guidance
  - Formalin fixation generally adequate but frozen (for immunofluorescence) and gluteraldyhyde fixed specimens (for ultrastructure) may be obtained if disease other than rejection is suspected
  - five or more glomeruli considered adequate for diagnosis

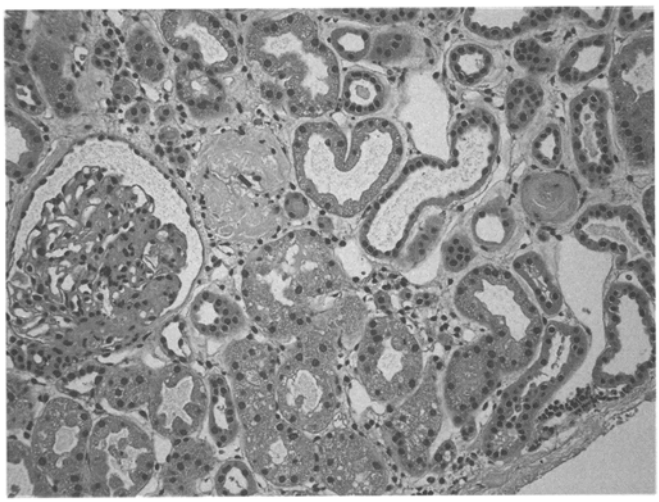


Fig. 9. Wedge biopsy of kidney before transplantation to evaluate extent of sclerosis. Capsule is seen in lower right corner. There is patchy interstitial fibrosis, a senescent glomerulus and hyaline arteriolosclerosis. The organ was used successfully for transplantation.

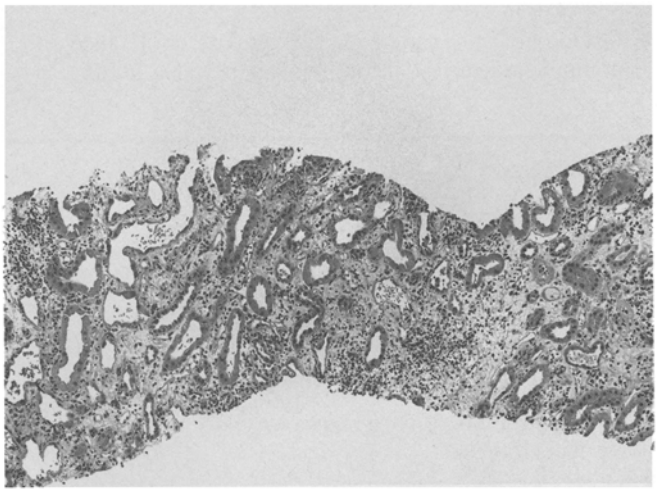


Fig. 10. Allograft kidney showing a mixture of grade I antibody-mediated rejection and Grade IB acute cellular rejection. There is extensive interstitial edema and an infiltrate in >25% of the parenchyma.

Banff Criteria: Consensus diagnostic criteria for renal allograft rejection (Racusen et al.)

- Normal
- Antibody-mediated rejection:
  - Rejection due in part to antidonor antibodies—may also show changes of No. 3–5 below
- Type (Grade):
  - ATN-like – C4d + in peritubular capillaries, minimal inflammation **(Figures 10–12)**
  - Capillary margination and/or thromboses, C4d +
  - Arterial—transmural / necrotizing arteritis, C4d +

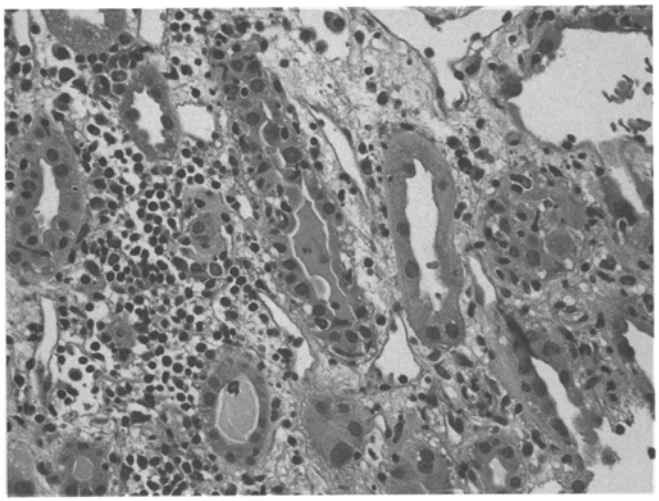


Fig. 11. Higher power of Fig. 10 showing tubulitis.

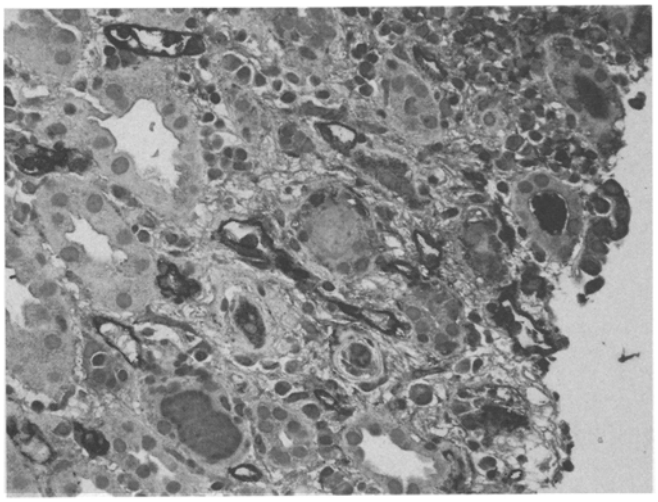


Fig. 12. Immunoperoxidase stain for C4d showing positive staining in peritubular capillaries consistent with antibody mediated rejection.

- Borderline changes, "suspicious for acute rejection":
  - 1–4 mononuclear cells per tubular cross section in up to 25% of the parenchyma
  - No arteritis
- Acute rejection:
  - Grade:
    - IA—Interstitial mononuclear infiltrate in >25% of the parenchyma with mild tubulitis (>4 mononuclear cells per tubule)
    - IB—Interstitial mononuclear infiltrate in >25% of the parenchyma with moderate tubulitis (>10 mononuclear cells per tubule) **(Figures 13, 14)**
    - IIA—mild to moderate intimal arteritis
    - IIB—Severe intimal arteritis compromising >25% of the luminal area

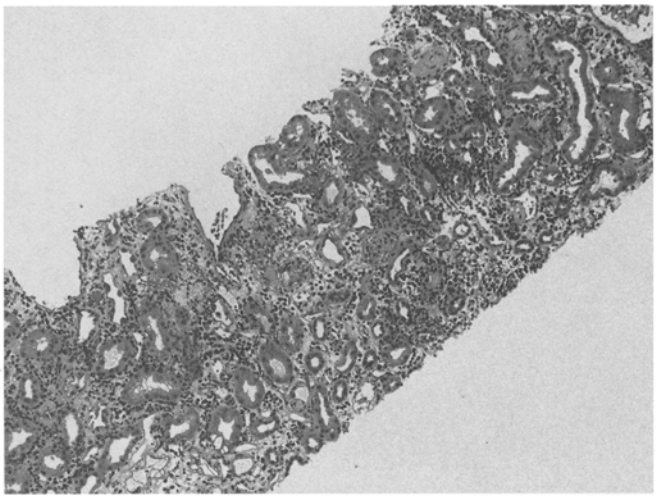


Fig. 13. Allograft kidney showing Grade IA acute cellular rejection without a component of vascular rejection (C4d staining not shown). There is extensive interstitial edema and an infiltrate in >25% of the parenchyma.

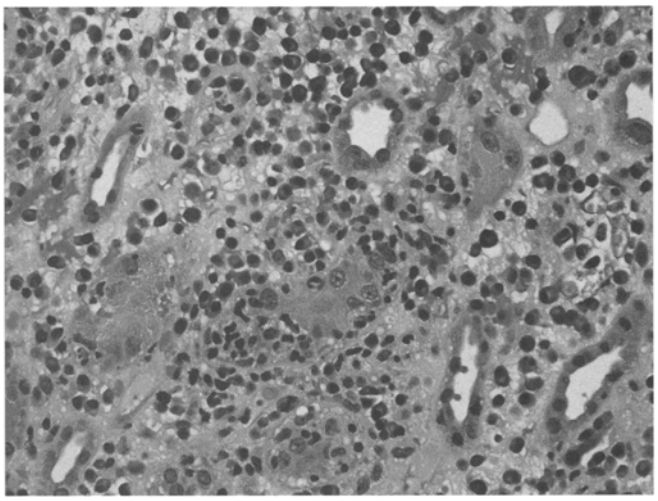


Fig. 14. Higher power of Fig. 13 showing 4–6 mononuclear cells per tubule cross section.

  - III—Transmural arteritis and or arterial fibrinoid change and necrosis of medial smooth muscle cells
- ♦ Chronic/sclerosing allograft nephropathy:
  - Grade:
    - Mild—Mild interstitial fibrosis and tubular atrophy with or without arteriopathy
    - Moderate—Moderate interstitial fibrosis and tubular atrophy with or without arteriopathy **(Figure 15)**
    - Severe—Severe interstitial fibrosis, tubular atrophy and tubular loss with or without transplant arteriopathy
- ♦ Other changes not considered rejection

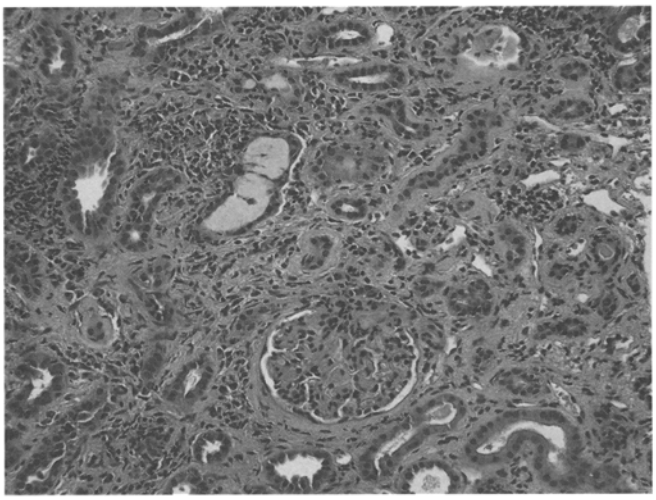


Fig. 15. Kidney allograft with moderate interstitial fibrosis, mononuclear infiltrate, and tubular atrophy consistent with Grade II chronic nephropathy.

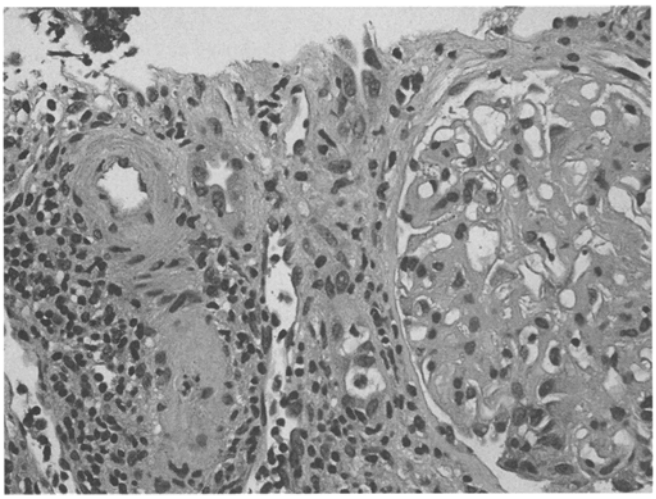


Fig. 16. Higher power of Fig. 14 to show changes in the glomerulus. Without additional studies one can not distinguish chronic nephropathy from recurrent or de novo glomerulonephritis.

Transplant Nephropathy/Glomerulopathy

- ♦ Present with increasing creatinine and proteinuria
- ♦ Glomerulosclerosis typically seen 1 year or more after transplantation
- ♦ Must distinguish chronic hypertensive change/chronic rejection from recurrent or de-novo glomerular disease **(Figure 16)**
- ♦ Requires biopsy with immunofluorescence and ultrastructural examination

Recurrent Disease

- ♦ Glomerulonephritis (GN) recurs in 5–20% of allografts, causing graft failure in <10%

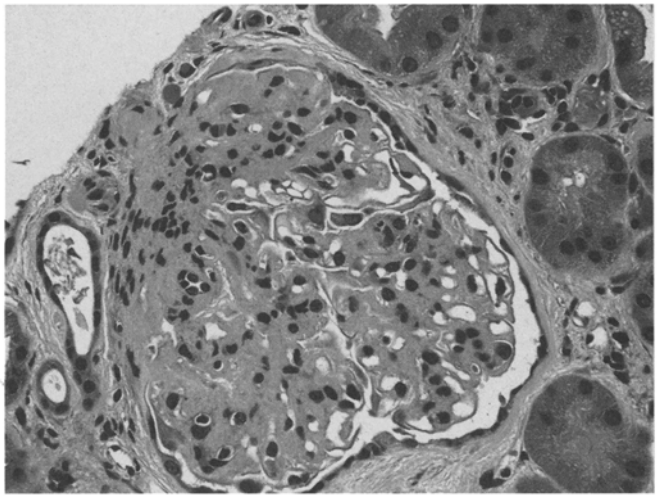


Fig. 17 . Allograft kidney with glomerular sclerosis from a patient originally transplanted for IgA nephropathy.

- Variable timing, months to years after transplant
- Often present with proteinuria, hematuria, and renal insufficiency
- Requires immunofluorescence and ultrastructural examination to diagnose accurately—same criteria for diagnosis as in native kidney:
  - IgA nephropathy (**Figures 17, 18**):
    - Recurs 3 months and later after transplant
    - 25–60 % incidence of recurrence
  - Necrotizing crescentic glomerulonephritis (Wegeners granulomatosis, microscopic polyangiitis):
    - Clinical factors (cANCA, pANCA levels, disease subtype, type of transplant) not useful for predicting recurrent disease
    - Recurrence seen in up to 18%
  - Anti-glomerular basement membrane (GBM) disease:
    - 50% recurrence rate when antiGBM antibodies in serum
    - 5–15% recurrence rate when serum cleared of anti-GBM antibodies for more than 6 months
  - Hemolytic uremic syndrome:
    - Clinical presentation of recurrence gradual or abrupt
    - Thrombocytopenia, hemolysis, progressive renal dysfunction
    - 30% recurrence rate with poor graft survival after recurrence
  - Focal segmental glomerulosclerosis:
    - Recurrence is typically early mean 14 days after transplant
    - Proteinuria, hypertension, increased creatinine
    - 20–30% recurrence in first transplant with 40–50% graft loss
    - 75% recurrence in subsequent transplant if initially lost to recurrent disease
  - Membranous glomerulonephritis:
    - ~ 30% recurrence rate
  - Membranoproliferative glomerulonephritis:
    - Type I:
      - Underlying circulating immuncomplexes usually persist after transplant
      - 20–30% recurrence with 40% graft loss, higher with subsequent grafts
      - HLA matched grafts said to be more susceptible to recurrence
    - Type II:
      - Recurs in 50–100% of grafts
      - Presents after 1 year posttransplant with hematuria and proteinuria
    - Lupus nephritis:
      - <10 % recurrence rate, all pattern types recur
      - Usually seen 3 or more years after transplantation
    - Diabetes:
      - Changes often recur, typically >1 year after transplant
      - Present with progressive renal dysfunction typically with out or only mild proteinuria
- De Novo Glomerulonephritis:
  - Uncommon, when seen—most commonly membranous glomerulonephritis

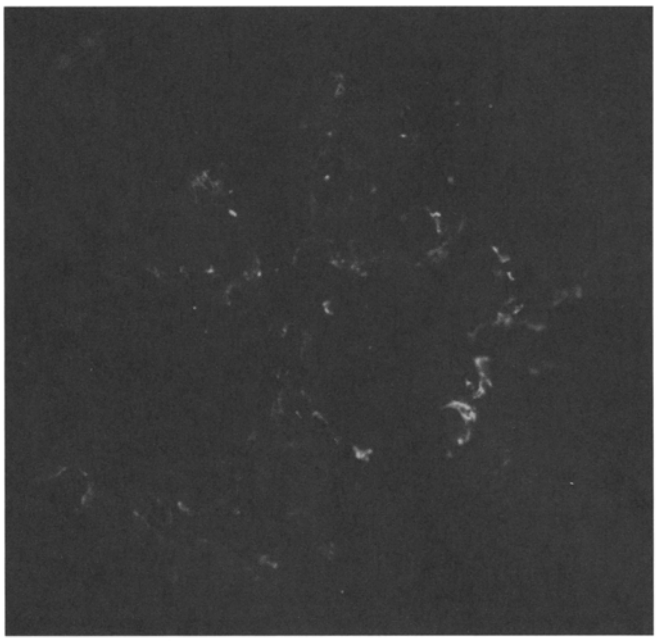


Fig. 18. Immunofluorescence for IgA on kidney from Fig. 17 indicating recurrent IgA nephropathy.

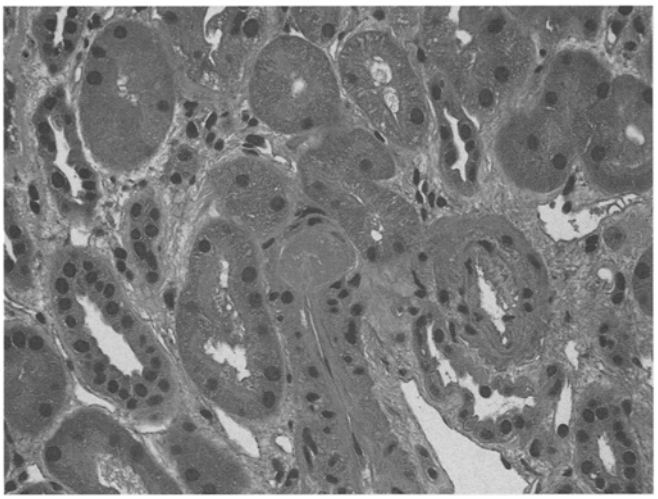


Fig. 19. Small arteriole from an allograft kidney showing intramural hyaline globule consistent with calcineurin inhibitor toxicity. Note the lack of an interstitial infiltrate.

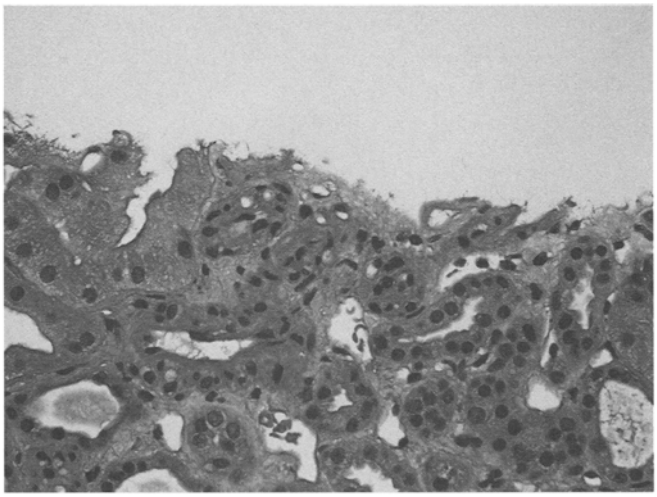


Fig. 20. Small arteriole from an allograft kidney showing vacuolization of the smooth muscle cytoplasm within the wall of the vessel. This finding is suggestive of calcineurin inhibitor toxicity. Note the lack of an interstitial infiltrate.

- ♦ Drug toxicity:
  - Cyclosporine or FK506 toxicity:
    - Presents with increased creatinine
    - Minimal interstitial inflammation
    - Nodular, new onset, arteriolar hyaline change is suggestive of toxicity **(Figure 19)**
    - Also vacuolization of smooth muscle cytoplasm in arteriole wall **(Figure 20)**
  - Antibiotics, etc.:
    - Variable interstitial infiltrate often with eosinophils **(Figure 21)**

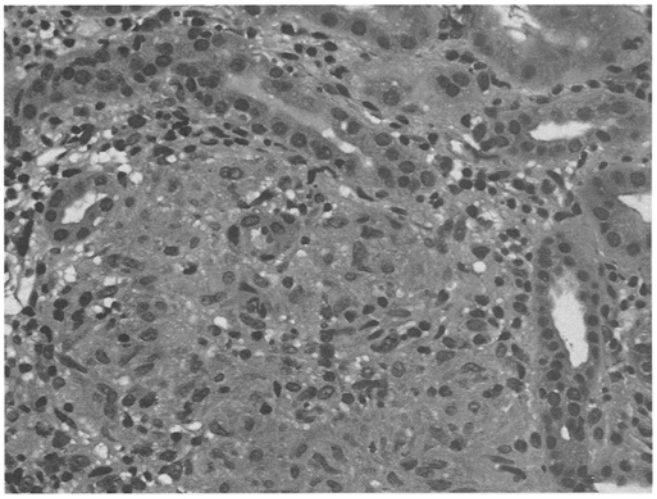


Fig. 21. Interstitium of a renal allograft expanded by a mononuclear infiltrate including numerous macrophages and eosinophils. Some tubular damage is present. The patient presented with creatinine elevation which resolved with discontinuation of antibiotic therapy—a drug toxicity.

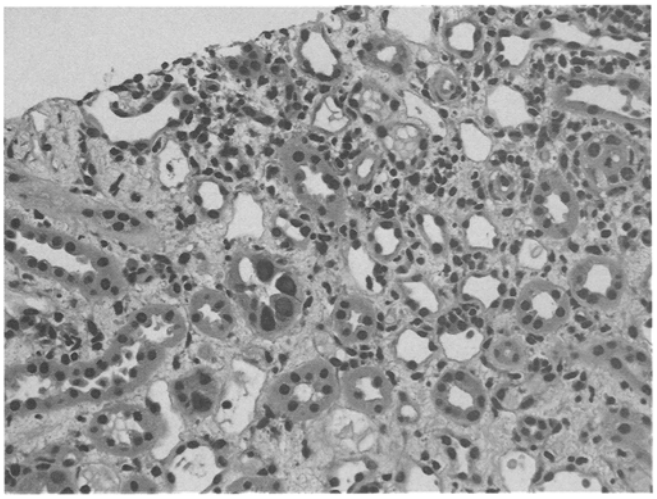


Fig. 22. An allograft kidney with a mild to moderate interstitial infiltrate. Two tubules exhibit enlarged nuclei with amphophilic inclusions very suggestive of BK virus infection. Some tubular damage is present which might be errantly diagnosed as rejection if the viral inclusions are not noted.

Virus Infection

- ♦ BK virus:
  - Small nonenveloped double stranded DNA virus of the polyomavirus family
  - Latent infection present in at least 50% of the population
  - Usual onset within 3 months posttransplant but can be seen years later
  - Present with graft dysfunction
  - Histology is the polymorphous interstitial infiltrate associated with tubulitis mimicking rejection **(Figure 22)**

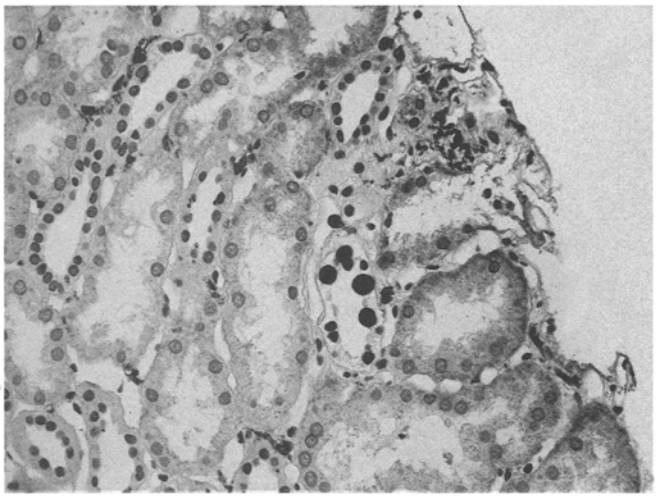


Fig. 23. Immunoperoxidase-type staining using antibodies to the BK virus on the same patient as seen in Fig. 22. The nuclear inclusions are nicely highlighted.

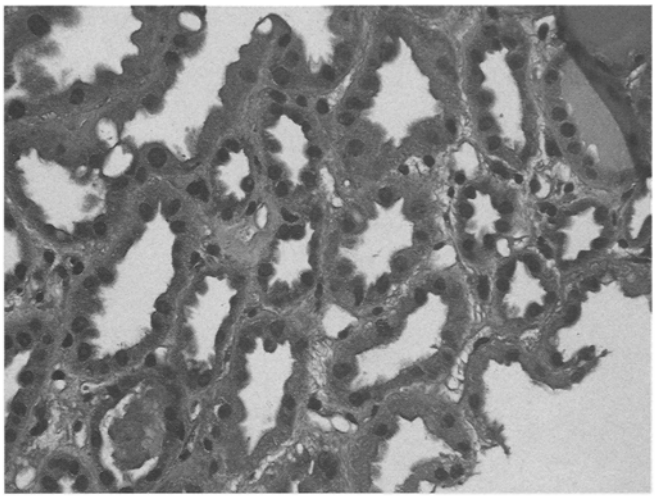


Fig. 24. A kidney allograft several days after implantation showing enlarged tubular nuclei with scattered mitotic figures consistent with recovering ATN.

- Characteristic ground glass to lavender ntranuclear inclusions often associated with nuclear enlargement of the tubular epithelium
- Virus can be confirmed with immunohistochemistry **(Figure 23)** or ultrastructural examination
- Treated with decreased immunosuppression

♦ Cytomegalovirus (CMV):
- Typically seen 30 days after transplant
- Presents with graft dysfunction
- Histology is the polymorphous interstitial infiltrate associated with tubulitis may mimic rejection
- Characteristic nuclear enlargement with prominent intranuclear and cytoplasmic inclusions
- Inclusions may be found in the tubular epithelium, endothelial cells in veins and glomerular capillaries and in stromal cells

Acute Tubular Necrosis

♦ Seen early after transplant, consistent with preservation effect **(Figure 24)**

♦ May be seen late as a manifestation of hypotension or drug effect

Ureter Obstruction/Pyelonephritis

♦ Common, variable timing

♦ Presents with fever, increased creatinine, pyuria

♦ Interstitial infiltrate of neutrophils with edema

Posttransplant Lymphoproliferative Disorder

♦ Atypical interstitial mononuclear infiltrate with mitotic figures

♦ EBV often can be demonstrated

♦ Treated with decreased immunosuppression

HEART TRANSPLANTATION

Indication for Transplantation

♦ Chronic severe heart failure: coronary artery disease, myocardial infarction, myocarditis, congenital malformations, etc.

Clinical Considerations

♦ Contraindications to transplantation: Malignancy, active infection (HIV), amyloidosis

♦ Cadaveric organs are ABO matched to donor

♦ Orthotropic transplant—Recipient atria (with cavae and pulmonary veins) are anastamosed to donor atria creating slightly enlarged composite atria. Donor aorta above the level of the coronaries anastomosed to recipient aorta; pulmonary artery to pulmonary artery

♦ Treatment for acute cellular rejection is institution specific:
- At our institution, in adults, grade 3A and above rejection is treated with increased immune suppression, lower grades generally not treated
- Grade 2 may be treated if clinically symptomatic

Rejection

♦ Hyperacute rejection:
- Rare

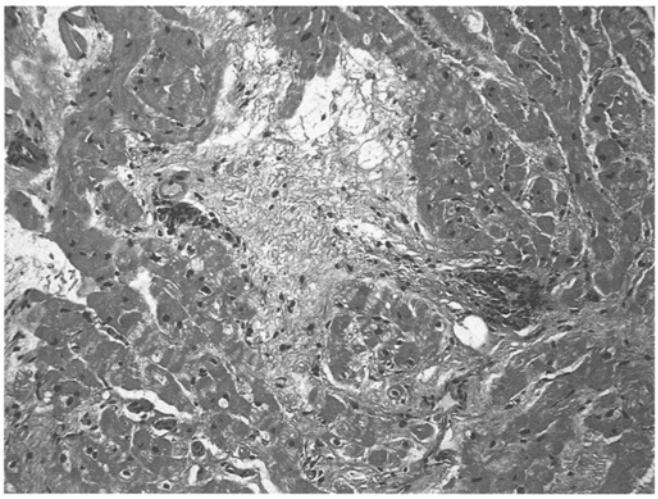


Fig. 25. Allograft heart showing two small perivascular infiltrates characteristic of grade I acute rejection.

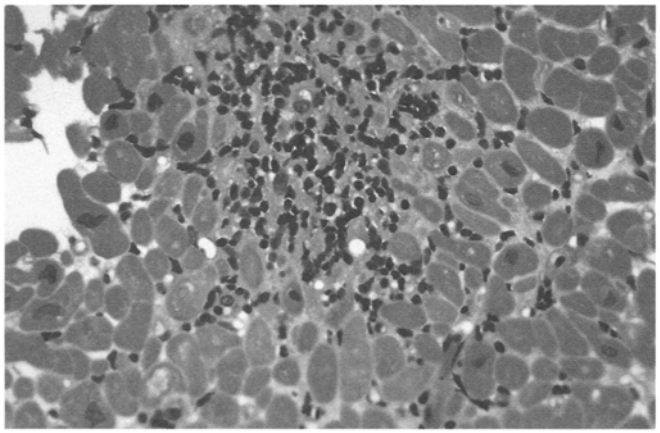


Fig. 26. A single moderately dense lymphocytic infiltrate characteristic of grade 2 rejection. One should examine multiple levels though a lesion like this to exclude the possibility of tangentially cut Quilty effect.

- Graft becomes dusky and ceases pumping shortly after revascularization
- Due to preformed antibodies producing microvascular injury
- Immunofluorescence shows immunoglobulin and compliment deposition in capillaries
- Histology shows marked congestion

♦ Acute cellular rejection:

- Acute cellular rejection first occurs 7–10 days after transplantation
- May present with elevated right side heart pressures and or malaise
- No clinical parameter correlates well with rejection so right-sided myocardial biopsy performed at regular intervals to look for rejection—protocol biopsies

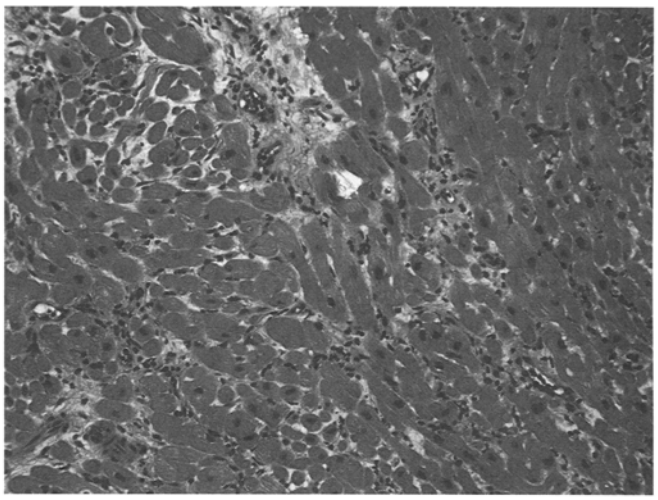


Fig. 27. Diffuse interstitial infiltrate that was noted in all five fragments in the biopsy specimen consistent with moderate acute rejection 3A.

- A minimum of five formalin fixed myocardial fragments are considered adequate for evaluation
- Consensus criteria for diagnosis of rejection developed by the International Society for Heart and Lung Transplantation (ISHLT) (Rodriguez, 2003):
  - Grade 0—no rejection
  - Grade 1—focal myocardial infiltrates without myocyte damage **(Figure 25)**
  - Grade 2—One focus only of aggressive mononuclear cell infiltration; may or may not show myocyte damage; must distinguish from penetrating Quilty effect **(Figure 26)**
  - Grade 3A—Multifocal aggressive infiltrates with or without myocyte damage **(Figure 27)**
  - Grade 3B—Diffuse inflammatory process with necrosis **(Figure 28)**
  - Grade 4—Diffuse aggressive infiltrates with polymorphonuclear cells, edema, hemorrhage, vasculitis and necrosis

Transplant Coronary Artery Disease (Cardiac Transplant Vasculopathy/Chronic Rejection)

♦ ~ 10% of heart transplant patients develop clinically significant vessel disease

♦ Risk factors include acute rejection, CMV infection, hyperlipidemia, and glucose intolerance

♦ Early—foamy endothelial changes

♦ Late—circumferential fibrointimal proliferation that obliterates the lumen leading to infarction—as the lumen narrows predisposes to thrombosis **(Figure 29)**

♦ Difficult to diagnose without angiogram—some advocate immunofluorescence studies of biopsy material

♦ No known treatment—leads to graft failure

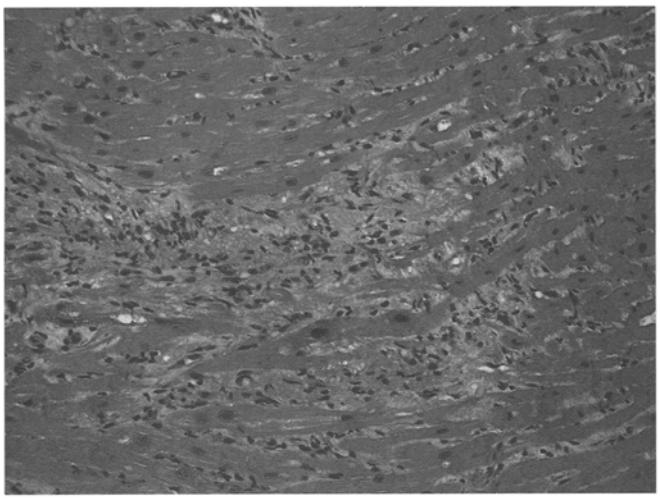


Fig. 28. Interstitial infiltrate associated with myocyte necrosis a feature of Grade 3B rejection.

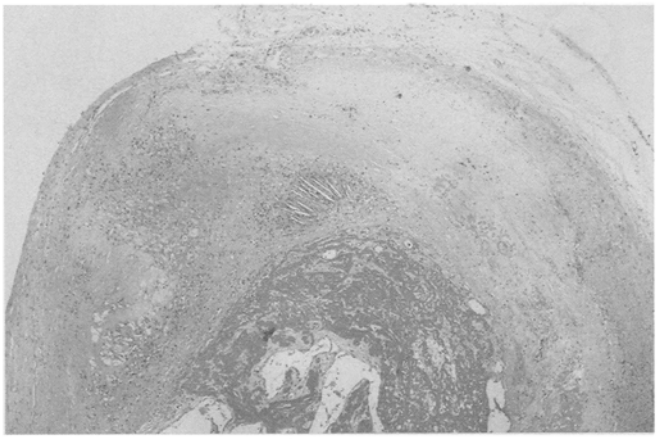


Fig. 29. An epicardial coronary artery from an explanted cardiac allograft showing classic transplant vascular disease of chronic rejection. There is marked fibrointimal thickening of the wall in a concentric fashion with an acute thrombus in the lumen.

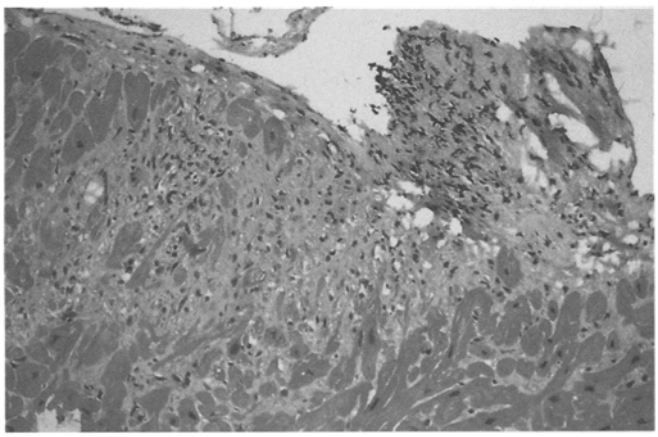


Fig. 30. Fibrosis and granulation tissue consistent with a previous biopsy site in a cardiac allograft.

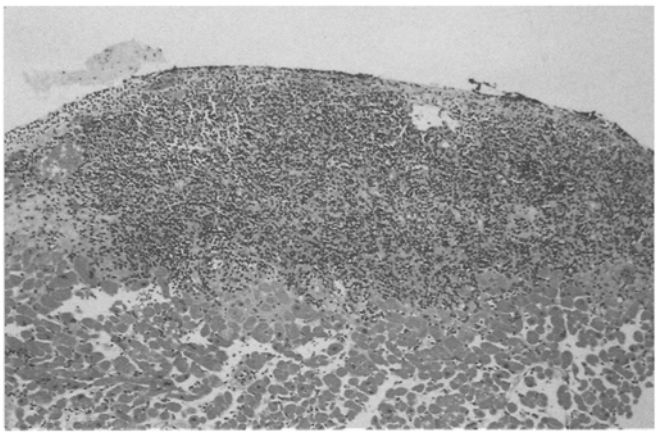


Fig. 31. Classic appearance of Quilty effect. The lesions can be quite variable in size.

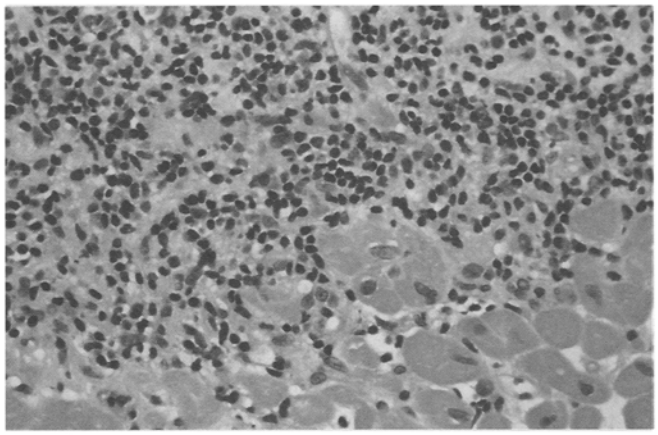


Fig. 32. High power view of the base of the infiltrate seen in figure 31. Note the myocyte damage at the interface. This is not an indication of rejection. Imagine how this focus would look if cut tangentially.

Other Biopsy Findings

- Focal subendocardial layer of myocyte necrosis is early biopsies consistent with preservation effect; goes on to fibrosis with time; thinner the necrotic layer the better
- Granulation tissue with or without chronic inflammatory cells = biopsy site, not rejection **(Figure 30)**
- Quilty effect:
  - A nodular collection of lymphocytes involving the endocardium **(Figure 31)**
  - May extend into the endocardium with damage to adjacent myocytes (penetrating Quilty effect) **(Figure 32)**
  - Small vessels often seen in the infiltrate
  - Mixture of T and B cells without prominent nucleoli, mitoses or atypia
  - Associated with cyclosporine immunosuppression but etiology not known
  - Not rejection
  - Note: if tangentially cut, penetrating Quilty effect my be confused for grade 2 rejection

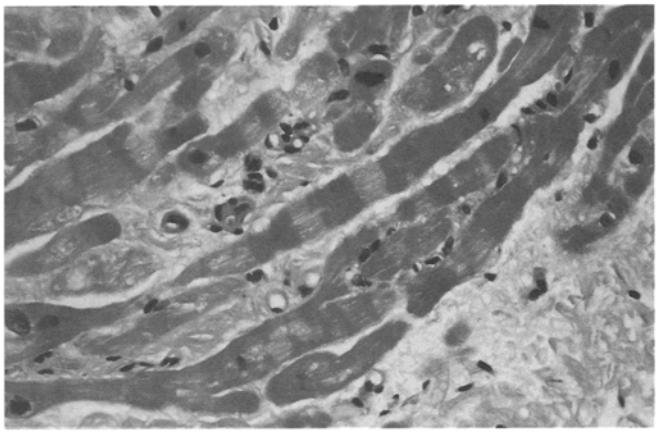


Fig. 33. Artifactual contraction bands. Note that there is no pyknosis. This artifact is present in almost all cardiac biopsies.

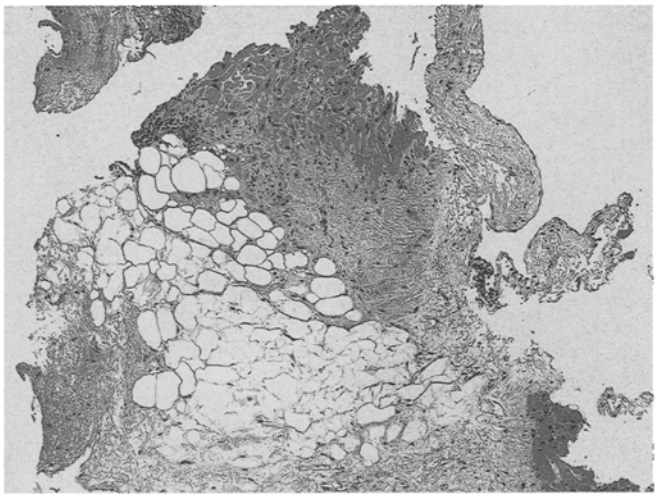


Fig. 34. A large amount of adipose tissue in a cardiac biopsy raises the possibility of perforation.

- Levels through the block may be helpful with this distinction
- Differential Diagnosis:
  - Lymphoma

♦ Myocytes with cytoplasmic contraction bands (without nuclear pyknosis) are present in every biopsy and are not significant **(Figure 33)**

♦ Extensive adipose tissue **(Figure 34)** or mesothelium **(Figure 35)** suggests myocardial perforation

♦ Endocardial thrombi should be reported but are not usually significant

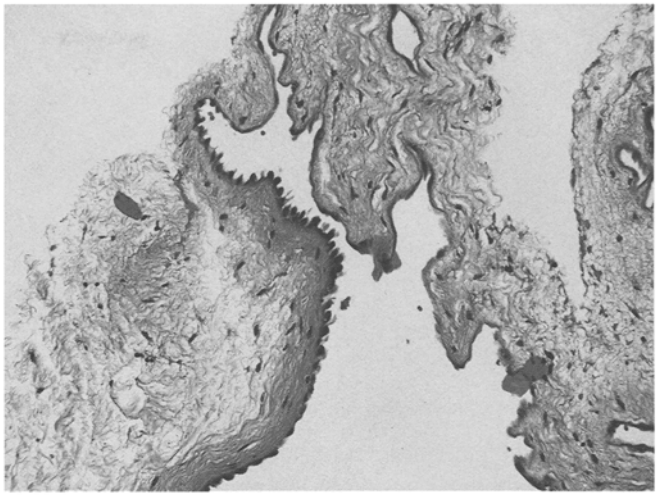


Fig. 35. A strip of mesothelium from a right ventricular biopsy is a sure indicator of perforation. The patients usually do not feel the cardiac biopsies because the allograft is de-innervated. However, biopsy of an innervated structure may be felt.

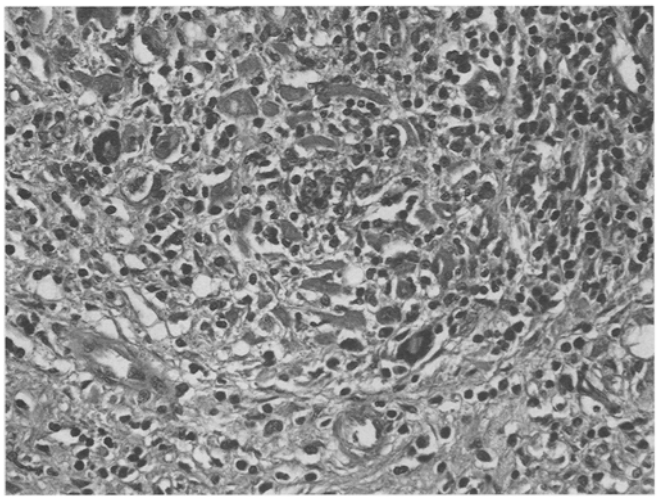


Fig. 36. Recurrent giant cell myocarditis in a failed allograft.

♦ CMV or toxoplasma inclusions may be seen in patients without previous exposure, usually within the first year after transplantation

♦ Extensive fibrosis suggests cyclosporine toxicity but is seldom seen with current immunosuppresion regimens

♦ Giant cell myocarditis may recur in the allograft **(Figure 36)**

LUNG TRANSPLANTATION

Indication for Transplantation

♦ Chronic pulmonary failure: Chronic obstructive pulmonary disease (COPD)/emphysema, cystic fibrosis, idiopathic pulmonary fibrosis (usual interstitial pneumonia), pulmonary hypertension (often with heart transplant because of congenital heart disease)

Clinical Considerations

♦ Allograft is matched for size and side

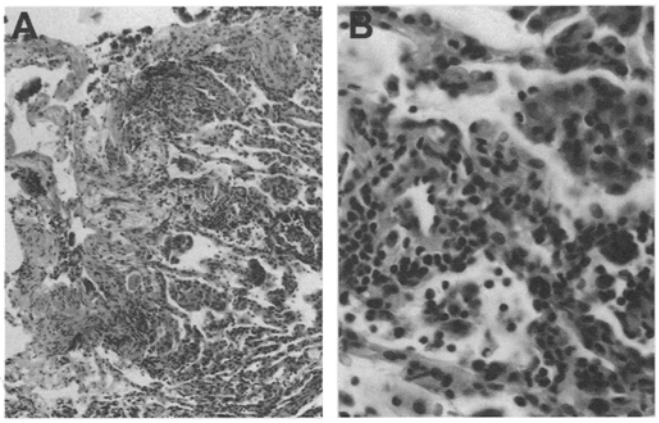


Fig. 37. Mild pulmonary rejection characterized by small perivascular infiltrates visible at low power without extension into the alveolar wall. Low power magnification on the left, higher power on the right.

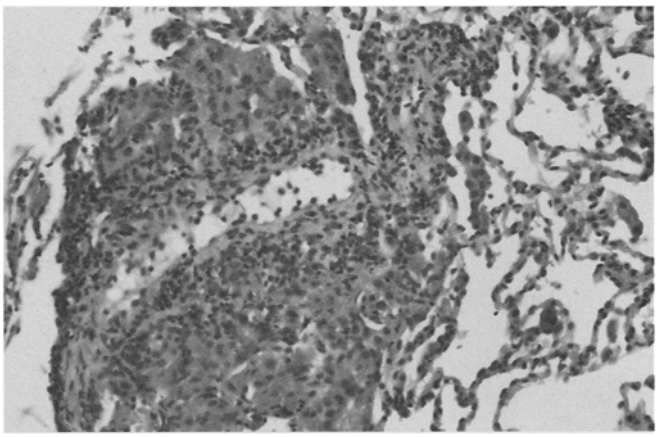


Fig. 38. Moderate pulmonary rejection showing a large perivascular infiltrate with extension into the surrounding alveolar walls.

♦ One or both lungs may be transplanted; if bilateral, done as two single lungs

Rejection

♦ Acute cellular rejection:
- Typically seen 7–10 days after transplant
- May present with malaise, fever, shortness of breath and pulmonary infiltrates on chest radiographs
- Increased immunosuppression usually improves acute rejection
- Four, formalin fixed transbronchial biopsy fragments are considered adequate for diagnosis
- International Society for Heart and Lung Transplantation (ISHLT) criteria for rejection (Yousem et al. 1996):
  - Grade A0 = none
  - Grade A1= minimal rejection:
    - Rare perivasuclar mononuclear infiltrates that are not notable at low power

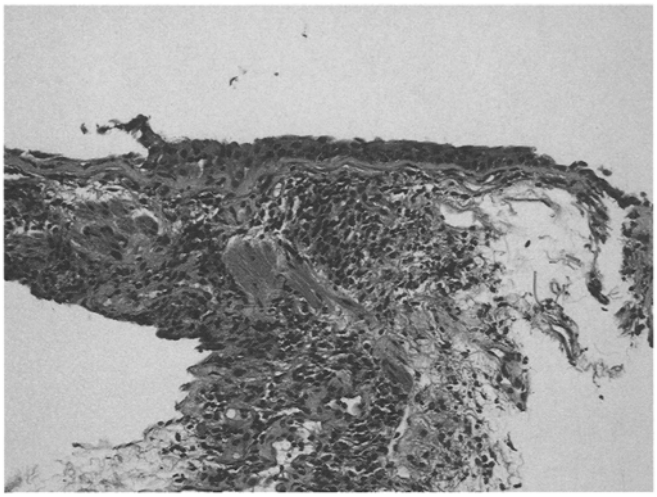


Fig. 39. Chronic, moderate to severe bronchitis from a pulmonary allograft biopsy. Bronchitis should be noted in reports in addition to the perivascular infiltrates.

  - Grade A2 = mild rejection:
    - Frequent perivasuclar mononuclear infiltrates that are easily seen at low power **(Figure 37)**
  - Grade A3 = Moderate rejection:
    - Frequent perivasuclar mononuclear infiltrates that are easily seen at low power
    - Often with endotheliitis, with extension into the surrounding interstitium **(Figure 38)**
  - Grade A4 = Severe rejection:
    - Changes seen in moderate rejection plus alveolar wall damage with hyaline membranes and neutrophils
    - Necrosis and vasculitis may be present
- Lymphocytic bronchitis/bronchiolitis may be seen with any of the above grades of rejection and the report should also include its absence or presence (lymphocytic bronchitis/bronchiolitis may be graded B1–B4) **(Figure 39)**

♦ Chronic Rejection:
- Increasing shortness of breath with obstructive spirometry
- No pulmonary infiltrates
- Histology = bronchiolitis obliterans (active or inactive, grade Ca or Cb respectively) **(Figure 40)**
- Usually associated with chronic transplant vasculopathy **(Figure 41)**
- Generally, does not respond to treatment

Early Posttransplant Changes

♦ Diffuse alveolar damage:
- May be seen in early posttransplant biopsies
- Must distinguish from grade A4 rejection
- Hyaline membranes present but no mononuclear infiltrate

♦ Cryptogenic organizing pneumonia (Bronchiolitis obliterans—organizing pneumonia, BOOP):

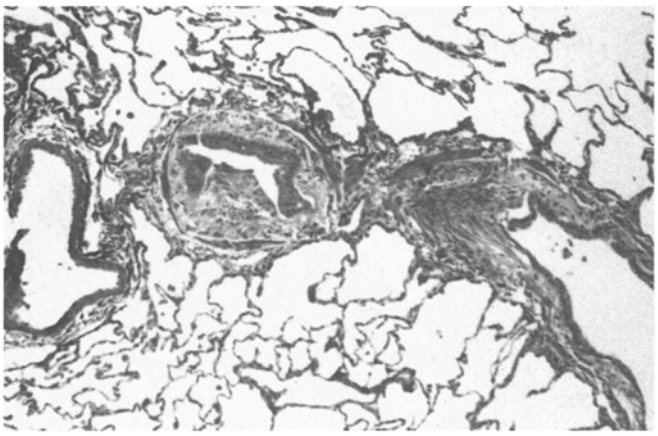


Fig. 40 . Trichrome stained section showing early bronchiolitis obliterans. There is a mural fibrous proliferation obscuring the lumen of this small membranous bronchiole. The pulmonary artery branch is visible to the extreme left and is without arteriopathic changes.

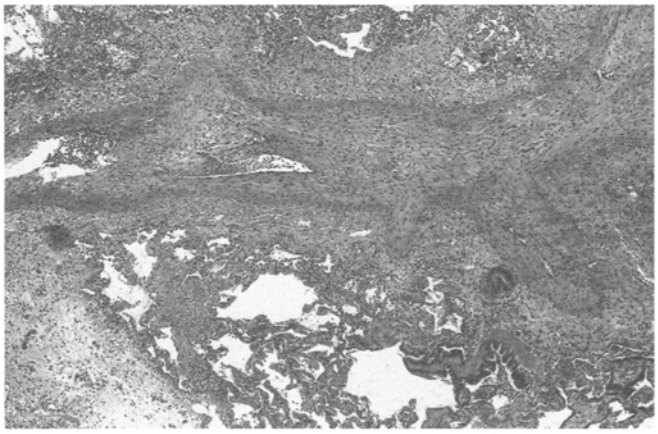


Fig. 41. A pulmonary allograft with severe transplant vasculopathy consistent with chronic rejection.

- May be seen in early posttransplant biopsies
- Usually resolves
- Must distinguish from bronchiolitis obliterans **(Table 2)**
- Bronchiolitis obliterans can be diagnosed in transbronchial biopsies but it is difficult or impossible in many cases—open biopsy may be necessary
- Chronic transplant vasculopathy usually only seen in resected explants

Table 2. Bronchiolitis Obliterans vs Cryptogenic Organizing Pneumonia

	Timing	*Appearance*	*Location*
Bronchiolitis Obliterans	Late	Mural fibrosis, compressing lumen	Membranous bronchial and above
Cryptogenic organizing pneumonia	Early	Airspace granulation tissue	Respiratory bronchiole and below

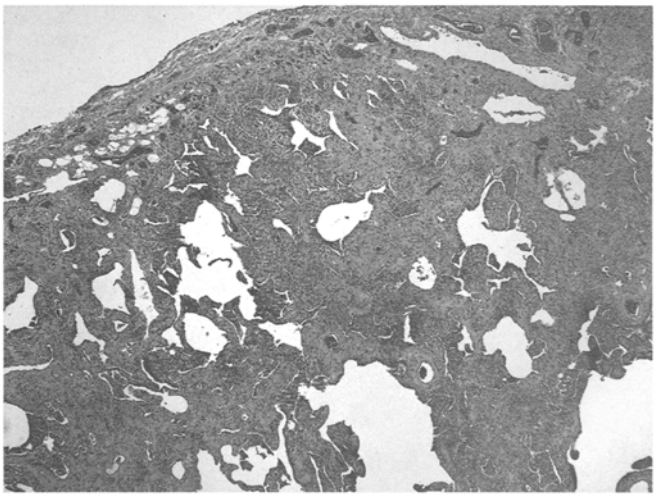


Fig. 42. Explanted allograft lung showing early honeycomb change consistent with recurrent usual interstitial pneumonia. Other foci show fibrosis that is variable in time and place (not shown).

Infection

- Bacterial pneumonia, but also opportunistic pathogens including CMV, pneumocystis, aspergillous and candidia.
- Pseudomonas is a common infection of the bronchi

Nonhealing Bronchial Margin

- Common clinical problem
- Biopsy shows nonspecific chronic inflammation

Recurrent Disease

- Uncommon; Eosinophilic granuloma, leiomyomatosis, sarcoidosis, unsual interstitial pneumonia **(Figure 42)**

LIVER TRANSPLANTATION

Indication for Transplantation (acute and chronic liver failure, others)

- Acute—Drugs and toxins; fulminate viral hepatitis HBV >> HBA > HBC; fulminate autoimmune hepatitis
- Chronic—cirrhosis of any etiology; HCV, EtOH, chronic cholestatic disorders are common causes
- Other—primary metabolic disease, e.g., hereditary hyperoxyaluria

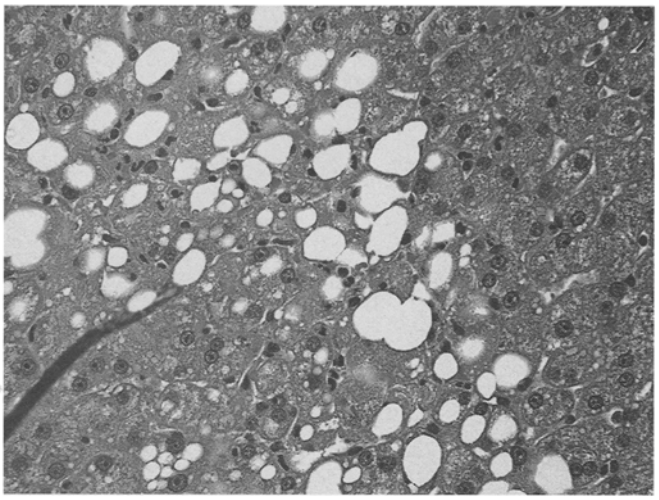


Fig. 43. Approximately 50% macrovesicular fatty change in a potential liver allograft. Some would consider this liver unsuitable for transplantation.

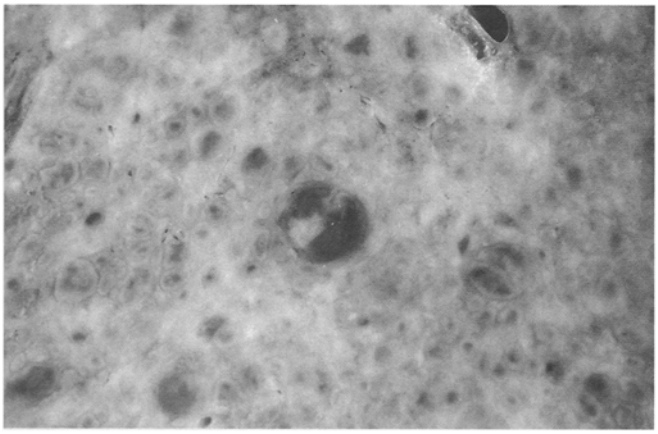


Fig. 44. Cut section of a native liver with end stage liver disease secondary to HCV infection and alcohol toxicity. Note the nodule that is larger and a different color from its neighbors—it's an incidental hepatocellular carcinoma.

Clinical Considerations

- Small **(under ? 4 cm)** hepatomas are common in cirrhotic patients and are not a contraindication for transplantation
- Cadaveric donors are generally used with some facilities doing rare living donor partial liver transplants
- Recipient and organ are size (usually by weight) and ABO matched
- Donor liver sometimes evaluated by frozen section before transplant
- Chronic liver disease (significant fibrosis), or macrovesicular fatty liver >50% may not be suitable for transplant (at the surgeon's discretion) **(Figure 43)**

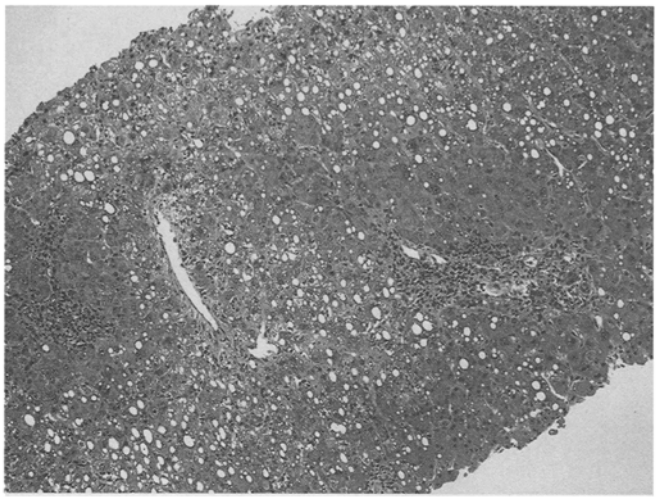


Fig. 45. Liver biopsy 3 days after transplantation. The lobule shows numerous changes including cholestasis, slight centrilobular ballooning, moderate fatty change, and Kupffer cell prominence. Most of the changes are consistent with preservation effect. The portal tracts have a sprinkling of neutrophils, lymphocytes, edema, and slight ductular proliferation, consistent with borderline rejection.

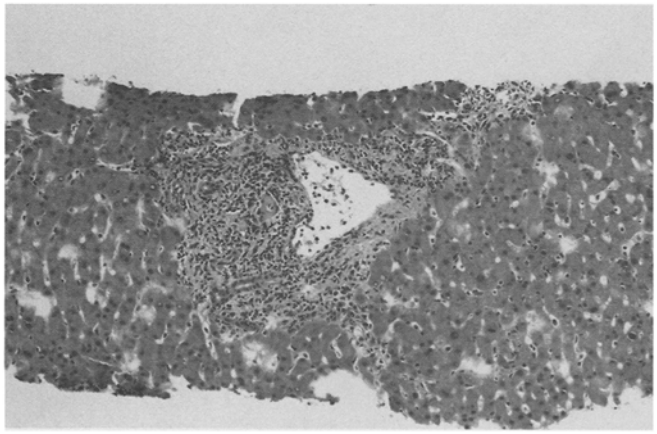


Fig. 46. Portal tract expanded by a mixed infiltrate with bile duct damage and endotheliitis consistent with acute cellular rejection.

- Orthotropic transplant with caval, portal and arterial anastomoses; donor bile duct usually sewn end-to-end of recipient, except with chronic cholestatic disease where bile duct is sewn to Roux-limb (hard to do ERCP):
  - Donor cholecystectomy usually performed
- Explanted liver should be examined carefully for incidental hepatocellular carcinoma:
  - Gross: Soft, bulge above the cut surface, often a different color from surrounding nodules **(Figure 44)**
  - Number, size, presence, or absence of vascular invasion, lymph note status should be noted in report

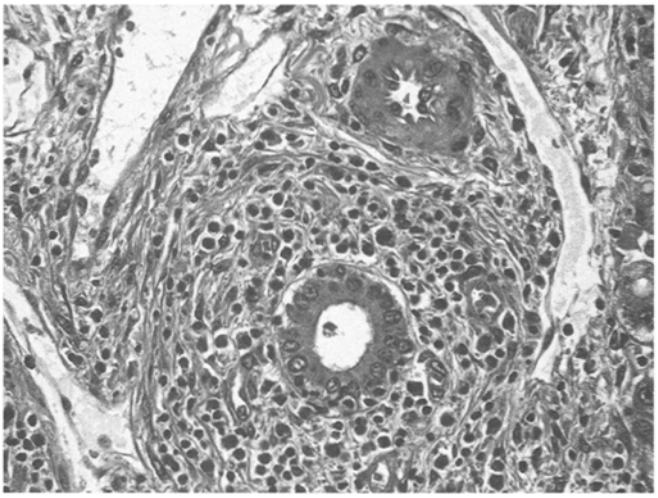


Fig. 47. Interlobular bile duct damage consistent with acute cellular rejection.

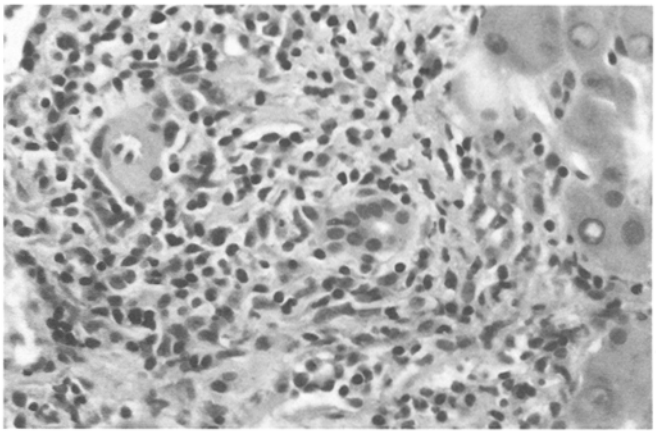


Fig. 48. Interlobular bile duct damage consistent with acute cellular rejection, with more duct injury and unrest.

- An explanted allograft liver should be carefully examined, especially the artery, for etiology of graft failure

Rejection

- Acute rejection:
  - Usually present 7–10 days after transplantation
  - Elevated liver function tests, primarily alkaline phosphatase and γ glutamyl transpeptidase (GGT)
  - May have fever and or peripheral eosinophilia
  - Formalin fixed liver biopsy adequate if five or more portal tracts are present
  - Characterized by (1) mixed but predominantly mononuclear portal infiltrate, (2) manifestations of interlobular bile duct damage, (3) endotheliitis
  - Two of these three factors must be present to diagnose cellular rejection
  - An unusual manifestation of rejection, especially among children, is a mononuclear infiltrate around the central veins with little or no portal changes (not taken into account in the below noted classification)
  - Moderate to severe acute rejection is a predictor for the development of chronic rejection
  - Acute rejection must be differentiated from:
    - Viral and drug induced hepatitis, mechanical bile duct obstruction, recurrent cholestatic disease (PBC, PSC)
    - Posttransplant lymphoproliferative disorder: only rejection associated with arteriopathy

Consensus Banff Criteria (Demetris et al., 1997)

- Acute cellular rejection:
  - Indeterminate—portal infiltrates that fail to meet the criteria for rejection **(Figure 45)**
  - Mild—Infiltrates in a minority of tracts with little tract expansion
  - Moderate—Infiltrates expanding most or all the portal tracts
  - Severe—at least moderate portal infiltrates plus central perivenular infiltrates with hepatocyte damage

* The Banff committee also suggested that a Rejection Activity Index score be given, 3–9, by adding together the scores for the three below noted categories

- Portal Inflammation:
  - Lymphocytes involving but not noticeably expanding a minority of triads = 1
  - Most triads expanded with mixed infiltrate **(Figure 46)** = 2
  - Marked expansion of most triads with spill-over into lobule = 3
- Bile duct changes:
  - Minority of ducts cuffed and infiltrated by inflammatory cells = 1
  - Most or all ducts infiltrated by inflammatory cells **(Figures 47, 48)** = 2
  - As in 2 with degenerative changes or focal luminal disruption = 3
- Venous endothelial inflammation:
  - Endotheliitis involving some portal or hepatic veins = 1
  - Endotheliitis involving most or all portal or hepatic veins **(Figure 49)** = 2
  - As in 2, with inflammation that extends into the parenchyma with necrosis = 3
- Chronic rejection:
  - Marked elevation of canilicular enzymes
  - Early changes include oncocytic change and disruption of bile duct epithelium

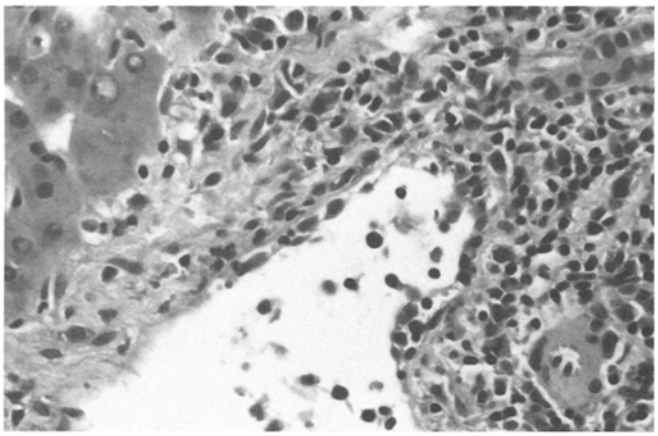


Fig. 49. Hepatic allograft with classic endotheliitis of rejection involving a portal vein.

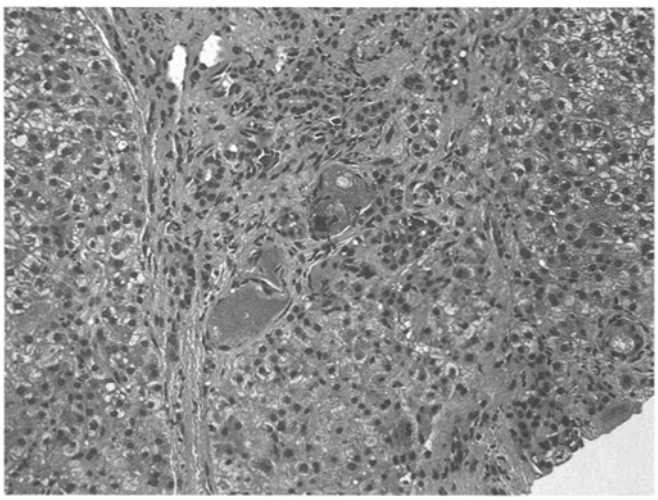


Fig. 50. Explant liver allograft showing a portal tract devoid of a bile duct. Here is cholestasis and centri-lobular hepatocyte dropout. The centri-lobular region is not cellular and this may represent ischemia from chronic transplant vasculopathy as much as direct immunologic injury.

- Progressive loss of interlobular bile ducts **(Figure 50)**
- Usually associated with chronic transplant arteropathy (seldom seen in biopsies) and fibrosis **(Figure 51)**
- Centrilobular hepatocyte dropout/inflammation/fibrosis marked:
  - Maybe because of cellular rejection or ischemia secondary to arteriopathy
- Cholestasis is marked with numerous collection of foamy Kuppfer cells
- Does not respond to therapy resulting in graft loss

Mechanical bile duct obstruction

- Can mimic acute rejection exquisitely

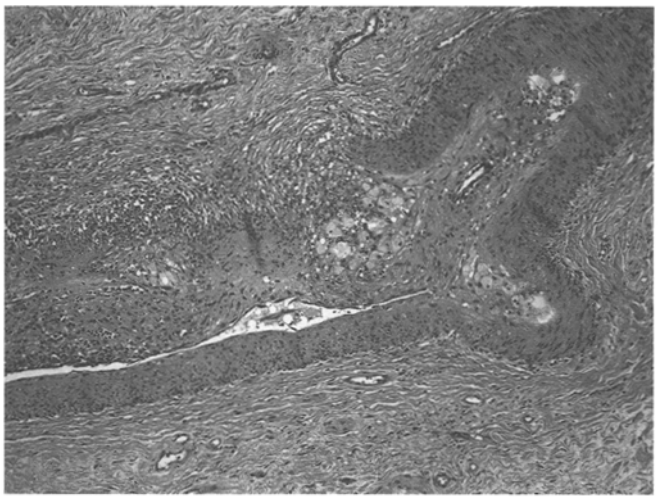


Fig. 51. Explant liver allograft showing classic transplant vasculopathy of chronic rejection.

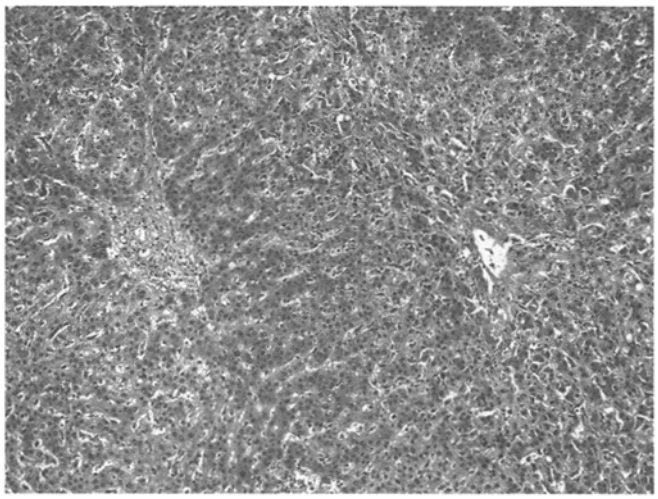


Fig. 52. Liver allograft with marked bile ductular proliferation and cholestasis. Differential diagnosis would include extra-hepatic duct obstruction and sepsis. This is not typical of acute rejection.

- Mixed portal infiltrate, may show bile duct damage
- Increased number of neutrophils and bile ductular proliferation more suggestive of obstruction than rejection **(Figure 52)** not typically associated with endotheliitis—no arteriopathy
- ERCP diagnostic

CMV infection

- Seen approx 30 days after transplant
- Elevated LFTs
- Histology is the "microabscesses" in the lobule associated with rare hepatocyte inclusions **(Figure 53)**

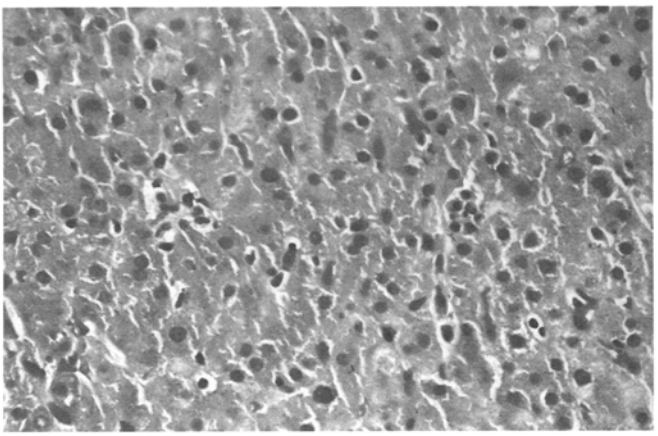


Fig. 53. Allograft liver with scattered "microabscesses" small collections of neutrophils in the lobule are a marker for CMV infection. When microabscesses are noted, there should be a careful search for the virus.

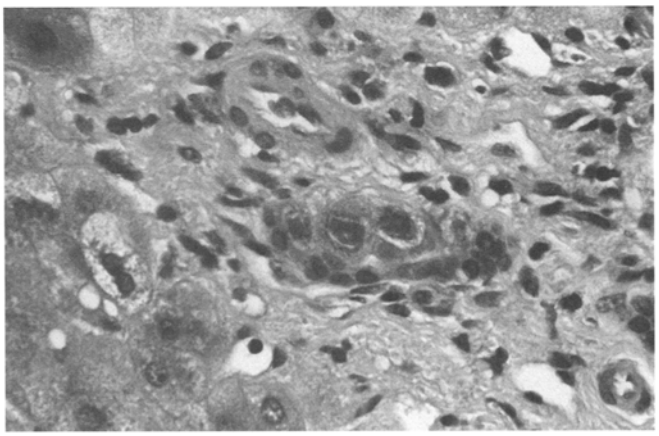


Fig. 54. Two classic CMV inclusions in the interlobular duct epithelium of a liver allograft. The inclusions can also be seen hepatocytes, endothelial cells and in stromal cells (not illustrated).

- Can exhibit a portal infiltrate if bile duct epithelium infected **(Figure 54)**

Preservation effect

- Vacuolization of central hepatocyte cytoplasm with or without cannilicular cholestasis, acidophil bodies (*see* **Figure 45**)
- Usually resolves after 7 days
- Can persist for 30 days

Recurrent disease

- Congenital diseases manifested in the liver do not recur, i.e., α 1 antitrypsin deficiency
- Recurrent disease has the same histologic features in the allograft as in the native liver

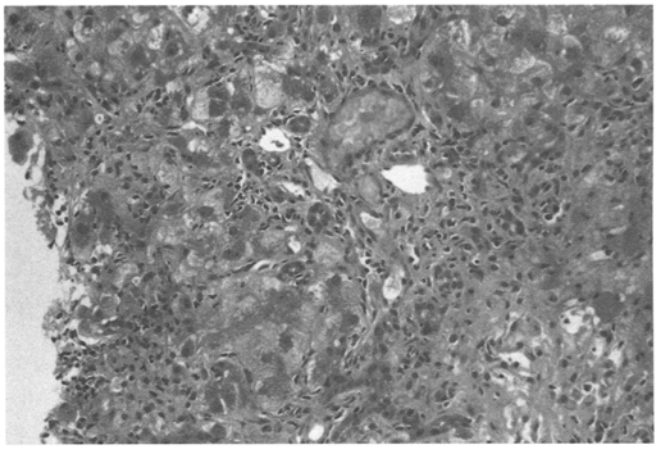


Fig. 55. Fibrosing cholestatic hepatitis secondary to HBV. The patient is over immunosuppressed and the virus is likely directly cytotoxic. HBV was very hard to manage before to the use of lamavudine.

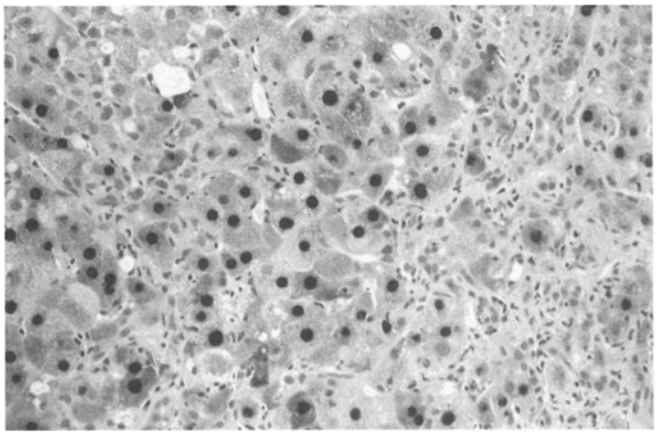


Fig. 56. Immunoperoxidase stain for hepatitis B core antigen from patient seen in Fig. 55. Core antigen is present in almost every cell.

- Hepatitis B:
  - Often recurs, clinically noted 30+ days after transplant
  - Portal chronic inflammatory cell infiltrate usually without bile duct damage, with or without lobular inflammation
  - New nucleoside analogues control the disease
  - If over immunosuppressed, fibrosing cholestatic hepatitis (FCH) may develop:
    - FCH characterized by a paucity of inflammation, cholestasis and marked portal and bridging fibrosis **(Figure 55)**
    - High viral titer—HB core and surface antigen in every hepatocyte **(Figure 56)**

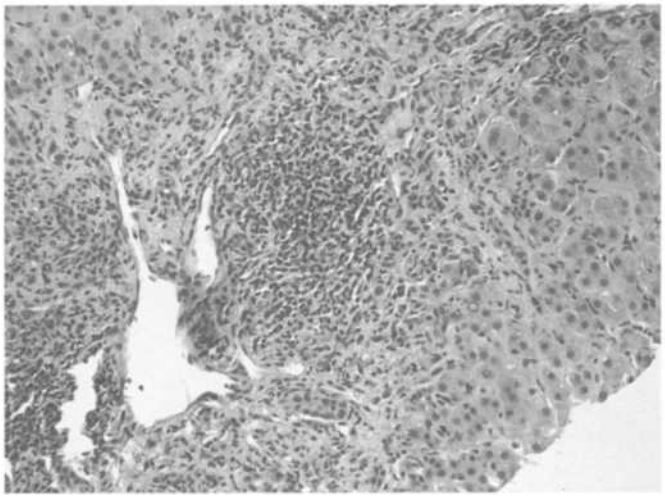


Fig. 57. Classic nodular portal infiltrate of recurrent HCV hepatitis in the allograft. There is slight injury to the interlobular duct, but if only focal, not considered rejection in our institution.

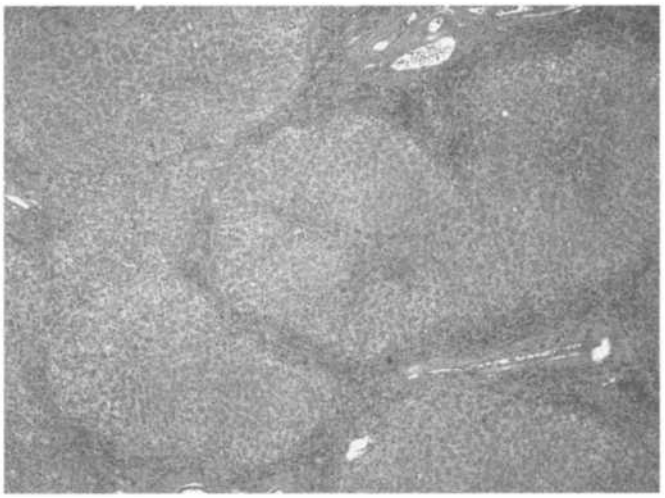


Fig. 58. Allograft liver 8 months after transplantation for HCV showing a well developed cirrhosis with ongoing inflammation and ductular proliferation. All hepatic artery branches were normal and there was no bile duct loss. The findings are typical of fibrosis cholestatic hepatitis secondary to unchecked HCV infection. There is often more inflammation compare to cases associated with HBV. The patient was pulsed with steroids 6 weeks after transplantation for "rejection." The LFTs and viral titers increased and were no longer responsive to interferon or lowered immunosuppression.

- Hepatitis C:
  - Almost always recurs, clinically noted 30+ days after transplant
  - Initially mild lobular inflammation and slight disarray
  - Later, classic nodular portal infiltrates appear, fat usually inconspicuous **(Figure 57)**
  - Occasional bile duct infiltrates are not rejection (Poulsen lesion)
  - Over immunosuppression leads to marked viral proliferation and FCH which may no longer respond to lower immunosuppression and/or interferon **(Figure 58)**
  - May exhibit marked bile ductular proliferation with high viral titers
  - Classic rejection may seen in the first 2 weeks after transplant, after that only florid bile duct damage should be diagnosed as rejection (very dependent on immunosuppression protocol used)
- Autoimmune Hepatitis:
  - Classic appearance
  - May occur *de novo*
- Primary Biliary Cirrhosis:
  - Can not follow AMA levels—often do not return to normal after transplant
  - Histology is the chronic portal infiltrate, bile duct damage plus granuloma (florid duct lesion)
- Primary Sclerosing Cholangitis:
  - Probably does recur
  - No pathomnemonic findings, must exclude rejection, mechanical duct obstruction, vascular stricture, etc.
- Alcoholic Hepatitis and non alcoholic steatohepatitis (NASH):
  - May recur—classic histology
- Neoplasms:
  - Often recur in allograft or other sites (lung, lymph nodes, bone)
  - Hepatoma <4 cm low incidence of recurrence, >4 cm greatly increased incidence of recurrence
  - Behave in an aggressive manner

Drug Effect

- May exhibit increased eosinophilia compared with other processes
- Often a diagnosis of exclusion

Posttransplant Lymphoproliferative Disorder

- Dense portal infiltrates of atypical mononuclear cells are described previously
- Easily found mitotic figures a strong clue
- No bile duct damage
- EBV demonstrated by immunohistochemistry

PANCREAS/ISLET CELL TRANSPLANTATION

Indication for Transplantation

- Treatment of Type I diabetes

Clinical Considerations

- 60% graft survival at 5 years
- Procedure: Cadavaric duodenum with attached pancreas is anastomosed to the recipient urinary bladder; donor splenic artery anastomosed to recipient iliac artery; portal vein to the iliac vein:
  - The graft is ectopic but is easily biopsied via cystoscope
  - Urinary amylase levels can be monitored; increase levels indicate graft dysfunction
- Alternatively the allograft can be sewn to a Roux-limb and mesenteric vessels:
  - Thought to be more physiologic
  - Hard to biopsy
  - Serum lipase, amylase and glucose followed to indicate rejection
- Pure Islet cells may be transplanted under renal capsule or injected into portal vein

Rejection

- No consensus grading system
- Nakhleh grading system (Nakhleh et al., 1992) for pancreatic allograft rejection:
  - Mild—patchy mild or polymorphous infiltrates with possible acinar destruction and endotheliitis
  - Severe—patchy or diffuse polymorphous infiltrates with acinar destruction and vasculitis with or without fibrinoid necrosis
  - Chronic—fibrointimal vascular proliferation or intimal foam cell accumulation
- Drachenberg grading system (Drachenberg et al. 1998) for pancreatic allograft rejection:
  - Grade I:
    - Inflammation of unknown significance
    - Sparse septal mononuclear inflammation no venous endotheliitis or acinar involvement
  - Grade II (Minimal rejection):
    - Septal inflammation with venous endotheliitis
    - Or, in the absence of endotheliitis, three of the following:
      - Mixed septal infiltrates
      - Eosinophils
      - Acinar inflammation in rare foci
      - Ductal inflammation
  - Grade III (Mild rejection):
    - Mixed septal infiltrates with acinar inflammation in multiple foci
    - Eosinophils, endotheliitis and ductal injury may also be seen **(Figures 59–62)**
  - Grade IV (Moderate rejection):
    - Arterial endotheliitis and/or necrotizing arteritis. Grade III features are usually present
  - Grade V (Severe rejection):
    - Extensive acinar inflammatory infiltrates with mutifocal or confluent acinar necrosis; vascular and ductal lesion may also be seen

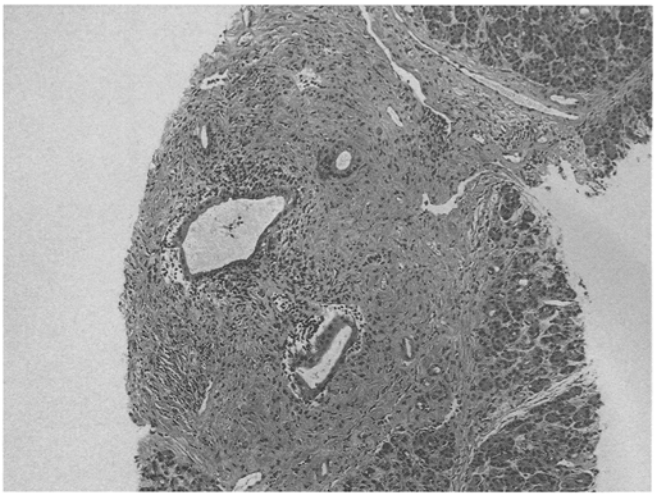


Fig. 59. Pancreas allograft showing septal inflammation and duct damage consistent with mild acute rejection.

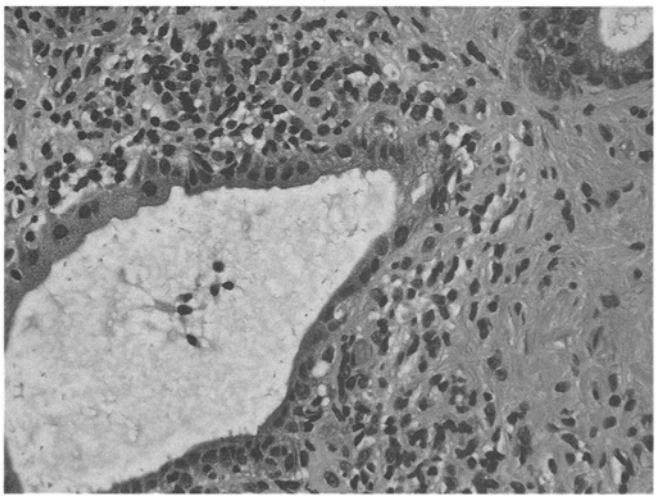


Fig. 60. Higher magnification of Fig. 59 showing the duct injury.

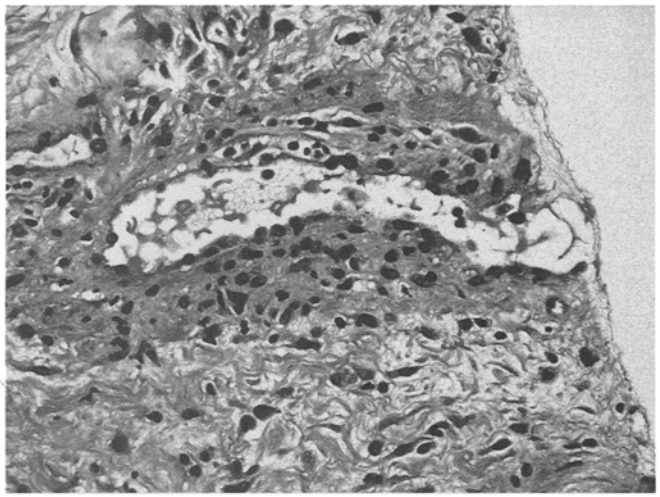


Fig. 61. Focal venulitis in the pancreas allograft from Fig. 59.

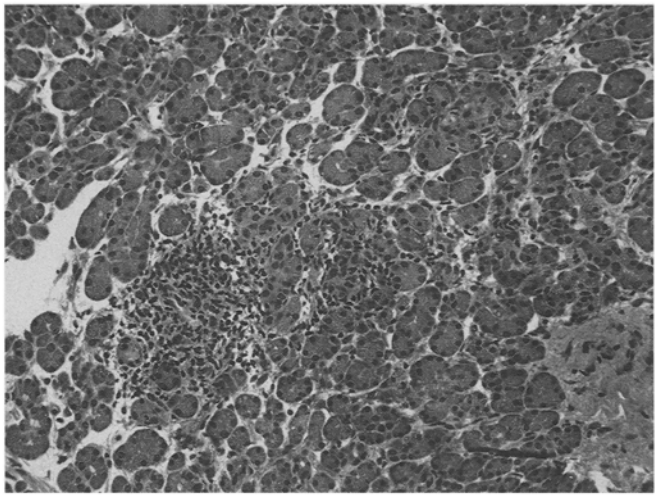


Fig. 62. Pancreas allograft with acinar damage in the pancreas from Fig. 59. Together these are the findings of mild acute cellular rejection after pancreas transplantation.

CMV Infection

- May show many features of rejection
- Careful search for viral inclusions to exclude infection
- Immunohistochemistry or in-situ hybridization may be used to identify MCV markers

Posttransplant Lymphoproliferative Disorder

- Atypical lymphoid infiltrates as previously described

BONE MARROW TRANSPLANTATION (BMT)

Indication for Transplantation

- Bone marrow failure: Usually clinically induced to destroy bone marrow disease such as leukemia

Clinical Considerations

- Active infection—HIV, is a general contra-indications for transplantation
- Living donors are used
- Recipient and organ are HLA and ABO matched,
- Donor marrow may be manipulated, i.e., T-cell depletion
- Stem cells only may be used, including cord blood stem cells

Graft vs Host Disease (GVHD)

- Generally affects the gastro intestinal (GI) tract, skin, and liver although any organ can be affected
- Graft lymphocytes attack host organs as foreign tissue
- May be seen in immunosuppressed patients without a bone marrow transplant after transfusion and rare patients with thymoma or lymphoma
- Occasionally seen in solid organ transplant patients involving nongrafted organs
- Approximately one-half of HLA match BMT patients develop GVHD
- Skin:
  - Acute GVHD presents with erythematous maculopapular rash on the trunk, soles, palms and ears 21–100 days posttransplant
  - Often associated with GI and liver symptoms
  - Histology is the pauci cellular, mononuclear, dermal infiltrate associated with vacuolization and apoptosis of basal keratinocytes
- Grading:
  - Grade 0 = normal skin
  - Grade 1 = basal vacuolar change
  - Grade 2 = dyskeratotic cells in epidermis and follicle
  - Grade 3 = fusion of basal vacuoles to form clefts and microvesicles
  - Grade 4 = separation of epidermis from dermis
- DDx = drug reaction, eosinophils favor drug reaction
- Grading correlates poorly with clinical severity of rash
- Chronic GVHD is seen as early as 80 days post transplant:
  - Lichen planus like skin changes including oral involvement
  - Histology is the lichenoid infiltrates with marked atrophy of epidermis

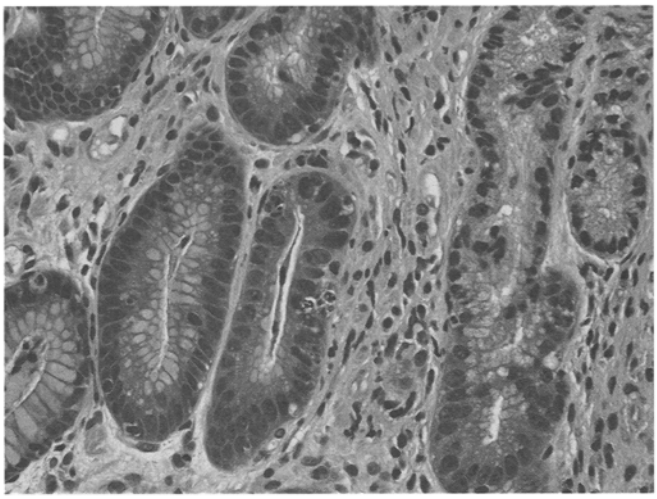


Fig. 63. Grade I graft vs host disease in the stomach. There is patchy crypt apoptosis.

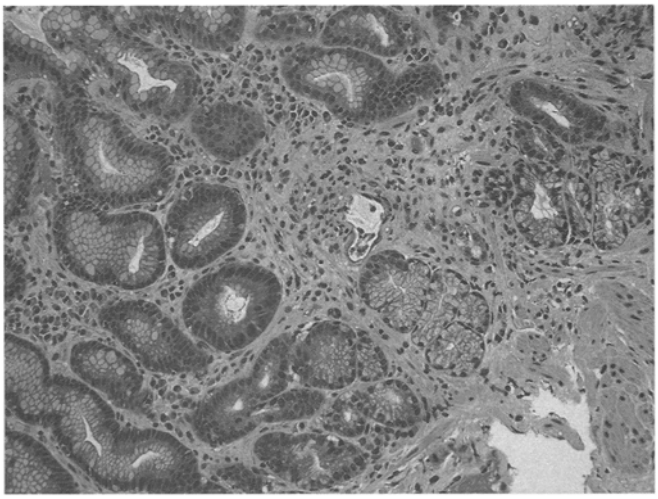


Fig. 64. Grade II graft vs host disease in the stomach. There is crypt apoptosis and focal crypt dropout.

- Gut:
  - Usually presents with crampy abdominal pain, nausea, vomiting, and watery diarrhea
  - Histology is the pauci-cellular infiltrate associated with apoptosis at the base of crypts-stomach through rectum
  - Esophagus shows changes similar to skin
  - Grading (Snover DC. Am J Surg Pathol 1990;14:101-108):
    - Grade 1 = apoptosis but no crypt loss **(Figure 63)**
    - Grade 2 = individual missing crypts **(Figure 64)**
    - Grade 3 = more than 2 contiguous missing crypts
    - Grade 4 = complete loss of mucosa **(Figure 65)**
  - DDx = CMV colitis – look carefully for viral inclusions
- Liver:
  - Usually presents 30+ days after the transplant, often with involvement of skin and GI tract

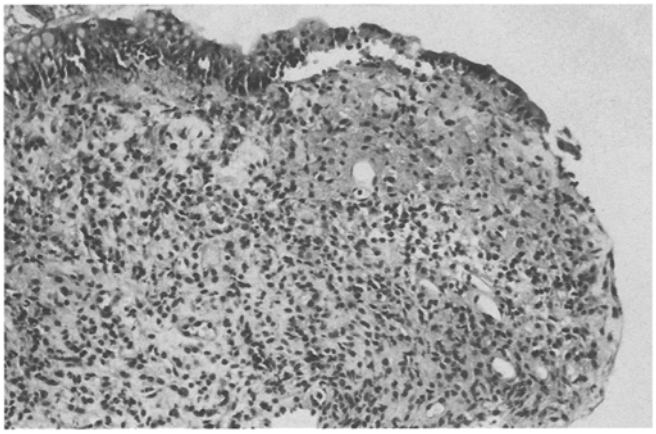


Fig. 65. A colon biopsy from a patient with severe diarrhea after bone marrow transplantation. The crypts are completely destroyed showing only a focus of re-epithelization. There was ongoing crypt apoptosis in other sites—Grade IV graft vs host disease in the colon.

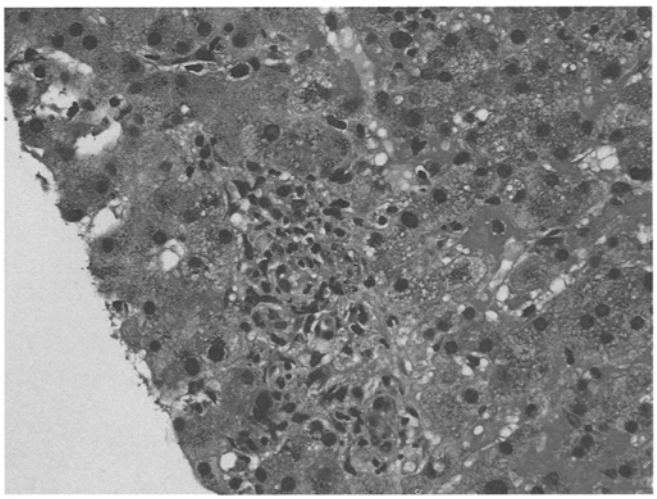


Fig. 66. Liver biopsy from a liver transplant patient showing a scant portal infiltrate but severe injury to the bile duct epithelium. There is no grading system for graft vs host disease changes in the liver. Note the surrounding increase in hepatocyte iron storage.

  - May be seen without skin or gut disease
  - Presents with increasing bilirubin progressing to jaundice and elevations of the canilicular enzymes (alkaline phosphatase and GGT)
  - Histology is the scant mononuclear infiltrate associated with interlobular bile duct injury (nuclear irregularity, hyperchromasia, cytoplasmic vacuoles) **(Figure 66)**
    - The density of the portal infiltrate is dependent on the immunosuppression regimen used—denser infiltrates can be seen with lowered immunosuppression
    - Endotheliitis can be seen but uncommon

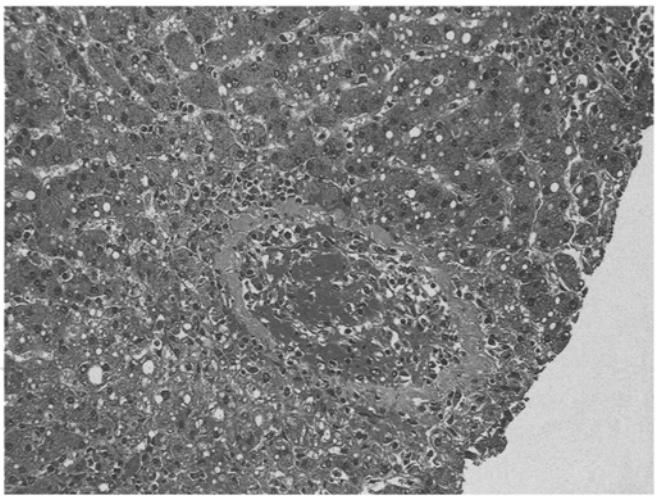


Fig. 67. Liver biopsy from a BMT patient showed central hepatic vein occluded with a granulation tissue like proliferation and sinusoidal congestion consistent with veno-occlusive disease.

- No established grading system
- If untreated leads to duct paucity (chronic liver GVHD), fibrosis and cholestasis:
  - Transplant arteriopathy is NOT a feature of chronic GVHD of the liver
- Liver usually also shows hemosiderosis (not a feature of GVHD)
- DDX = CMV infection (look carefully for inclusions):
  - Chronic viral hepatitis (B,C):
    - Careful management of immunosuppression required with concomitant viral hepatitis and BMT
  - Drug induced liver disease
- Veno-occlusive disease (VOD):
  - Secondary to cytoreductive chemotherapy toxicity
  - Presents with hepatomegaly, sudden weight gain and jaundice
  - Serum bilirubin >10 mg/dL often fatal
  - Histology is the fibrinoid occlusion of central veins associated with congestion **(Figure 67)**
  - Best seen with trichrome stain
  - May or may not see hepatocyte necrosis
  - May be patchy
  - DDX is the heart failure, ischemia, herpetic viral hepatitis
  - Recurrent leukemia can be seen in the sinuses
- Lung:
  - Pulmonary involvement is not a common acute presentation of GVHD
  - Usually presents with increasing shortness of breath
  - Classic histology = bronchiolitis obliterans (*see* **Figure 68**)

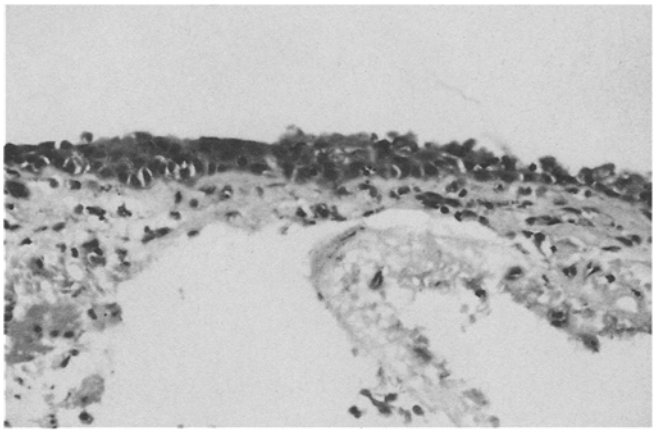


Fig. 68. Bronchial biopsy from a BMT patient showing atrophy, squamoid metaplasia and apoptosis consistent with graft vs host disease.

Table 3. Pulmonary Manifestations of Graft vs Host Disease (Yousem et al., 1995)

Pattern of injury	*Onset*	*Potentially Reversibility*
Diffuse alveolar Damage	Early	Yes
Cryptogenic organizing pneumonia (BOOP)	Early	Yes
Lymphocytic bronchitis/ bronchiolitis (Fig. 68)	Early	Yes
Cellular interstitial pneumonia	Early	Yes
Bronchiolitis with interstitial fibrosis	Late	No
Bronchiolitis obliterans	Late	No

  - Recently broadened findings of Pulmonary GVHD **(Table 3)**
  - When a BMT patient has a lung biopsy with pattern of injury noted in the table, we report out the pattern with a note that it has been associated with GVHD

Posttransplant Lymphoproliferative Disorder

- Risk factors: T-cell depletion, HLA mismatching, specific antilymphocyte therapy, primary immunodeficiency as an indication for transplantation
- Median onset 70–90 days posttransplant
- May present as adenopathy, mass lesion, fever, unexplained pain or weight loss
- Histology, as previously described with a tendency to the monomorphic variant being more common
- More fulminate disease with up to 90% mortality, improved recently with advent of donor lymphocyte infusion therapy

SMALL BOWEL TRANSPLANTATION

Indication for Transplantation

- Small bowel failure (SBF) results when there is too little small bowel to absorb nutrition—transplantation may be an alternative to total parenteral nutrition (TPN)
- Adults require a minimum of 100 cm of small bowel with no colon; 60 cm with intact colon
- Children require at least 20% functioning small bowel
- Causes of SBF in children: intestinal atresia, necrotizing enterocolitis, gastroschisis, volvulus
- Children with small bowel failure often develop end-stage liver disease secondary to TPN
- Causes of SBF in adults: ischemia, trauma, Crohn's disease
- Graft survival 50–60% at 2 years

Clinical Considerations

- Two clinical procedures:
  - Small bowel combined with liver (head of pancreas and duodenum are included) leaves liver hilum undisturbed
  - Isolated small bowel (ileum and jejunum)—arterial inflow from recipient infra renal aorta, venous outflow to the inferior cava or splanchnic veins

Preservation Injury

- Epithelial denudation with regenerative changes ± superficial inflammation (often acute)

Rejection

- No good clinical markers—often followed with protocol biopsies
- No consensus criteria for diagnosis of rejection
- Pittsburgh histologic criteria (Wu et al., 2003) for grading of small bowel allograft rejection
- Indeterminate—Minimal localized infiltrate, minimal crypt injury, or apoptosis (<6 apoptotic bodies per 10 crypts) , minimal architectural changes, no ulceration
- Mild—Mild localized infiltrate, mild crypt injury or apoptosis (>6 apoptotic bodies per 10 crypts), mild architectural changes, no ulceration **(Figures 69,70)**
- Moderate—Widely dispersed infiltrate, diffuse crypt injury and increased sometime confluent apoptosis, more prominent architectural changes, possible mild-to moderate intimal arteritis, no ulceration
- Severe—Features of moderate rejection plus ulceration; possible severe or transmural arteritis

Chronic rejection

- Obliterative arteriopathy ± mucosal injury

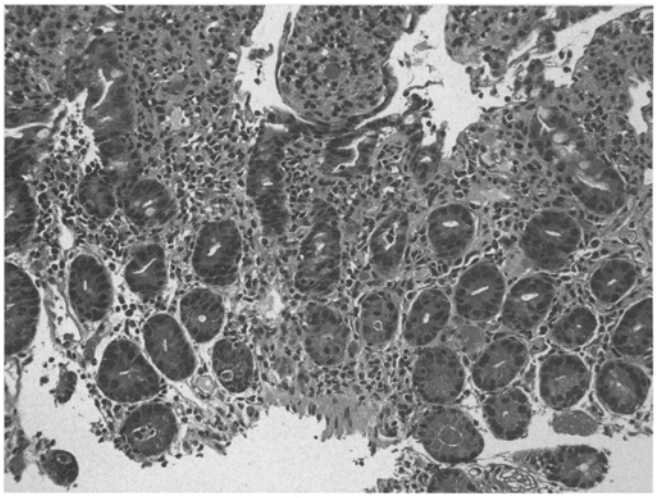


Fig. 69. Small bowel allograft showing apoptosis but no crypt loss consistent with Grade I rejection.

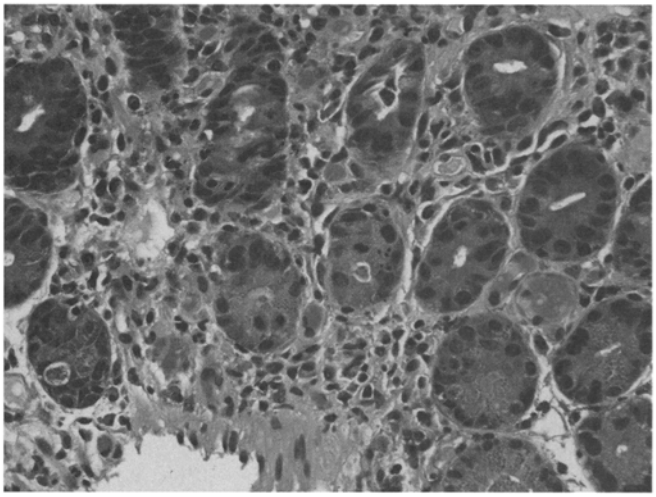


Fig. 70. Small bowel allograft showing crypt apoptosis consistent with mild acute cellular rejection.

CMV infection

- May show many features of rejection
- Careful search for viral inclusions to exclude infection
- Immunohistochemistry or in-situ hybridization may be used to identify MCV markers

Posttransplant Lymphoproliferative Disorder

- Atypical lymphoid infiltrate as previously described

CORNEA TRANSPLANTATION

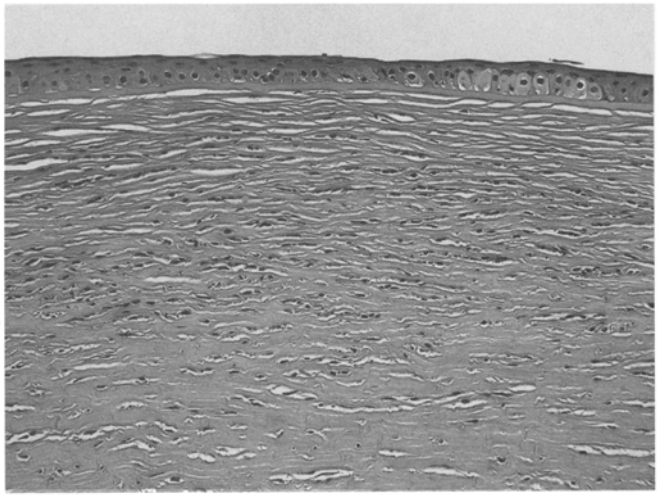


Fig. 71. Rejected corneal allograft showing marked edema, vascularization and a mononuclear infiltrate.

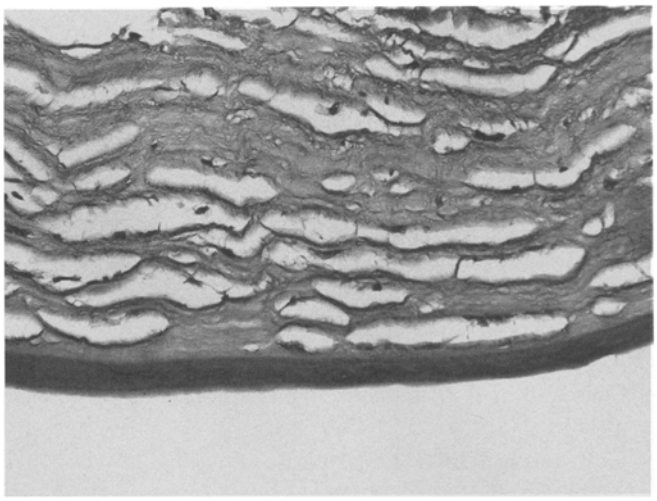


Fig. 72. PAS stain highlights Descemets membrane in this rejected cornea allograft. Note the marked edema and loss of endothelial cells.

Indication for Transplantation

- Indicated for blindness secondary to corneal edema—aphakic or pseudoaphakic bullous keratopathy, Fuch's dystrophy and keratoconus

Clinical Considerations

- Penetrating keratoplasty used to remove old cornea
- Not typically treated with immunosuppression—anterior chamber = privileged site
- 10–20% develop rejection over 10 years, good response to topical immunosuppression
- Risk factors for rejection: Young recipient, concurrent intraocular inflammation, Glaucoma, previous surgery, anterior synechiae
- Most common cause of graft failure is rejection—diagnosed and managed clinically
- Failed grafts show peripheral scar with or without vascularization, marked edema, endothelial loss, mononuclear infiltrates (**Figures 71, 72**)

OTHER TRANSPLANTS

Hand

- To restore limb function
- Complications of heavy immunosuppression
- Rejection similar in appearance to GVHD in the skin

Xenotransplantation

- Experimental work to develop animal organs for transplantation into humans, i.e., baby Jessica and the baboon heart
- Would alleviate organ shortage
- Problems with rejection control and possible trans-species viral transmission

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7

Cytopathology

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CONTENTS

PART A: GYNECOLOGIC CYTOLOGY

I. The 2001 Bethesda System 7–6
Specimen Type 7-6
General Categorization (Optional) 7-6
Descriptive Interpretations/Results 7-6
Non-Neoplastic 7-6
Epithelial Cell Abnormalities 7-6

II. Specimen Adequacy Terminology/ Reporting 7-6
Unsatisfactory Specimen 7-7
Endocervical/Transformation Zone Component (TZ) 7-7

III. Infections 7-7
Trichomonas vaginalis 7-7
Candida albicans 7-7
Bacterial Vaginosis 7-7
Actinomyces 7-7
Herpes simplex virus (HSV) 7-7
Doderlein bacilli (Lactobacillus acidophilus) 7-8
Leptothrix 7-8
Molluscum contagiosum (Pox Virus) 7-8
Enterobias vermicularis (Pinworm) 7-8
Entamoeba histolytica 7-8
Contaminants 7-8

IV. Reactive Changes 7-8
Typical Repair 7-8
Radiation Effect 7-9
IUD-Associated Change 7-9
Other Reactive Changes 7-9
Hyperkeratosis (HK) 7-9
Parakeratosis (PK) 7-9
Chronic Follicular (Lymphocytic) Cervicitis 7-9

V. Pregnancy-Related Changes 7-9
Folic Acid Deficiency 7-9
Navicular Cells 7-9
Decidual Cells 7-9
Syncytiotrophoblasts 7-10

VI. Squamous Cell Abnormalities 7-10
Atypical Squamous Cells (ASC) 7-10
Atypical Squamous Cells of Undetermined Significance (ASC-US) 7-10
Atypical Squamous Cells; Cannot exclude HSIL (ASC-H) 7-10
Squamous Intraepithelial Lesion (SIL) 7-11
Keratinizing Dysplasia 7-12
Cervical Squamous Cell Carcinoma (SCC) 7-12

VII. Normal and Reactive Endocervical Cytology 7-13
Normal Endocervical Cells 7-13
Endocervical Cells, Reactive Changes 7-13
Tubal Metaplasia 7-13
Microglandular Hyperplasia 7-13
Arias-Stella Reaction 7-13
Glandular Cell Abnormalities 7-13
Atypical Endocervical Cells 7-14
Atypical Endocervical Cells, Favor Neoplastic 7-14

Endocervical Adenocarcinoma *In Situ* (AIS) 7-14
HSIL with Endocervical Involvement.... 7-14
Endocervical Adenocarcinoma 7–15

VIII. Endometrial Cytology 7-15
Cytologically Normal Endometrial Cells 7-16
Atypical Endometrial Cells 7-16
Endometrial Adenocarcinoma 7-16
Papillary Serous Adenocarcinoma 7-17
Extra-Uterine Metastatic Adenocarcinoma.... 7-17
Malignant Mixed Müllerian Tumor 7-17
Lymphoma/Leukemia Cervix 7-17

PART B: NON-GYNECOLOGIC CYTOLOGY

I. Overview 7-36
Evaluation of Cytologic Smear 7-36
Key Cellular Features 7-36
Cellular Patterns 7-37

II. Respiratory Cytology 7-38
Overview 7-38
Normal Cellular Components of Lung Cytology 7-38
Types of Cellular Specimens 7-38
Spectrum of Cytologic Changes in Various Preparations 7-38
Benign Lesions 7-39
Pulmonary Infarct 7-39
Pneumonia 7-39
Creola Bodies 7-39
Cigarette and Habitual Marijuana Smoking 7-39
Radiation and Chemotherapy-Induced Atypia 7-39
Amiodarone (Antiarrhythmic Drug)-Induced Changes 7-39
Hemosiderin-Laden Macrophages 7-39
Lipid-Laden Macrophages in Bronchial Lavage 7-40
Corpora Amylacea 7-40
Sarcoidosis 7-40
Ferruginous Bodies 7-40
Ciliocytophthoria 7-40
Asthma 7-40
Infectious Processes 7-40
Cytologic Features of Viral Infection 7-40
Aspergillosis 7-40
Cryptococcosis 7-40
Histoplasmosis 7-40
Phycomycosis/Zygomycetes (Mucor, Rhizopus, etc.) 7-40
Coccidiodomycosis 7-40
Blastomycosis 7-40
Candidiasis 7-41
Tuberculosis 7-41
Pneumocystitis carinii (PCP) 7-41
Neoplastic Lesions 7-41
Keratinizing Squamous Cell Carcinoma (SCC) 7-41
Non-Keratinizing Squamous Cell Carcinoma 7-41
Adenocarcinoma 7-41
Large Cell Undifferentiated Carcinoma 7-43
Pulmonary Neuroendocrine Tumors 7-43
Metastatic Carcinoma 7-44

III. Salivary Gland and Head/Neck Cytology 7-44
Statistics 7-44
Salivary Glands 7-44
Normal Findings 7-44
Non-Neoplastic Lesions 7-45
Sialadenosis 7-45
Sialadenitis 7-45
Benign Neoplastic Lesions 7-45
Pleomorphic Adenoma (Benign Mixed Tumor) 7-45
Warthin's Tumor (Papillary Cystadenoma Lymphomatosum) 7-45
Malignant Neoplasms 7-46
Mucoepidermoid Carcinoma 7-46
Adenoid Cystic Carcinoma 7-46
Acinic Cell Carcinoma 7-46
Polymorphous Low Grade Adenocarcinoma 7-46
Salivary Duct Carcinoma 7-46
Head and Neck 7-46
Non-Neoplastic Lesions 7-46
Neoplastic Lesions 7-47

IV. Thyroid 7-47
Overview 7-47
Benign Lesions 7-47
Thyroid Cysts 7-47
Thyroiditis 7-48
Black Thyroid Nodule 7-48
Nodular Goiter and Colloid Nodule 7-48
Toxic Diffuse Hyperplasia (Graves' Disease) 7-49
Neoplastic Lesions 7-49
Follicular Neoplasm Favor Benign 7-49
Hürthle Cell Neoplasm 7-49
Papillary Carcinoma 7-49

Follicular Carcinoma 7-50
Medullary Carcinoma 7-50
Anaplastic Carcinoma 7-50
Metastatic Carcinoma 7-50

V. Breast 7-50
Overview 7-50
Benign Lesions 7-51
Fat Necrosis 7-51
Subareolar Abscesses 7-51
Lactational Changes 7-51
Fibrocystic Changes 7-51
Fibroadenoma 7-51
Gynecomastia 7-52
Intraductal Papilloma 7-52
Ductal Carcinoma *In Situ* and Invasive Carcinoma 7-52
Ductal Carcinoma *In Situ* (DCIS) 7-52
Lobular Carcinoma *In Situ* 7-52
Intracystic Papillary Carcinoma 7-52
Invasive Ductal Carcinoma 7-53
Lobular Carcinoma 7-53
Mucinous (Colloid) Carcinoma 7-53
Medullary Carcinoma 7-53
Tubular Carcinoma 7-53
Apocrine Carcinoma 7-54
Phyllodes Tumor 7-54
Metaplastic Carcinoma 7-54

VI. Lymph Node 7-54
Reactive Hyperplasia 7-54
Acute Lymphadenitis 7-54
Necrotizing Granulomatous Lymphadenitis 7-54
Cat Scratch Disease 7-54
Non-Necrotizing Granulomatous Lymphadenitis 7-55
Infectious Mononucleosis 7-55
Malignant Lymphoma 7-55
Common Variants of Lymphoma 7-55

VII. Skin, Soft Tissue, Bone, and Cartilage 7-56
Skin 7-56
Pilomatrixoma (Calcifying Epithelioma of Malherbe) 7-56
Squamous Cell Carcinoma 7-56
Basal Cell Carcinoma 7-56
Malignant Melanoma 7-56
Merkel Cell Carcinoma 7-56
Soft Tissue 7-57
Adipose Tissue Tumors 7-57
Fibrous and Fibrohistiocytic Lesions 7-57
Neural Tumors 7-58
Miscellaneous 7-59
Bone and Cartilage 7-59
Chondroma 7-59
Chondroblastoma 7-59
Giant Cell Tumor 7-59
Chondrosarcoma 7-60
Osteosarcoma 7-60
Ewing's Sarcoma and PNET 7-60
Langerhans' Cell Histiocytosis (Eosinophilic Granuloma) 7-60

VIII. Esophagus, Stomach, Colon, Liver, and Pancreas 7-60
Esophagus 7-60
Normal Components 7-60
Infection 7-60
Reflux Esophagitis 7-60
Radiation Change 7-60
Barrett's Esophagus 7-61
Dysplasia 7-61
Squamous Cell Carcinoma 7-61
Adenocarcinoma 7-61
Stomach 7-61
Normal Cytology 7-61
Gastric Ulcer 7-61
Chronic Gastritis 7-61
Hyperplastic or Regenerative Polyp 7-61
Adenocarcinoma 7-61
Lymphoma 7-61
Colon 7-61
Normal Cytology 7-61
Adenomatous Polyp 7-62
Adenocarcinoma 7-62
Liver 7-62
Normal Components 7-62
Benign Lesions 7-62
Malignant Lesions 7-63
Pancreas 7-64
Normal Components 7-64
Acute Pancreatitis 7-64
Chronic Pancreatitis 7-64
Pseudocyst 7-64
Tumors 7-64

IX. Ovary 7-65
Overview 7-65
Selected Lesions 7-65
Follicular Cyst 7-65
Corpus Luteum Cyst 7-65
Endometriotic Cyst 7-66
Mature Cystic Teratoma 7-66
Cystic Granulosa Cell Tumor 7-66
Serous Cystadenoma 7-66

Mucinous Cystadenoma 7-66
Papillary Serous Cystadenocarcinoma 7-66
Mucinous Cystadenocarcinoma 7-66
Endometrioid Carcinoma 7-66
Clear Cell Carcinoma 7-66
Granulosa Cell Tumor 7-66
Brenner's Tumor 7-66
Fibrothecoma 7-66
Carcinoid 7-67
Dysgerminoma 7-67

X. Kidney 7-67
Simple Cyst 7-67
Oncocytoma 7-67
Angiomyolipoma 7-67
Clear Cell Renal Cell Carcinoma 7-67
Papillary Renal Cell Carcinoma 7-68
Chromophobe Renal Cell Carcinoma 7-68
Collecting Duct Carcinoma 7-68
Wilms' Tumor 7-68

XI. Urinary Bladder 7-68
Overview 7-68
Benign Lesions and Mimics of Malignancy 7-69
Reactive Urothelial Cells 7-69
Instrument Artifact and Lithiasis 7-69
Decoy Cells 7-69
Ileal Conduit 7-69
Treatment Effect 7-69
Urothelial Papilloma 7-70
Malignant Lesions 7-70
General Features 7-70
Urothelial Carcinoma *In Situ* (CIS) 7-70
Urothelial Carcinoma 7-70
Urothelial Adenocarcinoma 7-71

XII. Pleural and Peritoneal Fluid 7-71
Reactive Mesothelial Cells 7-71
Rheumatoid Pleuritis/Pericarditis 7-72
Tuberculosis 7-72
Mesothelioma 7-72
Metastatic Adenocarcinoma 7-72

XIII. Cerebrospinal Fluid (CSF) and Central Nervous System 7-73
Specimen Preparation of CSF 7-73
Normal Components of CSF 7-73
Ependymal Cells 7-73
Choroid-Plexus Cells 7-73
Pia-arachnoid (Leptomeningeal) Cells 7-73
Brain Parenchyma 7-73
Primitive (Blast-like) Cells of Neonates 7-73
Inflammatory Conditions 7-73
Mollaret Meningitis 7-74
Acute Lymphocytic Leukemia/Malignant Lymphoma 7-74
Astrocytoma 7-74
Ependymomas 7-74
Choroid Plexus Papilloma 7-74
Craniopharyngioma 7-74
Germinoma 7-74
Meningioma 7-75
Retinoblastoma 7-75
Medulloblastoma 7-75
Metastatic Carcinoma 7-75

XIV. Suggested Reading 7-75

Part A

Gynecologic Cytology

THE 2001 BETHESDA SYSTEM

Specimen Type

- Conventional smear, liquid based preparation, or other

Adequacy

- Satisfactory for evaluation (describe presence or absence of endocervical/transformation zone component and any other quality limiting factors)
- Unsatisfactory for evaluation (specify reason):
  - Specimen rejected (specify reason)
  - Specimen processed and examined, but unsatisfactory for evaluation of epithelial abnormality because of (specify reason)

General Categorization (optional)

- Negative for Intraepithelial Lesion or Malignancy
- Epithelial Cell Abnormality: see interpretation/result (specify "squamous" or "glandular" as appropriate)
- Other: see interpretation/result (e.g. endometrial cells in a woman >40 years of age)

Descriptive Interpretations/Results

Non-Neoplastic

- Negative for intraepithelial lesion or malignancy (when there is no cellular evidence of neoplasia, state this in the General Categorization above and/or in the Interpretation/Result section of the report, whether or not there are organisms or other non-neoplastic findings)

Organisms

- *Trichomonas vaginalis*
- Fungal organisms morphologically consistent with *Candida spp*
- Shift in vaginal flora suggestive of bacterial vaginosis
- Bacteria morphologically consistent with *Actinomyces spp*
- Cellular changes associated with Herpes simplex virus

Other Non-Neoplastic Findings (Optional to report; not inclusive)

- Reactive cellular changes associated with:
  - Inflammation (includes typical repair)
  - Radiation
  - Intrauterine contraceptive device (IUD)
- Benign-appearing glandular cells status post hysterectomy
- Atrophy
- Endometrial cells (in a woman >40 years of age)

Epithelial Cell Abnormalities

Squamous Cell

- Atypical squamous cells:
  - Of undetermined significance (ASC-US)
  - Cannot exclude HSIL (ASC-H)
- Low grade squamous intraepithelial lesion (LSIL):
  - Encompassing: HPV/mild dysplasia/CIN1
- High grade squamous intraepithelial lesion (HSIL):
  - Encompassing: moderate and severe dysplasia, CIS/CIN2 and CIN3
  - With features suspicious for invasion (if invasion is suspected)
- Squamous cell carcinoma

Glandular Cell

- Atypical:
  - Endocervical cells (NOS or specify in comments)
  - Endometrial cells (NOS or specify in comments)
  - Glandular cells (NOS or specify in comments)
- Atypical glandular/endocervical cells, favor neoplastic
- Endocervical adenocarcinoma *in situ*
- Adenocarcinoma:
  - Endocervical
  - Endometrial
  - Extrauterine
  - Not otherwise specified (NOS)

Other Malignant Neoplasms: (specify)

SPECIMEN ADEQUACY TERMINOLOGY/REPORTING

Adequate Pap Test

- An adequate test has well visualized and well-preserved squamous cells with an estimated minimum of 8–13,000 cells (conventional Pap) and >5,000 (liquid based Pap)—This minimum cell range should be an estimate aided by published diagrams of representations of microscopic fields with different parameters of microscope objectives/oculars/field number and number of cells-10 endocervical/squamous metaplastic cells (Transformation zone components) per smear and no other limiting factors

- Describe presence or absence of endocervical/transformation component and any other quality indicators immediately after Satisfactory and Unsatisfactory terms. The list of quality indicators might include: absence of pertinent clinical information (such as LMP, age, etc), air drying, or poor preservation of cellular material, excessive blood/mucous/exudates, thick cell groups, scant cellularity, and excessive cytolysis
- Any specimen with abnormal cells is by definition satisfactory for evaluation

Unsatisfactory specimen

- Clarify laboratory's role in processing/evaluation of specimen in the report
- Suggested wording to clarify report:
  - Rejected Pap:
    - Specimen rejected (not processed) because (specimen not labeled, slide broken, etc.)
  - Fully evaluated unsatisfactory Pap:
    - Specimen processed and examined, but is unsatisfactory for evaluation of epithelial abnormality because of obscuring-blood, inflammation (>75% of the cells are obscured), etc
  - Additional comments or recommendations are suggested, as appropriate: An excessively bloody or inflamed Pap test may mask the screener's ability to detect an underlying abnormality and a repeat examination/evaluation is suggested

Endocervical/Transformation Zone Component (TZ)

- At least 10 well-preserved endocervical and/or squamous metaplastic cells should be observed to report that a transformation zone component is present. In a negative Pap test, its absence does not necessarily mean that the patient requires early repeat testing especially if the patient has a negative Pap history. However, attention to regular screening is suggested. If there is a history of abnormal Pap, incomplete visualization of cervix, immunocompromised status, or poor screening history, repeat in 6 months is suggested

INFECTIONS

Organisms

Trichomonas vaginalis

- 25% of women are carriers
- Often coexist with leptothrix and other coccoid bacteria
- Small, pear-shaped, faintly stained organism with small, oval, eccentric hyperchromatic nuclei and eosinophilic granules
- Cannonball cell with agglomeration of neutrophils onto squamous cells
- Small, perinuclear halo, cytoplasmic vacuolization, and polychromasia "moth eaten" squamous cells
- Granular debris and inflammation in background

Candida albicans

- 10% of females are carriers
- Incidence increased with pregnancy, oral contraceptives use, and diabetes
- Yeast form and pseudohyphae in inflammatory background
- Torulopsis glabrata: lack pseudohyphae

Bacterial Vaginosis

- Occurs in 10% to 30% of general population
  - Patients have exponentially more anaerobes per ml of vaginal fluid than normal
- Etiology includes *Gardnerella vaginalis,* anaerobic lactobacilli and *Bacteroid* and *Mobiluncus* species
- *Gardnerella vaginalis* (*haemophilus-corynebacterium-vaginalis*):
  - May be cultured in 30% to 50% of asymptomatic women
  - Absence of lactobacilli
  - Whiff test on KOH preparation is positive
  - Minute rod-shaped gram variable bacillus
  - Clue cell:
    - Epithelial cell covered by adherent, small, uniformly spaced bacilli
    - Neither specific nor sufficient for the diagnosis of bacterial vaginosis

Actinomyces

- Gram positive filamentous organisms
- Associated with the use of IUD and vaginal pessaries
- Isolated aggregates of basophilic filamentous structures with radiating pattern
- Dirty, necrotic, inflammatory background
- Sulfur granules

Herpes Simplex Virus (HSV)

- 80% develop infection following exposure; 60% recurrence rate

- Multinucleation (90%), ground glass nucleus (90%), and intranuclear inclusion (20%); multinucleation, nuclear molding, and chromatin margination
- Cannot cytologically distinguish between type I and type II (genital) herpes, or between primary or secondary infection

Chlamydia trachomatis

- The intracytoplasmic vacuoles containing eosinophilic dots (elementary particles) are not specific for C. trachomatis, as they probably represent mucinous or other vacuoles
- the Pap test has no role in the diagnosis of this infection

Doderlein bacilli (Lactobacillus acidophilus)

- Heterogeneous group of bacilli
- Function to maintain an acid vaginal pH (3.5–4.5)
- Only species capable of causing cytolysis of intermediate squamous cell by hydrolyzing intracyto-plasmic glycogen
- Results in cytolysis of intermediate squamous cells

Leptothrix

- Filamentous rods with or without branching
- Often associated with the presence of another organism (trichomonas, Candida)

Molluscum contagiosum (Pox Virus)

- Large cells with cosinophilic intracytoplasmic inclusions and pyknotic degenerative nuclei

Enterobias vermicularis (Pinworm)

- Ovoid-shaped eggs with double-walled shell and flattened on one side

Entamoeba histolytica

- Large trophozoites with large nuclei and dot-like central karyosome
- Vacuolated cytoplasm containing ingested RBC

Contaminants

- Alteneria:
  - Short yellow brown conidiospores and transversely and longitudinally septate conidia (snow shoe-like)
- Pollen
- Vegetable cells:
  - Dense cell walls and structureless nuclei
  - May be observed in patients with rectovaginal fistulas along with goblet cells, inflammation, and necrotic debris
- Graphite-pencil markings
- Lubricant jelly:
  - Not recommended for gynecologic examination prior to Pap smear
- Cotton, cardboard, and tampon fibers
- Trichome: "Octopus-like" structure derived from leaves of arrowhead tree
- Cockleburs:
  - Associated with IUD, oral contraceptive use, and second half of pregnancy
  - Related to cellular degeneration
  - Composed of nonimmune glycoprotein, lipid, and calcium
  - Cytologic findings:
    - Golden refractile crystalline rays surrounded by histiocytes
- Hematoidin crystals:
  - Indicative of previous hemorrhage, but do not contain iron
  - Composed of bile-like pigment formed from hypoxic tissue
  - Cytologic findings:
    - Finer crystalline rays with different shape
- Talc particles
- Fern:
  - Arborizing, palm leaves-like pattern of cervical mucus that occurs at ovulation

REACTIVE CHANGES

Typical Repair

- Cells in cohesive sheets with rare or absence of isolated cells
- Streaming of cells and pseudopodia
- Nuclear enlargement with fine chromatin and smooth nuclear contour
- Prominent nucleoli, often multiple and regular
- Delicate, cyanophilic cytoplasm without differentiation; streaming cytoplasm
- No tumor diathesis

Differential Diagnosis

- Squamous cell carcinoma:
  - Discohesive abnormal cells
  - Irregular chromatin distribution

- Multiple irregular nucleoli
- Tumor diathesis

♦ Acantholytic cells in pemphigus vulgaris:
- Usually observed in vaginal smear
- Increased number of single isolated cells (tombstone cells-Tzank cells)
- Correlate with clinical history

Radiation Effect

♦ Cellular enlargement (macrocytosis), nuclear enlargement, normal N/C ratio
♦ Nuclear and cytoplasmic vacuoles, large perinuclear halos
♦ Finely granular or degenerative "smudged" chromatin; karyorrhexis and karyopyknosis
♦ Binucleation and multinucleation; micro- and macro-nucleoli
♦ Large bizarre cells; polychromasia
♦ Peripheral cytoplasmic projections (pseudopodia) and cytophagocytosis

IUD-Associated Change

♦ Small clusters of hypersecretory endocervical cells
♦ Abundant cytoplasm with distinct cell borders
♦ Large cytoplasmic vacuoles (bubble-gum cytoplasm)
♦ Large, uniform nuclei that may contain prominent nucleoli
♦ Inflammatory/reparative squamous changes
♦ Clean or inflammatory background
♦ ± actinomycotic colonies

Differential Diagnosis

♦ Adenocarcinoma of endometrium:
- Occurs in older patients (postmenopausal)
- Generally many abnormal cells present with tumor diathesis
- Irregular chromatin pattern and prominent nucleoli

Other Reactive Changes

Hyperkeratosis (HK)

Etiology

♦ Non-specific chronic cervicitis
♦ Uterine prolapse
♦ Reaction to previous biopsy, cryosurgery, or instrumentation
♦ In utero diethylstilbestrol (DES) exposure
♦ Pessary use
♦ SIL (approximately 10%); HK may represent a reparative surface reaction overlying SIL, usually LSIL or a reaction to persistent disease in patients with prior biopsy/cytology-proven SIL
♦ The presence of anucleated squamous cells during pregnancy suggests ruptured fetal membrane

Cytologic Features

♦ Cluster or group of anucleated and granular superficial polygonal squamous cells
♦ Rare, isolated anucleated cells probably represent contaminants

Parakeratosis (PK)

♦ PK represents a reactive surface process similar to HK
♦ Persistence of PK without a known etiology may warrant further investigation to exclude an associated squamous intraepithelial lesion

Cytologic Features

♦ Isolated or loose sheets of miniature round to oval superficial cells with dense orangeophilic cytoplasm
♦ Small uniform pyknotic nuclei

Chronic Follicular (Lymphocytic) Cervicitis

♦ Polymorphous population of mature lymphocytes, plasma cells, and histiocytes
♦ No clinical significance; reporting is optional

PREGNANCY-RELATED CHANGES

Folic acid deficiency

♦ Cytologic finding similar to those of early radiation effect
♦ Nuclear and cellular enlargement; nuclear enfolding; binucleation and multinucleation
♦ Hypochromatic nuclei with smooth nuclear contour
♦ Cytoplasmic vacuolization and cytoplasmic polychromasia

Navicular Cells

♦ Observed with pregnancy
♦ Boat-like intermediate cells with ecto-endoplasmic differentiation and glycogen
♦ Seen in late menstrual cycle, pregnancy, and high progesterone medications
♦ Cytolysis may be prominent under same conditions

Decidual Cells

♦ Maybe seen in smears from pregnant women and women on birth control pills or progesterone agents. Clinical history is important

Cytologic Features

- Loose sheets of large, polygonal or round cells
- Abundant, delicate, eosinophilic or amphophilic cytoplasm
- Slight to moderate nuclear enlargement, but N/C ratio remains low
- Round nuclei with smudged and degenerative changes
- Nucleoli may be prominent

Syncytiotrophoblasts

- Rarely seen in normal pregnancy
- May indicate threatened abortion in 6% of patients when observed in the first trimester
- Suspect partial premature separation of the placenta when observed in the third trimester
- Suspect retained placental tissue when observed 4 weeks, after termination of pregnancy

Cytologic Features

- Cells with abundant cyanophilic cytoplasm, distinct cell border and peripheral condensation
- Round to oval nuclei with nuclear overlapping but without molding
- Finely granular, evenly distributed chromatin with inconspicuous nucleoli

SQUAMOUS CELL ABNORMALITIES

Atypical Squamous Cells (ASC)

Definition

- Cytologic changes suggestive of a squamous intraepithelial lesion (SIL) that are quantitatively or qualitatively insufficient for a definitive interpretation
- Does not represent a single biologic entity
- Subdivided: ASC-US and ASC-H

Atypical Squamous Cells of Undetermined Significance (ASC-US)

- 90% of all ASC
- Approximately 50% have oncogenic (High risk) HPV types

Cytologic features of ASC-US may be observed in

- Intermediate or superficial squamous cells :
  - Cells usually isolated and few cells in smear
  - Size and shape of superficial or intermediate cells
  - Nuclear size 2–3x (or 2 1/2–3x) size of intermediate cell nucleus or 2x size of nucleus of immature squamous metaplastic cells
  - Slight increase in N/C ratio
  - Minimal nuclear hyperchromasia, irregularity, clumping, smudging or multinucleation
  - Does not include inflammatory, reparative/reactive "atypia"
- Squamous metaplastic cells:
  - Similar enlarged nuclei to ASC-US in intermediate or superficial cells (70–120 μm^2)
  - Finely granular, evenly distributed chromatin
  - Cytoplasm less abundant, more cynaophilic
  - Cells are more round and N/C ratio higher than conventional ASC-US in intermediate or superficial squamous cells
- Atypical cells in an atrophic smear:
  - Nuclear enlargement with concomitant hyperchromasia
  - More marked irregularities in cell shape, nuclear contours or chromatin distribution may be observed
  - Possible recommendation:
    - Repeat Pap after short course of intravaginal estrogen therapy
- Atypical parakeratosis:
  - Nuclear abnormalities noted above associated with dense orangiophilic cytoplasm
  - Spindled and variable/irregular outlines may be observed
  - High N/C ratio with irregular nuclear contours
  - Dark nuclei with dense or smudged chromatin may be observed
- Cells with equivocal changes for HPV:
  - Partial koilocytosis/perinuclear halos
  - Bi- or multinucleation
  - Spindled nuclei
  - Mild hyperchromasia

Atypical Squamous Cells; Cannot exclude HSIL (ASC-H)

- 5% of all ASC
- Cytologic changes that are suggestive of high grade squamous intraepithelial lesion (HSIL), but lack criteria for definitive interpretation
- The association with underlying CIN2 and CIN3 for ASC-H is lower than for HSIL, but sufficiently higher than for ASC-US to warrant consideration of different management recommendations
- Approximately 70–80% have oncogenic (High risk) HPV types

Cytologic features of ASC-H may be observed in

- Atypical immature metaplastic cells
- Small cells as single or in tight clusters of usually <1 0 cells:
  - Nuclear size 1.5–2x that of metaplastic cells
  - Round to oval cells with dense amphophilic cytoplasm
  - Ectoplasm and endoplasm may be distinctive
  - High N/C ratio similar to HSILwith mildly hyperchromatic nuclei
  - Numerous cells hyperchromasia, chromatin irregularity and abnormal nuclear shapes favor HSIL
- Markedly typical Repair:
  - Cohesive sheets with nuclear pleomorphism or some loss of cohesion
  - Repair-like clusters that raise the possibility of HSIL or carcinoma
- Thick tissue fragments/crowded sheet pattern:
  - Microbiopsy of crowded cells
  - Loss of polarity or difficult to see
- Rare isolated atypical small cells:
  - High N/C ratio
  - Nuclear irregularities//grooves
  - Hyperchromasia

Squamous Intraepithelial Lesions (SIL)

Definition

- SIL encompasses a spectrum of non-invasive cervical epithelial abnormalities traditionally classified as flat condyloma, dysplasia/carcinoma in-situ, and CIN. Low-grade lesions include the cellular changes associated with HPV cytopathic effect and mild dysplasia/CIN1. High-grade lesions encompass moderate dysplasia, severe dysplasia, and carcinoma in situ (CIN2,3)

Low Grade Squamous Intraepithelial Lesion (LSIL)

- Transition from ASC-US to LSIL involves increase in nuclear size, nuclear hyperchromasia, N/C ratio and nuclear envelope irregularities. HPV cytopathic effect is synonymous with SIL not ASC

Cytologic features of LSIL

- Single or sheets of large polygonal cells
- Nuclear enlargement (>150 μm^2): 3–6x size (usually 4–5xs) of normal intermediate cell nucleus or 2–4x size of normal immature squamous metaplastic cell nucleus
- Mild nuclear hyperchromasia and moderate variation in nuclear size
- Mild nuclear envelope irregularities in some nuclei
- Chromatin pattern usually finely granular and uniformly distributed
- Nucleoli are generally absent
- Binucleation/multinucleation may be present
- Human Papillomavirus induced cytological changes: The most common low-risk HPV types are 6, 11, 42, 43, 44 and high risk HPV types are 16, 18, 31, 35, 39, 45, 51, 58, 59, 68
- Koilocytes with perinuclear halos surrounded by dense peripheral cytoplasm
- Enlarged and hyperchromatic nuclei with slight irregular contour
- Dyskeratosis, binucleation and multinucleation, nuclear pleomorphism
- In liquid based cytology the cytologic features of LSIL are similar to those of conventional preparations. There may be however:
  - Decreased hyperchromasia
  - Increased nuclear detail
  - More apparent nuclear membrane irregularities

Differential Diagnosis of LSIL

- HSIL:
  - Increase in N/C ratio
  - Hyperchromasia
  - Marked chromatin abnormalities and irregularities
  - Cell arrangements usually change from sheets to syncytial aggregates
- ASC-US:
  - Few cells (x2–3 intermediate cell nucleus)
  - Slight nuclear enlargement (x2–3 intermediate cell nucleus)
  - Stippled chromatin
  - Smooth nuclear membranes

High Grade Squamous Intraepithelial Lesion (HSIL)

Cytologic Features – Compared to LSIL

- Increased frequency of cell aggregates and syncytial-like arrangements
- Immature cytoplasmic characteristics or pleomorphic keratinized configurations
- Increased nuclear hyperchromasia
- Increased chromatin clumping and coarsening of chromatin
- Increased irregularities of nuclear outline
- Increased N/C ratio (cell and nuclear size however smaller than LSIL)
- Round to oval cells with lacy, delicate or metaplastic cytoplasm
- No tumor diathesis
- In liquid based cytology:
  - Fewer numbers of abnormal cells may be present
  - Cells tend to be more isolated or present in small groups

- The nuclear membrane irregularities are prominent
- Hyperchromasia is often observed as coarsening of chromatin material rather than darkening

"Keratinizing Dysplasia"

- Refers to the pleomorphic appearance of cells rather than cytoplasmic staining
- Severity determined by degree of pleomorphism rather than cytological atypia but difficult to predict: Cellular pleomorphism with marked anisonucleosis Caudate (spindle, elongated, tadpole, or bizarre forms), coarsely granular or smudged chromatin, dense orangeophilic cytoplasm with distinct borders
- Maybe difficult to distinguish from keratinizing squamous cell carcinoma (KSCC): KSCC generally has more discohesive cells, and more marked nuclear pleomrphism
- Usually viewed as HSIL to obtain biopsy and evaluate severity/exclude more advanced process

Differential Diagnosis of HSIL

- Invasive SCC:
  - Marked cellular pleomorphism
  - Irregular chromatin pattern distribution
  - Nucleoli
  - Tumor diathesis
- Endocervical adenocarcinoma *in situ*:
  - Picket fence arrangement of columnar cells with peripheral palisading ("feathering") and granular cytoplasm
  - Columnar configuration
  - Monotonous population of hyperchromatic oval nuclei
- Repair:
  - Cohesive, flat monolayer sheets of polygonal cells with distinct cell borders
  - Single nucleolus in every cell
  - No tumor diathesis

Cervical Squamous Cell Carcinoma (SCC)

Cytologic Features

- Many discohesive abnormal cells, some in aggregates
- Loss of cellular and nuclear polarity
- Cell size: 1/5 or less of normal superficial or intermediate squamous cell
- Nuclear size: x2–4 nucleus of intermediate squamous cell
- Chromatin: coarse and irregular distributed with parachromatic clearing
- N/C ratio: over 60% (30–90%)
- Tumor diathesis
- In liquid based cytology:
  - There may be a greater depth to focus of cell groups
  - The nuclei maintain features indicative of malignancy but are usually less hyperchromatic
  - More prominent nucleoli
  - A distinctive necrotic background pattern may be observed

Classification of SCC

- Keratinizing Squamous Cell Carcinoma:
  - Keratinizing cell with significant pleomorphism (Spindle, bizarre, tadpole, and caudate cells)
  - Dense orangeophilic cytoplasm with distinct cell border
  - Hyperchromatic, coarsely clumped chromatin with inconspicuous nucleoli
  - Anucleated squames and atypical parakeratotic cells
- Large Cell Non-Keratinizing Squamous Cell Carcinoma (LCNK):
  - Less anisocytosis and anisonucleosis than keratinizing carcinoma
  - Numerous single cells and syncytial groups of cells with indistinct borders
  - High N/C ratio
  - Round to oval nuclei
  - Nuclear overlapping
  - Coarse granular chromatin with chromatin clearing
  - Macronucleoli
- Small Cell Type:
  - Most are neuroendocrine carcinomas
  - Single cells and syncytial groups of small, cuboidal or round cells
  - High N/C ratio with scant cyanophilic cytoplasm
  - Large, round to oval nuclei with hyperchromatic, coarsely granular chromatin
  - Nuclear molding and small nucleoli

Differential Diagnosis of SCC

- Endometrial cells:
  - Three-dimensional cluster of cells with kidney bean shaped nuclei, evenly distributed chromatin, smooth nuclear contours
  - Foamy cytoplasm without macronucleoli
  - Lack tumor diathesis
- HSIL:
  - Loose aggregates and syncytial-like arrangement
  - Round to oval cells with delicate cytoplasm
  - Lack nuclear molding
  - No chromatin clearing
  - No tumor diathesis

NORMAL AND REACTIVE ENDOCERVICAL CYTOLOGY

Normal Endocervical Cells

Cytologic Features

- Cells may occur singly or in strips, rosettes, or sheets
- They are usually elongated and columnar. When viewed on end, they are smaller, polygonal or cuboidal, and demonstrate the typical "honeycomb" arrangement
- The cytoplasm is usually described as granular, but it may show fine vacuolization. The nuclei are round to oval and are often indented or possess a nuclear nipple-protrusion of the nuclear contents at one end
- The nuclear chromatin is finely granular and evenly dispersed
- Multiple small chromocenters and one or more small eosinophilic nucleoli may be present
- Binucleation or multinucleation is not uncommon
- Variability observed in cells derived from various regions of the endocervical canal

Endocervical Cells, Reactive Changes

General Cytologic Features

- Cells occur in sheets and strips with minor degrees of nuclear overlap
- Nuclear enlargement, up to three to five times the area of normal endocervical nuclei, may be seen
- Mild variation in nuclear size and shape occurs
- Slight hyperchromasia frequently is evident
- Nucleoli often are present
- Abundant cytoplasm and distinct cell borders often are discernible

Tubal Metaplasia

- Normal finding especially upper endocervical canal
- May be related to unopposed estrogen

Cytologic Features

- Small crowded cellular strips, clusters, or flat honeycomb sheets
- Evenly spaced uniform, basally oriented round to oval nuclei
- Large stripped nuclei may be observed
- Finely granular, evenly distributed or washed-out chromatin
- Small inconspicuous nucleoli
- Terminal bars/cilia, and mucus depletion
- Ciliocytophthoria

Differential Diagnosis

- Endocervical adenocarcinoma in situ (AIS):
  - Lack terminal bars or cilia
  - Nuclear hyperchromasia and coarse chromatin pattern
  - Nuclear feathering and rosettes
  - Apoptosis

Microglandular Hyperplasia

- Related to progesterone effect (may be observed in pregnancy, birth control pills and postmenopausal women on estrogen)

Cytologic Features

- Usually indistinguishable from those of reactive hyperplasia and regeneration/repair
- Associated endocervical changes:
  - Large sheets of polygonal or columnar cells with minimal stratification
  - Pseudoparakeratosis: degenerative changes in endocervical cells
- Spindle and elongated metaplastic cells
- Terminal bars and cilia may be present

Arias-Stella Reaction

- A non-neoplastic hormone related phenomenon usually observed in pregnancy. Clinical correlation is essential for diagnosis

Cytologic Features

- Single or small groups of "atypical" glandular cells
- Low N/C ratio with abundant clear or faintly eosinophilic cytoplasm
- Nuclear enlargement, hyperchromasia, pleomorphism and nuclear groove
- Granular, evenly distributed chromatin, often smudged with ground-glass appearance

Benign Glandular Cells in the Specimens from Post-Hysterectomy Women

- The likely source of these benign cells include: prolapse of uterine tube, vaginal endometriosis, fistula, vaginal adenosis not associated with DES exposure, or glandular metaplasia associated with prior radiation or chemo-therapy. These findings are considered benign and do not warrant an interpretation/diagnosis of "atypical glandular cells"

Glandular Cell Abnormalities

- Whenever possible, atypical glandular cells should be qualified as to endocervical or endometrial. When the

distinction cannot be made, the cytology report of "atypical glandular cells-AGS" indicates the uncertainty as to the source of these cells. Atypical glandular cells rates in the typical cytology laboratory are usually infrequent with compiled data showing means between 0.3 and 1%

Atypical Endocervical Cells

Cytologic Features

- Changes beyond those encountered in reactive processes, but are insufficient for favoring neoplasia or an unqualified diagnosis of adenocarcinoma *in situ* (AIS)
- Mild cellular crowding without nuclear pseudo-stratification
- Nuclear enlargement, hyperchromasia, and anisocytosis

Follow-up of Atypical Endocervical Cells

- Normal, reactive or benign process: 20–40%
- Endocervical neoplasia: 0–11%
- Squamous neoplasia: 35–80%:
  - This points to the difficulties inherent in interpretation of these lesions. SIL which may involve endocervical gland necks and mimic glandular cells
  - Features that should favor SIL include the presence of syncytial groups, opaque hyperchromatic nuclei, dense cytoplasm, and the presence of individual SIL cells

Atypical Endocervical Cells, Favor Neoplastic

Cytologic Features

- The presence of some but not all the criteria as outlined for adenocarcinoma In Situ (AIS) or other "atypical" presentation which should be individually and specifically categorized in a qualifying statement

Endocervical Adenocarcinoma In Situ (AIS)

Cytologic Features in Conventional Smears

- These features are for the most common "endocervical" form of AIS
- Moderate to highly cellular smear composed of tight clusters and cohesive sheets of glandular cells
- Pseudostratification, rosette formation and feathering at the edge of sheets
- Uniform nuclear enlargement, hyperchromasia, nuclear irregularities, and crowding with elongate configuration
- Coarsely granular, evenly distributed chromatin
- Mitosis and apoptotic bodies may be present
- Micronucleoli may be observed
- Delicate, finely vacuolated cytoplasm with diminished mucin production
- Clean or inflammatory background
- About 50% of AIS are associated with SIL

Cytologic Features in Liquid-Based Preparations: Differences from Conventional Smears

- Hyperchromatic crowded groups become denser and more three dimensional with greater nuclear overlap, increased apparent hyperchromasia of nuclei, and with increased difficulty in visualization of individual nuclei in the groupings
- "Disordered honeycomb" arrangement may be the only feature present in some cases
- Key architectural features may be more subtle than in conventional smears
- Margins of the groups become smoother and sharper with lesser degrees of nuclear protrusion (feathering)
- Pseudo stratified strips of cells are often the most prominent architectural arrangement

Differential Diagnosis of AIS

- Tubal metaplasia:
  - Terminal bars, cilia, flat sheets
  - More evenly spaced nuclei, resemble honeycomb pattern
  - Absence of mitosis, apoptosis, or nuclear hyperchromasia
- Lower uterine segment endometrium:
  - Mixture of glandular and stromal cells
  - Large cell aggregates with tubular branched glands
  - Cell polarity retained
  - Smaller nuclei with finely granular chromatin
- Repair/reactive processes:
  - Flat sheet of polygonal cells in a honeycomb arrangement
  - Lack of single cells
  - Abundant cytoplasm and distinct cell borders often are discernable
  - Uniform cells with low N/C ratio
  - Minor degrees of nuclear overlap
  - Nuclear enlargement, up to three to five times the area of normal endocervical nuclei, may be seen
  - Mild variation in nuclear size and shape occurs
  - Slight hyperchromasia may be seen
  - Nucleoli often are present

HSIL with endocervical gland involvement

- Feathering may occur but often restricted to one end of crowded sheet
- Syncytial arrangement
- Hyperchromatic nuclei
- Dense cytoplasm
- No strips, rosettes or pseudo stratified atypical columnar cells

- Individual cells with dysplasia in background
- Normal endocervical cells are numerous
- AIS is much less frequent than HSIL

Endocervical Adenocarcinoma

Cytologic Features

- Features of AIS, highly cellular smear
- Isolated strips and single or discohesive sheets of columnar or cuboidal cells
- Two and three dimensional clusters
- Round to oval nuclei with coarse granular chromatin and chromatin clearing
- Marconucleoli
- Round to oval nuclei. Nuclear size, and nuclear pleomorphism increase in less differentiated tumors. Multinucleation, and mitotic figures may be present
- More abundant foamy or finely vacuolated cytoplasm than AIS
- Necrotic granular (tumor) diathesis

Minimal deviation adenocarcinoma (adenoma malignum)

- Can be a very difficult diagnosis. May be suspected in the proper clinical context
- Hyper cellular smear
- Strips, honeycomb sheets, and three dimensional clusters of cell with distinct cell border, abundant lacy cytoplasm and occasional nucleoli

Table 1. Endocervical Adenocarcinoma vs. Endometrial Adenocarcinoma

Endocervical Adenocarcinoma (Endocervical Type)	*Endometrial Adenocarcinoma (Endometrioid Type)*
Younger patients	Elderly patients
Strips, rosette and feathering arrangement	Syncytial arrangement
Larger columnar cells	Smaller cell with indistinct cell border
Granular cytoplasm	Amphophilic cytoplasm
Solitary macronucleoli	Multiple small nucleoli
Necrotic dirty background	Watery diathesis

Note: The cytologic findings of moderately and poorly differentiated endocervical adenocarcinoma often overlap with those of endometrial adenocarcinoma. Other histologic types are identical to their endometrial counterpart

- Round to oval nuclei (rather than elongated) nuclei with coarse granular chromatin

Differential Diagnosis of Endocervical Adenocarcinomas

- Endometrial adenocarcinoma: (see **Table 1**)

ENDOMETRIAL CYTOLOGY

Cytologically Normal Endometrial Cells

Cytologic Features

- Endometrial epithelial cells:
  - Loose clusters and cell balls
  - Cells are small, cuboidal to round
  - Scant amphophilic and often finely vacuolated cytoplasm
  - Round or bean shaped nuclei, slightly eccentric
  - Nuclear size similar to that of intermediate cell nucleus
  - Uniform finely powdered chromatin pattern
- Superficial endometrial stromal cells:
  - Individually the cells resemble and may be indistinguishable from histiocytes
  - Identify as stromal cells when numerous and loosely clustered
  - Round oval or reniform nuclei
  - Nucleus is usually centrally located but may be eccentric
  - Chromatin finely granular
  - Micronucleoli may be observed
- Deep endometrial stromal cells:
  - Loose aggregates late in the menstrual flow
  - Spindle or oval cells
  - Ill defined cytoplasmic borders
  - Nuclei reniform or cigar shaped, often with nuclear enfolding (grooves)
  - Nuclear chromatin finely granular, sometimes hyperchromatic
  - Small chromocenters may be observed
- Exodus:
  - Occur on days 6–10 of menstrual cycle
  - Cells balls composed of stromal cells surrounded by peripheral larger epithelial cells

- The presence of endometrial cells is related to:
  - Site of origin of endometrium
  - Days of menstrual cycle
  - The environment into which they are shed and interval that has elapsed since the cells were shed
  - Collection method
  - Processing techniques
- The significance of endometrial cells is in part dependent on:
  - Age of the patient
  - Day of last menstrual cycle
  - Menopausal state
  - Hormonal usage
  - Intrauterine devices
  - Recent instrumentation
- Note:
  - Endometrial cell peak at day 4–5 and may persist till day 12–14 of a 28 day menstrual cycle
  - Presence of endometrial cells after day 12–14 or in menopausal women is associated with an age-dependent (endometrial pathology more likely to be detected after age 40) increased detection of endometrial pathology (endometrial polyp, hyperplasia or adenocarcinoma)
- Abnormal shedding of cytologically normal endometrial cells may be associated with a 35–40% risk of endometrial pathology (of any kind)). There is advancing risk with age especially over age 40years. Changes /lesions that may be associated with endometrial cells may include: IUD use, hormonal effect, immediate postpartum period, impending or early abortion, acute and chronic endometritis, recent intrauterine instrumentation, endometriosis, polyps and sub mucosal leiomyoma
  - Because of the lack of clinical impact and the unreliable clinical data often supplied with the sample, cytologically normal endometrial cells may need not be reported in women less than 40 years.

Bethesda 2001 Reporting of Endometrial Cells

- Cervical/vaginal cytology is a screening tool for squamous cell carcinoma and its precursor lesions. It is a sensitive or accurate screening test for detection of endometrial lesions and should not be used to evaluate suspected endometrial abnormalities
- Suggested reporting of benign appearing endometrial cells in all women from the age of 40 onward, regardless of hormonal therapy using the following format:
- General Categorization: Negative for squamous intraepithelial lesion. Other
  - Descriptive Interpretation: Endometrial cells present. See "Comment"
- An educational comment appropriate for the local laboratory practice, such as the following, may be used. For example, "Endometrial cells after age 40, particularly out of phase or after menopause, may be associated with benign endometrium, hormonal alterations and less commonly, endometrial/ uterine abnormalities. Clinical correlation is recommended"

Atypical Endometrial Cells

- No well defined criteria to separate reactive vs. pre-neoplastic endometrial cells
- Should not be subdivided into categories
- May be seen in:
  - Endometrial polyp
  - Endometritis, acute and chronic
  - Endometrial metaplasia
  - Endometrial hyperplasia
  - Well-differentiated adenocarcinoma (FIGO grade 1)

Cytologic Features

- Cells occur in small groups, usually 5 to 10 cells per group
- Mild cellular crowding without nuclear pseudostratification
- Nuclei are slightly enlarged with mild hyperchromasia, and anisocytosis
- Small nucleoli may be present
- Cell borders are ill-defined
- Compared with endocervical cells, these cells have scant cytoplasm, which occasionally is vacuolated

Endometrial Adenocarcinoma

Cytologic Features

- Shedding is sparse and irregular especially for low-grade tumors
- Small cells that may be difficult to detect. Cell size increases from low to high-grade tumors
- Scant cyanophilic cytoplasm with fine vacuolization
- Loss of cell polarity
- Nuclear enlargement (>70 μm^2) and high N/C ratio
- Nuclear crowding and overlapping (3-D cell ball)
- Chromatin is not usually hyperchromatic
- Powdered chromatin with parachromatin clearing
- Nucleolar enlargement proportional to grade of tumor
- Singly or loose clusters of foamy histiocytes and lipophages
- Watery granular tumor diathesis
- In liquid based cytology:
  - The groups may be more spherical or clustered
  - The nuclei present in groups may show less visual accessibility due to overlap and increased cytoplasmic thickening
  - The nuclear features are usually well preserved
  - Nucleoli are prominent
  - Distinction between endocervical adenocarcinoma maybe more difficult

Differential Diagnosis

- Normal endometrial cell:
  - Round nucleus similar in size to intermediate squamous cell nucleus
  - No cytological features of malignancy
- Atypical endometrial:
  - Cytological changes may overlap with those of low-grade endometrial adenocarcinoma
  - Cell polarity maintained
  - Nuclear size less than that of adenocarcinoma
  - No tumor diathesis
- Endocervical adenocarcinoma (see **Table 1**)

Papillary Serous Adenocarcinoma

Cytologic Features

- Cells usually shed in papillary aggregates and have all the features of a poorly differentiated carcinoma
- Small compact cell balls elongated groups with peripheral molding or irregular tight clusters of cells may be identified
- Occasionally, the central connective tissue core may be seen. Psammoma bodies can be observed
- The cytologic features of papillary serous carcinoma of the endocervix , endometrium or tubes/ovaries are indistinguishable
- Poorly differentiated endometrioid carcinoma FIGO Grade III and with extra uterine papillary carcinoma cannot be distinguished cytologically

Extra-Uterine Metastatic Adenocarcinoma

- Important to consider clinical history
- Ovarian carcinoma most common primary site (papillary serous carcinomas)
- Other sites include fallopian tubes, gastrointestinal tract, pancreas and breast
- Presence of ascites and patent fallopian tubes increases yield
- Most are poorly differentiated adenocarcinomas

Cytologic Features

- Three-dimensional, tubular, spherical or papillary tissue fragments
- Large cells with high N/C ratio, nuclear hyper-chromasia and macronucleoli
- Generally, no specific cytological features point to the primary site
- Exceptions include the presence of psammoma bodies (favor ovarian), columnar cells with brush borders (favor GI) , and cords of cells (favor breast)
- Absence of tumor diathesis, provided implantation has not occurred

Malignant Mixed Müllerian Tumor

Cytologic Features

- Two distinct tumor cell populations: malignant poorly differentiated glandular component with or with squamous differentiation, and pleomorphic spindle or multinucleated sarcomatous component
- Heterologous elements are rare and are cytologically difficult to recognize
- The malignant epithelial component sheds as single cells or in aggregates, whereas the sarcomatous cells usually occur as single cells and, rarely, in aggregates
- Tumor diathesis is usually evident

Lymphoma/Leukemia Cervix (also see Chapters 7 and)

Cytologic Features

- Vary with the type of lymphoma
- Complete lack of intercellular cohesion among the tumor cells. Some of the cells may appear to cluster, but no true aggregates are present
- The tumor cell population is monomorphic
- The cells have high N/C ratios. In most lymphoma cells, the cytoplasm is barely visible; however, a minority have a plasmacytoid appearance with more abundant cytoplasm
- The nuclear membrane usually shows marked convolutions and may show a nipple-like protrusion
- The chromatin is coarse with regular clumps
- Nucleoli are not common, except in the immunoblastic lymphoma category
- The subtyping of lymphomasis not reliable

ABBREVIATIONS

CP:	Conventional preparation
LBP:	Liquid-based preparation
ASC-US:	Atypical squamous cells of undetermined significance
ASC-H:	Atypical squamous cells cannot exclude high-grade squamous intraepithelial lesion
SIL:	Squamous intraepithelial lesion
LSIL:	Low-grade squamous intraepithelial lesion
HSIL:	High-grade squamous intraepithelial lesion
HPV:	Human papillomavirus
CIS:	Carcinoma *in situ*
AIS:	Adenocarcinoma *in situ*

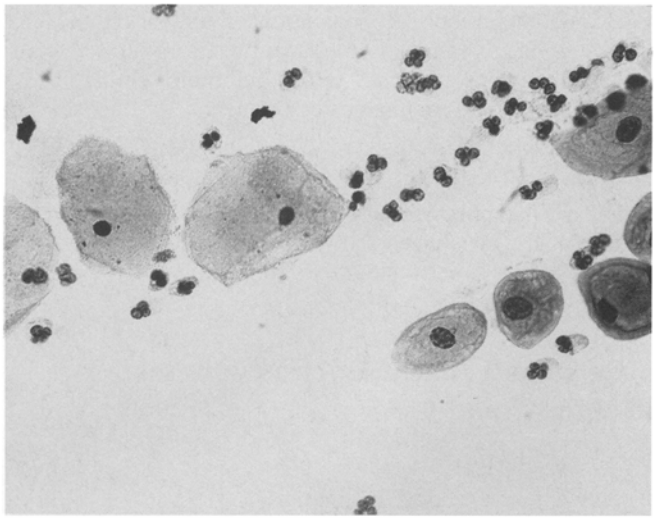


Fig. 1. Satisfactory for evaluation. Negative for Intraepithelial lesion or Malignancy. Superficial squamous cells, metaplastic cells and intermediate squamous cells (LBP).

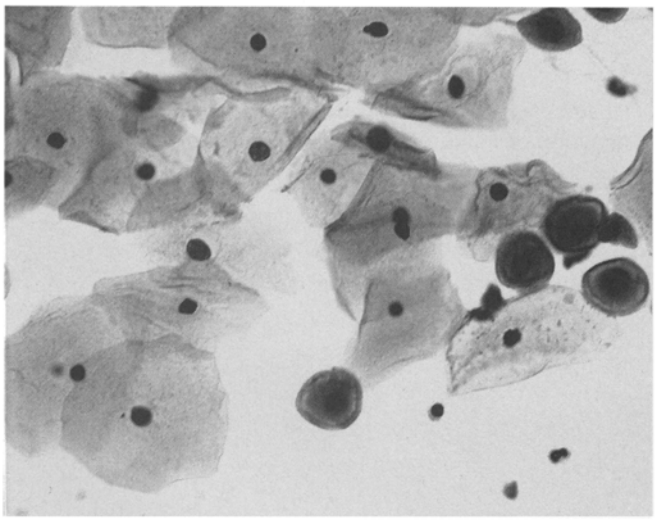


Fig. 2. Satisfactory for evaluation. Negative for Intraepithelial lesion or Malignancy. Superficial, intermediate and metaplastic squamous cells (LBP).

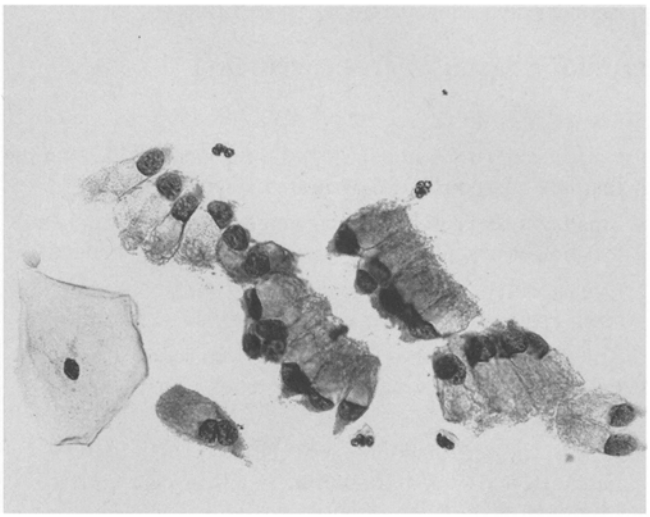


Fig. 3. Satisfactory for evaluation. Endocervical-transformation zone component present. Normal endocervical cells (CP).

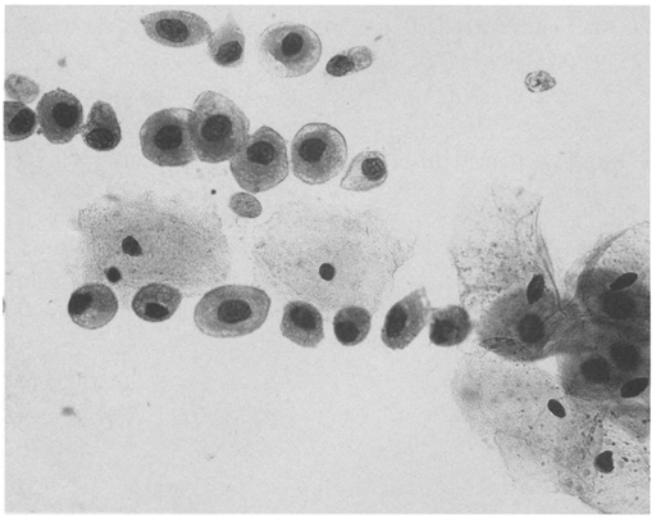


Fig. 4. Satisfactory for evaluation. Endocervical transformation zone component present. Immature and mature metaplastic cells (CP).

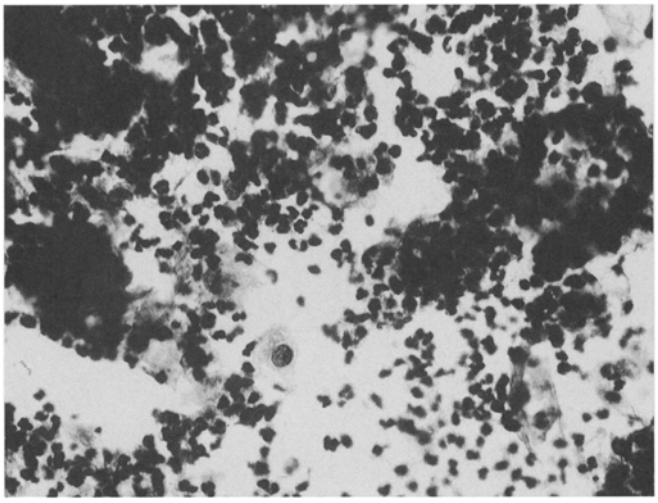


Fig. 5. Unsatisfactory for evaluation, obscuring exudates. The specimen is totally obscured by acute inflammatory cells precluding evaluation. Greater than 75% obscuring is considered unsatisfactory if no abnormal cells are identified (CP).

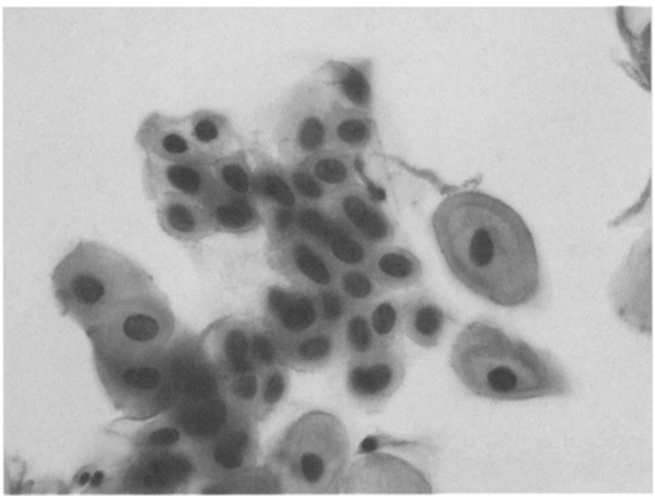


Fig. 6. Negative for Intraepithelial lesion or Malignancy. Atrophy. Maturation is not observed. Smear consists predominantly of parabasal cells (LBP).

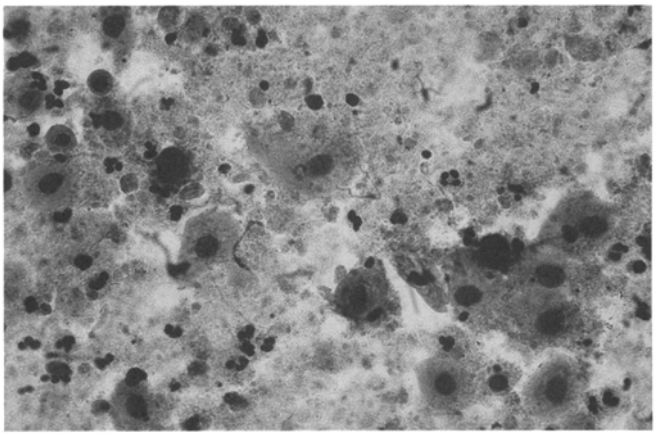


Fig. 7. Negative for Intraepithelial lesion or Malignancy. Atrophy. Granular backround,basal cells and "blue blobs" (CCP).

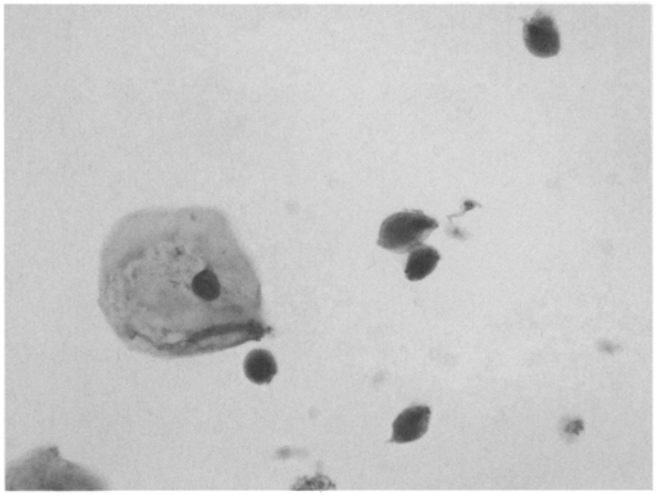


Fig. 8. Trichomonas vaginalis. Pear-shaped organisms with eccentrically located nucleus and granular cytoplasm (LBP).

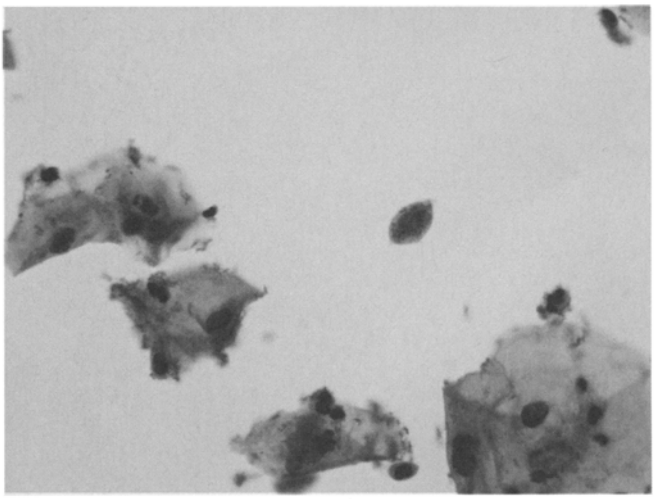


Fig. 9. Trichomonas vaginalis (LBP).

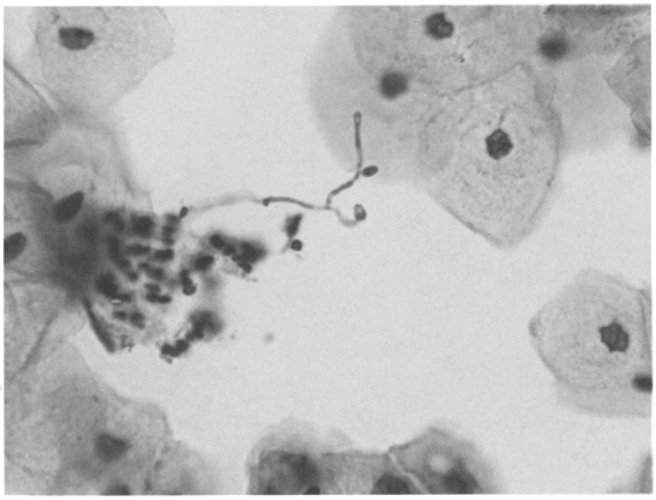


Fig. 10. Fungal organisms morphologically consistent with Candida species. Pseudohyphae and spores are present (LBP).

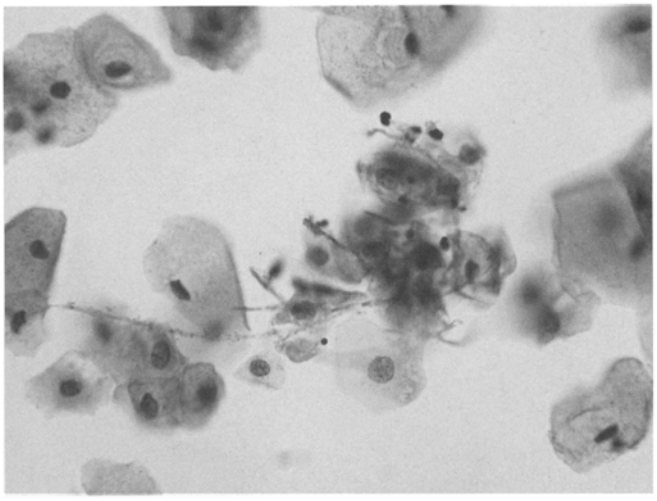


Fig. 11. Fungal organisms morphologically consistent with Candida species (LBP).

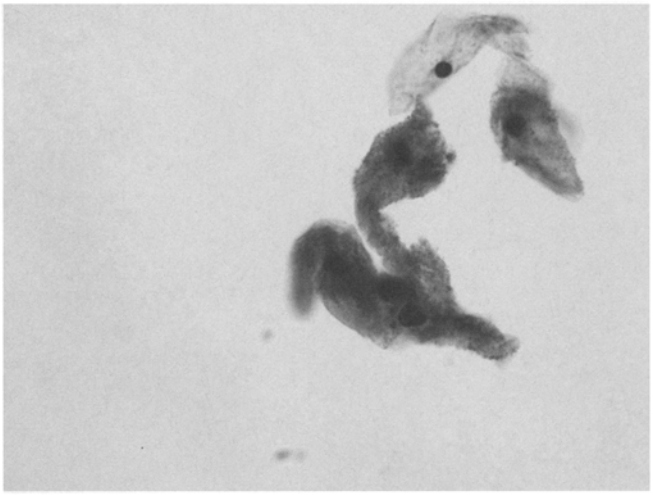


Fig. 12. Shift in flora suggestive of bacterial Vagenosis. Clue cells with cocobacilli covering the cytoplasm (LBP).

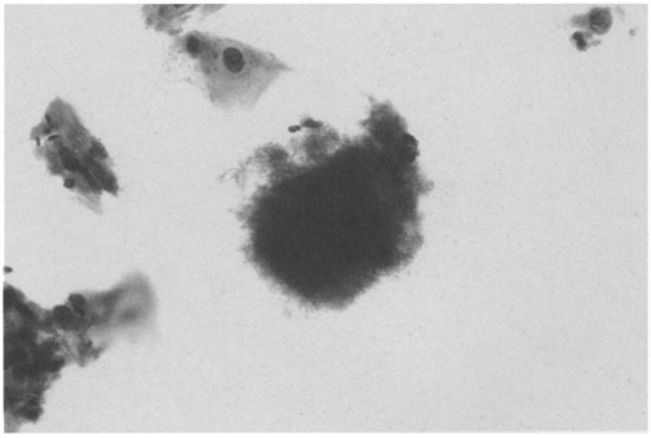


Fig. 13. Bacteria morphologically consistent with Actinomycis species.A cluster of thin filamentous bacilli are present (LBP).

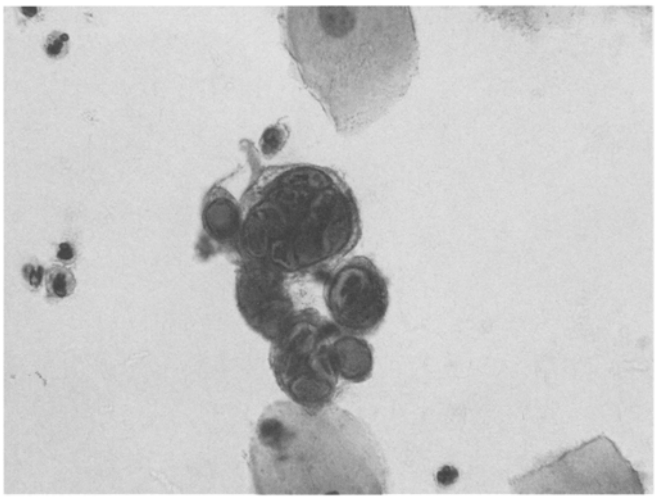


Fig. 14. Cellular changes consistent with herpes simplex virus. Multinucleated giant cell with molding, ground-glass nuclei and intranuclear inclusions (LBP).

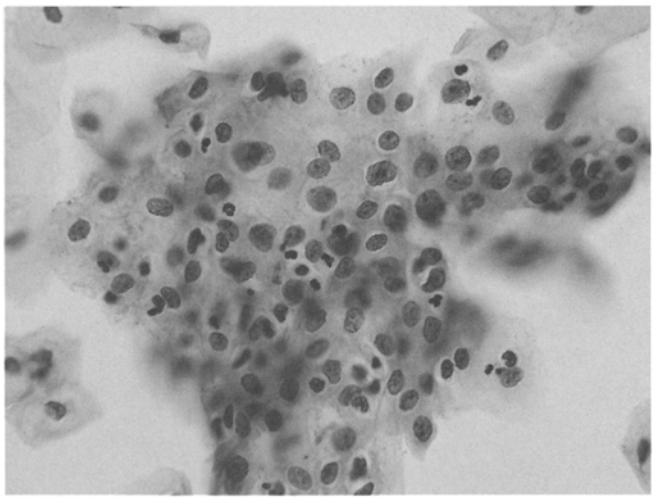


Fig. 15. Reactive cellular changes associated with inflammation. Sheet of cells with slightly enlarged uniform nuclei and abundant cytoplasm. Polymorphonuclear leukocytes are present in the sheet. Elsewhere in this slide fungal organisms consistent with Candida species were observed (LBP).

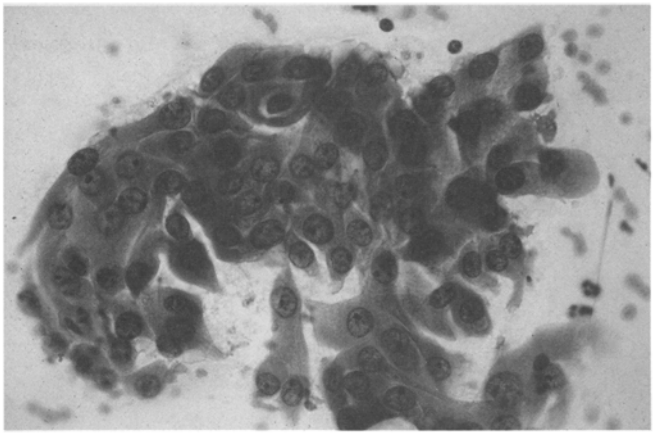


Fig. 16. Reactive cellular changes associated with inflammation. Sheet of squamous cells with distinct borders, abundant cytoplasm, enlarged uniformly round nuclei and nucleoli. Isolated atypical cells are not observed (CP).

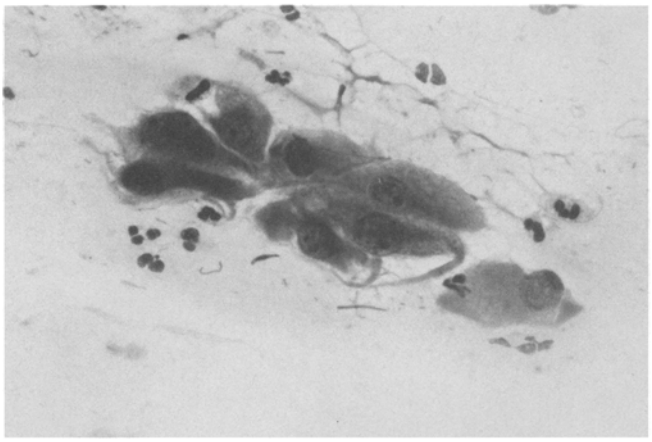


Fig. 17. Reactive cellular changes associated with inflammation. Typical repair characterized by a sheet of cells with distinct borders, abundant cytoplasm and slightly enlarged nuclei with uniform chromatin pattern and nucleoli (CP).

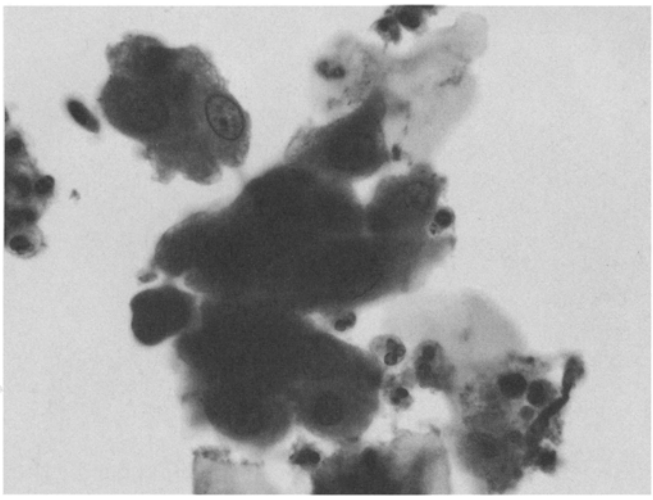


Fig. 18. Reactive cellular changes associated with inflammation. Typical repair (LBP).

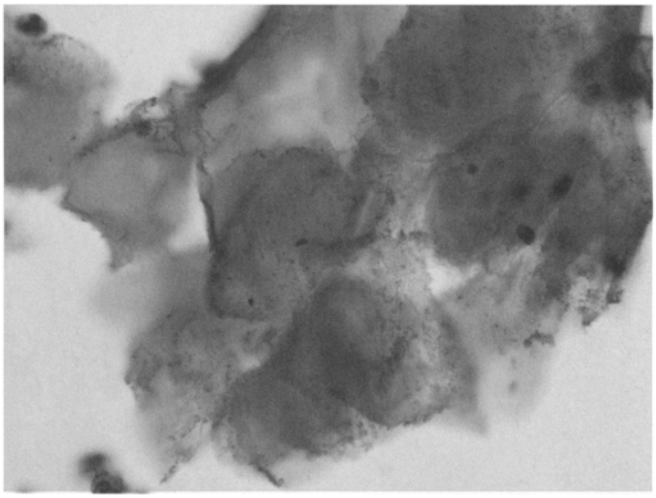


Fig. 19. Reactive cellular changes. Hyperkeratosis. Anucleated mature squamous cells with absent ghost-like nuclei (LBP).

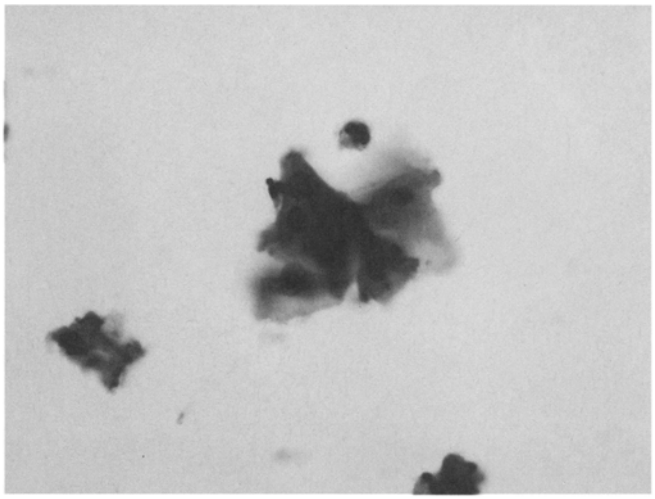


Fig. 20. Reactive cellular changes. Parakeratosis. Miniature brightly orangophilic cells with small hyperchromatic nuclei (LBP).

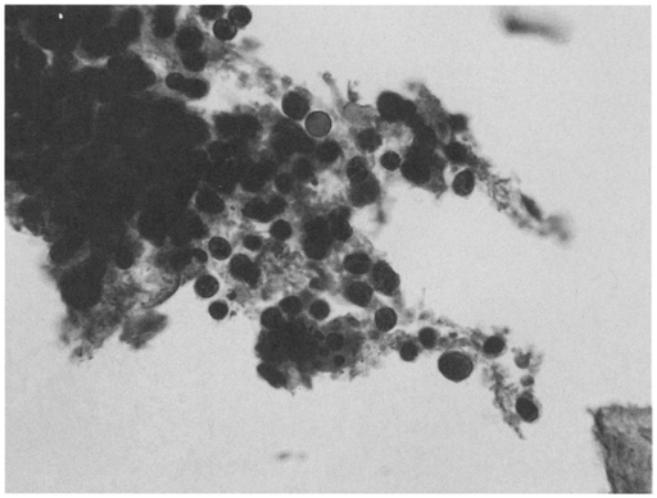


Fig. 21. Reactive cellular changes. Chronic lymphocytic cervitis. Polymorphous population of lymphoid cells with tingible body macrophages (LBP).

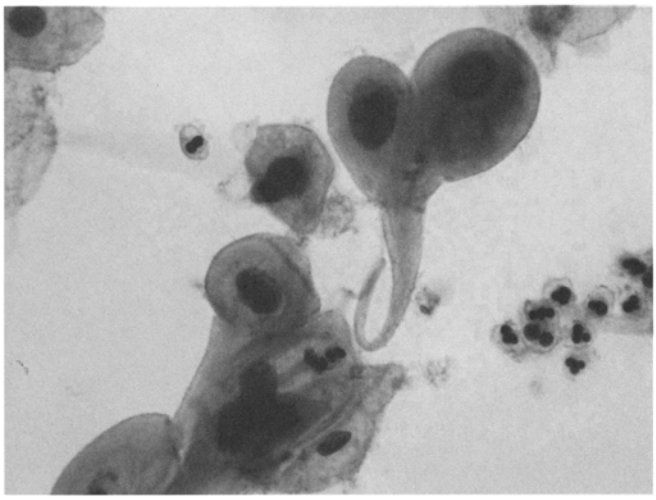


Fig. 22. Reactive cellular changes associated with radiation effect. Large intermediate and metaplastic cells with enlarged nuclei and abundant cytoplasm. Note the polymorphous staining and vacuolization (LBP).

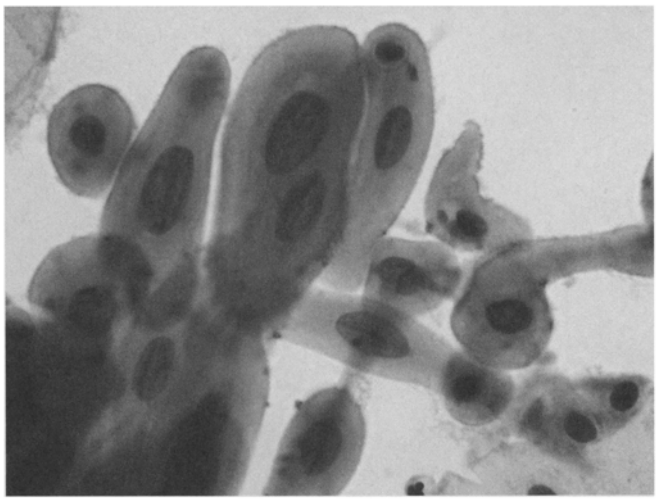


Fig. 23. Reactive cellular changes associated with radiation effect (LBP).

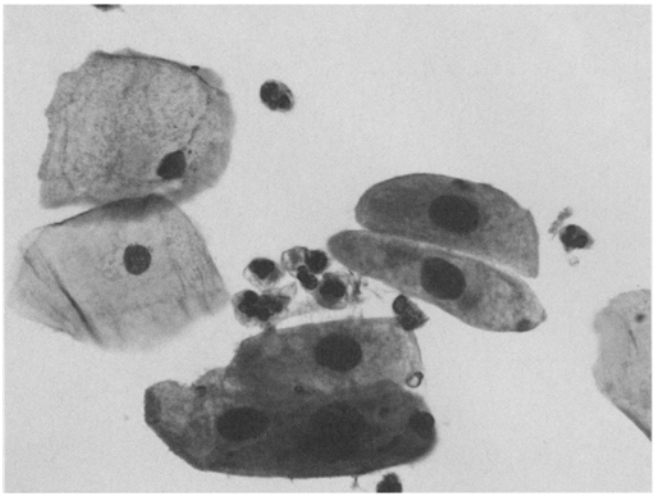


Fig. 24. ASC-US (LBP)Atypical intermediate squamous cells with round hypochromatic nuclei that are 2–3 times the size of the adjacent normal intermediate cell nuclei (LBP).

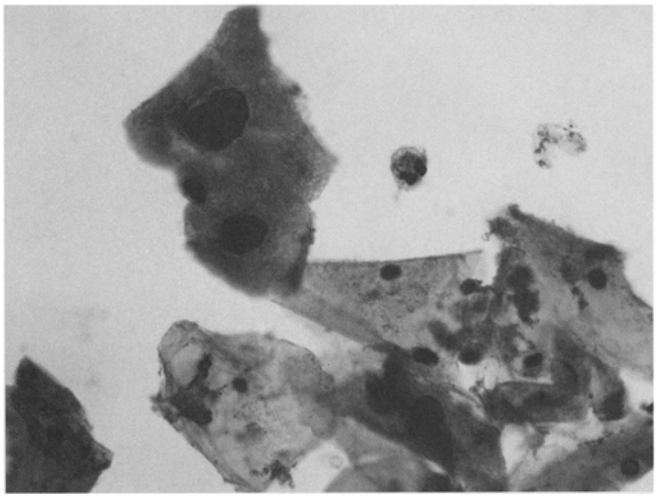


Fig. 25. ASC-US. Intermediate cells with nuclear enlargement (2–3x) intermediate cell nuclei and minimal hyperchronasia. No inflammation is present in the backround (LBP).

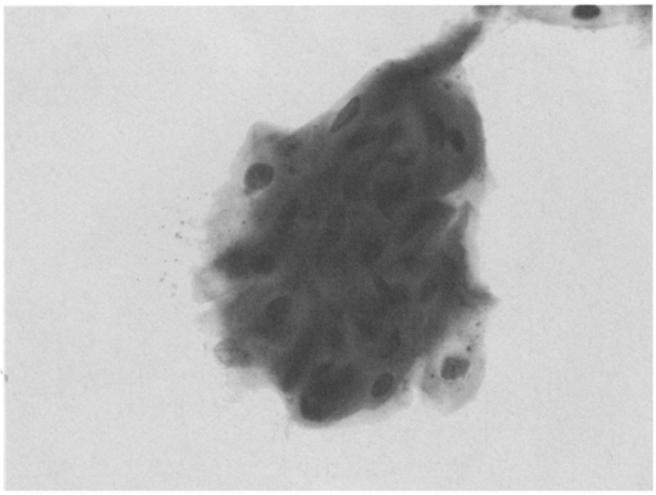


Fig. 26. ASC-US. Atypical Parakeratosis. Spindled and slightly pleomorphic orangophilic parakeratotic cells with mild nuclear enlargement (LBP).

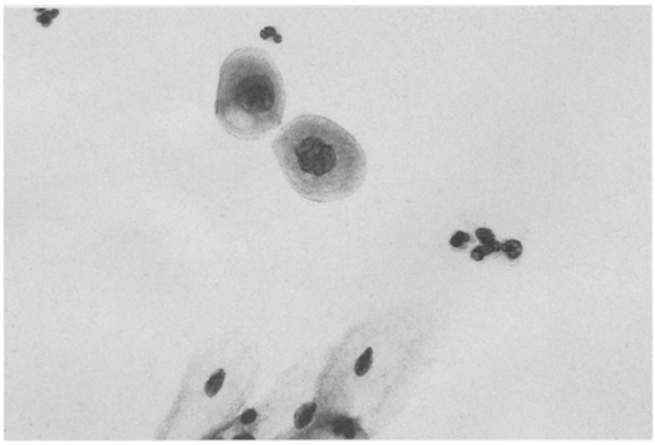


Fig. 27. ASC-H. Atypical immature metaplastic cells with enlarged nuclei and nuclear irregularity. The findings are not diagnostic of HSIL. Only rare atypical cells were present (LBP).

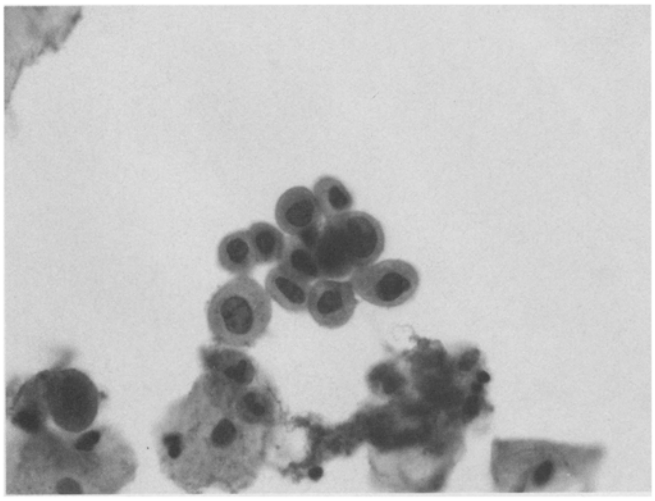


Fig. 28. ASC-H. Atypical immature metaplastic cells (LBP).

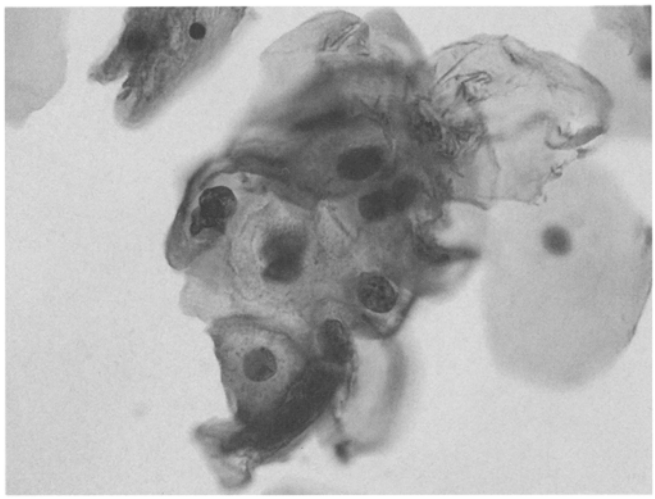


Fig. 29. LSIL (mild dysplasia with HPV effect). Intermediate cells with mild nuclear enlargement and nuclear contour irregularities. Perinuclear halos consistent with HPV effect are present (LBP).

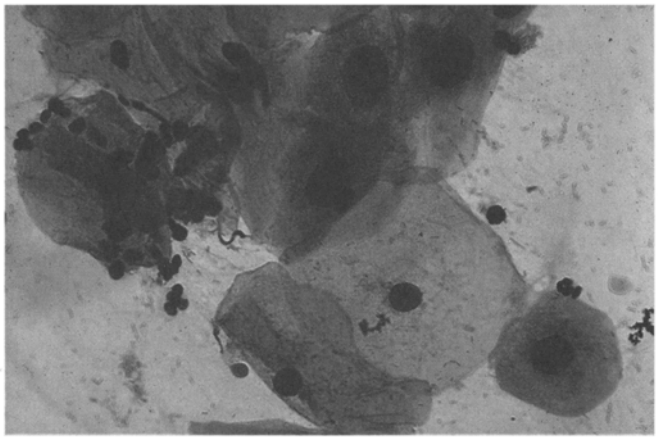


Fig. 30. LSIL (mild dysplasia). Intermediate squamous cells with mildly enlarged nuclei and slight hyperchromasia (LBP).

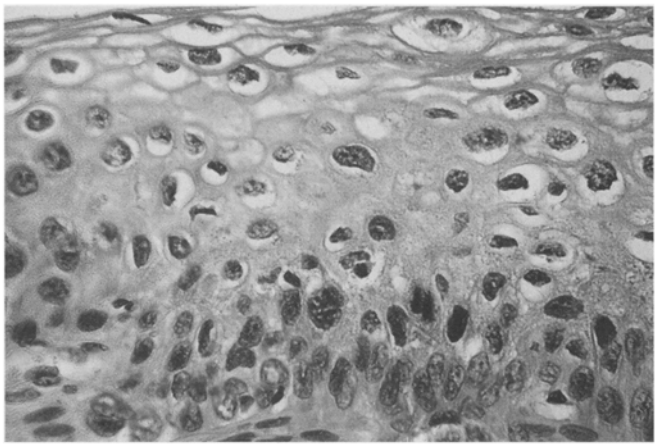


Fig. 31. Mild dysplasia with evidence of HPV infection. Disordered proliferation of dysplastic cells in the lower third of the epithelium and HPV effect towards the surface (Histology).

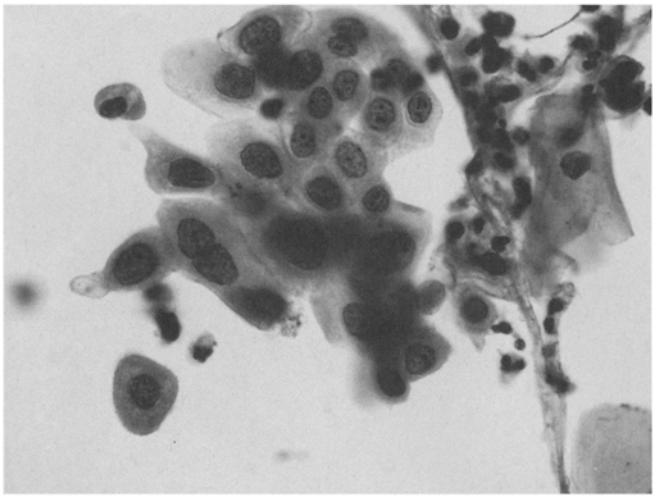


Fig. 32. HSIL (moderate dysplasia). Sheet of cells with enlarged nuclei, irregularities of nuclear contour and coarse chromatin pattern (LBP).

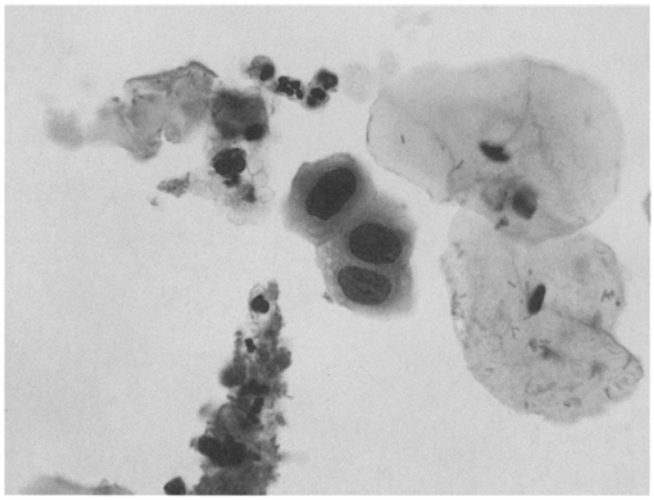


Fig. 33. HSIL (moderate dysplasia). Metaplastic cells with enlarged nuclei, irregular nuclear contours and coarse chromatin pattern (LBP).

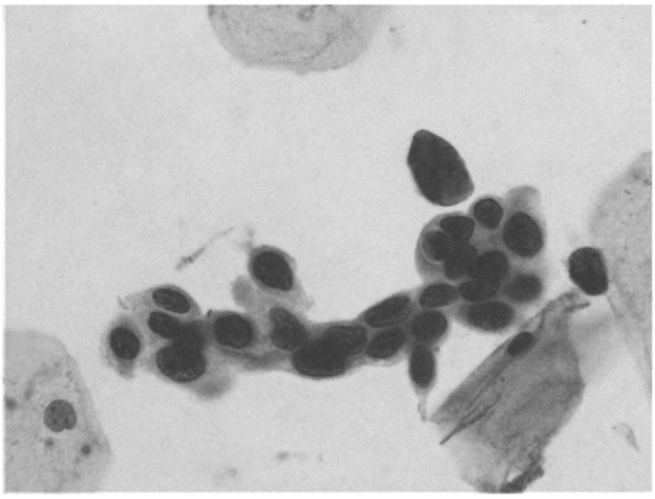


Fig. 34. HSIL (severe dysplasia-cis). Syncytial cluster of small cells with very high nuclear to cytoplasmic ratio, markedly irregular nuclear contours and coarse but equally distributed chromatic pattern (LBP).

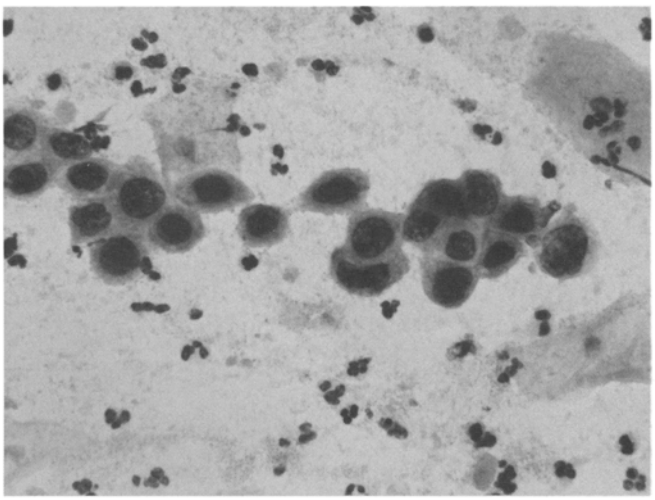


Fig. 35. HSIL (severe dysplasia-cis). Loose arrangement of small immature cells with high nuclear to cytoplasmic ratio, markedly irregular nuclear contours and coarsely granular chromatic pattern (CP).

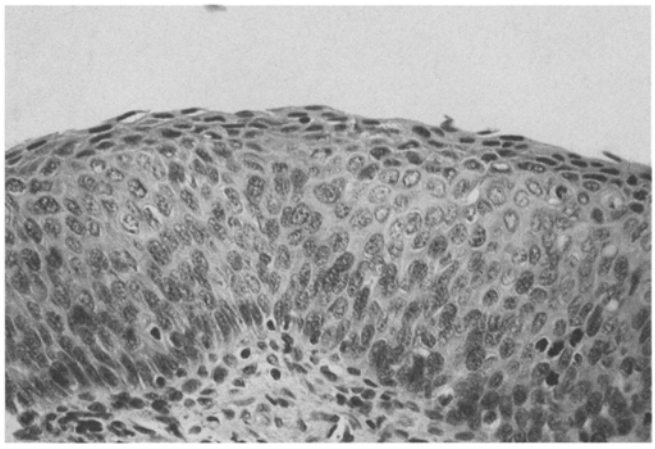


Fig. 36. Severe dysplasia-cis (Histology). Full-thickness disordered maturation with dysplastic cells showing hyperchromatic nuclei and high nuclear: cytoplasmic ratio.

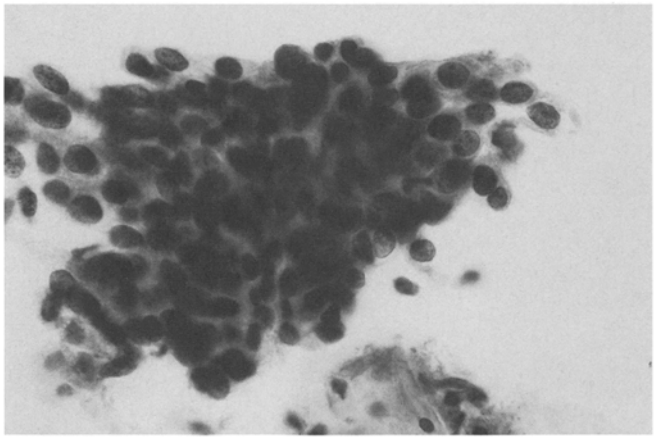


Fig. 37. HSIL involving endocervical glands mimicking AIS. Syncytial cluster of HSIL in a tight cluster with rounded contour (LBP).

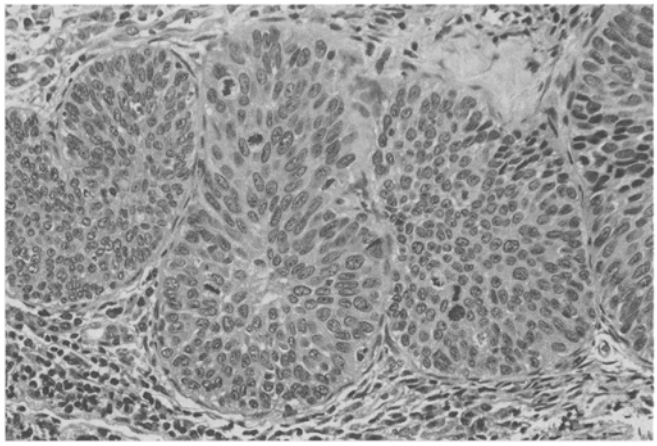


Fig. 38. Severe dysplasia/carcinoma *in situ* involving endocervical glands. The endocervical glands are occupied by dysplastic squamous cells extending from the surface Histology).

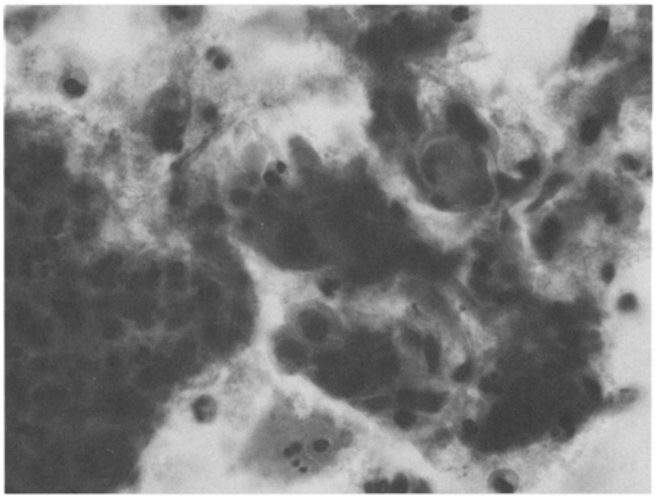


Fig. 39. Squamous cell carcinoma, keritinizing type. Markedly pleomorphic orangophilic cells are present. The nuclei are irregular with enlarged hyperchromatic nuclei and irregular coarse chromatin pattern (CP).

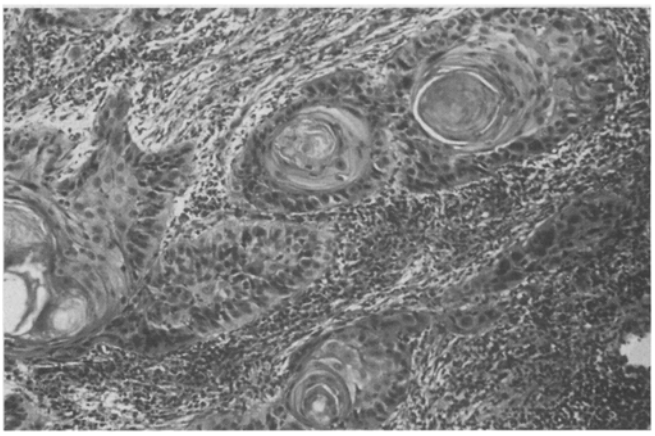


Fig. 40. Invasive squamous cell carcinoma, keratinizing type. Keratin pearls are present in this invasive moderately differentiated squamous cell carcinoma (Histology).

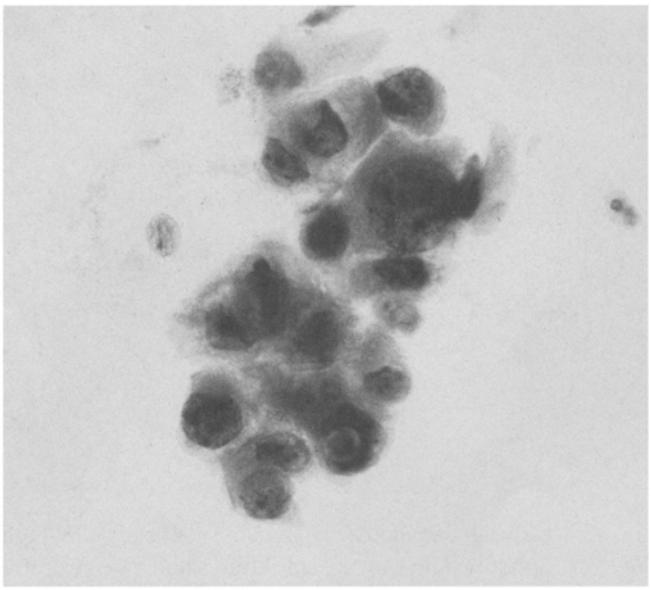


Fig. 41. Squamous cell carcinoma, large cell non-keratinizing type. Cluster of malignant cells with pleomorphic nuclei, irregular chromatin pattern and nucleoli (LBP).

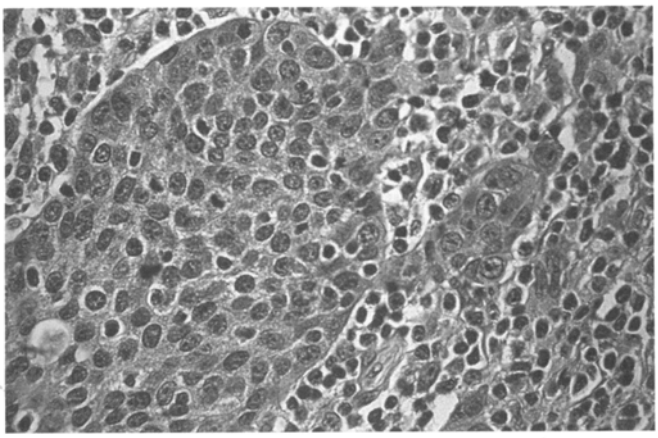


Fig. 42. Squamous cell carcinoma, large cell non-keratinizing type. Invasive squamous cell carcinoma that lacks squamous pearls (Histology).

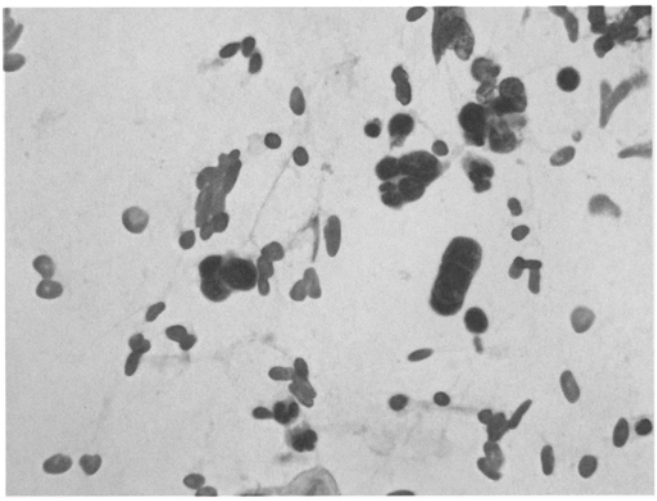


Fig. 43. Small cell carcinoma. Malignant small cells with high nuclear: cytoplasmic ratio, molding and single file arrangement (LBP).

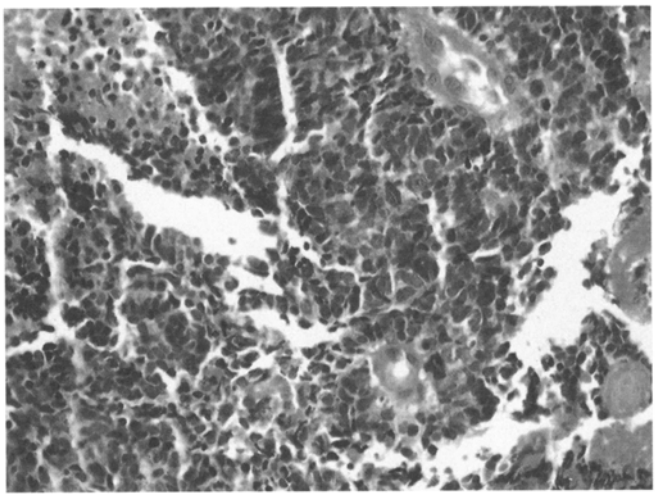


Fig. 44. Small cell carcinoma. Small blue cells with molding and necrosis (Histology).

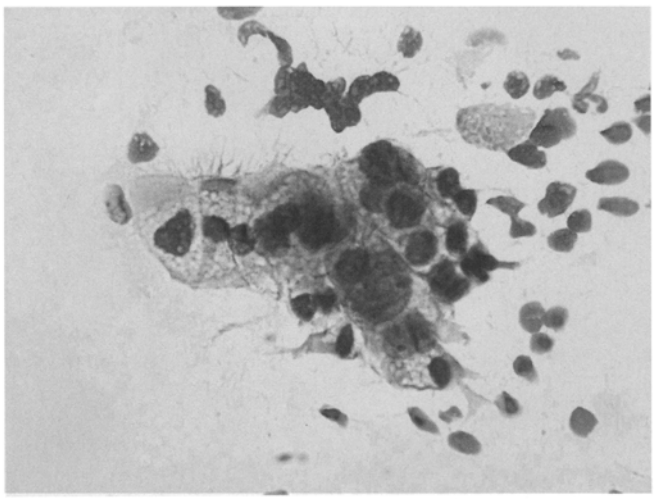


Fig. 45. Endocervical cells, tubal metaplasia. A strip of ciliate columnar endocervical cells (CP).

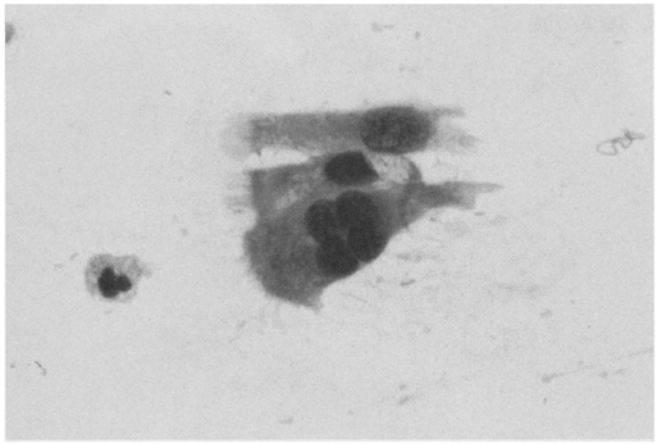


Fig. 46. Endocervical cells, tubal metaplasia. Columnar endocervical cells, one multinucleated, with celia (CP).

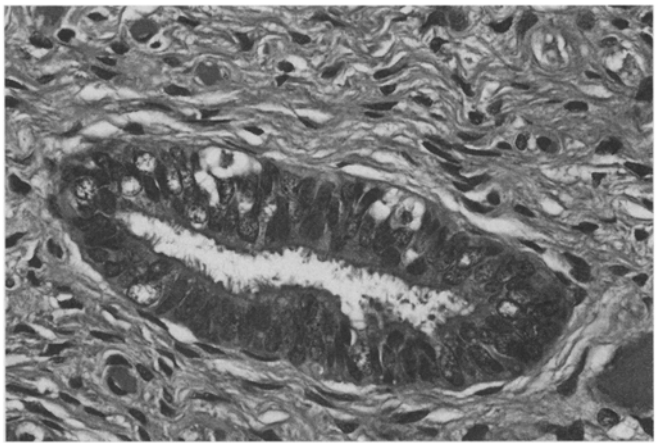


Fig. 47. Tubal metaplasia. Ciliated tubal epithelium lines an endocervical gland (Histology).

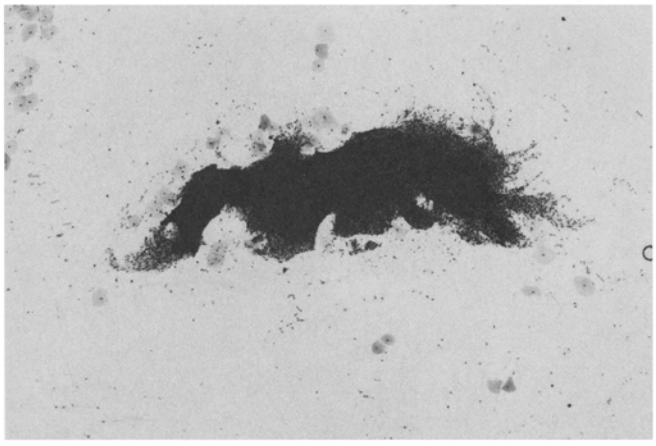


Fig. 48. Lower uterine segment endometrium can mimic AIS. Branching fragment of epithelial and stromal cells (CP).

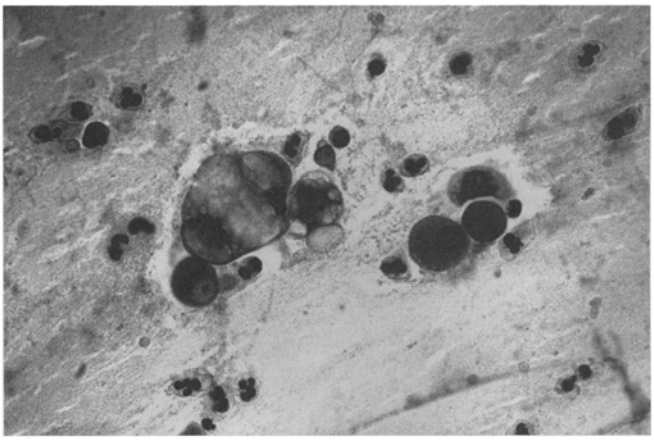


Fig. 49. Reactive cellular changes associated with intrauterine contraceptive device. Glandular cells with cytoplasmic vacuoles displacing the nuclei (CP).

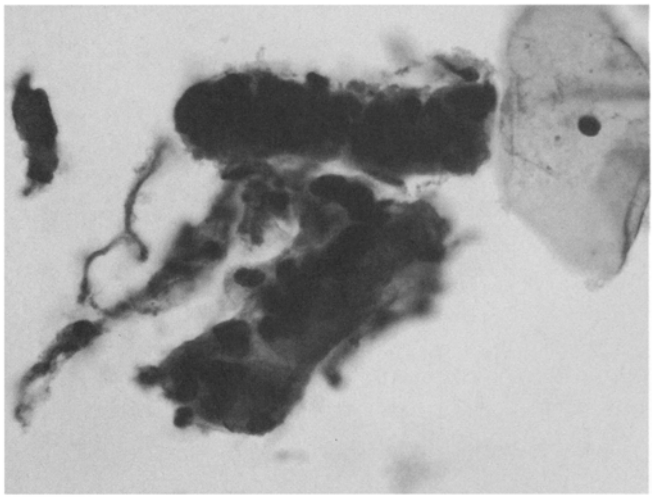


Fig. 50. Atypical endocervical cells, favor neoplastic. Crowding and pseudostratification of two strips of atypical endocervical cells. Follow-up biopsy showed AIS (LBP).

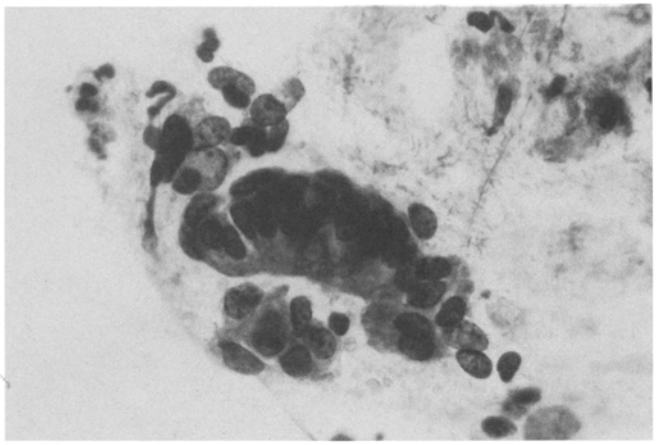


Fig. 51. Atypical endocervical cells, favor neoplastic. A strip of pseudostratified atypical endocervical cells and a disorganized cluster of similar cells. The findings fall short of those characteristic of AIS (LBP).

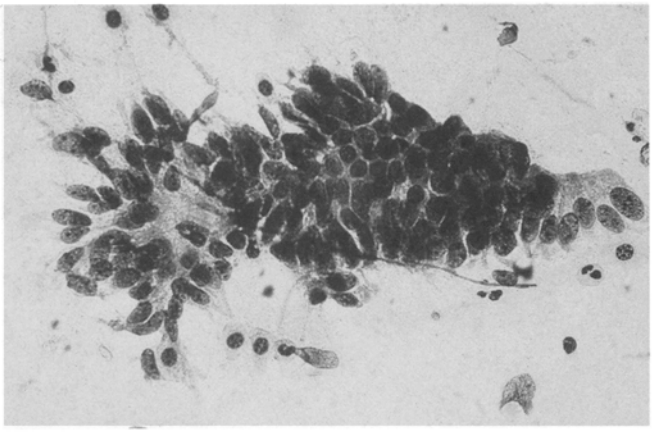


Fig. 52. AIS. Hyperchromatic endocervical cells with pseudostratification, rosette-like arrangement and feathering.

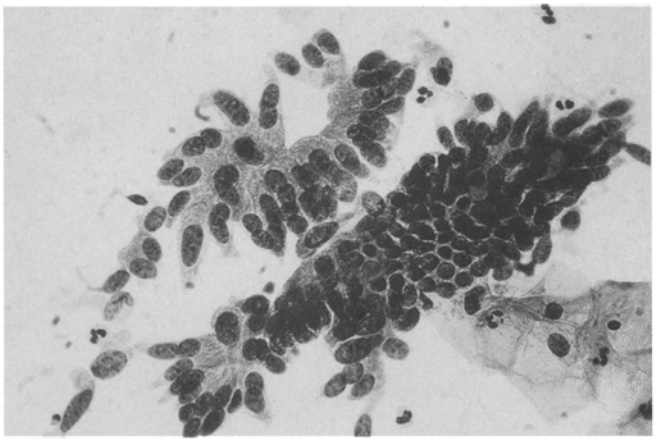


Fig. 53. AIS. Pseudostratified hyperchromatic endocervical cells with rosette-like arrangement and feathering (CP).

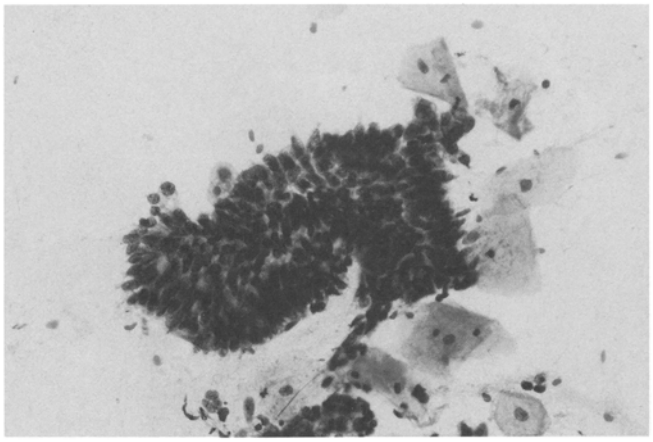


Fig. 54. AIS. Crowded three-dimensional clusters of endocervical cells with enlarged elongated nuclei and coarsely granular chromatin. Feathering is noted (LBP).

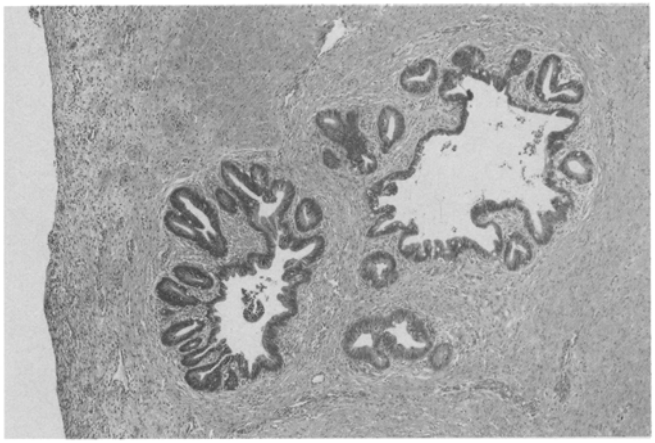


Fig. 55. AIS. Endocervical gland with stratified neoplastic lining (History, low power).

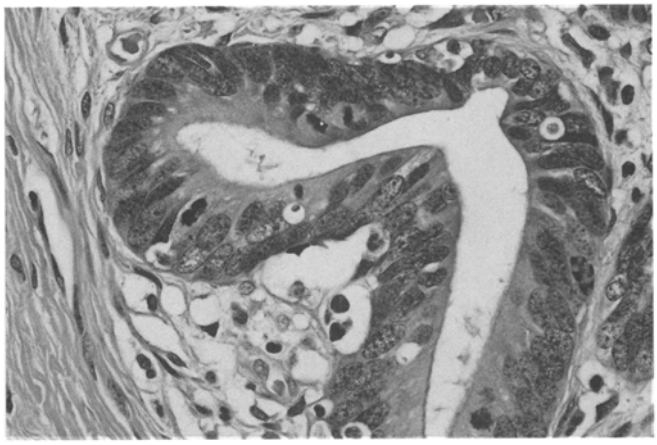


Fig. 56. AIS. Endocervical gland with pseudostratification of enlarged hyperchromatic elongated nuclei and mitotic figures (Histology, high power).

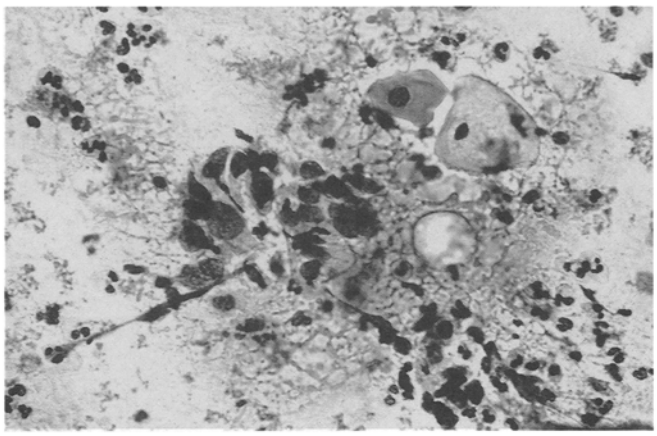


Fig. 57. Adenocarcinoma, endocervical. Columnar cells with eccentric large round to oval nuclei, irregular chromatin pattern, nucleoli and eosinophilic granular cytoplasm. Tumor diathesis is present in the backround (CP).

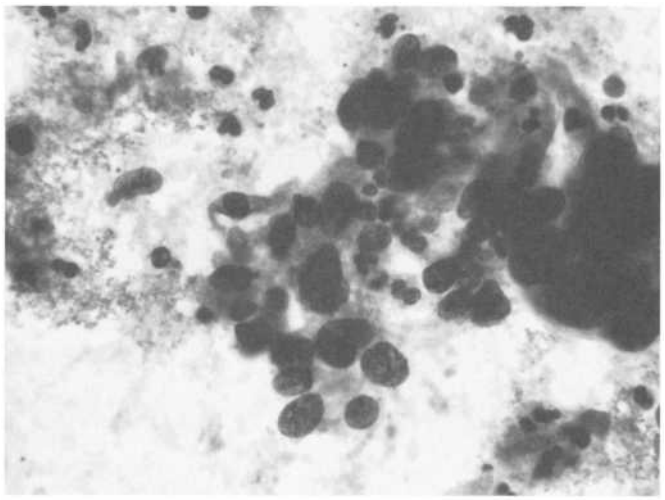


Fig. 58. Adenocarcinoma, endocervical. Adenocarcinoma cells with suggestion of a columnar configuration and glandular formation. The nuclei are elongated and hyperchromatic with irregularly distributed chromatin pattern and nucleoli. The cytoplasm is basophilic and granular. Tumor diathesis is present in the backround (CP).

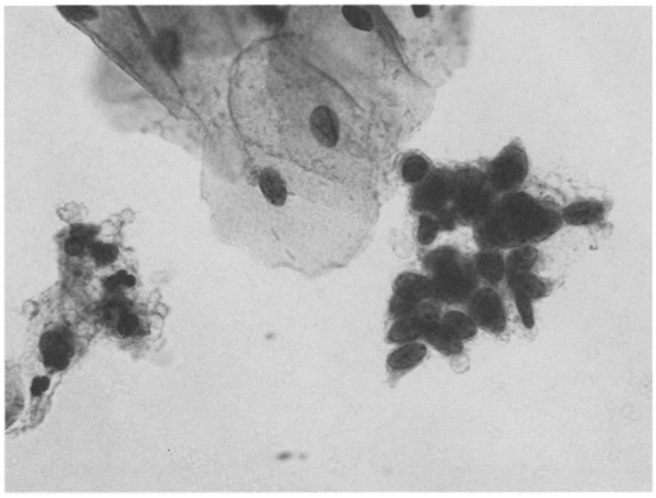


Fig. 59. Endometrial cells cytologically normal. LBP.jpg.

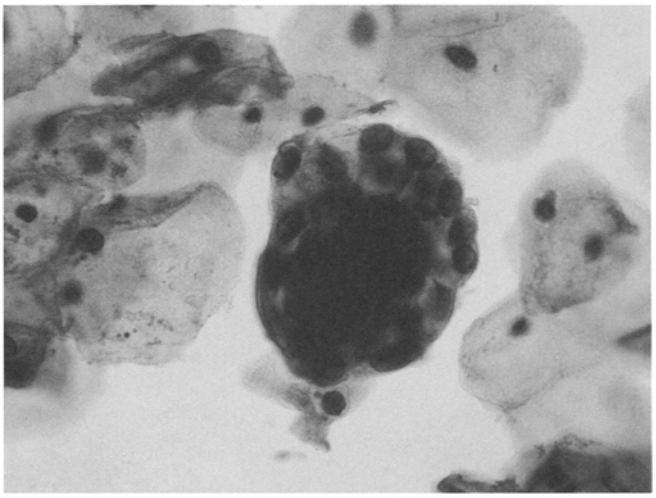


Fig. 60. Endometrial cells, cytologically normal-exodus. A tight ball of cells with central epithelial and peripheral stromal cells (LBP).

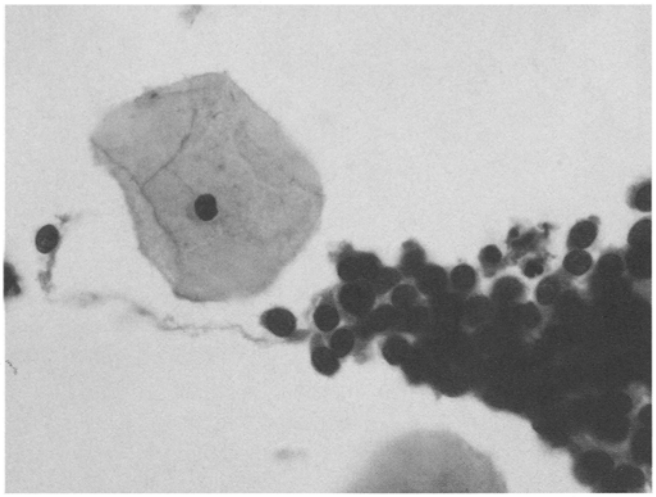


Fig. 61. Endometrial cells, present in 40 years and older. Tight cluster of small glandular cells with eccentric nuclei and scant cytoplasm. The nuclei are uniformly round and have regularly distributed chromatin pattern (LBP).

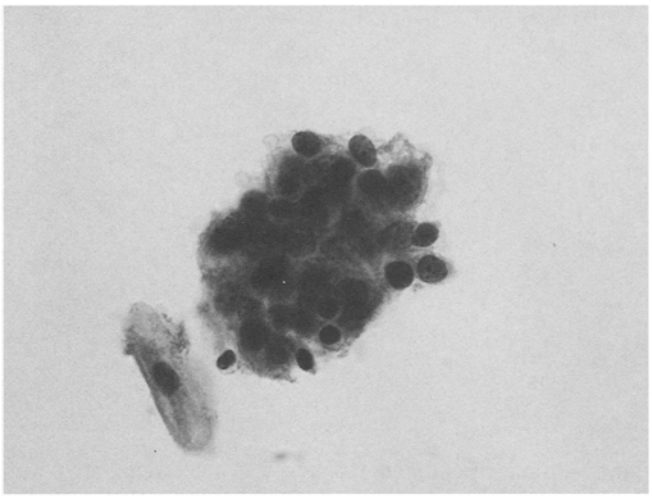


Fig. 63. Atypical endometrial cells. Tight cluster of endometrial cells with loss of polarity, variation in nuclear size and shape, coarse chromatin pattern and scattered small nucleoli (LBP).

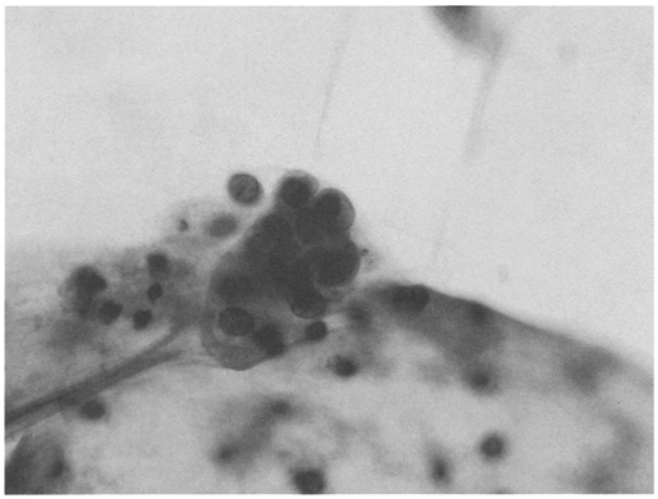


Fig. 62. Atypical endometrial cells. A cluster of atypical endometrial cells with slight variation in size and shape, loss of polarity, and mild nuclear enlargement (LBP).

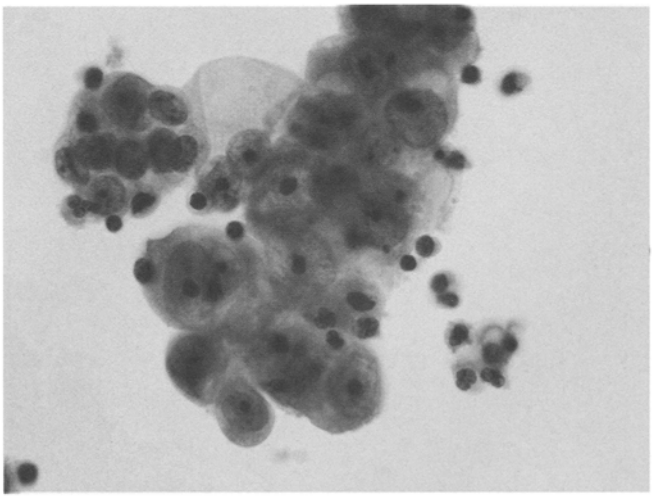


Fig. 64. Adenocarcinoma, endometrial. Three-dimensional cluster of malignant glandular cells with round eccentric nuclei, vacuolated basophilic cytoplasm and nucleoli (LBP).

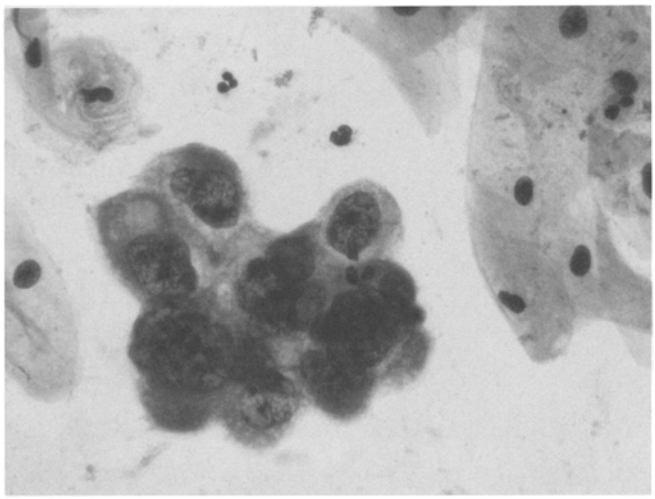


Fig. 65. Adenocarcinoma, endometrial. A cluster of pleomorphic malignant glandular cells with eccentric irregular nuclei, irregular chromatin pattern of nucleoli (LBP).

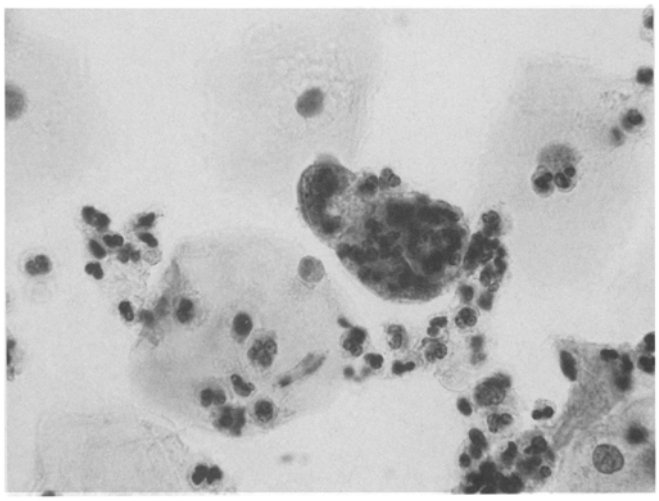


Fig. 66. Adenocarcinoma, endometrial. Malignant glandular cells in a papillary configuration (LBP).

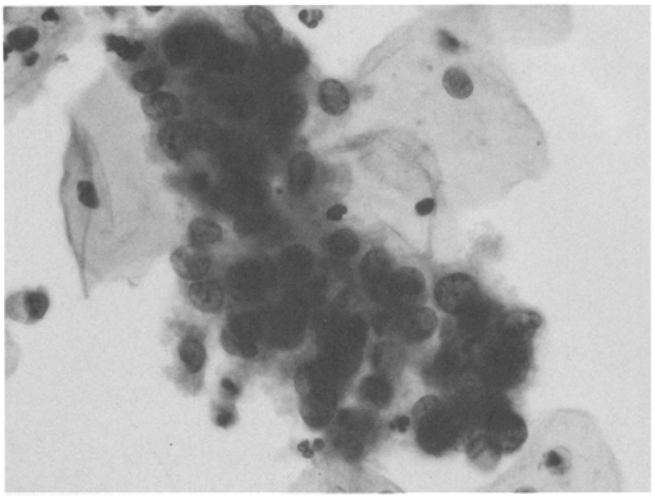


Fig. 67. Adenocarcinoma, not otherwise specified. The cluster of high-grade adenocarcinoma has papillary features. The primary carcinoma was endometrial with secondary involvement of the endocervix (LBP).

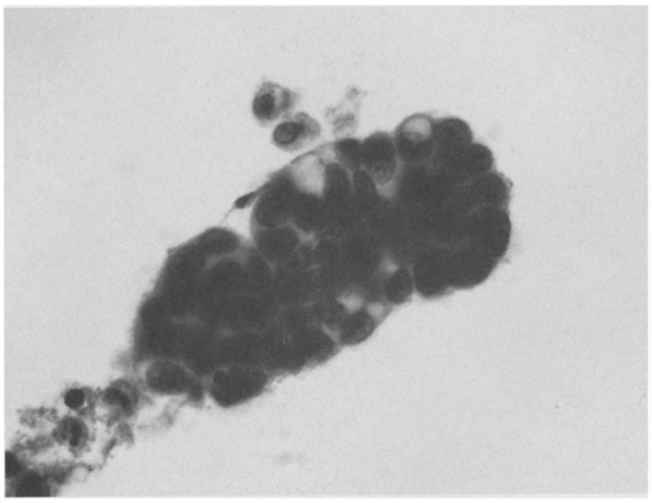


Fig. 68. Vaginal specimen. Adenocarcinoma, metastatic to vagina from primary ovarian papillary serous carcinoma. Three-dimensional cluster of malignant glandular cells with prominent nucleoli (LBP).

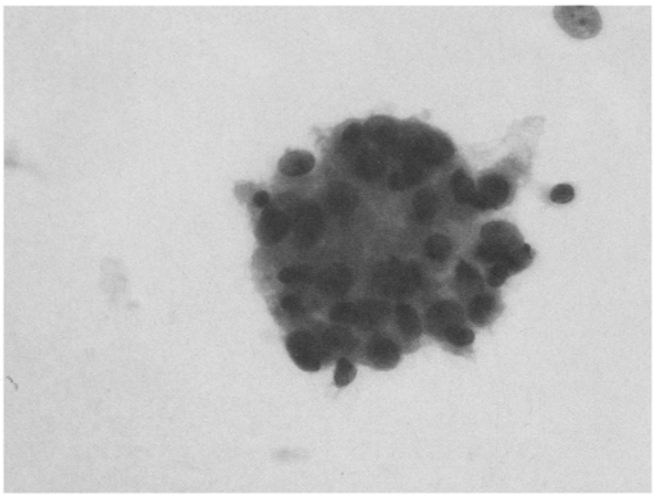


Fig. 69. Vaginal specimen. Adenocarcinoma, metastatic from primary adenocarcinoma of endometrium. A cluster of malignant glandular cells. The patient had previously a hysterectomy for deeply invasive endometrial adenocarcinoma (LBP).

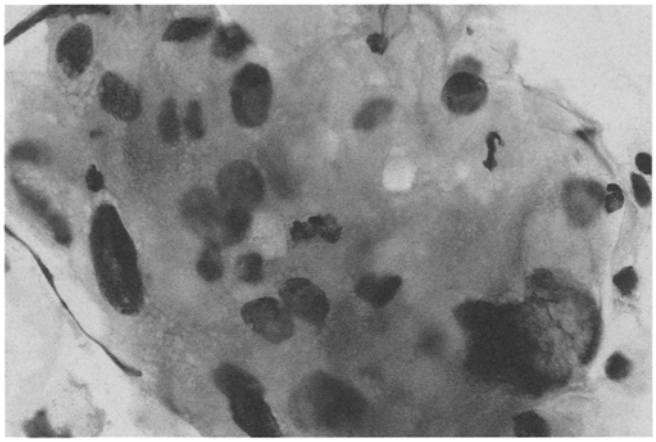


Fig. 70. Decidua. These cells were observed on a Pap smear from a pregnant woman. They show abundant eosinophilic to amphophylic cytoplasm and enlarged nuclei with smudged chromatin pattern (CP).

Part B

Non-Gynecologic Cytology

OVERVIEW

Evaluation of Cytologic Smear

- Cellularity
- Are the cells representative of a lesion?
- Type of cells (epithelial, mesenchymal or lymphopoietic)
- Architectural arrangement of tissue fragments
- Relationship of cells
- Cellular changes: Nuclear to cytoplasmic (N/C) ratio, cytoplasm, nuclear change (chromatin, nuclear membrane, and nucleoli)
- Background: bloody, granular, watery proteineous, inflammatory, granuloma, mucoid, diathesis, etc

Key Cellular Features

Benign Cellular Features

- Centrally located, single or multiple, round to oval nuclei
- Chromatin finally granular and evenly distributed
- Nuclear membrane smooth
- Single or multiple, small, rounded nucleoli
- Normal N/C ratio
- Well defined cytoplasmic border
- Tissue fragments are one to two cell layers with good polarity or honeycomb pattern

Reactive Cellular Features Due to Inflammation

- Centrally located, single or multiple, round to oval nuclei
- Nuclei enlarged with slightly enlarged nucleoli
- N/C ratio normal or slightly increased
- Chromatin slightly more granular and may be hyperchromatic
- Nuclear membrane may be wavy but uniform in thickness
- Background with inflammation, granular and cellular debris

Degenerative Changes Due to Reversible Injury

- Nuclear enlargement due to swelling (karyolysis)
- Chromatin smudged or washed out
- Nuclear membrane may be uneven in thickness
- Nucleoli may be indistinct
- Cells may become more rounded due to swelling
- Cytoplasmic disintegration and fraying (moth-eaten appearance)
- Cell borders not well defined
- Normal N/C ratio
- Background may or may not be inflamed

Degenerative Features Due to Irreversible Injury

- Nucleus wrinkled and decreased in size
- Loss of chromatin detail
- Pyknotic and smudged chromatin
- Fragmentation and condensation of chromatin (karyorrhexis)
- Hyperchromasia
- Nucleolus invisible
- Cytoplasmic borders not well defined and disintegrated
- N/C ratio may be increased due to loss of cytoplasm or decreased due to nuclear shrinkage

Cellular Features of Repair

- Monolayer sheets of well organized cells and very few single cells
- Cells bear striking resemblance to each other
- Little or no cellular overlap
- Enlarged cells with centrally located round nuclei
- Enlarged nuclei
- Prominent nucleoli/cherry red single macronucleoli
- Marginated chromatin (swelling)
- Well defined, uniform, thick nuclear membrane
- Well defined cell borders
- Cytoplasm may be streaming in the same direction (school of fish)

Atypical Repair

- Areas of atypical repair usually merge or coexist with typical repair
- Anisonucleosis within the monolayer sheet
- Increased cellular overlap within the sheet
- Increased number of single cells
- Increase chromatin granularity
- Altered nuclear polarity
- Hyperchromasia
- Cell borders blurred

General Features of Malignancy

- Increase N/C ratio (with few exceptions)
- Nuclei are round to oval, single or multiple, and frequently irregular
- Marked variation in nuclear size and shape (anisonucleosis)
- Chromatin is crisp and may vary from finely granular and evenly distributed to coarsely granular and unevenly distributed
- Chromatin rim may be irregular in thickness
- Nuclear membrane may be smooth but frequently irregular with grooves and sharp notches
- Nucleoli may vary from inconspicuous to prominent. They may be angulated or irregular
- Cellular discohesion with many single cells

- Cells within aggregates lose their polarity and form pseudosyncytia (cells blend with each other and lose their well defined borders)
- Background may contain tumor diathesis which appears as granular material with cellular debris and old blood

Cellular Patterns

Mixture of Epithelial Cells/Lymphocytes

- Branchial cleft cyst
- Sialadenitis
- Lymphoepithelial lesion
- Warthin's tumor
- Hashimoto's thyroiditis
- Thymoma
- Seminoma
- Medullary carcinoma of the breast
- Nasopharyngeal lymphoepithelioma-like carcinoma

Mixture of Epithelial Cells/ Spindle Cells (biphasic)

- Pleomorphic adenoma
- Tumors with marked stromal fibrosis
- Neuroendocrine tumors (e.g. carcinoid)
- Synovial sarcoma
- Malignant schwannoma
- Mesothelioma (biphasic)
- Phyllodes tumor
- Brenner's tumor
- Malignant mixed mullerian tumor
- Leiomyoblastoma
- Wilms' tumor
- Hepatoblastoma
- Epithelioid sarcoma
- Epithelioid leiomyosarcoma
- Melanoma

Plasmacytoid Cells

- Multiple myeloma
- Lymphoma (lymphoplasmacytic and Waldenstrom's lymphoma)
- Carcinoid
- Medullary thyroid carcinoma
- Islet cell tumor
- Breast carcinoma. lobular and ductal
- Urothelial/carcinoma
- Melanoma

Tumor with Discohesive Pattern

- Lymphoma
- Melanoma
- Sarcoma
- Squamous cell carcinoma
- Signet ring carcinoma
- Lobular carcinoma of the breast
- Seminoma
- Neuroendocrine tumors
- Small blue cell tumors: Ewing's sarcoma, primitive neuroectodermal tumor (PNET), neuroblastoma, and rhabdomyosarcoma

Tumors with Acinar Pattern

- Prostate carcinoma
- Thyroid follicular tumor
- Carcinoid and neuroendocrine tumor

Tumor with Trabecular Pattern

- Hepatic tumor (hepatocellular carcinoma, hepatic adenoma)
- Thyroid follicular tumor
- Breast carcinoma
- Carcinoid
- Merkel cell carcinoma

Granuloma

- Infectious (e.g. fungal, mycobacterium etc.)
- Non-infectious (e.g. sarcoidosis, Wegener's granulomatosis etc.)
- Reaction to foreign body (e.g. keratin, amyloid, suture material)
- Tumors with granulomatous component:
  - Squamous cell carcinoma
  - Seminoma
  - Hodgkin lymphoma
  - T-cell lymphoma

Intranuclear Cytoplasmic Inclusions

- Papillary thyroid carcinoma
- Medulllary carcinoma of the thyroid
- Hurthle cell neoplasm
- Hyalinizing trabecular adenoma of the thyroid
- Parathyroid adenoma
- Bronchioalveolar carcinoma
- Hepatocellular carcinoma
- Melanoma
- Meningioma
- Sclerosing hemangioma
- Breast carcinoma
- Adrenal cortical carcinoma

Intracytoplasmic Inclusions/Hyaline Globules

- Papillary thyroid carcinoma (septate vacuoles)
- Bronchioalveolar carcinoma, clara cell type (sufactant)

- Squamous cell carcinoma (keratin)
- Adenocarcinoma (mucin droplets)
- Hepatocellular carcinoma (Mallory bodies or inspissated secretions)
- Melanoma
- Yolk sac tumor (alpha-fetoprotein or human chorionic gonadotropins)
- Pleomorphic liposarcoma (sarcoma bodies)
- Rhabdoid tumor (intermediate filaments)

Extracellular Hyaline Globules

- Corpora amylacea
- Collagenous spherules
- Liesegang rings
- Alveolar proteinosis
- Amyloid (irregular and thick)
- Mesothelial hyperplasia and mesothelioma (collagen balls)
- Clear cell carcinoma of the kidney or ovary
- Adenoid cystic carcinoma (smooth globules)
- Monomorphic adenoma (irregular globules)

Signet Ring Cells

- Goblet cells
- Mesothelial cells
- Gastrointestinal tract carcinoma
- Mucinous carcinoma of the breast, ovary
- Mucinous carcinoid

Mucinous/Myxoid Background

- Mucinous carcinoma
- Pleomorphic adenoma
- Chondroid hamartoma
- Chondroid tumors
- Myxoid tumors

Psammoma Bodies

- Papillary carcinoma of thyroid, breast, ovary
- Bronchoalveolar carcinoma
- Malacoplakia
- Meningioma
- Endosalpingiosis
- Mesothelial hyperplasia and mesothelioma

RESPIRATORY CYTOLOGY

Overview

Normal Cellular Components of Lung Cytology

- Squamous cells
- Alveolar macrophages
- Bronchial epithelial cells
- Terminal bronchiolar and alveolar lining cells (pneumocytes)
- Inflammatory cells
- Megakaryocytes and mesothelial cells

Types of Cellular Specimens

Exfoliate

- Sputum
- Bronchial Brushings (BB)
- Bronchoalveolar lavage (BAL)

Fine needle aspiration

- Fine needle aspiration (FNA)
- Transbronchial needle aspirate

Spectrum of Cytologic Changes in Various Preparations

Sputum

- Adequacy of sputum specimen: macrophages must be present (exception: acute pneumonia)
- When positive, often shows small number of single or small tight clusters of tumor cells with frequent degenerative changes
- Often obscured by inflammatory exudate or food contamination
- Tumor diathesis is indistinguishable from inflammatory exudate or pneumonia
- May contain large number of squamous cells from oral cavity

Bronchial Brushings

- Contain large number of cells and tissue fragments with few macrophages
- Large number of columnar ciliated bronchial epithelial cells with or without reactive change
- Profuse mucus, and tumor diathesis well demonstrated

Bronchial Washings and Bronchoalveolar Lavage (BAL)

- Small number of tumor cells
- Large number of macrophages (many pigmented and multinucleated)
- Degenerative/distorted bronchial epithelial cells in tight clusters/balls which may have lost their cilia and stain hyperchromatic

Fine Needle Aspiration (FNA)

- Excellent cellular preservation and good representation of lesion (if smear is cellular)
- Large number of cells seen singly or in fragments
- Few macrophages and bronchial epithelial cells and rare mucus
- Pneumocytes may be abundant with reactive changes
- Mesothelial cells may be seen
- Tumor diathesis is well demonstrated

Transbronchial FNA

- Performed to sample a bronchial mass for primary diagnosis or hilar lymph nodes for staging and/or primary diagnosis
- Contain many bronchial cells, histiocytes, and mucin in addition to the lesional cells
- Aspirates of hilar lymph nodes should contain lymphocytes to document adequate sampling of the node when the aspirate is negative

Benign Lesions

Pulmonary Infarct

- Maximum atypia is seen during 2nd–3rd post-infarction weeks
- Sheets and papillary grouping of reactive pneumocytes
- Granular or vacuolated cytoplasm
- Nuclear and nucleolar enlargement
- Degenerative changes and metaplastic squamous cells
- Hemosiderin-laden macrophages

Pneumonia

- Numerous polymorphous leukocytes
- Cell debris
- Degenerative changes of the epithelial cells
- Bacterial colonies are significant only in FNA
- Carefully screen FNA with purulent materials to exclude carcinoma associated with obstructive pneumonia
- Culture suspicious FNA

Creola Bodies

- Benign reactive columnar cell hyperplasia, often seen in asthma
- Papillary tissue fragments or three-dimensional cell balls
- Smaller, less differentiated peripheral palisading cells with terminal plates and cilia
- Goblet cells may be seen within the peripheral palisading cells

Cigarette and Habitual Marijuana Smoking

- The earliest change in squamous metaplasia is reserve cell hyperplasia
- Reserve cell hyperplasia consists of tight clusters of uniform small cells with hyperchromatic nuclei
- Single or monolayered sheets of metaplastic cells with dense cyanophilic cytoplasm
- Immature squamous metaplasia
- Numerous multinucleated histiocytes

Radiation and Chemotherapy-Induced Atypia

- Cytomegaly, nucleomegaly, multinucleation and normal N/C ratio
- Cytoplasmic vacuolization and cytoplasmic polychromasia
- Bizarre cells with amphophilic cytoplasm, indistinct cell border, and cytophagocytosis of neutrophils
- Nuclear degeneration (karyorrhexis and karyolysis), hyperchromasia, and prominent nucleoli
- Smudged chromatin and poor nuclear detail

Amiodarone (Antiarrhythmic Drug)- Induced Changes

- Foamy alveolar macrophages with uniform, ill-defined, and smaller vacuoles than the coarse vacuoles seen in lipoid pneumonia
- Negative oil-red O stain
- Atypical pneumocytes with increased N/C ratio, hyperchromasia, and nuclear pleomorphism
- Cells retain cohesiveness, smooth or flattened cell border, and regular nuclear membranes
- Background of increased lymphocytes, neutrophils, and eosinophils
- Electron microscopy: osminophilic lamellar cytoplasmic inclusions

Hemosiderin-Laden Macrophages

Pediatric Patients

- Idiopathic pulmonary hemosiderosis (isolated)
- Pulmonary hemosiderosis associated with sensitivity to cow's milk
- Glomerulonephritis
- Collagen vascular and pruritic disease
- Cardiac diseases, intravascular lesions or malformations

Adult Patients

- Diffuse interstitial pulmonary disease
- Sarcoidosis
- Hypersensitivity pneumonitis
- Fibrosis associated with rheumatoid arthritis
- Radiation or chemotherapy

Quantitation of Hemosiderin-Laden Macrophages

- Percentage of cells containing hemosiderin (Prussian blue or Perl stain):
  - Result of >20% has a sensitivity of 10% and specificity of 92% for detecting pulmonary hemorrhage and hemosiderosis

- Hemosiderin score:
  - Adding staining intensity score (0–3) for each 100 cells measured
  - A score of >50 has a high sensitivity and specificity in the proper clinical setting

Lipid-Laden Macrophages in Bronchial Lavage

- Associated with tracheal aspiration in children with gastroesophageal reflux (GER) or lobular consolidation distal to an obstructed bronchus
- Aspiration of mineral oil
- Quantitation may be of value for predicting recurrent aspiration

Corpora Amylacea

- Seen in:
  - Heart failure
  - Pulmonary infarction
  - Chronic bronchitis

Sarcoidosis

- May see loose clusters of epithelioid cells and giant cells intermingled with lymphocytes
- Schaumann's bodies may be noted in the giant cells
- Asteroid bodies are not specific

Ferruginous Bodies

- General term that implies a variety of mineral fibers that have been inhaled and sheathed with golden brown iron-protein complex
- Asbestos bodies (consist of a clear colorless central fiber of uniform thickness within a golden brown iron-protein complex):
  - Indicative of occupational asbestos exposure
- Non-asbestos bodies: have a black or yellowish center and is not uniform in thickness

Ciliocytophthoria

- Anucleated cytoplasmic fragments bearing cilia
- Suggestive of viral infection (e.g. respiratory syncytial virus)

Asthma

- Curschmann's spiral:
  - Coiled strands of inspissated mucus
- Charcot-Leydin crystals:
  - Elongated red crystalline structure derived from eosinophil (lyso)phospholipase B, involved in prostaglandin metabolism
- Eosinophils and goblet cell hyperplasia
- Creola bodies (see description above)

Infectious Processes

Cytologic Features of Viral Infection

- Intranuclear inclusion bodies
- Loss of nuclear chromatin patterns
- Multinucleation
- Cytoplasmic inclusions
- Ciliocytopthoria
- Necrosis and inflammation
- Bronchial and alveolar hyperplasia

Aspergillosis

- Thick, uniform, septate hyphae 3–6 μm in width
- Dichotomous branching at 45° angle
- Birefringent needle-like crystals (calcium oxalate) produced by A. niger and others
- Fruiting heads form in aerobic conditions
- Stained by Papanicolaou, Periodic acid-Schiff (PAS) and Grocott methods
- Potentially a contaminant but should always be reported

Cryptococcosis

- Seen extracellularly or intracellularly within macrophages
- Yeast cells 5–10 μm in size surrounded by thick mucoid capsule (clear zone)
- Single narrow-based budding with tear drop appearance
- Green cytoplasm with clear capsule on Papanicolaou staining
- PAS, alcian blue and mucicarmine stain the capsule
- Gomori's methenamine silver (GMS) stains the organism
- Background inflammation varies from mild to necrosis

Histoplasmosis

- Readily recognized on methenamine silver stain
- Oval, single budding, yeast like organism (2–5 μm) in macrophages and neutrophils

Phycomycosis/Zygomycetes (Mucor, Rhizopus etc.)

- Occur in severely immunocompromised, diabetics, renal failure and patients with severe burns
- Non-septae broad hyphae of variable width (5–20 μm), resembling ribbons
- Irregular branching at up to 90° angles
- Pale staining with most staining methods

Coccidiodomycosis

- Endemic in western and southern states
- Intact or collapsed large thick-walled spherules 20–60 μm in diameter (empty or contain endospores, resemble a bag of marbles)
- Round, non-budding, nucleated endospores 2–5 μm in size
- Eosinophilic staining in Papanicolaou preparations
- Strongly stained by Grocott's method

Blastomycosis

- Yeast cells 8–15 μm in diameter
- Refractile thick cell wall (double contour), poorly stained in Papanicolaou samples

- Strong staining with Grocott's method
- Single broad-based budding
- No hyphae
- Suppurative granulomatous inflammation in background

Candidiasis

- Candida species are part of the normal flora of the oropharynx
- Diagnosis requires histologic demonstration of pulmonary parenchymal invasion or identification of materials from FNA
- Small spherical to oval yeast like cell 2–6 μm in diameter
- Pseudohyphae and spores (sticks and stones)
- Should see both pseudohyphae and inflammatory response to diagnose as pathogenic

Tuberculosis

- A mixed inflammatory exudate
- Epithelioid histiocytes and giant cells
- Langerhan's giant cells (peripheral nuclei) are infrequently found
- Fragmented granuloma may be seen in FNA material
- Caseation ranges from absent to conspicuous
- Organisms may be demonstrated in FNA samples
- Requires acid fast staining, yield is higher when necrosis is present

Pneumocystitis Carinii (PCP)

- Eosinophilic foamy alveolar exudate
- Cluster of organisms with round clear spaces within the eosinophilic material (overlapping ringlets)
- Tiny basophilic dots are frequently seen in the clear spaces
- Cysts are 4–8 mm, spherical or cup shaped
- Trophozoites are 8/cyst
- Capsule/cyst stain: GMS, PAS, and toluidine blue
- Romanovsky (includes Diff-Quik, Geimsa and Wright stains) results in empty spaces against a purple background
- Trophozoites stain: Gram, Romanovsky (tiny purple dots)

Neoplastic Lesions

Keratinizing Squamous Cell Carcinoma (SCC)

Cytologic Findings

- Discohesive squamous cells with abnormal keratinization, pearls, and intercellular bridges
- Abundant orangeophilic waxy cytoplasm (Papanicolaou stain), pure blue (Romanovsky stain)
- Marked nuclear and cellular pleomorphism with variable N/C ratio
- Bizarre cell shapes including caudate and tadpole cells
- Irregular pyknotic nuclei with marked nuclear hyperchromasia
- Tumor diathesis

Differential Diagnosis

- Atypical squamous metaplasia:
  - Lack cellular and nuclear pleomorphism
- Vegetable cell contaminants:
  - Rectangular cell, refractile cellulose cell wall, and amorphous nuclei
- Pulmonary infarct:
  - Reparative features
  - Reactive type II pneumocytes
  - Hemosiderin-laden macrophages
- Necrosis in other carcinomas and cells heavily blood stained may acquire orangiophilia and mimic keratinization (look for viable cells and evidence of other differentiation)

Non-Keratinizing Squamous Cell Carcinoma

Cytologic Findings

- Irregular cohesive sheets
- Prominent nucleoli
- Clues to squamous differentiation:
  - Perinuclear halos and condensation of peripheral cytoplasm
  - Dense cytoplasm and well defined cell borders
  - Nucleoli vary in size and number
  - Chromatin is coarse and varies in density among cells

Differential Diagnosis

- Other poorly differentiated carcinomas:
  - Lack clues to squamous differentiation
- Adenocarcinoma:
  - Most adenocarcinomas have vacuolated cytoplasm and syncytial appearance with ill-defined cell borders
  - Prominent nuclei that tend to be more monotonous
  - Chromatin more vesicular
- Large cell undifferentiated carcinoma:
  - Highly atypical and discohesive
  - Lack clues to squamous differentiation

Adenocarcinoma

Cytologic Findings

- Isolated cells in columnar configuration with altered polarity
- Sheets, rosettes, acinar, syncytial grouping, cell balls, and papillary structures with smooth community border
- Abundant pale or vacuolated cyanophilic cytoplasm
- Intracytoplasmic lumens in certain types
- Peripherally located round nuclei with coarse granular chromatin

Table 2. Staining Characteristics of Mesothelioma and Adenocarcinoma

Stain	*Mesothelioma*	*Adenocarcinoma*
Routine stains	Two-tone appearance with Papanicolaou	Homogeneously distributed stain
	Peripheral blebs with Diff-Quik	No peripheral blebs noted
Special stains	PAS + digestible material (glycogen)	Glycogen content is small
	Coalesced vacuoles may appear sausage-shaped	PAS + material not digested
Immunostains	Extracellular alcian blue+ material removable by hyaluronidas	No hyaluronic acid present
CEA	Consistently negative	Consistently positive
EMA	Variably positive with frequently "thick" membrane	Frequently positive in cytoplasm and cell periphery
LMWK and HMWK	Positive for both	Positive only for LMWK
Leu Ml	Invariably negative	Occasionally positive
HBME-l	Positive in many cases (cytoplasmic or membranous)	Occasionally positive
Calretinin	Positive in many cases	Usually negative

- Chromatin more vesicular than SCC
- Single prominent maronucleoli
- Frequent nuclear pseudoinclusions in bronchoalveolar carcinoma
- Clean or mucinous background

Variants

- Bronchoalveolar carcinoma:
  - Cellular smear with monotonous cell population
  - Sheets of slightly atypical cells with no cilia
  - Arrangements in cell ball, sheets or papillae
  - Cell balls with flower-petal like knobby border
  - Mucinous variants often display vacuolated or abundant foamy cytoplasm
  - Round to oval eccentrically located nuclei with prominent nucleoli
  - Occasional nuclear folds and intranuclear cytoplasmic inclusions
  - Variable pleomorphism and atypia among cells
  - Psammoma bodies

Differential Diagnosis

- Mesothelioma:
  - Flat sheets of uniform population of cells with dense two-tone type cytoplasm
  - Scalloped borders, thick cell membrane and cytoplasmic blebs
  - Centrally placed nuclei
  - Lack hyaluronidase resistant alcian blue staining
  - See **Table 2**
- Squamous cell carcinoma (see non-keratinizing SCC)
- Hyperplastic type II pneumocyte proliferations and reactive/reparative changes:
  - Smooth outlined spherical clusters and cohesive sheets of cells
  - Scalloped borders and intercellular windows (gap) typical of reactive type II pneumocytes
  - Spectrum of reactive changes and continuity with recognizable benign cells
  - Rectangular or columnar cells with cilia and shows terminal plates
  - Normal N/C ratio with abundant cytoplasm, uniform nuclei, and prominent nucleoli
  - Multinucleated cells and degenerative changes with smudged chromatin
  - Lack of necrosis and tumor diathesis
  - Sputum and BAL may contain numerous clusters
- Creola body:
  - Benign reactive columnar cell hyperplasia, often seen in asthma
  - Papillary tissue fragments or three-dimensional cell balls
  - Smaller, less differentiated peripheral palisading cells with terminal plates and cilia

- Pap cell:
  - Derived from squamous metaplasia/parakeratosis in pharynx or upper respiratory tract
  - Small angulated cells with degenerative nuclei (pseudokeratosis)
- Granular cell tumor:
  - Isolated or small clusters of cells with a finely granular cytoplasm
  - Uniform round to oval nuclei frequently eccentric
  - Small nucleoli
  - Some spindled cells
  - S-100 protein +

Large Cell Undifferentiated Carcinoma

Cytologic Findings

- Single or disorganized groups of large malignant cells with pleomorphic cell population
- High N/C ratio with variable cytoplasm and intracytoplasmic neutrophils
- Nuclear enlargement with multiple large prominent nucleoli
- Thickened irregular nuclear membrane and coarse clumped chromatin pattern
- Delicate cyanophilic cytoplasm without evidence of squamous or glandular differentiation
- May contain giant cells (<25% of total cells)
- Tumor diathesis

Differential Diagnosis

- Giant cell carcinoma:
  - Neutrophil infiltrate and emperipolesis
  - Pronounced nuclear pleomorphism with multiple nuclei and nucleoli
  - Multinucleated cells constitute more than 25% of total cell population
- Metastatic Melanoma:
  - Dusty cytoplasm
  - Intranuclear pseudoinclusions
  - Positive staining to S-100 protein, HMB-45, and Melan-A (Mart-1)

Pulmonary Neuroendocrine Tumors

- Typical carcinoid
- Atypical carcinoid
- Large cell neuroendocrine carcinoma
- Small cell carcinoma

Typical Carcinoid

- Highly cellular smears
- Monotonous population of small round to oval cells
- Cells may have plasmacytoid appearance
- Occasional intranuclear inclusions
- Cohesive clusters, loosely cohesive sheets and single cells
- Acinar structures, papillae, cords of cells, interconnecting trabeculae, and nuclear palisading
- Low nuclear to cytoplasmic ratio
- No chromatin smearing
- Prominent capillaries

Atypical Carcinoid

- Slight to moderate nuclear pleomorphism
- More prominent nucleoli
- Occasional mitotic activity
- Single cell necrosis

Spindle Cell Carcinoid

- Common in peripheral carcinoid
- Can be typical or atypical
- Monotonous population of fusiform cells forming arches and coma shapes
- Single cells or loose aggregates
- Moderate cytoplasm with elongated processes that may show interconnection
- Small nuclear indentation
- Single small nucleoli
- Prominent capillaries

Large Cell Neuroendocrine Carcinoma

- Large polygonal to oval cells
- Some discohesion
- Nuclei are more than three times the size of a resting lymphocyte
- Nuclei variable in size and shape:
  - Large vesicular nucleus and prominent nucleoli similar to adenocarcinoma
  - Coarse stippled nucleus and occasional nucleoli similar to small cell carcinoma
- Obvious mitotic figures
- Obvious necrosis
- Nuclear molding variable
- Capillaries present surrounded by palisading cells

Small Cell Carcinoma

Cytologic Findings

- Cellular smears
- Dimorphic population of large cohesive sheets in a background of small blue cells with discohesion
- Background of single cells, doublets and short cords
- High N/C ratio with scant cytoplasm and coarsely clumped, "salt and pepper" chromatin

- Bare nuclei and elongated cells with pointed and angulated nuclei
- Nuclear size is equal or less than three times the size of a resting lymphocyte
- Paranuclear cytoplasmic inclusion (blue body)
- Chromatin smearing
- Pleomorphic, hyperchromatic, stippled nuclei with no nucleoli
- Extensive cellular molding
- Very obvious mitotic activity
- Necrotic background

Differential Diagnosis

- Reserve cell hyperplasia:
  - More cohesive, uniform cuboidal cells with smooth nuclear contours
  - Peripheral cells may have columnar configuration with cilia or terminal bars
  - Round uniform nuclei sometimes with very tight molding or crushing
  - Lack of discohesion or single cells
  - Lack tumor diathesis
- Benign lymphocytes and follicular bronchitis:
  - Small lymphocytes without anisonucleosis
  - Sharp demarcation of the euchromatin from heterochromatin
- Lymphoma/Leukemia:
  - Loosely aggregated lymphoid cells with intact cytoplasm
  - Vesicular nuclei, and visible nucleoli, no molding
  - Subtyping possible in BAL and FNA materials

Metastatic Carcinoma

- Metastatic Colon Carcinoma:
  - Geographic sheets in a background of extensive necrosis
  - Columnar cells with elongated hyperchromatic nuclei in a picket-fence or rosette pattern
  - Cytoplasmic vacuoles and prominent nucleoli may be seen
  - Prominent tumor necrosis
- Renal Cell Carcinoma:
  - Discohesive sheets of monotonous cells with uniform nuclei
  - Clear or granular cytoplasm
  - Numerous bare nuclei (due to fragile cytoplasm)
- Prostatic Adenocarcinoma:
  - Acinar arrangement of uniform cells with prominent nucleoli
- Breast Carcinoma:
  - Isolated cells or cell balls with eccentric nuclei imparting plasmacytoid appearance
  - Occasional cytoplasmic vacuoles and signet ring cells

SALIVARY GLAND AND HEAD/NECK CYTOLOGY

Statistics

- Most common salivary gland tumor:
  - Pleomorphic adenoma
  - Warthin's tumor (2nd most common)
- Most common parotid cancer in adults:
  - Mucoepidermoid carcinoma
- Most common malignancy of salivary glands other than parotid location:
  - Adenoid cystic carcinoma
  - Polymorphous low grade adenocarcinoma (2nd most common)
- Most common salivary gland malignancy in child:
  - Mucoepidermoid carcinoma
  - Acinic cell carcinoma (2nd most common)
- Most common cystic lesions of salivary glands:
  - Warthin's tumor
  - Mucoepidermoid carcinoma (2nd most common)
- Most common bilateral tumors of salivary glands:
  - Warthin's tumor
  - Acinic cell carcinoma (2nd most common)
- Most common bilateral cancer of salivary glands:
  - Acinic cell carcinoma
- Most common radiation induced malignancy:
  - Mucoepidermoid carcinoma

Salivary Glands

NORMAL FINDINGS

- Acinar cells (serous or mucinous):
  - Cohesive tissue fragments of spherical acini outlined by their basement membrane
  - Often held together by small amount of fibro-vascular tissue
  - May be connected by small ductular structure
  - Serous glands:
    - Abundant finely vacuolated cytoplasm
    - Small round basal nuclei

- May result in numerous bare nuclei (not to be confused with lymphocytes)

♦ Ductal cells:
- Small cohesive flat sheets
- Small cells with dense cytoplasm
- Round to oval nuclei

Non-Neoplastic Lesions

Sialadenosis

♦ Often bilateral enlargement of the parotid glands
♦ Numerous acinar epithelial cells
♦ Cells may appear normal or enlarged

Sialadenitis

Cytologic Findings

♦ Infective sialadenitis:
- Tender swollen glands
- Purulent material comprised of neutrophils, foamy cells, and endothelial cells

♦ Chronic sialadenitis:
- Key features are interstitial fibrosis and atrophy
- Hypocellular smear of cohesive clusters of epithelial cells with reactive changes
- Fibroblasts and admixtures of polymorphous inflammatory cells
- Oncocytic or squamous metaplasia (may have some atypia)

♦ Necrotizing sialometaplasia:
- Mainly affect the minor salivary glands
- Squamous metaplasia with atypia

Differential Diagnosis

♦ Benign lymphoepithelial lesions:
- Admixtures of polymorphous lymphoid cells and myoepithelial islands
- Few oncocytes and multinucleated histiocytes
- Absence of acute inflammatory cells

♦ Malignant lymphoma:
- Monotonous population of isolated lymphoid cells
- Absence of oncocytes and multinucleated histiocytes

♦ Intraparotid lymph node:
- Hypercellular smear of heterogeneous elements of lymphoid tissue

Benign Neoplastic Lesions

Pleomorphic Adenoma (Benign Mixed Tumor)

Cytologic Findings

♦ Biphasic population of epithelial cells and spindle stromal cell components
♦ Trabeculae, acinar and solid branching arrangement of epithelial cells
♦ Many single cells
♦ Cells may be plasmacytoid or vacuolated (sometimes signet ring)
♦ Well defined cytoplasmic border
♦ Round nuclei with finely granular chromatin
♦ Fibrillar chondromyxoid metachromatic stroma with irregular feathery outline on Romanovsky
♦ Tyrosine-rich crystals and metaplastic goblet or squamous cells may be seen

Differential Diagnosis

♦ Malignant mixed tumor:
- Malignant components (glandular, squamous, small cell or sarcomatous)

♦ Epithelial-myoepithelial carcinoma:
- Biphasic population of dark and clear cells
- Numerous bare nuclei or bipolar cells
- Absence of mesenchymal stromal component

♦ Mucoepidermoid carcinoma:
- Goblet cells, columnar cells and intermediate cells

♦ Well differentiated adenoid cystic carcinoma:
- Small cells with high N/C ratio
- Hyperchromatic nuclei
- Scant cytoplasm

♦ Basal cell (monomorphic) adenoma:
- Numerous epithelial clusters and few single cells
- Finely granular chromatin and scant cytoplasm
- Variable amount of stromal material
- Membranous variant: clusters surrounded by hyaline material (opposite to what is seen in adenoid cystic carcinoma)

Warthin's Tumor (Papillary Cystadenoma Lymphomatosum)

Cytologic Findings

♦ Orderly cohesive flat sheets and clusters of oncocytes intermixed with many lymphocytes
♦ Occasional aspirates may be dominated by lymphocytes

Differential Diagnosis

♦ Brachial cleft cyst:
- Anucleated squamous cells and cholesterol cleft

♦ Benign lymphoepithelial lesions:
- Myoepithelial islands and less frequent oncocytes

♦ Acinic cell carcinoma:
- More cellular, sheets and acinar glandular structures, lymphocytes inconspicuous

- Numerous bare nuclei
- PAS-positive and diastase resistant

♦ Oncocytoma:
- More abundant eosinophilic cytoplasm, lymphocytes inconspicuous

♦ Mucoepidermoid carcinoma:
- Coexistence of glandular and squamous components with intermediate cells

Malignant Neoplasms

Mucoepidermoid Carcinoma

Cytologic Findings

♦ Discohesive sheets and clusters of glandular and squamous cells
♦ Intermediate cell differentiation is pathognomonic
♦ Dirty background containing mucus and debris
♦ Low grade: predominantly glandular component
♦ High grade: squamous component often predominant

Differential Diagnosis

♦ Mucocele:
- Hypocellular smear with necrotic debris, inflammatory cells and mucoid material

♦ Warthin's tumor:
- Admixture of oncocytic cells and lymphocytes

♦ Chronic sialadenosis
♦ Necrotizing sialometaplasia
♦ Pleomorphic adenoma
♦ Metastatic squamous cell carcinoma:
- Abundant keratinized cells and keratin pearls, lack intermediate cells

Adenoid Cystic Carcinoma

Cytologic Findings

♦ Cellular smear of tight three dimensional cell balls
♦ Small uniform basaloid hyperchromatic cells surrounding smooth rounded hyaline globules composed of homogenous basement membrane material
♦ No squamous differentiation

Differential Diagnosis

♦ Monomorphic adenoma (trabecular adenoma):
- Irregular interface between tumor cells and collagenous stroma
- Tubular and branching growth pattern and more abundant finely fibrillar stroma
- Round to oval uniform nuclei with inconspicuous nucleoli

♦ Monomorphic adenoma (membranous):
- Clusters outlined by membranous material

Acinic Cell Carcinoma

Cytologic Findings

♦ Highly cellular material in a clean background
♦ Sheets and cords of monotonous cells with nuclear enlargement and nuclear pseudoinclusions
♦ Cohesive clusters sometimes with fibrovascular cores
♦ Poorly formed acinar structures
♦ Moderate sized nuclei with variable pleomorphism
♦ Abundant vacuolated or oncocytic cells
♦ Vacuolated cytoplasm (PAS-positive, diastase resistant)
♦ Stripped nuclei and lymphocytes
♦ Lack of ductal sheets

Differential Diagnosis

♦ Benign salivary gland acini:
- Less cellular
- Ductal epithelial cells, and fat present

Polymorphous Low Grade Adenocarcinoma

♦ Poorly cohesive clusters
♦ Small cells with scant cytoplasm and oval nuclei
♦ Finely granular chromatin and inconspicuous nucleoli
♦ Small hyaline oval globules

Salivary Duct Carcinoma

♦ Cytologic findings resemble those of comedocarcinoma of the breast
♦ Sheets of obviously malignant cells with high N/C ratio and pleomorphic nuclei
♦ Necrotic background

Head and Neck

Non-Neoplastic Lesions

Thyroglossal Duct Cyst

♦ Midline location and movable in a cranial direction when swallowing
♦ Hypocellular smear with squamous and glandular cells admixed with lymphocytes
♦ Thyroid follicular epithelium and variable colloid may be seen
♦ Occasional ciliated columnar respiratory epithelium

Epidermal Inclusion Cyst

♦ Abundant anucleated squames, inconspicuous lymphocytes
♦ Superimposed infection with neutrophils and multinucleated histiocytes

Brachial Cleft Cyst

Cytologic Findings

♦ Aspirate results in a thick yellow fluid
♦ Admixtures of numerous anucleated squamous cells and squamous cells of variable maturity, cholesterol clefts,

elements of reactive lymphoid tissue, foamy histiocytes and acellular debris
- Occasional ciliated columnar respiratory epithelium

Differential Diagnosis
- Metastatic squamous cell carcinoma with cystic degeneration (diagnosis rests on finding few highly atypical or bizarre cells with abnormal keratinization)
- Suppurative lymphadenitis
- Thyroglossal duct cyst (distinguished by anatomic site)
- Epidermal inclusion cyst

NEOPLASTIC LESIONS

Paraganglioma (Carotid Body and Glomus Jugulare Tumors)

Cytologic Findings
- Single or poorly cohesive cells with vague follicular pattern
- Abundant pale cytoplasm with fine red garanules on Romanovsky
- Round to oval nuclei with finely granular chromatin
- Intranuclear pseudoinclusions may be seen
- Aspirates are very bloody

Differential Diagnosis
- Medullary carcinoma of the thyroid:
  - Aspirates are usually more cellular and less bloody
  - Amyloid may be seen
  - Part of multiple neuroendocrine tumor syndrome

Neurilemmoma/Schwannoma
- Frequently occur in the head and neck (45%) particularly lateral aspect
- More often in women than men
- Should always be included in the differential of head and neck lesions

Meningioma
- Extracranial tumors appear in relation to the base of skull, the scalp, orbit, nasal cavity, paranasal sinuses, and middle ear
- Should always be included in the differential diagnosis of any head and neck lesion

Squamous Cell Carcinoma
- Most common carcinoma in the head and neck region
- Lymph node metastasis of well differentiated carcinoma have a tendency for cystic degeneration
- Few atypical cells in a dirty background may be all that is seen in a cystic or necrotic mass (look for abnormal dense keratin and bizarre shaped cells)
- Cytologic features are similar to those described in the respiratory section

Nasopharyngeal Carcinoma

Cytologic Features
- Undifferentiated malignant cells in small clusters and single cells
- High N/C ratio and scant eosinophilic cytoplasm
- Lymphoepitheliomatous type:
  - Large open nuclei and prominent nucleoli
  - Well defined eosinophilic cytoplasm
- Undifferentiated type:
  - Basaloid cells with hyperchromatic nuclei
- Numerous benign lymphocytes in the background

Differential Diagnosis
- Undifferentiated type from basal cell carcinoma
- Lymphoepitheliomatous type from Hodgkin's lymphoma or large cell lymphoma

Olfactory Neuroblastoma
- Occurs in the upper nasal cavity and may metastasize to cervical lymph nodes
- Small blue cells forming pseudorosettes
- Bland nuclei with finely granular chromatin
- Fibrillary material may be seen in the center of rosettes

THYROID

Overview
- Reporting Terminology (Diagn Cytopathol 15:84-9, 1996)
  - Unsatisfactory for interpretation (specify reasons)
  - Benign thyroid nodule/colloid nodule/nodular goiter
  - Cyst/cystic goiter, with or without hemorrhage
  - Thyroiditis, specify type
  - Cellular follicular lesion, favor nonneoplastic process
  - Follicular neoplasm
  - Hürthle cell neoplasm
  - Malignant, specify type if possible
  - Other

Benign Lesions

THYROID CYSTS
- Majority are benign
- Result in degenerative, necrosis, or hemorrhage within adenomatous nodule or neoplasm

- Benign cysts collapse after aspiration
- Variable number of histiocytes, +/– hemosiderin
- Multinucleated foreign body giant cells may be present
- Occasionally lined by squamous or columnar cells (thyroglossal duct cyst)
- Mainly lack epithelial cell component
- Beware of cystic papillary carcinoma

THYROIDITIS

Acute Thyroiditis

Cytologic Findings

- Enlarged gland with multiple abscesses
- Abundant neutrophils, macrophages, cellular debris, and fibrin
- Scant follicular cells

Differential Diagnosis

- Infected thyroglossal duct cyst:
  - Columnar ciliated or squamous cells
- Carcinoma with necrosis

Subacute Thyroiditis

- Common in middle age woman
- Resolve spontaneously in most cases
- Initial stage: degenerated follicular cells, multinucleated giant cells, epithelioid histiocytes, lymphocytes and neutrophils; background dirty
- Late stage: low cellularity with few inflammatory cells and active fibroblasts

Subacute Lymphocytic Thyroiditis

- Painless swelling that resolves spontaneously
- May develop in postpartum women
- Moderate lymphocytes and no Hurthle cells

Chronic Thyroiditis

- Chronic granulomatous thyroiditis e.g. tuberculous, mycotic, etc
- Reidel's thyroiditis:
  - Chronic fibrosing multifocal inflammation
  - Probably autoimmune
  - Sudden painless enlargement of a long standing mass
  - Dysphagia or dyspnea
  - Aspirates are poorly cellular and frequently non-diagnostic
  - May contain few lymphocytes, degenerated follicular cells and fibroblasts

Hashimoto's Thyroiditis

Clinical

- Middle aged women present with hypothyroidism
- Moderate generalized enlargement, micronodules can develop in late lesions

Cytologic Findings

- Acute phase: mostly lymphocytes
- Hypertrophic phase: admixture of lymphocytes and Hurthle cells
- Atrophic phase: admixture of cells but much lower in cellularity
- Microtissue fragments composed of Hurthle cells and hyperplastic follicular epithelium
- Admixture of inflammatory cells with germinal center (immature) lymphocytes, small lymphocytes, plasma cells and histiocytes
- Characteristically the lymphocytes infiltrate the Hurthle cells
- The Hurthle cells can occasionally be quite bizarre
- Inconspicuous colloid component

Differential Diagnosis

- Hürthle cell neoplasm:
  - Large sheets of Hurthle cells with syncytial arrangement and lack of lymphocytes
  - Numerous discohesive Hurthle cells
  - Prominent Hurthle cell nodules that do not have lymphocytes can be indistinguishable from Hurthle cell neoplasms
- Riedel's thyroiditis:
  - Fewer follicular center cells and absence of squamous metaplasia or Hurthle cells
  - More abundant neutrophils and eosinophils
- Subacute (Dequervain's) granulomatous thyroiditis:
  - Follicular center (immature) lymphocytes and Hurthle cells uncommon
  - Admixtures of follicular epithelium, small lymphocytes, epithelioid histiocytes, and foreign-body giant cells
  - Foreign body reaction "ingesting" colloid
  - Fibroblast and inflammatory debris
- Graves' disease:
  - Hypercellular smear with hyperplastic follicular epithelium
  - Inconspicuous colloid and inflammatory components
  - Flame cells

Black Thyroid Nodule

- Due to administration of minocyclines and tetracyclin
- Intracytoplasmic deposits of brown pigment in follicular cells
- Pigment consists of neuromelanin and lipofuscin

Nodular Goiter and Colloid Nodule

*Cytologic Findings (see **Table 3**)*

- Abundant colloid and variable number of follicular cells
- The presence of a labrithin of a rouloux of red blood cells and empty spaces with scant follicular cells suggests washed-out colloid

Table 3. Differential Diagnosis of Follicular Lesions

Colloid Nodule/Goiter	*Follicular Neoplasm*
Abundant colloid and scanty cellularity	Cellular specimen with scant colloid
Honeycomb sheets of follicular cells	Syncytial sheets and microfollicles
Regenerative and degenerative changes	

- Microtissue fragments, small follicles, and honeycomb sheets of follicular epithelium
- Nuclei are round with smooth contours
- Minor variation in nuclear size in the sheet may be observed
- Degenerative changes common (histiocytes, ± hemosiderin, giant cells, and fibroblasts
- Regenerative (reparative) changes
- Hurthle cell change, foam cells, and giant cells with foamy cytoplasm
- Stromal calcification

Toxic Diffuse Hyperplasia (Graves' disease)

- Highly cellular smears consisting of colloid and follicular/Hürthle cells
- Flame cells (key feature):
  - Follicular cells with metachromatic materials in apical cytoplasm
  - Secondary to hyperfunctioning of endoplasmic reticulum
  - May also be present in aspirates from active nodules
  - Paravacuolar granules
  - Non-specific findings, composed of lysosome with hemosiderin or lipofuscin
  - Seen best on Romanovsky stain

Differential Diagnosis of Hyperplastic lesions

- Follicular neoplasm (see **Table 3**)
- Follicular variant of papillary carcinoma:
  - Nuclear features of papillary carcinoma are preserved

Neoplastic Lesions

Follicular Neoplasm Favor Benign

*Cytologic Findings (see **Table 3**)*

- Hypercellular smear, microfollicles, and microfollicular complexes
- Uniform nuclei. and orderly cellular arrangement
- Syncytial tissue fragments with loss of honeycomb pattern
- Rarely markedly atypical or bizarre cells may be observed in atypical adenoma
- Scant colloid

Differential Diagnosis

- Parathyroid adenoma:
  - High cellularity with microfollicular pattern
  - Indistinguishable from follicular neoplasm
- Nodular goiter (*see* **Table 3**):
  - Admixture of colloid and follicular epithelial cells with small nuclei
  - Honeycomb sheets

Hürthle Cell Neoplasm

- Cellular smear of monomorphic discohesive cells
- Sheets and single isolated large oval or polygonal cells with abundant eosinophilic cytoplasm
- Uniform small round nuclei with fine granular chromatin and single prominent nucleoli
- Adenomas may not be reliably distinguished from well-differentiated carcinoma on FNA biopsies
- Carcinoma often more discohesive with numerous isolated smaller cells with high N/C ratio, nuclear pleomorphism, nuclear overlapping, coarsely granular chromatin and multiple nucleoli

Papillary Carcinoma

- Microtissue fragments of monolayer sheets, syncytium, and papillae with or without fibrovascular core
- Follicular structures observed especially in follicular variant
- Dispersed cell pattern may rarely be observed
- Numerous oval nuclei with irregular nuclear membranes (nuclear grooves imparting a coffee bean appearance)
- Any intranuclear cytoplasmic inclusions (diagnostic of papillary carcinoma, but may be observed in medullary carcinoma)
- Nuclei with fine granular chromatin and multiple small nucleoli
- Nuclear molding and crowding
- Septated cytoplasmic vacuoles seen on Romanovsky stain
- Squamous differentiation with dense metaplastic cytoplasm
- Psammoma bodies: colorless and refractile on Romanovsky, but laminations can still be appreciated
- "Bubble gum" colloid: metachromatic on Romanovsky stain and stringy on papanicolau stain (sticky and stretch out)
- Lymphocytosis may be seen (uncommon in other thyroid tumors)
- Giant cells with epithelioid cytoplasm (giant cells with foamy cytoplasm may be observed in goiter)

Follicular Carcinoma

Cytologic Findings

- Well differentiated carcinoma may be indistinguishable from adenoma
- Cellular smear with syncytial microtissue fragments and small follicles
- Disordered cellular pattern with crowding and pilling
- Nucleomegaly with coarse granular chromatin and prominent nucleoli
- Loss of polarity within the cell aggregates with cellular crowding
- Scant colloid

Medullary Carcinoma

Cytologic Findings

- Discohesive clusters and isolated spindle or plasmacytoid cells
- Pale delicate cytoplasm with red azurophilic cytoplasmic granules (calcitonin)
- Eccentric round to oval nuclei with salt and pepper chromatin
- Bi- or multinucleation, and intranuclear cytoplasmic inclusions
- Fluffy, granular or acellular amyloid stroma, positive for Congo red stain
- Fine red metachromatic (neurosecretory) granules on Romanovsky stain
- Large atypical cells and giant cells may be observed

Differential Diagnosis

- Malignant lymphoma:
  - Numerous isolated monotonous cells and lymphoglandular bodies on Romanovsky stain
  - Lack germinal center cells and epithelial components
  - Lack of salt and pepper chromatin

Anaplastic Carcinoma

- Isolated or discohesive clusters of cells
- Marked nuclear pleomorphism and large bizarre cells with prominent macronucleoli
- Tumor diathesis

Metastatic Carcinoma

- Consider this diagnosis when the cytologic features are not consistent with conventional thyroid neoplasms
- Metastatic renal carcinoma with granular cytoplasm may be difficult to differentiate from Hurthle cell neoplasms

BREAST

Overview

Stromal and Epithelial Cells

- Fibroadenoma
- Phyllodes tumor
- Periductal stromal sarcoma
- Carcinosarcoma
- Adenocarcinoma with marked stromal fibrosis

Squamous Cells

- Subareolar abscess
- Fibrocystic change (rare)
- Phyllodes tumor (rare)
- Gynecomastia
- Infarcted papilloma (rare)
- Cysts (epidermal inclusion cyst and fibrocystic change)
- Metaplastic carcinoma

Apocrine Cells

- Fibrocystic changes
- Fibroadenoma
- Benign phyllodes tumor
- Apocrine carcinoma

Giant Cells

- Duct ectasia
- Granulomatous mastitis
- Foreign body reaction (e.g. suture material, silicon)
- Fat necrosis
- Medullary carcinoma

Small Cells

- Ductal carcinoma
- Tubular carcinoma
- Lobular carcinoma
- Lymphoma
- Carcinoid

Reporting Terminology (Diagn Cytopathol 1997;16:295–311)

- Benign: no evidence of malignancy
- Atypical/indeterminate: cellular findings are not diagnostic, clinical and radiologic correlation is warranted
- Suspicious/probably malignant: Highly suggestive of malignancy, recommend tissue biopsy
- Malignant: findings diagnostic of malignancy. Qualify further with specific diagnosis

- Unsatisfactory (due to):
  - Scant cellularity
  - Airdrying or distortion artifact
  - Obscuring blood or inflammaation
  - Other

Benign Lesions

Fat Necrosis

- Foreign body reaction with foamy histiocytes and giant cells
- Isolated atypical fibroblast with enlarged nuclei and fine vesicular chromatin
- Atypical ductal cells with reparative changes and granulation tissue
- Hemosiderin-laden macrophages indicate old blood
- Disrupted fat and dystrophic calcifications

Subareolar Abscesses

- Thick material obtained by aspiration
- Suppurative granulomatous inflammation
- Anucleated squamous cells in granular, necrotic dirty inflammatory background
- May contain mature metaplastic or parakeratotic cells
- Reactive and reparative epithelial changes

Lactational Changes

Cytologic Findings

- Moderate cellularity with uniform cell population
- Numerous bare nuclei (fragile hypervacuolated cytoplasm)
- Discohesive cells with prominent nucleoli and foamy vacuolated cytoplasm in a granular proteinaceous background (milky)
- Intranuclear pseudoinclusion and minimal nuclear pleomorphism
- Naked bipolar myoepithelial cells with prominent nucleoli

Differential Diagnosis

- Lactating adenoma:
  - More cellular
  - Numerous strips of epithelial clusters with foamy vacuolated cytoplasm
- Lobular carcinoma and signet ring cell carcinoma:
  - Significant cytologic atypia, nuclear pleomorphism, necrosis and loss of polarity

Fibrocystic Changes

- Triad of epithelial hyperplasia, cyst formation, and stromal fibrosis

Cytologic findings

- Cohesive sheets of ductal epithelial cells with honey comb arrangement
- Polymorphous population of cells is a key feature
- Bipolar/myoepithelial cells within the sheets and in the background
- Apocrine metaplasia
- Foamy histiocytes (content of cyst)
- Occasional fibroblasts in the background depending on the extent of fibrosis

Differential diagnosis

- Fibroadenoma:
  - Branching complex sheets
  - More bare nuclei in the background
- Well differentiated ductal carcinoma:
  - More irregular sheets with frayed edges and pointed borders
  - More pronounced nuclear atypia
  - Striped fibroblasts may mimic bipolar cells

Fibroadenoma

- Triad of complex epithelial fragments, myoepithelial cells, and fibromyxoid stroma

Cytologic Findings

- Cellular smear with a clean background
- Tight branching cohesive sheets of polymorphous cells forming antler horn or mitten-like papillary fronds
- Large monolayer and folded sheets
- Numerous striped bipolar naked myoepithelial cells
- Fragments of fibromyxoid stroma
- Occasional multinucleated giant cells (stromal origin)
- Mild nuclear and nucleolar enlargement and rare mitotic figures
- Occasional nuclear overlapping and few isolated cells
- Apocrine metaplastic cells and foamy histiocytes not uncommon

Differential Diagnosis

- Phyllodes tumor:
  - Dimorphic population of epithelium and stroma
  - Highly cellular stroma, with or without squamous metaplasia
  - Epithelial fragments similar to fibroadenoma
  - Cytologic atypia in naked bipolar cells and stromal fragments
  - Stromal fragments tend to be more cellular than fibroadenoma
  - Blood vessels across the stromal fragments
- Well differentiated ductal carcinoma:
  - Epithelium with pointed edges and irregular borders
  - Cytologic atypia with nuclear overlapping and nuclear membrane irregularity
  - Lack of stripped bipolar nuclei

- Tubular carcinoma:
  - Low cellular smears
  - Three dimensional tubular structures with angulated appearance
  - Less frequent bipolar cells
- Fibromatosis, nodular fasciitis, and mammary fibrosis:
  - Often indistinguishable on FNA biopsy
  - Hypocellular smear of isolated spindle fibroblasts and syncytial stromal fragments
  - Lack epithelial components
  - Myxoid stroma in an inflammatory background more common in nodular fasciitis
  - Fragments of mature adipose tissue and stromal fragments common in mammary fibrosis
- Fibrocystic changes:
  - Apocrine metaplasia, foamy macrophages, and epithelial hyperplasia
  - Granular, proteinaceous secretion
  - Lack of characteristic epithelial fragments

Gynecomastia

- Findings similar to fibroadenoma, but less cellular
- Branching, cohesive sheets of hyperplastic polymorphous cells and naked bipolar cells
- Frequent discohesive isolated columnar cells
- Cytologic atypia may be striking

Intraductal Papilloma

Cytologic Findings

- Cellular smear composed of sheets of polymorphous cells and few singly scattered cells
- Papillae and columnar cells with eccentric nuclei
- Minimal nuclear pleomorphism and nuclear membrane irregularity
- Mixtures of apocrine metaplasia, foamy macrophages and sheets of hyperplastic ductal cells

Differential Diagnosis

- Intracystic papillary carcinoma:
  - Branching three-dimensional papillae with more complex architecture and monomorphic cell population
  - Numerous single papillae
  - Increased discohesiveness, nuclear pleomorphism, and mitotic figures
  - Some cases may have numerous columnar cells

Ductal Carcinoma *In Situ* and Invasive Carcinoma

- Carcinoma *in situ* cannot be reliably separated from invasive carcinoma by cytology. The following are characteristic features suggested by the literature

Ductal Carcinoma In Situ (DCIS)

Cytologic Findings

- Monotonous discohesive isolated cells often >10% of the atypical cell population
- Three-dimensional clusters of cells with papillary, solid or cribriform configuration
- Rare bipolar cells or bare nuclei
- Cytologic atypia with nuclear pleomorphism, nuclear hyperchromasia, coarsely granular chromatin, prominent macronucleoli, and necrosis in comedo-type DCIS

Differential Diagnosis

- Ductal hyperplasia without atypia:
  - Clusters and crowded sheets of cells in a complex arrangement with cellular streaming, nuclear spindling, and irregular lumen formation
  - Bipolar bare nuclei
- Atypical ductal hyperplasia:
  - Often indistinguishable from low grade DCIS
  - Clusters and flat sheets of epithelial cells with regular lumen formation
  - Loss of polarity and cell cohesion with increased isolated monotonous cells
  - Nuclear enlargement, crowding, and overlapping
  - Admixture of benign stromal cells and apocrine metaplastic cells
- Low grade ductal carcinoma:
  - Increased discohesive isolated monotonous cells
  - Absence of benign cellular components
  - Dirty, inflammatory background

Lobular Carcinoma In Situ

Cytologic Findings

- Hypocellular smear of single isolated uniform small cells and three dimensional cell balls
- Indian filing and nuclear molding
- Eccentric nuclei and intracytoplasmic vacuoles (signet ring cells)
- Irregularly rounded and large bare nuclei, inconspicuous nucleoli

Differential Diagnosis

- Atypical lobular hyperplasia:
  - Often indistinguishable from LCIS
- Invasive lobular carcinoma:
  - More cellular, more discohesive, more cytologic atypia

Intracystic Papillary Carcinoma

Cytologic Findings

- Cellular smear of isolated monomorphic cells and branching papillae with smooth border

- Tall columnar cells with cytologic atypia and nuclear pleomorphism
- Increased mitotic figures and discohesiveness
- Numerous histiocytes, hemosiderin-laden macrophages and hemorrhagic background
- Arborized thin-walled blood vessels
- Irregularly rounded and large bare nuclei

Differential Diagnosis

- Intraductral papilloma:
  - More cohesive, lack cytologic atypia, round to oval nuclei
  - Apocrine metaplasia, foamy histiocytes and small bipolar bare nuclei
- Fibroadenoma:
  - Dimorphic populations of cells without cytologic atypia
  - Larger, more complex cellular fragment
  - Numerous stripped bipolar nuclei

Invasive Ductal Carcinoma

Cytologic Findings

- Cellular smear composed of discohesive single cells with plasmacytoid appearance
- Sheets and syncytial fragments of malignant cells with nuclear overlapping
- Monotonous population of atypical cells
- Irregular contours of nuclear membrane, coarsely clumped chromatin
- Nucleomegaly and prominent nucleoli, and anisonucleosis
- Lack of naked bipolar myoepithelial cells and loss of polarity
- Background of necrosis and tumor diathesis (nuclear and cytoplasmic debris, ghosts of cells, and old blood)

Differential Diagnosis

- Cellular fibroadenoma:
  - Dimorphic populations of bipolar naked cells and branching tight clusters and sheets of epithelial cells with fenestration
  - Preserved cellular polarity
  - Absence of prominent nucleoli and nuclear overlapping

Lobular Carcinoma

Cytologic Findings

- Low to moderately cellular smear of discohesive small cells
- Indian filing of cell arrangement and numerous isolated single cells
- High N/C ratio, nuclear membrane irregularity, nuclear hyperchromasia, small nucleoli
- Targetoid intracytoplasmic vacuoles with eccentric nuclei, imparting signet ring appearance

Differential Diagnosis

- Mucinous (colloid) carcinoma:
  - Cellular clusters and single mildly atypical cells
  - Mucoid background

Mucinous (Colloid) Carcinoma

Cytologic Findings

- Cellular smear of numerous isolated cell, discohesive sheets and cell balls
- Mucoid background (pink by Papanicolaou and blue by Romanovsky stain)
- Arborized thin-walled blood vessels within the mucus
- Intracytoplasmic vacuoles and eccentric uniform nuclei

Differential Diagnosis

- Mucocele:
  - Scant cellularity, few clusters and cohesive flat sheets of cells
  - Lack three-dimensional cell balls and arborized thin-walled blood vessels
  - No cytologic atypia
  - Abundant extracellular mucin and scattered histiocytes and fibroblasts
- Cystic hypersecretory duct carcinoma:
  - Scattered isolated, clusters and sheets of epithelial cells
  - Pink bubbling secretions with cracked artifact imparting mosaic plate appearance

Medullary Carcinoma

Cytologic Findings

- Cellular smear of isolated cells and discohesive clusters and syncytial fragments
- Large pleomorphic cells with nucleomegaly, anisonucleosis and prominent nucleoli (may be bizarre)
- Inflammatory background with lymphocytes and plasma cells

Tubular Carcinoma

Cytologic Findings

- Low to moderately cellular smear of discohesive isolated monotonous cells and angulated glands
- Three dimensional tubular structure with central lumens and loss of polarity
- Bipolar naked myoepithelial cells present in 25–50% of the cases
- Numerous uniform isolated small cells with small nucleoli and vacuolated cytoplasm

Differential Diagnosis

- Fibroadenoma:
  - Flat branching sheets with honeycomb pattern and staghorn configuration
  - Bipolar bare nuclei and fibrous stroma fragments

Apocrine Carcinoma

Cytologic Findings

- Cellular smear of isolated cells and discohesive clusters and syncytial fragments
- Apocrine differentiation with dense waxy eosinophilic cytoplasm and apocrine snouts
- Cytoplasm heavily granular (rich in mitochondria)
- Nucleomegaly, nuclear pleomorphism, and prominent nucleoli

Differential Diagnosis

- Fibrocystic change:
  - Less cellular, more cohesive, lack cytologic atypia or anisonucleosis
  - No significant nuclear pleomorphism and lack marconucleoli

Phyllodes Tumor

Cytologic Findings

- Cellular smear of two cell population (epithelial and stromal)
- Bipolar naked nuclei with cytologic atypia
- Branching tight clusters of epithelial cells
- Squamous metaplasia (rare)
- More abundant and cellular stroma
- Spindle cells embedded in metachromatic staining stroma
- Stromal overgrowth and/or stromal atypia with increased mitosis suggest malignancy

Differential Diagnosis

- Fibroadenoma:
  - Less cellular stromal fragments, clean background, lack cytologic atypia
- Juvenile cellular fibroadenoma:
  - Stromal elements may be abundant, no significant cytologic atypia
- Ductal carcinoma:
  - Lack bipolar cells and hypercellular stromal fragments

Metaplastic Carcinoma

Cytologic Findings

- Hypercellular smear of mixtures of poorly differentiated malignant cells and areas of squamous, sarcomatous, chondroid or osseous metaplasia
- Squamous metaplasia is the most common type of metaplasia
- Dense waxy eosinophilic cytoplasm and anucleated keratinous debris
- Multinucleated giant cells with intracytoplasmic vacuoles and phagocytic debris

Differential Diagnosis

- Fibromatosis and nodular fasciitis:
  - Less cellular smear, lack cytologic atypia

LYMPH NODE

Reactive Hyperplasia

- Polymorphous mixed cell population with predominant mature small lymphocytes admixed with tingible body macrophages, plasmacytoid lymphocytes, and immunoblasts
- Lymphoglandular bodies in background
- Lymphohistiocytic aggregate (follicular center fragment):
  - Consisting of dendritic cells associated with centroblasts and centrocytes.
  - Indicative of benign process or follicular lymphoma
  - Differential diagnosis: granuloma, carcinoma
- Russell body: intracytoplasmic inclusion bodies seen in reactive plasma cells
- Mott cell: plasma cells with large numbers of Russell bodies appearing as hyaline globules (immunoglobulin in the endoplasmic reticulum)

Acute Lymphadenitis

- Sheets of neutrophils and heterogeneous lymphoid cells in a necrotic background
- Varying degree of cell necrosis
- Bacteria and fungi may be identified

Necrotizing Granulomatous Lymphadenitis

- Etiology includes cat scratch disease, mycobacterial infection, Yersinia, tularemia, brucellosis and fungal infection
- Varying number of granuloma: loose or tightly clustered epithelioid histocytes
- Variable degree of background necrosis and neutrophils (the latter are less conspicuous in aspirates from mycobacterium infection)

Cat Scratch Disease

- Polymorphous cell populations of lymphocytes, plasma cells, and neutrophils
- Poorly formed granuloma with scattered epithelioid histiocytes
- Some of the granuloma may show a stellate configuration with central scattering of neutrophils
- Dirty necrotic background

Non-Necrotizing Granulomatous Lymphadenitis

- Etiology includes sarcoidosis, toxoplasmosis, infectious mononucleosis, tuberculosis, drug reactions, syphilis, berylliosis, foreign body reaction, lymphoma (especially Hodgkin lymphoma and T-cell lymphoma), and lymph node draining malignancies (especially squamous cell carcinoma and seminoma)
- Granuloma without background of necrosis
- Numerous multinucleated giant cells

Infectious Mononucleosis

- Predominantly immunoblasts with cellular elements of reactive hyperplasia
- Immunoblasts have pale or deep blue cytoplasm on Romanovsky
- Round nuclei with fine chromatin and regular prominent nucleoli
- Frequent tingible body macrophages and plasmacytoid lymphocytes
- Lymphoglandular bodies may be seen

Malignant Lymphoma (see Chapter 7)

- Highly cellular smear
- Discohesive cells
- Usually relatively monomorphic population of abnormal lymphocytes
- Lymphoglandular bodies:
  - Fragments of lymphocyte cytoplasm
  - Seen in both benign and malignant lesions
  - Rare in T-cell lymphoma
  - Best appreciated on Romanovsky as light-blue or blue-gray globular or flakelike structure
- Dutcher body:
  - Intranuclear inclusion bodies (versus Russell bodies: intracytoplasmic inclusions, nonspecific)
  - Often seen in Waldenstrom's macroglobulinemia
  - May indicate neoplastic processes
- Flame cell: often seen in IgA producing myeloma

Common Variants of Lymphoma

Small Lymphocytic Lymphoma

- Monomorphic population of small round lymphocytes
- Uniform round nuclei with regular nuclear borders, and coarsely granular chromatin, and inconspicuous nucleoli
- Scant basophilic cytoplasm
- Lack tingible body macrophages and mitotic figures inconspicuous

Mantle Cell Lymphoma

- Monomorphic population of small lymphocytes that are larger than mature lymphocytes
- Nuclei with irregular nuclear contours and irregularly distributed chromatin
- Some nuclei have marked indentation/cleaves with deep fold ("coffee bean" nuclei)
- Lack tingible body macrophages

Burkitt's Lymphoma

- Cells 2–3x larger than mature lymphocytes
- Predominantly round nuclei
- Clumped chromatin pattern
- One or several prominent nucleoli
- Moderate amount of cytoplasm with frequent lipid vacuoles
- High mitotic figures
- Tingible body macrophages and necrosis common (indicate rapid turn over of cells)

Diffuse Large B-cell Lymphoma

- Cells 3x larger than mature lymphocytes, more variable in cell size
- Round or convoluted nuclei; nuclei may have projections (nipple)
- Variable chromatin pattern
- Nucleoli invariably present with variable number and size, usually prominent
- Moderate to abundant cytoplasm with inconspicuous vacuoles
- Mitotic figures variable
- Tingible body macrophages often seen

Adult T-cell Lymphoma

- Round nuclei, may be variably convoluted
- Cell 2x larger than mature lymphocytes
- Delicate chromatin pattern with inconspicuous nucleoli
- Scant cytoplasm, abundant or inconspicuous vacuoles
- Hand-mirror cells often seen in lymphoblastic lymphoma and Ki-1 lymphoma
- High mitotic figures
- Variable number of tingible body macrophages and necrosis

Anaplastic Large Cell Lymphoma

- Large pleomorphic cells with irregular nuclear contours, coarsely granular chromatin, and prominent nucleoli
- Bi- or multinucleation, wreath-like nuclei may be seen

- Moderate amounts of pale to basophilic cytoplasm with projections (hand-mirror cells)

Hodgkin Lymphoma

- Heterogeneous population of lymphoid cells with background eosinophils, plasma cells, similar to reactive process
- Reed-Sternberg cells with gray cytoplasm, mirror-image nuclei, irregular nuclear membrane, coarse chromatin, and prominent nucleoli
- Atypical mononuclear Reed-Sternberg cells
- Lacunar cells (large cells with hyperchromatic single or multinucleated and lobulated nuclei) often seen in nodular sclerosing variant
- Popcorn cells (pale multinucleated giant cell with lobulated nucleus and lack prominent nucleoli) often seen in lymphocyte-rich variant
- Epithelioid histiocytes and collagen fragments may be observed

SKIN, SOFT TISSUE, BONE, AND CARTILAGE

Skin (see Chapter 9)

Pilomatrixoma (Calcifying Epithelioma of Malherbe)

- Sheets of degenerated, anucleated squamous cells (ghost cells)
- Clusters of basaloid small cells
- Background of calcification, nuclear debris, inflammatory cells, and foreign body giant cells

Squamous Cell Carcinoma

- See previous discussion

Basal Cell Carcinoma

Cytologic Features

- Tight cell aggregates and some discohesive cells
- Palisading nuclei at periphery of aggregates
- Small cells with scant cyanophilic cytoplasm (Pap stain) and indistinct cell borders
- Small hyperchromatic nuclei with inconspicuous nucleoli
- No nuclear molding

Differential Diagnosis

- Basaloid squamous cell carcinoma:
  - Generally exhibit more discohesion, occasional dense cytoplasm, and more prominent nucleoli
- Merkel cell carcinoma:
  - Predominantly discohesive population of small cells
  - Neuroendocrine features

Malignant Melanoma

- This tumor should be considered in the differential diagnosis of every tumor of unknown primary

Cytologic Features

- Smears are highly cellular
- Predominantly discohesive population and many single cells
- Occasionally tight clusters
- Plamacytoid appearance with eccentric nuclei
- Abundant dense or slightly vacuolated cytoplasm, frequently has a dusty quality
- Melanin pigment within the cytoplasm, loose, and in the background histiocytes (melanotic melanoma)
- Marked nuclear pleomorphism
- Binucleated and multinucleated cells
- Intranuclear cytoplasmic inclusions
- Prominent nucleoli
- Spindle cell variant present with numerous spindle cells, sometimes intermixed with few classic cells
- Myxoid stroma may be seen in occasional cases
- Small cell variant consists of relatively smaller cells than the epithelioid variant
- Positive for S-100, HMB-45, and Melan-A/Mart-1

Differential Diagnosis

- Spindle cell tumors
- Anaplastic large cell carcinoma
- Myxoid soft tissue tumors
- Small cell tumors

Merkel Cell Carcinoma

- Highly cellular smears
- Discohesive cell population of small abnormal cells
- Some nuclear molding, pseudorosettes, or acinar forms
- Scanty cyanophilic cytoplasm
- Round to oval nuclei
- Finely granular chromatin (neuroendocrine pattern)
- Intracytoplasmic red granules seen by Romanovsky
- Discrete intracytoplasmic dots (keratin buttons by electron microscopy)
- Cytokeratin 20 shows characteristic dot pattern corresponding to the keratin buttons

Soft Tissue (see Chapter 12)

Adipose Tissue Tumors

Lipoma

Cytologic Findings

- Microtissue fragments and tight clusters of adipocytes
- Round cells with single large clear cytoplasmic vacuoles and distinct cell borders
- Small round to oval nuclei, often eccentrically located
- Background of lipid droplets

Differential Diagnosis

- Normal subcutaneous tissue:
  - Indistinguishable from lipoma, clinical findings important
- Well-differentiated liposarcoma:
  - Atypical lipocytes (lipoblasts) with irregular and enlarged hyperchromatic nuclei
  - Prominent plexiform capillary network

Liposarcoma

Cytologic Findings

- Lipoblasts in a finely vascular stroma
- Lipoblasts often arranged around a delicate branching capillary network
- Lipoblasts may have variable cytologic appearance: spindle or stellate cells with small lipid droplets, single large cytoplasmic vacuoles (signet-ring type), or multivacuolated cytoplasm
- Nuclei may show indentation or scalloping
- Lipid droplets are usually sharply outlined and best appreciated on Romanovsky
- Myxoid liposarcoma contains a matrix rich in acid mucopolysaccharide that appears magenta to purple on Romanvsky and is alcian blue positive and mucin negative
- Round liposarcoma composed of densely packed small round cells with finely vacuolated cytoplasm and pleomorphic nuclei
- Pleomorphic liposarcoma often yield highly cellular smear composed of bizarre microvacuolated pleomorphic giant cells

Differential Diagnosis

- Lipid laden histiocytes (lipophages):
  - Foamy cytoplasm with fine vacuoles and indistinct vacuoles
  - Bean-shaped nuclei that are rounded rather than scalloped
  - Background of hemorrhage, necrosis, inflammation, lipids and giant cells
  - Lack characteristic features of lipoblast and plexiform capillary network
- Angiolipoma:
  - Monomorphic univacuolated adipocytes with uniform nuclei
  - Branching vascular pattern
  - Lack lipoblasts
- Pleomorphic lipoma:
  - Pleomorphic single and multinucleated giant cells
  - Peripheral circular arrangement of nuclei (floret cells)
  - Mature adipose tissue
  - No necrosis, mitotic figures and true lipoblasts
  - Complete excision for histologic examination is necessary due to sampling variation in order to avoid underdiagnosis
- Lipoblastomatosis:
  - Occurs in children <3 years
  - Identical cytologic findings as myxoid liposarcoma
- Hibernoma:
  - Small round centrally located nuclei without scalloping
  - Multiple small uniform cytoplasmic vacuoles
- Signet ring cell carcinoma:
  - Mucin positive
  - Lack lipoblast and plexiform capillary network

Fibrous and Fibrohistiocytic Lesions

Nodular Fasciitis

- Hypocellular smear of spindle to ovoid cells in a mucoid or metachromatic stroma
- Discohesive large plump myofibroblasts
- Oval nuclei with evenly distributed granular chromatin and inconspicuous nucleoli
- Tissue fragments containing fibrin and metachromatic mucoid substances may be observed
- Inflammatory background (lymphocytes, mast cells, and lipophages)

Fibromatosis

- Low to moderate cellularity with isolated cells or in loose clusters
- Spindled to oval uniform nuclei with finely granular chromatin, smooth nuclear contours and inconspicuous nucleoli
- Pale, delicate cyanophilic cytoplasm with tapered ends
- Stripped nuclei can be numerous
- Fragments of collagenous metachromatic stroma with mucoid ground substance
- Atrophic skeletal muscle cells may be present
- Scattered lymphocytes and variable number of histiocytes may be observed

Dermatofibroma (Benign Fibrous Histiocytoma)

- Numerous oval to spindle cells arranged in a vague storiform pattern
- Lack significant cytologic atypia
- Occasional inflammatory cells (lymphocytes, lipophages, hemosiderin-laden macrophages)
- Foreign body type giant cells and Touton cells may be seen

Dermatofibrosarcoma Protuberans

- Individual or loose clusters of spindle cells with storiform pattern arrangement (best appreciated in tissue fragments)
- Uniform oval to elongated nuclei with smooth nuclear contour and finely granular chromatin
- Finely fibrillar metachromatic stroma, best appreciated on Romanovsky

Fibrosarcoma

- Single or loose clusters of oval to spindle cells
- Nuclear pleomorphism dependent on tumor grade, but generally, unlike MFH, bizarre giant cells are not observed
- Coarsely granular chromatin and indistinct nucleoli, variable mitotic figures
- Tapered scant cytoplasm
- Scant metachromatic collagenous stroma

Malignant Fibrous Histiocytoma (MFH)

Cytologic Findings

- Hypercellular smear of dimorphic population of histiocytes and spindle cells
- Storiform growth pattern in myxoid or inflammatory background
- Multinucleated giant cells with irregular nuclei and coarsely granular chromatin
- Bizarre pleomorphic cells often clustered around vessels
- Frequent atypical mitotic figures

Differential Diagnosis

- Liposarcoma:
  - Isolated or discohesive sheets of pleomorphic cells in a metachromatic background
  - Lipoblasts and fine vasculature
  - Well define (discrete) lipid vacuoles with nuclear scalloping

Neural Tumors

Neurofibroma

- Variable cellularity
- Cells isolated or in small aggregates in the background of abundant myxoid stroma
- Elongated spindle cells with wavy serpentine nuclei
- Finely granular chromatin, scant pale cytoplasm with indistinct cell borders
- Lack prominent nucleoli
- Naked nuclei with blunt or tapered ends are common

Schwannoma (Neurilemmoma)

- Cellular smear of uniform spindle cells with elongated wavy nuclei in a fibrillar (or metachromatic) background
- Ancient schwannoma may show cytologic atypia with large pleomorphic hyperchromatic or multilobulated nuclei displaying intranuclear cytoplasmic inclusions and smudgy chromatin
- Lack prominent nucleoli and mitotic figures
- Antoni A: Anastomosing and intervening fascicles of spindle cells with nuclear palisading
- Antoni B: Poorly cellular area with myxoid degeneration and scattered spindle cells with indistinct cell borders and vacuolated cytoplasm

Granular Cell Tumor

- Cellular smear composed of single and loose clusters of large polygonal, elongated, or rounded cell
- Dirty granular background
- Cells have abundant eosinophilic or granular cytoplasm and indistinct cell border
- Uniform small centrally located nuclei with prominent nucleoli
- S-100 protein positive

Malignant Peripheral Nerve Sheath Tumors

Cytologic Findings

- Cellular smear composed of single and loose clusters of cells with irregular contours
- Irregular nuclei are wavy, buckled or comma shaped
- Atypical mitotic figures
- Pale cytoplasm with indistinct cell borders and long cytoplasmic processes
- Metachromatic fibrillary matrix

Differential Diagnosis

- Fibrosarcoma or monophasic synovial sarcoma:
  - May be cytologically indistinguishable, consider clinical presentation and relation to major nerves
  - More regular cell contours with tapered nuclei rather than wavy nuclei
  - S-100 protein negative

Primitive Neuroectodermal Tumors (PNET)

- See discussion for Ewing's sarcoma

Neuroblastoma

- Cellular smear of discohesive cell clusters and isolated single cells
- Cells with high N/C ratio, finely granular chromatin, and inconspicuous nucleoli
- Nuclear molding may be seen
- Polygonal ganglion cells with clear cytoplasm may be noted
- Bi- or multinucleation, eccentric nuclei, and prominent nucleoli
- Neuropils (tangles of neuritic processes) and occasional Homer-Wright rosettes

Ganglioneuroma

- Large polygonal ganglion cells with abundant amphophilic cytoplasm and eccentric nuclei

- Spindle stromal cells with wavy nuclei in a fibrillary background

MISCELLANEOUS

Giant Cell Tumor of Tendon Sheath

- Cellular smears composed of 2 cell populations with similar nuclear features
- Small round to oval or spindle mononuclear cells similar to synnovial lining cells or osteoblasts
- Large multinucleated osteoclastic-type giant cells
- Moderate amount of distinct cytoplasm with hemosiderin deposition
- Uniform eccentrically located nuclei with fine granular chromatin and inconspicuous nucleoli
- Background of hemosiderin-laden macrophages, xanthoma cells, and inflammatory cells

Synovial Sarcoma

- Hypercellular smear of single cells and cell clusters
- Uniform spindle cells predominate
- Scant cytoplasm with tapered ends and oval or elongate nuclei with inconspicuous nucleoli
- Difficult to differentiate monophasic synovial sarcoma from low-grade fibrosarcoma
- Biphasic population of epithelioid cells and spindle cells in a metachromatic stromal background
- Occasional glandular arrangement of cuboidal or columnar cells in biphasic synovial sarcoma
- Increased mitotic figures
- Focal immunoreactivity for cytokeratin in the epithelial elements

Leiomyosarcoma

- Cellular smear composed of uniform spindle cells arranged as tightly woven fascicles
- Centrally located cigar-shaped nuclei with blunted ends
- Cytoplasmic vacuoles may result in a blunt or concave nuclear contours
- Variable degree of nuclear pleomorphism and necrosis

Angiosarcoma

- Hemorrhagic cellular smear composed of branching papillary clusters of spindle, polygonal or rounded cells
- Concentrically arranged whorls (pseudoacini or rosette-like) of endothelial cells may be observed
- Moderate amount of pale cytoplasm and occasional nuclear groove
- Nuclear pleomorphism and prominent nucleoli
- CD31 and CD34 positive

Kaposi's Sarcoma

- Isolated single and loosely cohesive clusters of spindle cells with well defined borders
- Elongate nuclei with finely granular chromatin and inconspicuous nuclei
- Pale delicate cytoplasm that may contain hemosiderin pigments
- Cells may contain characteristic diastase-resistant PAS positive hyaline globules
- Inflammatory background

Rhabdomyosarcoma

- Cellular smear of isolated or loose aggregates of round or spindle cells
- Scant cytoplasm that taper from nucleus as a "tadpole-shape" or as a broad bands (strap cell)
- Cytoplasmic cross striation is rarely observed
- Oval to round eccentric nuclei with variable nuclear pleomorphism, frequently eccentric
- Concentrically arranged fibrillary materials around the nucleus
- Variable mitotic figures and tumor diathesis
- Desmin +, muscle-specific actin +, and MyoD1+

Bone and Cartilage

Chondroma

- FNA not generally indicated and not performed
- Cytology cannot differentiate chondroma from low grade chondrosarcoma
- Hypocellular smear composed of fragments of cartilage
- The presence of cartilage indicates that the lesion is cartilaginous (or has a cartilaginous component), and assists in determining if the lesion is benign or malignant
- Small uniform chondrocytes in lacunae
- Lack mitotic figures or significant nuclearpleomorphism
- Metachromatic fibrillary matrix, best appreciated on Romanovsky

Chondroblastoma

- Variable cellularity with single isolated and discohesive clusters of uniform round to polygonal cells
- Single or binucleated cells with dense glassy eosinophilic cytoplasm
- Evenly distributed fine granular chromatin and inconspicuous nucleoli
- Occasional nuclear groove and intranuclear cytoplasmic inclusions may be observed
- Multinucleated osteoclasts and vacuolated histiocytes
- Metachromatic amorphous chondroid stroma

Giant Cell Tumor

- Numerous large osteoclastic-type giant cells
- Mononuclear cells with eosinophilic cytoplasm and nuclei that are similar to those of giant cells
- Cells with abundant eosinophilic cytoplasm

Chondrosarcoma

- Not generally aspirated as diagnosis is made radiographically and aspirates may not be representative
- Aspirates of possible lytic areas may be performed to exclude dedifferentiated chondrosarcoma
- Cellular smear composed of single isolated cells and discohesive clusters
- Mononuclear or binuclear cells in lacunae embedded in metachromatic stromal matrix
- Oval to polygonal cells with distinct cell border and abundant vacuolated cytoplasm
- Variable degree of cytologic atypia and mitotic figures
- Bi- and multinucleation are common

Osteosarcoma

- Numerous discohesive cells with marked nuclear pleomorphism and bizarre cells
- Multinucleated tumor cells and occasional osteoclast-like cells are observed
- Nucleoli may be prominent
- Cells with moderate to abundant eosinophilic granular cytoplasm
- Increased mitotic figures and abnormal mitotic figures may be seen
- Eosinophilic metachromatic osteoid matrix are best seen on Romanovsky

Ewing's Sarcoma and PNET

Cytologic Findings

- Cellular smear with tight clusters and isolated single monotonous cells (2–3x size of mature lymphocytes)
- Uniform round to oval nuclei with finely granular chromatin and inconspicuous nucleoli
- Nuclear molding with crush artifact, bare nuclei common
- Variable cytoplasmic vacuoles containing glycogen (PAS positive)
- Frequent mitotic figures and occasional Homer-Wright rosettes
- "Tigroid" background (also seen in seminoma)
- Mic2 (HBA71) protein positive

Differential Diagnosis

- Metastatic neuroblastoma:
  - Background of fibrillary neuropil
  - Ganglion cell differentiation and frequent Homer-Wright rosettes

Langerhan's Cell Histiocytosis (Eosinophilic Granuloma)

- Cellular smear composed of numerous isolated large histiocytes admixed with eosinophils
- Nuclei of histiocytes are round or reniform
- Finely granular chromatin, nuclear grooves
- Granular, occasionally vacuolated cytoplasm
- Variable number of eosinophils
- Occasional multinucleated osteoclast-like cells
- Birbeck granules (tennis racket-like structure) on electron microscopy are diagnostic
- CD1a positive

ESOPHAGUS, STOMACH, COLON, LIVER, AND PANCREAS

Esophagus

Normal Component

- Superficial and intermediate squamous cells
- Parabasal cells may be seen in ulcer or vigorous brushing
- Gastric cells may be noted in samples from gastroesophageal junction

Infection

(Findings Similar to Those Described in Respiratory Tract)

- Candida esophagitis
- Herpes simplex virus

Reflux Esophagitis

- Sheets of loosely cohesive squamous cells with reactive/regenerative atypia
- Normal polarity and N/C ratio retained
- Regular nuclear membranes and uniformly distributed fine chromatin
- Abundant cyanophilic cytoplasm
- Rare isolated single cells and lack significant nuclear pleomorphism
- Inflammatory cells (lymphocytes, eosinophils, and histiocytes) may be observed

Radiation Change

- Cytomegaly with normal N/C ratio
- Nuclei enlarged, hypochromatic and have prominent nucleoli (may be irregular)
- Degenerative change with nuclear pyknosis, smudging and karyorrhexis
- Nuclear and cytoplasmic vacuoles, multinucleation

- Dense amphophilic cytoplasm
- Granulation tissue formation with spindle fibroblasts and endothelial cells

Barrett's Esophagus

- The brushing should be taken several centimeters above gastroesophageal junction
- Isolated single cells and small clusters of columnar mucin-producing cells
- Interspersed goblet cells
- Lack significant cytologic atypia
- Suspect dysplasia when cytologic atypia is observed

Dysplasia

- Loosely cohesive sheets of hyperplastic epithelial cells with cytologic atypia
- Enlarged nuclei with nuclear hyperchromasia, irregular nuclear contours
- Low-grade dysplasia may be indistinguishable from reactive atypia
- High-grade dysplasia displays:
  - Increased N/C ratio
  - Increased hyperchromasia
  - Increased nuclear membrane irregularity
  - Increased nuclear pleomorphism and prominent nucleoli
- Lack tumor diathesis or numerous isolated single cells

Squamous Cell Carcinoma

- Discohesive clusters, syncytial sheets and isolated cells with orangeophilic waxy cytoplasm
- Keratin pearls, intercellular bridges and distinctive cell border
- Marked variation in size and shape and bizarre cells
- Nuclear pyknosis, karyorrhexis, and apoptosis
- Nuclear pleomorphism, hyperchromasia, irregular nuclear membrane, and coarse clumped chromatin

Adenocarcinoma

- Discohesive sheets, acini, papillae and isolated single columnar cells
- Loss of polarity and cellular cohesion with single isolated cells
- Nuclear pleomorphism, nucleomegaly with open chromatin and prominent nucleoli
- Indistinct cell border, cytoplasmic vacuoles (mucin)

Stomach

Normal Cytology

- Columnar cells in sheets with honeycomb pattern
- Round to oval basal nuclei with finely granular and evenly distributed chromatin
- Granular or vacuolated mucus-filled cytoplasm
- Degenerative epithelial changes are frequently observed

Gastric Ulcer

- Fibrinous exudate with sheets and islands of regenerative epithelial cells
- Spectrum of reactive atypia in the epithelial fragments
- Granulation tissue formation with plump spindle fibroblasts and endothelial cells
- Knowledge of clinical findings is essential for proper interpretation
- For gastric adenocarcinoma diagnosis, require nondegenerated cells with malignant cytologic features to avoid overdiagnosis ulcer-related atypia/regeneration

Chronic Gastritis

- Cell polarity maintained with relative normal N/C ratios
- Even chromatin distribution, regular smooth nuclear contour
- Lack significant nuclear pleomorphism
- Inflammatory background and cellular debris
- Helicobactor pylori may be seen in Pap-stained smears of gastric blushings, especially in mucus and are better appreciated on Romanovsky stain

Hyperplastic or Regenerative Polyp

- No specific cytologic features
- Microtissue fragments of normal gastric epithelium
- Honeycomb sheets of mucous epithelial cells with fine chromatin

Adenocarcinoma

- Hypercellular smear of discohesive sheets, three-dimensional clusters and isolated single cells
- Loss of nuclear polarity
- Nuclear pleomorphism, chromatin clumping and clearing, and prominent nucleoli
- Granular and vacuolated cytoplasm
- Signet ring cells should be distinguished from vacuolated histiocytes (muciphages)

Lymphoma

- Highly cellular smear with a monotonous population of small or large cleaved or non-cleaved lymphocytes
- Relatively clean background
- Negative reaction to mucin and immunostaining for keratin and leukocyte common antigen are extremely helpful in the differential diagnosis from poorly differentiated adenocarcinoma

Colon

Normal Cytology

- Honeycomb or picket-fence arrangement
- Tall columnar cells with brush borders and goblet cells
- Elongated nuclei with regular outline and finely granular chromatin

Adenomatous Polyp

- Microtissue fragments and strips of columnar cells with peripheral feathering
- Nuclear polarity and cell cohesion retained
- Even chromatin distribution, regular smooth nuclear membrane, and micronucleoli
- Lack prominent nucleoli, significant nuclear pleomorphism, or tumor diathesis

Adenocarcinoma

- Hypercellular smear of discohesive geographic sheets, clusters and isolated single columnar cells
- Loss of nuclear polarity with nuclear pleomorphism, uneven chromatin distribution, and prominent nucleoli
- Granular and vacuolated cytoplasm
- Signet ring cells should be distinguished from vacuolated histiocytes (muciphages)
- Tumor diathesis

Liver

Normal Components

Normal Hepatocytes

- Polygonal cells arranged in sheets, clusters or as single cells
- Eosinophilic or basophilic cytoplasm that may show vacuoles or pigment (hemosiderin, lipofuscin or bile)
- Round nuclei, central or slightly eccentrically located
- Smooth nuclear contour and evenly distributed finely granular chromatin
- Anisonucleosis common as well as bi- or multinucleation
- Nucleoli usually present, and may be prominent

Bile Duct Cells

- Honeycomb sheets or tightly packed glandular clusters
- Low columnar or cuboidal cells with basophilic cytoplasm
- Round to oval nuclei, often eccentric, with evenly distributed finely granular chromatin and micronucleoli

Kupffer Cells

- Single, bare, comma shaped nuclei between hepatocytes

Benign Lesions

Cysts

- Congenital cyst:
  - Clear fluid
  - Few uniform cuboidal cells and some macrophages
- Ciliated hepatic foregut cyst:
  - Located beneath the falciform ligament
  - Clusters of ciliated columnar cells
  - Macrophages
- Hydatid cyst:
  - Thick turbid fluid
  - Fragments of laminated cyst wall
  - Scolices and/or hooklets demonstrated with Pap stain

Reactive/Regenerative Changes

- Cell cohesion and nuclear polarity retained
- Normal N/C ratio, lack significant nuclear pleomorphism
- Significant variation between cells usually indicate benignity
- Occasional binucleation, and prominent nucleoli
- Bile duct epithelium and lipofuscin, and hemosiderin

Steatosis

- Cytoplasmic (fat) vacuoles

Hepatocellular Adenoma

Cytologic findings

- Clearly defined focal mass
- Sheets and clusters of monotonous polygonal normal hepatocytes or hepatocytes with slight nuclear enlargement
- Lack nuclear pleomorphism
- Glycogen, hemosiderin, and fatty change may be observed
- Absence of glandular cells of bile duct origin

Differential Diagnosis

- Well differentiated hepatocellular carcinoma:
  - Very subtle difference
  - Less fragile cytoplasm in adenoma with more distinct cell border
  - Low N/C ratio in adenoma
  - Fewer bare nuclei in adenoma
- Regenerative nodule and cirrhosis:
  - Marked anisokaryosis
  - Scattered cells with nuclear pleomorphism and high N/C ratio

Focal Nodular Hyperplasia

- Admixtures of fragments of bile ducts, fibrous stromal tissue, and hepatocytes
- The cytologic findings are not specific
- The presence of admixture of hepatocytes and bile duct cells in the proper clinical setting support the diagnosis of focal nodular hyperplasia

Hemangioma

- Bloody background, fibrovascular tissue fragments, vascular walls, and occasional fibrin
- Few scattered endothelial cells with elongated normochromatic nuclei

Bile Duct Hamartoma

- Admixtures of benign bile ductal cells and strands of fibrous stroma

Malignant Lesions

Hepatocellular Carcinoma

Cytologic Findings

- Findings dependent on degree of differentiation
- Cellular smear with predominantly trabecular pattern (>3–4 cell layers in thickness), mostly seen in well-differentiated tumors
- Sinusoidal endothelial cell lining surrounding and/or traversing the trabeculae
- Numerous single discohesive polygonal cells with round central nuclei, high N/C ratio, binucleation, smooth nuclear membrane, and prominent nucleoli
- Intranuclear cytoplasmic inclusions and intracytoplasmic bile
- Abundant granular cytoplasm
- Cytoplasmic eosinophilic hyaline globule (alpha feto-protein, AFP)
- Mallory hyaline may be observed
- Small nuclear fragments, satellite nuclei and atypical naked nuclei
- Absent bile duct epithelium
- Canalicular polyclonal CEA and CD10 staining pattern

Variants

- Fibrolamellar hepatocellular carcinoma:
  - Large polygonal cells with eosinophilic granular cytoplasm
  - Nuclear enlargement with single prominent nucleoli and intranuclear cytoplasmic inclusions
  - Pale body (fibrinogen) and PAS-positive hyaline globules
  - Rows of fibroblasts may be observed

Differential Diagnosis

- Metastatic adenocarcinoma and cholangiocarcinoma:
  - Often indistinguishable based on cytologic findings
  - Lack sinusoidal endothelial cell lining, AFP, alpha-1-antitrypsin, intracytoplasmic Mallory hyaline, and bile production
  - Trabecular growth pattern and intranuclear inclusion are uncommon
  - Mucin production and diffuse cytoplasmic CEA staining pattern

Hepatoblastoma

Cytologic Findings

- Hypercellular smear with trabeculae, cords, tubular, acinar and papillary arrangement of cells covered by sinusoidal lining cells
- Mixture of fetal/embryonal type primitive cells and mesenchymal elements similar to other small round cell tumors of childhood
- Nuclei usually smaller than normal hepatocytes
- High N/C ratio, round, central, normochromatic or slightly hyperchromatic chromatin
- Smooth nuclear membrane and inconspicuous nucleoli
- Scant to moderate finely granular cytoplasm
- Small cytoplasmic vacuoles maybe noted but bile is rare
- Positive for low molecular weight keratin, and negative for vimentin, high molecular weight cytokeratin, and epithelial membrane antigen
- Extramedullary hematopoiesis may be seen (very rare)
- Cartilaginous or osseous metaplasia may be observed

Differential diagnosis

- Hepatocellular carcinoma:
  - Larger cells with more pleomorphism
  - Broader trabeculae than those seen in hepatoblastoma
- Hepatocellular adenoma:
  - Less cellular than hepatocellular carcinoma or hepatoblastoma
  - Unremarkable appearing hepatocytes

Cholangiocarcinoma

Cytologic Findings

- Well differentiated ones present as sheets and clusters of atypical cells that resemble bile duct epithelium
- The findings in less differentiated ones are those of adenocarcinoma, not otherwise specified
- Hypercellular smear of discohesive sheets, three-dimensional clusters and isolated single glandular cells
- Loss of nuclear polarity with nuclear pleomorphism, irregular nuclear membrane, chromatin clumping and clearing, atypical mitotic figures, and prominent nucleoli
- Cellular borders usually indistinct
- Granular and vacuolated cytoplasm, may contain mucin
- Tumor diathesis

Differential Diagnosis

- Reactive/regenerative atypia:
  - Cohesive monolayer sheets of cells with normal N/C ratios
  - Regular nuclear membrane, and evenly distributed chromatin
  - Cell polarity maintained and lack significant nuclear pleomorphism
  - Inflammatory background and cellular debris
- Hepatocellular carcinoma:
  - Cell balls and trabeculae with peripheral endothelium

Metastatic Adenocarcinoma

- Findings in metastatic adenocarcinoma from lung, stomach or pancreas are indistinguishable from cholangiocarcinoma

- Metastatic colon adenocarcinoma typically shows tall columnar cells with luminal borders and elongate or spindled hyperchromatic stratified nuclei

Metastatic Carcinoid

- Cellular smear of loosely arranged round monotonous cells
- Occasional rosette formation
- Basophilic or slightly granular cytoplasm
- Nuclei 2–3x normal lymphocytes, round regular central or slightly eccentric (plasmacytoid)
- Evenly distributed finely or coarsely chromatin (salt and pepper)
- Inconspicuous nucleoli
- Immunohistochemical staining for neuroendocrine makers (chromogranin A, synaptophysin and neuron specific enolase) helpful

Pancreas

Normal Components

Acinar cells

- Small clusters of cells with dense granular cytoplasm
- Round small peripherally located regular nuclei
- Evenly distributed finely granular chromatin

Ductal Cells

- Columnar or cuboidal cells in sheets (honeycomb pattern)
- Pale cytoplasm and round to oval uniform nuclei with fine granular chromatin and small nucleoli

Islet cells

- Isolated and loose clusters of cells with round to oval nuclei
- Uniform nuclei with finely granular chromatin (salt and pepper)
- Usually few cells and may not be distinguishable from acinar cells

Acute Pancreatitis

- Hypocellular smear with admixtures of ductal/acinar cells, neutrophils, and histiocytes in a dirty necrotic background
- Degenerative/regenerative epithelial cells with reactive atypia (may mimic adenocarcinoma)
- Lipophages and amorphous basophilic materials associated with fat necrosis

Chronic Pancreatitis

- Hypocellular smear with cohesive honeycomb sheets of ductal cells with reactive/reparative changes
- Lack nuclear pleomorphism and presence of single cells
- Acinar components less conspicuous
- Stromal fragments with myofibroblasts and variable chronic inflammatory background
- Ductal and acinar cells may show degenerative change

Pseudocyst

- Hypocellular smear of lipid-laden histiocytes, neutrophils, plasma cells, and lymphocytes in a dirty background
- Occasional atypical mesenchymal cells and myofibroblasts
- Flecks of calcification
- Possibly necrotic fat cells
- No or rare epithelial elements
- Fluid content positive for amylase and negative for CEA
- Purulent fluid should be cultured

Tumors (also see Chapter 29)

Microcystic Adenoma

- Microcysts lined by bland, uniform cells
- Aspirates result in clear watery fluid
- Hypocellular smear with flat sheets of low columnar or cuboidal cells with honeycomb arrangement
- Amphophilic cytoplasm with fine vacuolization containing glycogen
- Small uniform round to oval nuclei and inconspicuous nucleoli
- Lack cytologic feature of malignancy
- Scattered foamy or hemosiderin-laden macrophages
- Positive staining for glycogen and negative for mucin

Mucinous Cystic Neoplasm

- Low cellularity
- Findings ranged from cohesive sheets and papillary clusters of cells resemble benign endocervical cells to cells clearly derived from mucinous adenocarcinoma
- Single cells may resemble goblet cells
- Intracellular mucin deposition and mucin in the background
- Scattered muciphages and chronic inflammation
- Even if cytologically benign, these neoplasms require total resection
- CEA elevated in the cyst fluid

Ductal Adenocarcinoma

Cytologic Findings

- Cellular smear of sheets and clusters of cells with abortive lumen formation
- Loosely cohesive ductal cells arranged in "drunken honey comb" pattern
- Nuclear pleomorphism (nuclear size variation >4:1)
- Nuclear enlargement with increased N/C ratio
- Nuclear overlapping and crowding, nuclear membrane irregularity, irregular chromatin distribution ("washed-out" nuclear chromatin with rimming of nuclear membrane)
- Prominent macronucleoli, increased mitotic figures, and loss of nuclear polarity
- Multinucleation and frequent mitotic figures

- Cytoplasmic vacuolization, sometimes acquires squamoid appearance
- Tumor diathesis
- Lack acinar or islet cells

Differential Diagnosis

- Chronic pancreatitis
  - Reactive ductal cells are uniform in size and shape

Acinar Cell Carcinoma

- Clusters and isolated monotonous acinar cells; predominantly cohesive
- Uniformly hyperchromatic, centrally placed enlarged nuclei with irregular nuclear membrane and prominent nucleoli
- Moderate amount of granular eosinophilic cytoplasm
- PAS+ cytoplasmic staining
- Absence of benign ductal components

Islet Cell Tumors

- Hypercellular smear of loose clusters, rosettes and isolated round uniform cells
- Eccentric nuclei imparting a plasmacytoid appearance
- Uniform nuclei with salt and pepper chromatin
- Small to inconspicuous nucleoli
- Pale delicate basophilic granular cytoplasm
- Positive staining for PAS and alpha-antitrypsin
- Positive immunostaining for neuroendocrine markers
- Neurosecretory granules observed on electron microscopy

Solid-Pseudopapillary Tumor (Solid and Papillary Epithelial Neoplasm)

- Loosely cohesive microtissue fragments and cells with acinar-like arrangement
- Branching papillae with delicate fibrovascular cores, myxoid stroma and one to several layers of cells
- Uniform oval nuclei with fine chromatin and characteristic nuclear grooves
- Inconspicuous small nucleoli
- Variable amount of pale amphophilic cytoplasm
- Metachromatic material in fibrovascular cores and hyaline globules in some acinar-like structures on Romanovsky stain

OVARY

Overview

Sampling Method

- Transvaginal sonographically guided aspiration (most common route)
- Transabdominal
- Transrectal
- Laproscopic visualization and aspiration

Parameters to be Considered in FNA of Ovary

- At least 2 of these parameters must be consistent to establish the correct diagnosis:
  - Ultrasound and laparoscopic findings
  - Cytologic examination
  - Estradiol level in the fluid

Contaminants that may be Observed in FNA of Ovaries

- Squamous cells from skin or vaginal mucosa
- Colonic epithelium:
  - May be seen in transrectal and transabdominal aspirates
  - Usually few cells
  - May not indicate perforation of bowels
- Mesothelial cells
- Mesenchymal cells:
  - Adipose tissue
  - Smooth and skeletal muscle
  - Collagen
- Note: it is important to ascertain the route of the needle and which form of possible contaminants may be present

Selected Lesions

Follicular Cyst

- Isolated single cells and tight clusters of granulosa cells of variable size
- Round to oval nuclei with nuclear grooves and coarse granular chromatin
- Occasional large polygonal luteinized granulosa cells with abundant granular or vacuolated cytoplasm
- Eccentric nuclei with finely granular chromatin and prominent nucleoli
- Lack ciliated bodies
- Estradiol level in fluid >20 nmol/L in 90% of follicular cyst

Corpus Luteum Cyst

- Numerous luteinized granulosa cells
- Abundant granular cytoplasm with indistinct cell borders and large nuclei with nucleoli

- Blood, fibrin, hemosiderin laden macrophages and fibroblast
- Abundant fibroblasts and hematoidin-laden macrophages suggest a regressing corpus luteum
- "Atypia" that mimics carcinoma may be noted in aspirates performed in postpartum period

Endometriotic Cyst

- Bloody smear with numerous hemosiderin laden macrophages
- Rare isolated or clusters of endometrial cells
- Marked degenerative changes may be observed

Mature Cystic Teratoma

- Abundant anucleated squames, mesenchymal cells, and columnar cell
- Viscous amorphous debris representing sebaceous secretion

Cystic Granulosa Cell Tumor

- May be indistinguishable from follicular cyst
- Follicular or trabecular arrangement of uniform granulosa cells
- Call-Exner bodies may be seen

Serous Cystadenoma

- Mildly cellular
- Clusters and groups with sheet-like (honeycomb) and papillary configuration
- Uniform columnar epithelial cells
- Lacks cytologic atypia
- Cilliary bodies (tufts of cilia) may be observed

Mucinous Cystadenoma

- Mildly cellular
- Honeycomb sheets of columnar mucin producing cells
- Uniform nuclei with finely granular evenly distributed chromatin
- Mucin background best appreciated on Romanovsky stain

Papillary Serous Cystadenocarcinoma

Cytologic Findings

- Hypercellular smear composed of isolated cells and branching papillary group of columnar or cuboidal cells with eosinophilic cytoplasm
- Eccentric hyperchromatic nuclei with irregularly distributed chromatin
- Nuclear pleomorphism and prominent nucleoli
- Psammoma bodies
- Cytologic features of borderline tumors (low malignant potential) vary from completely bland cells to highly atypical and almost indistinguishable from those of carcinoma

Differential Diagnosis

- Serous cystadenoma:
  - Less cellular
  - Clusters and groups of uniform columnar epithelial cells
  - Lacks cytologic atypia
- Atypical luteinized cells
- Endometriosis

Mucinous Cystadenocarcinoma

Cytologic Findings

- Numerous clusters of columnar cells with picket-fence configuration and cell balls
- Cytoplasmic vacuoles and eccentrically located nuclei
- Mucinous background

Differential Diagnosis

- Colonic cell contaminants from transrectal aspirates
- Mucinous cystadenoma:
  - Less cellular
  - Honeycomb sheets of columnar mucin producing cells
  - Uniform nuclei with finely granular evenly distributed chromatin

Endometrioid Carcinoma

- Clusters, sheets and syncytial groups of cells with acinar configuration
- Cuboidal to polygonal cells with low N/C ratio
- Abundant granular eosinophilic cytoplasm, fine cytoplasmic vacuoles, prominent nucleoli
- May be indistinguishable from serous adenocarcinoma

Clear Cell Carcinoma

- Sheets and clusters of large cells with abundant pale cytoplasm
- Nuclear pleomorphism and irregularity with hobnailing
- Cherry red macronucleoli

Granulosa Cell Tumor

- Cellular smear with solid, follicular and trabecular arrangement of cells
- Uniform cells with indistinct cell border, nuclear grooves, evenly distributed chromatin, and small nucleoli
- Occasional Call-Exner bodies: acinar-like structure with central amorphous reddish material

Brenner's Tumor

- Biphasic populations of epithelial and mesenchymal cells
- Sheets of polygonal to cuboidal epithelial cells
- Oval nuclei, nuclear groove and cytoplasmic eosinophilic globules

Fibrothecoma

- Hypocellular smear of spindle cells
- Elongated nuclei with evenly distributed chromatin

Carcinoid

- Discohesive cells with eccentric nuclei and plasmacytoid appearance
- Granular "salt and pepper" chromatin
- Bilateral ovarian involvement represents metastasis to the ovaries

Dysgerminoma

- Discohesive isolated large cells with abundant amphophilic cytoplasm
- Nucleomegaly, coarse clumped chromatin and macronucleoli
- Numerous lymphocytes and occasional histiocytes and giant cells
- Tigroid Background seen on Romanovsky:
  - Composed of interwoven lacy, PAS+ materials
  - Related to extracellular glycogen
  - Also occur in rhabdomyosarcoma and glycogen-rich clear cell tumors

KIDNEY

Simple Cyst

- Hypocellular smear with scant epithelial cells
- Pyknotic degenerative nuclei
- Scattered macrophages with finely vacuolated cytoplasm ("foamy cells")
- Amorphous proteineous materials and inflammatory cells
- More than 50% of men over age 50 may have cysts and 1–5% of cysts may harbor cancer

Oncocytoma

- Sheets and isolated polygonal cells with abundant eosinophilic cytoplasm
- Cells have normal N/C ratio and resemble proximal tubular cells
- Single or multiple nuclei with fine granular chromatin and inconspicuous nucleoli
- Occasional degenerative bizarre nuclei, bi- and/or multinucleation

Angiomyolipoma

- Microtissue fragments with few single or isolated cells
- Triphasic tumors:
  - Smooth muscle cells: spindle cells with cigar-shaped nuclei (smooth muscle)
  - Adipocytes
  - Blood vessels
- Smooth muscle cells may have epithelioid appearance mimicking sarcoma
- Bloody background
- Immunostaining for HMB-45+ (in smooth muscle)

Clear Cell Renal Cell Carcinoma

Cytologic Findings

- Smears can either be highly cellular or very bloody/necrotic and hypocellular
- Isolated cells, floral grouping and three-dimensional clusters of large columnar cells
- Tumor cells are larger than adjacent proximal tubular cells
- Variable nuclear pleomorphism depending on the tumor grade
- Nuclei with irregular nuclear membrane and coarsely granular chromatin
- Intranuclear vacuoles common
- Abundant vacuolated cytoplasm positive for glycogen or hemosiderin
- Metachromatic basement membrane-like material on Romanovsky
- Negative mucin

Variants

- Multilocular cystic renal cell carcinoma:
  - Isolated cells and discohesive sheets, papillae and loose clusters
  - Low nuclear grade, irregular nuclear borders
  - Intranuclear cytoplasmic inclusions
  - Granular vacuolated cytoplasm with glycogen and hemosiderin
  - Necrotic debris, foamy histiocytes, degenerating blood and inflammatory background

Differential Diagnosis

- Benign hepatocytes:
  - Cohesive sheets of polygonal cells with central nuclei and low N/C ratio
  - Cytoplasmic lipofuscin and bile production
- Normal adrenal cortical cells:
  - Cells with uniform nuclei and abundant vacuolated cytoplasm
- Vacuolated macrophages:
  - Single isolated cells, no clustering or grouping
- Adrenocortical neoplasm:
  - Lack metachromatic basement membrane-like material
  - Nuclear pleomorphism

- Pheochromocytoma:
  - Isolated single cells and loose clusters of variable sized cells
  - Nuclear pleomorphism and salt-pepper chromatin
  - Abundant red granules on Romanovsky
- Retroperitoneal seminoma:
  - Discohesive cells admixed with lymphocytes
  - Tigroid background composed of irregular, lacy PAS+ material
  - Thick irregular nuclear membrane and prominent nucleoli

Papillary Renal Cell Carcinoma

- Cellular smear of papillae with true fibrovascular cores
- May present as spherules or tubules
- Cuboidal or columnar cells with high N/C ratio
- Delicate basophilic cytoplasm with intracytoplasmic hemosiderin
- Relatively uniform nuclei with evenly distributed fine granular chromatin in most cases
- Psammoma bodies, scattered foamy histiocytes, and hemosiderin-laden macrophages
- Distorted aspirated normal glomeruli may mimic papillary renal cell carcinoma

Chromophobe Renal Cell Carcinoma

- Cellular smear composed of isolated and tight clusters of large polygonal cells
- Cells have distinct cell border and pale granular or vacuolated cytoplasm (Hale's colloidal iron+)
- Nuclei are enlarged and irregular with coarsely granular chromatin and occasional nucleoli
- Bi- and/or multinucleation

Collecting Duct Carcinoma

- Isolated cells and tubulo- papillary groups of pleomorphic cells with mucin production
- Cells have high N/C ratio and granular cytoplasm
- Hyperchromatic nuclei with coarsely granular chromatin and prominent nucleoli
- Metachromatic stromal fragments and inflammatory background (neutrophils may be numerous)

Wilms' Tumor

Cytologic Findings

- Microtissue fragments with tightly packed tubular structure surrounded by small blastemal cells
- Triphasic tumor with blastema, epithelial cells and spindle stromal cells
- Blastemal cells are small with high N/C ratio and hyperchromatic nuclei
- Epithelial components may form glands, complex branching tubules and glomeruloid bodies intermixed with metachromatic materials
- Small cuboidal or columnar cells with scant cytoplasm
- Skeletal muscle, cartilage and fat may be seen

Differential Diagnosis

- Neuroblastoma:
  - Isolated cells, loose clusters, and frequent Homer-Wright rosettes
  - Neuropil and occasional polygonal ganglion cells
- Rhabdoid tumor:
  - Clusters and isolated round to oval cells with macronucleoli and abundant cytoplasm
  - Intracytoplasmic eosinophilic globular hyaline inclusions
- Clear cell sarcoma:
  - Clusters and isolated polygonal or spindle cells with uniform nuclei
  - Fine vasculature
- Rhabdomyosarcoma:
  - Rhabdomyoblasts and absence of triphasic composition
- Teratoma:
  - Lack blastemal cells

URINARY BLADDER

Overview

Types of Cellular Specimens

- Spontaneous voided urine
- Instrumentation (catheterization/cystoscopy)
- Bladder washing
- Ureteral and pelvic brushing and washing
- Urethral brushing
- Ileal conduit urine

Specimen Preparation

- Direct smear
- Membrane filtration
- Cytocentrifugation
- Monolayer thin preparation
- Paraffin cell block (rarely used mainly for tissue fragments)

Cellular Components of Urinary Cytology

- Urothelial cells:

- Superficial umbrella cells, large and often multinucleated (more frequent in washings and catheterized urine)
- Intermediate pyramidal cells
- Cuboidal basal cells

♦ Squamous cells:
- May be due to contamination
- Normally found in women and would show cyclic changes
- In males their presence indicate squamous metaplasia

♦ Renal epithelial cells (indicates renal disease or injury)
♦ Intestinal epithelial cells in ileal conduit specimens
♦ Endometrial cells (endometriosis)
♦ Prostatic or seminal vesicle epithelial elements, spermatozoa (particularly following prostatic massage)
♦ Red cells and inflammatory cell

Reporting Terminology

♦ Unsatisfactory for evaluation
♦ Negative for malignancy
♦ Reactive urothelial cells
♦ Atypical urothelial cells, favor reactive
♦ Atypical urothelial cells of undetermined significance (including dysplastic cells)
♦ Atypical urothelial cells, suspicious for malignancy
♦ Malignant cells are present:
- Derived from low grade urothelial carcinoma
- Derived from high grade urothelial carcinoma
- Derived from carcinoma in-situ
- Derived from adenocarcinoma
- Others (e.g. small cell and squamous cell carcinoma)

Benign Lesions and Mimics of Malignancy

Reactive Urothelial Cells

♦ Nuclei are relatively uniform with smooth contours, finely granular chromatin
♦ Peripheral condensation of chromatin
♦ Cytoplasmic vacuolization and prominent nucleoli (not seen in low grade urothelial carcinoma)

Instrument Artifact and Lithiasis

♦ Increased cellularity
♦ Cohesive, ball-shaped and papillary tight clusters with cytoplasmic collar and smooth border
♦ Flattened urothelial cell at periphery of cell balls
♦ Cytoplasmic vacuolization usually occur in reactive urothelium or high grade carcinoma, but rarely occur in low grade carcinoma
♦ Numerous multinucleated superficial cells

Decoy Cells

♦ Indicative of polyoma virus (Papovavirus) infection
♦ Infection may be asymptomatic or associated with hematuria
♦ Some patients are immunocompromised e.g. AIDS, diabetes mellitus, cancer or post-transplantation
♦ Many patients have no known predisposing factor
♦ Spontaneously resolves
♦ May have aneuploid DNA pattern
♦ Discohesive isolated enlarged cells without clustering
♦ High N/C ratio with eccentric nuclei and peripheral ring of chromatin
♦ Single intranuclear dense dark ink-black large smudgy inclusion (decoy cell)
♦ Some may have a thin halo around the inclusion (not to be confused with the conspicuous halo of cytomegalovirus)
♦ Some have short cytoplasmic tails (comet cells)

Ileal Conduit

♦ Columnar (colonic) degenerative epithelial cells without atypia
♦ Mucoid dirty background
♦ Eosinophilic cytoplasmic inclusions may be seen

Treatment Effect

Radiation

♦ Cytomegaly and bizarre cells (may be spindled)
♦ Multinucleation
♦ N/C ratio normal and nuclear degeneration with a smudged chromatin pattern
♦ Macronucleoli
♦ Cytoplasmic polychromasia, vacuolization, and cytophagocytosis

Chemotherapeutic effect

♦ N/C ratio normal or high, degenerative intranuclear and cytoplasmic vacuoles
♦ Multinucleation

Cyclophosphamide (Cytoxan) and Busulphan (Myleran) therapy

♦ Produce highly atypical cells that mimic high-grade urothelial carcinoma
♦ Cytomegaly
♦ High nuclear to cytoplasmic ratio
♦ Markedly hyperchromatic chromatin (frequently smudged)
♦ One or two large irregular nucleoli

Thiotepa and Mitomycin C

♦ Cause increased cell turnover and exfoliation in the initial stage
♦ Associated with reactive-like changes

Cyclosporine A

♦ Nephrotoxic and causes shedding of tubular cells, sometimes as papillary tissue fragments
♦ Cytoplasmic inclusions (giant mitochondria)

- Cytoplasmic vacuolization
- Microcalcifications may occur

Intravesical Bacilli Calmette-Guerin (BCG) Effect

- Multinucleated giant cells and lymphohistiocytic aggregates
- Mixed inflammatory cells and reactive urothelial cell
- Neutrophils (first week), lymphocytes and macrophages (later)

Laser Effect

- Spindled cells occur singly or in groups
- Elongated nuclei with uniform dense chromatin

Urothelial Papilloma

- Often indistinguishable from low grade papillary urothelial carcinoma
- Less cellular, small cells with hyperchromatic nuclei

Malignant Lesions

General Features

- May detect urothelial carcinoma long before it is detected clinically or confirmed histologically
- False positive cytology is truly false positive after extensive workup of the patient
- Urine cytology is more predictive of carcinoma as the grade gets higher
- High false negative rate for low grade tumors
- Cannot distinguish between low grade intraepithelial lesions, papilloma, and low grade urothelial carcinoma
- Cannot distinguish between high grade intraepithelial lesions, carcinoma in situ and high grade urothelial carcinoma
- Papillary clusters in voided urine are highly suspicious for carcinoma in the absence of infection or stone

Urothelial Carcinoma In Situ (CIS)

- Often indistinguishable from high grade urothelial carcinoma
- Predominantly isolated highly atypical single cells with cytoplasmic vacuolization (usually have more monotony than invasive high grade carcinoma)
- Enlarged nuclei with irregular nuclear contour, coursely granular chromain and prominent nucleoli
- Lack tumor diathesis

Urothelial Carcinoma

- 1998 International Society of Urologic Pathology Classification of Papillary Bladder Neoplasms (also see Chapter 25):
  - Papilloma
  - Papillary neoplasm of low malignant potential (formerly WHO grade 1 urothelial carcinoma)
  - Urothelial carcinoma, low grade (formerly WHO grade 2 urothelial carcinoma)
  - Urothelial carcinoma, high grade (formerly WHO grade 3 carcinoma)

Cytologic Findings

- Classification and grading of urothelial carcinoma is difficult based on cytology
- WHO Grade 1:
  - May be indistinguishable from benign reactive urothelial cells or papilloma
  - Lack cytoplasmic vacuolization and prominent nucleoli
- WHO Grade 2:
  - Papillary and three-dimensional clusters with ragged border
  - True papillary frond with fibrovascular core are pathognomonic
  - Increased N/C ratio with slight irregular nuclear contours and finely granular chromatin
  - Cytoplasmic homogeneity
  - Lack prominent nucleoli and cytoplasmic vacuolization
  - Umbrella cells are still present
- WHO Grade 3:
  - High grade urothelial carcinoma and CIS are often indistinguishable cytologically
  - Discohesive clusters and isolated single cells
  - Cytoplasmic vacuolization, lack surface maturation
  - Increased nuclear overlapping and crowding
  - High N/C ratio, nuclear pleomorphism, irregular nuclear contours, chromatin clumping and clearing, prominent nucleoli
  - Dirty inflammatory background with necrotic debris

Differential Diagnosis

- Reactive urothelial cells:
  - Cytoplasmic vacuolization and prominent nucleoli may be seen (incompatible with low-grade urothelial carcinoma)
- Instrument artifact and lithiasis:
  - Increased cellularity, multinucleated superficial cells
  - Flattened urothelial cells at periphery of cell balls
  - Cytoplasmic vacuoles (cytoplasmic vacuolization usually occur in reactive urothelium or high grade carcinoma, but rarely occur in low grade carcinoma)
- Decoy cells:
  - Discohesive isolated enlarged cells with high N/C ratio
  - Peripheral condensation of chromatin, dense smudgy intranuclear inclusion, and occasionally a thin halo

- Treatment effect:
  - N/C ratio normal, cytoplasmic vacuoles, cytoplasmic polychromasia
  - Multinucleated giant cells and reactive urothelial cells
  - Smudged chromatin
- Seminal vesicles:
  - Lipofuscin pigment
- Malacoplakia:
  - Macrophages containing Michaelis-Gutmann bodies
- Reactive renal tubular epithelium:
  - Suspect renal parenchymal ischemic necrosis
  - Round oval cells with small eccentric nuclei and granular cytoplasm
- Renal collecting duct epithelium:
  - Microtissue fragments or isolated small polygonal cells with scant cytoplasm
  - Centrally placed small nuclei with dense chromatin
- Urothelial papilloma:
  - Often indistinguishable from low grade papillary urothelial carcinoma
  - Less cellular, small cells with hyperchromatic nuclei

Urothelial Adenocarcinoma

Cytologic Findings

- Three dimensional grouping with nuclear palisading
- High N/C ratio, eccentric nuclei, irregular nuclear contours, prominent nucleoli
- Intracellular and extracellular mucin production

Differential Diagnosis

- Prostatic adenocarcinoma:
  - Acini and syncytial groups of cells with nucleomegaly and prominent nucleoli
  - Lack mucin
- Herpes simplex virus-induced changes
- Decoy cells
- Glandularis cystitis:
  - Glandular cells with cytoplasmic vacuoles, lack cytologic atypia
- Renal cell carcinoma:
  - Frequently degenerated
  - Single cells or small groups of abnormal cells
  - Nuclei round to oval, eccentric, hyperchromatic, with prominent nucleoli
  - Cytoplasm appears more granular than expected due to degeneration
- Nephrogenic adenoma:
  - Single or small groups of vacuolated cells
  - Polygonal to columnar in shape
  - Uniform nuclei
- Ileal conduit:
  - Columnar (colonic) degenerative epithelial cells without atypia
  - Mucoid dirty background
  - Eosinophilic cytoplasmic inclusions may be seen
- Renal rejection:
  - Numerous renal tubular cells and T-lymphocytes
  - Casts and renal red blood cells with thick outer border and clear center

PLEURAL AND PERITONEAL FLUID

Reactive Mesothelial Cells (See Tables 4 and 5)

- Loose aggregates of cells with demarcation lines or "windows" between cells
- Fluffy cytoplasmic border (cilia) and centrally placed nuclei
- Ill-defined, fine, small centrally placed vacuoles with signet-ring change and peripheral PAS staining (glycogen)
- Two-tone cytoplasm staining with a rim of lighter blue cytoplasm around nucleus
- Bi- and multinucleation with similar nuclear size
- Continuum or spectrum of changes ranging from normal to atypia
- Psammoma bodies and mitotic figures

Causes of mesothelial hyperplasia:

- Heart failure
- Infection (pneumonia, lung abscess)
- Infarction
- Liver disease (hepatitis, cirrhosis)
- Collagen disease
- Renal disease (uremia, dialysis)
- Pancreatic disease
- Radiation
- Chemotherapy (Bleomycin, Cytoxan)
- Traumatic irritation (hemodialysis, surgery)
- Chronic inflammation (pleuritis)

Table 4. Features of Quiescent and Reactive Mesothelial Cells

Cytologic feature	*Quiescent*	*Reactive Hyperplastic*
Pattern	Sheets, closely apposed to one another Break off in small groups	Doublets or triplets with windows between them May form papillary groups Connections by clasp like articulation
Shape and size	Round to oval 15–20 mm	Round to oval 20–40 mm
Nucleus	Monotonous Oval to round Mononuclear or binuclear Evenly distributed chromatin	Variable Oval to round Multinucleation Variable
Nucleolus	Inconspicuous	Variable
Cytoplasm	Moderate amount Translucent Peripheral vacuoles containing glycogen	Abundant Endo-ectoplasmic demarcation Peripheral vacuoles containing glycogen
Cell border	Fuzzy border due to microvilli	Cytoplasmic protrusions distal to cellular connections

Table 5. Comparison Between Transudate and Exudate

	Transduate	*Exudate*
Appearance	Clear	Turbid
Specific gravity	<1.015	>1.015
Protein	<3 gm/dl	>3 gm/dl
Fluid/serum protein ratio	<0.5	>0.5
Fluid/serum LOH ratio[1]	<0.6	>0.6

[1]*LOH = lactate dehydrogenase*

- Underlying neoplasm (fibroid, hamartoma)
- Foreign substance (talc, asbestos)

Rheumatoid Pleuritis/Pericarditis

- Pink necrotic granular debris (key feature)
- Elongated spindle epithelioid histiocytes with dense granular eosinophilic cytoplasm
- Multinucleated giant cells, neutrophils, lymphocytes and scattered reactive mesothelial cells

Tuberculosis

- Predominant lymphocytes without mesothelial cells in the pleural fluids
- Entrapment of mesothelial cells in the fibrinous exudate

Mesothelioma

- Grouping of cells:
  - Excessive number of malignant cells
  - No evidence of two-cell population
  - Cohesive, three dimensional clusters with thick cell membrane (cellular spheres)
  - High number of cells in the cellular spheres
  - Doublets and triplets still recognizable
- Individual cells:
  - Ecto-endoplasmic demarcation (two tone cytoplasmic staining with denser, more eosinophilic perinuclear staining)
  - Fuzzy border around entire perimeter
  - Clasp-like articulation between two cells
  - Protrusion from pinched member of the pair
  - Window-like spaces between the cells
  - Peripheral vacuolization and bleb formation
  - Bland nuclei resembling one another

Metastatic Adenocarcinoma (See Table 2)

Cytologic Findings

- Two-cell population
- Papillary acinar structures and cell balls with smooth community border
- Three dimensional tight clusters with nuclear overlapping and nuclear molding
- Large, well-defined, smooth edged and eccentrically placed vacuoles
- Some types present as single large abnormal cells

- Diffuse (instead of peripheral) PAS (+diastase) staining and mucin production and positive hyaluronidase resistant alcian blue
- Bizarre cells, multinucleation with atypia and variable nuclear size
- High N/C ratios, irregular nuclear contours, anisonucleosis, prominent nucleoli, and mitotic figures
- Intranuclear or intracytoplasmic inclusions

Differential Diagnosis

- Reactive mesothelial cells:
  - "Windows" between cells and cilia, two-tone cytoplasm staining
  - Negative mucin staining
- Malignant mesothelioma (see **Tables 2** and **3**):
  - Hypercellular smear with one cell population
  - Three-dimensional cohesive clusters of cells two-tone cytoplasm staining
  - Lack hyaluronidase resistant alcian blue staining
- Collagen ball:
  - Collagen covered by mesothelial cells, may be detached from the serosal surface or the ovary
  - Appear as smoothly contoured green bodies, naked or covered by a layer of mesothelial cells
- Ciliocytophthoria (ascites):
  - Detached cilliary tufts
  - Derived from fallopian tube lining cells, often seen in later half of menstrual cycle or after surgical manipulation
- LE cells:
  - Seen in patients with systemic lupus erythematosis
  - A neutrophil or sometimes a macrophage ingesting a denatured nucleus of an injured cell
- Tart cells:
  - Seen in patients with systemic lupus erythematosis
  - A macrophage that ingested a nonhomogenized nucleus of a dead cell

CEREBROSPINAL FLUID (CSF) AND CENTRAL NERVOUS SYSTEM

Specimen Preparation of CSF

- Cytospin
- Monolayer preparation
- Filter preparation:
  - More cells retained, but less optimal preservation and staining

Normal Components of CSF

- Usually no more than 5 cells/mm3
- Few lymphocytes and histiocytes
- Occasional neutrophils and eosinophils may be present after operative procedure involving subarachnoid space
- Contaminants include: cutaneous squamous cells, adipose tissue, skeletal muscle, cartilage, and vessels
- Hematopoietic precursors from bone marrow contaminants
- Corpora amylacea
- Talc powder
- Ventricular lining cells

Ependymal Cells

- Cuboidal to columnar cells with indistinct cell border, cytoplasmic vacuoles, and microcilia
- Difficult to differentiate from choroid plexus cell (not important)
- Less cohesive than choroid plexus cells with amphophilic cytoplasm
- May be pleomorphic in reactive conditions
- Phosphotungstic acid hematoxylin (PTAH) stains basal bodies of cilia

Choroid-Plexus Cells

- Often have papillary or microacinar configuration with dense eosinophilic cytoplasm
- Cell outline sharper than ependymal cells
- Cytoplasm may contain yellow pigment

Pia-arachnoid (Leptomeningeal) Cells

- Small round to spindle cells with abundant foamy cytoplasm and less defined cell border, resemble mesothelial cell

Brain Parenchyma

- Often seen in patients with ventricular shunts, intracranial hemorrhage, and head injury

Primitive (Blast-like) Cells of Neonates

- Probably derived from the subependymal germinal matrix
- Often seen in CSF of neonates with hydrocephalus or intraventricular hemorrhage
- Cohesive clusters of cells with high N/C ratio
- Neuron specific enolase positive and leukocyte common antigen negative

Inflammatory Conditions

- Neutrophils followed by mononuclear inflammatory cells in acute meningitis

- Viral infection characteristically shows mild lymphocytosis and rarely viral inclusions
- Mixed inflammation with lymphocytes may be observed in tuberculosis

Mollaret Meningitis

- Recurrent self-limiting aseptic meningitis
- Mollaret cell (activated monocytes), pleocytosis with increased lymphocytes and neutrophils

Acute Lymphocytic Leukemia/Malignant Lymphoma

Cytologic Findings

- Monotonous population of singly malignant cells with high N/C ratio, irregular nuclear contours, open chromatin, and prominent nucleoli
- Ancillary studies may be essential for diagnosis

Differential Diagnosis

- Reactive lymphocytes (due to intrathecal chemotherapy, viral infection, etc)
- Plasmacytoid and immunoblastic lymphocytes
- Puncture of marrow space
- Hematopoietic precursors at different stage of development
- Nucleated red cells and megakaryocytes
- Ventricular lining cells
- Primitive cells of neonates
- Medulloblastoma:
  - Tight clusters or single isolated small blue cells with nuclear molding

Astrocytoma

Cytologic Findings

- Low grade:
  - Hypocellular smear composed of dispersed small cells in a fibrillar background
  - Round nuclei with finely granular chromatin
  - Pale cyanophilic cytoplasm with indistinct cell borders
  - Long or blunt cytoplasmic processes may be seen in cells on FNA
  - Fibrillary background with small blood vessels in close association with tumor cells seen on FNA
- High grade:
  - Hypercellular smear
  - Nuclear hyperchromasia and nuclear pleomorphism
  - Tumor giant cells, bizarre nuclei, and prominent nucleoli
  - Endothelial proliferation best appreciated on Romanovsky
  - Degenerative changes and necrosis prominent
  - Atypical mitotic figures

Differential Diagnosis

- Reactive gliosis:
  - May be indistinguishable from low grade astrocytoma
  - Less cellularity, polymorphous population of cells
  - Admixtures of lymphocytes, histiocytes, and gemistocytes
  - Lack atypical mitoses and endothelial proliferation

Ependymomas

Cytologic Findings

- Honeycomb sheets or cohesive three dimensional aggregates of columnar and polygonal cells
- Low N/C ratio, small polarized round nuclei with finely to coarsely granular chromatin
- Cells with distinct cell borders and abundant eosinophilic cytoplasm
- Flexner-Wintersteiner (true) rosette and perivascular pseudorosette

Differential Diagnosis

- Normal ependymal Cells:
  - Often occur as singly isolated cells without clustering

Choroid Plexus Papilloma

Cytologic Findings

- Papillary and cohesive aggregates of cuboidal cells with distinct cell border
- Cells with low N/C ratio, uniform nuclei, smooth nuclear contours and fine chromatin
- Small or inconspicuous nucleoli

Differential Diagnosis

- Primitive Neuroectodermal tumors (PNET):
  - Small blue cells with hyperchromatic angulated nuclei and nuclear molding
  - Nuclei with course granular chromatin and smooth nuclear membrane
- Metastatic adenocarcinoma

Craniopharyngioma

- Anucleated squamous cells, lipid-laden macrophages, keratin pearls, and cholesterol crystals

Germinoma

- Isolated single cells and loosely cohesive sheets of large tumor cells admixed with lymphocytes
- Large vesicular uniform nuclei with prominent nucleoli

- Scant to moderate, delicate, occasionally vacuolated cytoplasm with distinct cell borders
- Granulomatous inflammation and tigroid background in Romanovsky stain
- Positive for placental alkaline phosphatase (PLAP)

Meningioma

- Cohesive clusters and syncytial arrangement of uniform spindle cells
- Cells with abundant eosinophilic cytoplasm
- Small nuclei with smooth nuclear contour and fine granular chromatin
- Psammoma bodies, whorls and intranuclear cytoplasmic inclusions
- Positive for epithelial membrane antigen (EMA)

Retinoblastoma

- Tight clusters of small blue cells with irregular coarsely granular chromatin
- Occasional rosette formation
- Tumor diathesis and inflammatory background

Medulloblastoma

Cytologic Findings

- Cellular smear composed of uniform population of small blue cells
- Nuclear molding
- Cells are isolated or as tight clusters
- Round hyperchromatic nuclei, high N/C ratio,
- Coarse granular chromatin and inconspicuous nucleoli
- Pseudorosette and nuclear molding

Differential Diagnosis

- Normal cerebellum:
  - Uniform cells of granular layer with smooth nuclear contours

Metastatic Carcinoma

- Variable number of cells
- Clusters of malignant cells with features that may be reminiscent of primary cancer
- Immunohistochemical staining is often helpful

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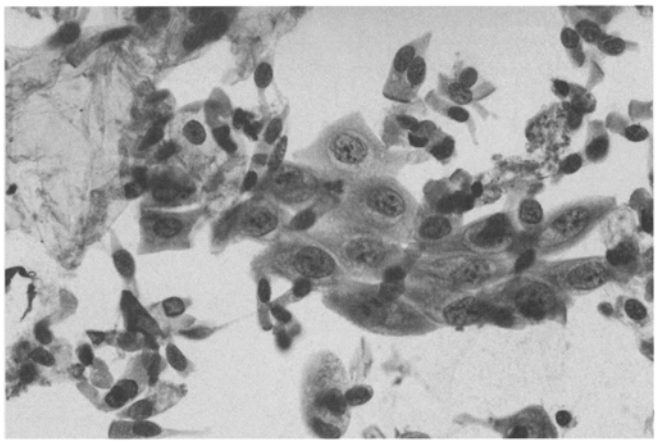


Fig. 71. Repair, gastric brush. Monolayer sheet of well-organized cells with striking resemblance to each other. No cellular overlap. The nuclei are enlarged with prominent nucleoli and marginated, pale chromatin. The cell borders are well defined, and the cytoplasm shows streaming in the same direction. Papanicolaou stain, high power view.

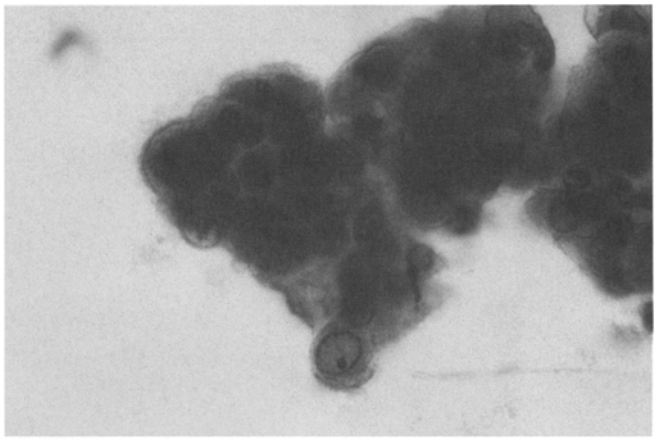


Fig. 72. Creola body, bronchoalveolar lavage. Three-dimensional, tightly cohesive clusters bordered by cilia. Papanicolaou stain, high power view.

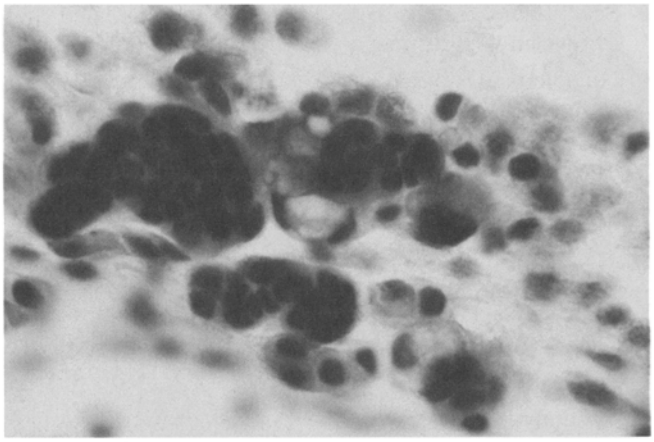


Fig. 73. Reserve cell hyperplasia, bronchial wash. Tightly cohesive small blue cells with no cytologic atypia or discohesion. The presence of contiguous goblet cells is a clue of their origin. Papanicolaou stain, high power view.

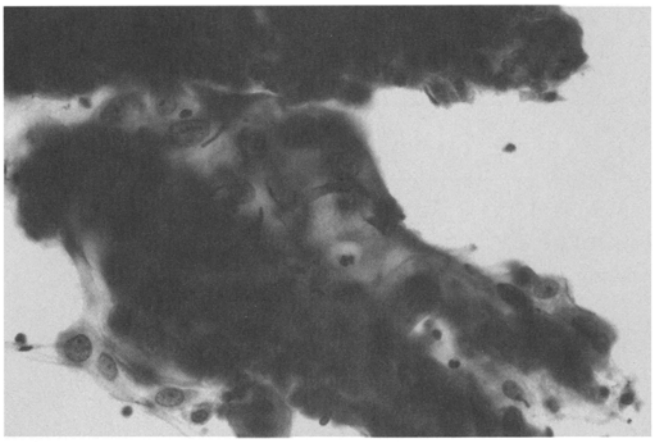


Fig. 74. Radiation therapy change, lung, FNA. Cytomegallic cells arranged in a syncytium. The cells are bizarre with amphophylic, frequently vacuolated, cytoplasm and ingested neutrophils. The chromatin is frequently smudged and difficult to read. Papanicolaou stain, high power view.

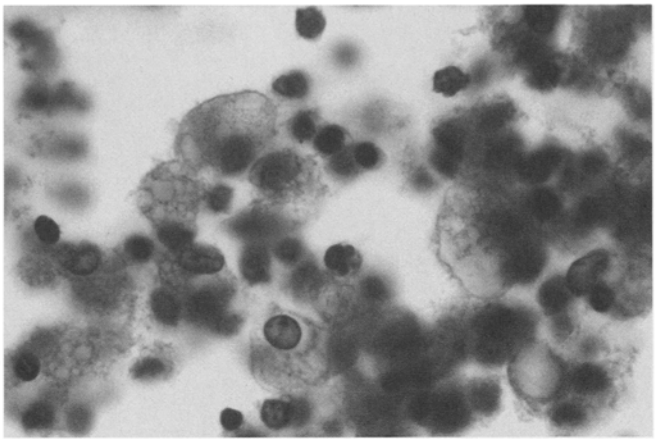


Fig. 75. Lipoid pneumonia, bronchoalveolar lavage. Highly vacuolated cytoplasm of these lipid ladened macrophages. Papanicolaou stain, high power view.

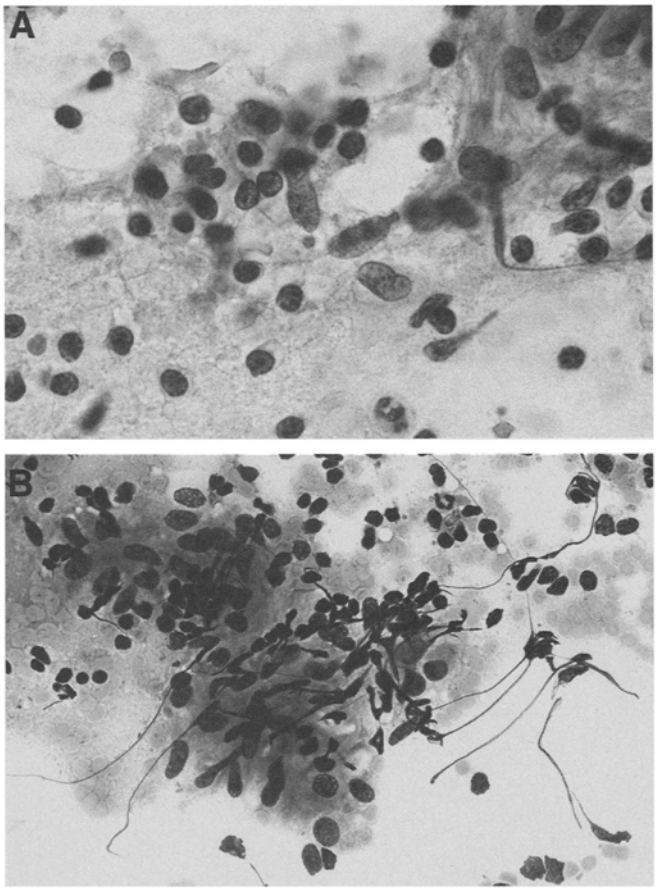


Fig. 76. Sarcoidosis, FNA of lung. **A.** Clusters of epithelioid histiocytes mixed with lymphocytes, Papanicolaou stain. **B.** Diff-Quik stain, high power view.

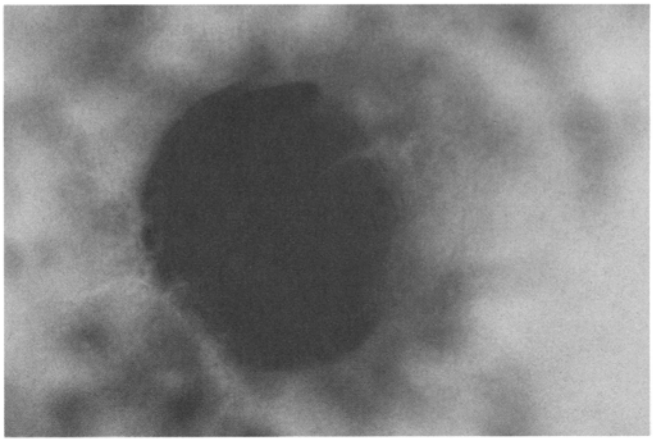


Fig. 77. Corpora amylacia, bronchial wash. Thick amorphous material with internal rings. Note the crack induced during preparation and the surrounding giant cell. Papanicolaou stain, high power view.

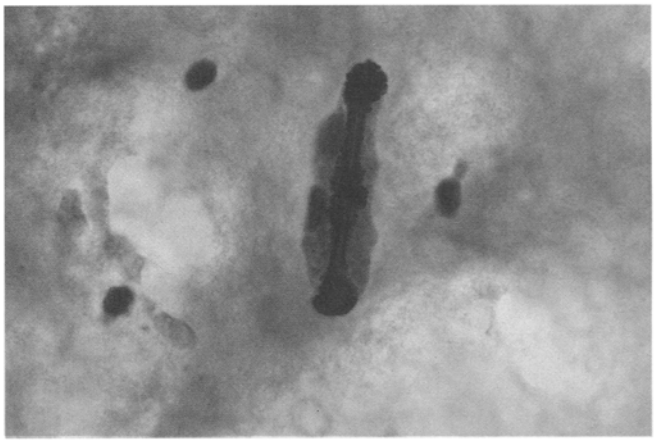


Fig. 78. Asbestos body, bronchial wash. Fiber with a clear, colorless center, and uniform thickness. Papanicolaou stain, high power view.

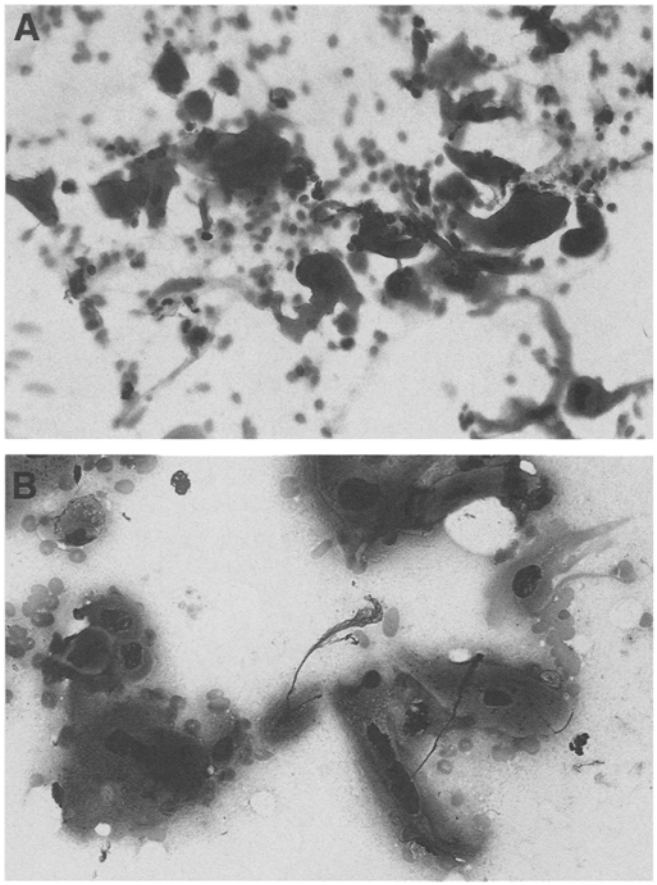


Fig. 79. Well differentiated squamous cell carcinoma, lung, FNA. **A.** Atyical cells with moderate orangeophilic cytoplasm indicating keratinization, Papanicolaou stain, medium power view. **B.** The keratinizing cells have a robin blue cytoplasm. Diff-Quik stain, high power view.

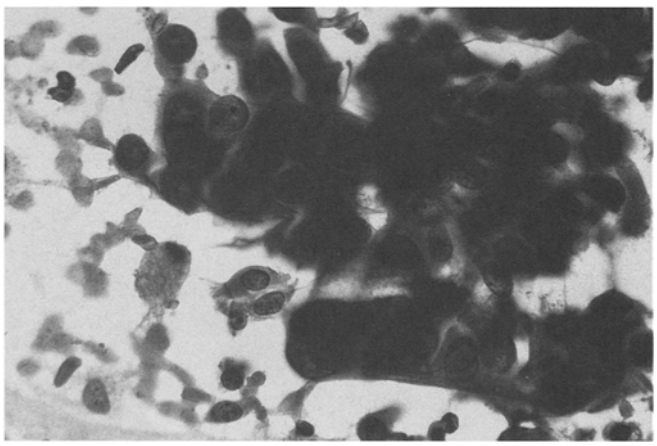


Fig. 80. Adenocarcinoma, bronchial brushing. Atypical cells arranged in sheets with a common cell border and areas with depth of focus. The nuclei are enlarged with prominent nucleoli. Compare the cytologic features of these malignant cells to the neighboring bronchial epithelium with ciliated cells in the center of the field. Papanicolaou stain, medium power view.

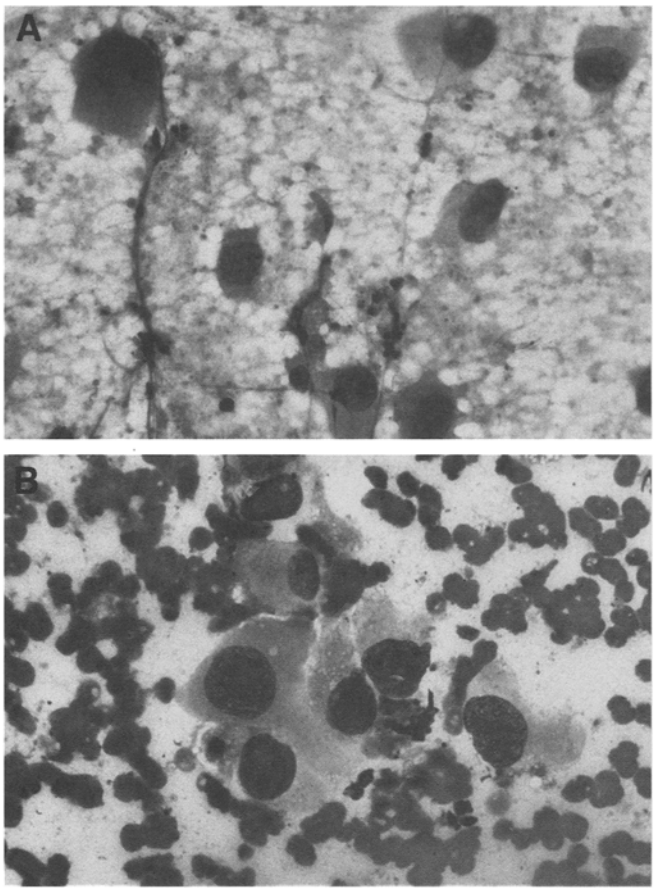


Fig. 81. Large cell anaplastic carcinoma, lung, FNA. Large single, disorganized malignant cells with pleomorphic nuclei and abundant cytoplasm. **A.** Papanicolaou stain, **B.** Diff-Quik stain, high power view.

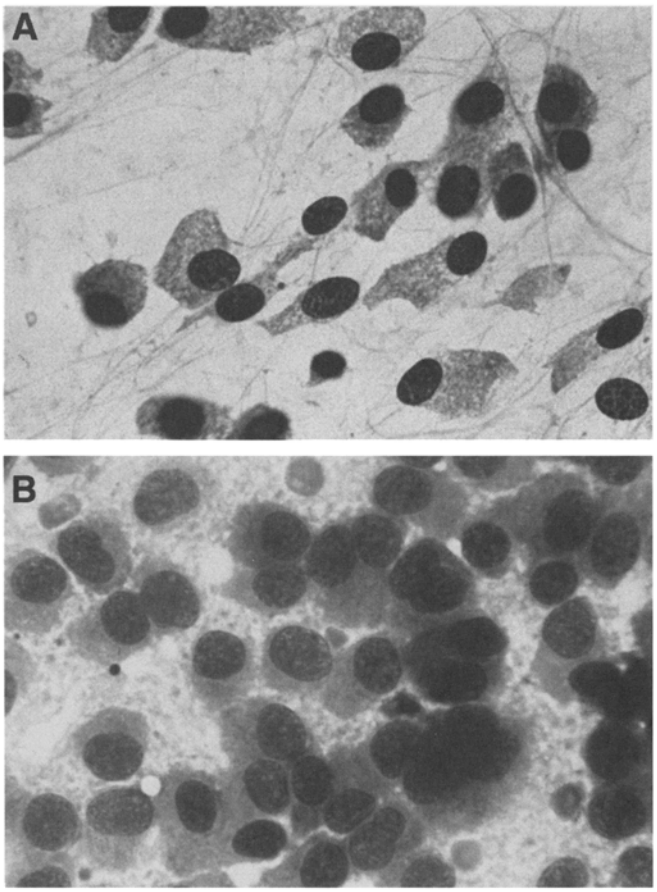


Fig. 82. Typical carcinoid, lung, FNA. **A.** Monotonous population of small plasmacytoid-appearing cells with a moderate amount of cytoplasm. Chromatin has a salt and pepper appearance. Papanicolaou stain. **B.** Occasional binucleation and multinucleation. Diff-Quik stain, high power view.

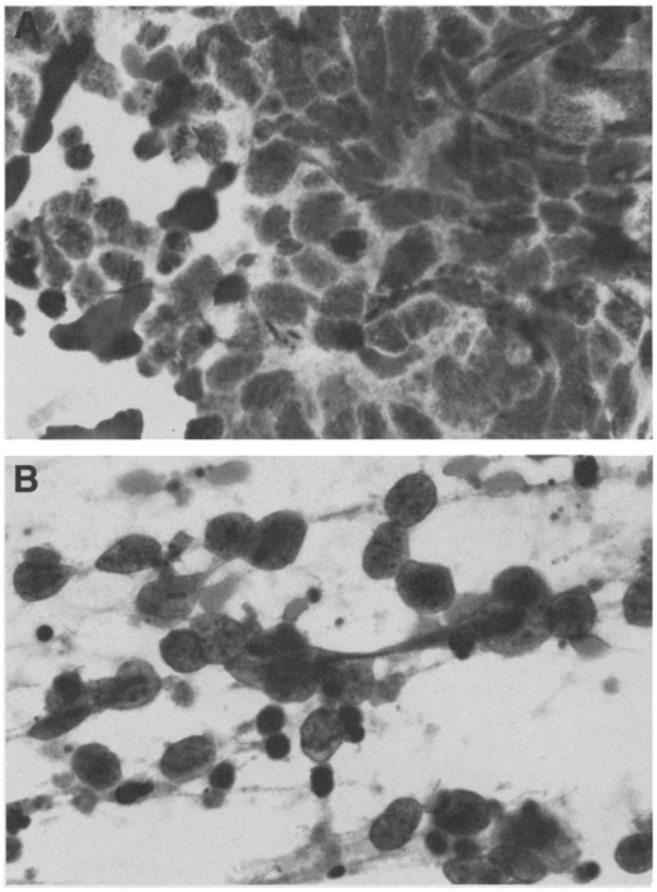


Fig. 83. Small cell carcinoma, lung, FNA. **A.** Small cells with extensive molding, salt and pepper nuclei, and no distinct nucleoli. Chromatin smearing and apoptotic cells in the background. Papanicolaou stain. **B.** Highly cellular smear showing extensive molding, focal pallisading of the nuclei and chromatin smearing. Diff-Quik stain, medium power view.

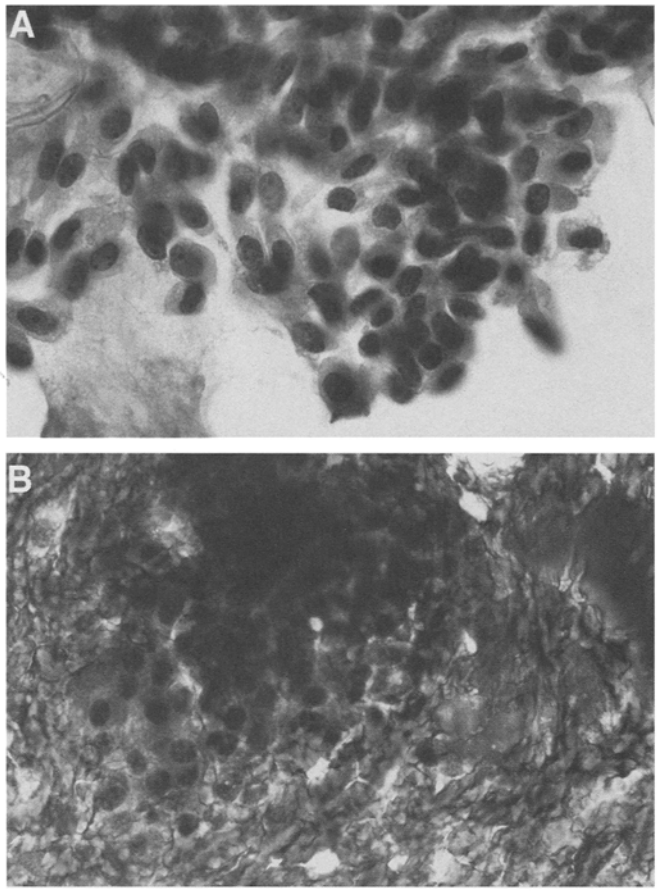


Fig. 84. Pleomorphic adenoma, parotid gland, FNA. **A.** Cluster of epithelial cells with plasmacytoid appearance in a background of cyanophillic staining myxoid stroma. Papanicolaou stain. **B.** Myxoid stroma staining as dark magenta. Diff-Quik stain, medium power view.

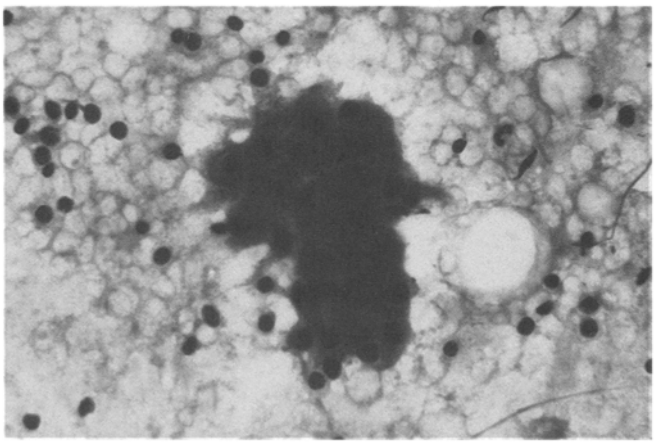


Fig. 85. Warthin tumor, salivary gland, FNA. A tight cluster of oncocytic cells with abundant granular cytoplasm in the background of numerous lymphocytes and mucoid background. Papanicolaou stain, medium power view.

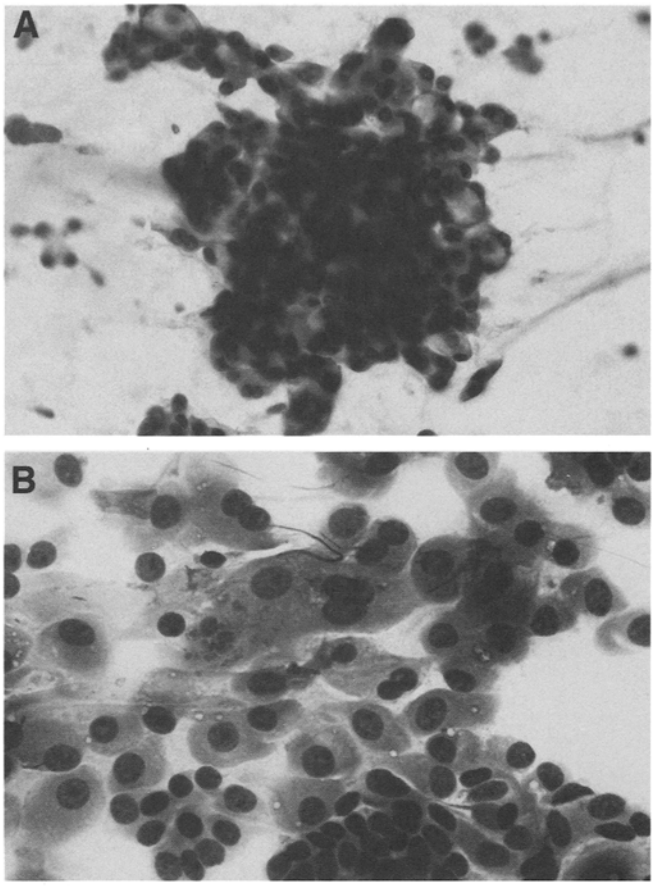


Fig. 86. Well differentiated mucoepidermoid carcinoma, salivary gland, FNA. **A.** Cellular aggregate of intermediate cells and glandular cells. Glandular differentiation is evidenced by the appearance of intracytoplasmic vacuoles and attempt to form glands (microacinar formation). Background mucin staining light pink. Papanicolaou stain. **B.** Most of the cells are showing intermediate differentiation, note the fine vacuolization in some of these cells and the intracellular mucin seen in the center. Diff-Quik stain, medium power view.

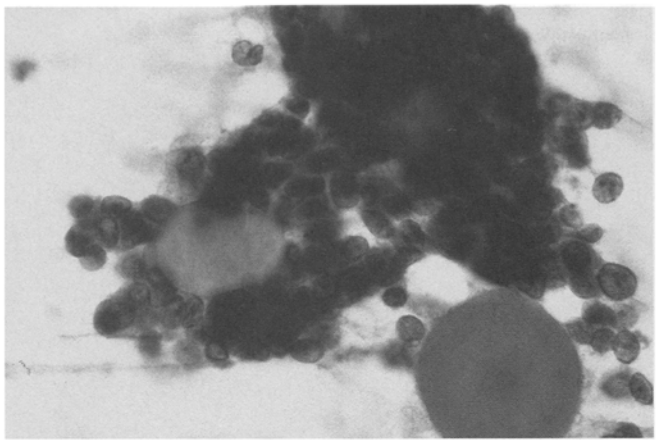


Fig. 87. Adenocystic carcinoma, salivary gland. Cylindrical material appearing as rounded globules with well-defined borders surrounded by small, uniform basaloid hyperchromatic cells. Papanicolaou stain, medium power view.

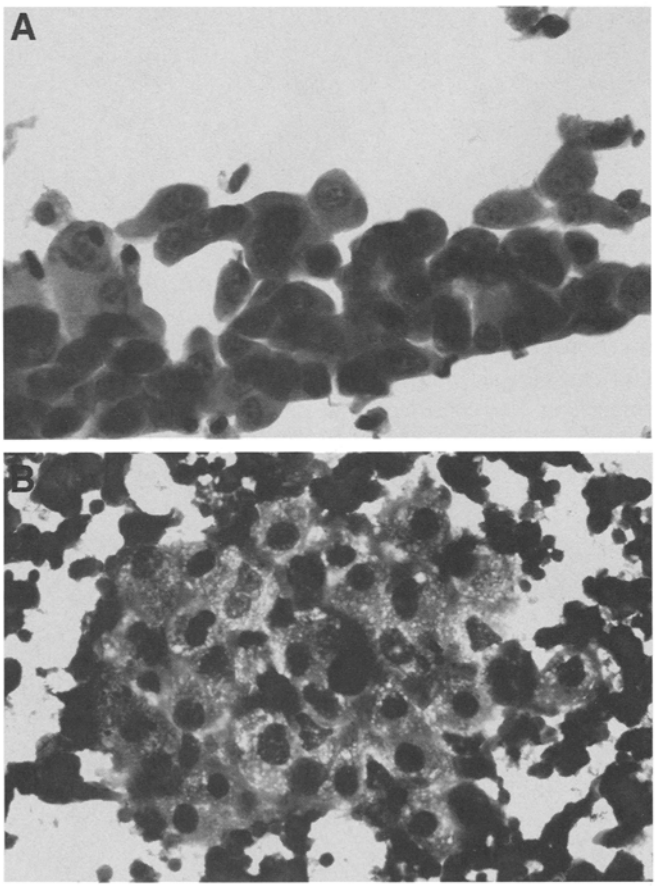


Fig. 88. Acinic cell carcinoma, salivary gland, FNA. **A.** Sheets of monotonous cells with enlarged nuclei and moderate to abundant cytoplasm. Papanicolaou stain. **B.** similar cells with obvious granular cytoplasm. Diff-Quik stain, high power view.

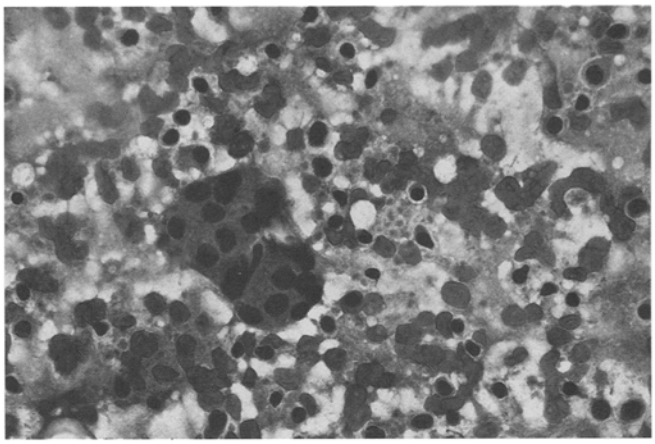


Fig. 89. Lymphocytic thyroiditis (Hashimoto's). A cluster of Hurthle cells in a background of numerous lymphocytes and plasma cells. Papanicolaou stain, medium power view.

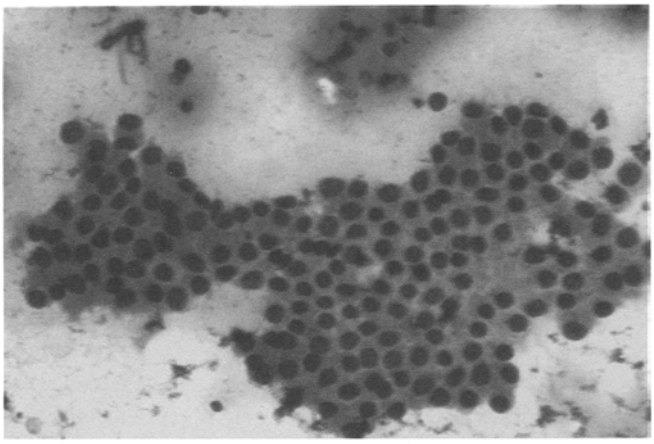


Fig. 90. Nodular hyperplasia (goiter). Large monolayer sheet of follicular/Hurthle cells showing a well organized, honeycombed arrangement with abundant cytoplasm in a background of metachromatically stained colloid. Diff-Quik stain, high power view.

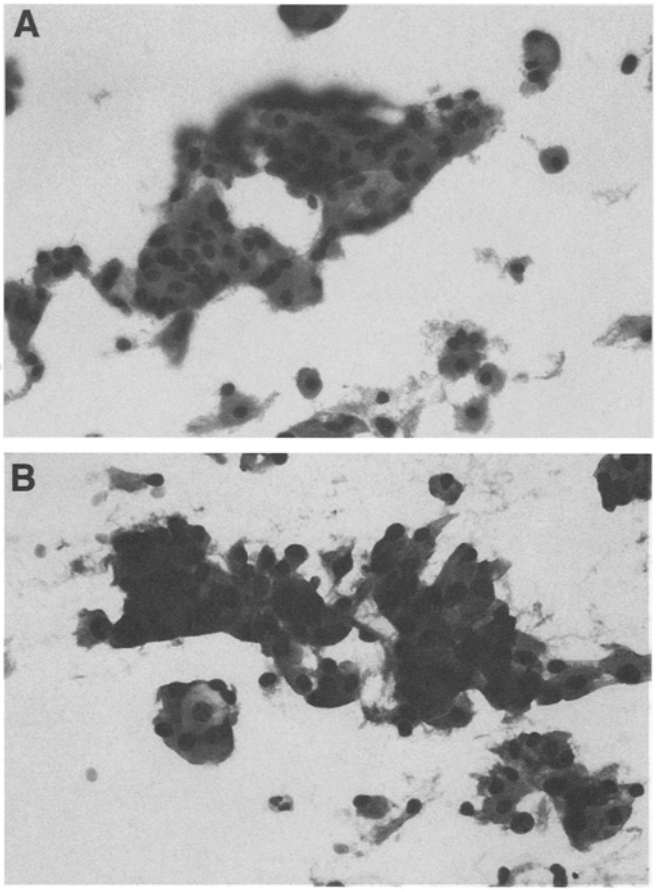


Fig. 91. Follicular neoplasm (adenoma), thyroid, FNA. **A.** Syncytial fragment of follicular cells with disordered arrangement and some nuclear variation. Notice the small micro-follicles in the upper right corner. **B.** Papanicolaou stain. Diff-Quik stain, medium power view.

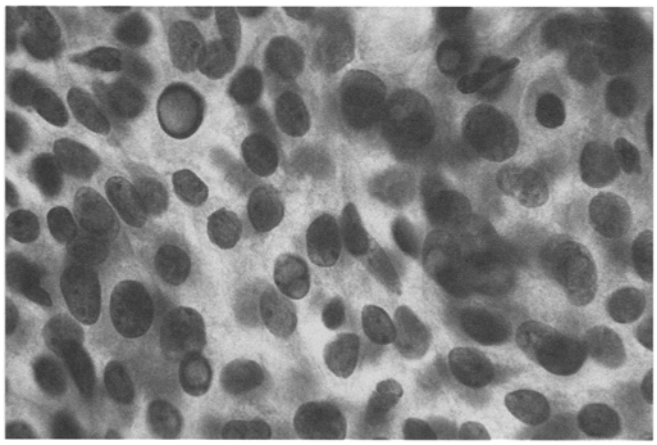


Fig. 92. Papillary carcinoma, thyroid, FNA. Follicular cells with monotonously enlarged nuclei and disordered arrangement of the cells. Notice the frequent overlapping and molding of cells, the intranuclear inclusions and the frequent nuclear grooves. Papanicolaou stain, high power view.

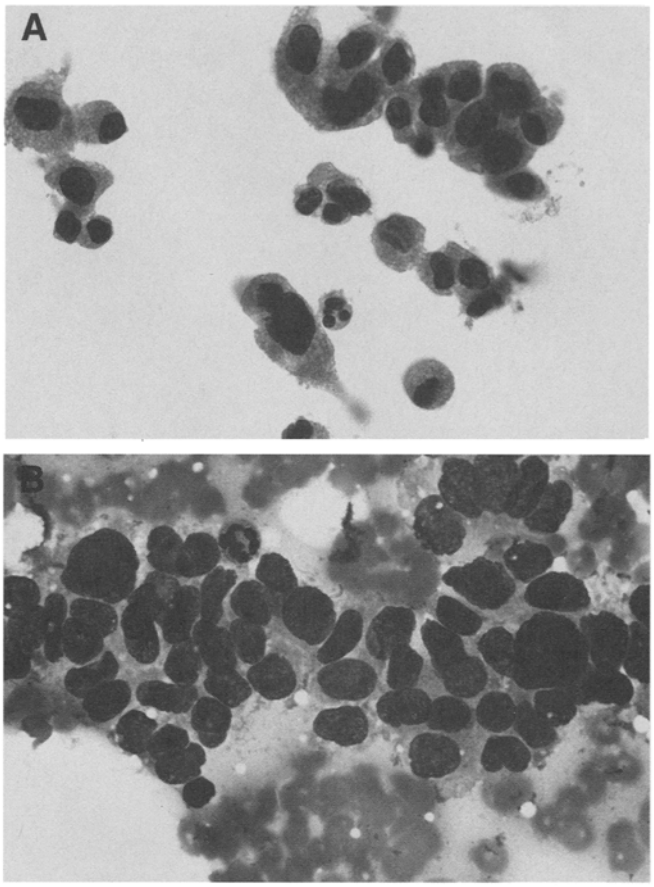


Fig. 93. Medullary carcinoma, thyroid, FNA. **A.** Discohesive small plasmacytoid cells with round to oval nuclei, and occasional binucleation. Chromatin is finely granular and evenly distributed. Papanicolaou stain. **B.** Occasional out of proportion enlarged nuclei consistent with neuroendocrine lesions. Note also the pallisading of nuclei in the upper right corner attempting to form rosettes. Diff-Quik stain, high power view.

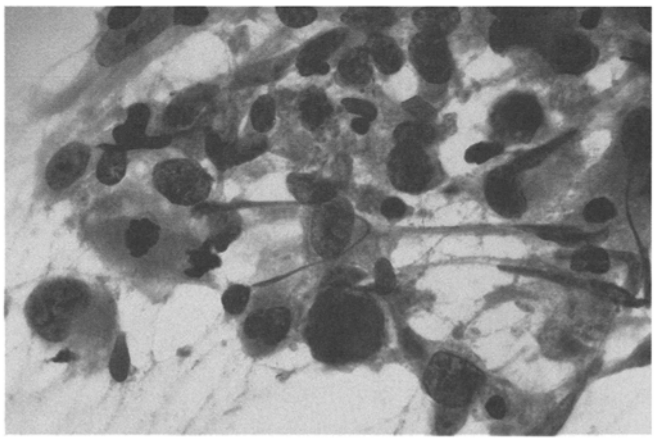


Fig. 94. Anaplastic carcinoma, thyroid, FNA. Discohesive, large, markedly pleomorphic cells. Papanicolaou stain, high power view.

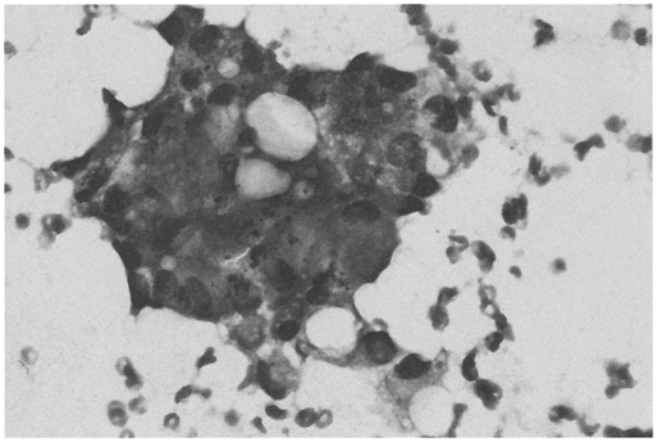


Fig. 95. Fat necrosis,breast, FNA. Disrupted fat surrounded by histiocytes and hemosiderin laden macrophagues. Diff-Quik stain, high power view.

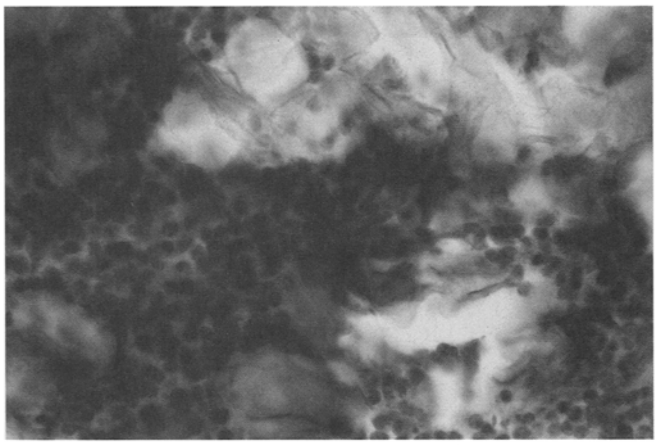


Fig. 96. Subareolar abscess, breast, FNA. Purulent exudate admixed with numerous annucleated squames. Papanicolaou stain, medium power view.

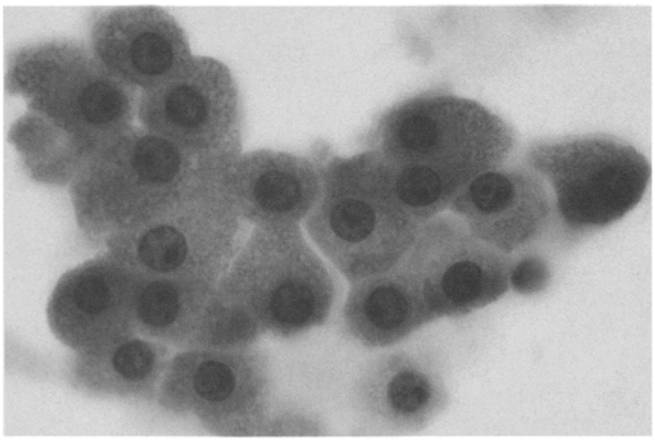


Fig. 97. Apocrine metaplasia, breast, FNA. Monolayer sheet of large cells with enlarged nuclei, prominent nucleoli and abundant granular cytoplasm. Papanicolaou stain, high power view.

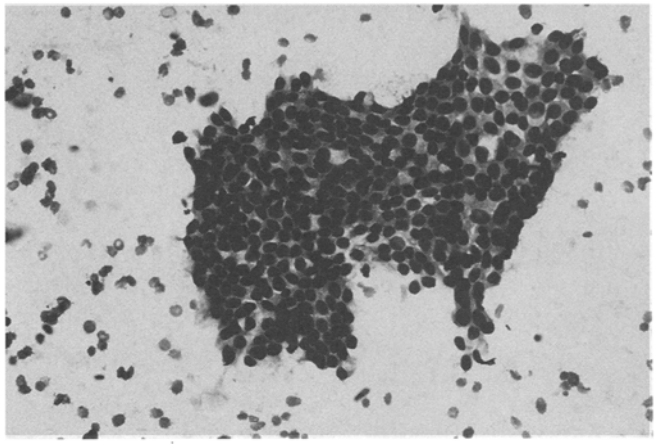


Fig. 98. Fibrocystic changes, breast, FNA. Large folded sheet of benign mammary epithelium in a background of few stripped nuclei. Diff-Quik stain, medium power view.

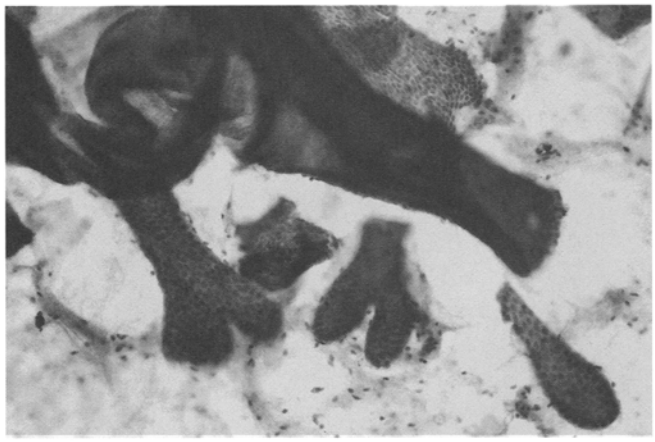


Fig. 99. Fibroadenoma, breast, FNA. Cellular smear with tight branching, cohesive sheets of cells forming antler horn and papillary-like fronds in a background of numerous small stripped nuclei. Papanicolaou stain, low power view.

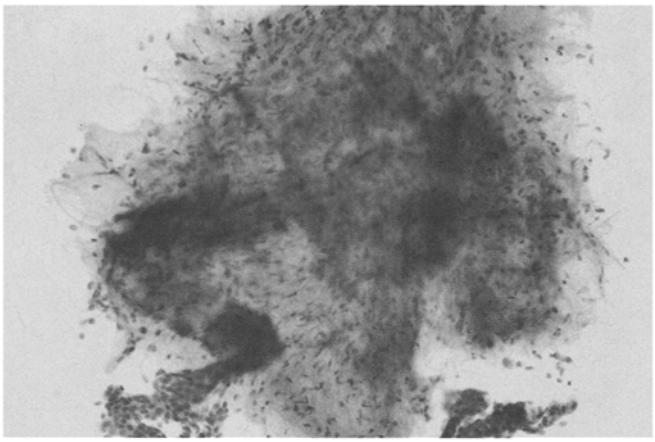


Fig. 100. Fibroadenoma, breast, FNA. Fibromyxoid stroma admixed with few clusters of benign mammary epithelium. Papanicolaou stain, medium power view.

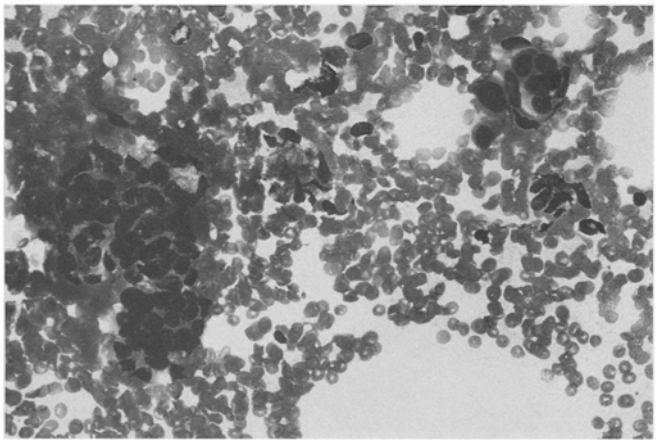


Fig. 101. Gynecomastia, male breast, FNA. Several tight clusters of benign mammary epithelium in a background of few stripped nuclei and a small fragment of myxoid stroma in the center. Diff-Quik stain, lower power view.

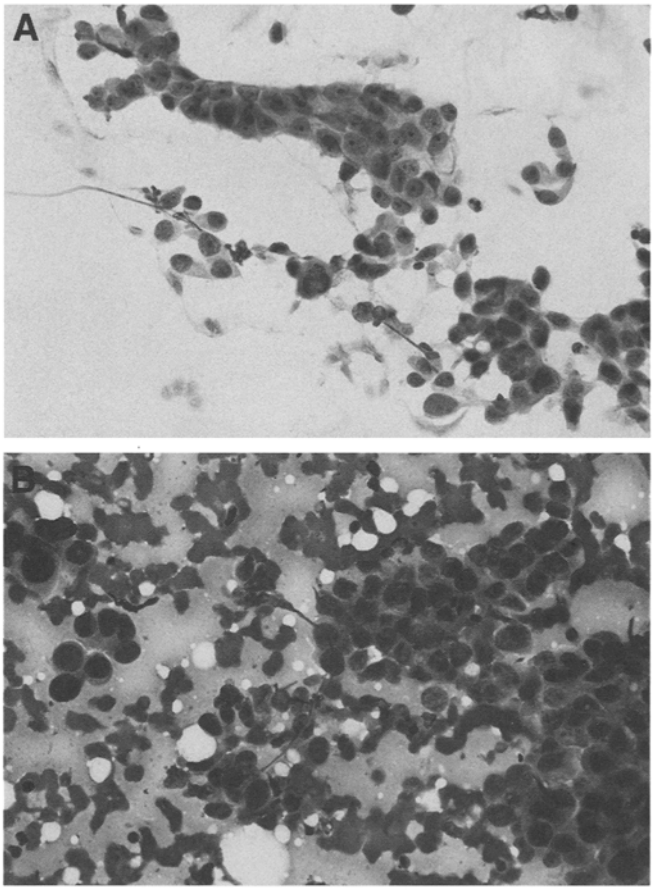


Fig. 102. Invasive ductal carcinoma, breast FNA. **A.** Small cluster and trabeculae of atypical cells with enlarged nuclei and prominent nucleoli. Note the presence of numerous atypical discohesive single cells. Papanicolaou stain. **B.** Diff-Quik stain, medium power view.

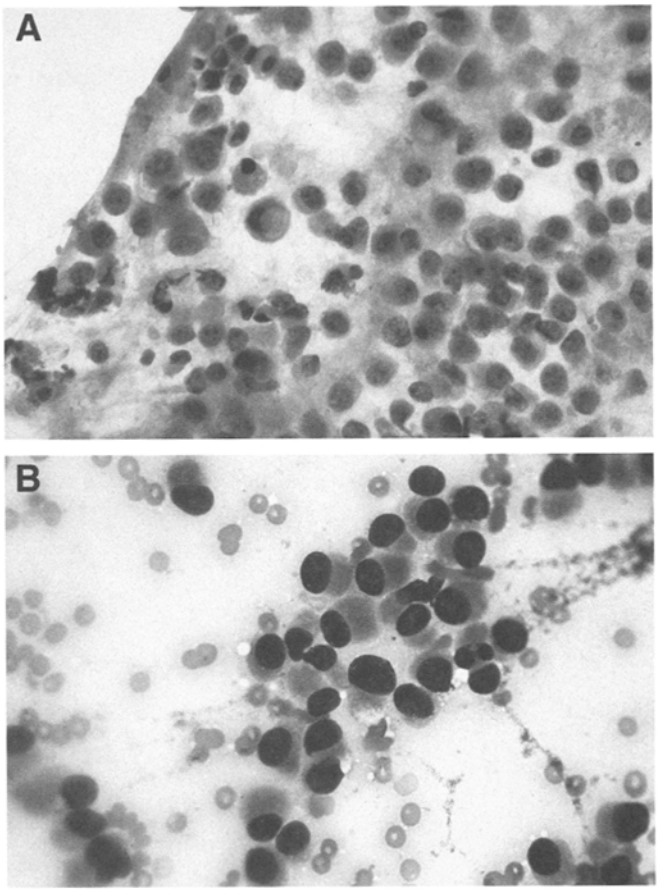


Fig. 103. **A.** Invasive lobular carcinoma, breast, FNA. Discohesive atypical single cells, some with intracytoplasmic vacuoles (signet ring cells). Papanicolaou stain. **B.** Single cells have a plasmacytoid appearance. Diff-Quik stain, high power view.

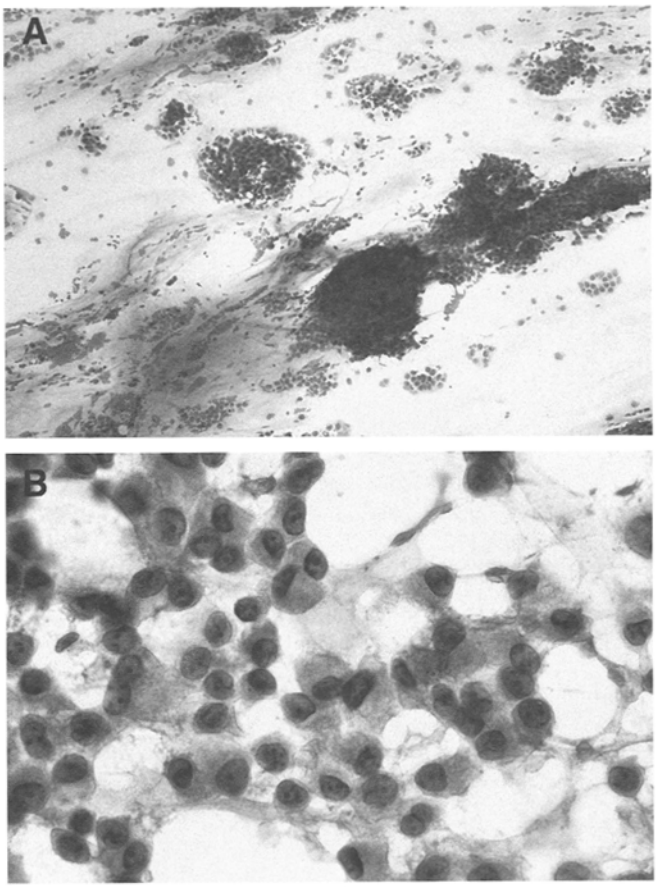


Fig. 104. **A.** Mucinous carcinoma, breast, FNA. Tight and discohesive clusters of malignant cells in a background of abundant mucin. Papanicolaou stain, low power view. **B.** Another presentation with numerous single plasmacytoid cells. Notice the occasional binucleation and the mild nuclear atypia. The background is rich in pale staining mucin. Papanicolaou stain, high power view.

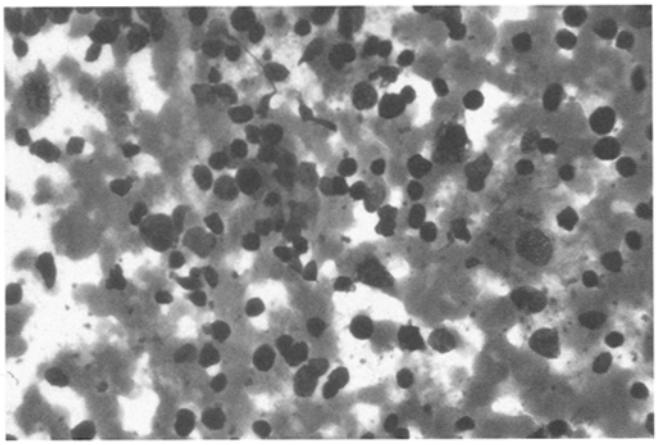


Fig. 105. Reactive lymph node, FNA. A polymorphic population of lymphocytes and tingible body macrophage. Small blue droplets represent broken lymphocytic cytoplasm i.e. lymphoglandular bodies. Diff-Quik, medium power view.

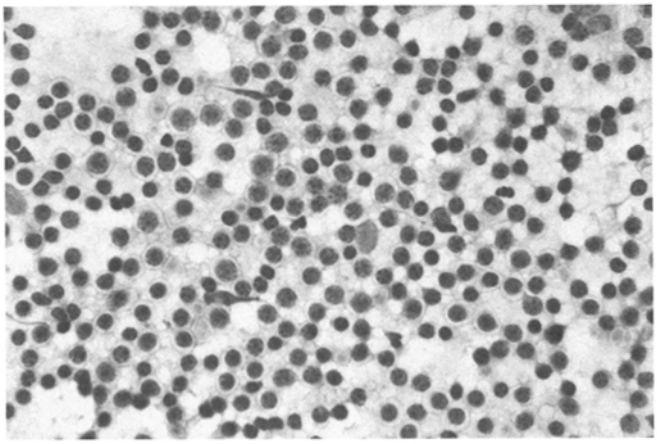


Fig. 106. Small lymphocytic lymphoma, FNA. A monotonous population of small lymphocytes. Papanicolaou stain, medium power view.

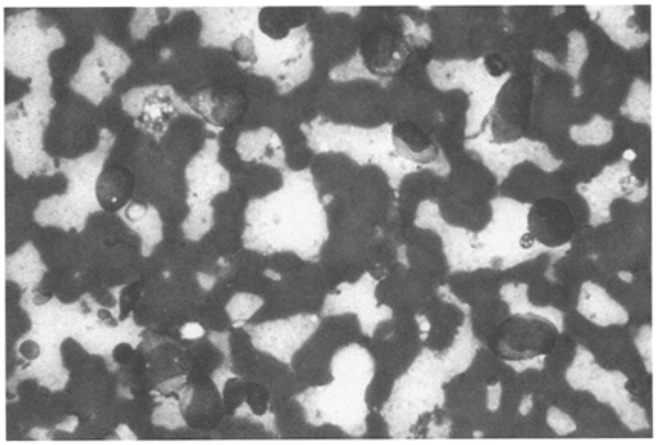


Fig. 107. Large B-cell lymphoma. Monotonous population of large atypical lymphocytes with obvious nuclear irregularity and high N/C ratio. Diff-Quik stain, high power view.

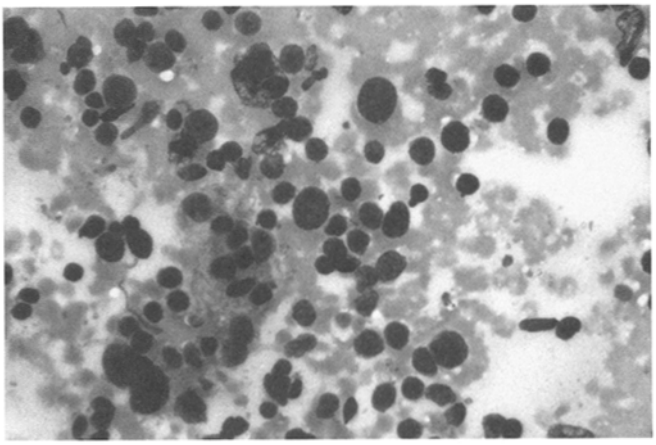


Fig. 108. Follicular center lymphoma, follicular grade II. The smear consists of a mixture of follicle center cells, consisting of centrocytes (cleaved follicle center cells) and centroblasts (large noncleaved follicle center cells). Diff-Quik stain, high power view.

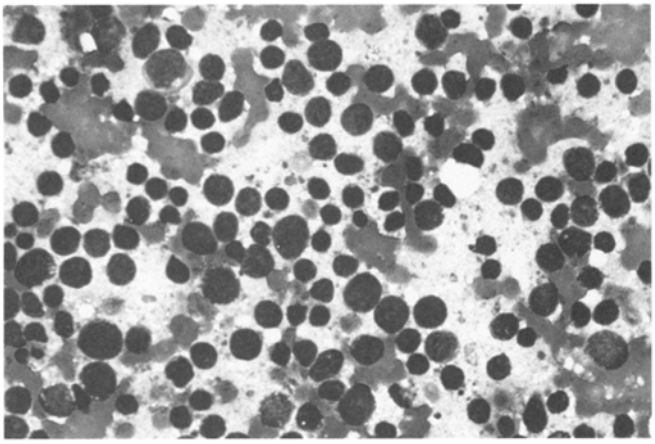


Fig. 109. Burkitt's lymphoma, abdominal mass, FNA. Monotonous population of predominantly enlarged cells with round nuclei, and a rim of cytoplasm with peripheral vacuoles. Diff-Quik stain, high power view.

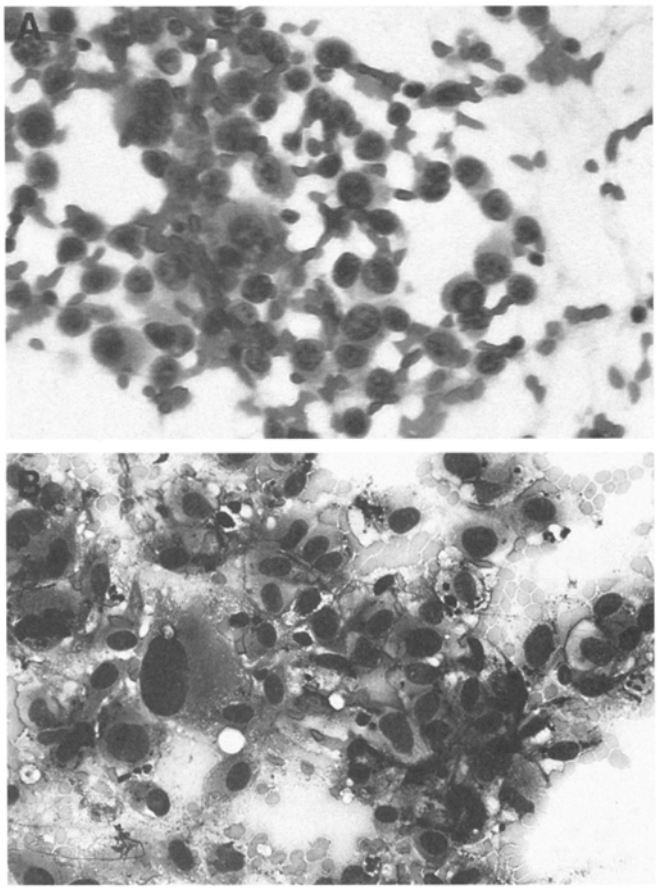


Fig. 110. Malignant melanoma. **A.** Amelanotic variant with single discohesive, markedly atypical cells with plasmacytoid appearance and occasional intranuclear inclusion. Notice the binucleation and multinucleation. Papanicolaou stain. **B.** In this aspirate, the melanin is seen both intracellularly and as loose pigment in the background. Diff-Quik stain, high power view.

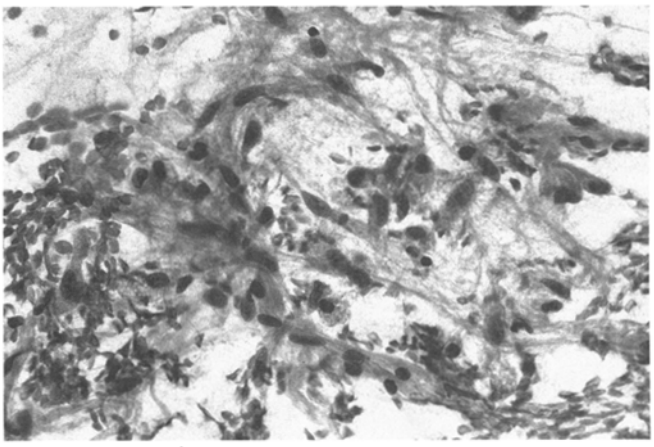


Fig. 111. Nodular fasciitis, anterior chest wall, FNA. Large plump myofibroblasts appearing admixed with lightly straining eosinophilic stroma. Papanicolaou stain, high power view.

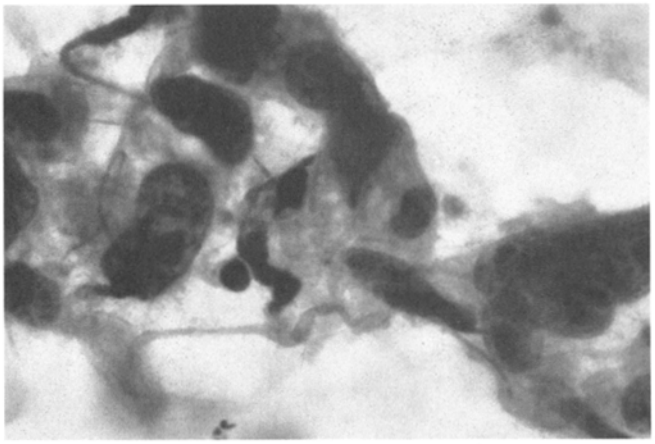


Fig. 112. Malignant fibrous histiocytoma. Large bizarre cells with irregular nuclei and coarsely granular chromatin. Papanicolaou stain, high power view.

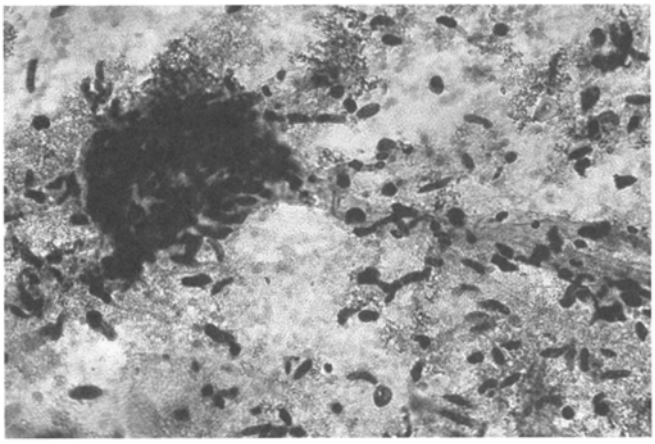


Fig. 113. Neurolemmoma (schwannoma). Cellular smear of uniform spindle cells with elongated, wavy nuclei. Papanicolaou stain, medium power view.

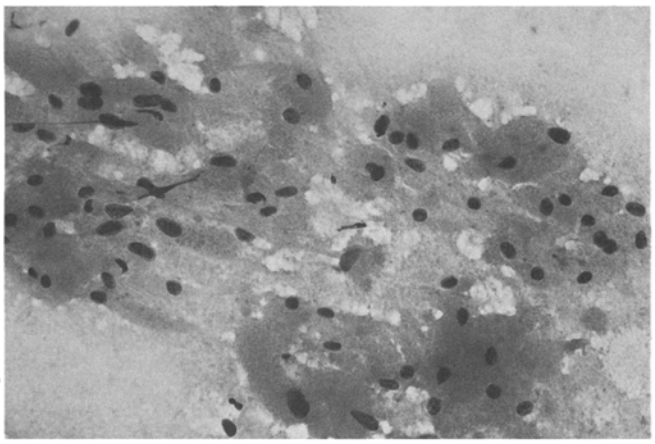


Fig. 114. Granular cell tumor, neck mass, FNA. Cellular smear of loosely cohesive large polygonal cells. The cytoplasm is abundant and eosinophilic, with obvious granularity that blurs with the background. Papanicolaou stain, medium power view.

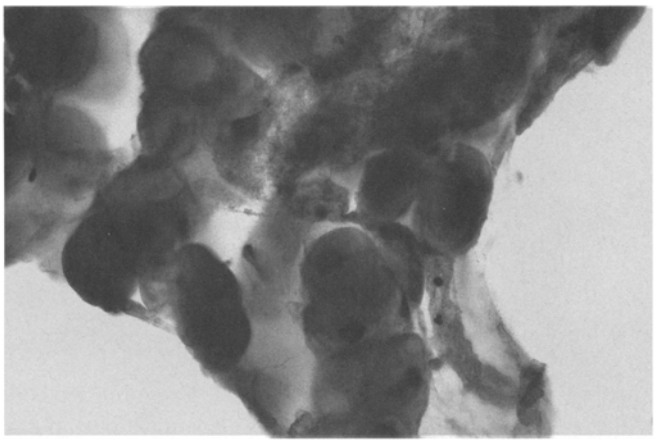


Fig. 115. Encondroma, knee joint, FNA. Fragments of cartilage with good preservation of the lacunae. Note the small uniform chondrocytes within lacunae and lack of mitotic Figs. or significant pleomorphism. Papanicolaou stain, high power view.

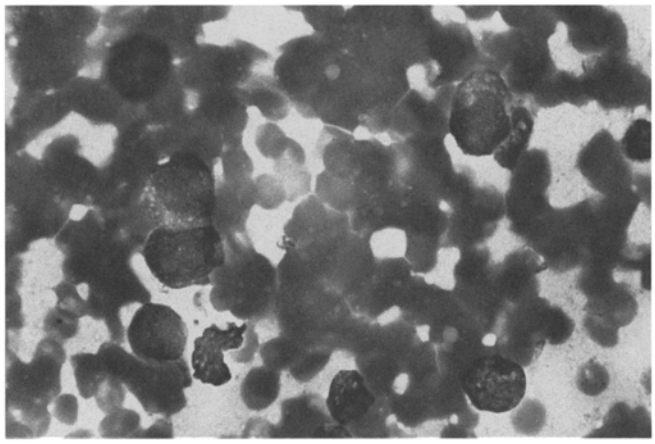


Fig. 116. Metastatic Ewing's sarcoma, lung, FNA. Isolated single monotonous cells with round nuclei. The chromatin is finely granular. Variable amount of cytoplasm is present with vacuoles. Diff-Quik, high power view.

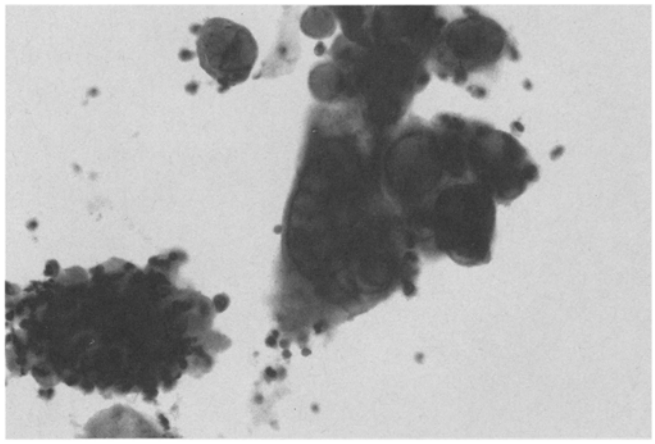


Fig. 117. Herpes simplex virus effect, Esophageal brush. Single and multinucleated cells showing nuclear molding and ground glass nuclei with a small intranuclear inclusion. Papanicolaou stain, high power view.

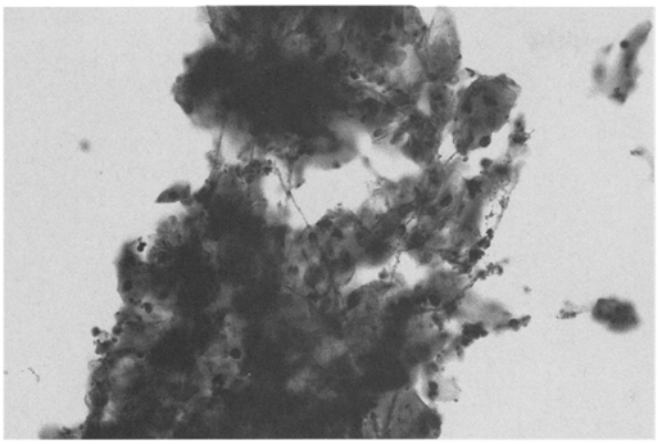


Fig. 118. Candida albicans. A cohesive sheet of squamous cells admixed with thin, uniform candidal pseudohyphae. Such pseudohyphae can frequently be seen at the edges of the affected clustered epithelial cells. Papanicolaou cells, medium power view.

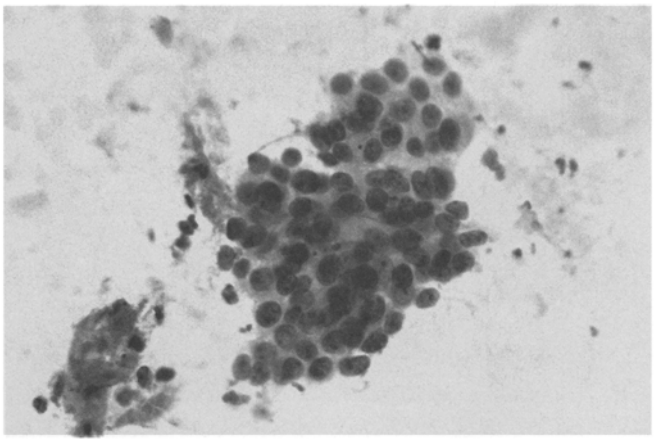


Fig. 119. Adenocarcinoma, gastric brush. Sheet of irregularly arranged cells with depth of focus. Note the cellular crowding and attempt to form glands within the sheet. Papanicolaou stain, high power view.

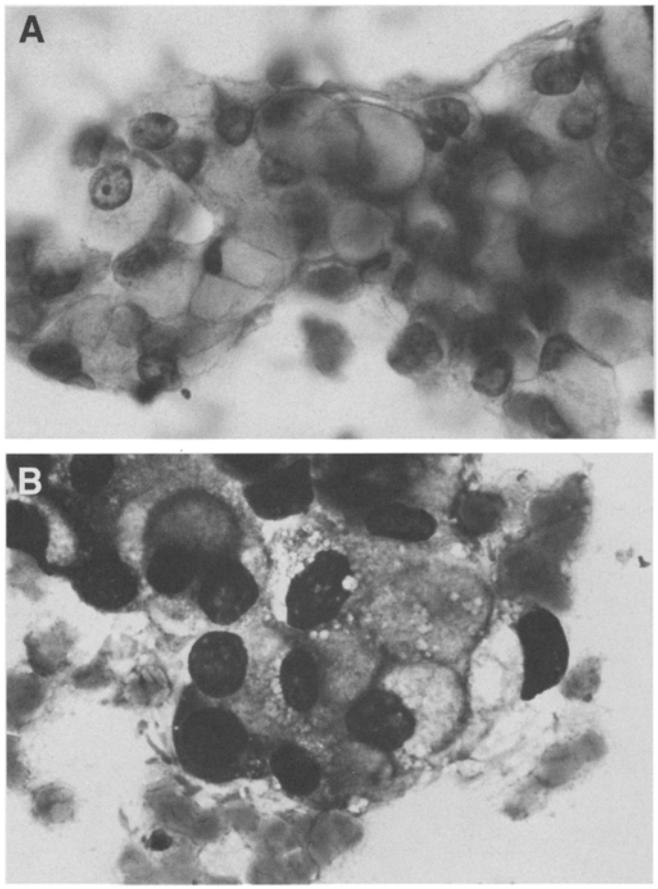


Fig. 120. Mucinous carcinoma arising from Barrett's mucosa, esophageal brush. **A.** signet ring cells with highly vacuolated abundant cytoplasm and mild nuclear atypia The disordered orientation of these atypical cells distinguish them from simple goblet cells. Papanicolaou stain. **B.** Diff-Quik stain, high power view.

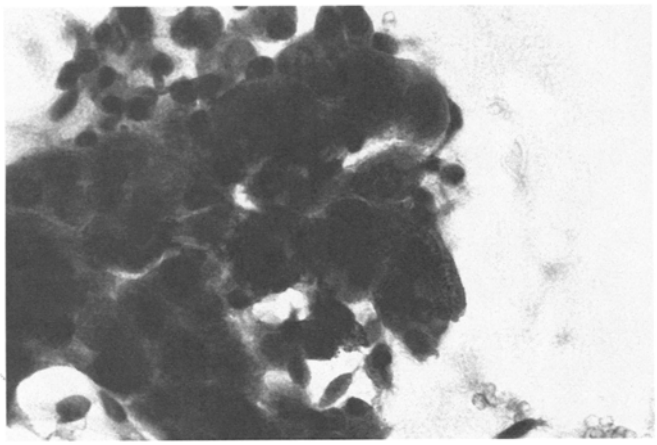


Fig. 121. Hepatocellular carcinoma, liver, FNA. Monotonous population of atypical cells with slight increase of N/C ratio growing as clusters and trabeculae surrounded by endothelial cells. The polygonal shape and granular cytoplasm indicate the hepatocellular origin. Papanicolaou stain, medium power view.

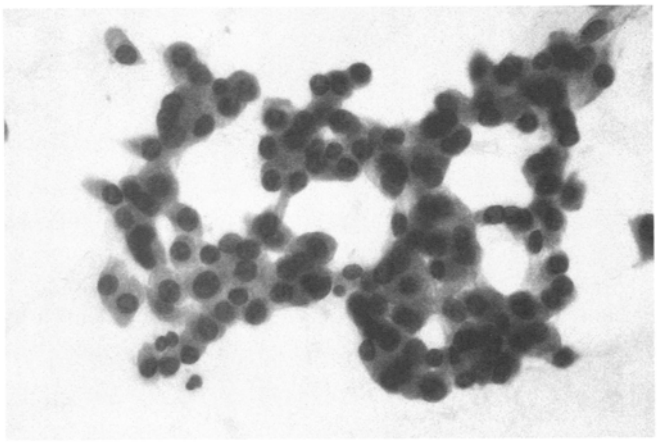


Fig. 122. Islet cell tumor, pancreas, FNA. A monotonous population of plasmacytoid cells with eccentric nuclei, and moderate amount of cytoplasm. The nuclei have fine chromatin and very small nucleoli.

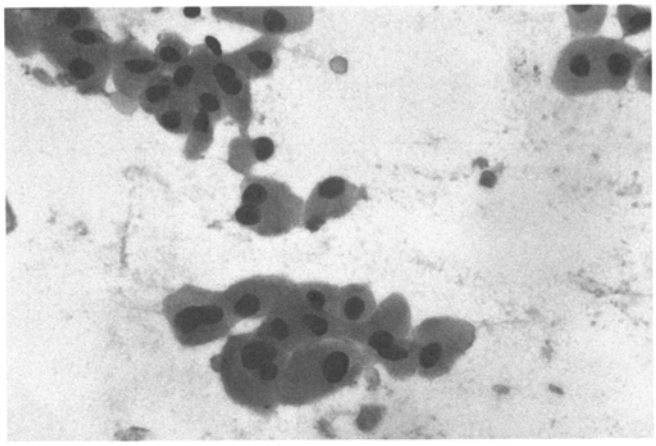


Fig. 123. Oncocytoma, kidney, FNA. Cellular smear containing a monotonous population of cells with little cytologic atypia. The nuclei are round and small, and the cytoplasm is abundant and granular. Papanicolaou stain, high power view.

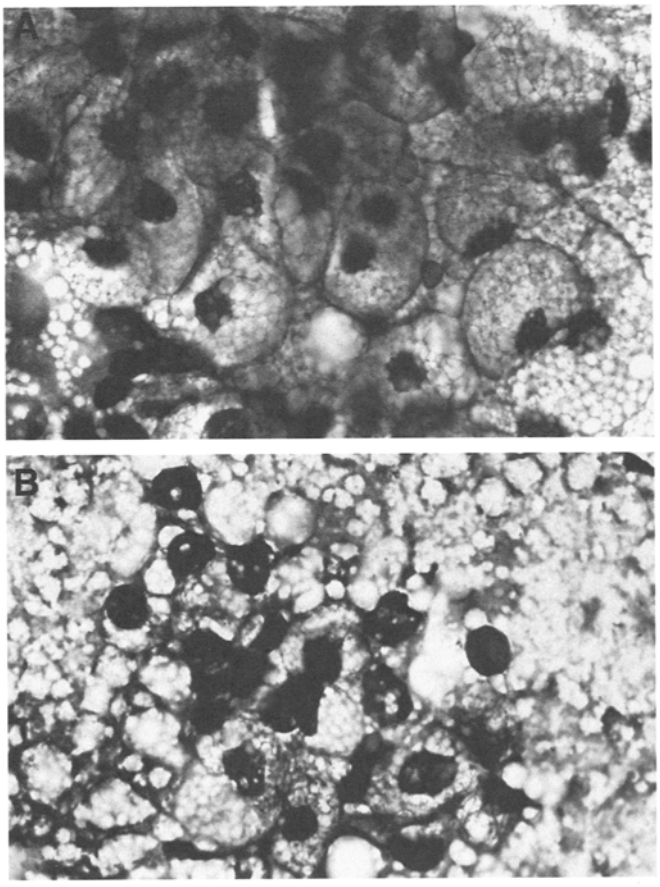


Fig. 124. Renal cell carcinoma, kidney, FNA. **A.** Sheet of cells with slight nuclear atypia, and abundant vacuolated cytoplasm mimicking histiocytes. The disorganization of these cells and the nuclear indentation by the vacuoles and nuclear irregularity distinguish this from a sheet of histiocytes. Papanicolaou stain. **B.** Diff-Quik stain, high power view.

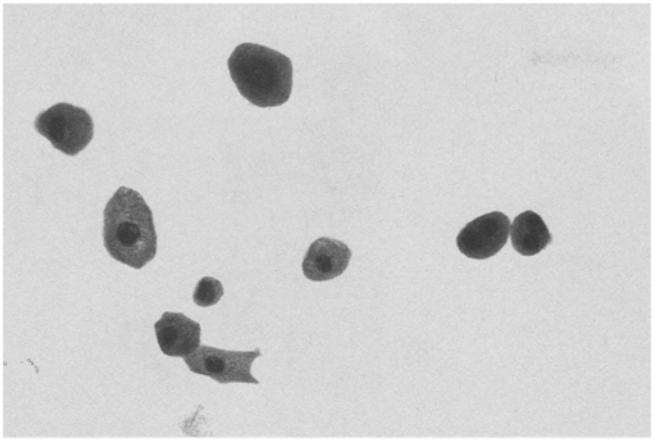


Fig. 125. Normal voided urine. Low cellular smear with urothelial cells that are single or binucleated with abundant cytoplasm. Papanicolaou stain, medium power view.

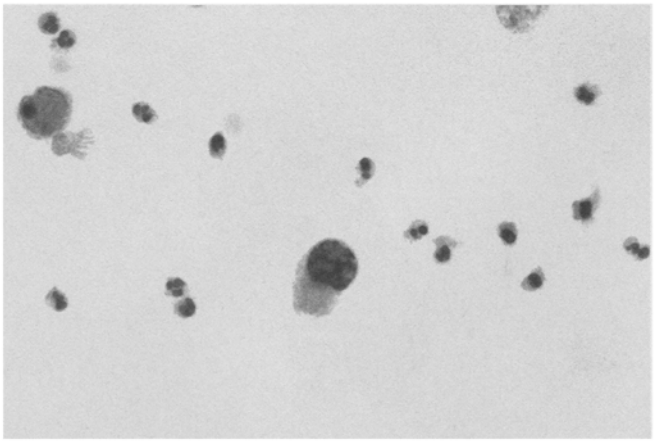


Fig. 126. Polyoma virus effect, urine. Note the enlarged, eccentric nuclei with ground glass appearance due to the intranuclear inclusion. Sometimes the nuclei appear hyperchromatic, but the smudged dark chromatin should be distinguished from that of the urothelial carcinoma. Papanicolaou stain, high power view.

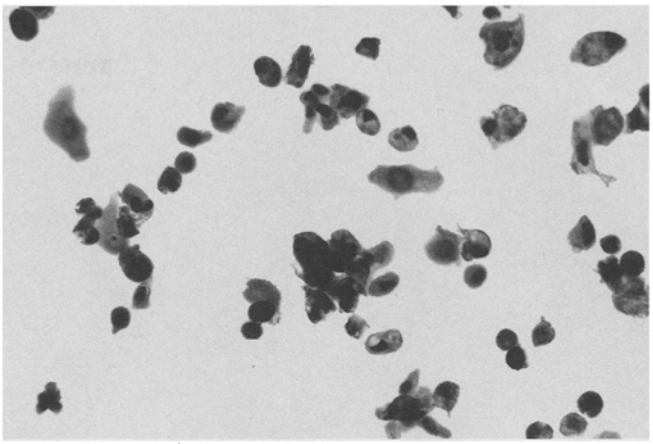


Fig. 127. Urothelial carcinoma, high grade, voided urine. Cellular preparation with numerous highly atypical cells containing eccentric hyperchromatic and irregular nuclei. Papanicolaou stain, medium power view.

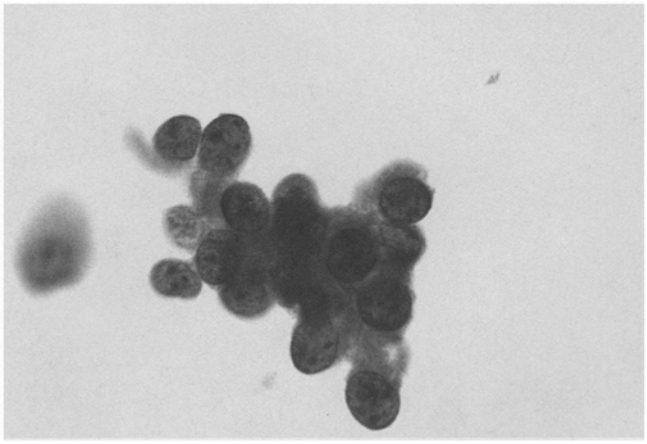


Fig. 128. Urothelial carcinoma, voided urine. Cluster of highly atypical cells with eccentric hyperchromatic enlarged nuclei. Papanicolaou stain, high power view.

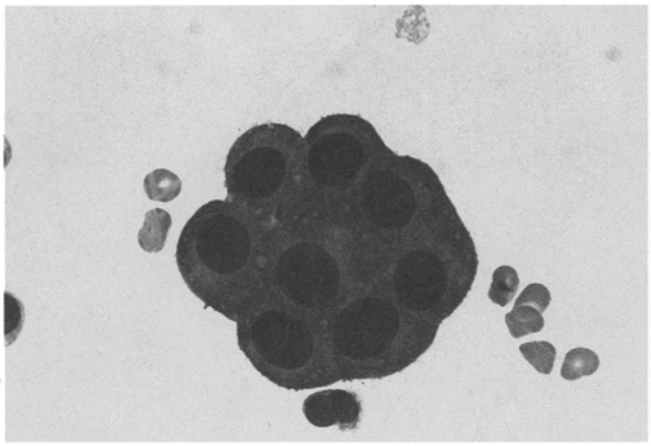


Fig. 129. Benign reactive mesothelial cells, pleural fluid. Tight cluster with scalloped borders and uniformly arranged monotonous nuclei. The cytoplasm has two- tone staining indicative of the endo-ectoplasmic differentiation and small windows are apparent between the cells. Diff-Quik stain, high power view.

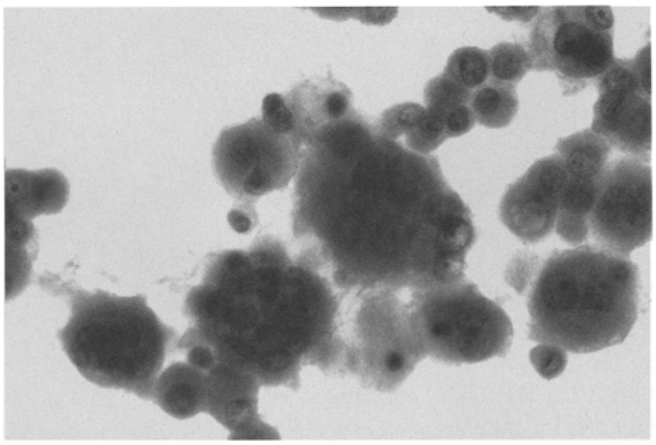


Fig. 130. Malignant mesothelioma, pleural fluid. Highly cellular smear with numerous cellular clusters (morules) in the background of single and multinucleated cells. Note the gigantic size of some of the single cells. Also notice the enlarged nuclei with prominent nucleoli. Papanicolaou stain, medium power view.

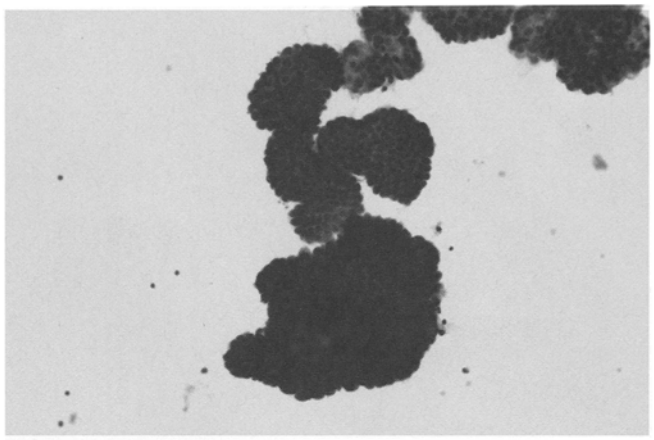


Fig. 131. Metastatic papillary serous carcinoma of ovary, peritoneal fluid. A cellular smear with highly atypical cells arranged in complex papillae. Psammoma bodies are frequent. Papanicolaou stain, low power view.

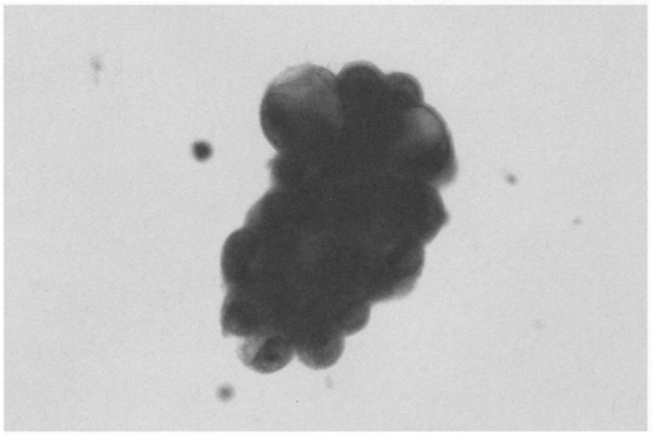


Fig. 132. Metastatic clear cell carcinoma of the ovary, peritoneal wash. Highly atypical cells arranged in tight clusters with abundant clear cytoplasm. Papanicolaou stain, high power view.

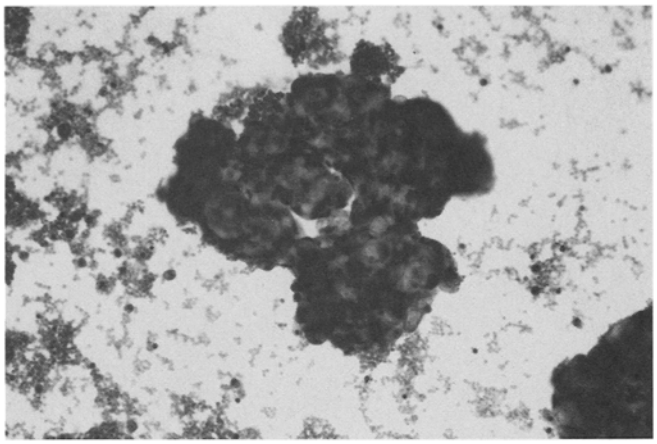


Fig. 133. Metastatic mucinous carcinoma of ovary, peritoneal fluid. Malignant cells arranged in tight papillary clusters. Cells present as signet ring cells with eccentric nuclei and abundantly vacuolated cytoplasm.

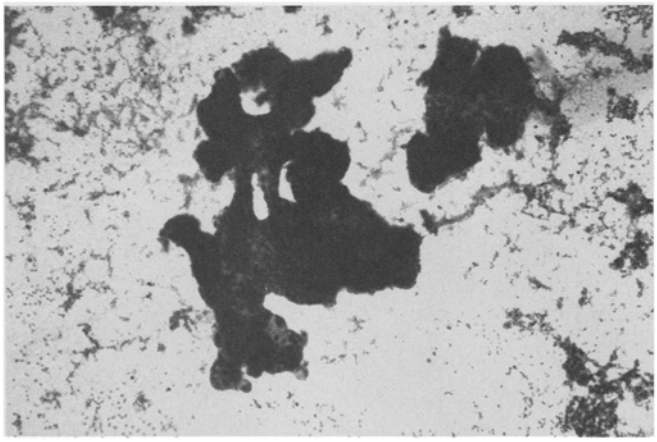


Fig. 134. Metastatic adenocarcinoma of breast (ductal), pleural fluid. The clusters may show bridging and cribriform appearance. Papanicolaou stain, medium power view.

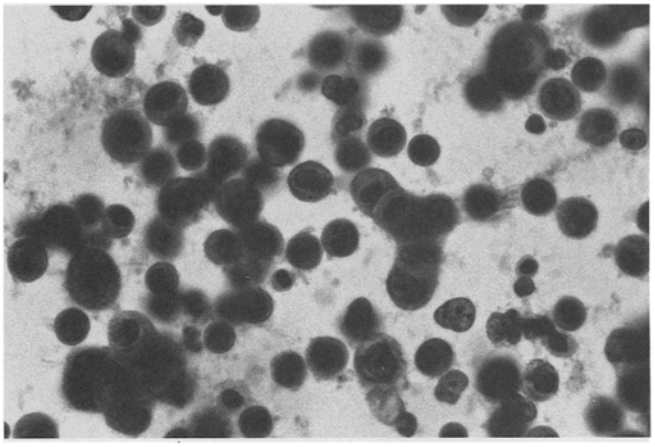


Fig. 135. Metastatic adenocarcinoma of breast (ductal or lobular), pleural fluid. Another common appearance of breast carcinoma presenting with small clusters, short cords (Indian filing) and as cell within cell arrangement. Papanicolaou stain, high power view.

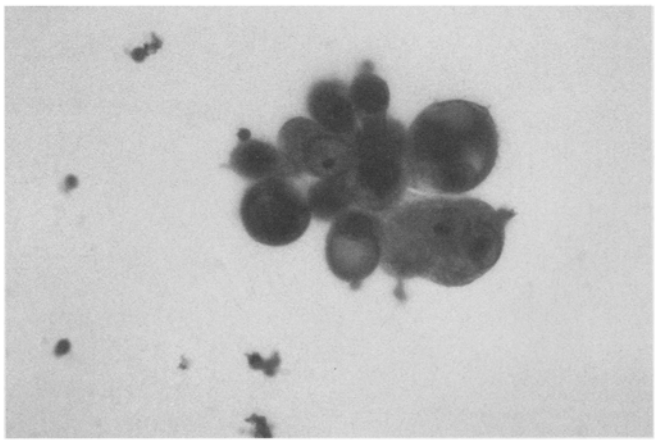


Fig. 136. Metastatic adenocarcinoma of the lung, pleural fluid. Large atypical cells appearing as small clusters or singularly scattered cells. Papanicolaou stain, high power view.

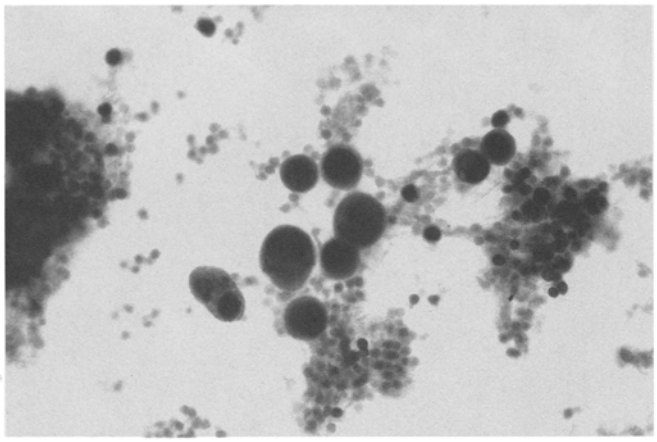


Fig. 137. Metastatic Gastric adenocarcinoma, poorly differentiated, pleural fluid. The cells appear as small atypical cells with eccentric, highly atypical nuclei. These cells could easily be dismissed if the smear is not screened meticulously at the higher magnification. Papanicolaou stain, high power view.

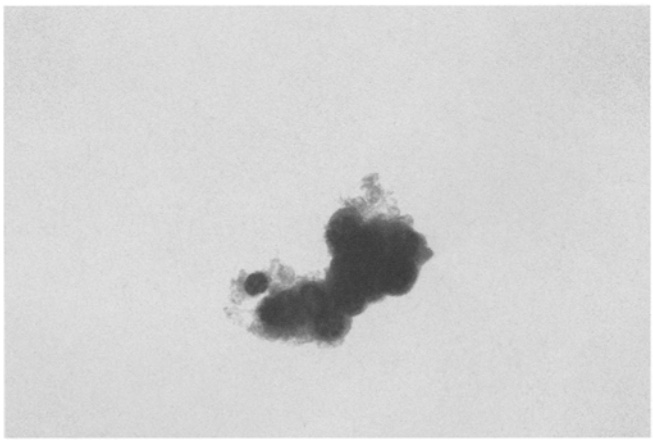


Fig. 138. Benign ependymal cells, CSF. Cluster of cuboidal cells with distinct cell borders. Papanicolaou stain, high power view.

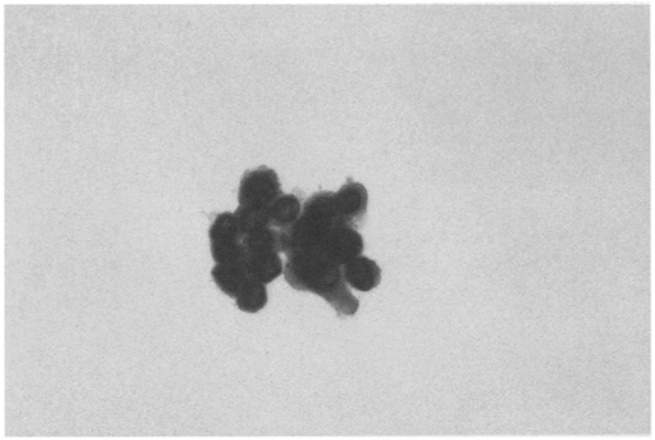


Fig. 139. Choroid plexus cells, CSF. Cuboidal to columnar cells with sharp cell borders. Note how they appear in a cluster with somewhat acinar-like formation that could be mistaken for metastatic adenocarcinoma. Papanicolaou stain, high power view.

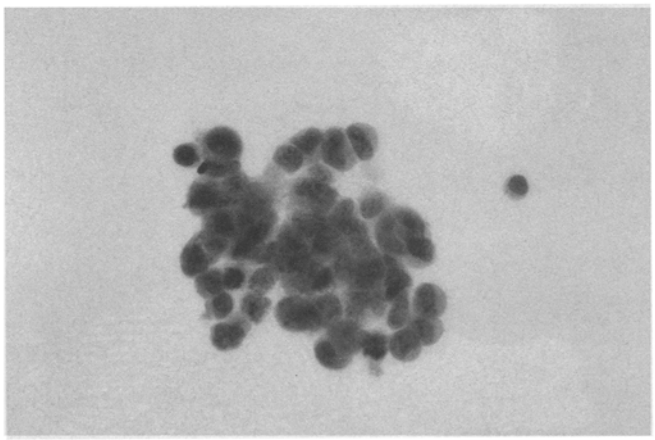


Fig. 140. Metastatic medulloblastoma, CSF. A somewhat cohesive group of small blue cells with hyperchromatic angulated nuclei and nuclear molding. Papanicolaou stain, high power view.

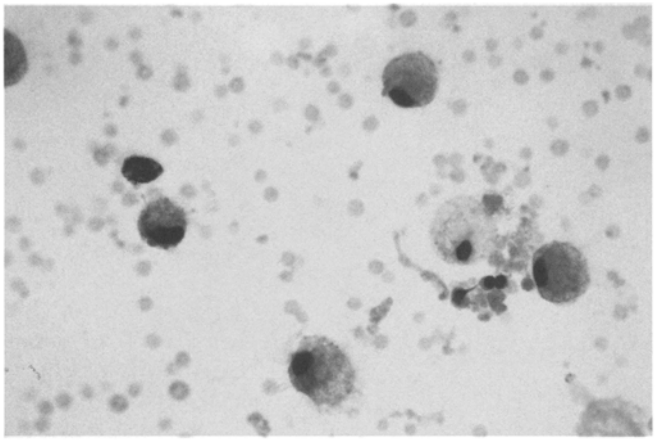


Fig. 141. Metastatic gastric carcinoma, CSF. Signet ring cells with eccentric hyperchromatic atypical nuclei and vacuolated abundant cytoplasm. Papanicolaou stain, high power view.

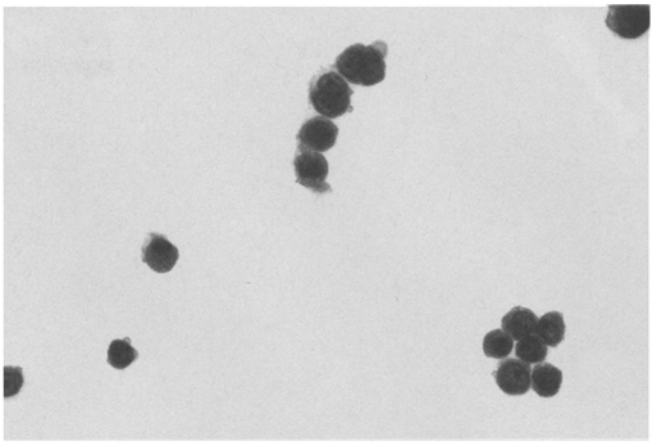


Fig. 142. Metastatic adenocarcinoma of breast, CSF. Malignant cells appearing in cell clusters or as long cellular cords (Indian filing). Papanicolaou stain, high power view.

Part II

Organ Systems

8

Neuropathology

Arie Perry, MD,
and Bernd W. Scheithauer, MD

CONTENTS

I. General Reactions to Injury 8-5
Macrophage/Microglial Reactions 8-5
Gliosis (Reactive Astrocytosis) 8-5
Acute/Subacute Gliosis 8-5
Chronic Gliosis 8-5
Pilocytic Gliosis 8-5
Cerebral Edema 8-5
Vasogenic Edema 8-5
Cytotoxic Edema 8-5
Hydrocephalus 8-5
Herniation Syndromes 8-6
Cingulate (Subfalcine) Herniation 8-6
Uncal (Transtentorial) Herniation 8-6
Tonsillar Herniation 8-6
Duret (Secondary Brainstem) Hemorrhage 8-6

II. Gliomas 8-6
Key Features in Differential Diagnosis of CNS Tumors 8-6
Diffuse (Infiltrative) Astrocytomas 8-8
Cytologic/Histologic Variants 8-8
Prognostic Variables 8-8
Grading Schemes 8-10
Grade II Astrocytoma (Astrocytoma) 8-10
Grade III Astrocytoma (Anaplastic Astrocytoma) 8-11
Grade IV Astrocytoma (Glioblastoma Multiforme) 8-11
Circumscribed Astrocytomas 8-12
Pilocytic Astrocytoma (WHO Grade I) 8-12
Pleomorphic Xanthoastrocytoma (PXA) (WHO Grade II–III) 8-13
Subependymal Giant Cell Astrocytoma (SEGA) (WHO Grade I) 8-14
Oligodendroglioma 8-15
Mixed Oligoastrocytoma 8-17
Ependymoma 8-17
Subependymoma (WHO Grade I) 8-18
Choroid Plexus Neoplasms 8-19
Choroid Plexus Papilloma (WHO Grade I) 8-19
Choroid Plexus Carcinoma (WHO Grade III) 8-20

III. Neuronal/Glioneuronal Neoplasms 8-21
Derivations/Definitions Used in Neuronal Tumors 8-21
Ganglion Cell Tumors (Ganglioglioma/Gangliocytoma) (WHO Grade I) 8-21
Central Neurocytoma (WHO Grade II) 8-21
Pineal Parenchymal Tumors 8-21
Pineocytoma 8-21
Pineoblastoma 8-22
Dysembryoplastic Neuroepithelial Tumor (DNT) (WHO Grade I) 8-23
Paraganglioma (WHO Grade I) 8-23
Embryonal Tumors 8-24
Medulloblastoma/PNET (WHO Grade IV) 8-24
Atypical Teratoid/Rhabdoid Tumor 8-25
Olfactory Neuroblastoma (WHO Grade III) 8-26
Retinoblastoma 8-26

IV. Meningeal Neoplasms 8-27
Meningioma (WHO Grade I).....8-27
Atypical Meningioma (WHO Grade II).....8-27
Malignant (Anaplastic) Meningioma (WHO Grade III).....8-28
Hemangiopericytoma (WHO Grade II or III).....8-28
Other Primary Mesenchymal Neoplasms 8-29
Benign.....8-29
Sarcomas.....8-29
Dural Metastases 8-29
Inflammatory Pseudotumors 8-30

V. Other Non-Glial Neoplasms 8-30
Hemangioblastoma (WHO Grade I) 8-30
Craniopharyngioma 8-31
Adamantinomatous Craniopharyngioma (WHO Grade I) 8-31
Papillary Craniopharyngioma (WHO Grade I) 8-32
Germ Cell Tumors 8-32
Lymphoma/Leukemia.....8-32
Primary CNS Lymphoma 8-32
Secondary (Systemic) Lymphoma/Leukemia 8-33
Metastases 8-33

VI. Trauma.....8-34
Closed Head Injury 8-34
Open Head Injury.....8-34
Blunt Head Injury.....8-34
Skull Fractures 8-34
Epidural Hematoma 8-34
Subdural Hematoma 8-34
Subarachnoid Hemorrhage 8-34
Cortical Contusion 8-34
Pontomedullary Transection (Brainstem Avulsion).....8-34
Gunshot Wounds 8-34
Penetrating Wound 8-34
Perforating Wound 8-34
Entrance Wound 8-34
Exit Wound 8-34
Bullet Track: Low Velocity Missiles 8-34
Secondary Track 8-34
Spinal Cord Trauma 8-34
Upper Cervical Injuries 8-35
C4-C8 Injuries 8-35
Cervical Spondylosis 8-35
Central Cord Necrosis 8-35
Post-Traumatic Syringomyelia 8-35

VII. Ischemic/Anoxic/Vascular Disorders....8-35
Cerebral Infarct [Cerebrovascular Accident (CVA) "Stroke"] 8-35
Anoxic Encephalopathy (Global Ischemic Injury).....8-35
Hippocampal Necrosis 8-36
Purkinje Cell Necrosis (Cerebellar Cortex) 8-36
Watershed (Borderzone) Infarct 8-36
Selective Neuronal Necrosis.....8-36
Laminar/Pseudolaminar Necrosis.....8-36
Brain Death Syndrome ("Respirator Brain").....8-36
Multi-infarct Dementia 8-38
Venous Infarcts.....8-38
Small Vessel Disease/Deep Infarcts 8-38
Arteriolosclerosis 8-38
Binswanger's Disease.....8-38
CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy) 8-38
Leukoaraiosis 8-38
Related Disorders (Patterns of Selective Vulnerability).....8-38
Hypoglycemic Brain Injury 8-38
Carbon Monoxide Poisoning 8-38
Methanol Poisoning 8-38
Intracranial Hemorrhage 8-38
Berry (Saccular) Aneurysm/ Subarachnoid Hemorrhage (SAH)....8-38
Hypertensive Intracerebral Hemorrhage 8-39
Cerebral Amyloid Angiopathy (CAA) and Superficial Lobar Hemorrhage....8-39
Vascular Malformations 8-39
Berry (Saccular) Aneurysm 8-39
Arteriovenous Malformation (AVM) 8-39
Cavernous Angioma ("Cavernoma") 8-39
Others 8-40
Other Vascular Disorders 8-40
Vasculitis 8-40
Intravascular Lymphoma 8-40

VIII. Neurodegenerative Disorders 8-40
Summary Table.....8-40
Alzheimer's Disease (AD) 8-40
Frontotemporal Lobar Degeneration (FTLD) 8-40
Multi-infarct Dementia.....8-40
Idiopathic Parkinson's Disease (IPD) 8-40
Huntington's Disease (HD) 8-43
Pick's Disease (Lobar Atrophy).....8-43
Creutzfeldt-Jakob Disease (CJD)/ Spongiform Encephalopathies (SE) 8-43
Other Spongiform Encephalopathies (SE).....8-43
New Variant CJD (nvCJD) 8-43

Gerstmann-Sträussler-Scheinker Disease (GSS) 8-44
Fatal Familial Insomnia (FFI)....8-44
Kuru 8-44
Progressive Supranuclear Palsy (PSP; Steele-Richardson-Olszewski Disease)....8-44
Corticobasal (Ganglionic) Degeneration (CBD) 8-44
Multisystem Atrophy (MSA) 8-44
Amyotrophic Lateral Sclerosis (ALS)/ Motor Neuron Disease (MND) 8-44
Spinal Muscular Atrophy (SMA)....8-46
Friedreich's Ataxia 8-46
Spinocerebellar Ataxia (SCA) 8-46
Neuroaxonal Dystrophy 8-46
Lafora's Disease (Myoclonic Epilepsy)....8-46

IX. Inflammatory/Infectious Diseases 8-46
Acquired Demyelinating Disorders 8-46
Multiple Sclerosis (MS) 8-46
Acute Disseminated Encephalomyelitis (ADEM)/Perivenous Encephalomyelitis 8-47
Guillain-Barré Syndrome (GBS)/Acute Inflammatory Demyelinating Polyneuropathy (AIDP) 8-47
Demyelinating Viral Infections....8-47
Paraneoplastic Encephalomyelitis 8-48
Neurosarcoidosis 8-48
Bacterial Infections 8-48
Meningitis 8-48
Abscess 8-48
Tuberculosis (TB)....8-49
Neurosyphilis 8-49
Whipple's Disease 8-49
Fungal Infections 8-49
Meningitis 8-49
Granuloma/Abscess 8-49
Angioinvasive Forms 8-49
Viral Infections....8-50
Encephalitis....8-50
Herpes Simplex (HSV)....8-50
HIV Encephalitis/AIDS Dementia Complex....8-50
Vacuolar Myelopathy of AIDS....8-50
Cytomegalovirus (CMV) 8-50
JC Virus/Progressive Multifocal Leukoencephalopathy (PML) 8-51
Subacute Sclerosing Panencephalitis (SSPE) 8-51
Rabies 8-51
Poliomyelitis....8-51
Parasites 8-51
Cysticercosis....8-51
Toxoplasmosis 8-51
Amebic Meningoencephalitis....8-52
Cerebral Malaria....8-52

X. Pediatric and Seizure Neuropathology 8-52
Malformations 8-52
Neural Tube Defects....8-52
Holoprosencephaly 8-52
Congenital Hydrocephalus 8-52
Migrational/Gyral Defects 8-53
Destructive Malformations 8-54
Agenesis of Corpus Callosum 8-54
Syringomyelia/Syringobulbia....8-55
Fetal/Perinatal Insults....8-55
Intraventricular Hemorrhage....8-55
Gray Matter Ischemia....8-55
White Matter Ischemia/Periventricular Leukomalacia (PVL) 8-55
Kernicterus 8-55
Chromosomal Syndromes 8-55
Down Syndrome (Trisomy 21)....8-55
Edward Syndrome (Trisomy 18) 8-55
Patau Syndrome (Trisomy 13) 8-55
Fragile X....8-55
Seizure-Associated Pathology 8-55
Malformations....8-56
Tuberous Sclerosis 8-56
Tumors 8-56
Inflammatory/Infectious 8-56
Vascular Malformations 8-56

XI. Toxic/Metabolic Disorders.....8-57
Alcohol- (and/or Malnutrition-) Related Pathology 8-57
Trauma 8-57
Wernicke-Korsakoff Syndrome 8-57
Cerebellar Degeneration....8-57
Peripheral Neuropathy 8-57
Central Pontine Myelinolysis (CPM)....8-57
Hepatic Encephalopathy....8-57
Subacute Combined Degeneration of Spinal Cord 8-57
Fetal Alcohol Syndrome....8-57
Other Toxic Injuries 8-57
Carbon Monoxide....8-57
Methanol 8-57
Arsenic Poisoning....8-57
Lead Poisoning 8-59
Methotrexate Toxicity....8-59
Metabolic Disorders....8-59
Lysosomal (Enzyme) Storage Disorders 8-59
Mucopolysaccharidoses 8-59
Peroxisomal Disorders 8-59

Leukodystrophies 8-59
Adrenoleukodystrophy (ALD) 8-59

XII. Sellar/Suprasellar Pathology 8-59
Pituitary Adenomas 8-59
General Features 8-59
Prolactinoma (Lactotrophic Adenoma) 8-60
Corticotrophic (ACTH) Adenomas 8-60
Growth Hormone and Prolactin-Producing Adenomas 8-61
Gonadotrophic (FSH/LH) and Null Cell (IP-) Adenomas 8-61
Thyrotrophic Adenoma/Hyperplasias 8-61
Atypical Pituitary Adenoma 8-61
Pituitary Carcinoma 8-61
Pituitary Hyperplasia 8-61
Apoplexy 8-61
Craniopharyngioma 8-61
Rathke's Cleft Cyst 8-61
Granular Cell Tumor 8-61
Histiocytosis X (Langerhans' Cell Histiocytosis) 8-61
Hypothalamic Hamartoma 8-61
Other Tumors 8-62
Lymphocytic Hypophysitis 8-62
Empty Sella Syndrome 8-62

XIII. References 8-62

GENERAL REACTIONS TO INJURY

Macrophage/Microglial Reactions

Gitter Cells (Figure 1)

- Central nervous System (CNS) macrophages recruited from native microglia or systemic circulation
- Large accumulations in infarcts and demyelinating disease
- Wide range of morphology with accompanying subacute gliosis and occasional mitoses; commonly leads to a misdiagnosis of glioma

Microglial Activation (Figure 2) (Rod Cells, Microglial Nodules)

- Microglia are specialized antigen-presenting mononuclear cells of the CNS that: a) become elongated when activated (rod cells); b) surround dying neurons, a process known as neuronophagia; and c) cluster to form microglial nodules, a characteristic response in viral and paraneoplastic (autoimmune) encephalitis

Gliosis (Reactive Astrocytosis) (Figure 1)

- Accompanies all forms of brain injury

Acute/Subacute Gliosis

- Astrocytic hypertrophy with prominent radially oriented, stellate processes and often plump eccentric cytoplasm (gemistocytes, gemistos = full in Greek); cells are evenly distributed (as opposed to astrocytoma) and have no mitoses. Glial fibrillary acidic protein (GFAP) immunostains highlight reactive astrocytes

Chronic Gliosis

- Difficult to discern individual processes, dense fibrillary background, other signs of chronic injury (neuronal loss, rarefaction, hemosiderin, etc.); grossly firm, rubbery, atrophic, and/or dark, associated T2 MRI changes

Pilocytic Gliosis

- Chronic gliosis with Rosenthal fibers
- Common adjacent to cysts and slow-growing neoplasms, especially craniopharyngioma, pineal cyst, ependymoma, hemangioblastoma, and syrinx
- Potential confusion with pilocytic astrocytoma on small suprasellar, posterior fossa, or spinal cord biopsies, but less cellular and lacks microcystic component and eosinophilic granular bodies

Cerebral Edema

- Component of most forms of brain injury occurs in; two types (often admixed)

Vasogenic Edema

- Most common type, predominantly extracellular, results from breakdown of blood-brain barrier (BBB)

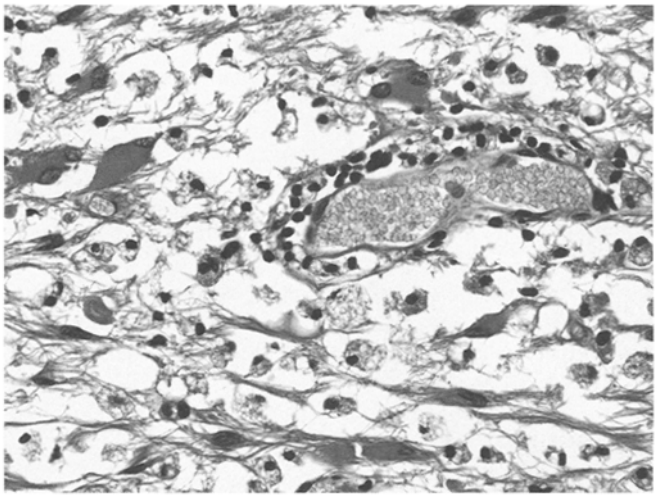


Fig. 1. Active demyelination with foamy macrophages, reactive astrocytes with abundant eosinophilic cytoplasm, and perivascular lymphoplasmacytic inflammation.

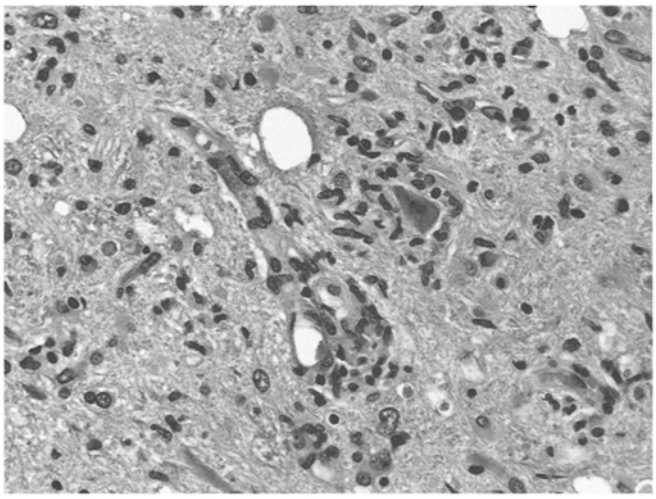


Fig. 2. Encephalitis with perivascular inflammation, microglial activation (rod cells), microglial nodules, and neuronophagia.

Cytotoxic Edema

- Intracellular, generally ischemic or toxic etiology (osmotic imbalance, ionic pump failure, etc.)

Hydrocephalus

Acute

- Often due to intraventricular hemorrhage or meningitis; life-threatening

Chronic

- Most are caused by obstruction to flow, e.g., tumor; increased cerebral spinal fluid (CSF) production also a factor in choroid plexus papilloma

Obstructive Hydrocephalus

- Obstruction within ventricular system

Non-obstructive Hydrocephalus

- Extraventricular obstruction (e.g., arachnoid granulations blocked by hemorrhage)

Hydrocephalus Without Increased Intracranial Pressure

- Ex vacuo: secondary to parenchymal loss (e.g., Alzheimer's disease)
- Normal pressure hydrocephalus: clinical triad of dementia, gait disturbance, and urinary incontinence; etiology unclear; some clinical evidence of intermittently raised CSF pressure

Herniation Syndromes

- Secondary to mass effect from edema, hemorrhage, tumor, abscess, etc.; high mortality
- Result of unyielding surrounding structures (skull, dural folds), therefore more common after closure of sutures

Cingulate (Subfalcine) Herniation

- Inferomedial herniation of cingulate gyrus (above corpus callosum) under falx cerebri; occasional superimposed anterior cerebral artery infarct from arterial compression

Uncal (Transtentorial) Herniation (Figure 3)

- Inferomedial herniation of uncus (posteromesial temporal structure) under tentorium cerebelli
- Compression of adjacent optic tract results in "blown pupil" because parasympathetic fibers run along the periphery of the nerve
- Compression of adjacent vessel leads to posterior cerebral artery infarct
- Displacement of opposite cerebral peduncle (corticospinal tract) into tentorium results in Kernohan's notch, with false lateralizing hemiplegia on same side as herniation



Fig. 3. Closed head injury from motor vehicle accident with marked edema, right uncal herniation, and Duret (secondary brainstem) hemorrhage involving central portion of midbrain.

Tonsillar Herniation

- Downward herniation of cerebellar tonsils into foramen magnum
- Resulting compression of medulla can lead to respiratory arrest
- Tonsils may fragment and fall into spinal subarachnoid space

Duret (Secondary Brainstem) Hemorrhage (Figure 3)

- Downward herniation of brainstem results in kinking of penetrating arteries (perpendicular branches off basilar artery) with acute hemorrhagic infarctions in pons, (characteristically narrow and medial in anteroposterior plane)
- In contrast, primary hypertensive brainstem hemorrhages are often globular and internal contusions (diffuse axonal injury) are typically posterolateral

GLIOMAS

Key Features in Differential Diagnosis of CNS Tumors

Precise Location

- Intra-axial (parenchymal) vs. extra-axial (dural)
- Superficial (cortical) vs. deep
- Intraventricular vs. paraventricular
- Supratentorial vs. infratentorial
- Sellar, suprasellar, hypothalamic
- Pineal region
- Cerebellar vs. cerebellopontine angle vs. brainstem (ventral or dorsal)
- Spinal cord: intradural vs. extradural; intramedullary vs. extramedullary

Age/Sex (Imaging Appearance = "Equivalent to Gross Examination" for Biopsy Specimens)

- Site of origin or epicenter
- Mass effect

Table 1. Typical Immunoprofiles of CNS Neoplasms

Tumor	+	±	−
Astrocytoma	S-100, GFAP		CK[1], LCA, SYN, HMB-45
Oligodendroglioma	S-100	GFAP[2]	CK[1], LCA, SYN
Ependymoma	S-100, GFAP	EMA(lumens), CK	LCA, SYN
Choroid plexus tumors	CD99 (membrane and lumens) S-100, CK, VIM, Transthyretin[3]	GFAP	EMA, CEA
Metastatic carcinoma	EMA and CK, CK7 TTF1(Lung), CK20 (colon)	CEA, S-100, SYN	GFAP, LCA, HMB-45
Melanoma	S-100, HMB-45, melan A		GFAP, CK, LCA
Lymphoma	LCA, CD20 (L26)	EMA[4]	CK, GFAP, HMB-45, SYN
Meningioma	EMA, VIM , Claudin	S-100, CD34, CK[5]	GFAP, HMB-45
Hemangiopericytoma	VIM, CD99, bc1–2, factor XIII[6]	CD34	EMA, CK, GFAP, S-100
Medulloblastoma	SYN, BAF 47 (lost in AT/RT)	S-100, GFAP	CK, LCA, EMA
Atypical teratoid/ rhabdoid tumor	EMA, CK, actin	SYN, GFAP, desmin, AFP	PLAP, β-hCG, LCA, BAF 47
Ganglioglioma	SYN, NF, CG, GFAP, CD34		Neu-N, CK, EMA, PLAP
Central neurocytoma	SYN, Neu-N	GFAP, S-100	NF, CG, CK, LCA
Schwannoma	S-100[7], CD34, Coll 4	GFAP, HMB-45[8]	EMA, NF, CK
Paraganglioma	SYN, CG, S-100[9]	NF	GFAP, CK, HMB-45
Hemangioblastoma	S-100, NSE, inhibin	GFAP	CK, EMA
Germinoma	PLAP, OCT4, CD117 (C-kit)	β-hCG, CK	AFP, EMA, HMB-45, LCA
Yolk sac tumor	AFP, CK	PLAP, EMA	β-hCG, GFAP CD30
Choriocarcinoma	β-hCG, CK,EMA	PLAP	AFP, GFAP, HMB-45, LCA
Embryonal carcinoma	CK, PLAP, OCT4, CD30		β-hCG, AFP, EMA, LCA, CD117(c-Kit)
Teratoma	CK, PLAP, EMA	AFP	β-hCG

[1]CAM 5.2 recommended because AE1/AE3 frequently stains gliomas; [2]Strongly positive in microgemistocytes; [3]Not specific for choroid plexus; [4]Positive in myeloma; [5]Positive in secretory variant; [6]Characteristic pattern of scattered, individual immunoreactive cells; [7]Diffuse, strong expression; [8]Positive in melanocytic variant; [9]Positive in sustentacular cells.

Note: GFAP = glial fibrillary acidic protein, CK = cytokeratin, LCA = leukocyte (Common antigen, SYN = synaptophysin, EMA = epithelial membrane antigen, VIM = vimetin, CEA = carcinoembryonic antigen, PLAP = placental alkaline phosphatase, AFP = α-fetoprotein, β-hCG = β-human chorionic gonadotrophin, CG = chromogranin, Coll 4 = collagen type IV, NSE = neuron specific enolase, NF = neurofilament

- Edema
- Infiltrative vs. discrete
- Enhancing: uniform vs. irregular; focal mural nodule vs. ring; nonenhancing
- Cystic vs. solid
- Single vs. multiple
- Calcified vs. noncalcified
- Tumoral seeding (leptomeningeal or nerve root enhancement)
- Other: melanin, lipid, hemorrhage (MRI), calcium (CT)

Histology/Immunohistochemistry

- *See* **Table 1**

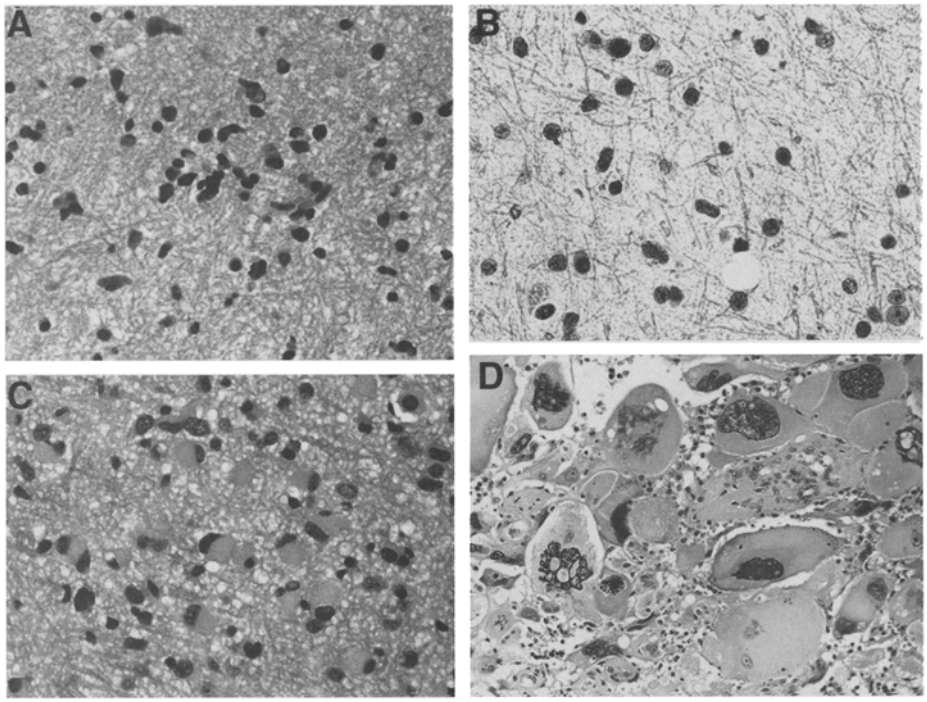


Fig. 4. Diffuse astrocytomas of various grade and variant morphology. Low grade (WHO II) fibrillary astrocytoma displays nuclear clustering, irregular shape, and hyperchromasia with minimal cytoplasm imparting the appearance of "naked nuclei" **(A)**. Immunoreactivity of p53 protein further supports the diagnosis **(B)**. Gemistocytic astrocytoma with similar nuclear features, but eccentric bellies of eosinophilic cytoplasm **(C)**. Bizarre mono- and multinucleate giant cells characterize the giant cell glioblastoma **(D)**.

Diffuse (Infiltrative) Astrocytomas

Cytologic/Histologic Variants

Fibrillary (Figure 4A-B)

- Most common cell type. Elongate or irregular, hyperchromatic nuclei. Cytoplasm varies from indiscernible and GFAP– to apparent as processes and GFAP+

Gemistocytic (Figure 4C)

- Abundant, eccentric, eosinophilic, GFAP-rich cytoplasm; short, eccentric cytoplasmic processes; round, variably hyperchromatic nuclei; irregular distribution of tumor cells (unlike reactive gemistocytic astrocytes); often associated perivascular inflammation; infrequent mitoses, but high-grade examples frequently associated with proliferating small cell astrocytes; high rate of anaplastic transformation

Giant Cell (Figure 4D)

- Multinucleate astrocytes with abundant cytoplasm and bizarre nuclei; GFAP+; often deceptively circumscribed grossly; usually Grade IV

Small Cell (Figure 5)

- Small cells with minimal cytoplasm and oval mildly hyperchromatic nuclei that may resemble oligodendroglioma; high mitotic index, usually Grade IV, differential diagnosis = other small cell malignancies or anaplastic oligodendroglioma; GFAP often highlights thin processes; genetically, 70% have EGFR amplification and >95% have chr. 10q deletion

Gliosarcoma (Figure 6)

- A variant of GBM with both astrocytic and sarcomatous elements
- Sarcoma derived by metaplasia from glioma (analogous to carcinosarcoma)
- Sarcoma usually fibrosarcoma or malignant fibrous histiocytoma, but may include bone, cartilage, muscle, and even epithelium
- Often superficial and deceptively circumscribed

Architectural Variants

Gliomatosis Cerebri

- A clinicopathologic diagnosis indicating extensive tumoral involvement of the CNS, in some cases the entire neuraxis. Most often it manifests as involvement of more than two cerebral lobes. Cytologically, nuclei are typically elongate, twisted, and bland. May be associated with multiple foci of dedifferentiation to glioblastoma

Prognostic Variables

- Patient age: strongest predictor in many series; survival time decreases with advancing age
- Histologic grade

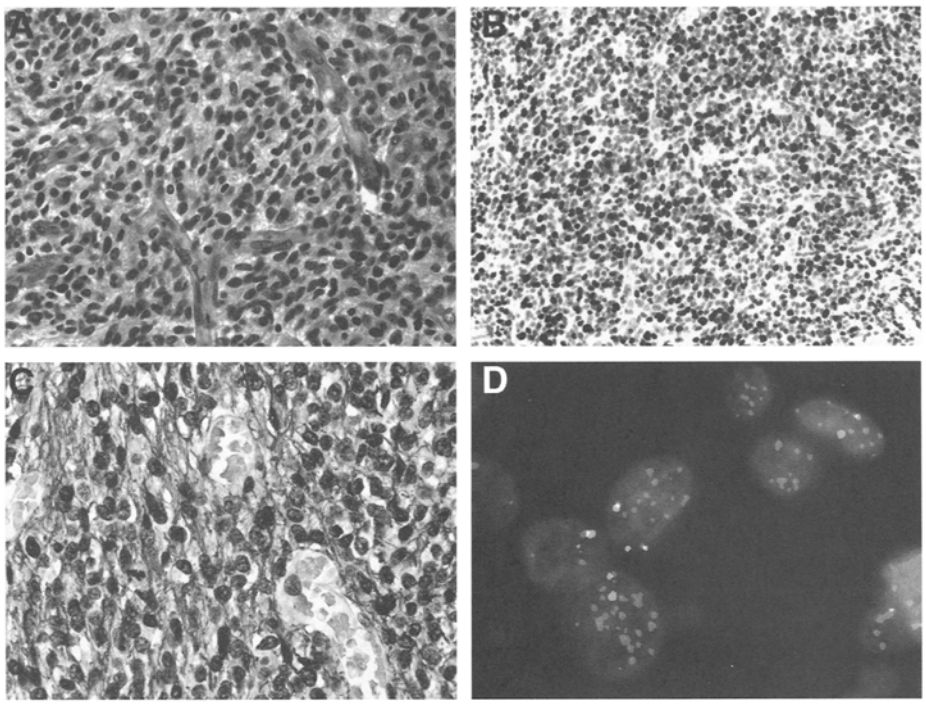


Fig. 5. The small cell glioblastoma is defined by monomorphous oval nuclei **(A)**, high proliferative index **(B;** MIB-1), minimal cytoplasm with thin GFAP+ processes **(C)**, and EGFR gene amplification in ~70% of cases **(D;** FISH analysis with EGFR in red and the chromosome 7 centromere in green).

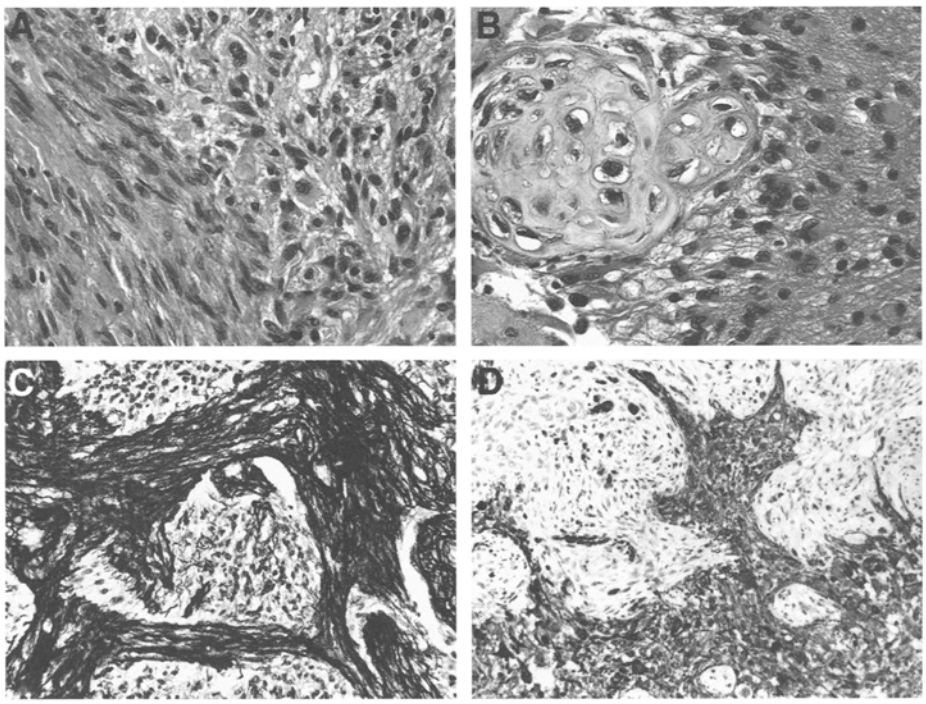


Fig. 6. Gliosarcoma with alternating zones of glial (upper right) and sarcomatous (lower left) differentiation **(A).** A focus of chondrosarcoma is seen **(B).** The sarcomatous and glial elements are individually highlighted by reticulin **(C)** and GFAP **(D)** stains, respectively.

Table 2. Grading Schemes for Astrocytoma

Three-tiered	*Four-tiered*
Ringertz	Kernohan
Modified Ringertz (Burger)	St. Anne-Mayo (see below)
WHO (see below)	

St. Anne-Mayo (functionally 3-tiered) (AMEN)

Criteria	*Scoring*
Atypia (nuclear)	Grade 1 = 0 criteria (very rare)
Mitoses (1 is enough)	Grade 2 = 1 criterion (nearly always atypia)
Endothelial proliferation	Grade 3 = 2 criteria (usually addition of mitoses)
Necrosis	Grade 4 = 3 or 4 criteria
Equivalents in terms of WHO grade:	Grade 1 has no WHO equivalent
	Grade 2 = (Differentiated) Astrocytoma
	Grade 3 = Anaplastic astrocytoma
	Grade 4 = Glioblastoma multiforme (GBM)

WHO (1993 Revision)

Adopted the morphologic parameters of the St. Anne-Mayo scheme but doesn't score and uses Roman numerals (II, III, IV) instead

Gr. II defined by atypia only

Gr. III defined by mitotic activity (number not specified)

Gr. IV defined by necrosis or endothelial proliferation, typically in association with atypia and mitoses (Note: Kernohan, Ringertz, and modified Ringertz schemes require necrosis for GBM)

Note: WHO Grade I corresponds to pilocytic astrocytoma.

- Histologic cell type: Oligo better than Oligoastro better than astrocytoma
- Preoperative performance status (better neurologic function relates to better prognosis)
- Extent of resection: variable conclusions among series, but gross total resection likely beneficial

Grading Schemes

- *See* **Table 2**
- World Health Organization (WHO) most commonly used

Grade II Astrocytoma (Astrocytoma)

Clinical

- Age peak = 30–40 years old
- Insidious onset
- Seizures > functional deficits
- Survival 5–8 years
- High rate of anaplastic transformation in adults, Death due to infiltration of vital structures or to herniation

Imaging/Gross (Figure 7A–C)

- Ill-defined low-density lesion on CT or T1 MRI; nonenhancing
- Bright T-2 on MRI
- Non-circumscribed; rubbery
- Epicenter in white matter; variable obliteration of grey-white matter junction

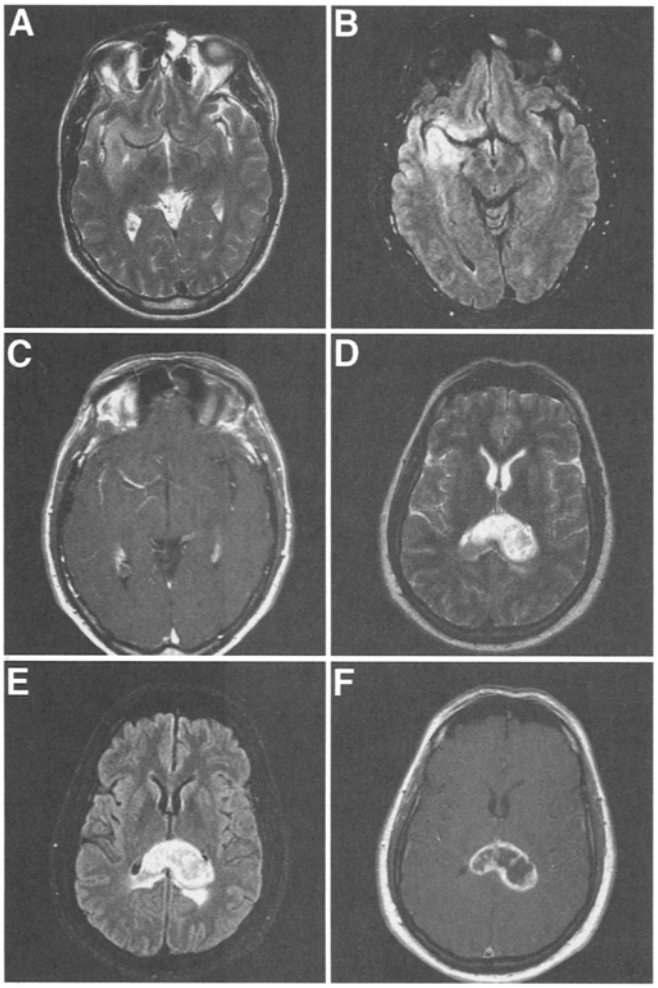


Fig. 7. T2 **(A,D)**, FLAIR **(B,E)**, and T1-gadolinium **(C,F)** MRI sequences from cases of diffuse astrocytoma, grade II **(A–C)** and glioblastoma, grade IV **(D–F)**. The former is non-enhancing, whereas the latter shows ring enhancement.

Smear

- Minimal to mild hypercellularity
- Nuclear atypia (hyperchromasia, cigar shape or pleomorphism)
- Variable cytology: inconspicuous cytoplasm ("naked nuclei") to variable size cell body or process formation

Microscopic (Figure 4A)

- Same features as above plus:
  - Predominantly white matter involvement but cortical infiltration also common
  - Uneven distribution of cells
  - "Secondary structures"—perivascular, perineuronal, subpial or subependymal cell accumulation

Grade III Astrocytoma (Anaplastic Astrocytoma)

Clinical

- Age peak = 40–50 years old
- Often more rapid onset than Grade II
- Seizures less common; deficits more frequent
- High rate of transformation to GBM
- Survival 2–3 years

Imaging/Gross

- Similar to Grade II astros; often show focal enhancement on CT/MRI but no ring enhancement
- May cross corpus callosum

Smear

- Increased cellularity
- Like Grade II but often with greater atypia

Microscopic (Figure 8A)

- Same features as above plus:
  - Mitotic activity
  - No endothelial proliferation or necrosis
  - May have a lower grade component

Grade IV Astrocytoma (Glioblastoma Multiforme)

Clinical

- Age peak = 50–60 years old
- Rapid onset with functional deficits, when primary GBM (i.e., de novo); slower evolution when secondary GBM (i.e., arising from a lower grade precursor)
- Survival is age dependent, but often short (<1 year)

Imaging/Gross (Figure 7D–F)

- Deceivingly circumscribed
- Ring enhancing
- Variegated gross appearance due to hemorrhage/necrosis
- May cross corpus callosum (butterfly lesion)

Smear

- Marked pleomorphism frequent but not invariable; may be monomorphous (e.g. small cell variant)
- Variable process formation and cytoplasm
- Endothelial proliferation and/or necrosis

Microscopic (Figure 8B–D)

- Same as above plus:
  - Endothelial proliferation = apparent multilayering of endothelium; not simply glomeruloid capillaries with numerous tiny lumens as seen commonly in pilocytic astrocytomas
  - Necrosis usually but not invariably associated with nuclear pseudopalisading

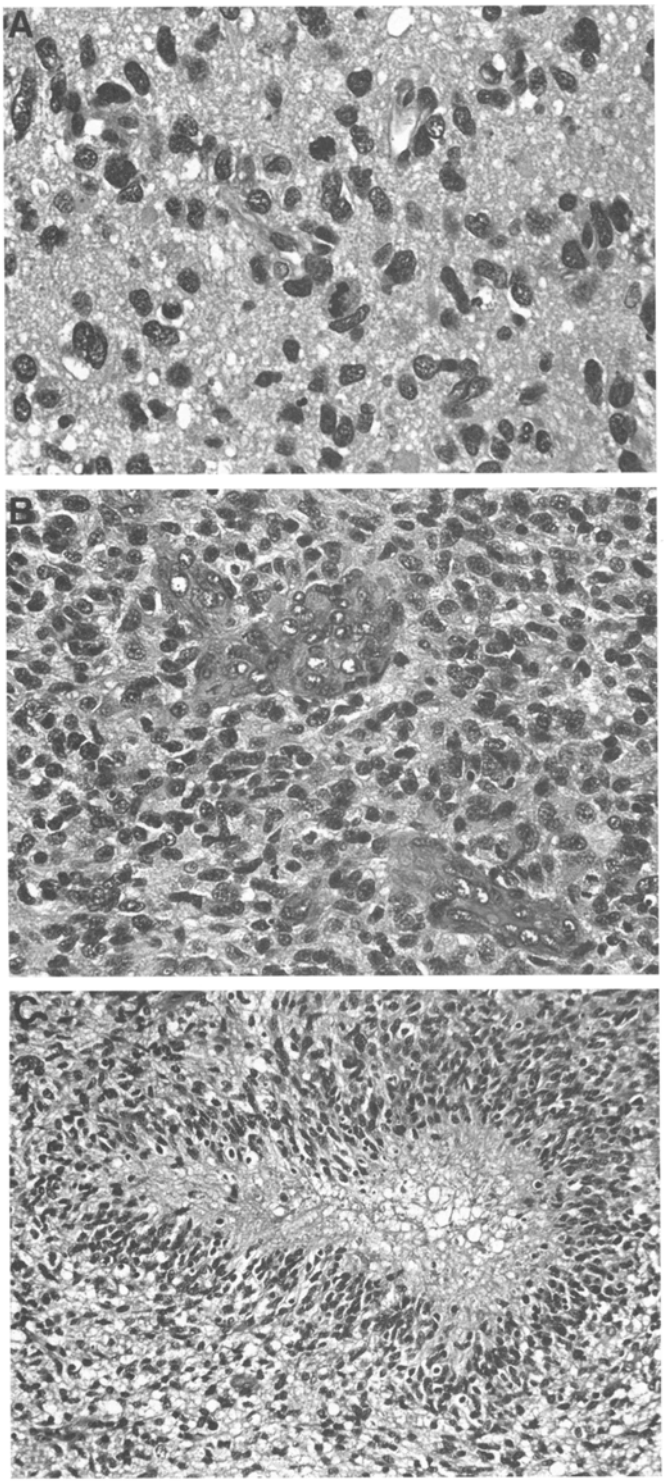


Fig. 8. Grading of diffuse astrocytomas relies on the presence or absence of mitoses (**A**), endothelial hyperplasia (**B**), and necrosis (**C**), the latter often associated with nuclear pseudopalisading.

Table 3. Common Differential Diagnoses of Astrocytomas

Common diagnosis	*Useful stains*
Astrocytoma vs. Reactive gliosis	GFAP shows equally spaced astrocytes with radiating processes, MIB-1 = low
Astrocytoma vs. Demyelinating disease	LFB-PAS shows myelin loss; Bielschowsky or Neurofilament IPs show axonal sparing; KP-1 shows numerous macrophages
Diffuse vs. Circumscribed astrocytoma	PAS with diastase highlights EGBs; Neurofilament IPs = relatively solid growth (i.e., rare axons within the tumor)
Recurrent tumor vs. Radiation Necrosis	H&E shows coagulative necrosis without pseudopalisading; dystrophic Ca^{2+}; vascular hyalinization/telangiectasias; MIB-1 = low
GBM vs. Metastasis vs. Lymphoma vs.small cell carcinoma	CAM 5.2 (epithelial), EMA (epithelial, meningothelial), S-100 (melanocytic, glial), HMB-45 (melanocytic),GFAP (glial),LCA (lymphoid), CD20 (B-cell), Cytokeratin (CK) 7 (lung or breast primary), CK 20 (GI, especially colon primary), Synaptophysin (SYN) (PNET, Neuroendocrine-ex. small cell carcinoma)

Note: Some keratins (e.g., AE1/AE3) stain neoplastic and nonneoplastic glial cells.

- Infiltrative margin (relative circumscription may be seen in primary GBM)
- Frequent presence of lower grade component in secondary GBM

Differential Diagnosis

♦ *See* **Table 3**

Circumscribed Astrocytomas

Pilocytic Astrocytoma (WHO Grade I)

Clinical

♦ Children/young adults

♦ Predilection: Cerebellum, hypothalamus third ventricle, optic nerve, cerebral hemisphere, spinal cord

♦ Slowly progressive symptoms

- Excellent prognosis (80% 20-year survival)
- Malignant transformation exceedingly rare

Imaging/Gross (Figure 9)

- Demarcated
- Enhancing
- Bright T-1 MRI signal due to mucinous/proteinaceous fluid in cystic element
- Often partially cystic with mural nodule

Smear

- Bipolar cells with bland, oval to elongated nuclei and long piloid (hair-like) processes
- Note: cytology similar to fibrillary astrocytoma in many cases
- Rosenthal fibers (RFs)
- Eosinophilic granular bodies (EGBs)
- Bizarre or multinucleated cells ("pennies on a plate" arrangement of nuclei)
- Glomeruloid vessels, no prognostic significance

Microscopic (Figure 10)

- Variable: same as above plus:
  - Often biphasic compact (piloid) and loose (micro-cystic) pattern; either pattern may predominate
  - "Diffuse" variant may simulate Grade II fibrillary astro
  - Oligodendroglioma-like regions may be seen
  - Note: *Pilomyxoid astrocytoma* is a monomorphous more aggressive pilocytic variant occurring in infants. Frequent hypothalamic involvement, lack of RFs/EGBs, and vague perivascular pseudorosettes (Figure 10D) Tendency to leptomeningeal seeding

Differential Diagnosis

- Pilocytic gliosis (other underlying lesion; no microcysts or EGBs)
- Ganglioglioma (dysmorphic neurons)
- Pleomorphic xanthoastrocytoma (more pleomorphic, occasional lipidized giant cells, partly reticulin-rich, EGBs)
- Fibrillary astrocytoma (non-enhancing, generally noncystic, no RFs or EGBs)
- Oligodendroglioma (lacks piloid component, RFs and EGBs; rarely in cerebellum or spinal cord)

Pleomorphic Xanthoastrocytoma (PXA) (WHO Grade II–III)

Clinical

- Children/young adults
- Chronic seizures
- Very good prognosis in most cases
- Worse prognosis with anaplastic transformation (15%); still far more favorable prognosis than GBM

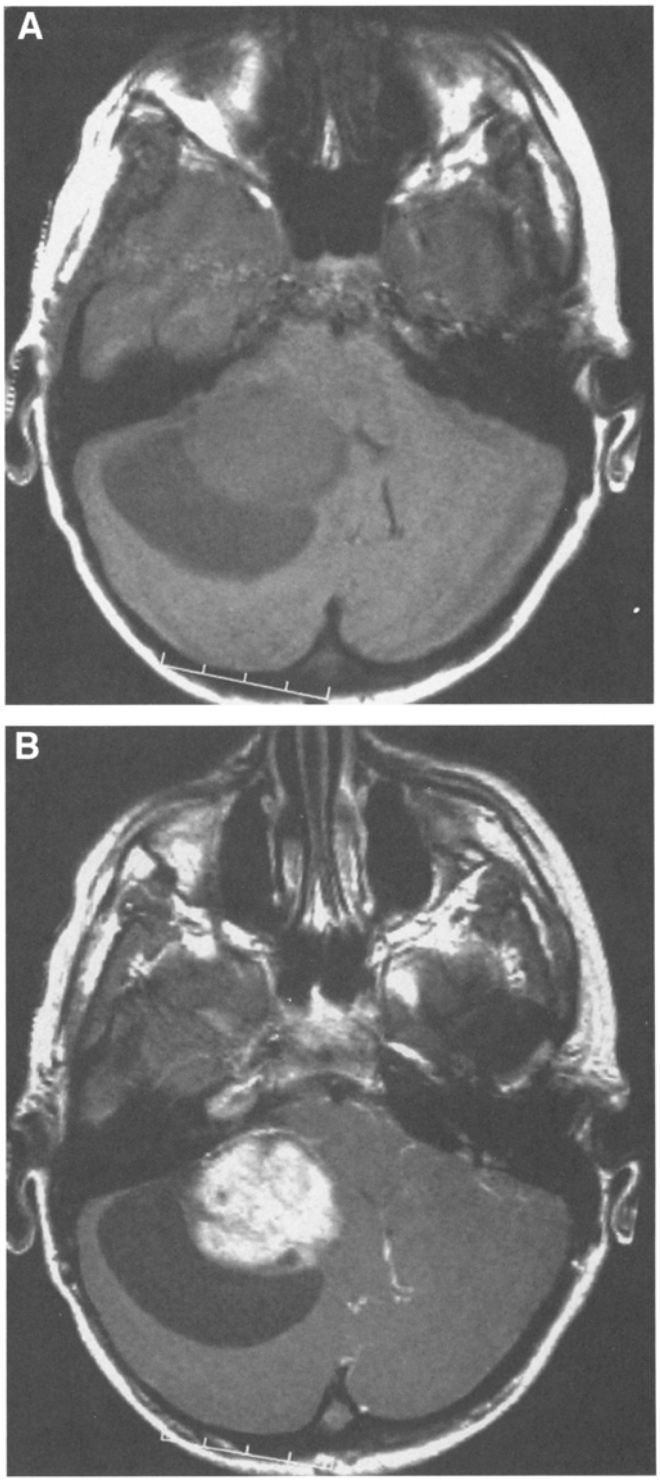


Fig. 9. Typical MRI appearance of cerebellar pilocytic astrocytoma with sharp demarcation and a cystic mass with a mural contrast enhancing nodule. T1-weighted images without (**A**) and with (**B**) gadolinium (images courtesy of Dr. Robert McKinstry, Mallinckrodt Institute of Radiology, St. Louis, MO).

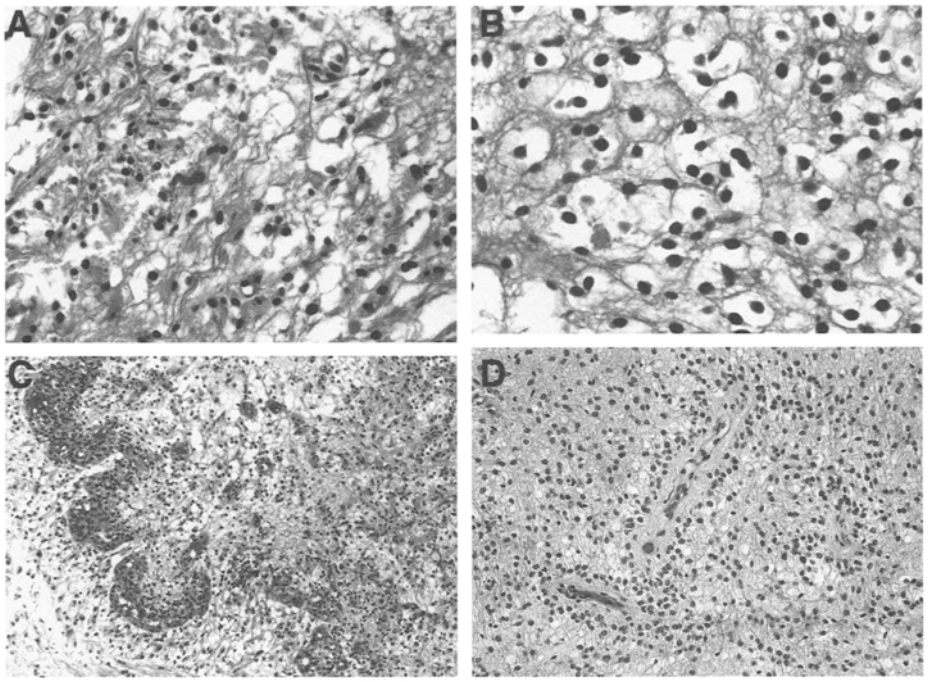


Fig. 10. Pilocytic astrocytoma is most commonly characterized by limited cellularity, thin hair-like processes, and Rosenthal fibers **(A)**. An oligodendroglioma-like component is not uncommon, though other features of pilocytic astrocytoma, such as EGBs help to establish the diagnosis **(B)**. Endothelial hyperplasia is common in pilocytic astrocytoma **(C)**, but has no prognostic significance. Pilomyxoid astrocytoma appears similar, but forms ependymoma-like perivascular pseudorosettes and lacks Rosenthal fibers and EGBs **(D)**.

Imaging/Gross

- Cyst with enhancing mural nodule
- Superficial; often with leptomeningeal component
- Temporal lobe (less often parietal)

Smear

- Marked cellular pleomorphism; bizarre nuclei, nuclear-cytoplasmic pseudoinclusions
- Glial appearance
- Eosinophilic granular bodies

Microscopic (Figure 11)

- Same as above plus:
  - Xanthomatous cells variable, often few
  - Perivascular lymphocytic cuffing
  - Spindled, mesenchymal-like cells
  - Scant mitoses
  - No endothelial proliferation or necrosis
  - Anaplastic transformation (15%) = monomorphic smaller, often epithelioid cells, frequent mitoses, necrosis, and occasional endothelial proliferation

Differential Diagnosis

- Ganglioglioma (dysmorphic neurons)
- Pilocytic astrocytoma (less pleomorphic, reticulin poor)
- GBM (Situated deeper in brain; brisk mitotic activity, endothelial proliferation, necrosis, no EGBs)
- Dural-based sarcoma, e.g., MFH (GFAP–, mitoses)

Subependymal Giant Cell Astrocytoma (SEGA) (WHO Grade I)

Clinical

- Children/young adults
- Obstructive hydrocephalus
- Tuberous sclerosis associated (may be first manifestation); rarely syndrome-unassociated
- Excellent prognosis (possibly hamartomatous in nature)

Imaging/Gross (Figure 12A)

- Intraventricular (anterior within lateral ventricles, typically near foramen of Monro)
- Large, sharply demarcated, solid, often calcified
- "Candle guttering"-associated

Smear

- Large spindled to epithelioid cells with primarily glial and less often neuron-like features

Microscopic (Figure 12B)

- Same as above plus:
  - Truly giant cells uncommon

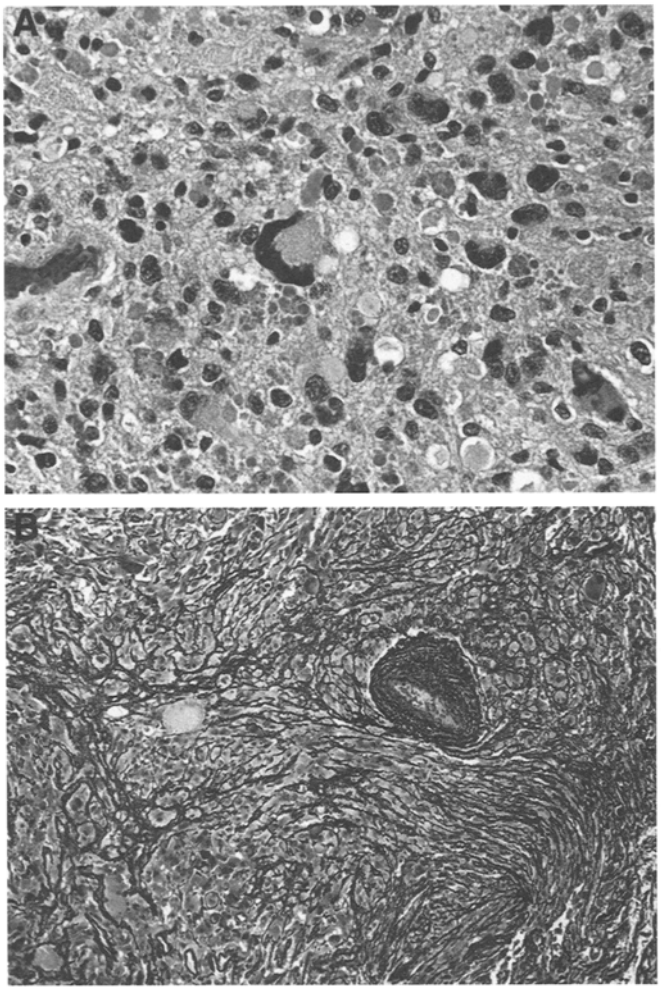


Fig. 11. PXA with multinucleate giant cells, EGBs **(A)**, and increased reticulin deposition **(B)**.

- Perivascular pseudorosettes
- Non-infiltrative of surrounding tissue (NF stain)
- Scattered mast cells
- Variable GFAP staining; ± minor NF, synaptophysin or neurotransmitter substance staining

Differential Diagnosis

- Gemistocytic astrocytoma (infiltrative, more uniformly GFAP+, white matter epicenter; no syndrome association)
- Giant cell astrocytoma (often at least partly infiltrative, somewhat more GFAP+, white matter epicenter; no syndrome association)
- Ependymoma (no syndrome association; more GFAP+, periventricular rather than intraventricular)

Oligodendroglioma

Clinical

- 30–40 years old

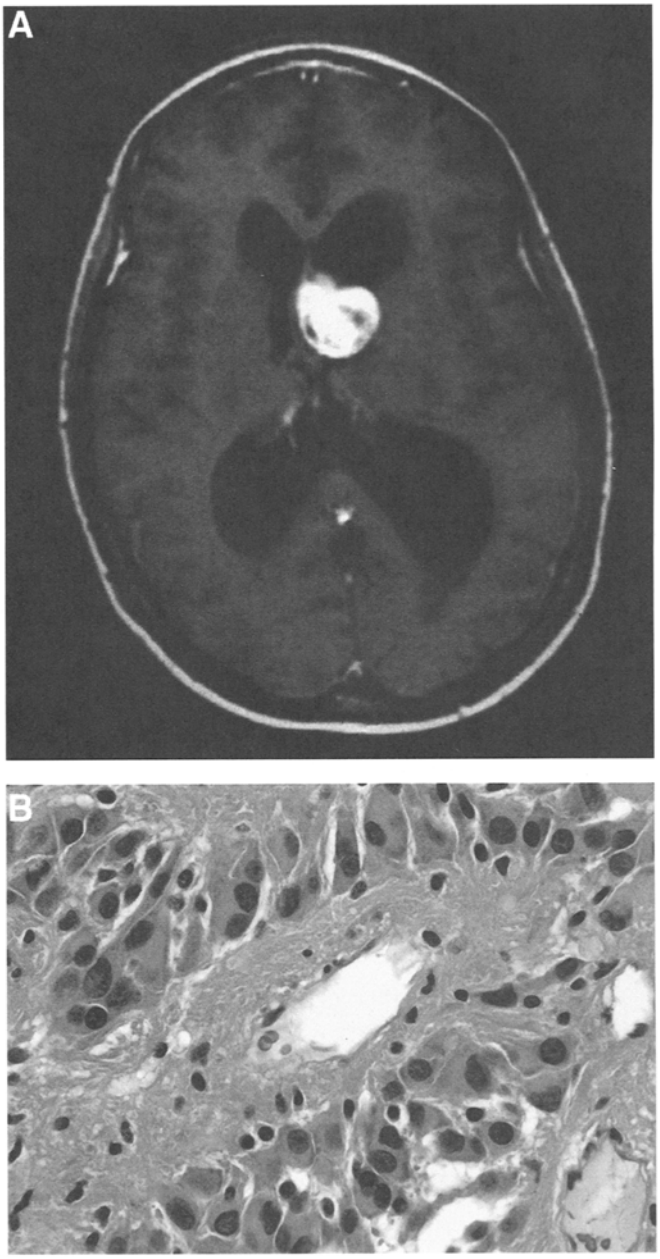


Fig. 12. SEGA presenting as an enhancing intraventricular mass **(A)**. Histologically, it is characterized by cells with neuron-like nuclei (vesicular with nucleoli) and astrocyte-like cytoplasm (eosinophilic), sometimes arranged in perivascular pseudorosettes **(B)**.

- History of seizures > focal neurologic deficits
- Survival:
  - Grade II: 10–15 years
  - Grade III: 3–5 years
- Treated with radiation ± chemotherapy (e.g. PCV, temozolamide)
- Anaplastic transformation less frequent and slower than in diffuse astrocytoma

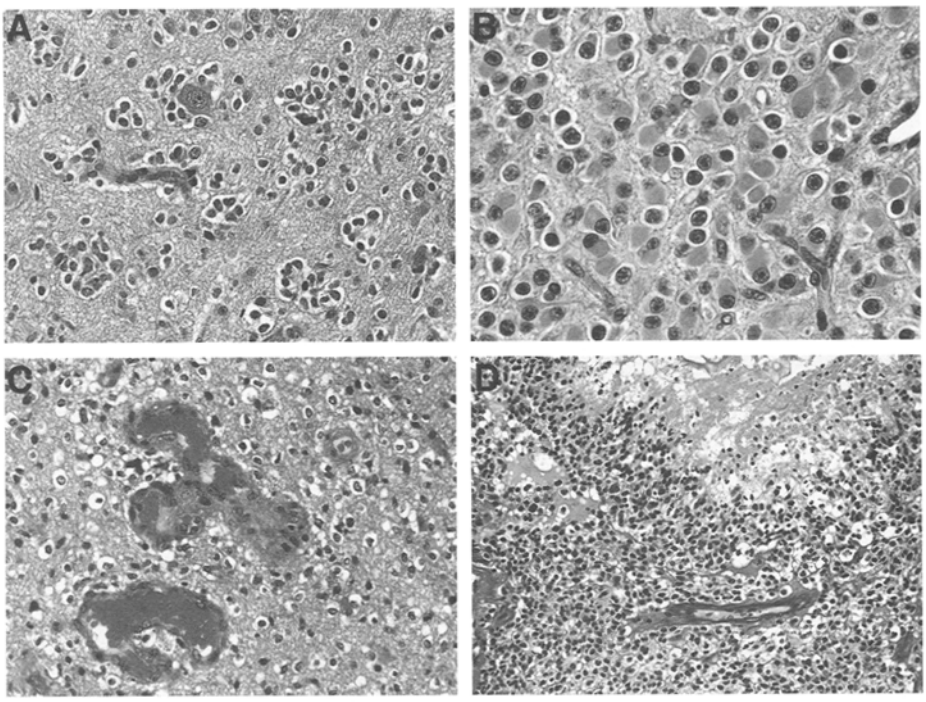


Fig. 13. Oligodendrogliomas with uniform rounded nuclei, clear perinuclear haloes, perineuronal satellitosis **(A)**, and minigemistocytes with small rounded bellies of eosinophilic cytoplasm **(B)**. Endothelial hyperplasia **(C)** and necrosis **(D)** may be seen in high-grade examples.

Imaging/Gross

- Cerebral hemisphere, especially frontal lobes
- Extensive cortical involvement
- Demarcated relative to deeper white matter
- Calcification common

Smear

- Uniform round nuclei in a loose background of axons
- Bland chromatin, small nucleoli
- Small skirt of cytoplasm; occasional "minigemistocytes"
- Few cytoplasmic processes
- Microcalcifications common

Microscopic (Figure 13)

- Same as above plus:
  - Perinuclear clear halo artifact (lacking in frozen sections and promptly fixed specimens)
  - "Chicken-wire" capillary pattern
  - Microgemistocytes (GFAP+; smaller and rounder than gemistocytes; nuclei round and regular)
  - Gliofibrillary oligodendrocytes (small GFAP+ cytoplasmic rim, torch-shaped process) (Figure 14A)
  - Extensive cortical infiltration with secondary structures:
    - Perineuronal satellitosis
    - Subpial condensation
    - Perivascular aggregation
    - Hypercellular, patternless nodules (occasional)

Grading

- WHO: high mitotic index (e.g. >5/10 HPF) and/or endothelial hyperplasia = anaplastic oligo (III)
- WHO = oligo (II) vs. anaplastic oligo (III)
- Gr II: conventional oligodendroglioma
- Gr III: anaplastic oligo: hypercellular, mitotically active, endothelial proliferation or necrosis; high MIB-1 (Ki-67) proliferative index also helpful (Figure 14B)

Genetics

- Chromosome 1p and 19q codeletions in 70–85% (Figure 14C–D): constitutes a "genetically favorable":
  - Pattern associated with longer survival and enhanced therapeutic sensitivity

Differential Diagnosis

- Demyelinating disease/infarct (Many KP-1+ macrophages; axonal sparing in demyelination, axonal loss in infarct)
- Pilocytic astrocytoma (classic locations and imaging, macrocysts, RFs, EGBs)
- Central neurocytoma (intraventricular, neuropil containing rosettes)
- Clear cell ependymoma (perivascular pseudorosettes, sharp demarcation, solid, no axons on NF stain)

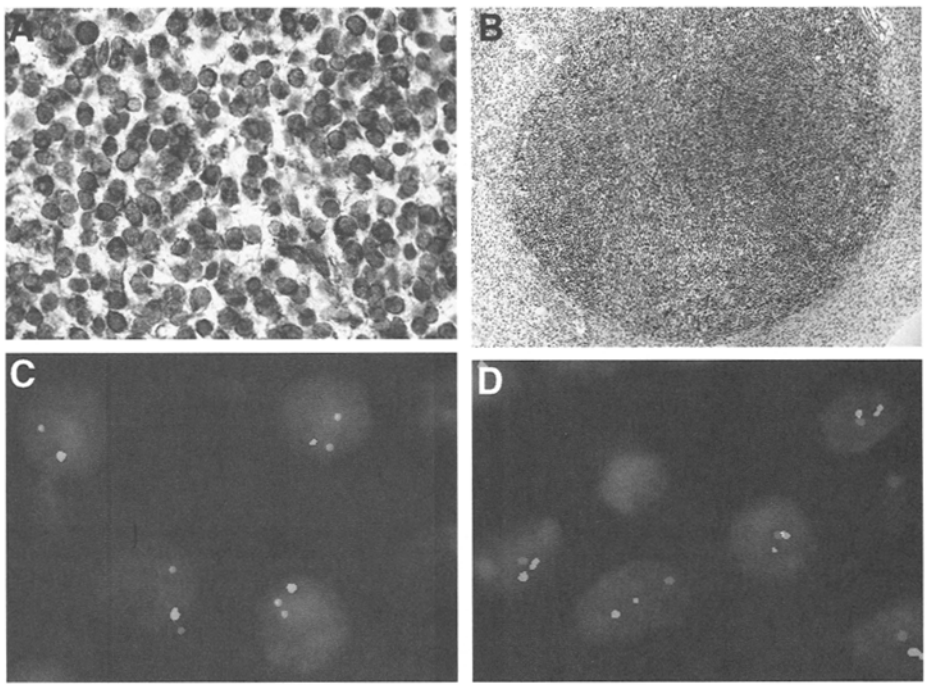


Fig. 14. Special studies in oligodendrogliomas. GFAP is typically negative or highlights minigemistocytes and gliofibrillary oligodendrocytes with a thin rim of cytoplasmic reactivity **(A)**. Anaplasia may be focal and is often accompanied by an elevated MIB-1 labeling index **(B)**. FISH analysis reveals codeletion of 1p (C; 1p32 in green and 1q42 in red) and 19q (D; 19p13 in green; 19q13 in red) in roughly 80% of cases.

- Dysembryoplastic neuroepithelial tumor (intracortical, patterned nodules, floating neurons)
- Mixed glioma (oligo and astro elements)

Mixed Oligoastrocytoma

- Controversial entity with varying definitions among experts
- For example:
  - Diffuse glioma with separate discrete oligodendroglial and astrocytic zones
  - Both clearly recognizable cell types intermixed
  - Single cell type with features intermediate between oligodendroglioma and astrocytoma
- Similar presentation, imaging, and therapy as pure oligodendroglioma; graded the same way as pure oligodendrogliomas
- Generally behave better than pure astrocytoma and worse than pure oligo; however, difficult to predict on histology alone
- There is no convincing evidence for the existence of other types of mixed gliomas, such as "oligoependymoma" or "astroependymoma"

Ependymoma

Clinical

- Children/young adults
- Paraventricular, or even cortical in supratentorial brain
- Fourth ventricle favored in children, spinal cord favored in adults
- May cause obstructive hydrocephalus
- Prognosis difficult to predict; age >2 years and gross total removal are favorable factors
- Spinal ependymomas have a better prognosis, particularly myxopapillary tumors
- CSF dissemination in <5% of ependymomas, usually those of high grade

Imaging/Gross

- Sharp demarcation
- Calcification (intracranial)
- Cyst formation (supratentorial)
- Enhancement on CT/MRI

Smear

- Often cohesive cells
- Uniform round nuclei in fibrillary background
- Distinct nucleolus
- Perivascular pseudorosettes

Microscopic (Figure 15)

- Same as above plus:
  - Ependymal true rosettes or canals (infrequent) (5–10%)
  - Sharp demarcation

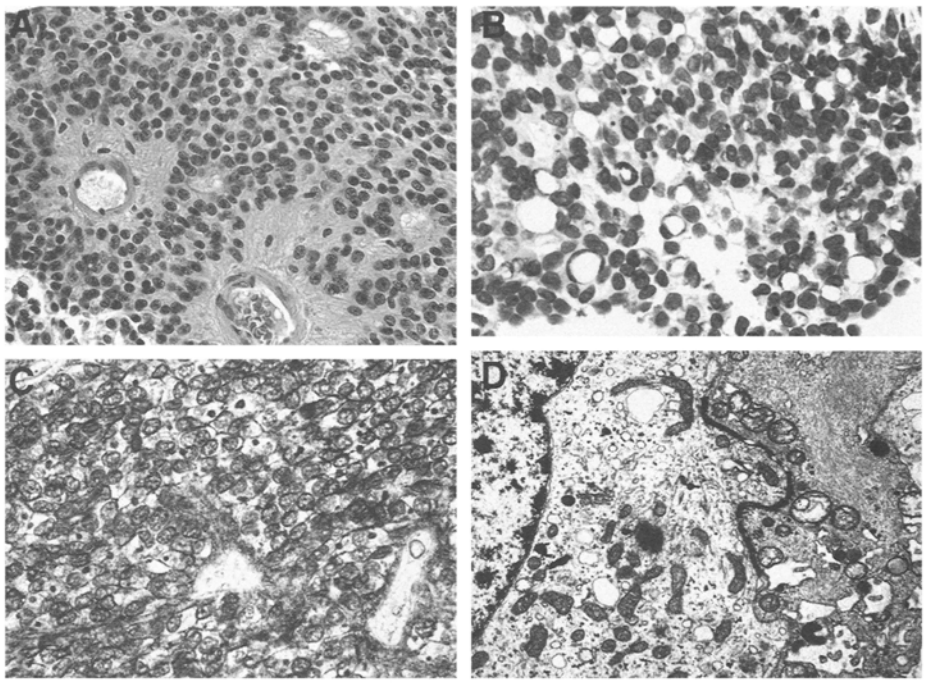


Fig. 15. Ependymomas are characterized most commonly by perivascular nuclear-free zones or pseudorosettes **(A)**. True rosettes with lumens are rarer but more specific **(A)**. Intracellular lumina occasionally yield intracytoplasmic EMA (B) and CD99 **(C)** positive dot-like structures. Ultrastructural features include long zipper-like intercellular junctions **(D)**.

- May have membrane and/or cytoplasmic dot-like EMA and CD99 immunopositivity
- Diagnostic ultrastructural features include zipper-like intercellular junctions and intra/intercellular lumina containing cilia and microvilli

Grading

- ♦ No consensus; less correlation with clinical behavior than in astrocytoma and oligodendroglioma
- ♦ WHO Grading = ependymoma (II) vs. anaplastic ependymoma(III):
  - Gr I: only applied to myxopapillary variant
  - Gr II: ependymoma: few mitoses
  - Gr IIII: anaplastic ependymoma: numerous mitoses, ± endothelial proliferation. Necrosis not important unless associated with palisading

Variants

- ♦ Clear Cell Ependymoma:
  - Mimics oligodendroglioma; look for demarcation and perivascular pseudorosettes
- ♦ Papillary Ependymoma:
  - Papillary cores are glial rather than fibrovascular as seen in choroid plexus tumors
- ♦ Myxopapillary Ependymoma:
  - WHO Grade I variant, filum terminale, myxoid perivascular stroma, thin capsule; excellent prognosis if resected intact; may seed spontaneously or if ruptured intraoperatively. Rare primary pre- or postsacral soft tissue examples show a tendency to undergo lung metastases
- ♦ Tanycytic Ependymoma:
  - Extremely long, thin processes forming vague pseudorosettes

Differential Diagnosis

- ♦ Medulloblastoma/PNET (synaptophysin+)
- ♦ Oligodendroglioma (lacks sharp circumscription and pseudorosettes)
- ♦ Central neurocytoma (origin in septum pellucidum, synaptophysin+)
- ♦ Choroid plexus papilloma (origin in choroid plexus, connective tissue stroma; strong uniform cytokeratin staining)
- ♦ Papillary meningioma (falls apart to form pseudo-papillae, EMA+, GFAP–)
- ♦ Pilocytic astro (some infiltration on NF stain; frequent biphasic pattern, RFs and EGBs)
- ♦ Schwannoma of cauda equina region (nerve origin; reticulin-rich, collagen IV+, may be GFAP+)
- ♦ Paraganglioma of cauda equina region (origin in filum or nerve root; Zellballen or carcinoid-like pattern; chromogranin+)

Subependymoma (WHO Grade I)

Clinical

- ♦ Usually older patient

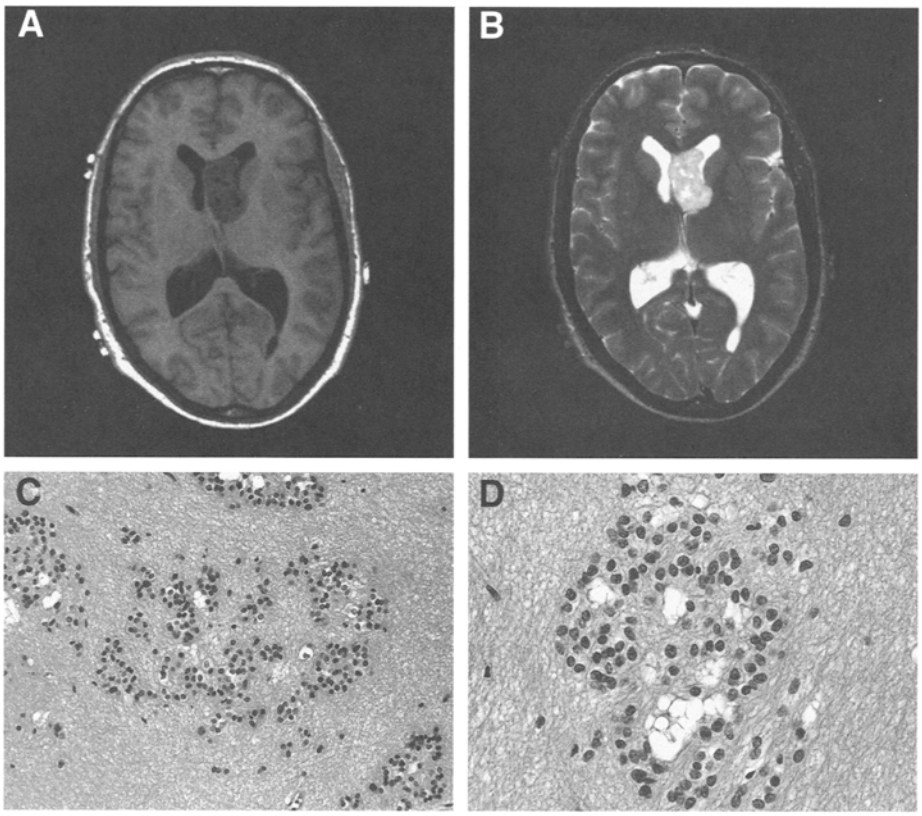


Fig. 16. Intraventricular subependymoma detected on T1 **(A)** and T2 **(B)** weighted MR images. Histologically, there are clusters of ependymoma-like nuclei embedded in a densely fibrillary background **(C,D)**.

- Often incidental; otherwise hydrocephalus-associated
- Benign despite occasional mitoses
- Intratumoral hemorrhage in large examples is rare; may be life-threatening

Imaging/Gross (Figure 16A–B)

- Intraventricular: lateral > 4th > 3rd; rare in spinal cord
- Sessile and demarcated
- Often calcified

Smear/Histology (Figure 16C–D)

- Ependymoma-like nuclear features, lobulated
- Immediately subependymal
- Microcysts
- Paucicellular with prominent clustering of cells
- Clusters surrounded by skeins of glial cell processes
- Degenerative features: nuclear atypia, hyalinized vessels, calcium, hemosiderin deposits
- May have minor component of ependymoma with pseudorosettes if more than minor, they are termed "mixed subependymoma-ependymoma" WHO Grade II

Differential Diagnosis

- Ependymoma: more cellular, occasional true rosettes
- Fibrillary astrocytoma: intraparenchymal, infiltrative, lacks distinctive clustering

Choroid Plexus Neoplasms

Choroid Plexus Papilloma (WHO Grade I)

Clinical

- Hydrocephalus (mechanisms: both obstruction and increased CSF production)
- Lateral ventricle in congenital/childhood cases
- Fourth ventricle in adults
- Benign/surgically curable

Radiology/Gross

- Intraventricular
- Enhancing
- Polypoid/papillary ("cauliflower" appearance)
- Discrete
- Often calcified

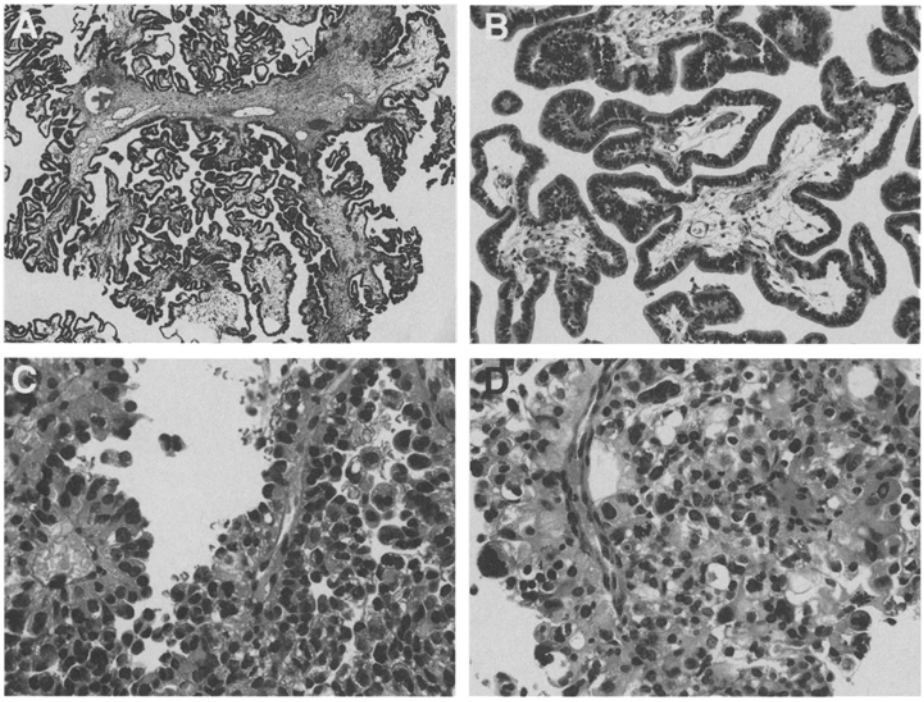


Fig. 17. Choroid plexus papillomas show well formed fibrovascular cores and typically a single layer of cuboidal to columnar epithelium **(A,B)**. Choroid plexus carcinomas have solid foci, typically a high-grade cytology, and numerous mitoses **(C,D)**.

Smear/Histology (Figure 17A–B)

- True papillae (fibrovascular cores)
- Simple cuboidal to columnar epithelium lacking "cobblestone" cell surfaces characteristic of normal choroid plexus
- Limited architectural complexity
- Low mitotic rate
- Occasionally necrosis or calcification (no prognostic significance)
- Focal ependymal differentiation common (GFAP+ tapered processes)
- IHC = S-100+, CAM 5.2+, Transthyretin (prealbumin)+, GFAP ±, EMA–, CEA–

Differential Diagnosis

- Normal choroid plexus (smaller cells, "cobblestone" epithelial lining)
- Papillary ependymoma (falls apart to form pseudo-papillae, lack collagenous papilla stroma, fibrillary processes, GFAP+, CAM 5.2–)
- Choroid plexus carcinoma (more solid, complex, infiltrative, mitotically active)

Choroid Plexus Carcinoma (WHO Grade III)

Clinical

- Rare
- Vast majority age <3 years; some congenital
- Highly aggressive/nearly uniformly fatal
- High rate of metastasis, mainly cerebrospinal
- Rare long-term survivors with complete excision

Radiology/Gross

- Intraventricular
- Enhancing
- Infiltrative
- CSF seeding in some

Smear/Histology (Figure 17C–D)

- More solid and complex than papillomas
- High mitotic rate
- High grade cytology
- Infantile examples may be markedly pleomorphic with eosinophilic globules
- IHC = S-100+, CAM 5.2+, Transthyretin (prealbumin)+, GFAP±, EMA–, CEA–

Differential Diagnosis

- Anaplastic ependymoma (GFAP+, non-uniform CK+)
- GBM (GFAP+, CAM 5.2–)
- Medulloblastoma/PNET (synaptophysin+, CK–)
- Atypical teratoid/rhabdoid tumor (paranuclear inclusions, EMA+, actin+)
- Metastatic carcinoma (adult patient, EMA+, CEA–, S-100±)

NEURONAL/GLIONEURONAL NEOPLASMS

Derivations/Definitions Used in Neuronal Tumors

- Ganglio = ganglion cell
- Neurocyte = small mature neuron (e.g., cerebellar internal granular layer, dentate fascia)
- Neuroblast = primitive small cells with "neuropil" or Homer Wright rosette formation
- Medulloblast = theoretical cerebellar precursor cell (?external granular layer)
- Paraganglio = specialized autonomic neuroendocrine cell
- Medullo (neuro) epithelium = primitive epithelial tubules/canals resembling the embryonic neural tube
- Pineo, Esthesio, Retino = derived from or differentiating toward specialized neuronal receptor cells
- Cytoma = mature; blastoma = primitive

Ganglion Cell Tumors (Ganglioglioma/ Gangliocytoma) (WHO Grade I)

Clinical

- Children/young adults
- Chronic seizures
- Benign/surgically curable
- Hamartomatous versus tumoral nature of the lesion is unsettled
- Rare malignant transformation (usually astrocytic component): WHO Grade III

Imaging/Gross

- Superficial
- Temporal lobe favored
- Demarcated
- Cystic with enhancing mural nodule or solid and variably enhancing

Smear/Histology (Figure 18)

- Lobular/nodular
- Spongy/microcystic
- Dysmorphic/binucleate ganglion cells (SYN/NF/CG+, Neu-N usually–)
- Perivascular chronic inflammation
- Eosinopilic granular bodies/Rosenthal fibers
- Collagen containing stroma in some (reticulin, trichrome+)
- Glial component: pilocytic or fibrillary in nature; oligodendroglial elements rare
- CD34+ cells often present (?progenitor cells)

Special Variants

- Desmoplastic infantile ganglioglioma (DIG):
  - Age <2, supratentorial, hemispheric, cyst-mural nodule architecture. Nodule firm, often dura attached. Spindle cells far exceed prevalence of ganglion-like cells
- Dysplastic cerebellar gangliocytoma (Lhermitte-Duclos disease):
  - Unilateral expanded folia with replacement of internal granular layer by dysmorphic ganglion cells; associated with Cowden's syndrome (PTEN gene)

Differential Diagnosis

- Infantile desmoplastic astrocytoma of infancy—identical but without ganglion-like cells
- Pilocytic astrocytoma (no ganglionic-like cells, contains RFs and EGBs)
- Pleomorphic xanthoastrocytoma (bizarre, multinucleate astrocytic cells, rare ganglion cells)

Central Neurocytoma (WHO Grade II)

Clinical

- Young/middle-age adults
- Signs/symptoms of obstructive hydrocephalus
- Vast majority surgically curable
- Rare atypia, mitoses, and/or MIB-1 >2% (atypical central neurocytoma)

Imaging/Gross (Figure 19A–B)

- Lateral ventricle near foramen of Monroe; origin in septum pellucidum
- Rarely extraventricular; most hemispheric, rare at other sites
- Often large and globular
- Calcified

Smear/Histology (Figure 19C–D)

- Uniform, round nuclei; speckled chromatin (oligo-like)
- Streaming and vague perivascular pseudorosettes
- Fine neuropil-like background
- Calcification
- Synaptophysin+, Neu-N+, neurofilament ±

Differential Diagnosis

- Oligodendroglioma (superficial, synaptophysin–)
- Cellular or clear cell ependymoma (paraventricular, GFAP +)

Pineal Parenchymal Tumors

Pineocytoma

Clinical

- Middle to late adulthood

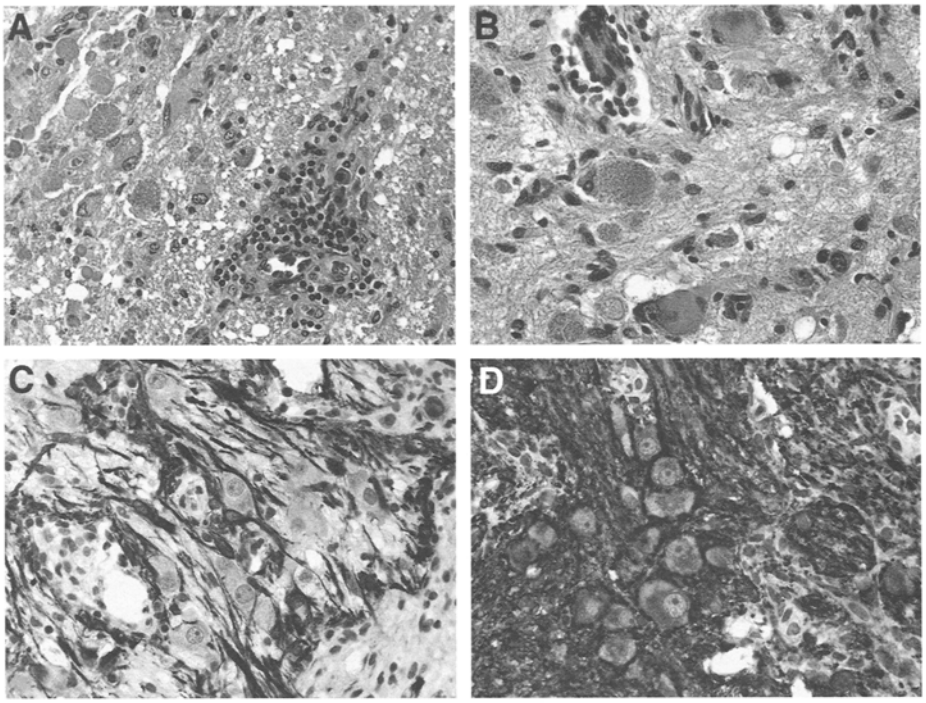


Fig. 18. Gangliogliomas are characterized by dysmorphic ganglion cells, perivascular lymphocytes, and EGBs **(A,B)**. The glial component is highlighted with GFAP **(C)**, whereas the neuronal element is positive for synaptophysin, chromogranin, and neurofilament **(D)**.

- Pineal region symptoms (Parinaud's syndrome i.e. paralysis of upward gaze, etc.)
- "Favorable prognosis" in comparison to pineoblastoma

Imaging/Gross

- Globular, discrete
- Contrast enhancing, variable calcification

Smear/Histology

- Round salt and pepper nuclei
- Loss of normal lobularity
- Solid sheets of cells
- Pineocytic rosettes (large, exaggerated Homer Wright rosettes)
- Argyrophilic, club-shaped neuritic processes (Bodian, Bielschowsky)
- Synaptophysin+, Neu-N+ in most

Differential Diagnosis

- Normal pineal (no rosettes, may be difficult diagnosis on small biopsy)
- Pineoblastoma (scant cytoplasm, PNET-like, no pineocytic rosettes, increased proliferation, necrosis, CSF seeding common)
- Pineal parenchymal tumor, intermediate type (lacks pineocytomatous rosettes, scant mitoses, only occasional seeding)
- Ependymoma (GFAP+, synaptophysin–)

Pineoblastoma

Clinical

- Childhood
- CSF seeding
- Rapid recurrence
- Association with bilateral retinoblastoma ("trilateral retinoblastoma")

Imaging/Gross

- Enhancing
- Infiltrative, CSF seeding

Smear/Histology

- Small "blue cell tumor"
- No pineocytomatous rosettes
- Occasional Homer Wright rosettes
- Occasional photoreceptor differentiation ("fleurettes")
- Rare glial or mesenchymal differentiation

Differential Diagnosis

- Pineocytoma (low proliferation, pineocytomatous rosettes)
- Cellular ependymoma (low proliferation, GFAP+)
- Seeding from medulloblastoma (clinicopathologic correlation required)
- Malignant germ cell tumor (PLAP, AFP, β-hCG, CK, etc.)

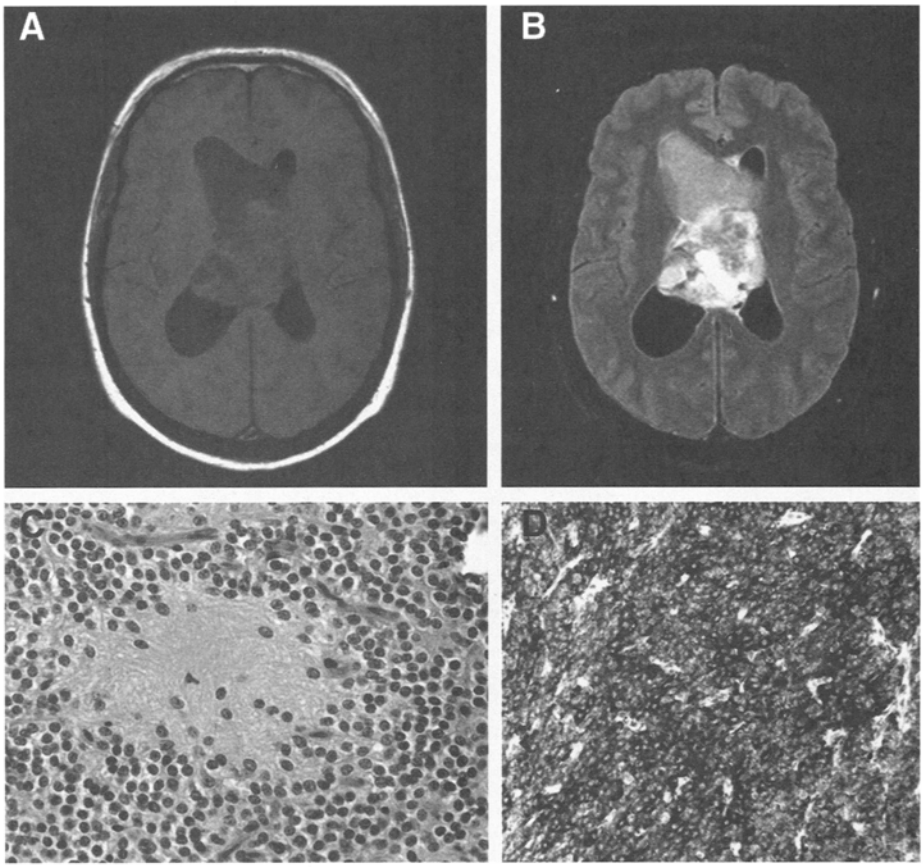


Fig. 19. Enhancing intraventricular mass in a case of central neurocytoma detected by T1-weighted MRI without **(A)** and with **(B)** gadolinium. Cytologically, it resembles oligodendroglioma but is associated with neurocytic rosettes with central neuropil **(C)**. The neuronal character is confirmed with a synaptophysin stain **(D)**.

Dysembryoplastic Neuroepithelial Tumor (DNT) (WHO Grade I)

Clinical

- Age of onset <20 years
- Longstanding chronic seizures (partial complex type)
- Slow or no growth
- Benign/surgically curable
- Hamartoma vs. neoplasm; nature of tumor unsettled

Imaging/Gross

- Supratentorial; temporal lobe, infrequent at other sites
- Intracortical
- Multinodular
- May be "cystic appearing" on imaging due to high mucin content, infrequent calcification

Microscopic (Figure 20)

- Patterned, mucin-rich intracortical nodules
- "Specific glioneuronal element" between nodules features both:
  - "floating neurons" and oligo-like cells
- Minimal perineuronal satellitosis
- Cortical dysplasia may be seen at periphery of the lesion

Differential Diagnosis

- Oligodendroglioma (white matter involvement, occasional nonpatterned nodules, perineuronal satellitosis, subpial tumor cell accumulation, no floating neurons)
- Oligoastrocytoma (same as above)
- Ganglioglioma (cyst-mural nodule, lymphocytic infiltrate, no floating neurons)

Paraganglioma (WHO Grade I)

Clinical

- Adults
- Back pain, radiculopathy, or incontinence
- Almost always benign/surgically curable

Imaging/Gross

- Filum terminale or nerve root (rarely skull base or sella)
- Enhancing/discrete
- Large feeder vessels

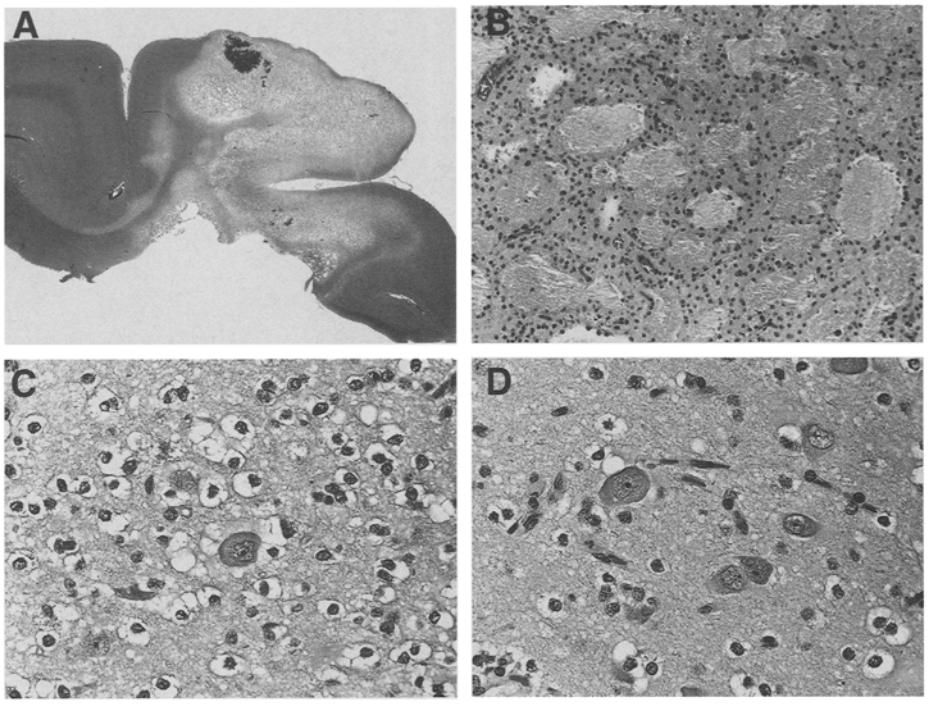


Fig. 20. DNT is an intracortical mass **(A)** with patterned mucin-rich nodules **(B)**, oligodendroglioma-like cells, and floating neurons **(C,D)**.

Smear/Histology

- Zellballen and/or carcinoid-like pattern
- Neuroendocrine cells with salt and pepper chromatin
- Ganglion cells in 50% ("gangliocytic paraganglioma")
- Synaptophysin/chromogranin+; neurofilament±
- S-100 + sustentacular cells

Differential Diagnosis

- Myxopapillary ependymoma (GFAP+, synaptophysin–, chromogranin–)

Embryonal Tumors

Types

- Medulloepithelioma (age <5, epithelial canals)
- Medulloblastoma and variants:
  - Classic (vermis, infiltrative, PNET cytology)
  - Nodular/Desmoplastic (reticulin-rich between nodules, most advanced neuroglial differentiation within nodules)
  - Large cell (vesicular nuclei with large nucleoli, "cannibalization," aggressive variant prone to seed)
  - Medullomyoblastoma (rhabdomyoblastic differentiation; may also be anaplastic)
  - Melanotic (pigmented, aggressive)
  - Extensively nodular (bunch of grapes appearance on MRI, extensive neurocytic neuronal differentiation, less aggressive)
- Primitive neuroectodermal tumor (PNET) = medulloblastoma-like tumor outside the cerebellum
- Ependymoblastoma (PNET with well differentiated ependymal true rosettes)
- Pineoblastoma (pineal region, neuroblastic/retinal differentiation)
- Neuroblastoma/ganglioneuroblastoma
- Olfactory neuroblastoma (esthesioneuroblastoma, paraganglioma-like)
- Retinoblastoma (eye, Flexner-Wintersteiner rosettes, fleurettes)
- Atypical teratoid/rhabdoid tumor (carcinoma-like, PNET-like element, spindle cells, clear cells, rhabdoid cells may be rare)

Medulloblastoma/PNET (WHO Grade IV)

Clinical

- Children/young adults
- Rapid, aggressive clinical course
- Rapidly fatal without therapy (Rx)
- 5-year survival with Rx = 60% to 70% in medulloblastoma; less with PNET
- Rx = surgery, craniospinal radiation, multidrug chemotherapy

Imaging/Gross

- Solid

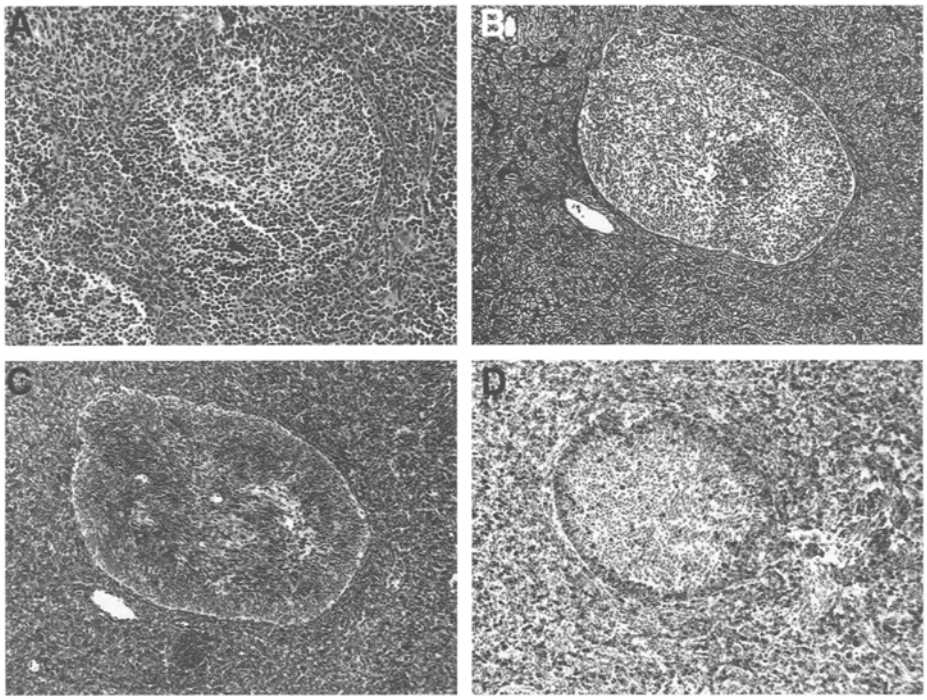


Fig. 21. Pale nodule in a nodular/desmoplastic Medulloblastoma **(A)**. There is increased internodular reticulin deposition **(B)**, intranodular synaptophysin positivity **(C)**, and internodular MIB-1 labeling **(D)**.

- Noncalcified
- Homogeneously enhancing
- CSF spread /drop metastases

Smear/Histology (Figure 21)

- Small "carrot-shaped" to round nuclei, inapparent nucleoli (except in large cell anaplastic variant), scant cytoplasm
- Classic pattern: reticulin-free sheets
- Nodular/Desmoplastic variant: reticulin-rich internodular regions, "germinal center-like" nodules with evidence of neuronal differentiation, "Indian filing"
- Undifferentiated or with lines of differentiation
- Neuroblastic differentiation (fibrillarity, Homer Wright rosettes)
- Glial, mesenchymal, or melanocytic differentiation less common
- Subarachnoid invasion
- Synaptophysin+, GFAP±

Differential Diagnosis

- Small blue cell tumors (primary or metastatic)
- Cellular ependymoma (lower proliferation, GFAP+, SYN–)
- Atypical teratoid/rhabdoid tumor, variable cytology including (rhabdoid, epithelioid, spindle cells; EMA+, CK+, actin+, desmin±)

Atypical Teratoid/Rhabdoid Tumor

Clinical

- Infants <2 years old
- Rapid, highly aggressive clinical course
- CSF seeding seen at presentation in 35%
- Almost uniformly fatal within 1 year, minimal therapeutic response

Imaging/Gross

- Similar to medulloblastoma/PNET
- All sites; cerebellum most common

Smear/Histology (Figure 22)

- Epithelioid component resembles carcinoma or malignant rhabdoid tumor of kidney
- PNET component in 65%
- Spindled cells or even chondroid foci may be seen
- Vimentin, EMA+, CK+, actin+ in majority of cases
- Synaptophysin+, GFAP+ in some cases
- β-HCG–, PLAP– (i.e., not a germ cell tumor despite occasional AFP+)
- Immunohistochemically detectable loss of INI1/hSNF5 protein (Figure 22C)
- Chromosome 22q loss or monosomy 22 in 70–80% (Figure 22D)

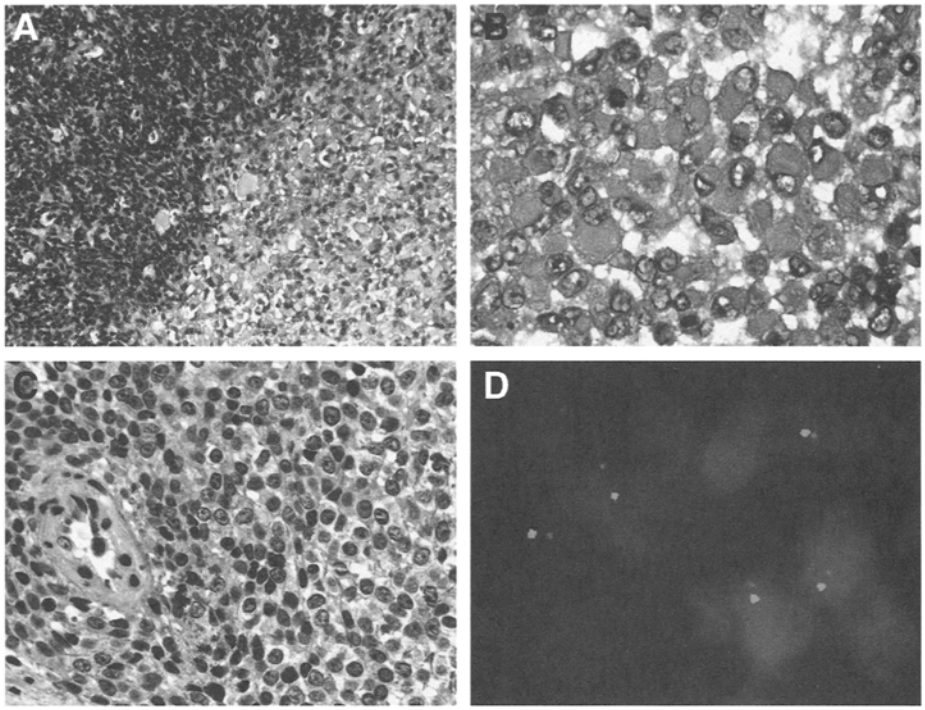


Fig. 22. AT/RTs often have a small round cell component **(A)**, though the diagnostic cell type is the rhabdoid cell with an eccentrically placed vesicular nucleus and a globular parnuclear inclusion **(B)**. The diagnosis is supported by loss of INI1 protein expression **(C)** and a chromosome 22q deletion by FISH **(D;** BCR in green, NF2 in red).

Differential Diagnosis

- Small blue cell tumors (primary or metastatic)
- Cellular ependymoma (low proliferation, EMA–, CK–, actin–, synaptophysin–)
- Medulloblastoma/PNET (more uniformly small cells, EMA–, CK–, actin–, INI1 retained expression)

Olfactory Neuroblastoma (WHO Grade III)

Clinical

- Bimodal peaks, adolescence and elderly
- Epistaxis, nasal obstruction
- Favorable prognosis in most, especially with gross total resection
- Subset is aggressive, difficult to predict
- Metastases, neuroblastic predominance, and high MIB-1 equate with lower survival

Imaging/Gross

- Cribriform plate
- Polypoid intranasal extension
- Intracranial extension

Smear/Histology

- Mixed patterns of paraganglioma and neuroblastoma
- Nests/lobules/sheets
- "Neuroendocrine nuclei"
- Delicate fibrillary background may be seen
- Rare rosettes (Homer Wright or Flexner types)
- Synaptophysin/neurofilament/chromogranin+
- Usually CK–
- S-100 + sustentacular cells in paraganglioma like pattern

Differential Diagnosis

- Sinonasal undifferentiated carcinoma (large anaplastic cells; CK+, synaptophysin–, S-100–)
- Neuroendocrine carcinoma (CK+, synaptophysin + S-100 –)
- Small cell melanoma (HMB-45+)

Retinoblastoma

Clinical

- Age <3
- Leukocoria, strabismus
- Sporadic or familial; linked to Rb gene on 13q14
- Favorable prognosis in developed countries due to early stage at detection and effective adjuvant therapy
- Familial cases at risk for other neoplasms, especially osteosarcoma

Macroscopic

- Arise in retina
- Often bilateral and multifocal in familial form
- Gray-white

- Fleshy
- Necrotic with dystrophic calcification
- Optic nerve margin important

Smear/Histology

- Small blue cell tumor
- Flexner-Wintersteiner rosettes
- Homer Wright rosettes (rare)
- Fleurettes (extremely rare)

Spread

- Along optic nerve
- Leptomeningeal spread or cerebrospinal deposits
- Extraocular extension
- Lymphatic and/or hematogenous metastases

Differential Diagnosis

- Lymphoma (LCA+, synaptophysin–)

MENINGEAL NEOPLASMS

Meningioma (WHO Grade I)

Clinical

- Adults
- F:M ratio = 1.5 intracranial, 10:1 spinal (possible hormonal basis)
- NF2 gene (chromosome 22) implicated in most familial and half of sporadic cases
- Insidious/asymptomatic onset
- Occasionally radiation-induced
- Slow growth (unless atypical or malignant)
- Recurrence:
  - 5% to 10% in gross totally resected, benign (WHO I) meningiomas
  - 40% to 60% in subtotal resection or atypical/malignant grade (WHO II/III) meningiomas
- Decreased survival in atypical and malignant meningioma

Imaging/Gross

- Extra-axial location
- "Dural tail" sign (wisp of enhancement around base of tumor; represents either tumor or hypervascular dural tissue)
- Hyperostosis of adjacent skull related to bone invasion in most cases

Smear

- Cellular smears with 3D clusters; fibrous tumors smear poorly
- Epithelioid to spindle cells
- Nuclear pseudoinclusions

Microscopic (Figure 23)

- Highly variable
- Polygonal epithelioid to elongated cells
- Nuclear pseudoinclusions
- Stroma scant, collagenous, or mucinous
- Whorls
- Psammoma bodies
- Hyalinized vessels

Immunohistochemistry

- *See* **Table 4**

Variants (Figure 24)

- Meningothelial (WHO I)
- Fibrous (WHO I)
- Transitional (WHO I)
- Psammomatous (WHO I)
- Microcystic (WHO I)
- Secretory (WHO I)
- Lymphoplasmacytoid (WHO I)
- Angiomatous (WHO I)
- Metaplastic
- Chordoid (WHO II)
- Clear cell (WHO II)
- Rhabdoid (WHO III)
- Papillary (WHO III)

Differential Diagnosis

- Metastatic carcinoma (strong, uniform CK+)
- Melanoma (HMB-45+)
- Hemangiopericytoma/other sarcoma (reticulin rich, EMA–)
- Solitary fibrous tumor (strong and diffuse CD34+, EMA–)
- Schwannoma (strong and diffuse S-100 and collagen IV+, EMA–)
- Inflammatory pseudotumor (entrapped microscopic meningothelial nests only)
- Glioma with dural invasion (GFAP+, EMA–)

Atypical Meningioma (WHO Grade II) (Figure 23B,C)

- High risk (65%) of recurrence even after gross total resection

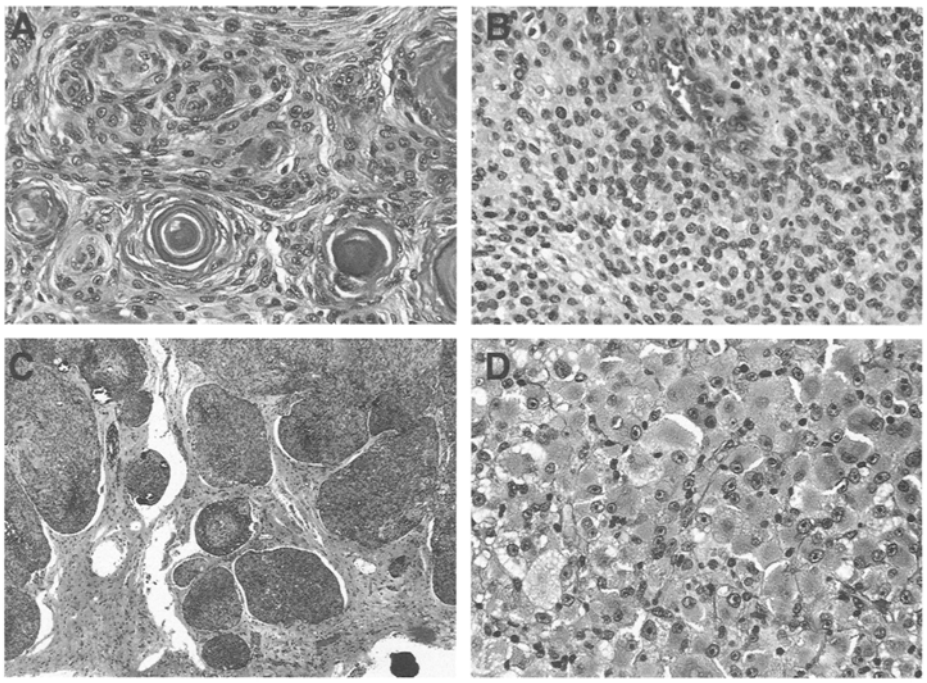


Fig. 23. Meningioma, grade I, with whorl formation and psammoma bodies **(A)**. An atypical meningioma, grade II, with sheeting architecture and numerous mitotic figures **(B)**. Brain invasion **(C)** is another criterion for a grade II designation. Anaplastic meningioma, grade III, with melanoma-like cytology **(D)**.

Table 4. Immunohistochemistry of Meningiomas

Positive	*Negative*
EMA (weak; membrane pattern)	Estrogen Receptor
CK (secretory variant; otherwise rare)	GFAP
Progesterone Receptor	CD34 (±)
Vimentin	
S-100 (20%; 80% fibrous variant)	
CEA (secretory variant)	
Claudin	
Prostaglandin D Synthase	

- Note: Nuclear hyperchromasia/pleomorphism is unimportant, since it is often a degenerative phenomenon similar to that seen in ancient schwannoma!
- WHO definition:
  - High mitotic index, e.g. ≥4/10 HPF (may be focal) or
  - Brain invasion or
  - Three of these five features
    - Sheeting (patternless growth with loss of whorls and fascicles)
    - Small cells (lymphocyte-like nests with high N/C ratio)
    - Hypercellularity
    - Macronucleoli
    - Spontaneous necrosis not induced by embolization or radiation

Malignant (Anaplastic) Meningioma (WHO Grade III)

- Definitions vary
- Extracranial metastasis. Note: So-called "benign metastasizing meningioma" may be indolent
- Anaplasia:
  - Carcinoma, sarcoma, or melanoma-like appearance, focally or diffusely (requires IHC or EM demonstration of meningothelial features) (Figure 23D)
- High mitotic index (e.g., >20/10 HPF)
- Median survival <2 years

Hemangiopericytoma (WHO Grade II or III)

Clinical

- Adults

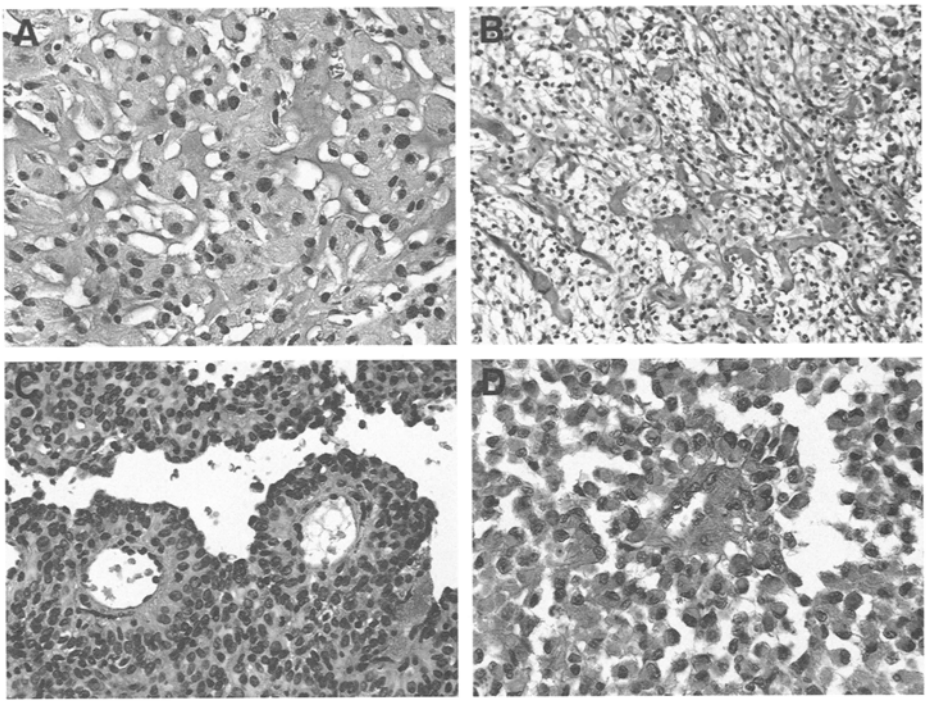


Fig. 24. Aggressive variants include chordoid, grade II **(A)**, clear cell, grade II **(B)**, papillary, grade III **(C)**, and rhabdoid, grade III **(D)** meningiomas.

- F : M = 1
- No chromosome 22 abnormality
- Considered a meningeal sarcoma
- Recurrence rate = 60%
- Metastases 25%
- Mean survival 7 years

Imaging/Gross

- Extra-axial, densely contrast-enhancing on CT/MRI
- Highly vascular on angiogram
- Frequently invades adjacent bone
- No associated hyperostosis

Smear

- Cellular without the molding/whorling of meningiomas

Microscopic (Figure 25)

- Monotonous, patternless cellularity
- Staghorn vessels
- Pale zones
- Only minor collagen deposition, if any
- Variable mitotic rate
- Intercellular reticulin staining, variable but usually dense
- EMA – (except in rare examples with focal staining), S-100–
- CD34– or patchy+
- Strongly bcl-2 and CD99+ in most cases

Differential Diagnosis

- Meningioma (tight whorls, psammoma bodies, reticulin poor, EMA+)
- Solitary fibrous tumor (strong, diffuse CD34+; malignant examples may be difficult to differentiate from hemangiopericytoma)
- Other sarcomas (e.g., mesenchymal chondrosarcoma)

Other Primary Mesenchymal Neoplasms

Benign

- Generally rare; includes most soft tissue neoplasms (e.g., chondroma, fibrous histiocytoma, hemangioma, solitary fibrous tumor, etc.)

Sarcomas

- Typically high-grade malignant; includes fibrosarcoma, MFH, osteosarcoma, chondrosarcoma (especially mesenchymal chondrosarcoma), etc.
- Some are radiation-induced
- Poor prognosis

Dural Metastases

- Lung or breast carcinoma, melanoma, leukemia/ lymphoma most common

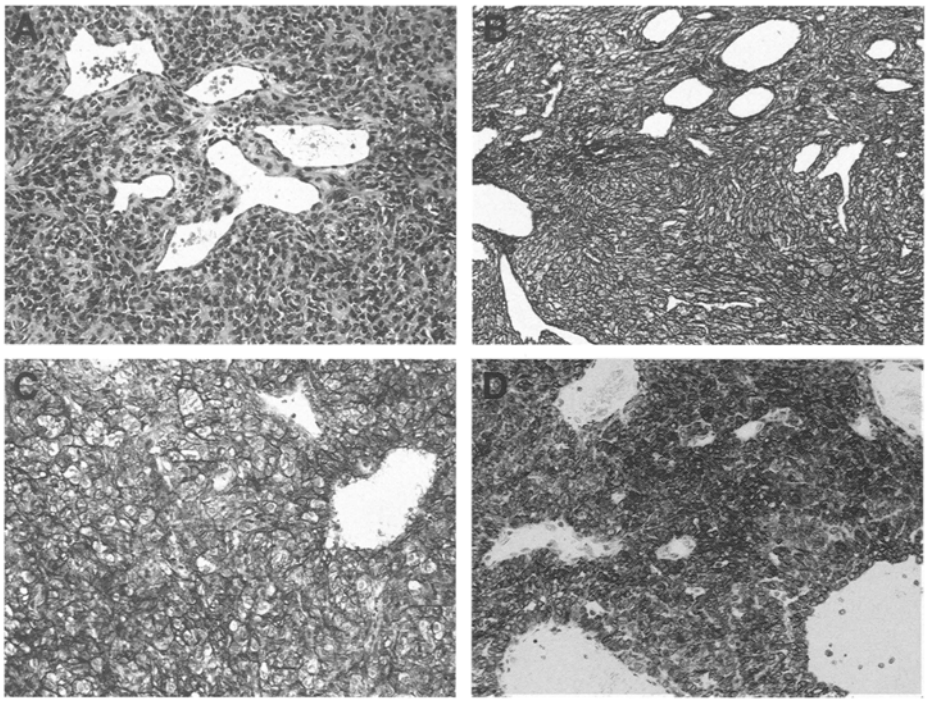


Fig. 25. Hemangiopericytoma with increased cellularity, oval to spindled cells, arborizing thin-walled vessels (**A**), increased reticulin deposition (**B**), and immunoreactivity for CD99 (**C**), and bcl-2 (**D**).

Inflammatory Pseudotumors/Inflammatory Myofibroblastic Tumor (IMT)

- Unknown etiology, but probably neoplastic in some cases
- Clinically and radiologically mimic meningioma
- Dura-based nonspecific plasma cell-rich fibro-inflammatory masses; differential diagnosis includes rheumatoid arthritis, Rosai-Dorfman disease, Erdheim-Chester disease, and a variety of granulomatous disorders

OTHER NON-GLIAL NEOPLASMS

Hemangioblastoma (WHO Grade I)

Clinical

- Adults (30–65)
- Polycythemia (10%)
- Sporadic or von Hippel-Lindau (VHL) disease associated (~20% of cases, gene on chromosome 3p)
- Single or multiple
- Multiple, supratentorial, or occurrences outside the CNS favors VHL association
- Benign

Imaging/Gross

- Intra-axial
- Cerebellum, less often brainstem or cord
- Rare supratentorial or peripheral nerve involvement
- Cyst with enhancing mural nodule

Smear

- Misleading pseudofibrillarity may mimic astrocytoma
- Variable nuclear pleomorphism
- Lipidized stromal cells

Microscopic (Figure 26)

- Highly vascular
- Lipidized stromal cells
- Reticulin rich (reticular variant) or poor (cellular variant featuring lobules)
- Foci of extramedullary erythropoiesis (~10–15%)
- May incite marked intra- and peritumoral pilocytic gliosis
- Inhibin+, NSE+, S-100+, GFAP±, EMA–

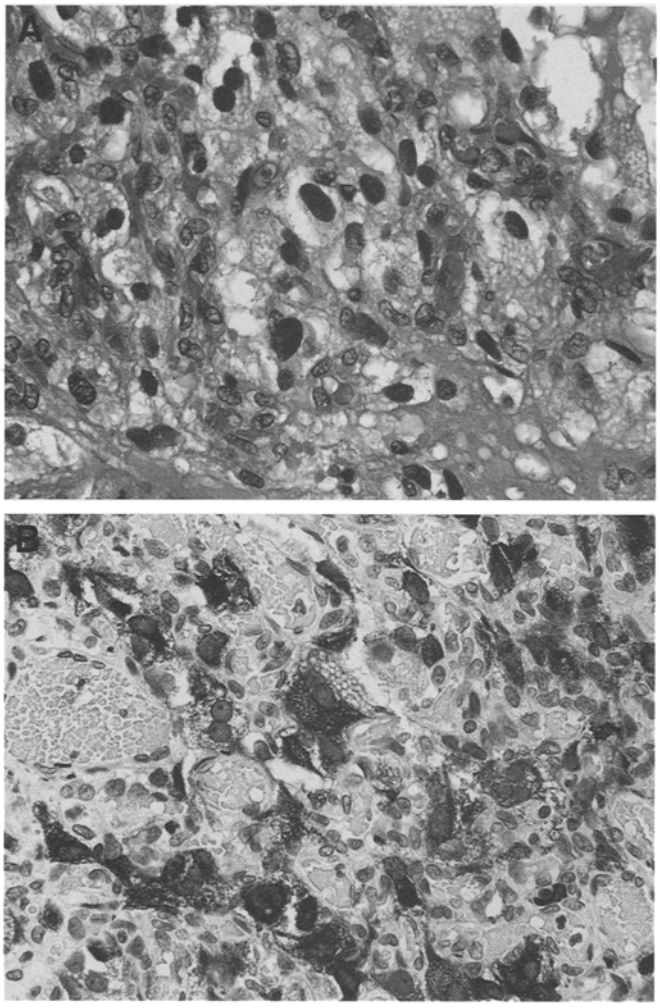


Fig. 26. Hemangioblastoma with foamy stromal cells **(A)** and inhibin positivity **(B)**.

Differential Diagnosis

- Pilocytic astrocytoma (reticulin–; lacks lipidized cells)
- Metastatic renal cell carcinoma (EMA and/or CK+, CD10+, Inhibin–)

Craniopharyngioma

Adamantinomatous Craniopharyngioma (WHO Grade I)

Clinical

- Children/occasional adults
- Diabetes insipidus
- Frequently recurs
- Significant morbidity and long-term mortality due to hypothalamic injury, despite benign histology

Imaging/Gross

- Suprasellar/3rd ventricle
- Cystic

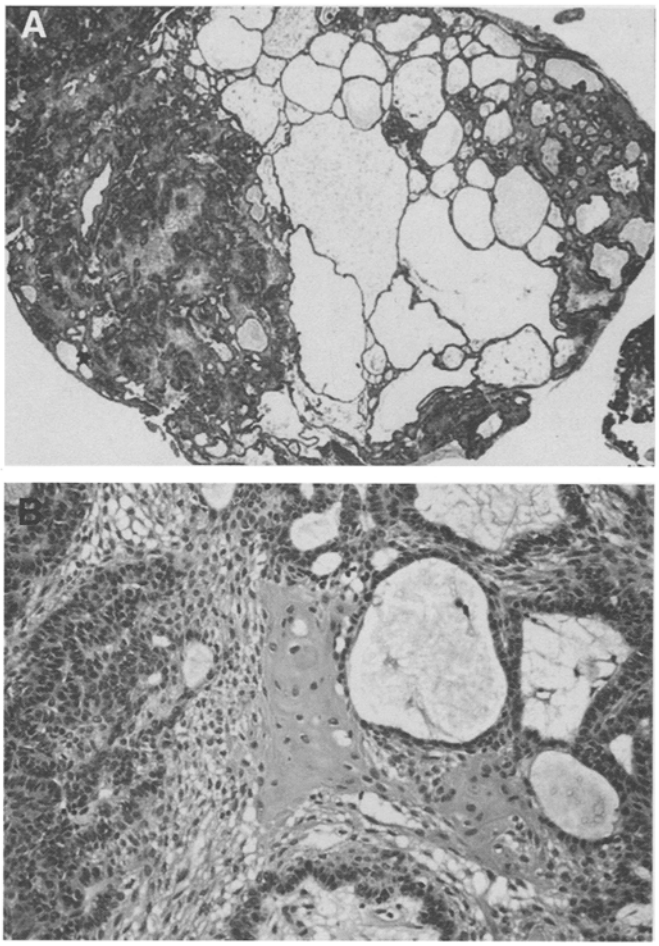


Fig. 27. Craniopharyngioma with cystic degeneration, stellate reticulin, and basal palisading of epithelium **(A,B)**.

- "Motor oil" contents
- Calcifications

Smear

- 3D clusters
- Squamous cells with intercellular bridges
- Wet keratin (diagnostic; resembles ghost cells of pilomatrixoma)
- Cholesterol crystals (well seen in polarized light)

Microscopic (Figure 27)

- Resembles adamantinoma of bone and ameloblastoma of jaw
- Complex layered squamous epithelium consisting of: basal palisading columnar cells, loosely disposed cells with processes (stellate reticulum), a malpighian-like layer, and a keratin producing layer.
- Wet keratin that may undergo calcification
- Xanthogranulomatous, cholesterol-rich debris
- Infiltrative growth
- Accompanying pilocytic gliosis

Differential Diagnosis

- Papillary craniopharyngioma (nonkeratinizing squamous epithelium)
- Rathke's cleft cyst (ciliated and mucin-producing respiratory type epithelium. Mucin content common. Squamous metaplasia

Papillary Craniopharyngioma (WHO Grade I)

Clinical

- Adult
- More resectable than adamantinomatous variant
- Lower recurrence rate (4%) than adamantinomatous variant (20%)

Imaging/Gross

- Third ventricle, suprasellar
- Solid/cystic
- Noncalcified
- Cyst fluid clear

Histology

- Demarcated
- Solid sheets undergoing papillary dehiscence
- Nonkeratinizing squamous epithelium
- No granular layer
- Mucin containing goblet cells are a common focal feature

Differential Diagnosis

- Adamantinomatous craniopharyngioma (infiltrative growth, complex, epithelium, wet keratin undergoing calcification, "machine oil-like" cyst content)
- Rathke's cleft cyst (squamous metaplasia beneath respiratory epithelium)

Germ Cell Tumors

Clinical

- Children/young adult
- Parinaud's syndrome (paralysis of upward gaze) in pineal examples
- Precocious puberty (even in non-suprasellar/third ventricular examples)
- Male predilection of pineal region lesions
- Treatment varies
- Germinoma radioresponsive
- Mature teratoma resectable
- Nongerminomatous germ cell tumors variably chemosensitive

Imaging/Gross

- Pineal and/or suprasellar location
- Solid or cystic
- Calcification common in teratomas

Smear/Histology

- Both identical to lesions in testis
- Immature teratoma = primitive (fetal-like) tissue; often feature CNS elements
- Malignant teratoma = carcinoma/sarcoma elements supervening upon a teratoma

Prognosis

- Good: pure germinoma, mature teratoma
- Intermediate: immature teratoma, mixed germ cell tumor (predominantly germinoma or teratoma)
- Poor: choriocarcinoma, yolk sac tumor, embryonal carcinoma, malignant teratoma, mixed germ cell tumor (predominantly malignant, non-germinomatous mixtures)

Lymphoma/Leukemia

Primary CNS Lymphoma

Clinical

- Elderly or immunosuppressed patients
- Steroid responsive initially
- Death within 2 years in most, though prognosis improving with methotrexate-based therapy

Imaging/Gross

- Single or multiple, homogenously enhancing lesions
- Periventricular
- Supra- and/or infratentorial
- Brainstem and spinal cord uncommon
- Disappearance of lesions after steroid therapy

Smear/Histology (Figure 28)

- Infiltrative
- Angiotropic, but permeates parenchyma
- >95% are diffuse large B-cell type
- Component of small, reactive CD3+ T cells
- Necrosis and EBV-immunopositivity often seen in AIDS/immunosuppression

Differential Diagnosis

- Oligodendroglioma (superficial, S-100+, LCA–, CD20–)
- Inflammatory/demyelinating process demarcated plaques, uniform myelin loss, numerous KP-1+ macrophages)
- Small cell carcinoma (CAM5.2+, SYN+, CD20–)
- Small cell GBM (GFAP±, S-100+, CD20–)
- Medulloblastoma/PNET (SYN+, CD20–)
- Melanoma (HMB-45+, S-100+, CD20–)

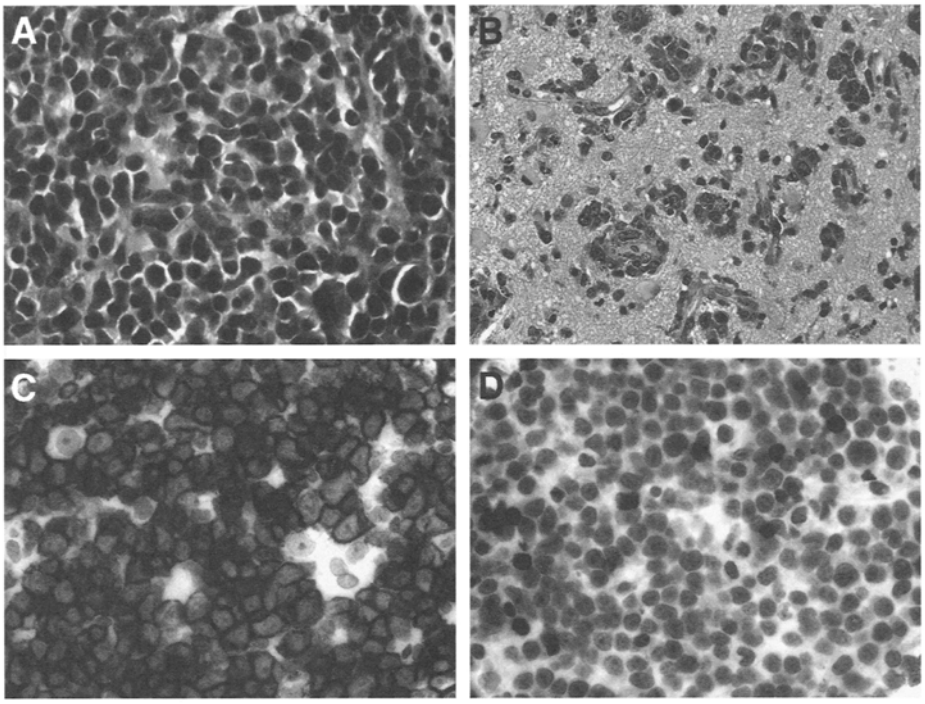


Fig. 28. Primary CNS lymphoma is typically a diffuse large cell lymphoma with discohesive **(A)** and perivascular or angiocentric **(B)** growth patterns. Nearly all are positive with the B-cell marker, CD20 **(C)**, though small mature CD3-positive T-cells are also invariably present **(D)**.

Secondary (Systemic) Lymphoma/Leukemia

- Epidural, dural or leptomeningeal are principle sites
- Cranial or spinal nerve roots involvement common
- Parenchymal involvement is secondary by inward extension along perivascular spaces
- Intravascular lymphoma: rare form of lymphoma featuring infarcts due to plugging of vessels (see Vascular Disorders)

Metastases

Clinical

- Hematogenous (parenchymal: lung primary; meningeal: breast/GI/prostate primary)
- Perineural (direct extension from head and neck primary)
- Direct extension from bone
- Poor prognosis
- Overall improved survival may be seen with resection of solitary metastases (e.g., renal cell carcinoma, melanoma)

Imaging/Gross

- Single or multiple
- Gray-white junction
- Leptomeningeal carcinomatosis is recognized clinicopathologic variant; often gastric carcinoma
- Contrast enhancing

Smear/Histology

- Discrete margin
- Limited parenchymal spread in small cell carcinoma and melanoma
- Adenocarcinomas most common; other carcinomas less so
- Melanoma relatively common
- Sarcomas rare

Patterns

- Hemorrhagic:
  - Melanoma
  - Renal cell carcinoma
  - Choriocarcinoma
- Young patient:
  - Germ cell tumors
  - Alveolar soft parts sarcoma
- Unknown primary:
  - Adenocarcinoma (lung or breast are CK7+, lung is often TTF1+, GI are CK20+ (seeTable 25-2)
  - Melanoma (skin; primary may have regressed)

TRAUMA (SEE CHAPTER 3)

Closed Head Injury

- Most common form
- Dura intact; may be associated with serious brain injury despite minor or no external injuries

Open Head Injury

- Dura breached and brain exposed to environment; increased risk of infection in survivors

Blunt Head Injury

- Common cause of traumatic death
- Generally multilevel, involving external to internal structures (e.g., scalp laceration, skull fracture, subdural hematoma, cortical contusion, internal contusion)

Skull Fractures

- Need to strip dura for adequate examination
- Linear: follows direction of force and spreads along paths of least resistance
- Depressed: impact over small surface (e.g., hammer)
- Comminuted: impact over larger surface (e.g., brick)
- Compound: associated with scalp laceration
- Basilar: often complex, patterns include hinge and ring fractures (e.g., MVA, landing on feet from high fall, or forceful hyperextension)
- "Raccoon eyes": hemorrhage into eyelids due to orbital roof fracture
- "Battle sign": hemorrhage overlying mastoid region due to petrous temporal fracture

Epidural Hematoma

- Relatively uncommon: usually result of skull fracture with laceration of middle meningeal artery
- Lens-shaped with depression of convexity

Subdural Hematoma (Figure 29A)

- Common, often fatal, usually traumatic; skull fracture in 50%
- Caused by tearing of bridging veins
- Direct impact not necessary (e.g., shaken infant); common in child abuse
- Organized examples have thin inner membrane and a thick outer membrane attached to dura may coexist with diffuse axonal injury (DAI)

Subarachnoid Hemorrhage (Figure 29B)

- Trauma is the most common cause; may accompany contusion, laceration, or subdural hematoma
- Nontraumatic form is associated with ruptured aneurysms and other vascular malformations
- Hemorrhage extends into sulci and Virchow-Robin spaces

Cortical Contusion

- Maximum damage over gyral crests with sparing of sulci (opposite of pattern in infarct):
  - Coup: adjacent to point of impact; most prominent with mobile object striking stationary head (e.g., hammer)
  - Contacoup: opposite point of impact; prominent when mobile head hits stationary object (e.g., frontal lobe injury when hitting back of head during fall):
    - Common sites include fronto-orbital and temporal poles where they contact irregular bony surfaces of the skull base

Pontomedullary Transection (Brainstem Avulsion)

- Results from extremely forceful hyperextension
- Partial or complete; instantly fatal in most cases

Gunshot Wounds (see Chapter 3)

- An unfortunately common cause of death in urban American life, damage generally described in terms of direction of missile trajectory (e.g., entrance wound, bullet tract, exit wound)

Penetrating Wound

- Bullet enters, but doesn't exit

Perforating Wound

- Bullet enters and exits

Entrance Wound

- Abrasion ring:
  - Close or contact: soot deposits and burns
  - Intermediate: "powder tattoo"
  - Distant: no deposits
  - Skull surface bevels in at entrance (wider inner table defect)

Exit Wound

- Skull defect bevels out (wider outer table defect)

Bullet Track: Low Velocity Missiles

- Associated with contusion-lined cavity; high-velocity missiles: extensive damage (avulsion, "burst lobe")

Secondary Track

- Caused by ricochet of bullet off inner table of skull

Spinal Cord Trauma

- Motor vehicle accident and falls most common cause

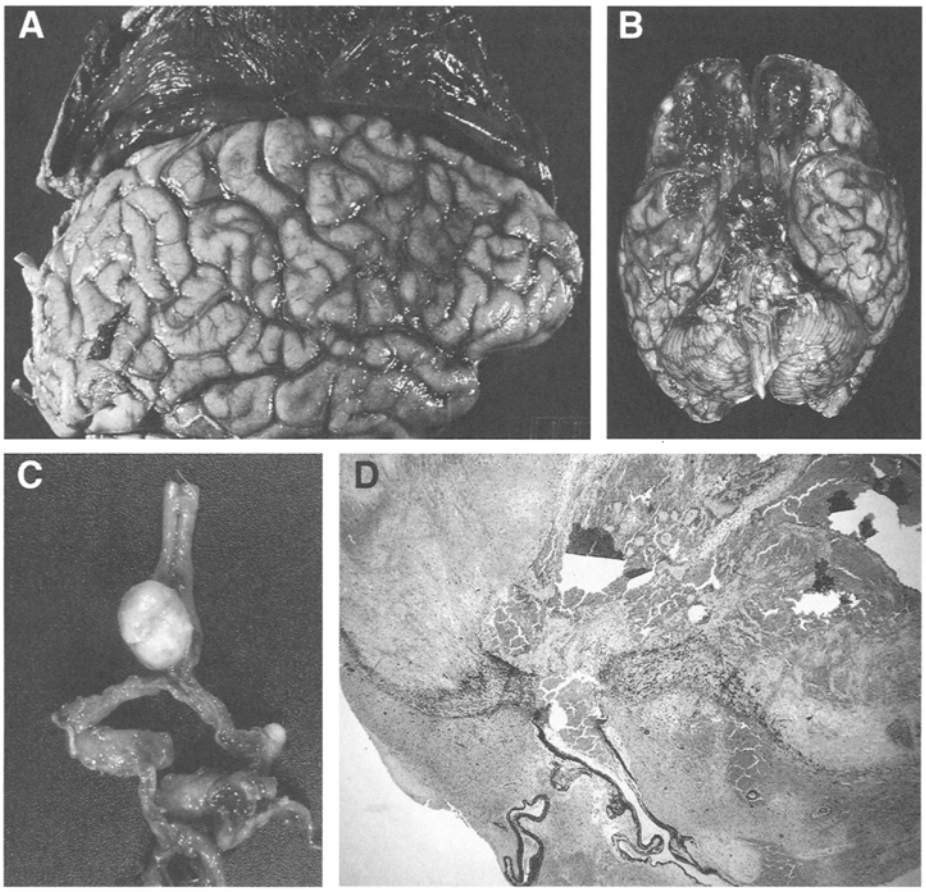


Fig. 29. Chronic subdural hematoma with typical attachment to overlying dura **(A)**. Subarachnoid hemorrhage at the base of the brain **(B)** is often due to a rupture Berry aneurysm, in this case located around the anterior communicating artery **(C)**. A stain with smooth muscle actin shows the thinning and disruption of the vascular wall within the aneurysmal dilatation **(D)**.

Upper Cervical Injuries

- Usually instantly fatal and associated with brain injury

C4-C8 Injuries

- Most common site of nonfatal trauma; region susceptible to hyperextension, hyperflexion, etc.

Cervical Spondylosis

- May predispose to hyperextension injuries

Central Cord Necrosis

- Common in non-penetrating injury; generally fusiform and extending over multiple segments

Post-Traumatic Syringomyelia

- Late complication of central cord necrosis; may extend rostrally over time, causing neurologic deterioration in paraplegics

ISCHEMIC/ANOXIC/VASCULAR DISORDERS

Cerebral Infarct [Cerebrovascular Accident (CVA) "Stroke"] (Figure 30)

- Obstruction of major arterial (ACA, MCA, PCA, basilar, vertebral) or smaller branch (e.g., PICA, cortical/leptomeningeal) vascular distributions
- Cerebral atherosclerosis, thromboembolic disease, or combination; individual susceptibility due to variations in anatomy of circle of Willis anatomy and its collaterals
- Embolic disease from heart or neck vessels (e.g., carotid bifurcation); MCA territory most common (straight shot); often multiple and hemorrhagic
- Time course of infarct (*see* **Table 5**)

Anoxic Encephalopathy (Global Ischemic Injury)

- Systemic circulatory failure/hypotension (e.g., resuscitation after cardiac arrest)

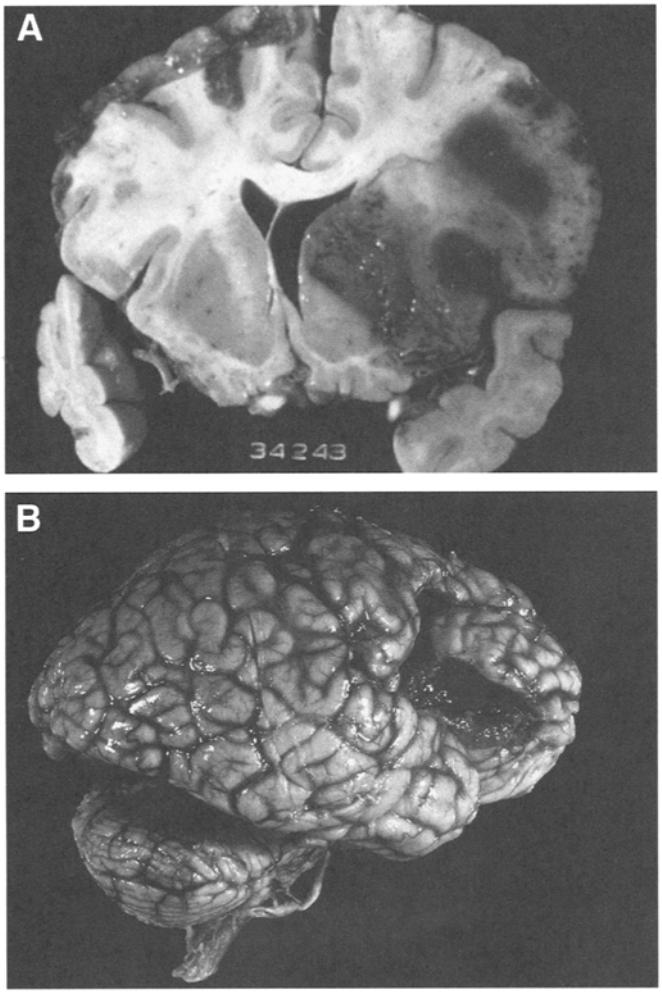


Fig. 30. Typical wedge shaped distribution of this acute hemorrhagic infarct involving the MCA territory **(A)**. Remote infarcts undergo cystic degeneration **(B)**.

- "Selective Vulnerability" = regional (e.g., hippocampus CA1 and CA4 > CA2 and CA3) and cellular (e.g., neuronal > glial) variations in susceptibility to ischemia
- Includes hippocampal necrosis, Purkinje cell necrosis, watershed infarcts, selective neuronal necrosis, laminar/pseudolaminar necrosis, and "brain death syndrome" (see below)

Hippocampal Necrosis (Figure 31A–B)

- Affects pyramidal neurons of Sommer's sector (CA1) and sometimes endplate (CA4) with relative sparing of CA2 and CA3

Purkinje Cell Necrosis (Cerebellar Cortex)

- Red Purkinje cells with intact internal granular cell neurons

Watershed (Borderzone) Infarct

- Typically linear and hemorrhagic, between two or all three of the major arterial zones of vascular supply (e.g., ACA and MCA territories)
- Susceptibility of endarterial vascular supply (i.e., tissue farthest from arterial source is ischemic first)

Selective Neuronal Necrosis

- Scattered necrotic neurons in cortex (especially depths of sulci) and/or deep gray matter with preservation of intervening cells

Laminar/Pseudolaminar Necrosis (Figure 31C–D)

- Extensive, typically bilateral linear intracortical infarcts involving entire cortex (laminar) or the middle to deeper layers (pseudolaminar)

Brain Death Syndrome ("Respirator Brain")

- Extensive global ischemic insult
- Marked edema results in increased intracranial pressure (ICP) rising above systemic blood pressure, thus preventing brain perfusion

Table 5. Gross and Micro Features of Cerebral Infarct

	Gross features	*Micro features*
Acute (hrs-days)	Soft, edematous; Anemic = non-reperfused Hemorrhagic = reperfused	Coagulative necrosis, "red dead" neurons, spongy neuropil, mild neutrophil response
Subacute (days-wks)	Partially liquefied	Liquefactive necrosis, neuronal and glial dropout, marked macrophage (Gitter cell) response, reactive capillaries and gliosis at periphery
Chronic (mos-yrs)	Cystic cavity with collapse of surrounding tissue	Cyst lined by "gliotic scar" (no collagen), parenchymal loss in vascular distribution, subpial sparing (as opposed to old contusion); ± hemosiderin, ± scattered macrophages

- If "life" maintained by respirator (too philosophical to discuss here, but legally, brain death = patient death), brain autolysis occurs in vivo. Note: respirator does not cause the injury, thus the objection to the term "respirator brain"
- Gross and microscopic appearance is identical to postmortem autolysis (i.e., without reactive changes)

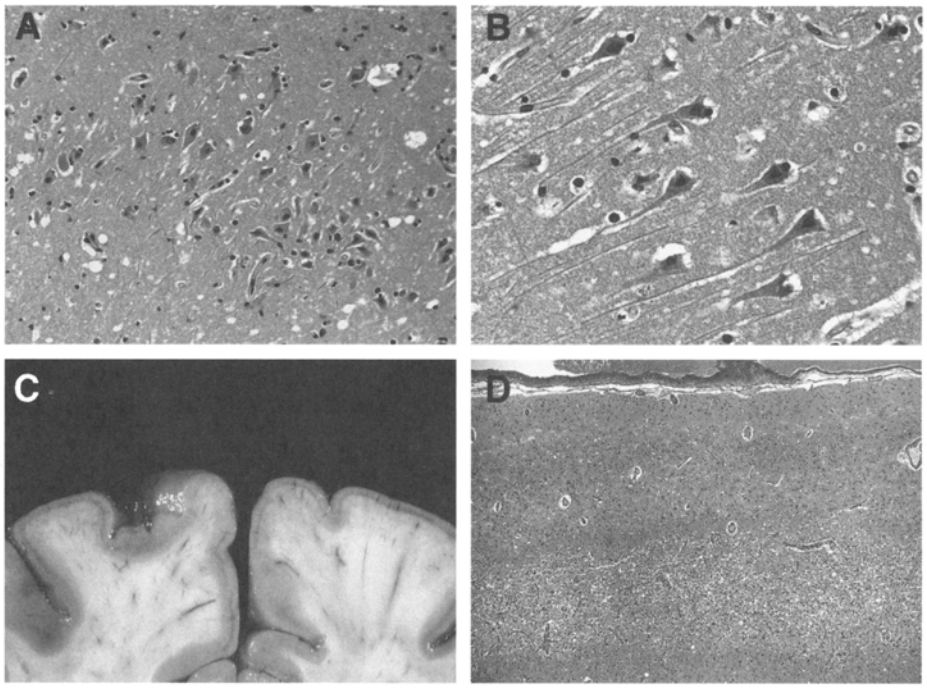


Fig. 31. Patterns of selective vulnerability associated with global hypoxia include eosinophilic neuronal necrosis of hippocampal sector CA1 **(A,B)** and laminar cortical necrosis with middle to deeper cortical layers most affected **(C,D)**.

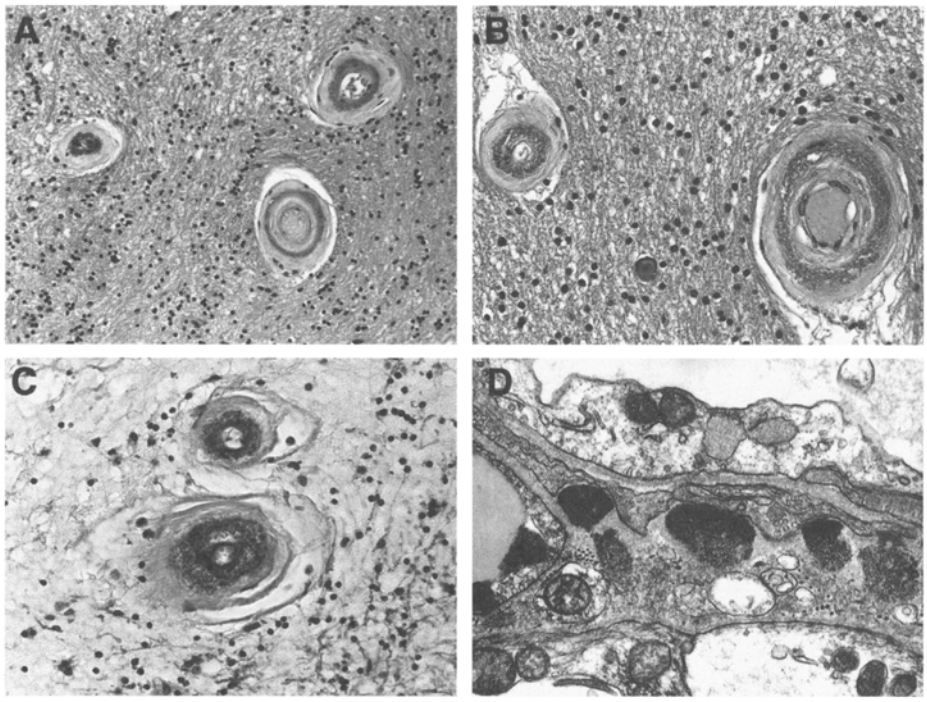


Fig. 32. CADASIL is characterized by vascular thickening with granular eosinophilic deposits in the media or arteries and arterioles **(A,B)**. They are PAS positive **(C)** and correspond to pockets of granular osmiophilic deposits at the edges of smooth muscle cells ultrastructurally **(D)**.

Multi-infarct Dementia

- Overdiagnosed clinically; many have Alzheimer's Disease with one or more incidental infarcts at autopsy; diagnosis requires extensive cortical damage, typically with a stepwise clinical course
- Rare cases are due to extensive cortical microinfarcts secondary to small vessel leptomeningeal disease with gross appearance of "granular atrophy"

Venous Infarcts

- Thrombosis of dural sinuses or cerebral veins; may complicate infection or hypercoagulable state
- Typically hemorrhagic, bilateral, and affects white > grey matter

Small Vessel Disease/Deep Infarcts

- Arteriolar disease with deep grey and white matter infarcts, myelin rarefaction, and/or frank demyelination

Arteriolosclerosis

- Associated with hypertension, diabetes, and advanced age

Binswanger's Disease

- Rare complication of hypertension with diffuse cerebral white matter disease and clinical dementia

CADASIL (Cerebral Autosomal Dominant Arteriopathy With Subcortical Infarcts and Leukoencephalopathy) (Figure 32)

- Familial neurodegenerative disorder associated with missense mutations in the Notch 3 gene on chromosome 19q
- Mid-late adult onset dementia and/or pseudobulbar palsy; infrequent hemorrhage
- Identical distribution to Binswanger's disease, except no hypertension
- Pathognomonic PAS+; granular, electron dense deposits in media of small and perforating arterioles

"Leukoaraiosis"

- Radiologic term for white matter changes often incidentally found in elderly; thought to represent small vessel ischemic changes

Related Disorders (Patterns of Selective Vulnerability)

Hypoglycemic Brain Injury

- Rare in pure form
- Resembles ischemia except no gross infarcts; relative sparing of Purkinje cells
- Pseudolaminar necrosis affects superficial laminae (rather than the middle/deep layers as in hypoxia)

Carbon Monoxide Poisoning

- CO outcompetes O_2 for hemoglobin binding

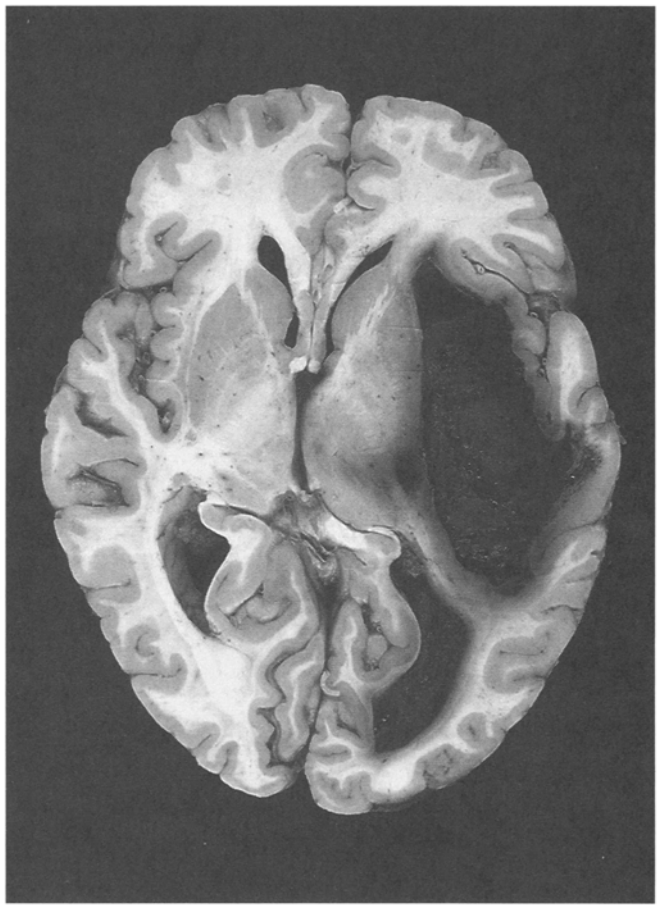


Fig. 33. Large hypertensive intracerebral hemorrhage with displacement, rather than destruction of adjacent parenchyma.

- Resembles hypoxia except that there is selective vulnerability for globus pallidus and white matter
- Acute death: cherry red discoloration, body and brain
- Delayed death: pallidal necrosis, white matter necrosis/demyelination, and/or cortical, hippocampal, and cerebellar ischemic damage

Methanol Poisoning

- Metabolized by liver to formaldehyde and formic acid, which causes most of the damage
- Selective vulnerability (necrosis): retinal ganglion and photoreceptor cells (blindness); basal ganglia (putamen and claustrum)

Intracranial Hemorrhage (also see Trauma)

Berry (Saccular) Aneurysm/Subarachnoid Hemorrhage (SAH) (Figure 29B–D)

- Saccular outpouchings (as opposed to fusiform atherosclerotic aneurysms of posterior circulation) at bifurcations in circle of Willis, especially the anterior circulation
- Risk of rupture is proportional to size and is associated with high mortality/morbidity

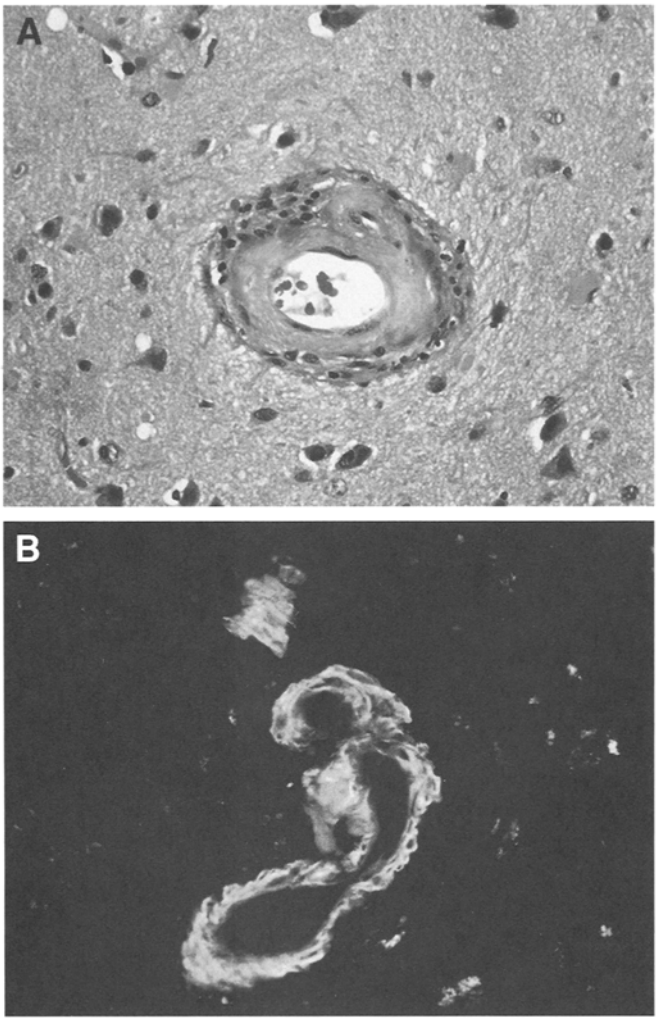


Fig. 34. Amyloid angiopathy involving a superficial cortical vessel (**A;** photo courtesy of Dr. Ben Tu, Washington U., St. Louis, MO), with confirmation on thioflavin S stain **(B)**.

- Higher incidence in polycystic kidney disease, Ehlers-Danlos syndrome, Marfan syndrome and neurofibromatosis type 1 (NF1)

Hypertensive Intracerebral Hemorrhage (Figure 33)

- Deep, especially basal ganglia, thalamus, cerebellum, and pons
- Displaces, rather than destroys tissue (unlike hemorrhagic infarct); thus, once resolved/resorbed, leaves a slit-like (rather than rounded) space

Cerebral Amyloid Angiopathy (CAA) and Superficial Lobar Hemorrhage (Figure 34)

- Affects the elderly
- βA4 amyloid (CNS form, identical to that in neuritic plaques) deposited in leptomeningeal and superficial cortical vessels
- Most Alzheimer's patients have CAA, but those presenting with lobar hemorrhage are not always demented

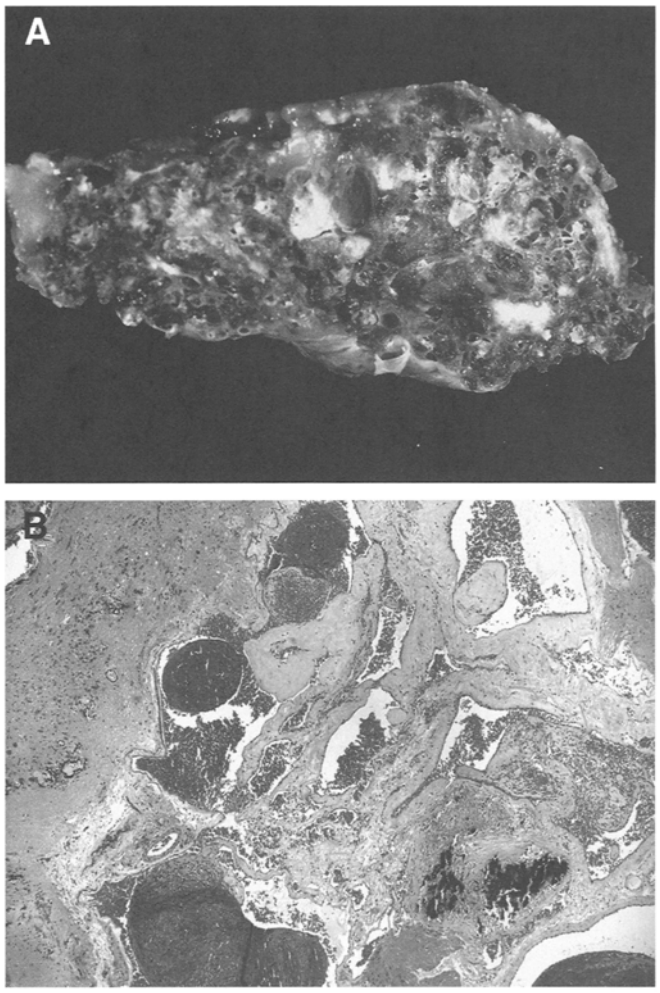


Fig. 35. Large cavernous angioma yielding sponge-like gross appearance **(A)** with dilated, partially hyalinized vascular spaces and surrounding hemosiderin deposition histologically **(B)**.

- Clinical differential includes intratumoral hemorrhage, so it may be seen as a surgical specimen

Vascular Malformations

Berry (Saccular) Aneurysm

- *See* **Figure 29C,D**

Arteriovenous Malformation (AVM)

- Mostly intracerebral, occasionally spinal
- Present with hemorrhage in more than half; seizures and headaches are also common
- Consist of tortuous arterial, venous, and arteriovenous vessels, often with chronic degenerative changes (hyalinization, Ca^{2+}, thrombosis, hemosiderin, gliosis)
- Extensive intervening brain parenchyma; arterial component is elastin+

Cavernous Angioma ("Cavernoma") (Figure 35)

- Large, thin-walled, elastic stain and actin immunonegative vessels, and often minimal intervening brain parenchyma

- Grossly spongy, chronic degenerative changes (hyalinization, Ca^{2+}, thrombosis, hemosiderin, gliosis)
- Incidental finding or associated with hemorrhage and/or seizures; 1% chance of bleed/year

Others

- Venous angiomas and capillary telangiectasias consist of thin-walled vessels with intervening brain parenchyma devoid of reactive or degenerative changes
- Typically cerebral white matter or pons; often incidental

Other Vascular Disorders

Vasculitis

- Often secondary to meningitis or other inflammatory/infectious process
- Primary CNS vasculitis is commonly granulomatous; probably autoimmune; inflammation confined to vessel wall and causes secondary infarcts in young to middle aged adults:
  - Poor prognosis unless treated aggressively with immunosuppressives
  - May be missed on biopsy due to patchy distribution; angiography helpful

Intravascular Lymphoma

- Previously termed "angioendotheliomatosis," but it is not an endothelial tumor
- Rather, it is a highly aggressive, systemic lymphoma largely confined to intravascular spaces of various organs including the CNS
- Most present with confusing neurologic manifestations due to vascular occlusion with multiple infarcts
- Diagnosis is often missed antemortem
- Usually large cell morphology, B-cell phenotype

NEURODEGENERATIVE DISORDERS

Summary Table (Table 6)

- Neurodegenerative disorders are progressive, fatal, and usually idiopathic with regional atrophy, neuronal loss, and gliosis

Alzheimer's Disease (AD) (Figure 36)

- Most common neurodegenerative disorder
- Incidence increases with age
- Varying criteria, but diagnosis based on neocortical (not hippocampal) burden of neuritic plaques (NP) and/or neurofibrillary tangles (NFT), highlighted by silver stains (Bielschowsky, Bodian, Gallyas, etc.) or immunostains for Tau (microtubule associated protein)
- Coexistent cerebral amyloid angiopathy (CAA) in most (Figure 34)
- βA4 amyloid (CNS form of amyloid) in both NPs and CAA
- NFTs in neuronal perikarya and neuritic processes are composed of paired helical filaments on EM
- Majority are sporadic
- Higher risk associated with apoE4 and lower risk with apoE2 alleles
- ~10% familial forms (autosomal dominant in most) with younger age of onset; AD1 (APP or amyloid precursor protein) gene on chr. 21, AD2 on chr. 19, AD3 on chr.14, AD4 on chr. 1
- Down syndrome patients get early onset AD, probably due to overexpression of AD1 gene

Frontotemporal Lobar Degeneration (FTLD)

- Third most common cause of dementia after AD and DLBD in some series
- Frontal lobe symptoms include personality changes, dysinhibition, etc.
- Nonspecific pathology (neuronal loss and gliosis) without NFTs, NPs, Lewy bodies, Pick bodies, swollen neurons, etc. (i.e., diagnosis of exclusion)
- Generally sporadic and idiopathic
- Considered by some to be a form of Pick's disease without Pick bodies (analogous to solid variants of cysts in surgical pathology)
- Occasionally associated with MND (ALS/frontal lobe dementia)

Multi-infarct Dementia

- Overdiagnosed clinically; many have AD changes with one or more incidental infarcts at autopsy
- Requires extensive damage with stepwise clinical course
- Rare cases grossly associated with "granular atrophy" due to extensive cortical microinfarcts secondary to small vessel leptomeningeal disease

Idiopathic Parkinson's Disease (IPD) (Figure 37)

- Most common cause of parkinsonism (masked facies, shuffling gate, resting tremor, etc.)
- Other forms of parkinsonism are usually associated with additional symptoms and are typically not L-Dopa

Table 6. Neurodegenerative Disorders, The Minimalist's Approach

Disorder	*Clinical*	*Regions of pathology*	*Histology*	*Genetic/other associations*
Alzheimer's Ds. (AD)	Dementia	Cortex, Mesial temperal lobe, Nucleus basalis	Neurofibrillary tangles, plaques, amyloid angiopathy	Apo E4 allele, Ad1 (APP) gene-chr. 21 (Down syn.), AD2-AD4 genes
Frontotemporal lobar degeneration	Dementia, frontal lobe sx's	Frontotemporal cortex	Neuronal loss and gliosis only (Dx of exclusion)	ALS/dementia complex (Rare)
Pick's Ds.	Dementia, frontal lobe sx's	Frontotemporal cortex	Pick bodies, swollen neurons (Pick cells)	Rare familial associations
Parkinson's Ds. (IPD)	Parkinsonism, ± Dementia	Subst. Nigra, Locus ceruleus	Lewy bodies (LB)	Combined AD/IPD, DLBD, LB variant of AD
Huntington's Ds. (HD)	Chorea, Dementia	Caudate, Putamen	Neuronal loss and gliosis only	Huntington gene (chr 4p), aut.dom., triple repeat expansion
Creutzfeldt-Jakob Ds. (CJD)	Dementia, myoclonus, EEG findings	Gray matter (cerebral/ cerebellar cortex, deep gray)	Spongiform change, amyloid (Kura) plaques	PrP gene/protein (all forms), Bovine SE and nvCJD, GH extracts, grafts, etc. Also iatrogenic CJD, cannibalism and Kuru
Progressive Supranuclear Palsy (PSP)	Parkinsonism, upward gaze palsy, ± dementia	Subcortical, esp. brainstem nuclei, globus pallidus, and dentate	Neurofibrillary tangles, (globose type), glial inclusions, neuropil threads	
Corticobasal Degen. (CBD)	Dementia, "alien limb" syndrome, parkinsonism	Frontotemporal cortex, subst. nigra, other subcortical nuclei	Swollen neurons, neurofibrillary tangles, glial inclusions, nueropil threads	
Multisystem atrophy (MSA)	Striatonigral degeneration (parkinsonism) ± olivoponto-cerebellar atrophy (ataxia), ± Shy-Drager syn (autonomic dysfunction)	Putamen, subst. nigra, locus ceruleus, basis pontis, Purkinje cells	Glial inclusions, neuropil threads	
Amyotrophic Lateral Sclerosis (ALS)/MND	Upper and lower motor neuron disease (weakness, hyperreflexia, fasciculations)	Ant. horns and roots, lat. columns, XII cr. n.	Myelin pallor, neuronal loss, Bunina bodies, LB-like inclusions	5–10% familial; minority with superoxide dismutase (SOD) gene mutations
Spinal muscular atrophies (SMA)	Type 1 infantile (Werdnig-Hoffman)-floppy infant, LMN only	Ant. horns + roots, skeletal muscle atrophy	Myelin pallor, neuronal loss, characteristic muscle histology in infantile form	Aut. rec., gene(s) on chr. 5q
Friedrich's ataxia	Ataxia, cardiac dz, neuropathy	Post. columns + roots, periph. n., lat. columns, dentate, sup. cerebellar ped.	Myelin pallor, neuronal loss	Aut. rec., frataxin gene (chr. 9q), triple repeat expansion
Spino-cerebellar ataxias (SCA)	Ataxia, variable sx's depending on variant, some overlap with MSA	Variable, Purkinje cells, OPCA, spino-cerebellar tracts, MND (type 3)	Myelin pallor, neuronal loss	Aut. dom. in most, caused by triple repeat expansion
Neuroaxonal dystrophies	Infantile and adult forms, Hallervorden-Spatz Dz (HSD)	Widespread in infantile, Globus pallidus in HSD	Axonal spheroids (swellings) + iron deposition in HSD	Aut. rec. in most, genes not yet identified
Lafora's dz (Myoclonic epilepsy)	Seizures, myoclonus, dementia, visual sx's	Cortex, globus pallidus, nigra, thalamus, PNS, cerebellum	Lafora body	Aut. rec., gene on chr. 6q

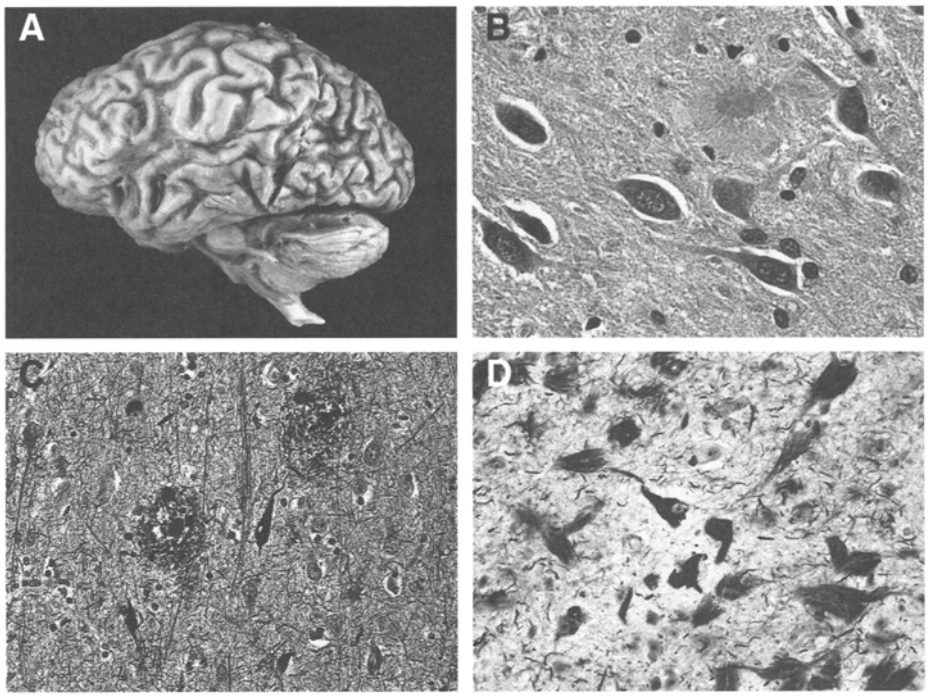


Fig. 36. Alzheimer's disease characterized by generalized cortical atrophy **(A)**, a neuritic plaque with an amyloid core on H&E **(B)**, and cortical plaques and tangles on Bielschowski silver stain **(C)**. The latter also highlights more lightly stained ghost tangles in the hippocampus, where neurons have died off **(D)**.

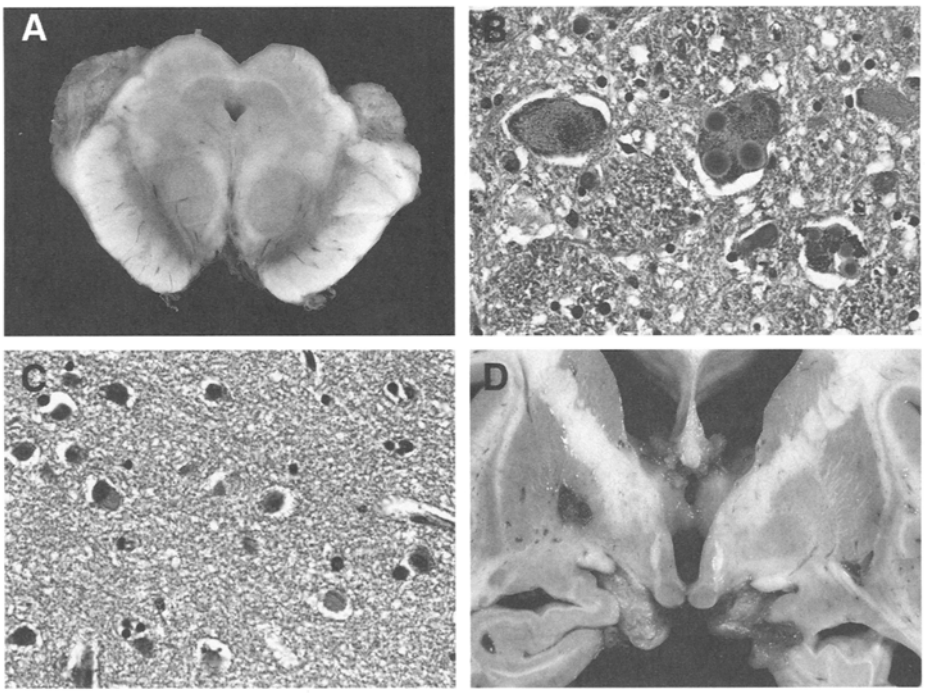


Fig. 37. Idiopathic Parkinson's disease and diffuse Lewy body disease are characterized by pallor of the substantia nigra, particularly the lateral portions **(A)**, Lewy bodies in residual nigral neurons **(B)**, and more subtle Lewy bodies in small cortical neurons, particularly in the cingulated gyrus **(C)**. Pallidotomy is a common surgical approach for alleviating some of the involuntary movements **(D)**.

responsive ("Parkinson's Plus"), including PSP, CBD, MSA, postencephalitic parkinsonism, ALS/dementia/ Parkinsonism of Guam, dementia pugilistica, drug-induced (MPTP) parkinsonism, etc.

- Often affects lateral substantia nigra most severely (Lateral = Least pigment, Medial = Most pigment)
- Lewy body (LB) = diagnostic hallmark; immunoreactive for ubiquitin and alpha-synuclein
- Dementia not uncommon; most due to coexistent AD (AD/IPD) and/or cortical Lewy bodies, others likely subcortical in nature
- If cortical LBs also found, diagnosis = diffuse Lewy body disease (DLBD) and is often associated with psychiatric symptoms; if AD changes as well, diagnosis = Lewy body variant of AD
- Some of the symptoms are also partially treated surgically with either ablative techniques (e.g., pallidotomy; Figure 37D) or via deep brain stimulators (e.g. placed into subthalamic nuclei)

Huntington's Disease (HD) (see Chapter 2)

- Autosomal dominant; average onset in fourth to sixth decade (i.e., after procreation, thus allowing for gene survival)
- Slowly progressive; uniformly fatal
- Chorea usually precedes dementia
- Atrophy, neuronal loss, and gliosis of neostriatum (caudate and putamen); some cortical atrophy in late stage disease
- Huntington gene on chr 4q with CAG triple repeat expansion (<37 copies = normal; >37 copies = disease)
- Genetic anticipation = younger onset and increased severity with each generation due to continued expansion of triple repeat
- Repeat expansion most likely to occur in paternal transmissions (i.e., during spermatogenesis)
- Lateral ventricles have "bat wing" configuration due to atrophy of caudate head

Pick's Disease (Lobar Atrophy)

- Rare form of dementia; usually sporadic, <20% familial
- Earlier onset than AD (45–65 years)
- Frontotemporal disease with symptoms similar to frontotemporal lobar degeneration (see above)
- Sparing of precentral gyrus and posterior 2/3 of superior temporal gyrus
- Striking cortical atrophy described as "knife edge" or "walnut brain;" typically asymmetric
- Pick bodies = round, silver stain and Tau immunopositive neuronal inclusions in cortex and mesial temporal structures (hippocampus, amygdala, entorrhinal cortex)
- Pick cells = swollen (achromatic or chromatolytic) cortical neurons which appear large and pink; neurofilament (NF) + and devoid of Nissl substance (thus resembles central chromatolysis)

Creutzfeldt-Jakob Disease (CJD)/ Spongiform Encephalopathies (SE) (Figure 38)

- Rapidly fatal form of dementia
- Uniform worldwide incidence of 1/1,000,000 per year
- Majority are sporadic (i.e., no evidence of infectious or genetic cause)
- 10% familial (PrP gene mutations)
- Rare cases are iatrogenic (infectious) due to inadvertent inoculation of contaminated tissue such as dural graft, corneal transplant, EEG electrodes, or human growth hormone extracts
- Transmissible agent is protease-resistant prion protein (PrP)
- Disease occurs with conformational change of PrP structure into β-pleated sheet (amyloidogenic)
  - Some gene mutations increase likelihood of this conversion (familial)
  - Single pathogenic PrP can induce further protein conversions of wild type protein, thus creating a chain reaction
- Etiology of sporadic CJD is poorly understood, but most likely represents somatic age-related gene mutation or spontaneous protein conversion; homozygosity for Met or Val at codon 129 increases risk of sporadic CJD
- Classic cases have triad of rapid dementia, myoclonus, and periodic short wave activity on EEG
- Classic histology shows triad of neuronal loss, gliosis, and spongiform change (often patchy) defined by small, "sharply defined, punched out" vacuoles in gray matter (cortex and/or deep nuclei)
- Differential Diagnosis includes
  - Status spongiosus: superficial cortical vacuolation commonly seen in end-stage AD; in comparison, CJD typically affects deep cortex or entire cortex
  - Edema or ischemia: vacuoles larger and more ill-defined
  - Artifacts: vacuoles larger and ill-defined; also affects white matter
- Cerebellar amyloid plaques in ~5%

Other Spongiform Encephalopathies (SE)

New Variant CJD (nvCJD)

- Cluster of cases reported from England with epidemiologic link to bovine spongiform encephalopathy (BSE)
- Unusually young age of onset (<40 years)
- Prolonged clinical course
- Dementia less prominent; behavioral changes
- Numerous cerebral cortical and cerebellar amyloid plaques (unique histology among the SEs)
- Patients homozygous for Met at codon 129
- Link to BSE puzzling because bovine skeletal muscle contains little to no pathogenic PrP (as compared to brain)

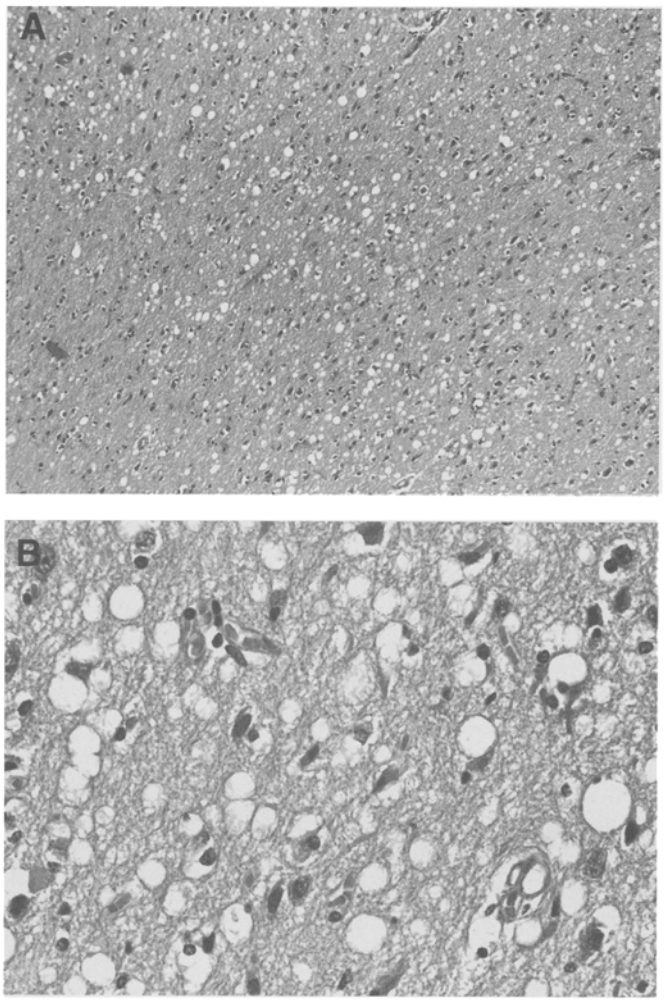


Fig. 38. Creutzfeld-Jacob disease (CJD) is recognized as the prototype spongiform encephalopathy with numerous small punched out vacuoles in regions of both cortical and subcortical gray matter **(A,B)**.

Gerstmann-Sträussler-Scheinker Disease (GSS)

- Rare familial SE with cerebellar ataxia and amyloid plaques in cerebellar molecular layer ("GSS plaques"); various PrP gene mutations

Fatal Familial Insomnia (FFI)

- Autosomal dominant SE with rapid course, sleep disturbances, hallucinations, motor and autonomic symptoms, prominent thalamic, and inferior olive disease; PrP gene mutations

Kuru

- Literally "trembling disease" in the Fore language of New Guinea
- Largely of historic interest; it established the "transmissible agent" from diseased brains
- Linked to cannibalistic ritual involving brains of deceased; now discontinued, the disease is disappearing
- Predominantly a cerebellar disease with "spiked-ball" amyloid ('Kuru") plaques

Progressive Supranuclear Palsy (PSP; Steele-Richardson-Olszewski Disease)

- Supranuclear (upward) gaze palsy due to involvement of oculomotor (CN III) nucleus (similar to Parinaud's syndrome, see pineal tumors)
- Parkinsonism and/or dementia (subcortical), clinical syndrome nonspecific: overlaps with IPD, CBD, MSA, etc.
- Subcortical NFTs with globose configuration
- Tau immunopositive glial cytoplasmic inclusions (GCI) and neuropil threads (overlap with CBD and MSA)

Corticobasal (Ganglionic) Degeneration (CBD)

- Relative newcomer to neurodegenerative world; mostly sporadic
- Cortical and subcortical (basal ganglia, substantia nigra) pathology
- Overlap with Pick's disease; = asymmetrical frontal lobe dementia with swollen neurons
- Overlap with PSP; subcortical NFTs, neuropil threads, and GCIs with parkinsonism
- "Alien limb" syndrome typical, but not always present

Multisystem Atrophy (MSA) (Figure 39)

- Three clinical syndromes, though they often coexist; mostly sporadic:
  - Striatonigral degeneration (SND): putamen and nigra = parkinsonism
  - Olivopontocerebellar atrophy (OPCA): inf. olives, basis pontis, Purkinje cells = ataxia
  - Shy-Drager: intermediolateral spinal columns (thoracic cord) = autonomic dysfunction
- Gross atrophy with subcortical Gallyas and Tau positive GCIs and neuropil threads
- Some overlap with inherited SCAs, PSP, and CBD

Amyotrophic Lateral Sclerosis (ALS)/Motor Neuron Disease (MND) (Figure 40)

- Combined upper (UMN) and lower motor neuron (LMN) disorder, but occasionally only one level is involved
- Weakness, wasting, fasciculations, hyperreflexia, Babinski sign, EMG signs of denervation, etc.
- 5% to 10% familial, of which a minority have mutation in superoxide dismutase (SOD) gene (i.e., most cases are sporadic/idiopathic)
- Clinical mimics may include polio, HIV, HTLV-1, lead poisoning, autoimmune disease, etc. ("Secondary MND")
- Grossly, atrophy of anterior spinal roots is the most prominent pathologic feature

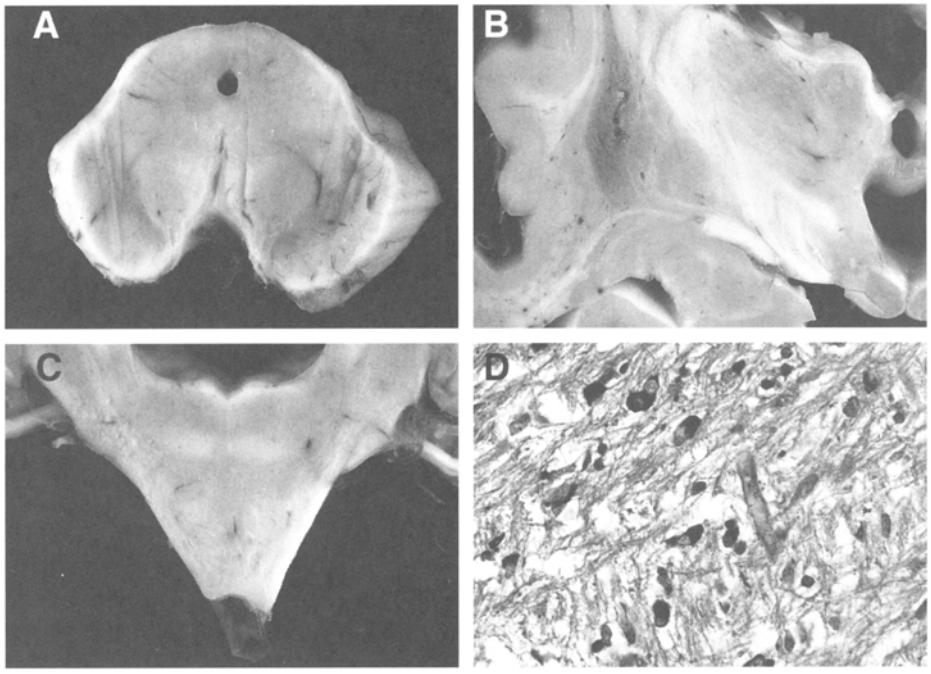


Fig. 39. Multiple systems atrophy (MSA) is another parkinsonian disorder with striatonigral degeneration **(A,B)** and olivopontocerebellar atrophy (**C**; pontine component) representing the two most common gross patterns of involvement. A Gallyas silver stain highlights the typical glial cytoplasmic inclusions **(D)**.

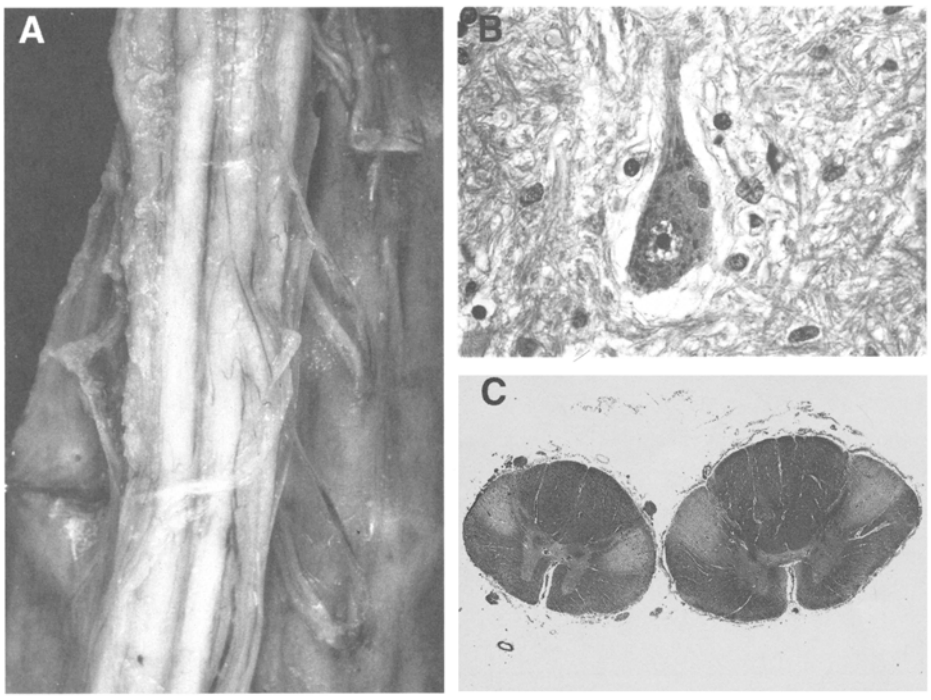


Fig. 40. ALS characterized by atrophy of anterior nerve roots **(A)**, a Bunina body within a motor neuron of the anterior horn **(B)**, and marked pallor of the corticospinal tracts on LFB-PAS stain **(C)**.

- ♦ Histology shows myelin pallor (LFB-PAS or other myelin stain) of lateral columns and anterior roots, loss of anterior horn neurons, Bunina bodies (small eosinophilic cytoplasmic inclusions), Lewy body-like inclusions, and neurogenic pattern of muscle fiber atrophy
- ◆ Rare cases are associated with frontal lobe dementia

Spinal Muscular Atrophy (SMA)

- Group of autosomal recessive MNDs (LMN only), one or more genes on chr. 5q (also see Chapter 2)
- Histology shows loss of anterior horn neurons, atrophy of anterior nerve roots, and neurogenic muscle fiber atrophy
- Variants:
  - Type 1 = infantile (Werdnig-Hoffman disease): most common SMA, "floppy baby," die within a couple of months from respiratory failure; characteristic skeletal muscle histology with large group neurogenic atrophy (small and round, not angulated) and scattered round hypertrophic fibers
  - Type 2 = chronic infantile: intermediate severity with survival into teens
  - Type 3 = chronic, proximal (Kugelberg-Welander syndrome); clinical presentation similar to muscular dystrophy

Friedreich's Ataxia (see Chapter 2)

- Most common form of inherited ataxia; autosomal recessive inheritance
- GAA triple repeat expansion (see HD) in frataxin gene, chr 9q
- Onset in childhood or teens with variable survival (rarely past 30s)
- Cardiomyopathy typical (unlike SCA, see below)
- Ataxia due to combined peripheral neuropathy, atrophy of spinocerebellar tracts (cerebellar afferents), and degeneration of superior cerebellar peduncle (efferents)
- Myelin pallor in posterior columns, dorsal nerve roots, lateral columns, spinocerebellar tracts, superior cerebellar peduncles, and peripheral nerve
- Neuronal loss in dentate nucleus and others

Spinocerebellar Ataxia (SCA)

- Group of inherited, mostly autosomal dominant forms of ataxia
- Number of variants growing (see Chapter 2)
- CAG triple repeat expansions
- Genetic anticipation (see HD)
- Some overlap with MSA, but no GCIs or neuropil threads
- Machado-Joseph disease = form of SCA 3 with parkinsonism, bulging eyes, and anterior horn cell loss (MND) that may mimic ALS

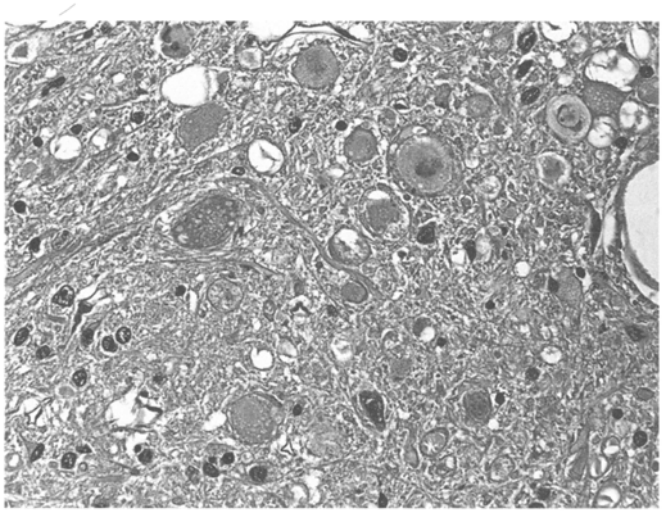


Fig. 41. Infantile neuroaxonal dystrophy (NAD) with numerous axonal swellings or spheroids.

Neuroaxonal Dystrophy (Figure 41)

- Group of neurodegenerative disorders characterized by axonal spheroids (swellings)
- Infantile form = autosomal recessive; widespread CNS and PNS disease; death in early childhood; diagnosis can be made on skin, nerve, conjunctival or rectal biopsy
- Hallervorden-Spatz disease is autosomal recessive in most; early and late onset variants; movement disorder and dementia; characteristic "eye of tiger" sign on MRI; spheroids and iron accumulation in globus pallidus and substantia nigra

Lafora's Disease (Myoclonic Epilepsy)

- Rare neurodegenerative disorder of carbohydrate metabolism
- Autosomal recessive, gene on chromosome 6q
- Onset in childhood or teens; death in early adulthood
- Myoclonic seizures, cerebellar symptoms, dementia
- Widespread CNS and PNS disease
- PAS+ Lafora body (similar to corpora amylacea, polyglucosan bodies, brain sand, "blue balls") that normally accumulates in brain with age, except that they are intracytoplasmic (neuronal processes, glia, Schwann cells, endothelium, skeletal and cardiac muscle, hepatocytes, sweat ducts) and surrounded by haloes
- Diagnosis can be made on skin, liver, or nerve bx

INFLAMMATORY/INFECTIOUS DISEASES

Acquired Demyelinating Disorders

Multiple Sclerosis (MS) (Figure 42)

- Prototypic CNS demyelinating disorder
- Idiopathic, probably multifactorial with genetic and environmental components
- Young adults, multifocal, remitting-relapsing disease, but many exceptions

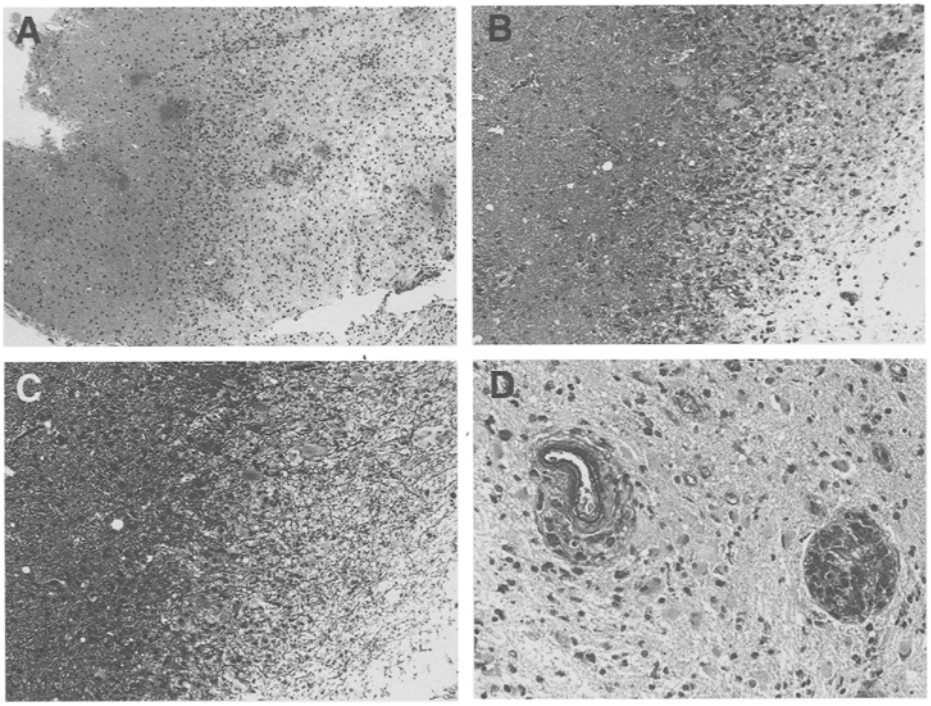


Fig. 42. Biopsy from a patient with active demyelinating disease **(A)**, showing marked loss of myelin on an LFB-PAS stain **(B)** with relative preservation of Bielschowski-positive axons **(C)**. At higher magnification, PAS-positive myelin debris is seen within macrophages **(D**; LFB-PAS stain). See also Figure 1.

- Periventricular, subcortical, optic pathway, brainstem, spinal cord lesions
- Gross = sharply demarcated gray, translucent plaques (i.e., white matter without myelin resembles gray matter)
- Histology = triad of numerous macrophages, perivascular lymphocytes, and gliosis
- LFB-PAS and Bielschowsky or NF immunostain useful to show loss of myelin with relative sparing of axons (in contrast to infarcts); PAS + myelin debris in macrophages
- Activity of plaques relates to degree of inflammation
- "Shadow plaques" represent partial remyelination

Variants

- Marburg's variant = acute fulminant MS; severe, rapid course, often fatal: some overlap with ADEM (see below); occasional solitary lesion mimics tumor
- Devic's variant = optic pathway and spinal cord affected
- Schilder's variant = giant, bilateral plaques, usually in children; some cases have turned out to represent adrenoleukodystrophy (see metabolic disorders)
- Balo's concentric sclerosis = rare pattern with alternating rings of myelin loss and preservation/remyelination

Acute Disseminated Encephalomyelitis (ADEM)/Perivenous Encephalomyelitis

- Spectrum of disorders including postinfectious/ postvaccinial encephalomyelitis and acute hemorrhagic encephalomyelitis (AHEM):
  - Research model = experimental allergic encephalomyelitis (EAE)
- Often, but not invariably associated with inciting viral infection or vaccination
- Acute, fulminant course, though most patients recover
- Probably autoimmune attack against CNS myelin or related antigen (analogous to GBS and PNS myelin) due to cross reactivity with viral antigen
- Widespread, perivenous demyelination, inflammation, and/or hemorrhage
- Brainstem and spinal cord involvement is common and may predominate

Guillain-Barré Syndrome (GBS)/Acute Inflammatory Demyelinating Polyneuropathy (AIDP)

- Rapid, progressive radiculopathy/polyneuropathy with paralysis
- Analogous to ADEM, except PNS
- Inciting events include viral infection, vaccination, surgery, trauma, and neoplastic disease
- Research model = experimental allergic neuritis (EAN)
- CIDP = chronic form with onion bulbs in nerve biopsy representing multiple bouts of demyelination and remyelination

Demyelinating Viral Infections

- HIV, HTLV-1, JC virus (PML), Measles virus (SSPE)

Paraneoplastic Encephalomyelitis

- Rare complication of neoplasia, especially lung (small cell), ovarian, and breast carcinomas
- Associated with serologically detectable antibodies in most; e.g., anti-neuronal antibody (ANNA-1 or anti-Hu)
- Probably cross reactivity of neuronal and tumor antigens; therefore, primary tumor is often small, low stage, and associated with inflammation
- Affects any level of CNS, PNS, and/or muscle; combinations common
- Histology is identical to viral encephalitis
- Clinical disease patterns include limbic, cerebellar, or brainstem encephalitis; opsoclonus/myoclonus; myasthenic syndromes; gastric paresis; etc.
- Lambert-Eaton myasthenic syndrome due to effects of presynaptic calcium channel antibodies
- Patients often die of paraneoplastic disease rather than of tumor

Neurosarcoidosis

- CNS disease in ~5%, though systemic disease may not be obvious
- Predilection for basal meninges, thus affecting cranial nerves, optic pathway, and hypothalamus
- Parenchymal (brainstem, spinal cord, or cerebral) disease may also occur
- Granulomas tend to spread into deeper brain along Virchow-Robin spaces
- Variable clinical course; some fatal despite therapy

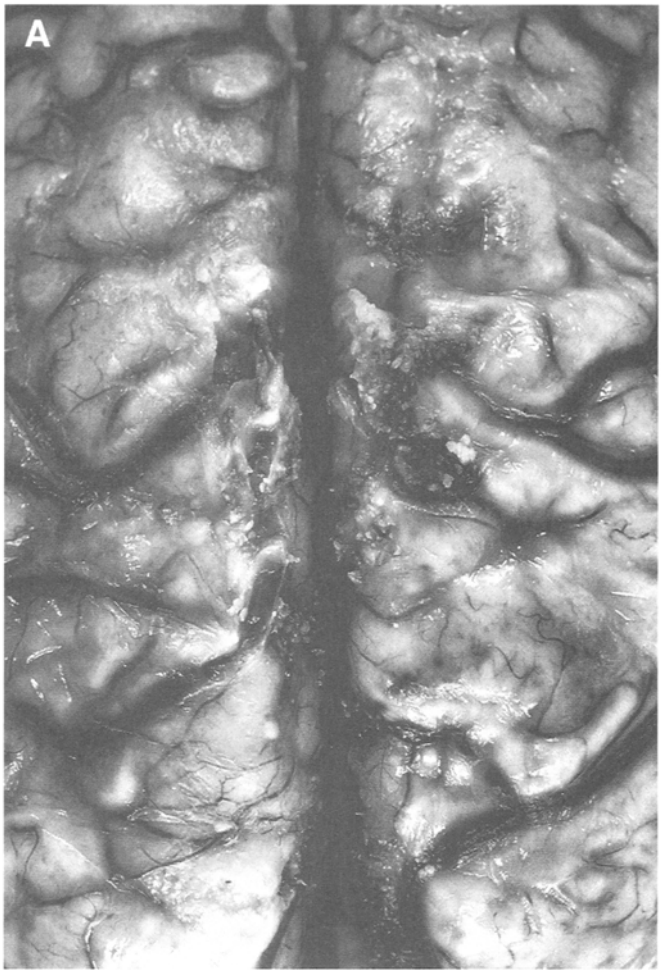
Bacterial Infections

Meningitis (Figure 43)

- Purulent leptomeningeal inflammation, often with secondary vasculitis and infarcts
- Typically due to hematogenous source with initial access to the CSF via the choroid plexus where there is no BBB; therefore, there is frequently a coexisting ependymitis/plexitis
- Neonates = group B strep; E. coli, other Gram negative rods
- Children = H. influenza (less common now due to vaccination), N. meningitidis
- Adults = strep pneumonia, N. meningitidis
- Complications = venous infarcts, hydrocephalus, deafness, cranial palsies, postmeningitic epilepsy, developmental delays, and cognitive deficits

Abscess

- Usually hematogenous (e.g., septic emboli); occasionally due to contiguous spread
- Predisposing factors = endocarditis, heart valve disease, congestive heart disease with L to R shunt, IV drug abuse, periodontal disease, dental work, sinus infection, and mastoiditis



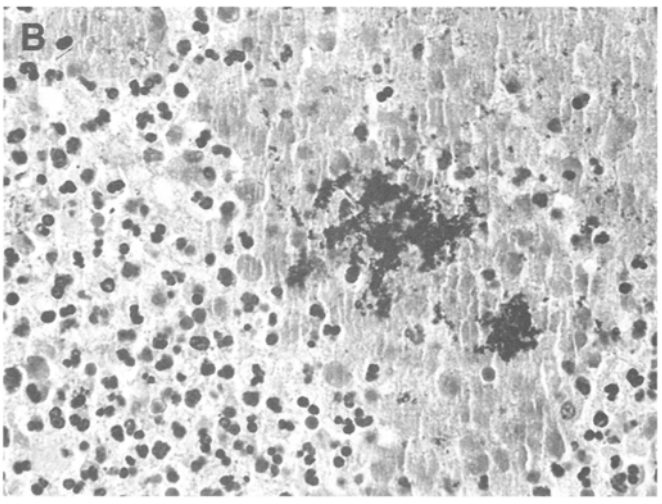


Fig. 43. Acute bacterial meningitis with leptomeningeal opacification **(A)**, a neutrophil-rich subarachnoid infiltrate, and gram-positive organisms **(B)**.

- Tend to lodge at microvascular branch points near cortical gray-white junction, especially in MCA territory

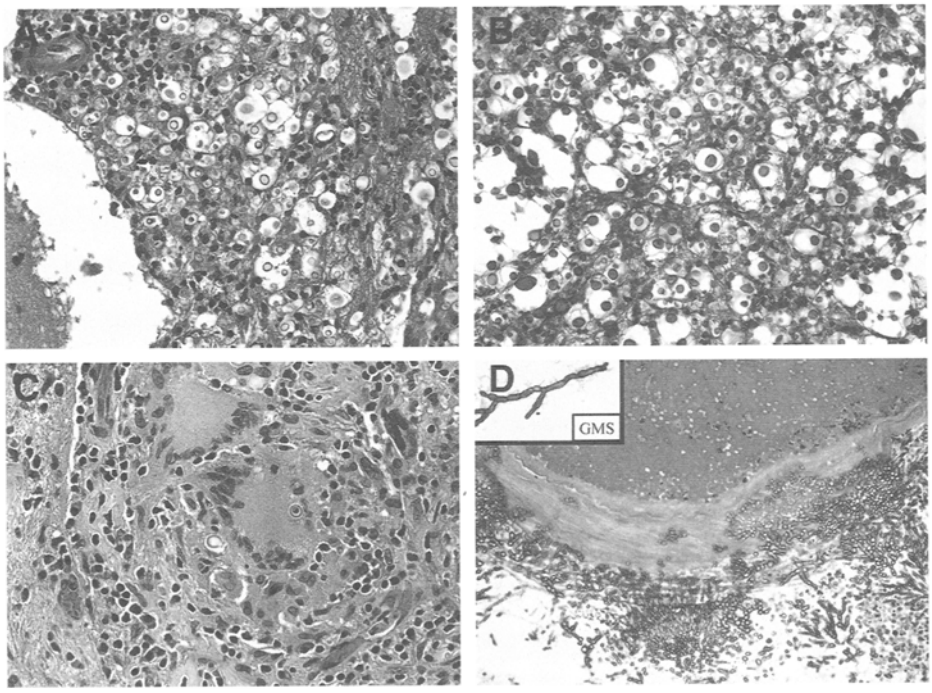


Fig. 44. Patterns of fungal CNS infections, including cryptococcal meningitis (**A,B**: PAS stain), granulomatous blastomycosis **(C)**, and angioinvasive Aspergillosis **(D)**.

- Early cerebritis (presuppurative) progresses to microabscess, which progresses to walled-off abscess
- Neuroimaging may mimic primary or metastatic neoplasm

Tuberculosis (TB)

- Basal meninges and cranial nerves
- Parenchymal disease = tuberculoma; cerebellum and pons commonly affected
- May develop secondary vasculitis with multiple infarcts
- High mortality without early treatment

Neurosyphilis

- Typically presents in late tertiary stage
- Meningeal and/or parenchymal involvement; spinal cord and/or brain
- Hallmark = microglial activation and endarteritis obliterans with secondary infarcts
- Paretic dementia (general paresis of insane) = meningeal fibrosis, hydrocephalus, and cortical atrophy with perivascular lymphoplasmacytic cellular inflammation, and microglial activation (i.e., encephalitis); organisms demonstrable on silver stains
- Tabes dorsalis = atrophy of posterior nerve roots, DRGs, and posterior spinal columns, especially lumbosacral and/or cervical; no organisms, no inflammation, so etiology is uncertain

Whipple's Disease

- CNS disease rare, but may occur without obvious systemic findings
- Cortical subpial, basal ganglia, hypothalamus, brainstem, and cerebellum
- Inflammatory nodules
- Hallmark = perivascular macrophages stuffed with PAS + bacilli (Tropheryma whippelii); free organisms may also be found
- EM or PCR may be helpful

Fungal Infections

Meningitis (Figure 44A–B)

- Cryptococcus most common; especially frequent in AIDS patients:
  - Yeast with thick polysaccharide-rich capsule results in grossly mucoid exudate
  - Process extends deep within Virchow-Robin spaces to form microabscesses
  - Minimal inflammatory response
  - High mortality

Granuloma/Abscess (Figure 44C)

- Candida, coccidiodomycosis, and histoplasmosis are most common.
- Organism load and inflammatory response varies with immunocompetence

Angioinvasive Forms (Figure 44D)

- Aspergillus and mucor (zygomycetes)
- Hemorrhagic and necrotizing due to vascular involvement

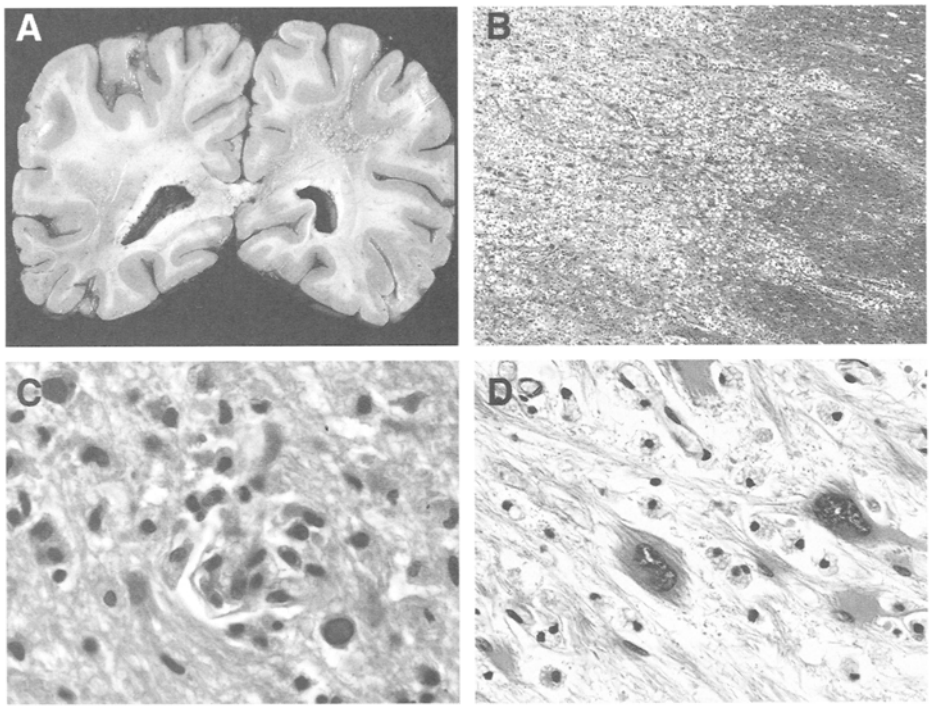


Fig. 45. PML with multiple, bilateral foci of demyelination **(A)**, a macrophage-rich infiltrate within demyelinating foci **(B)**, plumb-colored viral inclusions within oligodendrocytes **(C)**, and bizarre, virally infected astrocytes **(D)**.

- Mucor likes low pH and high glucose, therefore increased incidence in diabetics with ketoacidosis: frontal lobe disease results from spread of primary sinus infection

Viral Infections

- Characterized by microglial nodules, microglial activation, perivascular lymphocytes, and/or viral inclusions

Encephalitis (Figure 2)

- Herpes is the most common cause of sporadic cases (see below)
- Arboviruses is the most common cause of epidemic cases
  - Transmitted to humans from animal reservoirs (e.g., horse) via arthropods (e.g., mosquito)
  - No inclusions, specific diagnosis depends on serology
  - Variable mortality rates

Herpes Simplex (HSV)

- Mostly Type 1; Type 2 occurs in infants exposed during vaginal delivery
- Temporal lobes almost always involved; bilateral, asymmetric
- Hemorrhagic and necrotizing
- Cowdry A and B nuclear inclusions, may be difficult to find in biopsy; immunostains helpful, though most cases are now diagnosed clinically with CSF PCR studies
- Most cases fatal unless treated early (acyclovir)

HIV Encephalitis/AIDS Dementia Complex

- Common complication of AIDS with cognitive, behavioral, and motor deficits
- Mild cerebral atrophy grossly
- Abnormalities in white matter, thalamus, and basal ganglia (subcortical dementia)
- Hallmark = macrophage-derived multinucleated giant cells (HIV+)
- Perivascular lymphocytes and macrophages, microglial nodules (i.e., encephalitis), myelin rarefaction, or frank white matter necrosis

Vacuolar Myelopathy of AIDS

- Less common, but also felt to represent direct consequence of HIV infection
- Vacuolation of myelin in posterior and lateral columns, mainly thoracic cord, with minimal to no inflammation; resembles vitamin B12 deficiency
- Paraparesis, ataxia, and incontinence
- Most patients have coexisting HIV encephalitis

Cytomegalovirus (CMV)

- Common opportunistic infection, especially in AIDS patients and in neonates
- Represents "reactivation disease" in most adult cases
- Ventriculitis, choroid plexitis, and encephalitis (especially periventricular regions)

- Nuclear and cytoplasmic inclusions in glial, neuronal, choroid plexus, endothelial, and histiocytic cells
- Represents the "C" in TORCH; results in microcephaly, chorioretinitis, hydrocephalus, periventricular calcifications, and CNS malformations

JC Virus/Progressive Multifocal Leukoencephalopathy (PML) (Figure 45)

- Papovavirus named after the first described patient's initials (JC) (nothing to do with CJD)
- Virtually uniformly fatal infection of immunocompromised, especially AIDS
- Is a "reactivation disease"; most of population is seropositive
- Hallmark = demyelinating (or frankly necrotizing) plaques featuring enlarged, nuclear-inclusion bearing oligodendrocytes
- Also typical are large, bizarre astrocytes that may mimic astrocytoma on biopsy
- Minimal inflammation
- EM and/or in situ hybridization is diagnostically useful

Subacute Sclerosing Panencephalitis (SSPE)

- Rare reactivation disease of children who had measles years earlier
- Generally fatal with gray and white matter involvement
- Encephalitis histology with intranuclear oligodendroglial and neuronal inclusions; neuronophagia common
- Patients typically have high measles antibody titers
- EM and PCR also diagnostically useful

Rabies

- Single stranded RNA virus
- Enters CNS via axonal transport from peripheral nerves; therefore incubation period relates to site of inoculation
- Typically, but not invariably, transmitted through bite of rabid animal
- Histology = encephalomyelitis pattern and/or neuronophagia
- Hallmark = Negri body (one or more eosinophilic, bullet-shaped cytoplasmic inclusions) in hippocampal, neocortical, or Purkinje cell neurons

Poliomyelitis

- CNS disease develops in <10% of patients with enteric infection
- Rare in USA because of widespread vaccination
- Same syndrome may occur with a variety of enteroviruses
- Hemorrhagic, necrotizing myelitis involving predominantly lower motor neurons of anterior horns; microglial nodules, neuronophagia
- Brain involvement in some fatal cases

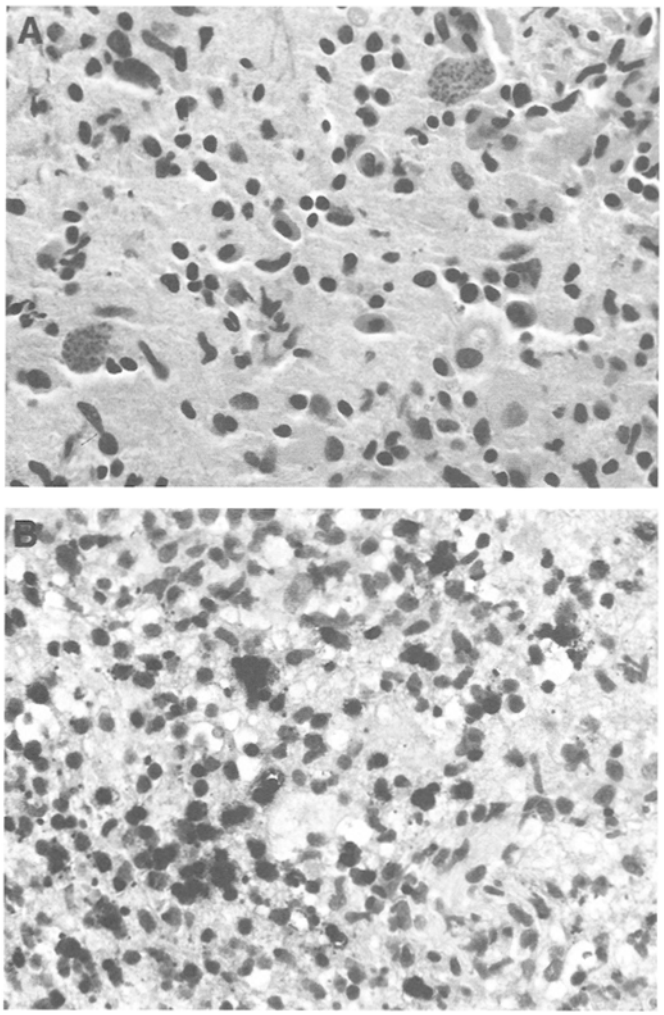


Fig. 46. Encysted forms of toxoplasma on a brain biopsy **(A)**, with additional tachyzoites identified on an immunostain **(B)**.

Parasites

Cysticercosis

- Most common CNS parasitic infection
- Most common cause of epilepsy in Mexico
- Encysted larval form of the pig tapeworm Taenia solium
- Becomes symptomatic when organism dies and elicits a host inflammatory response
- Multiloculate cysts often at base of brain or in subarachnoid space/fourth ventricle = racemose form
- Single or multiple; parenchymal or intraventricular, and/or hydrocephalus
- Gross = cyst with larval nodule
- Micro = larva with diagnostic scolex

Toxoplasmosis (Figure 46)

- Common opportunistic infection of AIDS patient and of neonates ("T" in TORCH)
- Represents a "reactivation disease" in adults

- One of the only treatable CNS disorders in AIDS; therefore, often treated empirically prior to resorting to biopsy
- Multiple, enhancing deep and cortical lesions; main differential diagnosis = lymphoma
- Necrotizing encephalitis with microglial nodules, macrophages, secondary vasculitis, and/or abscess formation
- Chorioretinitis also common
- Encysted and free organisms seen at periphery necrosis on H&E stain
- Immunostains useful for confirmation
- Healed lesions show abundant lipid-laden macrophages and dystrophic calcification

Amebic Meningoencephalitis

- Rare disorder usually due to Naegleria fowleri
- Lethal, hemorrhagic meningoencephalitis at base of brain (frontotemporal)
- Children/young adults diving/swimming in warm fresh water
- Gains access through nose to region of cribriform plate
- Acanthameba species is a rare cause of granulomatous encephalitis in the immunocompromised or of keratitis in contact lens users

Cerebral Malaria

- Most serious complication of malaria; associated with high mortality
- P. falciparum most common; lesions due to high parasite load creating sticky red cells that occlude microcirculation
- Ring hemorrhages are typical

PEDIATRIC AND SEIZURE NEUROPATHOLOGY

Malformations

Neural Tube Defects

Anencephaly (Figure 47A)

- Most common brain malformation
- Frog-like facies; sphenoid wing deformity resembles "bat with folded wings"
- Area cerebrovasculosa = ectatic vessels and brain remnants
- Underdeveloped hypothalamus/pituitary leads to adrenocortical hypoplasia
- Interaction of environmental/genetic factors poorly understood
- Associated with high amniotic fluid AFP

Craniorachischesis (Figure 47B)

- Anencephaly and lack of spinal closure, flattened, malformed spinal cord or area medullovasculosa (tissue similar to area cerebrovasculosa)

Encephalocele

- Herniation of brain through skull defect
- Usually occipital; occasionally anterior (frontal) at bridge of nose
- Typically asymmetric and/or overlying skin ulceration
- Neurologic deficit depends on extent of herniation and other malformations

Myelomeningocele

- Herniation of malformed spinal cord and meninges through a vertebral defect and/or overlying skin ulceration
- Usually associated with Arnold-Chiari malformation and hydrocephalus
- Neurologic deficit depends on level of defect and associated rostral spinal malformations; lumbosacral level is most common

Spina Bifida Occulta

- Minor lumbosacral defect with intact overlying skin

Holoprosencephaly

- Failure of cerebral hemispheres to separate: "face predicts brain"; cyclopia, proboscis, agnathia, cleft lip/palate, etc.
- Most cases are sporadic
- Common associations = maternal diabetes, TORCH infections, fetal alcohol syndrome, and trisomy 13
- Variations:
  - Alobar = small, monoventricular brain, no interhemispheric fissure, olfactory aplasia, fused basal ganglia and thalami, thin membrane over posterior ventricle (posterior cyst)
  - Semilobar = shallow interhemispheric fissure, minimal gyration
  - Lobar = normal interhemispheric fissure, well-developed gyration, fusion of midline structures
  - Arrhinencephaly = olfactory aplasia with lack of bulbs, tracts, and gyrus rectus (i.e., no olfactory sulcus)

Congenital Hydrocephalus

Arnold-Chiari (Chiari II) Malformation

- Elongated, S-shaped brainstem with herniation of medulla and cerebellar vermis below foramen magnum



Fig. 47. Frog facies **(A)** and lack of spinal fusion **(B)** encountered in anencephaly with craniorachischesis.

- "Beaking" of quadrigeminal plate with fusion of inferior colliculi
- Compressed fourth ventricle with obstructive hydrocephalus
- Associated myelomeningocele in most
- Associated migrational/gyral defects in some

Dandy Walker Malformation (Figure 48)

- Agenesis of cerebellar vermis with dilated fourth ventricle cyst covered by thin membrane (easily torn)
- Large posterior fossa
- Etiology of hydrocephalus uncertain; aqueductal stenosis in some
- Associated malformations common (e.g., polymicrogyria, agenesis of corpus callosum, etc.)

Aqueductal Stenosis

- Rare cause of hydrocephalus
- Histologically associated with atresia, forking, etc.
- Ependymal granulations and gliosis suggest prior infection (TORCH)

Migrational/Gyral Defects

- Often associated with seizures, mental/psychomotor retardation, learning disorders, etc.
- Timing of insult (ischemic, infectious, genetic, etc.) determines abnormality
- Normally, neuroblasts migrate from periventricular germinal matrix to cortex and other sites; excess neurons are removed by apoptosis and the remaining neurons mature

Polymicrogyria (Figure 49)

- Most common gyral abnormality
- Small gyri with shallow sulci and "fused" molecular layers
- Cortical dysplasia (architectural distortion) with simplified 2- to 4-layer neocortex

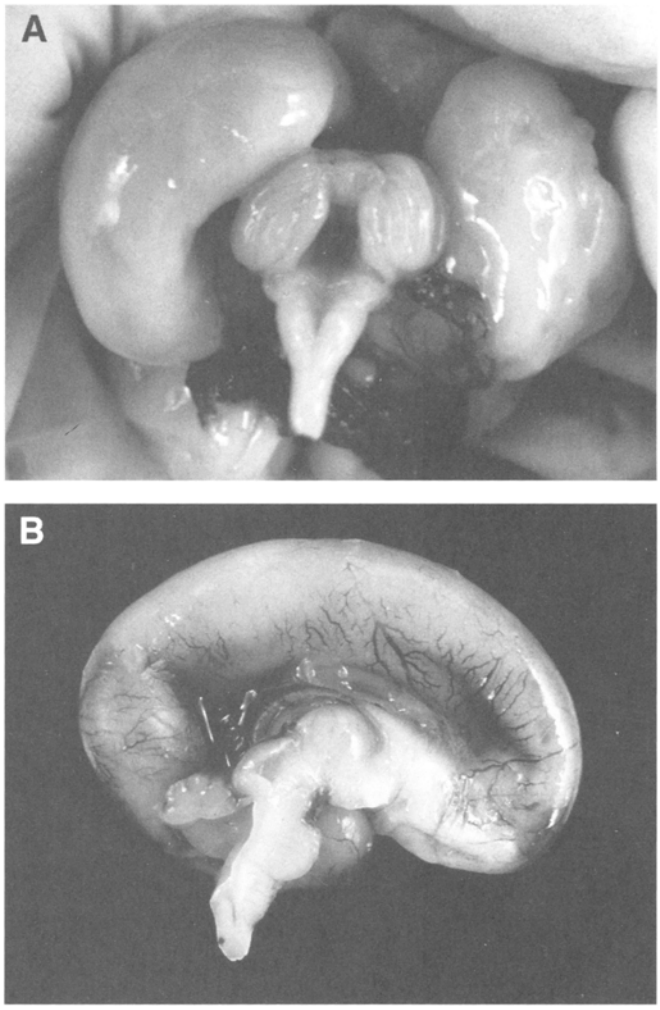


Fig. 48. Dandy-Walker malformation in a fetus, showing nearly complete agenesis of the cerebellar vermis **(A,B)**. The delicate, thin-walled meningeal lining covering the posterior fossa cyst ruptured during extraction of the brain.

- Underlying neuronal heterotopias common ("migrational arrest")
- Commonly seen at the edge of a porencephalic cyst

Lissencephaly/Pachygyria

- Small brain (microcephaly) with broad or no gyri
- Thick cortex extending almost all the way down to ventricles (minimal white matter)
- Other coexisting malformations common
- Sporadic or familial
- Miller-Diecker syndrome associated with LIS-1 gene on 17p

Gray Matter Heterotopia (Figure 49A)

- Defect of neuroblast migration (get stuck before reaching cortex)
- Diffuse neuronal heterotopia = numerous neurons scattered throughout white matter

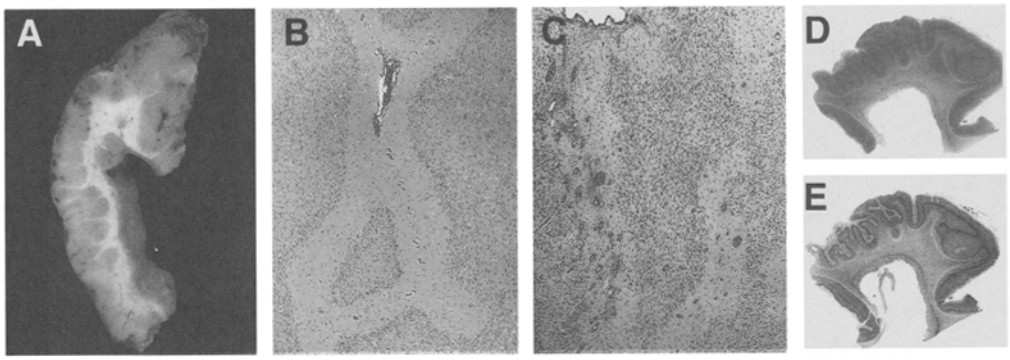


Fig. 49. Polymicrogyria and nodular gray matter heterotopia adjacent to the ventricle (**A**). Note the shallow-appearing sulci and reduction of white matter development. Microscopically, polymicrogyria is characterized by hypergyration and the appearance of fused molecular layers resulting from the lack of adequate sulcal formation (**B, C:** H&E and LFB-Cresyl violet stains) (**D,E**: H&E and Neu-N stains, courtesy of Dr. Robert Schmidt, Washington U., St. Louis, MO).

- Nodular heterotopia = subcortical or subependymal nodules, most common form
- Laminar heterotopia = band of gray matter between cortex and ventricle ("double cortex")

Cortical Dysplasia (Figure 50)

- Umbrella term for all forms of disordered neuronal architecture; microdysgenesis and hamartia represent subtle microscopic forms

Destructive Malformations

- Intrauterine ischemia, infections (TORCH), etc.

Sclerotic Ulegyria

- Mushroom-shaped gyri ("ulegyria")
- Cortical microinfarcts of sulcal depths (narrow) with sparing of gyral crests (wide)
- Associated neuronal loss and gliosis ("sclerotic")

Porencephaly

- Large area of cystic degeneration (intrauterine infarct), often MCA territory
- Result of liquefactive necrosis
- Large cyst, often extending from meninges to ventricle
- Polymicrogyria common at edge of cyst

Hydranencephaly

- "Basket brain"
- Severe, bilateral cerebral damage
- Most of cortex and white matter lost resulting in large, bilateral thin cysts
- Thalamus usually preserved

Agenesis of Corpus Callosum

- Complete vs. partial (posterior portion only)
- No overlying cingulate gyrus (helpful in distinguishing postmortem artifacts)

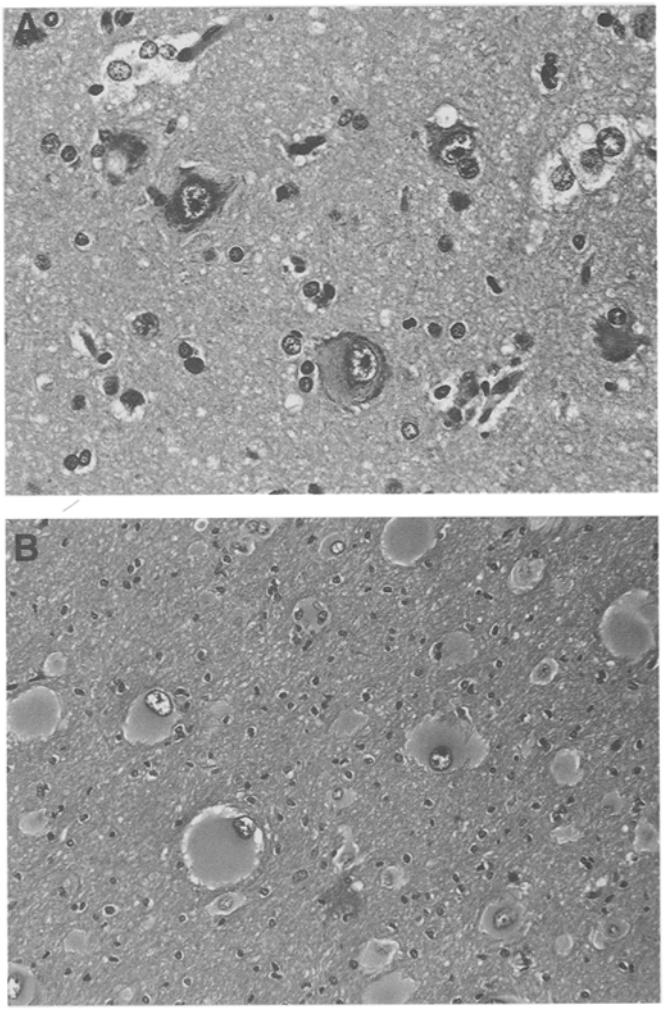


Fig. 50. Focal cortical dysplasia or tuber (in a patient with tuberous sclerosis) is characterized by both neuronomegaly (**A**) and balloon cells containing neuron-like nuclei and eccentric collections of astrocyte-like cytoplasm (**B**).

- "Bat's wing"-shaped lateral ventricles
- Probst bundles = callosal remnants in lateral roof of ventricle
- May be associated with callosal lipoma

Syringomyelia/Syringobulbia

- Cystic cavity in spinal cord or brainstem
- Variants:
  - Hydromyelia = distension of central canal (ependymal lining may slough, so often lumped with syringomyelia or syrinx)
  - Idiopathic or primary type usually associated with Chiari Type I malformation (chronic cerebellar tonsillar herniation and/or hydrocephalus) with cerebellar ataxia and dissociated sensory loss from cervical syrinx; young adult, often progressive
  - Secondary types associated with tumor, trauma, infarcts, etc.

Fetal/Perinatal Insults

Intraventricular Hemorrhage (Figure 51)

- Premature infants <32 weeks estimated gestational age most commonly affected
- Usually arise from dissection of germinal matrix hemorrhage (poorly developed capillaries presumably undergoing involution)
- Associated with perinatal ischemia/respiratory distress syndrome
- Choroid plexus hemorrhage is more common source in term infants
- High mortality unless it is a small, contained hemorrhage

Gray Matter Ischemia

- Produces ulegyria, porencephaly, and migrational defects (see above)
- Status marmoratus (marbled state):
  - Ischemic damage to basal ganglia and/or thalamus prior to myelination
  - Abnormal myelination occurs over gliotic fibers resulting in marbled appearance
  - Common in cerebral palsy
- Pontosubicular necrosis: reflects perinatal selective vulnerability with pontine nuclei and subiculum being more sensitive than CA1 of hippocampus

White Matter Ischemia/Periventricular Leukomalacia (PVL)

- White matter is a site of selective vulnerability in premature infants
- Sharply demarcated infarcts
- Become cystic upon resolution
- Often coexists with other ischemic lesions



Fig. 51. Fetus with bilateral intraventricular hemorrhages. These hemorrhages start in the subependymal germinal matrix, typically near the head of the caudate (see right side).

Kernicterus

- Necrosis of globus pallidus and hippocampus in premature infants
- Unconjugated bilirubin (immature liver) crosses BBB to produce bright yellow gross appearance
- Rare today due to "bilirubin lights" and other preventive therapies

Chromosomal Syndromes (see Chapter 2)

Down Syndrome (Trisomy 21)

- Gross changes not always obvious
- Brain short and blunted in AP direction
- Narrow superior temporal gyrus
- Small cerebellum and brainstem
- Premature Alzheimer's (see Neurodegenerative section)

Edward Syndrome (Trisomy 18)

- Microcephaly, gyral defects

Patau Syndrome (Trisomy 13)

- Holoprosencephaly in most

Fragile X

- Most common form of familial mental retardation
- M > F (i.e., X-linked)
- Associated with triple repeat expansion of FMR-1 gene on Xq
- Microcephaly, neuronal heterotopias

Seizure-Associated Pathology

- Increasingly seen in surgical specimens (refer to individual lesions in previous sections for details)

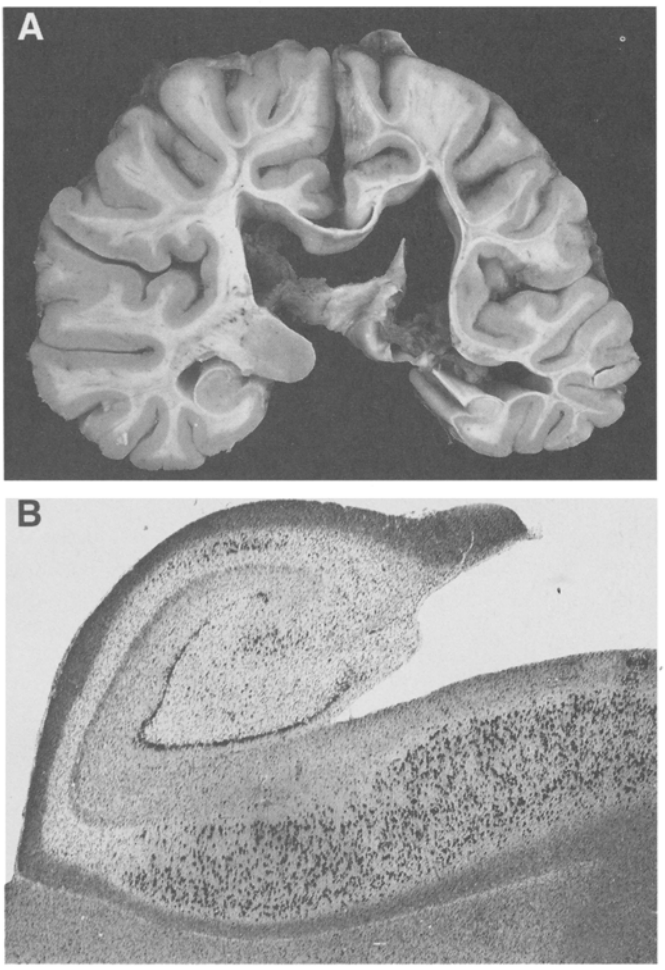


Fig. 52. Mesial temporal sclerosis with marked hippocampal atrophy (**A;** right side) and loss of neurons in the CA4 and CA1 sectors (**B**) Neu-N stain; photo courtesy of Dr. Robert Schmidt, Washington U., St. Louis, MO).

Mesial Temporal Sclerosis (MTS; Hippocampal Sclerosis) (Figure 52)

- Most common form of pathology in surgical specimens from patients with temporal lobe seizures
- Hippocampus atrophic with variable degrees of neuronal loss and gliosis, most commonly involving CA1 and CA4 sectors (same regions of selective vulnerability to ischemia)
- Long standing debate about whether MTS is the cause or the result of the seizure disorder, since patients often suffer hypoxic injury during prolonged seizures
- High likelihood of seizures being cured or reduced in frequency after surgery

Malformations

- Any of ones previously discussed; most common are polymicrogyria and neuronal heterotopias

Tuberous Sclerosis

- Triad of seizures, resultant mental retardation, facial angiofibromas
- Tubers = cortical dysplasia with balloon cells (**Figure 50**), mono- and multinucleated dysmorphic glioneuronal cells, associated gliosis and/or calcification firm, "potato-like" cortical lesion with subcortical degenerative changes
- Gray matter heterotopias = similar histology (balloon cells) to tubers, but deeper and often perivascular
- Subependymal giant cell astrocytoma (SEGA) = malformative intraventricular tumor near foramen of Monro composed of spindle, epithelioid, and occasional giant cells forming sweeping fascicles and perivascular pseudorosettes; neuron-like cells less common; calcification; noninfiltrative growth pattern
- Candle gutterings = identical to SEGA, but smaller, waxy subependymal nodules throughout lateral ventricles (precursors to SEGA)
- Continuous, radial abnormalities from cortex to ventricle suggest migrational disturbance
- Non-CNS lesions = cutaneous angiofibroma, renal angiomyolipoma, pulmonary lymphangioleiomyomatosis (LAM), and cardiac rhabdomyoma
- Two genes identified: TSC1 on 9q, TSC2 on 16p

Tumors

- Dysembryoplastic neuroepithelial tumor (DNET): quasihamartomatous intracortical lesion featuring patterned mucin-rich nodules and "floating neurons" (*see* **Figure 20**):
  - Often misdiagnosed as oligodendroglioma or oligoastro; common in epilepsy specimens (7%)
  - Excellent prognosis
- Low-grade diffuse gliomas: oligodendroglioma, oligoastrocytoma, astrocytoma
- Pilocytic astrocytoma
- Ganglioglioma
- Pleomorphic Xanthoastrocytoma (PXA)

Inflammatory/Infectious

Cysticercosis

- Most common cause of epilepsy in Mexico

Rasmussen's Encephalitis

- Progressive, unilateral process often associated with intractable seizures in young patients
- Hemispherectomy may be necessary for seizure control
- Histology identical to viral encephalitis
- Autoimmune vs. infectious; associated with autoantibodies to glutamate receptor in some patients

Vascular Malformations

- Most commonly cavernous angioma or AVM

TOXIC/METABOLIC DISORDERS

Alcohol- (and/or Malnutrition-) Related Pathology

- Not restricted to alcoholics

Trauma

- Alcoholics fall a lot; subdural hematomas and cortical contusions are common

Wernicke-Korsakoff Syndrome

- Due to thiamine (vitamin B_1) deficiency
- Wernicke's encephalopathy = nystagmus, ataxia, confusion, and stupor
- Korsakoff's psychosis = anterograde and retrograde amnesia, confabulation (e.g., "Yes, I see the invisible pink thread you're holding.")
- Mamillary bodies/periventricular thalamus and brain-stem affected
- Acute-subacute = petechial hemorrhages, capillary proliferation, gliosis, and/or necrosis with neuronal sparing
- Chronic = atrophy, hemosiderin, axonal/myelin loss, and vascular prominence

Cerebellar Degeneration

- Due to thiamine (vitamin B_1) deficiency
- Atrophy of anterior superior cerebellar vermis with Purkinje cell loss and Bergmann layer gliosis
- Truncal ataxia

Peripheral Neuropathy

- "Glove and stocking" distal (dying back) neuropathy with axonal degeneration
- Etiology poorly understood; may be multifactorial
- Yet another source of ataxia
- Associated tract degeneration of posterior spinal columns

Central Pontine Myelinolysis (CPM) (Figure 53)

- Most often associated with too rapid correction of hyponatremia (an iatrogenic process)
- Symmetric, triangle-shaped zone of demyelination in central basis points
- Relatively high mortality
- Extrapontine lesions noted in 10%

Hepatic Encephalopathy

- Liver failure with hyperammonemia
- Dementia/delirium/stupor/coma
- Grossly, the brain is normal to edematous; bilirubin staining (jaundice) of dura, meninges, and choroid plexus (i.e., sites lacking BBB)

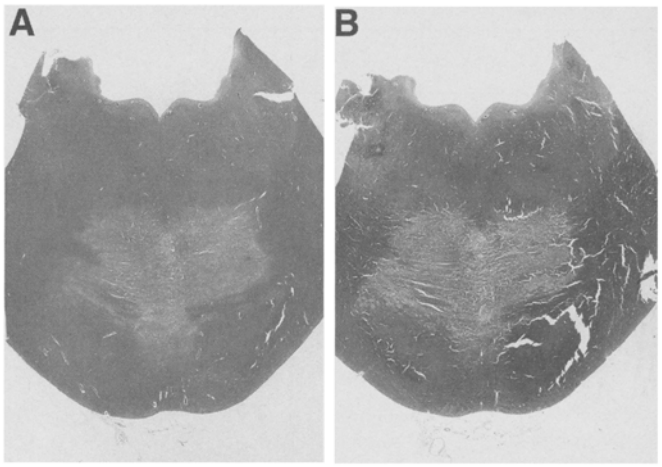


Fig. 53. Characteristic central triangular shaped region of myelin pallor in a case of central pontine myelinolysis. **(A)** H&E stain; **(B)** LFB-PAS stain.

- Micro = Alzheimer Type 2 astrocytes (enlarged nuclei with pale, open chromatin and little cytoplasm) in gray matter, especially deep cortex, globus pallidus, and dentate nucleus

Subacute Combined Degeneration of Spinal Cord

- Due to vitamin B_{12} deficiency
- Vacuolation/myelin pallor of posterior and lateral columns; thoracic levels emphasized in books, but cervical levels are also involved frequently (identical to vacuolar myelopathy in AIDS)
- Combined sensory and upper motor neuron deficits
- Similar, but reversible symptoms can be seen with folate deficiency

Fetal Alcohol Syndrome

- Complex etiology related to timing and volume consumed during pregnancy, genetic influences, etc.
- Common cause of mental retardation
- Facial abnormalities
- Growth retardation

Other Toxic Injuries

Carbon Monoxide

- See "Patterns of selective vulnerability" (p. 8–38)

Methanol

- See "Patterns of selective vulnerability" (p. 8–38)

Arsenic Poisoning

- GI symptoms, sensory neuropathy, weakness
- No morphologic CNS changes

Table 7. Metabolic Disorders

Disease	*Clinical*	*Genetics*	*Enzyme*	*Accumulations*	*Pathology*
Wilson's disease	Liver failure, movement disorder	AR, Chr. 13	Cu transporting ATPase (not ceruloplasmin)	Copper ↓ serum ceruloplasmin)	Cystic deg. of putamen, Alz. Type 2 astros, perivascular copper + iron deposits
Tay-Sachs disease	Ashkenazi Jews; death < age 5, cherry-red macula	AR, Chr. 15	Hexosaminidase A	GM2-ganglioside	Foamy CNS, PNS, + retinal neurons; LFB+, PAS + granules. EM-MCBs
GMl-ganglio-sidosis	Like Tay-Sachs plus dysmorphism and visceromegaly	AR, Chr. 3	β-galactosidase	GMl-ganglioside	Like Tay-Sachs + foamy hepatocytes, macrophages and endothelial cells
Ceroid lipofuscinosis	Various subtypes, ages, and severity	AR, Multiple	Various enzyme defects	"Lipofuscin"	Cerebral atrophy, thick dura, N. loss, PAS +, EMfinger print + curvilinear bodies
Niemann-Pick Disease (Type A)	Visceromegaly, cherry-red macula, death < age 5	AR, Chr. 11	Sphingomyelinase	Sphingomyelin	Foamy neurons, endothelial cells and macrophages
Gaucher's Disease (Type 2)	Neuronopathic, CNS + visceral, death < age 2	AR, Chr. 1	Glucocerebrosidase	Glucocerebroside	Perivasc. PAS + Gaucher cells (macrophages) with "crumpled tissue paper"; neuronal loss
Mucopoly-saccharidoses	Hurlers (I) + Hunters (II-males), MR, dysmorphic	AR, except 11 = XL	Various enzyme defects	Glycosamino-glycans (GAG) high in urine	Thick skull and dura, perivasc. "pits" = GAG deposits. EM = "zebra bodies"
Fabry's disease	Males, renal/heart failure, p. neuropathy, death ~age 40	XL, Chr. Xq	α-galactosidase A	Ceramides	Vascular dz. with cerebral infarcts, PAS + deposits in meninges, vessel walls, and other cells
Glycogen storage ds (II-Pompes)	Limb-girdle + resp. weakness, death < age 2	AR, Chr. 17	Acid maltase	Glycogen	Vacuolar myopathy. In infantile form: heart, liver, neurons, and astrocytes affected
Zellwegers Syndrome	Dysmorphic, floppy, FTT, liver dz, death < age 1	AR	Peroxisomes absent (along with enzymes)	Numerous biochemical abnormalities	Migrational defects (patchy/ polymicrogyria, hetero-topia), myelin loss, cirrhosis
Adrenoleuko-dystrophy	Boys ("Lorenzo's oil"), rapid course, CNS + adrenal disease	XL, Chr. Xq	Peroxisomal membrane protein	Very long chain fatty acids	Diffuse myelin loss and inflam.; mimics MS. Adrenal atrophy with "balloon cells"
Metachromatic leukodystrophy	Usually infants/ kids, early bone marrow Tx helpful	AR, Chr. 22	Arylsulfatase A	Sulfatides	Diffuse myelin loss; metachromasia on frozen sections. EM-prismatic inclusions
Krabbes leuko-dystrophy	Death < age 2, cherry-red macula	AR, Chr. 14	Galactocerebrosidase	Galactocerebro-side + psychosine	Diffuse myelin loss, "Globoid cells" = clusters of macrophages with eccentric nuclei

AR = autosomal recessive, XL = X-linked, TX = transplant, FTT = failure to thrive, Alz = Alzheimer's, N = neuron, MCB = membranous cytoplasmic bodies, MS = multiple sclerosis, MR = mental retardation

- Peripheral neuropathy with segmental demyelination, axonal degeneration, and occasionally onion bulb formation (repeated exposures)

Lead Poisoning

- Usually children ingesting lead-based paint from old houses
- Cerebral edema and petechial hemorrhages associated with lead encephalopathy
- Peripheral neuropathy with segmental demyelination and/or axonal degeneration
- Anemia, renal and GI symptoms, lead lines in bone on X-ray

Methotrexate Toxicity

- Follows intrathecal or IV therapy for leukemias, lymphomas, etc.
- May cause a necrotizing leukoencephalopathy, especially when combined with radiation therapy

Metabolic Disorders

- Generally due to enzyme defects with accumulation of toxic byproducts
- Almost always autosomal recessive
- Diagnosed by biochemical analyses, biopsy of skin, conjunctiva, rectum, etc.
- Almost all exist as variants wherein youngest age = most severe, oldest age = least severe
- Table 7 summarizes the most common and most severe CNS forms
- Lipid accumulations may be seen in frozen sections, but are often lost in processing of paraffin sections
- Variable gross appearance: encephalomegaly from storage vs. microcephaly from atrophy

Lysosomal (Enzyme) Storage Disorders (see Table 7)

- Involve CNS and/or other organs
- Enlarged lysosomes often result in the formation of PAS + granules
- EM shows membranous cytoplasmic bodies (MCBs) often morphologically nonspecific, but supportive of a storage disorder

Mucopolysaccharidoses

- Include many subtypes: Gargoyle-like dysmorphism, Hurler (Type I) = most severe, Hunter (Type II) = X-linked: "Hunters are men"

Peroxisomal Disorders (see Table 7))

- Due to absence or decreased numbers of peroxisomes vs. abnormality of peroxisomal protein

Leukodystrophies (see Table 7))

- Metabolic disorder of myelin synthesis/breakdown
- Dysmyelination (abnormal formation) instead of demyelination (loss of normally formed myelin as in MS)
- Diffuse, symmetric, and bilateral, with sparing of subcortical U-fibers

Adrenoleukodystrophy (ALD)

- X-linked, peroxisomal disorder/leukodystrophy with inflammation that can mimic MS (e.g., many cases of "Shilder's variant of MS" have turned out to be ALD)

SELLAR/SUPRASELLAR PATHOLOGY

Pituitary Adenomas (Figure 54)

General Features

- Most common sellar neoplasm; 20% incidental autopsy finding
- Hormonally functional tumors often present at microadenoma (<1 cm) stage, especially patients with Cushing's disease
- Non-functional tumors present as macroadenoma (>1 cm) due to mass effects, including visual deficits and/or hypopituitarism
- "Stalk effect" = mild prolactin (PRL) elevation due to compression of stalk (blocks transport of dopamine, the normal PRL-inhibiting factor from the hypothalamus to the pituitary)
- "Invasive adenoma" = gross intraoperative or radiologic descriptor; affects management and likelihood of recurrence. Simple microscopic invasion of dura alone is unimportant
- Differential Diagnosis only theoretically includes ependymoma (perivascular rosettes), and olfactory neuroblastoma (involves cribriform plate). Small cell carcinoma is simulated by crush artifact of normal or adenomatous tissues
- Loss of acinar architecture and the presence of prominent nucleoli are helpful in distinguishing adenoma from normal pituitary
- Reticulin stain helpful to highlight architecture, especially in crushed specimens or with freezing artifacts; adenomas are reticulin-poor compared to normal adenohypophysis which features reticulin encircled acini

Histology Clues (Often True)

- Psammomatous calcification = prolactinoma
- Spherical lamellated amyloid bodies (rare) = prolactinoma
- High N/C ratio and fibrosis = result of medical treatment of prolactinomas with dopamine agonists
- Perivascular rosettes or papillae = gonadotrophic adenoma

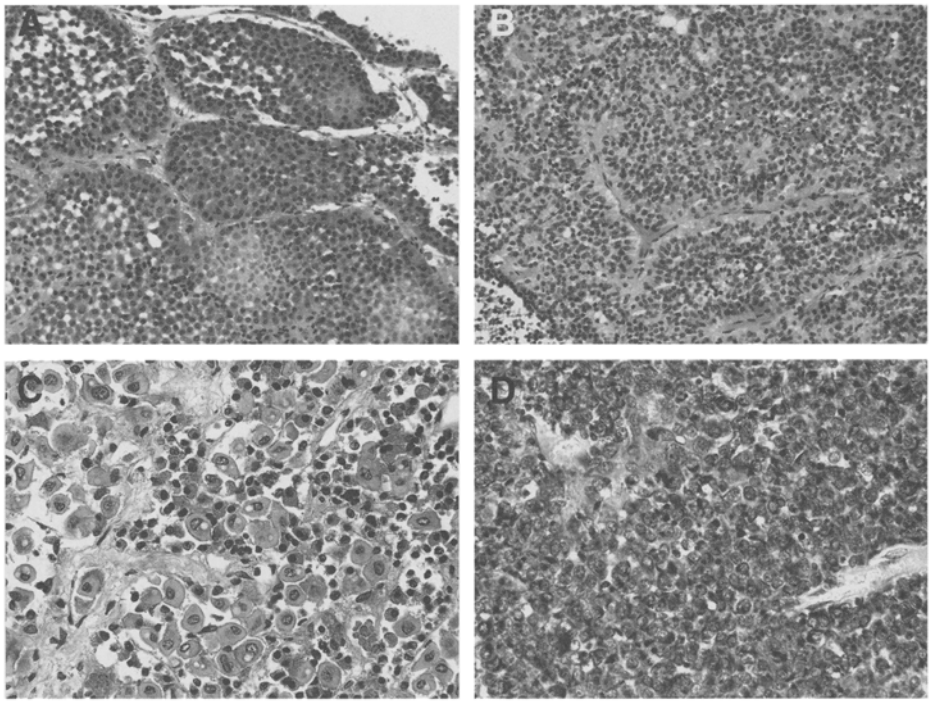


Fig. 54. Nesting **(A)** and pseudorosette-like **(B)** patterns in cases of pituitary adenoma. Crooke's hyalin is characterized by rings of eosinophilic material in the non-neoplastic corticotroph cells of the adenohypophysis **(C)**, which are reacting to the negative feedback stimuli from the patient's hypercortisolism. Cytokeratin-positive fibrous bodies forming paranuclear balls of staining in a growth hormone producing adenoma **(D)**.

- Crooke's hyaline change in normal pituitary = results from hypercortisolism of any cause
- Strong PAS+ = corticotroph adenoma
- Weak PAS+ = glycoprotein adenoma (FSH, LH, TSH)
- CK+ paranuclear "fibrous bodies" = GH-producing adenoma
- Immunostaining for hormones most useful in confirming prolactinoma (a medically treatable tumor) or in establishing the pituitary origin of tumor outside the sella
- EM is most useful in cases where immunostains are non-confirmatory or equivocal, as well as in establishing the diagnosis of rare aggressive forms such as acidophil stem cell or silent subtype III adenomas

Prolactinoma (Lactotrophic Adenoma)

- F > M; women present with amenorrhea and/or galactorrhea while tumor is still small
- In males, the tumor is often asymptomatic until large; decreased libido is only symptom
- Medically treatable with dopamine agonists which cause cellular atrophy and decreased cell proliferation

Corticotrophic (ACTH) Adenomas

Cushing's Syndrome

- Clinical manifestations of hypercortisolism of any cause

Nelson's Syndrome

- Bilateral adrenalectomy in setting of Cushing's disease wherein microadenoma is undetected. Results in uncontrolled tumoral growth due to the loss of end-organ feedback
- Most are aggressive and difficult to manage
- May undergo progression to pituitary carcinoma

Crooke's Hyaline Change

- Ring-like, keratin accumulations in normal ACTH cells
- Result of hypercortisolism of any cause

Silent Corticotroph Adenoma

- ACTH + adenoma unassociated with clinical and/or biochemical evidence of Cushing's disease; often invasive macroadenomas

Growth Hormone Adenoma

- Three forms: 1) Densely granulated GH adenoma, 2) Sparsely granulated GH adenoma which features cytoplasmic "fibrous bodies," 3) Plurihormonal
- adenomas which produce multiple hormones (GH, PRL, TSH-producing) and
- may consist of 1 to 3 separate cell types. All cause acromegaly. About 50% invasive

Growth Hormone and Prolactin-Producing Adenomas

- Three types
- Mixed GH cell-PRL cell adenoma. Two distinct cell types present. Relatively indolent
- Mammosomatotroph adenoma = GH and PRL produced by same cells. Signs of GH excess. Relatively indolent
- Acidophil stem cell adenoma = Rare variant. Serum PRL >GH level. Clinically mimics prolactinoma. Infrequent acromegaly. Features giant mitochondria and misplaced exocytosis at EM level:
  - Aggressive and relatively non-responsive to dopamine agonists

Gonadotrophic (FSH/LH) and Null Cell (IP-) Adenomas

- Elderly, M > F
- Clinically nonfunctioning; macroadenomas
- Most indolent and least invasive adenomas

Thyrotrophic Adenoma/Hyperplasias

- Rarest of the adenomas in pure form
- Many arise due to the loss of T_3/T_4 feedback in primary hypothyroidism

Atypical Pituitary Adenoma

- New diagnostic category
- Increased proliferative activity (mitoses, MIB-1 >3%); often p53 immunoreactive
- Thought to have increased risk of recurrence and, rarely, transformation to pituitary carcinoma
- Usually PRL+, GH+, or ACTH+ (functioning adenomas)

Pituitary Carcinoma

- Rare
- Brain invasion (exceptional finding during life) or intracranial (CSF) and/or extracranial metastases
- Most PRL+ or ACTH+. (latter often occur in setting of Nelson's syndrome)
- Usually p53+ and high MIB-1 index
- High morbidity/mortality

Pituitary Hyperplasia

- Diffuse form is difficult to document
- Nodular form features expanded acini filled by disproportionate number of one cell type; reticulin stain useful to show acinar enlargement
  - PRL: pregnancy, estrogen therapy
  - GH: hypothalamic or ectopic (neuroendocrine tumor) source of growth-hormone-releasing hormone
  - ACTH: hypothalamic or ectopic (neuroendocrine tumor) source of corticotropin-releasing hormone
  - FSH/LH: Klinefelter's and Turner's syndrome due to gonadal nonfunction
  - TSH: hypothyroidism: also associated with PRL hyperplasia since thyrotropin-releasing hormone stimulates not only TSH cells but PRL cells as well

Apoplexy

- Spontaneous hemorrhagic infarction of pituitary adenoma; usually large, nonfunctioning
- Surgical emergency
- Reticulin stains still show vessels and effaced acinar architecture
- Immunostains may be helpful in partly preserved tissue

Craniopharyngioma

- See "Other Nonglial Neoplasms" section, p. 8–31

Rathke's Cleft Cyst

- Developmental lesion; small examples often an incidental autopsy finding between anterior and posterior pituitary lobes
- Symptomatic lesions generally >1 cm; cause hyper-prolactinemia and/or visual disturbance
- Slow growing, surgically curable
- Clear, mucoid cyst contents
- Cuboidal to columnar, ciliated and nonciliated cells, goblet cells:
  - Same histology as colloid cyst of third ventricle and enterogenous cyst of spinal cord
- Squamous metaplasia in some; differential diagnosis includes craniopharyngioma

Granular Cell Tumor

- Benign tumor of pituicytes (specialized astrocytes in the posterior pituitary and stalk)
- Small, incidental examples common at autopsy; symptomatic lesions rare
- Identical morphology to granular cell tumors elsewhere
- Packed with PAS+ lysosomes, S-100 protein+
- Differential diagnosis includes pituitary adenoma with oncocytic change (mitochondria instead of lysosomes; secretory granules and hormones are demonstrable)

Histiocytosis X (Langerhans' Cell Histiocytosis)

- Most represent secondary CNS involvement from skull base
- Predilection for hypothalamus/infundibulum
- ± Diabetes insipidus
- May appear xanthomatous; differential diagnosis includes Rosai-Dorfman disease; Erdheim Chester disease

Hypothalamic Hamartoma

- Uncommon, incidental autopsy finding. Rarely symptomatic. Malformative in nature.

- Some present with precocious puberty or gelastic seizures (uncontrollable laughter). Rare pituitary hyperfunction due to releasing hormone production
- Sessile or pedunculated attachment to floor third ventricle; some lie separate from brain
- Resembles normal hypothalamus, but less organized
- Surgically curable

Other Tumors

- Covered elsewhere; include pilocytic astrocytoma, meningioma, hemangioma, sarcoma (often post-irradiation), and metastases

Lymphocytic Hypophysitis

- Autoimmune disorder associated with hypopituitarism
- Almost exclusively in postpartum women
- Other minor coexistent autoimmune disorders in some
- Lymphoplasmacytic infiltrate without granulomas
- Treated with surgery and hormone replacement; fatal if untreated

Empty Sella Syndrome

Primary

- Congenital defect in diaphragma sella permits downward herniation of leptomeninges ("arachnoidocele") with resulting compression of pituitary

Secondary

- "ex vacuo," (i.e., parenchymal loss):
  - Sheehan's syndrome = infarction due to postpartum shock
  - Apoplexy of an intrasellar adenoma
  - Post-surgical or post-irradiation loss of sellar volume

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9

Lymph Node

Ellen D. Remstein, MD and Paul J. Kurtin, MD

CONTENTS

I. How to Work Up a Lymph Node 9-3

II. Classification of Diseases.....9-3

Lymphoid Hyperplasias 9-3
Follicular Hyperplasias.....9-3
Sinus Hyperplasias 9-3
Paracortical Hyperplasias 9-3
Necrotizing Granulomatous Lymphadenitis 9-3
Necrotizing Nongranulomatous Lymphadenitis 9-3

III. Malignant Lymphoma/Leukemia (WHO Classification).....9-3

Precursor B- and T- cell Neoplasms.....9-3
Mature B-Cell Neoplasms 9-3
Mature T-Cell and NK-Cell Neoplasms 9-3
Hodgkin Lymphoma.....9-4
Histiocytic Lymph Node Tumors.....9-4
Spindle Cell Lesions of Lymph Node 9-4

IV. Lymphoid Hyperplasias 9-4

Follicular Hyperplasias 9-4
Reactive Follicular Hyperplasia 9-4
Toxoplasmosis 9-4
Cytomegalovirus (CMV) 9-4
Human Immunodeficiency Virus (HIV)....9-4
Rheumatoid Arthritis 9-4
Syphilis (Luetic Lymphadenitis) 9-5
Progressive Transformation of Germinal Centers 9-5
Castleman's Disease, Hyaline Vascular Type 9-6
Castleman's Disease, Plasma Cell Variant 9-6
Sinus Hyperplasias 9-6
Lymphangiogram Effect 9-6
Whipple's Disease 9-6
Hemophagocytic Syndrome 9-7
Vascular Transformation of Lymph Node Sinuses 9-7
Paracortical Hyperplasias.....9-7
Infectious Mononucleosis.....9-7
Atypical Immunoblastic Reaction 9-7
Dermatopathic Lymphadenopathy 9-8
Necrotizing Granulomatous Lymphadenitis 9-8
Cat Scratch Disease 9-8
Lymphogranuloma Venereum (LGV).....9-8
Tularemia 9-8
Yersinia.....9-8
Tuberculosis (TB).....9-8
Fungal Infection 9-9
Necrotizing Nongranulomatous Lymphadenitis 9-9
Kikuchi-Fujimoto Disease 9-9
Systemic Lupus Erythematosis (SLE) 9-9

V. Malignant Lymphoma/Leukemia (WHO Classification).....9-9

Precursor B- and T-Cell Neoplasms.....9-9
Precursor B-Lymphoblastic Leukemia (B-ALL)/Lymphoblastic Lymphoma (B-LBL) 9-9
Precursor T-Lymphoblastic Leukemia/Lymphoma (T-ALL/T-LBL) 9-10
Mature B-Cell Neoplasms 9-11
Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) 9-11

B-Cell Prolymphocytic Leukemia (B-PLL) 9-13
Lymphoplasmacytic Lymphoma/ Waldenström Macroglobulinemia 9-13
Splenic Marginal Zone Lymphoma 9-14
Hairy Cell Leukemia (HCL)....9-15
Plasma Cell Neoplasms 9-16
Extranodal Marginal Zone B-cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma) 9-16
Nodal Marginal Zone B-Cell Lymphoma 9-18
Follicular Lymphoma (FL) 9-18
Mantle Cell Lymphoma (MCL) 9-21
Diffuse Large B-Cell Lymphoma....9-23
Mediastinal (Thymic) Large B-Cell Lymphoma 9-24
Burkitt Lymphoma/Leukemia....9-25
Mature T-Cell and NK-Cell Neoplasms....9-26
T-Cell Prolymphocytic Leukemia (T-PLL) 9-26
Large Granular Lymphocytic (LGL) Leukemia 9-27
Aggressive NK-Cell Leukemia....9-27
Adult T-Cell Leukemia/ Lymphoma (ATL/L)....9-27
Extranodal NK/T-Cell Lymphoma, Nasal Type 9-28
Enteropathy-Type T-Cell Lymphoma 9-28
Hepatosplenic T-Cell Lymphoma....9-28
Subcutaneous Panniculitis-Like T-Cell Lymphoma 9-29
Blastic NK-Cell Lymphoma....9-30
Mycosis Fungoides/Sézary Syndrome (MF/SS) 9-30
Angioimmunoblastic T-Cell Lymphoma 9-31
Peripheral T-Cell Lymphoma, Unspecified 9-31
Anaplastic Large Cell Lymphoma (ALCL) 9-32
Hodgkin Lymphoma (HL) 9-33
Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)....9-33
Nodular Sclerosis Hodgkin Lymphoma 9-35
Mixed Cellularity Hodgkin Lymphoma (MCHL) 9-35
Lymphocyte-Rich Classical Hodgkin Lymphoma (LRCHL) 9-36
Lymphocyte Depleted Hodgkin Lymphoma (LDHL)....9-36

VI. Histiocytic Lymph Node Tumors 9-37
Langerhans Cell Histiocytosis 9-37
Sinus Histiocytosis with Massive Lymphadenopathy (SHML)....9-37
Histiocytic Sarcoma 9-38

VII. Spindle Cell Lesions of Lymph Nodes....9-38
Bacillary Angiomatosis 9-38
Palisaded Myofibroblastoma 9-39
Inflammatory Pseudotumor of Lymph Node 9-40
Follicular Dendritic Cell Sarcoma 9-40
Interdigitating Dendritic Cell Sarcoma 9-40

VIII. Suggested Reading.....9-40

HOW TO WORK UP A LYMPH NODE

- Receive lymph node fresh
- Ensure excellent fixation (B5 or zinc sulfate formalin preferred)
- Snap freeze a portion (for frozen immunoperoxidase stains and molecular genetics)
- Virtually all diagnostic problems involving hematolymphoid neoplasms can be resolved by a combination of paraffin section immunoperoxidase stains, frozen section immunoperoxidase stains, and/or molecular genetics studies
- Flow cytometry (selected cases)
- Phenotypic approach: Most cost effective approach should be driven by the morphologic differential diagnosis. Remember: reimbursement is not guaranteed if ancillary studies cannot be shown to be diagnostically justified

CLASSIFICATION OF DISEASES

Lymphoid Hyperplasias

Follicular Hyperplasias

- Reactive follicular hyperplasia
- Toxoplasmosis
- Cytomegalovirus
- Human immunodeficiency virus
- Rheumatoid arthritis
- Syphilis
- Progressive transformation of germinal centers
- Castleman's disease, hyaline vascular type
- Castleman's disease, plasma cell type

Sinus Hyperplasias

- Lymphangiogram effect
- Whipple's disease
- Hemophagocytic syndrome
- Vascular transformation of lymph node sinuses

Paracortical Hyperplasias

- Infectious mononucleosis
- Atypical immunoblastic reaction
- Dermatopathic lymphadenopathy

Necrotizing Granulomatous Lymphadenitis

- Cat scratch disease
- Lymphogranuloma venereum
- Tularemia
- Yersinia
- Tuberculosis
- Fungal infection

Necrotizing Nongranulomatous Lymphadenitis

- Kikuchi-Fujimoto disease
- Systemic lupus erythematosis

MALIGNANT LYMPHOMA/LEUKEMIA (WHO CLASSIFICATION)

Precursor B- and T-Cell Neoplasms

- Precursor B-lymphoblastic leukemia/lymphoma
- Precursor T-lymphoblastic leukemia/lymphoma

Mature B-Cell Neoplasms

- Chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- Lymphoplasmacytic lymphoma/Waldenström macroglobulinemia
- Splenic marginal zone lymphoma
- Hairy cell leukemia
- Plasma cell neoplasms
- Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
- Nodal marginal zone B-cell lymphoma
- Follicular lymphoma
- Mantle cell lymphoma
- Diffuse large B-cell lymphoma
- Mediastinal (thymic) large B-cell lymphoma
- Burkitt lymphoma/leukemia

Mature T-Cell and NK-Cell Neoplasms

- T-cell prolymphocytic leukemia
- Large granular lymphocytic leukemia
- Aggressive NK-cell leukemia

- Adult T-cell leukemia/lymphoma
- Extranodal NK/T-cell lymphoma, nasal type
- Enteropathy-type T-cell lymphoma
- Hepatosplenic T-cell lymphoma
- Subcutaneous panniculitis-like T-cell lymphoma
- Blastic NK-cell lymphoma
- Mycosis fungoides/Sézary syndrome
- Angioimmunoblastic T-cell lymphoma
- Peripheral T-cell lymphoma, unspecified
- Anaplastic large cell lymphoma

Hodgkin Lymphoma

- Nodular lymphocyte predominant Hodgkin lymphoma
- Classical Hodgkin lymphoma:
  - Nodular sclerosis Hodgkin lymphoma
  - Mixed cellularity Hodgkin lymphoma
  - Lymphocyte-rich classical Hodgkin lymphoma
  - Lymphocyte depleted Hodgkin lymphoma

Histiocytic Lymph Node Tumors

- Langerhans' cell histiocytosis
- Sinus hyperplasia with massive lymphadenopathy
- Histiocytic sarcoma

Spindle Cell Lesions of Lymph Node

- Bacillary angiomatosis
- Kaposi's sarcoma
- Palisaded myofibroblastoma
- Inflammatory pseudotumor of lymph node
- Follicular dendritic cell sarcoma
- Interdigitating dendritic cell sarcoma

LYMPHOID HYPERPLASIAS

Follicular Hyperplasias

Reactive Follicular Hyperplasia

Differential Diagnosis

- Follicular lymphoma (*See* **Table 1**)

Toxoplasmosis

Clinical

- Mostly young females (if pregnant, may result in birth defects in developing fetus)
- Transmitted by exposure to oocysts in cat feces or by ingestion of poorly-cooked meat
- Symptoms: flu-like or asymptomatic
- Site of involvement: posterior cervical nodes most common

Microscopic ***(Figure 1)***

- Toxo Triad:
  - Florid follicular hyperplasia
  - Monocytoid B-cell hyperplasia expanding and surrounding sinuses
  - Paracortical epithelioid histiocyte clusters that encroach on germinal centers:
    - No necrosis
- Confirm diagnosis with serologic studies

Cytomegalovirus (CMV)

Microscopic

- Florid follicular hyperplasia
- Monocytoid B-cell hyperplasia expanding sinuses (CMV inclusions may sometimes be identified here)
- +/– immunoblastic proliferation (may be atypical)
- Confirm diagnosis serologically, immunohistochemically, or by *in situ* hybridization techniques

Human Immunodeficiency Virus (HIV)

Microscopic ***(Figure 2)***

- Early stage:
  - Florid reactive lymphoid hyperplasia with absent mantle zones and follicle lysis of germinal centers (germinal centers disrupted by hemorrhage, disrupted FDC [follicular dendritic cell] meshwork, and increased T-cells)
  - Monocytoid B-cell hyperplasia expanding sinuses
  - Epithelioid histiocyte clusters
  - Increased plasma cells and polykaryocytes (large multinucleated giant cells) in interfollicular zones
- Late stage:
  - Regressively transformed germinal centers
  - Depletion of lymphocytes from paracortex

Differential Diagnosis

- Castleman's disease, hyaline vascular type: Expanded mantle zones, hyalinized vessels

Rheumatoid Arthritis

Microscopic

- Florid follicular hyperplasia
- Marked interfollicular plasmacytosis (plasma cells also present within follicles)
- Clusters of neutrophils in sinuses

Table 1. Follicular Hyperplasia vs Follicular Lymphoma

Follicular Hyperplasia	*Follicular Lymphoma*
Younger patients	Older patients
Normal follicle density	Increased follicle density (back to back)
Follicles vary in size and shape	Follicles homogeneous
Well-defined mantle zone	Thin or absent mantle zone
Cellular polarization present	Cellular polarization absent
Heterogeneous follicle cells	Homogeneous follicle cells
Tingible body macrophages present	Tingible body macrophages absent
Mitoses common	Mitoses uncommon
Follicles confined to node	Follicles may be seen in perinodal tissue
No atypical cells between follicles	Interfollicular regions may contain neoplastic cells
Follicle center cells (FCC) bcl-2 negative	Follicle center cells (FCC) bcl-2 positive (usually)
FCC not light chain restricted	FCC light chain restricted
Ig/bcl-2 genes not rearranged	Ig/bcl-2 genes rearranged (Southern blot or PCR or FISH)

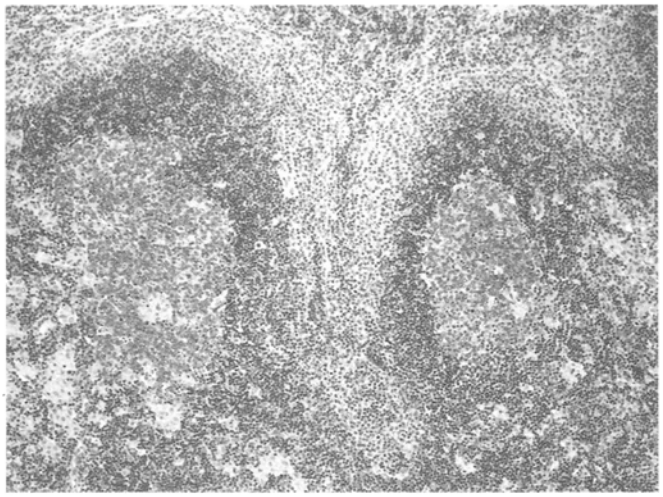


Fig 1. Toxoplasmosis lymphadenitis.

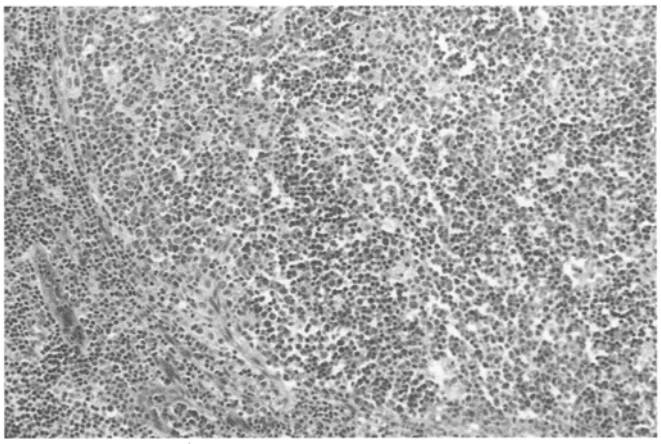


Fig 2. Human immunodeficiency virus lymphadenitis.

Differential Diagnosis

- Other inflammatory disorders (e.g., Sjögren's syndrome, Felty's syndrome, Still's disease)
- HIV infection
- Syphilis
- Castleman's disease, plasma cell type (this is a clinicopathologic diagnosis)

Syphilis (Luetic Lymphadenitis)

Microscopic

- Florid follicular hyperplasia
- Interfollicular plasmacytosis
- Epithelioid granulomas
- Thick, fibrotic capsule—perivascular plasma cells
- +/– arteritis/phlebitis
- Confirm diagnosis serologically

Progressive Transformation of Germinal Centers

- Rarely precedes, accompanies, or succeeds nodular lymphocyte predominant Hodgkin lymphoma (NLPHL)

Microscopic

- Associated with reactive follicular hyperplasia in the same node
- Large follicles with indistinct germinal center/mantle zone borders due to infiltration of germinal centers by mantle zone lymphocytes
- Residual large germinal center cells (EMA–) may mimic L&H cells (usually EMA+) of NLPHL

Differential Diagnosis

- NLPHL:
  - Neoplastic Hodgkin cells have nuclear lobulation, centroblasts usually do not
  - Hodgkin cells usually EMA+
- Follicular lymphoma, floral variant:
  - Neoplastic follicle center cells usually bcl-2+ and exhibit kappa or lambda light chain restriction
- Mantle cell lymphoma:
  - Neoplastic cells surround atrophic follicles
  - Monoclonal B-cells CD5+, cyclin D1+

Castleman's Disease, Hyaline Vascular Type

Clinical

- Usually solitary mediastinal mass, may involve other sites

*Microscopic (**Figure 3**)*

- Atrophic germinal centers (regressively transformed) with expanded mantle zones composed of concentric layers of lymphocytes
- Multiple regressively transformed germinal centers in one "cloud" of mantle zone lymphocytes
- Hyalinized blood vessels penetrate into follicles; interfollicular vascularity increased
- Few interfollicular plasma cells or transformed lymphocytes

Differential Diagnosis

- HIV infection:
  - Absent mantle zones
  - Increased interfollicular plasma cells and polykaryocytes

Castleman's Disease, Plasma Cell Variant

Clinical

- Patients may have POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin lesions) or a variety of other signs and symptoms
- Sites of involvement: abdominal cavity and mediastinum, peripheral lymph nodes, extranodal sites
- Clinicopathologic diagnosis

Microscopic

- Florid follicular hyperplasia with regressive transformation of germinal centers

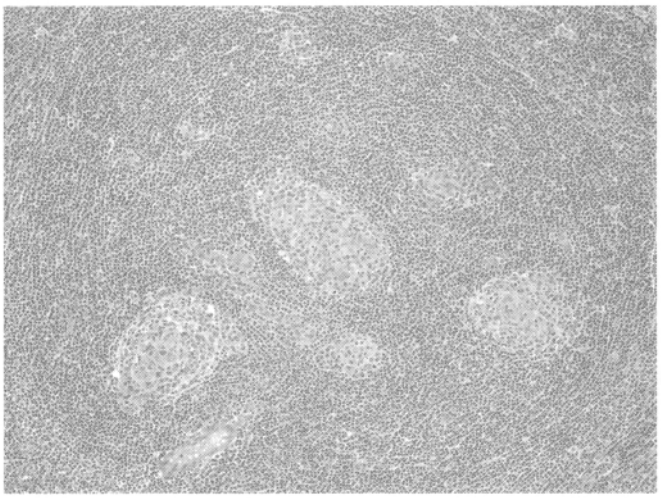


Fig 3. Castleman's Disease, hyaline vascular type.

- Marked interfollicular plasmacytosis that extends to the lymph node capsule

Differential Diagnosis

- Rheumatoid arthritis
- HIV infection
- Syphilis

Sinus Hyperplasias

Differential Diagnosis of All Sinus Hyperplasias

- Metastatic carcinoma
- Metastatic malignant melanoma
- Anaplastic large cell lymphoma (ALCL)

Lymphangiogram Effect

Clinical

- Sites of involvement: Abdominal lymph nodes

Microscopic

- Sinuses distended by lipid vacuoles surrounded by histiocytes and multinucleated giant cells

Whipple's Disease

Clinical

- Age: middle-aged adults
- Sex: M > F
- Etiology: infectious disease of small bowel (etiologic agent: Tropheryma whippelli)
- Site of involvement: small bowel, abdominal lymph nodes, +/– peripheral lymph nodes

Microscopic

- Sinuses distended by large lipid vacuoles surrounded by vacuolated histiocytes

- PAS+ bacilli present within histiocyte cytoplasm in sinuses and in germinal centers
- Confirm diagnosis by PCR or electron microscopy

Differential Diagnosis

- Mycobacterium avium intracellulare (MAI):organisms are acid-fast + as well as PAS+
- Lymphangiogram effect: histiocytes are PAS–, acid-fast –
- Lipogranuloma: diagnosis of exclusion
- Silicon

Hemophagocytic Syndrome

Synonym

- Virus-associated hemophagocytic syndrome

Clinical

- Immunocompromised host
- Usually due to viral infection, may result from bacterial, fungal, or parasitic infection
- May complicate certain lymphomas:
  - Subcutaneous panniculitis-like T-cell lymphoma
  - ALCL
  - Extranodal NK/T-cell lymphoma, nasal type
- Sites of involvement: lymph nodes, spleen, bone marrow

Microscopic

- Sinuses distended by benign-appearing histiocytes containing phagocytized erythrocytes or other hematopoietic elements

Vascular Transformation of Lymph Node Sinuses

Clinical

- Lymph node enlargement
- Sometimes associated with deep venous thrombosis in adjacent vein

Microscopic

- Sinuses distended by proliferating anastamosing vascular channels, often with fibrosis
- Capsule spared

Differential Diagnosis

- Kaposi's sarcoma:
  - Capsular/subcapsular involvement
  - Spindle cell proliferation without distinct vascular channels
  - PAS+ hyaline globules

Paracortical Hyperplasias

Differential Diagnosis of all Paracortical Hyperplasias

- Peripheral T-cell lymphoma
- Interfollicular Hodgkin lymphoma

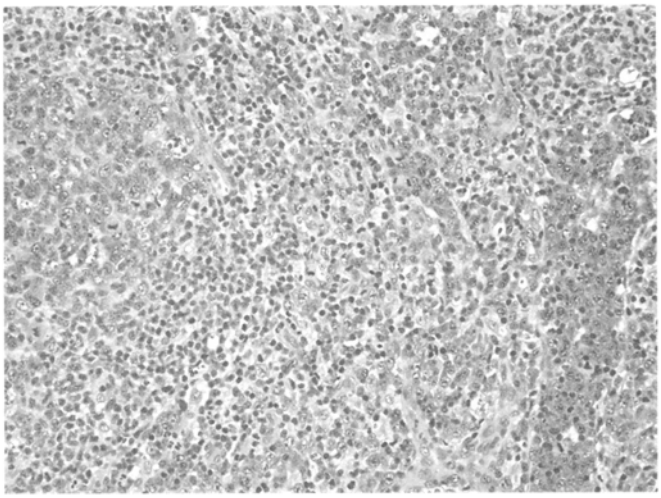


Fig. 4. Infectious mononucleosis.

Infectious Mononucleosis

Microscopic ***(Figure 4)***

- Paracortical expansion (EBV+ cells located in paracortex)
- Focal necrosis
- Sinuses distended by atypical lymphocytes, monocytoid B-cells, and/or immunoblasts
- +/– follicular hyperplasia
- Cytology: polymorphous population of transformed lymphocytes, immunoblasts, RS-like cells, plasma cells, and histiocytes
- Confirm diagnosis by serologic studies or blood findings (lymphocytosis with >50% lymphocytes, >10% atypical lymphocytes)

Differential Diagnosis

- Diffuse large B-cell lymphoma: monoclonal
- Classical Hodgkin lymphoma: Hodgkin cells CD15+, CD30+, CD45–
- Viral infection (e.g., CMV)
- Drug reaction (especially hydantoin)

Atypical Immunoblastic Reaction

Microscopic

- Similar to infectious mononucleosis

Causes

- Drug reaction (especially hydantoin): eosinophils often numerous
- Herpes simplex: viral inclusions may be seen in and around necrotic areas
- CMV: accompanied by monocytoid B-cell hyperplasia, CMV inclusions
- Postvaccinial (smallpox vaccine): RARE

Dermatopathic Lymphadenopathy

Clinical

- Usually associated with skin lesions

Microscopic

- Subcapsular paracortical regions expanded (often focally) by small lymphocytes, some with convoluted nuclei resembling small Sézary cells, interdigitating reticulum cells, Langerhans cells, and histiocytes containing melanin, lipid, and hemosiderin
- Residual node displaced centrally

Differential Diagnosis

- Mycosis fungoides:
  - more architectural effacement, large and medium-sized pleomorphic lymphocytes present
  - aberrant T-cell phenotype
  - may require molecular genetics

Necrotizing Granulomatous Lymphadenitis

Cat Scratch Disease

Clinical

- Sites of involvement: axillary and cervical lymph nodes
- Etiologic agent: Bartonella henselae

Microscopic

- Central stellate abscesses containing neutrophils, surrounded by palisaded histiocytes and fibroblasts; sparse to no multinucleated giant histiocytes
- +/– follicular hyperplasia
- +/– monocytoid B-cells distending sinuses
- Bacilli (found in necrotic areas) stain positively with Warthin-Starry stain

Differential Diagnosis

- Lymphogranuloma venereum, Tularemia, Yersinia– all – on Warthin-Starry stain
- Toxoplasmosis: No necrosis, Warthin-Starry–
- Hodgkin lymphoma

Lymphogranuloma Venereum (LGV)

Clinical

- Sexually transmitted disease caused by chlamydia trachomatis
- Involves inguinal lymph nodes in males, pelvic lymph nodes in females

Microscopic

- Morphologically indistinguishable from cat scratch disease, tularemia, yersinia
- Confirm diagnosis serologically

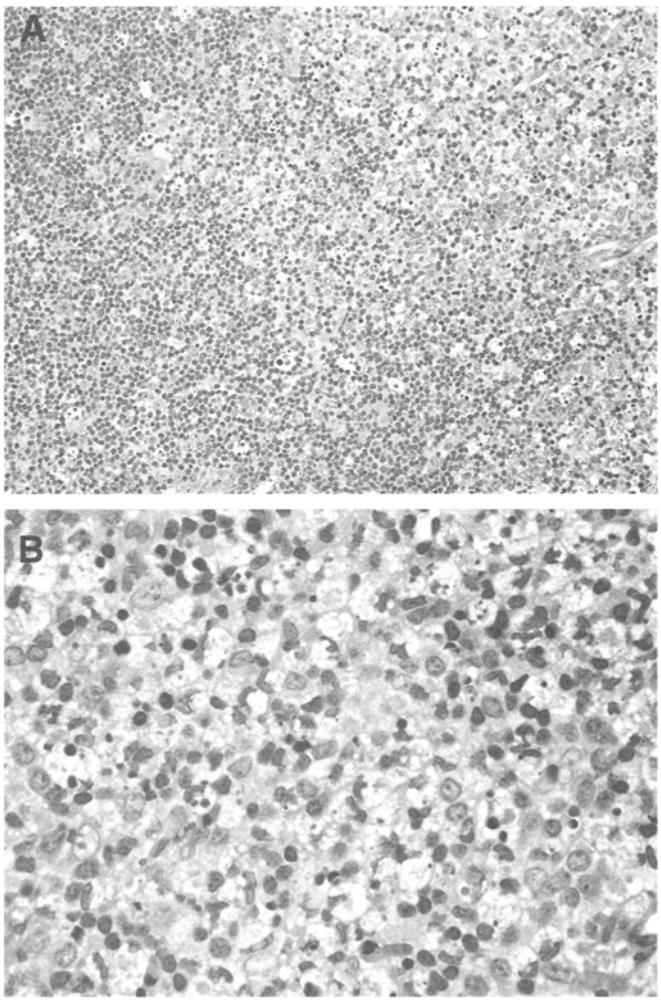


Fig. 5. Kikuchi-Fujimoto disease (**A** and **B**).

Tularemia

- Often history of tick bite
- Involves axillary lymph nodes
- Morphologically indistinguishable from cat scratch disease, LGV, yersinia
- Confirm diagnosis by serology or cultures

Yersinia

- Clinical history of abdominal pain and diarrhea, signs suggesting appendicitis
- Involves mesenteric lymph nodes
- Morphologically indistinguishable from cat scratch disease, LGV, tularemia

Tuberculosis (TB)

Microscopic

- Necrotizing granulomas with central caseous necrosis without neutrophils
- AFB+ bacilli present in necrotic areas (may be difficult to find); PCR may help

Fungal Infection

- Morphologically similar to TB, but granulomas more commonly contain neutrophils and karyorrhectic nuclear debris
- Organisms GMS+, PAS+

Necrotizing Nongranulomatous Lymphadenitis

Kikuchi-Fujimoto Disease

Synonym

- Histocytic necrotizing lymphadenitis

Clinical

- Young adult females
- Involves cervical lymph nodes

*Microscopic (**Figure 5**)*

- Patchy cortical and paracortical necrosis with extensive karyorrhectic debris and histiocytes centrally
- Immunoblasts, histiocytes, and plasmacytoid monocytes peripherally
- No granulocytes, few plasma cells

Systemic Lupus Erythematosis (SLE)

Clinical

- Young adult females
- Cervical or generalized lymphadenopathy

Microscopic

- Follicular hyperplasia
- Interfollicular zones contain increased plasma cells and immunoblasts
- Areas of necrosis may contain neutrophils or plasma cells
- Hematoxylin bodies (composed of DNA aggregates, polysaccharides, and immunoglobulin) found within areas of necrosis as well as in walls of blood vessels

MALIGNANT LYMPHOMA/LEUKEMIA (WHO CLASSIFICATION)

Precursor B- and T-Cell Neoplasms

Precursor B-Lymphoblastic Leukemia (B-ALL)/ Lymphoblastic Lymphoma (B-LBL)

Synonyms

- Rappaport: lymphoblastic (formerly diffuse poorly differentiated lymphocytic [PDL])
- Kiel: lymphoblastic, B-cell type
- Lukes-Collins: undefined cell
- Working Formulation:lymphoblastic
- FAB: L1 and L2
- REAL: precursor B lymphoblastic leukemia/lymphoma

Clinical

- Age: children > adults
- Presentation:
  - Acute lymphoblastic leukemia (bone marrow and peripheral blood involvement) — more common. Pancytopenia, adenopathy, hepatosplenomegaly, bone pain
  - Lymphoblastic lymphoma (solid tumor [lymph node, skin, bone], +/– minimal bone marrow or peripheral blood involvement [≤25% lymphoblasts in bone marrow - arbitrary cut-off]; mediastinum rarely involved in B-LBL) — less common
- Clinical course:
  - Highly aggressive
  - Often curable with chemotherapy
  - Better prognosis:
    - >50 chromosomes
    - t(12;21)(p13;q22)
  - Poorer prognosis:
    - t(1;19), t(9;22), t(4;11)(q21;q23), hypodiploidy
    - lack of CD10, CD34, or CD24 expression
    - CD13 or CD33 expression

Postulated Cell of Origin

- Precursor B-lymphoblasts

Microscopic

- Low power:
  - Architecture effaced
  - Invasion of perinodal fat common
  - Tumor involves paracortex, may spare reactive follicles
- High power (**Figure 6**):
  - Monotonous population of lymphoblasts:medium-sized cells with round or convoluted nuclei, fine chromatin, inconspicuous nucleoli, scant cytoplasm
  - Frequent mitoses
  - +/– starry sky pattern (tingible body macrophages)
  - T and B phenotypes morphologically indistinguishable

Immunophenotype

- CD19+, CD79a+

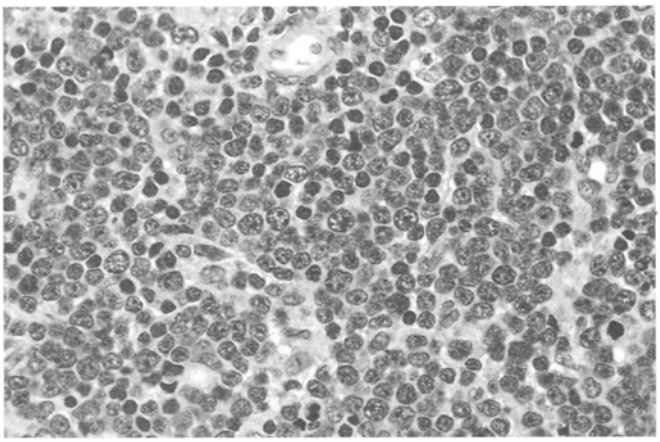


Fig. 6. Precursor B-lymphoblastic leukemia/lymphoma.

- CD43+
- TdT (terminal deoxynucleatidyl transferase)+
- CD34 usually+
- CD20, CD22 usually+
- CD10 usually+
- Surface immunoglobulin (sIg)–
- CD13 and/or CD33 may be present

Genetics

- Ig heavy chain genes rearranged
- Light chain genes may be rearranged (~50%)
- T-cell receptor gene may be rearranged in B-LBL

*Differential Diagnosis (**Table 2**)*

- More mature B-cell neoplasms (e.g., blastoid variant of mantle cell lymphoma):
  - TdT and CD34–
  - sIg+
- Precursor T-lymphoblastic leukemia/lymphoma:
  - B-cell associated antigens–
  - CD3, CD7+
  - CD34–
- Myeloid sarcoma (extramedullary myeloid tumor, granulocytic sarcoma):
  - CD13, CD33, myeloperoxidase (MPO), CD68, lysozyme +
  - CD19, CD22, CD10, CD79a–
- Burkitt lymphoma:
  - More prominent starry-sky pattern, coarser chromatin, multiple nucleoli, amphophilic, agranular cytoplasm
  - sIg+
  - CD34, TdT–

Precursor T-Lymphoblastic Leukemia/Lymphoma (T-ALL/T-LBL)

Synonyms

- Rappaport: poorly differentiated lymphocytic, diffuse (modified to lymphoblastic)
- Kiel: T-lymphoblastic
- Lukes-Collins: convoluted T-lymphocytic
- Working Formulation: lymphoblastic, convoluted or nonconvoluted

Clinical

- Age: adolescents and young adults
- Sex: M > F
- Presentation: rapidly enlarging mediastinal (thymic) mass, +/– lymphadenopathy, SVC syndrome, pericardial and pleural effusions
- Bone marrow involvement >25% = precursor T-lymphoblastic leukemia
- Clinical course: highly aggressive but potentially curable

*Microscopic (**Figure 7**)*

- Monotonous population of lymphoblasts (medium-sized cells with round nuclei, fine chromatin, inconspicuous nucleoli, and scant cytoplasm)
- Numerous mitoses, tingible body macrophages (starry sky)
- Morphologically indistinguishable from B-LBL

Immunophenotype

- Mirrors stages of intrathymic T-cell ontogeny
- CD7+, CD3+ (cytoplasmic + even if surface–), CD2+, CD5+
- Subset of cases expresses CD1, CD4 and CD8
- TdT+
- Immunoglobulin–
- B-cell associated antigens–

Genetics

- T-cell receptor gene rearrangement variable
- Immunoglobulin heavy chain gene rearrangement may be present

Differential Diagnosis

- B-LBL:
  - B-cell associated antigens+
  - T-cell associated antigens–
  - CD10+
- Mature B-cell lymphoma:
  - Lacks blastic cytology
  - B-cell associated antigens+
  - T-cell associated antigens–
  - TdT–

Table 2. Paraffin Section Immunophenotype of Blastic Hematolymphoid Malignancies

Disorder	*TdT*	*CD34*	*CD43*	*MPO/Lys*[1]	*CD3*	*CD79a*	*CD20*	*Cyclin D1*
Precursor T-lymphoblastic leukemia/lymphoma	+	–	+	–	+	–	–	–
Precursor B-lymphoblastic leukemia/lymphoma	+	+	+	–	–	+	+/–	–
Myeloid sarcoma	+/–	+/–	+	+/–	–	–	–	–
Burkitt lymphoma	–	–	+	–	–	+	+	–
Blastoid mantle cell lymphoma	–	–	+	–	–	+	+	+

[1]*MPO/Lys: myeloperoxidase/lysozyme.*

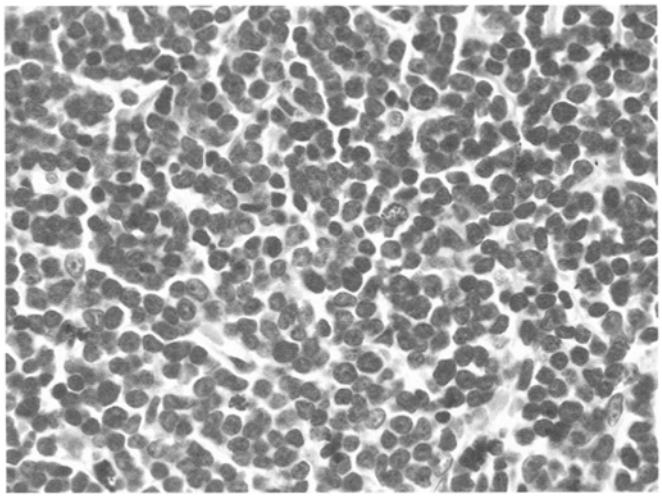


Fig. 7. Precursor T-lymphoblastic leukemia/lymphoma.

- Mature T-cell lymphoma:
  - Heterogeneous cell population that lacks blastic cytology
  - TdT–
- Myeloid sarcoma (extramedullary myeloid tumor, granulocytic sarcoma):
  - Eosinophilic cytoplasm
  - Myeloperoxidase (MPO)+, lysozyme +, CD68+
  - T-cell associated antigens –

Mature B-Cell Neoplasms

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

Synonyms

- Rappaport: well-differentiated lymphocytic, diffuse
- Kiel: CLL
- Lukes-Collins: small lymphocytic B, CLL
- Working Formulation: small lymphocytic, consistent with CLL
- REAL: B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma

Clinical

- Age: older adults (median age 60–65 yrs)
- Sex: M > F (slight)
- History of waxing and waning adenopathy common
- Usually disseminated at presentation (involvement of bone marrow, multiple lymph nodes, spleen, and liver common)
- ~30% of patients with SLL progress to CLL
- CLL criteria: >10,000/mm^3 circulating lymphocytes
- CLL: lymph nodes (in addition to bone marrow and peripheral blood) usually involved
- SLL and CLL morphologically indistinguishable on lymph node biopsy
- Clinical course:
  - Indolent but not curable with available therapy
  - Median survival: 60–70 months
  - May transform to large cell lymphoma; risk increases over time
  - Poorer prognosis:
    - Extensive clinical disease
    - Increased number of large cells (prolymphocytes and paraimmunoblasts)
    - Trisomy 12, 17p deletion, 11q deletion
    - Germline variable region genes (consistent with naive B-cell derivation)—may correlate with CD38/ZAP70 expression
  - Better prognosis:
    - 13q deletion

- Postulated cell of origin:
  - 40–50%—naïve B-cell (germline variable region genes)
  - 50–60%—post-germinal center B-cell (variable region genes contain somatic mutations)

Microscopic

- Low power:
  - Effaced architecture (75% of cases)
  - Extensive involvement of perinodal fat in one third of cases
  - May be interfollicular
  - Pale zones (proliferation centers) alternating with darker zones **(Figure 8A)**
- High power:
  - Monotonous population of small lymphocytes (rounded nuclei, clumped chromatin, scant cytoplasm, inconspicuous to small nucleoli, and infrequent mitotic figures)
  - Most cases also contain larger lymphoid cells (prolymphocytes and paraimmunoblasts), frequently forming indistinct nodules known as pseudofollicles, proliferation centers or growth centers **(Figure 8B)**

Immunophenotype

- CD19, CD20, CD79a+
- CD23+
- CD5+, CD43+
- sIg weakly + (M +/– D), immunoglobulin light chain restricted
- CD10–
- cyclin D1–

Genetics

- Ig heavy and light chain genes are rearranged
- Trisomy 12
- 13q abnormalities (13q14)—most common-slightly better prognosis
- 11q deletion—poorer prognosis
- 17p deletion—poorer prognosis

Variant

- Interfollicular small lymphocytic lymphoma:
  - Microscopic: numerous residual follicles (tumor will subsequently spread through lymph node to obliterate architecture)

*Differential Diagnosis (See **Tables 3** and **4**)*

- Lymphoplasmacytic lymphoma:
  - Monoclonal plasmacytoid lymphocytes and plasma cells present; Dutcher bodies
- Mantle cell lymphoma (MCL):
  - Slightly larger lymphocytes with cleaved nuclei; no proliferation centers
  - CD23–

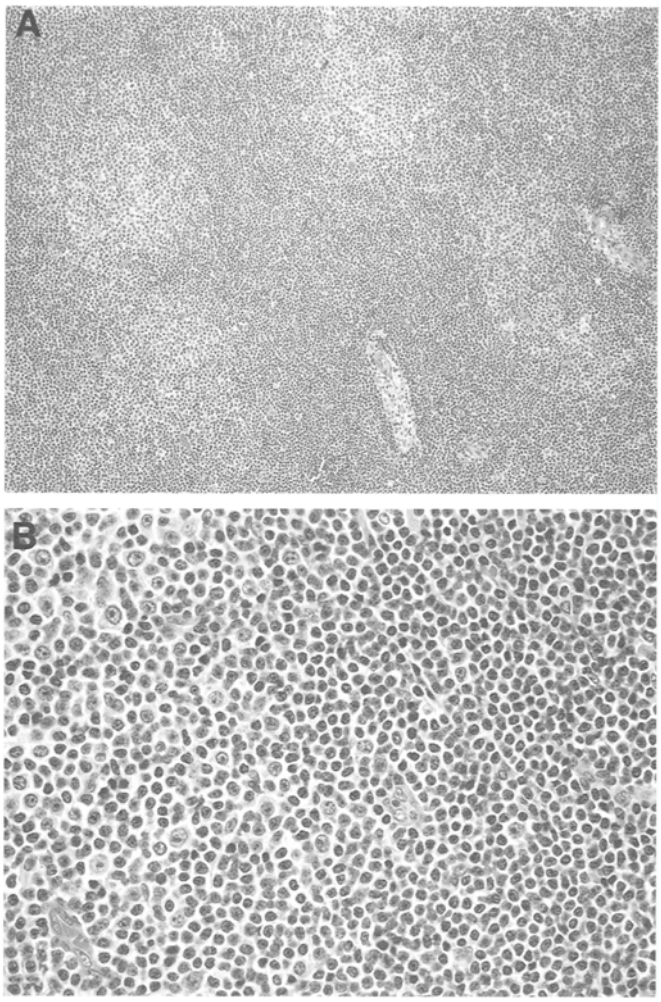


Fig. 8. Chronic lymphocytic leukemia/small lymphocytic lymphoma. **A.** low power; **B.** high power—proliferation centers.

  - Cyclin D1+
  - t(11;14) present
- Follicular lymphoma (FL):
  - Follicular pattern (at least partially), centrocytes usually predominate, no proliferation centers
  - CD5–, CD43–, CD23 usually–
  - CD10+
  - Cyclin D1–
  - t(14;18) common
- Marginal zone B-cell lymphoma:
  - Cellular heterogeneity, reactive follicles usually present, no proliferation centers
  - CD5 usually–, CD23–
- T-cell prolymphocytic leukemia:
  - T-cell associated antigens+
  - B-cell associated antigens–
- B-cell prolymphocytic leukemia (see below)

Table 3. Morphologic Differential Diagnosis of B-cell Lymphoproliferative Disorders in Lymph Node, Spleen and Bone Marrow Histologic Sections

	Lymph Node	*Spleen*	*Bone Marrow*	*Cytology*
Chronic lymphocytic leukemia/small lymphocytic lymphoma	Diffuse pattern, proliferation centers	Red pulp cords and sinusoids	Intertrabecular nodules and interstitial	Small lymphocytes, prolymphocytes, and paraimmunoblasts
Lymphoplasmacytic lymphoma	Diffuse pattern	Red pulp cords and sinusoids, encroaches on borders of white pulp	Intertrabecular nodules and interstitial, may be paratrabecular	Small lymphocytes, plasmacytoid lymphocytes, plasma cells, Dutcher bodies
Mantle cell lymphoma	Diffuse or nodular pattern with atrophic germinal centers	White pulp with atrophic germinal centers and obliterated marginal zone	Intertrabecular nodules and paratrabecular aggregates	Small lymphocytes with nuclear irregularity. No large cells
Nodal marginal zone lymphoma	Perisinusal or surrounding benign germinal centers and mantle zones	White pulp with small germinal centers and residual non-neoplastic mantle cells	Intertrabecular nodules and paratrabecular aggregates	Medium size cells with irregular nuclei, abundant pale cytoplasm. Occasional large transformed cells
Hairy cell leukemia	Rarely involved. Hilum, perinodal soft tissue involvement	Red pulp cords and sinusoids. Blood lakes	Interstitial	Small to medium size lymphocytes with abundant pale cytoplasm
Follicular lymphoma	True follicular nodularity	White pulp germinal centers expanded with benign mantle and marginal zone cells	Intertrabecular nodules and paratrabecular aggregates	Small cleaved cells and large non-cleaved cells in varying proportions

B-Cell Prolymphocytic Leukemia (B-PLL)

Clinical

- Often present with higher WBC count and splenomegaly

Microscopic

- >50% of blood lymphocytes have clumped chromatin with prominent single nucleolus (defined on the basis of peripheral blood involvement, not tissue sections)

Immunophenotype

- Strong sIg+, CD5 may be –, CD23 usually absent

Prognosis

- More aggressive clinical course

Lymphoplasmacytic Lymphoma/Waldenström Macroglobulinemia

Synonyms

- Rappaport: well-differentiated lymphocytic, plasmacytoid, diffused mixed lymphocytic and histiocytic
- Kiel: immunocytoma, lymphoplasmacytic type
- Lukes-Collins: plasmacytic-lymphocytic
- Working Formulation: small lymphocytic, plasmacytoid, diffuse mixed small and large cell
- REAL: lymphoplasmacytoid lymphoma/immunocytoma

Clinical

- Age: older adults (median 63 years)
- Sex: M > F (slight)
- Monoclonal immunoglobulin in serum or urine (usually IgM, occasionally IgG or IgA) usually present
- Waldenström macroglobulinemia: monoclonal IgM serum immunoglobulin
- Autoimmune hemolytic anemia, autoimmune thrombocytopenia, coagulation factor inhibitors, and cryoglobulinemia may be seen
- Sites of involvement:
  - Lymph nodes, bone marrow, spleen (usually stage III or IV at presentation)
  - Peripheral blood lymphocytosis may be present
- Clinical Course:
  - similar to CLL/SLL
  - indolent but not curable with available therapy

Table 4. Immunophenotypic Features of Small B-Cell Lymphoproliferative Disorders

	SIg	*CD19*	*CD20*	*CD23*	*CD10*	*CD5*	*CD3*
Chronic lymphocytic leukemia/ small lymphocytic lymphoma	Monoclonal (dim)	+	+ (dim)	+	–	+	–
Lymphoplasmacytic lymphoma	Monoclonal cIg in plasma cells	+	+	–/+	–	–/+	–
Mantle cell lymphoma[1]	Monoclonal (bright)	+	+ (bright)	–	–	+	–
Marginal zone lymphoma	Monoclonal (bright)	+	+ (bright)	–	–	–/+	–
Hairy cell leukemia[2]	Monoclonal (bright)	+	+	–	–	–	–
Follicular lymphoma	Monoclonal (bright)	+	+ (bright)	–/+	+	–	–

[1]In addition, mantle cell lymphoma is the only lymphoma + for cyclin D1.
[2]The cells of hairy cell leukemia characteristically and brightly co-express CD22 and CD11c and are + for CD103.

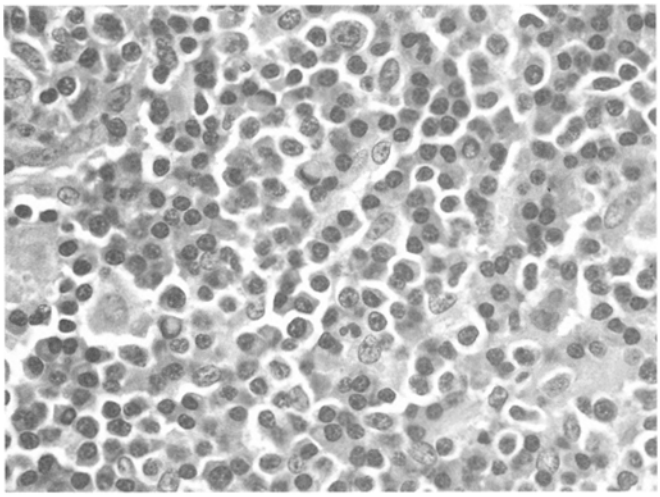


Fig. 9. Lymphoplasmacytic lymphoma.

- may transform to diffuse large B-cell lymphoma (~10%)—poor prognosis

*Microscopic (**Figure 9**)*

- Diffuse or parafollicular proliferation of small lymphocytes, plasmacytoid lymphocytes (lymphocyte-like nuclei, plasma cell-like cytoplasm), and plasma cells
- Abnormal immunoglobulin production manifest by:
  - Dutcher bodies (intranuclear immunoglobulin inclusions)
  - Russell bodies (extracellular hyaline immunoglobulin bodies)
  - Crystalline immunoglobulin deposits (intracytoplasmic or extracellular)
  - Amyloid deposits
  - Intercellular light chain deposits, mimicking amyloid
- Sinuses spared (may contain immunoglobulin)
- Mast cells frequently seen
- Iron-containing epithelioid histiocytes may be present

Immunophenotype

- Monoclonal sIg present (usually IgM; IgD absent), monoclonal cIg in plasma cells
- CD19, CD20, CD22, CD79a+
- CD23 usually–
- CD43– or+
- CD5 usually–, occasionally+
- CD10 usually–

Genetics

- Ig heavy and light chain genes are rearranged

Differential Diagnosis

- CLL/SLL:
  - Monoclonal plasmacytoid lymphocytes and plasma cells absent
  - CD5+, CD23+, sIg weakly+

Splenic Marginal Zone Lymphoma

Synonyms

- Rappaport: (not specifically listed) WDL or WDL-plasmacytoid
- Kiel: not specifically listed
- Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small
- Lymphocyte B, monocytoid

- Working Formulation: (not specifically listed) SLL
- REAL: splenic marginal zone lymphoma, with or without villous lymphocytes

Clinical

- Age: older adults (median seventh decade)
- Sex: M > F
- Marked splenomegaly, often without adenopathy
- Bone marrow and peripheral blood usually involved
- May present as leukemia (+/– villous lymphocytes: lymphoid cells with abundant cytoplasm and small thin villi, often concentrated at one pole, as seen on peripheral blood smear)
- Clinical course: indolent
- Splenectomy may be treatment of choice (+/– chemotherapy)

Microscopic (Spleen)

- Low power:
  - Both mantle and marginal zones involved
  - Residual germinal centers atrophic or hyperplastic
  - Red pulp may be involved—sinusoidal involvement correlates with leukemic phase
- High power:
  - Mantle zone: Small neoplastic lymphoid cells with little cytoplasm
  - Marginal zone: Medium-sized neoplastic cells with moderate-abundant pale cytoplasm and scant large transformed lymphocytes with round nuclei, prominent nucleoli, dispersed chromatin and abundant cytoplasm
  - Plasmacytic differentiation may be present

Immunophenotype

- sIg+ (M > G or A), cIg may be +; light chain restricted
- CD19, CD20, CD22, CD79a+
- CD5 and CD43 usually –, CD10– (may be + on flow cytometry)
- May be weakly TRAP
- CD23–, cyclin D1–
- CD11c usually+
- CD103–

Genetic Features

- loss of 7q21-32 common

Differential Diagnosis

- Splenic marginal zone hyperplasia:
  - sIg—polyclonal
- Hairy cell leukemia (HCL):
  - Red pulp process, blood lakes common, monotonous tumor cells
  - CD103+, TRAP+, DBA.44+
- CLL/SLL
  - Red pulp process, architecture effaced, proliferation centers present, cells have scant cytoplasm
  - CD5+, CD43+, CD23+
- MCL:
  - Architecture effaced, monotonous cells with scant cytoplasm
  - CD5+, CD43+, cyclin D1+
- FL:
  - Follicular pattern, at least partially; germinal centers expanded
  - CD10 and bcl-6 usually+

Hairy Cell Leukemia (HCL)

Clinical

- Age: middle-aged to older adults
- Sex: M > F
- Presentation:
  - Splenomegaly, pancytopenia, monocytopenia
  - Hepatomegaly variable, although liver is usually involved
  - Lymphadenopathy is uncommon
- Peripheral blood: always involved, but characteristic hairy cells (lymphoid cells with abundant pale cytoplasm with circumferential hairy projections) may be hard to find
- Bone marrow: always involved, may be inaspirable due to increased reticulin fibrosis
- Clinical course:
  - Indolent, may remit spontaneously
  - Infection—common complication
  - Median survival: 4–5 years
- Treatment:
  - Splenectomy +/– nonconventional lymphoma chemotherapy (interferon, 2-CDA, deoxycoformycin)

Microscopic

- Spleen:
  - Low power:
    - Involves red pulp cords and sinusoids, white pulp atrophic
    - Blood lakes (variable size) lined by neoplastic cells common
  - High power:
    - Monotonous population of small-medium lymphoid cells with oval-reniform nuclei and abundant pale cytoplasm
    - Cells appear widely spaced
- Lymph node (uncommonly involved):
  - Diffuse involvement, prominent hilar and perinodal fat involvement, may spare follicles

Immunophenotype

- sIg+, light chain restricted
- CD19, CD20, CD22, CD79a+
- CD11c+ (strong), CD25+ (strong)
- CD103+ (most specific marker)
- DBA.44+ (tissue sections)
- TRAP+
- CD5–, CD10–, CD23–, cyclin D1–

Genetics

- Ig heavy and light chains rearranged (proves B-cell lineage)

Electron Microscopy

- Long microvilli with broad base and ribosome-lamella complexes
- Characteristic but not pathognomonic

Differential Diagnosis

- Splenic marginal zone lymphoma:
  - Involves white pulp mantle and marginal zones, blood lakes absent
  - CD103–, TRAP weakly + in cell subset
- Mastocytosis:
  - Tryptase +, CD103–, TRAP–
- CLL/SLL:
  - Architecture effaced, proliferation centers present, cells have scant cytoplasm
  - CD5+, CD43+, CD23+
  - CD103–, TRAP–
- MCL:
  - White pulp process, architecture effaced, monotonous cells with scant cytoplasm
  - CD5+, CD43+, cyclin D1+
- FL:
  - Follicular pattern, at least partially; germinal centers expanded
  - Involves splenic white pulp
  - CD10, bcl-6 usually+
  - CD103 –, TRAP–

Plasma Cell Neoplasms

Clinical

- Plasma cell myeloma (multiple myeloma)—disseminated bone marrow tumor—common
- Plasmacytoma—uncommon:
  - Solitary plasmacytoma of bone:
    - Age: median sixth decade
    - Sex: M > F
    - Solitary bone lesion
    - 40–50% progress to multiple myeloma
  - Extraosseous plasmacytoma:
    - Age: median seventh decade
    - Sex: M > F
    - Usually involves upper aerodigestive tract, can arise in any organ
    - Regional lymph nodes may be involved
    - Primary plasmacytoma of lymph node extremely rare
    - 10-20% progress to multiple myeloma

Microscopic

- Monotonous infiltrate of mature to immature plasma cells
- No admixed lymphoid cells

Immunophenotype

- sIg–, cIg+ (G, A or light chain only; M, D or E rare), light chain restricted
- CD19, CD22– (CD79a often +); CD20 may be+
- CD45 usually–
- CD38+, CD138+

Genetics

- Ig heavy and light chain genes rearranged or deleted

Differential Diagnosis

- Reactive plasmacytosis:
  - Background of hyperplastic lymphoid follicles
  - Heterogeneous population of plasma cells
  - cIg not light chain restricted
- Lymphoplasmacytic lymphoma (and other low grade B-cell lymphomas):
  - Plasma cells admixed with small B-lymphocytes (not pure plasma cell population)
- Diffuse large B-cell lymphoma (immunoblastic/ plasmacytoid type):
  - CD19, CD20+
  - CD45+
  - CD38–, CD138–
- Osteosclerotic myeloma (POEMS syndrome)
- Heavy chain disease (HCD):
  - Gamma HCD
  - Mu HCD
  - Alpha HCD

Extranodal Marginal Zone B-Cell Lymphoma of Mucosa-Associated Lymphoid Tissue (MALT Lymphoma)

Synonyms

- Rappaport: (not specifically listed) well differentiated lymphocytic (WDL) or WDL-plasmacytoid, IDL, ILL, PDL, mixed lymphocytic-histiocytic (nodular or diffuse)

- Kiel: monocytoid B-cell, immunocytoma (some cases previously classified as centroblastic/centrocytic or centrocytic)
- Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small lymphocyte B, monocytoid
- Working Formulation: (not specifically listed) SLL (some consistent with CLL, some plasmacytoid), small cleaved or mixed small and large cell (follicular or diffuse)
- REAL: extranodal marginal zone B-cell lymphoma

Clinical

- Age: adults (median age approximately 60 years)
- Sex: F > M (slight)
- May occur in patients with autoimmune disorder (e.g., Sjogren's syndrome) or chronic antigenic stimulation (e.g., helicobacter gastritis)
- Sites of involvement:
  - stomach, salivary gland, lung, thyroid, skin, etc
  - may secondarily involve regional lymph nodes
  - bone marrow involvement uncommon (15–20%); peripheral blood involvement rare
- Clinical course:
  - indolent; when disseminated, usually incurable with available therapy
  - 5 year survival 75–80%
  - may recur in other extranodal sites
  - may transform to large B-cell lymphoma

*Microscopic **(Figure 10)***

- Low power: perisinusoidal, parafollicular, or marginal zone distribution; mantle zone preserved. Tumor gradually effaces architecture, circumscribing and infiltrating germinal centers (follicular colonization)
- High power: heterogeneous population of marginal zone cells (small-medium lymphoid cells with round-slightly indented nuclei, clumped chromatin, abundant pale cytoplasm, and well-defined cytoplasmic membranes), monocytoid B-cells, small lymphocytes, and plasma cells (plasma cells usually located in interfollicular zones). Occasional large transformed cells may be seen
- Lymphoepithelial lesions (marginal zone cells infiltrating epithelium) typically seen
- Plasma cells often located in subepithelium

Immunophenotype

- sIg+ (M > G or A), cIg may be + (40%)
- CD19, CD20, CD22, CD79a+
- CD5, CD43 usually–

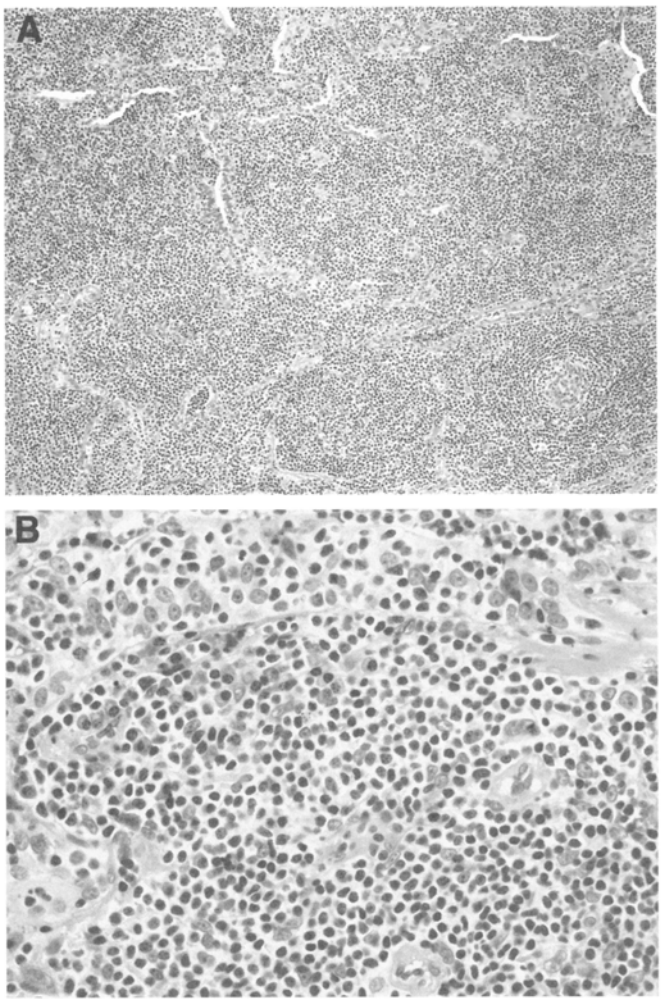


Fig. 10. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) (**A** and **B**).

- CD10, CD23, cyclin D1 –
- CD11c may be weakly +, CD25–

Genetics

- t(11;18)(q21;q21)/API–MALTI—20–50% of cases
- t(1;14), t(3;14), t(14;18)/IGH–MALT1 less common
- Trisomy 3 (12–85%)
- Trisomy 18 (7–36%)

Differential Diagnosis

- CLL/SLL:
  - Architecture effaced, proliferation centers present, cells have scant cytoplasm
  - CD5+, CD43+, CD23+
- MCL:
  - Architecture effaced; monotonous cells with scant cytoplasm
  - CD5+, cyclin D1+

- FL:
  - Follicular pattern, at least partially; centrocytes and centroblasts
  - CD10 and bcl-6 usually+
- Monocytoid B-cell hyperplasia:
  - Germinal centers intact—not invaded by neoplastic monocytoid cells
  - sIg—polyclonal

Nodal Marginal Zone B-Cell Lymphoma

Synonyms

- Rappaport: (not specifically listed) well differentiated lymphocytic (WDL) or
- WDL-plasmacytoid, IDL, ILL, PDL, mixed lymphocytic-histiocytic (nodular or diffuse)
- Kiel: monocytoid B-cell, immunocytoma (some cases previously classified as centroblastic/centrocytic or centrocytic)
- Lukes-Collins: small lymphocyte B, lymphocytic-plasmacytic, small lymphocyte B, monocytoid
- Working Formulation: (not specifically listed) SLL (some consistent with CLL, some plasmacytoid), small cleaved or mixed small and large cell (follicular or diffuse)

Clinical

- Localized or generalized lymphadenopathy

*Microscopic **(Figure 11)***

- Low power:
  - Parafollicular or marginal zone distribution
- High power:
  - Marginal zone B-cells and/or monocytoid B-cells, +/– occasional large transformed cells

Immunophenotype

- sIg + (M > G or A), light-chain restricted
- CD19, CD20, CD22, CD79a+
- CD5, CD43 usually–
- CD10, CD23, cyclin D1–
- CD11c may be weakly +, CD25–

Follicular Lymphoma (FL)

Synonyms

- Rappaport: nodular poorly differentiated lymphocytic (PDL), mixed lymphocytic-histiocytic, or histiocytic
- Kiel: centroblastic/centrocytic follicular, follicular centroblastic
- Lukes-Collins: small cleaved, large cleaved or large noncleaved follicular center cell (FCC), follicular
- Working Formulation: follicular, small cleaved mixed, or large cell

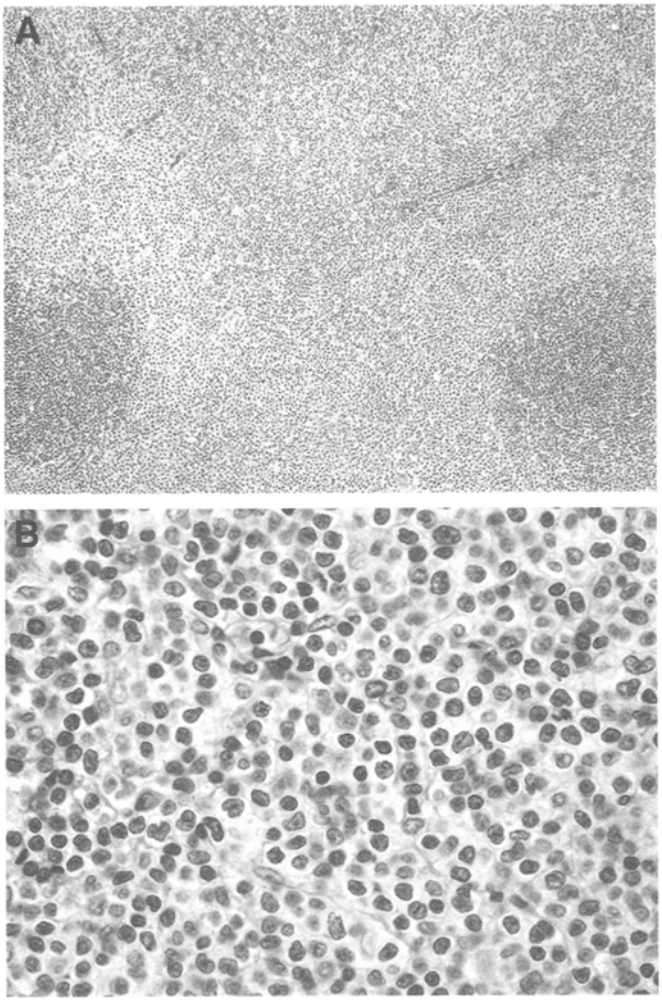


Fig. 11. Nodal marginal zone B-cell lymphoma (**A** and **B**).

- REAL: follicular center lymphoma, follicular

Clinical

- Age: adults (median age 55–59 years)
- Sex: M = F
- Comprises 35–40% of non-Hodgkin lymphomas in U.S. (less common in other countries)
- Usually disseminated at presentation (>80% stage III/IV)
- Sites of involvement:
  - lymph nodes, spleen (25–55%), liver, bone marrow (40%), peripheral blood (uncommon)
  - Extranodal presentation without lymph node involvement uncommon (exception: primary follicular lymphoma of the skin)
- Clinical course:
  - Indolent but usually not curable with available therapy (grade 3: more aggressive but potentially curable with aggressive therapy)

- Repeated relapses despite achievement of complete remission with or without therapy (23% remit spontaneously)
- Transformation to large B-cell lymphoma common (up to 60–80% overall), regardless of treatment status
- 5 year overall survival 72%; 5 year failure-free survival 40%

♦ Adverse prognostic indicators:
- Increased number of centroblasts
- Increased proportion of tumor with diffuse pattern (controversial)

Terminology

♦ Subtype according to architectural pattern and follicular center cell composition:
- Architecture: state approximate percent follicular pattern in report:
  - follicular (>75% follicular pattern)
  - follicular and diffuse (25–75% follicular pattern)
  - focally follicular (<25% follicular pattern)
- Follicular center cell composition:
  - Grade 1 = predominantly small cleaved cells (centrocytes) **(Figure 12)**:
    - 0–5 noncleaved cells (centroblasts)/40 × high power field (hpf) by counting method—must count cells in 10 follicles
  - <25% large noncleaved cells by estimation method
  - Grade 2 = mixed small cleaved (centrocytic) and large cell (centroblastic)

    6–15 large noncleaved cells/hpf by counting method

    25–50% large noncleaved cells by estimation method
  - Grade 3 = predominantly large cell:
    - >15 large noncleaved cells/hpf by counting method
    - >50% large noncleaved cells by estimation method
    - Counting method cut-offs are based on hpf of 0.159 mm^2. Compensatory factor must be used for different oculars
    - Grade 3a: >15 noncleaved cells/high power field but small cleaved cells still present **(Figure 13A)**
    - Grade 3b: solid sheets of centroblasts **(Figure 13B)**

Microscopic

♦ Follicular pattern (at least partially); diffuse areas may be present **(Figure 14)**

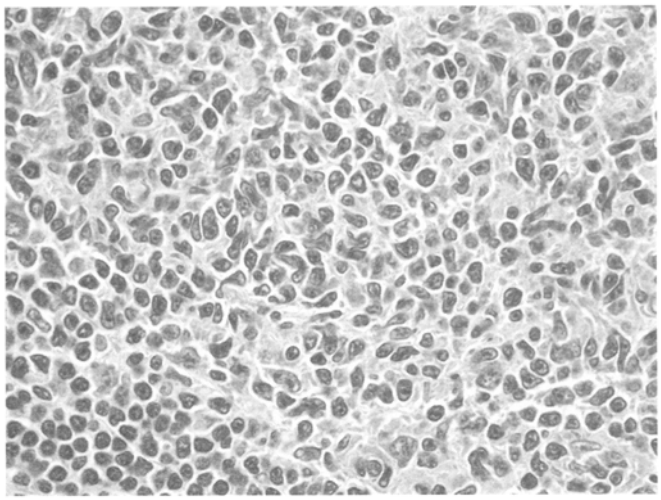


Fig. 12. Follicular lymphoma, grade 1.

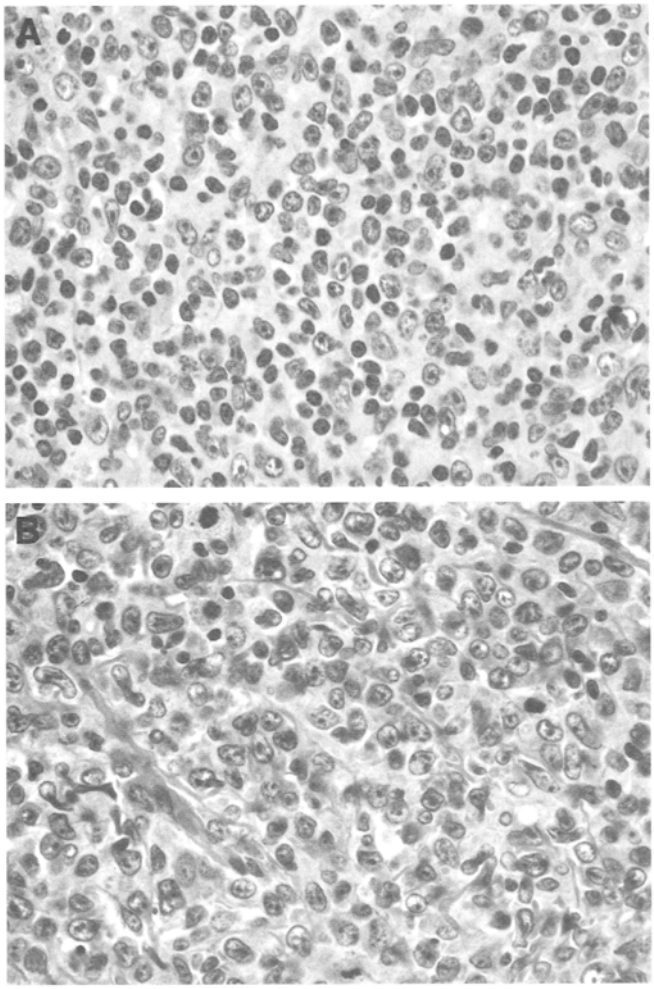


Fig. 13. Follicular lymphoma, grade 3a **(A)** and grade 3b **(B)**.

♦ Back to back arrangement of relatively uniform follicles (increased follicle density); intervening lymphoid stroma compressed



Fig. 14. Follicular lymphoma with follicular and diffuse architecture.

- Tumor may infiltrate nodal capsule, perinodal blood vessels, and perinodal fat
- Limited or absent mantle zone
- Follicles lack cellular polarization
- Follicles composed of centrocytes (small cleaved follicular center cells—usually predominate) and centroblasts (large noncleaved follicular center cells—usually in the minority)
- Follicles lack tingible body macrophages (may be present in grade 3 subtype)
- Low mitotic rate in follicles (may be high in grade 3 subtype)

Immunohistochemistry

- sIg+ (usually IgM)
- Ig light chain restricted
- bcl-6+, CD10 usually + (75%), interfollicular neoplastic cells also usually CD10+ (albeit more weakly)
- CD19, CD20, CD22, CD79a+
- CD5–, CD43–
- CD23 usually–
- Cyclin D1–
- Intrafollicular lymphocytes bcl-2+ (83–100% of grade 1, 52-85% of grade 3)
- N.B.:bcl-2 is + in many other small B-cell lymphomas (as well as normal B and T-cells, normal hematopoietic precursors, and many other nonhematopoietic cells and tumors), therefore bcl-2 is:
  - useful in distinguishing FL from follicular hyperplasia
  - not useful in distinguishing FL from other small B-cell lymphomas

Genetics

- t(14;18)(q32;q21): bcl-2 gene (chromosome 18) juxtaposed to J-region of immunoglobulin heavy chain gene (chromosome 14) leading to increased bcl-2 protein expression
- bcl-2 protein: prevents B-cell apoptosis (programmed cell death) leading to extended B-cell survival
- t(14;18) also present in 30% of diffuse large B-cell lymphomas
- Additional genomic defects (e.g., involving 3q27 or 17p, del 6q, trisomy 2,3,7,12,18, or 21, dup 2p) may be associated with grade 2 or 3 subtypes and more aggressive clinical course

Variants

- FL in children (rare):
  - Localized disease
  - Head and neck or inguinal region
  - Grade 2 or 3 subtypes common
  - Favorable outcome
- Sclerotic:
  - Synonym: nodular sclerotic lymphosarcoma
  - Broad collagenous bands or fine sclerotic compartmentalization
  - No prognostic significance
- Follicular signet ring cell lymphoma:
  - Lymphoid cells (usually centrocytes) contain cyto-plasmic clear vacuoles (usually monoclonal IgG) or Russell body-like inclusions (usually monoclonal IgM)
- Multilobated nuclei:
  - Most common in grade 3 subtype
- Plasmacytic differentiation:
  - Large number of plasma cells
  - Plasma cells—polyclonal > monoclonal
  - Usually interfollicular, may be intrafollicular
  - May contain Russell bodies or Dutcher bodies
- Floral variant:
  - Mimics progressive transformation of germinal centers (PTGC)
  - Floral/serrated appearance due to regular invasion of neoplastic follicles by small lymphocytes (B and T)
  - Usually grade 3
- FL with hyaline vascular follicles (rare):
  - Neoplastic follicles with concentrically arranged lymphoid cells and hyalinized venules
- Diffuse follicle center lymphoma:
  - Synonyms:
    - Rappaport:diffuse poorly differentiated lymphocytic
    - Kiel:centroblastic/centrocytic, diffuse
    - Lukes-Collins:diffuse small cleaved FCC
    - Working Formulation:diffuse small cleaved cell
    - REAL:follicle center lymphoma, diffuse (predominantly small cell)
  - Microscopic:

- Diffuse architecture
- Majority of centrocytes with occasional centroblasts
- Immunophenotype of follicle center cells (pan B-antigen+, sIg+, CD10+, bcl-2+, bcl-6+)

Differential Diagnosis

- Follicular Hyperplasia (FH):
  - See **Table 1**
- Castleman's disease, hyaline vascular type:
  - Reactive condition
  - Broad mantle zones with onionskin pattern
  - Small (regressively transformed) germinal centers containing hyalinized vessels
  - Intrafollicular lymphocytes bcl-2–, polyclonal
  - Interfollicular lymphocytes CD10–
- PTGC:
  - Reactive condition, rarely associated with NLPHL
  - Expansile follicles in background of reactive follicles
  - No atypical cells in interfollicular zones or perinodal tissue
  - Intrafollicular lymphocytes bcl-2–, polyclonal
  - Interfollicular lymphocytes CD10 –
- NLPHL:
  - nodules larger than follicles of FL
  - centrocytes scant
  - L&H cells may resemble centroblasts, but have more pronounced nuclear lobulation, delicate chromatin, small nucleoli, wispy pale cytoplasm
  - L&H cells are usually EMA+ and are often surrounded by CD57 + T-cells
  - nodular lymphocytes CD10–
- MCL:
  - diffuse or vaguely nodular pattern, cells homogeneous
  - CD5+, CD43+
  - CD10–, bcl-6–
  - cyclin D1+
- MALT lymphoma:
  - Lymphoepithelial lesions in extranodal sites
  - Perifollicular growth pattern
  - More abundant pale cytoplasm in centrocyte-like cells
  - Monoclonal plasma cells common
  - Neoplastic cells CD10—(although residual normal follicle center cells may be CD10 +)
  - CD43 may be+
- CLL/SLL with prominent proliferation centers:
  - Proliferation centers composed of prolymphocytes and paraimmunoblasts
  - CD5+, CD43+, CD23+
  - CD10 –
- Lymphoblastic lymphoma with lobular pattern:
  - blast-like cytology
  - TdT+, sIg–
  - both may be CD10+

Mantle Cell Lymphoma (MCL)

Synonyms

- Rappaport: intermediately or poorly differentiated lymphocytic, diffuse or nodular (ILL/IDL/PDL)
- Kiel: centrocytic (mantle cell) lymphoma
- Lukes-Collins: small cleaved follicular center cell (FCC)
- Working Formulation: small cleaved cell, diffuse or nodular; rarely diffuse mixed xor large cleaved cell
- Other: mantle zone lymphoma

Clinical

- Age: older adults (median age 63 years)
- Sex: M > F
- Sites of involvement:
  - High stage at presentation: lymph nodes, spleen (~60%), peripheral blood (at least 25%)
  - Extranodal sites, especially GI tract (lymphomatous polyposis) and Waldeyer's ring
- Clinical course:
  - Moderately aggressive, incurable with available therapy
  - Median survival: 3–5 years
  - May progress to blastoid variant
- Adverse prognostic indicators:
  - Blastoid subtype
  - High mitotic rate
  - Peripheral blood involvement

Microscopic (Lymph Node)

- Low power:
  - Architecture effaced
  - Diffuse or vaguely nodular pattern **(Figure 15)**
  - Tumor may involve or expand mantle zones of some reactive follicles (pure mantle zone pattern less common)
  - Hyalinized small capillaries in ~75%
  - Scattered epithelioid histiocytes without tingible bodies common (starry sky pattern on low power)
  - Monotonous population of small to medium-sized lymphoid cells without proliferation centers, paraimmunoblasts, or transformed cells **(Figure 16)**
- High power:
  - Neoplastic cells: round to irregular nuclei (+/– clefts), clumped chromatin, scant cytoplasm
  - Few mitoses



Fig. 15. Mantle cell lymphoma.

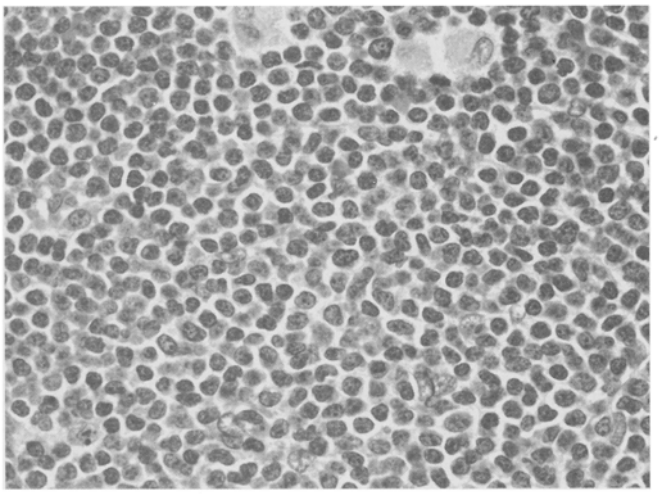


Fig. 16. Mantle cell lymphoma.

Immunophenotype

- sIg+ (M +/– D)
- Immunoglobulin light chain restricted (lambda > kappa)
- CD19, CD20, CD22, CD79a+
- Cyclin D1+ (specific for MCL)
- CD5 +, CD43+
- CD23–, CD10–

Genetics

- t(11;14)(q13;32) demonstrable in up to 75% of cases by Southern blot analysis or conventional cytogenetics, and in nearly 100% of cases by fluorescence *in situ* hybridization:
  - translocation of CCND1 (bcl-1) oncogene (chromosome 11) into Ig heavy chain locus (chromosome 14) results in overexpression of cyclin D1 (bcl-1 [PRAD-1]) gene product-required for progression from G1 to S phase in cell cycle; not normally over-expressed in lymphoid cells
- Variable region genes unmutated in most cases, consistent with pre-germinal center B-cell derivation

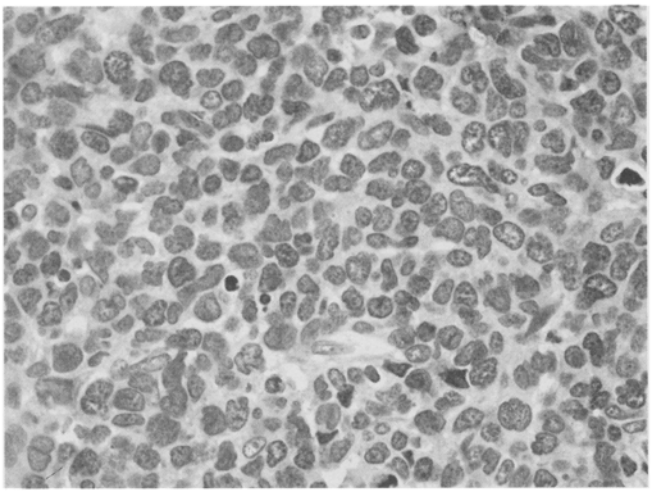


Fig. 17. Mantle cell lymphoma, blastoid variant.

Variants

- Blastoid type (synonyms: lymphoblastoid **(Figure 17)**, blastic, anaplastic, pleomorphic, centrocytoid-centroblastic):
  - Composed of lymphoblast-like cells with dispersed chromatin, small nucleoli, and high mitotic rate (+/– starry-sky pattern)
  - May indicate progression/transformation
- Monocytoid-like: abundant pale cytoplasm

Differential Diagnosis

- CLL/SLL:
  - Proliferation centers
  - Dim sIg expression, CD23+
  - Cyclin D1–
- Marginal zone B-cell lymphoma:
  - Parafollicular proliferation of monocytoid-like cells
  - CD5 usually–, may be CIg+ (40%), CD43 usually–, CD23 may be + (<50%)
  - Cyclin D1–
- Follicular lymphoma:
  - Follicular architecture, at least partially
  - CD5 –, CD10 and bcl-6 usually +, CD23 may be + (<50%)
  - Cyclin D1–
  - t(14;18) usually present
- Large B-cell lymphoma:
  - Larger cells, prominent nucleoli, mitoses common
  - CD5–, CD43–
  - Cyclin D1–

- Lymphoblastic lymphoma:
  - Lymphoblastic cytology, numerous mitoses
  - TdT+, sIg–
  - CD34 usually+
  - Cyclin D1–

Diffuse Large B-Cell Lymphoma

Synonyms

- Rappaport: diffuse histiocytic, occasionally diffuse mixed lymphocytic-histiocytic
- Kiel: centroblastic, B-immunoblastic, large cell anaplastic (B-cell)
- Lukes-Collins: large cleaved or large noncleaved FCC, B-immunoblastic
- Working Formulation: diffuse large cell cleaved, noncleaved or immunoblastic, occasionally diffuse mixed small and large cell

Clinical

- 30–40% of all adult non-Hodgkin lymphomas
- Age: median seventh decade (wide age range)
- Sex: M > F (slight)
- Most arise de novo
- Some result from transformation of lower grade lymphoma (e.g., FL, CLL/SLL)
- May occur in patients with AIDS
- Presentation:
  - Rapidly enlarging mass (up to 40% extranodal)
  - 30% have B symptoms (fever, night sweats, or weight loss)
  - Bone marrow involvement less frequent (10%) than in low grade lymphomas
- Clinical course:
  - Aggressive but potentially curable

Microscopic (Lymph Node)

- Low power:
  - Complete, partial, sinus, or interfollicular involvement
  - Infiltration of perinodal tissue, sclerosis, necrosis (apoptosis or coagulative necrosis) common
- High power:
  - Variable cytology
  - Large cells with vesicular nuclei, prominent nucleoli, cytoplasm variable
  - Bizarre cells may be present
  - Mitoses common

Immunophenotype

- CD19, CD20, CD22, CD79a+
- CD45 usually+
- May express CD10 (25-50%) or CD5 (10%)
- Bcl-2 expressed in 30–50%

Genetics

- Bcl-2 gene (18q21) rearranged in 20–30% (e.g., t(14;18))
- Bcl-6 gene (3q27) rearranged in a third; point mutation in 70%
- Three different subtypes (germinal center B-cell-like, activated B-cell-like, and type 3) suggested by gene expression profiling

Differential Diagnosis

- Carcinoma:
  - CD45–, B-cell associated antigens–, keratin+
- Malignant melanoma:
  - CD45–, B-cell associated antigens–, S100+, HMB45 usually+
- Hodgkin lymphoma (classical):
  - Neoplastic (Hodgkin) cells larger with more prominent nucleoli
  - CD45–, B-cell associated antigens – or weakly + in Hodgkin cell subset
  - CD15 usually+, CD30 usually +
  - Inflammatory background present
- Anaplastic large cell lymphoma (ALCL):
  - CD30+ (diffuse)
  - B-cell associated antigens
  - CD45 +/–
  - ALK-1 +/–
- Kikuchi-Fujimoto disease:
  - Zonation phenomenon, with karyorrhectic debris and phagocytic histiocytes in center, and immuno-blasts, lymphocytes and plasmacytoid monocytes at periphery
- Atypical immunoblastic reaction (infections, mononucleosis, other viral infection, drug reaction, etc.):
  - Partial preservation of lymph node architecture
  - Large cells admixed with small lymphocytes and plasma cells
  - Immunohistochemically, large cells are predominantly T-cells or mixture of T and B-cells
  - B-cell polyclonal

Variants

- WHO classification suggests that subclassifying large B-cell lymphoma is impractical (due to poor interobserver reproducibility) and irrelevant (as treatment is currently similar for all types)
- Centroblastic (**Figure 18**):
  - Composed of centroblasts (medium to large lymphoid cells with vesicular chromatin and multiple nucleoli)
  - Monomorphous or polymorphous (may be multilobate)

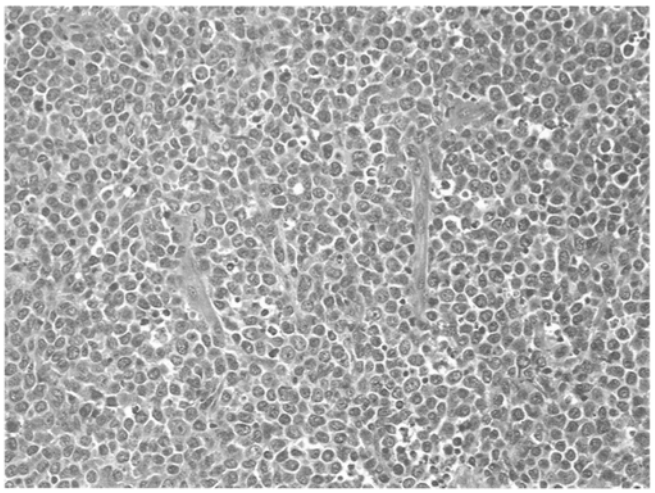


Fig. 18. Diffuse large B-cell lymphoma, centroblastic variant.

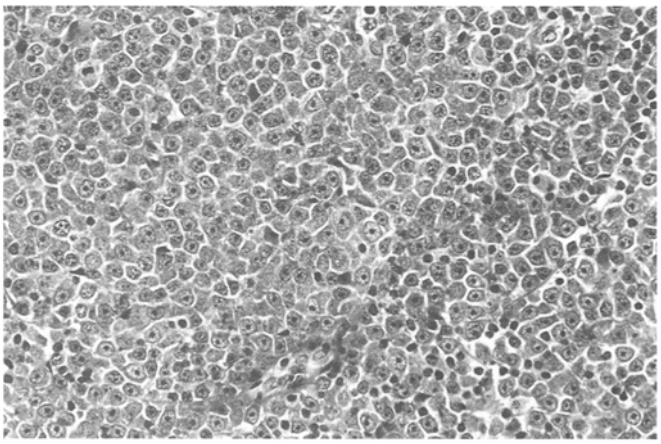


Fig. 19. Diffuse large B-cell lymphoma, immunoblastic variant.

- Immunoblastic (**Figure 19**):
  - >90% of cells are immunoblasts (single central nucleolus, ample basophilic cytoplasm)
- Anaplastic:
  - Large bizarre cells
  - May grow in sheets and/or have sinusoidal growth pattern
  - Unrelated to T-cell anaplastic large cell lymphoma

T-Cell/Histiocyte Rich Variant

Clinical

- Age: older adults (mean age 56 years)
- Sex: M > F (slight)
- Presentation:
  - Lymphadenopathy more common than extranodal involvement
  - Usually high stage at presentation (spleen, bone marrow involvement common)

Microscopic

- Low power: diffuse architecture
- High power:
  - Predominantly small lymphoid cells (T >> B) +/– histiocytes interspersed by individual or small groups of large lymphoid B-cells with variable appearance (may resemble Reed-Sternberg cells)

Immunophenotype

- Small lymphocytes:
  - Mostly T-cells (immunologically normal)
- Large lymphoid cells:
  - React with B-cell markers, usually CD30–, light chain restricted (golgi or perinuclear staining)

Differential Diagnosis

- NLPHL:
  - Macronodular architecture
  - L&H cells may be surrounded by CD57+ T-cells
  - Follicular dendritic cells (CD21+) may be prominent
- Other mature B-cell neoplasms
- ALCL
- Classical Hodgkin Lymphoma
- Carcinoma
- Melanoma

Mediastinal (Thymic) Large B-Cell Lymphoma

Synonyms

- Mediastinal large cell lymphoma with sclerosis
- Mediastinal clear cell lymphoma

Clinical

- Age: young adults (median age fourth decade, mean 32 years)
- Sex: F > M (2:1)
- Presentation:
  - Locally invasive anterior mediastinal mass (derives from thymus)
  - Superior vena cava (SVC) syndrome, cough, dyspnea, chest pain
- Relapses: extranodal (kidney, adrenal, liver, skin, brain, etc.)

Microscopic

- Thymus usually (if not always) involved
- Diffuse infiltrative growth into anterior mediastinal soft tissue
- Fine, compartmentalizing sclerosis common

Cytology

- Large cells with variable appearance
- Cells uniform to pleomorphic

- Nuclei round, elongate, folded, multilobated, or multinucleated
- Chromatin vesicular or granular, often with distinct nucleoli
- Moderate-abundant cytoplasm (formalin artifact)
- Associated small lymphocytes and histiocytes may be present

Immunophenotype

- sIg usually–
- CD19, CD20, CD22, CD79a+
- CD45 usually+
- CD30 usually – (may be weakly+)
- CD15–, CD5–, CD10–

Genetics

- Ig heavy and light chains rearranged
- Molecular signature by gene expression profiling shares features with classical HL but differs from other DLBCL

Differential Diagnosis

- Thymic carcinoma:
  - More cohesive growth pattern, nuclei less irregular
  - Keratin+, CD45–
- Classical Hodgkin Lymphoma (e.g., syncytial variant of nodular sclerosis classical Hodgkin Lymphoma):
  - Larger neoplastic cells with prominent nucleoli
  - Inflammatory background (eosinophils, neutrophils, plasma cells)
  - CD15+, CD30+, CD45–
- Anaplastic large cell lymphoma:
  - Larger neoplastic cells with bizarre nuclei
  - CD30+, p80/ALK-1 may be+, T-cell or null cell phenotype
- Seminoma:
  - Male predominance
  - CD45–, PLAP (placental alkaline phosphatase)+

Burkitt Lymphoma/Leukemia

Synonyms

- Rappaport: undifferentiated lymphoma, Burkitt's type
- Kiel: Burkitt's lymphoma
- Lukes-Collins: small noncleaved FCC
- Working Formulation: small noncleaved cell, Burkitt's type

Clinical

- Endemic (African):
  - Age: young children (mean age 4–7 years)
  - Sex: M > F (2-3:1)
  - Geography: equatorial Africa (may be associated with both malaria and EBV)
  - Majority (95%) are EBV-associated (clonally homogeneous EBV genomes present in tumor cells)
  - Sites of involvement: extranodal:
    - Jaws and other facial bones
    - Ovary, testis, thyroid, salivary gland, kidney, CNS
    - Bone marrow involvement rare (<10%)
    - Lymph nodes and mediastinum spared
- Sporadic (nonendemic):
  - Age: older children
  - Sex: M > F
  - Minority (<20%) associated with EBV
  - Sites of involvement: extranodal:
    - Abdominal cavity: intestine (especially terminal ileum, cecum, and mesentery), also stomach, peritoneum, and retroperitoneal tissue
    - Facial bones, ovary, testis, CNS, lymph nodes less common
    - Bone marrow involvement in 10-30%
    - Rarely presents as Burkitt leukemia
    - Mediastinal involvement infrequent
- Immunodeficiency associated (primarily associated with AIDS):
  - Age: middle age
  - Sex: M > F
  - EBV + in up to 50%
  - Sites of involvement: extranodal (CNS, GI tract)
  - Occurs early in course of AIDS
- Clinical course:
  - Aggressive but potentially curable
- Adverse prognostic indicators:
  - Large tumor bulk
  - CNS or bone marrow involvement
  - High pretreatment serum LDH

*Microscopic **(Figure 20)***

- Low power:
  - Diffuse, infiltrative growth pattern
  - Cells appear cohesive (jigsaw-puzzle-like appearance)
  - Starry sky pattern due to macrophages ingesting apoptotic tumor cells
- High power:
  - Monotonous population of medium-sized cells with round nuclei, multiple nucleoli, and basophilic cytoplasm
  - Numerous mitoses

Immunophenotype

- SIg+ (usually IgM), light chain restricted
- CD10 and bcl-6 usually+
- TdT–, CD34–, MPO–, cyclin D1–
- CD5–

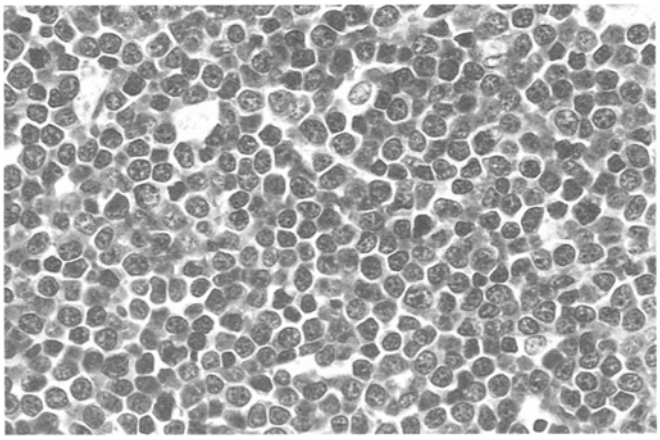


Fig. 20. Burkitt lymphoma.

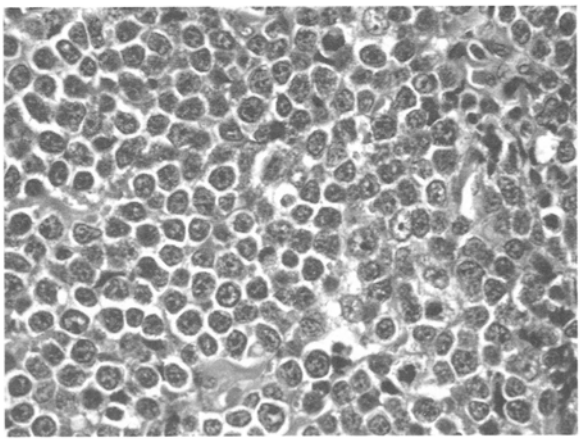


Fig. 21. Atypical Burkitt/Burkitt-like lymphoma.

Genetics

- 75–80%: t(8;14)(q24;q32) = translocation of c-myc (chr 8) to Ig heavy chain region (chr 14)
- 16%: t(8;22) = translocation of c-myc (chr 8) to Ig lambda light chain region (chr 22)
- 8%: t(2;8) = translocation of c-myc (chr 8) to Ig kappa light chain region (chr 2)
- Results in deregulation of myc gene leading to altered B-cell growth and differentiation

Differential Diagnosis

- Lymphoblastic lymphoma:
  - Mediastinum—most common site
  - Blastic cytology (dispersed chromatin, inconspicuous nucleoli, scant cytoplasm)
  - TdT+, sIg–, usually T-cell lineage
- Large B-cell lymphoma:
  - Uncommon in children
  - Larger, more heterogeneous cells
  - Fewer, more prominent nucleoli
- Myeloid sarcoma (extramedullary myeloblastic , granulocytic sarcoma):
  - Eosinophilic cytoplasm
  - Myeloperoxidase (MPO)+, lysozyme+, CD68+
  - CD34+, TdT may be+
- Atypical Burkitt/Burkitt-like (**Figure 21**):
  - Tumor of adults
  - Medium-sized lymphocytes with slight pleomorphism
  - May have c-MYC translocation +/– complex karyotype

Mature T-Cell and NK-Cell Neoplasms

T-Cell Prolymphocytic Leukemia (T-PLL)

Synonyms

- Rappaport: WDL, PDL
- Kiel: T-cell prolymphocytic leukemia/T-cell lymphocytic leukemia
- Lukes-Collins: small lymphocyte T, prolymphocytic
- Working Formulation: small lymphocytic, consistent with CLL, diffuse small cleaved cell
- French-American-British (FAB): T-PLL
- REAL: T-cell chronic lymphocytic leukemia/ prolymphocytic leukemia

Clinical

- 1–2 % of all small lymphocytic leukemias:
  - Age: older adults
  - Presentation: marked lymphocytosis (>100,000/mm^3)
  - Sites of involvement:
    - Skin and mucosa
    - Bone marrow, spleen, liver, lymph nodes
  - Clinical course:
    - Aggressive
    - Median survival <1 year

Microscopic (Lymph Nodes)

- Architecture:
  - Diffuse or paracortical involvement
  - Pseudofollicles absent
  - +/– numerous prominent small vessels
- Cytology:
  - Morphologically similar to B-CLL, although nuclear contours usually more irregular and nucleoli often present
  - "small cell" variant—small cell size, nucleoli often not visible
  - "cerebriform" (Sézary cell-like) variant—very irregular nuclear contours

Immunophenotype

- CD2, CD3, CD5, CD7+
- CD4+ (65%) or CD4 and CD8+ (20%) or CD8+ (15%)

Genetics

- T-cell receptor gene rearranged
- Inv 14(q11;q32) common

Differential Diagnosis (all are + for B-cell associated antigens)

- CLL/B-PLL
- MCL
- FL
- Marginal zone B-cell lymphoma

Large Granular Lymphocytic (LGL) Leukemia

Synonyms

- Rappaport: SLL, CLL
- Kiel: T-CLL
- Lukes-Collins: small lymphocyte, T
- Working Formulation: small lymphocytic, consistent with CLL
- FAB: T-CLL, T-LGL

Clinical

- Presentation:
  - LGL lymphocytosis (>1000/mm^3)
  - Neutropenia +/– anemia
  - May be associated with rheumatoid arthritis or + rheumatoid factor
- Sites of Involvement:
  - Peripheral blood
  - +/– mild-moderate splenomegaly
  - No lymphadenopathy or hepatomegaly
- Clinical course:
  - Indolent

Microscopic

- Peripheral blood smear: lymphoid cells with round nuclei, rare nucleoli, and eccentric abundant pale blue cytoplasm with azurophilic granules
- Spleen: red pulp involvement, small lymphocytes, can be subtle

Immunophenotype

- T-cell lineage:
  - CD2+, CD3+, CD8+, CD5 and CD7 often dim by flow cytometry
  - CD16+, CD56–, CD57 +/–
  - TIA-1+, granzyme B+
- NK-cell lineage:
  - CD2+, CD7+, CD3–, CD5–, CD8–
  - CD16 +, CD56 usually +, CD57 usually–
  - TIA-1+, granzyme B+

Genetics

- T-cell lineage: T-cell receptor genes rearranged
- NK-cell lineage: Germline T-cell receptor genes

Aggressive NK-Cell Leukemia

Clinical

- Rare overall (more common in Asia)
- Age: young adults
- Presentation: fever, hepatosplenomegaly +/– lymphadenopathy, leukemia blood picture +/– cytopenias
- Strongly associated with EBV
- Clinical course: aggressive/fulminant

Microscopic

- Peripheral blood:
  - Large granular lymphocytes with atypical features

Immunophenotype

- CD2+, CD56+
- CD3 –
- cytotoxic granule associated protein-+ (e.g., TIA-1, granzyme B)
- EBV usually+

Genetics

- T-cell receptor genes germline
- EBV commonly in clonal episomal form

Adult T-Cell Leukemia/Lymphoma (ATL/L)

Synonyms

- Rappaport: diffuse PDL, mixed lymphocytic-histiocytic, or histiocytic
- Kiel: pleomorphic small, medium, and large cell types (HTLV1+)
- Lukes-Collins: T-immunoblastic sarcoma
- Working Formulation: diffuse small cleaved cell, mixed small and large cell, diffuse large cell, large cell immunoblastic
- REAL: adult T-cell lymphoma/leukemia

Clinical

- Age: adults
- All are HTLV-1+
- Geography: Japan, Caribbean, Brazil; sporadic in U.S.
- Acute variant (most common):
  - Presentation: marked lymphocytosis, hypercalcemia
  - Sites of involvement: liver, spleen, lymph nodes, skin, bone marrow, bone (lytic bone lesions), lung, peripheral blood
  - Clinical course: highly aggressive, rapidly fatal

- Lymphomatous variant:
  - Prominent lymphadenopathy, no leukemia phase
  - Aggressive course
- Chronic variant:
  - Presentation: mild lymphocytosis, skin rashes
  - Sites of involvement: lymph nodes, lung, skin, bone marrow, peripheral blood
  - Clinical course: less aggressive, but may transform to acute phase
- Smoldering variant:
  - Skin or lung involvement, normal white blood cell count
  - Less aggressive, but may transform to acute phase

Microscopic

- Peripheral blood: lymphoid cells with hyperlobated nuclei ("flower" cells)
- Lymph nodes:
  - Low power: diffuse involvement
  - High power: markedly pleomorphic small and large lymphoid cells

Immunophenotype

- CD2, CD3, CD5+, CD7 usually–
- Most are CD4+
- CD25+

Genetics

- T-cell receptor genes rearranged
- HTLV-1 genomes present

Extranodal NK/T-Cell Lymphoma, Nasal Type

Clinical

- Age: adults > children
- Geography: Asia and Latin America > US/Europe
- Virtually all cases associated with EBV
- Sites of involvement: Destructive nasal or midline facial tumor most common ("nasal NK/T-cell lymphoma"); may involve other extranodal sites (e.g., skin, soft tissue, testis, upper respiratory tract, gastrointestinal tract)
- May be complicated by hemophagocytic syndrome - adversely affects survival
- Treatment: radiotherapy and chemotherapy

Microscopic

- Low power: angiocentric/angioinvasive lymphoid infiltrate
- High power: broad cell spectrum: small, medium, and/or large atypical cells, any of which may predominate. A prominent inflammatory infiltrate may be present early in course of disease

Immunophenotype

- CD2 and CD56 usually+
- Surface CD3 (detected by monoclonal anti-CD3 antibodies) usually – (cytoplasmic CD3ε, detected by polyclonal anti-CD3 antibodies, often +)
- Other T-cell associated antigens including CD5 and CD7 occasionally+
- CD16, CD57 usually–
- Cytotoxic granule associated proteins (TIA-1, granzyme B, perforin) usually+

Genetics

- EBV genome virtually always present, therefore *in situ* hybridization with probes to EBV-encoded small nuclear RNA may be helpful
- T-cell receptor and Ig genes usually germline

Enteropathy-Type T-Cell Lymphoma

Clinical

- Age: adults
- Most patients have history of gluten-sensitive enteropathy (celiac disease)
- Presentation: abdominal pain, jejunal perforation, peritonitis
- Clinical course: aggressive

Macroscopic

- Jejunal ulceration, often with perforation, +/– mass
- May be multifocal

Microscopic

- Ulcerated small bowel mucosa with underlying tumors composed of varying proportions of small, medium, and/or large/anaplastic atypical lymphoid cells
- +/– intraepithelial lymphoma cells
- +/– prominent inflammatory cells (histiocytes and eosinophils)
- +/– villous atrophy of adjacent small bowel mucosa

Immunophenotype

- CD3+, CD7+, CD103+
- CD5 often–

Genetics

- T-cell receptor genes are clonally rearranged

Hepatosplenic T-Cell Lymphoma

Clinical (γδ Type)

- Age: young adults
- Sex: M > F
- Presentation: fever, cytopenias
- Sites of involvement: spleen, liver, bone marrow, +/– peripheral blood; lymph nodes spared
- Clinical course: highly aggressive, usually incurable with available therapy

Microscopic

- Architecture: splenic, hepatic, and bone marrow sinusoids involved

- Cytology: monotonous population of medium-sized round or folded lymphoid cells with abundant pale cytoplasm
- Cells may appear cohesive

Immunophenotype

- CD2, CD3, and CD7+, CD5 usually–
- CD4, CD8 usually –
- Most cases are γδ T-cell receptor +; minority of cases are αβ T-cell receptor+

Genetics

- Clonal rearrangement of T-cell receptor genes
- Iso (7q) common

Differential Diagnosis

- Hairy cell leukemia:
  - Older adults
  - B-cell associated antigens +, T-cell associated antigens–
  - CD103+, TRAP+

Subcutaneous Panniculitis-Like T-Cell Lymphoma

Clinical

- Age: adults (median fifth decade, wide age range)
- Sex: F > M (slight)
- Presentation: Multiple red, painless, deep subcutaneous nodules, +/– ulceration
- Sites of involvement: Subcutaneous tissue (lower extremities > upper extremities > trunk)
- May be associated with systemic B symptoms
- May be complicated by hemophagocytic syndrome—frequently fatal
- Clinical course: aggressive
- Treatment: systemic chemotherapy

*Microscopic **(Figure 22)***

- Low power:
  - Lymphoid infiltrate involving subcutaneous fat septae and lobules (+/– fat necrosis), +/– extension into deep dermis. Neoplastic cells frequently rim individual fat cells
  - Epidermis and dermal appendages spared
- High power:
  - Neoplastic cells: Variable mixture of small, medium, and large lymphoid cells, often very atypical, especially with progression of disease. Transmural vascular infiltrates may be present. Karyorrhexis common
  - Background: Reactive histiocytes, +/– erythrophagocytosis (not necessarily indicative of clinical hemophagocytic syndrome)

Immunophenotype

- CD45+
- CD2, CD3, CD43+, +/– aberrant absence of CD5 or CD7
- Most are CD8+

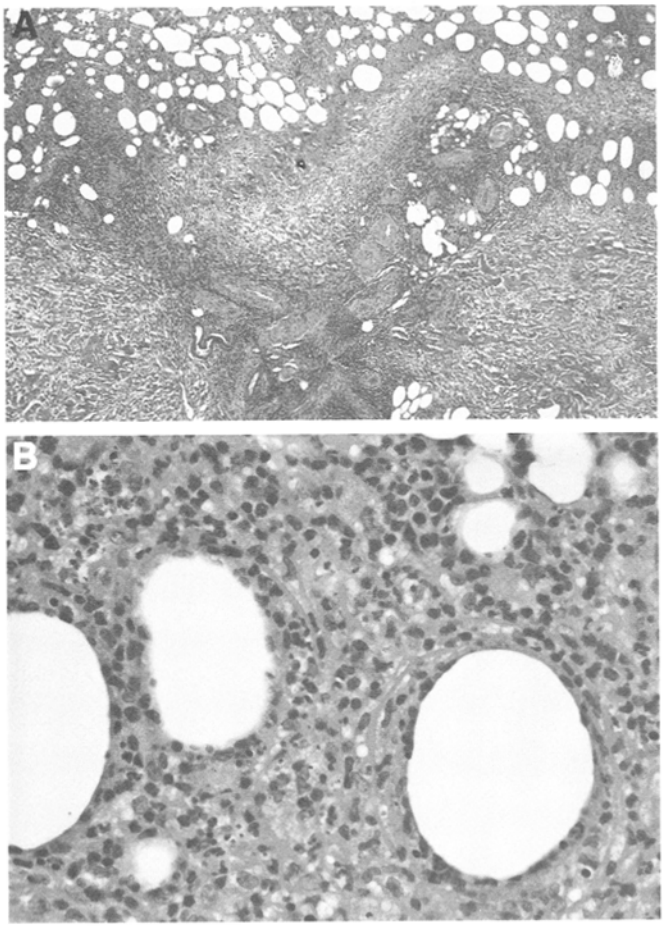


Fig. 22. Subcutaneous panniculitis-like T-cell lymphoma **(A,B)**.

- Cytotoxic granule associated proteins (Tia-1, granzyme B, perforin) +
- Most are αβ+
- Minority are γδ + (may correlate with CD56-+, CD4, CD8 double – phenotype and more aggressive course)

Genetics

- T-cell antigen receptor genes usually rearranged

Differential Diagnosis

- Mycosis fungoides/Sézary syndrome:
  - Involves dermal-epidermal junction—rarely extends to subcutaneous tissue
  - Histiocytic infiltrate absent
- Granulomatous slack skin syndrome (variant of cutaneous T-cell lymphoma):
  - Extensive dermal granulomas, few atypical lymphoid cells
  - Subcutaneous tissue spared
- FL:
  - B-cell process
- Infectious panniculitis

- Neutrophilic (bacterial/fungal) or granulomatous (mycobacterial) inflammation of fat septae and lobules; atypical lymphoid cells are rare/absent

♦ Erythema nodosum:
- Involves fat septae, not lobules. Ulceration absent
- Mixed inflammatory infiltrate (lymphocytes, histiocytes, giant cells, neutrophils)
- Heals spontaneously in 3–6 weeks

♦ Erythema induratum:
- Involves fat septae and lobules, and may cause medium and small-vessel vasculitis, but transmural vascular inflammation is mixed (neutrophils, histiocytes, giant cells); atypical lymphoid cells rare/absent

Blastic NK-Cell Lymphoma

♦ Synonym: agranular CD4+ CD56+ hematodermic neoplasms

Clinical

♦ Rare overall
♦ Age: middle-aged to elderly
♦ Sites: skin, lymph node, soft tissue, peripheral blood/bone marrow
♦ Clinical course: aggressive
♦ Cell of origin: plasmacytoid monocyte-like cell

Microscopic

♦ Monotonous infiltrate of blast-like cells

Immunophenotype

♦ CD56+, CD4 and CD43 usually+, CD123+
♦ CD3–, myeloperoxidase –, CD33–
♦ EBV–
♦ TdT may be+
♦ Extensive phenotyping required to exclude AML and T-ALL/T-LBL

Genetics

♦ Germline T-cell receptor genes

Mycosis Fungoides/Sézary Syndrome (MF/SS)

Synonyms

♦ Rappaport: mycosis fungoides/Sézary syndrome
♦ Kiel: small cell, cerebriform
♦ Lukes-Collins: cerebriform T
♦ Working Formulation: mycosis fungoides

Clinical

♦ Age: adults (median age 55 years)
♦ Sex: M > F (2:1)
♦ Sites of involvement:
- MF: multifocal skin lesions (patch, plaque, and tumor stages), +/– subtle peripheral blood involvement
- SS: diffuse skin involvement (erythroderma) with prominent peripheral blood involvement
- Lymph node and visceral organ (lung, liver, spleen) involvement occurs late in course of disease

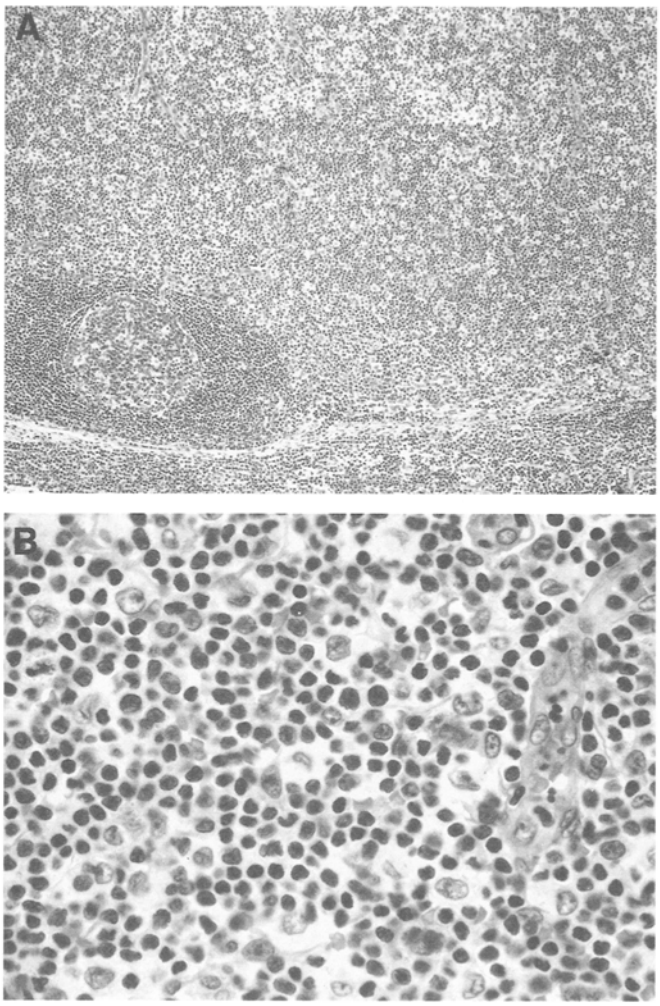


Fig. 23. Mycosis fungoides (**A** and **B**).

♦ Clinical course:
- MF: prognosis correlates with clinical stage
- SS: aggressive
- May eventually transform to LCL

*Microscopic (**Figure 23**)*

♦ Skin: band-like infiltrate at dermal-epidermal junction, epidermal infiltration (Pautrier's microabscesses)
♦ Lymph nodes: paracortical involvement initially, later becomes diffuse
♦ Cytology: predominantly small (and a minority of large) atypical lymphoid cells with convoluted, "cerebriform" nuclei associated with intermixed, non-neoplastic Langerhans' cells

Immunophenotype

♦ CD2, CD3, CD5+, often CD7– (other combinations of "aberrant" phenotypes may be seen)
♦ Usually CD4+

Genetics

- T-cell receptor genes clonally rearranged

Differential Diagnosis

- Skin:
  - Inflammatory dermatoses with lichenoid pattern of skin involvement (e.g., drug eruption, autoimmune diseases, actinic reticuloid, etc.)
  - Lymphomatoid papulosis
  - Other malignant lymphomas
- Lymph nodes:
  - Dermatopathic lymphadenopathy—normal T-cell phenotype, polyclonal T-cell receptor genes
  - Other malignant lymphomas

Angioimmunoblastic T-Cell Lymphoma

Synonyms

- Rappaport: not listed (diffuse mixed lymphocytic-histiocytic, histiocytic)
- Kiel: T-cell, angioimmunoblastic (AILD)
- Lukes-Collins: immunoblastic lymphadenopathy—like T-cell lymphoma
- Working Formulation: not listed (diffuse mixed small and large cell, diffuse large cell, large cell immunoblastic)

Clinical

- Age: adults (middle-age to elderly)
- Sex: M = F
- Presentation: fever, weight loss, skin rash, polyclonal hypergammaglobulinemia
- Sites of involvement: lymph nodes (generalized lymphadenopathy)
- Clinical course:
  - Moderately aggressive, may respond to treatment
  - Prone to infectious complications

*Microscopic **(Figure 24)***

- Architecture: paracortical to diffuse involvement; loss of germinal centers; sinuses open; tumor may invade perinodal fat
- Cytology: tumor composed of lymphoid cells including medium-sized cells with round nuclei and abundant clear cytoplasm, in background of small lymphocytes and immunoblasts, +/– epithelioid histiocytes, eosinophils, and/or plasma cells
- Follicular dendritic cell clusters surrounding arborizing high endothelial venules often prominent

Immunophenotype

- T-cell associated antigens+
- CD4 usually+
- Follicular dendritic cells CD21+
- Tumor cells may be CD10+

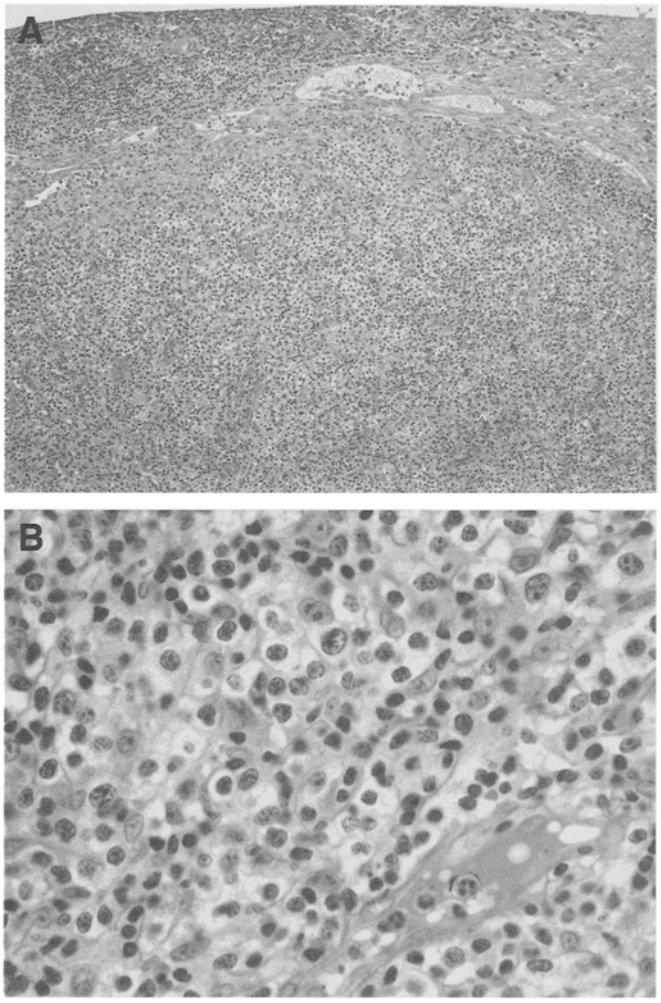


Fig. 24. Angioimmunoblastic T-cell lymphoma (**A** and **B**).

Genetics

- T-cell receptor genes usually rearranged
- Ig heavy chain genes occasionally rearranged (10–30%)
- EBV often present in scattered paracortical immunoblasts
- Trisomy 3, trisomy 5 may be present

Peripheral T-Cell Lymphoma, Unspecified

Synonyms

- Rappaport: diffuse PDL, diffuse mixed lymphocytic-histiocytic, histiocytic
- Kiel: T-zone lymphoma, lymphoepithelioid cell lymphoma, pleomorphic, small, medium, and large cell, T-immunoblastic
- Lukes-Collins: T-immunoblastic lymphoma
- Working Formulation: diffuse mixed small and large cell, large cell immunoblastic (polymorphous or clear cell)

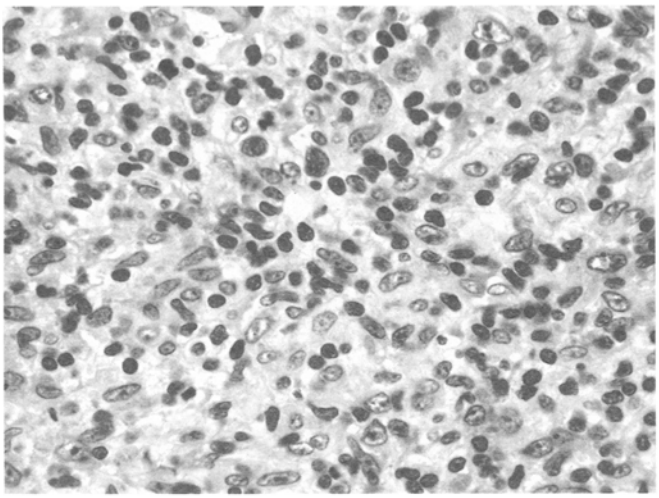


Fig. 25. Peripheral T-cell lymphoma, unspecified type.

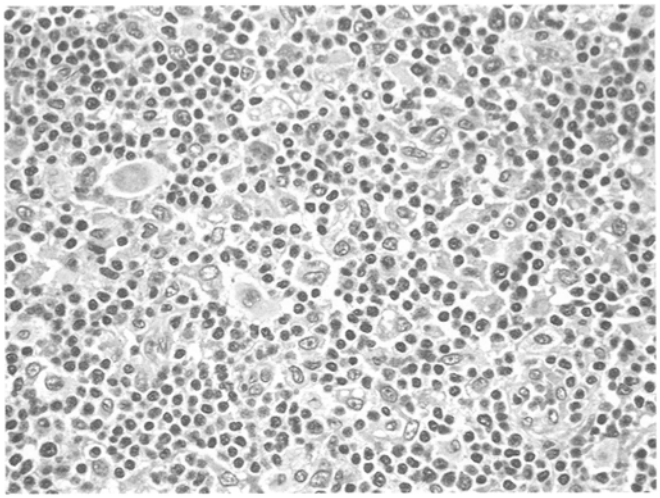


Fig. 26. Peripheral T-cell lymphoma, lymphoepithelial cell variant (Lennert lymphoma).

Clinical

- Age: adults
- Presentation: +/– eosinophilia, pruritus, or hemophagocytic syndrome
- Sites of involvement: lymph nodes, skin, subcutis, liver, spleen
- Clinical course: aggressive, usually incurable

Microscopic (Lymph Nodes)

- Architecture: paracortical or diffuse involvement
- Cytology (**Figure 25**):
  - Cell spectrum characterizes PTCL: small, medium, and large lymphocytes
  - Nuclear irregularity and hyperchromasia in small and medium-sized cells
  - Prominent nucleoli, dispersed chromatin, abundant clear cytoplasm in large cells
  - Variable number of eosinophils and/or epithelioid histiocytes may be present
  - Vascular proliferation may be seen

Variants

- T-zone variant:
  - Interfollicular growth pattern
  - Small to medium-sized tumor cells with little pleomorphism, +/– clusters of clear cells
  - Prominent high endothelial venules
  - Abundant reactive cells (eosinophils, plasma cells, histiocytes)
- Lymphoepithelial cell variant (Lennert lymphoma) (**Figure 26**):
  - Diffuse growth pattern
  - Small tumor cells with little pleomorphism
  - Prominent clusters of epithelioid histiocytes

Immunophenotype

- Aberrant T-cell phenotypes, defined by loss of a pan-T-cell antigen from a cell population, are frequent. Antigens absent: CD7 (75%), CD5 (50%), CD3 (10%), CD2 (10%)
- CD4 + more commonly than CD8
- B-cell associated antigens–

Genetic Features

- T-cell receptor genes usually clonally rearranged

Anaplastic Large Cell Lymphoma

Synonyms

- Rappaport: not listed (histiocytic, diffuse)
- Kiel: large cell anaplastic
- Lukes-Collins: T-immunoblastic sarcoma
- Working Formulation: not listed (diffuse large cell, immunoblastic)
- Other: malignant histiocytosis, sinusoidal large cell lymphoma, regressing atypical histiocytosis, Ki-1 lymphoma

Clinical

- Presentation: advanced stage disease, +/– B symptoms
- Sites of involvement: lymph nodes and extranodal sites (soft tissue, skin, bone, etc.)
- Age: bimodal:
  - Children/young adults: usually ALK+ (*See* Genetics following)
  - Older adults: usually ALK– (see genetic features below)
- Better prognosis: ALK+ (median survival 14 years)
- Poorer prognosis: ALK– (median survival 3 years)

Microscopic (Common Variant)

- Architecture:
  - Diffuse involvement, often with infiltration of sinuses
  - Cohesive growth pattern common

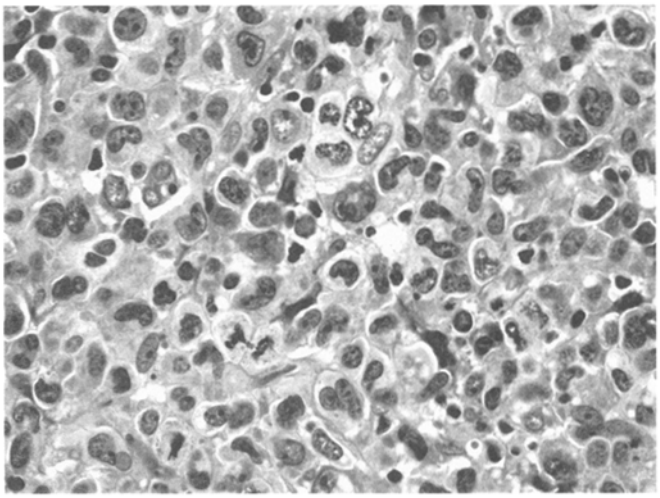


Fig. 27. Anaplastic large cell lymphoma.

- Cytology (**Figure 27**):
  - Very large pleomorphic cells with embryoid nuclei, multiple prominent nucleoli, and abundant cytoplasm
  - +/– background of granulocytes and macrophages

Immunophenotype

- CD30+ (cell membrane and Golgi staining)
- Tumor usually + for at least one T-cell antigen (CD2 and CD4 more often + than CD3, CD5, or CD7)
- CD45 usually+
- CD43, CD45RO often+
- EMA usually + in p80/ALK-1 + cases, EMA usually – in p80/ALK-1 – cases
- Fascin usually negative
- TIA-1, granzyme B often+
- B-cell associated antigens–

Genetics

- ALK+ cases: genetic alterations of ALK locus:
  - t(2;5)(p23;q35)—most frequent translocation → juxtaposition of nucleophosmin (NPM) gene on chromosome 5 and anaplastic lymphoma kinase (ALK) gene on chromosome 2 ⇒ hybrid NPM-ALK gene expressed
  - ALK antibody: detects ALK gene product:
    - Cytoplasmic and nuclear staining associated with t(2;5)
    - Cytoplasmic or membranous staining with variant translocations—e.g., t(1;2), t(2;3), t(2;17), inv(2)
  - ALK positivity associated with younger patients, EMA positivity, and better prognosis
  - EBV genome absent
- ALK– cases:
  - Genetic alterations of ALK locus absent
  - ALK negativity associated with older patients, EMA negativity, and poorer prognosis, or with primary cutaneous ALCL
- T-cell receptor gene rearranged in ~90% of cases, regardless of expression of T-cell antigens

Morphologic Variants

- Lymphohistiocytic variant:
  - Infrequent smaller neoplastic cells and rare cells with bilobed nuclei in histiocytic background. Histiocytes have a peculiar plasmacytoid cytology with eccentric round nuclei and abundant pink cytoplasm with perinuclear clearing
- Small cell variant:
  - Small to medium-sized neoplastic cells, often surrounding blood vessels

*Differential Diagnosis (**Table 5**)*

- Carcinoma: keratin +, CD45–
- Malignant melanoma: S-100 +, HMB45 usually +, CD45–
- Sarcoma: Vimentin+, CD45–
- Classical Hodgkin lymphoma: CD15+, CD45–, EMA–, ALK–, CD20 may be focally +

Hodgkin Lymphoma (HL)

Nodular Lymphocyte Predominant Hodgkin Lymphoma (NLPHL)

Synonyms

- Lukes et al: lymphocytic and/or histiocytic, nodular, lymphocytic and/or histiocytic, diffuse (some cases)
- Lennert and Mohri: paragranuloma, nodular or diffuse

Clinical

- Age: median mid 30's (wide age range)
- Sex: male > female (2.5:1)
- Presentation:
  - Localized involvement of peripheral lymph nodes (usually cervical, supraclavicular, axillary); mediastinum spared
  - 70–80% present at stage I or II
- Better prognosis: younger patients, presentation at low stage
- Poorer prognosis: older patients, presentation at high stage
- Occasionally preceded, accompanied, or succeeded by progressive transformation of germinal centers (PTGC)
- Clinical course:
  - Vast majority have complete response to therapy
  - May relapse or develop other lymphoma, especially large B-cell lymphoma

*Microscopic (**Figure 28**)*

- Low power: macronodules (may be highlighted by immunostains, particularly CD21, which stains follicular dendritic cells), +/– diffuse areas, often with rim of uninvolved lymph node
- High power:
  - Neoplastic cells:

Table 5. Differential Diagnosis of Poorly Differentiated Large Cell Neoplasms

	CD30	*Keratin*	*HMB-45/S-100*	*CD75*	*CD68/Lysozyme*	*CD45*
Anaplastic large cell lymphoma (ALCL)	+	–	–	–	–	+/–
Carcinoma	–	+	–/+	+/–	–	–
Melanoma	–	–	+	–	–[1]	–
Histiocytic sarcoma	–	–	–	–/+	+	+/–

[1]*Most cases of melanoma are CD68+, but they are lysozyme and CD45–*

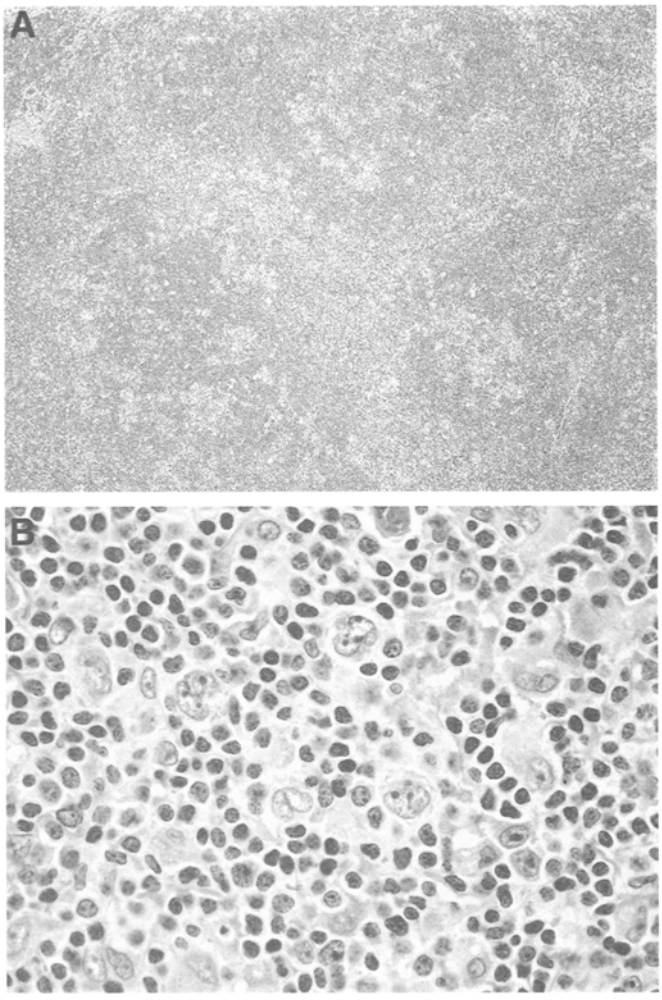


Fig. 28. Nodular lymphocyte predominant Hodgkin lymphoma (**A** and **B**).

- L & H cells (lymphocytic and /or histiocytic Reed-Sternberg [RS] cell variants; also called popcorn cells) may be numerous:large cells with multilobated vesicular nuclei, delicate chromatin, small nucleoli, and scant wispy cytoplasm
  - Classic RS cells rare or absent
- Background cells:
  - Lymphocytes (polyclonal, mostly B-cells) and groups of epithelioid histiocytes
  - L & H cells may be surrounded by CD57+ T-cells
  - Follicular dendritic cells (CD21+) often prominent
  - Rare plasma cells, eosinophils, or neutrophils

Immunohistochemistry

♦ L & H cells:
- CD45+
- CD19, CD20, CD22, CD79a+
- CD15–, CD30 usually–
- EMA often+
- Ig–

Genetics

♦ Whole tissue DNA: polyclonal

♦ DNA isolated from individually selected L&H cells: usually monoclonal Ig gene rearrangements

Differential Diagnosis

♦ Progressive transformation of germinal enters (PTGC):
- L & H cells have nuclear lobulation, centroblasts usually do not
- Centroblasts are EMA–

♦ Classical Hodgkin lymphoma, especially lymphocyte-rich type:
- Neoplastic cells are classic RS cells morphologically and immunohistochemically (CD15+, CD30+, CD45–, B-cell associated antigens–)

♦ FL, especially floral variant:
- Lymph node architecture usually completely obliterated
- Follicles/nodules composed predominantly of neoplastic B-cells (e.g., few normal lymphocytes or epithelioid histiocytes)
- Intrafollicular lymphocytes are bcl-2+, monoclonal sIg

- Large B-cell lymphoma, T-cell/histiocyte rich variant:
  - Diffuse architecture
  - Tumor cells may be arranged in clusters, without being surrounded by rosettes of CD57+ T-cells
  - No intermixed CD21+ FDC's
  - Tumor cells often show monoclonal sIg

Nodular Sclerosis Hodgkin Lymphoma

Clinical

- Age: young adults
- Sex: F > M (slight)
- Sites of involvement: lower cervical, supraclavicular, and anterior mediastinal lymph nodes most common
- Poorer prognosis: higher stage, greater bulk of disease
- Clinical course: often curable (95% of patients presenting at stage I and II, 50–70% of patients present at stage III and IV)

*Microscopic **(Figure 29)***

- Low power:
  - Nodular pattern with fibrous band separating nodules, +/– diffuse areas, +/– necrosis
  - May be interfollicular
- High power:
  - Hodgkin and Reed-Sternberg (HRS) cells:
    - Lacunar cells (RS cell variants) common: multilobated nuclei, small nucleoli, abundant pale cytoplasm that retracts with formalin fixation
    - Classic RS cells may be rare
  - Background cells:
    - Lymphocytes (mostly T-cells), eosinophils, histiocytes, plasma cells, neutrophils (associated with B symptoms), and fibroblasts
    - Broad range of appearances depending on relative contribution from different cell populations and degree of sclerosis. HL is classified as NS type whenever there are collagen bands and lacunar cells, regardless of all else

Immunophenotype

- HRS cells:
  - CD30+
  - Usually CD15+ (paranuclear, cytoplasmic, and/or membranous staining pattern), at least in a subset of HRS cells
  - CD45–
  - B-cell associated antigens weakly + in a subset of RS cell variants in some cases
  - T-cell associated antigens usually – in RS cell variants
  - EMA–
  - p80/ALK-1–
  - Fascin usually+

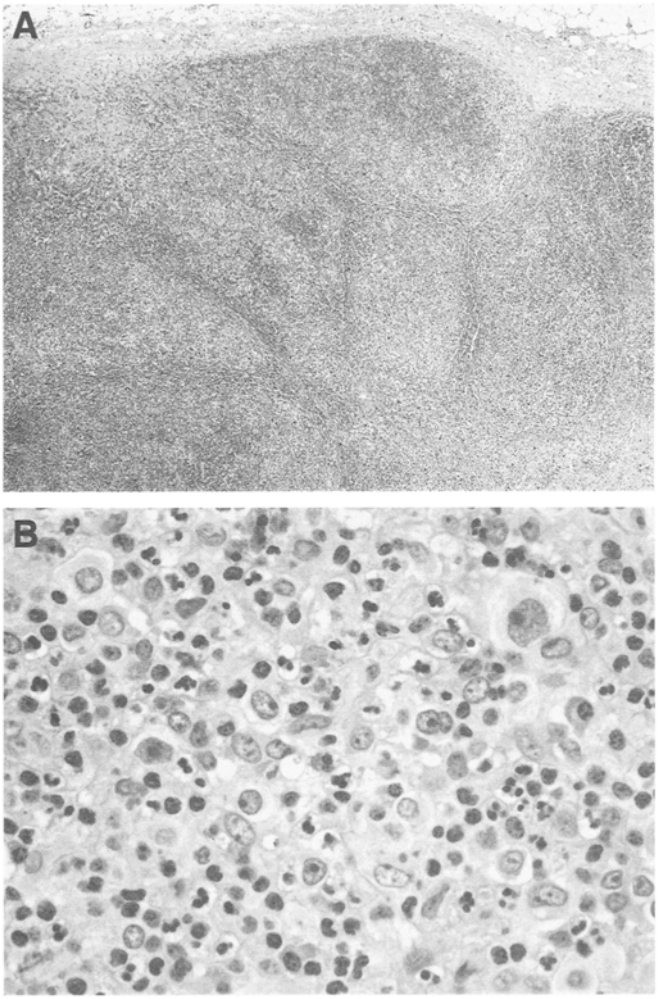


Fig. 29. Nodular sclerosis Hodgkin lymphoma (**A** and **B**).

Genetics

- DNA isolated from isolated single HRS cells: usually monoclonal Ig gene rearrangements

NSHL Grading, BNLI (British National Lymphoma Investigation) Criteria

- Grade II:
  - Sheets of RS cells in ≥ 25% of nodules (syncytial variant of NSHL)
- Grade I:
  - Scattered RS cells in mixed inflammatory background in >75 % of nodules. Prognostic significance of grading NSHL is controversial

Mixed Cellularity Hodgkin Lymphoma (MCHL)

Clinical

- Age: adults (wide age range)
- Sex: M > F

♦ Presentation: higher stage (lymph nodes, spleen, liver, bone marrow often involved)

Microscopic

♦ Architecture:
- Diffuse or vaguely nodular
- Lymph node capsule intact
- No broad bands of fibrosis
- May be interfollicular

♦ Cytology
- HRS cells:
  - Classic RS cells common: large cells with large single or multiple nuclei that often have more than one lobe, a single prominent eosinophilic nucleolus per lobe, and abundant cytoplasm
- L & H cells, lacunar cells absent
- Background cells:
  - Lymphocytes, epithelioid histiocytes, eosinophils, neutrophils, and plasma cells

Immunophenotype

♦ HRS cells:
- CD30+
- Usually CD15+ (paranuclear, cytoplasmic, and/or membranous staining pattern)
- CD45–
- B-cell and T-cell associated antigens usually–
- EMA–
- p80/ALK-1–

Differential Diagnosis

♦ Large B-cell lymphoma, T-cell/histiocyte-rich type
- Immunophenotyping essential to make distinction

Lymphocyte-Rich Classical Hodgkin Lymphoma (LRCHL)

Clinical

♦ Age: adults

♦ Sex: M > F

♦ Presentation: lymphadenopathy; usually lower stage (I or II)

Microscopic

♦ Architecture:
- Nodular or diffuse involvement

♦ Cytology:
- Neoplastic cells: infrequent classic RS cells, +/– lacunar variants
- Background cells: numerous lymphocytes with occasional histiocytes, eosinophils, or plasma cells

Immunophenotype

♦ HRS cells:

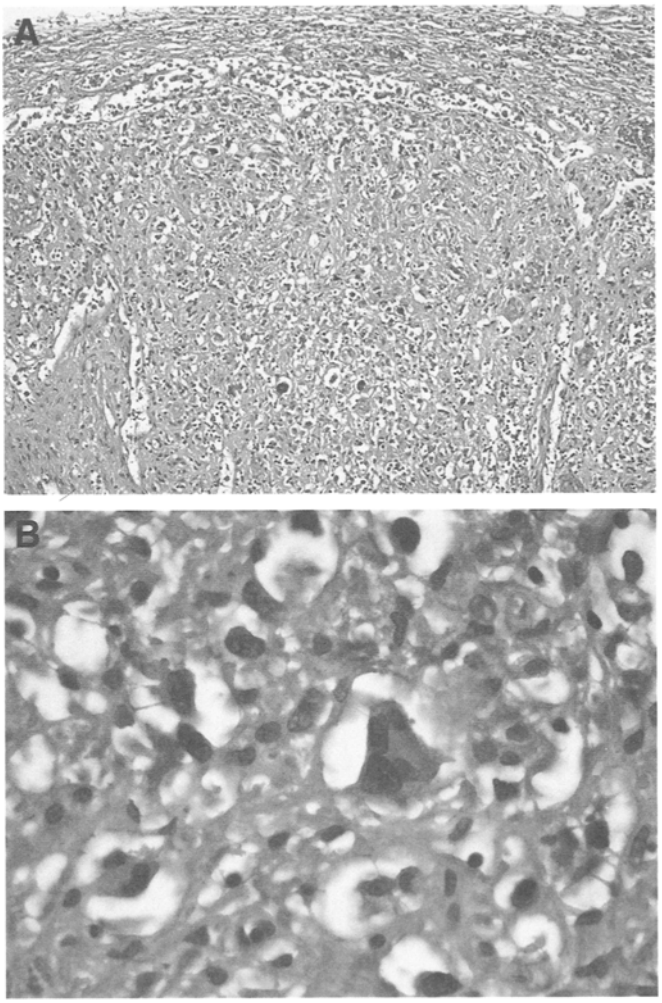


Fig. 30. Lymphocyte depleted Hodgkin lymphoma (**A** and **B**).

- CD30+
- CD15+ (paranuclear, cytoplasmic, and/or membranous staining pattern)
- CD45–
- B-cell and T-cell associated antigens usually–
- EMA–, p80/ALK-1–

Differential Diagnosis

♦ NLPHL:
- Immunophenotyping essential to make distinction

Lymphocyte Depleted Hodgkin Lymphoma (LDHL)

Clinical

♦ RARE

♦ Age: older adults

♦ Also seen in HIV+ patients and patients from developing countries

♦ Sites of involvement: abdominal lymph nodes, spleen, liver, bone marrow

- Extranodal sites involved in HIV+ individuals (usually EBV–/+)
- Presentation: high stage

*Microscopic (**Figure 30**)*

- Architecture:
  - Depleted appearance with disorganized collagen
- Cytology:
  - Innumerable RS cells, bizarre multinucleated cells and RS cell variants of no special type
  - Minimal reactive elements

Immunophenotype

- HRS cells:
  - CD30+
  - Usually CD15+ (paranuclear, cytoplasmic, and/or membranous staining pattern)
  - Fascin usually positive
  - CD45–
  - B-cell and T-cell associated antigens usually–
  - EMA–, p80/ALK-1–

Differential Diagnosis

- Diffuse large B-cell lymphoma:
  - CD45+
  - B-cell associated antigens+
  - CD15, CD30–

Table 6. Immunophenotypic Distinction Between Hodgkin Lymphoma and Anaplastic Large Cell Lymphoma

Marker	*Anaplastic Large Cell Lymphoma*	*Hodgkin Lymphoma*
CD30	+(strong, all cells)	+
CD45	+/–	–
CD15	–/+	+(80%)
Fascin	–/+	+
CD43	+(70%)	–
CD45RO	+(50%)	–
CD3 (paraffin)	+(50%)	–
EMA	+/–	–
P80 or ALK-1	+(50%)	–
CD20	–	–/+

- Anaplastic large cell lymphoma (**Table 6**):
  - CD45+, EMA+, ALK-1/p80+
  - CD15–
  - T-cell associated antigens often+
- Sarcoma

HISTIOCYTIC LYMPH NODE TUMORS

Langerhans' Cell Histiocytosis

Synonyms

- Langerhans' cell granulomatosis
- Histocytosis X

Clinical

- Age: children
- Sex: M > F
- Presentation: unifocal disease (solitary eosinophilic granuloma), multifocal unisystem disease (previously called Hand-Schuller-Christian syndrome), or multifocal multisystem disease (previously known as Letterer-Sewe syndrome)
- Sites of involvement:
  - Lymph nodes or other organs (skin, bone, lungs, etc.)
- Prognosis: related to number of affected organs at presentation

Microscopic

- Sinuses distended by Langerhans' cells (mononuclear cells with fine chromatin, nuclear grooves, moderate eosinophilic cytoplasm)
- Background cells:
  - +/– eosinophils, which may form microabscesses
  - +/– mononuclear and multinuclear histiocytes
  - +/– neutrophils and lymphocytes

Immunophenotype

- Langerhans' cells:
  - S-100 protein+
  - CD1a+
  - PLAP (placental alkaline phosphatase) usually+

Electron Microscopy

- Langerhans' cells contain Birbeck granules (racket- or rod-shaped structures with osmiophilic core and double outer sheath)

Sinus Histiocytosis with Massive Lymphadenopathy (SHML)

Synonym

- Rosai-Dorfman disease

Clinical

- Age: mean age 20 years (wide age range)
- Sex: M > F (slight)
- Sites of involvement:
  - Bilateral cervical lymphadenopathy most common; may involve other lymph nodes or other sites (e.g., skin, upper respiratory tract, bone)
- Clinical course: most cases spontaneously regress

*Microscopic **(Figure 31)***

- Capsular fibrosis
- Sinuses distended by large histiocytes containing intact intracytoplasmic lymphocytes as well as intracytoplasmic plasma cells and erythrocytes ("emperipolesis")
- Medullary cords contain numerous plasma cells

Immunohistochemistry

- Histiocytes: S-100+, CD68+, CD1a–

Histiocytic Sarcoma

Clinical

- RARE
- Age: adults; wide age range
- Sites of involvement: lymph nodes, skin, extranodal sites
- Clinical course: aggressive

Microscopic

- Low power:
  - Diffuse proliferation of large atypical cells
- High power:
  - Large pleomorphic cells with ample eosinophilic cytoplasm, +/– reactive cells (small lymphocytes, eosinophils, benign histiocytes)

Immunophenotype

- + for histiocytic markers (CD68, lysozyme, CD11c, CD14)
- – for myeloid markers (myeloperoxidase, CD33, etc.), B-cell markers, and T-cell markers
- CD45 may be+

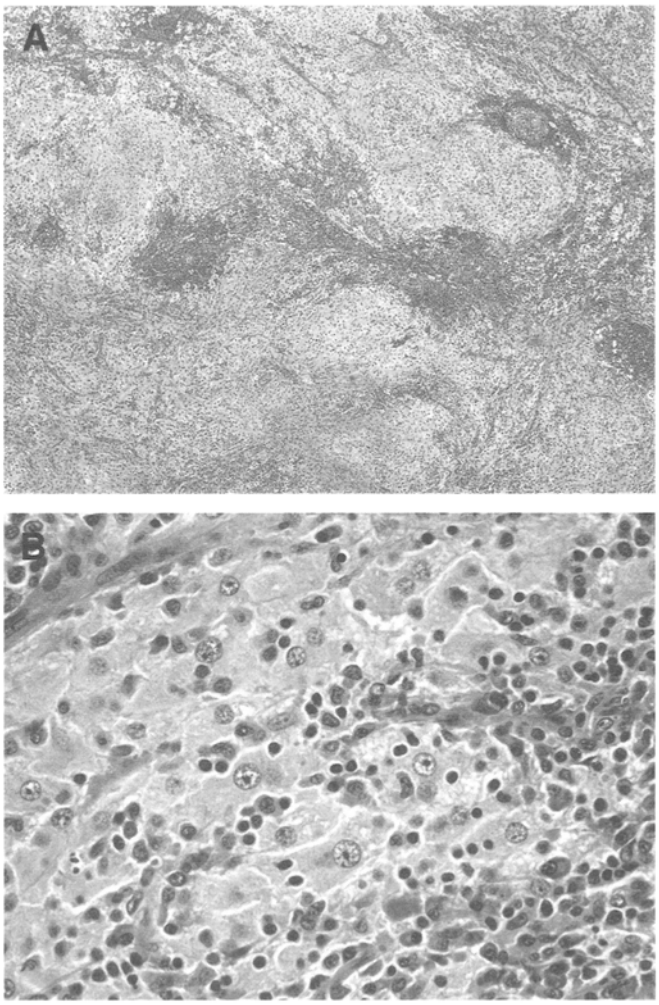


Fig. 31. Sinus histiocytosis with massive lymphadenopathy (**A** and **B**).

Differential Diagnosis

- Diffuse large B-cell lymphoma: CD20+
- Carcinoma: keratin+
- Melanoma: S-100, HMB-45+; may be CD68+; CD45 and lysozyme–

SPINDLE CELL LESIONS OF LYMPH NODES

Bacillary Angiomatosis

Clinical

- Etiologic agent: Bartonella henselae
- Patients are immunosuppressed (especially AIDS)
- Sites of involvement: skin, lymph nodes, spleen
- Treatment: antibiotics

Microscopic

- Multiple nodules composed of proliferating vessels lined by plump, +/– pleomorphic endothelial cells with pale, vacuolated cytoplasm
- Interstitium contains distinctive eosinophilic granular material (= aggregates of bacilli), +/– neutrophils
- +/– foamy macrophages, granulomas, or peliotic spaces

- Bacilli + on Warthin-Starry stain and Giemsa stain (less sensitive)

Differential Diagnosis

- Epithelioid hemangioma/hemangioendothelioma:
  - Cells have eosinophilic cytoplasm without vacuoles
  - No extracellular granular material made up of aggregates of bacilli, Warthin-Starry stain–
- Kaposi's sarcoma:
  - Based in lymph node capsule
  - Fascicles of spindle cells present
  - Warthin-Starry stain—for bacilli

Kaposi's Sarcoma

Clinical

- Classic: most common presentation is lower extremity skin lesions in elderly Jewish or Mediterranean men. Indolent clinical course
- African (endemic): Equatorial Africa:
  - Cutaneous: most common in young men; uncommon regional lymph node involvement
  - Lymphadenopathic:most common in children, M > F; localized or generalized lymphadenopathy. Aggressive clinical course
- Epidemic:Common in HIV+ patients, especially gay men. Involves lymph nodes, mucocutaneous sites, gastrointestinal tract, lung

Etiologic Agent

- Human herpes virus 8 (HHV8)

Microscopic

- Low power:
  - Single or multiple nodules, or extensive replacement of lymph node
  - Capsular/subcapsular involvement
- High power:
  - Fascicles of spindle cells with vascular slits containing extravasated red blood cells
  - Mitoses common
  - +/– lymphocytes, plasma cells, histiocytes, and hemosiderin deposits
  - Eosinophils hyalin globules (PAS-D+) often seen within spindle cells or histiocytes

Immunophenotype

- CD31+, CD34+, Factor VIII+/–
- Actin

Differential Diagnosis

- Vascular transformation of lymph node sinuses
  - Capsule spared, distinct vascular channels, no PAS+ hyaline globules
- Inflammatory pseudotumor of lymph node:
  - No vascular slits, no PAS+ hyaline globules
  - Follicular hyperplasia and plasmacytosis are prominent
- Palisaded myofibroblastoma:
  - No vascular slits, no PAS+ hyalin globules
  - Actin +, Factor VIII–
- Epithelioid hemangioma/hemangioendothelioma
- Bacillary angiomatosis:
  - No spindle cell fascicles; bacilli Warthin-Starry+

Palisaded Myofibroblastoma

Synonym

- Hemorrhagic spindle cell tumor with amianthoid fibers

Clinical

- Age: wide age range
- Sex: M > F (slight)
- Location: inguinal lymph nodes most common; cervical, mediastinal nodes rare
- Clinical course: benign; no local recurrences or metastases

Microscopic

- Short fascicles of bland spindle cells (+/– perinuclear vacuoles), palisaded nuclei
- Intersitial hemorrhage and/or hemosiderin
- Stellate foci of collagen (amianthoid-like fibers)
- Periphery of tumor often hemorrhagic, with compressed rim of residual lymph node
- Mitoses rare

Immunophenotype

- Actin +, Vimentin+
- Desmin –, S-100–, Factor VIII–

Differential Diagnosis

- Kaposi's sarcoma:
  - Lymph node capsule based
  - Red cells within vascular slits; PAS+ hyaline globules common; CD31, CD34+
- Intranodal schwannoma:
  - Distinct Antoni A and B areas; S-100+
- Vascular transformation of lymph node sinuses
- Inflammatory pseudotumor of lymph nodes
- Follicular dendritic cell sarcoma:
  - Nests of plumper cells; no amianthoid-like fibers or hemorrhage; CD21, CD35+

Inflammatory Pseudotumor of Lymph Node

Clinical

- Age: young adults
- Presentation: lymphadenopathy (superficial or deep), often with constitutional symptoms
- Treatment: excision of node is often curative

Macroscopic

- Enlarged lymph node(s), may be matted

Microscopic

- Proliferation of spindle cells (histiocytes and fibroblasts) and blood vessels, with acute and chronic inflammation and sclerosis
- Primarily involves hilum, trabeculae, and capsule

Differential Diagnosis

- Kaposi's sarcoma:
  - Vascular slits and PAS+ hyaline globules present
  - Sclerosis less prominent
- Castleman's disease
- Hodgkin lymphoma

Follicular Dendritic Cell Sarcoma

Microscopic

- Partial to complete replacement of lymph node
- Fascicles and nests of oval to spindle shaped cells with bland vesicular nuclei, inconspicuous nucleoli, and pale cytoplasm
- Few mitoses
- Scattered small lymphocytes present

Immunophenotype

- CD21, CD35 usually+
- CD68 usually+
- S-100 usually–
- Clusterin+

Interdigitating Dendritic Cell Sarcoma

Microscopic

- Histologic spectrum from spindle cells to rounder, lymphoid-like cells

Immunophenotype

- S-100 +, CD68 usually+
- Clusterin usually negative
- CD21–, CD35–

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10

Spleen

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CONTENTS

I. General Considerations 10-2
Examination and Evaluation of the Spleen 10-2
Splenomegaly 10-2
Splenic Rupture 10-3
Splenic Ectopia.....10-3

II. Lymphoid Neoplasms.....10-3
Lymphomas presenting predominantly in white pulp 10-3
Splenic Marginal Zone Lymphoma 10-3
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma 10-5
Lymphoplasmacytic Lymphoma.....10-6
Follicular Lymphoma 10-6
Mantle Cell Lymphoma 10-7
Nodal Marginal Zone Lymphoma 10-8
Lymphoid neoplasms presenting predominantly in red pulp 10-8
Hairy Cell Leukemia 10-8
Prolymphocytic Leukemia 10-9
Acute Lymphoblastic Leukemia.....10-9
Hepatosplenic T-Cell Lymphoma.....10-10
Large Granular Lymphocytic Leukemia 10-10
Other patterns of splenic involvement 10-11
Classical Hodgkin Lymphoma 10-11
Nodular lymphocyte-predominant Hodgkin lymphoma 10-11
Diffuse Large B-cell Lymphoma 10-12

III. Myeloid and Related Disorders 10-12
Extramedullary Hematopoiesis 10-12
Acute Myeloid Leukemia.....10-13
Myeloproliferative Disorders 10-13
Myelodysplastic Syndromes 10-14
Systemic Mastocytosis 10-14
Hemophagocytic syndrome 10-15

IV. Non-Hematopoietic Lesions 10-15
Cysts 10-15
Hamartoma 10-15
Inflammatory Pseudotumor 10-15
Follicular Dendritic Cell Tumor.....10-16
Inflammatory Myofibroblastic Tumor 10-16
Vascular Lesions.....10-17
Peliosis 10-17
Hemangioma.....10-17
Lymphangioma 10-17
Littoral Cell Angioma.....10-18
Hemangioendothelioma 10-19
Angiosarcoma 10-19
Metastatic disease.....10-19

V. Reactive Lesions including hyperplasias, infections, autoimmune and immunodeficiency.....10-20
Hyperplasias 10-20
Vascular/congestive disorders 10-20
Red blood cell disorders.....10-20
Infections 10-21
Storage disease 10-22
Other systemic disorders 10-23
Autoimmune conditions 10-23
Congenital immunodeficiency-related splenic disorders 10-24

VI. Suggested Reading.....10-24

GENERAL CONSIDERATIONS

Examination and Evaluation of the Spleen

The spleen as a specimen in anatomic pathology has several unusual features

- It is only rarely biopsied; it is almost always removed completely either intact or as multiple fragments
- Pathology findings are either incidental because of removal secondary to trauma, or are seen because of symptoms of splenomegaly associated with known disease
- Only occasionally is a spleen removed with pathology that is a significant diagnostic challenge due to: its rarity, its overlap with other pathologic entities or an unusual histologic appearance that requires ancillary studies for diagnosis
- The pattern of involvement of splenic pathology can be divided into four categories: white pulp lesions, red pulp lesions, focal lesions or a combination of these types **(Figure 1)**
- Normal spleen has small white flecks in a background of purple red, representing the white and red pulp, respectively
- The gross presentation of white pulp lesions is a caricature of the normal splenic appearance; the small white flecks expand in size and become readily visible grossly, which is described as a miliary pattern **(Figure 2)**
- In red pulp lesions, the spleen takes on a beefy red appearance, with the white pulp becoming inapparent
- Focal lesions can vary in size, consistency and circumscription of their boundaries; these may represent cystic or solid masses
- In masses, color and density depend on their cellular composition, although many focal lesions in spleen evoke a fibrosclerotic response from the splenic stroma, imparting a firm, yellow-tan appearance **(Figure 3)**

The spleen as an organ is unique in its combination of functions

- It serves as an 'agent' of both the immune system and the hematopoietic system
- As an immune organ, one of its functions is to serve as a very large lymph node, with immunologic responses comparable to those found in other lymphoid organs
- Its immunologic function also includes phagocytosis of cells or materials that are recognized as 'foreign'
- In a similar manner, the spleen serves to cull effete red blood cells as they pass through splenic sinuses into cords; red blood cells lacking appropriate membrane deformability will be repaired or destroyed as they transit through the acidotic environment
- The splenic architecture is composed of a fibrous capsule with an interconnected complex of support trabeculae, a network of arteries and arterioles, a complex arrangement of vascular sinuses with associated macrophages, and a complex arrangement of lymphoid tissue
- Because of this combination of tissues and functions, the spleen presents with diseases that are expressions of its similarities to other sites (lymphomas), its abundance of certain types of tissues (vascular tumors), and is related to its functions (extramedullary hematopoiesis, acute leukemias) and its unique anatomy (littoral cell angiomas)
- Because of its filtering function, it is not uncommon for the spleen to be a site of infection
- The microenvironment of the spleen is somewhat inhospitable, so the organisms that are present must be particularly good at evading immunologic destruction (e.g., encapsulated bacteria, fungi)

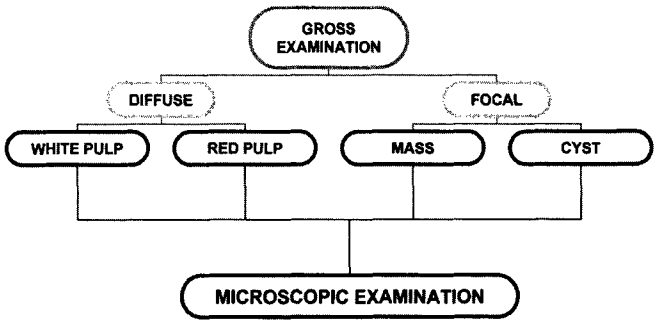


Fig. 1. Approach to examination of the spleen.

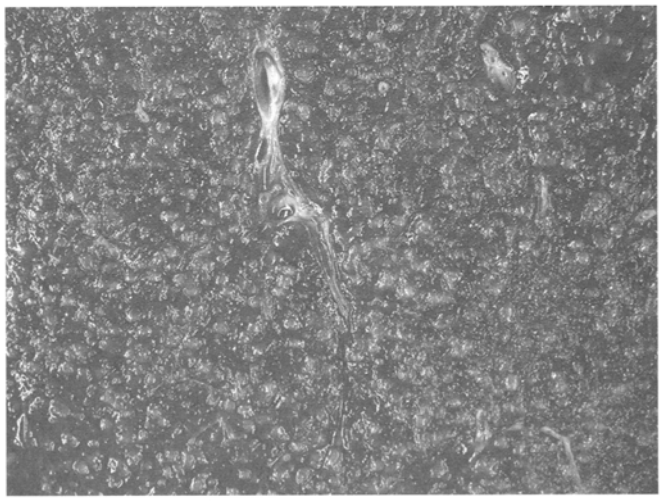


Fig. 2. White pulp: The miliary pattern is an accentuation of the normal splenic architecture. The white pulp components are enlarged and prominent.

Splenomegaly

- Splenomegaly may result from a variety of causes, both benign and malignant
- Some of the most common causes of splenomegaly are systemic disorders that merely represent hyperfunction of normal splenic activities and/or vascular congestion

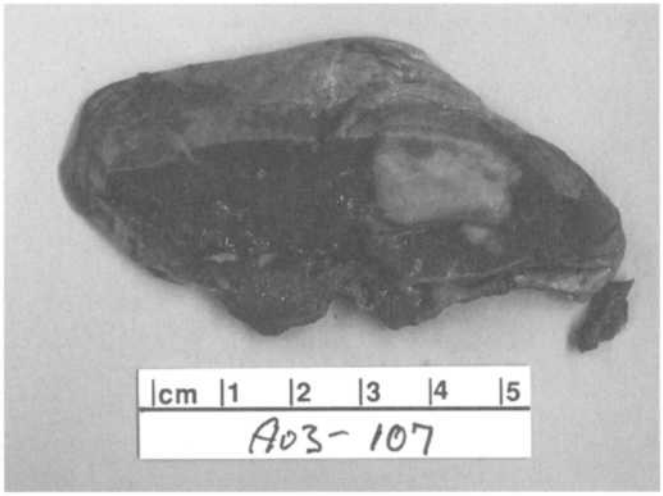


Fig. 3. Splenic infarction: The firm, tan wedge shaped mass is a splenic infarction. Microscopically, it is composed of macrophages, fibroblasts and benign vascular elements.

- Splenomegaly may result in clinical symptoms including early satiety, abdominal fullness, and pain
- Splenic enlargement is not an uncommon manifestation of systemic hematologic disease, however, the spleen is rarely removed as a diagnostic specimen
- It may be removed as a result of intractable symptoms, including patient discomfort or cytopenias
- Only rarely is the spleen removed for evaluation of an unknown cause of splenomegaly or a mass of uncertain etiology

Splenic Rupture (Figure 4)

- There are a wide variety of both non-neoplastic and neoplastic causes associated with splenic rupture
- The spleen is typically enlarged in these cases, sometimes massively. But the rapidity of enlargement may also play a role, with acute processes rupturing while the spleen is smaller
- Hemoperitoneum as a result of splenic rupture often leads to serious consequences including shock and death if not treated appropriately

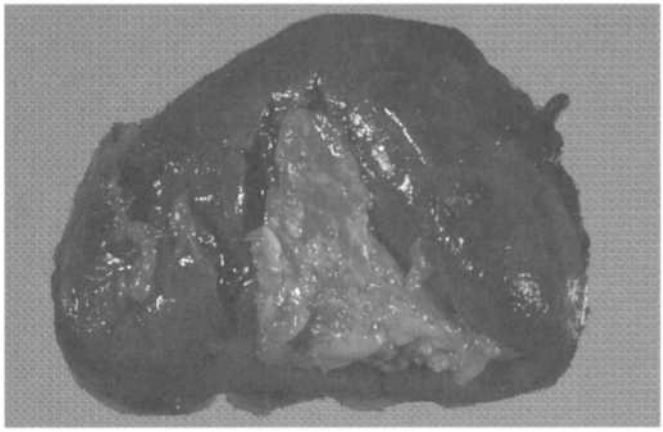


Fig. 4. Splenic rupture: This gross photograph shows several ruptures in the splenic hilum and with small amounts of adherent blood clot.

- In cases with an underlying neoplasm, spontaneous splenic rupture is associated with a high mortality rate. A list of causes associated with splenic rupture can be seen in **Table 1**
- One notable cause of "spontaneous" splenic rupture is infectious mononucleosis/acute Epstein-Barr virus infection

Splenic Ectopia

- Accessory spleens are not uncommon findings at autopsy and are typically located in the splenic region but can be more distant
- Accessory spleens have the normal architecture of spleen and are typically small
- Splenic-gonadal fusion is a rare developmental anomaly with portions of the spleen attaching to the left gonad +/– tissue connecting the normally located spleen with the wandering fragment
- Splenosis refers to the presence of multiple small foci of splenic tissue which are present throughout the abdominal cavity
- Splenosis usually arises after rupture of the spleen and seeding of the abdominal cavity with small fragments of splenic parenchyma

LYMPHOID NEOPLASMS

Lymphomas Presenting Predominantly in White Pulp

Splenic Marginal Zone Lymphoma (SMZL)

Definition

- B-cell lymphoma, thought to be derived from splenic marginal zone cells
- Splenic involvement is predominant, although marrow and peripheral blood involvement are present in virtually all cases
- Formerly known as 'splenic lymphoma with villous lymphocytes
- SMZL is a relatively common diagnosis made in spleens removed for undetermined causes of splenomegaly

Table 1. 'Spontaneous*' Splenic Rupture: Associations and Etiologies

I. Infectious
- A. Bacterial
  - i. Typhoid fever
  - ii. Q Fever
  - iii. Infectious endocarditis (various species)
  - iv. Tuberculosis and other mycobacteria
  - v. Numerous others
- B. Viral
  - vi. Epstein-Barr virus
  - vii. CMV
  - viii. HIV
  - ix. Others
- C. Parasitic/Protozoal
  - x. Malaria
  - xi. Others

II. Hematopoietic Diseases
- A. Acute leukemias
- B. Lymphoma
- C. Myeloma/ Amyloidosis (esp. plasma cell leukemia)
- D. CML and other myeloproliferative disorders (CIMF, ET, PV)

III. Vascular lesions
- A. Benign (e.g., peliosis, hemangioma)
- B. Neoplastic (e.g., littoral cell angioma, angiosarcoma)

IV. Cysts

V. Infarction

VI. Autoimmune including collagen-vascular diseases

VII. Hamartoma

VIII. Medications
- A. Anticoagulants and thrombolytics
- B. Cytokines including G-/GM-CSF

IX. Metastatic malignancy (carcinoma, melanoma, etc.)

X. Storage Diseases

XI. Coagulation Abnormalities
- A. Factor VIII deficiency
- B. Congenital dysfibrinogenemia

Table 1. *(Continued)*

XII. Pregnancy-related
- A. Post-partum
- B. Ectopic pregnancy ('splenic' pregnancy)

XIII. Miscellaneous
- A. Sarcoidosis
- B. Acute pancreatitis
- C. Cirrhosis of liver from any cause
- D. Mechanical (after vomiting, coughing)

**This may be better referred to as 'atraumatic' splenic rupture, as spontaneous rupture is sometimes defined as rupture associated with no specific underlying etiology.*

Clinical

- Patients most often present with asymptomatic splenomegaly

Laboratory

- Leukocytosis may be present. Lymphocytes in peripheral blood may have cytoplasmic projections, referred to as villous lymphocytes

Diagnosis

- Macroscopic: **(Figures 5,6)**
  - Spleens are typically enlarged, often massively, with prominent expansion of the white pulp in a miliary pattern
- Microscopic:
  - The white pulp is expanded and replaced by a population of predominantly small lymphocytes
  - These are typically round, with a relative increase in cytoplasm giving them a pale appearance; rare larger, transformed lymphocytes are also present
  - Occasionally there is plasma cell differentiation. In early involvement, they will expand the normal marginal zone
  - As the disease progresses, lymphocytes will invade and replace the mantle zone and follicle centers
  - Another diagnostic feature is colonization and replacement of the PALS with B-cells
  - As disease advances, small nodules of B-cells will be seen in the red pulp
  - High grade transformation is uncommon, but occurs
  - In transformation, the morphology will appear similar to diffuse large B-cell lymphoma +/– evidence of residual, low grade lymphoma as well
  - Bone marrow involvement may be subtle and have a intravascular pattern



Fig. 5. Splenic marginal zone lymphoma: Expansion of the white pulp by pale-appearing lymphocytes.

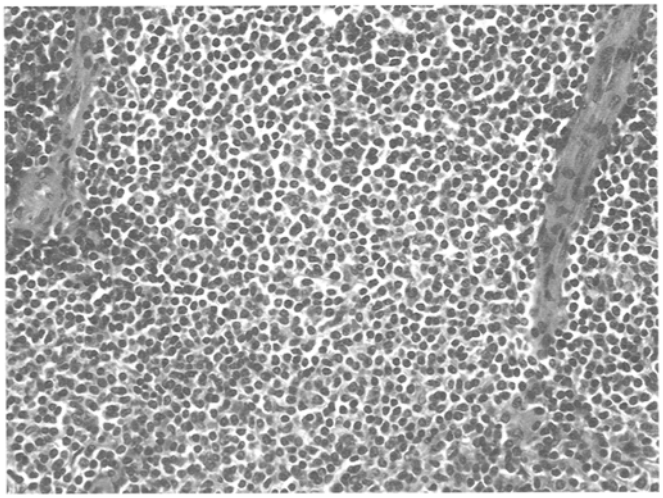


Fig. 6. Splenic marginal zone lymphoma: Predominantly small lymphocytes with moderate amounts of clear or pale cytoplasm.

Additional Studies

- FLOW: CD19+, CD20+, CD23+/–, CD5–, CD10–, FMC7+
- IHC: SMZL will be positive for B-cell markers and negative for markers associated with other specific lymphoma types: CD5, CD10, bcl-6, Cyclin D1, Overexpression of p53 is associated with transformation to higher grade tumor and a poor prognosis
- Molecular: IgH gene rearrangements often positive; allelic loss of 7p21–32; trisomy 3

Differential Diagnosis

- Benign: splenic marginal zone hyperplasia
- Malignant: other 'small B-cell' lymphomas with splenic involvement including follicular lymphoma, small lymphocytic lymphoma, mantle cell lymphoma and lymphoplasmacytic lymphoma

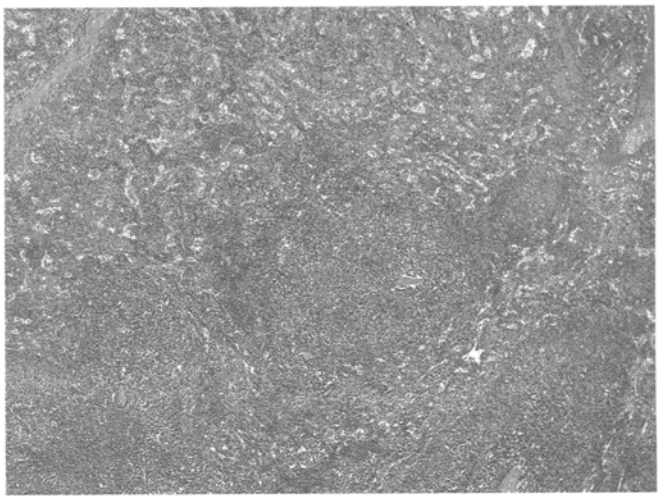


Fig. 7. CLL/SLL: Expansion of the white pulp with small satellite nodules. The cells are predominantly small, round lymphocytes with occasional prolymphocytes.

Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL) (Figure 7)

Definition

- Neoplastic proliferation of predominantly small, mature-appearing B-cells that co-express CD5 and CD19
- Typically there is peripheral blood involvement (CLL) and occasionally predominant nodal involvement (SLL)

Clinical

- Patients typically >50 years old
- Often asymptomatic but may have anemia, fatigue, infectious or symptomatic splenomegaly
- Splenic involvement can vary depending on presentation of disease. Most often splenic red pulp is more prominently involved (CLL-like presentation), in addition to white pulp involvement
- Rarely, the predominant involvement is in the white pulp (SLL-like presentation) with minimal red pulp involvement

Laboratory

- Peripheral blood and bone marrow involvement is common
- The usual presentation is isolated elevated WBC composed of small, mature lymphocytes

Diagnosis

- Macroscopic: Prominent white pulp involvement leads to miliary pattern grossly. Red pulp involvement leads to beefy appearance of spleen. May have both patterns of involvement
- Microscopic: White pulp is enlarged in size, with inconspicuous germinal centers. The predominant cell is small, round lymphocyte with scant cytoplasm and

condensed chromatin. Rare larger cells, with large open chromatin, prominent central nucleolus and moderate cytoplasm (prolymphocytes) are present

Additional Studies

- FLOW: CD5+, CD20(dim)+, CD23+. FMC7–, CD10–
- IHC: CD5+, CD20+, CD23+, CD43+, bcl-2+, CD10–, Cyclin D1–, bcl-6–
- Karyotype: trisomy 12 is present in a proportion of cases and can be associated with a poor prognosis
- Molecular: mutation status of the IgH genes is associated with prognosis. Those with unmutated IgH genes have a worse prognosis

Differential Diagnosis

- Malignant: other 'small B-cell' lymphomas with splenic involvement including follicular lymphoma, marginal zone lymphoma, mantle cell lymphoma and lymphoplasmacytic lymphoma
- Benign: white pulp hyperplasias

Lymphoplasmacytic Lymphoma (Figure 8)

Definition

- An indolent form of B-cell lymphoma composed of IgM secreting cells with lymphoid and plasmacytic features

Clinical

- Many patients have symptoms of hyperviscosity, termed Waldenstrom's macroglobulinemia caused by large amounts of serum monoclonal IgM protein
- Bone marrow and peripheral blood involvement are typical. Splenic involvement is not uncommon, but spleen is rarely removed for diagnostic purposes
- Considered a diagnosis of exclusion; must rule out other possible diagnoses including marginal zone lymphoma, CLL/SLL, plasma cell dyscrasias

Diagnosis

- Macroscopic:
  - Depends on type of microscopic involvement
  - Diffuse or focal
- Microscopic:
  - Most commonly infiltration of both white and red pulp by a mixture of small lymphocytes, lymphoplasmacytic cells and plasma cells
  - Dutcher bodies and Russell bodies not uncommon
  - Rarely involvement of white pulp with similar cells, without prominent red pulp involvement

Additional Studies

- FLOW: CD19+, light chain restricted, CD5–, CD10–, CD23–, FMC7+
- IHC: CD20+, Cyclin D1–, CD5–, CD10–
- Molecular: IgH gene rearrangement often present

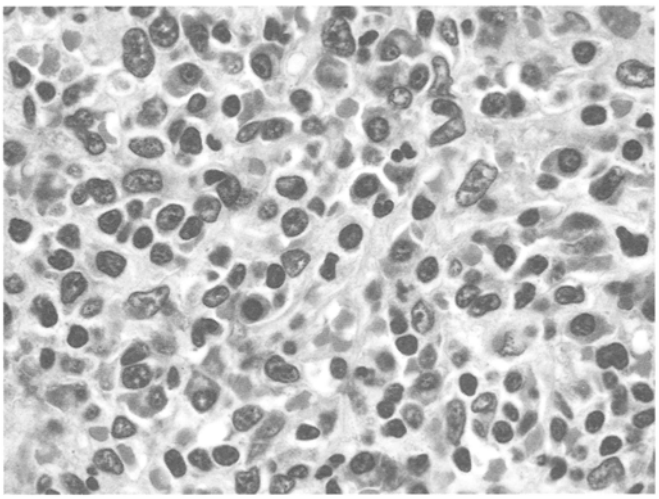


Fig. 8. Lymphoplasmacytic lymphoma: Red pulp infiltration by a combination of neoplastic lymphocytes, lymphoplasmacytic cells and plasma cells.

Differential Diagnosis

- Differentiation from splenic marginal zone lymphoma can be difficult

Follicular Lymphoma (Figure 9)

Definition

- A lymphoma derived from neoplastic follicle center cells

Clinical

- Low-grade follicular lymphomas (Grade 1 or 2) are typically indolent diseases with relentless growth. Grade 3 follicular lymphoma has a most aggressive clinical course and is more similar in behavior to diffuse large B-cell lymphoma. FL typically presents in Stage IV

Diagnosis

- Macroscopic:
  - Typical white pulp involvement, with a miliary pattern
  - Larger nodules (possibly with necrosis or hemorrhage) may represent sites of higher grade transformation
- Microscopic:
  - Increase in the size and density of white pulp nodules
  - Uniform nodules composed of: predominantly small, cleaved lymphocytes (Grade 1); large numbers of large lymphocytes with centroblasts features (Grade 3); or only occasional large cells combined with small, cleaved cells (Grade 2)

Additional Studies

- FLOW: CD19+, CD20+, CD10+, kappa OR lambda light chain+, CD5–, FMC7+

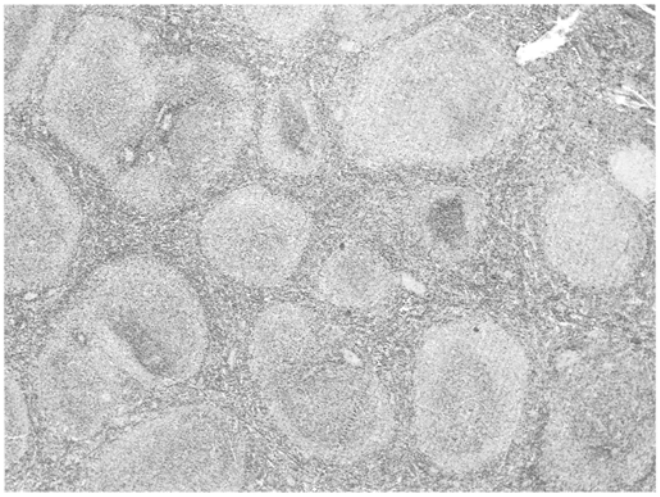


Fig. 9. Follicular lymphoma: Expansion and increase of white pulp/nodules with homogeneous, neoplastic lymphocytes that retain a follicular architecture.

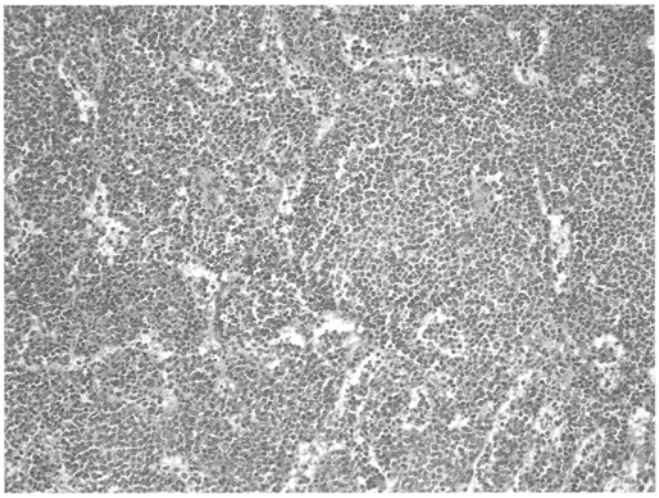


Fig. 10. Mantle cell lymphoma: Expansion of white pulp nodules with spill-over of lymphocytes into red pulp. Cytologically, the neoplastic mantle cells are small, with irregular nuclei and condensed chromatin.

- IHC: CD20+, CD10+, bcl-2+ (75%), bcl-6+, CD5–, CD23–, Cyclin D1–
- Molecular: rearrangement of bcl-2 gene

Differential Diagnosis

- Benign: follicular hyperplasia
- Malignant: other 'small B-cell' lymphomas with splenic involvement including small lymphocytic lymphoma, mantle cell lymphoma and lymphoplasmacytic lymphoma

Mantle Cell Lymphoma (Figure 10)

Definition

- A neoplastic proliferation of typically small lymphocytes which overexpress the Cyclin D1 gene product
- Splenic involvement is common

Clinical

- Often presents at high stage

Laboratory

- Peripheral blood involvement is not uncommon

Diagnosis

- Macroscopic:
  - Miliary pattern is most common, with expansion of the white pulp
- Microscopic:
  - Expansion of the splenic white pulp by small lymphocytes with irregular nuclear borders
  - Rarely, these may be confined to an expanded mantle zone
  - More often, they replace the normal germinal centers, making uniform nodules
  - It is not uncommon for there to be 'spill-over' into the red pulp with clusters of neoplastic mantle cells
  - There is a variant termed blastoid mantle cell lymphoma which encompasses two subtypes; one with blastic nuclear chromatin, the other, termed 'pleomorphic' which has larger cells size and more nuclear irregularities
  - Blastoid variant is associated with a more aggressive clinical course and similar patterns of involvement or may occasional have more diffuse involvement of the spleen

Additional Studies

- FLOW: B-cells coexpressing CD19 and CD5, negative for CD23, light chain restricted (more often lambda), bright CD20 and sIg (compared to CLL/SLL with dim CD20 and sIg), FMC7+
- IHC: CD5+, CD20+, bcl-2+, CD43+, Cyclin D1+ (p53 often positive and Ki67 often increased in blastoid variant), CD10–, CD23–, bcl-6–
- Karyotype: t(11;14)
- Molecular: translocation of the bcl-1 gene and the Ig heavy chain gene. This leads to overexpression of Cyclin D1, a cell cycle regulator

Differential Diagnosis

- Benign: mantle cell hyperplasia
- Malignant: other 'small B-cell' lymphomas with splenic involvement including follicular lymphoma, small lymphocytic lymphoma, marginal zone lymphoma and lymphoplasmacytic lymphoma

Nodal Marginal Zone Lymphoma

Definition

- A B-cell lymphoma arising from cells with characteristics of marginal zone cells, but not those primary to the spleen

Diagnosis

- Splenic involvement by nodal or extranodal marginal zone lymphomas is quite rare compared to 'primary' splenic marginal zone lymphoma
- Although there are some subtle immunophenotypic differences, most cases with splenic involvement are of the splenic-type

Burkitt Leukemia/Lymphoma

Definition

- An aggressive, high-grade malignancy of B-cells

Clinical

- There are three clinical settings; 1) endemic type, 2) sporadic type, 3) immunodeficiency-related
- Typically occurs in young patients (<20 years) except in immunodeficiency related group
- Splenic involvement is not common and is typically part of high-stage disease

Diagnosis

- Macroscopic:
  - Miliary pattern; may have larger expansive nodules or diffuse disease, due to rapidity of cell growth
- Microscopic:
  - Intermediated sized lymphocytes expanding and replacing white pulp structures
  - Nuclei are generally round with small amounts of deeply staining cytoplasm
  - Mitotic/apoptotic bodies common
  - Tingible body macrophages may be present, imparting classic 'starry sky' appearance
  - Subtle cytoplasmic vacuoles may be seen in cytologic preparations

Additional Studies

- FLOW: CD19+, CD10+, CD20+, light chain restricted, TdT–, CD5–
- IHC: CD20+, CD10+, light chain restricted, TdT–, Ki67 near 100%, CD5–, Cyclin D1–, bcl-2–
- Karyotype: t(8;14) most common, t(2;8) or t(8;22) less common
- Molecular: translocation of c-myc gene at 8q24

Differential Diagnosis

- Blastic or blastoid appearing neoplasms including ALL, blastoid mantle cell, blastoid NK leukemia/lymphoma, hepatosplenic T-cell lymphoma

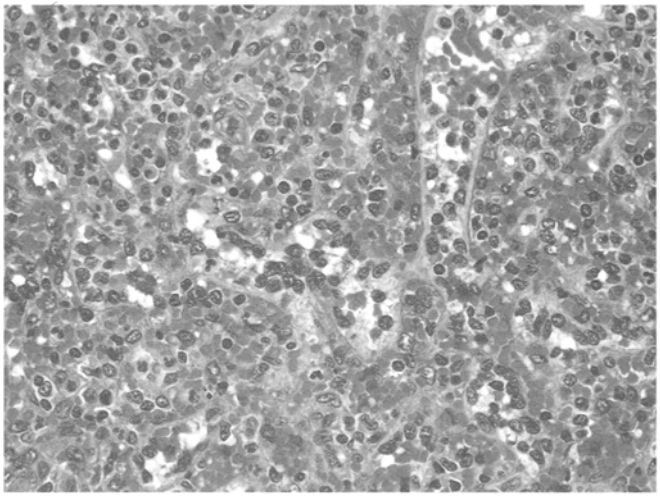


Fig. 11. Hairy cell leukemia: Red pulp infiltration by lymphocytes with moderate amounts of cytoplasm and relatively open chromatin.

Lymphoid Neoplasms Presenting Predominantly in Red Pulp

Hairy Cell Leukemia (Figure 11)

Definition

- An uncommon B-cell neoplasm that prominently involves spleen, bone marrow and peripheral blood

Clinical

- Usually indolent clinical behavior
- Present with symptoms related to marrow replacement (anemia) or symptoms associated with splenomegaly

Laboratory

- Increased circulating lymphocytes with characteristic 'hairy' cytoplasmic projections
- These cells are positive for tartrate-resistant acid phosphatase (TRAP), which is not seen in normal lymphocytes
- Monocytopenia is common

Diagnosis

- Macroscopic:
  - Massive splenomegaly is common and may be presenting sign
  - The spleen typically has a beefy appearance from expansion of the red pulp
- Microscopic:
  - The red pulp is expanded by a population of abnormal cells
  - These cells have round, centrally-placed nuclei, with moderate amounts of clear-to-pale cytoplasm
  - Blood lakes (small pockets of blood in spaces surrounded by elongated hairy cells) are seen in red pulp in most cases

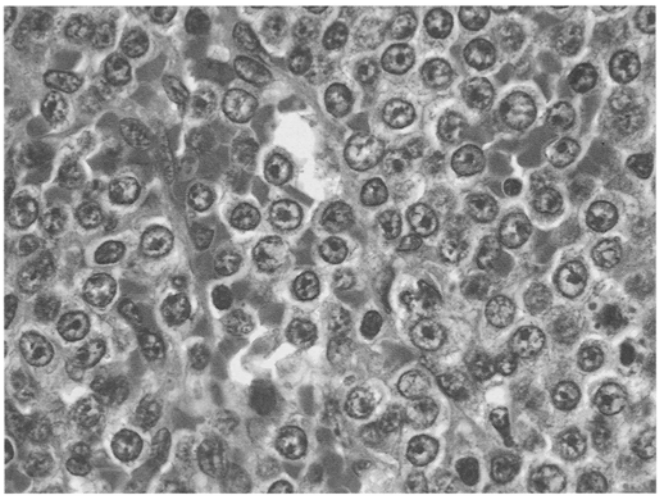


Fig. 12. Prolymphocytic leukemia: In this case there is extensive red pulp infiltration by intermediate-sized lymphocytes with prominent central nucleoli.

Additional Studies

- FLOW: B-cells positive for CD11c, CD22, CD25 and CD103
- IHC: CD20+, DBA.44+, TRAP+
- Molecular: IgH rearrangements present

Prolymphocytic Leukemia (PLL) (Figure 12)

Definition

- Most cases are T-cell derived leukemias; less commonly B-cell derived malignancies, some of which are a more aggressive variant of CLL

Clinical

- Patients present with high WBC, often over 100,000

Diagnosis

- Macroscopic:
  - Often both white and red pulp involvement
- Microscopic:
  - Involvement is in the red pulp with a uniform population of intermediate to large lymphocytes
  - They have round nuclei with prominent central nucleoli

Additional Studies

- FLOW: T-cell: CD3+, CD4+/–, CD8–/+, CD2+, CD7+, TdT–
- B-cell: CD5–/+, CD20+, sIg + (bright), FMC-7–/+, CD23+/–
- IHC: T-cell: CD3+, CD4+/–, CD8–/+, CD2+, CD7+, TdT–
- B-cell: CD5–/+, CD20+, sIg + (bright), FMC-7–/+, CD23+/–, CyclinD1–
- Karyotype: T-cell: abnormalities of 14q11 common

Differential Diagnosis

- Need to consider variants of mantle cell lymphoma with leukemic/splenic presentation; Cyclin D1 stain is necessary to evaluate the possibility of mantle cell lymphoma

Acute Lymphoblastic Leukemia

Definition

- A neoplasm of lymphoid precursor cells (lymphoblasts), of either B-cell origin (~90%) or T cell origin (10%)

Clinical

- Most often occur in pediatric patients. B-cell type has prominent bone marrow involvement, +/– blood involvement
- T-cell type often is associated with a mediastinal mass, +/– blood /bone marrow involvement
- Splenic involvement is common, but significant splenomegaly is rare

Laboratory

- Elevated WBC with blasts

Diagnosis

- Macroscopic:
  - Expansion of red pulp by neoplastic lymphoblasts in sinuses; rarely, white pulp involvement
- Microscopic:
  - Intermediate sized lymphocytes with blastic chromatin and little cytoplasm

Additional Studies

- FLOW: B-cell type—CD19+, CD10+, CD34+/–, TdT+, sIg–*
- T-cell type—CD3+, CD2/5/7+, CD4/8 often–, TdT+, CD10–/+*
- IHC: B-cell type—CD20–, CD10+, CD34+/–, TdT+, CD79a+
- T-cell type—CD3+, CD2/5/7+, CD4/8 often–, TdT+, CD10–/+

*Aberrant expression of myeloid markers may be observed

- Karyotype: T-cell type -variable cytogenetic abnormalities present
  - B-cell type— t(9;22)(q34;q11.2); BCR/ABL
    (v;11q23); MLL rearranged
    t(12;21)(p13;q22); TEL/AML1
    t(1;19)(q23;p13.3); PBX/E2A
    hypodiploid
    hyperdiploid >50

Differential Diagnosis

- Other blastic and blastoid neoplasms in splenic red pulp

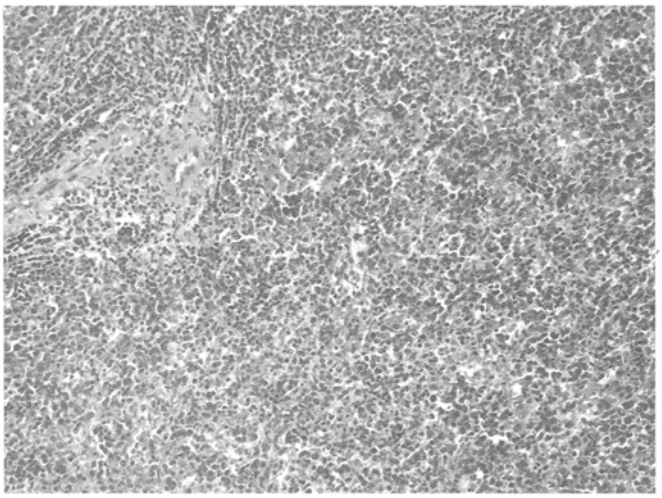


Fig. 13. Hepatosplenic T-cell lymphoma: This lymphoma shows extensive infiltration of the red pulp, predominately in sinuses. The malignant lymphocytes can range from small cells with condensed chromatin to intermediate or large cells with more blastic chromatin.

Hepatosplenic T-cell lymphoma (Figure 13)

Definition

- Neoplasm of T-cells that characteristically affects spleen, liver and bone marrow
- Often have surface expression of gamma/delta T-cell receptor, which normally accounts for only a very small percentage of T-cells

Clinical

- Most commonly in young males
- Also increased in incidence in post-transplant setting
- Bone marrow involvement is generally present and will most often show characteristic intrasinusoidal pattern of involvement

Laboratory

- Often thrombocytopenia and anemia

Diagnosis

- Macroscopic:
  - Spleen is usually markedly enlarged, with typical expanded red pulp appearance
  - Liver is also diffusely enlarged
- Microscopic:
  - Marked increase in lymphocytes in the red pulp. Infiltration is most prominent in the sinusoids
  - Cytology can vary from small, mature appearing lymphocytes, to larger more blastic appearance

Additional Studies

- FLOW: CD3+, CD56+/–, typically CD4–/CD8–. Most cases express surface gamma/delta T-cell receptor, rare cases are alpha/beta

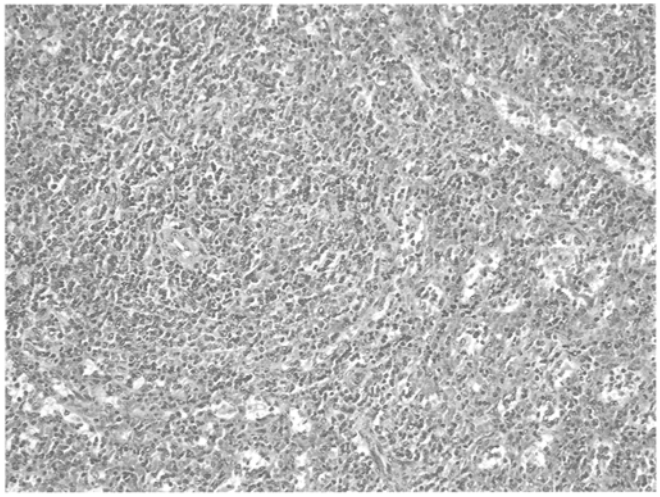


Fig. 14. Large granular lymphocytosis: These small, irregular T cells infiltrate the red pulp and expand the PALS in the white pulp.

- IHC: CD3+, CD56+/–, CD4–, CD8–, CD5–, TIA-1+
- Karyotype: Isochromosome 7q is found in almost all cases
- Molecular: Clonal rearrangement of T-cell receptor

Differential Diagnosis

- Histologic evaluation includes several disorders including splenic involvement by leukemias, B-cell lymphomas involving the red pulp and other T-cell lymphomas

Large Granular Lymphocytic Leukemias (Figure 14)

Definition

- A proliferation of cytotoxic T lymphocytes (85% of cases), or more rarely NK cells
- In many cases, these proliferations are non-neoplastic and associated with autoimmune diseases such as rheumatoid arthritis
- Occasionally, these proliferations are neoplastic

Clinical

- There is a strong association with autoimmune disease. Among the more common associations are: Felty Syndrome, rheumatoid arthritis, Sjogren Syndrome, SLE

Laboratory

- Review of the peripheral blood often reveals neutropenia.
- There is an increase in large granular lymphocytes
- If less than 2.0×10^9/L, the diagnosis requires confirmation of clonality by molecular techniques

Diagnosis

- Macroscopic: Enlarged spleen. Red pulp expansion
- Microscopic: Increased lymphocytes and expansion of the red pulp, typically with relative sparing of the white pulp

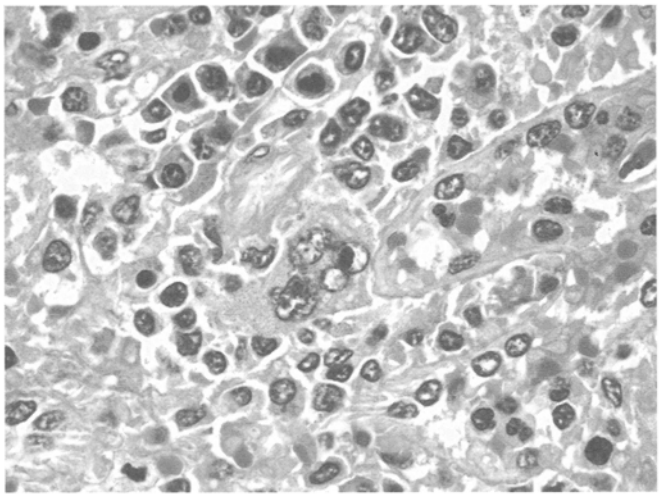


Fig. 15. Hodgkin lymphoma: A diagnostic Reed-Sternberg cell is seen in the splenic red pulp.

Additional Studies

- LGL disease of cytotoxic lymphocytes (T-LGL) most often positive for: pan-T-cell markers (CD2, CD3, CD5, CD7), CD8, cytotoxic markers (e.g. TIA-1), CD57; CD56 usually negative
- LGL disease of NK cells are positive for CD56; CD57 usually negative
- Molecular:
  - Increases in CD8-positive LGL disease is associated with clonal T-cell receptor gene rearrangements
  - NK-types do not have clonal rearrangements of the T-cell receptor; clonality can be assessed by X-linked gene analysis or cytogenetics

Differential Diagnosis

- It is possible to confuse LGL of the spleen with other T-cell disorders involving the splenic red pulp
- Among these would be involvement by mycosis fungoides, hepatosplenic T-cell lymphoma and other T-cell lymphomas

Other Patterns of Splenic Involvement

Classical Hodgkin Lymphoma (Figure 15)

Definition

- A malignancy of 'crippled' B-cells which produce large characteristic malignant cells, Reed-Sternberg and Hodgkin cells
- The malignant cells are typically rare, but produce a characteristic background

Clinical

- Patients may have "B" symptoms; fever, night sweats, weight loss
- Prognosis depends on stage, but is generally excellent
- Splenic involvement usually implies at least Stage II disease

Diagnosis

- Macroscopic:
  - These most often present as focal, fibrotic nodules of varying sizes
  - Rarely, they can be massive or very small-sized
- Microscopic:
  - Neoplastic cells are large, often binucleate (Reed-Sternberg cells), with large nucleoli
  - The background cells may consist of a mixture of small lymphocytes, eosinophils (often prominent), plasma cells, macrophages and neutrophils
  - Fibrosis may also be a prominent microscopic feature

Additional Studies

- FLOW: typically non-contributory in the diagnosis of Hodgkin lymphoma
- IHC: Hodgkin and R-S cells: CD15+, CD30+, CD45–, PAX-5+, CD20–/+, CD3–

Differential Diagnosis

- Macroscopic differential diagnosis includes other focal processes in the spleen both benign and malignant
- Microscopic differential includes other neoplasms with rare, large malignant cells with a polymorphous background including considerations include T-cell/histiocyte-rich B cell lymphoma, anaplastic large cell lymphoma and others

Nodular Lymphocyte-Predominant Hodgkin Lymphoma (NLPHL)

Definition

- A neoplasm of B-cells, with a characteristic background, composed of small lymphocytes
- The neoplastic cells are large and share some features with Hodgkin and R-S cells, but NLPHL is distinct disease for 'classical' Hodgkin lymphoma
- Spleen involvement is very rare

Diagnosis

- Macroscopic:
  - Most often focal disease with variable sized nodules
- Microscopic:
  - Malignant cells are large, pale lymphocytes, usually in the center or periphery of nodules of reactive, small, round, dark blue lymphocytes
  - The neoplastic cells have delicate nuclear chromatin and sometimes lobated nuclei, which can be called 'popcorn' cells

Additional Studies

- FLOW: non-contributory in the diagnosis of Hodgkin lymphoma
- IHC: Neoplastic cells are strongly positive for CD20, CD45 (LCA), often surrounded by collar of T-cells which often are CD57+

Differential Diagnosis

- Differential includes classical Hodgkin lymphoma and other B-cell lymphomas such as T-cell rich DLBCL

Diffuse Large B-cell Lymphoma (DLBCL) (Figure 16)

Definition

- A heterogeneous category inclusive of several malignancies of large B cells
- There are a variety of methods for subtyping such as cell derivation, immunophenotype, and distinctive clinical features
- DLBCL may be de novo or arise as a transformation of a low-grade B-cell lymphoma

Clinical

- Primary diagnosis rarely made in spleen
- Prognosis is dependent on stage
- Of lymphomas seen in spleen, DLBCL is relatively common

Diagnosis

- Macroscopic:
  - Most often presents as focal disease (nodules or mass). Rarely may have diffuse involvement
- Microscopic:
  - Usually diffuse sheets of large lymphoid cells
  - There may be considerable variation in specific cytologic detail, some may appear centroblastic (more irregular nuclear contours, coarse chromatin, inconspicuous nucleoli, scant pale cytoplasm) or immunoblastic (round nuclei, more open chromatin, prominent nucleoli, variable deeply staining cytoplasm)

Additional Studies

- FLOW: CD19/20+, often light chain restricted, CD10+(40%), CD5+(10%)
- IHC: CD20+
- Karyotype: abnormalities of 3q27; t(14;18), others
- Molecular: IgH gene rearrangements often present; BCL-2 rearrangement

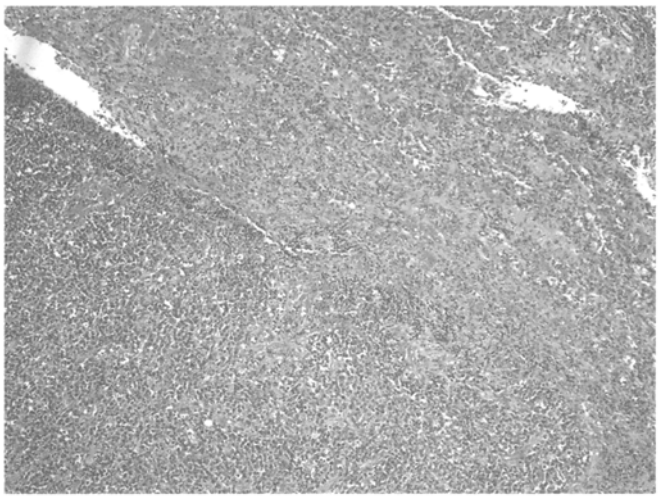


Fig. 16. Diffuse large B-cell lymphoma: Lymphoma (lower left) is composed of large lymphocytes. This mass is compressing the normal splenic structures.

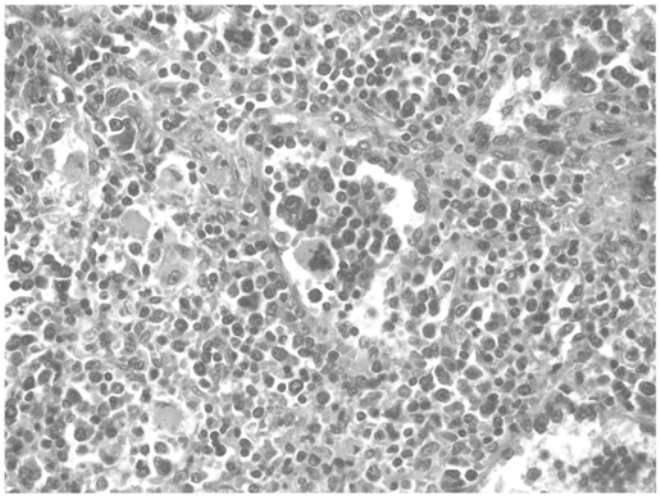


Fig. 17. Extramedullary hematopoiesis - benign: This spleen shows a cluster of hematopoietic elements (erythroid and megakaryocyte) in a sinus. There is no cytologic atypia seen, in contrast to MPD or MDS.

MYELOID AND RELATED DISORDERS

Extramedullary Hematopoiesis (EMH) (Figure 17)

Definition

- Proliferation of neoplastic or non-neoplastic bone marrow elements in the spleen

Clinical

- Can occur in a variety of clinical settings but most often seen in myeloproliferative disorders or severe anemias (e.g., hemoglobinopathies)
- May also be seen as a consequence of treatment with marrow stimulating cytokines such as G-CSF or GM-CSF **(Figure 18)**

Diagnosis

- Microscopic:
  - Trilineage EMH: Clusters of maturing erythroid, granulocytic precursors and megakaryocytes in red pulp

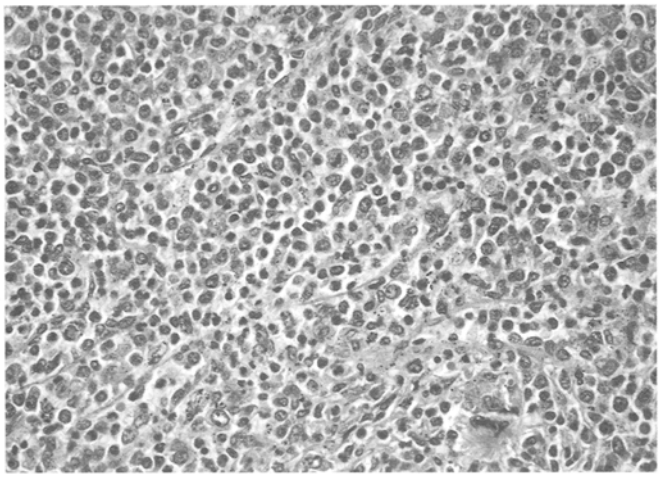


Fig. 18. G-CSF effect: The splenic red pulp is expanded by massive increase in maturing granulocytic elements.

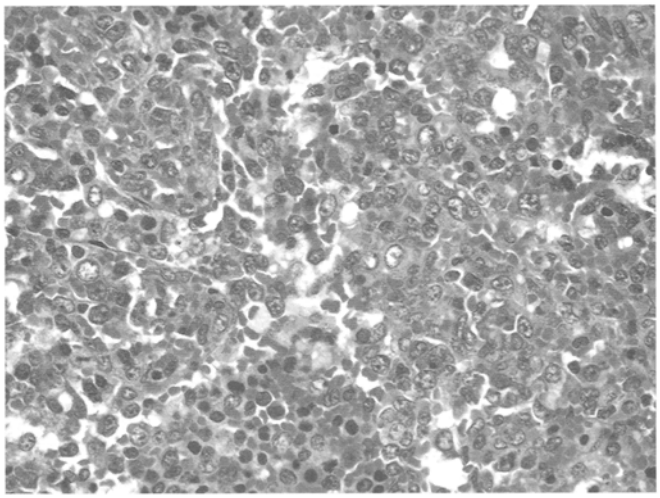


Fig. 19. Acute myeloid leukemia: Intermediate-sized blastic cells characterize AML which preferentially infiltrates the red pulp.

- Unilineage EMH: Most often a single lineage in reactive cases (e.g., erythroid in thalassemia). No excess of immature elements (e.g. blasts) or dysplastic forms is seen

Additional Studies

- IHC: No increase in CD34 or CD117 positive cells seen

Differential Diagnosis

- If marrow elements are markedly increased or dysplastic, myeloproliferative disorders, myelodysplastic disorders or acute leukemias should be considered

Acute Myeloid Leukemia (AML) (Figure 19)

Definition

- Malignancy of myeloid progenitor/early precursor cells
- Most often blasts of granulocytic or monocytic lineage
- Several subtypes based on cytogenetic findings, lineage and phenotypic variation

Clinical

- Variable
- WBC usually elevated (blasts)
- Splenic involvement is not unusual; massive splenomegaly is quite rare

Diagnosis

- Macroscopic:
  - Red pulp involvement imparting "beefy" appearance
- Microscopic:
  - Red pulp sinuses expanded by blastic-appearing intermediate sized cells
  - Occasionally more mature forms, with cytoplasmic granules (promyelocytes) or eosinophils and eosinophilic precursors may be seen

Additional Studies

- FLOW: Positive for a variety of myeloid antigens, depending on subtype including: CD117, CD13, CD33, cytoplasmic myeloperoxidase, CD34+/–
- IHC: variably positive for CD34, CD117, myeloperoxidase, lysozyme
- Karyotype: Characteristic abnormalities may be seen in several subtypes of AML. Cytogenetic subtypes include cases with t(8;21), inv(16), t(15;17) and 11q23 abnormalities

Myeloproliferative Disorders (MPD) (Figure 20)

Definition

- Neoplastic proliferations of hematopoietic stem cells, typically producing increased numbers of one or more of the myeloid lineages in the blood and bone marrow
- Subtypes include chronic myelogenous leukemia (CML), chronic idiopathic myelofibrosis (CIMF), polycythemia vera (PV) and essential thrombocythemia (ET)

Clinical

- Splenic enlargement is common all MPDs except ET. Splenomegaly is typically massive in CIMF
- Sudden increase in spleen size in any MPD may herald an accelerated phase/blast transformation

Diagnosis

- Macroscopic:
  - CML/PV: Enlargement with expansion of the red pulp, with typical 'beefy' appearance
  - CIMF: As above but may have distinct, purple nodules (so-called 'plums') in addition
- Microscopic:
  - CML: Typically massive expansion of red pulp cords and sinuses by maturing granulocytes. Eosinophils may be prominent. In chronic phase CML, blasts are

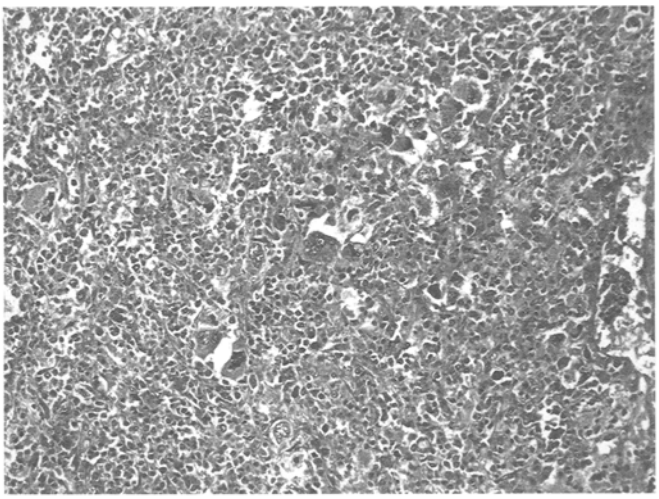


Fig. 20. Extramedullary hematopoiesis neoplastic: In this case of chronic idiopathic myelofibrosis, these are numerous hematopoietic elements, predominantly megakaryocytic and granulocytic. The megakaryocytes showed marked cytologic atypia.

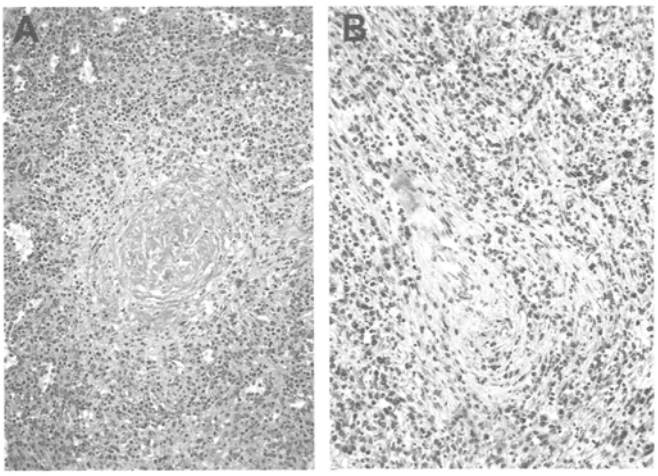


Fig. 21. Mastocytosis: A fibrous lesion composed of spindled mast cells with other inflammatory elements including eosinophils and plasma cells. These lesions are common in spleen trabecular, perivascular and perifollicular areas. An immunohistochemical stain for tryptase highlights the mast cells.

not numerous. Erythroid and megakaryocytic elements may be seen, but are not usually prominent

- CIMF: Massive expansion of red pulp by a variety of trilineage marrow elements. Megakaryocytes, in particular, may be increased and present in clusters or large nodules. The megakaryocytes are cytologically atypical with large, bizarre nuclei

Additional Studies

- IHC: increased blasts may be highlighted in cases of accelerated phase/blast transformation by myeloperoxidase, CD117 or rarely CD34
- Cytogenetics: Cytogenetic progression in spleen may herald disease progression in the bone marrow

Myelodysplastic Syndromes (MDS)

Definition

- A group of clonal disorders of hematopoietic stem cell, associated with ineffective hematopoiesis, peripheral cytopenias and increased risk of progression to AML

Clinical

- Cytopenias common

Diagnosis

- Splenic enlargement rare
- Expansion of red pulp by immature, dysplastic marrow elements
- Transformation to acute leukemia may occur

Systemic Mastocytosis (Figure 21)

Definition

- Abnormal proliferation and accumulation of mast cells in multiple sites
- Systemic types are clonal disorders

Clinical

- Constitutional symptoms may be prominent as well as mast cell cytokine mediated symptomatology
- Mastocytosis can also be seen in association with other hematopoietic malignancies including myeloproliferative disorders, myelodysplastic syndromes, acute myeloid leukemias

Laboratory

- Elevated serum tryptase levels are almost always seen, but are not entirely specific for mastocytosis
- Splenomegaly is common in systemic mastocytosis (~70%)

Diagnosis

- Macroscopic:
  - Variable
- Microscopic:
  - Mastocytosis may involve any compartment in the spleen and present as diffuse or focal disease
  - Trabecular involvement is common. On routine H&E stains, mast cells are inconspicuous
  - Mast cells are round with moderate amounts of cytoplasm or occasionally unremarkable spindle cells
  - Cytoplasmic granules may be inapparent
  - Mast cell infiltrates are associated with polymorphous infiltrates of inflammatory cells including lymphocytes, plasma cells and often prominent eosinophils
  - Fibrosis is common
  - Polychromatic stains (Giemsa, toluidine blue) will highlight mast cells and their granules

Additional Studies

- FLOW: typically non-contributory due to associated fibrosis
- IHC: positive for tryptase, CD117, CD43, CD2, CD25

Hemophagocytic Syndrome (HPS)

Definition

- Consumption of hematopoietic elements by macrophages, secondary to a variety of causes
- Etiologies including congenital disorders, infection-associated and those associated with other malignancies, especially T-cell lymphomas

Clinical

- Often patients are very ill due to profound cytopenias
- Bone marrow is also a prominent site of involvement of these disorders
- Splenic involvement and enlargement is common

Diagnosis

- Macroscopic:
  - Congestion of the red pulp
- Microscopic:
  - Expanded red pulp cord and sinuses
  - Macrophages with ingest blood elements numerous
  - Erythrophagocytosis most common, but all circulating blood elements can be seen in macrophages
  - Clusters of histiocytes may be seen
  - In cases of T-cell lymphoma-associated HPS, infiltrate of cytologically abnormal T-cells may be appreciated

Differential Diagnosis

- HPS needs to be distinguished from the exceptionally rare true histiocytic sarcoma (malignant histiocytosis)

NON-HEMATOPOIETIC LESIONS

Cysts

Definition

- Space occupying lesions of spleen, typically fluid filled
- Some may be caused by infectious etiologies
- True cysts have an epithelial lining, usually of flattened, bland epithelium. This lining is keratin positive
- Others that lack epithelial linings are termed 'false cysts' and often represent resolution of splenic hematomas

Differential Diagnosis

- Lymphangioma

Hamartoma (Figure 22)

Definition

- Non-neoplastic mass lesion composed of normal red pulp components

Clinical

- Often incidental findings by imaging or at splenectomy for other causes

Diagnosis

- Macroscopic:
  - Usually well-circumscribed nodule which resemble red pulp
- Microscopic:
  - Histologic appearance resembles red pulp, and typically lacks white pulp or trabecular components
  - Narrow vascular spaces are lined by typical, plump littoral type endothelial cells
  - Occasionally macrophages or fibrosis may be prominent

Additional Studies

IHC: Vascular spaces lined by CD8+/CD68+/CD34– endothelial cells

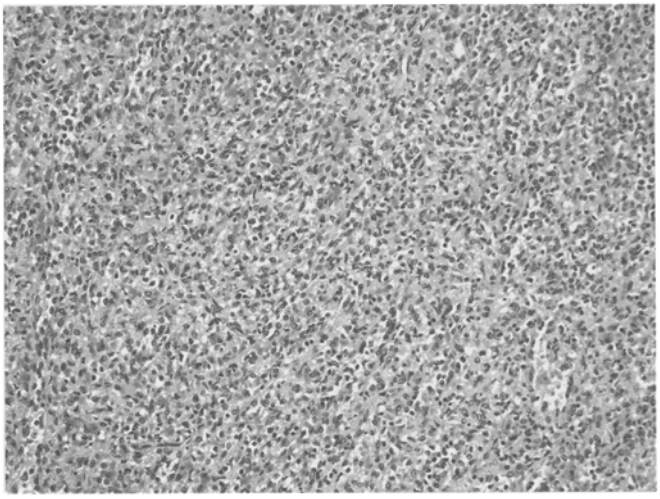


Fig. 22. Splenic hamartoma: The lesions are usually well-circumscribed, but not encapsulated. They are composed predominately of benign red pulp elements.

Differential Diagnosis

- Inflammatory pseudotumor, vascular lesions, capillary hemangioma with prominent sclerosis, in particular

Inflammatory Pseudotumor (IPT) (See Table 2)

Definition

- Nodular proliferation of benign-appearing spindle cells with a mixture of inflammatory components including lymphocytes, macrophages, neutrophils and plasma cells

Clinical

- Typically present as mass lesion
- Often an incidental finding

Table 2. Differential Diagnosis of Splenic Inflammatory Pseudotumor

	Etiology	*Distinguishing Features*
Inflammatory pseudotumor	Reactive, most probably secondary to infectious causes.	Prominence of inflammatory and/or sclerotic changes. Clinical history.
Inflammatory pseudotumor-like follicular dendritic cell tumor	Neoplasm of follicular dendritic cells; EBV-associated.	Spindle cells are CD21/CD35 positive. EBV positive.
Inflammatory myofibroblastic tumor	Neoplasm of myofibroblastic cells.	Increased smooth muscle actin/HHF-35 positive spindle cells. Occasionally ALK positive. Cytogenetic abnormalities mat be present.
Capillary hemangioma with prominent sclerosis	Benign neoplasm of vascular components.	Simulates IPT but with prominent vasculature. Lobular nature of involvement is a diagnostic clue. Vascular markers highlight prominent capillaries (CD34+).

- Rarely able to elicit a specific history of previous infection (bacterial, fungal, etc.)

Diagnosis

- Macroscopic:
  - Focal lesions that are firm and fibrotic
  - Borders may be well- or ill-defined
- Microscopic:
  - These masses are a combination of fibrotic stromal elements (spindle cells), acellular sclerosis, and varying degrees of mixed inflammatory elements including lymphocytes, granulocytes and polyclonal plasma cells
- Differential diagnosis:
  - Lesions that closely mimic IPT include: inflammatory pseudotumor-like follicular dendritic cell tumor, inflammatory myofibroblastic tumor, and occasional vascular lesions including hamartoma and capillary hemangioma with prominent sclerosis

Dendritic Cell Tumors

- Including follicular dendritic cell tumor, interdigitating dendritic cell tumor, inflammatory pseudotumor-like follicular dendritic cell tumor

Definition

- Neoplasms of immune accessory cells, follicular dendritic cells or interdigitating dendritic cells

Clinical

- Very rare
- The inflammatory pseudotumor-like follicular dendritic cell tumor (IPTLFDCT) has only been described in the spleen
- Variable prognosis
- Locally aggressive behavior has been reported in a significant percentage of cases; metastases are rare

Diagnosis

- Macroscopic:
  - Typically present as focal mass lesions that are firm, tan and usually have well-defined borders
- Microscopic:
  - Follicular dendritic cell tumor (FDCT) and interdigitating dendritic cell tumor (IDCT) are composed of masses of blunt-ended spindle cells
  - Spindle cells form whorls and fascicles
  - FDCT may often mimic a nodular/follicular growth pattern, including infiltrating lymphocytes
  - IPTLFDCT has spindle cells with large numbers of infiltrating inflammatory elements including lymphocytes, granulocytes and polyclonal plasma cells

Additional Studies

- IHC: FDCT: CD21+, CD35+, CD23+/–
- IDCT: S100+, CD68+/–
- IPTLFDCT: CD21+, EBV+

Differential Diagnosis

- Other spindle cell lesions including infectious etiologies, true inflammatory pseudotumor, inflammatory myofibroblastic tumor

Inflammatory Myofibroblastic Tumor (IMT) (See Table 2)

Definition

- Neoplastic proliferation of bland-appearing spindle cells of myofibroblastic derivation, often with associated inflammatory elements

Table 3. Vascular Disorders of the Spleen

	Diagnosis	*Features*	*Immunos*
Non-neoplastic	Peliosis	Rare. Unknown etiology. Ectatic sinusoids and blood-filled spaces.	Endothelial lining positive for CD31/FVIII/Ulex
	Hamartoma	Red pulp, very little or no white pulp seen.	CD31+, FVIII+, CD8+
Benign neoplasms	Hemangioma	Most common vascular neoplasm of spleen. Cavernous or capillary. Single or multiple. Similar features to other body sites.	CD31+, FVIII+, CD34+
	Lymphangioma	Thin lining, not keratin positive. Filled with proteinaceous fluid. Rarely single, more often part of multisystem lymphangiomatosis	Must rule out mesothelial cyst which are keratin+. Lined by CD31+ FVIII+ cells.
	Littoral cell angioma	Neoplasm of sinus lining cells. Larger, plump cells. May have papillary features and form cystic spaces. Focal hemophagocytosis	CD31+, FVIII+, CD34–, CD68+, often CD21+
Malignant neoplasms	Angiosarcoma	Vascular malignancy. May have solid areas. Anaplasia, mitoses, necrosis not uncommon.	CD31/FVIII/Ulex variably positive. CD34+ in 50%. CD8 variable.

Clinical

- Often incidental findings by imaging or at splenectomy for other causes

Diagnosis

- Macroscopic:
  - Usually well-circumscribed nodule tan nodule
- Microscopic:
  - Bland spindle cells, often in sheets or fascicles
  - Varying degrees of mixed inflammatory elements including histiocytes, lymphocytes, neutrophils and plasma cells

Additional Studies

- IHC: Spindle cells are strongly positive for actin, may be ALK positive

Vascular Lesions (*See* Table 3)

Peliosis

Definition

- Vascular lesion composed of ectatic sinusoids and blood-filled cysts
- Cysts are lined by sinusoidal endothelium (CD8+)

Hemangioma—Cavernous, Capillary (Figures 23,24)

Definition

- Vascular neoplasms which occur in diverse sites throughout the body
- Cavernous hemgiomas are composed of large, thick-walled vascular spaces
- Capillary hemangiomas are composed of proliferation of small caliber, thin walled elements

Clinical

- Cavernous type may be associated with cytopenias, especially thrombocytopenia, due to trapping of blood elements in the distended vascular spaces

Diagnosis

- Macroscopic:
  - Focal of diffuse lesions; red pulp based
  - Cavernous types are composed of larger blood filled spaces
  - Capillary types may appear more fibrotic
- Microscopic:
  - Spaces are lined by unremarkable endothelial cells
  - Rarely, capillary hemangiomas may have extensive sclerotic changes, histiocytic infiltrates and mimic IPT

Additional Studies

- IHC: positive for CD31/CD34/Ulex/vWF. Negative for CD8

Differential Diagnosis

- Other benign and malignant vascular proliferations are the most common considerations (Refer to Table 3)

Lymphangioma

Definition

- Rare, benign proliferation of lymphatic-lined spaces
- Most often as part of systemic disorder of diffuse lymphangiomatosis

Diagnosis

- Macroscopic:
  - Cysts containing clear, watery fluid
  - May be smooth or have papillary projections

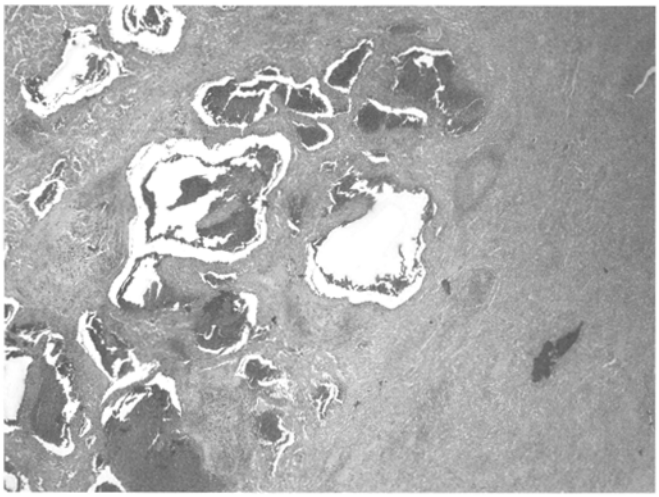


Fig. 23. Cavernous hemangioma: Large blood-filled spaces. Examination at higher magnification reveals these spaces to be lined with flattened, bland endothelial cells.

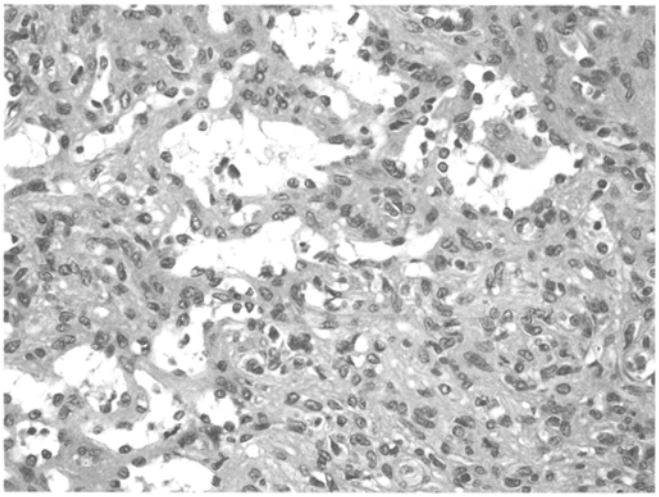


Fig. 24. Capillary hemangioma: Note the bland cytology of the endothelial cells and narrow vascular spaces.

- Microscopic:
  - Lining cells are flattened and cytologically bland
  - Occasionally papillary projections of lining cells into lumen
  - Foamy macrophages and cholesterol clefts are not uncommon

Additional Studies

- IHC: positive for vascular markers and negative for keratin

Differential Diagnosis

- Often confused with mesothelial-derived cysts, which are lined by keratin positive cells

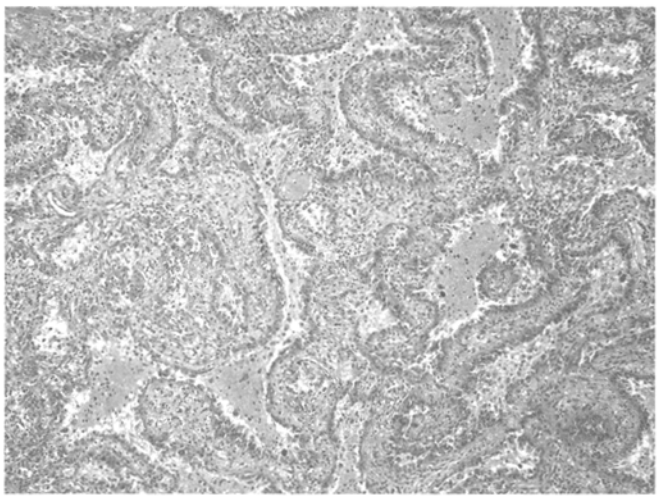


Fig. 25. Littoral cell angioma: This distinctive-appearing vascular neoplasm of spleen has patent, interconnected vascular spaces lined by plump endothelial-derived cells (i.e. littoral cells).

Littoral Cell Angioma (Figure 25)

Definition

- Neoplastic vascular proliferation, unique to the spleen, of specialized cells which line splenic sinuses
- These cells have features of endothelial cells and express some features of the macrophage lineage

Clinical

- Benign, often present as clinically asymptomatic mass or a multinodular lesion found on imaging
- Rarely present with mass symptoms or unusually with rupture
- Benign lesions that are cured by excision
- Malignant versions have been described, see description of angiosarcoma
- Some association with second malignancies (carcinomas, lymphomas)

Diagnosis

- Macroscopic:
  - Most common presentation is multiple, spongy, cystic masses in red pulp
- Microscopic:
  - Endothelial cells lining cysts are plump and cuboidal
  - There may be papillary projections of the sinus lining cells into the lumens of cysts often associated with luminal desquamation. Interstitial spaces contain varying amounts of sclerosis and fibrosis

Additional Studies

- IHC: Stains positive for CD31/vWF/Ulex but negative for CD34, CD8 –/+, CD21+/–

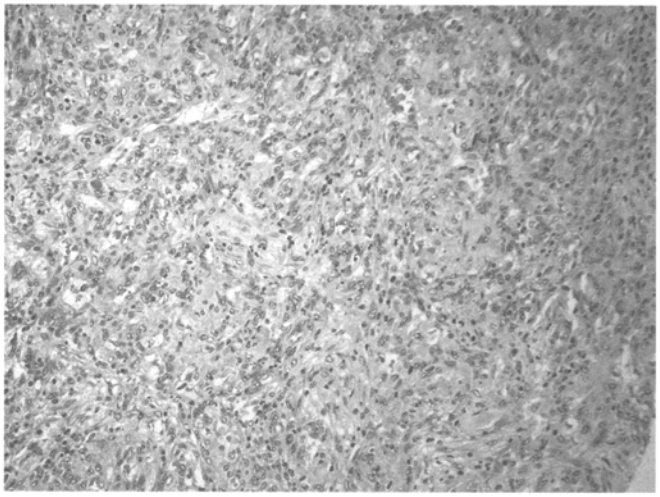


Fig. 26. Hemangioendothelioma: Irregular, interconnected vascular spaces are lined by plump, spindled cells.

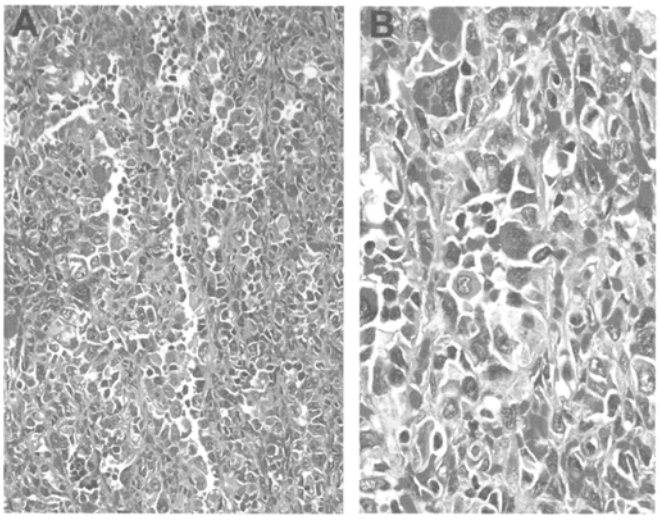


Fig. 27. Splenic angiosarcoma: Malignancy of vasoformative elements. The cells are markedly pleomorphic with irregular, randomly arranged vascular spaces.

Differential Diagnosis

- Other vascular neoplasms

Hemangioendothelioma (Figure 26)
Angiosarcoma (Figure 27)

Definition

- Malignancy of vasoformative elements

Clinical

- Older adults
- Patients are usually symptomatic

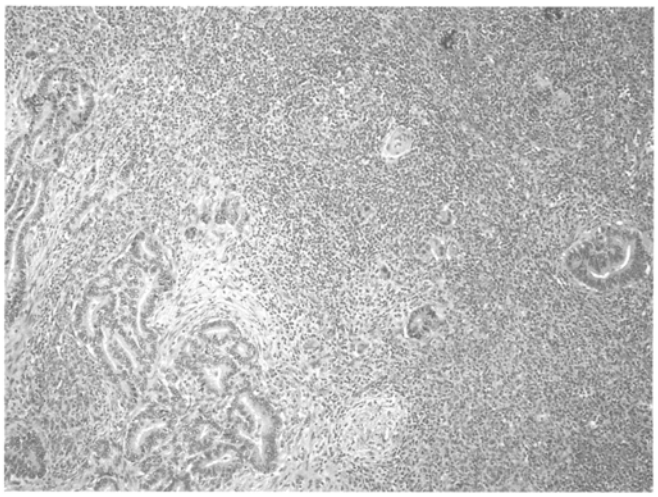


Fig. 28. Metastases: Metastases are rarely identified in the spleen. Metastatic tumors often induce significant stromal fibrosis.

Diagnosis

- Macroscopic:
  - Usually large tumor masses
  - Often with extensive hemorrhage and necrosis
- Microscopic:
  - Anastomosing vascular channels with lined with pleomorphic endothelial cells
  - Solid or spindled areas may be seen
  - Mitoses and pleomorphism variable, but usually present at least focally

Additional Studies

- IHC: Variably positive for vascular markers CD31/CD34/Factor VIII/Ulex; rare cases may be littoral cell derived and be CD8+, CD68+/– and are termed "littoral cell angiosarcoma"

Metastatic Disease (Figure 28)

Definition

- Metastatic tumors from a variety of sites

Clinical

- Prognosis depends on the type of tumor
- However, metastases to the spleen are uncommon and typically occur late in the course of disease

Diagnosis

- Macroscopic:
  - Usually form grossly visible mass lesions
- Microscopic:
  - These features are dependent on the type of tumor
  - Most often, there is a characteristic fibrotic stromal response to metastatic epithelial malignancy

REACTIVE LESIONS INCLUDING HYPERPLASIAS, INFECTIONS, AUTOIMMUNE AND IMMUNODEFICIENCY

Hyperplasias

- Follicular: Expansion and increase of reactive germinal centers in the spleen due to a variety of immunologic stimuli - as in lymph node, features of benign follicles include: polarization, tingible-body macrophages, variation in size and shape, well-formed mantle zones, etc
- Localized (nodular) hyperplasia (**Figure 29**): focal nodule(s) that grossly mimic lymphoma and composed of benign follicular elements microscopically
- Marginal Zone (**Figure 30**): Expansion of the 'third' layer of the follicle, which surround the mantle zone; cells often have a monocytoid appearance but lacks features of marginal zone lymphoma (*See* **Table 4**)
- Non-follicular/Immunoblastic: Proliferation of large transformed lymphocytes; can be seen in both the white pulp (PALS) and red pulp and may mimic large cell lymphoma (most commonly in association with viral etiologies)
- T-cell: Expansion of the PALS that often includes a mixture of large and small cells, with some intermixture of plasma cells (variety of etiologies including congenital immunodeficiencies, drug reactions [Ex. phenytoin], etc.)

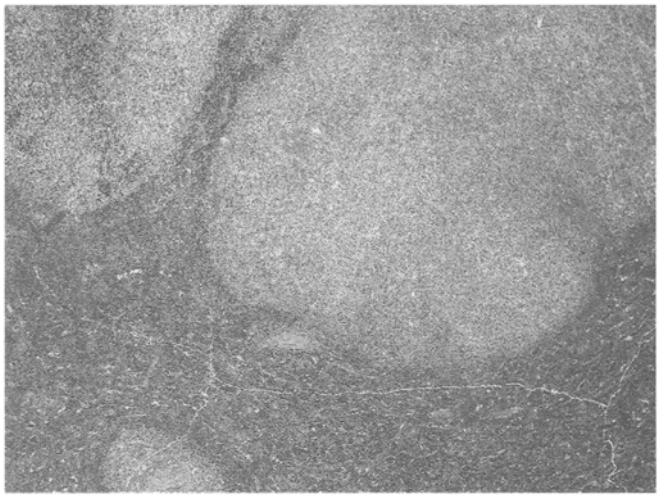


Fig. 29. Localized (nodular) lymphoid hyperplasia: Nodules may grossly mimic lymphoma, but have microscopic features of benign follicles.

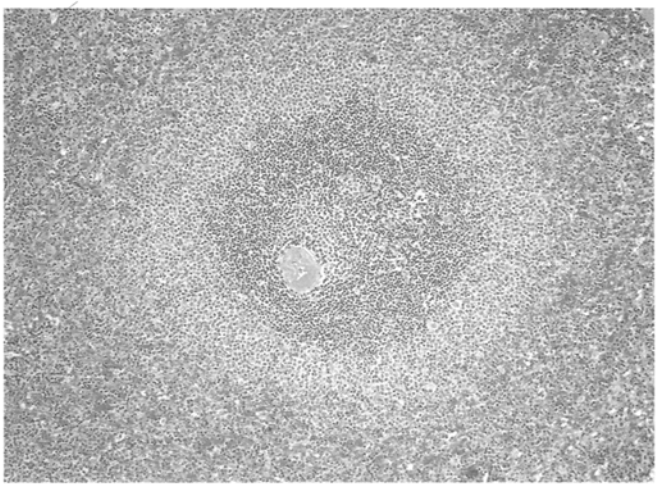


Fig. 30. Marginal zone hyperplasia: Atypical, three-layered follicle of spleen with an expanded marginal zone. Marginal zone hyperplasia can be difficult to distinguish from marginal zone lymphoma.

Vascular/Congestive Disorders

Definition

- Red blood cell congestion of the spleen due to vascular disturbances of various etiologies

Clinical

- May cause moderate splenomegaly depending on duration of vascular disturbance
- Common etiologies include: portal hypertension, splenic vein obstruction, hepatic vein obstruction, congestive heart failure, and liver disease

Diagnosis

- Microscopic:
  - Red pulp shows increase in red blood cells
  - Stromal elements may proliferate as a result of chronic congestion and causes splenic fibrosis
  - Gamna-Gandy bodies (nodules of iron deposition) may be present

Red Blood Cell Disorders (Figure 31)

Definition

- Defects of red blood cells can result in splenic changes due to increase in modification and destruction of red blood cells
- Several types of red blood cell disorders can induce splenomegaly and congestion including: membrane defects (e.g., hereditary elliptocytosis), enzyme defects (e.g., G6PD), as well as qualitative (Hemoglobin SS—sickle cell disease) and quantitative (e.g., thalassemias) hemoglobin abnormalities
- Similar changes can be seen due to excessive destruction of 'normal' red blood cells with antigen-driven destruction such as transfusion and autoantibodies

Clinical

- Symptomatology varies with type of disorder

Table 4. Marginal Zone Hyperplasia Versus Marginal Zone Lymphoma

Features	*MZH*	*MZL*
Expanded MZ (>12 cell layers)	Yes	Yes
Numerous B-cells in PALS	No	Yes
Follicles	3 layers	Loss of layers; often uniform single layer
Red pulp	No increase in red pulp B-cells	Often has clusters of red pulp B-cells
Kappa/lambda	Polyclonal	Monoclonal
Ki67	Normal secondary follicles with high proliferation	Colonized follicles have low proliferation in neoplastic cells
IgH rearrangements	No	Yes

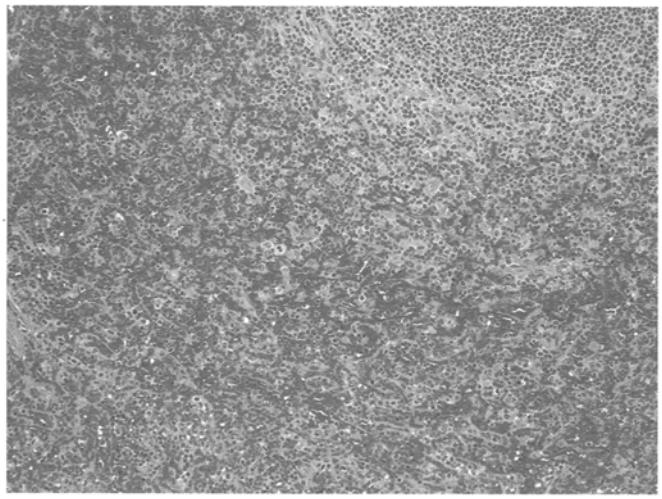


Fig. 31. Vascular congestion: In this case of hereditary spherocytosis, there is severe congestion of the red pulp. Red pulp congestion can be the result of a variety of conditions.

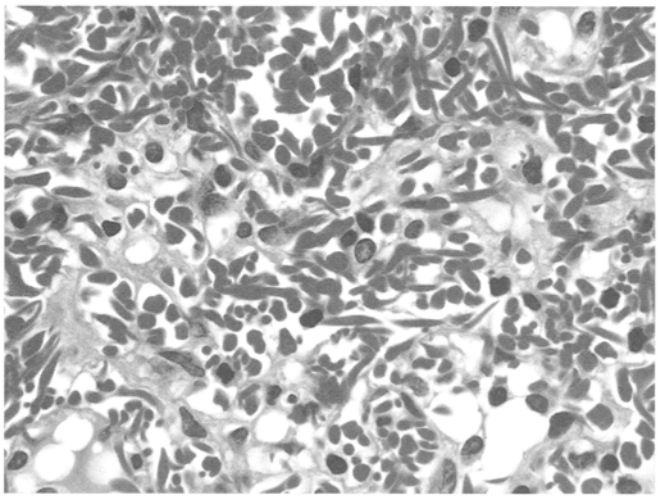


Fig. 32. Sickle cell disease: Note the sickled red blood cells distending the cords and sinuses.

Diagnosis

- Sickle cell disease (**Figure 32**):
  - Loss of marginal zones is an early occurrence in Sickle cell disease
  - Splenic micro-infarcts are common (Gamna-Gandy bodies), eventually, the spleen becomes a small, fibrotic, non-functional mass due to repeated infarction
  - Occasionally, children may present with an enlarged, painful spleen that is acutely infarcted
- Other red blood cell disorders may have erythrophagocytosis in cords

Infections

Definition

A variety of infectious organisms may affect the spleen. Several of these are discussed briefly below

- "Septic Spleen": Non-specific findings in spleen of patients with systemic infections - grossly may be congested and soft but no specific microscopic findings
- Infectious mononucleosis/acute EBV infection (**Figure 33**): Splenomegaly is common and may be especially susceptible to rupture with an increase in immunoblasts, especially in PALS, invasion of vessel walls, trabeculae and capsule by lymphocytes (a key microscopic feature)
- Tuberculosis: Miliary involvement in disseminated disease, characteristic granulomas, +/– caseation are present



Fig. 33. Infectious mononucleosis/EBV: There is an increase in lymphocytes and immunoblasts with characteristic infiltration of vascular walls and trabeculae.

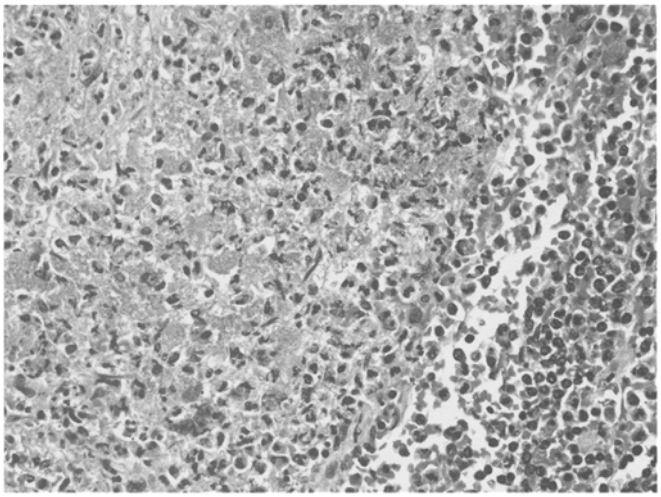


Fig. 34. Mycobacterium avium-intracellulare: Granulomas composed of macrophages filled with granular material that represents numerous organisms. M. a-i. is positive for both AFB and PAS.

- *Mycobacterium-avuim intracellulare* **(Figure 34)**: Not uncommon in HIV/AIDS patients with focal or diffuse increase in plump histiocytes filled with granular material that stain positively for AFB and PAS (may mimic a storage disease)
- Malaria: Splenomegaly common; often a combination of red pulp congestion and increased macrophages, with prominence of parasitized red blood cells and follicular and marginal zone hyperplasia may also be seen
- *Tropical splenomegaly* is progressive massive splenomegaly associated with malaria or other infections of unknown mechanism

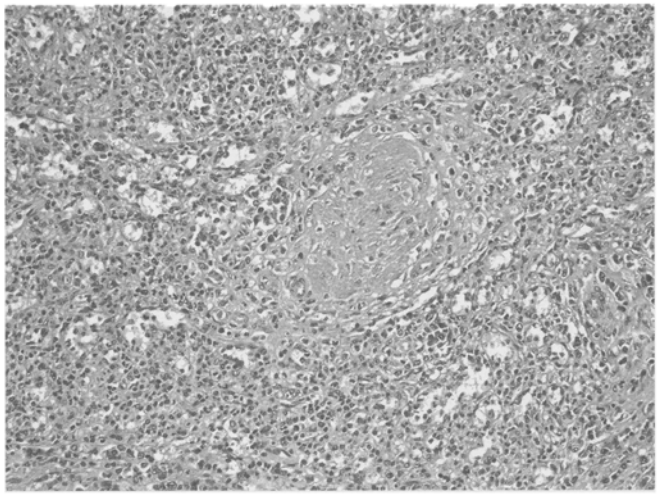


Fig. 35. HIV: This spleen shows some of the changes associated with HIV. In this late-stage case, the follicle (center) is depleted of lymphocytes. Plasmacytosis is also prominent.

- Leishmaniasis: Splenomegaly not uncommon in systemic Leishmaniasis; organisms can be seen in macrophages, especially with Giemsa stain
- HIV/AIDS (**Figure 35**): Splenic pathology dependent on stage of disease—early phase may have florid follicular hyperplasia, while late stage may have lymphoid depletion and regressed follicles, opportunistic infections increased
- Echinococcus (**Figure 36**): Cysts filled with debris and fragments of 'hydatid sand'; organisms may have prominent hooklets
- *Bartonella henselae* (bacillary angiomatosis): Seen in HIV/AIDS and other immunocompromised patients; forms granulomatous nodules in red pulp, numerous organisms can be demonstrated by Warthin-Starry stain
- Fungi (including Histoplasmosis, Blastomycosis, Coccidioidomycosis): Splenic involvement as part of disseminated disease; granulomas +/– caseation are present; organisms may be common or difficult to find; GMS and PAS stains may be of benefit

Storage Diseases (Figures 37,38)

Definition

- Abnormal products accumulate due to inherited biochemical abnormalities (e.g., Gaucher, Niemann-Pick, ceroid histiocytosis, mucopolysaccharidoses), neoplasms (e.g., primary amyloidosis) or other causes (e.g., secondary amyloidosis)

Clinical

- Variable depending on primary cause. Splenomegaly may be initial manifestation of adult-type of storage disorders

Diagnosis

- Macroscopic:
  - Amyloidosis associated with classic gross findings

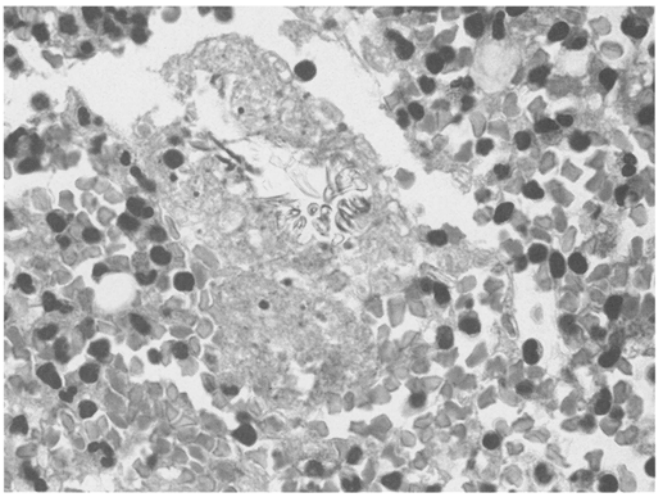


Fig. 36. Echinococcal cyst: Contents with the cyst may include fragments of organisms. In this case, prominent hooklets are seen.

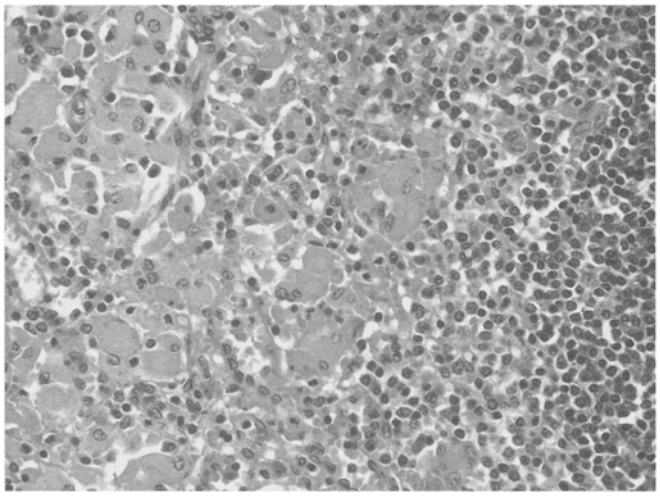


Fig. 37. Gaucher Disease: High magnification showing macrophages filled with excess metabolic product.

- *Sago spleen* refers accumulation of amyloid which appears as focal, solid waxy nodules in the spleen
- *Lardaceous spleen* refers to diffuse deposition of Amyloid throughout the spleen giving the entire organ a solid, waxy appearance

♦ Microscopic:
- Depends on type of accumulated product
- Both Gaucher and Neimann-Pick have massive accumulations of engorged macrophages in the red pulp with compression of white pulp structures
- In Gaucher's the classic 'folded tissue paper' appearance is seen
- In Niemann-Pick, macrophages will appear to have numerous small vacuoles.
- Amyloidosis shows accumulation of glassy, acellular pink matrix, initially most prominent in walls of vessels

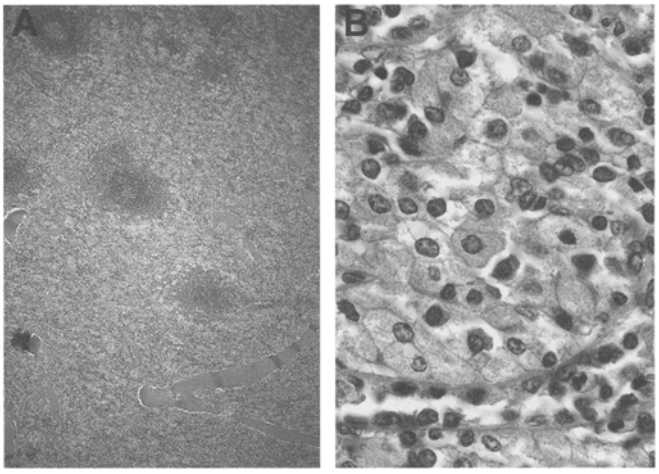


Fig. 38. Neimann Pick: Expansion of red pulp by numerous macrophages. These engorged macrophages lead to splenomegaly.

- In primary Amyloidosis, plasma cells are often quite rare

Additional Studies

♦ Positive staining for PAS diastase-resistant material can be seen in many storage disorders

♦ Amyloid will stain positive for Congo Red, with classic apple-green birefringence on polarization

Differential Diagnosis

♦ Deposition of material in macrophages can also be seen in several infectious disorders including *Mycobacterium avium-intracellulare,* fungal infections, etc

Other Systemic Disorders

♦ Sarcoidosis (**Figure 39**):
- Splenic involvement not uncommon
- Varying degrees of involvement
- Typically well-circumscribed, 'hard' granulomas composed of epithelioid histiocytes
- Negative for AFB/GMS stains

♦ Castleman Disease (**Figure 40**):
- Splenic involvement is rare; both hyaline-vascular type and plasma cell/systemic type have been reported

Autoimmune Conditions

♦ Immune thrombocytopenic purpura (ITP):
- Autoimmune destruction of platelets
- Significant splenomegaly uncommon
- Reactive follicular hyperplasia, increase of cordal macrophages, with occasional foamy histiocytes
- Occasionally see EMH, follicular hyperplasia, marginal zone hyperplasia

♦ Autoimmune hemolytic anemia: reactive follicular hyperplasia, vascular congestion of red pulp with plasmacytosis

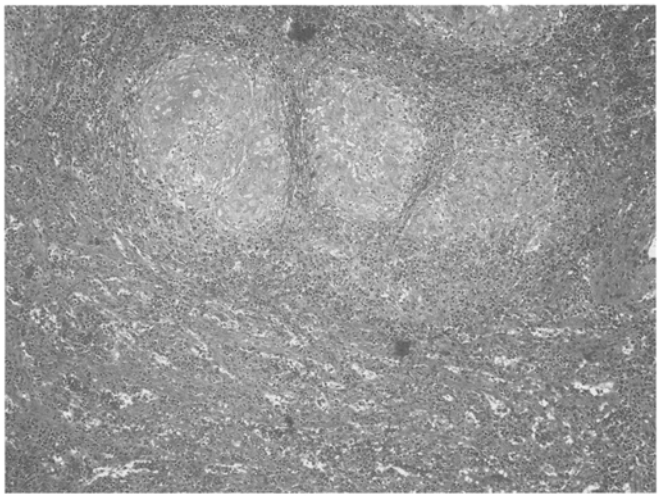


Fig. 39. Sarcoidosis: Well-defined granulomas composed of epithelioid macrophages.

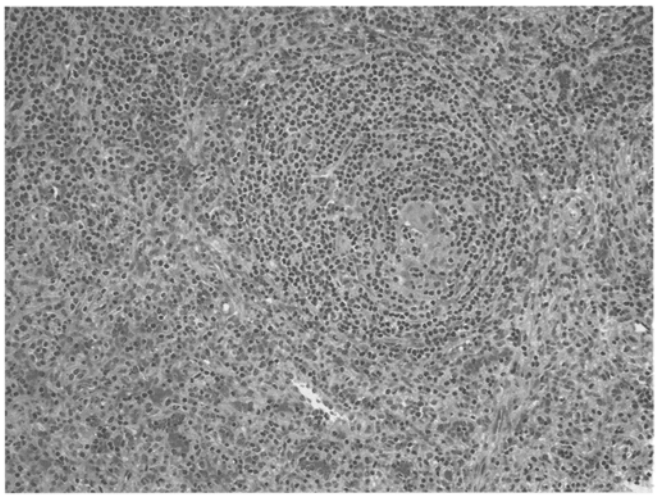


Fig. 40. Castleman Disease: Although quite rare, splenic involvement by Castleman Disease shares the same histologic features seen in lymph nodes.

- Systemic lupus: Can have prominent splenomegaly with red pulp expansion and white pulp hyperplasias; vasculitis, with onion-skin fibrosis of vessels is common and nearly pathognomonic
- Felty Syndrome (Rheumatoid arthritis, splenomegaly, neutropenia): May present with massive red pulp plasmacytosis (polyclonal).
- Other: Connective tissue diseases, polyarteritis nodosa, hyperthyroidism, juvenile rheumatoid arthritis may all present with splenomegaly

Congenital Immunodeficiency-related Splenic Disorders

Definition

- Several primary immunodeficiencies may present with prominent splenic findings or splenomegaly

Clinical

- Disorders with splenic involvement include autoimmune lymphoproliferative syndrome (ALPS), common variable immunodeficiency, selective IgA deficiency, hyper IgM syndrome, etc
- ALPS (**Figure 41**): Expansion of PALS and red pulp by CD4–/CD8– T cells. Variable plasmacytosis and follicular/marginal zone hyperplasias

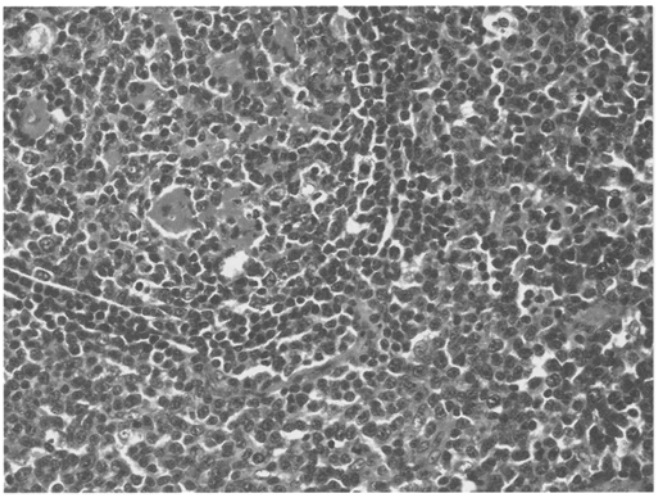


Fig. 41. Autoimmune Lymphoproliferative Syndrome: Spleen shows expansion by T-cells (CD4–/CD8–) and polyclonal plasma cells. Follicular and marginal zone hyperplasia may be seen.

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11

Bone Marrow

Dennis P. O'Malley, MD

CONTENTS

I. General Considerations 11-3
- Sampling 11-3
- Evaluation 11-3
- Ancillary Studies 11-3

II. Chronic Myeloproliferative Disorders 11-3
- Chronic Myelogenous Leukemia (CML), stable phase 11-3
- Chronic Myelogenous Leukemia (CML), accelerated phase (CML-AP)/ blast phase 11-4
- Polycythemia Vera (PV) 11-5
- Chronic Idiopathic Myelofibrosis (CIMF) 11-5
- Essential Thrombocythemia (ET) 11-6
- Chronic Eosinophilic Leukemia (CEL) /Hypereosinophilic Syndrome (HES) 11-7
- Chronic Neutrophilic Leukemia 11-7
- Myeloproliferative Disorder, Unclassifiable 11-7
- Systemic Mastocytosis 11-8

III. Acute Myeloid Leukemia 11-8
- Acute Myeloid Leukemia (AML) 11-8
- AML with Recurrent Cytogenetic Abnormalities 11-9
- AML (and MDS), Therapy-Related 11-10
- AML, Not Otherwise Categorized 11-11

IV. Acute Lymphoblastic Leukemia 11-15
- Precursor B-cell Acute Lymphoblastic Leukemia (B-ALL) 11-15
- Burkitt Leukemia/Lymphoma and Burkitt-like Leukemia/Lymphoma (BL/BLL) 11-16
- Precursor T-cell Acute Lymphoblastic Leukemia (T-ALL) 11-16

V. Myelodysplastic Syndromes 11-17
- Myelodysplastic Syndromes (MDS) 11-17
- Refractory Anemia (RA) 11-17
- Refractory Anemia with Ringed Sideroblasts (RARS) 11-18
- Refractory Cytopenia with Multilineage Dysplasia (RCMD) 11-19
- Refractory Anemia with Excess Blasts (RAEB) 11-19
- 5q- Syndrome 11-19
- MDS, Unclassifiable (MDS, U) 11-20

VI. Myelodysplastic/Myeloproliferative Diseases 11-20
- Chronic Myelomonocytic Leukemia (CMML) 11-20
- Atypical Chronic Myeloid Leukemia (aCML) 11-21
- Juvenile Myelomonocytic Leukemia 11-21
- MDS/MPD, Unclassifiable 11-22

VII. B-Cell Lymphoproliferative disorders 11-22
- Chronic Lymphocytic Leukemia (CLL) 11-22
- B-cell Prolymphocytic Leukemia (B-PLL) 11-23
- Lymphoplasmacytic Lymphoma/ Leukemia 11-23
- Marginal Zone Lymphoma (MZL) 11-24
- Follicular Lymphoma 11-24
- Mantle Cell Lymphoma (MCL) 11-25
- Hairy Cell Leukemia 11-25
- Diffuse Large B-cell Lymphoma (DLBCL) 11-26

VIII. T- and NK-Cell Lymphoproliferative disorders 11-26
T-cell Prolymphocytic Leukemia (T-PLL) 11-26
Anaplastic Large Cell Lymphoma (ALCL) 11-27
Sezary Syndrome (SS)/ Mycosis Fungoides (MF) 11-28
Adult T-cell Leukemia/ Lymphoma (ATLL) 11-28
Hepatosplenic T-cell Lymphoma 11-29
Large Granular Lympocytic Leukemias 11-29
Other Types T-cell lymphomas (PTCL, AILT, etc.) 11-30
Natural Killer (NK) Leukemias and Lymphomas 11-30

IX. Hodgkin Lymphoma 11-31
Classical Hodgkin Lymphoma (CHL) 11-31
Nodular Lymphocyte-predominant Hodgkin Lymphoma (NLPHL) 11-31

X. Plasma Cell Disorders 11-32
Reactive Plasmacytosis 11-32
Plasma Cell Myeloma (PCM) 11-32
Monoclonal Gammopathy of Undetermined Significance (MGUS) 11-33
Primary Amyloidosis 11-33
Plasma Cell Leukemia 11-34

XI. Histiocytic and Macrophage Disorders 11-34
Langerhans Cell Histiocytosis (LCH) 11-34
Hemophagocytic Syndrome (HPS) 11-34
Storage Diseases 11-35

XII. Metastases 11-36

XIII. Infections 11-36

XIV. Anemias 11-36
Iron Deficiency 11-36
Anemia of Chronic Disease 11-37
Megaloblastic Anemia 11-37
Paroxysmal Nocturnal Hemoglobinuria (PNH) 11-38
Congenital Dyserythroblastic Anemias (CDA) 11-38

XV. Reactive Conditions, Treatment Changes, MISC 11-38
Aplastic Anemia (AA) 11-38
Cytokine Effects 11-39
Granulomas 11-39
Immune Thrombocytopenic Purpura (ITP) 11-39

XVI. Suggested Reading 11-40

GENERAL CONSIDERATIONS

Sampling

- Peripheral blood smear with associated CBC results are critical in adequately evaluating hematologic disorders
- Aspirate smears allow for examination of cytomorphology; differential counts of 200 cells or more should be routinely performed on marrow aspirates
- Touch preparations of core biopsies should be performed in all cases of inaspirable bone marrows
- Core biopsies are necessary to evaluate the architecture of bone marrows; in some cases, fibrosis prevents aspiration and core biopsy may be the only pathologic specimen available; some focal pathology, such as paratrabecular lymphoid aggregates, is not typically observed in marrow aspirates
- Clot sections are fixed specimens made from aspirate smears; they are not decalcified and lack some architectural information present in core biopsy

Evaluation

- Bone marrow examination should include all of the following elements when possible: adequate clinical history (including presence of previous hematologic disease or indication for biopsy), CBC results, other pertinent laboratory results (e.g., SPEP), peripheral blood smear, aspirate smear, clot section, core biopsy; additional testing may be performed on these samples (see below)
- Similar to gynecologic cytology, bone marrow reports should include statement of specimen adequacy; if the specimen is inadequate, the reason for this should be stated (e.g., sample too small, sample crushed, etc.)
- Standard staining for peripheral blood and aspirate smears are the Wright or Wright-Giemsa stains
- Prussian blue stains of aspirate smears are used to evaluate iron stores and the presence of ringed sideroblasts; more than rare ringed sideroblasts are indicative of a pathologic condition; iron stain can be performed on core biopsy or clot sections
- H&E is the standard for core biopsies and clot sections; PAS (which highlights erythroid precursors) or Giemsa stains are used occasionally
- Reticulin staining is commonly performed on core biopsies to evaluate reticulin fibrosis; reticulin fibrosis of the bone marrow is a common finding in pathologic conditions, but is not specific for any entity

Ancillary Studies

- Flow cytometry is often performed on bone marrow aspirates to evaluate for the presence of disease; it is most useful for establishing clonality and immunophenotype in lymphoproliferative disease and in evaluating the presence, immunophenotype and amount of a blast population in acute leukemias
- Currently flow cytometric diagnosis of MDS and MPD is limited; however, new studies suggest that flow may play a greater role in prognostication and diagnosis in future
- Cytogenetics are often a cornerstone in the diagnosis of several neoplastic bone marrow disorders; if a neoplastic diagnosis is considered, cytogenetics should be performed on the bone marrow
- FISH studies are becoming more important in hematologic disease; these probes allow rapid, efficient testing of specific cytogenetic abnormalities in hematologic disease

CHRONIC MYELOPROLIFERATIVE DISORDERS

Myeloproliferative disorders (MPD)

Definition

- Neoplastic proliferations of hematopoietic stem cells, typically producing increased numbers of one or more of the myeloid lineages in the blood and bone marrow

Clinical

- Splenic enlargement is common in MPDs (see Chapter 9)

Chronic Myelogenous Leukemia (CML), stable phase (Figure 1)

Definition

- Myeloproliferative disease associated with the *BCR1/ABL* gene fusion of marrow stem cells, leading most often to blood and marrow expansion of predominantly granulocytic elements

Clinical

- Clinical presentation: fatigue (anemia), fullness/LUQ pain (splenomegaly), fever, malaise
- Disease of adults, most often sixth decade; very rarely occurs in children

Diagnosis

- Peripheral Blood:
  - Leukocytosis, often >100 x 10^9/L, with immature forms (predominantly neutrophilic) but less than 10% blasts
  - Often has prominent basophilia, a characteristic finding when present

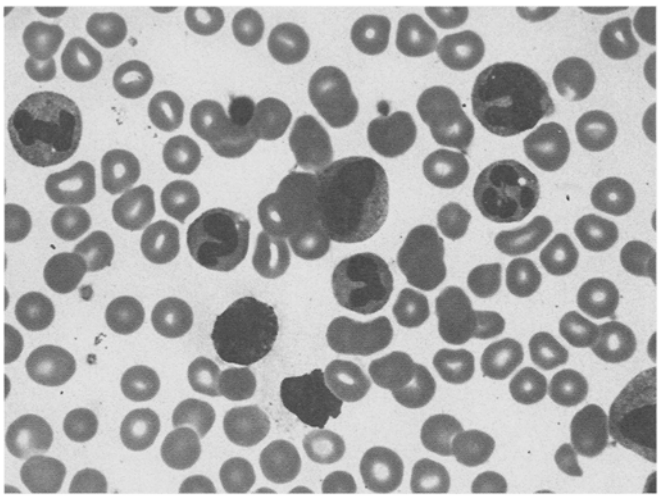


Fig. 1. Chronic Myelogenous Leukemia. Peripheral blood smear with increased granulocytes with left shift, including increased basophils.

  - Eosinophilia may also be prominent
  - Immature erythroid elements and thrombocytosis are variably present
  - Leukocyte alkaline phosphatase (LAP) score markedly decreased
- Aspirate Smear:
  - Hypercellular
  - Consists of numerous maturing granulocytic elements. M:E ratio >10 : 1. Dysplasia is not typically present
  - Blasts <10%
  - Megakaryocytes often increased
  - Pseudo-Gaucher cells may be seen
- Biopsy:
  - Hypercellular, often approaching 100%
  - Numerous myeloid precursors (M:E >10 : 1)
  - Paratrabecular expansion of immature myeloid elements, causing "myeloid bulge"
  - Dwarf (small, hypolobated) megakaryocytes common
  - Sinuses dilated, often with intrasinusoidal hematopoiesis

Additional Studies

- FLOW: typically non-contributory
- IHC: Rarely used. CD34 staining may highlight increased blasts (see accelerated phase, below)
- Cytogenetics/Molecular:
  - Characteristic translocation between chromosomes 9 and 22, leading to formation of Philadelphia chromosome, t(9;22) (q34;q11). Transposition of *BCR1/ABL* genes leading to overactive tyrosine kinase
  - p210 gene product: most common (95%)—typical CML
  - p190 gene product: rare (~5%)—morphology similar to CMML (also seen in ALL)
  - p230 gene product: very rare (<1%)—morphology ET-like or very rarely CNL-like

Differential Diagnosis

- Leukemoid reaction: reactive increase of granulocytes, without cytogenetic change; normal or increased LAP
- Chronic neutrophilic leukemia (see later), chronic eosinophilic leukemia (see later section), atypical CML (lacks cytogenetic AND molecular evidence of *BCR1/ABL* translocation)

Treatment and Prognosis

- Relatively specific treatment for CML, Gleevec, inhibits abnormal tyrosine kinase activity in many cases
- BMT may be therapy of choice in some patients

Chronic Myelogenous Leukemia (CML), accelerated phase (CML-AP)/blast phase

Definition

- Aggressive forms of CML, with associated worse prognosis
- Accelerated phase: advancement of clinical and laboratory features associated with a worsening prognosis
- Blast phase (blast crisis): clinical characteristics similar to poor-prognosis acute leukemia, with >20% blasts in blood or bone marrow; approximately 30% of blast phase transform to lymphoblastic leukemias

Clinical

- Features of accelerated phase include any of the following: 1) 10–19% blasts in blood or marrow, 2) blood basophils >20%, 3) persistent thrombocytopenia or thrombocytosis in spite of therapy, 4) increasing spleen size and WBC count in spite of therapy, 5) cytogenetic evidence of clonal evolution
- Criteria for blast phase include any of the following: 1) >20% blasts in blood or marrow, 2) extramedullary blast proliferation (e.g., spleen), 3) large clusters or aggregates of blasts in bone marrow (often identified by immunohistochemistry)

Diagnosis

- Peripheral Blood:
  - Increased blasts (10–19%)
  - Increased basophils (>20%)
  - The presence of dysplastic features in granulocytic elements
- Aspirate Smear:
  - Similar features to peripheral blood including increased blasts (>10%) and dysplastic features of marrow elements
- Biopsy:
  - Increased blasts

- If present, significant reticulin fibrosis may suggest accelerated phase
- Clusters or aggregates of blasts
- Increased numbers of megakaryocytes or large clusters of megakaryocytes may also indicate CML-AP

Additional Studies

- FLOW: Myeloid blasts (CD13, CD33, CD34, CD117) or lymphoid blasts (CD19, CD10, TdT) may be seen. Often mixed lineage leukemias with combination of myeloid and lymphoid antigens may be seen
- IHC: CD34/CD117 may highlight clusters of blasts
- Cytogenetics: In addition to t(9;22) additional abnormalities are often present. Most common findings include: double Philadelphia chromosome; iso(17q); trisomy 8

Polycythemia Vera (PV)

Definition

- Clonal myeloproliferative disease with predominant expression of erythroid proliferation

Clinical

- Diagnosed primarily by clinical criteria: Elevated RBC mass or Hgb >18.5 g/dL (men) or 16.5 g/dL (women) and no cause of secondary erythrocytosis AND any major (M) or two minor (m) criteria:
  - Splenomegaly (M)
  - Clonal genetic abnormality (other than *BCR1/ABL*) (M)
  - In vitro endogenous erythroid colony formation (m)
  - Thrombocytosis $>400 \times 10^9$/L (m)
  - WBC $>12 \times 10^9$/L (m)
  - Hypercellular bone marrow with panmyelosis (m)
  - Low serum erythropoietin (m)
- M : F = 1–2 : 1
- Post-polycythemic myelofibrosis and myeloid metaplasia (PPMM) characterized by marrow fibrosis, splenic enlargement and leukoerythroblastic peripheral blood
- Splenomegaly with extramedullary hematopoiesis common
- Thrombotic symptoms common

Diagnosis

- Peripheral Blood:
  - Leukocytosis and thrombocytosis common
  - Basophilia may be present
- Aspirate Smear:
  - Increase in all marrow elements (panmyelosis) lacking dysplasia
  - Stainable iron is absent
- Biopsy:
  - Normo- to hypercellular; if hypercellular, typically has increased erythroid elements

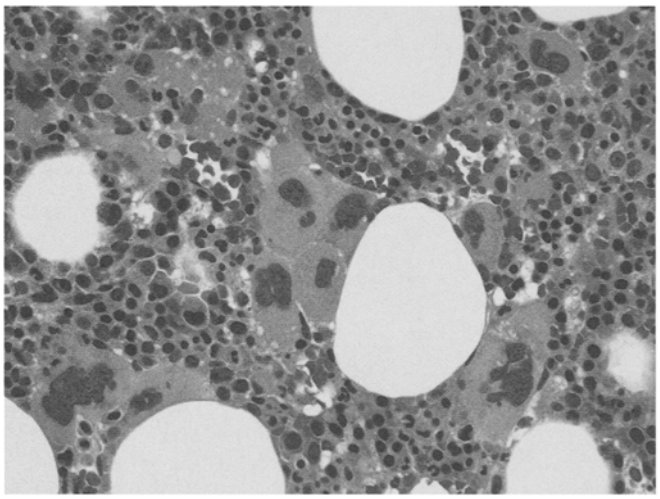


Fig. 2. Chronic Idiopathic Myelofibrosis. Note the clusters of morphologically atypical megakaryocytes. Extensive fibrosis would be seen on reticulin staining (not shown).

  - Megakaryocytes may be increased and have dysplastic appearance
  - Post-polycythemia myeloid metaplasia is a late development in PV with extensive fibrosis that has a morphologic appearance indistinguishable from CIMF,

Additional Studies

- Cytogenetics/Molecular: CD177 (*PRV-1*) is overexpressed in PV neutrophils and may increase in importance as a diagnostic test

Differential Diagnosis

- Reactive erythrocytosis, other MPD

Chronic Idiopathic Myelofibrosis (CIMF) (Figure 2)

Definition

- Clonal myeloproliferative disease characterized by proliferation of megakaryocytes with significant associated marrow fibrosis

Clinical

- Transformation to AML in 5–30% of patients
- Splenomegaly and hepatomegaly due to EMH
- "Prefibrotic stage" lacks splenomegaly and characteristic peripheral blood findings; lacks marrow fibrosis; has hypercellularity and megakaryocyte morphologic abnormalities

Diagnosis

- Peripheral Blood
  - Leukoerythroblastosis
  - Immature/nucleated erythroid precursors
  - Teardrop cells (dacrocytes)

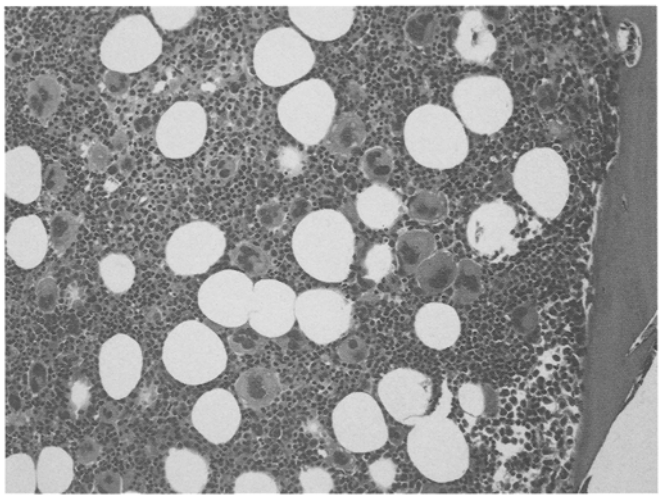


Fig. 3. Essential Thrombocythemia. Note increased megakaryocytes. In contrast to CIMF, fibrosis is rare.

- Immature neutrophilic elements, including rare blasts
- Increased platelets, abnormal hypogranulated or giant forms not uncommon
- Rarely, circulating megakaryocytes or megakaryoblasts

♦ Aspirate Smear:
- Most cases inaspirable due to marrow fibrosis

♦ Biopsy:
- Increased abnormal megakaryocytes, usually in tight clusters with enlarged, hyperchromatic nuclei
- Dilated sinuses
- Intrasinusoidal hematopoiesis common
- Blasts <10%
- Reticulin fibrosis usually present; often have trichrome (mature collagen) positive fibrosis
- Bone changes, including osteosclerosis are common

Additional Studies

♦ FLOW: typically not performed due to lack of aspirate

♦ IHC: CD34 may highlight blasts

♦ Cytogenetics/Molecular: no specific abnormalities. Most common include: del(13q); del(20q); partial trisomy (1q); +8; +9

Differential Diagnosis

♦ APMF

♦ Polycythemia vera/PPMM

♦ AML or MDS with fibrosis

♦ Autoimmune myelofibrosis: seen typically in young women with other autoimmune manifestations, lacks megakaryocytic abnormalities

Treatment and Prognosis

♦ Median survival 3–5 years from diagnosis

Essential Thrombocythemia (ET) (Figure 3)

Definition

♦ A neoplastic proliferation of marrow elements, with a predominance of megakaryocytes; these abnormal megakaryocytes produce large numbers of circulating platelets

Clinical

♦ Patients may be asymptomatic or present with consequences of thrombocytosis; these can include either bleeding (hypofunctional platelets) or thrombosis

♦ Transformation to AML is rare

Diagnosis

♦ Peripheral Blood:
- Sustained platelet count >600 × 10^9/L
- Platelets typically morphologically abnormal including variation in size, shape and granulation
- Typically lack elevated WBC or basophilia

♦ Aspirate Smear:
- Myeloid and erythroid elements typically normal
- Increased megakaryocytes
- Megakaryocytes are typically large in size with large nuclei and abundant cytoplasm
- Large clumps of platelets may occasionally be seen in aspirate smear

♦ Biopsy:
- Often normocellular
- Increase in number of megakaryocytes present in loose clusters
- Dysplastic megakaryocyte morphology includes very large size, with 'cloud-like' nuclei and large amounts of cytoplasm
- Myeloid and erythroid elements are often normal-appearing
- Reticulin fibrosis is absent or minimal

Additional Studies

♦ Flow/IHC: typically do not add to the diagnosis

♦ Cytogenetics/Molecular: abnormal cytogenetics rare but include del(13q22); +8; +9

Differential Diagnosis

♦ Reactive thrombocytosis—lack morphologic abnormalities in megakaryocytes; no abnormal cytogenetics

♦ Lacks features of other MPD including CML, CIMF, PV and MDS

Treatment and Prognosis

♦ Indolent disorder, transformation to AML quite rare (<5%)

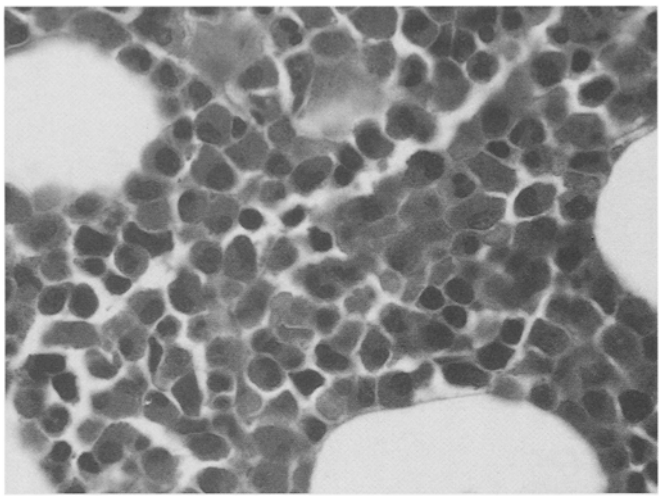


Fig. 4. Chronic Eosinophilic Leukemia. This bone marrow core biopsy shows a massive increased in eosinophils and precursors.

Chronic Eosinophilic Leukemia (CEL)/ Hypereosinophilic Syndrome (HES) (Figure 4)

Definition

- Autonomous proliferations of eosinophils with associated end-organ damage
- CEL has proven clonality or cytogenetic abnormality; HES lacks proof of clonality

Clinical

- CEL/HES are diagnoses of exclusion; other causes of eosinophilia (allergy, parasites, drug effects, secondary to neoplasms) must be excluded
- Eosinophils infiltration may lead to damage in lungs, heart, skin and GI tract
- M : F = 9 : 1
- Constitutional symptoms including diarrhea and pruritis common

Diagnosis

- Peripheral Blood:
  - >1.5 × 10^9/L eosinophils
  - Eosinophils may be dysplastic (abnormal granulation, hyperlobated), but these findings can be seen in reactive eosinophilia
- Aspirate Smear:
  - Increased eosinophils and precursors
  - Blasts <20%
  - May see Charcot-Leyden crystals
  - May see dysplastic features in other cell lineages
  - Eosinophils may be abnormally chloroacetate esterase positive
- Biopsy:
  - Hypercellular, predominantly due to increased eosinophils

Additional Studies

- Cytogenetics/Molecular: 5q33 associated with PDGF-beta; +8; 8p11; t(8;13), t(6;8)

Differential Diagnosis

- AML inv(16)—differentiate by cytogenetics and blast count; other MPD

Prognosis and Treatment

- Gleevec, most often used in CML, has activity in some cases of CEL/HES, including those with 5q33 abnormalities and others

Chronic Neutrophilic Leukemia

Definition

- Very rare disorder which consists of sustained proliferation of mature neutrophils, that lacks *BCR1/ABL* and other causes (e.g., paraneoplastic)

Clinical

- Possible association with plasma cell myeloma
- Hepatosplenomegaly
- Exceedingly rare

Diagnosis

- Peripheral Blood:
  - Numerous mature neutrophils (>25 × 10^9/L)
  - Immature granulocytes <10%
  - Blasts <1%
- Aspirate Smear:
  - Increased neutrophils
  - No dysplasia of neutrophils
  - Blasts <5%
- Biopsy:
  - Hypercellular
  - M : E >20 : 1
  - Fibrosis is uncommon

Additional Studies

- Cytogenetics/Molecular: Normal in most cases

Differential Diagnosis

- CML, CMML, MDS

Myeloproliferative Disorder, Unclassifiable

Definition

- Cases that have clinical or morphologic features of a MPD, but lack features of a specific entity OR have significant overlap between more than one entity AND lack evidence of *BCR1/ABL*

Other

- Features are variable
- May represent very early stages of PV or CIMF
- Features of MDS are lacking

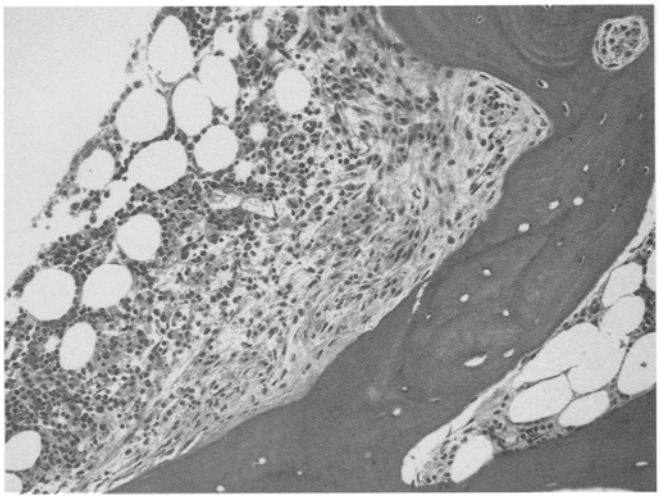


Fig. 5. Mastocytosis. This core biopsy shows a classic paratrabecular aggregate of fibrosis with mast cells. Tryptase, CD117, Giemsa or toluidine blue stains would highlight the mast cells.

Systemic Mastocytosis (Figure 5)

Definition

- Abnormal proliferation and accumulation of mast cells in multiple sites
- Systemic types are clonal disorders
- Mast cell leukemia is a very rare manifestation of mastocytosis with >10% mast cells in peripheral blood and diffuse infiltration of marrow by >20% mast cells

Clinical

- Constitutional symptoms may be prominent as well as mast cell cytokine-mediated symptomatology
- Mastocytosis can also be seen in association with other hematopoietic malignancies including myeloproliferative disorders, myelodysplastic syndromes, acute myeloid leukemias
- Elevated serum tryptase levels are almost always seen, but are not entirely specific for mastocytosis
- Other common sites of involvement include spleen, skin, GI tract

Diagnosis

- Peripheral Blood:
  - Circulating mast cells are rarely seen except in mast cell leukemia
- Aspirate Smear:
  - Mast cells are seen in increased numbers
  - In comparison to normal mast cells, neoplastic mast cells may be hypogranular or spindle-shaped
  - Increased numbers of eosinophils, lymphocytes or plasma cells may be seen
  - Because of association with other hematopoietic disorders, care must be taken when evaluating other marrow elements
- Biopsy:
  - Mast cells are round with moderate amounts of cytoplasm or occasionally unremarkable spindle cells
  - H&E stains, mast cells are inconspicuous; cytoplasmic granules may be inapparent
  - Giemsa or toluidine blue stains may highlight metachromatic granules of mast cells
  - Mast cell infiltrates are associated with polymorphous infiltrates of inflammatory cells including lymphocytes, plasma cells and often prominent eosinophils
  - Fibrosis is common

Additional Studies

- FLOW: often non-contributory due to associated fibrosis, mast cells positive for CD117, CD45, CD11c, CD33, CD43, CD2*, CD25*
- IHC: positive for tryptase, CD117, CD43, CD2*, CD25*

*Expression is seen in neoplastic mast cells and not normal mast cells

- Cytogenetic/Molecular: *KIT* gene mutations can be identified in many cases

ACUTE MYELOID LEUKEMIA

Acute myeloid leukemia (AML) (Figure 6)

Classification

- Malignancy of myeloid progenitor/early precursor cells
- Several subtypes based on cytogenetic findings, lineage and phenotypic variation
- The current WHO classification divides AML into four general groups: AML with recurrent cytogenetic abnormalities, AML with multilineage dysplasia, AML (and MDS)—therapy-related, AML not otherwise categorized
- AML, not otherwise categorized includes several clinical and/or morphologic entities, which make up the majority of cases of AML
- WHO terminology is used in this section, with the outdated FAB (French-American-British) classification system terminology included in parentheses for historical purposes

Clinical Findings

- Most often a disease of adults, 60 years and older

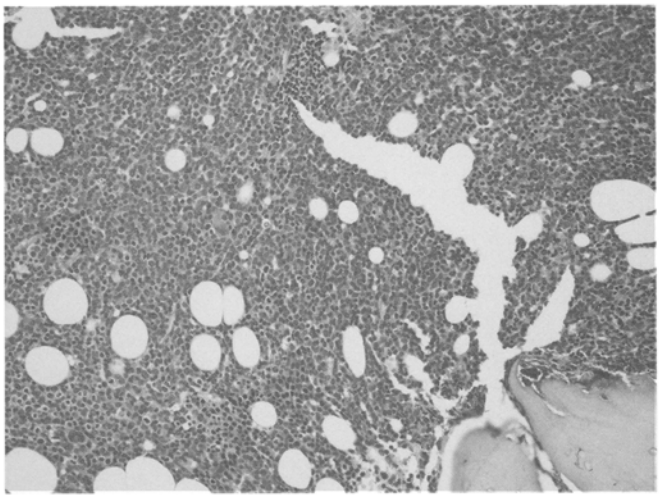


Fig. 6. Acute Myeloid Leukemia. This core biopsy shows extensive infiltration by myeloid blasts.

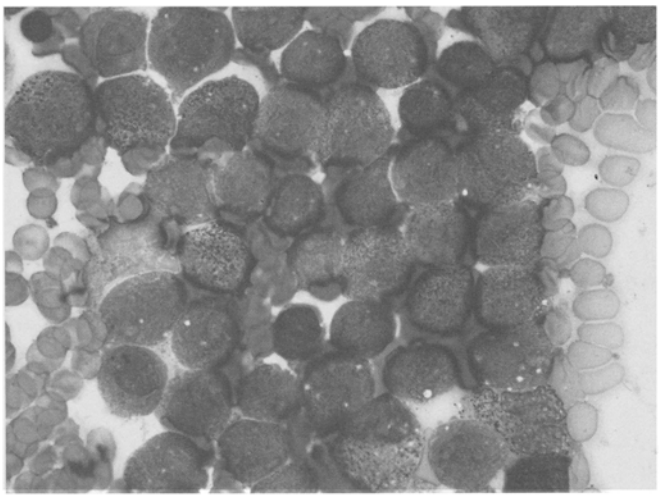


Fig. 7. Acute Promyelocytic Leukemia. This aspirate smear shows a large cluster of abnormal, granular promyelocytes.

- Contributing etiologies: viruses, ionizing radiation, cytotoxic chemotherapy, benzene, cigarette smoking

Diagnosis

- Auer rods are a fusion of primary granules, seen in the cytoplasm of blasts of granulocytic lineage; they are seen exclusively in a subset of cases of AML or high-grade MDS
- Cytochemical stains provide information on lineage of some AML types (*see* **Table 1**); for myeloperoxidase (MPO) or non-specific esterase (NSE) to be considered positive, at least 3% of the neoplastic cells (e.g. blasts) must stain positively

AML with recurrent cytogenetic abnormalities

In cases with recurrent cytogenetic abnormalities, even if blasts percentages do not reach 20%, they should still be diagnosed at AML rather than an MDS

AML with t(8;21)

- Translocation results in fusion of *AML1/ETO* genes
- Represents 5–12% of cases of AML
- Patients are typically younger than in other types of AML
- Morphology is most often large blasts, most often with numerous cytoplasmic granules and frequent Auer rods
- Maturing neutrophilic elements +/– dysplasia may be seen
- Strong cytoplasmic positivity for MPO is usually seen
- Flow: typically positive for CD34, CD13, CD33, often coexpress CD19, +/– CD56
- Prognosis: good, compared to other types of AML

AML with inv(16) and abnormal bone marrow eosinophils

- Most commonly results in fusion of *CBF beta/MYH11* genes
- Accounts for 10–12% of cases of AML
- Have features of myelomonocytic leukemia
- Most cases have atypical eosinophil precursors with heavy granulation and abnormally large granules
- Eosinophilia may or may not be present in the peripheral blood
- Cytochemistry: MPO is typically positive (at least 3%), and a component of monoblasts/promonocytes that are positive for NSE (*see* **Table 1**)
- Flow: component of myeloid blasts positive for CD13, CD33, MPO; monocytic elements are variable positive for CD11b, CD4, CD14, CD64
- Prognosis: good, compared to other types of AML

AML with 11q23 (MLL) abnormalities

- Translocations of *MLL* gene involved with several possible partner genes
- t(11;19); t(9;11), t(4;11), or several others
- 5–6% of cases of AML
- Occur more frequently in AML in infants and therapy-related AML (see later section)
- Monocytic morphology or, less commonly, myelomonocytic features are seen
- Cytochemistry: NSE positivity is seen in most cases
- Flow: there are no specific flow findings for AML with 11q23 abnormalities, but monocytic lineage markers (CD11b, CD4, CD14, CD64) are often positive

Acute Promyelocytic Leukemia (APML) (Figure 7)

Definition

- An acute myeloid leukemia with a predominance of promyelocytes

Table 1. Cytochemical Stains Useful in the Diagnosis of Hematopoietic Disorders

Stain	*Disorder*	*Staining Pattern*	*Comment*
Myeloperoxidase (MPO)	AML, myeloblastic AML, myelomonocytic APML	>3% blasts stain positive	
Sudan Black B (SBB)	AML, myeloblastic AML, myelomonocytic APML	Results parallel those of MPO	
Non-specific Esterase (NSE)	AML, monocytic AML, myelomonocytic AMkL	>3% of monoblasts or promonocytes stains positive	
Chloroacetate Esterase (CAE)	AML, myeloblastic APML	Less sensitive than MPO	Highlights Auer rods
PAS	ALL Erythroleukemia	Block positivity Perinuclear globules	
TRAP*	Hairy Cell Leukemia	Abnormal lymphocytes are positive	Some SMZL may also be positive
LAP**	CML	Low LAP score	PNH may also have low LAP score

** TRAP = tartrate resistant acid phosphatase; ** LAP = leukocyte alkaline phosphatase, test is performed by scoring 100 granulocytes 0-4, and adding scores.*

- There are two morphologic variants: hypergranular or "typical" type, and the microgranular or hypogranular type

Clinical

- Can be associated with DIC
- 5–8% of AML
- (FAB: AML-M3)

Diagnosis

- Peripheral Blood:
  - Microgranular variant typically has few cells with identifiable granules (Granules are present, but smaller than can be resolved by eye—they can be seen by EM)
  - Neoplastic promyelocytes are intermediate in size with irregular nuclei
  - Nuclei often have a "figure eight" or "dumbbell" shape
  - Auer rods may be seen; cells with numerous Auer rods are termed 'faggot cells'
- Aspirate Smear:
  - Myeloperoxidase cytochemistry strongly stains abnormal promyelocytes
  - Abnormal promyelocytes account for at least 20% of cells
  - Promyelocytes are intermediate sized cells with moderate amounts of cytoplasm and numerous granules; Auer rods may be present
  - Nuclear irregularities are common
- Biopsy:
  - Typically hypercellular
  - Promyelocytes usually replace marrow
  - Promyelocytes often have irregular, folded nuclear contours
- Additional Studies:
  - FLOW: positive for myeloid markers CD13, CD33, CD117. Almost always negative for CD34 and HLA-DR (in contrast to most other AML)
  - Cytogenetics/Molecular: classic translocation t(15;17)(q22;q12)—*PML/RARA*; t(11;17); t(5;17)
- Differential Diagnosis:
  - Other types of AML
- Prognosis and treatment:
  - Favorable prognosis AML
  - Treatment includes use of all-trans-retinoic acid (ATRA), which effects differentiation on neoplastic cells
  - t(11;17) variant appears to be resistant to ATRA

AML (and MDS), therapy-related

Alkylating agent-related AML

- Latency usually 5–6 years after treatment
- Often arises from a previous MDS or is associated with significant dysplastic features

- Morphology may be myeloid, monocytic, myelomonocytic or other types
- Marrow fibrosis is not uncommon
- Flow: an abnormal blast population will be present often expressing CD34, CD56+/–, CD7+/–
- Genetics: often complex cytogenetics; may include MDS-like changes including deletions/monosomies of chromosomes 5 and 7
- Prognosis: Poor

Topoisomerase type II inhibitor-related AML

- Latency of approximately 3 years after treatment
- Drugs associated with this type of leukemia include: epipodophyllotoxins, etoposide, teniposide
- Usually there is no preceding MDS phase
- Morphology almost always is monocytic or has a monocytic component
- Cytogenetics: typically abnormalities that involve the *MLL* gene at 11q23 including translocations: t(11;19); t(9;11); t(4;11)

AML, not otherwise categorized

- Listed below, these leukemias are classified based on morphologic, immunophenotypic or clinical findings, and lack features of other types of leukemias
- This large group accounts for the majority of cases of de novo AML

AML, myeloblastic

Definition

- As a group, these are acute leukemias with varying degrees of granulocytic lineage differentiation
- Acute myeloblastic leukemia, minimally differentiated (FAB:AML-M0)
- Acute myeloblastic leukemia, without maturation (FAB:AML-M1)
- Acute myeloblastic leukemia, with maturation (FAB:AML-M0)

Clinical

- Combined, these groups account for 45–60% of AMLs
- Typical symptoms of AML are often present

Diagnosis

- Peripheral Blood:
  - Varying numbers of blasts are seen
  - Blasts may be undifferentiated or have unequivocal features of myeloblasts including cytoplasmic granules +/– Auer rods
- Aspirate Smear:
  - Blasts comprise at least 20%, but are often more numerous
  - Cytochemistry: in minimally differentiated, there is no positivity for MPO; in cases without maturation and with maturation, MPO is positive in at least 3% (but usually more) blasts (*see* **Table 1**)
  - Minimally differentiated—blast are intermediate to large in size with open, delicate chromatin and small amounts of agranular cytoplasm
  - Without maturation—blasts account for >20% of the non-erythroid cells present; no myeloid maturation is identified
  - With maturation—blasts account for at least 20% of the cells present, at least 10% of the cells present display neutrophilic maturation, with less than 20% monocytic lineage cells; dysplastic features may be present in the neutrophilic series
- Biopsy:
  - Typically hypercellular with a prominent component of blasts

Additional Studies

- FLOW:
  - Minimally differentiated: positive for at least one pan-myeloid antigen CD13, CD33 or CD117; negative for B or T antigens; TdT positive in about 1/3 of cases; flow methods for MPO are more sensitive and positive even in cases with negative cytochemistry
  - Without and with maturation: typically positive for CD34, CD13, CD33; CD117 +/–
- IHC: often positive for CD34, but this marker lacks lineage specificity

Prognosis

- Minimally differentiated: associated with a poor prognosis
- With and without maturation: prognosis varies

AML, monocytic/monoblastic (Figure 8)

Definition

- An acute leukemia where more than 80% of the leukemic cells are of monocytic lineage; this includes monoblasts, promonocytes and mature monocytes. Neutrophils and precursors should be less than 20% (see AML, myelomonocytic)

Clinical

- Extramedullary disease is common including gum infiltrates, cutaneous, and CSF involvement
- 3–6% of AML
- (FAB:AML-M5a monoblastic; FAB: AML-M5b—monocytic)

Diagnosis

- Peripheral Blood:
  - Blasts are often present and varying from poorly differentiated to those with clear monocytic appearance

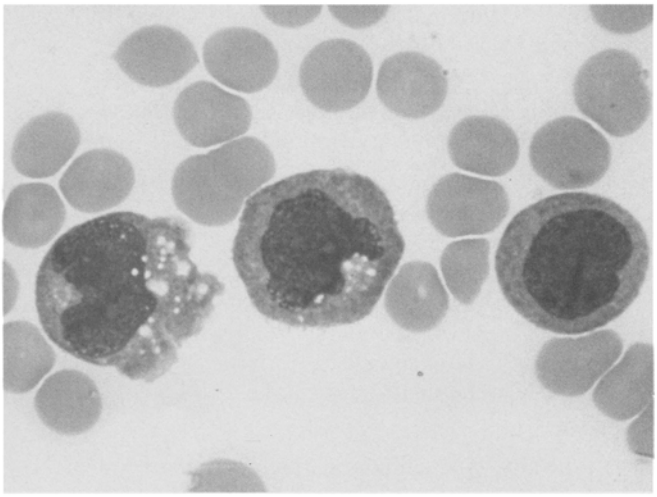


Fig. 8. AML, with monocytic/monoblastic differentiation. This peripheral blood smear illustrates monocytic differentiation in circulating blasts of AML.

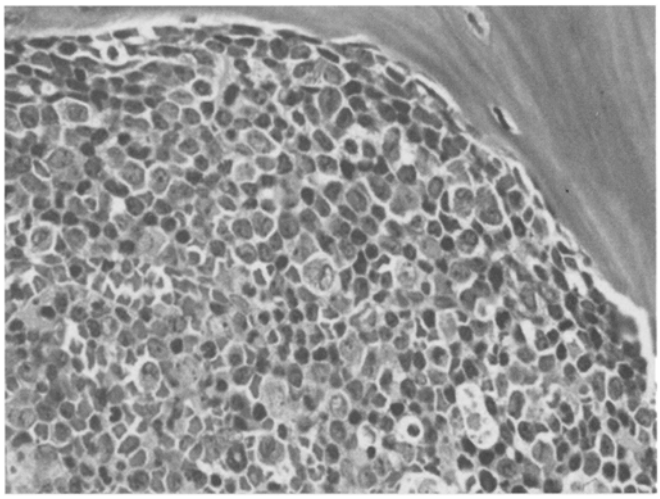


Fig. 9. AML, myelomonocytic. This core biopsy is infiltrated by blasts, some with irregular folded nuclei, suggesting monocytic differentiation.

  - Blasts of monocytic lineage often have nuclear folds or irregularities, increased amount of blue or blue-gray cytoplasm and lack cytoplasmic granules
- Aspirate Smear:
  - Blasts in aspirate (or PB) >20%
  - Monocytic differentiation may be less apparent in aspirate than in peripheral blood
  - Promonocytes (immature monocytic forms) are counted as blasts, but may be difficult to distinguish from other cells types unless numerous
  - Cytochemistry: NSE is typically positive in monoblasts and promonocytes (*see* **Table 1**)
- Biopsy:
  - Usually hypercellular
  - Infiltration of blasts usually apparent; promonocytes have somewhat folded irregular appearance of blast nuclei

Additional Studies

- FLOW: blasts population variable expresses monocytic/myeloid antigens including CD11b, CD14, CD4, CD64; CD117 is not uncommon, CD34 is less commonly positive
- IHC: monocyte/macrophage markers (e.g., CD68, lysozyme) may be negative in less differentiated forms
- Cytogenetics/Molecular: cytogenetics abnormalities vary

Differential Diagnosis

- AML with monocytic differentiation and 11q23 abnormalities should be classified with "AML with recurrent cytogenetic abnormalities" group

AML, myelomonocytic (Figure 9)

Definition

- An acute leukemia with proliferation of both monocytic and neutrophil precursors

Clinical

- 15–25% of AML
- May have extramedullary manifestations similar to monocytic/monoblastic leukemias
- (FAB:AML-M4)

Diagnosis

- Peripheral Blood:
  - Often large numbers of circulating monocytes
  - Circulating blasts common
- Aspirate Smear:
  - At least 20% blasts (or blasts + promonocytes)
  - In addition, there must be at least 20% monocytes and monocytic precursors, AND at least 20% neutrophils and precursors
  - Cytochemistry: distinct populations of MPO-positive and NSE-positive blasts are present, representing the myeloblastic and monoblastic components, respectively (see **Table 1**)
- Biopsy:
  - Typically hypercellular
  - Blasts population is often numerous and easily identifiable

Additional Studies

- FLOW: flow will typically show a component of myeloblasts (CD13, CD33, CD34) and monoblasts (CD11b, CD4, CD64, CD117)
- Cytogenetics/Molecular: abnormalities are often present but non-specific

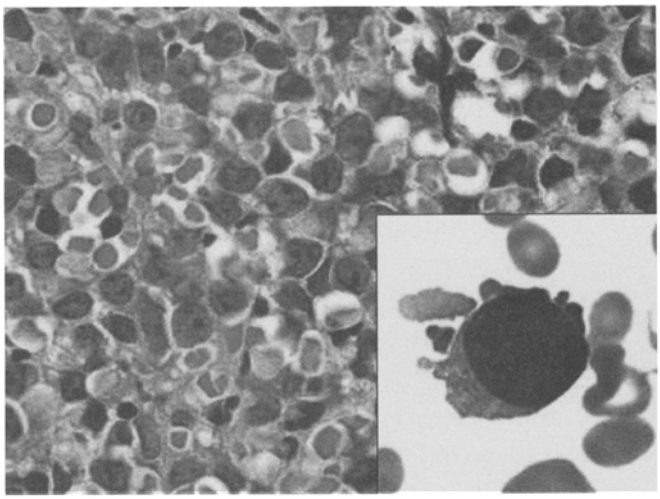


Fig. 10. Acute Megakaryoblastic Leukemia. The core biopsy is infiltrated by large, undifferentiated blasts. Inset: A single megakaryoblast, with cytoplasmic blebs.

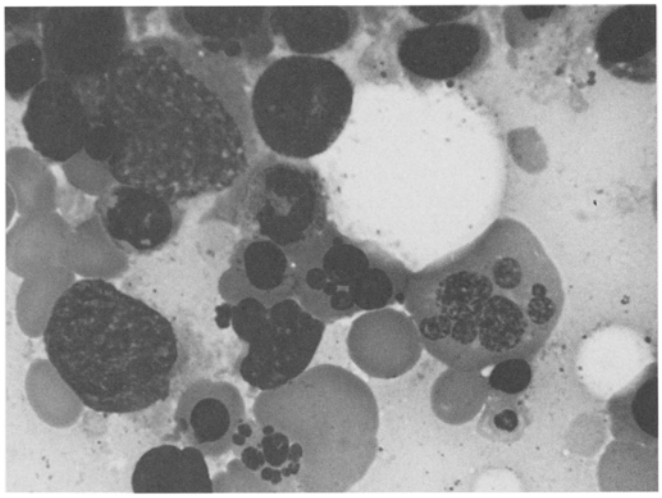


Fig. 11. Erythroleukemia. This aspirate smear shows the severe erythroid dysplasia often seen in erythroleukemia.

Differential Diagnosis

- AML with inv(16)

Acute Megakaryoblastic Leukemia (AMkL) (Figure 10)

Definition

- Leukemic proliferation of blasts, with >50% being of megakaryocytic lineage

Clinical

- 3–5% of cases of AML.
- (FAB:AML-M7)
- Increased incidence seen in patients with Down syndrome (trisomy 21)

Diagnosis

- Peripheral Blood:
  - Circulating blasts often present
  - Abnormal or bizarre platelets, or micromegakaryocytes may be seen
- Aspirate Smear:
  - Blasts of medium-large size
  - Classic appearance of blasts includes deep blue "blebs" of cytoplasm (ineffective formation of platelets)
- Biopsy:
  - Hypercellular; cellularity often composed of a uniform population of poorly differentiated, relatively large blasts
  - Severe reticulin fibrosis is common
  - Rarely, more mature, identifiable megakaryocytic forms are present

Additional Studies

- FLOW: megakaryoblasts express CD41 and/or CD61; other myeloid markers vary
- IHC: useful markers include Factor VIII, CD41, CD42
- Cytogenetics/Molecular: t(1;22)—seen in infants population, associated with poor prognosis; +21; inv(3); iso(12p)—seen exclusively in patients with mediastinal germ cell tumors

Differential Diagnosis

- Transient myeloproliferative disorder of Down Syndrome (TMPD): immature cells and blasts in peripheral blood of Down syndrome patients; most cases remit spontaneously, others progress to leukemia

Erythroleukemia (Figure 11)

Definition

- Very rare acute leukemia that consists of two main subtypes:
  - 1) erythroleukemia: presence of >50% erythroid precursors of all nucleated cells AND >20% myeloblasts of all non-erythroid cells present
  - 2) pure erythroid leukemia: marrow consists of >80% immature erythroid cells without significant numbers of myeloblasts

Clinical

- Profound anemia common
- May evolve from pre-existing MDS, leading to diagnostic overlap with AML, MLD and high-grade MDS
- 5–6% of AML; pure erythroid leukemia is extremely rare (<1%)
- (FAB:AML-M6)

Diagnosis

- Peripheral Blood

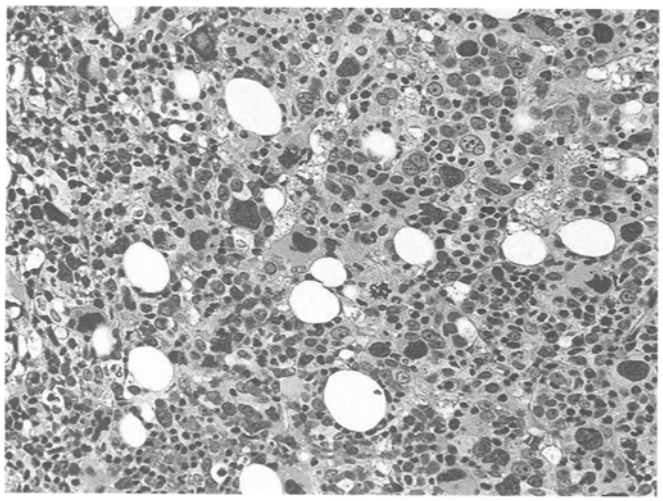


Fig. 12. Acute Panmyelosis with Myelofibrosis. This core biopsy is hypercellular, with abnormal-appearing megakaryocytes, and a population of blasts. Extensive fibrosis is present; the lineage of the blasts is usually characterized by immunohistochemistry.

- Severe RBC anisopoikilocytosis is not uncommon
- A component of circulating blasts may be present

♦ Aspirate Smear:
- Severe erythroid dysplasia is almost always present
- Erythroid dysplasia includes: megaloblastoid chromatin, multinucleation, nuclear fragmentation, giant erythroblasts, cytoplasmic vacuolation
- More common type does include component of typical myeloblasts (often with MPO positivity)
- Cytochemistry: vacuoles in abnormal erythroid precursors may have strong, abnormal PAS positivity; iron stain may highlight ringed sideroblasts
- Immature erythroid cells are increased

♦ Biopsy:
- Hypercellular, with increased erythroid elements
- Blasts variable depending on type
- Core biopsy morphology of immature erythroid elements can mimic other disorders and should be confirmed by smear morphology or immunophenotypic confirmation

Additional Studies

♦ FLOW: prominent population of erythroid cells present; myeloblasts variable

♦ IHC: anti-hemoglobin or anti-glycophorin antibodies useful in identifying immature erythroid cells

♦ Cytogenetics/Molecular: complex karyotypes common; abnormalities of chromosomes 5 and/or 7 common

Differential Diagnosis

♦ AML-MLD, MDS or other types of AML

Prognosis

♦ Often aggressive with a poor prognosis

Acute Panmyelosis with Myelofibrosis (Figure 12)

Definition

♦ AML subtype with proliferation of multilineage blasts and significant bone marrow fibrosis

Clinical

♦ Very rare (<1% of cases of AML)

♦ No or minimal splenomegaly—in contrast to CIMF

♦ Distinct from AMkL (see above) although historically cases may have been misclassified

♦ Previous names include acute myelofibrosis or acute myelosclerosis

Diagnosis

♦ Peripheral Blood:
- Often pancytopenia
- Occasional blasts may be seen
- Typically lacks anisopoikilocytosis of RBC

♦ Aspirate Smear:
- Usually inaspirable due to reticulin fibrosis

♦ Biopsy:
- Hypercellular
- Dysplasia of all cell lineages typically present, but most prominent in megakaryocytes
- Immature hematopoietic cells are present and represent immature myeloid, erythroid and megakaryoblastic elements (as identified by IHC)
- Severe fibrosis is present in all cases

Additional Studies

♦ FLOW: not usually available due to lack of aspirate

♦ IHC: CD34 positive in subpopulation of blasts; some immature cells or erythroid lineage (hemoglobin, glycophorin); component of immature cells of megakaryocytic/blastic lineage (Factor VIII, CD31, CD41, CD42)

Differential Diagnosis

♦ AMkL, AML with fibrosis or MDS with fibrosis

Prognosis

♦ Very poor, despite treatment

Other forms of AML

♦ Acute basophilic leukemia: very rare, blasts >20% with evidence of basophilic differentiation

♦ t(8;16): AML often association with hemophagocytosis

♦ del(12p): AML associated with increased bone marrow basophils

♦ t(6;9): AML associated with poor prognosis

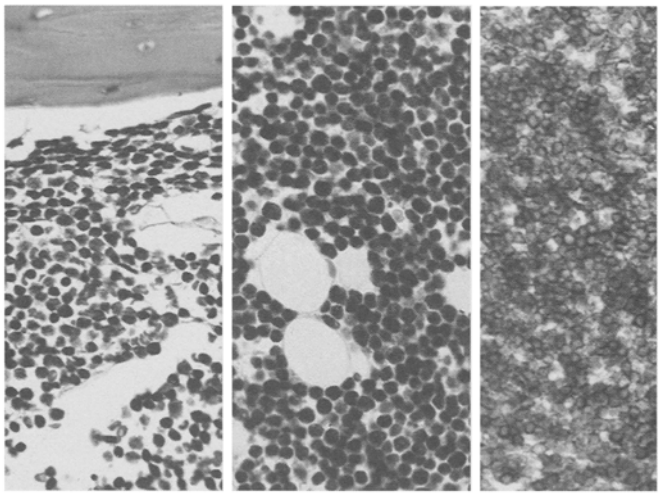


Fig. 13. Precursor B-cell Acute Lymphoblastic Leukemia. This composite photo shows (left to right) core biopsy, TdT staining, CD79a staining in precursor B-ALL.

Leukemias of Ambiguous Lineage

- Definition:
  - Acute leukemias which have morphologic, cytochemical or immunophenotypic features that either: 1) lack clear features of either myeloid or lymphoid origin, or 2) have characteristics of both myeloid and lymphoid lineage or both B-cell and T-cell lineage
- Undifferentiated acute leukemia: lacks lineage specific markers for B-ALL, T-ALL and AML
- Biphenotypic acute leukemia: blasts have characteristics of more than one lineage: B-lymphoid, T-lymphoid or myeloid; coexpression of multiple markers of more than one specific lineage must be present (a scoring system for this determination is used in the WHO classification)
- Bilineal acute leukemia: consists of two distinct populations of blasts with characters of B-ALL, T-ALL or myeloid leukemia
- Prognosis:
  - Prognosis appears to be poor, even compared to other types of acute leukemias

ACUTE LYMPHOBLASTIC LEUKEMIA

Precursor B-cell Acute Lymphoblastic Leukemia (B-ALL) (Figure 13)

Definition

- A neoplasm of lymphoid precursor cells (lymphoblasts) of B-cell origin which accounts for approximately 90% of cases of ALL

Clinical

- Common pediatric malignancy; rare in adults
- Extramedullary involvement (CSF, skin, gonads) is common
- May present as infection, due to underlying hematologic abnormalities

Diagnosis

- Peripheral Blood:
  - Anemia, and/or thrombocytopenia, and/or neutropenia are common
  - Circulating blasts common
- Aspirate Smear:
  - Blasts often numerous, usually small-intermediate in size, with delicate chromatin and variably prominent nucleoli; amount of cytoplasm varies but is usually scant and agranular
  - Rarely, B-ALL may have some cytoplasmic granules, but has immunophenotypic evidence of B-ALL and lacks cytochemical positivity for MPO or NSE
  - Cytochemistry: in many cases, there are small, paranucelar dots and blobs of PAS-positive material; negative for MPO and NSE (*see* **Table 1**)
- Biopsy:
  - Hypercellular; marrow often replaced by a homogeneous population of poorly-differentiated blasts

Additional Studies

- FLOW: CD19+, CD10+, CD34+/–, TdT+, sIg–, cCD22+, cCD79a
- IHC: CD20–, CD10+, CD34+/–, TdT+, CD79a+
- Karyotype: t(9;22)(q34;q11.2); *BCR/ABL* (unfavorable)
- (variable;11q23); *MLL* rearranged (unfavorable)
- t(12;21)(p13;q22); *TEL/AML1* (favorable)
- t(1;19)(q23;p13.3); *PBX/E2A* (unfavorable)
- hypodiploid (unfavorable)
- hyperdiploid >50 (favorable)

Differential Diagnosis

- Hematogones: Benign B-cell precursors, which are frequently present in pediatric bone marrows; when numerous, may mimic ALL; often are smaller than ALL blasts, but some may be larger and more immature; flow cytometry of hematogones can be similar to B-ALL, but has important differences in maturation and intensity of antigen expression **(Figure 14)**

Prognosis

- General prognosis of pediatric ALL is excellent
- Adult ALL typically has a poor prognosis
- Some cytogenetic subtypes, such as t(9;22)+ ALL, have a poor prognosis

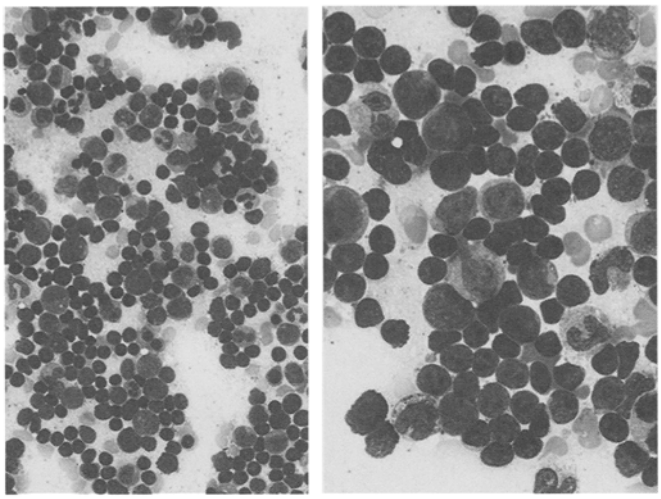


Fig. 14. Hematogones. Although there is some variation in size, the majority of the hematogones are small with condensed chromatin.

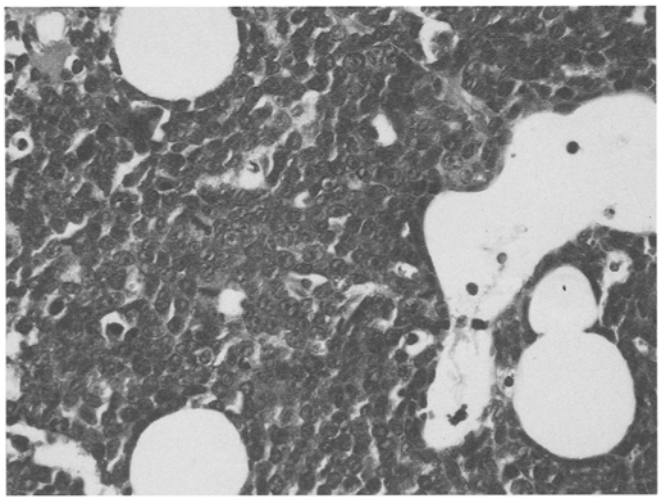


Fig. 15. Burkitt Leukemia. Extensive marrow infiltration by a monomorphic population of intermediate-size lymphocytes in an AIDS patient.

Burkitt leukemia/lymphoma and Burkitt-like leukemia/lymphoma (BL/BLL) (Figure 15)

Definition

- An aggressive, high-grade malignancy of B-cells (Although not a precursor lesion like ALL, discussed in this section for convenience.)
- Previously referred to as a type of ALL in the FAB classification (so-called FAB-ALL-L3)

Clinical

- There are three clinical settings; 1) endemic type, 2) sporadic type, 3) immunodeficiency-related
- Typically occurs in young patients (<20 years) except in immunodeficiency-related group
- Usually present with tissue masses (lymphomatous presentation) although rarely present as a leukemic form, seen more commonly in males

Diagnosis

- Peripheral Blood:
  - Circulating abnormal lymphocytes present
  - Various cytopenias may be seen
- Aspirate Smear:
  - Abnormal lymphocytes are often numerous
  - Abnormal lymphocytes are intermediate in size with round-to-irregular nuclear contours, and small to moderate amounts of vacuolated cytoplasm, chromatin is often more condensed-appearing than ALL
  - Cytochemistry: cytoplasmic vacuoles are PAS negative (in contrast to B-ALL) but stain positively for lipid stains including Oil Red O
- Biopsy:
  - Often hypercellular
  - Involvement by BL is often extensive; rarely, classic "starry sky" appearance is seen in marrow

Additional Studies

- FLOW: CD19+, CD10+, CD20+, light chain restricted, TdT-, CD5-
- IHC: CD20+, CD10+, light chain restricted, TdT–, Ki67 near 100%, CD5–, Cyclin D1–, bcl2–
- Cytogenetics/Molecular: t(8;14) most common, t(2;8) or t(8;22) less common; translocation of *c-MYC* gene at 8q24

Differential Diagnosis

- Blastic or blastoid-appearing neoplasms including ALL, blastoid mantle cell, blastoid NK leukemia/lymphoma

Prognosis

- Prognosis worse than ALL
- Bone marrow involvement is associated with poor prognosis

Precursor T-cell Acute Lymphoblastic Leukemia (T-ALL)

Definition

- A neoplasm of lymphoid precursor cells (lymphoblasts) of T-cell origin which accounts for 10–15% of cases of pediatric ALL

Clinical

- T-ALL often associated with a mediastinal mass (precursor T-cell lymphoblastic lymphoma), +/– blood /bone marrow involvement
- More common in adolescents or older children; M > F

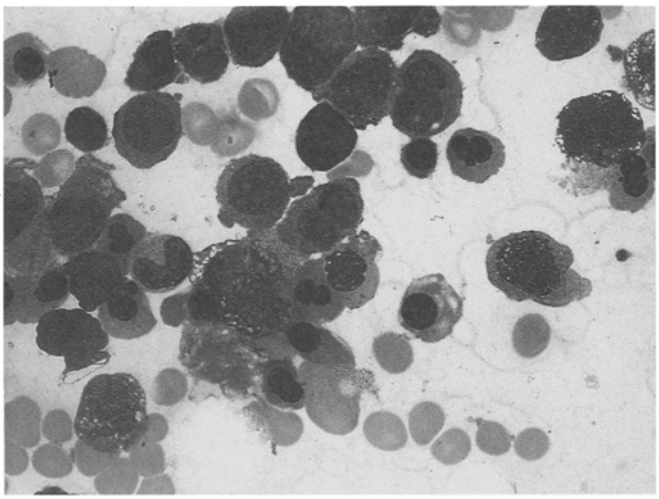


Fig. 16. Myelodysplastic Syndrome. Dyserythropoiesis in MDS.

Diagnosis

- Peripheral Blood:
  - High WBC count with numerous blasts is common
- Aspirate Smear:
  - Blasts are similar to B-ALL; intermediate size, blastic chromatin, scant cytoplasm
  - T-ALL often has more nuclear irregularity than B-ALL, but this is not a strong diagnostic criterion
  - Cytochemistry: cytochemical stains for acid phosphatase may show dot-like cytoplasmic positivity, but not specific for T-ALL
- Biopsy:
  - Degree of involvement varies; in cases with mediastinal mass, involvement may be minimal
  - Associated eosinophilia may be rarely seen

Additional Studies

- FLOW: CD3+, CD2/5/7+, CD4/8 often-, TdT+, CD10–/+
- IHC: CD3+, CD2/5/7+, CD1a+, CD4/8 often-, TdT+, CD10–/+
- Cytogenetics: rearrangements often involve the T-cell receptor genes at 14q11 and 7q35

Differential Diagnosis

- B-ALL, AML, and other 'small blue cell tumors' of childhood; all must be distinguished by immunophenotype

Prognosis

- Although formerly worse prognosis than B-ALL, T-ALL now has nearly equivalent excellent prognosis

MYELODYSPLASTIC SYNDROMES

Myelodysplastic syndromes (MDS)

Definition

- A group of clonal disorders of hematopoietic stem cell, associated with ineffective hematopoiesis, peripheral cytopenias and increased risk of progression to AML

Clinical

- Usually seen in older adults. Very rare in children
- Cytopenias common

Diagnosis

- Marrow elements involved are often increased in number in the marrow spaces but do not circulate (e.g. ineffective hematopoiesis)
- Bone marrow aspiration is most useful in assessing dysplastic features
- Dyserythropoiesis includes: megaloblastoid changes (lack of nuclear maturation with abnormal chromatin clumping relative to maturing cytoplasm), multinucleation, nuclear fragmentation (karyorrhexis), nuclear budding, cytoplasmic vacuolation (typically PAS positive), internuclear bridges **(Figure 16)**
- Dysgranulopoiesis includes: nuclear hypolobation (bilobed neutrophils, pseudo-Pelger-Huet), hypersegmentation (rare), hypogranulation, abnormal granules, donut or ring-shaped granulocytes/precursors
- Dysmegakaryopoiesis includes: small or large size, hypolobated or monolobated nuclei, separated nuclear lobes, abnormalities in cytoplasmic granulation **(Figure 17)**
- ALIP or "abnormal localization of immature precursors" can be seen. In normal marrows, immature granulocytes tend to be adjacent to bone trabeculae. In ALIP there are clusters of immature cells (blasts, promyelocytes) in interstitial spaces, not adjacent to bone
- MDS with fibrosis may prevent aspiration. In these cases assessment of dysplasia on core biopsy, evaluation of peripheral blood and immunohistochemistry should be evaluated for diagnosis

Prognosis

- Prognosis depends on specific diagnosis, percentage of blasts and cytogenetic defects (*see* **Table 1**)

Refractory Anemia (RA)

Definition

- A myelodysplastic syndrome characterized by symptoms and morphologic changes limited primarily to the erythroid lineage with a relatively low rate of progression to AML

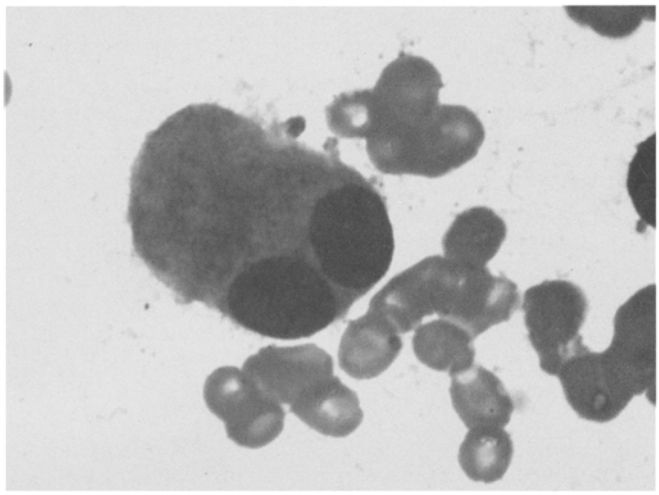


Fig. 17. Myelodysplastic Syndrome. A dysplastic megakaryocyte in MDS.

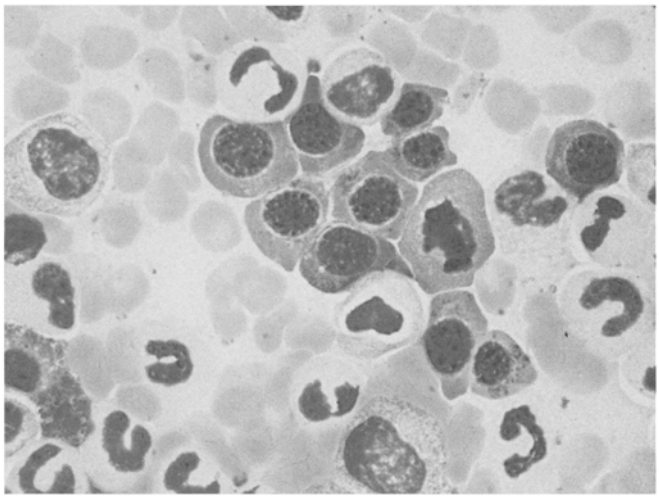


Fig. 18. Refractory Anemia with Ringed Sideroblasts. This iron stain illustrates several ringed sideroblasts in a case of RARS.

Clinical

- Accounts for 5–10% of cases of MDS
- Symptoms related to anemia, including fatigue and weakness

Diagnosis

- Peripheral Blood:
  - RBC are normocytic or slightly macrocytic
  - Anisocytosis and poikilocytosis may be present
- Aspirate Smear:
  - Usually have increased numbers of erythroid elements (ineffective erythropoiesis)
  - Dyserythropoiesis present
  - Blasts account for <5% of marrow cellularity
- Biopsy:
  - Often hypercellular due to increased ineffective erythropoiesis

Additional Studies

- Cytogenetics/Molecular: clonal abnormalities present in about 25% of cases including del(20q); +8; del/monosomy 5; del/monosomy 7

Differential Diagnosis

- Causes of anemia due to specific vitamin deficiencies (iron, B12, folate)
- Dyserythropoiesis from other causes including post-chemotherapy, medications, toxins, etc

Prognosis

- Progression to AML in approximately 5% of cases

Refractory Anemia with Ringed Sideroblasts (RARS)

Definition

- A myelodysplastic syndrome characterized by symptoms and morphologic changes limited primarily to the erythroid lineage, at least 15% ringed sideroblasts, and a relatively low rate of progression to AML

Clinical

- Similar to RA

Diagnosis

- Peripheral Blood:
  - Similar to RA
- Aspirate Smear:
  - The presence of ringed sideroblasts is primary to the diagnosis
  - Ringed sideroblasts are erythroid precursors with granules of stainable iron that surround at least 1/3 of nuclear circumference **(Figure 18)**
  - Iron stain shows at least 15% of erythroid precursors are ringed sideroblasts
  - Other features are the same as RA (see previous section)
- Biopsy:
  - Similar to RA
  - Rarely Prussian blue stain on core or clot section may reveal numerous ringed sideroblasts

Differential Diagnosis

- Other causes of ringed sideroblasts include: excessive alcohol intake, certain drugs (esp. anti-tubercular medications, chloramphenicol), excess of minerals (lead, copper, zinc) or rare inherited sideroblastic anemias

Prognosis

- Relatively good prognosis; only 1–2% of RARS eventually evolve into AML

Table 2. Cytogenetics in Myelodysplastic Syndromes

Relative Prognosis	*Cytogenetic Abnormalities*
Good	Normal, –Y, del(5q), del(20q)
Poor	Complex (>3 abnormalities), –7, or other abnormalities of chromosome 7
Intermediate	All other abnormalities

Refractory Cytopenia with Multilineage Dysplasia (RCMD)

Definition

- An MDS characterized by dysplasia of 2 or more cell lineages with bi- or pancytopenia

Clinical

- Accounts for 15% of cases of MDS

Diagnosis

- Peripheral Blood:
  - Less than 1% blasts
  - Monocytes $<1 \times 10^9$/L
  - Dysplastic features common in granulocytes; anisopoikilocytosis in RBC
- Aspirate Smear:
  - Less than 5% blasts
  - Dysplasia of myeloid, erythroid and megakaryocytic cell lines may be seen
  - Dysplastic changes are present in at least 10% of two cell lineages
  - If >15% ringed sideroblasts seen on iron stain, diagnosis would be "refractory cytopenia with multilineage dysplasia and ringed sideroblasts"
- Biopsy:
  - Hypercellular
  - Dysplastic features of megakaryocytes may be prominent

Additional Studies

- Cytogenetics/Molecular: karyotypic changes correlate with prognosis (*see* **Table 2**)

Prognosis

- Approximately 10% of cases progress to AML

Refractory Anemia with Excess Blasts (RAEB)

Definition

- MDS with dysplasia of multiple lineages and 5–19% blasts in bone marrow
- RAEB-1: 5–9% blasts in bone marrow, <5% blasts in PB
- RAEB-2: 16–19% blasts in bone marrow, 5–19% blasts in peripheral blood OR presence of Auer rods in cases with less than 20% blasts

Clinical

- Anemia

Diagnosis

- Peripheral Blood:
  - Dysplastic features common in granulocytes; anisopoikilocytosis in RBC
- Aspirate Smear:
  - Blasts increased
  - Multilineage dysplastic features common
- Biopsy:
  - Hypercellular
  - Dysplasia of megakaryocytes common
  - Blasts may be present in clusters, with ALIP formation

Additional Studies

- IHC: CD34 may be useful in identifying clusters of blasts
- Cytogenetics/Molecular: common karyotypic abnormalities include +8, monosomy /del(5q), monosomy/del(7), del(20q) (*see* **Table 2**)

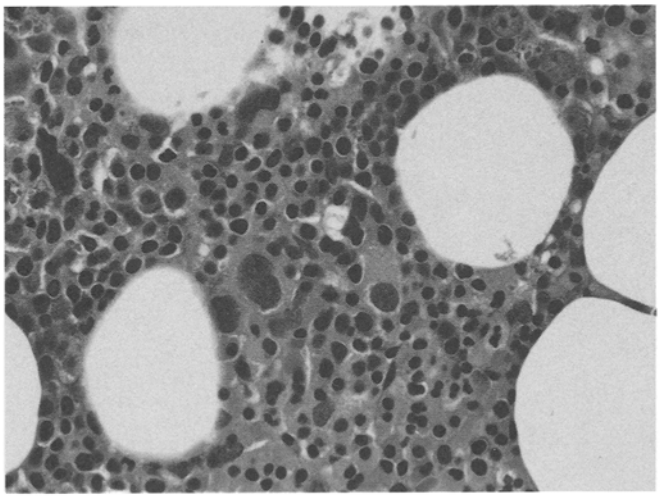


Fig. 19. 5q- Syndrome. Note the small, hypolobated megakaryocyte, which are common in this subtype of MDS.

5q- Syndrome (Figure 19)

Definition

- MDS associated with an isolated deletion of 5q, abnormal megakaryocytes, and a relatively good prognosis

Clinical

- Anemia common
- Occasionally thrombocytosis (unusual for an MDS which are most often associated with cytopenia)

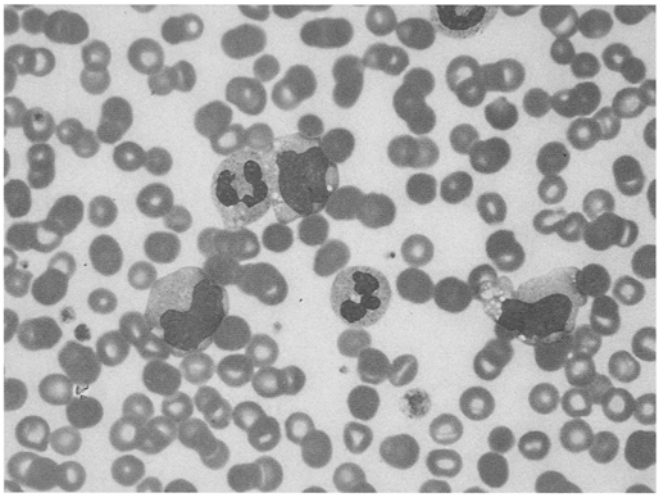


Fig. 20. Chronic Myelomonocytic Leukemia. Peripheral blood which shows increased monocytes and granulocytes.

Diagnosis

- Peripheral Blood:
  - Macrocytosis of RBC
  - Occasionally blasts may be seen (<5%)
  - Platelets normal or increased in number
- Aspirate Smear:
  - <5% blasts
  - Normal to increased numbers of megakaryocytes
  - Often have relatively small size and hypolobated/unilobate nuclei
- Biopsy:
  - Hypercellular
  - Increased numbers of hypolobated megakaryocytes that may be in clusters

Additional Studies

- Cytogenetics/Molecular: deletion of long arm of chromosome 5 involving bands q31-33. (If additional abnormalities are present, then case would be classified as another type of MDS)

MDS, unclassifiable (MDS,U)

Definition

- Similar to other MDS, but lacks features to make a diagnosis of a specific subtype

Clinical

- Similar to other MDS
- Cytopenias

Diagnosis

- Peripheral Blood:
  - No blasts are seen
- Aspirate Smear:
  - Lacks erythroid dysplasia (or consider a diagnosis of RA)
  - Dysplasia limited to neutrophils or megakaryocytes
- Biopsy:
  - Usually hypercellular
  - Megakaryocytic dysplasia may be prominent

Differential Diagnosis

- Typically a diagnosis of exclusion
- Must rule out other reactive conditions, MDS/MPD disorders, or specific types of MDS

MYELODYSPLASTIC/MYELOPROLIFERATIVE DISEASES

Chronic Myelomonocytic Leukemia (CMML) (Figure 20)

Definition

- A clonal stem cell disorder with a predominant proliferation of monocytic elements in the peripheral blood and bone marrow
- Features of dysplasia may be present or proliferative features without dysplasia may be seen
- CMML-1: blasts <5% in blood, <10% in marrow
- CMML-2: blasts 5–19% in blood or 10–19% in marrow

Clinical

- Monocytosis >1 × 10^9/L
- WBC often normal (~50% of patients)
- Fever, weight loss, fatigue, night sweats not uncommon
- Splenic enlargement is not uncommon

Diagnosis

- Peripheral Blood:
  - Monocytosis including immature forms (promonocytes) >10% of WBCs
  - May see dysgranulopoiesis (hypolobation, hypogranulation)
- Aspirate Smear:
  - Less than 20% blasts
  - Blast counts include myeloblasts, monoblasts and promonocytes
  - Monocytic elements may be difficult to appreciate by morphology—cytochemical stains (e.g. NSE) may be of benefit
  - Dyserythropoiesis (megaloblastoid changes, ringed sideroblasts, nuclear fragmentation, etc) may be seen in many cases

- Biopsy:
  - Hypercellular
  - Predominantly proliferation of granulocytic and monocytic elements, although monocytic elements may be difficult to appreciate
  - Dysplastic features may be seen in megakaryocytes
  - Fibrosis may be seen

Additional Studies

- FLOW: monocytic elements are positive for CD13, CD33, CD11b +/–, CD64 +/–, CD14 +/–; presence of CD34 or CD117 suggests immature cells
- IHC: CD34 may highlight blasts—clusters or >20% may suggest transformation to AML;
- Cytogenetics/Molecular: +8; –7/del(7q); 12p abnormalities; t(5;12)—CMML associated with eosinophilia

Differential Diagnosis

- CML—differentiated by cytogenetics
- AML of monocytic or myelomonocytic differentiation: blasts or blasts + promonocytes >20%

Treatment and Prognosis

- Progression to AML in 15–30% of cases

Atypical Chronic Myeloid Leukemia (aCML)

Definition

- Proliferative disorder of bone marrow elements, with a predominance of granulocytic forms in peripheral blood; lacks features of other MPDs or MDS, and lacks cytogenetic and molecular evidence *BCR1/ABL*

Clinical

- Anemia often present
- Splenomegaly common

Diagnosis

- Peripheral Blood:
  - WBC increased to varying degrees
  - Increased mature and immature neutrophils
  - Minimal absolute monocytosis account for <10% of total WBC
  - Basophilia should be minimal or absent
- Aspirate Smear:
  - Blasts <20%
  - Increased M:E ratio typical (often >10 : 1)
  - Dysgranulopoiesis common (including pseudo Pelger-Huet change, abnormal nuclear lobation, abnormal cytoplasmic granulation)
- Biopsy:
  - Hypercellular
  - Increased granulocytes and precursors
  - <20% blasts (or diagnose as AML)
  - Reticulin fibrosis may be present

Additional Studies

- FLOW/IHC: may show an increase in myeloid blasts
- Cytogenetics/Molecular: +8, del(20q), iso(17q), del(12p) can be found but are not specific for aCML

Differential Diagnosis

- CML: presence of *BCR1/ABL* translocation should differentiate CML from aCML
- MDS: typically have cytopenias rather than leukocytosis
- CMML: degree of monocytosis is critical for diagnosis of CMML

Treatment and Prognosis

- Prognosis is much worse compared to CML

Juvenile Myelomonocytic Leukemia

Definition

- Clonal hematopoietic disorder of children with proliferation of monocytes and granulocytes (lacking *BCR1/ABL*)
- Should have all major criteria (M) and at least two minor criteria (m) for diagnosis

Clinical

- May present with constitutional symptoms such as fever, pallor, weakness
- Often present as infection including bronchitis or tonsillitis
- Bleeding may be a presenting sign
- Leukemic infiltrates in tissues (esp. skin) can be seen

Diagnosis

- Peripheral Blood:
  - Monocytosis >1 × 10^9/L (M)
  - Hemoglobin F increased for age (m)
  - Immature granulocytes may be present in blood (m), but blasts <20%(M)
  - WBC count >10 × 10^9/L (m)
  - Anemia (often macrocytic) and thrombocytopenia common
  - Eosinophilia and basophilia may be seen
- Aspirate Smear:
  - Blasts (+ promonocytes) <20% (M)
  - Monocytes may be increased
  - Usually only minimal dyspoiesis
  - Cytochemical stains (NSE) may be useful in identifying monocytic elements

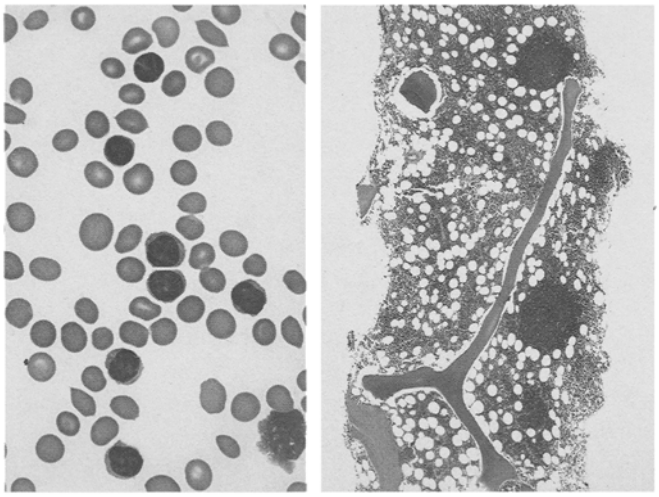


Fig. 21. Chronic Lymphocytic Leukemia. Peripheral blood in CLL (left) and nodular infiltration of bone marrow (right).

- Biopsy:
  - Hypercellular
  - Increased in granulocytic and monocytic elements
  - Megakaryocytes often decreased

Additional Studies

- Cytogenetics/Molecular: clonal chromosome abnormalities may be present including monosomy 7 (30–40%) (m); in vitro test shows myeloid progenitors hypersensitive to GM-CSF (m)

Differential Diagnosis

- CML: pediatric cases of CML exist but are rare. They do have *BCR1/ABL* translocation

Treatment and Prognosis

- Prognosis is poor, but better when patients are <1 year at time of presentation
- Bone marrow transplant is currently treatment of choice

MDS/MPD, unclassifiable

Definition

- A default diagnosis of a marrow disorder that shares features of both MDS and MPD, but lacks specific features for a diagnosis of a specific entity, such as CMML
- Refractory anemia with ringed sideroblasts and thrombocytosis is a provisional entity in the WHO classification. It is characterized by: persistent anemia, numerous ringed sideroblasts, dysplasia of granulocytic elements, marked thrombocytosis with abnormal-appearing platelets, +/– leukocytosis, +/– basophilia; because of its rarity, clinical behavior of this entity is uncertain

B-CELL LYMPHOPROLIFERATIVE DISORDERS

Chronic lymphocytic leukemia (CLL) (Figure 21)

Definition

- Neoplastic proliferation of predominantly small, mature-appearing B-cells that co-express CD5 and CD19; it is the blood and bone marrow counterpart to small lymphocytic lymphoma (SLL)
- >10% prolymphocytes, but <55% should be classified as "CLL with increased prolymphocytes" or CLL/PL, which has a more aggressive clinical course

Clinical

- Patients typically >50 years old
- Often asymptomatic but may have anemia, fatigue, infections or symptomatic splenomegaly

Diagnosis

- Peripheral Blood:
  - Clinical presentation is often isolated elevated WBC composed of small, mature lymphocytes
  - Lymphocytes may have characteristic clumped chromatin with "cracked earth" or "soccer ball" pattern
  - Lymphocytes are typically round with little cytoplasm, although rare cases may have irregular nuclear contours or, more rarely, plasmacytoid differentiation
  - Rare prolymphocytes (larger lymphocytes, with prominent single central nucleoli and increased amounts of amphophilic cytoplasm) are seen but usually number less than 10%
  - Smudge cells are often seen
- Aspirate Smear:
  - Increased number of small, round, mature-appearing lymphocytes are seen; variable numbers of prolymphocytes are also seen
- Biopsy:
  - Degree and pattern of lymphocytic infiltration varies
  - Infiltration may be nodular, interstitial or diffuse
  - Rarely, vague nodules, with increased large cells (pseudofollicles similar to those in lymph nodes) are seen

Additional Studies

- FLOW: CD5+, CD19+, CD20 (dim)+, CD23+, FMC7–, CD10–; CD38+ and ZAP-70+ cases may have a more aggressive clinical course

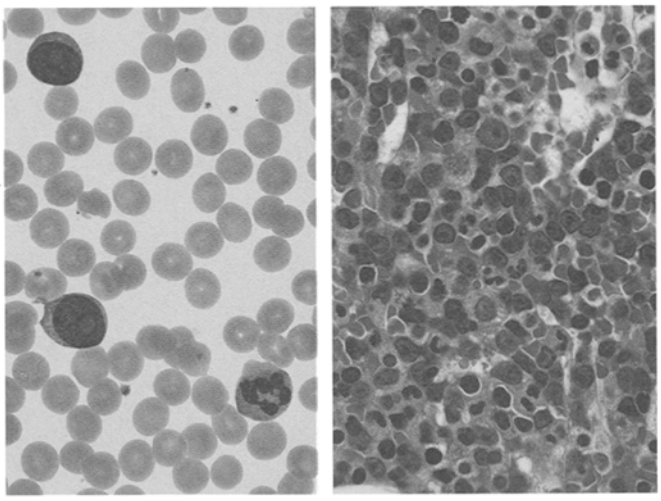


Fig. 22. B-Prolymphocytic Leukemia. Peripheral blood (left) showing two prolymphocytes (large size, prominent central nucleolus) and bone marrow infiltrated by B-PLL (right).

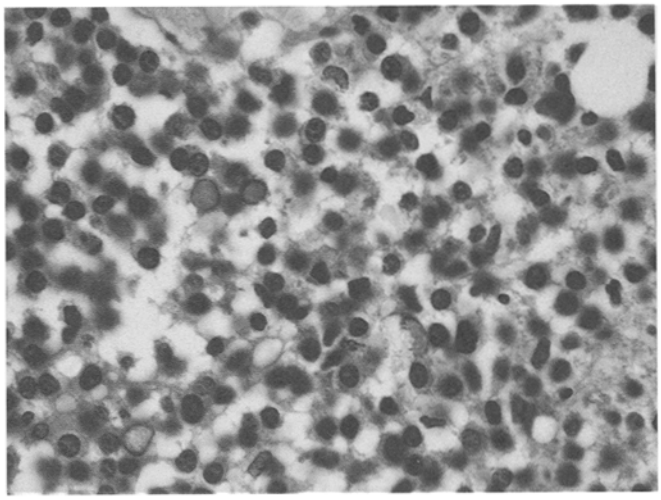


Fig. 23. Lymphoplasmacytic Lymphoma. Marrow infiltrated by LPL. A mixture of lymphocytes, plasma cells and lymphoplasmacytic cells are seen. Dutcher bodies (intranuclear immunoglobulin pseudoinclusions) can be seen.

- IHC: CD5+, CD20+, CD23+, CD43+, bcl2+, CD10–, cyclin D1–, bcl6–
- Cytogenetics/Molecular: trisomy 12 associated with a poor prognosis; unmutated IgH genes appear to have a worse prognosis

Differential Diagnosis

- Other 'small B-cell' lymphomas, including follicular lymphoma, marginal zone, mantle cell lymphoma and lymphoplasmacytic lymphoma

B-cell Prolymphocytic leukemia (B-PLL) (Figure 22)

Definition

- B-cell neoplasm consisting of predominantly prolymphocytes (>55% in blood); some cases are derived from pre-existing cases of CLL while other occur de novo

Clinical

- Patients present with high WBC, often $>100 \times 10^9$/L
- Splenomegaly is usually present

Diagnosis

- Peripheral Blood:
  - Numerous intermediate-large size lymphocytes, with mature chromatin, small-moderate amounts of amphophilic cytoplasm and a single, prominent, central nucleolus
- Aspirate Smear:
  - Cells similar to those in peripheral blood are seen
- Biopsy:
  - Typically hypercellular
  - Marrow infiltrated by population of intermediate-large size lymphocytes, many with prominent nucleoli
- Additional Studies
  - FLOW: CD5–/+, CD20+, sIg + (bright), FMC-7–/+, CD23+/–
  - IHC: CD5–/+, CD20+, sIg + (bright), FMC7–/+, CD23+/–, cyclin D1–

Differential Diagnosis

- Need to consider variants of mantle cell lymphoma with leukemic presentation; cyclin D1 stain is necessary to evaluate the possibility of mantle cell lymphoma
- CLL/PL: number of prolymphocytes in peripheral blood may be the only distinguishing criteria, making distinction from B-PLL occasionally difficult

Prognosis

- Poor prognosis

Lymphoplasmacytic lymphoma/leukemia (Figure 23)

Definition

- An indolent form of B-cell lymphoma composed of IgM secreting cells with lymphoid and plasmacytic features

Clinical

- Majority of patient have serum monoclonal protein
- Many patients have symptoms of hyperviscosity, termed Waldenstrom macroglobulinemia, caused by large amounts of serum monoclonal IgM protein
- Serum protein may result in autoimmune symptoms (hemolytic anemia, neuropathy, coagulopathy) or have cryoglobulin properties

Diagnosis

- Peripheral Blood:
  - Increased numbers of small lymphocytes, plasma cells and lymphoplasmacytoid cells are seen
  - Rouleaux formation may be severe due to paraprotein in blood
- Aspirate Smear:
  - Increased numbers of lymphocytes, lymphoplasmacytic cells, and plasma cells seen
  - Dutcher bodies (intranuclear Ig inclusions) and Russell bodies (intracytoplasmic Ig inclusions) not uncommon; inclusions often PAS positive
- Biopsy:
  - Nodular or interstitial infiltrates of lymphocytes, plasma cells

Additional Studies

- FLOW: CD19+, light chain restricted, CD5–, CD10–, CD23–, FMC7+
- IHC: CD20+, cyclin D1–, CD5–, CD10–
- Cytogenetics/Molecular: t(9;14) often present; *PAX-5* gene often overexpressed; IgH gene rearrangement often present

Differential Diagnosis

- Considered a diagnosis of exclusion; differential diagnoses include marginal zone lymphoma, CLL/SLL (with plasma cell differentiation), plasma cell dyscrasias

Marginal zone lymphoma (MZL)

Definition

- B-cell lymphoma, thought to be derived from marginal zone cells
- Different subtypes of MZL include splenic MZL (SMZL), nodal MZL (NMZL) and extranodal (MALT-type) MZL (EMZL)
- SMZL with peripheral blood involvement formerly known as 'splenic lymphoma with villous lymphocytes'

Clinical

- Degree of blood and bone marrow involvement varies with type; SMZL almost always has bone marrow +/- blood involvement; EMZL and NMZL, blood and bone marrow involvement is rare

Diagnosis

- Peripheral Blood:
  - Circulating abnormal lymphocytes, with increased amounts of cytoplasm, nuclear irregularities, plasmacytoid features or villous projections (SMZL) may be seen
- Aspirate Smear:
  - Varying numbers of abnormal lymphocytes including small mature forms, plasmacytoid lymphocytes, plasma cells, and larger transformed cells may be seen

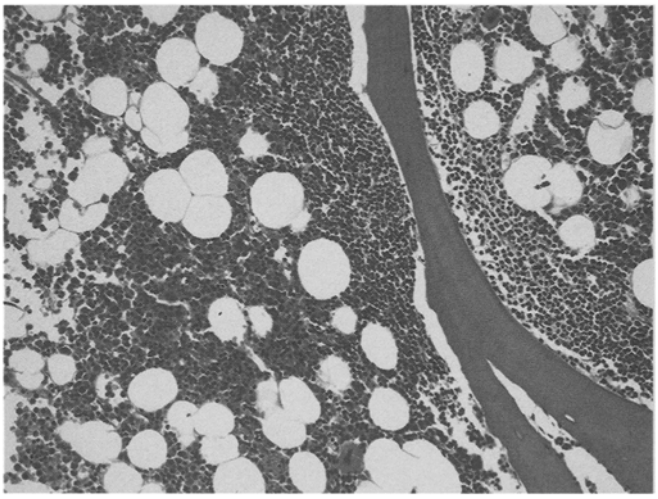


Fig. 24. Follicular Lymphoma. Classic paratrabecular lymphoid aggregate of follicular lymphoma in bone marrow biopsy.

- Biopsy:
  - Degree of involvement varies from subtle to extensive involvement
  - Pattern of involvement may be nodular, interstitial, diffuse; SMZL often has subtle intrasinusoidal infiltration (seen best by IHC)

Additional Studies

- FLOW: CD19+, CD20+, CD23+/–, CD5–, CD10–, FMC7+
- IHC: CD20+, CD10–, CD5–, bcl6–, cyclin D1–
- Cytogenetics/Molecular: IgH gene rearrangements often positive; allelic loss of 7p21-32; trisomy 3

Differential Diagnosis

- HCL
- FL
- Other "small cell" B-cell lymphomas

Follicular Lymphoma (Figure 24)

Definition

- A lymphoma derived from neoplastic follicle center cells with frequent marrow involvement (40%)

Clinical

- Low-grade follicular lymphomas (Grade 1 or 2) are typically indolent diseases with relentless growth. Grade 3 follicular lymphoma has a most aggressive clinical course and is more similar in behavior to diffuse large B-cell lymphoma. FL often presents in Stage IV

Diagnosis

- Peripheral Blood

- Significant numbers of circulating cells are seen in follicular lymphoma in about 10% of cases
- Morphology is typically small lymphocytes, with cleaved or notched nuclei

♦ Aspirate Smear
- Because of fibrosis, neoplastic lymphocytes may be rare or absent in aspirate smears
- Large clumps or aggregates of lymphocytes may be present in aspirate
- Cytology depends on grade, but is typically small to intermediate sized lymphocytes with irregular nuclei and scant cytoplasm

♦ Biopsy
- Cellularity varies; degree of involvement varies
- Lymphoid aggregates in FL are typically paratrabecular, hugging the contours of the bone
- Although typically small lymphocytes, large cells may be present
- Marrow may have discordant morphology compared to other sites of involvement; often marrow has low-grade appearance, with higher grade lymphoma at other site. Less often, marrow has higher-grade lymphoma (e.g., DLBCL) with low-grade in nodes

Additional Studies

♦ FLOW: because of fibrosis, flow cytometry may be negative. CD19+, CD20+, CD10+, light chain restricted, CD5–

♦ IHC: CD20 highlights B-cell aggregates, aggregates typically positive for bcl6 and CD10; bcl2 less specific, positive in most B-cell lymphomas; Cyclin D1-

♦ Cytogenetics/Molecular: t(14;18)(q32q21) *IgH/bcl-2*

Differential Diagnosis

♦ Paratrabecular aggregates are seen typically in FL, but are not specific for FL and can be seen in a number of other lymphoma types

Mantle Cell Lymphoma (MCL) (Figure 25)

Definition

♦ A neoplastic proliferation of typically small B-lymphocytes which overexpress the cyclin D1 gene product and express CD5

♦ Usually a tissue based disease, but peripheral blood and bone marrow involvement are not uncommon

♦ Blastoid variants have either: 1) blastic chromatin or 2) larger pleomorphic nuclei and are associated with a more aggressive clinical course

Clinical

♦ Typically seen in older, male patients

♦ Disseminated disease common at presentation

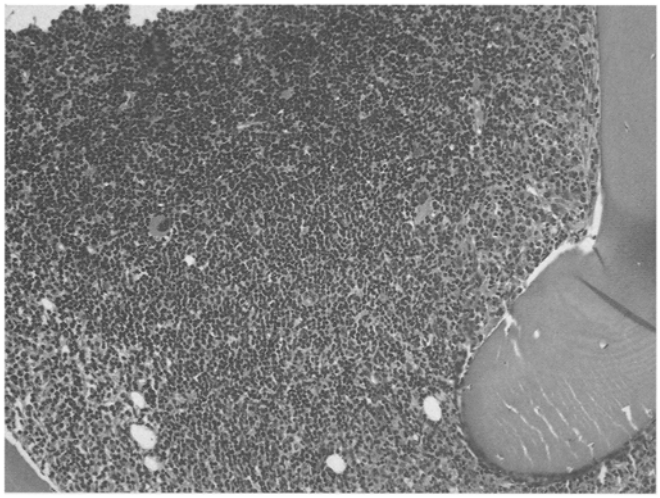


Fig. 25. Mantle Cell Lymphoma. Diffuse infiltration of bone marrow by MCL.

Diagnosis

♦ Peripheral Blood:
- Non-blastoid MCL lymphocytes in PB are small, with condensed mature chromatin and cleaved or notched nuclear contours and scant amounts of cytoplasm

♦ Aspirate Smear:
- Increased numbers of small lymphocytes with cleaved or irregular nuclei

♦ Biopsy:
- Infiltrates are nodular of diffuse, with varying degrees of involvement

Additional Studies

♦ FLOW: CD19+, CD5+, CD23–, light chain restricted (more often lambda), bright CD20 and sIg (compared to CLL/SLL with dim CD20 and sIg), FMC7+

♦ IHC: CD5+, CD20+, bcl-2+, CD43+, Cyclin D1+, CD10–, CD23–, bcl-6– (p53 often positive and Ki67 often increased in blastoid variant)

♦ Cytogenetics/Molecular: t(11;14); translocation of the *bcl-1* gene and the *IgH* gene leading to overexpression of cyclin D1, a cell cycle regulator

Hairy Cell Leukemia (Figure 26)

Definition

♦ An uncommon B-cell neoplasm that prominently involves spleen, bone marrow and peripheral blood with distinctive "hairy" appearance in peripheral blood

♦ Hairy cell variant has similar sites of involvement, but larger cells with prominent nucleoli, slightly different immunophenotype and a more aggressive clinical course

Clinical

♦ Usually indolent clinical behavior

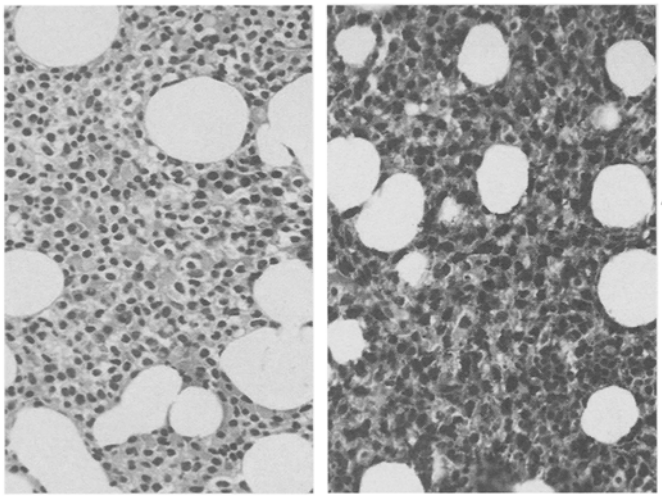


Fig. 26. Hairy Cell Leukemia. Bone marrow with "fried egg" appearance of HCL (left) and TRAP immunostain (right).

- Splenomegaly
- Present with symptoms related to marrow replacement (anemia) or symptoms associated with splenomegaly

Diagnosis

- Peripheral Blood:
  - Increased small-medium sized lymphocytes homogeneous, mature chromatin, inconspicuous nucleoli and characteristic 'hairy' cytoplasmic projections
  - Lymphocytes positive for tartrate-resistant acid phosphatase (TRAP), which is not seen in normal lymphocytes
  - Cytopenias common; monocytopenia most characteristic
- Aspirate Smear:
  - Often unavailable due to "dry tap"
  - Lymphocytes with round, centrally-placed nuclei, with moderate amounts of clear-to-pale cytoplasm
- Biopsy:
  - Variable degrees of infiltration by abnormal lymphocyte population
  - Almost invariably associated with severe reticulin fibrosis
  - Abnormal lymphocytes are often present in subtle interstitial infiltrates, with small, centrally-placed nuclei and moderate amounts of clear cytoplasm ("fried egg" appearance)

Additional Studies

- FLOW: CD19+, CD20+, CD11c+, CD22+, CD25+ and CD103+
- IHC: CD20+, DBA.44+, TRAP+, cyclin D1+/–
- Cytogenetics/Molecular: IgH rearrangements present

Treatment and Prognosis

- 2-chlorodeoxyadenosine (2-CDA) is an effective therapy
- Typically excellent prognosis with current therapies

Diffuse Large B-cell Lymphoma (DLBCL)

Definition

- A heterogeneous category inclusive of several malignancies of large B cells
- There are a variety of methods for subtyping such as cell derivation, immunophenotype, and distinctive clinical features
- DLBCL may be de novo or arise as a transformation of a low-grade B-cell lymphoma

Clinical

- Primary diagnosis rarely made in bone marrow
- Prognosis is dependent on stage

Diagnosis

- Peripheral Blood:
  - Rarely may have circulating large, atypical lymphoid cells
- Aspirate Smear:
  - Fibrosis often prevents DLBCL being present in aspirate
  - Touch preparation may be of benefit
  - Large lymphoid cells with immunoblastic features may be seen in some cases
- Biopsy:
  - Degree of marrow involvement varies
  - Cells are large in size, but may be intermixed with smaller lymphocytes (either reactive or low-grade component of lymphoma)
  - Distribution may be paratrabecular, interstitial or diffuse

Additional Studies

- FLOW: CD19/20+, light chain restricted (although occasionally no surface light chain expression), CD10+(40%), CD5+(10%)
- IHC: CD20+, other markers variable
- Cytogenetics/Molecular: abnormalities of 3q27; t(14;18), others; IgH rearrangements positive

T- AND NK-CELL LYMPHOPROLIFERATIVE DISORDERS

T-cell Prolymphocytic Leukemia (T-PLL) (Figure 27)

Definition

- Aggressive T-cell leukemia with prominent involvement of blood, bone marrow and spleen

Clinical

- Anemia and thrombocytopenia are common
- Splenomegaly always present, sometimes massive; may present with splenic infarct or rupture

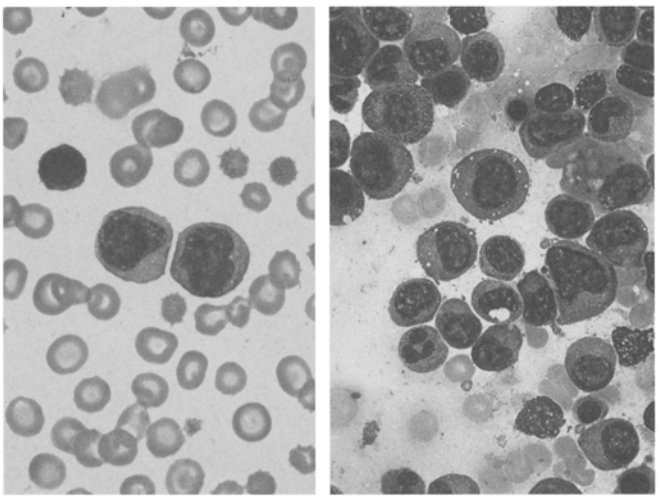


Fig. 27. T-Prolymphocytic Leukemia. Peripheral blood (left) and bone marrow aspirate (right) in T-PLL. Note differences from B-PLL (*see* Fig. 22).

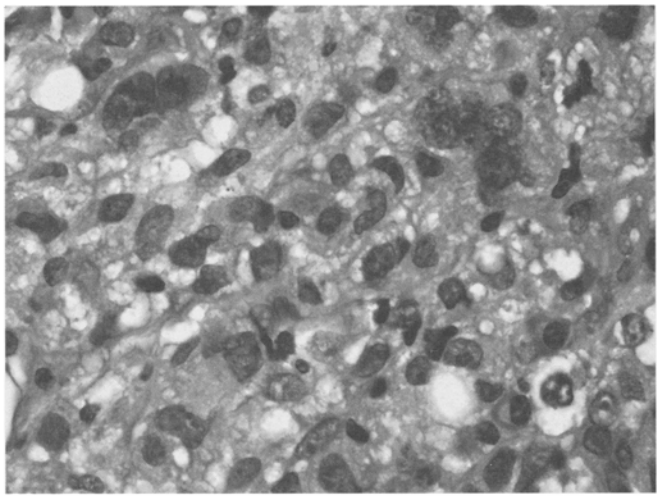


Fig. 28. Anaplastic Large Cell Lymphoma. Large, pleomorphic cells with multilobated nuclei infiltrating bone marrow.

- Cutaneous involvement not uncommon

Diagnosis

- Peripheral Blood:
  - Lymphocytes usually >100 × 10^9/L
  - Most often large sized lymphocytes, with single, prominent central nucleolus, round-to-irregular nuclear contours, condensed chromatin and a small-to-moderate amount of pale cytoplasm
- Aspirate Smear:
  - Typically a large population of uniform large-sized lymphocytes with mature chromatin, irregular nuclei, and prominent nucleoli
- Biopsy:
  - Often hypercellular
  - Interstitial or diffuse infiltrate of monotonous lymphoid cells

Additional Studies

- FLOW: CD3+, CD4+, CD8–, CD7+, CD56–; rarely CD4–/CD8+
- IHC: CD3+
- Cytogenetics/Molecular: TCR rearranged; inv 14(q11;q32) or t(14;14)(q11;q32); TCR alpha/beta loci

Differential Diagnosis

- T-cell CLL: controversial and not included as a separate entity in WHO classification

Anaplastic Large Cell Lymphoma (ALCL) (Figure 28)

Definition

- T-cell lymphoma with a wide spectrum of morphologic appearances, although most commonly consisting of large, pleomorphic cells which are, by definition, positive for CD30
- Two main types: ALK+ and ALK–

Clinical

- Marrow involved in 15–25% of cases

Diagnosis

- Peripheral Blood:
  - Leukemic forms rare; cells in blood typically large with irregular nuclei and may have blastic chromatin
- Aspirate Smear:
  - Unless extensive marrow involvement, tumor cells are only rarely seen in aspirate
- Biopsy:
  - Degree of involvement varies
  - Rare isolated tumor cells with extensive fibrosis may be present
  - Large clusters of lymphoma cells may be present
  - In small cell variant/leukemic forms, marrow may be diffusely involved with pleomorphic blast-like cells
  - Immunohistochemistry should be used in cases for staging, as marrow involvement may be subtle

Additional Studies

- FLOW: CD3+ (25%), CD4+, CD2+, CD7–, CD45 var.,
- IHC: CD30+, CD3+ (25%), CD45 +/–, TIA-1+; rare cases with "null" phenotype lack most hematopoietic markers, often positive for CD43
- Cytogenetics/Molecular: ALK+ will have t(2;5) *NPM/ALK*; or variants t(1;2), t(2;3), t(2;17), t(2;19) or other translocations involving *ALK* gene; clonal T-cell gene rearrangements in 90%

Differential Diagnosis

- Other T-cell lymphomas or Hodgkin lymphoma may have similar morphology

Treatment and Prognosis

- ALK+ cases have better prognosis (compared to ALK–) although leukemic forms have worse prognosis
- ALK– cases have poor prognosis similar to PTCL

Sezary Syndrome (SS)/Mycosis Fungoides (MF)

Definition

- Mycosis fungoides is a usually indolent, cutaneous neoplasm of T-cells
- Sezary syndrome is an advanced stage of MF, with systemic involvement including lymph nodes, blood and bone marrow, and an aggressive clinical course

Clinical

- SS occurs exclusively in adults
- Erythroderma common

Diagnosis

- Peripheral Blood:
  - Diagnostic criteria vary for SS, however, most agree that at least 1.0×10^9/L neoplastic lymphocytes are the minimum
  - Lymphocytes are often small with condensed chromatin and folded, cerebriform nuclei
  - Nuclear folds can be accentuated by using H&E or Pap stain on blood smear
- Aspirate Smear:
  - Increased numbers of small-medium sized lymphocytes with irregular nuclear contours
- Biopsy:
  - Hyper- or normocellular
  - Diffuse interstitial or nodular aggregates of lymphocytes

Additional Studies

- FLOW: preferred method for evaluating PB involvement in SS; CD4+, CD3+, CD2+, CD7–
- IHC: CD3
- Cytogenetics/Molecular: clonal rearrangement of T-cell receptor

Differential Diagnosis

- Infiltration of bone marrow by other T-cell lymphomas

Treatment and Prognosis

- Aggressive disease with poor (10–20%) five-year survival
- Transformation to large T-cell lymphoma has an especially grave prognosis

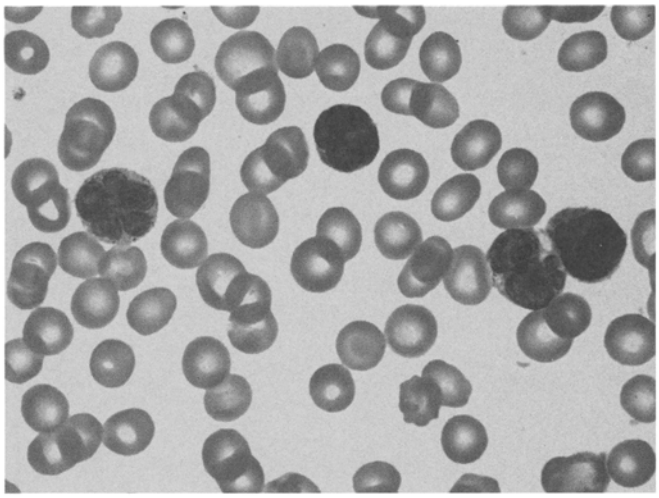


Fig. 29. Adult T-cell Leukemia/Lymphoma. This peripheral blood illustrates the classic "flower-like" appearance of lymphocytes in ATLL.

Adult T-cell Leukemia/Lymphoma (ATLL) (Figure 29)

Definition

- T-cell lymphoid proliferation associated with the HTLV-1 virus
- Variant based on clinical presentation include: acute; lymphomatous; chronic; smoldering

Clinical

- Associated with infection by HTLV-1
- Patients often from Japan, Caribbean or Central Africa
- Median age 55 years
- M : F = 1.5 : 1
- Hypercalcemia common (~70%)
- Lytic bone lesions and skin lesions common
- All patients present with disseminated disease
- Frequent opportunistic infections due to T-cell immunodeficiency

Diagnosis

- Peripheral Blood:
  - Medium to large-sized lymphocytes with mature, clumped chromatin
  - Lymphocyte nucleus have a characteristic polylobated or "flower" shape,
  - Rare cells are more blast-like
- Aspirate Smear:
  - Similar cells as peripheral blood, but marrow involvement may be less numerous than expected from blood involvement
  - Marrow involvement may be subtle

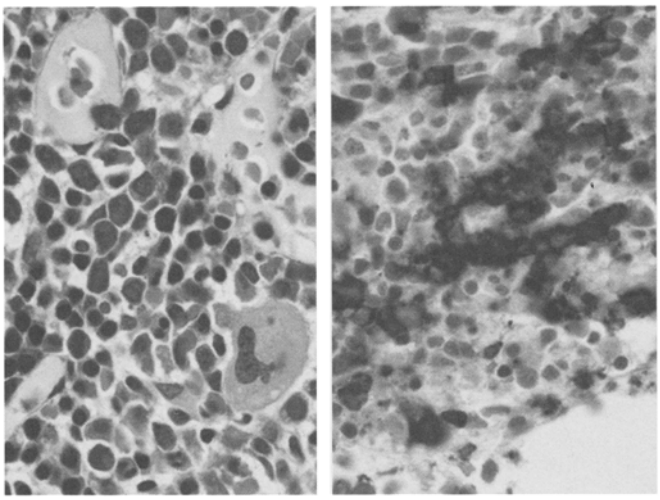


Fig. 30. Hepatosplenic T-cell Lymphoma. Bone marrow shows infiltration by abnormal lymphocytes (left), with an intrasinusoidal distribution, illustrated by CD2 stain (right).

- Biopsy:
  - Infiltrates vary in amount and may be subtle
  - Composed of small to intermediate sized lymphocytes with some nuclear pleomorphism
  - Bone changes, including prominent osteoblasts may be seen

Additional Studies

- FLOW: CD3+, CD2+, CD5+, CD4+, CD7–, CD8–
- IHC: CD3 may be necessary to appreciate subtle infiltrates in bone marrow
- Cytogenetics/Molecular: T-cell receptor rearranged; HTLV-1 present in all cases

Differential Diagnosis

- Other T-cell lymphoid proliferations with leukemic involvement

Treatment and Prognosis

- Depends on clinical variant
- Leukemic and lymphomatous variants tend to have a poor prognosis

Hepatosplenic T-cell lymphoma (Figure 30)

Definition

- Neoplasm of T-cells that characteristically affects spleen, liver and bone marrow
- Often have surface expression of gamma/delta T-cell receptor, which normally accounts for only a very small percentage of T-cells

Clinical

- Most commonly in adolescent and young adult males
- Increased in incidence in post-transplant setting
- Spleen and liver involvement are always present. Spleen often shows characteristic intrasinusoidal/red pulp pattern of involvement

Diagnosis

- Peripheral Blood:
  - Typically small to intermediate sized lymphocytes with mature-appearing chromatin, irregular nuclei and small amounts of chromatin
  - Rarely, more blastic-appearing with less condensed chromatin and larger size
- Aspirate Smear:
  - Increased numbers of atypical lymphocytes
- Biopsy:
  - Typically hypercellular
  - Prominent infiltrates of neoplastic lymphocytes
  - Intrasinusoidal distribution of lymphocytes typical in this disease
  - Infiltration may be subtle on H&E sections; immunohistochemistry is important to identify degree of infiltration

Additional Studies

- FLOW: CD3+, CD56+/–, typically CD4-/CD8–. Most cases express surface gamma/delta T-cell receptor, rare cases are alpha/beta
- IHC: CD3+, CD56+/–, CD4–, CD8–, CD5–, TIA-1+
- Cytogenetics/Molecular: Isochromosome 7q is found in all cases; clonal rearrangement of T-cell receptor

Differential Diagnosis

- Other T-cell leukemias/lymphomas
- Leukemia forms of NK malignancies—cytogenetics and clinical findings should differentiate

Prognosis

- Aggressive disease with poor prognosis
- Median survival <2 years

Large Granular Lymphocytic Leukemias (Figure 31)

Definition

- A proliferation of cytotoxic T lymphocytes (85% of cases), or more rarely NK cells
- In many cases, these proliferations are non-neoplastic and associated with autoimmune diseases such as rheumatoid arthritis
- Occasionally, these proliferations are neoplastic

Clinical

- There is a strong association with autoimmune disease, such as: Felty syndrome, rheumatoid arthritis, Sjogren syndrome, SLE

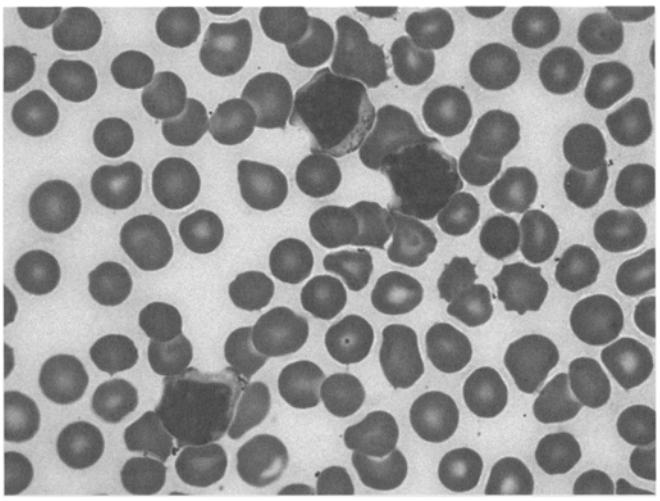


Fig. 31. Large Granular Lymphocytic Leukemia. Several abnormal lymphocytes, some with obvious cytoplasmic granules in the peripheral blood in a case of LGL leukemia.

Diagnosis

- Peripheral Blood:
  - Review of the peripheral blood often reveals neutropenia
  - Incrasedlarge granular lymphocytes
  - If less than 2.0×10^9/L, the diagnosis requires confirmation of clonality by molecular techniques
- Aspirate Smear:
  - May see increased small-medium sized lymphocytes with irregular nuclear contours +/– cytoplasmic granules
- Biopsy:
  - Often hypercellular
  - Interstitial infiltrates, with occasional aggregates of small-medium sized lymphocytes

Additional Studies

- FLOW: pan-T-cell markers (CD2, CD3, CD5, CD7) may be present; CD56 usually negative
- IHC: Lymphocytes may be positive for CD3, CD8, cytotoxic markers (e.g. TIA-1), CD57
- Cytogenetics/Molecular: clonal T-cell receptor gene rearrangements in CD8-positive LGL disease; NK-types do not have clonal rearrangements of the T-cell receptor; clonality can be assessed by X-linked gene analysis or cytogenetics

Differential Diagnosis

- Other T-cell lymphomas including mycosis fungoides, hepatosplenic T-cell lymphoma and other T-cell lymphomas

Other types of T-cell Lymphoma (PTCL, AILT, etc)

Definition

- Marrow or blood involvement by T-cell lymphomas occurs in high stage disease
- Marrow involvement common in angioimmunoblastic T-cell lymphoma

Diagnosis

- Peripheral Blood:
  - Variable involvement
  - Atypical lymphocytes may be present
- Aspirate Smear:
  - Variable degrees of atypical lymphocytes
- Biopsy:
  - Involvement may be nodular, interstitial of diffuse
  - May be associated with significant fibrosis
  - Neoplastic T-cells may also be seen associated with infiltrates including plasma cells, eosinophils or macrophages

Additional Studies

- FLOW: CD3+, other T-cell markers variable
- IHC: CD3+, variable positivity for other T-cell markers
- Cytogenetics/Molecular: TCR rearranged

Differential Diagnosis

- Primary diagnosis of T-cell lymphoma in marrow can be difficult; correlation with a diagnostic tissue biopsy is recommended

Prognosis

- Most T-cell lymphomas are aggressive and have a poor prognosis; marrow involvement usually implies high-stage disease

Natural Killer (NK) Leukemias and Lymphomas

Definition

- Two WHO entities are encompassed under this heading, Aggressive NK leukemia and Blastic NK lymphoma
- Distinct clinical entity, CD4+CD56+ hematodermic malignancy, which presents with both skin and bone marrow involvement, is probably derived from the dendritic cell precursors (plasmacytoid monocytes) and shares some clinical and immunophenotypic features with NK neoplasms

Clinical

- Typically very poor prognosis, with poor response to standard therapies

Diagnosis

- Peripheral Blood:
  - Blastic cells in peripheral blood
  - Rarely fine cytoplasmic granules identified
- Aspirate Smear:
  - Blastic cells present in smears, but can be difficult to positively identify

- Biopsy:
  - Infiltration of marrow can be focal or diffuse

Additional Studies

- FLOW: all entities lack surface CD3 expression, CD56+
- IHC: CD43+, CD56+, often CD3 (cytoplasmic) positive
- Cytogenetics/Molecular: no clonal rearrangements of TCR

Differential Diagnosis

- Other blastic malignancies, such as AML or ALL
- Other T-cell lymphomas

Prognosis

- Typically aggressive diseases with poor prognosis

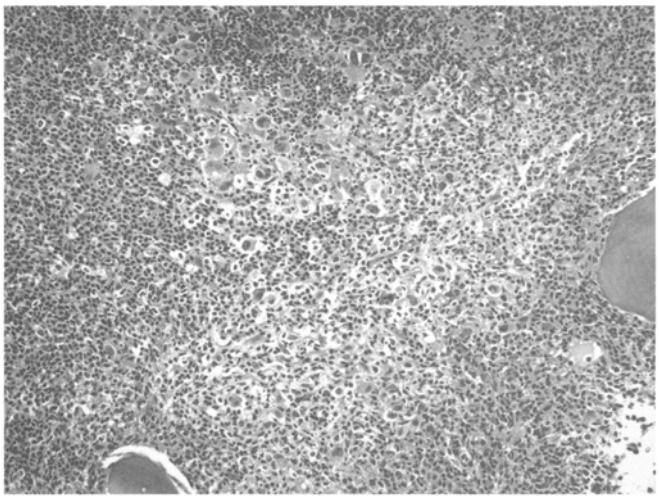


Fig. 32. Classical Hodgkin Lymphoma. Bone marrow involvement by CHL, with several Hodgkin and Reed-Sternberg cells.

HODGKIN LYMPHOMA

Classical Hodgkin lymphoma (CHL) (Figure 32)

Definition

- A malignancy of 'crippled' B-cells which produce large characteristic malignant cells, Reed-Sternberg (R-S) and Hodgkin cells and a characteristic background tissue reaction

Clinical

- Patients may have "B" symptoms; fever, night sweats, weight loss
- Marrow involvement implies Stage IV disease

Diagnosis

- Peripheral Blood:
  - PB involvement is almost never seen in CHL
- Aspirate Smear:
  - Because of associated fibrosis, little or no evidence of CHL is present in aspirate smears
  - Touch preparations may show Hodgkin or R-S cells
- Biopsy:
  - Degree of involvement is variable
  - Identification of fibrotic background with classic Hodgkin or R-S cells is diagnostic, although immunohistochemical confirmation is prudent
  - Presence of fibrosis without atypical large cells, necrosis, granulomas, or cellular background (histiocytes, eosinophils, plasma cells) without classic R-S cells should be considered suspicious for involvement by CHL

Additional Studies

- IHC: CD30 useful in identifying R-S cells, CD15/CD45 may be less helpful because of staining of background marrow elements

Differential Diagnosis

- Microscopic differential includes other neoplasms with rare, large malignant cells with a polymorphous background including: T-cell/histiocyte-rich B cell lymphoma, anaplastic large cell lymphoma and others

Treatment and Prognosis

- Prognosis is related to stage; marrow involvement usually implies higher stage disease

Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL)

Definition

- A neoplasm of rare, large, atypical B-cells, with a characteristic background composed of small lymphocytes
- The neoplastic cells are large and share some features with Hodgkin and R-S cells, but NLPHL is distinct disease from classical Hodgkin lymphoma
- Marrow involvement is very rare

Diagnosis

- Peripheral Blood:
  - PB involvement never seen
- Aspirate Smear:
  - Because of fibrosis, aspirate smear is usually uninformative
- Biopsy:
  - Findings similar to CHL
  - Fibrotic foci with large atypical cells
  - Immunohistochemistry helpful to confirm phenotype

Additional Studies

- IHC: Large atypical cells are CD20+, CD45+, CD30-, CD15-

Differential Diagnosis

- Differential includes classical Hodgkin lymphoma and other B-cell lymphomas such as T-cell rich DLBCL

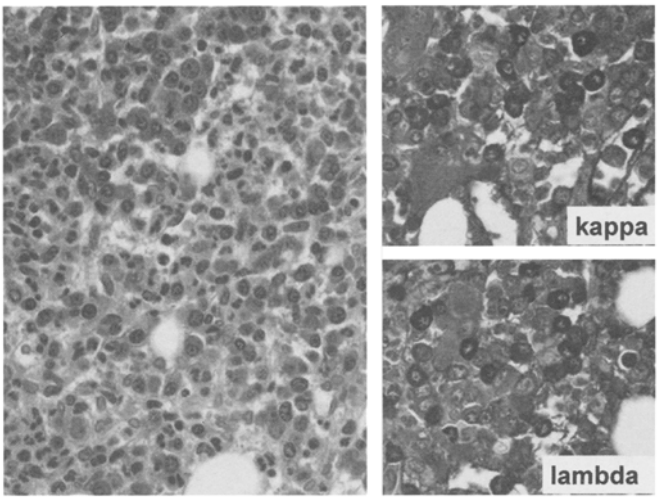


Fig. 33. Plasmacytosis. Polyclonal plasmacytosis in a patient with hepatitis.

PLASMA CELL DISORDERS

Reactive Plasmacytosis (Figure 33)

Definition

- Increases in benign bone marrow plasma cells that may simulate a neoplasm of plasma cells; rarely plasma cells may increase to 20% or higher in reactive conditions, simulating myeloma

Clinical

- Common associations include: alcoholism, autoimmune diseases, viral infections (esp. hepatitis viruses, HIV/AIDS), immune deficiency states, drugs

Diagnosis

- Although increased in number, plasma cells are cytologically mature
- Reactive plasma cells are polyclonal by kappa/lambda light chain analysis
- Patients do not have a monoclonal protein (M-protein) in serum or urine

Plasma Cell Myeloma (PCM) (Figure 34,35)

Definition

- Neoplastic proliferation of plasma cells

Clinical

- Twice as common in blacks as whites
- Common features include: anemia, bone pain, renal failure, neurologic symptoms
- Laboratory: presence of monoclonal immunoglobulin protein in serum (90%) or urine (75%)
- Monoclonal protein detectable by protein electrophoresis, immunolelectrophoresis, immunofixation
- Isotypes are variable: IgG (55%), IgA (22%), light chain only (18%), IgD (2%), IgE (<1%), IgM (<1%)
- Radiologic evidence of lytic lesions common
- Increased B2-microglobulin, hypercalcemia

Diagnosis

- Peripheral Blood:
  - Rouleaux may be present due to increased levels of serum immunoglobulin
- Aspirate Smear:
  - Plasma cells typically easily identified on Wright-Giemsa stained aspirates
  - Plasmacytic myeloma has predominance of mature plasma cells with eccentric round nuclei with condensed chromatin, and deep blue cytoplasm with a pale perinuclear hof
  - Immature morphology includes features such as prominent nucleoli, large nuclear size, central-placement of nuclei
  - Plasmablastic morphology is characterized by blastic chromatin with prominent nucleolus, small amounts of deep blue cytoplasm and large size; plasmablasts can be easily confused with erythroblasts
  - Anaplastic morphology includes wide variations in size, nuclear shape and cytologic detail of plasma cells; may be difficult to differentiate from carcinoma, melanoma, etc
- Biopsy:
  - Cellularity depends on degree of involvement

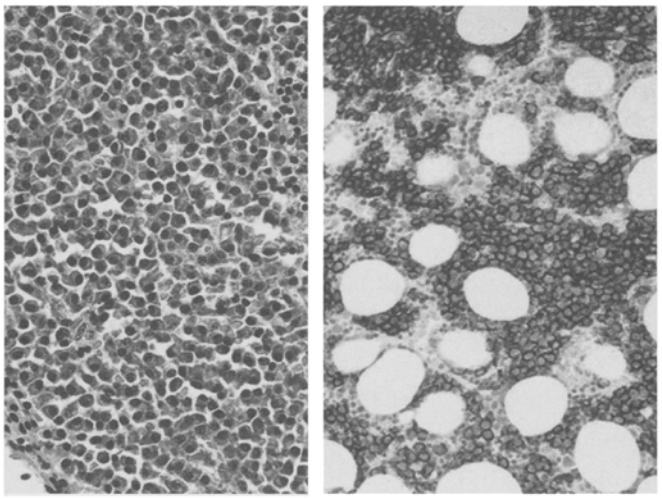


Fig. 34. Plasma Cell Myeloma. Marrow replacement by myeloma (left) and a CD138 stain, highlight plasma cells (right).

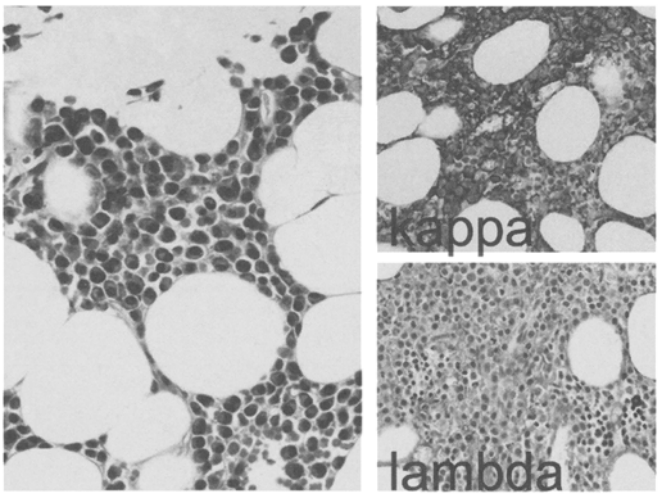


Fig. 35. Plasma Cell Myeloma. Marrow involvement may be patchy in myeloma (left); light chain stains may show clear evidence of monoclonality (right).

- Involvement may be patchy
- Plasma cells are often present in sheets and clusters
- Thin bone trabeculae, increased osteoblasts and osteoclasts may be seen

Additional Studies

- IHC: stains to identify/quantify plasma cells include CD138, VS38. Kappa and lambda light chains may be used to prove clonal nature of plasma cells. Ki67, p53, cyclin D1, CD117 may provide additional prognostic information in myeloma
- Cytogenetics/Molecular: complex karyotypes common; losses/del of 13q14 common

Differential Diagnosis

- Reactive plasmacytosis; MGUS; other lymphoproliferative disorders with plasma cell differentiation

Treatment and Prognosis

- Plasmablastic morphology (>2% plasmablasts) has been associated with a decidedly worse prognosis

Monoclonal Gammopathy of Undetermined Significance (MGUS)

Definition

- Clinical entity with production of a monoclonal serum protein (IgG in 75% of cases) without evidence of myeloma or other systemic lymphoproliferative disorder

Clinical

- Incidence increases with age; rare before age 50
- 25–30% of patients eventually develop myeloma, amyloidosis or other lymphoproliferative disorders
- Latency between MGUS and development of other disorders may be 10 years or more

Diagnosis

- Peripheral Blood:
  - No specific findings
- Aspirate Smear:
  - <10% plasma cells
  - Plasma cells are morphologically mature
- Biopsy:
  - Plasma cell infiltrates are usually small and scattered

Additional Studies

- IHC: CD138 or VS38c may be useful to enumerate plasma cells; kappa/lambda may show polyclonal or monoclonal plasma cells

Primary Amyloidosis (Figure 36)

Definition

- Primary amyloidosis is a disorder of abnormal deposition of monoclonal immunoglobulin protein in various tissues

Clinical

- Organ, vascular or coagulation dysfunction may be present due to amyloid deposition

Diagnosis

- Peripheral Blood:
  - Typically no significant PB findings
- Aspirate Smear:
  - In aspirate, amyloid may appear as waxy, homogeneous nodules
  - Plasma cells may be seen, but often in surprisingly low numbers

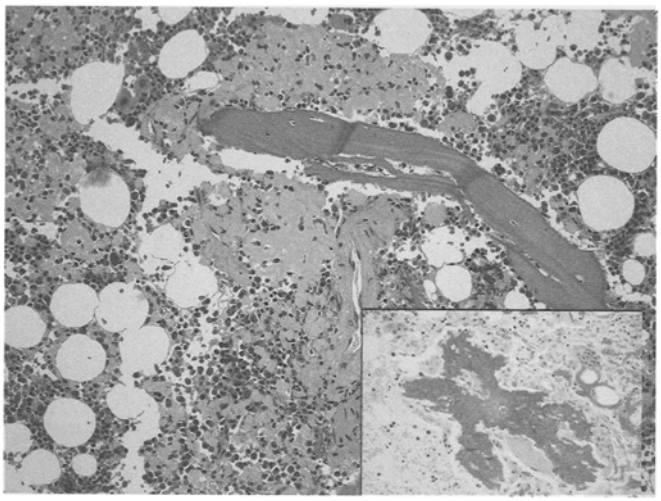


Fig. 36. Amyloidosis. Amyloid deposition in marrow, as an acellular, pink material. Inset. positive Congo Red stain.

- Biopsy:
  - Amyloid deposition is seen most often in walls of vessels, later in interstitial spaces
  - Amyloid appears as glassy, homogenous pink material on H&E
  - Congo red stains amyloid brick red, which shows characteristic apple-green birefringence on polarization

Additional Studies

- IHC: Plasma cells may be highlighted by CD38, CD138, VS38c; plasma cells are monoclonal for kappa or lambda

Plasma Cell Leukemia

Definition

- Rare manifestation of plasma cell malignancy associated with circulating neoplastic plasma cells and dismal prognosis

Clinical

- Occurs in about 2% of cases of PCM
- More frequent in light chain, IgE and IgD myeloma

Diagnosis

- Peripheral Blood:
  - Circulating plasma cells of at least 2×10^9/L
- Aspirate Smear/Biopsy:
  - Findings similar to plasma cell myeloma

Additional Studies

- Findings similar to plasma cell myeloma

Treatment and Prognosis

- Dismal prognosis, often a pre-terminal event in evolution of myeloma

HISTIOCYTIC AND MACROPHAGE DISORDERS

Langerhans Cell Histiocytosis (LCH) (Figure 37)

Definition

- Clonal proliferation of antigen-presenting type cell with a characteristic cellular background.

Clinical

- Variants are based on degree of involvement
- Unifocal disease (solitary eosinophilic granuloma)
- Multifocal, unisystem disease (Hand-Schuller-Christian disease)
- Multifocal, multisystem disease (Letterer-Siwe disease)
- Disease associations include Hodgkin and other lymphomas

Diagnosis

- Aspirate Smear:
  - May not be appreciated due to marrow fibrosis
  - Langerhans cells are macrophages with folded nuclei and moderate amounts of pale cytoplasm
  - Eosinophils may be increased
- Biopsy:
  - Nodules of pale, macrophages with associated eosinophils

Additional Studies

- IHC: S100+, CD1a+, CD68 +/–, CD45 +/–, lysozyme +/–
- Additional studies: Birbeck granules (characteristic pentilaminar lysosomes) are present by EM

Differential Diagnosis

- Involvement by Hodgkin lymphoma, histiocytic disorders, T-cell lymphomas

Treatment and Prognosis

- Excellent survival with limited involvement
- Worse prognosis with multisystem disease

Hemophagocytic Syndrome (HPS) (Figure 38)

Definition

- Ingestion of hematopoietic elements by macrophages, secondary to a variety of causes

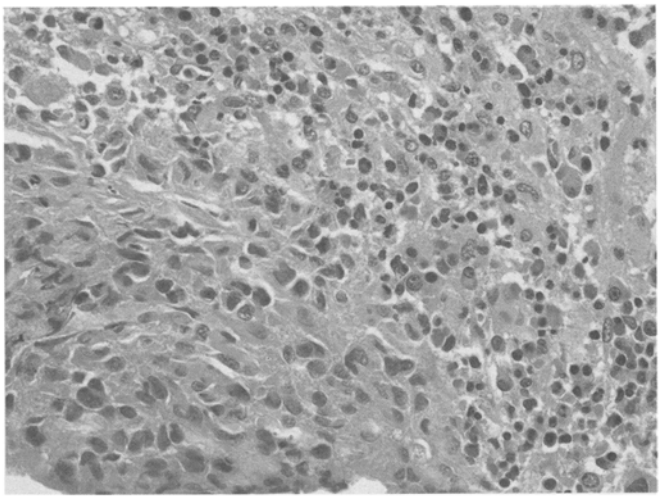


Fig. 37. Langerhans Cell Hsitiocytosis. Marrow infiltration by LCH, with pale pink histiocytes, some with grooved nuclei, and associated eosinophils.

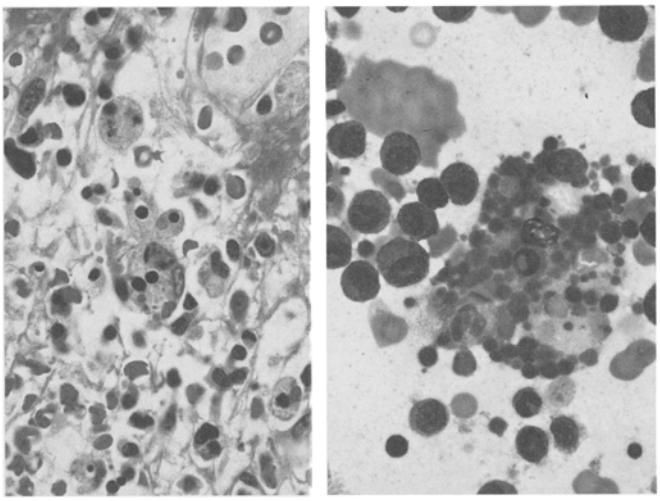


Fig. 38. Hemopahgocytic Syndrome. Marrow core (left) and aspirate (right) showing hemophagocytosis.

- Etiologies including congenital disorders, infection-associated and those associated with other malignancies, especially T-cell lymphomas

Clinical

- Often patients are very ill due to profound cytopenias
- Bone marrow is also a prominent site of involvement of these disorders
- Splenic involvement and enlargement is common

Diagnosis

- Peripheral Blood:
  - Atypical lymphocytosis may be present if infection-related or lymphoid malignancy

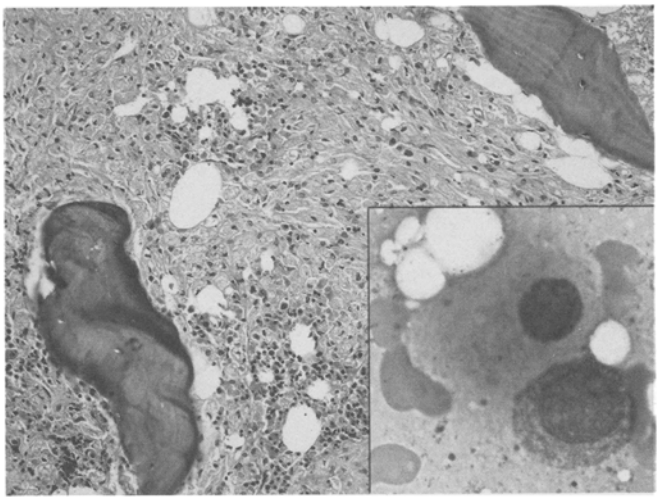


Fig. 39. Storage Disease. Gaucher disease, with numerous large, pink macrophages. Inset: Aspirate smear shows macrophage with pale blue color and "folded tissue paper" appearance in cytoplasm.

- Aspirate Smear/Core Biopsy:
  - Macrophages with ingested blood elements numerous
  - Erythrophagocytosis most common, but all marrow components can be seen in macrophages
  - Clusters of macrophages may be seen
  - In cases of T-cell lymphoma-associated HPS, infiltrate of cytologically abnormal T-cells may be appreciated

Additional Studies

- IHC: EBV by in situ hybridization or immunohistochemical stain may be positive in infection associated cases

Molecular: familial form may have perforin gene defects

Storage Diseases

Definition

- Abnormal products accumulate due to inherited biochemical abnormalities (e.g., Gaucher, Niemann-Pick, ceroid histiocytosis, mucopolysaccharidoses, etc.)

Diagnosis Depends on type of accumulated product

  - In Gaucher disease, the classic 'folded tissue paper' appearance is seen **(Figure 39)**
  - In Niemann-Pick, macrophages will appear to have numerous small vacuoles

Additional Studies

- Positive staining for PAS diastase-resistant material can be seen in many storage disorders

Differential Diagnosis

- Deposition of material in macrophages can also be seen in several infectious disorders including *Mycobacterium avium-intracellulare*, fungal infections, etc

METASTASES

Metastatic Disease (Figure 40)

Definition

- Metastatic tumors from a variety of sites involving the bone marrow

Clinical

- Prognosis depends on the type of tumor
- Metastases to the marrow are not uncommon

Diagnosis

- Peripheral Blood:
  - Exceedingly rare, presence of circulating malignant non-hematopoietic cells termed "carcinocythemia"
- Aspirate:
  - Often inaspirable due to associated marrow fibrosis
  - Touch preparations may shows clumps and aggregates of tumor cells
- Biopsy:
  - Metastatic disease often replaces marrow cellularity in a haphazard, pushing manner
  - Severe, marrow fibrosis common
  - Tumors may appear similar to primary site, but often appear less differentiated in marrow

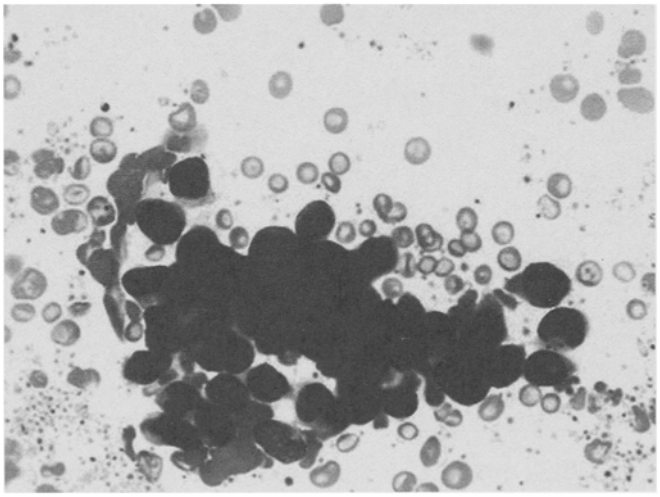


Fig. 40. Mestastic Disease. Cluster of breast carcinoma cells seen in bone marrow aspirate.

INFECTIONS

- Definition: A variety of infectious organisms may affect the bone marrow. Several of these are discussed briefly below
- Tuberculosis: Marrow involvement in disseminated disease, characteristic granulomas, +/– caseation, AFB stain rare organisms
- *Mycobacterium avuim-intracellulare*: Not uncommon in HIV/AIDS patients with focal or diffuse increase in plump histiocytes filled with granular material that stain positively for AFB and PAS (may mimic a storage disease) **(Figure 41)**
- Leishmaniasis: Marrow involvement not uncommon in systemic form; organisms can be seen in macrophages, especially in aspirate smear **(Figure 42)**
- HIV/AIDS: Marrow pathology dependent on stage of disease **(Figure 43)**; common changes include:
  - Hypercellularity
  - Lymphoid aggregates, often with atypical lymphocytes
  - Plasmacytosis
  - Dyserythropoiesis, including megaloblastoid changes
  - Megakaryocyte abnormalities including increased numbers, naked megakaryocyte nuclei, abnormally large megakaryocytes
  - Granulomas or histiocytic aggregates
  - Opportunistic infections including fungal, viral, parasitic/protozoal, etc
  - Increased incidence of neoplasia including high grade lymphoma (Burkitt), Hodgkin lymphoma, Kaposi sarcoma, etc
- Fungi (including Histoplasmosis, Blastomycosis, Coccidioidomycosis): granulomas +/– caseation are present; organisms may be common or difficult to find; GMS and PAS stains may be of benefit
- Parvovirus B19: viral infection seen predominantly in young or immunosuppressed patients leading to severe anemias due to red cell aplasia. Characteristic nuclear viral inclusions may be seen **(Figure 44)**

ANEMIAS

Iron Deficiency Anemia

Clinical

- Iron/ferritin studies helpful in diagnosis

Diagnosis

- Peripheral Blood:
  - Often microcytic, hypochromic anemia

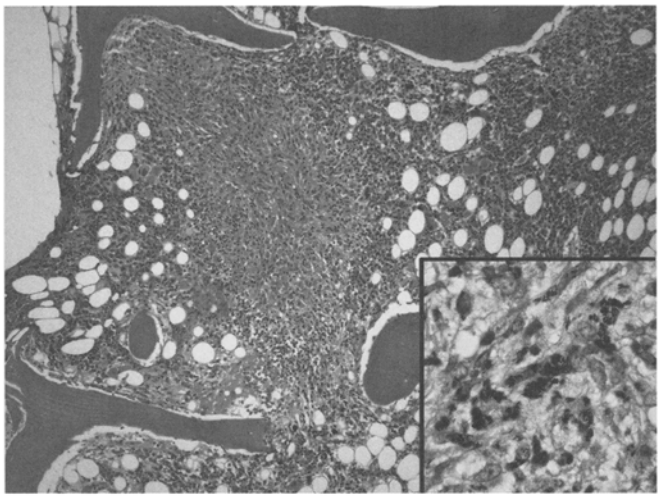


Fig. 41. Mycobacterium avium-intracellulare. Bone marrow infiltration showing granulomas composed of macrophages filled with M.a.-i. Inset: AFB stain.

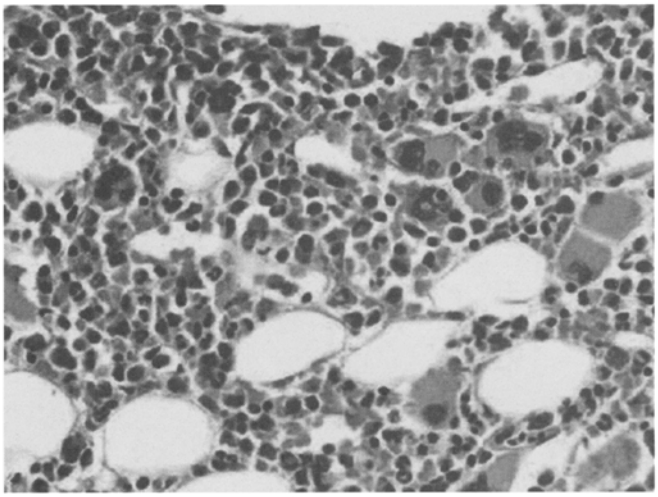


Fig. 43. HIV. Bone marrow of HIV patient, which is hypercellular, with increased megakaryocytes.

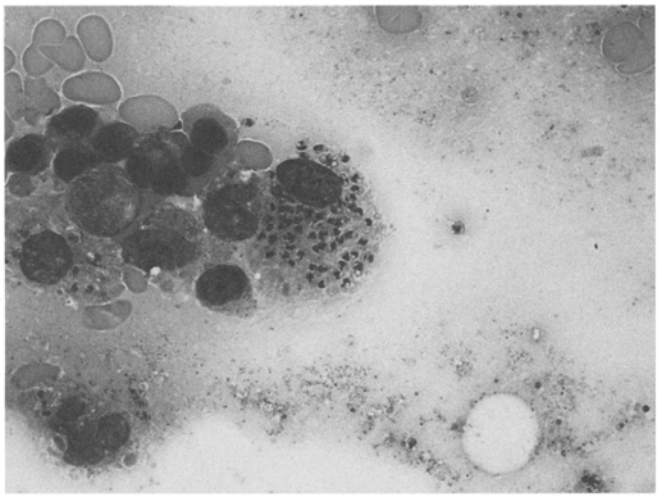


Fig. 42. Leishmania. Aspirate smear showing organisms within macrophage.

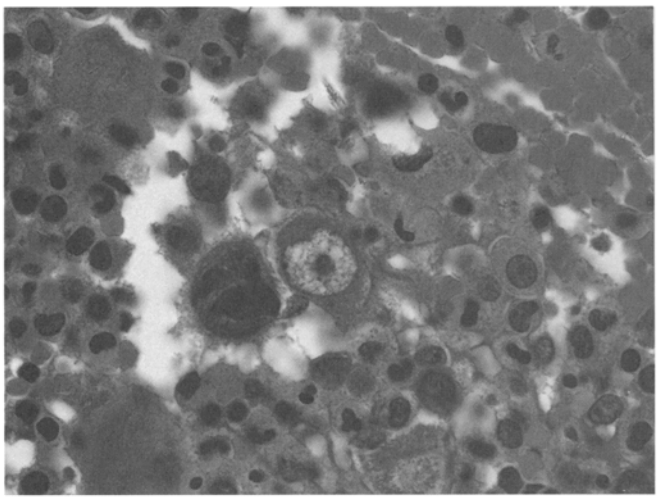


Fig. 44. Parvovirus. Giant pronormoblast seen in parvovirus-infected erythroid precursor.

- Aspirate Smear:
  - Absence of iron in Prussian blue stain

Anemia of Chronic Disease

Diagnosis

- Peripheral Blood:
  - Typically normochromic, normocytic mild-moderate anemia
- Aspirate Smear:
  - Stainable iron is typically increased

Megaloblastic Anemia (Figure 45,46)

Clinical

- B12/folate testing is useful for diagnosis

Diagnosis

- Peripheral Blood:
  - Macrocytic anemia is typical
  - Hypersegmented neutrophils seen
  - In severe cases, immature erythroid, and rarely myeloid, elements may be seen in blood

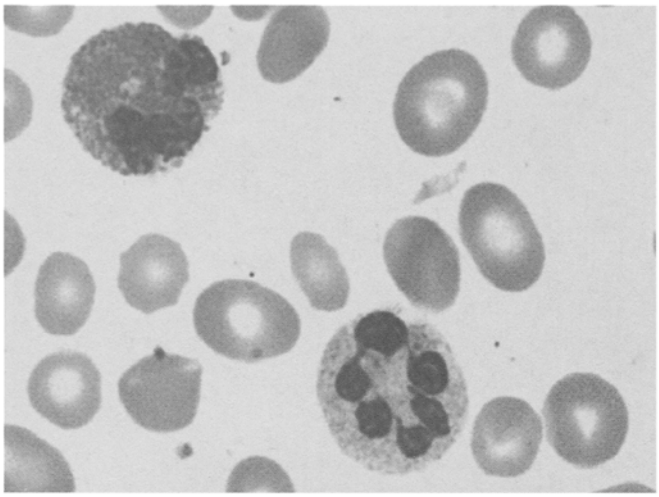


Fig. 45. Megaloblastic Anemia. Hyerpsegemented neutrophil.

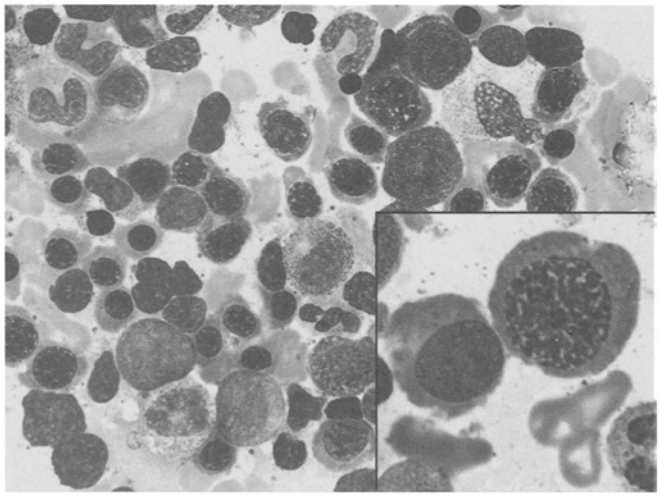


Fig. 46. Megaloblastic Anemia. Bone marrow aspirate with erythroid hyperplasia and Megaloblastic changes. Inset: Nuclear features of Megaloblastic anemia.

- Aspirate Smear:
  - Erythroid elements have characteristic nuclear/cytoplasmic dyssynchrony
  - Erythroid nuclear chromatin is less condensed and "ropy" compared to stage of development of cytoplasm
  - Other dyserythropoiesis including fragmentation, budding, multinucleation, etc., may be seen
  - Giant bands may be seen
- Biopsy:
  - Increases of immature erythroid elements may simulate blasts of leukemias

Paroxysmal Nocturnal Hemoglobinuria (PNH)

Definition

- Acquired clonal hematopoietic disorder, arising from mutation of gene leading to abnormal membrane proteins (PIG-A), leading to increased complement-mediated red cell hemolysis and increased risk of development of aplastic anemia, MDS and AML

Clinical

- Cytopenias and hemolysis common

Diagnosis

- Peripheral Blood:
  - Varying degrees of anisopoikilocytosis may be present
- Marrow:
  - May be hypoplastic or have significant erythroid hyperplasia
  - Varying degrees of dyserythropoiesis may be present; if severe, consider diagnosis of MDS

Additional Studies

- FLOW: abnormal decrease or lack of expression of CD55 and/or CD59 on surface of white blood cells is diagnostic test of choice

Congenital Dyserythroblastic Anemias (CDA)

- Group of rare erythroid maturation disorders; dyserythropoiesis common; CDA-II associated with positive Ham's test (AKA: HEMPAS); multinucleation and erythroid nuclear bridges may be seen

REACTIVE CONDITIONS, TREATMENT CHANGES, MISC

Aplastic Anemia (AA) (Figure 47)

Definition

- Pancytopenia with associated marrow hypoplasia; severe aplastic anemia is defined as less than 25% of age-normal marrow cellularity
- Etiologies include: constitutional defects (Fanconi anemia, dyskeratosis congenital, Schwachman-Diamond syndrome), infection-associated (EBV, parvovirus, HIV, hepatitis viruses), medication-related (chemotherapy, antibiotics, etc), toxins/exposures (benzene, insecticides, ionizing radiation), and a variety of other causes, although many cases are idiopathic

Clinical

- Absolute neutrophil counts are typically $<0.2 \times 10^9$/L

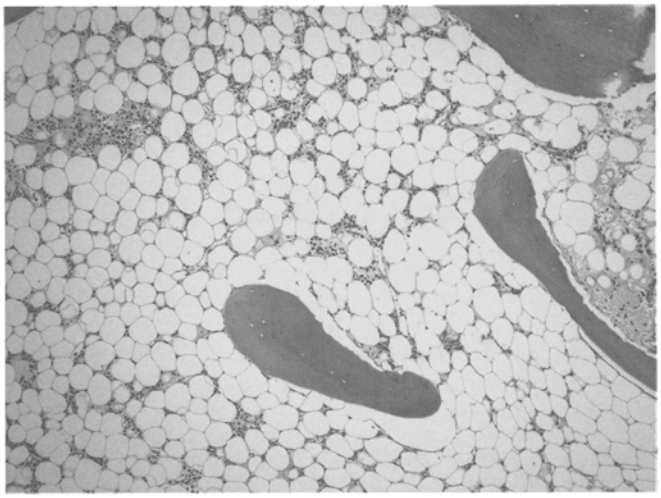


Fig. 47. Aplastic Anemia. Marked hypocellularity, with only rare hematopoietic elements.

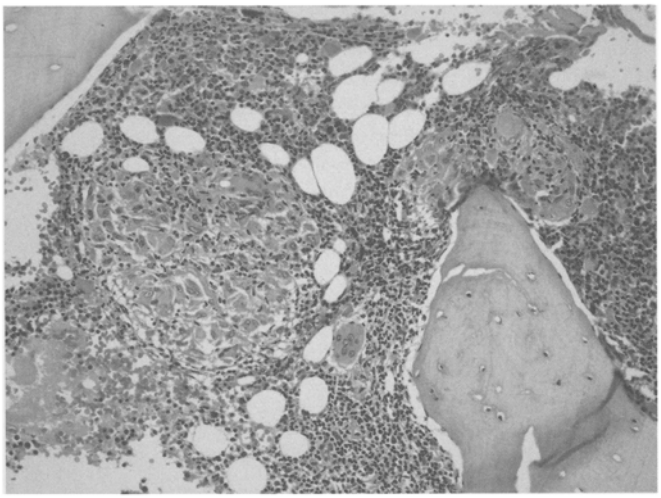


Fig. 48. Granuloma. Sarcoid granuloma seen in bone marrow biopsy.

- Platelets counts typically <20 x 10^9/L
- Anemia is often severe

Diagnosis

- Peripheral Blood:
  - Decreases in circulating blood cells
- Aspirate Smear:
  - Hypocellular, often consisting of only stromal elements, lymphocytes, plasma cells, and very rare hematopoietic elements
- Biopsy:
  - Hypocellular

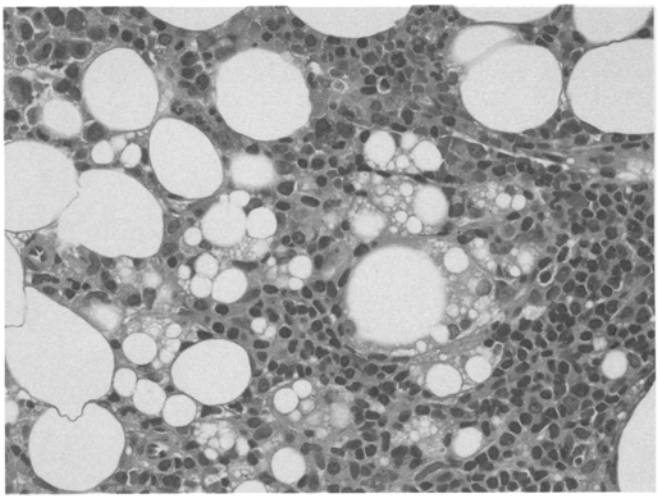


Fig. 49. Granuloma. Lipogranuloma.

  - Cellularity consists of stromal elements (+/– fibrosis); lymphoid aggregates may be seen; hematopoietic elements are decreased in number

Differential Diagnosis

- Hypoplastic MDS/AML: residual hematopoietic cells are immature, in hypoplastic AML and MDS CD34 is often positive, while it is absent/rare in AA

Prognosis and Treatment

- Recovery depends on underlying etiology of AA (if known)
- Treatment may include supportive therapy (transfusions, cytokines) or bone marrow transplant

Cytokine Effects

- G-CSF/GM-CSF: peripheral blood increase of granulocytes and sometimes monocytes with +/– immature forms, often with toxic granulation; marrow has increased M:E ratio, increased granulocytic and monocytic elements; may mimic an acute leukemia due to increase of immature-appearing forms
- Erythropoietin (EPO): typically causes erythroid hyperplasia in bone marrow; some dyspoiesis may be seen including megaloblastoid changes

Granulomas (Figure 48,49)

- Granulomas may be due to infections, neoplasms (Hodgkin lymphoma, other lymphomas, etc), systemic/autoimmune disorders (sarcoid, ulcerative colitis, etc), drug/therapy-related, immune-deficiencies
- Lipogranulomas are poorly formed foci of disrupted adipocytes with some surrounding macrophages

Immune thrombocytopenic purpura (ITP)

- Autoimmune destruction of platelets, with thrombocytopenia
- Marrow has increased numbers of megakaryocytes

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12

Neoplasms of the Skin and Immunodermatology

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CONTENTS

I. Cutaneous Neoplasms and Developmental Anomalies 12-3
Epithelial Neoplasms and Developmental Anomalies 12-3
Cystic Lesions: Neoplastic or Developmental.....12-3
Epidermal Tumors and Proliferations....12-5
Pilar and Pilosebaceous- Derived Tumors 12-9
Eccrine-Derived Tumors and Proliferations.....12-13
Apocrine-Derived Tumors and Proliferations.....12-19
Neuroendocrine-Derived Tumors 12-21

II. Soft Tissue Neoplasms and Developmental Anomalies 12-22
Adipocyte-Derived Tumors and Proliferations.....12-22
Neural-Derived Tumors and Proliferations.....12-23
Smooth Muscle-Derived Tumors and Proliferations.....12-26
Fibrohistiocytic, Histiocytic, and Langerhans' Cell-Derived Proliferations 12-28
Fibrous Proliferations and Tumors.....12-32

III. Vascular Proliferations, Malformations, and Tumors 12-36
Reactive, Nonneoplastic Vascular Proliferation and Telangiectasias....12-36
Benign Vascular Neoplasms 12-39
Vascular Tumors of Low-Grade Malignancy.....12-41
Malignant Vascular Tumors 12-42
Tumors of Perivascular Cells 12-43

IV. Melanocytic Proliferations and Pigmentary Disorders 12-43
Pigmentary Disorders of the Skin 12-43
Benign Melanocytic Proliferations.....12-44
Malignant Melanoma 12-48
Lymphoproliferative Disorders and Leukemias.....12-49

V. Immunodermatology 12-55
Methods, Terminology and Techniques 12-55
Direct Immunofluorescence (DIF) 12-55
Indirect Immunofluorescence (IIF) 12-55
Western Immunoblotting 12-55
ELISA 12-55
Immunobullous Diseases 12-55
Patterns of Antibody Deposition 12-55
Linear Deposition Along the Basement Membrane Zone.....12-55
Bullous Pemphigoid (BP).....12-55
Cicatricial Pemphigoid 12-56
Herpes Gestationis (Pemphigoid Gestationis) 12-56
Epidermolysis Bullosa Acquisita (EBA) 12-57

Bullous Systemic Lupus Erythematosus 12-58
Linear IgA Bullous Dermatosis (Chronic Bullous Disease of Childhood) 12-59
Deposition in Intercellular Spaces 12-61
Pemphigus Vulgaris 12-61
Pemphigus Foliaceus 12-62
Pemphigus Erythematosus 12-64
IgA Pemphigus 12-64
Paraneoplastic Pemphigus 12-65
Granular Deposition Along the Basement Membrane Zone: Lupus Erythematosus ..12-67
Discoid Lupus Erythematosus 12-67
Subacute Cutaneous Lupus Erythematosus (SCLE) 12-68
Bullous Systemic Lupus Erythematosus 12-69
Systemic Lupus Erythematosus 12-69

VI. Granular Deposition in the Dermal Papillae 12-70
Dermatitis Herpetiformis (DH) 12-70
Clumped Cytoid Bodies and Shaggy Deposition of Fibrogen Along the Basement Membrane Zone....12-71
Lichen Planus 12-71
Lupus Erythematosus 12-72
Dermatomyositis....12-72
Erythema Multiforme 12-72
Paraneoplastic Pemphigus 12-72
Lichenoid Dermatitis 12-72
Lichenoid Drug Reaction 12-72
Graft-vs-Host Disease....12-72

VII. Weak Thick Linear Deposition Along the Basement Membrane Zone and Perivascular Deposition 12-72
Porphyrias....12-72

VIII. Deposition on Eosinophils and Diffuse Deposition on Connective Tissue....12-74
Urticaria 12-74

IX. Deposition in Blood Vessels....12-75
Vasculitis....12-75

X. TNM Classification of Malignant Melanoma and Carcinoma of the Skin (2002 Revision) 12-75

XI. Suggested Reading....12-76

CUTANEOUS NEOPLASMS AND DEVELOPMENTAL ANOMALIES

Epithelial Neoplasms and Developmental Anomalies

CYSTIC LESIONS: NEOPLASTIC OR DEVELOPMENTAL

Epidermoid Cyst (Infundibular Cyst)

Clinical

- Dome-shaped lesions with central punctum; multiple lesions may be associated with Gardner's syndrome

Microscopic

- Dermal cyst with/without an epidermal connection lined by stratified squamous epithelium with a granular layer; cyst contains laminated keratin debris

Comedonal Cyst

Microscopic

- Similar to the epidermoid cyst but characterized by follicular plugging and hyperkeratosis; may be more superficial and typically has a larger epidermal ostia or punctum

Milia

Clinical

- Small white-yellow papules which may occur sporadically or in association with blistering diseases (epidermolysis bullosa, porphyria cutanea tarda, pemphigoid, etc.) which disrupt or occlude the eccrine ducts or hair follicles

Microscopic

- A small epidermoid-like cyst located in the superficial dermis

Steatocystoma (Figure 1)

Clinical

- May occur in a solitary form (simplex) or as multiple lesions inherited in a autosomal dominant fashion (multiplex)

Microscopic

- An irregular, collapsed, intradermal cyst lined by a stratified squamous epithelium with an irregular, corrugated internal cuticle. Sebaceous glands are usually evident in the duct walls, and the cyst contains proteinaceous debris but no keratin

Dermoid Cyst

Clinical

- An embryonic closure defect which typically involves the skin lateral to the eye, the scalp, neck or near the mastoid process. Usually detected early in life

Microscopic

- A unilocular dermal or subcutaneous cyst lined by stratified squamous epithelium and having hair follicles, glands and, sometimes, smooth muscle in the cyst wall

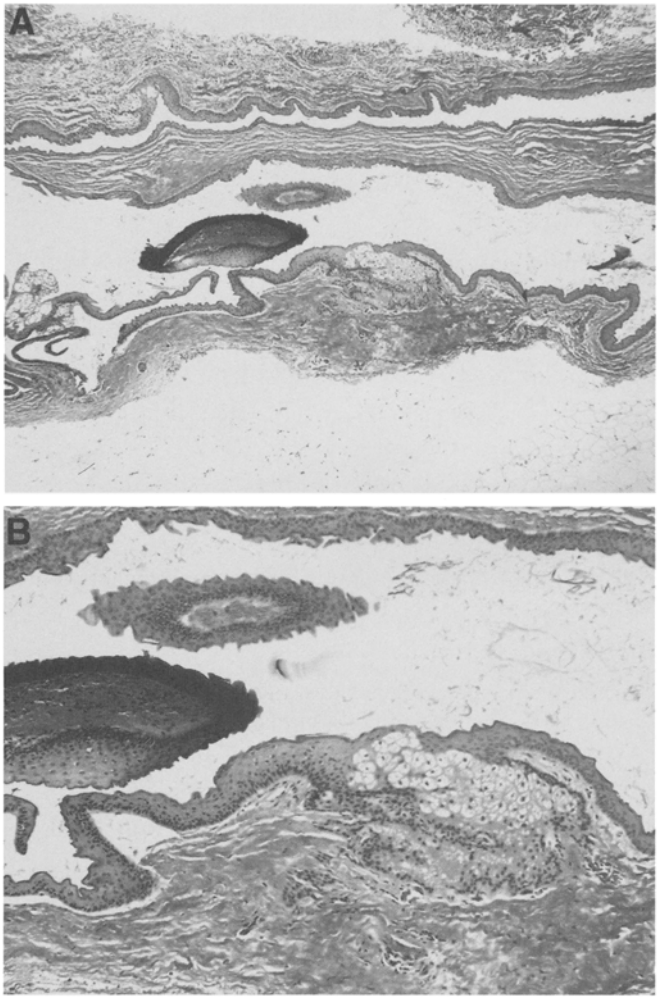


Fig. 1. Steatocystoma.

Cysts Associated With Branchial Cleft Deformities

Clinical

- Cystic lesions may be formed in and around the ear in association with branchial cleft deformities. These differ from the branchial cleft cyst of the neck by their location and their microscopic

Microscopic

- May be similar to an epidermoid cyst except for their tendency to collapse and assume a multiloculated appearance. Other forms, in addition to the above, have adnexal structures and even cartilage within their walls

Branchial Cleft Cyst

Clinical

- A developmental anomaly presenting as a cyst in the lateral aspect of the neck

Microscopic

- A lymphoepithelial cyst characterized by a stratified squamous or a pseudostratified ciliated lining with a dense lymphocytic infiltrate with germinal centers in the wall

Eruptive Vellus Hair Cyst

Clinical

- Small flesh-colored papules in children and young adults

Microscopic

- An epidermoid-like cyst that contains numerous, small vellus hairs

Pigmented Terminal Hair Cyst

Microscopic

- An epidermoid-like cyst containing numerous pigmented, terminal hairs

Trichilemmal (Pilar) Cyst

Clinical

- Dome shaped papules/nodules found predominantly on the scalp; may be single or multiple

Microscopic

- A dermal or subcutaneous cyst lined by an eosinophilic stratified squamous epithelium that lacks a granular layer. The cyst contents are composed of solid, nonlaminated keratin

Proliferating Trichilemmal Cyst/Tumor (Figure 2)

Clinical

- Multinodular scalp lesion more common in females

Microscopic

- Well-defined, multilobular tumor with trichilemmal keratinization; dense fibrous tissue surrounds the individual lobules; cystic areas may be inconspicuous
- Malignant forms occur but are rare
- More marked infiltration, cytologic atypia and mitotic activity characterize the malignant variants

Bronchogenic Cyst

Clinical

- A developmental cyst usually found near the precordium early in life

Microscopic

- This cystic lesion attempts to recapitulate the bronchi with a cyst lined by respiratory epithelium and a cyst wall with smooth muscle, glands and/or cartilage

Thryoglossal Duct Cyst

Clinical

- A developmental cyst found in the midline of the neck, near the hyoid bone

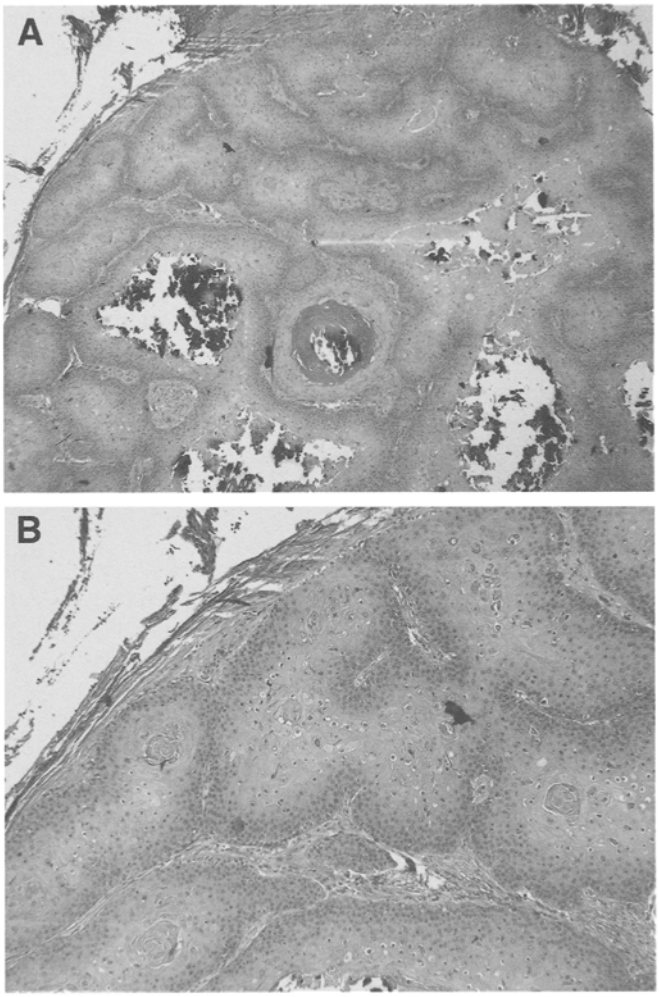


Fig. 2. Proliferating trichilemmal tumor.

Microscopic

- The cyst may be lined by cuboidal, columnar or stratified squamous epithelium
- The cyst wall contains thyroid follicles with or without skin appendages and lymphocytic inflammation
- Smooth muscle and cartilage are absent

Cutaneous Ciliated Cyst

Clinical

- Usually found on the lower extremities or buttocks of reproductive aged women

Microscopic

- Ciliated, cuboidal to columnar lined, multiloculated cyst surrounded by fibrous tissue
- No endometrial or fallopian tube type stroma is evident within the cyst walls

Endometriosis and Endosalpingiosis

Clinical

- Blue-red cysts/nodules most commonly seen in the vulvar or periumbilical regions of reproductive aged females

Microscopic

- Similar to the cutaneous ciliated cyst except that the cyst wall contains endometrial/fallopian tube type stroma with or without hemosiderin deposition

Hidrocystoma

Microscopic

- Unilocular or multilocular cysts lined by either apocrine or eccrine epithelium
- Apocrine: decapitation secretion (apical snouts) and a myoepithelial layer; may have papillary projections
- Eccrine: a two-layered cuboidal epithelium with no myoepithelial layer or decapitation secretion

Hybrid Cyst

Microscopic

- A cystic lesion combining the histologic features of more than one cyst type, usually trichilemmal and epidermoid cysts

Digital Mucous Cyst (Figure 3)

Clinical

- A fluctuant, sometimes tender, translucent nodule of the digits

Microscopic

- Dermal mucin deposited into a cyst-like space that may or may not also contain fibroblasts and collagen
- There is no true epidermal lining, and the cystic spaces may be multiloculated

Oral Mucocele

Clinical

- A translucent, blue nodule usually found on the lower lip

Microscopic

- A cystic space containing varying degrees of central mucin and lined by chronic inflammatory cells with numerous foamy histiocytes
- There is no true epithelial lining

Epidermal Tumors and Proliferations

Actinic Keratosis (Senile, Solar)

Clinical

- White-yellow, erythematous and scaly patches or plaques on sun damaged skin; some may be pigmented

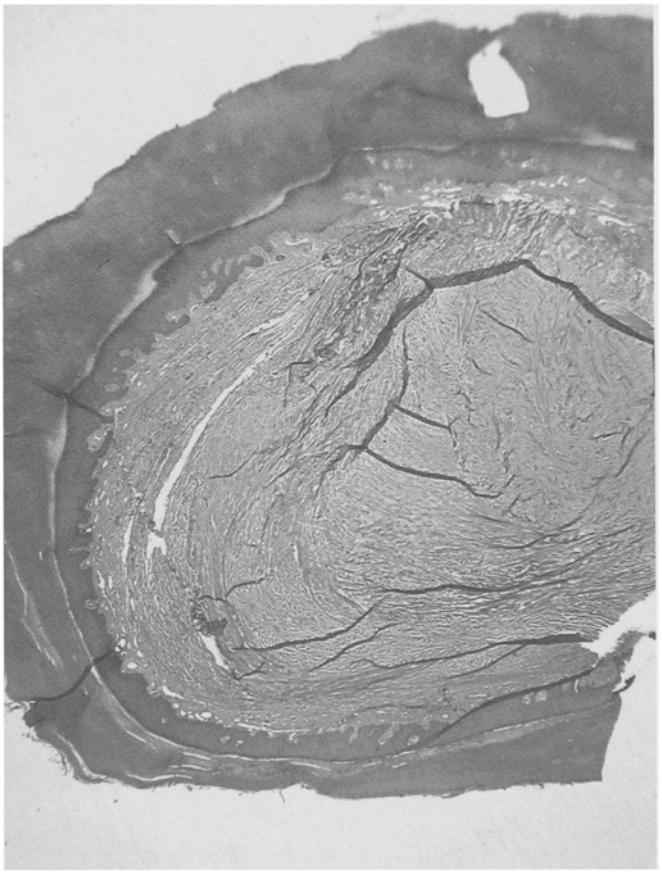


Fig. 3. Digital mucous cyst.

Microscopic

- While a variety of histologic types exist, all have in common epidermal dysplasia, which may also involve the hair follicles
- Hyperplastic, atrophic, acantholytic, epidermolytic, lichenoid, pigmented, bowenoid and clear cell categories exist and reflect additional alterations to the dysplastic epidermis (e.g., lichenoid variant = actinic keratosis with a band-like lymphocytic inflammatory infiltrate; bowenoid variant = actinic keratosis with full thickness dysplasia = carcinoma in-situ)

Benign Lichenoid Keratosis (Figure 4) (Lichen Planus-Like Keratosis)

Clinical

- Solitary papule or plaque found primarily on the trunk or upper extremities

Microscopic

- Very similar to lichen planus with a dense band-like lymphocytic infiltrate at the dermal-epidermal interface with basilar vacuolar degeneration and cytoid bodies

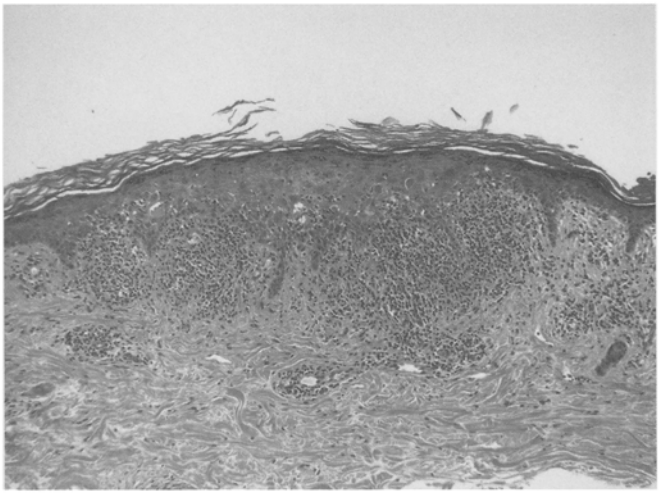


Fig. 4. Benign lichenoid keratosis.

- In contrast to lichen planus, eosinophils and parakeratosis may be seen
- In contrast to a lichenoid actinic keratosis, there is no keratinocyte dysplasia

Seborrheic Keratosis

Clinical

- Brown, elevated and sharply demarcated lesions which occur most commonly on the face, trunk and upper extremities
- These benign tumors often have a "stuck on" appearance and are more common in middle aged and older adults
- The sudden appearance of numerous seborrheic keratosis in association with visceral malignancy is referred to as the Leser-Trelat sign

Microscopic

- An epidermal proliferation of bland basaloid and polygonal keratinocytes associated with prominent keratin cyst formation
- The lesion is sharply delineated at its base and appears to grow up from the epidermis
- Irritated forms demonstrate more endophytic growth and form numerous squamous eddies
- Acanthotic, adenoid, clonal, pigmented and hyperkeratotic variants exist

Inverted Follicular Keratosis (Figure 5)

Microscopic

- An endophytic epidermal growth with numerous squamous eddies which, like seborrheic keratosis, is sharply delineated but is centered on the hair follicles
- Note: this entity is considered a variant of seborrheic keratosis by some experts and a viral induced lesion by others



Fig. 5. Inverted follicular keratosis.

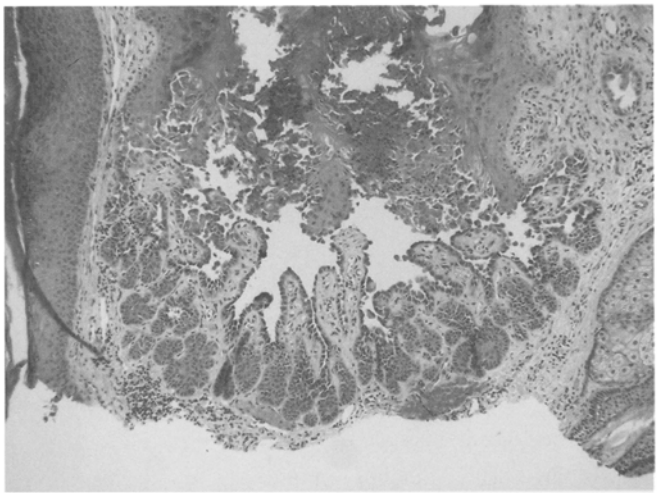


Fig. 6. Warty dyskeratoma.

Warty Dyskeratoma (Figure 6)

Clinical

- A benign, solitary, umbilicated nodule or papule on sun-exposed skin

Microscopic

- A hair follicle centered, endophytic squamous proliferation which is sharply delineated
- The base of the lesion typically reveals elongated trabeculae with varying degrees of dyskeratosis that underlies broad areas of acantholytic dyskeratosis located immediately below a keratin-filled, central crater

Linear Epidermal Nevus

Clinical

- Localized and systemic forms exist and are characterized by a linear arrangement of closely set papillomatous papules
- The systemic form may be associated with other defects, including skeletal and central nervous system abnormalities

Microscopic

- Both variants demonstrate epidermal papillomatosis, acanthosis and hyperkeratosis
- Many histologic variants exist, but, importantly, the presence of epidermolytic hyperkeratosis may be associated with systemic involvement

Nevus Comedonicus

Clinical

- Comedo-like papules with a central keratin plug usually in a linear arrangement on the palms, soles or other sites

Microscopic

- Deep epidermal invaginations with laminated keratin similar to a comedo
- Epidermolytic hyperkeratosis may be evident

White Sponge Nevus

Clinical

- Extensive, white patches and plaques involving mucosal sites (chiefly oral but also vaginal, rectal and esophageal) which are evident early in life and are inherited in an autosomal dominant pattern

Microscopic

- There is acanthosis and pallor of the mucosal lining due to prominent cytoplasmic clearing (intracellular edema) of the suprabasilar keratinocytes
- Similar changes are seen in leukoedema and pachyonychia congenita

Leukoedema

Clinical

- Patchy white plaques and patches of the oral mucosa with an adult onset
- These lesions remit and recur and are not inherited

Microscopic

- Similar to white sponge nevus from which it differs by clinical grounds

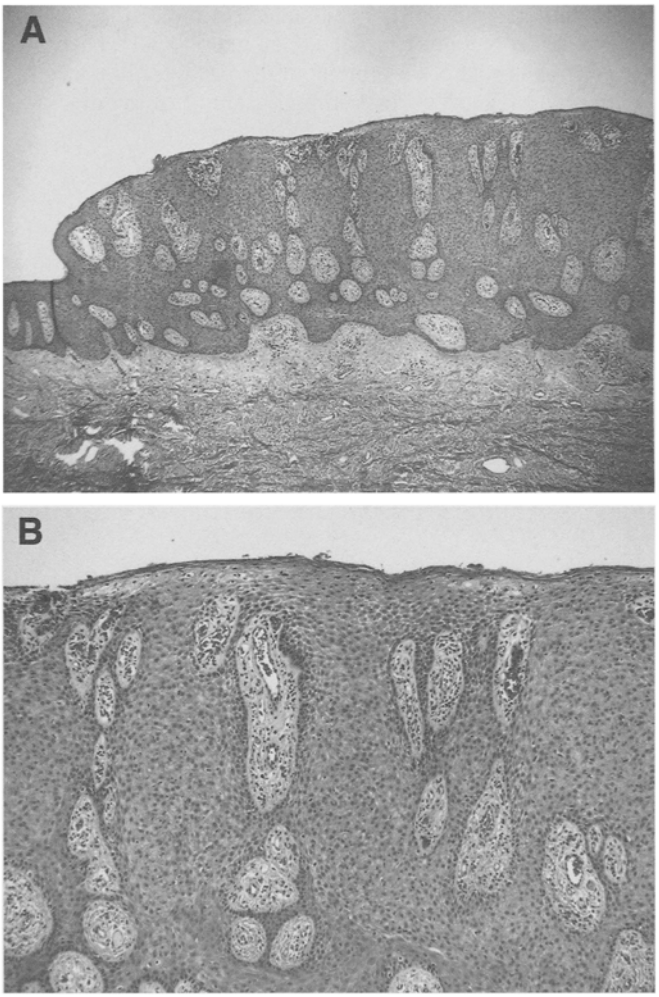


Fig. 7. Clear cell acanthoma.

Geographic Tongue (Lingua Geographica)

Clinical

- Irregular, erythematous patches with white borders on the tongue

Microscopic

- The erythematous areas show loss of the normal granular and horny layers while the white areas demonstrate acanthosis with neutrophilic inflammation

Clear Cell Acanthoma (Figure 7)

Clinical

- Solitary, slowly growing nodules or plaques with an oozing surface
- These lesions are most common on the lower extremities

Microscopic

- A plate-like epidermal thickening by a proliferation of clear, heavily glycogenated keratinocytes

- The tumors are sharply demarcated from the adjacent epidermis (eyeliner sign) and, characteristically, have neutrophils scattered throughout the proliferation, an important feature in separating this entity from other tumors with a plate-like growth pattern

Large Cell Acanthoma

Clinical

- Erythematous patches on sun-exposed skin

Microscopic

- A sharply defined epidermal proliferation of enlarged, pale keratinocytes with mild dysplasia
- Comment: these lesions are aneuploid and are best considered to be a variant of actinic keratosis

Squamous Cell Carcinoma In-Situ (Bowen's Disease)

Clinical

- Erythematous, irregular, scaly patches and plaques that may involve any skin surface as well as the mucous membranes
- Bowen's disease of the penis is often referred to as erythroplasia of Queyrat
- Sun-exposure, arsenic and other chemicals are associated with and increased risk of development of Bowen's disease
- Approximately 5% of these lesions develop an invasive component

Microscopic

- Epidermal acanthosis associated with full thickness epidermal dysplasia, which may involve the adnexa
- A dense lichenoid inflammatory infiltrate may also be present
- Intraepidermal spread (Borst-Jadassohn phenomena) may be prominent and should be differentiated from melanoma and Paget's disease

Bowenoid Papulosis

Clinical

- Red-brown papules or plaques on the external genitalia and perineum of young adults
- Lesions are frequently multiple, and there is a strong association with Human Papilloma Virus (HPV) types 16 and 18 with other types occurring less frequently
- Unlike Bowen's disease, these lesions may regress and are less likely to give rise to an invasive carcinoma

Microscopic

- Fairly discrete areas of epidermal acanthosis associated with varying degrees of epidermal dysplasia, koilo-cytosis, hypergranulosis and parakeratosis
- In-situ carcinoma may be present

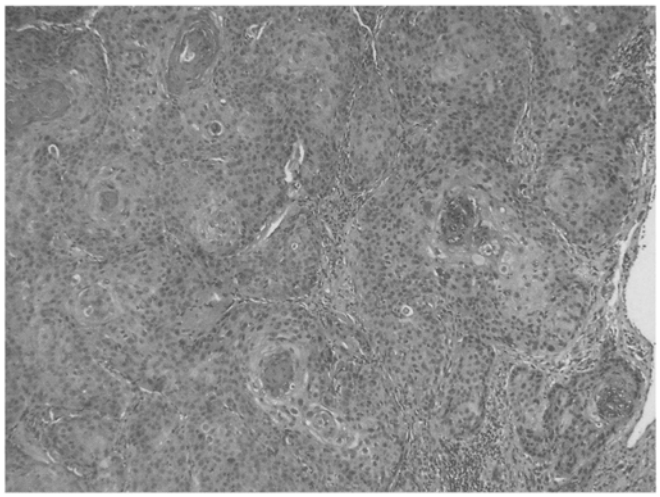


Fig. 8. Squamous cell carcinoma.

Squamous Cell Carcinoma (Figure 8)

Clinical

- Indurated, hyperkeratotic nodules which may show ulceration or verruciform changes
- Currently, squamous cell carcinoma is the second most common cutaneous malignancy
- The incidence is increasing
- While most are related to sun exposure, other risk factors include fair complexion, chronic inflammation, immunosuppression, burns, HPV infection and chemical exposure (e.g., arsenic)
- The overall rate of metastases is approximately 5% but is >10% at mucosal sites and the ear

Microscopic

- Atypical nests of epidermoid cells invasive into the dermis and, usually, with overlying epidermal dysplasia
- Differentiation varies from poorly differentiated (minimal keratin production, marked nuclear pleomorphism, high mitotic rate) to well differentiated (abundant keratin pearl formation, minimal cytologic atypia and few mitoses)
- The presence of keratin production, intercellular desmosomes ("spines") and overlying epidermal dysplasia are useful features in separating this tumor from other entities
- Variants include clear cell, spindle cell, acantholytic and verrucous tumors

Verrucous Carcinoma

Clinical

- A variant of squamous cell carcinoma that typically appears as a large hyperkeratotic nodule
- All cutaneous surfaces may be involved but plantar, oral (oral florid papillomatosis) and anogenital lesions are particularly common

- These tumors frequently recur but have little metastatic potential

Microscopic

- An endophytic and exophytic growth of well-differentiated squamous epithelium with extensive keratinization
- The deep component shows a broad, pushing front at its advancing edge
- If any significant nuclear dysplasia is present, a diagnosis of squamous cell carcinoma should be made

Keratoacanthoma

Clinical

- A rapidly growing, umbilicated nodule with a central keratin plug
- Multiple lesions may be present
- Typically, these tumors regress over the course of a few months, but they may recur
- These tumors are considered to be a variant of squamous cell carcinoma by some experts

Microscopic

- A well-defined, sharply demarcated, craterform squamous proliferation with a central keratin plug
- The squamous epithelium frequently has a glassy appearance and lacks significant cytologic atypia
- A lichenoid inflammatory infiltrate may be present
- The presence of cytologic atypia, infiltrative borders or atypical mitoses warrants a diagnosis of a squamous cell carcinoma

Pilar and Pilosebaceous-Derived Tumors

Dilated Pore of Winer

Clinical

- Flesh colored papule or cyst with a central keratotic plug found chiefly on the head and neck

Microscopic

- A cone-shaped dilatation of the follicular infundibulum with a central keratin plug
- The wall of the pore is proliferative with finger-like projections extending into the adjacent dermis
- No secondary hair follicles are evident within the cyst wall

Pilar Sheath Acanthoma

Clinical

- Small nodule with a central keratin filled pore on the upper lip

Microscopic

- Similar in architecture to the dilated pore but with a more proliferative wall

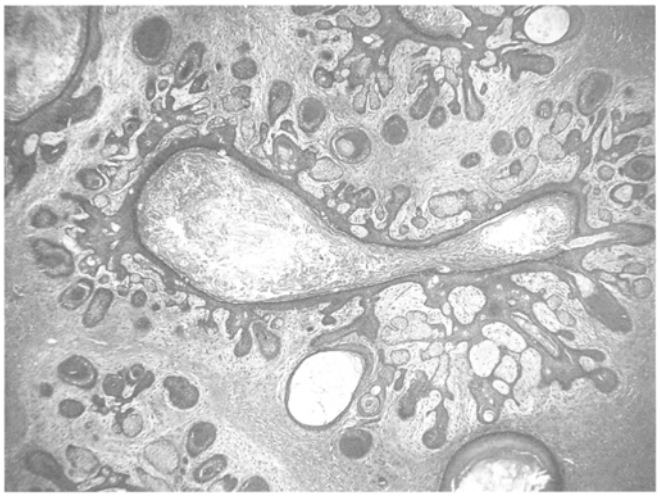


Fig. 9. Trichofolliculoma.

- The epithelium of the wall is paler than that of the dilated pore and may have some degree of peripheral palisading suggesting abortive hair follicle development
- No well-developed secondary hair follicles with hair formation are evident

Trichofolliculoma (Figure 9)

Clinical

- Solitary, flesh-colored nodules with a central pore from which numerous white hairs emerge

Microscopic

- Similar to the dilated pore, a central, elongated and dilated infundibulum is present
- Numerous secondary hair follicles radiate peripherally from the central cavity that is filled with laminated keratin and numerous hairs
- If sebaceous glands are evident within the secondary follicles, than a diagnosis of a sebaceous trichofolliculoma is appropriate

Tumor of the Follicular Infundibulum (Figure 10)

Clinical

- Small, hyperkeratotic papules or plaques on the head and neck

Microscopic

- A plate-like expansion of the epidermis by interanastomosing and interweaving trabeculae of glycogenated squamous epithelium within the superficial dermis
- The trabeculae show multiple attachments to the epidermis and to the hair follicles
- The trabeculae may show some peripheral palisading but lack mucin deposition or stromal retraction
- Elastic fibers are often condensed at the base of the lesion

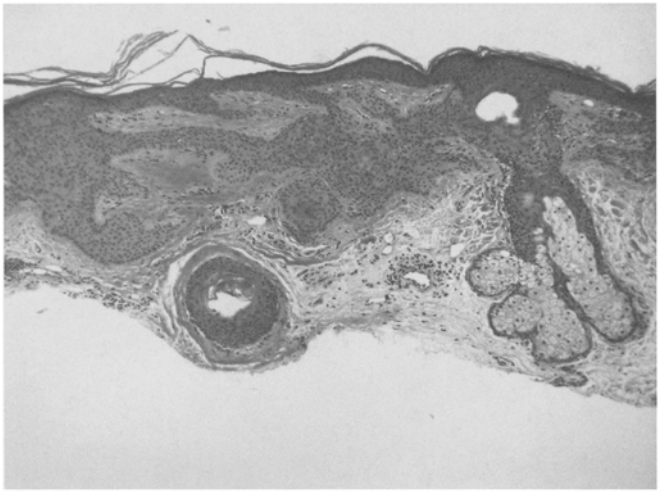


Fig. 10. Tumor of the follicular infundibulum.

Differential Diagnosis

- Fibroepithelioma of Pinkus and eccrine syringofibroadenoma
- Fibroepithelioma of Pinkus has narrower trabeculae with more pronounced basaloid differentiation while eccrine syringofibroadenoma shows scattered eccrine ducts within its trabeculae

Basaloid Follicular Hamartoma

Clinical

- Small, flesh-colored papules or plaques on the head and neck
- Solitary, multifocal and inherited variants have been described

Microscopic

- Small, starfish or octopus-like proliferations of basaloid cells within the dermis arranged as anastamosing trabeculae with peripheral palisading and surrounding fibrosis

Trichilemmoma (Figure 11)

Clinical

- Verrucous, hyperkeratotic papules usually found on the face
- Multiple trichilemmomas occur in the autosomal dominant disorder, Cowden's disease

Microscopic

- A single lobule or, occasionally, a multilobular proliferation of round, clear (glycogen rich) squamous cells giving a plate-like thickening to the epidermis
- There is usually a follicular accentuation to the proliferation with the pale cells growing down pre-existing follicular structures
- The lobules are surrounded by a PASD positive basement membrane



Fig. 11. Trichilemmoma.

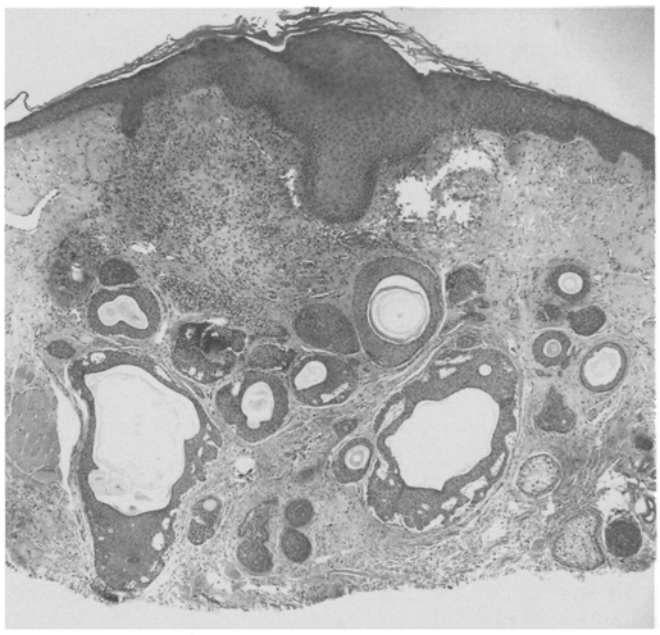


Fig. 12. Trichoadenoma.

- A desmoplastic variant exists which, in addition to typical trichilemmoma areas, has central trabeculae surrounded by a dense, hypocellular stroma

Trichoadenoma (Figure 12)

Clinical

- Yellow to flesh-colored papule on the face

Microscopic

- Numerous keratin filled cysts lined by a stratified squamous epithelium are evident within the dermis
- A granular layer is present (epidermoid keratinization), and the cysts have a surrounding fibrous stroma
- Solid trabeculae are rare

Trichoepithelioma

Clinical

- Small flesh-colored papules on the face of young to middle aged adults
- Solitary, desmoplastic and multiple (autosomal dominant inheritance) variants exist

Microscopic

- An admixture of keratin filled cysts and trabeculae of basaloid cells with peripheral palisading and a surrounding fibrous stroma
- Stromal retraction is not evident, and true hair bulb formation is rarely seen

Differential Diagnosis

- Keratotic basal cell carcinoma is different from trichoepithelioma by having stromal retraction, mucin deposition, individual cell necrosis and numerous mitoses
- Microcystic adnexal carcinoma differs from desmoplastic trichoepithelioma by the presence of deeper infiltration with eccrine ducts lined by an eosinophilic cuticle. A layered appearance with cysts predominating superficially and trabeculae predominating at the deep aspect of the tumor are characteristic

Trichoblastoma

Clinical

- A controversial entity having histologic and clinical overlap with trichoepithelioma and basal cell carcinoma

Microscopic

- A proliferation of germinative basaloid cells arranged in nests, sheets or trabeculae
- Conspicuous hair bulb differentiation is seen at the edge of the nests or sheets but also as single, primitive hair follicle-like structures surrounded by a dense fibrous sheath
- Stromal clefting and extensive mucin deposition are typically absent

Differential Diagnosis

- Basal cell carcinoma shows stromal clefting, mucin deposition, single cell necrosis and lacks primitive hair bulb structures
- Trichoepithelioma has admixed keratin-filled cysts and has few to no primitive hair bulbs

Trichodiscoma

Clinical

- A hamartomatous proliferation of the hair disc which presents as multiple flesh-colored papules on the face and also elsewhere on the body

Microscopic

- A nodular mesenchymal proliferation surrounded by an epidermal collarette
- Centrally there are stellate fibroblasts embedded in collagen, reticulin and elastic fibers with abundant mucin deposition
- Thin walled vessels with prominent basement membranes are seen within the proliferation

Perifollicular Fibroma and Fibrofolliculoma

Clinical

- Both occur as solitary and, more often, multiple flesh-colored papules on the face or neck

Microscopic

- Perifollicular fibromas show a loose, concentric proliferation of fibrous tissue around normal hair follicles while fibrofolliculomas show both a fibrous and a follicular proliferation centered on a dilated follicle
- The epithelial component of the latter consists of epithelial trabeculae that arise from the infundibulum and are surrounded by fibrous tissue

Pilomatricoma (Figure 13) (Calcifying Epithelioma of Malherbe)

Clinical

- Deep-seated, frequently calcified nodules on the head, neck and upper extremities of children and young adults
- These lesions may be solitary or multiple (autosomal dominant inheritance) or may be a marker of a systemic disease (Gardner's syndrome)

Microscopic

- A cystic or multinodular tumor with a biphasic epithelial growth pattern consisting of eosinophilic, ghosts or shadow cells centrally and basophilic, basaloid cells peripherally
- Granulomatous inflammation and calcification are frequent and may obscure the characteristic growth pattern

Basal Cell Carcinoma (Figure 14)

Clinical

- Well-delineated, pearly, translucent, pink-tan papules or nodules with telangiectasia
- Superficial, nodular/ulcerative, pigmented, diffuse, morpheaform and fibroepitheliomatous variants exist
- Most are found on sun-exposed skin of the elderly, but occasional cases are evident on non-sun-exposed skin
- Basal cell carcinoma is currently the most common cutaneous malignancy, and the incidence is increasing
- Risk of developing basal cell carcinomas is related to sun-exposure and skin type
- Multiple tumors are seen in Basex syndrome and basal cell carcinoma-nevus syndrome (Gorlin's syndrome), an autosomal dominant inherited disease also having odontogenic keratocysts, palmar-plantar pits, ectopic calcification and skeletal abnormalities

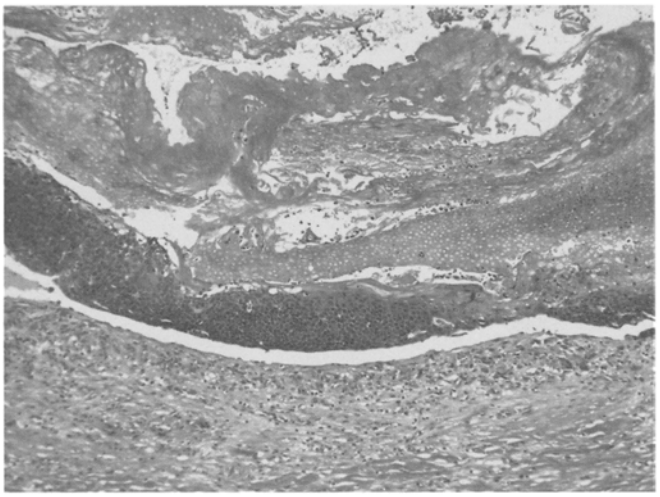


Fig. 13. Pilomatricoma.

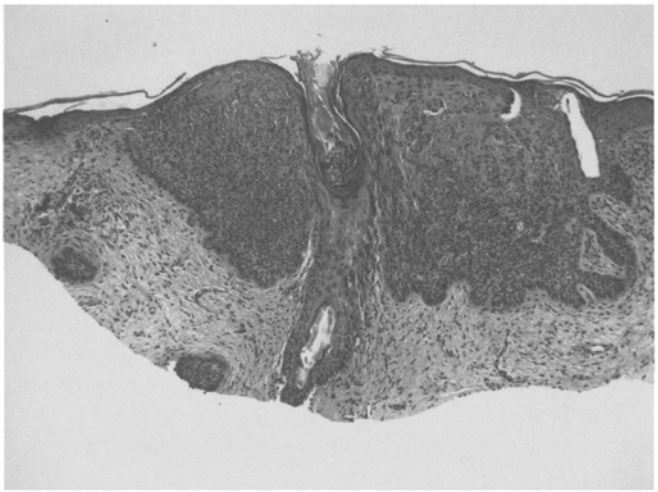


Fig. 14. Basal cell carcinoma.

- Basal cell carcinoma has little tendency to metastasize

Microscopic

- A proliferation of atypical basaloid cells in nests, trabeculae and/or cysts within the dermis but often demonstrating multifocal epidermal attachment
- Peripheral palisading, stromal retraction, mucin deposition, single cell necrosis and mitoses are characteristic and are useful in separating this tumor from other entities
- Nodulocystic, metatypical (keratotic), pigmented, adenoidal, infiltrating, superficial and morpheaform histologic variants exist with the latter two having an increased risk of recurrence

Fibroepithelioma of Pinkus (Figure 15)

Clinical

- Polypoid or plaque-like lesions on the thigh or trunk
- Considered a premalignant lesion by many experts

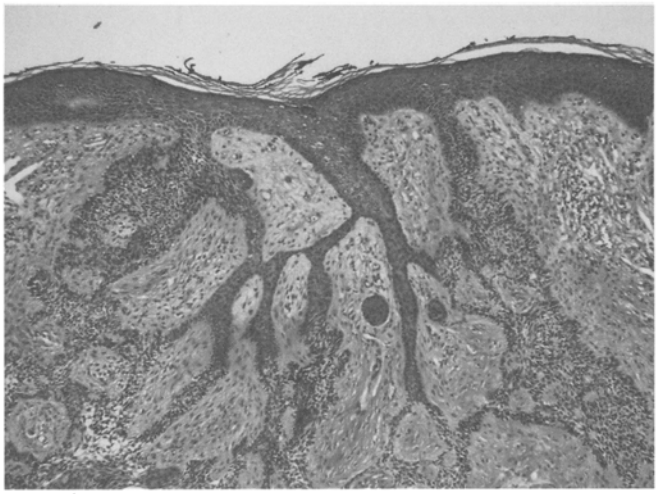


Fig. 15. Fibroepithelioma of Pinkus.

Microscopic

- Interanastomosing epithelial strands with multiple points of attachment to the epidermis and surrounded by a fibrous stroma
- The trabeculae are thinner than tumor of the follicular infundibulum, being 2-3 epithelial cells in thickness

Malignant Pilomatricoma

Clinical

- A rare tumor occurring as tumors or nodules on the face

Microscopic

- Similar to a benign pilomatricoma but showing areas with infiltration, mitoses and nuclear pleomorphism

Nevus Sebaceous (Figure 16)

Clinical

- Single or multiple, yellow papules to plaques with or without verruciform features on the head and neck of infants, adolescents and young adults
- A linear form exists
- Nevus sebaceous with cerebral abnormalities is referred to as the nevus sebaceous syndrome
- Basal cell carcinoma is the most common malignancy associated with nevus sebaceous while syringo-cystadenoma papilliferum is the most common benign proliferation associated with this condition

Microscopic

- The epidermis frequently demonstrates papillomatosis or verruciform change
- Numerous immature or abortive hair follicles are situated within the superficial dermis with a reduction in the number of mature terminal hairs

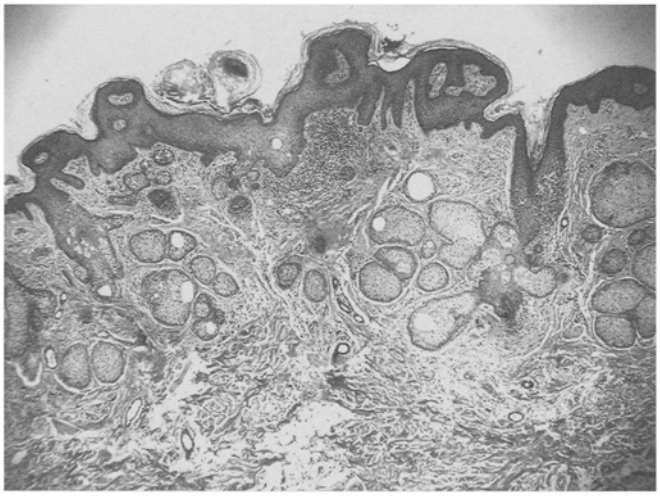


Fig. 16. Nevus Sebaceous.

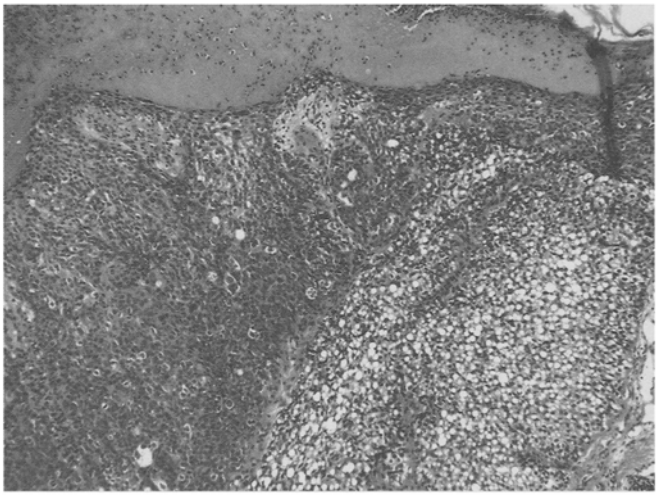


Fig. 17. Sebaceous carcinoma.

- The sebaceous glands appear haphazardly distributed within the dermis and may appear atrophic, hyperplastic or relatively normal in size
- Apocrine glands are a frequent finding in the deep dermis

Sebaceous Hyperplasia

Clinical

- Small yellow papules on the face and forehead of older adults

Microscopic

- Enlarged, hyperplastic sebaceous glands emptying into a central hair follicle often situated in the superficial dermis

Sebaceous Adenoma

Clinical

- Pink to yellow papules on the face and neck of older adults
- Multiple lesions are often associated with visceral malignancy (Muir-Torre syndrome)

Microscopic

- A multilobulated tumor often showing attachment to or emptying through the overlying epidermis
- The lobules are composed of basaloid cells peripherally and multivacuolated cells centrally
- By definition, the basaloid cells comprise less than 50% of cells of the individual lobules
- Infiltration, necrosis and frequent mitoses are absent

Sebaceous Epithelioma

Clinical

- Similar to sebaceous adenoma

Microscopic

- A faintly lobular tumor similar to the sebaceous adenoma
- Basaloid cells comprise more than 50% of the cells in the individual lobules
- While occasional mitotic Figures may be seen, abundant mitotic activity, infiltration, nuclear pleomorphism or necrosis should lead to a consideration of sebaceous carcinoma or basal cell carcinoma with sebaceous differentiation

Sebaceous Carcinoma (Figure 17)

Clinical

- Ulcerated or non-ulcerated nodules on the head and neck region of older adults
- The periocular region is a particularly common site where derivation from the meibomian gland occurs
- These tumors are associated with a high metastatic potential and increased mortality (~25%)

Microscopic

- These tumors may show irregular lobules or a diffuse infiltrating pattern
- Attachment to the overlying epidermis may be present, and pagetoid spread is common in the periocular variants
- These tumors show a spectrum of sebaceous differentiation varying from tumors composed predominantly of basaloid cells to tumors with numerous multi-vacuolated sebaceous cells
- Infiltration, necrosis, nuclear pleomorphism, nucleoli and mitoses are usually readily evident
- Perineural and capillary-lymphatic space invasion may be seen

Immunophenotype

- Cytokeratin and EMA+; S-100 protein and CEA–

Eccrine-Derived Tumors and Proliferations

Syringoma-Like Proliferations Associated with Alopecia

Clinical

- No specific clinical findings are associated with this lesion which presents simply as alopecia of any etiology

Microscopic

- This is a relatively rare, apparently, non-neoplastic proliferation of the eccrine ducts in response to alopecia
- The microscopic is that of the particular form of alopecia affecting the patient with the addition of a diffuse, haphazard proliferation of the eccrine ducts limited to the mid and upper dermis
- Ducts, trabeculae, comma and tadpole-shaped forms may all be seen
- No nuclear pleomorphism or perineural invasion is evident, but mitotic figures may be seen
- This proliferation may be seen throughout the scalp in cases of severe alopecia

Differential Diagnosis

- Syringoma is usually a more localized and circumscribed eccrine proliferation and lacks the haphazard appearance of the above
- Microcystic adnexal carcinoma and eccrine syringoid carcinoma are more infiltrative lesions that typically involve the lower dermis and the subcutis and show frequent perineural invasion

Eccrine Syringofibroadenoma (Figure 18)

Clinical

- Single or multiple papules or nodules with a wide age range and distribution
- The extremities are most commonly involved

Microscopic

- Interanastomosing cords and trabeculae of epithelial cells extending into the dermis with multiple points of attachment to the epidermis
- The cords are thin and surrounded by a fibrous stroma
- Scattered throughout the epithelial cords are areas of eccrine duct differentiation with prominent eosinophilic cuticles

Differential Diagnosis

- Tumor of the follicular infundibulum and fibro-epithelioma of Pinkus lack eccrine differentiation

Syringoma (Figure 19)

Clinical

- Multiple flesh-colored or faintly yellow papules on the eyelids or upper face
- Other sites may also be involved, and linear and eruptive variants occur
- Clear cell variants may be associated with diabetes

Microscopic

- A fairly well circumscribed but unencapsulated neoplasm involving the mid to upper dermis composed of eccrine derived cords and ducts



Fig. 18. Eccrine syringofibroadenoma.

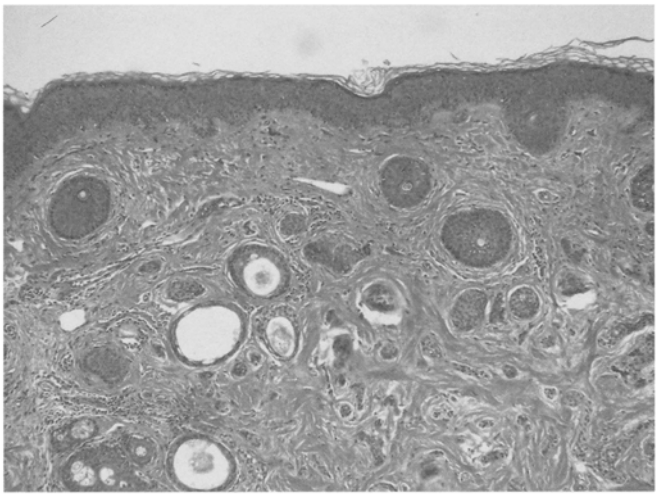


Fig. 19. Syringoma.

- The cords may show characteristic tadpole shaped forms
- Two or more cell layers with an internal eosinophilic cuticle and varying degrees of clear cell change line the ducts
- In general, the tumor does not infiltrate the deep dermis or subcutaneous fat, lacks mitotic activity and necrosis and has no significant pleomorphism

Immunophenotype

- Eccrine-derived tumors typically stain positively for the cytokeratins, EMA and CEA, which highlights the luminal aspect of the eccrine ducts

Differential Diagnosis

- Desmoplastic trichoepithelioma has numerous keratotic cysts, frequent calcification and lacks eccrine duct formation
- Microcystic adnexal carcinoma is much more infiltrative and typically involves the deep dermis and subcutaneous fat

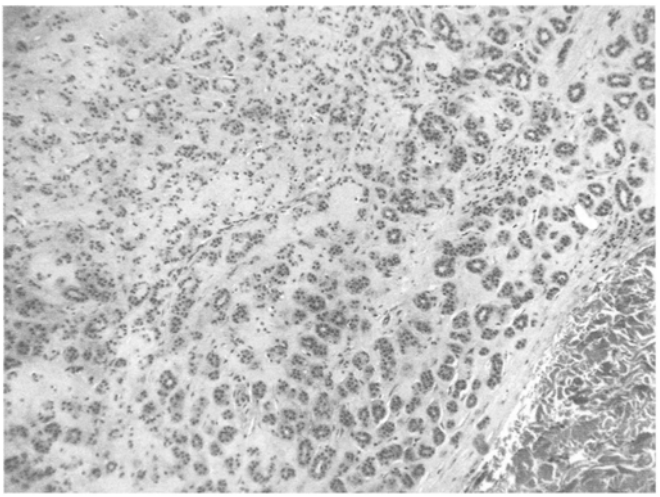


Fig. 20. Chondroid syringoma.

Chondroid Syringoma (Benign Mixed Tumor, Figure 20)

Clinical

- A benign, slowly growing, typically solitary tumor nodule on the head and neck; other sites may be involved

Microscopic

- A well-circumscribed, biphasic tumor nodule located within the dermis and/or the subcutaneous fat
- Epithelial cords, trabeculae and ducts are embedded in an abundant myxoid, fibromyxoid or cartilaginous matrix
- The epithelial component lacks nuclear pleomorphism, infiltration, necrosis and mitotic activity
- The ducts may show eccrine and/or apocrine differentiation

Differential Diagnosis

- Pleomorphic adenoma (benign mixed tumor of the salivary glands) should be differentiated from chondroid syringoma because of its tendency to recurrence and, possibly, malignant transformation
- As these tumors are similar histologically, location and the presence of adjacent normal salivary glands are the most reliable features used to separate these entities

Malignant Chondroid Syringoma

Clinical

- A rare, highly malignant tumor with a predilection for the distal extremities
- These tumors frequently recur and metastasize and are associated with increased mortality

Microscopic

- Malignant appearing, infiltrating epithelial cords, ducts and sheets that overgrow the benign mesenchymal matrix
- Necrosis, mitoses and nuclear pleomorphism are present
- An adjacent benign mixed tumor is not typically seen

Differential Diagnosis

- Carcinosarcoma shows a malignant mesenchymal component in addition to an epithelial malignancy

Papillary Eccrine Adenoma

Clinical

- A firm, pink to tan nodule on the distal extremities of adolescents and young adults with a female predominance
- Blacks are more commonly affected than whites

Microscopic

- A fairly well circumscribed but unencapsulated proliferation of eccrine ducts and duct-like structures within the dermis
- The ducts are lined by a multilayered cuboidal epithelium without apical snouts
- Micropapillary projections and transluminal bridging may be seen
- The tumor stroma is fibrotic and frequently hyalinized. Cribiform structures, necrosis, mitotic activity and nuclear pleomorphism are absent

Differential Diagnosis

- Aggressive digital papillary adenoma/adenocarcinoma (*see* below)

Aggressive Digital Papillary Adenoma/ Adenocarcinoma

Clinical

- Asymptomatic flesh-colored nodule on the digits of middle aged adults
- The recurrence rate is approximately 50% for these tumors, and the overtly malignant lesions have a metastatic rate of approximately 25–40%

Microscopic

- Generally, an unencapsulated and poorly circumscribed proliferation of eccrine ducts, tubules, cysts and nests within the dermis and/or subcutaneous fat
- The ducts and cystic structures are lined by a multilayered epithelium with abundant micro- and macropapillae
- Cribiform structures are frequently identified
- Varying degrees of nuclear pleomorphism, mitotic activity and necrosis may be seen
- Tumor grade correlates with metastatic potential, but all forms may metastasize
- Note: all of these lesions are best classified as adenocarcinomas due to their propensity for recurrence
- A histologic grade should be given as a prognostic indicator for the risk of metastases

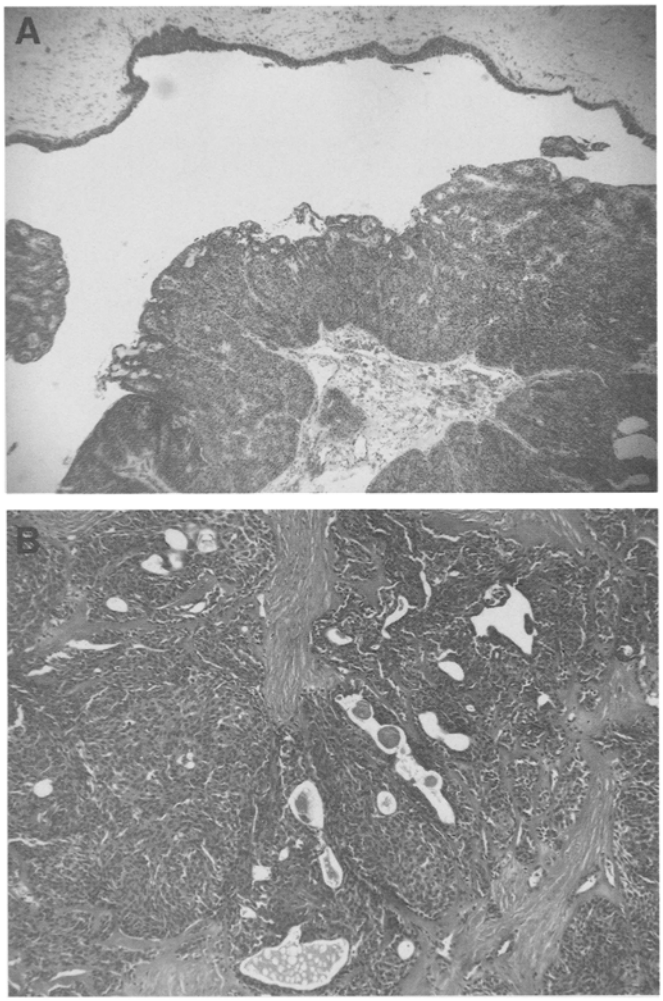


Fig. 21. Nodular hidradenoma.

Differential Diagnosis

- Papillary eccrine adenoma does not show the infiltration, nuclear atypia, mitotic activity or the cribiforming of the aggressive digital papillary adenocarcinoma

Nodular Hidradenoma (Clear Cell Hidradenoma, Solid-Cystic Hidradenoma and Eccrine Acrospiroma, Figure 21)

Clinical

- Solid or cystic, intradermal nodule 0.5–2.0 cm in diameter
- These tumors are usually solitary but may be multiple
- The head, neck and extremities are most commonly involved
- Predominates in young adults with a slight female predominance

Microscopic

- A well-circumscribed and often pseudoencapsulated tumor composed of a single lobule or, more often, multiple lobules of eosinophilic to clear cells in the dermis
- Cystic change may be prominent
- Tubular structures lined by cuboidal to columnar cells with an eosinophilic cuticle are evident in most tumors and are important in proper classification
- Foci of squamous and/or mucinous differentiation may be seen
- While this tumor is predominantly intradermal, occasional attachments may be seen to the overlying epidermis
- Necrosis, mitotic activity and nuclear pleomorphism are absent or minimal in extent

Hidradenocarcinoma (Malignant Nodular Hidradenoma)

Clinical

- Similar distribution to their benign counterparts but occur in older individuals (>50 years of age)
- Recurrence and metastatic rate is approximately 50%

Microscopic

- Like the hidradenoma, this tumor is composed of eosinophilic and/or clear cells forming lobules within the dermis
- The malignant variants, however, are asymmetrical, infiltrating, mitotically active and demonstrate nuclear pleomorphism and/or necrosis

Differential Diagnosis

- Clear cell squamous cell carcinoma, clear cell renal cell carcinoma, clear cell melanoma and trichilemmal carcinoma
- Look for tubular structures with an eosinophilic cuticle to confirm eccrine differentiation; CEA may be useful in that it highlights the luminal border of eccrine-derived structures

Hidroacanthoma Simplex (Intraepidermal Poroma)

Clinical

- A rare, benign variant of poroma typically involving the extremities of older individuals

Microscopic

- An intraepidermal proliferation (Borst-Jadassohn phenomenon) of round to faintly spindled cells with eosinophilic to faintly clear cytoplasm
- Intracytoplasmic glycogen is evident on PAS staining
- Rare eccrine ducts/tubules may be seen
- The individual cells are remarkably uniform and lack nuclear atypia
- The tumor cells are sharply demarcated from the squamous cells of the adjacent epidermis

Eccrine Poroma (Figure 22)

Clinical

- A red to flesh-colored tumor found most frequently on the sole of the foot or hand, but other sites may be involved
- These tumors may reach many centimeters in diameter and may be pedunculated



Fig. 22. Eccrine poroma.

- While the majority of these tumors are solitary, multiple lesions may be seen (eccrine poromatosis)

Microscopic

- This tumor is composed of numerous cords or trabeculae of small rounded tumor cells which rain down form the epidermis into the dermis in a fairly circumscribed manner
- The epidermal component is similar to hidroacanthoma simplex while the dermal component often shows numerous well-formed lobules with frequently conspicuous duct formation
- Cystic change is typically less than that seen in hidradenoma while the degree of epidermal involvement is significantly greater
- The tumor cells show intercellular bridges and should not be confused with squamous cells that are larger and more polygonal
- Poromatous lesions that are entirely limited to the dermis are often call dermal duct tumors

Porocarcinoma (Malignant Eccrine Poroma)

Clinical

- The malignant counterpart to the eccrine poroma affects similar sites but tends to occur in older individuals with a long history of progressive tumor growth

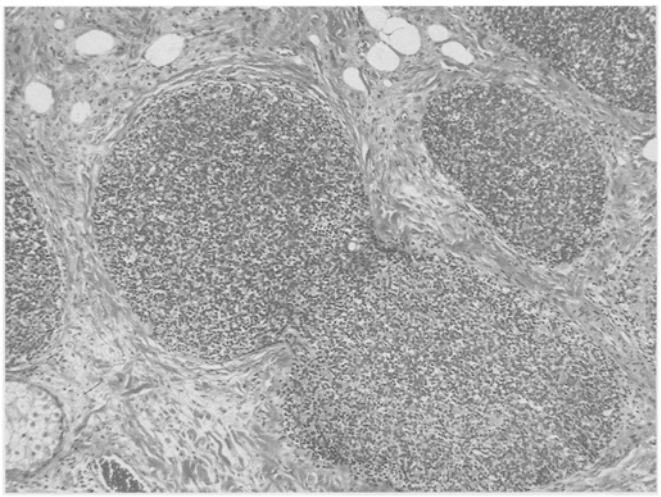


Fig. 23. Cylindroma.

- The recurrence and metastatic rate approaches 25%
- Multiple cutaneous metastases are not uncommon

Microscopic

- Like their benign counterparts, epidermal, dermal and mixed epidermal-dermal variants are seen
- The epidermal variants and the cutaneous metastases typically show frank pagetoidosis with scattered foci of ductal differentiation
- The mixed variants are by far the most common and have a similar architecture to their benign counterpart; however, these tumors are infiltrative, mitotically active and demonstrate nuclear pleomorphism and occasionally perineural and capillary-lymphatic invasion

Cylindroma and Malignant Cylindroma (Figure 23)

Clinical

- Solitary or multiple, red to purple nodules on the head, neck or scalp
- Multiple tumors (turban tumors) are inherited in a autosomal dominant fashion and may be associated with multiple trichoepitheliomas

Microscopic

- Multiple, dermal based lobules are found in the dermis and have an interlocking or "jigsaw puzzle" appearance
- The individual lobules are surrounded by an eosinophilic basement membrane
- Two cell types are evident within the lobules: a lymphocyte-like population of cells with hyperchromatic nuclei which predominate at the periphery of the lobules and a population of larger cells with oval, vesicular nuclei which predominate centrally
- Hylanizing basement membrane-like material is also frequently evident within the lobules

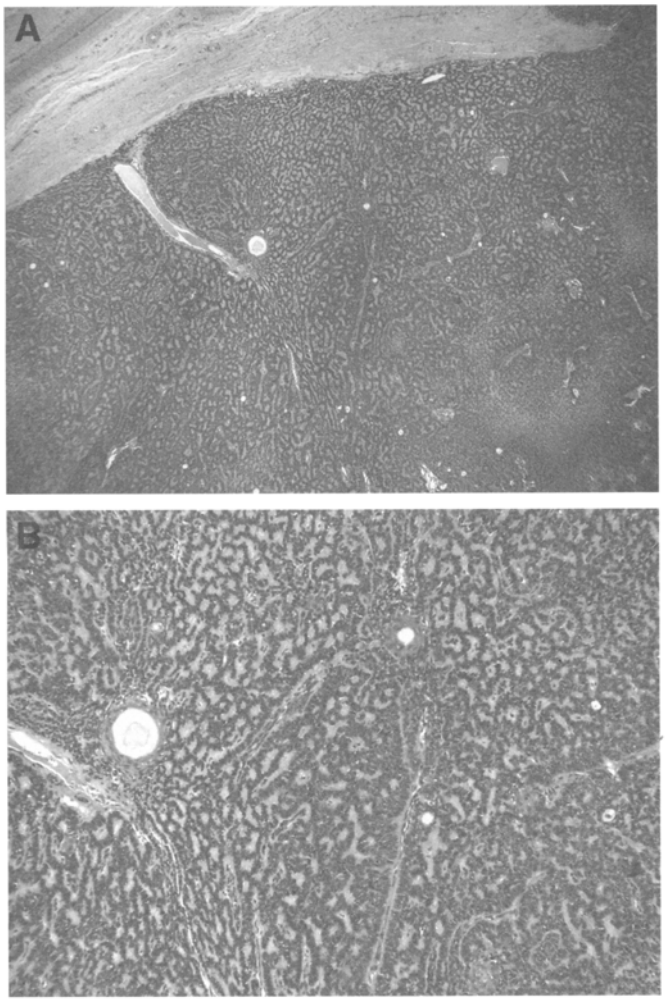


Fig. 24. Eccrine spiradenoma.

- Malignant variants demonstrate nuclear pleomorphism, mitotic activity, loss of the surrounding basement membrane and infiltration of adjacent tissue
- Malignant variants are rare and may arise in the background of multiple benign cylindromas

Eccrine Spiradenoma and Malignant Eccrine Spiradenoma (Figure 24)

Clinical

- Usually solitary, blue to flesh-colored, intradermal nodules on the ventral aspect of the body
- These tumors are frequently painful. Rarely, multiple tumors may be seen in a linear or zosteriform distribution

Microscopic

- One or more, basophilic tumor lobules are evident in the dermis and are usually encapsulated
- The lobules are composed of two cell types similar to the cylindroma: a small, lymphocyte-like population and a larger cell type with oval, vesicular nuclei
- Ductal differentiation may be conspicuous within the lobules, and pseudovascular spaces may give a hemangiomatous quality to the lesion
- The intervening stroma often demonstrates lymphangiectasia
- The rare malignant variants require an adjacent benign focus of typical microscopy for confident diagnosis
- The malignant variants are characterized by infiltration, mitoses, nuclear pleomorphism, necrosis and lymphatic invasion

Eccrine Duct Carcinoma

Clinical

- A nodular and often ulcerated lesion of long standing duration found most commonly on the head, neck and extremities of older adults
- Approximately 50% metastasize to lymph nodes or visceral sites

Microscopic

- An infiltrating dermal tumor composed of strands, trabeculae and tubules with varying degrees of lumen formation
- The histologic pattern is very similar to ductal carcinoma of the breast, which should always be excluded clinically
- There is at least some degree of nuclear pleomorphism, and nucleoli are frequently prominent
- Mitotic figures and necrosis may also be identified

Syringoid Eccrine Carcinoma (Eccrine Epithelioma)

Clinical

- Typically, a plaque or an ulcerated tumor of the scalp of middle-aged adults
- This tumor is locally aggressive with frequent recurrences, but metastases are rare

Microscopic

- A dermal-centered tumor showing extensive infiltration with involvement of the subcutaneous fat
- This tumor is composed of infiltrating cords and trabeculae with faint lumen formation and a dense, hyalinizing stroma
- Unlike microcystic adnexal carcinoma, keratocysts are rarely present
- The individual cells often have basaloid features but lack peripheral retraction
- Nuclear pleomorphism is mild, and mitotic figures are scarce
- Perineural invasion is frequent

Microcystic Adnexal Carcinoma (Figure 25)

Clinical

- A flesh-colored to yellow, slowly growing firm plaque or nodule involving the head, neck or face of older adults

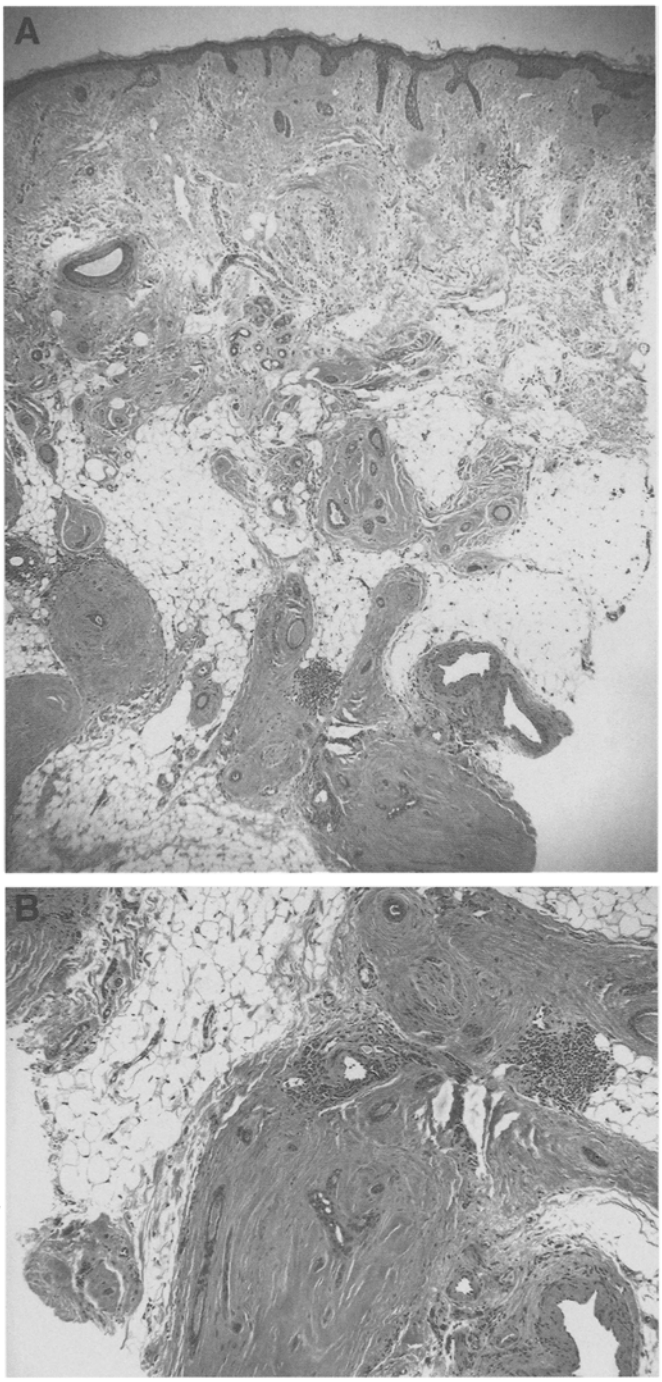


Fig. 25. Microcystic adnexal carcinoma.

- Like syringoid eccrine carcinoma, this is a locally aggressive tumor with frequent recurrences but with no tendency to metastasize

Microscopic

- A dermal-centered tumor showing extensive infiltration of the deep dermis and subcutaneous tissues
- Keratocysts, trabeculae and ductules are evident throughout the lesion, but keratocysts tend to predominate superficially while trabeculae predominate at the deeper aspect of the tumor
- The middle of the tumor shows an admixture of all forms giving this tumor a triphasic or trilayered look from superficial to deep
- The individual epithelial units are frequently invested by a dense fibrous stroma giving this tumor a sclerotic appearance
- Perineural invasion is common while nuclear pleomorphism and mitotic activity are rare

Mucinous Eccrine Carcinoma

Clinical

- A flesh-colored to blue nodule on the head and neck region (particularly the eyelid) of older adults with a male predominance

Microscopic

- A dermal based tumor showing islands of relatively bland epithelial cells floating in pools of mucin similar to colloid carcinoma of the breast

Adenoid Cystic Carcinoma

General

- A rare, primary cutaneous neoplasm showing a similar microscopic to its counterparts elsewhere but having a less aggressive course

Mucoepidermoid Carcinoma

General

- A rare primary tumor of skin showing similar histologic features to its salivary gland counterpart

Apocrine-Derived Tumors and Proliferations

Apocrine Nevus

Clinical

- A rare lesion typically presenting as a papule in the axilla or on the scalp

Microscopic

- An increase in the number or size of mature appearing apocrine glands

Syringocystadenoma Papilliferum (Figure 26)

Clinical

- Typically a solitary, verrucous to papillary lesion on the scalp, face or neck, but other sites may be involved
- In children, this tumor frequently arises within a nevus sebaceous

Microscopic

- A partially cystic, dermal centered tumor showing overlying epidermal invagination

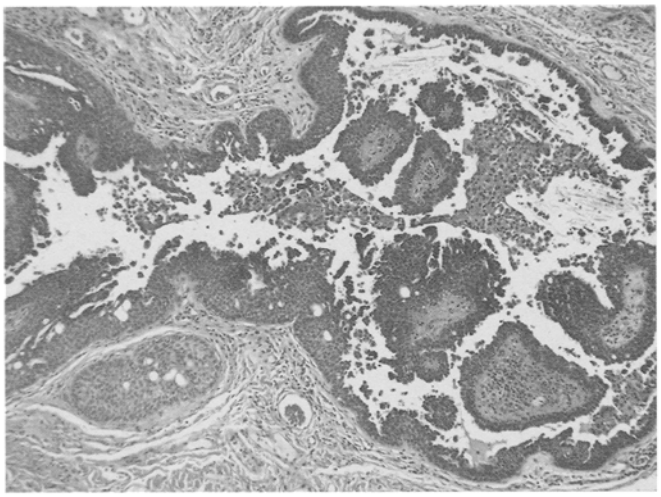


Fig. 26. Syringocystadenoma papilliferum.

- The cystic space contains abundant papillary structures lined by a bilayered epithelium with apical snouts, consistent with apocrine differentiation
- The fibrovascular cores contain abundant plasma cells

Hidradenoma Papilliferum

Clinical

- Typically a solitary, asymptomatic nodule presenting in the genital region of females
- Similar lesions have been described within the ear, nipple and eyelid

Microscopic

- A well demarcated, dermal-based neoplasm showing no involvement of the overlying epidermis
- This tumor is also frequently cystic in areas and is characterized by numerous trabeculae, epithelial fronds and papillary structures lined by a bilayered epithelium showing apocrine differentiation (apical snouts)
- The stroma is fibrovascular and lacks the plasma cells of syringocystadenoma papilliferum
- Occasional cases show a more pronounced fibrous stroma with a lobular architecture akin to fibroadenoma of the breast
- Rare cases show malignant transformation with high-grade nuclear features, frequent mitoses, necrosis and infiltration

Tubular Apocrine Adenoma (Figure 27)

Clinical

- A well-defined nodule occurring most commonly on the scalp of adults

Microscopic

- An unencapsulated, but well-demarcated proliferation of numerous ducts/glands lined by a bilayered to multilayered epithelium showing apocrine differentiation

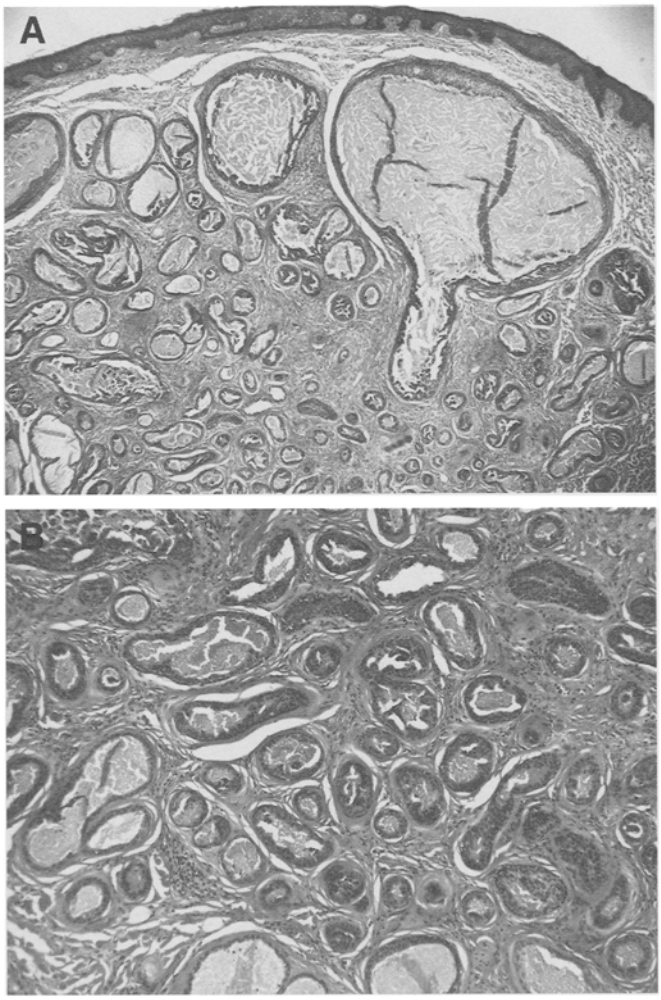


Fig. 27. Tubular apocrine adenoma.

- Small papillary structures and occasional cribiforming may be seen and resemble proliferative lesions in the breast
- These lesions may show some degree of nuclear atypia and mitotic activity but generally are not considered carcinomas unless obvious infiltration of surrounding tissues is seen

Apocrine Carcinoma

Clinical

- A rare primary tumor of skin that typically presents as an erythematous nodule with or without ulceration in older adults
- A variety of sites may be affected including the scalp, eye, ear and anogenital regions amongst others
- Recurrences and metastases may occur

Microscopic

- A variety of histologic appearances may be present including cystic, papillary, sheet-like and ductal variants

- Infiltration of adjacent tissues is seen, and pagetoidosis may be evident
- Nuclear pleomorphism may be mild to marked, and varying degrees of mitotic activity and necrosis may be evident:
  - By definition, areas of apocrine differentiation should be identified, at least focally

Differential Diagnosis

- Apocrine carcinoma of the breast has similar histologic and immunophenotypic characteristics and should be excluded clinically

Neuroendocrine-Derived Tumors

Merkel Cell Carcinoma (Figure 28)

Clinical

- An aggressive neoplasm typically presenting as a slowly growing nodule on the sun exposed skin (head and neck region) of older adults
- The recurrence and metastatic rate is approximately 40–50%

Microscopic

- A variety of histologic forms may be seen and include sheet-like, ribboned, nested, trabecular and organoid variants
- Pseudorosettes may be prominent
- These tumors are typically dermal based but frequently involve the subcutis and may show an intraepidermal growth pattern
- Focal areas of squamous, eccrine or sebaceous differentiation may be seen, and these tumors may arise in conjunction with another, histologically distinct neoplasm
- The cytologic and immunophenotypic appearance is characteristic and common to all variants
- Cytologically, the tumor cells have very high nuclear/cytoplasmic ratios, indistinct cell borders, hyperchromatic, and finely granular nuclei with inconspicuous nucleoli and thin nuclear membranes
- Nuclear molding and mitoses are abundant
- Immunophenotypically, the tumor cells express low molecular weight cytokeratin (CAM 5.2) in a perinuclear dot-like pattern which may also be seen with neurofilament staining
- Cytokeratin 20 staining is generally positive, and these tumors express a variety of neuroendocrine markers including neuron-specific enolase, chromogranin, synaptophysin and neurofilament, but are generally negative for S-100 protein and vimentin

Differential Diagnosis

- Merkel cell carcinomas must be differentiated from a variety of other neuroendocrine tumors of either metastatic or primary origin
- Small cell neuroendocrine carcinomas from visceral sites metastatic to skin have an essentially identical histologic appearance but are cytokeratin 20 negative
- Cutaneous neuroblastoma generally shows a filamentous background and/or focal ganglion cell differentiation and is typically cytokeratin negative (except for the olfactory variant)
- Primitive neuroectodermal tumors/extraosseous Ewing's sarcomas are usually cytokeratin negative and typically express MIC-2

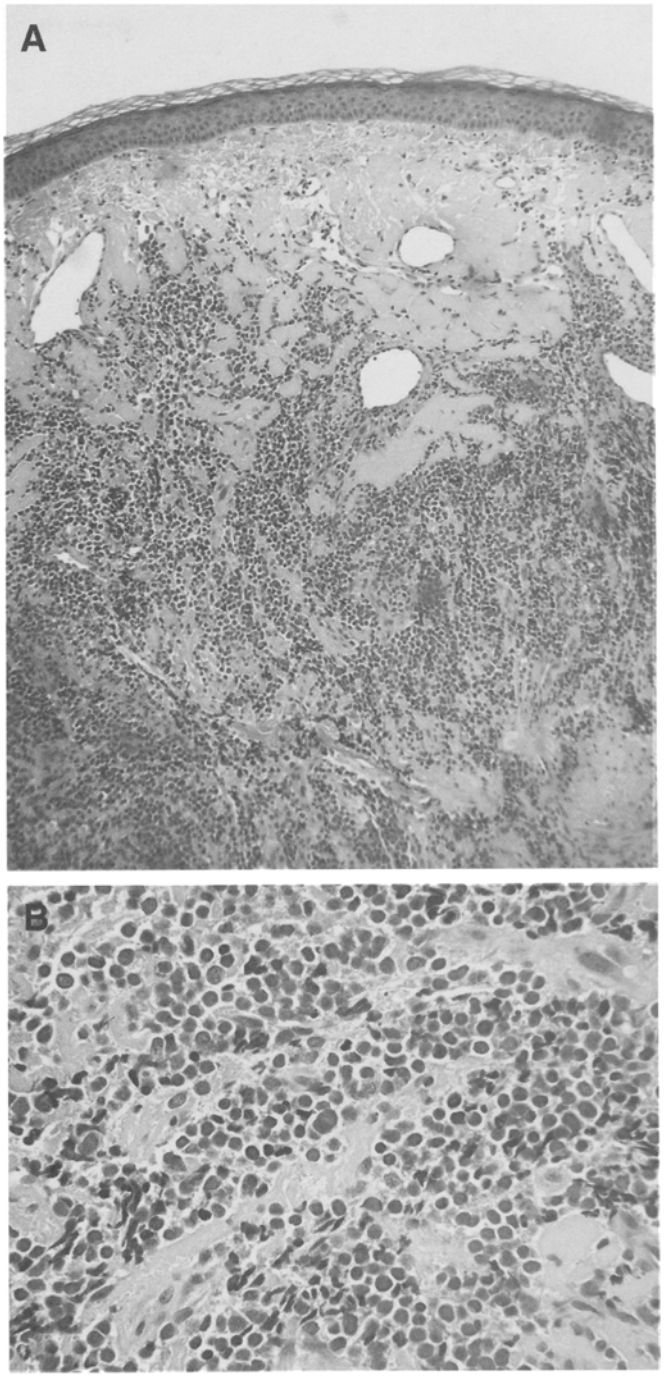


Fig. 28. Merkel cell carcinoma.

SOFT TISSUE NEOPLASMS AND DEVELOPMENTAL ANOMALIES

ADIPOCYTE-DERIVED TUMORS AND PROLIFERATIONS

Lipoma

Clinical

- A sporadic or multifocal tumor of the middle aged to elderly typically involving the trunk and/or extremities

Microscopic

- A thinly encapsulated proliferation of mature adipose tissue
- The adipose tissue may be accompanied by a wide variety of other types of mesenchymal-derived tissue: fibrous (fibrolipoma), bone (osteolipoma), cartilage (chondroid lipoma), bone marrow (myelolipoma), mucoid substances (myxoid lipoma), smooth muscle (myolipoma) and smooth muscle and vessels (angiomyolipoma)

Angiolipoma

Clinical

- A painful, subcutaneous nodule(s) involving the upper extremities of young adults

Microscopic

- Thinly encapsulated proliferations of mature adipocytes and variably sized, thin walled vessels Microthrombi are readily identified within the vessel lumina
- A cellular variant showing numerous small vessels with few adipocytes exists and must be differentiated from other vascular tumors that lack the proliferation of mature adipocytes

Spindle Cell Lipoma

Clinical

- A solitary, painless, subcutaneous nodule with a predilection for the base of the neck of middle aged to older adults

Microscopic

- An encapsulated proliferation of mature adipocytes and bland, bipolar spindle cells embedded in a myxoid matrix with collagen fibers
- The spindle cells may predominate and typically show bland, uniform features
- Lipoblasts and the plexiform capillary network of myxoid liposarcoma are absent
- Occasional cases show bizarre, multinucleated cells and merge with pleomorphic lipoma

Pleomorphic Lipoma

Clinical

- Similar to spindle cell lipoma

Microscopic

- Similar to spindle cell lipoma with the addition of numerous, multinucleated (floret cells) cells with hyperchromatic, peripherally situated nuclei

Lipoblastoma and Lipoblastomatosis

Clinical

- These are tumors of infants and young children and typically present as painless masses on the extremities in a localized (lipoblastoma) or diffuse (lipoblasto-matosis) fashion
- The latter may recur with incomplete excision

Microscopic

- Multilobular proliferations of immature and mature adipocytes embedded in a myxoid matrix and separated by thin fibrous septae
- The adipocytes may show a wide spectrum of differentiation from spindle cells to multivacuolated lipoblasts to mature, univacuolated adipocytes
- These lesions tend to mature histologically with time

Lipofibromatous Hamartoma of Nerve

Clinical

- A tumor-like condition that presents as a mass of the wrist and/or forearm
- Typically, these patients are young children, but adult presentations also occur
- Sensory defects, parathesias, pain and macrodactyly may be prominent
- Due to the intimate association of this proliferation with nerves, surgical excision is contraindicated and may lead to permanent sensorimotor impairment

Microscopic

- A proliferation of benign fibroadipose tissue is evident in and around nerve fibers which show secondary degeneration, atrophy and fibrosis

Lipomatosis

Clinical

- Multiple clinical forms exist including a diffuse variant typically involving the extremities or trunk of young children, a symmetrical variant (Madelung's disease) involving the neck region of middle-aged adult males as well as visceral and pelvic variants

Microscopic

- All are unencapsulated proliferations of mature adipose tissue involving the subcutis, skeletal muscle and, occasionally, other structures

Nevus Lipomatosus Superficialis

Clinical

- A hamartomatous proliferation typically presenting as multiple, polypoid papules or plaques on the buttocks, posterior trunk or thigh of children to young adults

Microscopic

- Small lobules of mature adipocytes are evident in the superficial and mid dermis and may be associated with keratin plugs and loss of adnexal structures

Hibernoma

Clinical

- A slow-growing, asymptomatic mass of the chest or upper back of young to middle-aged adults
- Other sites may also be affected

Microscopic

- An encapsulated, multilobular tumor composed of an admixture of multivacuolated and univacuolated adipocytes and large cells with eosinophilic cytoplasm and distinct cell membranes

Liposarcoma

Clinical

- These are rare tumors of skin that generally present as slowly growing subcutaneous masses in older adults

Microscopic

- The myriad of histologic types of liposarcoma are addressed in detail elsewhere
- Generally, the liposarcomas involving skin are of the well-differentiated (atypical lipoma) or myxoid types
- The former has lipoma-like, sclerosing and spindle cell variants which may recur but typically do not metastasize

Neural-Derived Tumors and Proliferations

Neurofibroma

Clinical

- Solitary and multiple forms exist
- The solitary variant is typically a soft, polypoid, flesh-colored tumor occurring in adults
- The multiple or diffuse variant has a strong association with neurofibromatosis type 1 and may show extensive, cosmetically deforming lesions with a bag of worms appearance and feel
- The diffuse variant is seen more frequently in childhood and adolescence
- The diffuse variant has definite malignant potential while the sporadic variant lacks this characteristic

Microscopic

- A variety of histologic subtypes exist, but all are characterized by a proliferation of wavy, pointed spindle cells embedded in a variably collagenous to myxoid matrix
- These tumors are unencapsulated but are generally well circumscribed
- They not infrequently incorporate dermal adnexal structures, but direct adnexal invasion is rare
- Plexiform, diffuse, myxoid and pacinian variants exist
- The plexiform variant is thought to be diagnostic of neurofibromatosis while the diffuse variant may also be associated with this disease at an increased rate

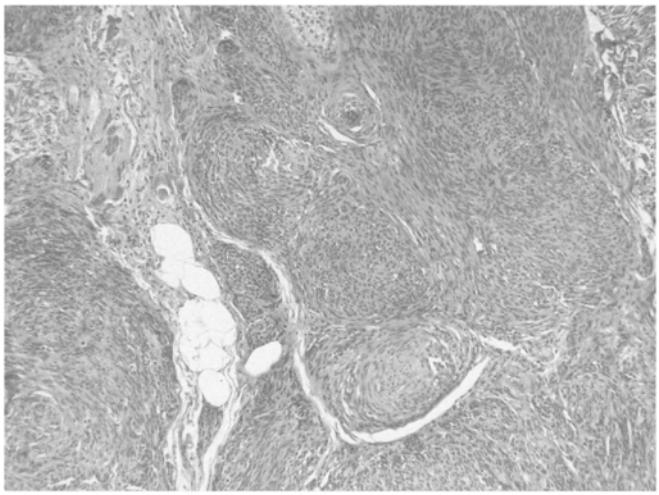


Fig. 29. Plexiform schwannoma.

Special Studies

- Neurofibromas are derived from nerve and, as such, demonstrate positive staining for axonal markers such as neurofilament and silver impregnation techniques
- Similar to other neural-derived tumors, these lesions are also positive for S-100 protein, CD57 and neuron-specific enolase

Schwannoma (Neurilemmoma, Figure 29)

Clinical

- A peripheral nerve sheath derived tumor that generally presents as a solitary nodule/mass on the head, neck or extremities of adults
- Rarely, multiple tumors may be evident (schwanno-matosis), and at least some of these cases are associated with neurofibromatosis type 2
- In general, schwannomas have little, if any, malignant potential

Microscopic

- A well-circumscribed, encapsulated tumor within the subcutis or deeper tissues
- Occasionally, dermal involvement may be evident
- The tumor is composed of spindle cells with wavy, pointed nuclei embedded in a collagenous and highly vascular stroma

- Classically, cellular, Antoni A areas with palisading, Verocay bodies are admixed with paucicellular, myxoid, Antoni B areas
- Degenerative changes are frequent findings and include hyalinization, vascular thrombosis, dystrophic mineralization and hemorrhage
- The ancient variants typically show some degree of nuclear pleomorphism and enlargement with a smudgy chromatin pattern
- Plexiform variants exist and typically present in childhood or adolescence
- These tumors are composed of multiple, cellular, Antoni A-like, encapsulated nodules that must be differentiated from plexiform neurofibroma and plexiform fibrohistiocytic tumor
- Cellular variants are moderately to markedly cellular and may have mitotic activity. Nuclear pleomorphism and necrosis, however, are absent. Melanotic variants also exist and must be differentiated from malignant melanoma

Special Studies

- Schwannomas are derived from the peripheral nerve sheath and, therefore, lack axonal differentiation; that is, they are neurofilament and silver staining negative
- Schwann cells are S-100 protein positive and are generally surrounded by type IV collagen-rich basement membrane
- Epithelial membrane antigen typically stains the capsule of schwannomas

Traumatic Neuroma

Clinical

- Reactive, nonneoplastic proliferations of nerve in response to injury
- Typically present as small, often painful, nodules at sites of previous injury

Microscopic

- A well-localized but unencapsulated, haphazard proliferation of nerve fibers associated with dermal fibrosis (scar)

Palisaded and Encapsulated Neuroma (Solitary Circumscribed Neuroma, Figure 30)

Clinical

- Solitary, flesh-colored papule on the face of middle-aged to older adults

Microscopic

- A nodular to multinodular, often dumbbell-shaped proliferation of spindle cells embedded in a collagenous matrix
- These lesions are well circumscribed but only partially encapsulated
- The superficial component generally lacks a true capsule and tends to resemble a neurofibroma while the deep component is encapsulated and resembles a schwannoma

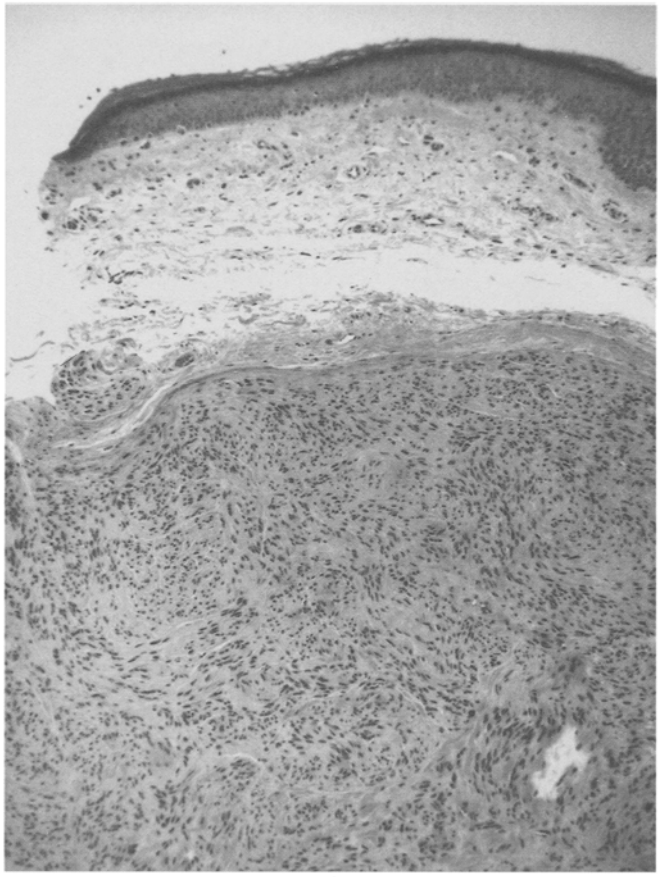


Fig. 30. Palisaded and encapsulated neuroma.

- The spindle cells demonstrate wavy, pointed nuclei and lack mitotic activity
- Contrary to its name, true nuclear palisading is rare in this lesion
- A nerve may be evident entering the base of the lesion

Special Studies

- Like neurofibroma, this lesion contains both axons and schwann cells and, hence, is S-100 protein and neurofilament positive

Granular Cell Tumor (Figure 31)

Clinical

- Slowly growing, sometimes painful, flesh-colored nodules with a predilection for the tongue, trunk and extremities of adults
- While usually solitary, multiple and familial variants exist

Microscopic

- Irregular fascicles and/or sheets of large, round to polygonal cells with eosinophilic, granular cytoplasm
- Cell borders are indistinct giving this tumor a syncytial appearance
- Nuclei are generally round to ovoid, central and monomorphic

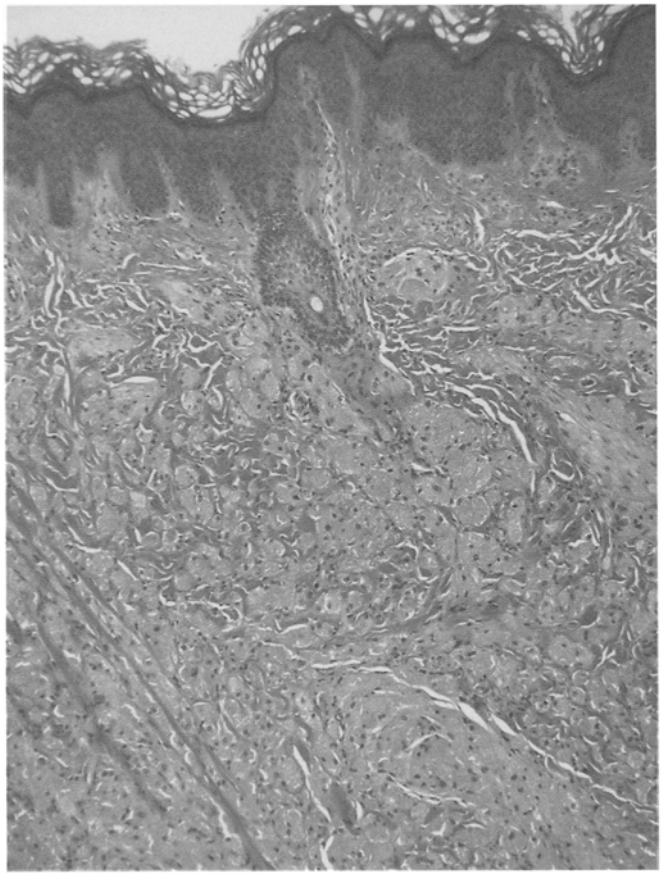


Fig. 31. Granular cell tumor.

- Nuclear pleomorphism, mitotic activity, necrosis and large tumor size may be associated with the rare malignant variants
- Prominent pseudoepitheliomatous hyperplasia of the epidermis is often seen overlying this tumor and must not be mistaken for squamous cell carcinoma

Special Studies

- While the cell of origin remains to be clarified, most authorities support a schwann cell derivation for these tumors
- Accordingly, these tumors are usually, but not always, S-100 protein and neuron specific enolase positive

Differential Diagnosis

- Secondary granular cell change is not an uncommon finding in other tumor types (dermatofibroma, neurofibroma, etc.) which should be excluded prior to making the diagnosis of granular cell tumor
- This tumor should also be differentiated from congenital epulis discussed below

Congenital Epulis

Clinical

- A polypoid gingival lesion in newborns that may spontaneously regress

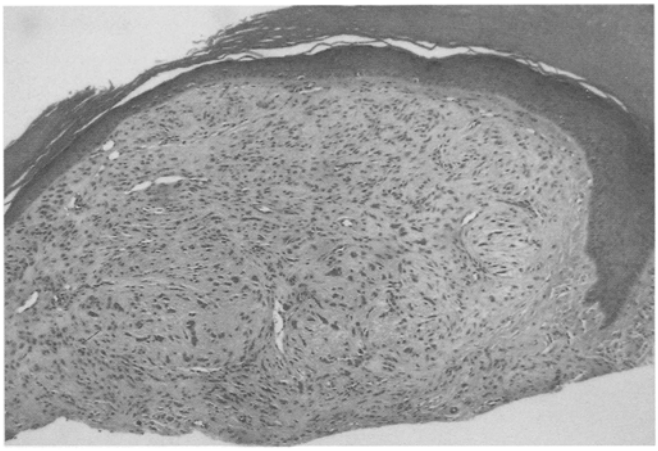


Fig. 32. Neurothekeoma.

Microscopic

- Similar to granular cell tumor, but these lesions are S-100 protein negative

Nerve Sheath Myxoma (NSM) and Cellular Neurothekeoma (Figure 32)

Clinical

- Soft, mobile, flesh-colored papules on the face or upper extremities of young adults
- These tumors may recur with incomplete excision

Microscopic

- NSM is a fascicular to lobular dermal tumor composed of spindle and stellate cells embedded in myxoid lobules which in turn are separated by fibrous septae
- Cellular neurothekeoma is composed of more uniform, epithelioid cells in nests and fascicles with minimal myxoid background material
- Mitotic activity and mild nuclear pleomorphism may be seen in both lesions

Special Studies

- NSM is typically S-100 protein+ and is likely derived from the peripheral nerve sheath
- Cellular neurothekeoma is S-100 protein– and its cell of origin is unclear
- The lack of S-100 protein positivity in the cellular variants allows these lesions to be readily distinguished from most melanocytic neoplasms

Perineurioma

Clinical

- A benign tumor of perineural origin that typically presents as a subcutaneous mass on the trunk and limbs of adults

Microscopic

- A well-circumscribed proliferation of bland spindle cells in fascicles with whorled and storiform areas

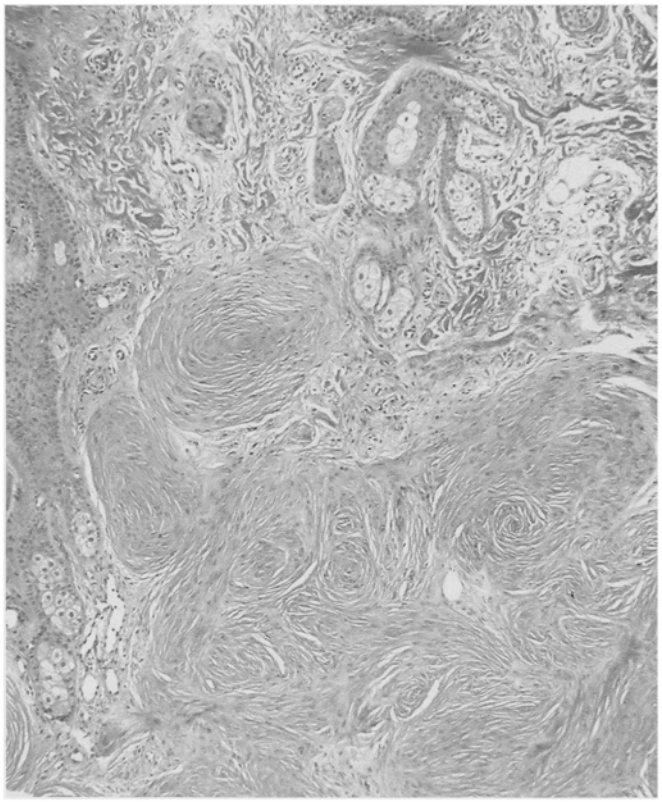


Fig. 33. Meningioma.

Special Studies

- Like perineural cells, this tumor is S-100 protien– and EMA+

Malignant Peripheral Nerve Sheath Tumor

General

- A rare, primary cutaneous malignancy frequently associated with neurofibromatosis type 1 when primary in the skin
- These lesions are discussed in detail in the soft tissue pathology chapter

Cutaneous Meningothelial Heterotopias/Meningiomas (Figure 33)

Clinical

- Classic meningocele is typically a transilluminating mass along the lower spine and represents a congenital defect
- Rudimentary meningocele is thought to be a herniation of the meninges into the superficial tissues of the scalp with a subsequent loss of its intracranial attachment
- Cutaneous meningioma comes in three forms: type I is congenital lesion involving the head and paravertebral regions of children and is secondary to misplaced arachnoid cells during embryogenesis; type II occurs on the head and neck region of adults and is thought to be secondary to a proliferation of arachnoid cells through a cranial foramina; type III represents a metastasis or direct extension of tumor into skin form an intracranial primary

Microscopic

- Meningoceles are typically cyst-like structures lined by arachnoid cells and having surrounding dense fibrous tissue with occasional collections of meningothelial cells in whorl-like structures
- Meningiomas are usually well-circumscribed deep dermal to subcutaneous proliferations composed of spindle cells arranged in fascicles and whorls with or without psammoma body formation
- Nuclear pleomorphism and mitotic activity may be seen, particularly in the type III variants
- Special studies
- Meningothelial proliferations are usually vimentin and EMA+
- Cytokeratin and S-100 protein may also be expressed by these tumors

Heterotopic Glial Tissue (Nasal Glioma)

Clinical

- Flesh-colored mass on the nasal bridge of infants to young adults Intranasal involvement may also be present
- Radiographic studies should be performed to exclude an intracranial attachment

Microscopic

- Nodules of benign eosinophilic, fibrillar, glial tissue within the deep dermis and subcutis
- Rarely, neuronal cells may also be seen

Smooth Muscle-Derived Tumors and Proliferations

Smooth Muscle Hamartoma

Clinical

- A congenital, sometimes pigmented, indurated plaque on the trunk which typically presents in infancy

Microscopic

- A haphazard proliferation of smooth muscle fascicles in the dermis with or without basilar epidermal hyperpigmentation

Becker's Nevus

Clinical

- An acquired, organoid, hyperpigmented plaque with hypertrichosis on the back of young adults and as adolescents
- This lesion may be associated with other congenital abnormalities

Microscopic

- Epidermal acanthosis and basilar hyperpigmentation occasionally associated with a mild haphazard proliferation of smooth muscle fascicles within the dermis

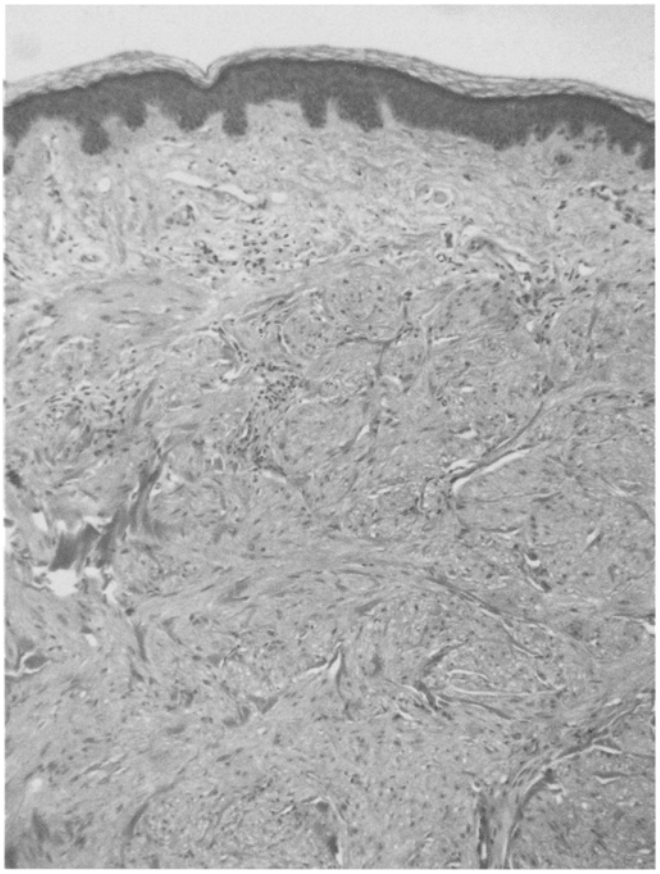


Fig. 34. Piloleiomyoma.

Piloleiomyoma (Pilar leiomyoma, Figure 34)

Clinical

- Multiple, somewhat painful papules or nodules on the trunk or extremities of young adults
- May be inherited in an autosomal dominant fashion

Microscopic

- A fairly well circumscribed yet irregular proliferation of smooth muscle fascicles within the dermis
- The individual cells have elongated eosinophilic cytoplasm and cigar-shaped nuclei
- No nuclear pleomorphism, mitotic activity or necrosis is evident

Angioleiomyoma (Figure 35)

Clinical

- A solitary, sometimes painful nodule on the extremities of adults

Microscopic

- A nodular, well-circumscribed proliferation of smooth muscle in fascicles admixed with numerous, variably sized vessels
- Degenerative changes are frequent

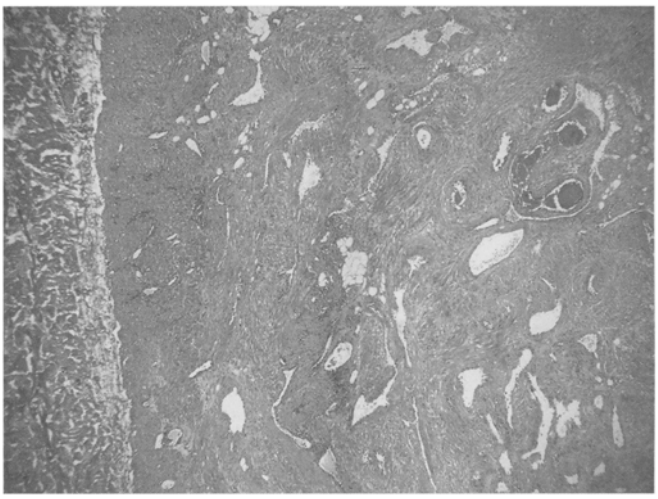


Fig. 35. Angioleiomyoma.

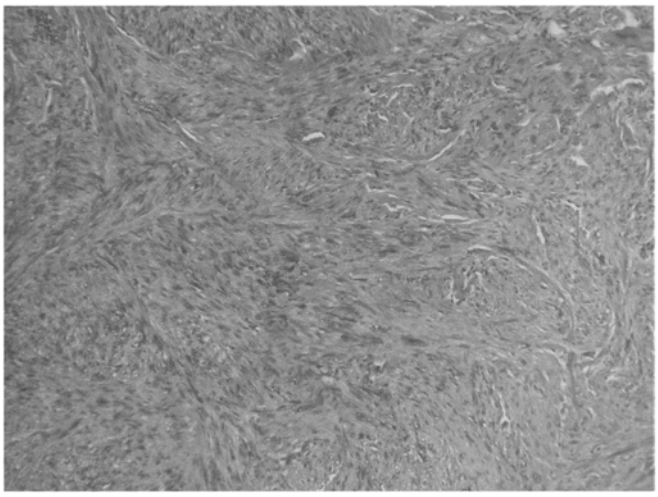


Fig. 36. Leiomyosarcoma.

Leiomyosarcoma (Figure 36)

Clinical

- Two clinical variants exist: a superficial or cutaneous variant and a deep or subcutaneous variant
- The former predominates on the limbs of young adults and is likely derived from the arrector pili muscle
- This variant may locally recur but generally does not metastasize
- The subcutaneous variant predominates on the limbs of the elderly and has both local recurrence and metastatic potential

Microscopic

- The cutaneous variant demonstrates an irregular, infiltrating and haphazard proliferation of smooth muscle bundles reminiscent of piloleiomyoma
- However, unlike piloleiomyoma, this tumor has low-grade nuclear pleomorphism, mitotic activity and, rarely, necrosis

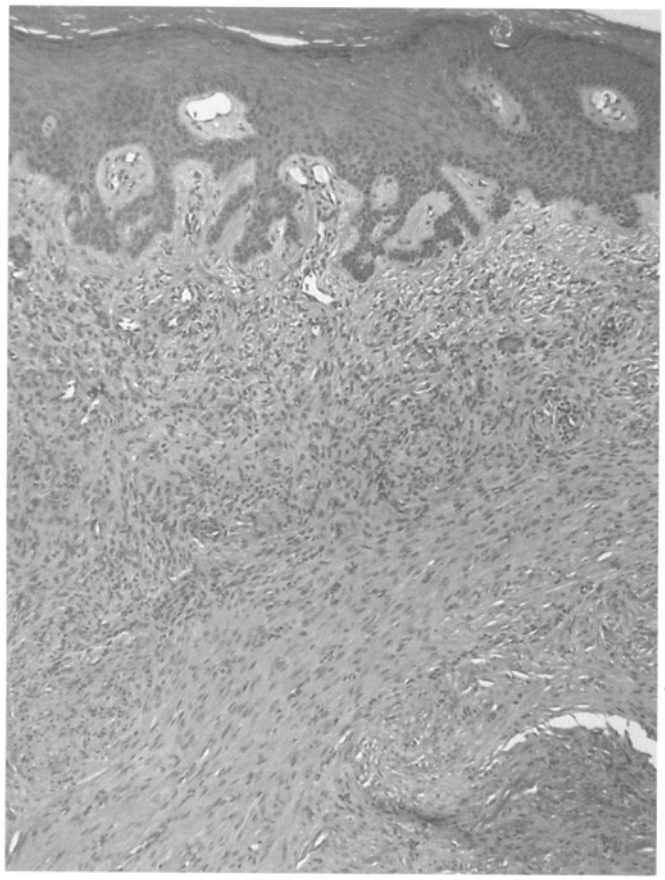


Fig. 37. Dermatofibroma.

- The deep or subcutaneous variant is akin to leiomyosarcomas arising elsewhere and consists of a nodular, at least focally infiltrating, proliferation of smooth muscle fibers in well-formed to ill-defined bundles with varying degrees of nuclear pleomorphism, mitotic activity and necrosis

Fibrohistiocytic, Histiocytic, and Langerhans' Cell-Derived Proliferations

Fibrous Histiocytoma (Dermatofibroma, Figure 37)

Clinical

- Usually single, occasionally multiple, slightly elevated, smooth, flesh-colored to hyperpigmented nodules on the extremities or trunk of adults

Microscopic

- Numerous subtypes have been described but all are generally made up of a proliferation of histiocytes, fibroblasts and collagenous tissue in varying proportions
- The prototypical lesion (dermatofibroma) consists of a fairly well circumscribed, unencapsulated, mid-dermal proliferation with feathery edges, an overlying Grenz zone and epidermal hyperplasia with basilar hyperpigmentation
- The cellular component consists of spindled, fibroblast-like cells admixed with plump histiocytic cells in an irregular fashion
- Storiform areas may be evident, and there may be focal extension into the subcutis
- Chronic inflammatory cells, multinucleated giant cells, xanthomatized histiocytes, and hemosiderin-laden histiocytes are also frequently identified within these lesions
- Important variants include atypical dermatofibroma (dermatofibroma with monster cells), aneurysmal fibrous histiocytoma and epithelioid cell histiocytoma, all of which may be mistaken for other more aggressive entities
- Atypical dermatofibroma is a lesion showing large, hyperchromatic, multinucleated giant cells in addition to typical dermatofibroma features and should be distinguished from atypical fibroxanthoma and malignant fibrous histiocytoma
- Aneurysmal fibrous histiocytoma is a fibrous histiocytoma with prominent intralesional hemorrhage and cystic, pseudovascular spaces
- This lesion should be distinguished from angiomatoid fibrous histiocytoma, a lesion of intermediate grade malignancy occurring in the pediatric population
- Epithelioid cell histiocytoma is composed of a polypoid well-circumscribed proliferation of angulated, epithelioid, histiocytic-appearing cells surrounded by an epidermal collarette
- This lesion should be distinguished from melanocytic tumors, both Spitz's nevus and melanoma

Special Studies

- Most fibrous histiocytomas express FXIIIa but are negative for CD34
- Dermatofibroma sarcoma protuberans tends to have the opposite staining pattern, but overlap and divergent staining patterns occasionally occur

Angiomatoid Fibrous Histiocytoma (Figure 38)

Clinical

- A fairly deep-seated, usually subcutaneous, nodule or mass within the extremities of children and adolescents
- This lesion is considered to be of borderline or intermediate malignancy and may recur and, rarely, metastasize

Microscopic

- A circumscribed, partially cystic and lobular mass usually centered on subcutaneous tissue
- This tumor is composed of an admixture of cystic, blood-filled pseudovascular spaces, myxoid lobules of histiocytic appearing cells and peripheral lymphocytic inflammation and fibrosis
- The neoplastic cells are somewhat spindled to plump, epithelioid cells with eosinophilic to amphophilic cytoplasm and mildly pleomorphic nuclei
- Mitotic figures may be evident

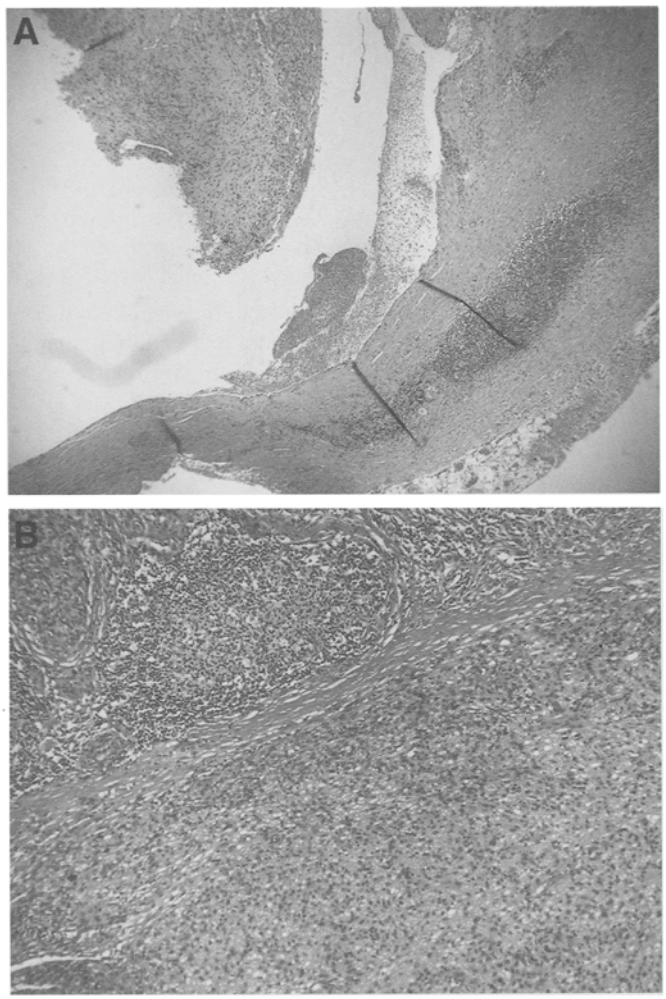


Fig. 38. Angiomatoid fibrous histiocytoma.

Special Studies

- The histiocytic-appearing cells often show expression of smooth muscle actin, desmin and CD34, suggesting to some a myofibroblastic derivation to this tumor

Plexiform Fibrohistiocytic Tumor

Clinical

- A slowly growing deep dermal to subcutaneous mass on the extremities of children to young adults
- This is a tumor of intermediate malignancy that may recur and rarely metastasizes

Microscopic

- An unencapsulated, irregular biphasic tumor consisting of short fibromatosis-like fascicles of plump spindle cells admixed with nodules of histiocytic and osteoclast-like giant cells with minimal nuclear pleomorphism
- The admixture of nodules and fascicles gives this tumor a plexiform appearance at low power

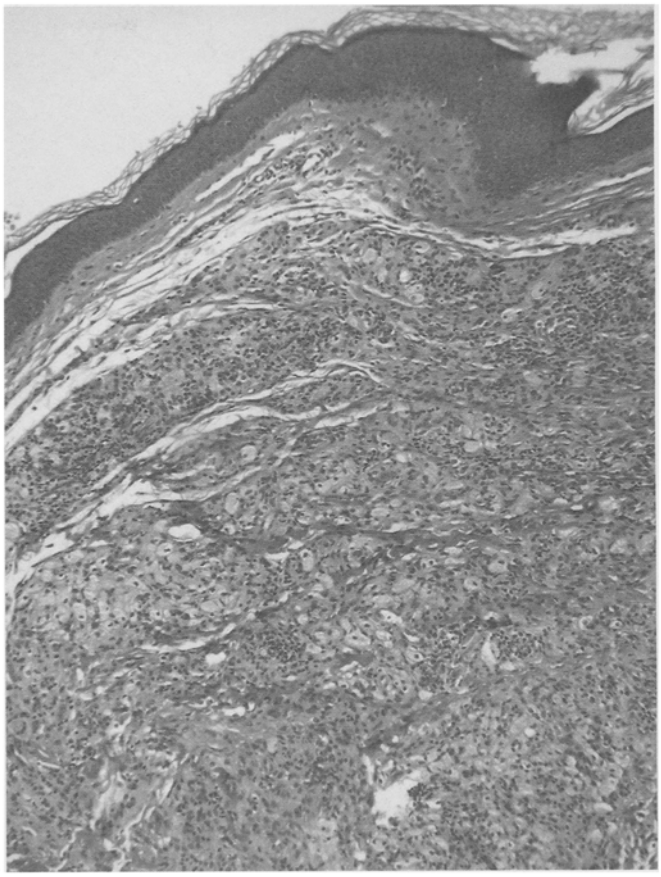


Fig. 39. Juvenile xanthogranuloma.

Juvenile Xanthogranuloma (Figure 39)

Clinical

- Solitary to multiple, yellow to red papules on the head and neck region of infants is the most common presentation
- However, adolescents and adults may also be affected, and other body sites may be involved
- Visceral involvement may be evident with the eye being the most common extracutaneous site of involvement
- Typically, the cutaneous lesions regress over time

Microscopic

- Fairly well circumscribed collection of histiocytes within the dermis admixed with Touton giant cells, xanthomatized histiocytes and chronic inflammatory cells
- The epidermis is spared, but periadnexal involvement is common
- Spindle cell and inflammatory cell rich variants exist

Reticulohistiocytoma and Multicentric Reticulohistiocytosis

Clinical

- Solitary and multicentric variants exist
- The former is usually a yellow to brown nodule on the upper body of adults while the latter shows multiple

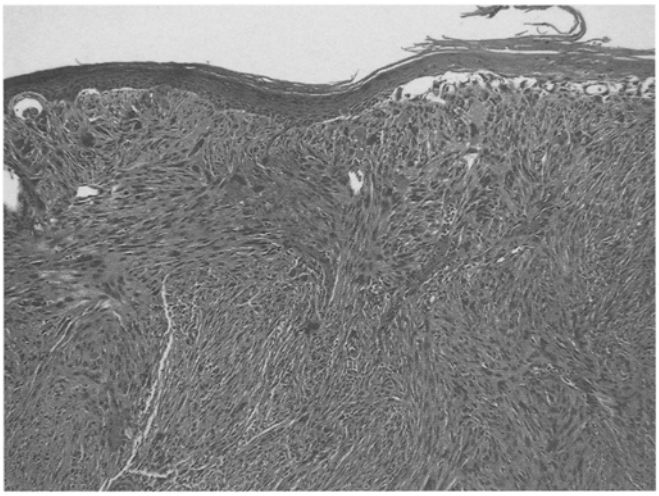


Fig. 40. Atypical fibroxanthoma.

lesions associated with a destructive arthritis and constitutional symptoms, also in adults

- Occasionally, the multicentric variant is associated with visceral neoplasia

Microscopic

- Both variants are characterized by fairly well circumscribed proliferations of large, eosinophilic histiocytes with "glassy" cytoplasm
- The individual cells may contain more than a single nucleus but Touton giant cells are usually absent, and xanthomatized histiocytes are not generally present
- Mild nuclear pleomorphism and admixed inflammation with eosinophils and lymphocytes may be evident

Atypical Fibroxanthoma (Figure 40)

Clinical

- Typically a solitary, often ulcerated polypoid nodule on the sun-exposed skin (head and neck) of the elderly
- A less common variant occurs on the trunk and extremities of young adults
- These tumors, when limited to superficial tissues, may locally recur but have minimal metastatic potential

Microscopic

- A nodular, often well circumscribed, proliferation of very pleomorphic epithelioid to spindle cells with frequent mitoses, often atypical
- These tumors are usually centered on the dermis and frequently abut the dermal-epidermal junction where they stop abruptly
- Epidermal ulceration is common, but true epidermal involvement with pagetoid spread should raise concerns about malignant melanoma or squamous cell carcinoma
- Rarely, the tumor is composed of spindle cells in poorly defined fascicles and may be mistaken for leiomyosarcoma
- While occasional tumors may show superficial involvement of the subcutaneous tissues, extensive subcutaneous involvement and/or prominent vascular invasion and necrosis should lead to an alternate diagnosis (e.g., malignant fibrous histiocytoma)

Special Studies

- This tumor is a diagnosis of exclusion; therefore, S-100 protein, cytokeratin and desmin should be negative by immunoperoxidase technique to exclude malignant melanoma, carcinoma and leiomyosarcoma, respectively
- Smooth muscle actin may be expressed by a subset of these tumors and is not indicative of smooth muscle differentiation (leiomyosarcoma) in the absence of desmin positivity

Malignant Fibrous Histiocytoma

General

- These tumors are rarely primary cutaneous lesions and have overlapping histologic features with atypical fibroxanthoma
- The latter tumor is often considered to be a superficial variant of malignant fibrous histiocytoma with minimal metastatic potential
- The term malignant fibrous histiocytoma should be used for those tumors that demonstrate deep tissue involvement, vascular invasion or extensive necrosis as detailed above
- The histologic subtypes and clinical distribution of this tumor are detailed in the soft tissue tumor chapter

Xanthomas and Xanthelasma (Figure 41)

Clinical

- Numerous clinical and histologic subtypes exist, many of which are related to systemic lipid abnormalities and represent storage disorders
- Eruptive:
  - Yellow papules on the buttocks and other sites associated with type I hyperliporoteinemia
- Tuberous:
  - Yellow papules and nodules on the extensor surfaces associated with hyperliporoteinemia types II-IV
- Tendinous:
  - Nodules or masses on the tendons of the extremities associated most frequently with type II hyperlipoproteinemia
- Planar:
  - Yellow papules and plaques that may involve intertriginous sites, palmar creases or more multiple sites in a diffuse fashion
  - The intertriginous variant is associated with type II hyperlipoproteinemia, the palmar variant with type III hyperlipoproteinemia, and the diffuse variant is often associated with hematopoeitic disorders
- Xanthelasma:
  - Yellow plaques on the eyelids, which are associated with lipid abnormalities in only approximately 50% of patients (type III hyperlipoproteinemia)
- Xanthoma disseminatum:

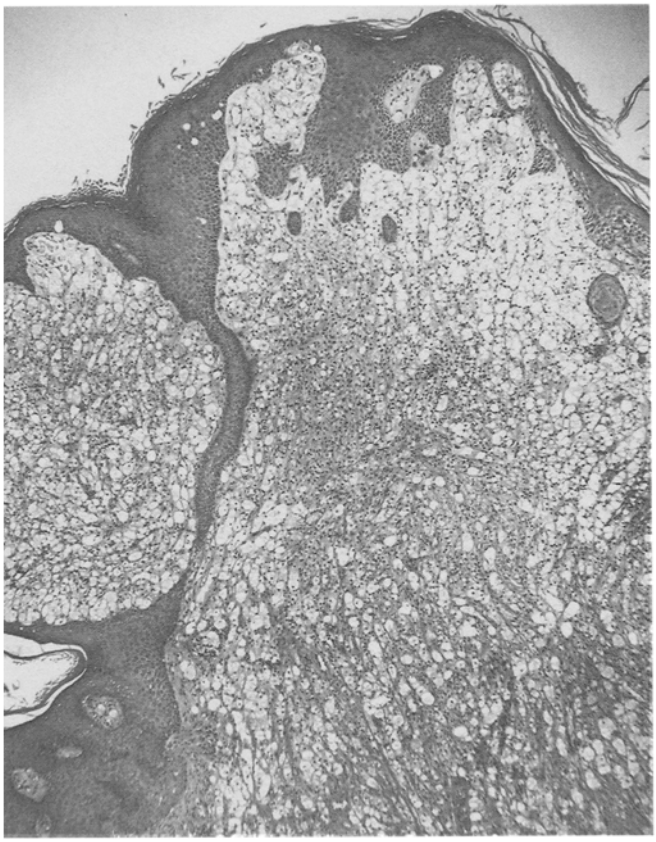


Fig. 41. Verruciform xanthoma.

- Not a true storage disorder but, rather, a non-X histiocytosis that presents as yellow-red papules and plaques on the flexural surfaces and mucosal membranes of young adults
- There is no association with lipid abnormalities with this disorder

♦ Verruciform xanthoma:

- Usually a solitary, yellow-red, papillomatous lesion of the mouth, this localized process may be seen at a number of cutaneous sites as a primary lesion or as a secondary phenomena in other disorders (e.g., squamous cell carcinoma, epidermal nevi, lupus erythematosus)

Microscopic

♦ All of the above lesions show an admixture of xanthomatized histiocytes, non-xanthomatized histiocytes and chronic inflammatory cells in varying proportions depending on the age and evolution of the lesion

♦ These lesions are typically dermal limited but, occasionally, show more extensive cutaneous involvement

♦ Epidermal involvement is not evident

♦ Occasional cases will have numerous multinucleated giant cells and/or Touton giants cells and, hence, show overlap with juvenile xanthogranuloma

♦ This is particularly true of xanthoma disseminatum, which should be distinguished by clinical criteria

♦ Verruciform xanthoma is a special histologic variant characterized by epidermal acanthosis, papillomatosis, parakeratosis, intraepidermal neutrophils and a sub-epidermal proliferation of markedly xanthomatized histiocytes

Special Studies

♦ Xanthomas and the non-X histiocytoses are S-100 protein–, CD1a–, macrophage markers+ (CD68) and Birbeck granule

Langerhans' Cell Histiocytosis (LCH, Histiocytosis X, Figure 42)

Clinical

♦ Three clinical variants of this disease have historically been described

♦ Letterer-Siwe disease is an acute disseminated form characterized by numerous brown papules on the scalp or face of infants with visceral involvement

♦ Hand-Christian-Schuller disease is a chronic, multifocal variant with osseous and localized visceral involvement that affects older children and adults and only occasionally involves the skin

♦ Eosinophilic granuloma is a chronic, focal variant that typically involves osseous sites in adults but may involve skin

♦ Many cases of LCH do not fit into the above categories and can show a wide spectrum of manifestations

Microscopic

♦ Nodular or loose aggregates of Langerhans cells within the dermis variably admixed with multinucleated cells, eosinophils, neutrophils and chronic inflammatory cells

♦ Epidermal involvement is common and aids in distinguishing this lesion from the non-X histiocytoses and urticaria pigmentosa

♦ Proper diagnosis rests on identifying the Langerhans' cell that is a histiocyte-like cell with abundant, eosinophilic to amphophilic cytoplasm and a reniform, sometimes twisted nucleus with occasional longitudinal grooves

Immunoperoxidase

♦ Langerhans' cells are S-100 protein+ and CD1a+

Electron Microscopy

♦ Birbeck granules are considered diagnostic of Langerhans' cell differentiation

Congenital Self-Healing Reticulohistiocytosis

Clinical

♦ Single or multiple, sometimes ulcerated, papules or nodules on the face, trunk and extremities of newborns

♦ Lesions are usually present at birth but occasionally will develop during the perinatal period

♦ Lesions typically regress within 2 to 4 months

Microscopic

♦ The histologic appearance of this lesion is similar to that of LCH, from which it cannot be reliably be separated on histologic grounds alone

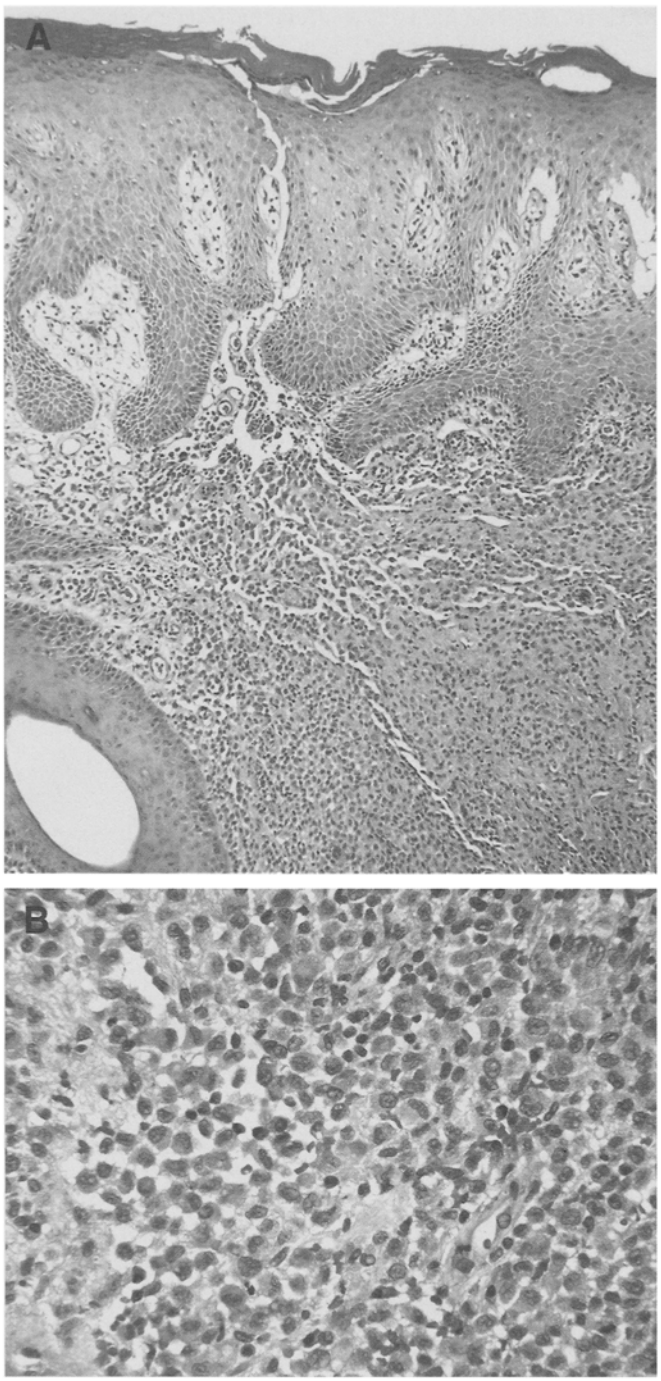


Fig. 42. Langerhans' cell histiocytosis.

- In general, this entity has larger, more eosinophilic cells with "glassy" cytoplasm than LCH
- PASD positive intracytoplasmic inclusions may be seen in this tumor but are apparently not present in LCH
- Epidermal involvement may rarely be present

Immunoperoxidase

- S-100 protein+, CD1a+

Electron Microscopy

- In addition to Birbeck granules, dense, myelin-like bodies with lamination are evident in this entity and may allow distinction from LCH

Differential Diagnosis

- This entity is best separated from LCH using clinical criteria; the electron microscopic findings may aid in this process

Indeterminate Cell Histiocytosis

General

- Occasional histiocyte-like proliferations demonstrate S-100 protein+ and CD1a+ on immunoperoxidase studies but no Birbeck granules on electron microscopy
- These proliferations have no distinct clinical or histologic characteristics at present

Benign Cephalic Histiocytosis

Clinical

- A non-X histiocytosis usually presenting as multiple yellow to red papules on the face of young children which completely regress with time

Microscopic

- A cellular, somewhat cohesive infiltrate of plump histiocytes often with admixed eosinophils is evident within the dermis
- The overlying epidermis may be attenuated or ulcerated, but epidermotropism is not evident
- Mild nuclear pleomorphism may be seen

Eruptive Histiocytoma

Clinical

- A non-X histiocytosis characterized by numerous, flesh-colored to red papules occurring in crops on the trunk, proximal extremities, and, occasionally, the mucosal membranes of adults
- Lesions may regress, persist and/or recur

Microscopic

- A bland infiltrate of histiocytes with or without coinfiltration of other inflammatory cells within the dermis

Fibrous Proliferations and Tumors

Hypertrophic Scar and Keloid

Clinical

- Hypertrophic scars are slightly raised, red, smooth and firm lesions at sites of previous injury which have no tendency for recurrence and no racial predilection
- Keloids are raised to polypoid, red to flesh-colored lesions usually, but not always, occurring at sites of injury and growing beyond the limits of the injured site
- These lesions may recur and are more common in blacks

Microscopic

- A fairly cellular, often nodular proliferation of dermal fibroblasts in a variably collagenized stroma with only minimal hyalinization characterizes the hypertrophic scar
- Keloids show more extensive, and often, less cellular nodular fibroblastic proliferations with extensive hyalinization of collagen

Nodular Fasciitis/Proliferative Fasciitis/Proliferative Myositis

Clinical

- Reactive, non-neoplastic proliferations presenting as rapidly growing, deep nodules or masses on the trunk or extremities of adults
- Virtually any site may be affected

Microscopic

- All are proliferations of bland, reparative, bipolar spindle cells embedded in a variably myxoid to collagenized stroma
- Most lesions are centered on the fascia/subcutaneous tissue interface, but dermal, vascular, and skeletal muscle variants are not uncommon
- The spindle cells have bland nuclear features, scattered normal mitotic figures and wispy, pointed cytoplasm giving these lesions a "tissue culture" appearance
- Extravasated erythrocytes and admixed chronic inflammatory cells are additional features
- The proliferative variants have, in addition to the above, a population of large, ganglion-like cells admixed within the spindle cells

Fibroma of Tendon Sheath

Clinical

- Slowly growing, benign fibrous nodule firmly attached to the tendon sheath on the distal extremities of adults

Microscopic

- A well-circumscribed, lobulated proliferation composed of densely hyalinized, paucicellular collagen centrally and more cellular fibroblastic proliferations peripherally
- The individual lobules often have peripheral stromal clefting but lack nuclear pleomorphism, mitotic activity or necrosis

Giant Cell Tumor of Tendon Sheath (Figure 43)

Clinical

- Similar to fibroma of tendon sheath (see above)

Microscopic

- A well-circumscribed, nodular to multilobular tumor composed of a proliferation of plump histiocyte-like cells admixed with multinucleated giant cells, spindle cells, foam cells and hemosiderin-laden cells in a variably collagenized matrix

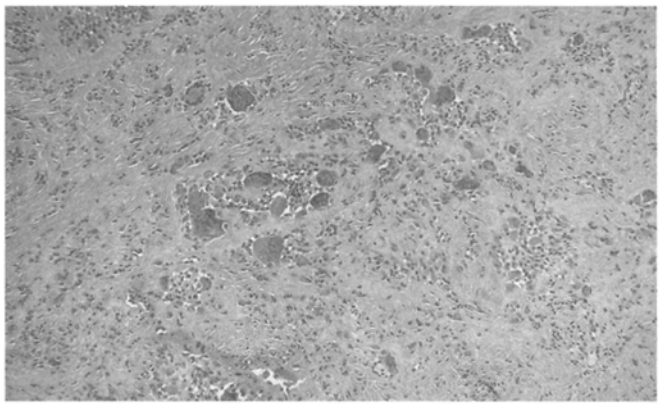


Fig. 43. Giant cell tumor of tendon sheath.

- Mitotic figures may be evident, but no cytologic atypia or necrosis is evident
- The latter aid in distinguishing this lesion from epithelioid sarcoma

Acrochordons (Soft Fibroma, Skin Tags, Fibroepithelial Polyps)

Clinical

- Polypoid, filiform or pedunculated flesh-colored lesions typically involving the groin, axilla and neck region of adults

Microscopic

- A polypoid lesion with epidermal acanthosis overlying a variably hyalinized fibrovascular core
- Adipocytes may be abundant in the central aspect of the lesion

Pleomorphic Fibroma

Clinical

- A benign polypoid to dome-shaped, flesh-colored lesion on the trunk or extremities of adults

Microscopic

- A paucicellular, polypoid proliferation of large, pleomorphic cells with hyperchromatic nuclei, small nucleoli and scant cytoplasm embedded in a fibrous stroma
- Rare mitotic figures may be seen in these lesions and do not imply an aggressive course

Sclerotic Fibroma

Clinical

- Usually a solitary, flesh-colored nodule in adult patients
- Multiple lesions may be associated with Cowden's disease

Microscopic

- A well-circumscribed, nodular proliferation of hyalinized, paucicellular fibrous tissue with laminated, cleft-like stromal spaces

Angiofibroma (Fibrous Papule, Oral Fibroma, Acquired Digital Fibrokeratoma, Pearly Penile Papules)

Clinical

- Papular to polypoid, flesh-colored lesions usually in adults

Microscopic

- A faintly polypoid, well-circumscribed proliferation of fibrovascular tissue with scattered hyperchromatic, occasionally multinucleated, stellate cells within the upper dermis
- In the digital variant there is overlying epidermal acanthosis and hyperkeratosis with the dermal collagen fibers oriented parallel to the long axis of the lesion

Elastofibroma

Clinical

- Typically a deep-seated, subscapular mass in older adults
- Occasionally other sites are involved

Microscopic

- An irregular, unencapsulated proliferation of paucicellular collagen admixed with enlarged and often globular elastic fibers best visualized with elastic stains

Dermatomyofibroma

Clinical

- A benign, solitary, flesh-colored to hyperpigmented plaque on the shoulder region of young adults

Microscopic

- A well-circumscribed proliferation of spindled, bland myofibroblastic cells in thin fascicles within the dermis
- The fascicles are oriented parallel to the epidermis except near adnexal structures where they assume a perpendicular growth pattern relative to the epidermis
- No nuclear pleomorphism, necrosis or significant mitotic activity is evident

Myofibroma/Myofibromatosis

Clinical

- Solitary and multifocal variants exist
- The solitary variants may be seen in infants, young children and adults and typically present as a dermal or subcutaneous nodule on the head, neck, trunk or extremities
- The multifocal variants are seen in infancy or as congenital lesions
- Multiple soft tissue lesions may be seen, and, if visceral involvement is present, there is increased morbidity and mortality
- The solitary variants in children, however, have a tendency to regress

Microscopic

- An unencapsulated, well-circumscribed, biphasic dermal and/or subcutaneous tumor composed of an admixture of peripheral smooth muscle-like fascicles admixed with more centrally located immature, mesenchymal-like spindle cells embedded in a myxoid background
- The latter component often has a hemangiopericytoma-like proliferation of blood vessels
- Mitotic figures and necrosis may be seen and usually do not herald an aggressive course

Infantile Digital Fibroma/Fibromatosis

Clinical

- A benign, rapidly growing nodule on the fingers or toes of infants and young children
- Lesions may be multiple and typically regress over time

Microscopic

- A moderately cellular, usually well circumscribed proliferation of spindled myofibroblasts embedded in a collagenous stroma
- The spindle cells have characteristic actin-positive intracytoplasmic eosinophilic inclusions

Fibrous Hamartoma of Infancy (Figure 44)

Clinical

- A hamartomatous lesion typically presenting as a deep dermal to subcutaneous nodule or plaque on the trunk of young children (usually less than 3 years of age)

Microscopic

- A deep dermal to subcutaneous, irregular, triphasic proliferation that merges with adjacent tissue
- The proliferation is composed of an admixture of densely collagenized, fibromatosis-like fascicles of bland spindle cells, myxoid, myofibroblastic lobules and adipocytes showing a range of differentiation from lipoblast-like to mature univacuolated cells
- The collagenized fascicles frequently appear to arise from the deep dermis and "rain down" into the subcutaneous tissue

Fibromatosis

General

- A variety of fibromatoses may present as cutaneous masses, and these are discussed within the soft tissue pathology chapter

Giant Cell Fibroblastoma (Figure 45)

Clinical

- A tumor of intermediate grade malignancy occurring almost exclusively in children as a nodule or plaque on the torso or extremities
- This tumor shows a tendency to local recurrence but has minimal to no metastatic potential
- Giant cell fibroblastoma is frequently associated with dermatofibroma sarcoma protuberans (see below) and may precede, follow or occur with this related lesion

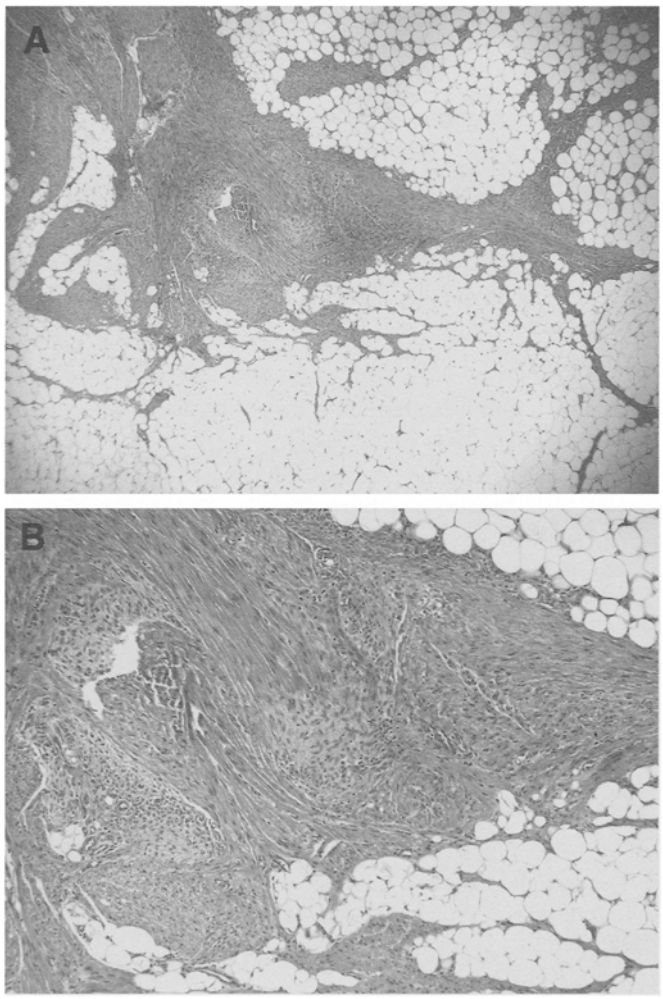


Fig. 44. Fibrous hamartoma of infancy.

Microscopic

- An infiltrative, dermal and often subcutaneous tumor composed of mildly pleomorphic spindle cells embedded in a variably myxoid stroma
- The hallmark of this tumor is the presence of pseudovascular spaces lined by pleomorphic, hyperchromatic and multinucleated-appearing cells that are not truly of endothelial origin

Special Studies

- Similar to DFSP, these tumors may express CD34

Dermatofibroma Sarcoma Protuberans (DFSP, Figure 46)

Clinical

- An indurated, red to blue, plaque-like or multinodular lesion on the trunk or extremities of young to middle aged adults
- Childhood variants also exist and may have coin-filtrating giant cell fibroblastoma

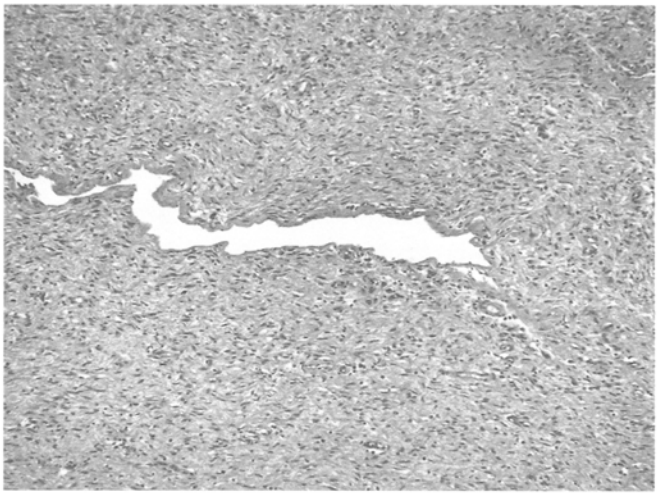


Fig. 45. Giant cell fibroblastoma.

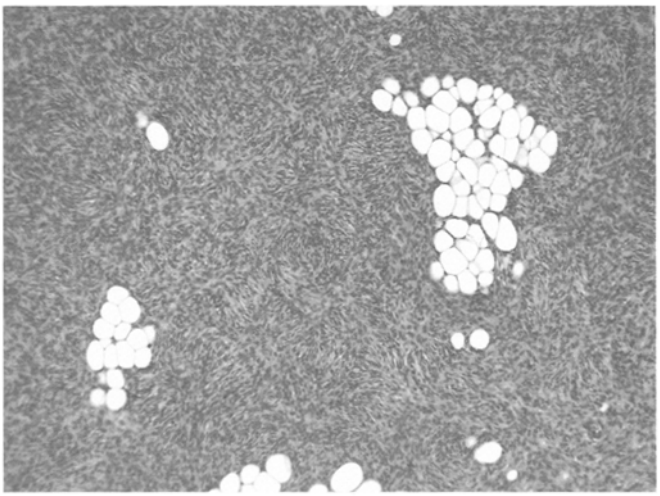


Fig. 46. Dermatofibrosarcoma protuberans.

- This tumor has a significant local recurrence rate but rarely metastasizes
- When a fibrosarcoma component is present, the risk of metastases increases significantly

Microscopic

- An infiltrative, dermal and subcutaneous proliferation of monotonous spindle cells in distinctly storiform pattern
- Unlike dermatofibroma, there typically is no epidermal hyperplasia, but basilar hyperpigmentation may be seen
- Tumor cells infiltrate the subcutaneous fat in a characteristic lace-like fashion
- The tumor cells are remarkably bland-appearing and monomorphic
- The mitotic rate is usually low
- Occasional tumors have a prominent myxoid background while others show transition to higher-grade fibrosarcoma

- DFSP usually lacks the coinfiltration of inflammatory cells, giant cells and xanthoma cells typically present in dermatofibroma
- A pigmented variant of DFSP, the Bednar tumor, exists and has in addition to the above, variable numbers of melanin-laden, dendritic appearing cells

Special Studies

- DFSP is typically CD34+, S-100 protein– and FXIIIa–

Fibrosarcoma

Clinical

- Two clinical variants exist: an infantile (congenital) form and an adult form
- The former typically presents as a large mass on the extremities of infants and has a relatively good prognosis compared to its adult counterpart
- The adult variant also typically involves the extremities but has a high recurrence and metastatic rate with subsequent increased mortality

Microscopic

- Both variants are characterized by a proliferation of mildly pleomorphic spindled cells embedded in a variably collagenized matrix
- The spindle cells are arranged in fascicles with a herringbone pattern that is more cellular than the fascicles of the fibromatoses
- Mitotic activity is always present but varies in quantity
- The infantile variant may have more immature rounded cells with a less prominent herringbone pattern
- Chronic inflammatory cells are frequently admixed within this variant

Special Studies

- Vimentin+, some are actin+
- This tumor is a diagnosis of exclusion, and other sarcomas and the fibromatoses should be considered prior to diagnosis

Epithelioid Sarcoma

Clinical

- A malignant tumor of uncertain origin typically presenting as firm, often ulcerated nodules on the hand, wrist or forearm of adolescents and young adults
- This tumor frequently shows multiple recurrences as well as metastases

Microscopic

- Usually a multinodular tumor involving the dermis and/or subcutaneous tissue
- The nodules frequently are well demarcated and have central necrosis, simulating necrotizing epithelioid granulomas
- The lesional cells are plump, round, histiocyte-like cells with abundant eosinophilic cytoplasm and relatively uniform ovoid nuclei
- An admixed spindle cell component may be evident
- There is usually a faint, collagenized stroma surrounding the individual cells
- Multinucleated giant cells are not typically seen in this tumor, a feature that aids in distinguishing this lesion from giant cell tumor of tendon sheath

Special Studies

- The lesional cells have a relatively unique immunophenotype being EMA+, vimentin+ and cytokeratin+

Synovial Sarcoma

General

- Synovial sarcoma may rarely present as a cutaneous mass and is discussed in detail in the soft tissue pathology chapter

VASCULAR PROLIFERATIONS, MALFORMATIONS, AND TUMORS

Reactive, Nonneoplastic Vascular Proliferations and Telangiectasias

Nevus Flammeus

Clinical

- A congenital vascular telangiectasia/malformation with many clinical forms including the salmon patch and the port-wine stain
- The former is a pink-red, macule/patch on the glabella that regresses during childhood
- The latter is a large, unilateral, red facial plaque that persists and may be associated with Sturge-Weber, Klippel-Trenaunay or other vascular syndromes

Microscopic

- Dilated (telangiectatic), thin-walled vessels are present within the papillary and superficial reticular dermis

Phakomatosis Pigmentovascularis

General

- A group of hamartomatous lesions consisting of nevus flammeus in combination with a variety of pigmented lesions (mongolian spot, nevus spilus, and nevus pigmentosus)

Eccrine Angiomatous Hamartoma

Clinical

- An angiomatous, sometimes painful, nodular lesion on the acral regions of children

Microscopic

- A hamartomatous proliferation of mature eccrine glands and thin-walled vessels in the deep dermis or subcutaneous fat
- Occasionally, other mesenchymal elements, particularly adipocytes, may also be admixed with the above

Nevus Anemicus

Clinical

- A solitary, circumscribed, pale, macule or patch on the torso thought to be secondary to vascular hyperreactivity to catecholamines

Microscopic

- No histologic abnormalities are evident within this clinical lesion

Lymphangioma Circumscriptum (Figure 47)

Clinical

- Grouped, vesicle-like lesions arranged in a plaque-like form on any cutaneous surface and appearing at birth or early in life

Microscopic

- Dilated, thin-walled lymphatic structures lined by flattened, bland endothelial cells are evident within the superficial dermis and are intimately associated with an acanthotic, surrounding epidermis
- Occasional cases have a deeper dermal component, and these variants may recur if superficially excised

Cavernous Lymphangioma

Clinical

- A congenital or infantile, doughy mass involving the head, neck or extremities which may recur if incompletely excised

Microscopic

- Numerous, variably sized lymphatic spaces are evident within the dermis and subcutaneous tissues
- The lymphatic spaces are lined by flattened, bland endothelium and are variably filled with eosinophilic proteinaceous material
- Chronic inflammatory cells may be seen within the vessel walls or the stroma of this proliferation

Cystic Hygroma

Clinical

- A large, cystic mass of the posterior neck of infants that is usually congenital and may be associated with Turner's syndrome

Microscopic

- Numerous, large and cystically dilated lymphatic spaces within the dermis and subcutaneous tissues are evident in this lesion

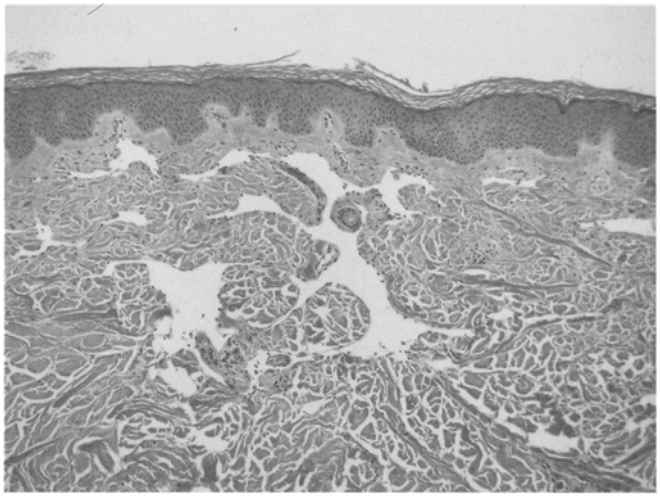


Fig. 47. Lymphangioma.

- Lymphoid aggregates are frequently present in the walls of these structures and aid in differentiating this lesion from other hemangiomatous processes

Lymphangiomatosis

Clinical

- A rare, often fatal, congenital disease which typically presents as sponge-like masses involving the skin of the extremities along with bone and visceral involvement
- Rare cases are limited to the extremities and a have a better prognosis than their systemic counterparts

Microscopic

- Infiltrating, interanastomosing and variably dilated lymphatic structures are evident in the dermis and underlying soft tissues in this entity

Spider Angioma (Nevus Araneus)

Clinical

- A red papule with "spidery" red legs on any cutaneous surface in both children and adults
- These lesions occur with an increased incidence in pregnancy, liver disease and thyrotoxicosis

Microscopic

- A central, dilated dermal arteriole is present and is interconnected to a superficial network of dilated capillaries

Venous Lake

Clinical

- A dark blue papule on the sun-damaged skin of older adults, especially the ears, lips and face

Microscopic

- A superficial, dilated venous structure is evident within the dermis

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Syndrome)

Clinical

- An autosomal dominant inherited disorder characterized by cutaneous and visceral telangiectasias beginning in childhood

Microscopic

- Telangiectatic superficial vessels are present in the dermis

Angiokeratoma (Figure 48)

Clinical

- Four clinical variants exist
- Fordyce:
  - Multiple, dark papules on the scrotum or vulva of the elderly
- Mibelli:
  - An autosomal dominant inherited disease characterized by warty papules on the extremities of children
- Angiokeratoma corporis diffusum:
  - Widespread cutaneous lesions with a bathing-trunk distribution and an association with Fabry's disease (x-linked, a-galactosidase deficiency)
- Solitary

Microscopic

- The microscopy of all these variants is similar consisting of superficial, thin-walled, ectatic vessels closely associated with an acanthotic epidermis
- The Fabry's-associated variant may show vacuolization of endothelial and smooth muscle cells which corresponds to glycolipid lamellar deposits on electron microscopy

Angiolymphoid Hyperplasia with Eosinophils (ALH, Epithelioid Hemangioma)

Clinical

- Red-blue, papules and nodules on the head of adults of uncertain etiology
- Occasional patients will have peripheral blood eosinophilia

Microscopic

- Well-circumscribed nodule or nodules are evident within the dermis and/or subcutaneous tissue and are composed of an admixture of variably sized vessels, a polymorphous lymphoid infiltrate and a variable number of eosinophils
- Enlarged, often vacuolated and hobnailed, endothelial cells line the vessels
- The lymphoid infiltrate is composed of an admixture of T and B-lymphocytes on immunoperoxidase studies and, rarely, forms germinal centers

Differential Diagnosis

- ALH should be distinguished from Kimura's disease, which it vaguely resembles clinically and histologically

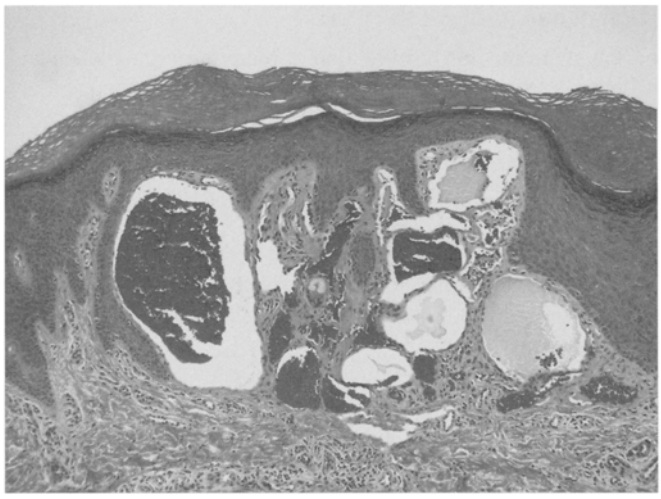


Fig. 48. Angiokeratoma.

- The latter is more common in adolescents and young adults of Asian descent and is characterized by cutaneous nodules with a wider cutaneous distribution associated with lymphadenopathy and peripheral eosinophilia
- Histologically, Kimura's disease lacks the vascular proliferation of ALH and has more prominent lymphoid follicles with germinal center formation

Pyogenic Granuloma (Lobular Capillary Hemangioma)

Clinical

- A hyperplastic, possibly neoplastic, lesion typically presenting as a solitary (occasionally multiple), polypoid, glistening red mass which may locally recur

Microscopic

- A polypoid, intradermal lesion frequently surrounded by an epidermal collarette and characterized by a lobular proliferation of bland capillaries and venules in a myxoid background
- Overlying ulceration and prominent inflammation are frequently present

Bacillary Angiomatosis

Clinical

- An infectious disease mimicking a vascular neoplasm, this lesion is most commonly seen as an angiomatous lesion in immunosuppressed patients but may also affect the immunocompetent. Bartonella quintana and henselae are the responsible organisms

Microscopic

- A pyogenic granuloma-like vascular proliferation with the additional features of numerous neutrophils, leukocytoclasia and granular, basophilic, intracytoplasmic masses within the endothelial cells lining the vascular proliferation
- The masses prove to be clumps of bacteria that stain nicely by the Warthin-Starry technique

Differential Diagnosis

- Verruga peruana is a related disease that is endemic in Peru and caused by Bartonella bacilliformis

Intravascular Papillary Endothelial Hyperplasia (Masson's Hemangioma)

Clinical

- A proliferative/reorganizing thrombus that may involve any cutaneous or mucosal surface but is frequently seen in rectal tissue

Microscopic

- Typically a localized process involving a single vessel or occasionally multiple adjacent vessels and characterized by numerous, intraluminal, endothelial-lined papillary structures with hylanized connective tissue cores
- The endothelial cells lack nuclear atypia or significant mitotic activity and, generally, do not "pile up" or stratify

Pseudo-Kaposi's Sarcoma

Clinical

- A group of pseudoneoplastic lesions including acroangiodermatitis and Stewart-Bluefarb syndrome
- The former is a variant of severe stasis dermatitis that typically involves the lower extremities of older adults
- The latter is an arteriovenous malformation unilaterally involving a lower extremity in a young adult

Microscopic

- Acroangiodermatitis is characterized by a relatively superficial proliferation of small, bland vascular structures which are often thick-walled and may be arranged in a lobular architecture
- There is associated chronic inflammation, dermal hemosiderin deposition, erythrocyte extravasation and overlying epidermal acanthosis and hyperkeratosis
- The Stewart-Bluefarb syndrome shows a transdermal proliferation of similar vessels and, occasionally, an arteriovenous malformation may identified in the deeper tissues

Differential Diagnosis

- These reactive proliferations should be distinguished from Kaposi's sarcoma which is characterized by a more infiltrative vascular proliferation which surrounds adnexa, dissects dermal collagen and shows a vessel around vessel growth pattern (the promontory sign)

Benign Vascular Neoplasms

Angioma Serpiginosum

Clinical

- Multiple, gyrate papules on the extremities of children and young adults

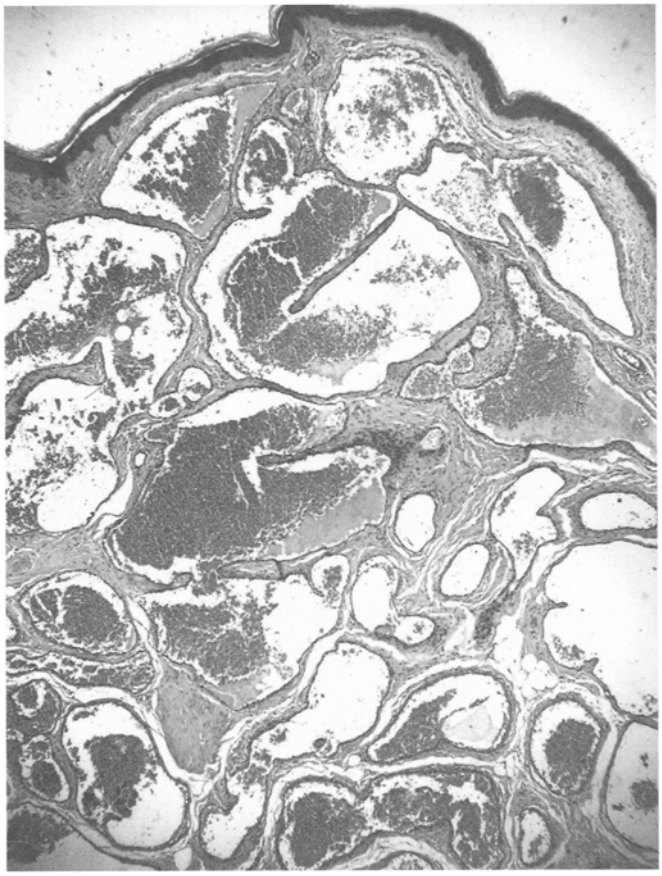


Fig. 49. Cavernous hemangioma.

Microscopic

- A clustered proliferation of thick-walled capillaries is evident within the papillae of the superficial dermis

Hemangiomas (Infantile, Cavernous, Capillary, Superficial, and Deep, Figure 49)

Clinical and General

- A variety of confusing terms have been utilized for hemangiomas rapidly developing in infancy, shortly after birth
- Traditionally, pathologists have classified these lesions as capillary or cavernous hemangiomas, with the thought that the former regress while the latter do not
- It is now clear that this division is erroneous and that, instead of representing distinct histologic entities, capillary and cavernous histologic changes are merely the histologic findings along points of time in the evolution of all infantile hemangiomas
- Dermatologists instead classify infantile hemangiomas as superficial or deep depending on whether the overlying skin surface is bright red or largely normal
- Further, almost all infantile hemangiomas experience some regression after their initial period of rapid growth, regardless of the histologic type

Microscopic

- Early lesions ("cellular hemangioma") show a highly cellular, often lobular proliferation of endothelial cells with indistinct lumina and scattered mitosis
- These lesions may be dermal limited or extend into the underlying soft tissue
- As the lesions age, vascular lumina become more apparent being composed of small capillary-sized vessels ("capillary hemangioma") which than progress to larger cavernous sized vessels ("cavernous hemangioma")

Cherry Angiomas

Clinical

- Acquired, small, red papules on the trunk of adults

Microscopic

- Dilated, mildly thickened capillary blood vessels in the papillary dermis

Acral A-V Tumor (Arteriovenous Hemangioma, Cirsoid Aneurysm)

Clinical

- Small, red-blue, papules on the head, neck or extremities of adults

Microscopic

- Localized, mid to upper dermal proliferation of variably sized, thick-walled vessels having features of both arteries and veins

Tufted Angioma (Tufted Angioblastoma)

Clinical

- Angiomatous appearing, red to brown, macules or plaques on the neck, torso and shoulders of children and young adults

Microscopic

- Multiple, cellular lobules of endothelial cells with peripheral, slit-like spaces are evident within the dermis and superficial subcutaneous tissue giving this lesion a "cannonball"-like pattern

Microvenular Hemangioma (Figure 50)

Clinical

- An acquired, slowly growing red-blue papule on the extremities of young adults

Microscopic

- A poorly circumscribed, dermal proliferation of monomorphic, thin-walled, branching venules lined by bland endothelium
- The venules dissect through the collagen raising some concern for Kaposi's sarcoma or low-grade angiosarcoma, but the atypia associated with these two lesions is absent

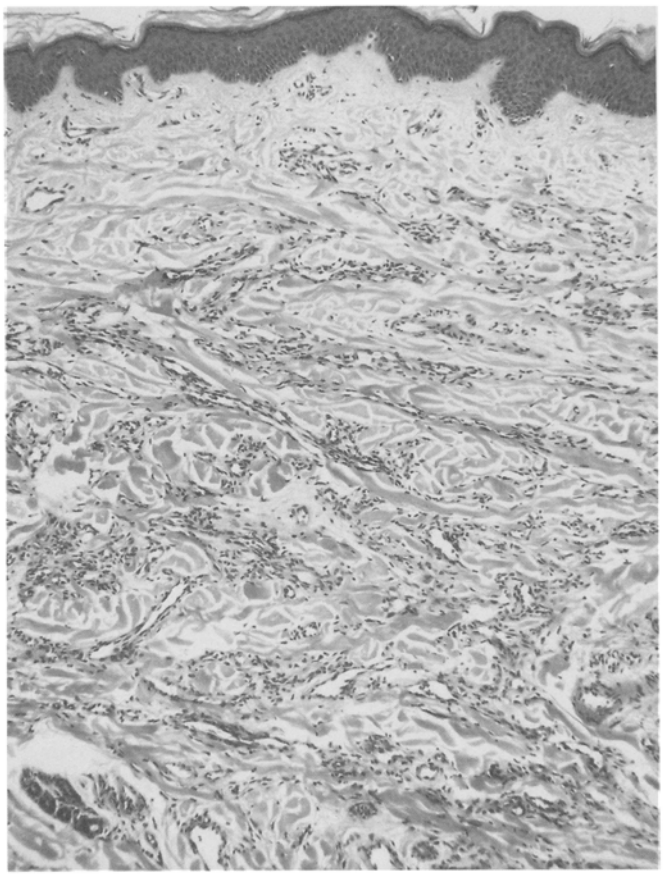


Fig. 50. Microvenular hemangioma.

Targetoid Hemosiderotic Hemangioma (Hobnail Hemangioma)

Clinical

- A red papule surrounded by clear and ecchymotic halos in succession on the trunk or extremities of adults

Microscopic

- Thin-walled, somewhat dilated vascular structures with intraluminal papillae and hobnailed endothelium characterize this lesion centrally
- The peripheral and deep aspects of this tumor show interanastomosing vascular spaces that dissect the dermal collagen in association with hemosiderin deposition and chronic inflammatory cells

Glomeruloid Hemangioma

Clinical

- An unusual vascular proliferation that occurs in the setting of POEMS syndrome, these lesions are typically red, dome-shaped to flat, papules and macules on the trunk and extremities of adults

Microscopic

- A glomerulus-like proliferation of tightly entwined capillary-sized blood vessels is present in the upper dermis

- The endothelial cells have characteristic, intracytoplasmic, eosinophilic, PAS+ inclusions that represent absorbed immunoglobulin

Kaposiform Hemangioendothelioma

Clinical

- A childhood neoplasm with a predilection for the retroperitoneum that rarely involves skin

Microscopic

- A multinodular, cellular neoplasm involving the dermis and underlying soft tissue
- The nodules are composed of fascicles of bland spindle cells, small congested capillaries, slit-like vascular spaces and epithelioid endothelial cells with hemosiderin, hyaline globules and primitive cytoplasmic lumina
- No significant mitotic activity is evident
- The multinodularity, the lack of plasma cells and the lack of atypia all aid in distinguishing this lesion from the histologically similar Kaposi's sarcoma

Spindle Cell Hemangioendothelioma

Clinical

- Single or multiple, red-blue, often painful nodules on the extremities of children and young adults

Microscopic

- A fairly well-circumscribed, dermal and/or subcutaneous, nodular tumor composed of an admixture of large, cavernous vascular spaces admixed with a spindle cell to faintly epithelioid, cellular component
- The large vascular spaces frequently have thrombosis with intravascular papillary projections
- The spindle cells often have vacuole-like, intracytoplasmic lumina

Acquired Progressive Lymphangioma (Benign Lymphangioendothelioma)

Clinical

- An acquired, slowly enlarging, bruise-like plaque on the extremities or trunk of young adults

Microscopic

- Thin-walled, anastomosing, irregular vascular channels are evident within the dermis and predominate superficially where they are oriented horizontally to the epidermis
- The deeper dermis also has scattered irregular lumina that are oriented haphazardly or perpendicularly to the overlying epidermis
- The vascular lumina are lined by bland, flattened endothelium and lack any significant intraluminal contents

Angiomatosis

Clinical

- A rare, benign, vascular proliferation of childhood characterized by an angiomatous growth involving a large area of the trunk and/or extremity with or without hypertrophy of the affected segment

Microscopic

- An irregular and haphazard proliferation of variably sized vessels and adipocytes is evident within the dermis and underlying soft tissues
- A characteristic finding is the presence of small vascular structures clustered near or within the wall of a large, thick-walled vein

Vascular Tumors of Low-Grade Malignancy

Epithelioid Hemangioendothelioma

Clinical

- Solitary or multiple, cutaneous and/or visceral masses with a wide age range and geographic distribution
- These lesions may recur and occasionally metastasize

Microscopic

- A proliferation of epithelioid to spindled endothelial cells as cords and nests in a myxoid to hylanized stroma
- Intracytoplasmic lumina with erythrocytes are evident within the epithelioid cells, but well-formed vascular structures are rarely identified
- The tumor often seems to arise from a large vessel wall, often preserving its vascular architecture

Retiform Hemangioendothelioma

Clinical

- A plaque-like or nodular tumor on the extremities of young adults characterized by frequent recurrences and low metastatic potential

Microscopic

- An irregular proliferation of branching, angulated blood vessels lined by hobnailed endothelial cells is present within the dermis and has been likened to similar appearing structures within the rete testis
- A deeper, more solid component with spindled and epithelioid cells and papillary structures may also be evident

Dabska's Tumor (Malignant Endovascular Papillary Angioendothelioma)

Clinical

- A rare, tumor typically presenting as a mass on the head, neck or extremities of children and adolescents

Microscopic

- An irregular, dermal proliferation of vascular structures lined by hobnailed endothelium and having numerous papillary, intraluminal projections lined by atypical, hyperchromatic endothelial cells with occasional mitoses
- Admixed lymphocytes are also frequently present

Kaposi's Sarcoma

Clinical

- Five different clinical subtypes exist
- Classic:
  - Red-blue plaques on the lower extremities of elderly men of Mediterranean descent
- African, endemic variants:
  - A nodular, indolent variant affecting the limbs of young to middle-aged men
  - A lymphoadenopathic, aggressive variant affecting young children
- Immunosuppression-associated variant:
  - Usually related to transplantation with a potentially aggressive course
- AIDS-related variant:
  - An aggressive variant that may involve any anatomic site
- Kaposi's sarcoma has been recently linked to human herpes virus type 8 which may play an important role in its pathogenesis

Microscopic

- The microscopic is similar in all of the above variants
- In the patch stage, a few, irregular and infiltrating small vessels are present predominantly within the superficial dermis
- The vessels infiltrate adnexa and frequently grow in a vessel-around-vessel pattern, the "promontory sign"
- Scattered lymphocytes, plasma cells and extravasated erythrocytes are evident within the dermis, and hemosiderin deposition is also frequently present
- The plaque stage shows, in addition to the above, a transdermal infiltrate with spindle cell areas arranged in irregular fascicles
- The spindle cell component has characteristic sieve-like spaces with extravasated erythrocytes, mild nuclear pleomorphism, occasional mitotic figures and eosinophilic hyaline globules
- The nodular variant is composed almost exclusively of a fairly well circumscribed, nodular, dermal and/or subcutaneous proliferation of spindle cells in fascicles with similar features to the plaque stage

Malignant Vascular Tumors

Angiosarcoma (Figure 51)

Clinical

- Three clinical variants exist
- Idiopathic angiosarcoma of the face and scalp of the elderly:
  - This variant presents as multiple bruise-like, infiltrating plaques and nodules
- Post-irradiation angiosarcoma:
  - Infiltrating, plaques, ulcers or nodules occurring years after radiation to the involved site

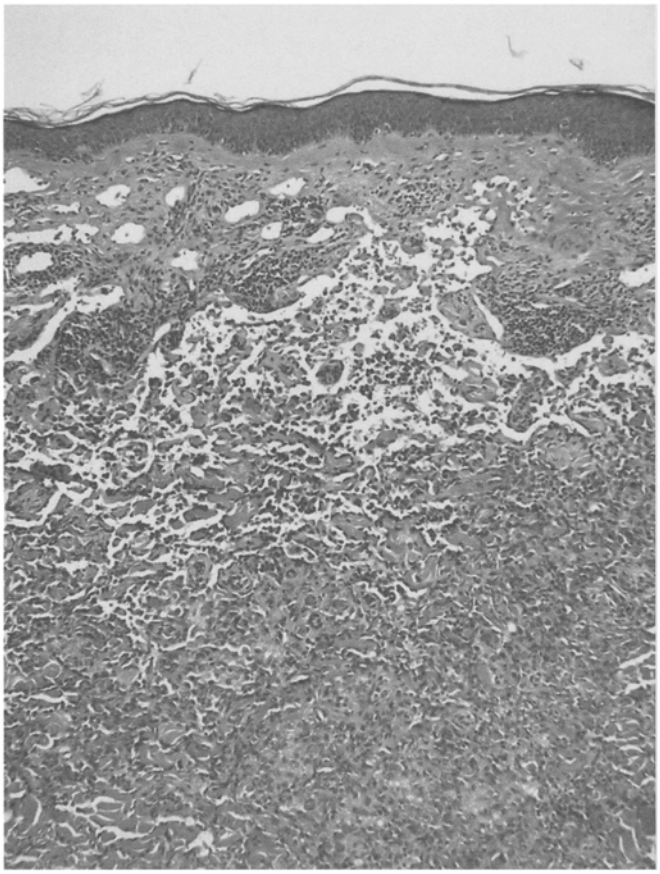


Fig. 51. Angiosarcoma.

- Lymphedema associated angiosarcoma (Stewart-Treves syndrome):
  - Angiosarcomas arising in the setting of prolonged lymphedema, usually post-mastectomy patients
- The overall survival for patients with cutaneous angiosarcoma is poor with frequent recurrences and early lymph node and visceral metastases characterizing their clinical course

Microscopic

- All three clinical variants of angiosarcoma show the same spectrum of histologic findings
- Well-formed, small, often slit-like, vessels that inter-anastomose and dissect the dermal collagen in an infiltrative fashion characterize the low-grade variants
- The endothelial cell lining may be flattened and nondescript, but areas with nuclear hyperchromasia, mitotic activity and stratification are usually evident
- A papillary network lined by atypical endothelial cells may be prominent
- High-grade lesions are typically more cellular and are composed of sheets or fascicles of polygonal, epithelioid or spindle cells with nuclear pleomorphism, mitoses and often prominent nucleoli

- Well-formed vascular structures may be scant, but intracytoplasmic lumina are often identified and aid in the differential diagnosis

Special Studies

- CD31, CD34, FVIII and Ulex europaeus I lectin stain, to a variable degree, endothelial-derived tumors
- CD31 is probably the most specific and sensitive endothelial cell marker amongst this group

Tumors of Perivascular Cells

Glomus Tumor (Figure 52)

Clinical

- These tumors of specialized arteriovenous anastomoses (Sucquet-Hoyer canal) most often present as painful, red-blue nodules on the fingers, but any cutaneous site may be involved
- A multicentric variant with autosomal dominant inheritance exists

Microscopic

- These tumors are characterized by a well-circumscribed, deep dermal proliferation of small vessels and a variable number of round to polygonal cells with eosinophilic cytoplasm and uniform, round to ovoid nuclei
- Rarely, mild, degenerative nuclear pleomorphism may be present
- The glomangioma, a common variant, has, in addition to the above, a component of large, cavernous vascular structures
- Tumors that also have a proliferation of smooth muscle, usually perivascular, have been called glomangiomyoma

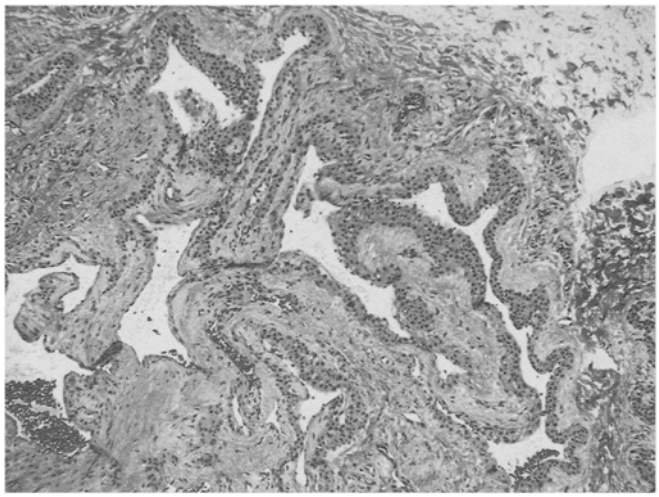


Fig. 52. Glomus tumor.

- Rare malignant glomus tumors have also been described

Special Studies

- The glomus cells are smooth muscle actin+, vimentin+ and may stain for desmin

Hemangiopericytoma

General

- A controversial neoplasm that rarely involves the skin, this tumor is a diagnosis of exclusion as its histologic pattern may be mimicked by a wide variety of neoplasms
- This tumor is discussed in more detail in the soft tissue pathology chapter

MELANOCYTIC PROLIFERATIONS AND PIGMENTARY DISORDERS

Pigmentary Disorders of the Skin

Melasma

Clinical

- An, acquired, symmetrical, brown hypermelanosis of the face that is more common in women

Microscopic

- An increase in melanin deposition within the basal epidermis and/or within dermal melanophages

Freckle (Ephelid)

Clinical

- Small, well-demarcated red-brown macules on sun-exposed areas. The lesions darken with sun exposure

Microscopic

- Basal keratinocyte hyperpigmentation without elongation of the rete ridges

Postinflammatory Hyperpigmentation

Clinical

- An acquired excess of melanin pigmentation in areas of preceding inflammation

Microscopic

- Increased melanophages within the superficial dermis with/without basilar keratinocyte hyperpigmentation

Dowling-Degos Disease

Clinical

- An autosomal dominant disorder characterized by reticulated, pigmented macules of the flexural areas in

combination with pitted, perioral, acneiform scars and comedone-like lesions on the neck and back

Microscopic

- Filiform to antler-like epidermal downgrowths in association with basilar keratinocyte hyperpigmentation, dermal melanosis and mild dermal lymphohistiocytic inflammation

Kitamura's Reticulate Hyperpigmentation

Clinical

- An autosomal dominant disorder characterized by reticulated, depressed pigmented macules on the dorsal hands and feet with pits and breaks on the palms and soles

Microscopic

- Basilar hyperpigmentation with elongation of the rete ridges and epidermal atrophy

Vitiligo

Clinical

- Acquired, depigmented, white patches surrounded by a normal or hyperpigmented border

Microscopic

- Absence of melanocytes within the depigmented areas

Albinism

Clinical

- An inherited disorder of the tyrosinase gene characterized by the lack of ocular pigment (ocular albinism; X-linked recessive) or the lack of ocular, follicular and cutaneous pigment (oculocutaneous albinism; autosomal recessive)

Microscopic

- Normal appearing epidermis containing a normal complement of melanocytes but a complete or markedly reduced amount of melanin production

Piebaldism

Clinical

- An autosomal dominant disorder with onset at birth characterized by a stationary hypomelanosis of the skin and hair involving the lateral trunk, arms, legs and forehead (white forelock)

Microscopic

- Absence of melanocytes and melanin within affected regions

Nevus Depigmentosus

Clinical

- A congenital, stable hypopigmented macule or patch on the trunk or extremities

Microscopic

- Normal number of melanocytes but reduced melanin production within the lesional areas

Idiopathic Guttate Hypomelanosis

Clinical

- Numerous, small hypopigmented macules on the sun-exposed surface of the extremities

Microscopic

- Marked reduction of melanin granules within lesional skin in association with epidermal atrophy and flattening of the rete ridges

Café-au-Lait Spot

Clinical

- Light brown, pigmented macule that may be found on any cutaneous surface and, if numerous, may be associated with neurofibromatosis

Microscopic

- Increased melanocytes and increased melanin production within the basal epidermis

Electron Microscopy

- Macromelanosomes

Becker's Nevus (Becker's Melanosis)

Clinical

- A hamartomatous lesion characterized by a hyperpigmented patch with hypertrichosis over the shoulder region or back

Microscopic

- Slight epidermal acanthosis/papillomatosis with basal keratinocyte hyperpigmentation and dermal melanosis
- A dermal, smooth muscle hamartomatous component may also be present

Mucosal Melanotic Macules

Clinical

- A pigmented macule/patch on the mucosa of the oral or genital region

Microscopic

- Basilar keratinocyte pigmentation with or without dermal melanosis

Benign Melanocytic Proliferations

Mongolian Spot

Clinical

- A slate-blue patch on the lower back of newborns and infants, often of Asian or African descent
- The lesions typically regress over time

Microscopic

- Long, wavy, variably pigmented, individual melanocytes are present within the deep dermis and are oriented parallel to the overlying epidermis

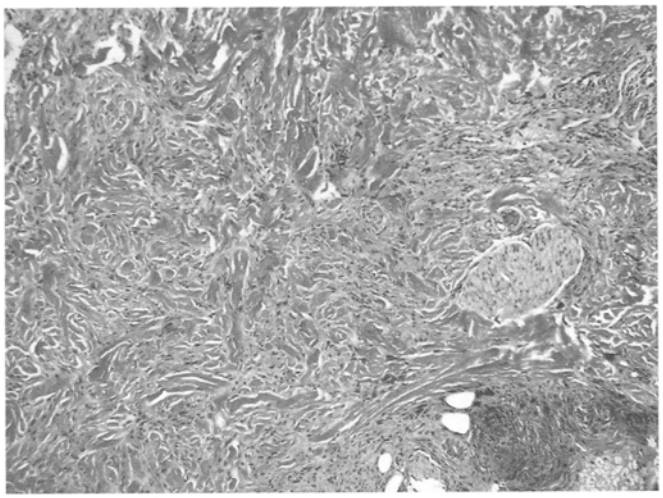


Fig. 53. Common blue nevus.

Nevus of Ito and Ota

Clinical

- Both of these lesions present as a slate-blue to mottled macule or patch which may be congenital or develop in adolescence
- The nevus of Ito typically involves the skin of the scapular, deltoid or supraclavicular regions while the nevus of Ota involves the skin of the face, usually in a unilateral fashion
- The nevus of Ota may be associated with ipsilateral scleral, conjunctival, corneal or retinal pigmentation
- The pigmentation persists
- These lesions may be present individually or in combination with one another or with the mongolian spot

Microscopic

- Both of these entities are characterized by the presence of pigmented, spindled and dendritic, individual melanocytes within the mid and upper dermis

Blue Nevi (Figures 53 and 54)

Clinical

- Two subtypes exist
- A small, well-circumscribed blue to blue-black papule on the hands or feet characterizes the common blue nevus
- A 1–3 cm or larger blue to blue-gray plaque on the sacrum or buttocks typifies the cellular blue nevus

Microscopic

- Common blue nevus: a symmetrical and fairly well circumscribed proliferation of spindled to dendritic nevomelanocytes within the dermis
- The dermis frequently is sclerotic within the lesional area
- Cellular blue nevus
- Typically a large, dermal and/or subcutaneous, symmetrical nodule composed of an admixture of spindled, dendritic, and rounded nevomelanocytes

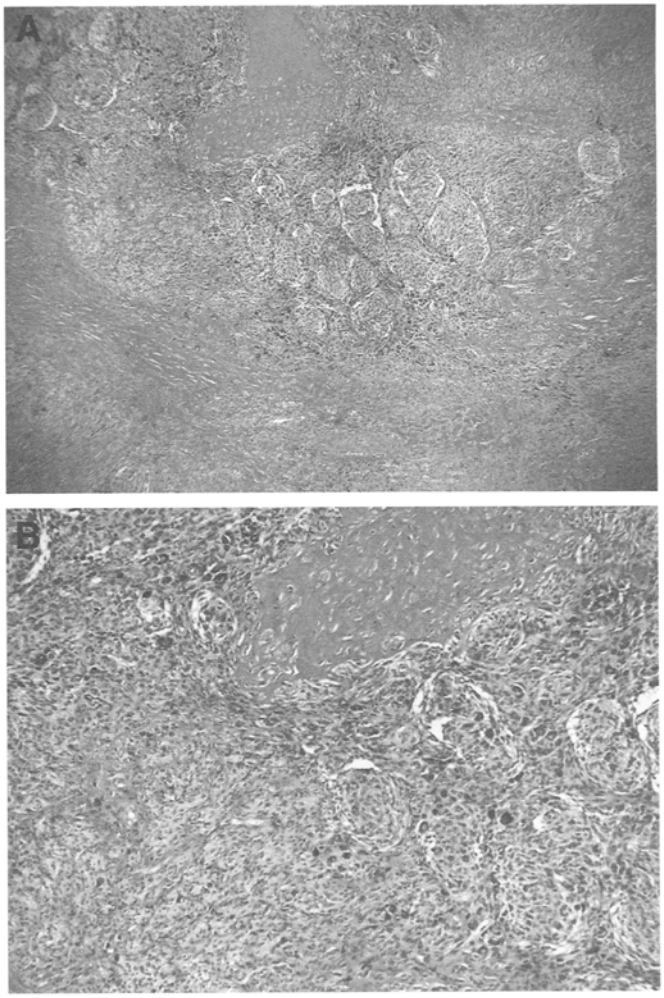


Fig. 54. Cellular blue nevus.

- The spindled and dendritic component predominates at the periphery of the lesion while nests of more rounded nevomelanocytes with melanophages are more common centrally
- Atypical variants may show nuclear pleomorphism, mitotic activity, an infiltrating architecture and even necrosis

Solar Lentigo

Clinical

- A uniformly pigmented macule/patch on areas chronically exposed to sunlight
- Solar lentigines are frequently multiple and are markers of increased risk of melanoma development

Microscopic

- Elongation of the rete ridges with basilar keratinocyte hyperpigmentation and a mild to marked proliferation of basilar melanocytes in a lentiginous (single cell, non-nested) fashion

Lentigo Simplex

Clinical

- A congenital or acquired, sharply demarcated, round to oval, macular area of hyperpigmentation, usually less than 5 mm in diameter
- Most lesions develop in childhood, but new lesions may form in adulthood
- Multiple lesions may be associated with the LEOPARD, NAME or Peutz-Jeghers syndromes
- The speckled lentiginous nevus (nevus spilus) is a variant characterized by a light brown patch with superimposed, darkly pigmented macules

Microscopic

- Mild to moderate elongation of the rete ridges in association with basilar and, often, suprabasilar keratinocyte hyperpigmentation and a lentiginous proliferation of bland nevomelanocytes
- Some lentigines show focal junctional nesting and, hence, overlapping features with a junctional nevus
- The term "jentigo" has, at times, been used for such lesions

Common Melanocytic Nevi

Clinical

- Benign, melanocytic proliferations that typically develop in childhood and adolescence
- The appearances of common melanocytic nevi vary from pigmented macules/papules to flesh-colored nodules to papillomatous lesions depending on the relative degree of junctional versus dermal activity and the site of origin
- These nevi are typically small (<1cm), evenly pigmented, symmetrical and sharply bordered
- The presence of large numbers of nevi on a single individual is a marker of increased risk of melanoma

Microscopic

- Common melanocytic nevi are characterized by symmetrical and well circumscribed proliferations of bland, round nevomelanocytes as nests along the dermal-epidermal junction and/or within the dermis
- The dermal component, if present, shows maturation and lacks significant mitotic activity or cytologic atypia
- The junctional component may show nevomelanocytic nests with or without an accompanying lentiginous melanocytic proliferation
- The nests within the junctional component are uniform in size and spacing and are typically limited to the basal epidermis

Dysplastic Nevus (Clark's Nevus, Atypical Nevus, B-K Mole)

Clinical

- A tan-brown to black, irregularly and asymmetrically pigmented macule/papule, usually >5 mm in diameter

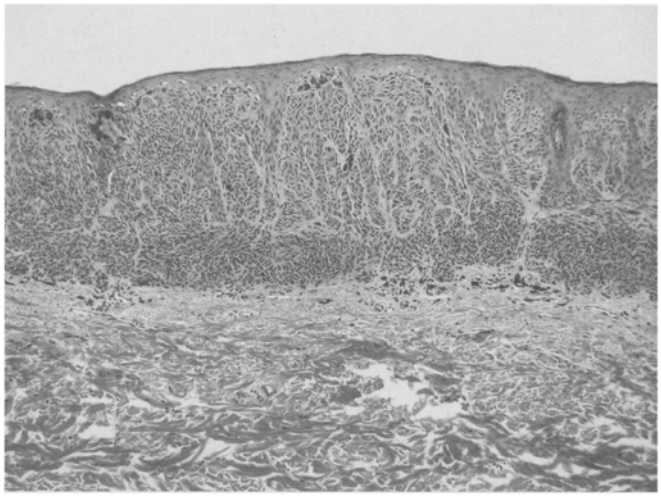


Fig. 55. Pigmented spindle cell nevus of Reed.

- Multiple lesions may be inherited as the B-K mole (dysplastic nevus) syndrome or the familial atypical mole syndrome
- This syndrome(s) is associated with a markedly increased risk of melanoma development. Most lesions are sporadic and are associated with a lesser risk of melanoma development

Microscopic

- Typically a compound nevomelanocytic proliferation showing a spectrum of architectural and cytologic features which include
- Junctional shouldering
- Lamellar dermal fibrosis
- Bridging of the rete ridges by melanocytic nests
- Melanocytic nuclear pleomorphism with nucleoli
- Early upward migration of melanocytes within the epidermis
- Perivascular chronic inflammation at the base of the lesion

Pigmented Spindle Cell Nevus of Reed (Figure 55)

Clinical

- Sharply defined, heavily pigmented, symmetrical papule on the trunk or extremities of adolescents/young adults

Microscopic

- Symmetrical and well-circumscribed proliferation of monomorphic, spindled melanocytes along the dermal-epidermal junction and, usually, the papillary dermis
- The individual melanocytes may have nucleoli , and mitotic figures are commonly seen
- There may be prominent upward migration of melanocytes within the epidermis
- Coarse melanin is frequently seen within the melanocytes and associated melanophages

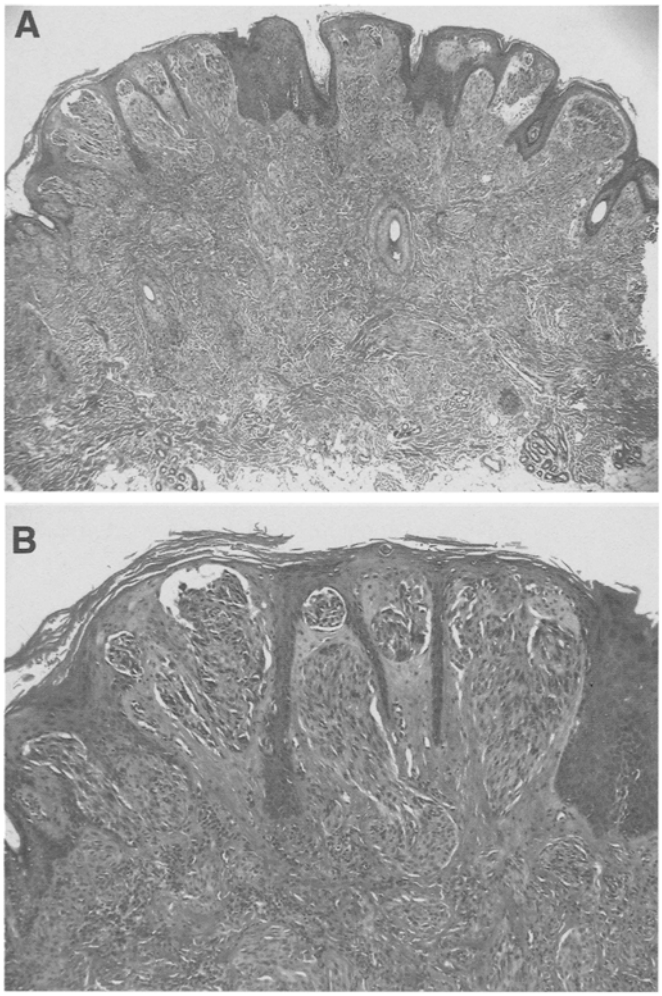


Fig. 56. Spitz nevus.

Spitz Nevus (Spindle and Epithelioid Cell Nevus, Figure 56)

Clinical

- Smooth-surfaced, round, sharply circumscribed, pink to red papule most commonly involving the face and/or the extremities of children to young adults

Microscopic

- Spitz nevi are generally well circumscribed and symmetrical proliferations which may be junctional, compound or dermal
- The nuclear pleomorphism that is present within these lesions may be mistaken for malignant melanoma
- The prototypical Spitz nevus has the following histologic features
- Epidermal hyperplasia
- Hypergranulosis
- Kamino bodies (cytoid bodies)
- Large junctional nests of epithelioid to spindled melanocytes
- Clefting between the junctional nests and the epidermis
- Deep dermal maturation
- Nuclear pleomorphism with nucleoli
- Additional features that may be present and may mimic melanoma include
- Brisk mitotic activity
- Upward epidermal migration of melanocytes
- Adnexal involvement

Congenital Nevus

Clinical

- A variant of the melanocytic nevus which is present at birth
- Congenital nevi are often divided into three groups based on their size: small (<1.5 cm), medium (1.5–20 cm) and large (>20 cm)
- These nevi are typically brown to black and frequently show an irregular surface with hypertrichosis
- Congenital nevi are associated with an increased risk of melanoma development; the risk is greatest for the large congenital nevi, which may show malignant transformation in up to 20% of cases

Microscopic

- Congenital nevi are similar to the common melanocytic nevi in that they are symmetrical, well-circumscribed proliferations with deep maturation
- They differ from common melanocytic nevi by having involvement of the deep reticular dermis/subcutis and by showing frequent involvement of adnexal structures

Deep Penetrating Nevus (Figure 57)

Clinical

- A darkly pigmented, uniform papule/nodule most often presenting on the trunk or extremities of young adults

Microscopic

- A distinctly, wedge-shaped proliferation of uniformly atypical melanocytes within the dermis and, occasionally, along the dermal-epidermal junction
- The nevomelanocytes are arranged into poorly formed nests and irregular fascicles which extend into the deep reticular dermis and/or subcutis without deep maturation
- These nevomelanocytes have nuclear pleomorphism and nucleoli, but mitotic figures are absent to scarce
- Dense melanin pigmentation is present throughout the lesion within the melanocytes and adjacent melanophages

Halo Nevus

Clinical

- A typical melanocytic nevus with a surrounding zone of depigmentation

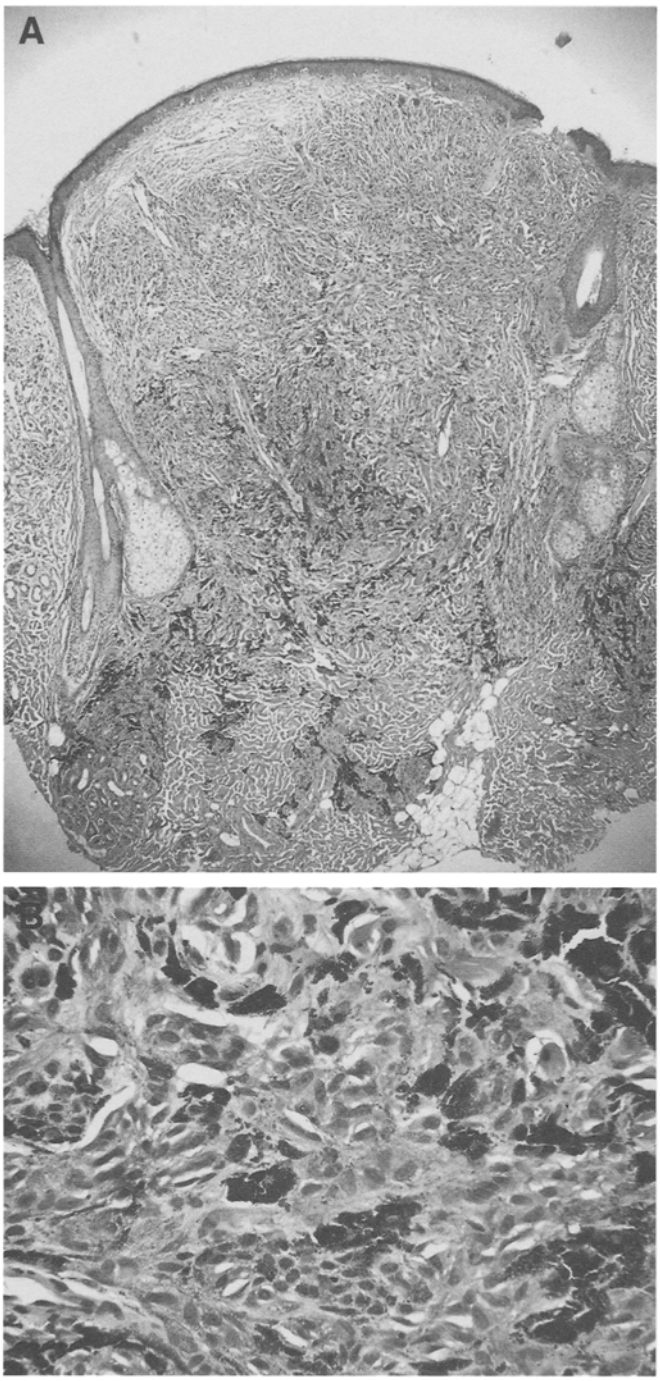


Fig. 57. Deep penetrating nevus.

Microscopic

- A chronically inflamed nevus of any type
- The lymphocytes are densely arranged within the dermal component of the nevus and may completely obscure the underlying melanocytic lesion
- The remaining melanocytes may show some degree of atypia and disorganization, but the typical features of a regressing melanoma are absent

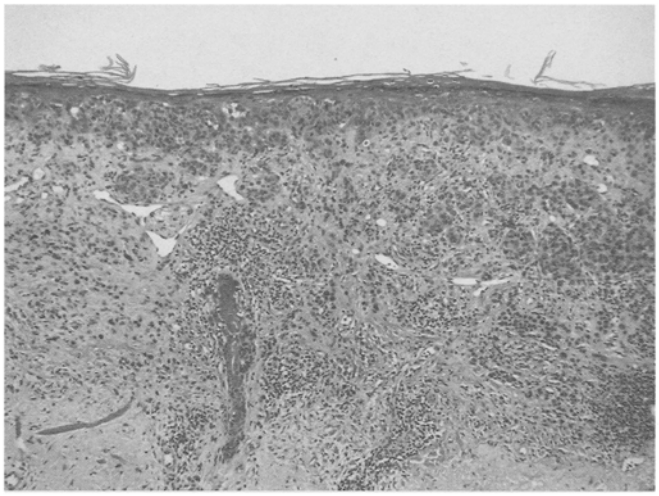


Fig. 58. Superficial spreading malignant melanoma.

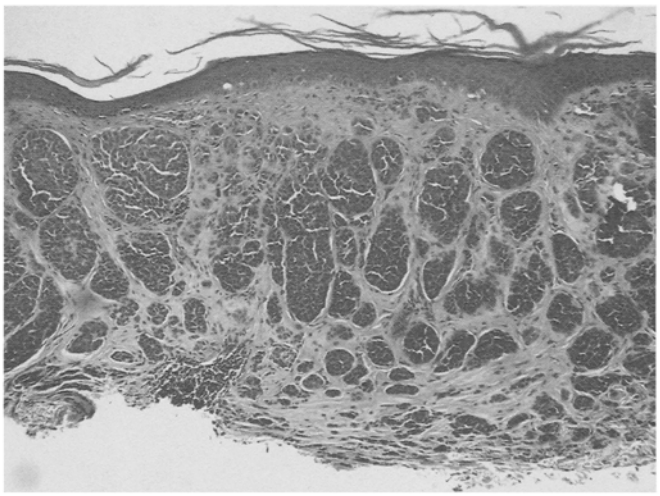


Fig. 59. Nevoid malignant melanoma.

Malignant Melanoma (Figures 58 and 59)

Clinical

- The majority of melanomas show a variegated, asymmetrical distribution of dark brown to black pigment within a lesion of greater than 0.5 cm in diameter
- However, amelanotic melanomas do exist and may mimic other neoplasms
- Melanomas are divided clinicopathologically into four basic subtypes
- Superficial spreading malignant melanoma:
  - Accounts for approximately 60% of melanomas
  - Related to sun exposure
  - Shows both a macular and a nodular appearance clinically
  - May affect all age groups but predominates in adults

- Lentigo maligna melanoma:
  - Accounts for approximately 10–15% of melanomas
  - Related to sun exposure
  - Largely a disease of the elderly
  - Grows initially as dark macule or patch (lentigo maligna) and develops a papular or nodular component when invasive (lentigo maligna melanoma)
  - Head and neck region most commonly affected
- Nodular malignant melanoma:
  - Accounts for approximately 10–20% of all melanomas
  - Nodular, often symmetrical appearance clinically
  - May be amelanotic
- Acral-lentiginous melanoma:
  - Accounts for 5–10% of all melanomas
  - Tumors of the palms, soles, nails, and genitalia
  - Most common melanomas of dark-skinned races

Prognostic Factors

- Tumor thickness is the most important prognostic factor at present, as measured by Clark level or Breslow depth
- Ulceration
- Lymphatic invasion
- Location of the primary melanoma
- Signs of regression
- Sex
- Age

Microscopic

- Almost all melanomas begin as epidermal proliferations which, if left unchecked, may invade into the dermis and underlying tissues
- Melanomas have a constellation of atypical cytologic and architectural features that may be present in varying portions within a given lesion including
- Architectural asymmetry
- Poor circumscription
- Upward epidermal migration of melanocytes, nested or single
- Melanocytic nests vary in size, shape and distribution
- No deep maturation of melanocytes
- Cytologic atypia in the form of nuclear pleomorphism, prominent nucleoli and mitotic figures
- Invasion of lymphatic spaces and nerves
- Adnexal involvement
- The lentiginous variants of melanoma show a predominant single, non-nested proliferation of melanocytes within the epidermis with or without upward epidermal migration
- The invasive component may be nested or may show a distinct spindled appearance with or without neurotropism (desmoplastic melanoma)
- The superficial spreading variant of melanoma shows a nested epidermal component with prominent upward epidermal migration, and the invasive component is typically nested but may be spindled
- The nodular melanoma is largely a dermal tumor with a minor, overlying epidermal component

Staging (see TNM Classifications)

- Stage I:
  - Tumor thickness 1.5 mm or less
- Stage II:
  - Tumor thickness 1.51–4.00 mm
- Stage III:
  - Tumor thickness greater than 4 mm or nodal and/or satellite metastases
- Stage IV:
  - Tumor metastatic to distant sites

Lymphoproliferative Disorders and Leukemias (also see Chapter 9)

Classification of Cutaneous Lymphomas

- A variety of cutaneous lymphomas exist, many of which differ significantly from their systemic counterparts in terms of histologic features, behavior and/or treatment
- In 1997, the European Organization for Research and Treatment of Cancer (EORTC) proposed a new, cutaneous lymphoma classification based on clinical, histologic and immunophenotypic criteria with an emphasis on disease entities rather than histologic subgroups
- While this is a significant departure from the REAL and WHO classifications of lymphoma, the EORTC classification is a significant advance in our understanding of cutaneous lymphomas and sets the groundwork for future lymphoma classification
- The following lymphoma discussion will focus on the EORTC classification of lymphoma, and the reader is urged to refer to the systemic lymphoma chapter for comparison (Chapter 7)

EORTC Classification

- Primary Cutaneous T-Cell Lymphoma (CTCL):
  - Indolent:
    - Mycosis fungoides (MF)
    - MF + follicular mucinosis
    - Pagetoid reticulosis
    - Large cell CTCL, CD30+:
      - Anaplastic
      - Immunoblastic
      - Pleomorphic
    - Lymphomatoid papulosis

- Aggressive:
  - Sézary syndrome
  - Large cell CTCL, CD30–:
    - Immunoblastic
    - Pleomorphic
- Provisional:
  - Granulomatous slack skin
  - CTCL, pleomorphic small/medium-sized
  - Subcutaneous panniculitis-like T-cell lymphoma

♦ Primary Cutaneous B-Cell Lymphoma:
- Indolent:
  - Follicular center cell lymphoma
  - Immunocytoma (marginal zone lymphoma)
- Intermediate:
  - Large B-cell lymphoma of the leg
- Provisional:
  - Intravascular B-cell lymphoma
  - Plasmacytoma

Primary Cutaneous Follicular Center Cell Lymphoma

Clinical

♦ Solitary or grouped papules, nodules or plaques
♦ Head and neck region most commonly involved
♦ May be associated with annular erythemas
♦ Rarely disseminate but frequently recur

Microscopic

♦ A tumor composed of follicular center cells either in the form of centrocytes (cleaved cells) or centroblasts
♦ Tumor cells are arranged into ill-defined nodules or diffuse sheets
♦ Germinal center formation may or may not be present

Immunophenotype

♦ CD20+, CD79a+, usually surface immunoglobulin (Sig)+
♦ CD5–, CD10–, bcl-2–

Differential Diagnosis

♦ Marginal zone lymphoma
♦ Lymphoid hyperplasia
♦ Systemic follicular lymphoma (bcl-2+)

Immunocytoma (Marginal Zone Lymphoma, Figure 60)

Clinical

♦ Solitary or multiple tumors/nodules
♦ Extremities most often involved
♦ Excellent long term survival ~100%

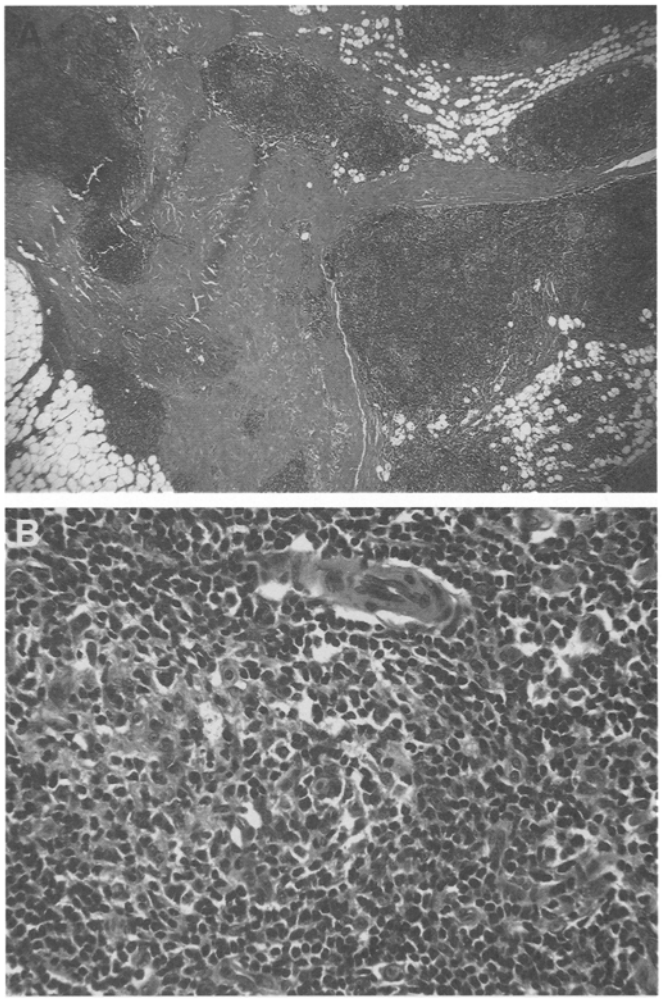


Fig. 60. Marginal zone lymphoma.

Microscopic

♦ Nodular or diffuse, often bottom-heavy infiltrates
♦ Benign germinal centers usually present
♦ Malignant small lymphocytes, plasmacytoid lymphocytes, plasma cells and centrocyte-like cells infiltrate diffusely outside of the germinal centers and may encroach upon the germinal centers
♦ Reactive T-cells, eosinophils and histiocytes are frequently admixed throughout the neoplasm

Immunophenotype

♦ CD20+, CD79a+, CD43+/–, Sig+, cytoplasmic immunoglobulin (Cig)+
♦ CD5–, CD23–, cyclinD1–

Differential Diagnosis

♦ Lymphoid hyperplasia
♦ Follicular lymphoma

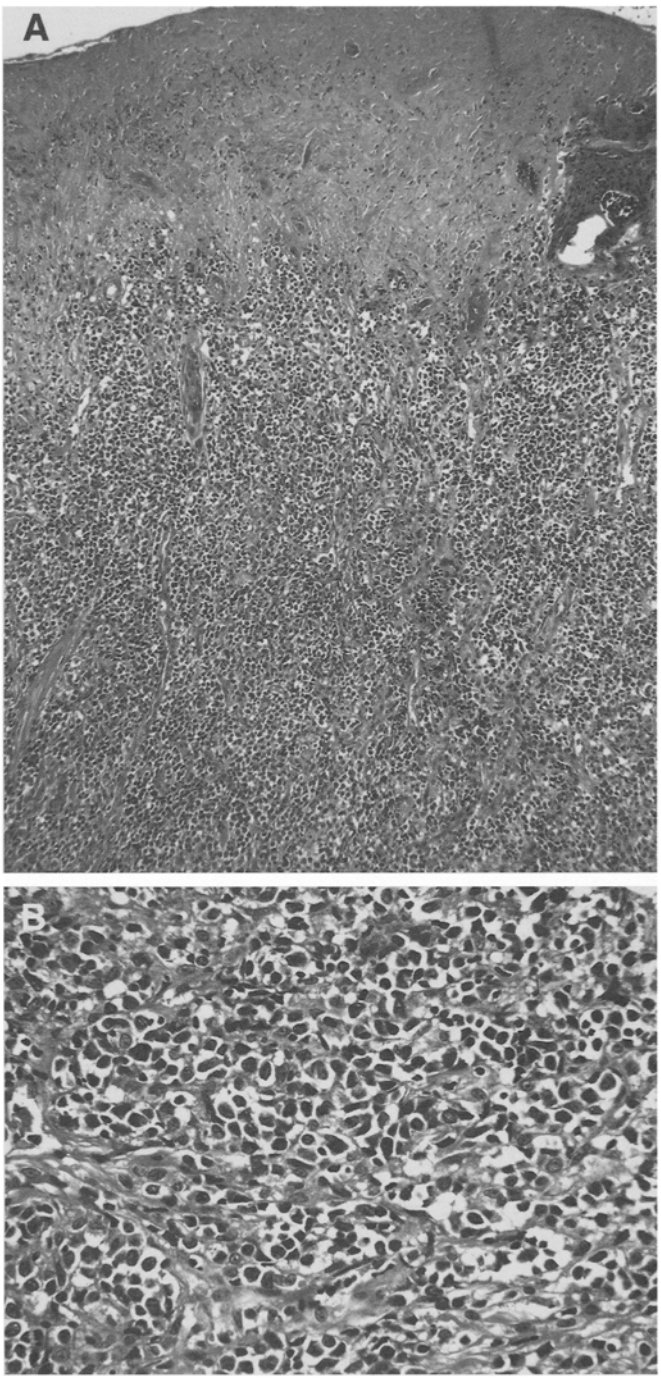


Fig. 61. Large B-cell lymphoma of the leg.

Large B-Cell Lymphoma of the Leg (Figure 61)

Clinical

- Red to blue nodules/plaques involving one or both legs
- Typically affects older patients, >70 y/o
- Frequently disseminates
- ~50% five year survival

Microscopic

- Diffuse, sheet-like proliferation of large atypical lymphocytes
- Epidermotropism is generally absent
- The large lymphocytes may have centrocytic, centro-blastic or immunoblastic features

Immunophenotype

- CD20+, CD79a+, bcl2+, Sig+/–

Genotype

- No t(14,18) translocation

Intravascular Large B-Cell Lymphoma

Clinical

- Violaceous, indurated plaques or patches
- Lower extremities most often involved
- Central nervous system involvement may also be present
- Poor prognosis

Microscopic

- Large atypical lymphocytes are present within dilated vessels of the dermis and/or subcutis
- Rarely, atypical lymphocytes may be present adjacent to the vessels

Immunophenotype

- CD20+, CD79a+, Sig+

Plasmacytoma

Clinical

- Solitary or multiple nodules involving any cutaneous surface
- Excellent prognosis
- No evidence of myeloma

Microscopic

- Diffuse sheets of mature or atypical plasma cells

Immunophenotype

- CD79a+, CD20–, Cig+

Mycosis Fungoides (Figure 62)

Clinical

- Persistent, erythematous patches and/or plaques which may progress to tumors over the course of many years
- Annular and serpiginous plaques may be present
- Trunk and extremities most commonly involved
- Generally an indolent disease with tumor formation and systemic spread occurring only after many years to decades

Microscopic

- A band-like, epidermotropic proliferation of variably sized lymphocytes is present in the superficial dermis

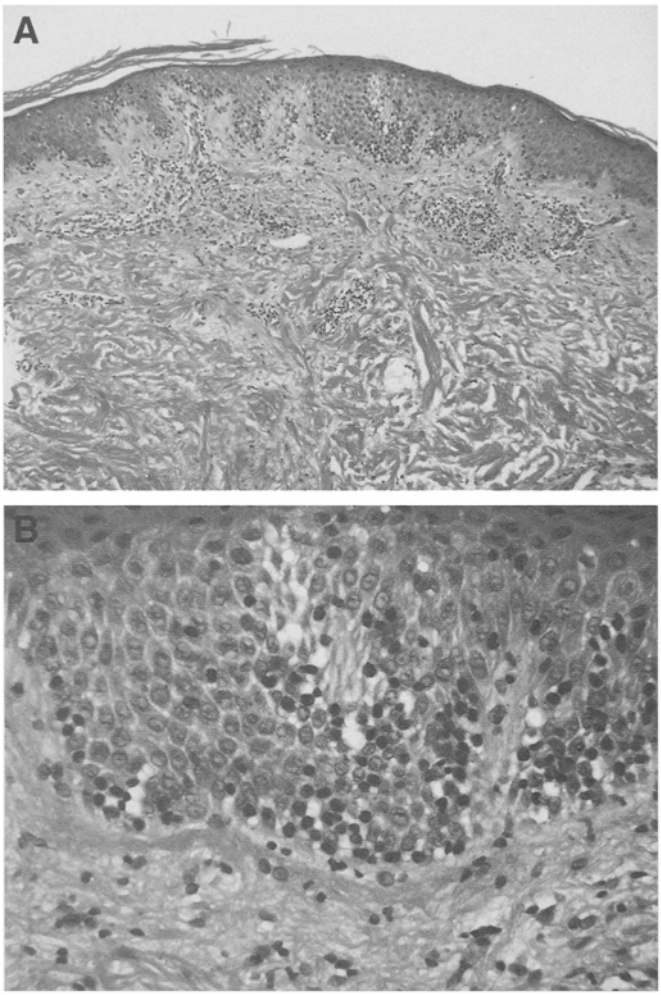


Fig. 62. Mycosis fungoides.

- The epidermotropic lymphocytes frequently populate the basal layer of the epidermis and are generally unassociated with spongiosis
- The epidermotropic lymphocytes may aggregate into intraepidermal microabscesses (Pautrier's microabscesses)
- The epidermotropic lymphocytes are frequently larger than those within the dermis and display varying degrees of nuclear convolution and cerebriform change
- The tumor stage shows a more diffuse, often sheet-like, proliferation of atypical, often large, lymphocytes with or without epidermotropism

Immunophenotype

- CD3+, CD4+, CD7+/–, CD8–, CD30–
- Rare CD8+ variants exist

Mycosis Fungoides With Follicular Mucinosis

Clinical

- Erythematous papules or plaques typically affecting the head and neck region
- Hair loss within the affected regions
- Typically affects adult patients

Microscopic

- Marked folliculotropism of atypical lymphocytes
- Mucinous degeneration of follicular epithelium
- Lymphocytes usually have the atypical nuclear features of mycosis fungoides, and epidermotropism may be evident
- Eosinophils are often present

Immunophenotype

- Similar to mycosis fungoides

Differential Diagnosis

- Primary (idiopathic) variants of follicular mucinosis affect younger individuals and appear unrelated to mycosis fungoides
- Other systemic diseases may show secondary follicular mucinosis (e.g., lupus erythematosus)

Pagetoid Reticulosis

Clinical

- Hyperkeratotic patches or plaques limited to a distal extremity (Woringer-Kolopp type)
- No systemic involvement present
- Excellent prognosis
- The systemic or disseminated form (Ketron-Goodman type) is best considered to be mycosis fungoides

Microscopic

- A distinctly epidermotropic proliferation of large atypical lymphocytes with irregular, often cerebriform, nuclei
- Minimal to no dermal component

Immunophenotype

- Similar to mycosis fungoides

CD30+ Lymphoproliferative Disorders Including Lymphomatoid Papulosis and CD30+ Large, T-Cell Lymphoma (Figure 63)

General

- Lymphomatoid papulosis (LyP) and CD30+, large, T-cell lymphoma are part of a spectrum of related clinicopathologic entities having in common a good prognosis and numerous CD30+ large lymphocytes histologically (*see* **Table 1**)

Sézary Syndrome

Clinical

- Generalized erythroderma in association with generalized lymphadenopathy and leukemic infiltration of the blood by malignant T-cells
- Alopecia, palmoplantar keratoderma and leonine facies are common findings
- Poor prognosis with a 5 year survival of less than 50%

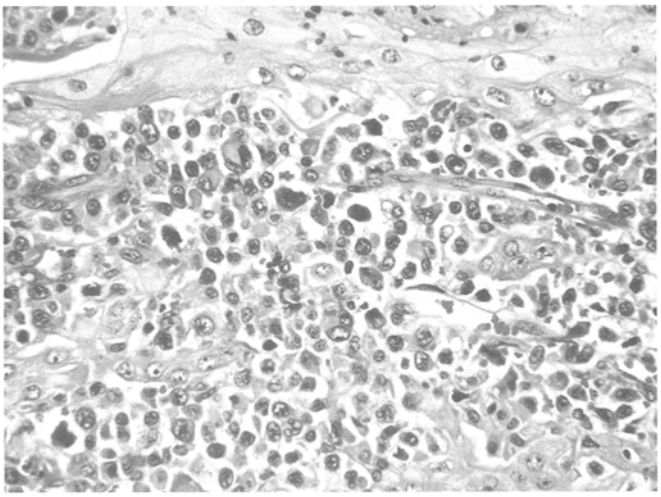


Fig. 63. CD30+ large T-cell lymphoma.

Microscopic

- Similar to mycosis fungoides but epidermotropism may be absent

Immunophenotype

- Similar to mycosis fungoides

Large Cell Cutaneous T-Cell Lymphoma, CD30–

Clinical

- Solitary, localized or generalized plaques, nodules or tumors
- Rapid development of generalized skin involvement is common
- No preceding mycosis fungoides
- Aggressive clinical course with a ~15% five year survival

Microscopic

- Diffuse to nodular infiltrates of medium to large-sized atypical lymphocytes
- Large cells comprise >30% of all cells
- Angiocentricity is common
- Epidermotropism may be present but is not marked

Immunophenotype

- CD3+, CD30–, CD4+/–

Granulomatous Slack Skin

Clinical

- Pendulous plaques involving the axilla and groin regions
- Probably a rare variant of mycosis fungoides
- Males are affected more often than females

Microscopic

- Dense, dermal, atypical lymphocytic infiltrate admixed with numerous multinucleated histiocytes
- Multinucleated cells often have a wreath-like arrangement of nuclei

Table 1. Comparison of Lymphomatoid Papulosis (LyP) and CD30+ Cutaneous T-Cell Lymphoma (CTCL)

	LyP	*CD30+CTCL*
Clinical		
• Lesion type	Multiple	Single or grouped
• Size of lesion(s)	<1 cm	>1 cm
• Distribution	WExtremities/ trunk	Extremities/ head/neck
• Remit	100%	25–50%
• Systemic spread	None	25%
• 5 yr Survival	100%	90%
• Age	Any age	Older adults
Microscopic		
• Pattern	Wedge-shaped	Diffuse sheet
• Subcutis	Spared	Involved
• Inflammation	Marked	Sparse
• Necrosis	Rare	Common
• Epidermotropism	Common	Rare
Immunophenotype and molecular genetics		
• CD30+ pattern	CD30+ clusters	CD30+ sheets
• Immunophenotype	CD3+, CD4+	CD3±, CD4±
• TCR clonality	10–20%	Usually+
• t(2,5) Translocation	–	–

- Elastolysis is frequently present
- Dermal lymphocytes are generally small and have cerebriform nuclear features

Immunophenotype

- Similar to mycosis fungoides

Pleomorphic Small/Medium-Sized Cutaneous T-Cell Lymphoma

Clinical

- One or more nodules/tumors without preceding mycosis fungoides
- Affects middle-aged to older adults

Microscopic

- Dense, diffuse or nodular infiltrate of small to medium-sized, atypical lymphocytes with or without subcutaneous involvement
- <30% large cells
- Epidermotropism may or may not be present

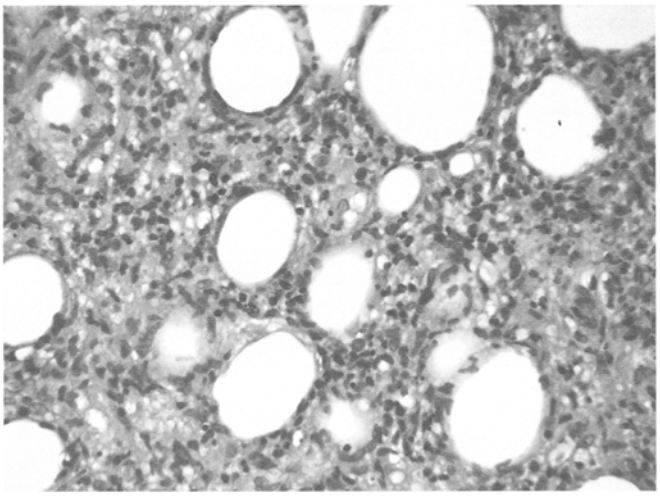


Fig. 64. Subcutaneous, panniculitis-like T-cell lymphoma.

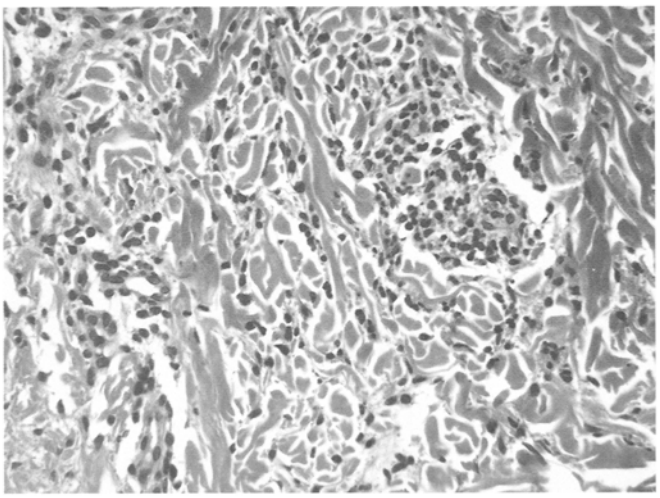


Fig. 65. Leukemia cutis.

Immunophenotype:

- CD3+, CD4+, CD30–

Subcutaneous, Panniculitis-Like T-Cell Lymphoma (Figure 64)

Clinical

- Subcutaneous nodules or plaques typically involving the lower extremities
- Frequent, severe constitutional symptoms
- Hepatosplenomegaly may be present
- Hemophagocytic syndromes are common
- Systemic dissemination is uncommon
- ~50% five year survival

Microscopic

- A variably dense, polymorphous, panniculitis-like infiltrate is present with no or minimal dermal involvement
- The pleomorphic lymphocytes may be small, medium or large T-cells which characteristically "ring" around the adipocytes
- Lipophages, plasma cells, eosinophils, neutrophils and, occasionally, lymphoid follicles may be present
- Necrosis, karyorrhexis, hemophagocytosis and angio-destruction are common

Immunophenotype

- CD3+, CD8+, Tia-1+, porin+, CD56–

Genotype

- Clonal T-cell receptor, alpha/beta genotype most common
- EBV negative

Leukemia Cutis (Figure 65)

General

- All forms of leukemia may involve the skin during the course of their evolution
- Most often, this occurs in patients with a known diagnosis of leukemia
- However, cutaneous disease may be the first manifestation of a leukemic process in evolution

Clinical

- Macules, papules, nodules, tumors, plaques and ulcers may all be manifestations of leukemia cutis
- Any cutaneous surface may be involved
- Gingival involvement is particularly characteristic of acute myelogenous leukemia of the monocytic type (AML, M5)

Microscopic

- The most common pattern of leukemic infiltration of skin is the diffuse dermal, reticular or splaying pattern where the neoplastic cells splay apart the dermal collagen fibers in a discohesive fashion
- Perivascular to angiocentric infiltrates are also seen frequently in chronic lymphocytic leukemia (CLL) and in AML
- Nodular patterns of infiltration are also common
- The cytologic features of a particular leukemic infiltrate reflect their systemic cell of origin
- *CLL: small, monotonous lymphocytes
- *AML: myeloblasts with or without eosinophilic myelocytes, differentiated monocytes, etc.
- *CML (chronic myelogenous leukemia): a spectrum of granulocytic cells and myeloblasts
- *ALL (acute lymphoblastic leukemia): medium-sized, fairly monotonous lymphoblasts

Immunophenotype

- CLL: CD20+, CD23+, CD5+, CD43+/–, CD3–
- AML: CD3–, CD20–, CD43+, MPO+/–, CD68+/–
- CML: CD3–, CD20–, CD43+, MPO+
- ALL: CD3 or CD20+, TdT+/–, MPO–

IMMUNODERMATOLOGY

Methods, Terminology, and Techniques

Direct Immunofluorescence (DIF)

- A skin biopsy that has been snap frozen or placed in transport media (such as Michel's media) is incubated with fluorescein conjugated antibodies against immunoglobulin and complement
- Standard panel of conjugates includes IgG, IgA, IgM, C3 and fibrinogen

Indirect Immunofluorescence (IIF)

- The patient's serum is incubated with normal human skin that has been split at the level of the lamina lucida using 1.0M NaCl (salt-split skin)
- Fluorescein conjugated antibodies to IgG are then added
- If circulating antibody to basement membrane zone is present, the conjugate will localize to the epidermal side, the dermal side or to both
- This pattern reflects the location of the immune deposits (for example hemidesmosome or sublamina densa) and allows distinction between certain immunobullous diseases
- The titer of the circulating antibody is determined by incubating the patient's serum with fluorescein conjugated antibodies to IgG on an epithelial substrate, usually monkey esophagus
- Other substrates may be used in specific conditions, such as rat bladder epithelium for paraneoplastic pemphigus or guinea pig esophagus for pemphigus foliaceus
- Progressively more dilute samples of patient serum are used (1:5, 1:10, 1:20, 1:40, 1:80 and so on)
- The dilution at which fluorescence can no longer be subjectively identified is the antibody titer
- Indirect immunofluorescence can also be performed using fluorescein conjugated antibodies to IgA
- This is helpful for diseases involving IgA, such as linear IgA bullous dermatosis and dermatitis herpetiformis

Western Immunoblotting

- A more specific technique to identify the antigens that the patient's antibodies are directed against

ELISA

- Enzyme linked immunosorbant assays have recently been developed for a number of immunobullous diseases
- These allow rapid, sensitive and specific identification of antibodies

Immunobullous Diseases

Patterns of Antibody Deposition

- A. Linear deposition along the basement membrane zone
- B. Deposition in intercellular spaces
- C. Granular deposition along the basement membrane zone
- D. Granular deposition in the dermal papillae
- E. Cytoid bodies and shaggy deposition along the basement membrane zone
- F. Thick linear deposition along the basement membrane zone and perivascular deposition
- G. Deposition on eosinophils and diffuse deposition on connective tissue
- H. Deposition in blood vessels

Linear Deposition Along the Basement Membrane Zone

Bullous Pemphigoid (BP)

Clinical

- Most commonly occurs in the elderly but has been reported in children and neonates
- Clinical presentation characteristic for pruritic tense bullae (negative Nikolsky sign) that heal without scarring
- The primary lesion is often urticarial
- Brunsting-Perry pemphigoid is a clinical subtype with scarring
- Distribution is mainly flexural, lower extremities and trunk
- Mucous membrane lesions occur in 10%–30%

Microscopic

- Typically shows subepidermal separation with inflammatory infiltrate of eosinophils and lymphocytes **(Figure 66)**
- Eosinophilic spongiosis may be present
- Neutrophils may also be seen, but are not prominent
- Basal layer spongiosis without frank separation may be seen in early or perilesional biopsies

Electron Microscopy

- Separation occurs within the lamina lucida

Immunopathology

- DIF on a perilesional skin biopsy specimen shows linear deposition of antibody (IgG > IgA) and complement at the basement membrane zone **(Figure 67)**
- Eosinophils are often prominent
- IIF using salt-split human skin demonstrates localization of the antibody to the epidermal side of the split **(Figure 68)**
- A combined pattern (epidermal and dermal) is occasionally seen
- Indirect immunofluorescence detects circulating IgG basement membrane zone antibodies in 50 to 70% of patients

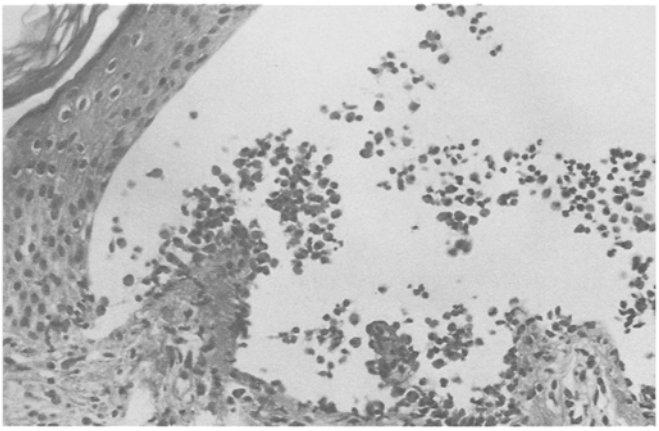


Fig. 66. Bullous pemphigoid. Subepidermal separation with eosinophils and lympocytes.

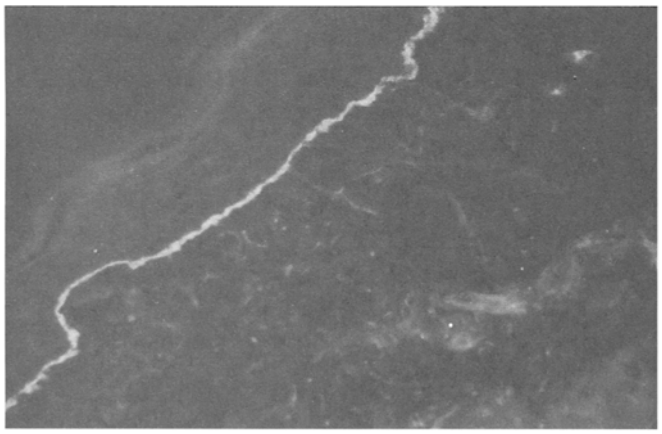


Fig. 67. Bullous pemphigoid. Linear deposition of IgG along the basement membrane zone.

- The antibody titer is not predictably correlated with disease activity or prognosis
- Implicated antigens:
  - Most commonly detected antigen is a 230-Kd hemidesmosomal cytoplasmic protein (BP antigen I)
  - The second most commonly detected is a 180-Kd hemidesmosomal transmembrane protein (BP antigen II)

Cicatricial Pemphigoid

Clinical

- Characterized by inflammation and scarring of the mucosal membranes, most commonly conunctiva
- May also involve oral and genital mucosa
- Primary oral lesion is often desquamative gingivitis
- Skin lesions are less common, but can occur
- Ocular scarring may lead to synblepharon, decreased tear production, entropion and blindness

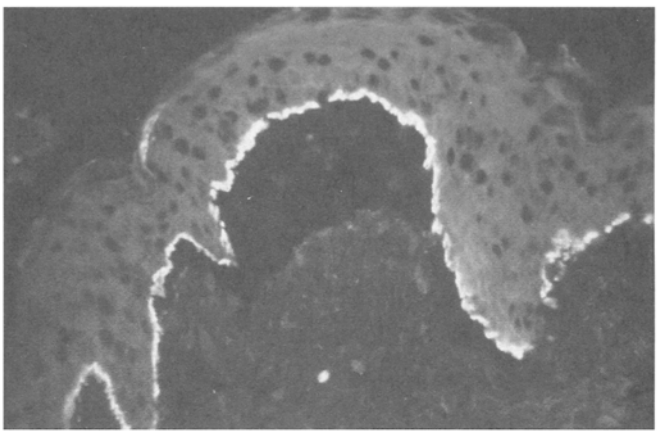


Fig. 68. Bullous pemphigoid. Antibody localizes to the epidermal side of salt split skin.

Microscopic

- May see subepithelial separation but usually see nonspecific mucositis with inflammatory infiltrate of eosinophils, plasma cells and lymphocytes
- Neutrophils may also be present, but are not prominent

Electron Microscopy

- Separation occurs at the level of the lamina lucida

Immunopathology

- DIF pattern is identical to that seen in bullous pemphigoid
- There is linear deposition of IgG, IgA and C3 along the basement membrane zone
- Eosinophils are often present in the lamina propria
- IIF usually does not detect circulating antibodies
- When antibodies are present, IIF using salt-split skin localizes the antibodies to the epidermal side in some cases, and to the dermal side in others

Implicated Antigens

- Most commonly implicated antigens are the same as for bullous pemphigoid (230-Kd and 180-Kd hemidesmosomal proteins), corresponding to the epidermal pattern of binding on salt-split skin
- Some patients have antibodies to epiligrin (laminin 5), a component of the anchoring filaments
- This subset of patients has been associated with the dermal pattern of binding on salt-split skin

Herpes Gestationis (Pemphigoid Gestationis)

Clinical

- Occurs exclusively in women
- Characterized by pruritic tense bullae (negative Nikolsky sign) that heal without scarring
- Primary lesion is often urticarial

- May begin around the umbilicus
- Usually most prominent on abdomen and flexural skin
- Mucosal lesions are very rare
- Most commonly occurs during the second or third trimester of pregnancy and resolves after delivery
- Post-partum flares can occur
- In subsequent pregnancies, the eruption occurs earlier and is more severe
- May also occur with hormonal medication or menses in susceptible women
- Has been reported with molar pregnancy and gestational malignancy

Epidemiology

- Increased frequency of HLA-B8, DR3 and DR4

Microscopic

- Usually identical to bullous pemphigoid
- Typically see subepidermal separation with inflammatory infiltrate of eosinophils, lymphocytes and occasionally neutrophils
- Early or perilesional biopsies may not show frank separation
- Basal cell necrosis may be more prominent than in bullous pemphigoid
- Might see eosinophilic spongiosis and/or an inverted tear-drop pattern of epidermal edema **(Figure 69)**

Electron Microscopy

- Separation occurs within the lamina lucida

Immunopathology

- DIF shows linear deposition of complement along the basement membrane zone **(Figure 70)**
- Linear deposition of IgG may also be present, but is less prominent than complement
- This pattern reflects the nature of the circulating antibody, referred to as "herpes gestationis factor" (HG factor)
- HG factor is an IgG antibody (usually IgG1) that avidly fixes complement
- It is often present in such low titers that DIF and IIF fail to identify it, but the complement it fixes can be detected
- IIF is usually negative
- Low titers of circulating IgG antibodies to basement membrane zone are identified in less than 20% of patients
- When present, salt-split skin localizes these antibodies to the epidermal side of the separation

Implicated Antigens

- The majority of patients have antibodies that are directed against the minor bullous pemphigoid antigen, BP antigen II (180-Kd transmembrane hemi-desmosomal protein)

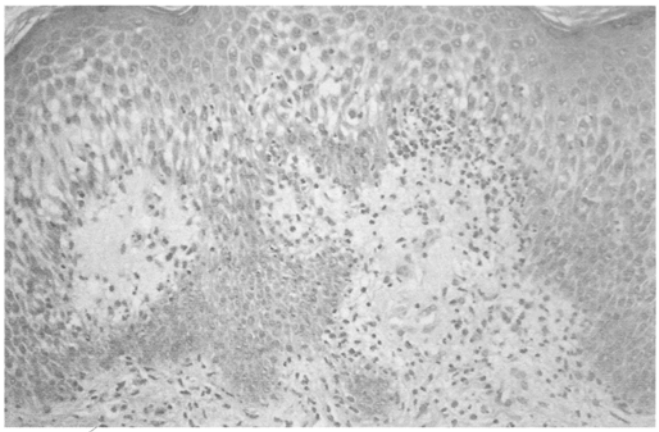


Fig. 69. Herpes gestationis. Eosinophilic spongiosis and subepidermal separation with eosinophils.

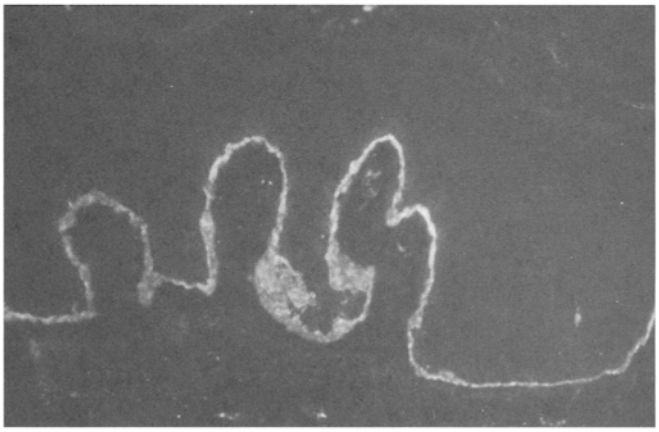


Fig. 70. Herpes gestationis. Linear deposition of complement along the basement membrane zone.

- A smaller group of patients have antibodies directed against the major bullous pemphigoid antigen, BP antigen I (230-Kd cytoplasmic hemidesmosomal protein)

Epidermolysis Bullosa Acquisita (EBA)

Clinical

- Adults are affected more commonly than children
- Racial differences are seen, with blacks affected more frequently
- Three different clinical patterns are observed
- A mechanobullous eruption with non-inflammatory blisters and increased skin fragility in an acral distribution, that heals with scarring and milia. This is the most frequent presentation
- An inflammatory ("bullous pemphigoid-like") vesico-bullous eruption that heals without scarring or milia
- Mucosal erosions with scarring ("cicatricial pemphigoid-like")
- All three types of lesions may be present; considerable overlap exists

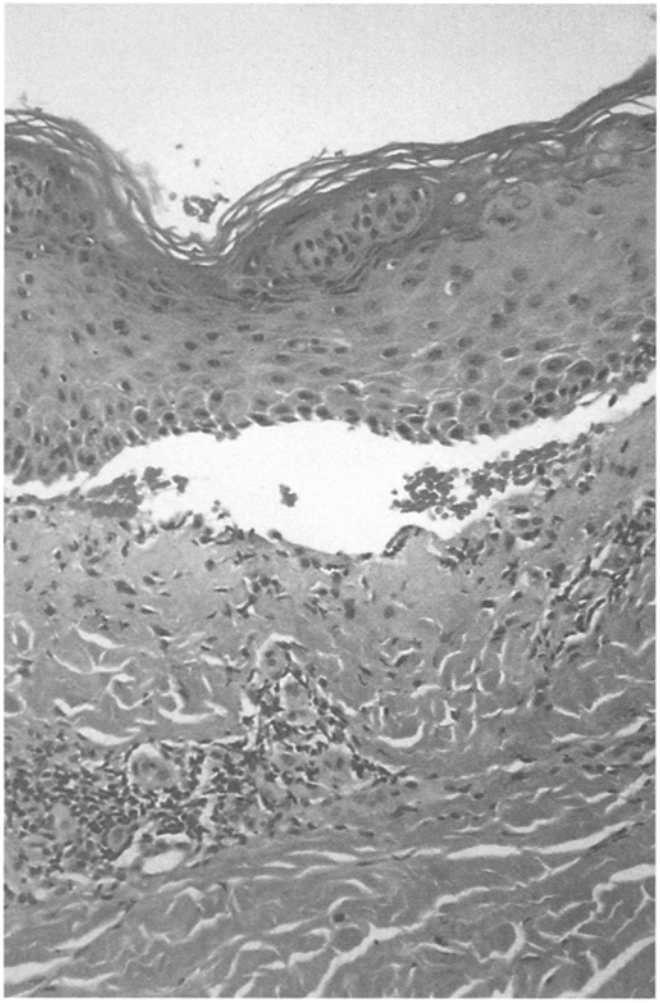


Fig. 71. Epidermolysis bullosa acquisita. Subepidermal separation wth minmal inflammation.

- Associated diseases include systemic lupus erythematosus, other diseases of autoimmunity (inflammatory bowel disease, Goodpasture's syndrome, glomerulonephritis, rheumatoid arthritis, thyroiditis, diabetes) and malignancy (multiple myeloma, chronic lymphocytic leukemia)
- Prognosis is generally poor

Epidemiology

- Increased incidence of HLA-DR2

Microscopic

- If a non-inflamed mechanobullous lesion is biopsied, microscopic will show a subepidermal separation with minimal inflammation **(Figure 71)**
- If clinical lesion is inflamed, biopsy will have subepidermal separation with neutrophils, eosinophils and lymphocytes along the basement membrane and in the upper dermis
- Neutrophils tend to predominate over eosinophils

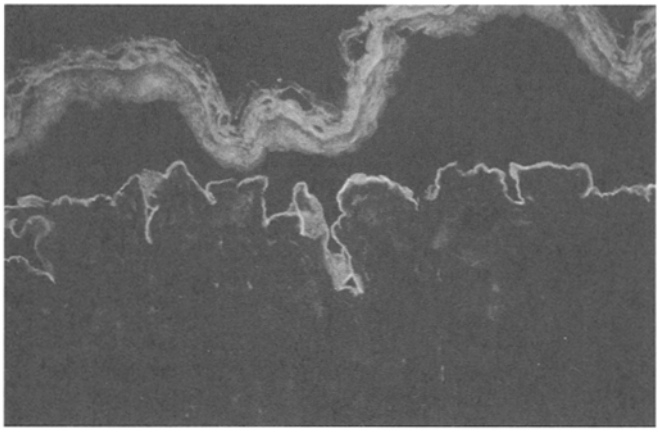


Fig. 72. Epidermolysis bullosa acquisita. Antibody localizes to the dermal side of salt split skin.

- Basal layer spongiosis without frank separation may be seen in early or perilesional biopsies

Electron Microscopy

- Separation usually occurs at the level of the lamina densa/sublamina densa
- Occasionally occurs in the lamina lucida

Immunopathology

- DIF has a pattern identical to bullous pemphigoid, with linear deposition of IgG and complement along the basement membrane zone
- IgA, IgM and fibrinogen are less commonly present. Indirect immunofluorescence is necessary to distinguish EBA from pemphigoid
- IIF on salt-split skin shows a dermal pattern of binding **(Figure 72)**
- Circulating IgG antibody to basement membrane zone is commonly present

Implicated Antigens

- The majority of patients have antibodies that are directed against the 290-Kd non-collagenous domain (NC-1) on the alpha chain of collagen type VII (anchoring fibrils)
- Rarely, antibodies to a 145-Kd non-collagenous globular domain on the alpha chain of collagen type VII have been identified

Bullous Systemic Lupus Erythematosus (BSLE)

Clinical

- Patients with systemic lupus erythematosus may also develop autoimmunity to basement membrane zone
- These patients present with a blistering eruption, especially on sun-exposed skin
- They will also have other signs and symptoms of systemic lupus
- They do not usually have other cutaneous manifestations of lupus

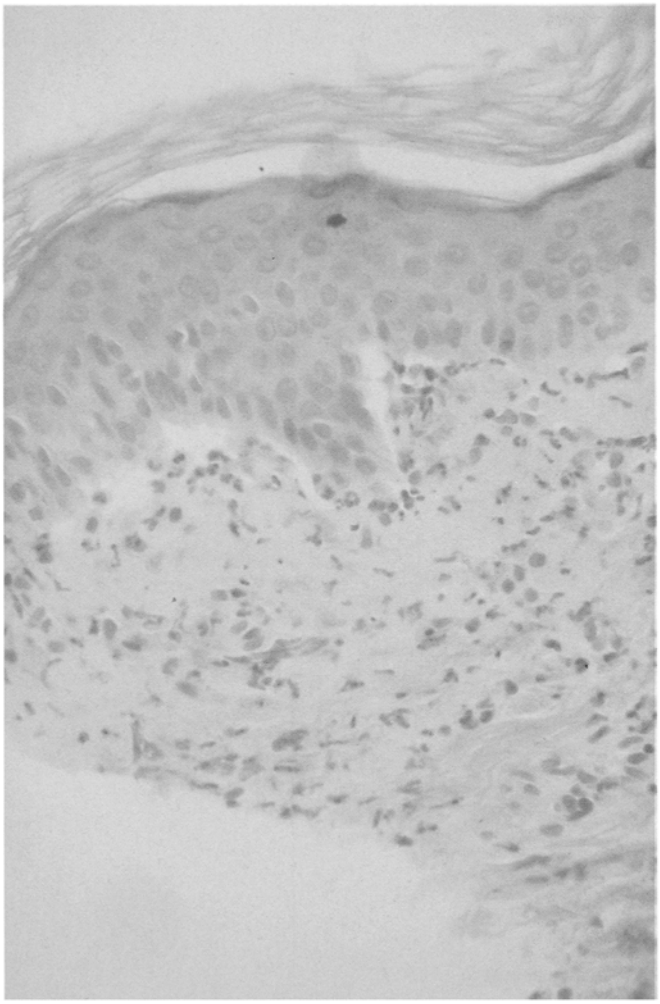


Fig. 73. Bullous systemic lupus erythamatosus. Subepidermal separation wih neutrophils and lymphocytes in dermal papillae and along the basement membrane zone.

- Patients with systemic lupus can also have blistering for other reasons, such as concurrent primary bullous disease or severe medication or photosensitivity reaction

Epidemiology

- Increased incidence of HLA-DR2

Microscopic

- Typically shows subepidermal separation with inflammatory infiltrate of neutrophils and lymphocytes in the dermal papillae (as in dermatitis herpetiformis) and along the basement membrane zone **(Figure 73)**
- Neutrophils predominate

Immunoelectron Microscopy

- IgG and complement are deposited in the sublamina densa
- Separation occurs at the level of the sublamina densa

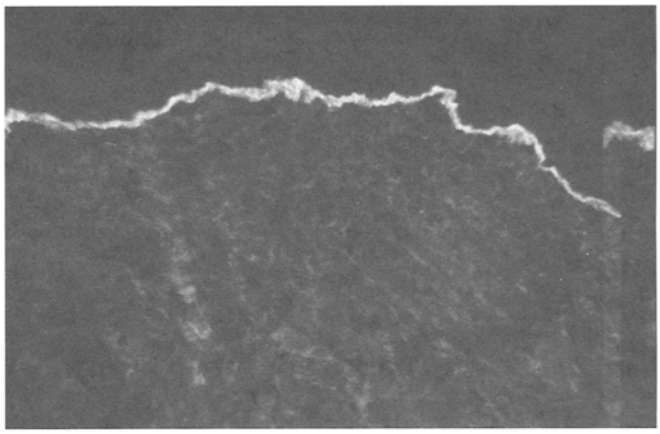


Fig. 74. Bullous systemic lupus erythamatosus. Linear deposition of IgG along the basement membrane zone.

Immunopathology

- DIF shows either linear **(Figure 74)** or granular to fibrillar deposition of IgG and complement along the basement membrane zone **(Figure 75)**
- IgM and IgA are occasionally present
- IIF using salt-split skin demonstrates immune deposits on the dermal side of the separation
- Circulating IgG to basement membrane zone is present in some but not all patients
- Antinuclear antibodies are often seen

Implicated Antigens

- As in EBA, the majority of patients have antibodies that are directed against the 290-Kd non-collagenous domain (NC-1) on the alpha chain of collagen type VII (anchoring fibrils)
- Rarely, antibodies to a 145-Kd non-collagenous globular domain on the alpha chain of collagen type VII have been identified
- Antibody specificity is the same as that seen in epidermolysis bullosa acquisita
- In some cases, antibodies to type VII collagen cannot be detected
- Some authors propose two subtypes, BSLE 1 and BSLE 2, based on the presence (BSLE 1) or absence (BSLE 2) of antibodies to type VII collagen

Linear IgA Bullous Dermatosis (Chronic Bullous Disease of Childhood)

Clinical

- Occurs in adults and children, probably more common in children and in women
- Clinically heterogeneous
- Clinical exam shows a vesiculobullous eruption on normal or erythematous skin
- May have a "cluster-of-jewels" appearance

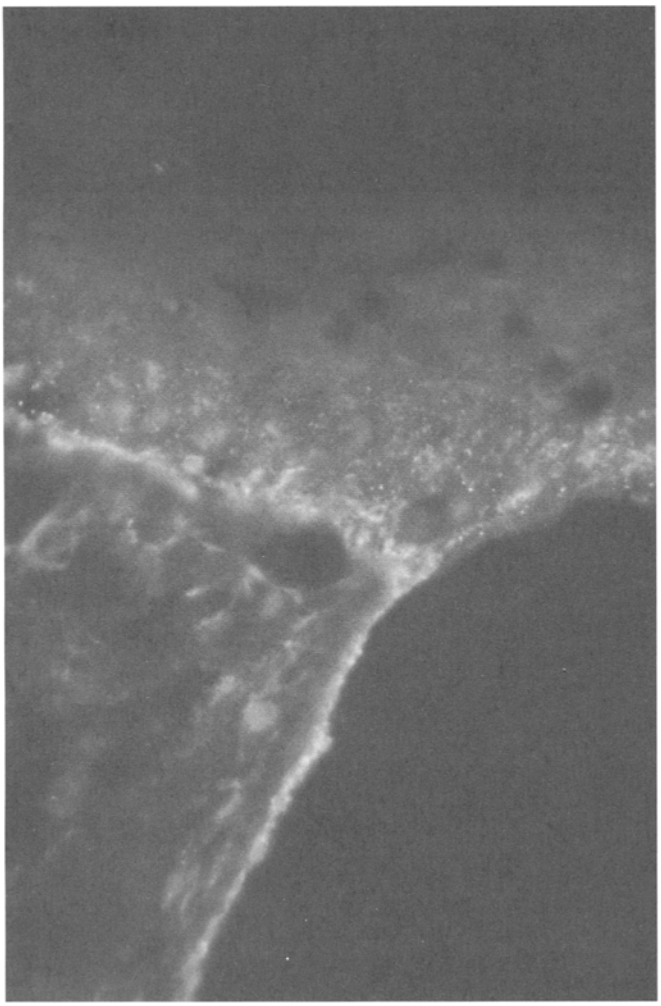


Fig. 75. Bullous systemic lupus erythamatosus. Linear to granular deposition of IgG along the basement membrane zone and epidermal ANA.

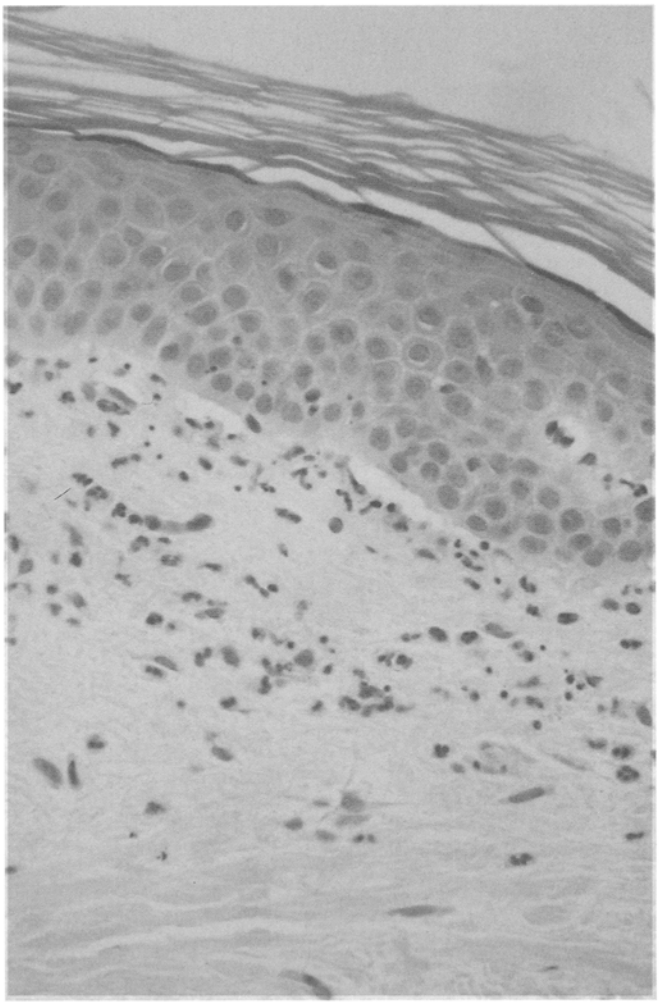


Fig. 76. Linear IgA bullous dermatosis. Subepidermal separation with neutrophils greater in number than lymphocytes and eosinophils.

- Commonly occurs on trunk and flexures in adults and on lower abdomen, groin and periorificial in children
- Oral lesions occur in about 70%
- Other mucosal surfaces, including conjunctivae, may be involved
- Disease associations include:
  - Medications (captopril, vancomycin, lithium), gastrointestinal diseases (inflammatory bowel disease, gluten sensitive enteropathy) malignancy (hematogenous, carcinoma, melanoma) various infections, other diseases of autoimmunity
- Prognosis is generally good

Microscopic

- Usually shows subepidermal separation with inflammatory infiltrate of neutrophils, eosinophils and lymphocytes **(Figure 76)**
- Neutrophils predominate over eosinophils, especially in early lesions
- Basal layer spongiosis without frank separation may be seen in early or perilesional biopsies
- May see neutrophilic microabscesses in dermal papillae, similar to dermatitis herpetiformis

Immunoelectron Microscopy

- Mixed findings occur
- In some cases, there is IgA deposition in the lamina lucida (beneath the hemidesmosomes)
- In others cases, IgA is found in the sublamina densa, in association with anchoring fibrils
- IgA may also be found deposited in both locations

Immunopathology

- DIF shows linear deposition of IgA along the basement membrane zone **(Figure 77)**

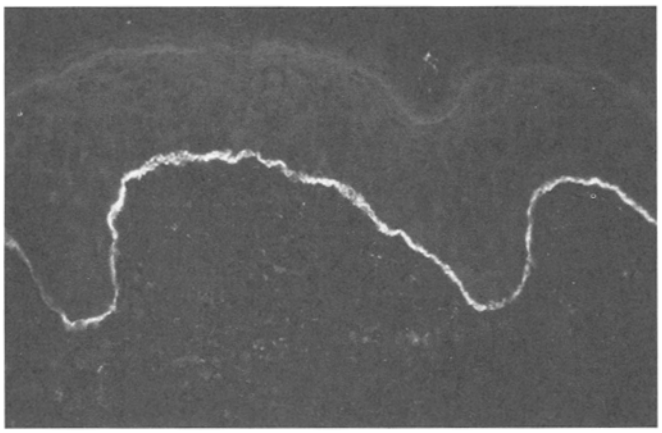


Fig. 77. Linear IgA bullous dermatosis. Linear deposition of IgA along the basement membrane zone.

- IgG, IgM, C3, and fibrinogen may be present but are of lower intensity than IgA
- IIF on salt-split skin may show an epidermal pattern (most common), a dermal pattern or both
- Circulating IgA antibodies (usually IgA1) to basement membrane zone can be identified in 60–70%

Implicated Antigens

- Several different antigens have been identified
- Most common is a 97-Kd component of the anchoring filaments termed LAD-1
- Immune deposition here corresponds to an epidermal pattern of binding on salt-split skin
- Antibodies to a 290-Kd component of collagen type VII have also been identified
- Epitope is different than that of EBA
- Immune deposition here corresponds to a dermal pattern of binding on salt-split skin
- Other antibodies have also been identified
- LABD is likely a heterogeneous group of diseases, with a variety of autoantibodies

Deposition in Intercellular Spaces

Pemphigus

- A group of diseases all characterized clinically by cutaneous and/or mucosal blistering or erosions and histologically by acantholysis
- Immunopathology:
  - Autoantibodies to epithelial cell surfaces giving an intercellular space pattern of antibody deposition (ICS pattern)

Pemphigus Variants

- Pemphigus vulgaris
- Pemphigus vegetans
- Drug-induced pemphigus
- Pemphigus foliaceus
- Pemphigus erythematosus
- IgA pemphigus
- Paraneoplastic pemphigus

Pemphigus Vulgaris

Clinical

- Most commonly occurs in adults (mean age 50–60) but has been reported in children
- Increased incidence with Ashkenazi jewish or Mediterranean heritage, but no race is exempt
- Oral lesions (erosions) usually develop first
- Disease may be confined to the oral cavity
- Skin lesions are typically flaccid bullae that rupture easily leaving erosions and crusts
- Gentle pressure on the blister roof will cause extension of the bulla (positive Nikolsky's sign) due to the fragility of the surrounding skin
- Any stratified squamous epithelial surface may be involved, including other mucosal surfaces
- Pemphigus vegetans is a clinical subtype characterized by chronic lesions that develop into hyperkeratotic plaques, often in intertriginous sites
- Most commonly implicated medications in drug-induced pemphigus are penicillamine and captopril

Microscopic

- Characteristic for suprabasilar separation with acantholysis **(Figure 78)**
- Basal layer remains attached, with separation at the lateral and apical margins ("tombstoning") **(Figure 79)**
- Acantholysis extending down hair follicles helps to distinguish pemphigus from other causes of acantholysis such as Hailey-Hailey and Darier's disease
- Eosinophilic spongiosis may be present
- There is a mixed inflammatory infiltrate in the dermis
- Pemphigus vegetans has more acanthosis and eosinophilic spongiosis with relatively subtle suprabasilar separation and acantholysis

Electron Microscopy

- First sign is loss of attachment of cell membrane between adjacent keratinocytes, at the level of the desmosome
- Widening of intercellular spaces follows, as desmosomes pull apart
- Intracellular keratin filaments begin to show perinuclear clustering and the acantholytic cells then "round up" and float free

Immunopathology

- DIF shows IgG and C3 bound to the keratinocyte cell surface in an ICS pattern; also referred to as intercellular substance **(Figure 80)**

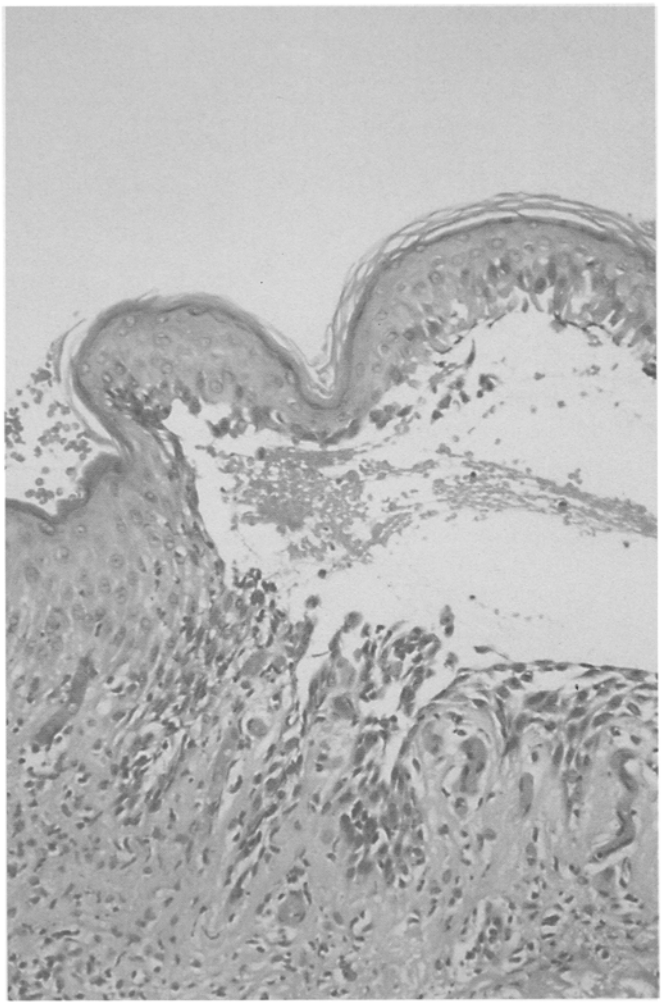


Fig. 78. Pemphigus vulgaris. Suprabasilar separation with acantholysis.

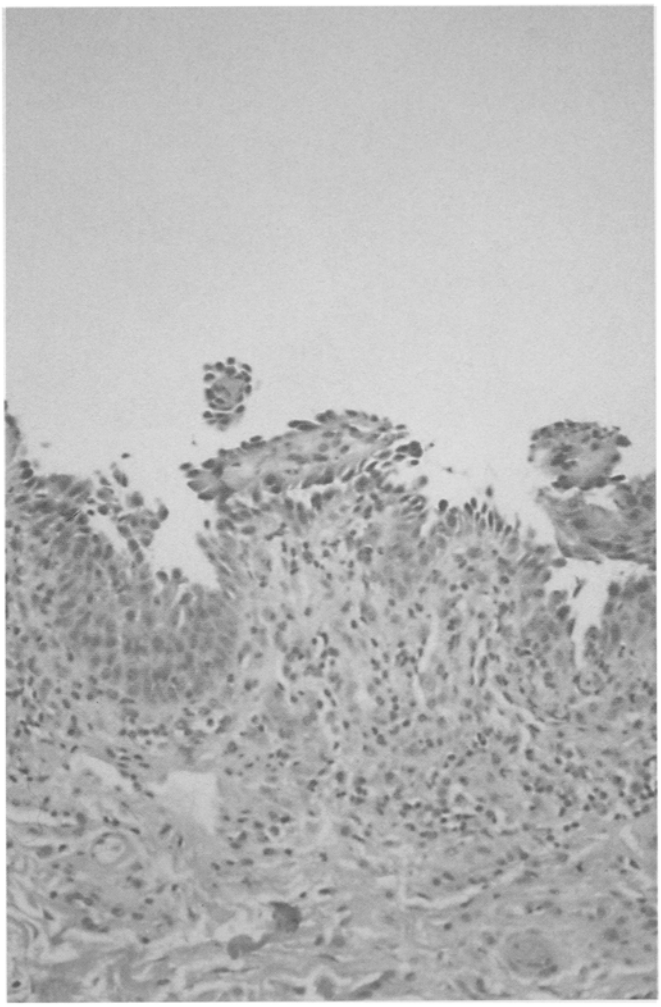


Fig. 79. Pemphigus vulgaris. "Tombstoning" of basal layer.

- ♦ May be seen throughout the thickness of the epidermis or only in the deeper levels
- ♦ In active disease, IIF is nearly always positive for circulating IgG antibodies to ICS **(Figure 81)**
- ♦ False negatives are more likely in drug induced and early disease
- ♦ Antibody titer correlates fairly well with disease activity
- ♦ False positive "pemphigus-like" antibodies are not uncommon and can be seen with medications (penicillin), infections (dermatophytes), and full thickness epidermal disruption (burns)
- ♦ The titer of false positive antibody is usually low (less than 1:80)

Implicated Antigen

- ♦ Autoantibodies (IgG4 > IgG1 and IgG3) are directed against desmoglein 3, a 130-Kd transmembrane glycoprotein located in desmosomes
- ♦ It exists in a molecular complex with plakoglobin, an 85-Kd intracellular protein

Pemphigus Foliaceus

Clinical

- ♦ Characterized by superficial erosions and crusts, flaccid vesicles or bullae may be present
- ♦ Usually begins on head/neck (seborrheic distribution) and spreads acrally
- ♦ Mucosal lesions are rare
- ♦ May be exacerbated by sunlight
- ♦ Clinical variants include a sporadic form, a drug-induced form, and an endemic form (Fogo selvagem)
- ♦ Fogo selvagem is seen in agricultural and poverty-stricken regions of Brazil and South America
- ♦ Familial cases are frequently seen
- ♦ Peak incidence in the second and third decade
- ♦ The black fly (Simulian pruinosum) has been epidemiologically implicated as a vector
- ♦ Sporadic form occurs in elderly patients with no family history

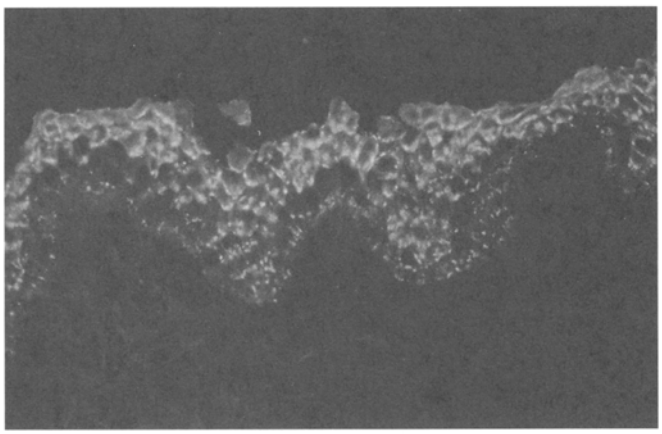


Fig. 80. Pemphigus vulgaris. IgG bound to keratinocyte cell surface in an ICS pattern.

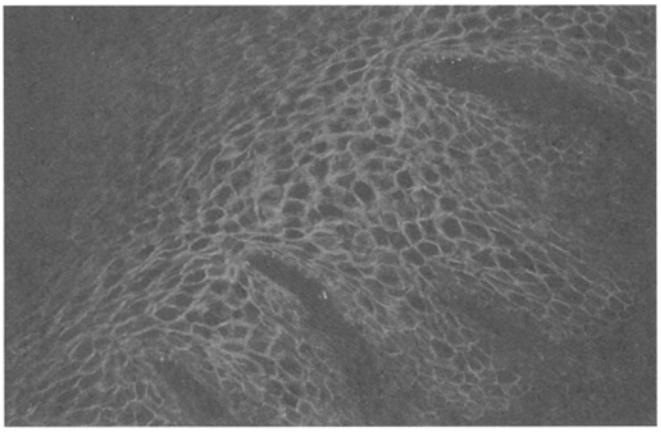


Fig. 81. Pemphigus vulgaris. Circulating IgG to ICS on monkey esophagus.

- No environmental factors have been implicated
- Drug-induced form most commonly linked to "thiol" drugs (penicillamine and captopril) but has also been seen with "masked thiols" (penicillins and cephalosporins) and non-thiols (enalapril)
- Other associations include myasthenia gravis and thymoma (benign and malignant)

Microscopic

- As in pemphigus vulgaris, but more superficially located
- Acantholysis occurs in a subcorneal or intraepidermal location (**Figure 82**)

Electron Microscopy

- Acantholysis affects ALL layers, including the basal layer

Immunopathology

- DIF and IIF have findings similar or identical to those seen in pemphigus vulgaris (**Figure 83**)

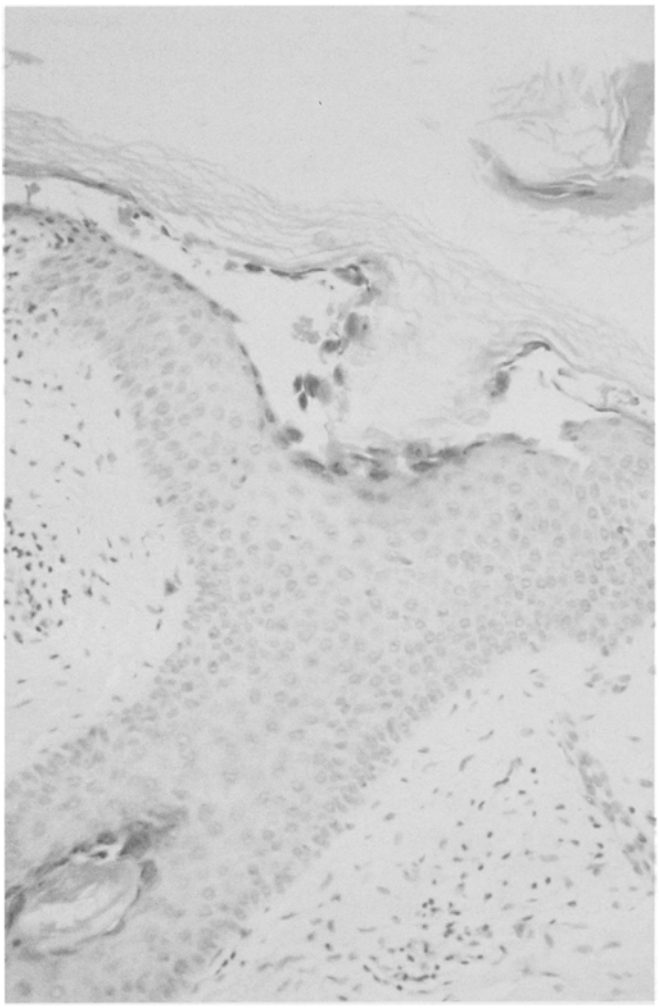


Fig. 82. Pemphigus foliaceus. Subcorneal acantholysis.

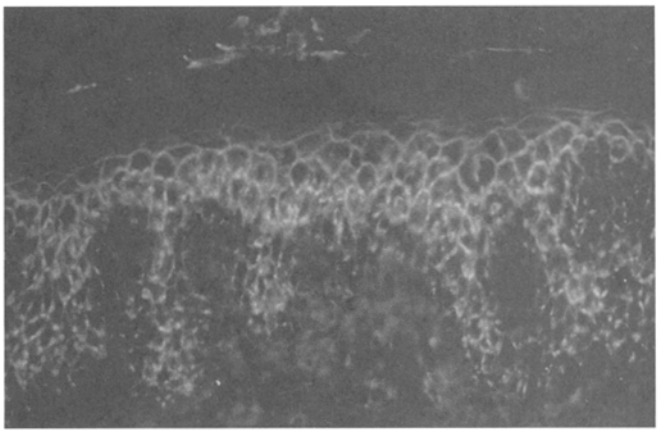


Fig. 83. Pemphigus foliaceus. IgG bound to keratinocyte cell surface in an ICS pattern.

- DIF cannot reliably distinguish P. vulgaris from P. foliaceus
- In active disease, IIF is nearly always positive for circulating IgG antibodies to ICS

- Antibody titer correlates fairly well with disease activity
- Guinea pig esophagus appears to be better than monkey esophagus as a substrate for detection of antibodies

Implicated Antigen

- Autoantibodies are directed against desmoglein 1, a 160-kd transmembrane glycoprotein located in desmosomes
- Like desmoglein 3 (antigen in P. vulgaris), desmoglein 1 exists in a molecular complex with plakoglobin

Pemphigus Erythematosus

Clinical

- A rare disease characterized by facial lesions with features of both lupus erythematosus and pemphigus foliaceus (or seborrheic dermatitis) and lesions on the trunk more suggestive of pemphigus (flaccid bullae, erosions and crusts)
- Usually photodistributed
- Mucosal lesions are rare
- May occur in any age; mean onset 40–60 years
- Clinical signs of lupus may be present, but usually are not
- When present, lupus is usually mild or localized only
- Antinuclear antibodies are present in 30–60%
- Most commonly associated medications are penicillamine and captopril
- Various autoimmune diseases (myasthenia gravis) and malignancies (bronchogenic carcinoma) have also been associated

Microscopic

- Superficial acantholysis (similar to P. foliaceus) is the main feature **(Figure 84)**
- A subcorneal separation or pustule may be present
- Lichenoid dermatitis may be seen, but changes characteristic of lupus are NOT usually found

Electron Microscopy

- Demonstrates findings similar to early pemphigus
- Most marked changes occur at the level of the stratum granulosum and upper stratum spinosum

Immunopathology

- DIF characterized by the combination of a typical ICS pattern with IgG and/or C3 **(Figure 85)**, as well as granular to linear deposition of IgM along the basement membrane zone **(Figure 86)**
- A lupus band is usually NOT present
- As in P. vulgaris and P. foliaceus, IIF is usually positive for circulating antibodies against ICS

Implicated Antigen

- Unknown

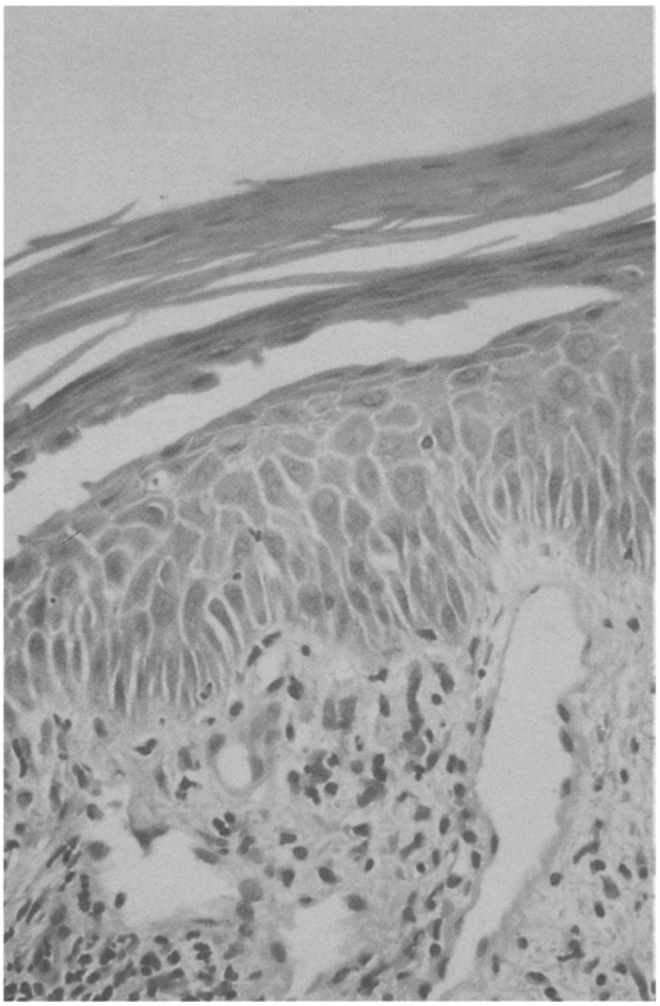


Fig. 84. Pemphigus erythematosus. Subcorneal acantholysis.

IgA Pemphigus (Numerous Synonyms: Intraepidermal Neutrophilic IgA Dermatosis, Atypical Neutrophilic Dermatosis, Intercellular IgA Vesico-pustular Dermatosis and IgA Pemphigus Foliaceus)

Clinical

- A rare disease, only reported in caucasians
- Has been reported in children
- Clinical lesions include flaccid vesicles and pustules, sometimes in an annular or circinate pattern
- Distribution is often central
- Mucosal lesions do not occur
- The clinical course is fairly mild
- Two subtypes are IgA pemphigus of the subcorneal pustular dermatosis type (SPD) and IgA pemphigus of the intraepidermal neutrophilic type (IEN)

Microscopic

- SPD-type has subcorneal separation with neutrophils **(Figure 87)**

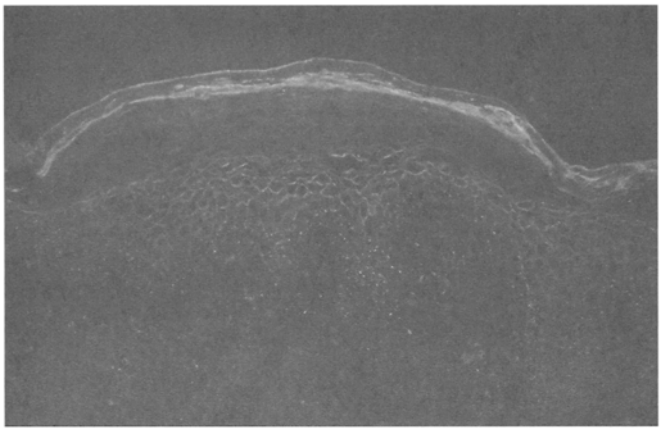


Fig. 85. Pemphigus erythematosus. IgG bound to keratinocyte cell surface in an ICS pattern.



Fig. 86. Pemphigus erythematosus. Granular deposition of IgM along the basement membrane zone and cytoids.

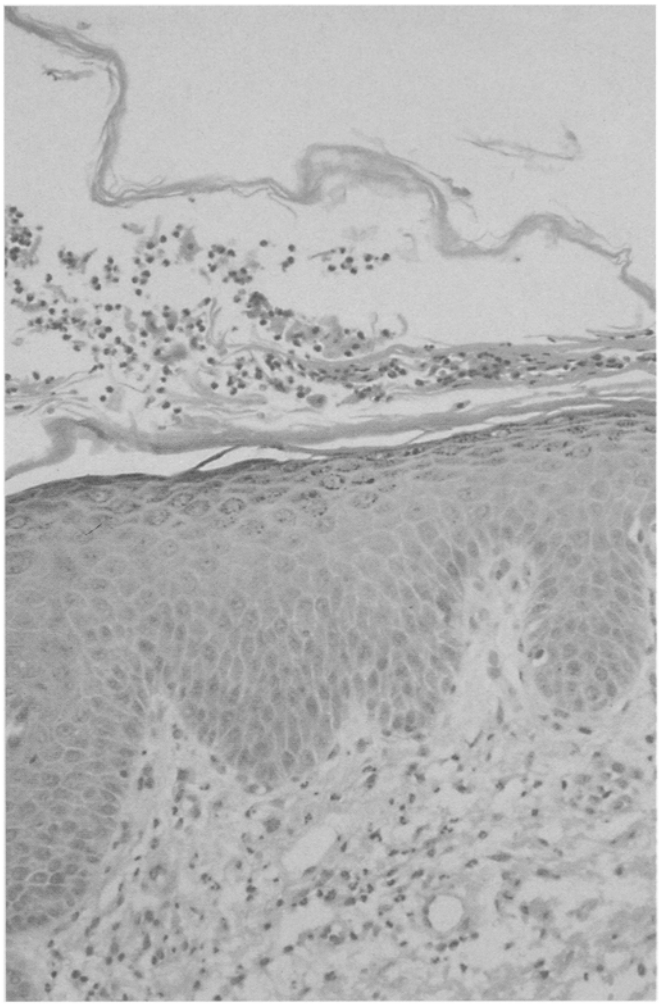


Fig. 87. IgA Pemphigus. Subcorneal separation with neutrophils.

- IEN-type has an intraepidermal cleft with neutrophils (slightly deeper than the SPD-type) **(Figure 88)**
- Suprabasilar separation may be seen
- In both types, acantholysis is sparse
- Neutrophilic microabscesses, as seen in dermatitis herpetiformis, have been reported

Immunopathology

- DIF is characterized by deposition of IgA in an ICS pattern **(Figure 89)**
- In general, deposition of C3 and other immunoglobulins does not occur
- Circulating IgA against ICS present in less than half of reported cases
- Circulating anti-ICS IgG (lower titer than anti-ICS IgA) has been rarely reported

Implicated Antigen(s)

- Most likely a heterogeneous group of diseases with antibodies directed against several different antigens
- Most strongly implicated antigen is desmocollin 1, a 115-Kd protein found on the extracellular surface of the desmosome, which has been linked to the SPD-type
- A 120-Kd protein has been linked to the IEN-type
- Other antigens, including some linked to P. vulgaris, have also been associated

Paraneoplastic Pemphigus

Clinical

- Association between pemphigus and malignancy has long been recognized
- Described as a distinct entity in 1990
- More common in older adults, but has been reported in children
- Malignancy usually presents first
- Prognosis is very poor; both malignancy and pemphigus are usually treatment resistant
- Hematopoeitic malignancies (CLL, Castleman's tumor, Waldenstrom's macroglobulinemia and non-Hodgkin's

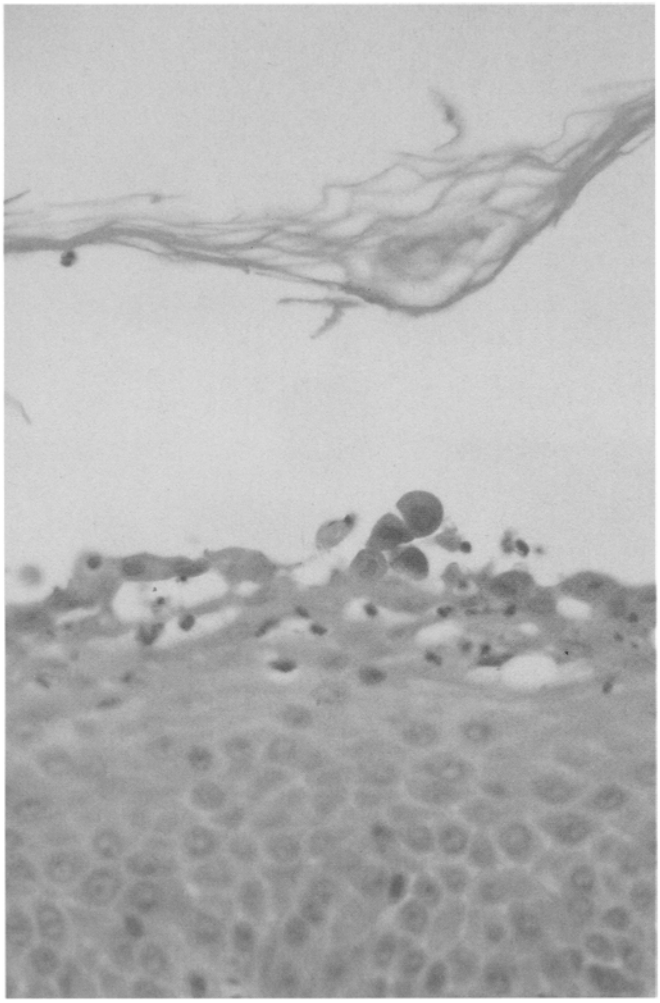


Fig. 88. IgA Pemphigus. Subcorneal separation with intraepidermal neutrophils.

lymphoma) have been most commonly associated, but poorly differentiated sarcomas, adenocarcinoma, and even benign thymoma have been linked

- Clinically characterized by severe, painful and recalcitrant erosions of mucosal surfaces
- Oral mucosa most commonly involved
- May also affect conjunctivae, genital mucosa and respiratory epithelium
- Cutaneous eruption is polymorphous
- Initially may have a pruritic papulosquamous eruption
- Blisters may later develop, including on palms and soles (reminiscent of erythema multiforme)
- Chronic lichenoid changes have also been described

Microscopic

- In about half of the cases, a combination of histologic features is seen, including:
- Suprabasilar separation and acantholysis **(Figure 90)**

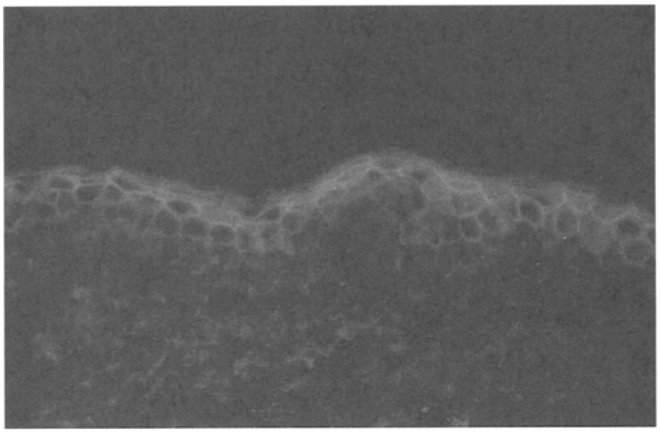


Fig. 89. IgA Pemphigus. IgA bound to keratinocyte cell surface in an ICS pattern.

- lichenoid changes (vacuolar degeneration, a band-like infiltrate and exocytosis of inflammatory cells) **(Figure 91)**
- Dyskeratotic and necrotic keratinocytes (as seen in erythema multiforme)
- Many cases will not have all of these features
- Eosinophilic infiltration is not typically seen
- Atypia of infiltrating cells also not seen

Immunoelectron Microscopy

- Immune complexes present in a variety of locations, including the hemidesmosomes, desmosomal plaques, keratinocyte plasma membrane and extracellular regions of desmosomes

Immunopathology

- DIF has the characteristic combination of an ICS pattern with IgG +/– C3, and linear to granular deposition of C3 +/– IgG along the basement membrane zone **(Figure 92)**
- Other lichenoid features, such as cytoids (dyskeratotic keratinocytes) and shaggy deposition of fibrinogen are variably present
- Circulating IgG against epithelial cell surfaces has been detected on many substrates, including stratified squamous (as in other forms of pemphigus) as well as transitional and columnar epithelium
- Best sensitivity/specificity profile in urinary bladder epithelium (rat and mouse)

Implicated Antigens

- Autoantibodies are directed against a complex of four antigens
- Most strongly and consistently detected are antibodies against a
- 190-Kd protein (identity unknown)
- 210-Kd protein (desmoplakin 2)
- Also detected are antibodies against a:

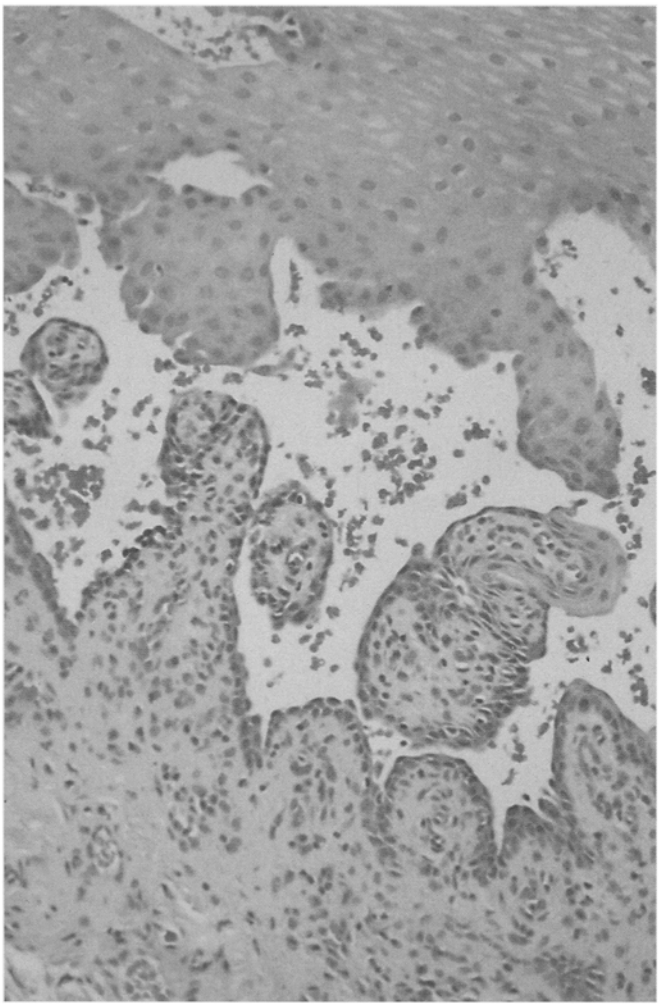


Fig. 90. Paraneoplastic pemphigus. Mucosa with suprabasilar separation and acantholysis.

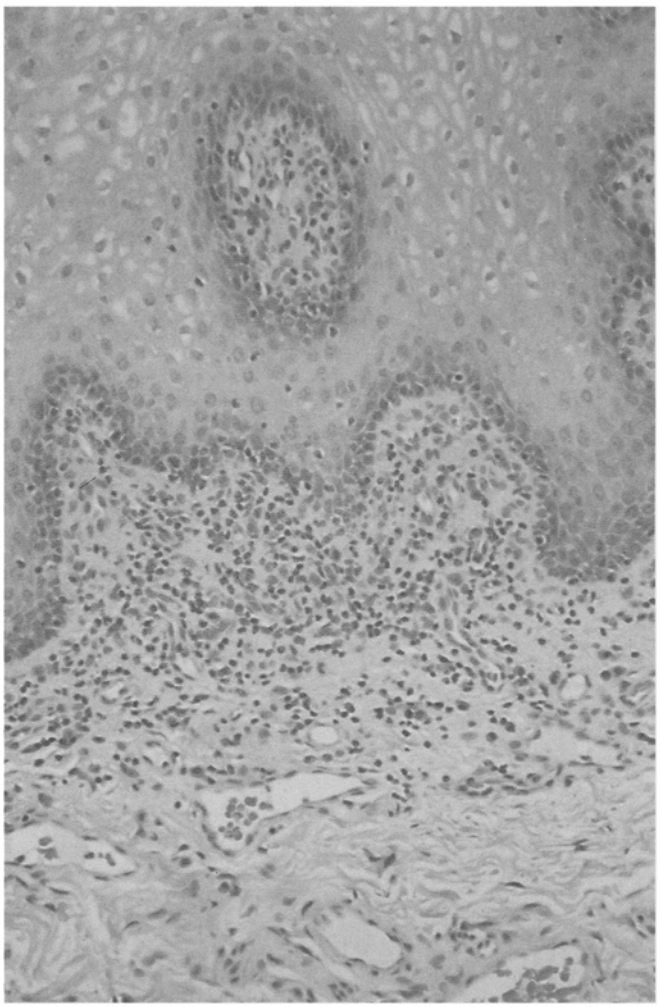


Fig. 91. Paraneoplastic pemphigus. Another zone with lichenoid mucositis.

- 230-Kd hemidesmosomal protein (bullous pemphgoid antigen 1)
- 250-Kd protein (desmoplakin 1)

Granular Deposition Along the Basement Membrane Zone: Lupus Erythematosus

Lupus Variants

- Discoid lupus erythematosus
- Localized
- Disseminated
- Subacute cutaneous lupus erythematosus
- Systemic lupus erythematosus
- Bullous systemic lupus erythematosus

Discoid Lupus Erythematosus (DLE)

Clinical

- DLE is a cutaneous disease, usually not accompanied by systemic signs of lupus
- It is photodistributed and thus typically affects the face, head and neck, chest and upper back
- Disease may be localized or widespread (disseminated)
- More common in young women
- Increased incidence in blacks
- Clinical lesions are patches, papules and plaques
- Characteristic features include telangiectasia, atrophy, scarring and follicular plugging
- Scalp involvement results in scarring alopecia
- Response to treatment (photoprotection, topical steroids and systemic antimalarials) is variable, but tends to be good

Microscopic

- Epidermal atrophy, hyperkeratosis, and thickening of the basement membrane accompany basal liquifactive degeneration, pigment incontinence and a variable degree of lichenoid inflammation **(Figure 93)**

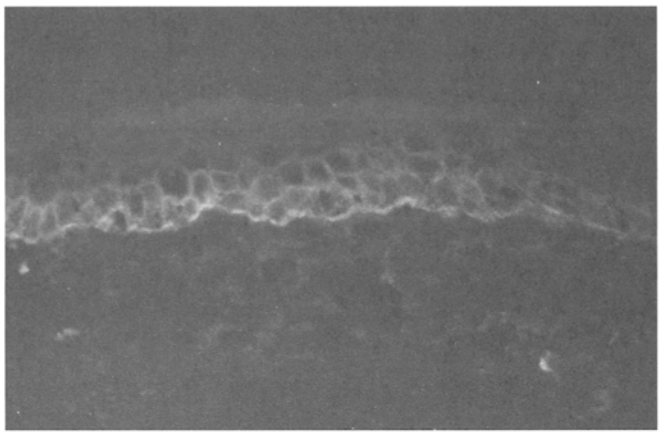


Fig. 92. Paraneoplastic pemphigus. Complement bound to cell surface in an ICS pattern and in a linear to granular pattern along the basement membrane zone.

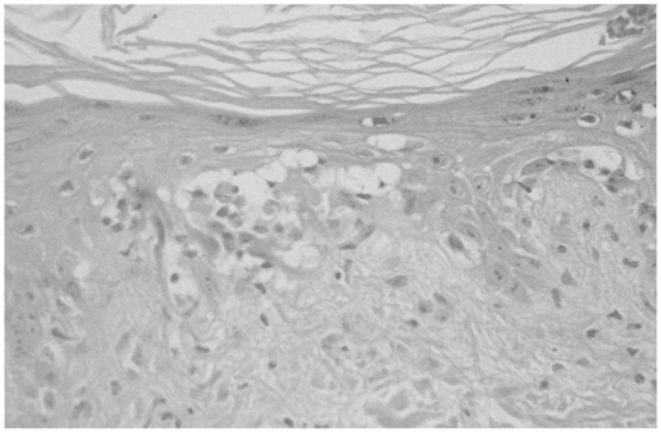


Fig. 93. Discoid lupus erythematosus. Interface dermatitis.

- Periadnexal and perivascular infiltrate is present in the upper and mid dermis
- Follicular infundibular plugging is often seen
- Dermal mucinosis often present

Immunopathology

- On involved or sun-exposed skin, DIF shows granular deposition along the basement membrane zone with IgM, sometimes referred to as a lupus band **(Figure 94)**
- The strict definition of a lupus band reserves the use of the term for the presence of granular IgM along the basement membrane zone in uninvolved and nonsunexposed skin, as seen in systemic LE **(Figure 95)**
- Granular deposition with other conjugates, including C3, IgA and IgG, is usually present, which helps to confirm the diagnosis
- Fibrinogen often forms a shaggy band along the basement membrane zone, typical for a lichenoid reaction

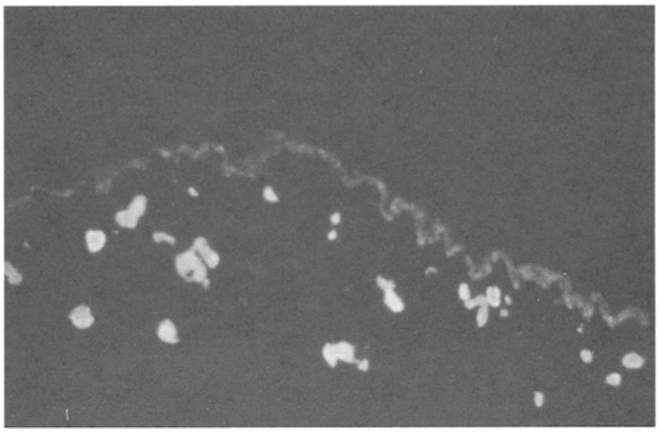


Fig. 94. Discoid lupus erythematosus. Granular deposition of IgM along the basement membrane zone and cytoids.

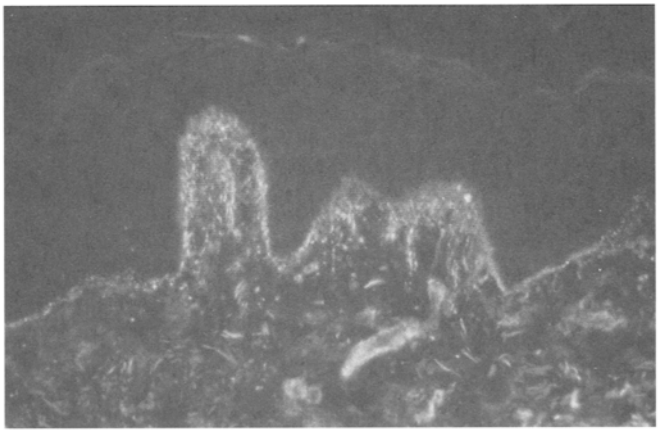


Fig. 95. Discoid lupus erythematosus. The "lupus band" of systemic lupus erythematosus is granular deposition of IgM along the basement membrane zone in nonsunexposed skin.

- DIF may be negative (or only have minimal granular IgM deposition) in a biopsy from an old "burned-out" lesion or from the atrophic center of a lesion, making site selection for biopsy critical for the diagnosis
- DIF is negative in uninvolved and nonsunexposed skin
- May also see epidermal antinuclear antibodies, most commonly with IgG
- Indirect immunofluorescence is negative

Subacute Cutaneous Lupus Erythematosus (SCLE)

Clinical

- SCLE is a photodistributed, symmetric and often widespread eruption, most commonly seen in females
- Mean age of presentation is around 40, which is slightly older than other types of LE
- There is a strong association with the presence of anti-Ro (SS-A) antibodies and Sjögren's syndrome

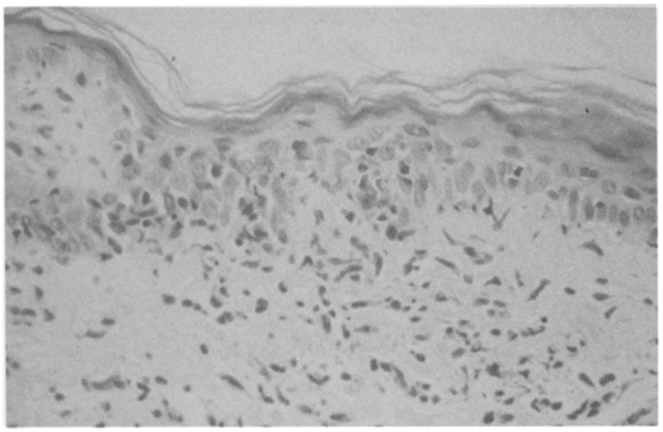


Fig. 96. Subacute cutaneous lupus erythematosus. Interface dermatitis.

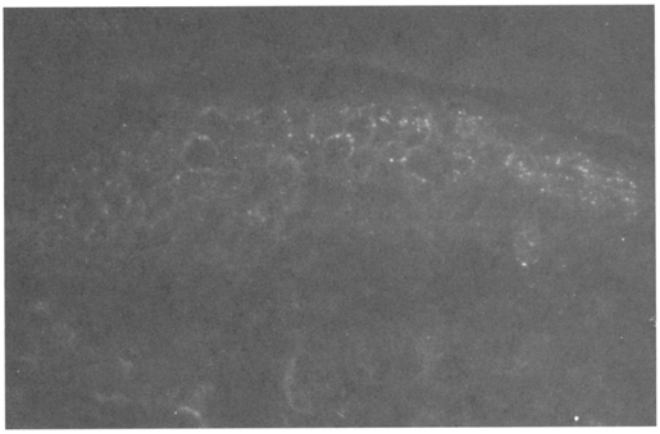


Fig. 97. Subacute cutaneous lupus erythematosus. Speckled or "particulate" pattern of intercellular epidermal IgG deposition.

- Systemic lupus erythematosus is present in 50%
- ANA is positive in about half; other antibodies including anti-La (SS-B), anti-thyroid and anti-cardiolipin are variably present
- Lesions are nonscarring and nonindurated
- May see annular/polycyclic plaques with central clearing or papulosquamous lesions (scaly pink-red papules)
- Lesions LACK atrophy, scarring, and follicular plugging
- Clinical course is usually relatively benign, but a subset of patients may go on to develop severe systemic disease

Epidemiology

- Increased incidence of HLA-DR3 and HLA-DR2 as well as inherited homozygous C2 and C4 deficiency

Microscopic ***(Figure 96)***

- Many features are similar to changes seen in discoid LE, but histologic distinction between the two can sometimes be made
- In general, SCLE has LESS:
  - Hyperkeratosis
  - Basement membrane thickening
  - Follicular involvement:
    - Follicular plugging
    - Dermal infiltrate, and it is more superficially located
- SCLE tends to have MORE:
  - Epidermal atrophy
  - Liquifactive degeneration
  - Cytoid bodies
  - Pigment incontinence
  - Satellite cell necrosis
  - Lymphocyte exocytosis
- Exceptions to these rules are frequent, and in many cases, SCLE cannot be histologically distinguished from other types of LE

Immunopathology

- DIF has findings that are distinct from other types of LE
- There is a discrete "particulate" or speckled pattern of epidermal deposition with IgG that occurs predominantly in the basal layer, and is associated with the presence of anti-Ro (SS-A) antibodies **(Figure 97)**
- Particulate dermal-epidermal deposition can be seen in other types of lupus and is NOT suggestive of SCLE
- Other DIF changes typical for LE (granular deposition along the basement membrane zone with IgM and other conjugates) may be present, but often are not
- May also see epidermal antinuclear antibodies, most commonly with IgG
- Circulating antinuclear antibodies are detected in 50%
- Indirect immunofluorescence is usually otherwise negative

Bullous Systemic Lupus Erythematosus

- DIF is characterized by linear OR granular deposition along the basement membrane zone
- See description under Linear deposition along the basement membrane zone

Systemic Lupus Erythematosus

Clinical

- SLE is an autoimmune disease with a wide variety of possible systemic manifestations
- Over 75% of patients will have some form of cutaneous involvement, including malar erythema, photosensitivity, oral involvement (cheilitis, ulcers, petechiae and gingivitis), or discoid lesions
- Non-specific lesions may be seen in SLE, but may also be seen in a variety of other conditions or in normal patients
- These include vasculitis and vasculopathy, Raynaud's phenomenon, livedo reticularis, perniosis, urticaria and urticarial vasculitis, nonscarring alopecia, and rheumatoid nodules

- Most common in women of childbearing age (F:M 9:1) and dark skinned patients (black, hispanic and so on)
- Increased incidence of complement deficiency, both due to excessive consumption by immune complexes and an increased incidence of inherited deficiencies of complement components (most commonly homozygous C2 deficiency)
- Mean age of onset is in the thirties
- May be induced by medication
- Clinical course is variable; may be mild and controlled with medication or severe and recalcitrant
- Most commonly affected systems include joints (90%), kidneys (50%), lungs (40%), and the central nervous system (30%), but a wide variety of other organs may also be affected
- Constitutional signs are frequent and include fatigue, fever, weight loss and malaise
- Most common cause of mortality is due to renal involvement

Microscopic

- Microscopic depends on the type of lesion biopsied
- No changes diagnostic for systemic LE exist
- Discoid lesions show changes as described for discoid LE
- Vasculitic lesions clinically associated with lupus anticoagulant syndrome show thrombotic microangiopathy, indistinguishable from other types of thrombotic microangiopathy (such as cryoglobulin associated microangiopathy)
- Biopsy of malar erythema is non-specific, with telangiectasia and rarely liquifactive degeneration or interface dermatitis

Immunopathology

- As discussed above, the strict definition of a positive lupus band test is the presence of granular deposition of IgM (and other conjugates) along the basement membrane zone in a biopsy from nonsunexposed and uninvolved skin **(Figure 95)**
- The presence of a lupus band is correlated with a higher incidence of systemic disease
- Granular deposition with other conjugates (IgG, IgA and C3) is usually seen
- Circulating antinuclear antibodies may be detected on indirect immunofluorescence, but IIF is otherwise negative

GRANULAR DEPOSITION IN THE DERMAL PAPILLAE

Dermatitis Herpetiformis (DH)

Clinical

- DH is a chronic, intensely pruritic eruption with usual onset in the second to fourth decade, though it may occur at any age
- Primary lesions are pruritic urticarial papules that develop into small tense vesicles
- Due to the intense pruritus of the lesion, an excoriation is usually all that remains at the time of exam
- Most commonly affects extensor surfaces, particularly on pressure points, including the extensor surfaces of the forearms (elbows), knees, back, buttocks and sacrum
- Associated with gluten-sensitive enteropathy which is clinically significant in 10% or less, but histologically detectable (by villous atrophy and increased lymphocytic infiltrate) in 60% to 70% of patients
- Cutaneous disease and small bowel disease both respond to gluten-free diet
- Also clinically characterized by a rapid (within 24 to 48 h) response to dapsone
- DH is also associated with an increased incidence of GI lymphoma and other malignancies
- Other organs with associated conditions include the thyroid (hyper and hypothyroidism, thyroid nodules and malignancy) and stomach (atrophy and hypochlorhydria)
- A variety of other autoimmune diseases have also been associated (Sjögren's syndrome, insulin dependent diabetes, rheumatoid arthritis, myasthenia gravis, and SLE, among others)

Epidemiology

- Increased frequency of HLA haplotypes B8, A1, DR3 and DQw2

Microscopic

- Early lesions show neutrophils along the basement membrane zone and in the dermal papillae, accompanied by fibrin deposition, leukocytoclasis and rare eosinophils
- Clefts appear at the sites of neutrophil accumulation, termed papillary microabscesses **(Figure 98)**
- Perivascular lymphohistiocytic infiltrate is often present in the upper and middle dermis
- As vesicles or bullae develop, findings become non-specific (subepidermal separation with neutrophils and eosinophils)

Immunopathology

- DIF characteristically has granular deposition of IgA in the dermal papillae and along the basement membrane zone **(Figure 99)**
- Granularity is most pronounced in the dermal papillae
- Granular deposition with other conjugates (C3, IgG and IgM) is rarely present, but has been reported

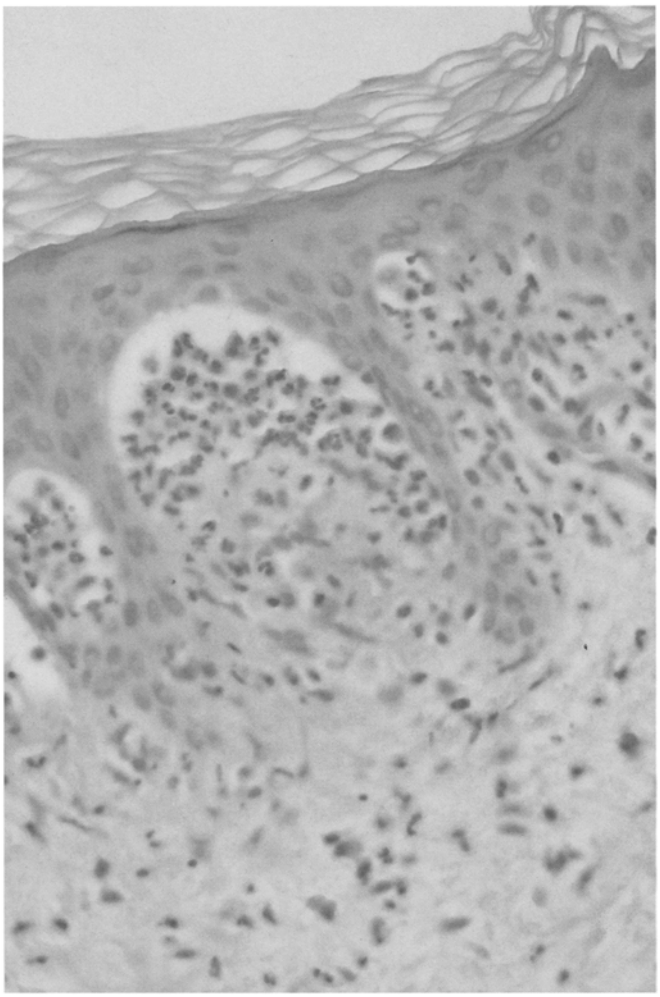


Fig. 98. Dermatitis herpetiformis. Papillary microabscesses.

- These changes are found in perilesional (within 3–5 mm) normal-appearing skin
- Several antibodies can be produced by patients with dermatitis herpetiformis and/or gluten sensitive enteropathy, including IgG and/or IgA anti-endomysial antibodies, anti-gliadin and anti-reticulin antibodies
- The patient's titer of IgA anti-endomysial antibody, detected using monkey esophagus substrate, correlates with disease activity as well as patient's compliance with the gluten-free diet

Implicated Antigen

- Unknown

Clumped Cytoid Bodies and Shaggy Deposition of Fibrinogen Along the Basement Membrane Zone

Lichenoid Tissue Reaction

- Cytoid bodies are round, homogeneously fluorescent cells that appear scattered as single cells or clumped in groups along the basement membrane zone



Fig. 99. Dermatitis herpetiformis. Granular deposition of IgA in dermal papillae and along basement membrane zone.

- They can also be seen in the epidermis (erythema multiforme) or upper dermis
- They are thought to represent necrotic keratinocytes and/or fragments of basement membrane
- Scattered cytoids can be seen nonspecifically in many conditions
- Shaggy deposition of fibrinogen along the basement membrane zone gives a pattern that has been likened to "dripping paint"
- While neither of these two findings is specific, the combination of clumped cytoids and shaggy deposition of fibrinogen is seen in lichenoid tissue reactions
- The diagnosis in each of these entities is dependent on the appropriate histopathology being present

Variants

- Lichen planus
- Lupus erythematosus
- Dermatomyositis
- Erythema multiforme
- Paraneoplastic pemphigus
- Lichenoid dermatitis
- Lichenoid drug reaction
- Graft vs Host Disease
- Other dermatoses

Lichen Planus

Immunopathology

- The "classic" lichenoid tissue reaction is often seen, with clumped cytoid bodies along the basement membrane zone and shaggy deposition of fibrinogen along the basement membrane zone **(Figure 100)**
- Mucosal lesions are less likely to have cytoid bodies; shaggy fibrinogen may be the only finding present
- Yeast (candida) can sometimes be found in mucosal lesions

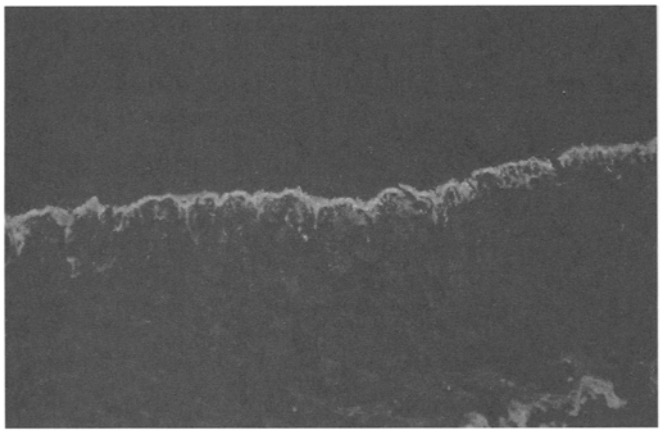


Fig. 100. Lichen Planus. Shaggy deposition of fibrinogen and clumped cytoids along the basement membrane zone.

- Although clumped cytoids are quite characteristic of LP, LP cannot be diagnosed on immunopathology alone. Microscopic consistent with LP must also be present to make the diagnosis

Lupus Erythematosus

- See section above

Immunopathology

- The typical features seen in lupus erythematosus are listed above. In addition, lupus may also demonstrate lichenoid features on immunopathology, often in combination with typical granularity along the basement membrane zone
- Immunofluorescence of aged or "burned out" lesions may only have lichenoid changes

Dermatomyositis

Immunopathology

- Although granularity along the basement membrane zone similar to that seen in lupus erythematosus (the lupus band) has been reported, immunofluorescence usually does NOT demonstrate these changes
- A lichenoid tissue reaction and nonspecific discontinuous granularity along the basement membrane zone are more commonly seen
- Subepidermal fibrin deposition may also be seen

Erythema Multiforme

Immunopathology

- Erythema multiforme is characterized by epidermal cytoid bodies and weak perivascular deposition of IgM in the superficial dermis
- Shaggy deposition of fibrinogen and cytoids in the dermis and at the dermal-epidermal junction may also be seen
- Granular deposition of IgM, C3 and fibrinogen along the dermoepidermal junction are occasionally present

Paraneoplastic Pemphigus

- See section B5 above

Immunopathology

- In addition to the characteristic features described above, clumped cytoids and shaggy deposition of fibrinogen along the basement membrane zone can also be seen

Lichenoid Dermatitis

Immunopathology

- Dermatitis due to any number of causes may also demonstrate a lichenoid tissue reaction
- This pattern is more likely to be seen in chronic dermatitis

Lichenoid Drug Reaction

Immunopathology

- In addition to lichenoid changes, drug reactions will also have eosinophils in the superficial and middle dermis

Graft vs Host Disease

Immunopathology

- Lichenoid features can occasionally be seen in chronic graft vs host disease
- Epidermal cytoids may also be observed
- Granular deposition of IgM along the basement membrane zone is observed in about 40% of patients with acute disease and around 85% of patients with chronic disease
- In addition, IgM and C3 can sometimes be found within dermal vessel walls

WEAK THICK LINEAR DEPOSITION ALONG THE BASEMENT MEMBRANE ZONE AND PERIVASCULAR DEPOSITION

Porphyrias

- The porphyrias are a group of inherited or acquired diseases that result from deficiency in the activities of enzymes of the heme biosynthetic pathway
- The characteristic clinical appearance of each of the subtypes results from accumulation of intermediaries or their byproducts
- While the clinical appearance, course and prognosis of the porphyrias with cutaneous manifestations varies

from type to type, the microscopic and immunofluorescence are the same or very similar. The variants tend to vary by degree

Variants

- Aminolevulinic acid dehydratase porphyria (ALA)
- Acute intermittent porphyria (AIP)
- Congenital erythropoietic porphyria (CEP)
- Porphyria cutanea tarda (PCT)
- Hepatoerythropoietic porphyria (HEP)
- Hereditary coproporphyria (HCP)
- Variegate porphyria (VP)
- Erythropoietic protoporphyria (EPP)
- Pseudoporphyria (drug-induced) (PP)

Clinical

- The following discussion pertains to the porphyrias with cutaneous manifestations
- Cutaneous changes can either be immediate or delayed
- An immediate reaction, as seen in EPP, includes erythema, pain, edema and purpura
- The other types of cutaneous porphyria show delayed phototoxicity, presenting as fragility, blistering, scarring and hypertrichosis
- Other reported clinical findings include sclerodermoid changes, alopecia and hyperpigmentation
- In inherited homozygous PCT, abnormal enzyme levels are seen in the liver and the red blood cells
- In heterozygous PCT, where abnormal enzyme levels are expressed in the liver, disease expression usually requires a "second hit" to the liver such as concomitant infection (hepatitis or HIV), alcohol ingestion, estrogen therapy or pregnancy
- Diagnosis and subtyping of porphyria is based in part on the clinical presentation, microscopic and immunofluorescence. However, the porphyrin levels in the urine, stool and red blood cells are the gold standard of diagnosis

Microscopic

- The subtypes demonstrate similar findings to varying degrees
- They are characterized by a pauci-inflammatory subepidermal separation with upward protrusion of the dermal papillae ("festooning") **(Figure 101)**
- There is homogeneous thickening of the blood vessels in the dermal papillae
- There is PAS positive deposition of material in and around the upper dermal blood vessels as well as along the basement membrane zone
- Actinic elastosis is usually present

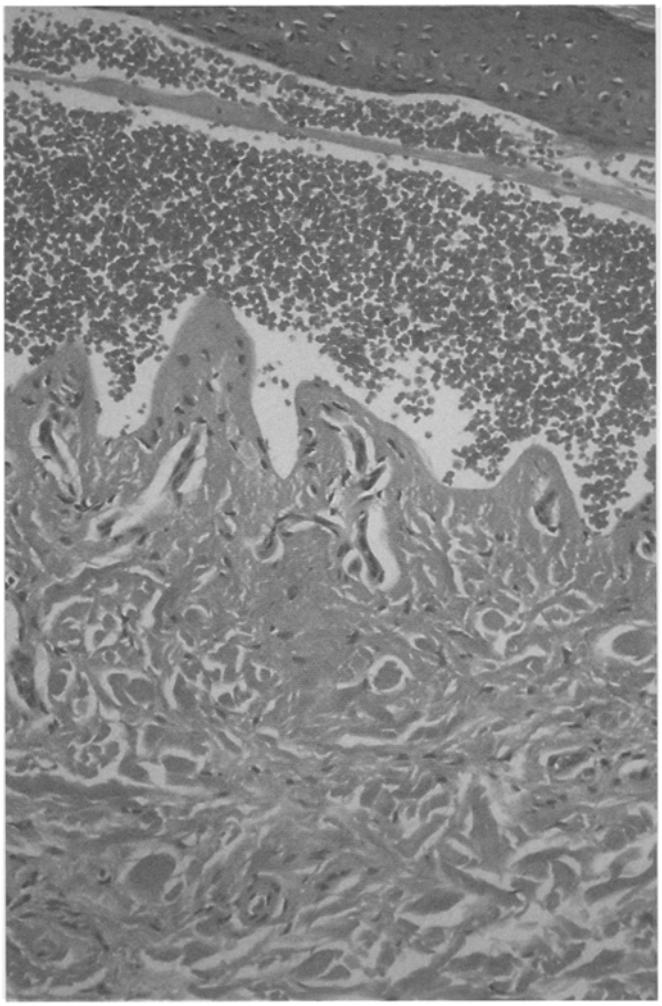


Fig. 101. Porphyria. Subepidermal separation with minimal inflammation and "festooning".

- Thickening of the basement membrane zone, hyperkeratosis, acanthosis and hypergranulosis are variably present
- Occasionally, PAS positive globules arranged in a linear fashion may be seen in the blister roof ("caterpillar bodies") **(Figure 102)**

Electron Microscopy

- EM shows extensive reduplication of the basal lamina of the upper dermal blood vessels and basement membrane zone
- There are widened perivascular spaces containing fibrillar material and small collagen fibrils
- In some cases there are irregular clumps of amorphous material embedded in the perivascular material
- The site of separation is the lamina lucida

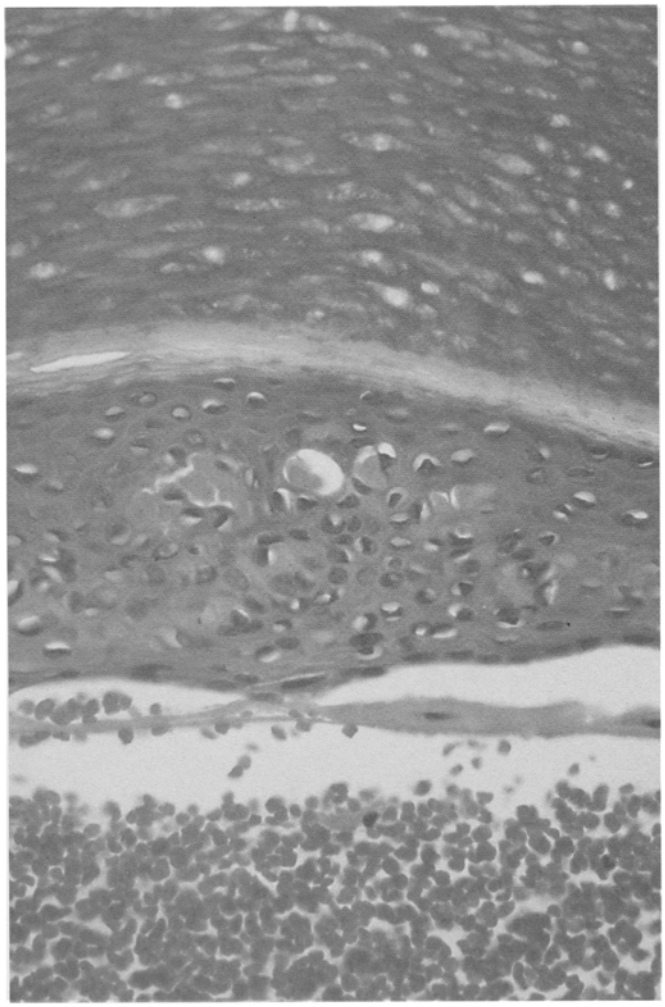


Fig. 102. Porphyria. Subepidermal separation and "Caterpillar bodies."

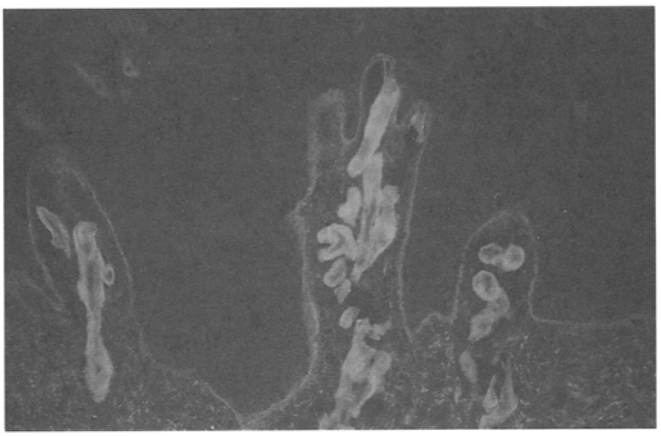


Fig. 103. Porphyria. Strong deposition of IgG in and adjacent to papillary dermal blood vessels and weak thick linear deposition along the basement membrane zone.

Immunopathology

- Again, the subtypes demonstrate similar findings to varying degrees
- There is marked deposition of immunoglobulin and complement (IgG, IgM, C3, IgA and fibrinogen) in and adjacent to the upper dermal blood vessels **(Figure 103)**
- In addition, there is weak thick deposition of immunoglobulin and complement along the basement membrane zone
- In general, these changes are more pronounced in involved sun-exposed skin, and in active lesions
- EPP demonstrates changes more marked than PCT, VP or PP

DEPOSITION ON EOSINOPHILS AND DIFFUSE DEPOSITION ON CONNECTIVE TISSUE

Urticaria

Clinical

- Referred to as hives or wheals, they are characterized by pruritic, erythematous or white, nonpitting edematous papules or plaques that change in size and shape over hours
- They vary in size from small papules to large plaques
- The depth of involvement varies from superficial to deep
- Episodes of urticaria are arbitrarily defined as either acute or chronic
- Chronic includes episodes persisting for longer than six weeks
- While the cause of acute urticaria is often established (usually food, drug or contact), the cause of chronic urticaria is usually not identified
- There are many implicated etiologic factors and associations, including foods and food additives, medications and hormonal perturbations, inhaled allergens, various internal diseases and malignancies, contactants (via both immunologic and nonimmunologic mechanisms), primary skin diseases (immunobullous diseases for example) and genetic diseases
- Urticaria may be separated into a variety of subtypes based on the etiology

Clinical Subtypes

- Physical urticarias
- Dermatographism
- Pressure urticaria
- Cholinergic urticaria

- Exercise-induced urticaria
- Solar urticaria
- Cold urticaria
- Heat, water and vibrational urticaria
- Aquagenic pruritus
- Angioedema
- Acquired angioedema
- Hereditary angioedema
- Contact urticaria
- Urticaria secondary to an ingested substance (food, medication or other)
- Pruritic and urticarial papules and plaques of pregnancy
- Urticarial vasculitis

Microscopic

- All of the subtypes of urticaria demonstrate similar histopathologic features
- Acute urticaria shows dermal interstitial edema, dilated venules with endothelial swelling and a minimal degree of inflammation, including intravascular neutrophils and perivascular lymphocytes and eosinophils
- In chronic urticaria, there is interstitial edema with a perivascular and interstitial polymorphous infiltrate of neutrophils, eosinophils and lymphocytes, as well as intravascular neutrophils
- The deeper the clinical form of urticaria, the deeper the extension of the histopathologic findings
- Angioedema extends into the subcutaneous tissue
- Hereditary angioedema demonstrates deep dermal and subcutaneous edema with minimal accompanying inflammation

Immunopathology

- DIF demonstrates deposition on eosinophils with IgA, and to a lesser degree with IgG, and IgM
- Fibrinogen shows diffuse deposition on the connective tissue throughout the dermis
- This pattern is nonspecific but consistent with the clinical diagnosis of urticaria

DEPOSITION IN BLOOD VESSELS

Vasculitis

Immunopathology

- In general, vasculitis is characterized by intravascular deposition of immunoglobulins and complement
- IgM is usually the predominant immunoglobulin deposited, but IgG and IgA are also seen
- Fibrinogen is often deposited in a perivascular pattern, with diffusion into the surrounding interstitial tissue
- The diagnosis of vasculitis should be reserved for specimens that show intravascular deposition with multiple immunoreactants
- Further, because vascular fluorescence can be seen nonspecifically in various inflammatory conditions, as well as in dependent locations (such as lower extremity), histopathology that is typical for vasculitis must also be present to justify the diagnosis
- Some of the clinical subtypes of vasculitis have more distinctive immunopathologic findings
- For example, Henoch-Schönlein purpura has a granular deposition of IgA in the superficial vessels that predominates over the deposition of other immunoglobulins
- Urticarial vasculitis has findings typical for urticaria in addition to immunoglobulin deposition in blood vessels
- Further, a subset of patients with urticarial vasculitis have systemic lupus erythematosus (either overt or in evolution) and demonstrate (in addition to features of urticarial vasculitis) granular deposition of IgM and other immune reactants along the basement membrane zone, typical for lupus erythematosus

TNM CLASSIFICATION OF MALIGNANT MELANOMA OF THE SKIN (2002 REVISION)

- T: Primary Tumor:
  - T0: No evidence of primary tumor
  - Tis: Melanoma in situ (Clark's Level I)
  - T1: Melanoma ≤1.0 mm in thickness with or without ulceration:
    - T1a: Melanoma ≤1.0 mm in thickness and level II (papillary dermis) or III (papillary-reticular dermal interface), no ulceration
    - T1b: Melanoma ≤1.0 mm in thickness and level IV (reticular dermis) or V (subcutaneous tissue) or with ulceration
  - T2: Melanoma 1.01–2 mm in thickness with or without ulceration:
    - T2a: Melanoma 1.01–2 mm in thickness, no ulceration
    - T2b: Melanoma 1.01–2 mm in thickness, with ulceration

- T3: Melanoma 2.01–4 mm in thickness with or without ulceration:
  - T3a: 2.01–4 mm in thickness, no ulceration
  - T3b: 2.01–4 mm in thickness, with ulceration
- T4: Melanoma greater than 4.0 mm in thickness with or without ulceration:
  - T4a: Melanoma >4.0 mm in thickness, no ulceration
  - T4b: Melanoma >4.0 mm in thickness, with ulceration

♦ N: Regional Lymph Nodes:
- NX: Regional nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastasis in one lymph node:
  - N1a: Clinically occult (microscopic) metastasis
  - N1b: Clinically apparent (macroscopic) metastasis
- N2: Metastases in two to three regional nodes or intralymphatic regional metastasis without nodal metastasis:
  - N2a: Clinically occult (microscopic) metastasis
  - N2b: Clinically apparent (macroscopic) metastasis
  - N2c: Satellite or in-transit metastasis without nodal metastasis
- N3: Metastasis in four or more regional nodes, or matted metastatic nodes, or in-transit metastasis or satellite(s) with metastasis in regional node(s)

♦ M: Distant Metastasis
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis
- M1a: Metastasis to skin, subcutaneous tissue or distant lymph nodes
- M1b: Metastasis to lung
- M1c: Metastasis to all other visceral sites or distant metastasis at any site associated with an elevated serum lactic dehydrogenase (LDH)

**The tumor thickness is measured from the superficial aspect of the granular cell layer of the epidermis (or the base of the lesion if the tumor is ulcerated) to the deepest point of tumor invasion*

***In transit metastasis involves skin or subcutaneous tissue more than 2 cm from the primary tumor but not beyond regional lymph nodes*

TNM CLASSIFICATION OF CARCINOMA OF THE SKIN (2002 REVISION)

♦ T: Primary Tumor:
- T0: No evidence of primary tumor
- Tis: Carcinoma in situ
- T1: Tumor 2 cm in greatest dimension
- T2: Tumor >2 cm, but <5 cm in greatest dimension
- T3: Tumor >5 cm in greatest dimension
- T4: Tumor invades deep extradermal structures (i.e., cartilage, skeletal muscle, or bone)

♦ N: Regional Lymph Nodes:
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

♦ M: Distant Metastasis:
- M0: No distant metastasis
- Distant metastasis

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13

Non-Neoplastic Skin Diseases

Steven D. Billings, MD
and Antoinette F. Hood, MD

CONTENTS

I. General Concepts 13-3
Pattern Recognition 13-3
Principle Patterns 13-3
Spongiotic Pattern.....13-3
Psoriasiform Pattern 13-3
Mixed Spongiotic and Psoriasiform 13-3
Interface Pattern 13-3
Superficial Perivascular 13-3
Superficial and Deep Perivascular 13-3
Interstitial Infiltrate.....13-3
Sclerosing Dermatitis 13-3
Panniculitis 13-3
Alopecia 13-3

II. Spongiotic Dermatitis 13-3
Acute Spongiotic Dermatitis 13-3
Subacute Spongiotic Dermatitis.....13-3
Chronic Spongiotic Dermatitis.....13-3
Types of Spongiotic Dermatitis 13-3
Eczematous Dermatitis.....13-4
Contact Dermatitis 13-3
Allergic Contact Dermatitis 13-3
Irritant Contact Dermatitis 13-4
Atopic Dermatitis 13-4
Pompholyx (Dyshidrotic Eczema) 13-4
Nummular Dermatitis
(Nummular Eczema) 13-4
Id Reaction 13-5
Eczematous Drug Reaction 13-5
Vesicular Dermatophytosis.....13-5
Pityriasis Rosea 13-5
Seborrheic Dermatitis.....13-5
Stasis Dermatitis.....13-5

III. Psoriasiform Dermatitis 13-5
Psoriasis Vulgaris 13-5
Psoriasis Variants (pustular and guttate) 13-6
Pityriasis Rubra Pilaris.....13-6
Lichen Simplex Chronicus/Prurigo
Nodularis 13-7
Secondary Syphilis.....13-7
Dermatophytosis.....13-8

IV. Interface Dermatitis 13-8
Erythema Multiforme.....13-8
Toxic Epidermal Necrolysis.....13-8
Lupus Erythematosus 13-8
Dermatomyositis 13-9
Graft vs Host Disease.....13-9
Morbilliform Drug Eruption 13-10
Viral Exanthem.....13-10
Lichen Planus 13-10
Lichenoid Drug Eruption 13-11
Fixed Drug Eruption.....13-11

V. Superficial Perivascular Dermatitis 13-11
Morbilliform Drug Eruption 13-11
Postinflammatory Pigment Alteration 13-12
Progressive Pigmented Purpuric Eruption
(Schamberg's Disease) 13-12
Urticaria 13-12
Urticaria Pigmentosa 13-12

VI. Superficial and Deep Perivascular Infiltrate 13-13
Lupus Erythematosus 13-13
Sweet's Syndrome 13-13
Pityriasis Lichenoides et Varioliformis Acuta (PLEVA) 13-13
Lymphomatoid Papulosis 13-13
Arthropod Bite Reaction 13-14

VII. Interstitial Pattern 13-15
Palisading Granulomatous Dermatitis 13-15
Granuloma Annulare 13-15
Necrobiosis Lipoidica 13-15
Rheumatoid Nodule 13-15
Nodular or Diffuse Infiltrate 13-15
Cutaneous Lymphoid Hyperplasia (Lymphocytoma cutis) 13-15
Eosinophilic Cellulitis (Wells' Syndrome) 13-16
Mastocytosis/Mastocytoma 13-16

VIII. Sclerosing Dermatoses 13-16
Scleroderma 13-16
Morphea 13-17
Lichen Sclerosus 13-17

IX. Panniculitis 13-17
General Comments 13-17
Erythema Nodosum 13-17
Lipodermatosclerosis (Lipomembranous Panniculitis, Sclerosing Panniculitis) 13-18
Subcutaneous Morphea (Morphea Profundus) 13-18
Nodular Vasculitis (Erythema Induratum) 13-18
Lupus Panniculitis (Lupus Profundus) 13-19
Polyarteritis Nodosa 13-19
Superficial Thrombophlebitis 13-19

X. Alopecia 13-20
Non-scarring Alopecia 13-20
Telogen Effluvium 13-20
Androgenetic Alopecia 13-20
Alopecia Areata 13-20
Trichotillomania 13-20
Scarring Alopecia 13-20
Lupus Erythematosus 13-20
Lichen Planopilaris 13-21
Follicular Degeneration Syndrome 13-21
Dissecting Cellulitis 13-21
Acne Keloidalis Nuchae 13-21
Folliculitis Decalvans 13-22
End-stage Scarring Alopecia 13-22

XI. Suggested Reading 13-22

GENERAL CONCEPTS

Pattern Recognition

- Skin has limited ways to react to a variety of inflammatory conditions
- Predominant pattern of inflammatory infiltrate helps define entities
- More than one pattern can co-exist in a lesion
- Some entities can have a variety of patterns

Principle Patterns

Epidermal Changes Predominant

Spongiotic Pattern

- Defined by intraepidermal edema (spongiosis)

Psoriasiform Pattern

- Defined by epidermal hyperplasia (acanthosis)

Mixed Spongiotic and Psoriasiform

- There is considerable overlap in spongiotic and psoriasiform dermatitis with most examples showing features of both

Interface Pattern

- Defined by vacuolization of basal layer of epidermis and either a perivascular or band-like (lichenoid) inflammatory infiltrate

Dermal Changes Predominant

Superficial Perivascular

- Inflammatory infiltrate concentrated around blood vessels in the upper dermis; little epidermal change

Superficial and Deep Perivascular

- As above but with infiltrate around deeper dermal vessels

Interstitial Infiltrate

- Nodular and diffuse infiltrate and palisading granulomatous

Sclerosing Dermatitis

- Dermal collagen changes predominate
- Inflammatory infiltrate variable

Panniculitis

- Septal: infiltrate predominantly involves the subcutaneous septae
- Lobular: infiltrate predominantly involves the subcutaneous lobules

Alopecia

- Non-inflammatory, non-scarring: little to no inflammation, no associated dermal fibrosis
- Non-inflammatory, scarring: little to no inflammation with associated dermal fibrosis
- Inflammatory, scarring: significant dermal inflammation associated with scarring
- End-stage scarring alopecia: prominent fibrosis with few if any remaining follicles. Inflammatory infiltrate variable

SPONGIOTIC DERMATITIS

Histologic Subtypes

Acute Spongiotic Dermatitis (Figure 1)

- Epidermis: normal "basket-weave" stratum corneum, pale keratinocytes, spongiosis with or without spongiotic vesicles
- Dermis: papillary dermal edema, superficial perivascular inflammatory infiltrate that is predominantly lymphocytic but often with some admixed eosinophils

Subacute Spongiotic Dermatitis (Figure 2)

- Epidermis: parakeratosis, acanthosis, diminished granular layer, spongiosis
- Dermis: similar to acute spongiotic dermatitis but usually less edema

Chronic Spongiotic Dermatitis (Figure 3)

- Epidermis: acanthosis, hyperkeratosis, parakeratosis, irregular granular layer, minimal to mild spongiosis
- Dermis: papillary dermis may become fibrotic, variable perivascular inflammatory infiltrate

Types of Spongiotic Dermatitis

- Eczematous dermatitis is a clinical term that describes a papular to vesicular erythematous rash. Distinct etiologies are not always apparent, but some have an identifiable cause (e.g., contact dermatitis). All have essentially indistinguishable histologic features, and may have features of acute, subacute, or chronic spongiotic dermatitis. Correlation with the clinical presentation is necessary. The most common clinical entities in the differential diagnosis of eczematous dermatitis are discussed below

Eczematous Dermatitis

Contact Dermatitis: Allergic Contact Dermatitis

Clinical

- Pruritic erythematous papules and vesicles

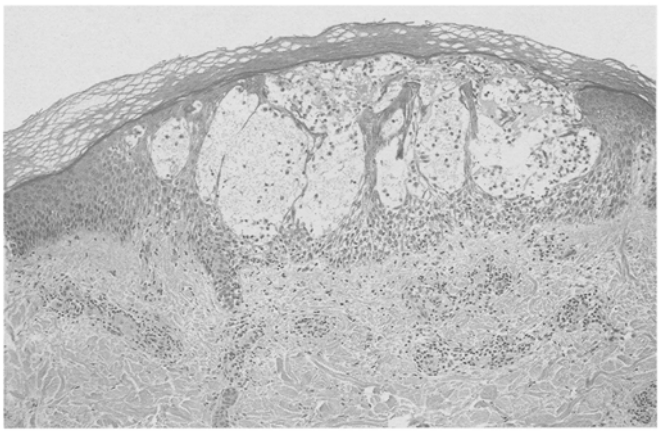


Fig. 1. Acute spongiotic dermatitis with spongiotic microvesicles.

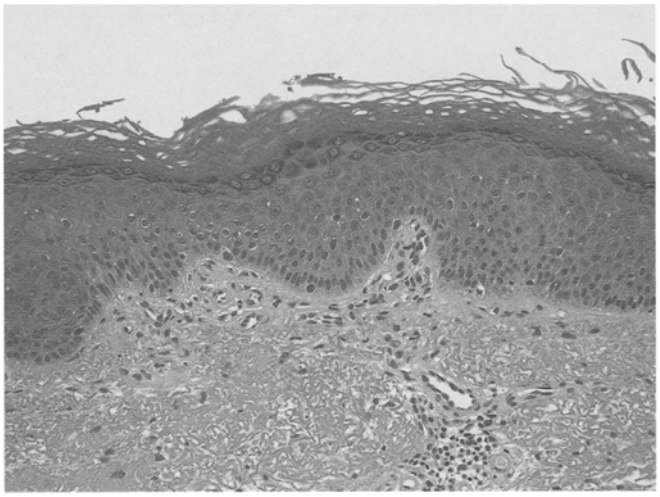


Fig. 2. Subacute spongiotic dermatitis.

- Secondary to type IV delayed hypersensitivity reaction
- Example: poison ivy

Microscopic

- Typical spongiotic dermatitis
- May have intraepidermal spongiotic microvesicles
- May have Langerhans cell microabscesses in epidermis
- Predominantly perivascular lymphocytic infiltrate with variable numbers of eosinophils:

Contact Dermatitis: Irritant Contact Dermatitis

Clinical

- Erythematous papules and vesicles
- Secondary to direct irritant effect of offending agent
- Example: diaper rash

Microscopic

- Subtle differences from allergic contact dermatitis

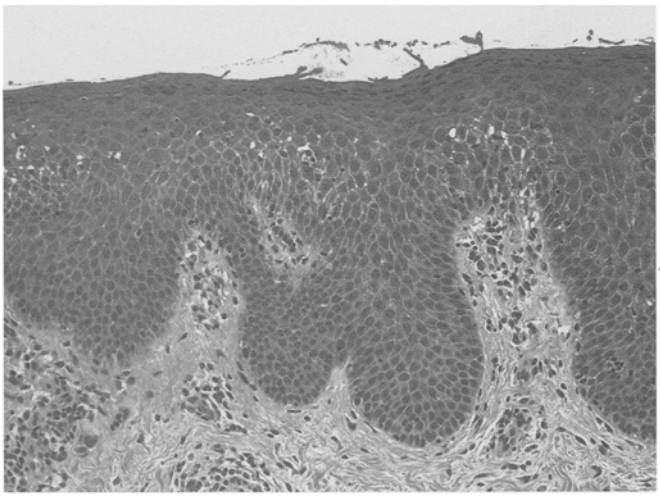


Fig. 3. Chronic spongiotic dermatitis.

- Ballooning degeneration of keratinocytes
- Focal necrotic keratinocytes
- May develop upper level epidermal necrosis

Atopic Dermatitis

Clinical

- Chronic pruritic, relapsing papular dermatitis
- Associated with history of asthma, allergic rhinitis (atopy)
- Predilection for flexural areas, especially in children

Microscopic

- Typically subacute to chronic spongiotic dermatitis

Pompholyx (Dyshidrotic Eczema)

Clinical

- Symmetric vesicular hand and/or foot dermatitis

Microscopic

- Subacute to chronic spongiotic dermatitis
- Spongiotic microvesicles are common
- May have features of either allergic contact or irritant contact dermatitis

Nummular Dermatitis (Nummular Eczema)

Clinical

- Round to oval pruritic patches to plaques
- Usually involves extremities

Microscopic

- Early: acute to subacute spongiotic dermatitis
- Late: chronic spongiotic dermatitis, may resemble psoriasis but with retention of granular layer, normal supra-papillary plate thickness and hyperkeratosis (see psoriasis below)

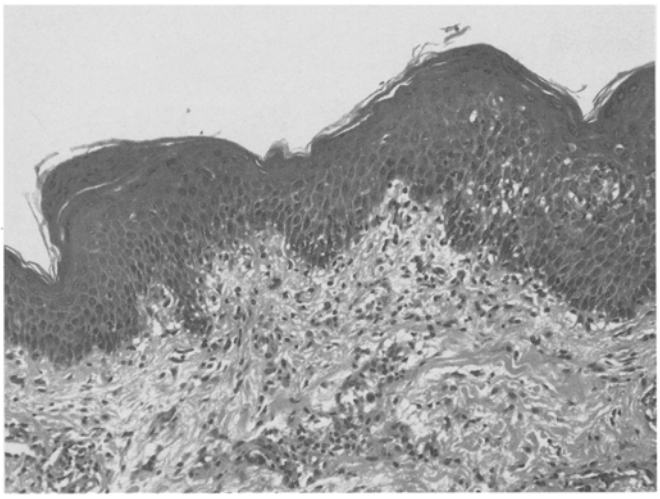


Fig. 4. Pityriasis rosea.

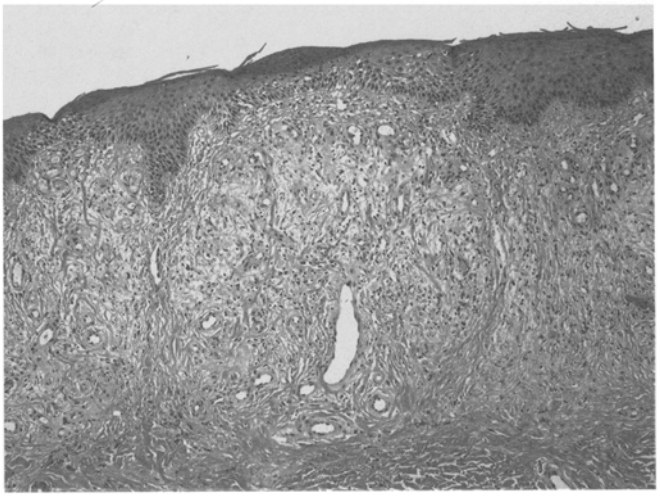


Fig. 5. Stasis dermatitis.

"Id" Reaction

Clinical

- Acute dermatitis that develops distal to the primary inflammatory focus
- Primary inflammatory lesion is frequently tinea pedis or impetiginized stasis dermatitis

Microscopic

- Typical spongiotic dermatitis

Eczematous Drug Reaction

Clinical

- 5–10% of drug reactions may be eczematous in nature

Microscopic

- Typical spongiotic dermatitis
- Often some perivascular eosinophils

Vesicular Dermatophytosis

Clinical

- Usually on feet
- Resembles pompholyx

Microscopic

- Spongiotic dermatitis
- Neutrophils in epidermis and/or stratum corneum
- Eosinophils often in dermis
- PAS or GMS stains demonstrate hyphae in stratum corneum

Pityriasis Rosea

Clinical

- Affects young adults
- Relatively asymptomatic
- Round to oval salmon-colored herald patch precedes widespread, symmetric eruption on trunk that follows skin lines

*Microscopic (**Figure 4**)*

- Subacute spongiotic dermatitis with mounds of parakeratosis and some dyskeratotic keratinocytes
- Mild to moderate mononuclear cell infiltrate often with some extravasation of erythrocytes in papillary dermis.

Seborrheic Dermatitis

Clinical

- Affects scalp (dandruff), ears, midface, upper chest
- Erythematous patches with greasy, yellow scale
- May be severe in AIDS patients and patients with neurologic disorders
- Rarely biopsied

Microscopic

- Subacute or chronic spongiotic dermatitis
- Parakeratotic mounds often with neutrophils around follicular ostia

Stasis Dermatitis

Clinical

- Eczematous dermatitis of the lower extremities associated with venous insufficiency
- Ulcers may be a complication

*Microscopic (**Figure 5**)*

- Subacute to chronic spongiotic dermatitis
- Significant acanthosis
- Lobular hyperplasia of superficial thick-walled dermal blood vessels with mild perivascular lymphocytic infiltrate, extravasated erythrocytes, and siderophages
- Variable dermal fibrosis

PSORIASIFORM DERMATITIS

- Pattern of acanthosis defined by elongation and widening of rete pegs

Psoriasis Vulgaris

Clinical

- Usually presents in 2nd–3rd decades
- Erythematous plaques with silvery scale on extensor surfaces, scalp, gluteal cleft, glans penis
- Nail pitting and yellow discoloration
- Arthritis present in 1–5% of patients

*Microscopic (**Figure 6**)*

- Uniform acanthosis with elongated rete ridges
- Absent granular layer
- Prominent parakeratosis
- Neutrophils in stratum corneum (Munro's microabcesses) and epidermis (pustules of Kogoj)
- Suprapapillary plate thinning
- Dilated, tortuous papillary dermal blood vessels
- Superficial perivascular lymphocytic infiltrate
- The presence of eosinophils is against the diagnosis of psoriasis

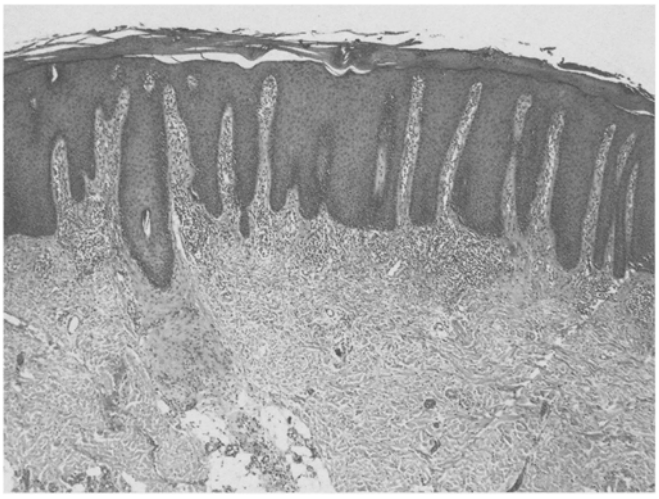


Fig. 6. Psoriasis vulgaris.

Variants: Pustular Psoriasis

Clinical

- Associated with pregnancy and discontinuation of systemic steroids

*Microscopic (**Figure 7**)*

- Only rarely has epidermal hyperplasia, granular layer diminished but not absent, large neutrophilic abscesses in epidermis and stratum corneum, little spongiosis

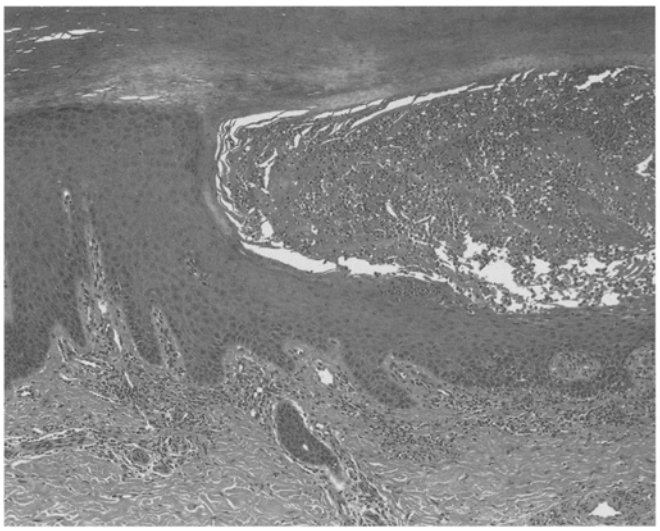


Fig. 7. Pustular psoriasis.

Variants: Guttate Psoriasis

Clinical

- Rapid onset of widespread disease characterized by small scaly plaques
- Associated with antecedent streptococcal infection

*Microscopic (**Figure 8**)*

- Minimal acanthosis, diminished granular layer, focal mounds of parakeratosis with neutrophils

Differential Diagnosis

- Psoriasis vulgaris: nummular dermatitis, contact dermatitis, seborrheic dermatitis, pityriasis rubra pilaris
- Pustular psoriasis: candidiasis, eczematous dermatitis with secondary impetiginization, Reiter disease
- Guttate psoriasis: pityriasis rosea

Pityriasis Rubra Pilaris

Clinical

- Hyperkeratotic perifollicular papules with surrounding yellow-orange erythema
- Islands of spared uninvolved skin
- Palmar and/or plantar keratoderma

*Microscopic (**Figure 9**)*

- Diffuse hyperkeratosis with parakeratosis alternatively arranged vertically and horizontally ("checkerboard pattern")
- Diffuse acanthosis very similar to psoriasis vulgaris
- Intact granular layer

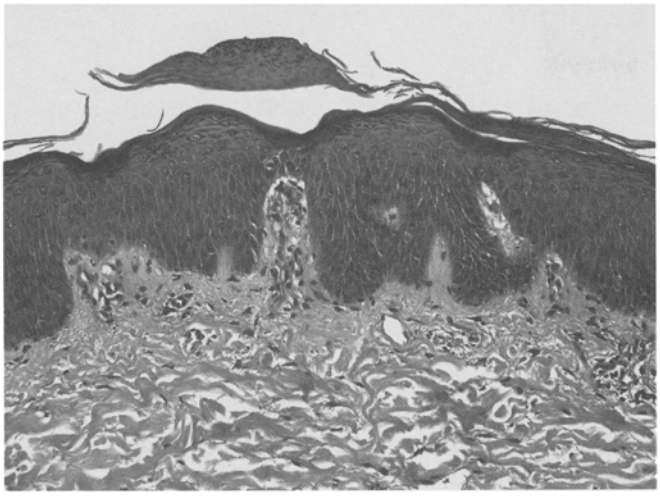


Fig. 8. Guttate psoriasis.

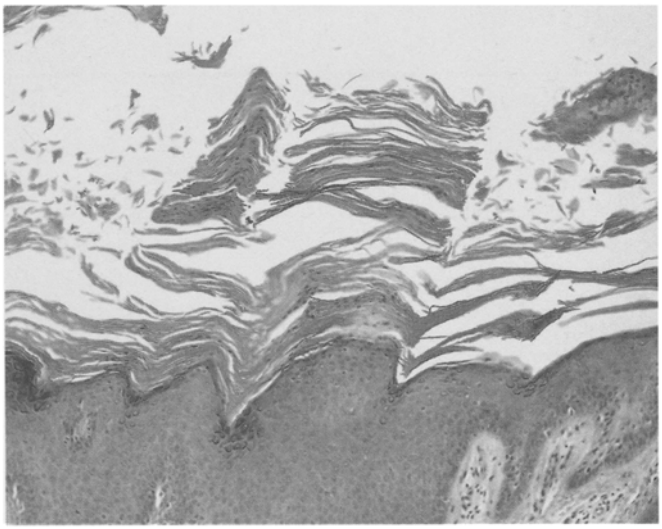


Fig. 9. Pityriasis rubra pilaris demonstrating the checkerboard pattern of parakeratosis.

- No suprapapillary thinning
- Mild lymphohistiocytic, superficial perivascular infiltrate

Differential Diagnosis

- Psoriasis, chronic eczematous dermatitis

Subacute and Chronic Eczematous Dermatitis

- Acanthosis often a prominent feature (see Spongiotic Dermatitis above)

Lichen Simplex Chronicus/Prurigo Nodularis

Clinical

- Spectrum of same dermatologic disease
- Secondary to persistent rubbing/scratching

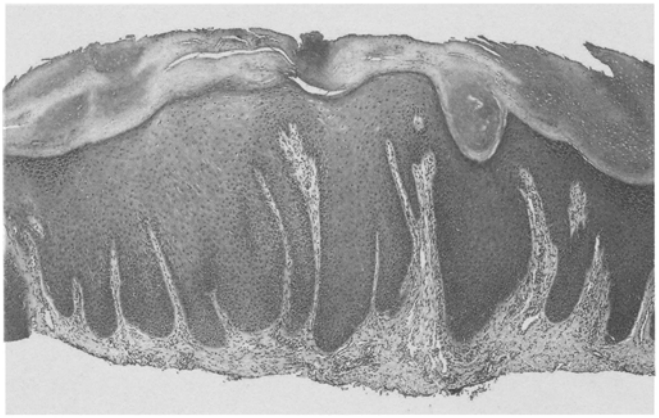


Fig. 10. Prurigo nodule.

- Lichen simplex chronicus presents as pruritic, lichenified, indurated plaques
- Prurigo nodularis presents as pruritic nodules
- Lesions occur only where the skin can be scratched or rubbed, especially posterior scalp, extremities, and genitalia
- Can develop as a secondary change in underlying dermatitis

*Microscopic (**Figure 10**)*

- Prominent compact hyperkeratosis
- Thickened granular layer
- Acanthosis, sometimes with pseudoepitheliomatous pattern
- Vertical fibrosis of papillary dermis
- Mild superficial perivascular lymphocytic infiltrate

Differential Diagnosis

- Psoriasis, lichen planus, verruca vulgaris, chronic spongiotic dermatitis, sometimes squamous cell carcinoma

Secondary Syphilis

Clinical

- Erythematous macular and/or papular eruption involving trunk, extremities, palms and soles
- Non-pruritic

Microscopic

- Parakeratosis
- Psoriasiform hyperplasia
- Lichenoid and or superficial and deep perivascular infiltrate
- Plasma cells

Differential Diagnosis

- Psoriasis, lichen planus, chronic spongiotic dermatitis, pityriasis rosea, mycosis fungoides

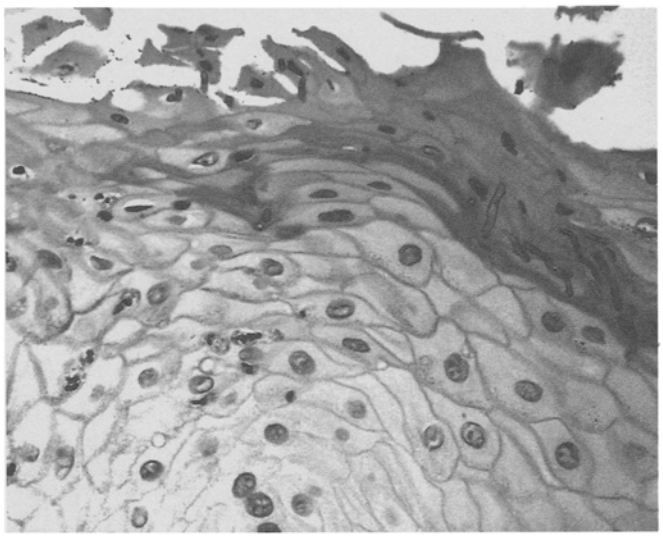


Fig. 11. Dermatophytosis. PAS stain demonstrating fungal hyphae in stratum corneum.

DERMATOPHYTOSIS

Clinical

- Annular scaly plaques with central clearing, usually on trunk
- On feet: confluent erythema with scale in moccasin distribution

*Microscopic (**Figure 11**)*

- Neutrophils in stratum corneum
- Parakeratosis
- Acanthosis
- +/– spongiosis
- Hyphae in stratum corneum (often only seen with PAS or GMS stain)

Differential Diagnosis

- Psoriasis, spongiotic dermatitis

INTERFACE DERMATITIS

Interface Dermatitis with Associated Perivascular Infiltrate

Erythema Multiforme

Clinical

- Self-limiting episodic eruptions
- Erythematous macules, papules and targetoid lesions usually on extensor surfaces, palms, soles, and oral mucosa
- Minor (erythema multiforme) and major (Stevens-Johnson syndrome) forms based on extent of mucosal involvement
- Associated with HSV and Mycoplasma infection and drugs (sulfonamides)

*Microscopic (**Figure 12**)*

- Normal basket-weave stratum corneum
- Spongiosis
- Scattered to confluent dyskeratotic cells
- Basal vacuolization
- Superficial perivascular lymphohistiocytic infiltrate
- Exocytosis of lymphocytes into epidermis
- Epidermal necrosis (seen in older lesions)

Differential Diagnosis

- Drug eruption, viral exanthem, dermatomyositis, lupus erythematosus, toxic epidermal necrolysis

Toxic epidermal necrolysis

Clinical

- Often drug-induced
- Widespread tender macular erythematous eruption with vesicles and bullae
- Nikolsky's sign (epithelial detachment with mild pressure)
- Mortality 25–50%

*Microscopic (**Figure 13**)*

- Similar to erythema multiforme with detachment of epidermis from dermis and scant superficial perivascular infiltrate

Differential Diagnosis

- Erythema multiforme, fixed drug eruption

Lupus Erythematosus

Clinical

- Chronic (discoid): well-demarcated scaly plaques, erythematous to hyperpigmented, usually on head; most patients with disease limited to skin
- Subacute: scaly erythematous, often annular plaques on upper trunk, extensor surfaces of arms; positive ANA 75% (cytoplasmic Ro and La)
- Acute: associated with systemic lupus erythematosus; erythematous lesions, malar rash; positive ANA and anti-DNA antibodies

*Microscopic (**Figures 14,15**)*

- Basal vacuolization
- Perivascular and periadnexal mononuclear cell infiltrate
- Epidermal atrophy (often)
- Increased dermal mucin
- Histologic overlap between subtypes

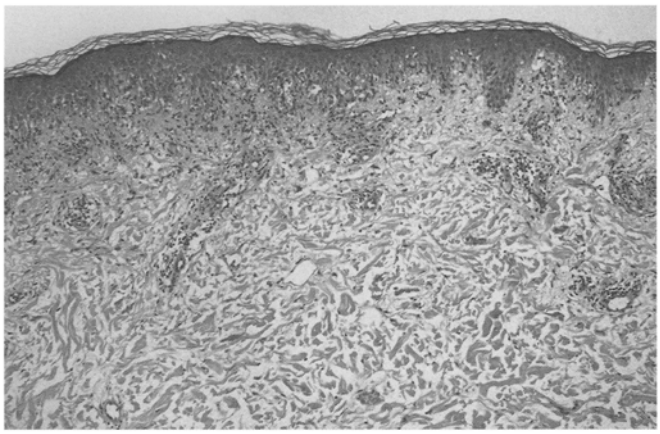


Fig. 12. Erythema multiforme.

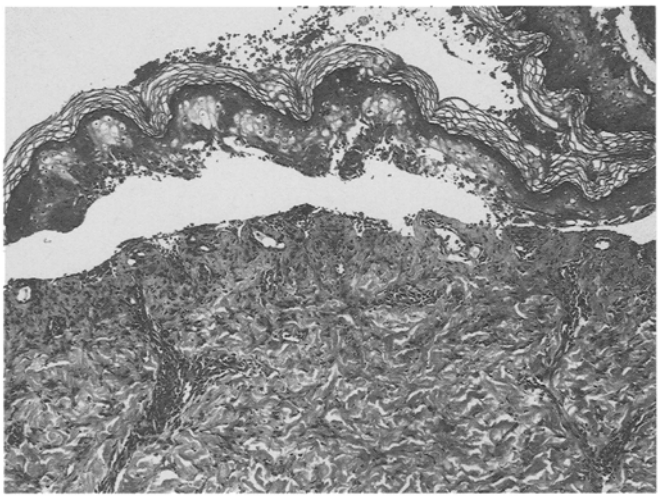


Fig. 13. Toxic epidermal necrolysis.

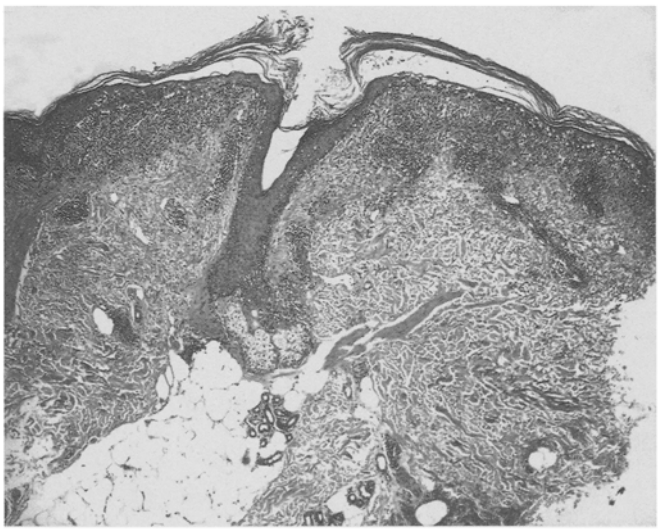


Fig. 14. Lupus erythematosus.

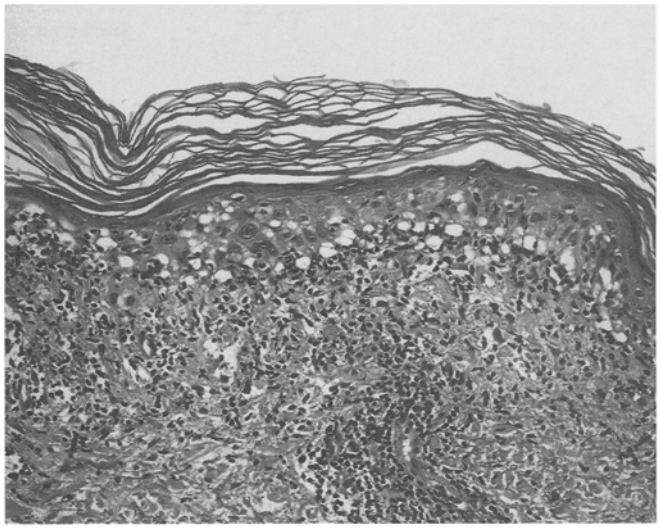


Fig. 15. Prominent interface change in lupus erythematosus.

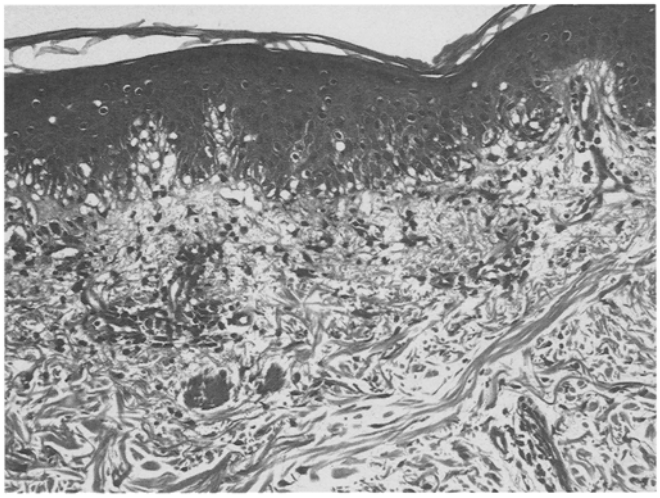


Fig. 16. Dermatomyositis.

Differential Diagnosis

- Dermatomyositis, erythema multiforme, lichen planus

Dermatomyositis

- Clinical: systemic disease with muscle weakness, heliotrope periorbital discoloration, violaceous rash on face and neck, periungual erythema, Gottron's papules on hands

*Microscopic (**Figure 16**)*

- Basal vacuolization
- Superficial perivascular mononuclear cell infiltrate, usually mild
- Increased dermal mucin

Differential Diagnosis

- Lupus erythematosus, graft vs. host disease

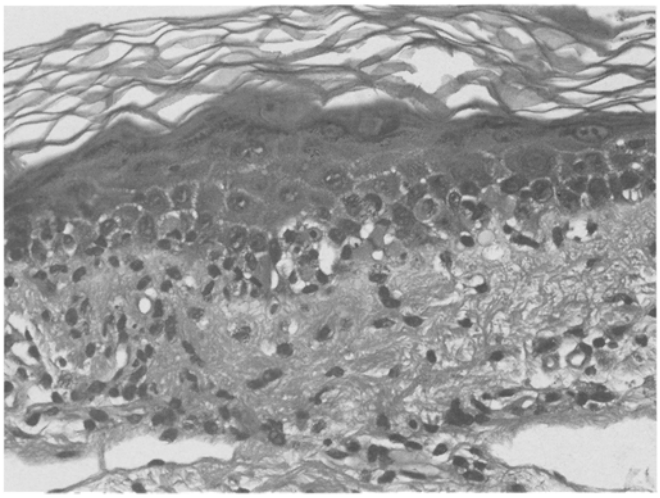


Fig. 17. Acute graft vs. host disease.

Graft vs. Host Disease

Clinical

- Acute: Usually 2–4 weeks after bone marrow transplant presents as macular erythema on trunk, neck, hands, and feet; may form blisters
- Chronic: Months to years after bone marrow transplant
  - Lichenoid form presents as violaceous papules and plaques on extremities, palms, and soles
  - Sclerodermoid form presents as widespread dermal sclerosis

Microscopic

- Acute (**Figure 17**)
  - Grade 0 : Normal epidermis
  - Grade 1: Basal vacuolization, mild superficial perivascular lymphocytic infiltrate
  - Grade 2: Basal vacuolization with dyskeratotic keratinocytes, excocytosis of lymphocytes, mild superficial perivascular lymphocytic infiltrate
  - Grade 3: Same as Grade 2 but with cleft formation between dermis and epidermis
  - Grade 4: Same as Grade 3 but with complete separation of epidermis and dermis
- Chronic
  - Lichenoid: resembles lichen planus
  - Sclerodermoid: resembles scleroderma/morphea

Differential Diagnosis

- Acute: drug eruption, viral exanthem, lupus erythematosus, dermatomyositis
- Chronic
  - Lichenoid: lichen planus
  - Sclerodermoid: scleroderma, morphea

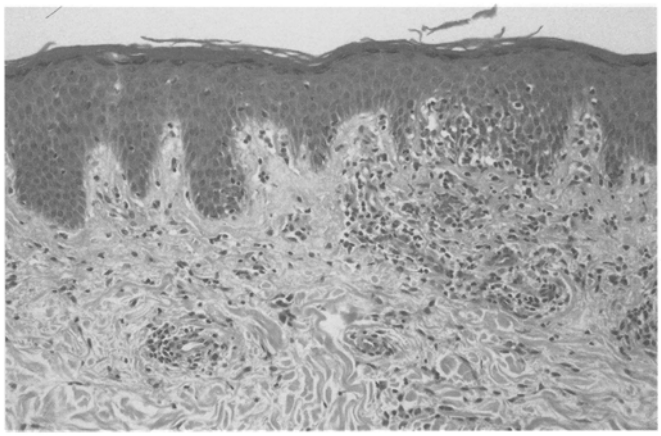


Fig. 18. Morbilliform drug eruption.

Morbilliform Drug Eruption

Clinical

- Blanchable symmetric, widespread macular or papular eruption

*Microscopic (**Figure 18**)*

- Mild vacuolar change (sometimes absent)
- Mild dyskeratosis
- Blood vessel ectasia
- Superficial perivascular infiltrate of lymphocytes and occasional eosinophils

Differential Diagnosis

- Graft vs. host disease, lupus erythematosus, dermatomyositis, viral exanthem

Viral Exanthem

Clinical

- Usually due to parvovirus, herpesvirus 6, HIV, enterovirus, EBV, hepatitis B, coxsackievirus

Microscopic

- Mild vacuolar change
- Variable dyskeratosis
- Papillary dermal edema
- Mild superficial perivascular lymphocytic infiltrate

Differential Diagnosis

- Graft vs. host disease, lupus erythematosus, dermatomyositis, drug eruption

Interface Dermatitis with Lichenoid (Band-Like) Infiltrate

Lichen Planus

Clinical

- Pruritic violaceous, polygonal papules

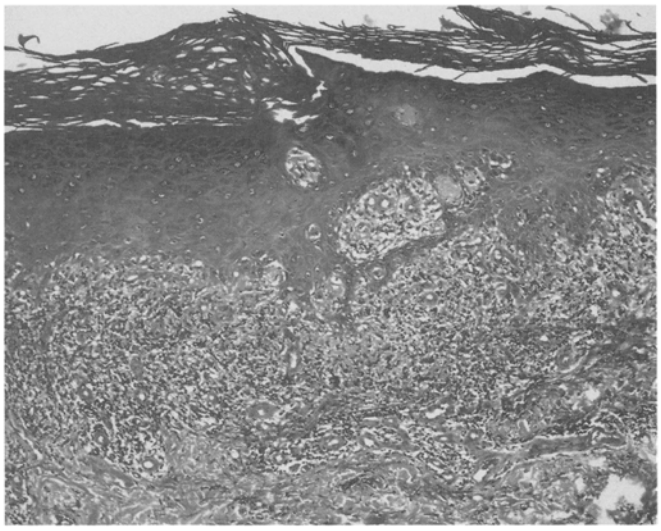


Fig. 19. Lichen planus.

- Predilection for flexural surfaces of wrists and ankles but may be widespread
- Mucosal involvement common

*Microscopic (**Figure 19**)*

- Hyperkeratosis without parakeratosis
- Acanthosis with wedge-shaped hypergranulosis
- Interface change with "saw-tooth" rete pegs, scattered dyskeratotic cells, and dense band-like lymphocytic infiltrate

Variants

- Atrophic lichen planus: thinned epidermis with subtle interface change and subtle wedge-shaped hypergranulosis
- Hypertrophic lichen planus: similar to classic lichen planus but with more prominent acanthosis
- Bullous lichen planus: subepidermal blister, wedge-shaped hypergranulosis, interface change at sides of blister

Differential Diagnosis

- Classic lichen planus: lichenoid benign keratosis, lichenoid graft vs. host disease, fixed drug reaction, lichenoid drug eruption, lichenoid pigmented purpuric dermatosis
- Atrophic lichen planus: resolving lichenoid benign keratosis, lupus erythematosus, dermatomyositis
- Hypertrophic lichen planus: lichenoid benign keratosis, squamous cell carcinoma

Lichenoid Drug Eruption

Clinical

- Widespread violaceous papules

Microscopic

- Very similar to lichen planus
- Occasional eosinophils
- May show parakeratosis

Differential Diagnosis

- Lichen planus

Fixed Drug Eruption

Clinical

- Well-demarcated erythematous plaques secondary to a drug reaction
- Most commonly involves hands, feet, genitalia, and face
- Often recurs in the same location on re-exposure to offending agent

Microscopic

- Basket-weave stratum corneum or parakeratosis
- Interface change with dyskeratotic keratinocytes
- Lichenoid infiltrate of lymphocytes admixed with some eosinophils
- Melanophages seen in older or recurrent lesions

Differential Diagnosis

- Erythema multiforme, lupus erythematosus

SUPERFICIAL PERIVASCULAR DERMATITIS

- Inflammatory infiltrate confined to upper dermis
- Little epidermal change

Morbilliform Drug Eruption

Clinical

- Most common type of cutaneous drug reaction
- Symmetric macular and papular rash
- Can occur with any drug
- Ampicillin in patients with mononucleosis is classic example

Microscopic

- May have mild vacuolar change (see Interface Dermatitis section)
- Superficial perivascular lymphocytic infiltrate with or without a few eosinophils or neutrophils

Differential Diagnosis

- Viral exanthem, tinea versicolor

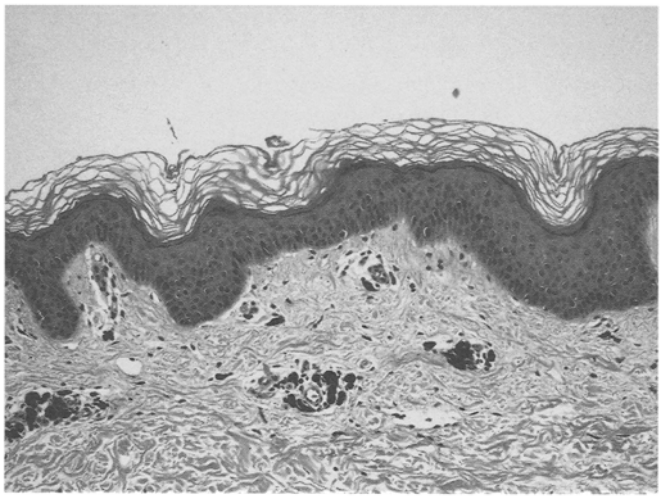


Fig. 20. Post-inflammatory pigment alteration.

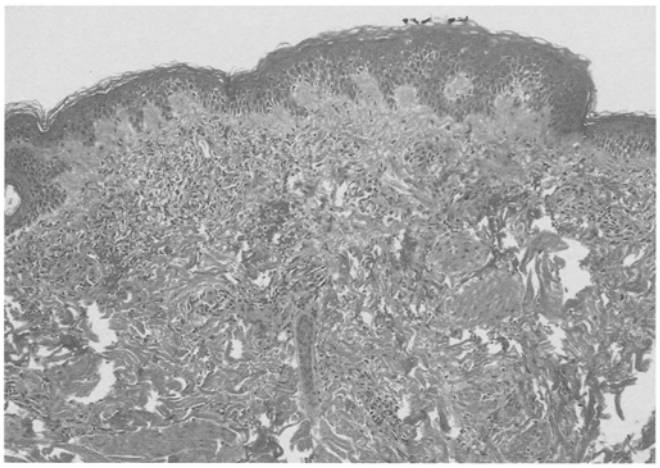


Fig. 21. Progressive pigmented purpuric dermatosis.

Postinflammatory Pigment Alteration

Clinical

- Hyperpigmented or hypopigmented macules and patches
- Sequelae of pre-existing inflammatory disorder

*Microscopic (**Figure 20**)*

- Mild superficial perivascular lymphohistiocytic infiltrate
- Scattered melanophages
- Typically little or no epidermal changes
- Melanocytes still present in epidermis

Differential Diagnosis

- Vitiligo, regressed melanocytic lesions, progressive pigmented purpuric eruption

Progressive Pigmented Purpuric Eruption (Schamberg's Disease)

Clinical

- Red-brown macules most commonly on lower legs

*Microscopic (**Figure 21**)*

- Little epidermal change; occasionally may have some spongiosis
- Mild superficial lymphocytic infiltrate with extravasated erythrocytes and siderophages; occasionally may have a lichenoid infiltrate
- No true vasculitis

Differential Diagnosis

- Stasis dermatitis, post-inflammatory pigment alteration

Urticaria

Clinical

- Transient edematous pruritic plaques (hives)
- Typically resolve within 24 hours

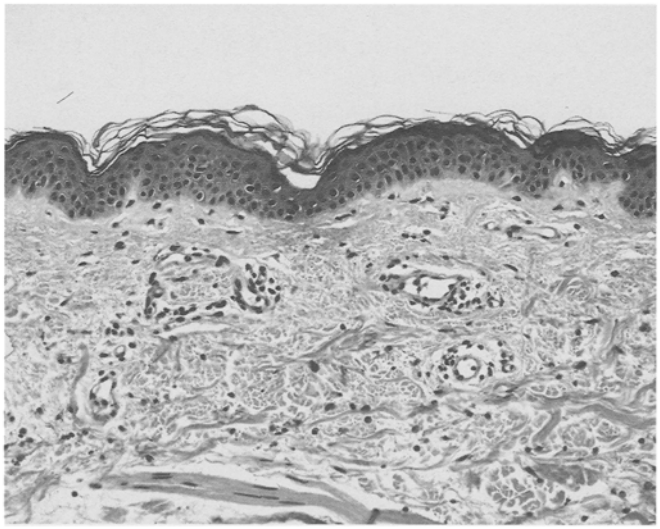


Fig. 22. Urticaria.

*Microscopic (**Figure 22**)*

- Normal epidermis
- Dermal edema
- Superficial perivascular infiltrate of lymphocytes and eosinophils and sometimes a few neutrophils

Differential Diagnosis

- Urticarial phase of bullous pemphigoid, arthropod bite reaction, drug eruption

Urticaria Pigmentosa

Clinical

- Persistent erythematous to tan macules and papules
- Solitary lesions called mastocytoma
- May present in childhood or adulthood

- Lesions urticate when stroked (Darier's sign)
- Rarely associated with systemic mast cell disease or mast cell leukemia

Microscopic

- Normal epidermis
- Superficial perivascular infiltrate predominantly composed of mast cells
- Mast cell infiltrate can be quite dense with a superficial and deep distribution
- Giemsa stain often necessary to demonstrate mast cells (**Figure 23**)

Differential Diagnosis

- Superficial perivascular pattern: viral exanthem, normal skin
- Dense superficial and deep pattern: intradermal nevus, Langerhans cell histiocytosis, lymphoma

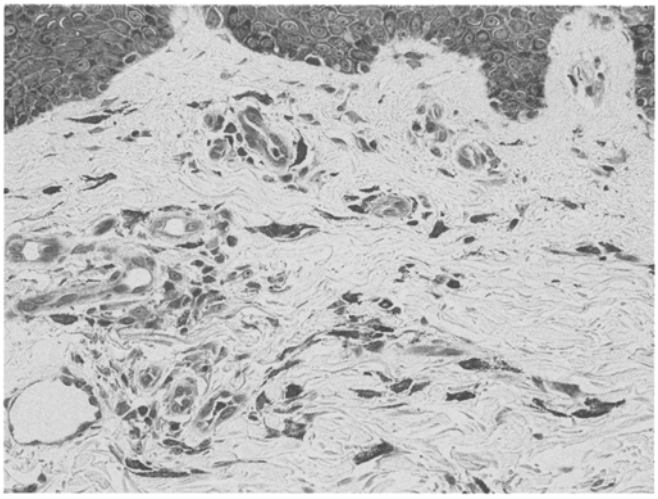


Fig. 23. Giemsa stain highlighting mast cells in urticaria pigmentosa.

SUPERFICIAL AND DEEP PERIVASCULAR INFILTRATE

- Lupus erythematosus (see also Interface Dermatitis section) may also exist without or with minimal interface change. This variant is called tumid lupus erythematosus

Sweet's Syndrome

Clinical

- Violaceous tender nodules or plaques
- May be associated with infections, myeloproliferative disorders, treatment with granulocyte colony-stimulating factors

*Microscopic (**Figure 24**)*

- No or minimal epidermal change
- Dense infiltrate of neutrophils in reticular dermis
- Leukocytoclasis but no true vasculitis

Differential Diagnosis

- Erythema elevatum diutinum, pyoderma gangrenosum, cellulitis

Pityriasis Lichenoides et Varioliformis Acuta (PLEVA)

Clinical

- Recurrent crops of flesh colored to erythematous papules
- Lesions evolve into vesicles, hemorrhagic lesions and crusted ulcerations
- Resolution leaves varioliform scars

*Microscopic (**Figure 25**)*

- Epidermal changes variable depending on stage of lesion including minimal to no epidermal changes, parakeratosis, focal dyskeratosis, basilar vacuolar change, epidermal ulceration
- Wedge-shaped perivascular and interstitial dermal infiltrate of small lymphocytes with occasional neutrophils and some dermal hemorrhage

Differential Diagnosis

- Pityriasis rosea, syphilis, lymphomatoid papulosis, pityriasis lichenoides chronica

Lymphomatoid Papulosis

Clinical

- Recurrent crops of papules that may vesiculate and become crusted
- Molecular studies have demonstrated T-cell clonality and some consider it a low grade T-cell dyscrasia/T-cell lymphoma
- Up to 20% of patients may develop a secondary lymphoid malignancy

*Microscopic (**Figure 26**)*

- Epidermal changes
  - Early: mild exocytosis of lymphocytes, parakeratosis

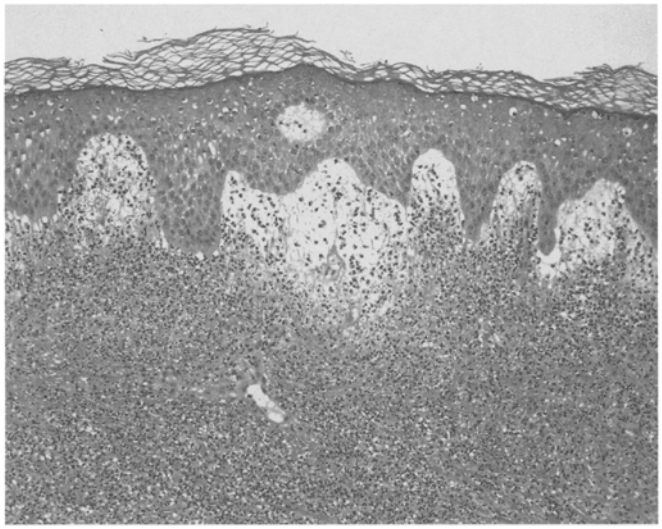


Fig. 24. Sweet's syndrome.

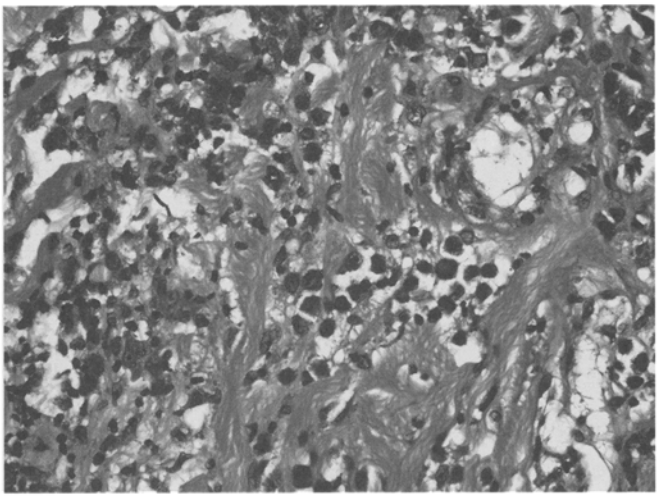


Fig. 26. Large atypical cells of lymphomatoid papulosis.

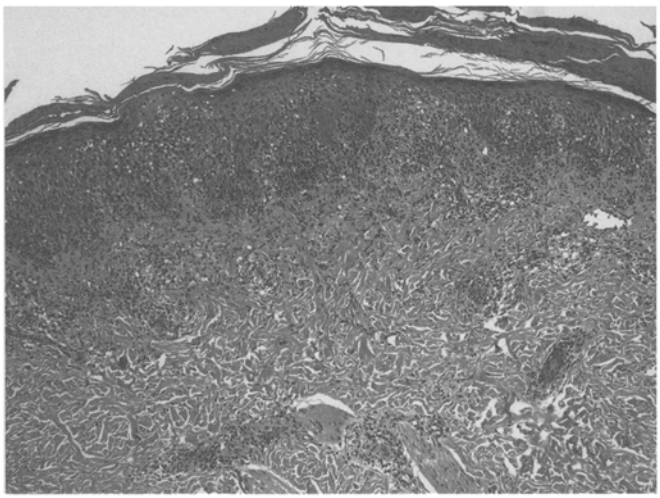


Fig. 25. Pityriasis lichenoides et varioliformis acuta (PLEVA).

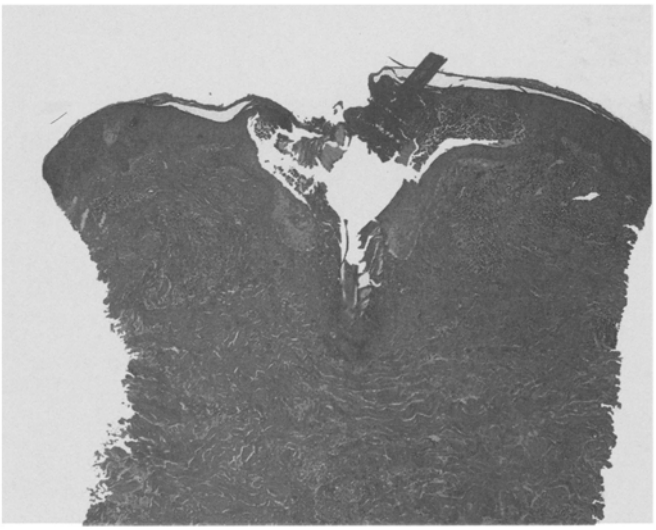


Fig. 27. Arthropod bite reaction.

- Late: more pronounced exocytosis, dyskeratotic cells, and necrosis

- Wedge-shaped dermal infiltrate of small and large lymphocytes with occasional plasma cells, eosinophils and neutrophils
- Large atypical CD30+ cells similar to those seen in anaplastic large cell lymphoma comprising greater than 25% of the infiltrate
- May be indistinguishable from cutaneous anaplastic large cell lymphoma (requires clinical information to distinguish)

Differential Diagnosis

- Anaplastic large cell lymphoma, PLEVA, arthropod bite reaction

Arthropod Bite Reaction

Clinical

- Variable, typically erythematous pruritic papule or papules

*Microscopic (**Figure 27**)*

- Epidermis may show acute necrosis or epidermal hyperplasia (chronic lesions)
- Papillary dermal edema
- Wedge-shaped superficial and deep perivascular and interstitial infiltrate of eosinophils and mononuclear cells

Differential Diagnosis

- PLEVA, lymphomatoid papulosis, deep fungal infection, eosinophilic cellulitis (Wells' syndrome)

INTERSTITIAL PATTERN

Palisading Granulomatous Dermatitis

- Characterized by interstitial histiocytic infiltrate surrounding altered collagen

Granuloma Annulare

Clinical

- Asymptomatic papules with annular configuration
- Usually on extremities

*Microscopic (**Figure 28**)*

- Most commonly involves upper and mid reticular dermis
- Central zone of altered collagen fibers with associated dermal mucin surrounded by a palisade of histiocytes with some giant cells
- Perivascular lymphocytic infiltrate with variable numbers of eosinophils
- Neutrophils may be prominent early
- Rarely may resemble sarcoidal granulomas
- Rarely may be confined to the subcutis

Differential Diagnosis

- Necrobiosis lipoidica, rheumatoid nodule

Necrobiosis Lipoidica

Clinical

- Yellow, indurated plaques usually on lower legs
- Two-thirds of patients have underlying diabetes mellitus

*Microscopic (**Figure 29**)*

- Epidermal atrophy
- Affects entire dermis
- Tiered arrangement of elongated zones of altered collagen (necrobiosis) separated by an interstitial infiltrate of histiocytes
- Multinucleated histiocytes common
- Aggregates of lymphocytes and plasma cells

Differential Diagnosis

- Granuloma annulare, sarcoidosis

Rheumatoid Nodule

Clinical

- Occurs in 20% of patients with rheumatoid arthritis
- Present most commonly as nodules on extensor surface of forearm

*Microscopic (**Figure 30**)*

- Subcutis and deep dermis most common sites of involvement
- Central zone of eosinophilic, degenerated collagen and nuclear debris surrounded by histiocytes

Differential Diagnosis

- Subcutaneous granuloma annulare



Fig. 28. Granuloma annulare.

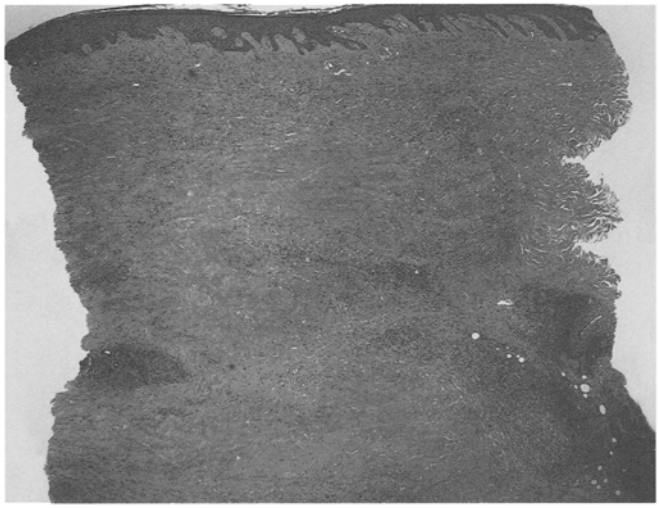


Fig. 29. Necrobiosis lipoidica.

Nodular or Diffuse Infiltrate

Cutaneous Lymphoid Hyperplasia (Lymphocytoma Cutis)

Clinical

- Solitary nodule or plaque most commonly on head and neck

*Microscopic (**Figure 31**)*

- Top-heavy nodular to diffuse lymphocytic infiltrate admixed with eosinophils and plasma cells
- Frequent germinal center formation

Differential Diagnosis

- Cutaneous marginal zone lymphoma, cutaneous follicular lymphoma

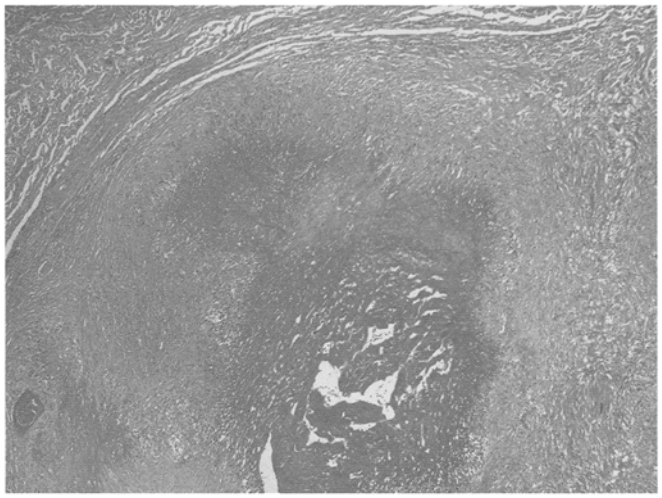


Fig. 30. Rheumatoid nodule.

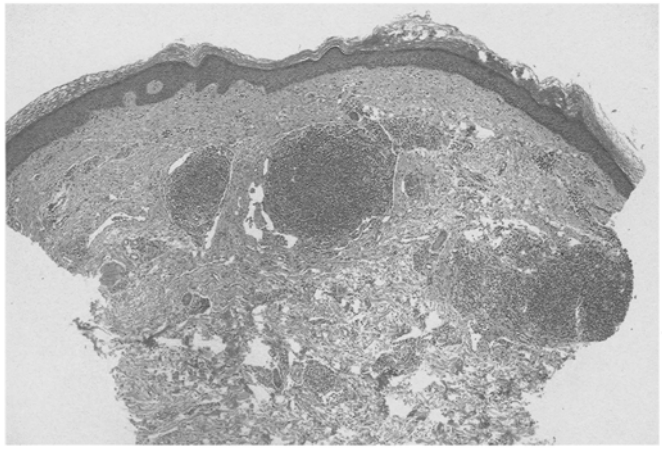


Fig. 31. Cutaneous lymphoid hyperplasia.

Eosinophils Cellulitis (Wells' Syndrome)

Clinical

- Erythematous painful or pruritic plaques resembling cellulitis or urticaria

Microscopic

- Edematous dermis
- Numerous interstitial eosinophils with flame figures (collagen fibers encrusted with eosinophilic granules) (**Figure 32**)

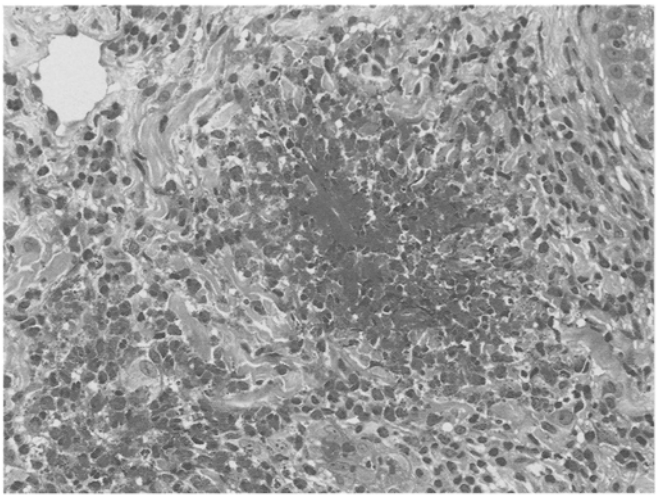


Fig. 32. Flame figure in Wells' syndrome.

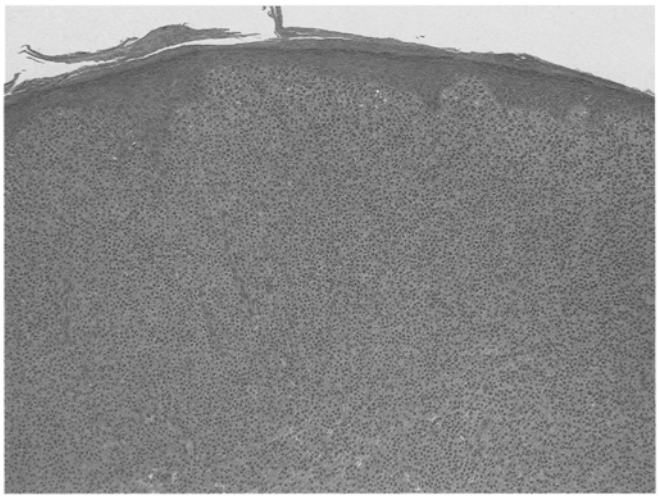


Fig. 33. Mastocytoma.

Differential Diagnosis

- Fungal infection, hypersensitivity reaction, arthropod bite reaction

Mastocytosis/Mastocytoma

- See also urticaria pigmentosa in superficial perivascular dermatitis section
- May be a dense interstitial infiltrate of mast cells (**Figure 33**)

SCLEROSING DERMATOSES

Scleroderma

Clinical

- Multisystem connective tissue disease
- Two major clinical groups
  - Group 1: Limited disease involving hands, forearms and face, often have CREST syndrome
  - Group 2: Diffuse cutaneous sclerosis and frequent visceral involvement

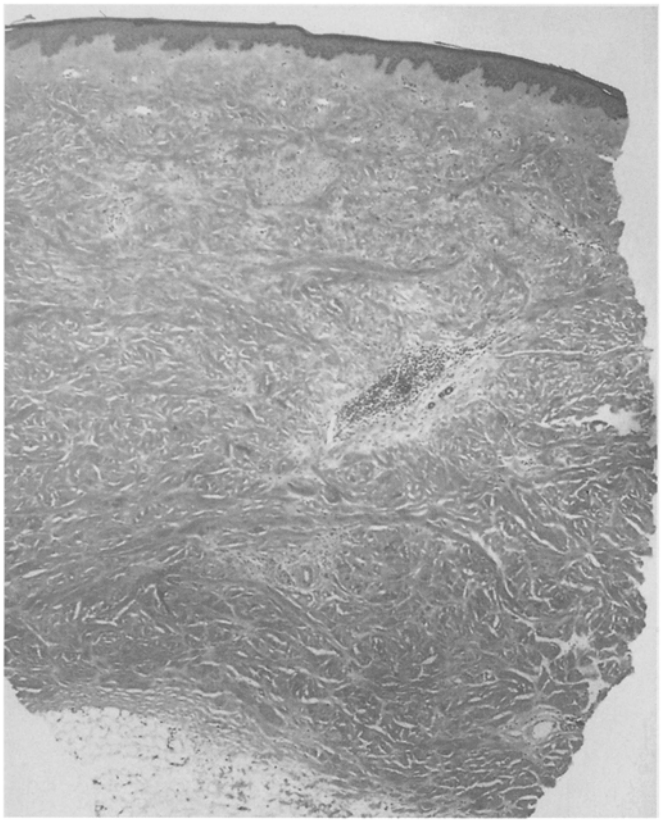


Fig. 34. Scleroderma/morphea.

- Indurated skin, sclerodactyly, hypopigmentation with perifollicular pigment retention, telangiectasias

*Microscopic (**Figure 34**)*

- Sclerosis and thickening of reticular dermis
- Entrapment of adnexal structures
- Lymphoplasmacytic infiltrate typically at dermal-subcutis junction

Differential Diagnosis

- Morphea, sclerodermoid graft vs. host disease

Morphea

Clinical

- Also known as localized scleroderma
- Most common on trunk

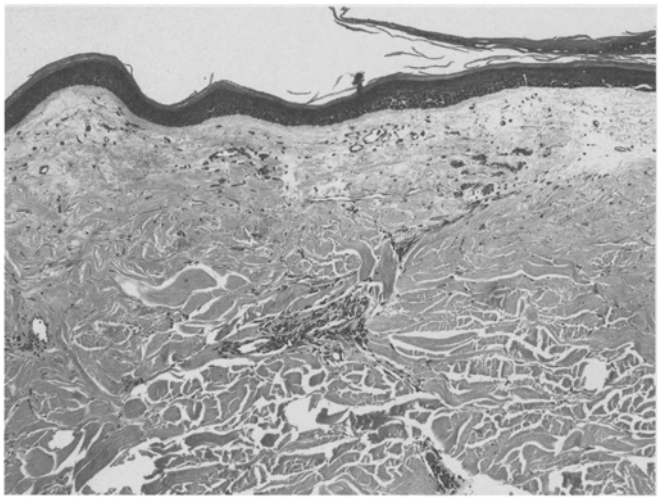


Fig. 35. Lichen sclerosus.

Microscopic

- Indistinguishable from scleroderma

Differential Diagnosis

- Scleroderma, sclerodermoid graft vs. host disease

Lichen Sclerosus

Clinical

- White papules and plaques, frequently with fine, crinkly scale
- Predilection for genital area

*Microscopic (**Figure 35**)*

- Atrophic epidermis with loss of normal rete peg pattern and hyperkeratosis
- Basal vacuolization (early lesions)
- Edematous and homogenized papillary dermis
- Variable lichenoid lymphocytic infiltrate beneath altered collagen

Differential Diagnosis

- Morphea, lupus erythematosus

PANNICULITIS

General Comments

- Two primary patterns: septal and lobular
- Most panniculitides usually have some septal as well as some lobular inflammation
- Categorization based on predominant pattern

Erythema Nodosum

Clinical

- Acute onset of tender, erythematous nodules
- Shins most common site, often bilateral

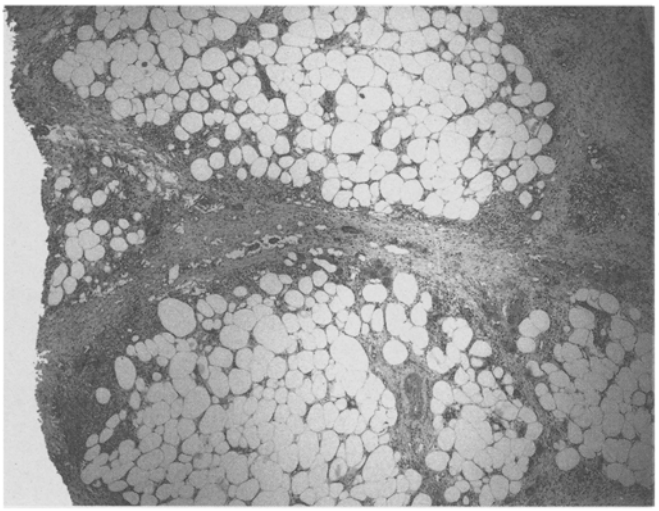


Fig. 36. Erythema nodosum.

- Subcutaneous hypersensitivity reaction that may be idiopathic or associated with infection (e.g., group A β-hemolytic streptococcus) or drugs (e.g., sulfa drugs, oral contraceptives)

*Microscopic (**Figure 36**)*

- Septal panniculitis
- Widened septae with edema, inflammation, and later fibrosis
- Lymphocytes, histiocytes and some neutrophils
- Small granulomas within septae
- Lobular inflammation at periphery of subcutaneous fat lobule

Differential Diagnosis

- Infection, trauma, nodular vasculitis, superficial migratory thrombophlebitis, lipodermatosclerosis, lupus panniculitis, subcutaneous morphea

Lipodermatosclerosis (Lipomembranous Panniculitis, Sclerosing Panniculitis)

Clinical

- Bilateral indurated plaques on medial aspects of lower legs
- Associated with stasis changes secondary to venous insufficiency and obesity

Microscopic

- Predominantly septal panniculitis but lobular component invariably present
- Widened septae
- Membranocystic fat necrosis (**Figure 37**)
  - Cystic cavities lined by a crenulated, hyaline membrane
- Mild perivascular lymphocytic infiltrate
- Overlying features of stasis change in dermis and epidermis

Differential Diagnosis

- Erythema nodosum, lupus panniculitis, subcutaneous morphea

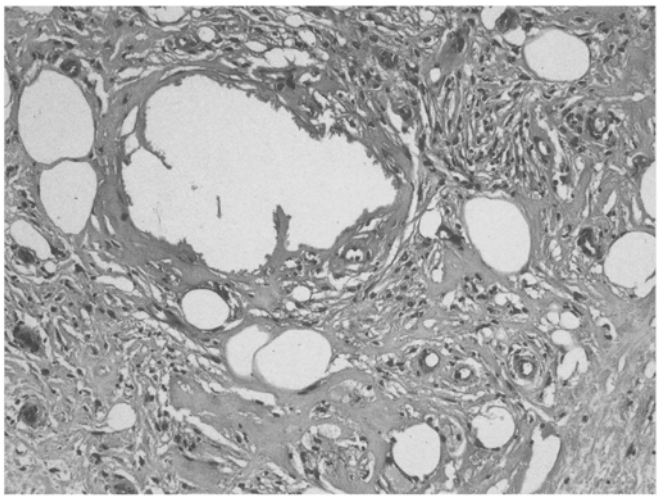


Fig. 37. Lipodermatosclerosis.

Subcutaneous Morphea (Morphea Profundus)

Clinical

- Multiple bound-down indurated plaques on extremities
- Overlying skin has dimpled appearance
- Frequent peripheral blood eosinophilia
  - When fascial involvement present may also be called eosinophilic fasciitis

Microscopic

- Septal panniculitis
- Thickened, hyalinized and compacted collagen fibers in subcutaneous septae and deep dermis
- Perivascular lymphoplasmacytic infiltrate
- Lymphoid aggregates without germinal centers

Differential Diagnosis

- Late stage erythema nodosum, lupus panniculitis, lipodermatosclerosis

Nodular Vasculitis (Erythema Induratum)

Clinical

- Chronic, recurring tender nodules on lower legs
- Calves most common site, often bilateral
- Subcutaneous hypersensitivity reaction that in some patients is a reaction to underlying infection with *M. tuberculosis*

*Microscopic (**Figure 38**)*

- Lobular panniculitis with fat necrosis
- Predominantly lymphocytes, histiocytes, and multinucleated histiocytes
- Irregular granulomas often present
- Acute vasculitis in septae

Differential Diagnosis

- Erythema nodosum, infection, polyarteritis nodosa, thrombophlebitis, lupus panniculitis

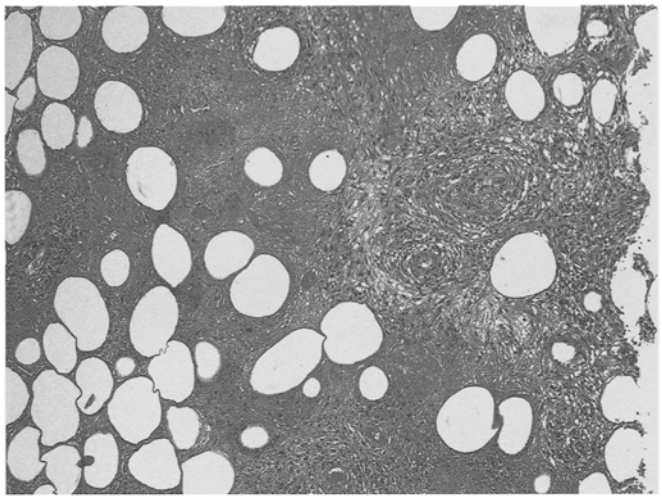


Fig. 38. Nodular vasculitis.

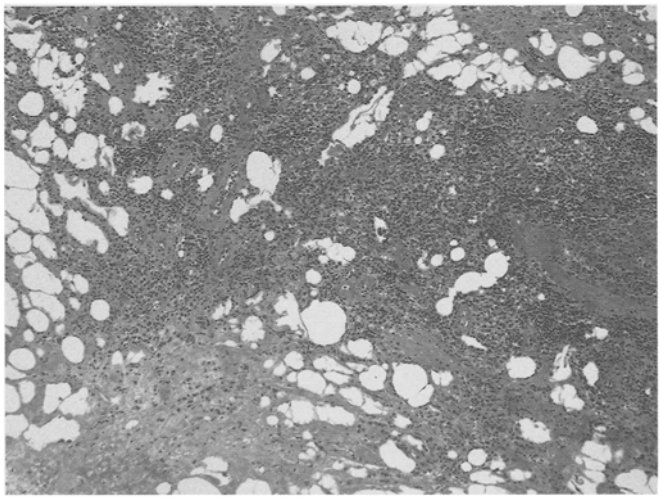


Fig. 39. Lupus profundus.

Lupus Panniculitis (Lupus Profundus)

Clinical

- Deep subcutaneous nodules and plaques on upper arms, thighs and trunk
- May or may not have other manifestations of cutaneous lupus erythematosus
- 10% have associated systemic lupus erythematosus

*Microscopic (**Figure 39**)*

- Predominantly lobular panniculitis
- Hyaline fat necrosis characterized by dense eosinophilic sclerosis around remnants of adipocytes
- Lymphoid nodules with germinal centers at periphery of fat lobules
- Sometimes lymphocytic vasculitis

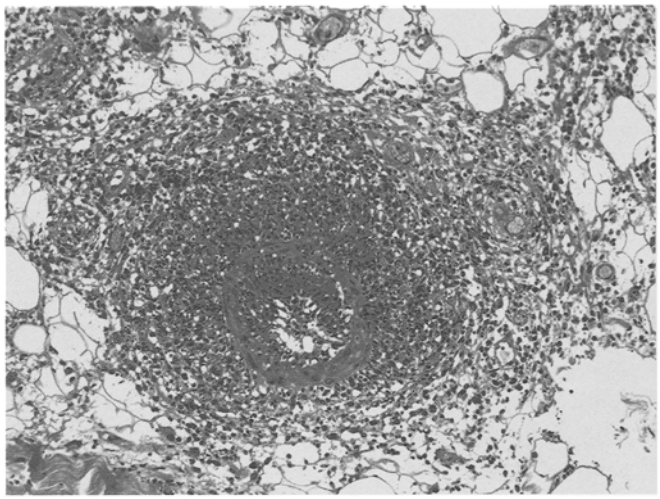


Fig. 40. Polyarteritis nodosa.

Differential Diagnosis

- Nodular vasculitis, subcutaneous morphea, lipodermatosclerosis

Polyarteritis Nodosa

Clinical

- Tender, erythematous nodules on extremities, especially legs
- Systemic (e.g., gastrointestinal or renal involvement) with skin involvement or localized to skin only
- Necrotizing vasculitis that affects small and medium sized arteries

*Microscopic (**Figure 40**)*

- Leukocytoclastic vasculitis involving small to medium sized artery in subcutis
- Focal lobular panniculitis surrounding affected vessel

Differential Diagnosis

- Superficial thrombophlebitis, nodular vasculitis

Superficial Thrombophlebitis

Clinical

- Cord-like arrangement of tender nodules most commonly on legs
- May be a paraneoplastic syndrome (Trousseau's sign)

Microscopic

- Inflammatory infiltrate involving wall of large vein in subcutis or deep dermis
- Composition of infiltrate varies with age of lesion (early neutrophils, later lymphocytes and histiocytes)

Differential Diagnosis

- Polyarteritis nodosa, erythema nodosum, nodular vasculitis

ALOPECIA

Non-Scarring Alopecia

Telogen Effluvium

Clinical

- Diffuse alopecia of rapid onset
- Preceding stressful event weeks to few months prior to onset (e.g., pregnancy, systemic illness)

Microscopic

- Acute phase: increased numbers of telogen phase follicles; normal total numbers of follicles
- Later stage: resembles normal scalp with primarily anagen phase follicles
- Patients more commonly biopsied in later stages of disease

Differential Diagnosis

- Normal scalp, alopecia areata

Androgenetic Alopecia

Clinical

- Male pattern baldness (bitemporal and occipital)
- Female pattern baldness (hair loss concentrated on scalp vertex)

*Microscopic (**Figure 41**)*

- Decreased numbers of follicles
- Miniaturized follicles, increased vellus hairs
- Sebaceous glands appear relatively enlarged
- Patchy mild perivascular lymphocytic infiltrate

Differential Diagnosis

- Telogen effluvium, alopecia areata

Alopecia Areata

Clinical

- Demarcated round area of hair loss typically localized to scalp but may become widespread

Microscopic

- Peribulbar lymphocytic infiltrate (**Figure 42**)
- Increased number of catagen and/or telogen follicles

Trichotillomania

Clinical

- Compulsive hair pulling
- More common in children and adolescents

Microscopic

- Distorted or fractured hair shafts (trichodystrophy) (**Figure 43**)

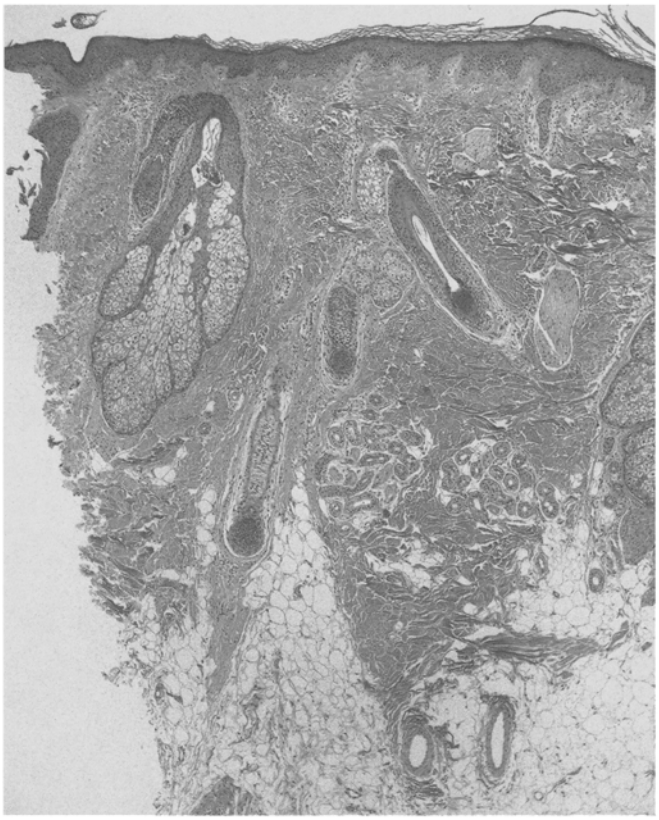


Fig. 41. Vellus hairs in androgenetic alopecia.

- Deposits of melanin within follicles (melanin casts) and stellae

Differential Diagnosis

- Alopecia areata

Scarring Alopecia

Lupus Erythematosus (see also Interface section)

Clinical

- Seen in setting of chronic discoid lupus erythematosus
- Variably hyperpigmented and hypopigmented plaques involving the scalp
- Follicular plugging, dilated follicles
- Women more commonly affected

Microscopic

- See earlier description of lupus erythematosus
- Interface change at follicular infundibulum
- Keratin plugs in follicles
- Variable perifollicular inflammation and fibrosis

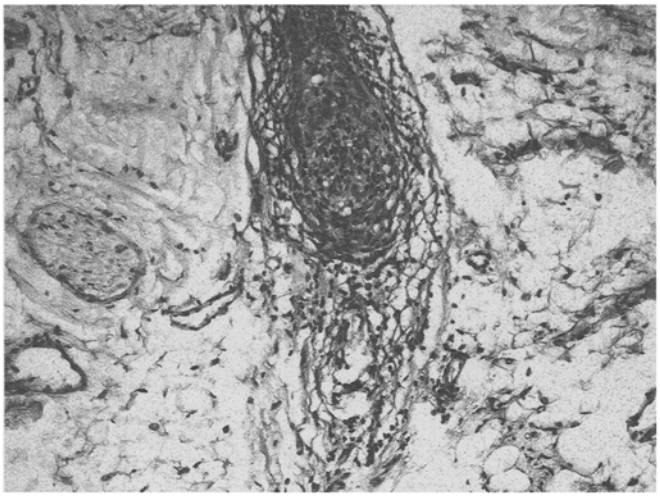


Fig. 42. Lymphocytic infiltrate around hair bulb in alopecia areata.



Fig. 43. Distorted hair shaft in trichotillomania.

Differential Diagnosis

- Lichen planopilaris

Lichen Planopilaris

Clinical

- Hyperkeratotic follicular papules
- May be associated with lichen planus elsewhere

*Microscopic (**Figure 44**)*

- Lichenoid interface change at follicular infundibulum
- Lichenoid interface change at dermal-epidermal junction often present
- Perifollicular fibrosis around infundibulum

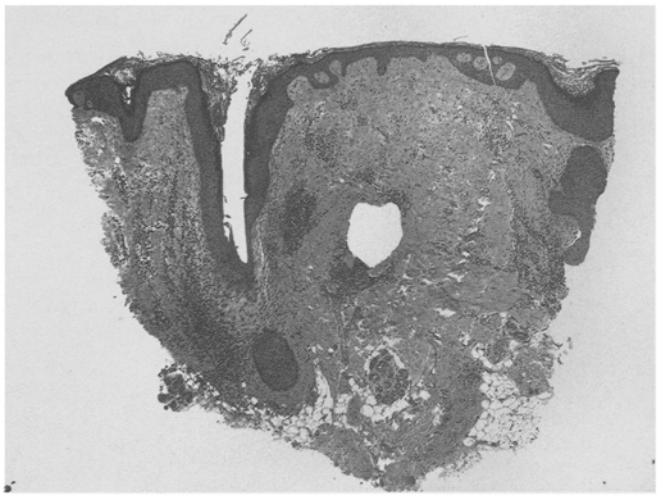


Fig. 44. Lichen planopilaris.

Follicular Degeneration Syndrome (Central Centrifugal Scarring Alopecia)

Clinical

- Most common in middle-aged black women
- Irregular patches of alopecia on frontal vertex or crown
- Some consider this chronic traction alopecia

Microscopic

- Concentric perifollicular fibroplasia with surrounding mild lymphocytic infiltrate
- Follicular atrophy with eccentric follicular canal

Differential Diagnosis

- Lichen planopilaris, lupus erythematosus

Dissecting Cellulitis

Clinical

- Most common in young black men
- Fluctuant nodules with follicular pustules

Microscopic

- Dilated follicles filled with neutrophils
- Keratotic plug in infundibulum
- Ruptured follicles
- Naked hair shafts in dermis
- Dermal abscesses

Differential Diagnosis

- Folliculitis decalvans, acne keloidalis nuchae

Acne Keloidalis Nuchae

Clinical

- Follicular pustules and perifollicular keloidal scars on occipital scalp
- Most common in black men

Microscopic

- Perifollicular fibroplasia, sometimes keloid-like
- Neutrophils and plasma cells within and around follicles

Differential Diagnosis

- Folliculitis decalvans, dissecting cellulitis

Folliculitis Decalvans

Clinical

- Well-demarcated, jagged patches of scalp alopecia with perifollicular pustules

Microscopic

- Perifollicular and intrafollicular neutrophilic infiltrates
- Some perifollicular fibroplasia
- Naked hair shafts surrounded by foreign body-type inflammatory response

Differential Diagnosis

- Dissecting cellulitis, acne keloidalis nuchae

End-Stage Scarring Alopecia and Pseudopelade (Idiopathic Scarring Alopecia)

Clinical

- Longstanding scarring alopecia
- Underlying etiology may be any of the forms of inflammatory scarring alopecia or idiopathic in nature

Microscopic

- Dermal fibrosis
- Residual lymphocytic or neutrophilic infiltrate
- Naked hair shafts

Differential Diagnosis

- Indistinguishable from end stage of other forms of scarring alopecia

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14

Endocrine Pathology

J. Aidan Carney, MD

CONTENTS

I. Thyroid Gland 14-3
- Non-Neoplastic Conditions 14-3
  - Heterotopic Thyroid 14-3
  - Thyroglossal Duct Cyst 14-3
  - Acute Thyroiditis 14-4
  - Granulomatous Thyroiditis (de Quervain's) 14-4
  - Fibrous Thyroiditis (Riedel's) 14-5
  - Lymphocytic Thyroiditis (Painless Thyroiditis) 14-6
  - Hashimoto's Thyroiditis 14-6
  - Graves' Disease 14-7
  - Nodular Hyperplasia 14-8
  - C-Cell Hyperplasia 14-9
- Neoplasms 14-11
  - Benign Tumors 14-11
    - Follicular Adenoma 14-11
    - Hürthle Cell Adenoma 14-12
  - Malignant Tumors 14-13
    - Papillary Carcinoma 14-13
    - Follicular Carcinoma 14-15
    - Insular Carcinoma 14-16
    - Anaplastic Carcinoma (Sarcomatoid Carcinoma) 14-16
    - Hürthle Cell Carcinoma 14-17
    - Medullary Carcinoma 14-17

II. Parathyroid Gland 14-19
- Non-Neoplastic Conditions 14-19
  - Parathyroid Cyst 14-19
  - Chief Cell Hyperplasia 14-19
  - Tumors 14-20
  - Parathyroid Adenoma 14-20
  - Parathyroid Carcinoma 14-22

III. Adrenal Gland 14-24
- Non-Neoplastic Conditions 14-24
  - Adrenal Heterotopia 14-24
  - Focal "Adrenalitis" 14-25
  - Adrenal Aplasia 14-25
  - Adrenal Cysts 14-25
  - Adrenal Cytomegaly 14-25
  - Beckwith-Wiedemann Syndrome 14-26
  - Adrenal Leukodystrophy 14-26
  - Congenital Adrenal Hyperplasia (Adrenogenital Syndrome) 14-26
  - Primary Adrenal Insufficiency (Idiopathic Addison's Disease) 14-27
  - Secondary Adrenal Insufficiency 14-28
  - Adrenal Cortical Hyperplasia 14-28
  - Cortical Hyperplasia Associated with Hyperaldosteronism 14-29
  - Cortical Macronodular Hyperplasia 14-29
  - Microadenomatous Hyperplasia (Primary Pigmented Nodular Adrenocortical Disease) 14-29
  - Ovarian Thecal Metaplasia 14-30
  - Adrenal Medullary Hyperplasia 14-30
- Neoplasms 14-31
  - Benign Tumors 14-31
    - Cortical Adenoma 14-31
    - Myelolipoma 14-34
    - Oncocytoma (Oncocytic Adenoma) 14-34
    - Pheochromocytoma 14-35
    - Ganglioneuroma 14-36
  - Malignant Tumors 14-37
    - Adrenal Cortical Carcinoma 14-37

Neuroblastoma (Stroma-Poor Neuroblastoma) 14-39
Ganglioneuroblastoma (Stroma-Rich Neuroblastoma) 14-41

IV. TNM Classification of Thyroid Carcinomas (2002 Revision) 14-41

V. Suggested Reading.....14-42

THYROID GLAND

Non-Neoplastic Conditions

Heterotopic Thyroid

Clinical

- Normal thyroid tissue found along course of thyroglossal duct (from foramen cecum in posterior tongue down along anterior midline to below cricoid cartilage); may rarely be seen in mediastinum
- Occurs in up to 10% of population, although usually subclinical due to small size
- Presents as nodule in midline neck or base of tongue (most common location)
- Patients with heterotopic thyroid (especially those with lingual thyroid) may lack a normal thyroid gland
- Heterotopic tissue can give rise to thyroid malignancies (usually papillary carcinoma)

Macroscopic ***(Figure 1)***

- May be encapsulated
- Resembles normal thyroid tissue

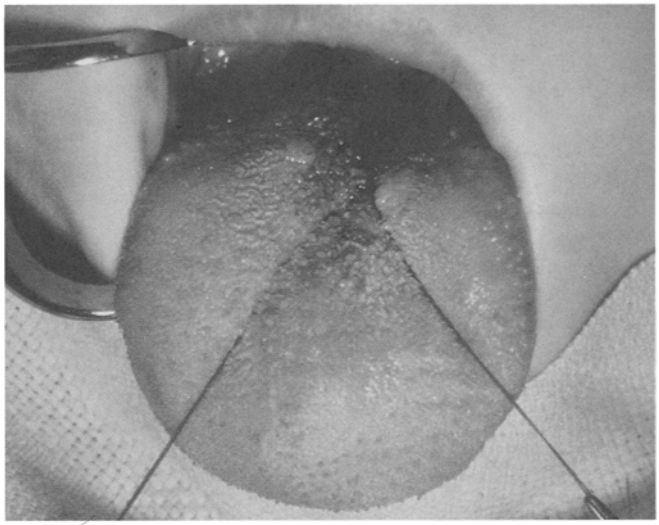


Fig. 1. Lingual thyroid. Depression at site of excision of lingual thyroid.

Microscopic ***(Figure 2)***

- Normal thyroid architecture that may manifest all pathologic processes that affect normally located thyroid gland (hyperplasia, neoplasia, inflammation, etc.)
- Individual follicles may proliferate between adjacent structures (such as muscle), a phenomenon that may simulate invasion

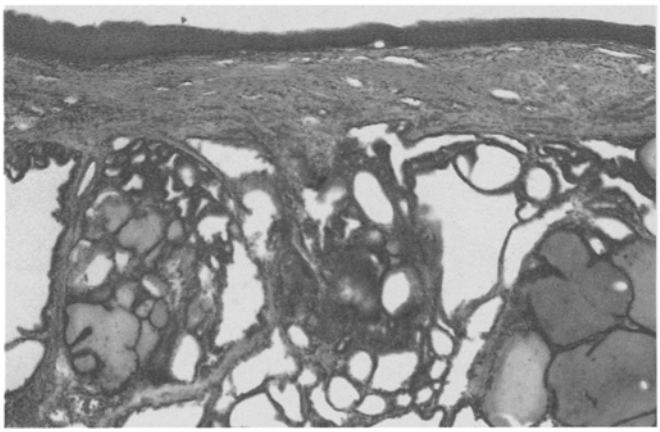


Fig. 2. Lingual thyroid. Variable sized hyperplastic follicles, some lined by cubical cells and featuring occasional papillary infoldings.

Differential Diagnosis

- Metastatic thyroid carcinoma:
  - Follicular carcinoma or follicular variant of papillary carcinoma may resemble normal thyroid
  - Careful examination may reveal solid areas, necrosis, mitoses, anaplasia, or true invasion

Thyroglossal Duct Cyst

Clinical

- Cystic dilation of remnant of thyroglossal duct, found along normal course of thyroglossal duct (from posterior tongue, along anterior midline to below cricoid cartilage)
- Duct may run anterior to, within, or posterior to hyoid bone
- Patients present during childhood with a midline nodule that may be tender and can be associated with the sinus tract
- Heterotopic thyroid tissue associated with the cyst may give rise to thyroid malignancies (usually papillary carcinoma)

Macroscopic

- Mucin-filled cyst, up to 3 cm in diameter
- Normal thyroid tissue may be seen in the wall of the cyst

Microscopic ***(Figures 3,4)***

- Cyst is usually lined by pseudostratified ciliated columnar or squamous epithelium
- If inflammation is prominent, lining may not be present.
- Surrounding stroma shows thyroid follicles and secondary inflammation

Differential Diagnosis

- Heterotopic thyroid:
  - Only thyroid tissue visible
  - No cyst or duct lining seen
- Branchial cleft cyst:
  - Location classically antero-lateral neck, not midline

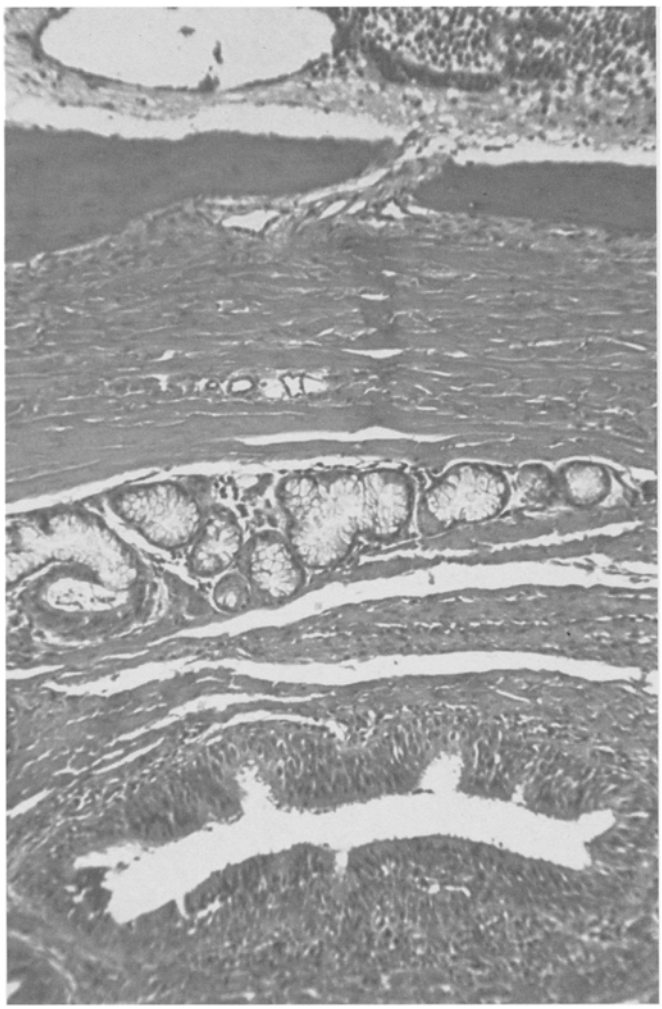


Fig. 3. Thyroglossal duct. Duct lined by columnar epithelium with lymphocytic infiltrate. Mucous glands and striated muscle separate the duct from the hyoid bone.

  - Lined by mixed squamous and respiratory-type epithelium
  - Many lymphoid follicles
  - No thyroid follicles seen
- Thyroid neoplasm with cystic degeneration:
  - Adenoma, adenomatous goiter, or carcinoma may show cystic degeneration
  - Careful examination of the cyst wall and surrounding tissue is important

Acute Thyroiditis

Clinical

- Acute inflammation usually due to infectious disease
- May be due to regional infection, general sepsis, or local trauma
- Usually due to gram+ bacteria, but gram– organisms or fungi may also be responsible

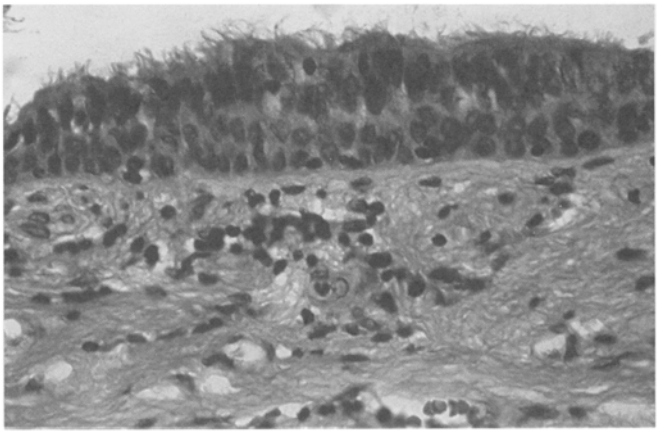


Fig. 4. Thyroglossal duct. Pseudostratified ciliated columnar epithelium line duct.

Macroscopic

- Thyroid may be enlarged, with areas of necrosis and abscess formation

Microscopic

- Acute inflammatory infiltrates with associated necrosis

Differential Diagnosis

- Other types of thyroiditis (granulomatous or lymphocytic):
  - In other types, predominant inflammatory cells are either histiocytes or lymphocytes (neutrophils, if present, usually in a minority)
  - Not associated with other acute infections or trauma

Granulomatous Thyroiditis (de Quervain's)

Clinical

- Granulomatous inflammation of thyroid of uncertain etiology; thought to be related to viral infection
- Seen in middle-aged women
- Patients present with fever and malaise, sore throat, thyroid enlargement and tenderness
- Early phase may show increased serum T3/T4 and decreased I^{131} uptake
- Usually resolves completely, but in some cases may result in some residual hypothyroidism

Macroscopic ***(Figure 5)***

- Thyroid enlargement (usually asymmetrical) up to twice normal size
- Cut surface shows areas of irregular firm tan tissue among more normal-appearing thyroid tissue

Microscopic ***(Figure 6)***

- Mixed inflammation, predominantly lymphocytic and histiocytic
- Microabcesses are common

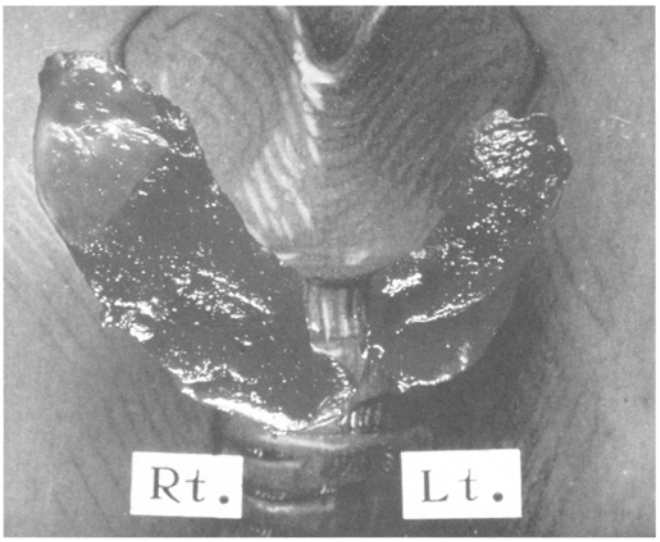


Fig. 5. Granulomatous thyroiditis. Localized involvement of the right upper lobe by a demarcated tan-yellow inflammatory mass.

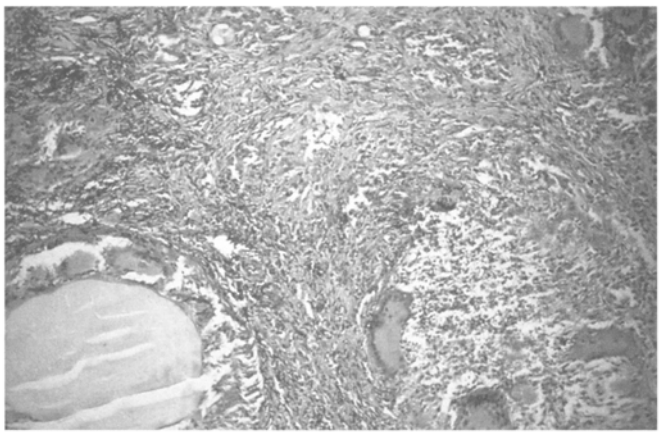


Fig. 6. Granulomatous thyroiditis. Normal thyroid parenchyma has largely been replaced by fibrosis and an inflammatory mass, including multinucleated giant cells. Thyroid follicles are in various stages of destruction.

- Vague, non-caseating granulomata with foreign body-type giant cells centered on and destroying follicles and engulfing colloid
- Patchy areas of fibrosis and regenerating follicles may be seen later in the disease

Differential Diagnosis

- Autoimmune thyroiditis:
  - Significantly less inflammation; predominantly lymphocytic with germinal centers
  - No gland destruction; rather, follicles show atrophy with Hürthle cell change
- Acute thyroiditis:
  - Inflammation predominantly neutrophilic rather than granulomatous
  - Usually associated with other infections (bacterial or fungal) or local trauma
- Tuberculosis or mycosis:
  - Rare, usually seen only in disseminated disease
  - Necrotizing granulomata
- Sarcoidosis:
  - Usually in patients with systemic disease
  - Granulomata are interstitial and do not result in follicular destruction
- Palpation thyroiditis:
  - Incidental finding as a result of vigorous palpation or minor trauma
  - Patchy, multifocal mixed lymphocytic and histiocytic inflammation involving isolated and widely distant follicles, in an otherwise histologically normal gland

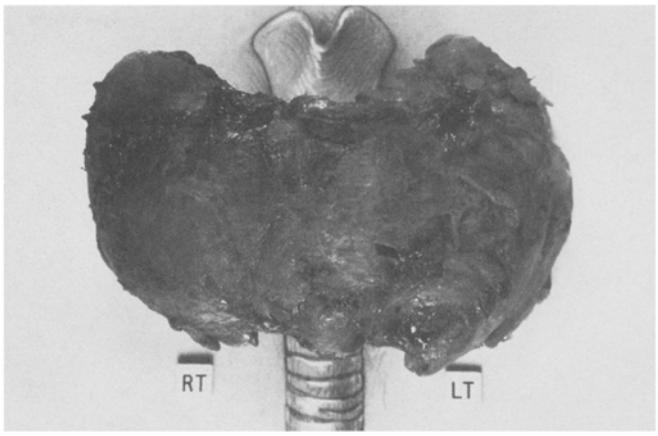


Fig. 7. Fibrous thyroiditis. Ragged external aspect of 230 gm thyroid gland. Portion of the strap muscles are inextricably attached to the left lobe.

Fibrous Thyroiditis (Riedel's Thyroiditis)

Clinical

- Rare, idiopathic process manifested by extensive fibrosis of the thyroid gland, extending beyond the gland into the surrounding tissue and usually involving the cervical musculature
- Thought to be related to fibrosing mediastinitis and retroperitoneal fibrosis (idiopathic fibrosclerosis)
- Patients tend to be adult or elderly (average age = 50 years), with slight female predilection
- Presents as poorly defined, rock-hard thyroid enlargement

*Macroscopic (**Figure 7**)*

- Gland enlarged with firm white tissue replacing parenchyma and extending into surrounding tissue, obliterating normal anatomic boundaries
- Fibrotic process pervades adjacent muscles, nerves, and vessels, making excision very difficult or impossible

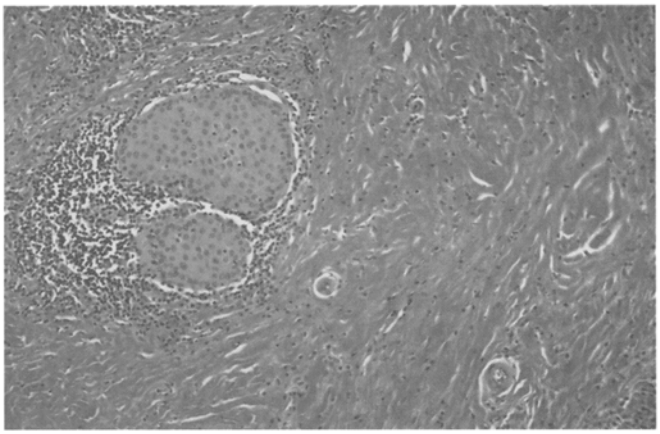


Fig. 8. Fibrous thyroiditis. Hyalinized fibrous proliferation has penetrated through the thyroid capsule and surrounds islands of metaplastic squamous epithelium. There is a lymphocytic infiltrate focally.

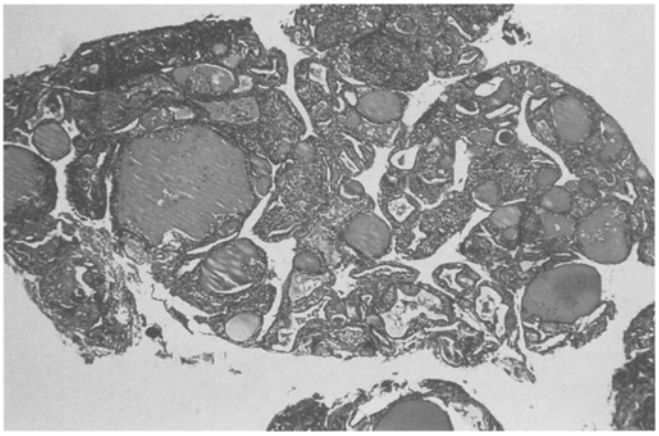


Fig. 9. Lymphocytic thyroiditis. Vim-Silvermann needle biopsy of a patient with transient hyperthyroidism. There is a moderately heavy lymphocytic infiltrate involving variable-sized thyroid follicles.

Microscopic ***(Figure 8)***

- Extensive fibrosis, infiltrating beyond the thyroid into the muscle and other tissue, with keloid-like hyalinized collagen
- Areas of more normal uninvolved thyroid are seen
- Patchy lymphoid and plasmacytic inflammation
- Involved vessels may show mural inflammation

Differential Diagnosis

- Fibrosing Hashimoto's thyroiditis:
  - Thyroid gland involved by fibrosis, but capsule intact and can be separated from adjacent structures by the surgeon
  - Microscopically, fibrosis appears more typical, rather than keloid-like

Lymphocytic Thyroiditis (Painless Thyroiditis)

Clinical

- Autoimmune thyroiditis caused by autoantibodies directed against thyroglobulin and other follicular cell antigens
- Usually seen in children and more common in women (F : M = 2 : 1)
- Patients present with asymptomatic goiter
- May be associated with transient hyperthyroidism
- Usually resolves within 1 year

Macroscopic

- Mild to moderate diffuse enlargement with slightly nodular appearance

Microscopic ***(Figures 9,10)***

- Scattered interstitial lymphoid follicles with germinal centers
- Follicles typically show minimal reaction to inflammation, but there may be some mild atrophy or Hürthle cell change

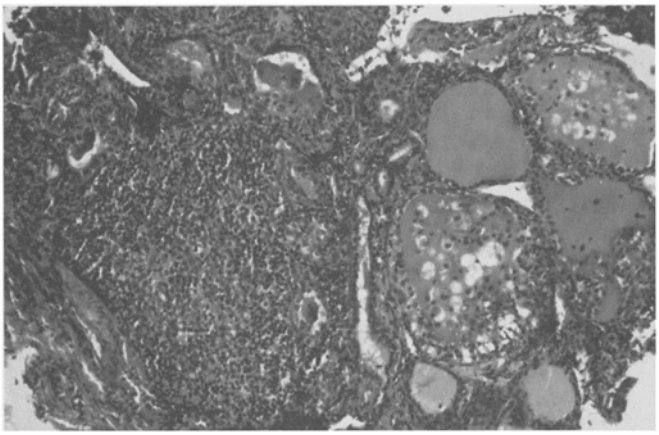


Fig. 10. Lymphocytic thyroiditis. Focal heavy lymphocytic infiltrate with follicles showing degenerative changes characterized by swelling of lining follicular cells and inflammatory infiltration.

Differential Diagnosis

- Hashimoto's thyroiditis:
  - Larger, more numerous lymphoid follicles and scattered plasma cells and histiocytes
  - Significant follicular changes with extensive atrophy and Hürthle cell change
- Grave's disease:
  - Associated with hyperthyroidism
  - Follicles are hyperplastic

Hashimoto's Thyroiditis

Clinical

- Autoimmune thyroiditis caused by autoantibodies directed against thyroglobulin, thyroid stimulating hormone

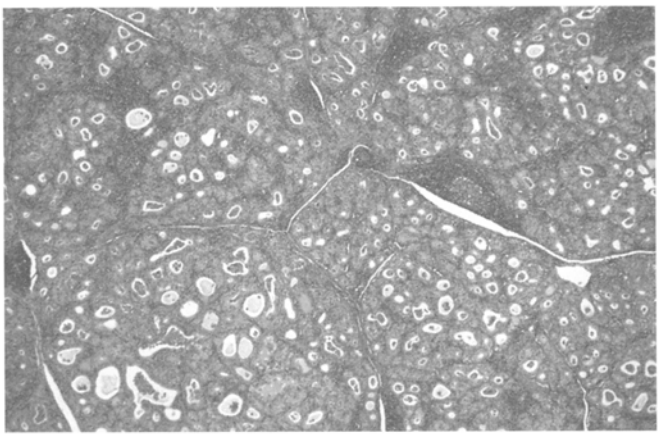


Fig. 11. Hashimoto's thyroiditis. The follicles are smaller than normal and lined by oxyphilic epithelium. There is a patchy lymphocytic infiltrate with germinal centers.

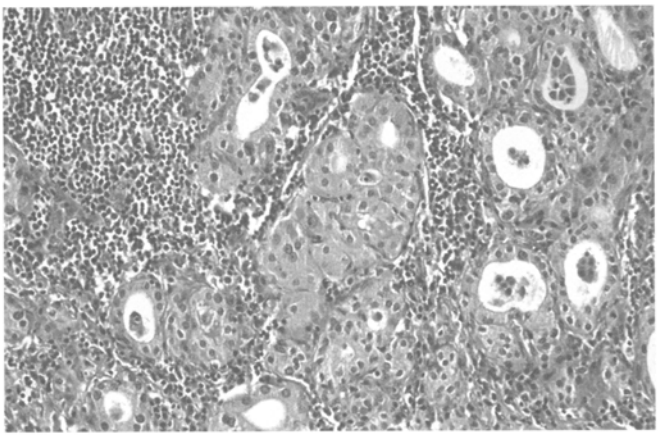


Fig. 12. Hashimoto's thyroiditis. Oxyphilic cells with granular cytoplasm together with a lymphocytic infiltrate.

receptors, and other follicular cell antigens, resulting in follicular damage

- Classically occurs in young to middle-aged females (30–50 years old; F : M = 10 : 1)
- Patients present with diffuse firm goiter, tenderness, and hyperthyroidism
- As the disease progresses, thyroid function decreases, eventually resulting in hypothyroidism
- A milieu of lymphocytic inflammation and regenerative hyperplasia results in increased risk of lymphoma, leukemia, and thyroid carcinoma
- May be associated with autoimmune disease of adrenals (Addison's disease), pancreas (diabetes), or stomach (pernicious anemia)

Macroscopic

- Diffuse firm enlargement
- Cut surface is soft and rubbery, vaguely nodular, with tan-gray appearance of hyperplastic lymphoid tissue

Microscopic ***(Figures 11,12)***

- Marked interstitial lymphocytic inflammation with prominent lymphoid follicles with germinal centers
- Small, atrophic thyroid follicles lined by oxyphilic epithelium (Hürthle cells)
- Scattered plasma cells (polyclonal) and histiocytes can be seen
- Interstitial fibrosis may accentuate lobular architecture
- Regenerative hyperplasia and squamous metaplasia may be seen

Variants

- Fibrosing Hashimoto's thyroiditis:
  - Represents ~10% of cases
  - Usually seen in elderly patients
  - Marked thyroid enlargement with some adhesion of gland to surrounding tissue (although surgical planes are readily identified)
  - Histologically shows extensive fibrosis, severe follicular atrophy with Hürthle cell change, and squamous metaplasia
  - Inflammatory cells include a mixture of lymphocytes and plasma cells
  - May be confused with Riedel's thyroiditis

Differential Diagnosis

- Lymphocytic thyroiditis:
  - Milder inflammation with scattered lymphoid follicles
  - Little or no reactive changes in thyroid follicles
- Grave's disease:
  - Follicles appear hyperplastic rather than atrophic

Graves' Disease

Clinical

- Autoimmune thyroiditis caused by autoantibodies directed against thyroid stimulating hormone receptors, resulting in chronic follicular stimulation and hyperthyroidism (diffuse toxic goiter)
- Seen in young females (20–40 years old; F : M = 4 : 1)
- Patients present with diffuse goiter and hyperthyroidism
- Thyroid studies show increased serum T3/T4 and decreased I^{131} uptake, with markedly depressed thyroid stimulating hormone

Macroscopic ***(Figure 13)***

- Mild to moderate diffuse enlargement with soft consistency and pink tan color

Microscopic ***(Figures 14–16)***

- Markedly hyperplastic follicles lined by active tall columnar cells showing clear, sometimes vacuolated, cytoplasm

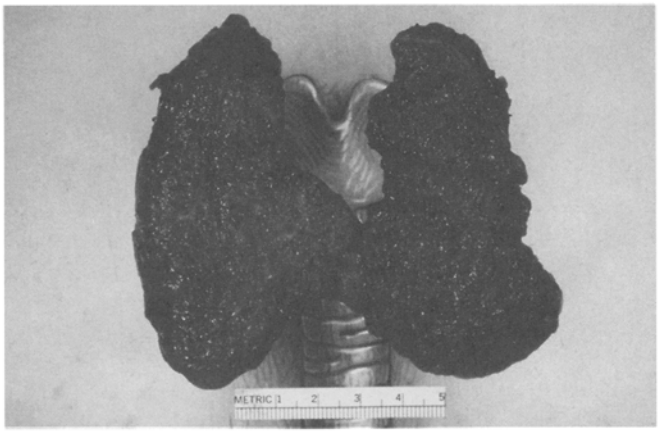


Fig. 13. Graves' disease. Enlarged thyroid (94 g) with a glistening, finely nodular cut surface.

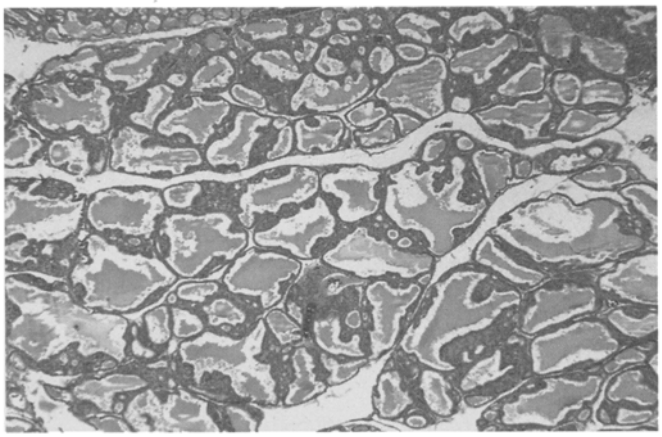


Fig. 14. Graves' disease. Irregularly shaped follicles are partially filled with pale colloid.

- Colloid appears pale and depleted, with scalloped edges at the epithelial border
- Epithelial hyperplasia results in papillary infolding of the follicles, resembling papillary carcinoma
- Interstitial lymphoid aggregates with germinal centers may be present
- Classic appearance is usually altered by preoperative medication:
  - Iodine therapy can greatly diminish hyperplasia, resulting in an almost normal-appearing gland
  - Propylthiouracil therapy increases hyperplasia

Differential Diagnosis

- Papillary thyroid carcinoma:
  - Presents as an expansile mass, rather than a diffuse process
  - Shows typical cytologic features (ground glass nuclei, nuclear grooves and nuclear pseudo inclusions)

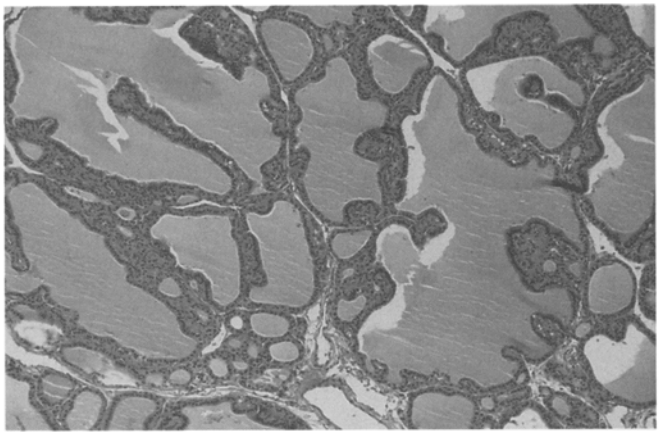


Fig. 15. Graves' disease. Follicles show multiple papillary infoldings and some scalloping of the colloid.

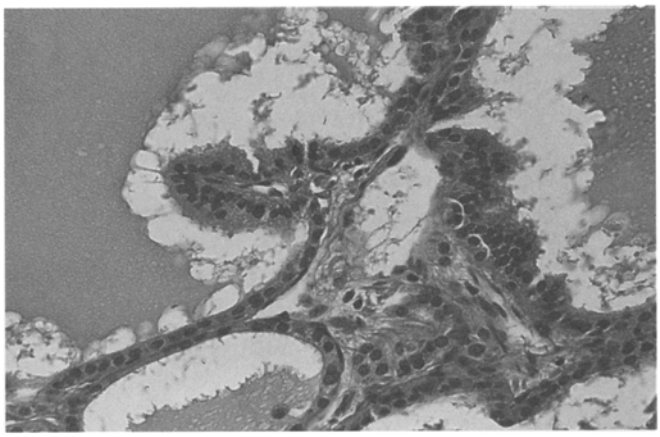


Fig. 16. Graves' disease. Cubical and low columnar eosinophilic epithelium lines follicles, one of which has a papillary infolding.

- Lymphocytic thyroiditis:
  - Young patients, usually euthyroid
  - Thyroid follicles appear normal or show only mild atrophy
- Hashimoto's thyroiditis:
  - Thyroid follicles show atrophy and Hürthle cell change, not hyperplasia

Nodular Hyperplasia

Clinical

- Hyperplastic process due to low dietary iodine (endemic goiter) or unknown causes (sporadic goiter)
- Synonyms: multinodular goiter, adenomatoid goiter, and adenomatous hyperplasia
- Endemic goiter:
  - Seen in regions with low environmental iodine, usually affecting entire population
  - Low iodine prevents adequate T3/T4 synthesis, leading to increased thyroid stimulating hormone secretion



Fig. 17. Nodular hyperplasia. Multiple degenerating and hemorrhagic nodules.

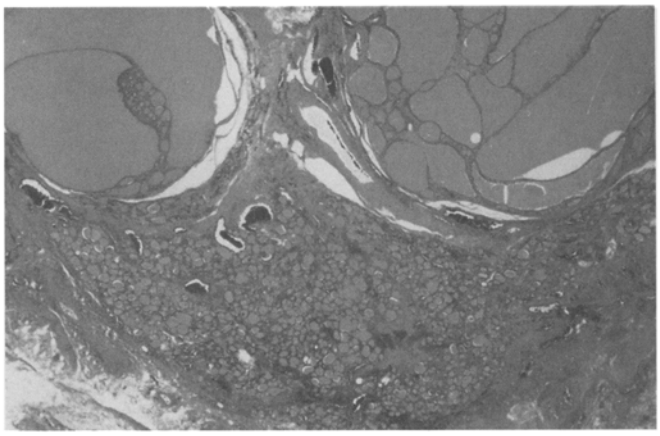


Fig. 18. Nodular hyperplasia. Macrofollicular nodule and colloid cyst in nodular hyperplasia.

- Increased circulating thyroid stimulating hormone (TSH) results in thyroid hyperplasia

♦ Sporadic goiter:
- Seen commonly in United States; ~5% incidence
- Exact etiology unknown, but pathogenesis probably similar to endemic form (inadequate T3/T4 secretion)
- May be due to more subtle abnormality in thyroid hormone synthesis, iodine metabolism, or other hormonal factors

♦ Majority of patients are euthyroid, presenting with symptoms of multinodular thyroid enlargement, which may be generalized or have dominant nodule

♦ Degenerative changes within nodules may result in pain and tenderness

♦ Nodules associated with hyperplasia tend to show increased I^{131} uptake

♦ Does not appear to be associated with increased risk of carcinoma

Macroscopic ***(Figure 17)***

♦ Gland enlarged and its normal smooth symmetrical appearance distorted by multiple nodules of varying size

♦ Larger nodules typically show degenerative changes typified by cysts, hemorrhage, and calcification

Microscopic ***(Figure 18)***

♦ Many nodules of different sizes, some encapsulated

♦ May be quite varied in composition:
- Highly cellular, with numerous small follicles
- Huge cystic follicles containing abundant colloid and lined by flattened epithelium
- Large cystic structures showing hyperplastic areas of follicles or papillary structures (foci of secondary proliferation)

♦ Hyperplasia may show varying degrees of Hürthle cell change

♦ Granulomatous inflammation may result from ruptured follicles

♦ Degenerative changes with hemorrhage, fibrosis, and calcification are seen in most cases

Differential Diagnosis

♦ Follicular adenoma:
- Usually single and completely encapsulated
- Microscopically, the nodule is composed of variably-sized, fairly uniform follicles that differ in appearance from the surrounding thyroid tissue
- Compresses surrounding tissue

♦ Follicular or papillary thyroid carcinoma:
- Tends to be solitary lesion, rather than multicentric process
- Microscopically, will show evidence of capsular or vascular invasion (follicular carcinoma) or diagnostic nuclear features (papillary carcinoma)

C Cell Hyperplasia

Clinical

♦ Hyperplasia of C cells seen in association with (and thought to be precursor of) medullary thyroid carcinoma

♦ Commonly associated with multiple endocrine neoplasia (MEN) Types 2A and 2B and familial medullary thyroid carcinoma

Macroscopic

♦ Not grossly evident

Microscopic ***(Figures 19,20)***

♦ Usually located at junction of upper and middle one-thirds of central portion of lateral lobes

♦ Interfollicular or intrafollicular clusters of C cells, numbering more than six cells per follicle

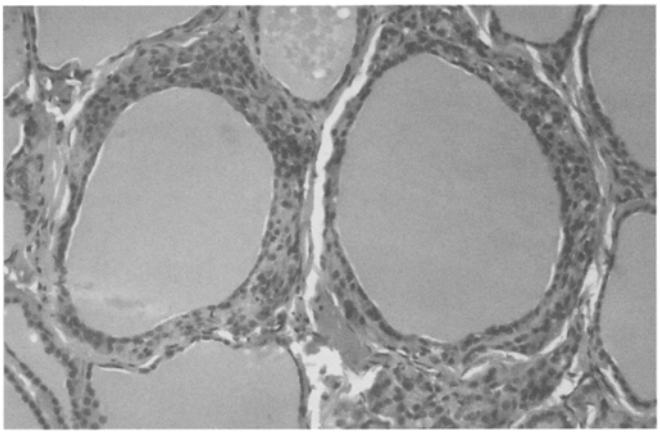


Fig. 19. C cell hyperplasia. Two follicles each exhibit a collar of sharply demarcated C cells.

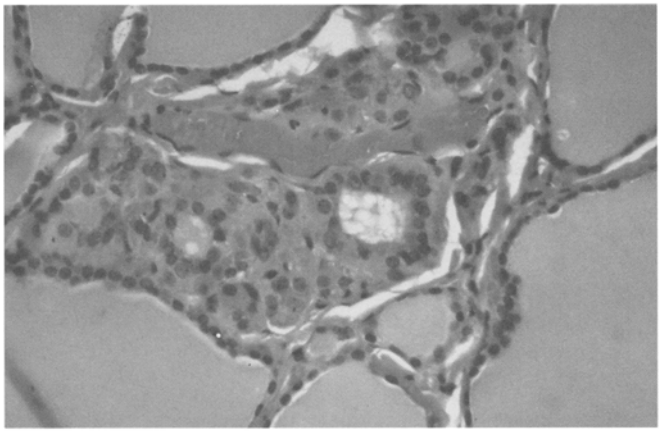


Fig. 20. C cell hyperplasia. C cells with ample slightly basophilic cytoplasm surrounding and between thyroid follicles.

- More rigid criteria require presence of expansile nodules of C cells
- No host fibrotic reaction

Immunohistochemistry

- Immunophenotype essentially same as for normal C cells:
  - Immunoreactive for calcitonin, low-molecular-weight cytokeratin (LMWK), synaptophysin, chromogranin, and carcinoembryonic antigen
- Hyperplastic C cells tend to show greater carcinoembryonic antigen immunoreactivity than normal C cells

Differential Diagnosis

- Reactive C-cell hyperplasia:
  - May be found in lymphocytic thyroiditis, secondary hyperparathyroidism, or adjacent to thyroid neoplasms (in these cases, significance of lesions in patients without family history or any other evidence of familial endocrine neoplasia is unknown)

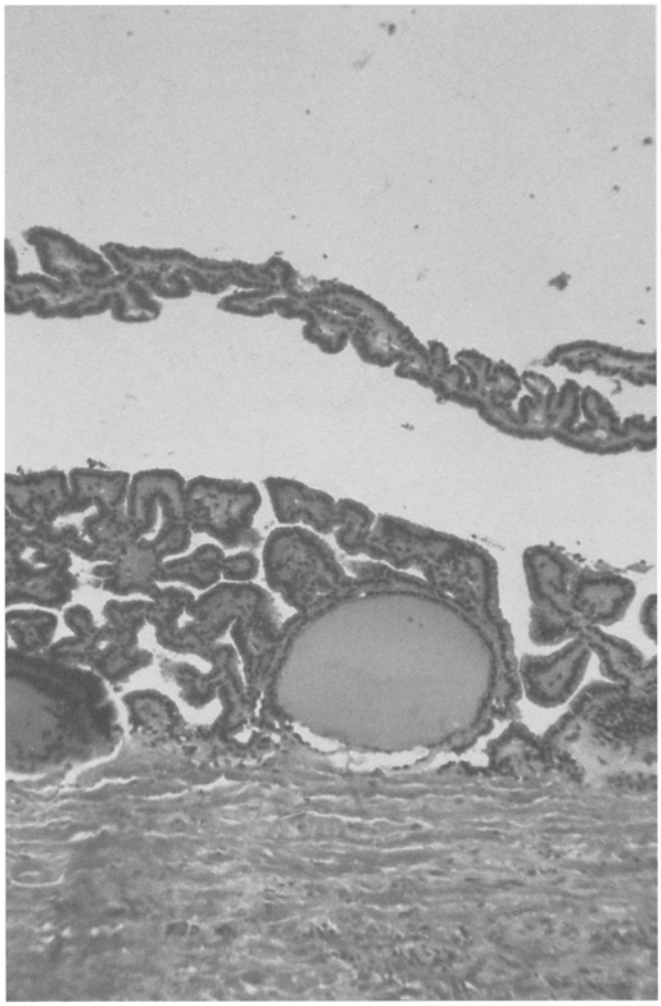


Fig. 21. Hyperplastic (papillary) adenoma. Cystic hyperplastic adenoma surrounded by a thick fibrous capsule.

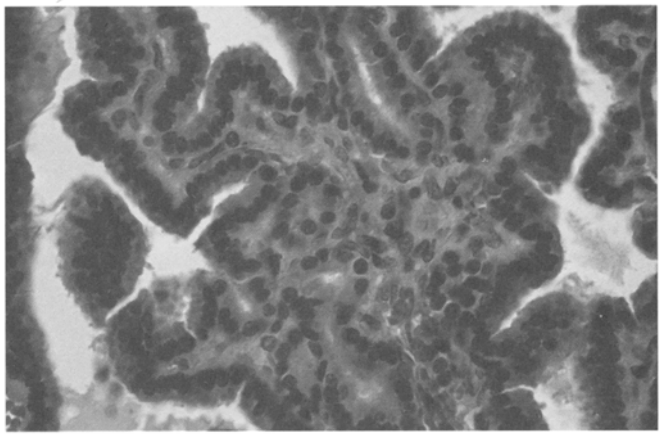


Fig. 22. Hyperplastic (papillary) adenoma. Papillations are lined by a uniform epithelium with basal hyperchromatic nuclei.

Table 1. Immunohistochemical Profiles of Thyroid Tumors

	Follicular adenoma	*Papillary carcinoma*	*Follicular carcinoma*	*Insular carcinoma*	*Anaplastic carcinoma*	*Hurthle cell tumor*	*Medullary carcinoma*
LMWK	+	+	+	+	+/–	+/–	+
HMWK	–	–/+	–	–	–/+*	–	–
Thyro globulin	+	+	+	+	–	+/–	–
EMA	+	+	+	–	–/+*	–	–
CEA	–	–/+	–	–	–/+*	–/+	+
CG	–	–	–	–	–	–	+
SYN	–	–	–	–	–	–	+
Calcitonin	–	–	–	–	–	–	+
S-100 protein	–	–/+	–	–	–	–/+	–

Note: LMWK = low-molecular-weight cytokeratin, HMWK = high-molecular-weight cytokeratin, EMA = epithelial membrane antigen, CEA = carcinoemhryonic antigen, CG = chromogranin, SYN = synaptophysin.

**Reactivity seen in areas of squamoid or other epithelial differentiation.*

Neoplasms

Benign Tumors

Follicular Adenoma

Clinical

- Neoplasm composed of benign thyroid follicles
- General incidence 5% to 10% of population
- More common in women
- Patients present with palpable nodule or asymmetrical thyroid enlargement
- Patients are typically euthyroid, although some cases are associated with hyperthyroidism ("toxic adenomas")
- Tumor usually shows little or no I^{131} uptake

Macroscopic

- Single encapsulated nodule, 1–3 cm in size
- Appearance of cut surface varies from gray-tan to pink and fleshy, depending on cellularity and colloid content
- Larger examples commonly show hemorrhage, cyst formation, fibrosis, and calcification

Microscopic

- Demonstrates complete capsule and compression of surrounding thyroid tissue
- A variety of growth patterns may be seen within the nodule (either as single pattern or mixture):
  - Follicles, ranging from tiny (microfollicular) to large and cystic (macrofollicular)
  - Areas of trabecular or solid growth
  - Focal hyperplasia with papillary or pseudopapillary architecture **(Figures 21,22)**
- Growth pattern of cells within nodule classically stand in sharp contrast to appearance of normal thyroid parenchyma outside capsule
- Rare examples may have clusters of cells with large hyperchromatic nuclei

Immunohistochemistry

- Similar to that of normal thyroid follicular cells; immunoreactive for thyroglobulin and LMWK (*see* **Table 1**)

Variants

- Hürthle cell adenoma:
  - Composed largely of Hürthle cells
- Hyperplastic (papillary) adenoma:
  - Prominent secondary hyperplastic changes result in predominantly papillary pattern of growth
- Hyalinizing trabecular adenoma **(Figures 23,24)**:
  - Features trabecular growth pattern with prominent intratrabecular hyaline material
  - Nuclei are similar to those of papillary carcinoma and occasional psamomma bodies may be seen
  - Low power view may resemble neuroendocrine neoplasm (paraganglioma or medullary thyroid carcinoma)
  - Immunoreactive for thyroglobulin and occasionally for chromogranin; no immunoreactivity for calcitonin



Fig. 23. Hyalinizing trabecular adenoma. Well circumscribed, solid, tan tumor.

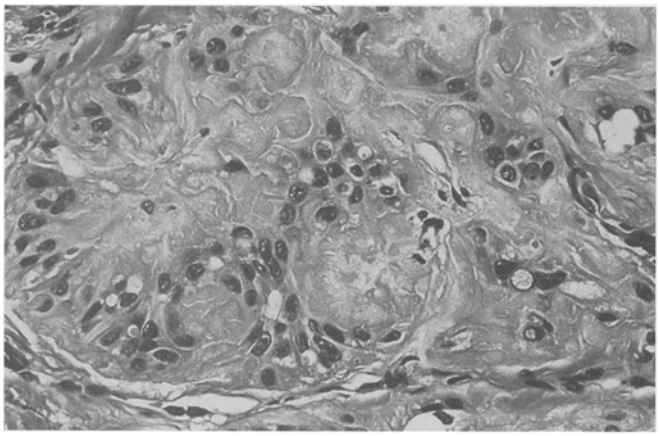


Fig. 24. Hyalinizing trabecular adenoma. Abundant intratrabecular hyaline material. Nuclei are polymorphic, many are oval. Intranuclear and cytoplasmic inclusions are present.

Differential Diagnosis

- Papillary or follicular thyroid carcinoma:
  - Evidence of capsular or vascular invasion or both
  - May also have increased mitoses and nuclear pleomorphism
  - Papillary carcinoma infrequently has a trabecular pattern
  - Does not feature formation of hyalin among tumor cells and is usually invasive
- Nodular hyperplasia:
  - Although a dominant nodule may be present, it is usually incompletely encapsulated
  - Surrounding thyroid shows hyperplastic changes similar to those seen within the nodule

Hürthle Cell Adenoma

Clinical

- Benign thyroid neoplasm composed of large follicular cells with granular eosinophilic cytoplasm
- Females affected more commonly than males
- Average age = 45 for adenoma and 55 for carcinoma
- Tumor usually shows little or no I^{131} uptake

*Macroscopic **(Figure 25)***

- Usually solid tumor with the typical brown cut surface seen in other oncocytic tumors
- Areas of hemorrhage, cyst formation, or calcification may be seen in larger tumors

*Microscopic **(Figures 26,27)***

- At least 75% of neoplasm composed of Hürthle cells
- Usually shows follicular growth pattern, although solid or papillary patterns also seen
- Characteristic polygonal cells with round regular nuclei with inconspicuous nucleoli and granular eosinophilic cytoplasm
- Some areas may show atypical nuclear features with occasional bizarre nuclei

Immunohistochemistry

- Immunoreactive for thyroglobulin, although staining not as strong as other thyroid follicular neoplasms
- Staining for carcinoembryonic antigen, S-100 protein, and HMB-45 protein also reported

Differential Diagnosis

- Follicular adenoma:
  - May show focal Hürthle cell features
- Follicular carcinoma:
  - May show Hürthle cell features
- Papillary carcinoma:
  - May show focal Hürthle cell features
  - Typical nuclear features (nuclear grooves, nuclear cytoplasmic inclusions, etc.)

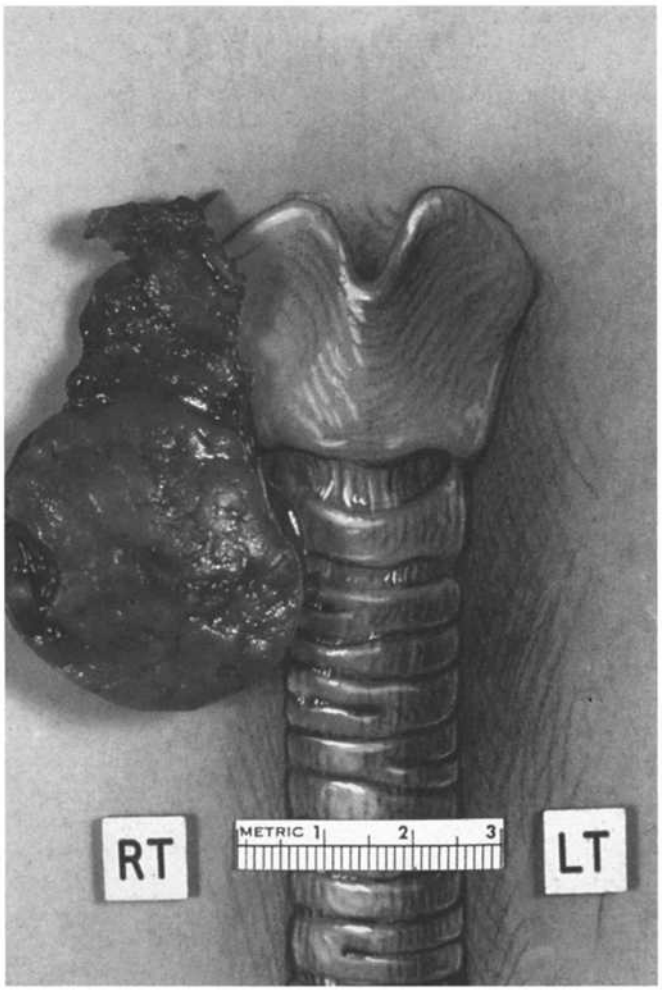


Fig. 25. Hürthle cell adenoma. Circumscribed slightly lobulated tan-colored tumor.

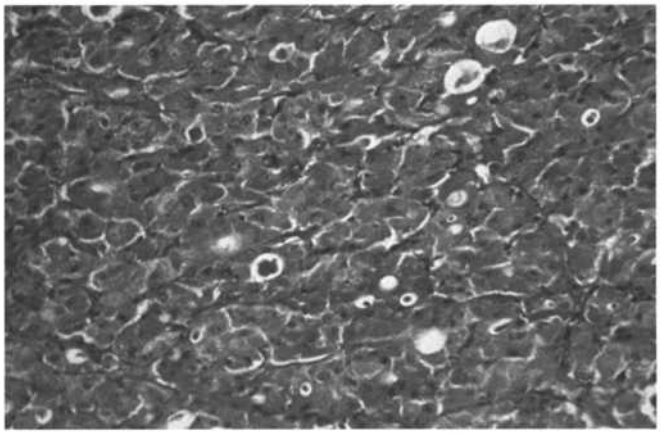


Fig. 26. Hürthle cell adenoma. Solid tumor composed of cells with eosinophilic cytoplasm and some follicle formation.

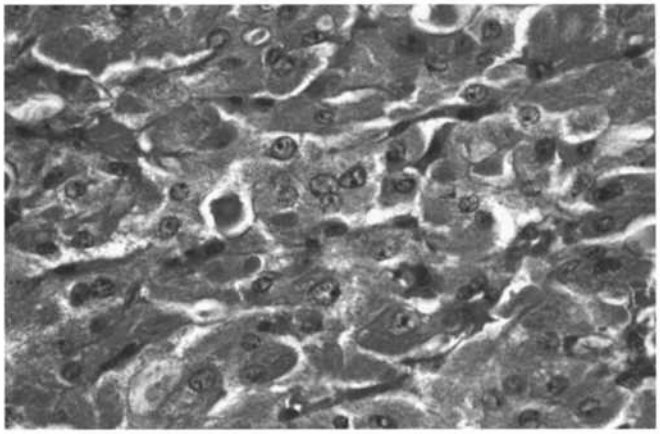


Fig. 27. Hürthle cell adenoma. Large, poorly demarcated cells with granular eosinophilic cytoplasm and vesicular nuclei with prominent nucleoli.

- Hashimoto's thyroiditis:
  - May show focal Hürthle cell features, but nearly always in background of lymphoplasmacytic inflammation (with lymphoid follicles), fibrosis, and atrophy

Malignant Tumors

Papillary Carcinoma

Clinical

- Low-grade carcinoma representing most common thyroid malignancy in both adults and children
- Average age = 40 years
- Females affected more commonly than males
- Tumor usually shows little or no I^{131} uptake
- Associated with radiation exposure and Hashimoto's thyroiditis
- Tends to spread by lymphatic route; at diagnosis, **33%** have lymph node metastases
- Prognosis generally very good, but related to:
  - Age: most deaths are in patients over 40
  - Stage: extrathyroidal extension has worse prognosis, distant metastases are worse still
  - Sex: males have slightly worse prognosis
  - Tumor size: larger tumors have a worse prognosis
  - Encapsulated tumors have better prognosis
  - Tumors with anaplastic or squamous foci have much worse prognosis
  - Variant: see below

Macroscopic

- Variably sized, from microscopic to >10 cm, usually 2–3 cm
- Appears as solid, white, infiltrating masses, often with granular cut surface
- Capsule, if present, is usually incomplete
- May undergo significant cystic degenerative changes

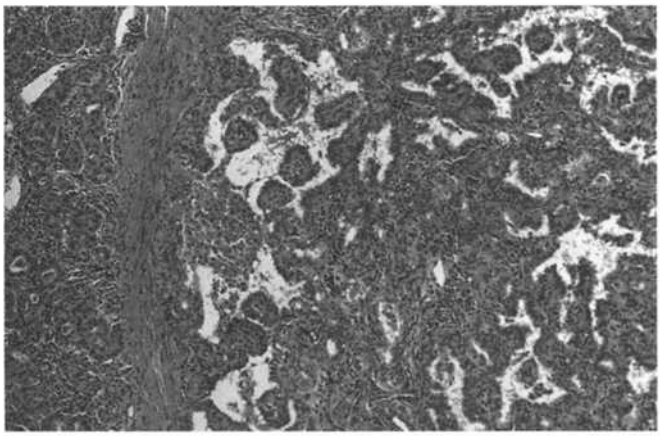


Fig. 28. Papillary carcinoma. The tumor has papillary and follicular components separated by a fibrous band.

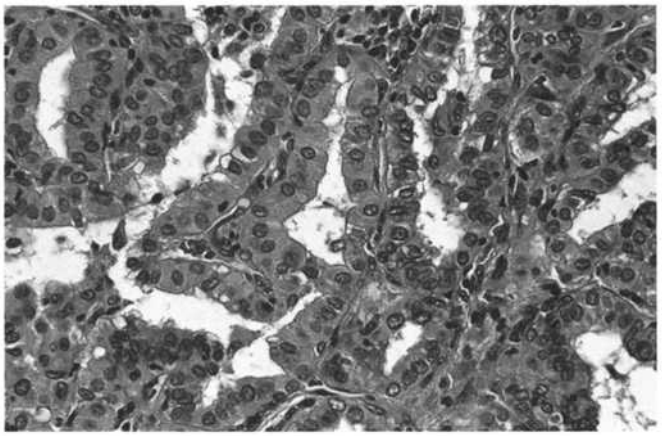


Fig. 29. Papillary carcinoma. Papillary processes with capillary cores mantled by medium-sized cells with eosinophilic cytoplasm and slightly irregular open nuclei with occasional grooves.

Microscopic ***(Figures 28,29)***

- Composed of large masses of complex papillae with single layer or stratified epithelial cells supported by branching fibrovascular cores
- Features of high-grade malignancy (increased mitoses, necrosis, vascular invasion) typically absent
- General papillary architecture may blend with variable component of follicular or solid growth
- Diagnostic nuclear features include:
  - Ground glass nuclei (large optically clear nuclei that tend to overlap)
  - Nuclear grooves (due to folded nuclear membrane)
  - Nuclear pseudoinclusions (due to intranuclear cytoplasmic invagination)
- Psammoma bodies (laminated basophilic bodies) occur in 50% of cases
- Significant number of cases (25% to 75% depending on sampling) show multiple tumor foci

Immunohistochemistry

- Similar to that of normal thyroid follicular cells
- Immunoreactive for thyroglobulin, thyroid transcription factor (TTF-1) and LMWK (*see* **Table 1**)
- May show areas of high-molecular-weight cytokeratin (HMWK) expression

Variants

- Encapsulated variant:
  - Tumor completely surrounded by capsule
  - Although regional nodal metastasis is seen, widespread metastases and death are very rare
  - May be confused with adenoma or hyperplastic nodule
- Papillary microcarcinoma:
  - Papillary carcinoma measuring <1 cm
  - May appear similar to typical papillary carcinoma or have features of sclerosing variant
  - Prognosis similar to that of encapsulated variant
- Follicular variant:
  - Growth pattern follicular rather than papillary
  - Differentiation from follicular carcinoma depends on finding diagnostic nuclear features and areas of papillary growth.
  - Metastatic tumor resembles classic papillary carcinoma
  - Prognosis similar to classic papillary carcinoma
- Diffuse sclerosing variant:
  - Marked fibrosis with lymphocytic infiltrate, extensively involving much of thyroid
  - Thyroid diffusely abnormal, with no dominant tumor evident
  - Numerous psammoma bodies
  - Areas of squamous metaplasia
  - Nodal and distant metastases common
  - Worse prognosis than classic papillary carcinoma
  - May be mistaken for Hashimoto's thyroiditis

Differential Diagnosis

- Follicular carcinoma:
  - May resemble follicular variant of papillary carcinoma
  - Does not show focal papillary architecture or specific nuclear features (nuclear grooves, intranuclear cytoplasmic inclusions)
- Follicular adenoma:
  - Areas of reactive hyperplasia within cysts may show papillary features
  - Papillary growth focal and lacks typical nuclear features

- Graves' disease:
  - Areas of reactive hyperplasia within cysts may show papillary features
  - Papillary growth focal and lacks typical nuclear features
- Hashimoto's thyroiditis:
  - May resemble diffuse sclerosing variant due to fibrosis, inflammation, and squamous metaplasia
  - Carcinoma will show other features of malignancy, such as invasion or nuclear changes

Follicular Carcinoma

Clinical

- Malignant thyroid neoplasm with follicular differentiation but without features of other follicular-derived thyroid malignancies (e.g., papillary carcinoma or Hürthle cell neoplasm)
- Usually presents as single palpable neck mass; patients may present with metastases
- Higher incidence in iodine-deficient regions
- Average age = 50 years
- Females affected more commonly than males
- Tumor usually shows little or no I^{131} uptake

Macroscopic

- Variable tumor appearance, ranging from encapsulated nodule (similar to adenoma) to poorly circumscribed mass with gross invasion of blood vessels and surrounding thyroid tissue
- Cut surface usually appears similar to follicular adenoma (gray-tan to pink and fleshy), with possible areas of hemorrhage or cyst formation

*Microscopic **(Figures 30,31)***

- Can be very difficult to distinguish encapsulated forms from follicular adenoma
- Malignancy determined by:
  - Vascular invasion (clusters of malignant cells covered with endothelium within and attached to wall of venules located in and outside tumor, usually near capsule)
  - Capsular invasion (penetration of full thickness of capsular wall)
- Increased mitotic activity (including atypical mitoses), widespread nuclear pleomorphism, and necrosis are also helpful features
- Growth pattern varies from well-differentiated follicular to solid or trabecular pattern; cribriform areas may also be seen
- Psamomma bodies, squamous metaplasia, and nuclear features of papillary carcinoma are not seen

Immunohistochemistry

- Similar to that of normal thyroid follicular cells
- Immunoreactive for thyroglobulin, thyroid transcription factor (TTF-1) and LMWK (*see* **Table 1**)

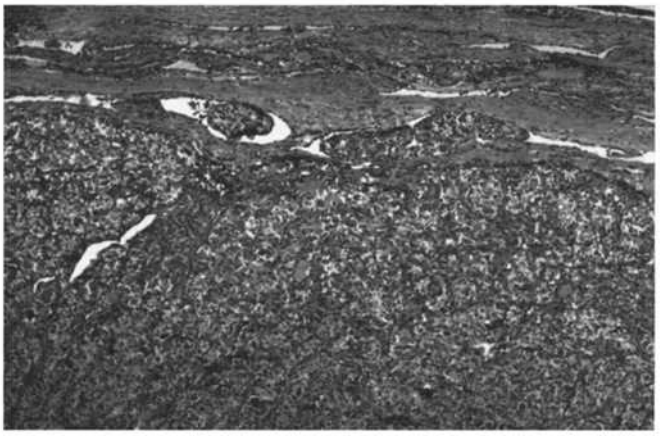


Fig. 30. Follicular carcinoma. The tumor shows invasion of a capsular blood vessel.

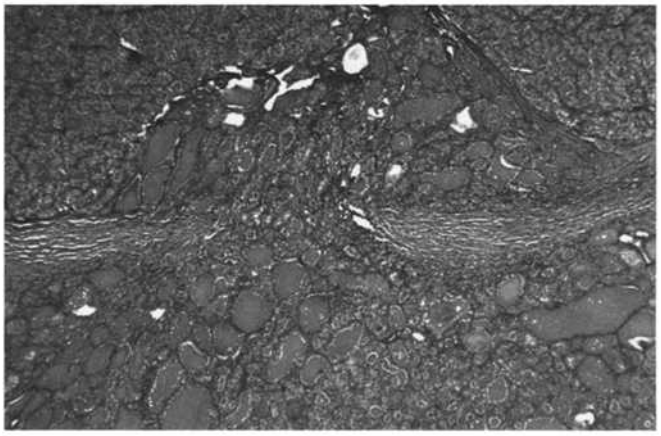


Fig. 31. Follicular carcinoma. The tumor has mushroomed through the wall of its fibrous capsule.

Variants

- Minimally invasive follicular carcinoma:
  - Grossly encapsulated
  - Usually shows microfollicular or trabecular growth pattern
  - Malignant features usually limited to foci of capsular and/or vascular invasion
  - Metastases occur in <5% and <1% of cases with vascular invasion and capsular invasion only, respectively
- Widely invasive follicular carcinoma:
  - Grossly non-encapsulated and infiltrative
  - Microscopically, shows extensive invasion of blood vessels and surrounding thyroid
  - Metastases occur commonly, usually to bones and lungs

Differential Diagnosis

- Follicular adenoma:
  - Shows similar encapsulation and growth patterns but no invasion

- Capsules of adenomas, on average, tend to be thinner than those of carcinomas
- The effects of fine-needle aspiration on an adenoma may mimic capsular invasion, but areas of hemorrhage and stromal repair should be evident

♦ Papillary carcinoma, follicular variant:
- Usually shows foci with some papillary differentiation
- Typical nuclear features (nuclear grooves, nuclear cytoplasmic inclusions, etc.)

Insular Carcinoma

Clinical

♦ Poorly differentiated thyroid carcinoma
♦ Average age = 55 years
♦ Patients usually present with palpable neck mass.
♦ Tumor usually shows good I^{131} uptake
♦ Relatively poor prognosis with lymph node and distant metastases common

Macroscopic

♦ Usually large (>5 cm) non-encapsulated tumor with infiltrative margins
♦ Cut surface usually pale gray-white, with areas of necrosis and calcification

Microscopic

♦ Distinctive nesting (insular) pattern of growth, reminiscent of carcinoid and medullary carcinoma
♦ Nests composed of sheets of cells with some micro-follicles
♦ Small uniform cells with mild to moderate nuclear pleomorphism
♦ Additional features may include increased mitotic rate and necrosis
♦ Growth may be in characteristic "peritheliomatous" pattern with extensive necrosis and preservation of viable cells around vessels

Immunohistochemical

♦ Similar to that of normal thyroid (immunoreactive for thyroglobulin and LWMK) (*see* **Table 1**)

Differential Diagnosis

♦ Medullary thyroid carcinoma:
- Cells tend to be more varied in morphology, with mixtures of round, polygonal, or spindled cells
- Atypical nuclear features, mitoses, and necrosis less prominent
- Immunostaining shows expression of calcitonin and neuroendocrine markers

♦ Follicular carcinoma (with solid or trabecular growth):
- Atypical nuclear features, mitoses, and necrosis less prominent features
- More typical areas of follicular growth normally seen

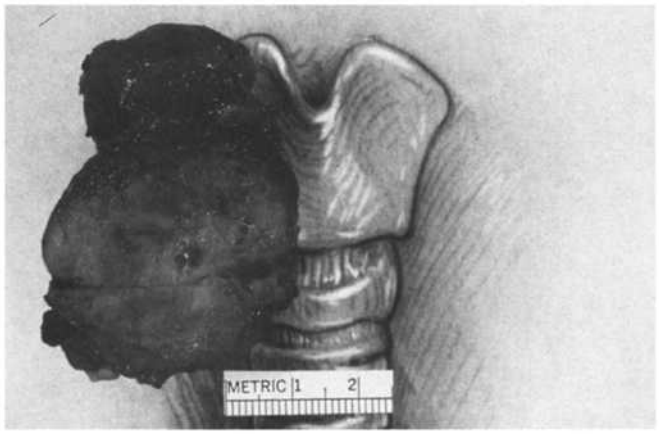


Fig. 32. Anaplastic carcinoma. The tumor occupies most of the right lobe of thyroid.

Anaplastic Carcinoma (Sarcomatoid Carcinoma)

Clinical

♦ Poorly differentiated thyroid carcinoma
♦ Seen in elderly patients
♦ Presents as rapidly expanding mass with symptoms of regional invasion (dysphagia, dyspnea or dysphonia)
♦ Tumor usually fails to show I^{131} uptake
♦ Very poor prognosis; mean survival = 6 months

*Macroscopic (**Figure 32**)*

♦ Grossly invasive mass replacing thyroid and extensively involving regional neck structures
♦ Areas of hemorrhage and/or necrosis common

*Microscopic (**Figure 33**)*

♦ Variable patterns, sometimes seen in combination:
- Squamoid: atypical epithelial cells that may show areas of keratinization
- Giant cell (pleomorphic): large cells with bizarre nuclei
- Spindle cell: atypical spindle cells growing in fascicular or storifom patterns, similar to sarcoma

♦ Tumors may show areas of cartilaginous or osseous metaplasia, myxoid stroma, or multinucleated giant cells, or may have prominent vascular patterns
♦ Areas of typical papillary or follicular carcinoma may be seen; in cases where anaplastic pattern represents minority of tumor, prognosis is somewhat better

Immunohistochemistry

♦ Most cases show immunoreactivity for LMWK and vimentin in spindle cells
♦ Areas of squamoid differentiation may show variable immunoreactivity for HMWK, epithelial membrane antigen, and carcinoembryonic antigen
♦ Negative for thyroglobulin; focal immunoreactivity result of entrapped normal follicles

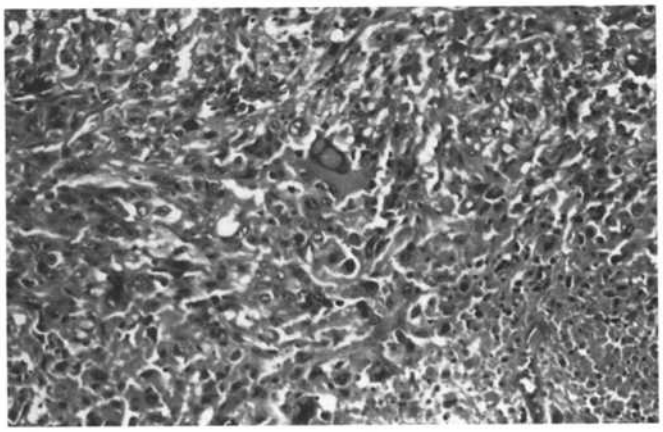


Fig. 33. Anaplastic carcinoma. Solid sheet of pleomorphic malignant cells with focal necrosis.

Differential Diagnosis

- Sarcoma:
  - Most cases of sarcomatous-appearing tumors of thyroid are, in fact, anaplastic carcinomas
  - May resemble malignant fibrous histiocytoma, angiosarcoma, hemangiopericytoma, or fibrosarcoma
  - Tumor should be extensively sampled to search for areas of epithelial differentiation
  - Cytokeratin immunoreactivity is very helpful in confirming a diagnosis of carcinoma

Hürthle Cell Carcinoma

Clinical

- Malignant thyroid neoplasm composed of large follicular cells with granular eosinophilic cytoplasm
- Females affected more commonly than males
- Average age 55
- Tumor usually shows little or no I^{131} uptake
- Has a relatively poor prognosis (5-year survival = 20–40%)

Macroscopic

- Usually solid tumor with typical brown cut surface seen in other oncocytic tumors
- Areas of hemorrhage, cyst formation, or calcification may be seen in larger tumors

Microscopic

- At least 75% of neoplasm composed of Hürthle cells
- Usually shows follicular growth pattern, although solid or papillary patterns may be seen
- Characteristic large polygonal cells with round nuclei with inconspicuous nucleoli and granular eosinophilic cytoplasm
- Areas may show atypical nuclear features with occasional bizarre nuclei
- Diagnosis of malignancy requires the same histologic findings as follicular carcinoma (vascular or capsular invasion)

Immunohistochemistry

- Immunoreactive for thyroglobulin, although staining not as strong as other thyroid follicular neoplasms (**Table 1**)
- Staining for carcinoembryonic antigen, S-100 protein, and HMB-45 protein have also been reported

Differential Diagnosis

- Follicular adenoma:
  - May show Hürthle cell features
- Follicular carcinoma:
  - May show Hürthle cell features
- Papillary carcinoma:
  - May show Hürthle cell features
  - Typical nuclear features (nuclear grooves, nuclear cytoplasmic inclusions, etc.)
- Hashimoto's thyroiditis:
  - Shows focal Hürthle cell features, but nearly always in a background of lymphoplasmacytic inflammation (with lymphoid follicles), fibrosis and atrophy

Medullary Carcinoma

Clinical

- Neuroendocrine carcinoma composed of malignant C cells (parafollicular cells)
- Commonly associated with multiple endocrine neoplasia Types 2A and 2B.
- Most tumors (80%) sporadic, usually presenting as solitary mass in patients in their fifth decade
- Tumor shows no I^{131} uptake
- Familial cases usually present earlier (mean age = 35), often as bilateral and multiple tumors
- An increasing number of cases are being detected as micro-tumors in closely monitored patients with family histories of multiple endocrine neoplasia
- May be associated with various ectopic hormone secretion syndromes (adrenocorticotrophic hormone, histamine, insulin, serotonin, etc.)

*Macroscopic **(Figure 34)***

- Non-encapsulated, firm gray mass, unilateral or bilateral

*Microscopic **(Figures 35–38)***

- Typically composed of round cells with granular amphophilic cytoplasm and round regular nuclei with coarse chromatin, growing in nests ("zellballen") separated by vascular septa and hyalinized collagen
- Tumor may show remarkable variety of growth patterns (trabecular, glandular, pseudo-papillary) and cell types (spindled, plasmacytoid, oncocytic, or squamoid)



Fig. 34. Medullary carcinoma. Poorly demarcated whitish tumor located at the upper pole of lateral lobe of thyroid. There is a degenerating adenoma in the mid-portion of the opposite lobe.

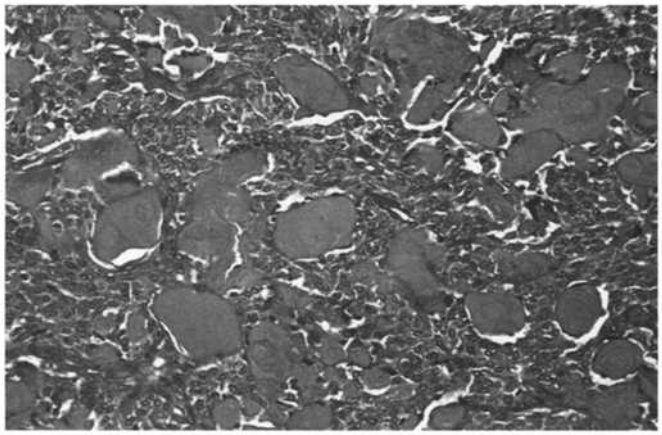


Fig. 35. Medullary carcinoma. Much solid, structureless eosinophilic material (amyloid) in a background of tumor cells without pattern.

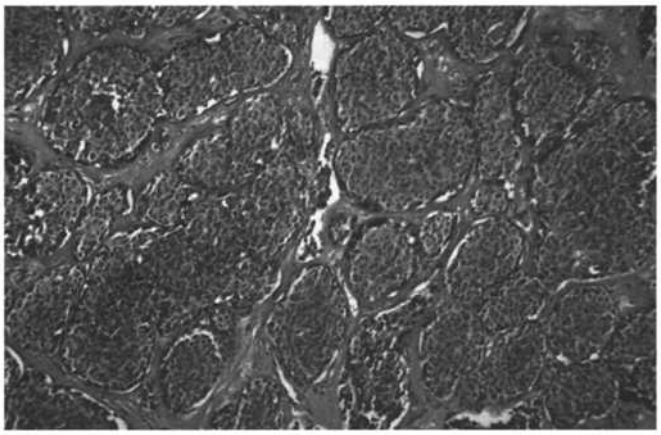


Fig. 36. Medullary carcinoma. Large aggregates of tumor cells create a carcinoid-like picture.

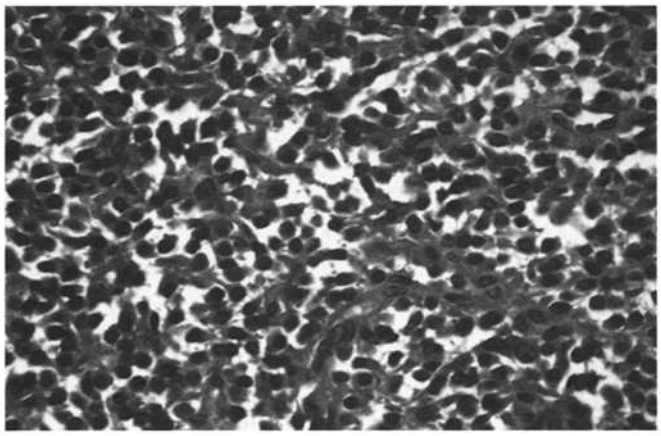


Fig. 37. Medullary carcinoma. Solid sheet of cells with eosinophilic cytoplasm and eccentric nuclei.

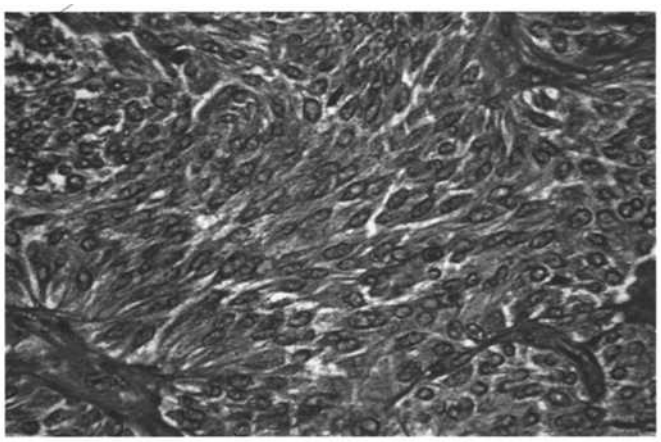


Fig. 38. Medullary carcinoma. Oval and spindling cells with vesicular nuclei.

- Amyloid (amorphous eosinophilic hyaline material) classically seen in stroma, although some tumors do not have any visible amyloid
- Calcification, sometimes coarsely laminated, may be present

Immunohistochemistry

- Immunoreactive for calcitonin, synaptophysin, chromogranin, cytokeratin, and carcinoembryonic antigen
- Usually – for thyroglobulin
- Amyloid stains positive with various reagents (cresyl violet, sulfated alcian blue) and demonstrates typical apple green birefringence with congo red under polarized light

Variants

- Variety of histologic architectures may be seen, including follicular, papillary, small cell, clear cell, giant cell, oncocytic, squamous, and melanotic

Differential Diagnosis

- Other thyroid carcinomas:
  - The wide spectrum of growth patterns seen in medullary carcinoma may lead to confusion with more common thyroid tumors (papillary, follicular, insular)
  - Atypical cell morphology or nuclear features may suggest the possibility of an unusual pattern of medullary carcinoma
  - Careful sampling of the entire tumor for more typical morphology and immunostaining is important in diagnosis
  - Other thyroid carcinomas are immunoreactive for thyroglobulin and negative for calcitonin
- Hyalinizing trabecular adenoma:
  - Intratrabecular hyaline material and nested growth pattern may resemble medullary carcinoma
  - Hyaline material – for amyloid
  - Tumor cells calcitonin – and immunoreactive for thyroglobulin

PARATHYROID GLAND

Non-Neoplastic Conditions

Parathyroid Cyst

Clinical

- Benign glandular cyst
- Usually asymptomatic and found incidentally
- No symptoms of hormone abnormality seen

*Macroscopic (**Figure 39**)*

- Solitary fluid-filled cyst, 1–6 cm in diameter
- Thin-walled
- Usually in inferior gland

*Microscopic (**Figure 40**)*

- Benign cyst lined by cuboidal epithelium with clear cytoplasm
- Associated adjacent normal parathyroid tissue

Differential Diagnosis

- Parathyroid adenoma:
  - Larger adenomas may undergo cystic degeneration
  - Clinical evidence of hyperparathyroidism usually seen
  - Surrounding tissue may show residual adenoma
- Thyroglossal duct cyst:
  - Seen in midline neck, usually at or above level of thyroid
  - Cyst wall usually demonstrates identifiable thyroid tissue
- Branchial cleft cyst:
  - Location classically antero-lateral neck
  - Lined by mixed squamous and respiratory epithelium

Chief Cell Hyperplasia

Clinical

- Diffuse parathyroid enlargement of all four glands due to autonomous hyperplasia (primary chief cell hyperplasia) or in response to chronically low serum calcium (secondary chief cell hyperplasia)
- Primary chief cell hyperplasia is commonly associated with multiple endocrine neoplasia Type I and IIA
- Secondary chief cell hyperplasia can be associated with kidney failure (renal loss of calcium) or calcium malabsorption

*Macroscopic (**Figure 41**)*

- Primary chief cell hyperplasia shows pronounced enlargement of all glands (up to 10 g each)
- Depending on degree of hypocalcemia, secondary chief cell hyperplasia is more variable in appearance, with glands ranging from normal size to significantly enlarged (up to 6 g each)

Microscopic (***Figure 42***)

- Hyperplasia principally of chief cells, although other cells types (oxyphil or water-clear) may be involved
- Cells typically grow in large hyperplastic nodules scattered throughout gland (nodular chief cell hyperplasia), giving it an irregular, asymmetrical appearance
- Diffuse growth pattern may be seen, especially in younger patients
- Other microscopic findings may include areas of fibrosis, acinar structures, or scattered atypical nuclear features (as in adenoma)

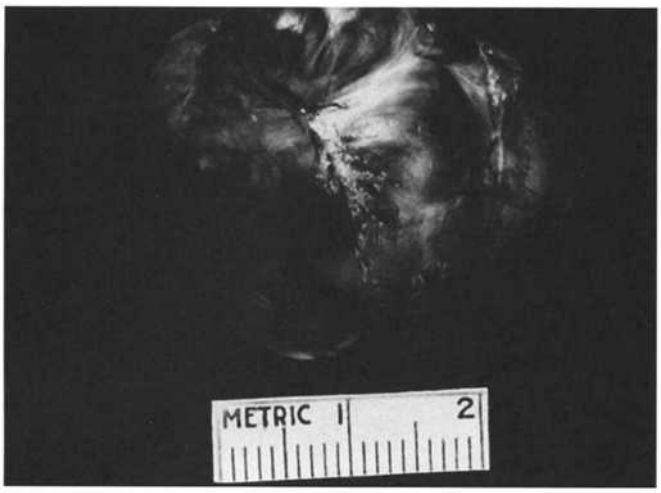


Fig. 39. Parathyroid cyst. Roughly spherical cyst with areas of ballooning of the cyst wall.

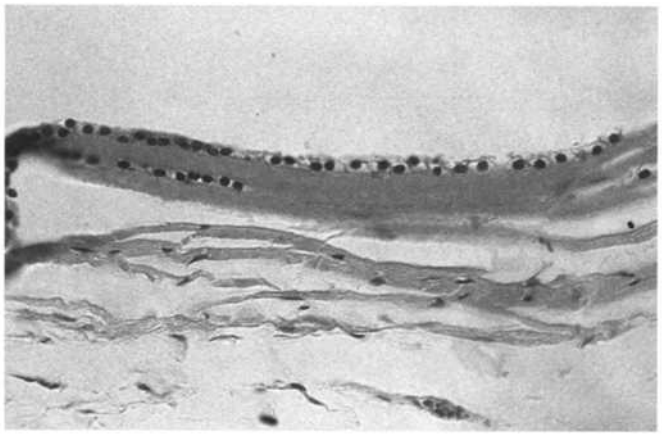


Fig. 40. Parathyroid cyst. The cavity is lined by cubical epithelium with clear cytoplasm.

- Distinction between primary and secondary chief cell hyperplasia cannot be made on morphologic grounds and is largely based on clinical findings

Variants

- Water-clear cell hyperplasia (**Figures 43,44**):
  - Rare sporadic variant of hyperplasia with marked parathyroid enlargement (combined weights may be >100 g) and associated primary hyperparathyroidism
  - Enlargement usually asymmetric, with upper glands considerably larger than lower pair
  - Cells are very large and ballooned, with finely vacuolated water-clear showing marked size variation and growing in alveolar pattern with delicate intervening stroma

Differential Diagnosis

- Parathyroid adenoma:
  - Enlargement involves only a single gland, with other glands usually appearing atrophic

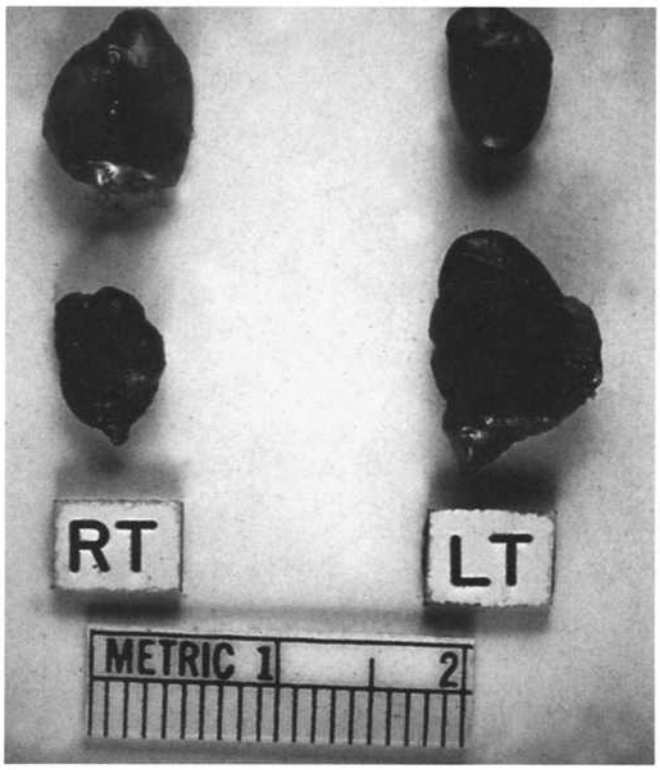


Fig. 41 Chief-cell hyperplasia. Four parathyroid glands are enlarged and together weigh 920 mg.

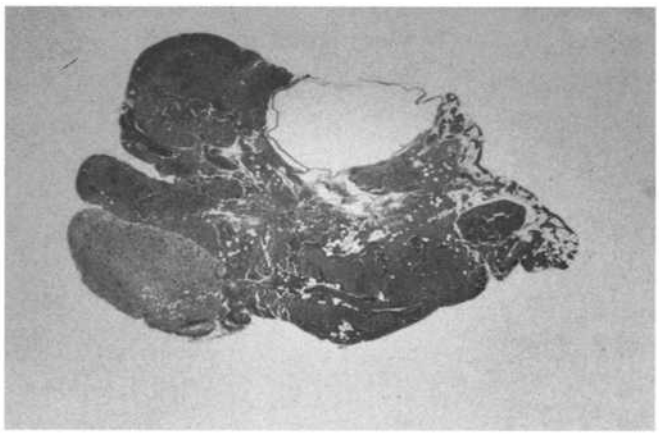


Fig. 42. Chief-cell hyperplasia. Hyperplastic parathyroid gland features multiple nodules and cyst.

  - Microscopically, shows an encapsulated expansive cellular nodule compressing normal, sometimes atrophic, parathyroid tissue

Tumors

Parathyroid Adenoma

Clinical

- Benign chief-cell neoplasm
- More common in women (F : M = 3 : 1)

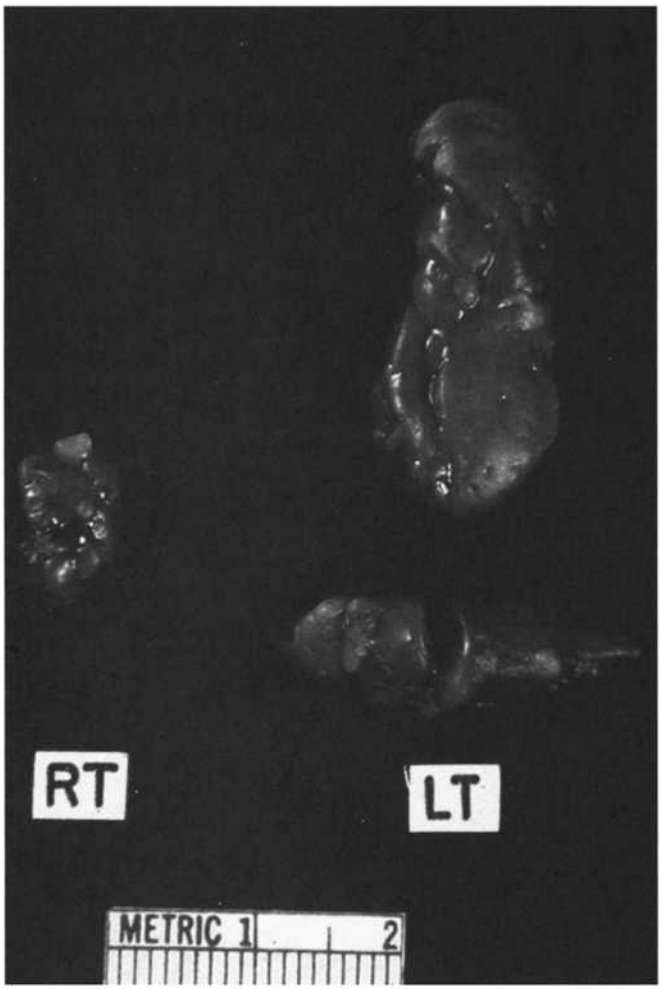


Fig. 43. Water-clear cell hyperplasia. Three glands are enlarged (the right superior and right inferior glands were fused). The cut surfaces are brown. Total parathyroid weight = 2.5 g.

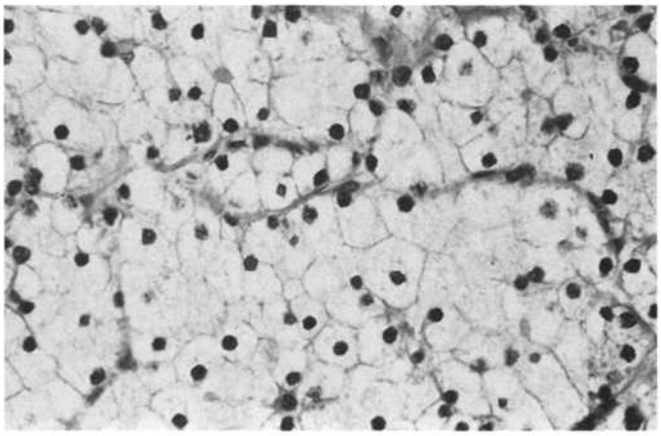


Fig. 44. Water-clear cell hyperplasia. Very large parathyroid cells with clear cytoplasm are sharply outlined and have generally central nuclei.



Fig. 45. Parathyroid adenoma. Cut surface of oval enlarged parathyroid gland is tan. Weight = 2.07 g.

- Usually too small and too soft to be found on physical examination
- Majority of tumors hormonally active; most patients present with symptoms of primary hyperparathyroidism (elevated serum calcium, bone loss)

Macroscopic ***(Figure 45)***

- Small, slightly lobulated nodules, with delicate capsules, weighing 0.5–5 g
- Smooth, shining exterior, without adjacent tissues attached
- Gray-brown in color, with soft, flabby consistency
- Other parathyroid glands appear normal or atrophic

Microscopic ***(Figures 46–49)***

- Encapsulated nodule of highly cellular parathyroid tissue
- Growth pattern is usually solid, but follicles or papillary structures can be seen
- Predominantly chief cells, but other cell types can be present
- Areas with nuclear pleomorphism can be seen
- Rare mitoses
- Remaining parathyroid tissue is compressed by the adenoma and may appear atrophic

Immunohistochemistry

- Identical to that of normal parathyroid chief cells

Variants

- Oxyphil adenoma:
  - Composed nearly entirely of oxyphil cells (**Figure 50**)
  - Usually non-functional
- Lipoadenoma (**Figures 51,52**):
  - Encapsulated nodular growth composed of islands or cords of chief cells separated by abundant mature-appearing adipose tissue

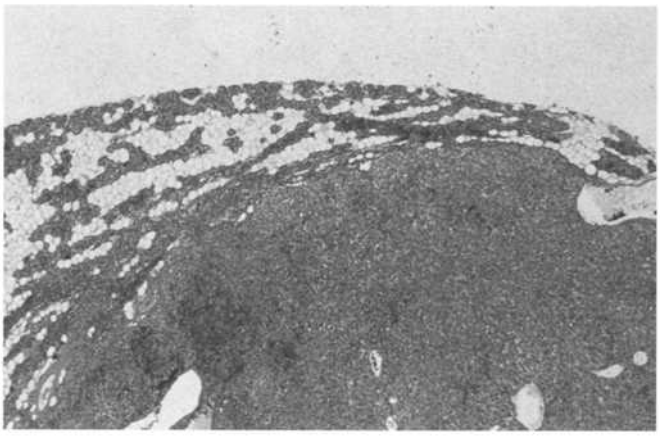


Fig. 46. Parathyroid adenoma. A mantle of normal parathyroid surrounds a sheet of adenoma cells.

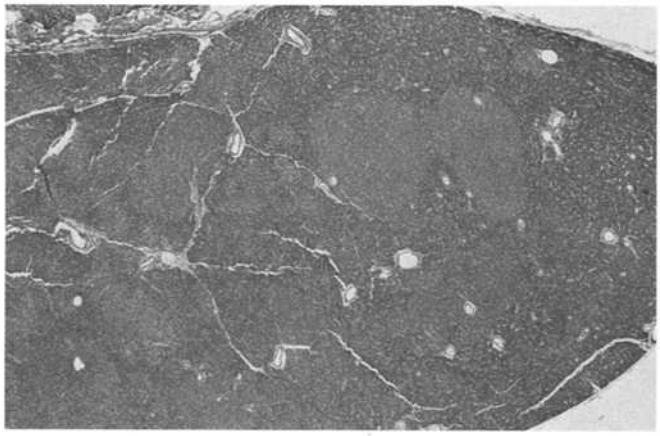


Fig. 47. Parathyroid adenoma. Tumor composed of chief cells features oxyphil cell nodules with eosinophilic cytoplasm.

Differential Diagnosis

- Parathyroid hyperplasia:
  - Involves all parathyroid glands
  - Microscopically, gland appears diffusely enlarged, with an even distribution of cellularity and adipose tissue
- Parathyroid carcinoma:
  - Can be very difficult to distinguish from adenoma
  - Clinical evidence of malignancy very important (palpable mass, vocal cord paralysis, adherence of gland to local structures, post-surgical recurrence)
  - Microscopic features of malignancy include fibrous bands, mitotic figures, and capsular or vascular invasion

Parathyroid Carcinoma

Clinical

- Malignant epithelial tumor composed of parathyroid chief cells

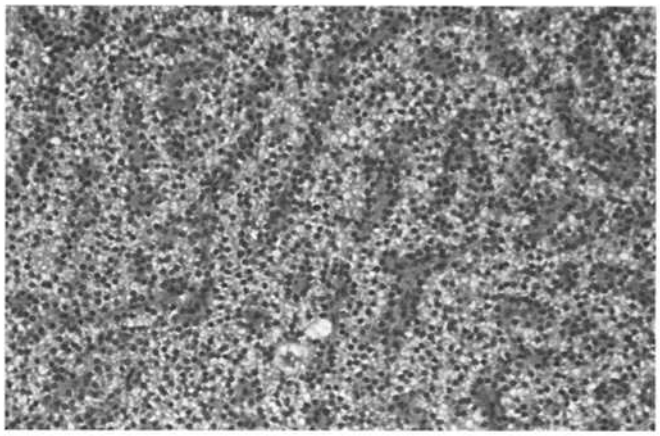


Fig. 48. Parathyroid adenoma. Adenoma features trabeculae of cells with clear cytoplasm and basal nuclei, supported by a delicate capillary network.

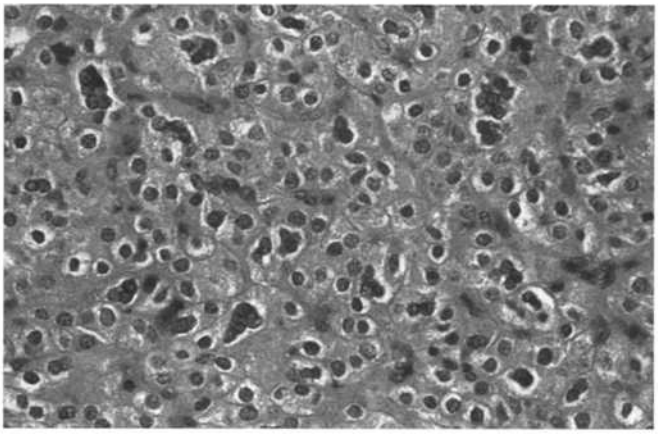


Fig. 49. Parathyroid adenoma. The adenoma features scattered multinucleated cells set in a background of cells with oxyphilic cytoplasm.

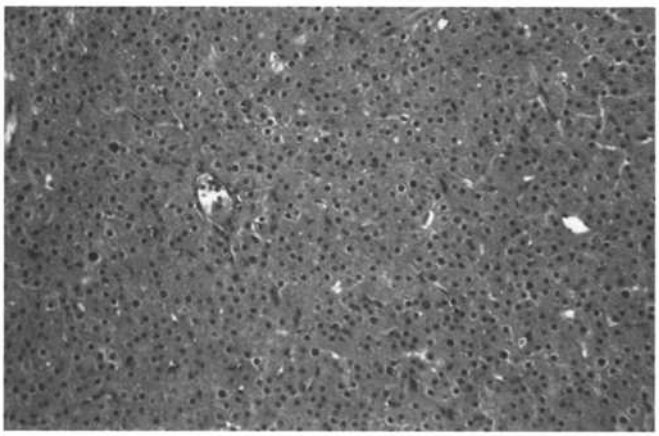


Fig. 50. Parathyroid adenoma. Oxyphil tumor with sharply outlined cells and clear granular eosinophilic cytoplasm.

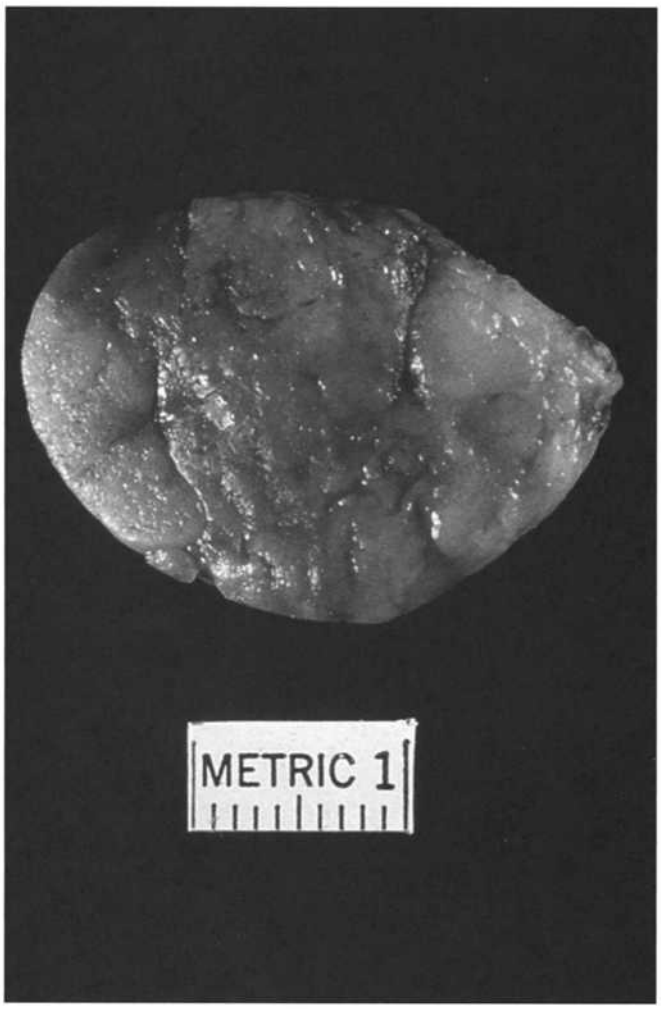


Fig. 51. Parathyroid lipoadenoma. Irregularly lobulated tumor with a yellow cut surface.

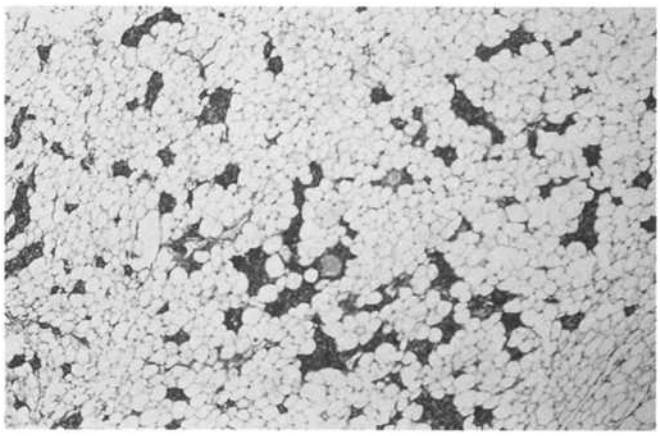


Fig. 52. Parathyroid lipoadenoma. Tumor is composed of an intimate mixture of mature fat and groups of parathyroid cells.



Fig. 53. Parathyroid carcinoma. Very ragged coarsely lobulated tumor.

- Similar to adenoma; majority of tumors hormonally active with patients usually presenting with symptoms of primary hyperparathyroidism (elevated serum calcium, bone loss)
- Additional clinical findings increase suspicion of malignancy:
  - Markedly elevated serum calcium
  - Palpable mass
  - Evidence of invasion (e.g., vocal cord paralysis)
- Prognosis generally good, although local recurrences common
- Death is usually a result of hypercalcemia rather than metastases

*Macroscopic **(Figure 53)***

- Gross appearance usually that of mass, firmly adherent to regional structures
- Tumor size ranges from 1–6 cm (mean = 3 cm) and weighs 1.5–30 g (mean 6.7 g)

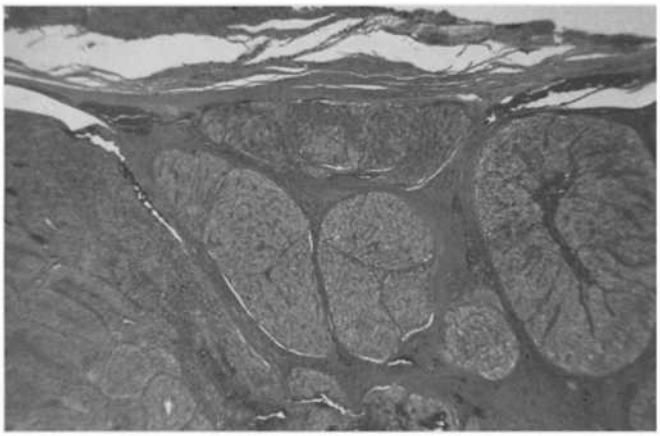


Fig. 54. Parathyroid carcinoma. Tumor composed of variable-sized masses of subtly invasive parathyroid cells.

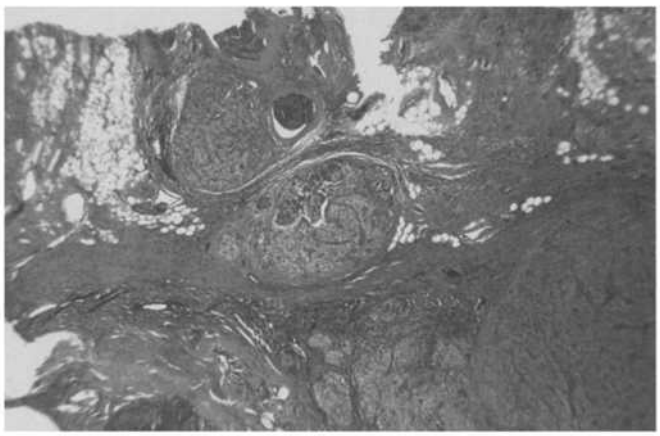


Fig. 55. Parathyroid carcinoma. Nodules of invasive tumor are present in the cervical fat.

*Microscopic **(Figures 54–56)***

- Often difficult to distinguish from adenoma because histologic features of malignancy may be focal and subtle
- Findings suspicious for malignancy include:
  - Solid or trabecular growth pattern
  - Dense fibrous bands

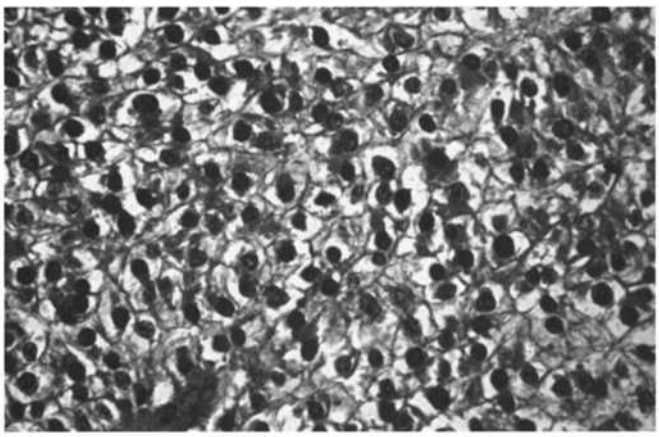


Fig. 56. Parathyroid carcinoma. Well-differentiated tumor with sharply outlined regular cells. Mitosis is present.

  - Increased mitotic activity
  - Capsular invasion
  - Vascular invasion
- It is important to note that some adenomas may show these features (fibrosis, rare mitoses, and solid growth); therefore, diagnosis of carcinoma must rely on both histologic and clinical features

Immunohistochemistry

- Identical to that of normal parathyroid chief cells

Differential Diagnosis

- Parathyroid adenoma:
  - May be very difficult to distinguish
  - Absence of suspicious clinical features (adherence to adjacent structures) and histologic features (mitoses, fibrosis, invasion) helpful in establishing benign diagnosis
- Parathyroid hyperplasia:
  - Involves all parathyroid glands
  - Microscopically, gland appears diffusely enlarged, with an even distribution of normal-appearing chief cells and adipose tissue

ADRENAL GLAND

Non-Neoplastic Conditions

Adrenal Heterotopia

Clinical

- Benign congenital anomaly with normal adrenal tissue appearing in abnormal locations
- Relatively common, seen in up to 30% of autopsy cases
- Usually located in retroperitoneal space near adrenals and kidneys, in pelvis, or in inguinal area
- May undergo hyperplasia in response to increased ACTH levels and rarely may give rise to cortical neoplasms

Macroscopic

- Small (<1 cm) nodules of yellow tissue resembling normal adrenal cortex

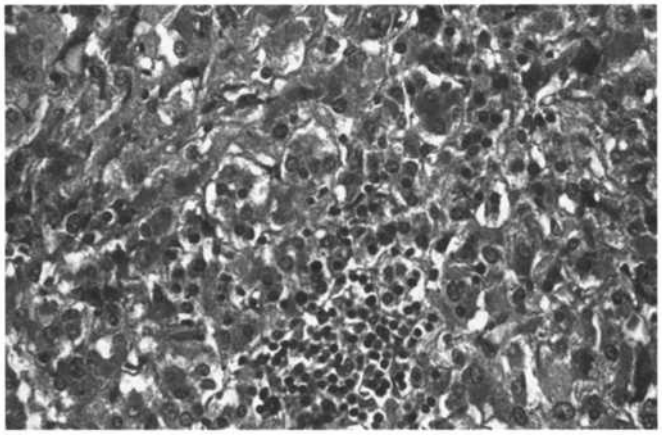


Fig. 57. Focal "adrenalitis." Foci of lymphocytes in the medulla have no known significance.

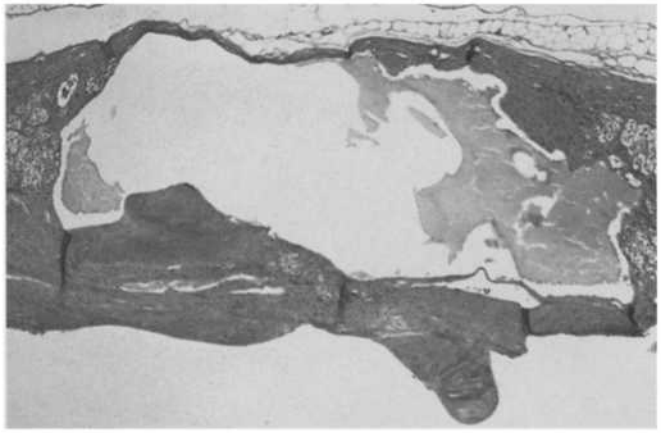


Fig. 58. Adrenal cyst. Fibrous-walled cyst partially filled with an amphophilic coagulum.

Microscopic

- Most consist of adrenal cortical tissue only, but some may also contain medulla

Focal "Adrenalitis"

Clinical

- Cortical and medullary lymphoplasmacytic aggregates of uncertain etiology
- Seen in up to 50% of autopsy patients and particularly common in elderly

*Microscopic (**Figure 57**)*

- Perivascular aggregates of lymphocytes and plasma cells

Differential Diagnosis

- Autoimmune adrenalitis:
  - Inflammatory response more diffuse
  - Marked cortical atrophy

Adrenal Aplasia

Clinical

- Unilateral or bilateral absence of adrenal gland, usually in setting of multiple congenital anomalies
- Seen in association with acardia, anencephaly, and renal agenesis

Adrenal Cysts

Clinical

- Benign pathologic finding
- Usually an incidental finding on CT or MRI
- Seen in adults in fourth to sixth decades
- May be simple developmental cysts or may arise from lymphangioendothelial cysts that undergo hemorrhage and fibrosis

Macroscopic

- Fluid-filled cysts ranging in size from 2–10 cm
- Walls may be focally calcified

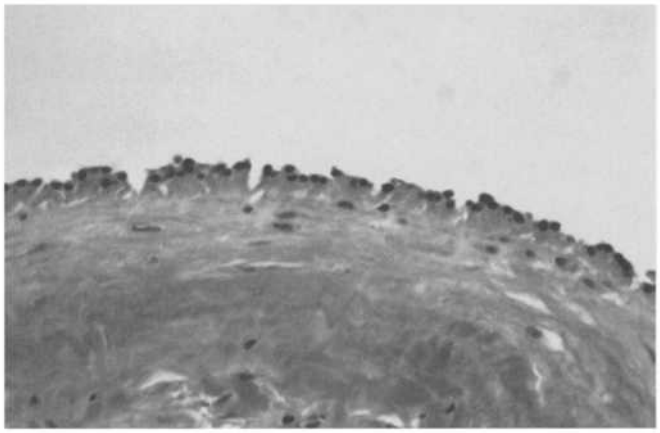


Fig. 59. Adrenal cyst. The cyst in Fig. 58 was partially lined by epithelioid cells, interpreted as plump endothelial cells.

*Microscopic (**Figures 58,59**)*

- Cyst walls composed of fibrous tissue with hemosiderin and elastic tissue occasionally identified
- Epithelial, endothelial, or no specific lining tissue

Differential Diagnosis

- Tumors such as adenoma, carcinoma, or pheochromocytoma may undergo cystic degenerative changes that may grossly mimic cyst

Adrenal Cytomegaly

Clinical

- An incidental histologic finding in up to 3% of newborns and 6.5% of stillborn fetuses
- Particularly prominent in infants with Beckwith-Wiedemann syndrome

*Microscopic (**Figure 60**)*

- Markedly enlarged cells (upto 120 μm) with marked nuclear enlargement, hyperchromasia, and pleomorphism

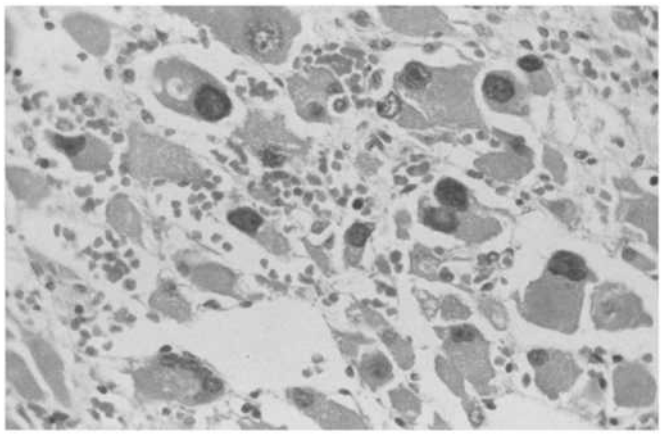


Fig. 60. Adrenal cytomegaly. enlarged cells with enlarged nuclei in provisional cortex of 7 month fetus.

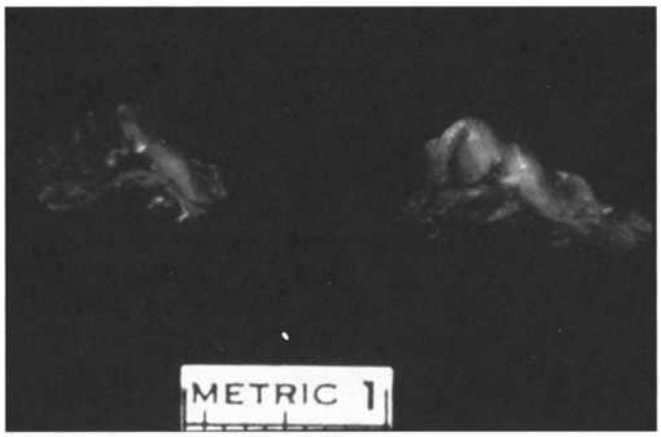


Fig. 61. Adrenal leukodystrophy. Slices of adrenal gland biopsy show much replacement of the yellow cortex by black and brown nodules.

- Nuclear cytoplasmic inclusions can occasionally be seen

Cytogenetics

- Cells may be polyploid/aneuploid, but are not considered neoplastic

Beckwith-Wiedemann Syndrome

Clinical

- Congenital disorder, sometimes familial, manifested by craniofacial abnormalities, abdominal wall defects, gigantism, macroglossia, and adrenal hyperplasia
- Estimated frequency = 1 in 13,000 births
- 7.5% of affected children develop a malignant neoplasm (usually nephroblastoma or adrenal cortical carcinoma)

Macroscopic

- Enlarged adrenals (upto 16 g) with cerebriform appearance

Microscopic

- Marked cytomegaly affecting nearly all cells of cortex
- Cortical microcysts may be seen
- Medullary hyperplasia

Adrenal Leukodystrophy

Clinical

- X-linked metabolic disorder characterized by:
  - Sensory and motor neuropathy
  - Spastic paraplegia
  - Adrenal insufficiency, culminating in Addison's disease

Macroscopic ***(Figure 61)***

- Cortical atrophy

Microscopic ***(Figure 62)***

- Attenuated cortex consisting of ballooned cells with abundant granular or hyaline eosinophilic cytoplasm
- Some cells may have cleared cytoplasm with intracytoplasmic striations

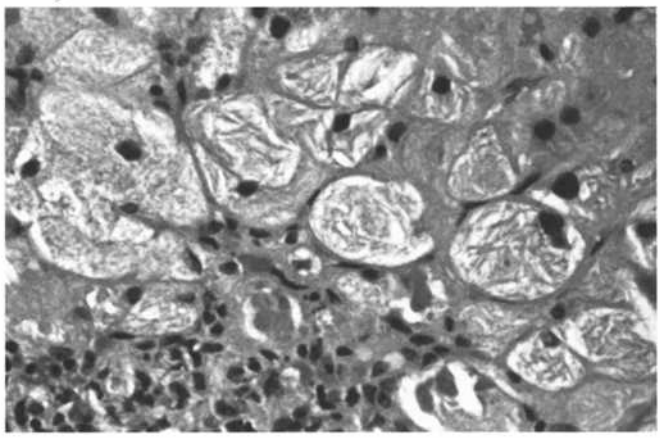


Fig. 62. Adrenal leukodystrophy. Ballooned cortical cells with somewhat clear cytoplasm and intracytoplasmic striations.

Electron Microscopy

- Cortical cells contain linear lamellar inclusions

Congenital Adrenal Hyperplasia (Adrenogenital Syndrome)

Clinical

- Pathologic manifestation of a group of autosomal recessive disorders characterized by enzymatic defects in cortisol synthesis
- Insufficient cortisol results in increased ACTH secretion and subsequent bilateral adrenal hyperplasia
- Biosynthesis pathway blockages result in shunting of steroids into other pathways, usually those for sex steroids
- Usually presents in first few years of life with findings related to abnormal hormone levels: sexual development abnormalities, hypertension, adrenal insufficiency, sodium imbalances

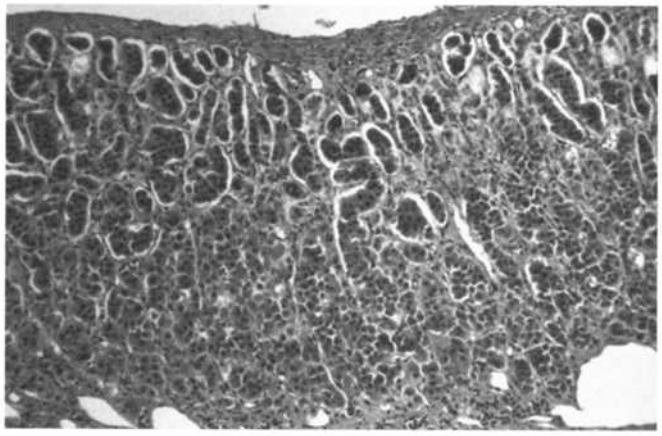


Fig. 63. Congenital adrenal hyperplasia. Normal cortex replaced by clear-cell nodules.

- Most common enzymatic defect is 21-hydroxylase deficiency (seen in >90% of cases)
- Patients affected with longstanding disease may develop steroid-type neoplasms (adrenal cortical and testicular) due to stimulatory effects of chronically increased adrenocorticotrophic hormone (ACTH) levels

Macroscopic

- Marked diffuse enlargement with tan-brown coloration and cerebriform appearance
- Glands usually weigh 10–15 g each

*Microscopic **(Figure 63)***

- Marked hyperplasia of zona fasciculata
- Compact cells with eosinophilic cytoplasm (lipid-depleted) replace normal vacuolated (lipid-laden) fasciculata cells

Differential Diagnosis

- Adrenal cortical hyperplasia:
  - Usually older patients
  - Hormonal syndromes usually associated with glucocorticoid or mineralocorticoid excess, rather than sex steroid excess
  - Commonly nodular or mixed diffuse and nodular
- Beckwith-Wiedemann syndrome:
  - Associated with multiple anatomic anomalies
  - Marked cortical cytomegaly

Primary Adrenal Insufficiency (Addison's Disease)

Clinical

- Adult autoimmune disease where antibodies directed against adrenal antigens result in cortical cell destruction and subsequent adrenal insufficiency
- More common in females (F : M = 2 : 1)
- Patients typically manifest signs and symptoms of deficiencies in glucocorticoids and mineralocorticoids, including fatigue, weight loss, hypotension, poor stress tolerance, and increased pigmentation (due to increased ACTH)
- Sometimes associated with autoimmune disease of thyroid (Hashimoto's thyroiditis resulting in hypothyroidism), stomach (chronic atrophic gastritis resulting in pernicious anemia), or pancreas (inflammation of islets causing diabetes mellitus)



Fig. 64. Primary adrenal insufficiency. Small normally shaped adrenal glands in primary adrenal atrophy. The two glands weighed 6 gm.

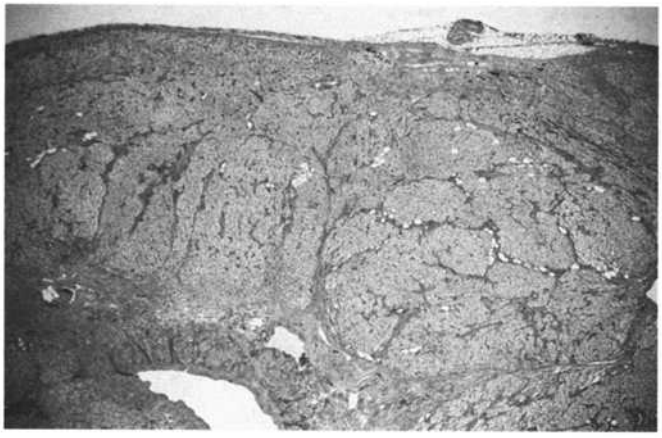


Fig. 65. Primary adrenal insufficiency. A thinned cortex shows loss of normal zona fasciculata with clear cells. The cortical cells are smaller than normal.

*Macroscopic **(Figure 64)***

- Marked cortical atrophy

*Microscopic **(Figure 65)***

- Marked cortical atrophy with remaining cortical tissue showing lymphocytic infiltrate
- Residual cortical cells are hypertrophied and have compact eosinophilic cytoplasm and enlarged nuclei (ACTH stimulation effect)
- Medulla uninvolved

Differential Diagnosis

- Other causes of adrenal cortical insufficiency:
  - Infectious agents such as mycobacteria, fungi, or viruses
  - Amyloid deposition

- Adrenal hemorrhage (Waterhouse-Friderichsen syndrome)
- Metastatic tumor
- Pituitary lesions (tumor, necrosis, hemorrhage)

Secondary Adrenal Insufficiency

Clinical

- Adrenal insufficiency and atrophy due to lack of ACTH stimulation
- Usually due to primary pituitary disease:
  - Pituitary neoplasm
  - Post-partum necrosis (Sheehan's syndrome)
- Patients present with hypocortisolism: anorexia, weight loss, hypotension, poor stress tolerance, and hyperpigmentation (due to increased ACTH)

Macroscopic

- Cortical atrophy
- Cortex appears bright yellow due to accumulation of lipid
- Brown zona reticularis (normally seen internal to yellow zona fasciculata) is not present
- Normal-appearing medulla

Microscopic

- Atrophy of zona fasciculata and reticularis with relative sparing of zona glomerulosa

Differential Diagnosis

- Primary adrenal insufficiency
- Exogenous steroid administration

Adrenal Cortical Hyperplasia

Clinical

- Enlargement of adrenal cortex with increased serum cortisol, usually due to above normal stimulation by ACTH, either from pituitary or ectopic sources
- Patients may present with extra-adrenal tumor (ectopic ACTH secretion) or with symptoms of hypercortisolism.
- Most common sources of ACTH include:
  - Pituitary adenoma (Cushing's disease)
  - Small cell lung carcinoma
  - Carcinoid tumor (lung, gastrointestinal tract, thymus, or pancreas)
  - Islet cell carcinoma
  - Medullary thyroid carcinoma

*Macroscopic (**Figure 66**)*

- Enlargement of cortex may be diffuse, nodular, or combination of both
- Diffuse hyperplasia results in moderate enlargement (12–24 g each) with uniform widening of cortex, which appears tan to brown

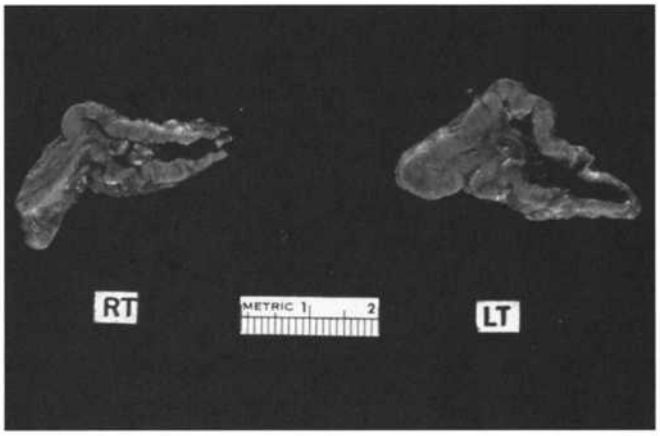


Fig. 66. Adrenal cortical hyperplasia. Generally thickened yellow-brown cortex in cortical hyperplasia. The glands together weighed 25.2 gm.

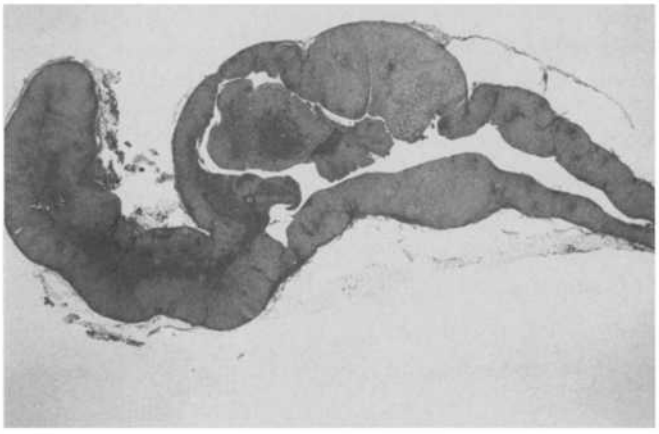


Fig. 67. Adrenal cortical hyperplasia. Irregular thickening with beginning nodularity of the cortex in diffuse cortical hyperplasia (Cushing syndrome).

- Nodular hyperplasia shows varying numbers of individual nodules in the cortex
- Nodules may measure up to 3 cm and adrenals may weigh upto 50 g
- Diffuse and nodular hyperplasia may co-exist in the same patient

*Microscopic (**Figure 67**)*

- Diffuse hyperplasia:
  - Expanded zona fasciculata with compact, lipid-depleted cells; zona glomerulosa cells appear vacuolated
- Nodular hyperplasia (**Figures 68,69**):
  - Nodules composed of clear cells, compact cells, or mixture of both

Differential Diagnosis

- Cortical adenoma

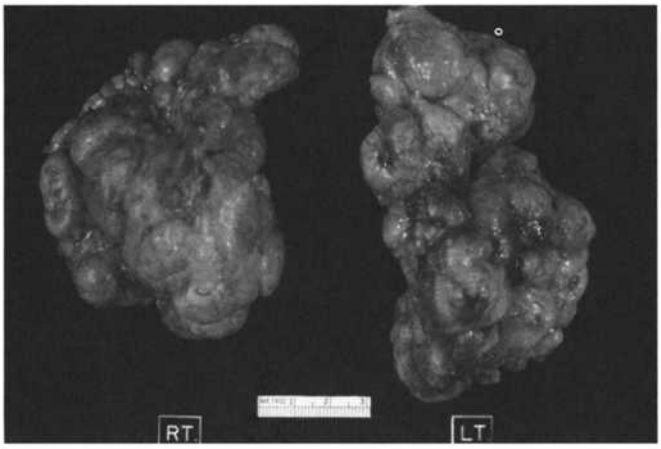


Fig. 68. Cortical macronodular hyperplasia. Bilateral macronodular cortical hyperplasia featuring massive enlargement of both adrenal glands. Total weight, 218 gm.

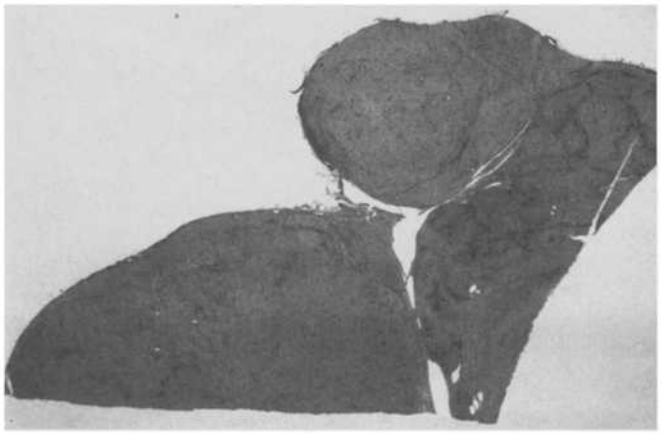


Fig. 69. Cortical macronodular hyperplasia. Low-power micrograph showing adjacent large cortical nodules that blend with a thickened cortex.

- Usually single dominant nodule, rather than multiple nodules
- Uninvolved cortex and contralateral adrenal are normal or show atrophy

Cortical Hyperplasia Associated with Hyperaldosteronism

Clinical

- Pathologic condition seen in ~40% of cases of primary hyperaldosteronism
- Patients exhibit typical manifestations of hyperaldosteronism: hypertension, weakness, hypokalemia, and hypernatremia

Macroscopic

- Cortex may be diffusely widened or have nodular appearance

Microscopic

- Cortical expansion due primarily to hyperplasia of zona glomerulosa with tongues of glomerulosa cells extending down into adjacent zona fasciculata
- In patients treated with diuretic spironolactone (Aldactone), cells may contain laminated eosinophilic inclusions ("spironolactone bodies")

Differential Diagnosis

- Typical adrenal cortical hyperplasia:
  - Associated with increased glucocorticoid levels
  - Hyperplastic cortex made up mostly of fasciculata cells rather than glomerulosa cells

Cortical Macronodular Hyperplasia

Clinical

- Rare type of primary adrenal hyperplasia with tumor-like enlargement of both glands
- Average age = 50 years
- Patients usually present with symptoms of hypercortisolism

Macroscopic

- Markedly enlarged adrenal glands (combined weight of 60–180 g), grossly distorted by multiple nodules ranging in size up to 3.5 cm
- On cross section, nodules are non-encapsulated and bright yellow in color

Microscopic

- Cortical cells are varied in appearance, predominantly large and vacuolated (lipid-laden) with some scattered, eosinophilic, compact (lipid-depleted) cells and rare balloon cells
- Pseudoglandular formations are occasionally present
- Focal lipomatous or myelolipomatous metaplasia can be seen

Differential Diagnosis

- Cortical carcinoma:
  - Unilateral
  - Typically >100 g
  - Cellular atypia, mitoses, necrosis, fibrous bands
  - Vascular or capsular invasion
- Typical adrenal hyperplasia:
  - Combined weight of adrenals usually <50 g
  - May have nodular appearance, but individual nodules are small (<0.5 cm)

Microadenomatous Hyperplasia (Primary Pigmented Nodular Adrenocortical Disease)

Clinical

- A type of primary adrenal hyperplasia with characteristic macroscopic findings
- More common in young women

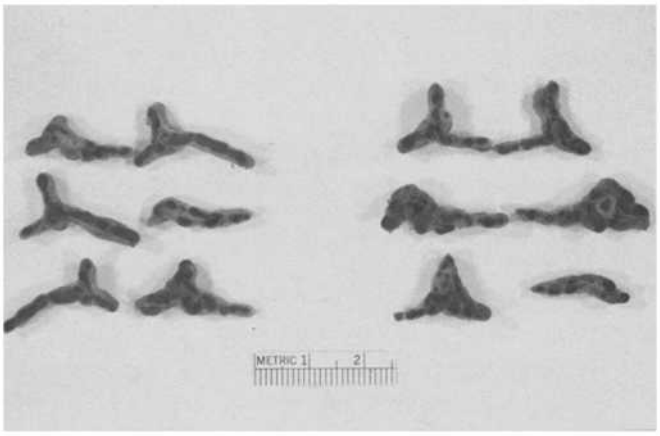


Fig. 70. Primary pigmented nodular adrenocortical disease. Slices of formalin-fixed right and left adrenal glands show multiple small brown and black nodules.

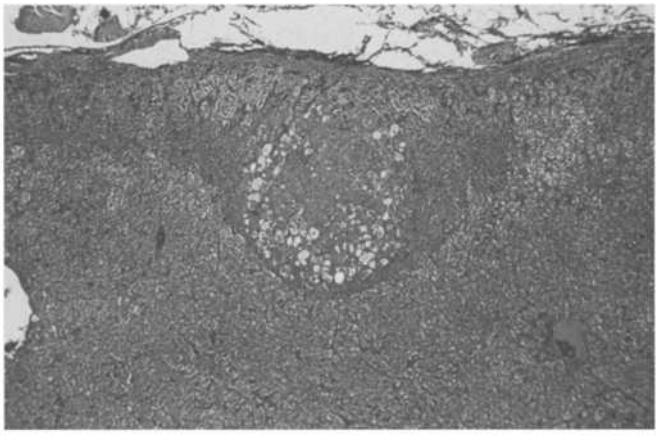


Fig. 71. Primary pigmented nodular adrenocortical disease. A nodule composed of cells with eosinophilic and clear cytoplasm straddles the corticomedullary function. The extranodular cortex is atrophic.

- Patients show typical signs and symptoms of hypercortisolism: truncal obesity, muscle weakness, hypertension, abdominal striae, menstrual abnormalities/impotence
- Osteoporosis often prominent feature
- Familial forms are associated with:
  - Myxomas (cardiac, cutaneous, and mammary)
  - Spotty cutaneous pigmentation (ephelides, lentigines, and blue nevi)
  - Endocrine overactivity (acromegaly due to pituitary adenoma and sexual precocity due to large-cell calcifying Sertoli cell tumor of testes)
  - Schwannomas (psammomatous melanotic type)

Macroscopic ***(Figure 70)***

- Multiple pigmented cortical nodules (1–3 mm in size) situated in an atrophic cortex
- Glands are usually normal size, but may be smaller or larger than normal

Microscopic ***(Figure 71)***

- Small nodules composed of large granular eosinophilic cells, some with large hyperchromatic nuclei and prominent nucleoli
- Cells contain lipofuscin pigment

Differential Diagnosis

- Pigmented cortical adenoma:
  - Larger, single nodule, usually 3–6 cm in size
- Cortical carcinoma:
  - Single, dominant mass, rather than multiple nodules
  - Marked cellular atypia, mitoses, necrosis, fibrous bands
  - Vascular or capsular invasion

Ovarian Thecal Metaplasia

Clinical

- Benign cortical proliferation resembling ovarian stroma

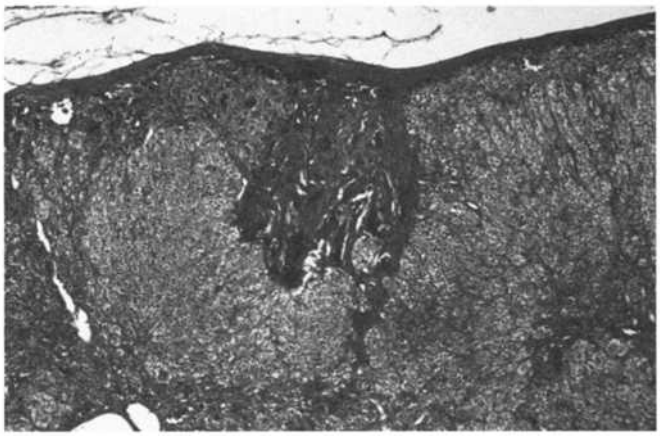


Fig. 72. Ovarian thecal metaplasia. A dense fibrous proliferation emanating from the adrenal capsule penetrates into the cortex.

- Seen in <5% of females, usually postmenopausal, may also occur rarely in males
- No known significance

Macroscopic

- Small (<2 mm) firm fibrous nodule, usually wedge-shaped, attached to adrenal capsule
- Occasionally multiple foci may be present

Microscopic ***(Figures 72,73)***

- Subcapsular proliferation of spindle cells that resembles normal ovarian stroma
- Scattered cortical cells may be entrapped within proliferation
- Fibrosis common; may be calcified

Adrenal Medullary Hyperplasia

Clinical

- Uncommon hyperplastic expansion of medulla

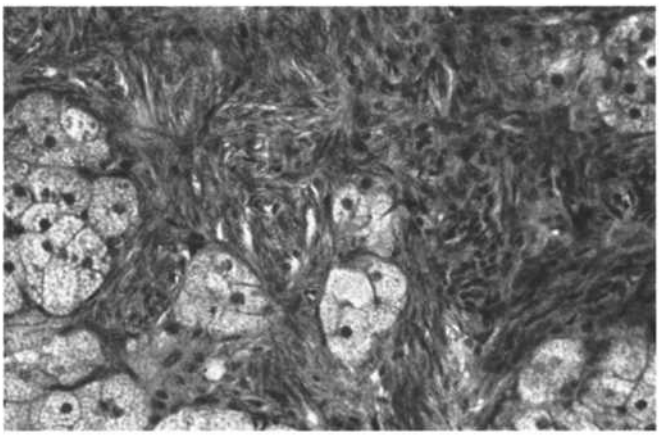


Fig. 73. Ovarian thecal metaplasia. Clusters of cortical cells with clear cytoplasm are surrounded by a cellular spindle cell proliferation.

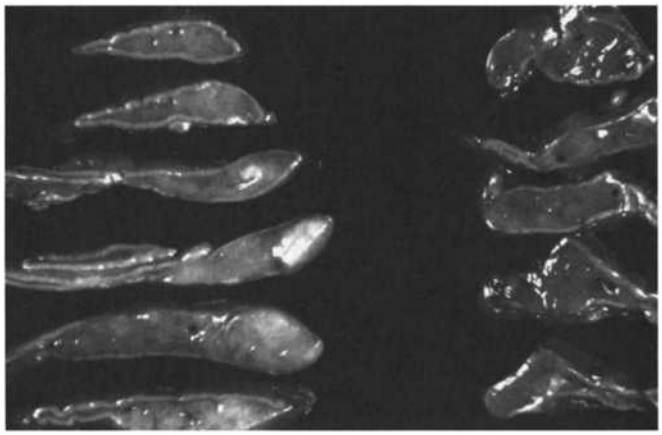


Fig. 74. Adrenal medullary hyperplasia. Slices of both adrenal glands show that the medulla is massively expanded and dwarfs the cortex.

- Typically associated with multiple endocrine neoplasia Types 2A and 2B
- May rarely be sporadic
- Thought to be precursor lesion to pheochromocytoma, especially in patients with multiple endocrine neoplasia

Macroscopic ***(Figure 74)***

- Increased adrenal medullary volume with pearly gray color
- Enlargement may be uniform or have a somewhat nodular appearance
- Medullary tissue may extend beyond its normal location (normally restricted to head and body of adrenal) and be found within alar and tail regions

Microscopic ***(Figure 75)***

- Increased numbers of cells, either in sheets or nodules, expanding medulla



Fig. 75. Adrenal medullary hyperplasia. Diffuse enlargement of the medulla without nodules.

- There may be significant cellular pleomorphism and some nuclear pleomorphism as well

Differential Diagnosis

- Adrenal cortical atrophy:
  - May mimic medullary hyperplasia grossly by making medulla appear relatively large compared to thin, attenuated cortex
- Pheochromocytoma:
  - Nodular hyperplasia may look similar to early pheochromocytoma and, indeed, is thought to be a possible precursor of pheochromocytoma

Neoplasms

Benign Tumors

Cortical Adenoma

Clinical

- A benign cortical neoplasm, often associated with hormonal secretion
- Signs and symptoms related to specific hormones elaborated by adenoma:
  - Hypercortisolism (Cushing's syndrome), hyperaldosteronism (Conn's syndrome), or increased androgenic or estrogenic steroids (adrenogenital syndrome)
  - Some adenomas secrete multiple hormones and others are non-functional
- Identified incidentally on MRI or CT ("incidentalomas")
- Autopsy series show 10% to 20% incidence

Macroscopic

- Well-circumscribed, encapsulated masses, well-demarcated from surrounding cortex
- Size varies from several grams up to 500 g in rare cases
- Cortical tumors >100 g should be carefully evaluated for presence of malignancy and, even if benign-appearing

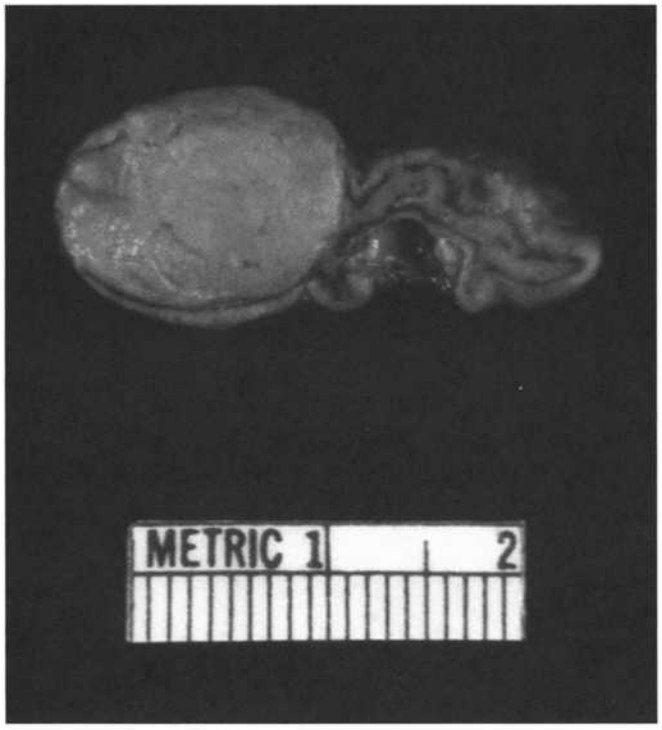


Fig. 76. Aldosterone-secreting adenoma. Yellow-orange tumor and associated cortex (showing outer zona fasciculata and inner zona reticularis) and medulla. The adrenal gland weighed 5.5 gm.

histologically, should be regarded as having an indeterminate biological potential

- Necrosis rare, but cystic degeneration commonly occurs in larger tumors
- In cases of cortisol-secreting tumors, the adjacent cortex and contralateral adrenal gland are atrophic due to suppression of pituitary ACTH secretion by the tumor's hormone secretion

Microscopic

- Well-circumscribed, usually encapsulated, tumors composed of nests and cords of cells resembling those normally found in glomerulosa, fasciculata, or reticularis
- Adenomas may be a mixture of cell types
- Some tumors may contain significant nuclear pleomorphism, thought to be degenerative
- In pediatric patients, benign adenomas may demonstrate increased mitotic rate, fibrosis, necrosis, and nuclear pleomorphism

Variants

- Adenomas associated with Conn's syndrome (**Figures 76–79**):
  - Small (<2 cm), bright yellow, often poorly demarcated from surrounding cortex
  - Tumor cells resemble those of glomerulosa or fasciculata (clear cells) or a combination of the two



Fig. 77. Aldosterone-secreting adenoma. The tumor is almost entirely composed of cells with clear cytoplasm. The attached cortex and medulla are normal.

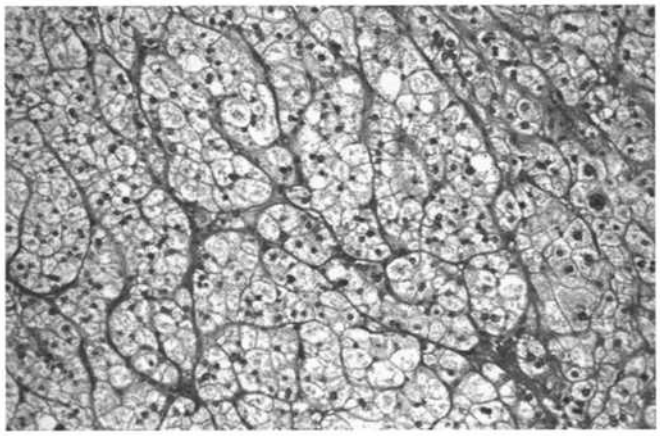


Fig. 78. Aldosterone-secreting adenoma. The tumor features large clear cells arranged in trabeculae supported by a minimal fibrovascular stroma. There is focal nucleomegaly.

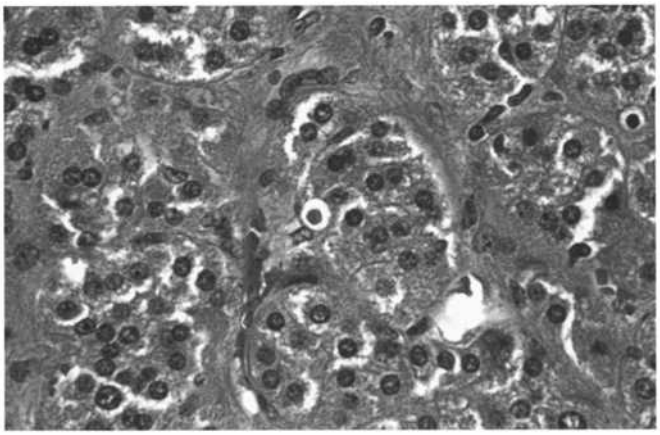


Fig. 79. Spironolactone bodies. There are scattered laminated eosinophilic structures in a group of cells with eosinophilic cytoplasm (the latter unusual in an aldosterone-secreting adenoma).

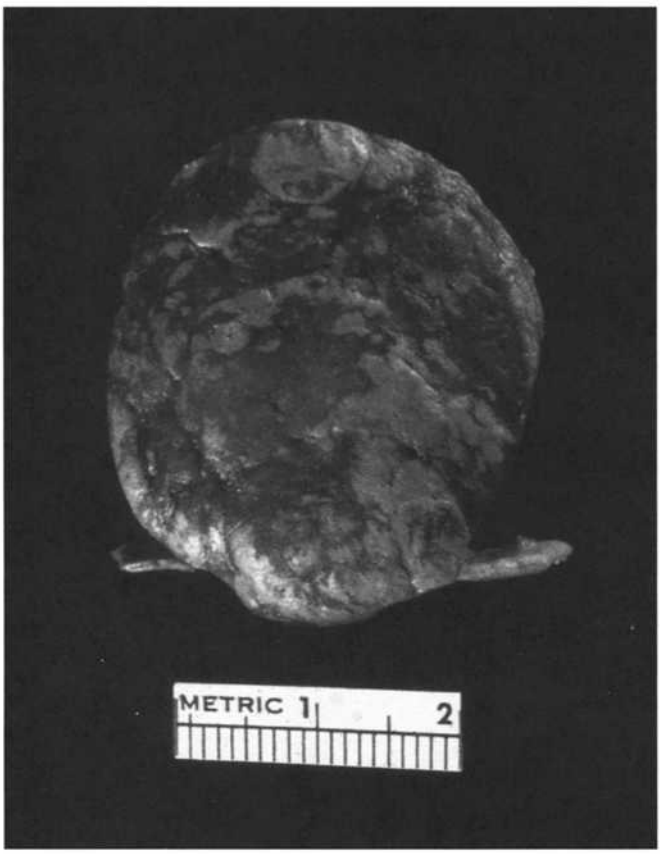


Fig. 80. Cortisol-secreting adrenal adenoma. The cut surface of the adenoma is marbled yellow and brown. The cortex protruding on both sides of the tumor is very thin (atrophic).

- In patients treated with diuretic spironolactone (Aldactone), tumor cells (and sometimes extratumoral zona glomerulosa cells) may contain eosinophilic inclusions ("spironolactone bodies")
- Zona glomerulosa of nearby cortex may be hyperplastic

♦ Adenomas associated with Cushing's syndrome (**Figures 80–83**):
- Usually measure 3–4 cm in diameter and weigh 10–50 g
- Usually appear as mixture of colors (yellow to brown) and may occasionally be darkly pigmented ("black adenoma")
- Cells resemble zona reticularis and fasciculata with lipid-depleted (dark) and lipid-rich (clear) cytoplasm
- Fatty or myeloid metaplasia common
- Cells of "black adenoma" contain abundant lipofuscin
- Adjacent cortex (and that of contralateral adrenal) typically appears atrophic, with absence of normal zona reticularis

♦ Adenomas associated with adrenogenital syndromes:
- Tend to be larger and may have red-brown appearance

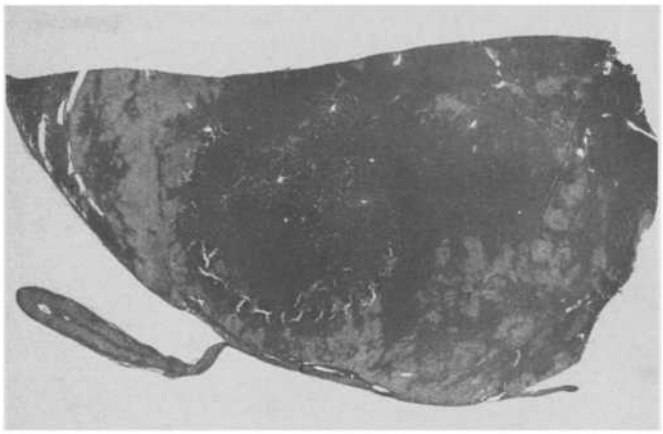


Fig. 81. Cortisol-secreting adenoma. Adenoma is composed of populations of cells with eosinophilic and clear cytoplasm.

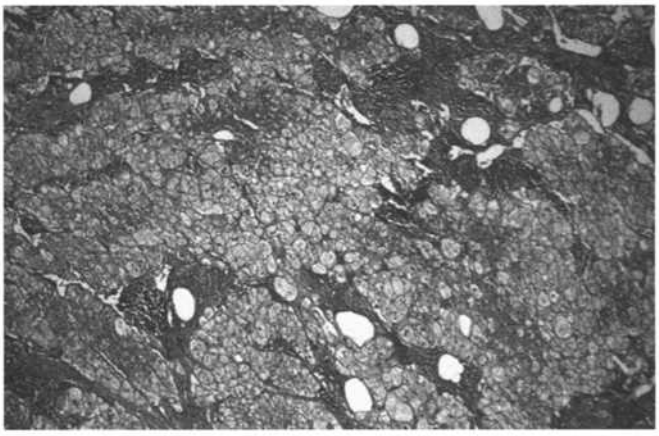


Fig. 82. Cortisol-secreting adenoma showing cells with clear and dark cytoplasm and foci of myeloid metaplasia.

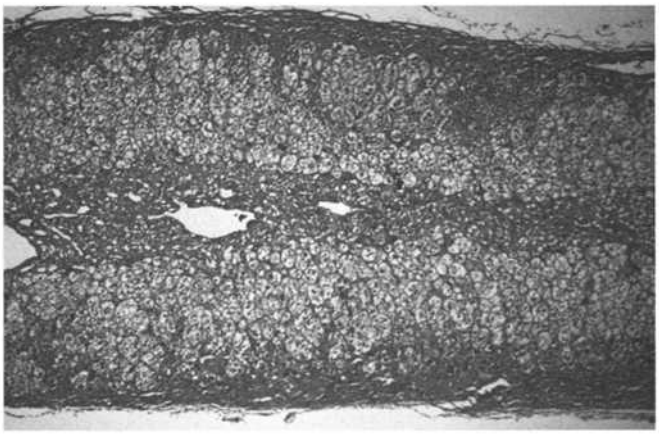


Fig. 83. Cortical atrophy in association with cortisol-secreting adenoma. The thin extratumoral cortex has lost normal zonation and is largely composed of large cells with clear cytoplasm.

- Are relatively uncommon and must be carefully distinguished from cortical carcinoma
- Not associated with atrophy of normal cortical tissue

♦ Non-functional adenomas and cortical nodules:
- Small (>3 cm), yellow to brown in color, and may be multicentric
- Not associated with atrophy of normal cortical tissue

Differential Diagnosis

♦ Nodular or macronodular hyperplasia:
- Usually multiple nodules rather than single dominant nodule
- Adjacent cortex and contralateral adrenal gland will commonly appear hypertrophic, not atrophic

♦ Cortical carcinoma:
- Typically >100 g
- Nuclear atypia, mitoses, necrosis, fibrous bands
- Vascular or capsular invasion

♦ Pheochromocytoma:
- Arising from adrenal medulla with normal adrenal cortex stretched out over its surface
- Red-brown in color with areas of hemorrhage or cystic degeneration if large
- Organoid growth pattern with nests of cells ("zell-ballen") and delicate vascular septa
- Immunohistochemistry: immunoreactive for neuro-filament, chromogranin, synaptophysin and S-100 (in sustentacular cell pattern); – for vimentin

Myelolipoma

Clinical

♦ Benign mixed stromal tumor composed of mature adipose and myeloid elements

♦ Usually incidental finding at autopsy or adrenalectomy

♦ Small foci of myelolipomatous transformation are commonly seen within adenomas or cortical hyperplasia

Macroscopic ***(Figure 84)***

♦ Small, non-encapsulated spongy lesion, bright yellow with scattered small red-brown foci

Microscopic ***(Figure 85)***

♦ Mature adipose tissue with scattered normal-appearing hematopoietic islands

Oncocytoma (Oncocytic Adenoma)

Clinical

♦ Benign epithelial adrenal cortical neoplasm

♦ Usually asymptomatic, but may be associated with hormonal syndrome

Macroscopic ***(Figure 86)***

♦ Variably sized (60–850 g), well-circumscribed, often encapsulated



Fig. 84. Myelolipoma. Bulging juxtapposed myelolipomas with a dark red appearance.

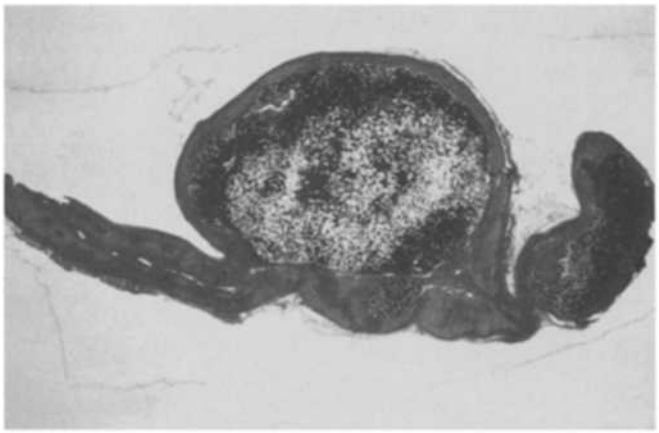


Fig. 85. Myelolipoma. Panoramic view of tumor with a large fatty core surrounded by a cellular collar (bone marrow cells).

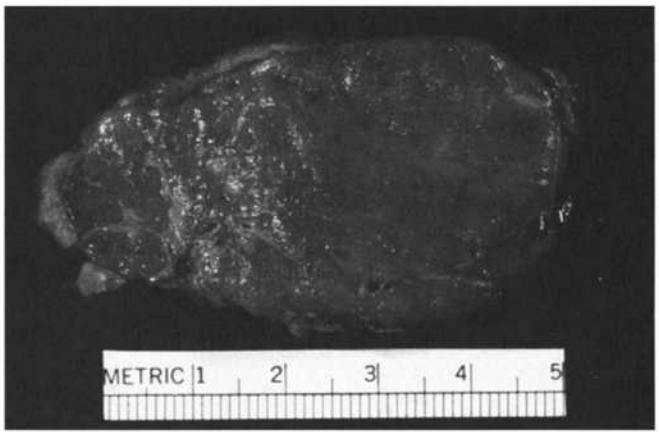


Fig. 86. Oncocytoma. Brown cut surface with some gaping vessels.

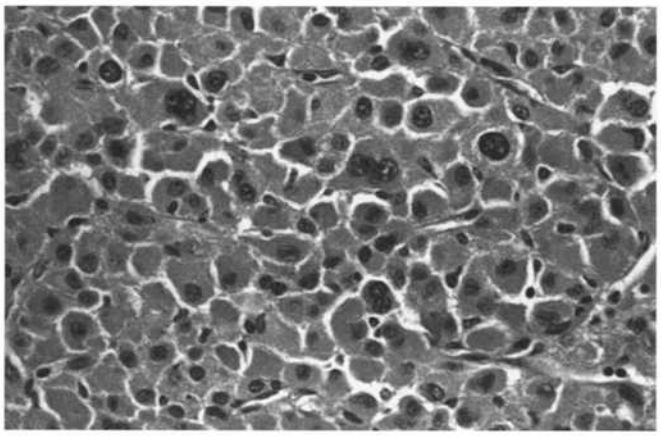


Fig. 87. Oncocytoma. Moderately large cells with eosinophilic cytoplasm and nuclei are central and eccentric. Multinucleation is present.

- Typical tan-brown color
- Central scarring common, but also may see hemorrhage or cystic change

*Microscopic **(Figure 87)***

- Composed of sheets of large regular polygonal cells with abundant granular eosinophilic cytoplasm
- Some nuclear pleomorphism common

Electron Microscopy

- Granular cytoplasm features many mitochondria that demonstrate both lamellar and tubular cristae
- May contain small electron-dense inclusions

Differential Diagnosis

- Adrenal cortical carcinoma:
  - Often associated with hormonal syndrome (but not always)
  - Gross invasion or necrosis
  - Increased mitoses, areas of necrosis, marked nuclear pleomorphism, invasion
- Pheochromocytoma:
  - Cells can sometimes appear oncocytic, with abundant granular cytoplasm
  - Immunohistochemistry: immunoreactive for S-100 in sustentacular cell pattern

Pheochromocytoma

Clinical

- Benign tumor composed of adrenal medullary chromaffin cells
- Highest incidence in fourth and fifth decades, although 10% occur in children
- Patients present with signs and symptoms of catecholamine secretion (hypertension, cardiac dysrhythmias, and diaphoresis)

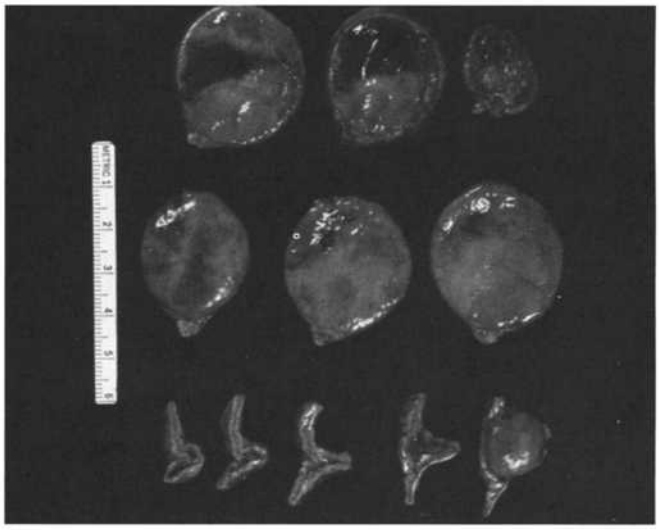


Fig. 88. Pheochromocytoma. The soft fleshy-pink tumor shows an area of hemorrhage.

- Ectopic hormones may be produced as well (ACTH, somatostatin, or calcitonin)
- Usually within adrenal glands, but 10% to 20% of cases elsewhere in retroperitoneum, mediastinum, neck, or bladder (at these extra-adrenal sites, referred to as paragangliomas)
- 10% to 20% of cases associated with familial syndromes: MEN Type 2A and 2B (roughly half of patients affected, usually multicentric and bilateral), von Hippel-Lindau disease, von Recklinghausen's disease, and Sturge-Weber syndrome (1% to 5% of patients)

*Macroscopic **(Figure 88)***

- Encapsulated mass usually 3–5 cm, weighing <100 g
- Gray-pink to tan-brown in color
- Soft consistency
- Areas of hemorrhage and cyst formation can be seen with larger tumors

*Microscopic **(Figure 89)***

- Tumor grows in cords or nests (zellballen = "cell balls"), with delicate fibrovascular septa
- Variably-sized cells with generally basophilic granular cytoplasm that may be vacuolated in some cases
- Occasional spindled cells
- PAS+ cytoplasmic hyaline globules in up to 60% of cases
- Round to oval, slightly irregular nuclei with coarsely clumped chromatin (salt and pepper chromatin) and single, ordinarily inconspicuous nucleoli
- Moderate nuclear pleomorphism may be present
- Mitoses possible, but rare

Immunohistochemistry

- Tumor cells immunoreactive for chromogranin, synaptophysin, and neurofilament

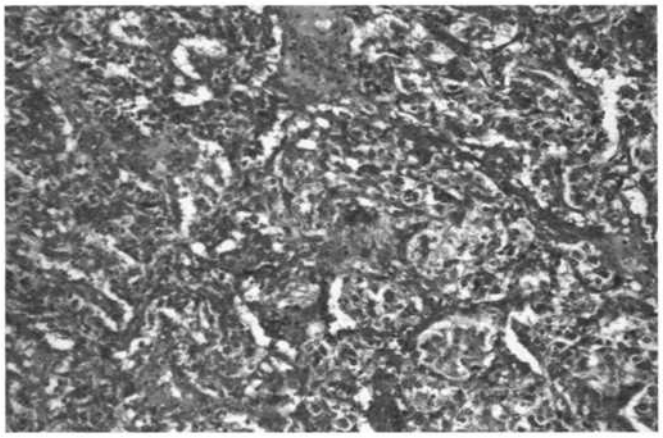


Fig. 89. Pheochromocytoma. Clusters of cells with granular slightly basophilic cytoplasm are surrounded by a fibrovascular stroma.

- S-100 staining of thin, spindled sustentacular cells (not tumor cells) in characteristic pattern (**Table 2**)
- Negative for cytokeratin and vimentin

Electron Microscopy

- Cytoplasm contains membrane-bound dense-core secretory granules that contain epinephrine or norepinephrine

Variants

- Malignant pheochromocytoma:
  - Estimated 5% to 10% of pheochromocytomas are malignant
  - Females more often than males
  - No reliable gross or histologic criteria exist for malignancy
  - Suspicious features include extra-adrenal location, large tumor weight, confluent areas of necrosis, and vascular invasion or extensive local invasion
  - 5-year survival = 50%

Differential Diagnosis

- Adrenal cortical adenoma:
  - Small (3–6 cm) with bright yellow to tan-brown color
  - Uninvolved adrenal cortical tissue appears normal or atrophic
  - Immunohistochemistry: immunoreactive for vimentin and possibly synaptophysin; no reactivity with S-100 or chromogranin
- Adrenal cortical carcinoma:
  - High-grade nuclear pleomorphism, necrosis, invasion
  - Increased mitoses
  - Immunohistochemistry: immunoreactive for vimentin and possibly S-100 protein (no sustentacular staining pattern), neurofilament, or synaptophysin
- Metastatic carcinoma:
  - Common primary sites include lung, breast, gastrointestinal tract, thyroid, and kidney
  - Growth pattern usually solid rather than nested
  - Immunohistochemistry: immunoreactive for cytokeratin, epithelial membrane antigen, and/or carcinoembryonic antigen
- Melanoma:
  - May be primary, or more commonly metastatic from an occult primary
  - Melanin pigment
  - Immunohistochemistry: tumor cells immunoreactive for S-100 protein and HMB-45

Ganglioneuroma

Clinical

- Benign neurogenic tumor arising in adrenal medulla and sympathetic ganglia
- Older children (>7 years) and young adults
- Varied presentation; may present as mass or be seen as an incidental finding on CT or MRI or at autopsy
- May be associated with clinical syndromes such as hypertension, diarrhea, and/or hypokalemia (95% of patients have detectable elevations in catecholamine metabolites in urine)
- May be solitary or associated with other neurogenic tumors
- <30% of cases located in adrenal glands
- Most found in posterior mediastinum or in retroperitoneum, particularly presacral region

Macroscopic

- Large (average size = 8 cm), sharply circumscribed firm masses
- Homogenous gray-white appearance
- May contain small hemorrhagic or necrotic areas that may represent less differentiated foci

Microscopic ***(Figures 90,91)***

- Stroma closely resembles neurofibroma, with thin wavy spindled cells (Schwann cells) in collagenous matrix
- Scattered mildly atypical to normal ganglion cells with abundant cytoplasm and multiple nuclei
- May contain lymphocytic infiltrates that may be confused with neuroblasts

Immunohistochemistry

- Stroma immunoreactive with S-100 protein (**Table 2**)
- Ganglion cells: immunoreactive with neurofilament, chromogranin, and neuron-specific enolase

Table 2. Immunohistochemical Profiles of Adrenal Tumors

	Cortical carcinoma	*Neuro-blastoma*	*Ganglio-neuroma*	*Pheochromo-cytoma*	*Metastatic carcinoma*	*Malignant melanoma*	*Lipo-sarcoma*
LMWK	–	–	–	–	+	–	–
VIM	+		+	–	±	+	+
NF	+	+	+ (ganglion cells)	+	–	–	–
S-100	+	+ (stroma)	+ (stroma)	+ (sustentacular cells)	–	+	+
EMA	–		–	–	±	–	–
CG	–	+	+ (ganglion cells)	+	–	–	–
SYN	±	–	+ (ganglion cells)	+	–	–	–
CEA	–		–	–	±	–	–

LMWK = low-molecular-weight cytokeratin, VIM = vimentin, NF = neurofilament, EMA = epithelial membrane antigen, CG = chromogranin, SYN = synaptophysin, CEA = carcinoemhryonic antigen.

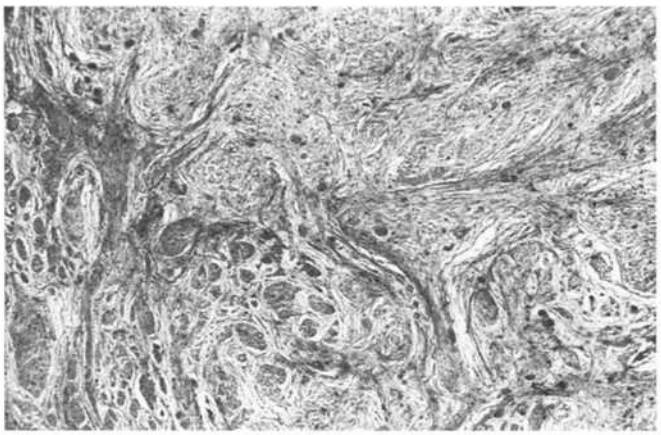


Fig. 90. Ganglioneuroma. Ganglion cells, their processes and ensheathing Schwann cells.

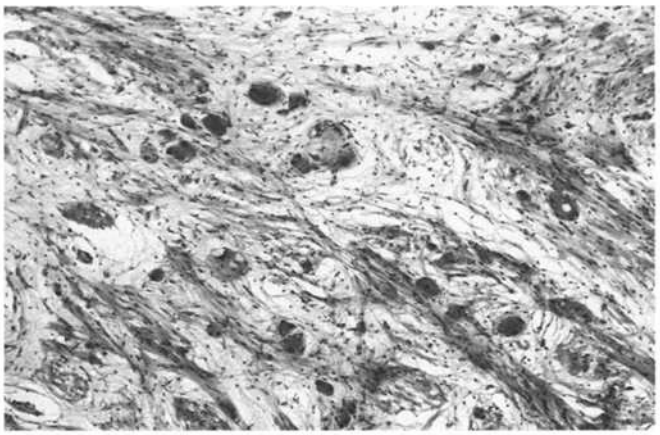


Fig. 91. Ganglioneuroma. Appearance is reminiscent of a neurofibroma except for the presence of abnormal and mature ganglion cells.

Electron Microscopy

- Ganglion cells closely resemble those found in normal sympathetic ganglia

Differential Diagnosis

- Neurofibroma:
  - Stroma appears identical, however, no ganglion cells seen
- Ganglioneuroblastoma:
  - Contains less differentiated foci of neuroblasts (with typical microscopic and immunohistochemical features)

Malignant Tumors

Adrenal Cortical Carcinoma

Clinical

- Malignant epithelial neoplasm, commonly associated with hormone secretion
- Typically presents in fourth to fifth decade; F : M = 2 : 1
- Patients usually present with syndromes associated with hormone excess (usually Cushing's syndrome or sex steroid overproduction), intra-abdominal mass, or metastases (lungs, retroperitoneal nodes, and liver most common)
- Median survival = 14 months; 5-year survival = 24%



Fig. 92. Adrenal cortical carcinoma. The tumor which weighed 870 gm shows variable sized lobules and a zone of necrosis.

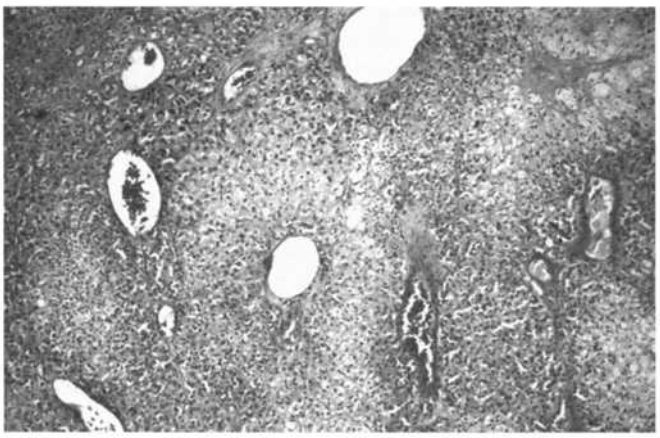


Fig. 93. Adrenal cortical carcinoma. A sheet of relatively uniform cells with clear to dark cytoplasm and dilated blood vessels.

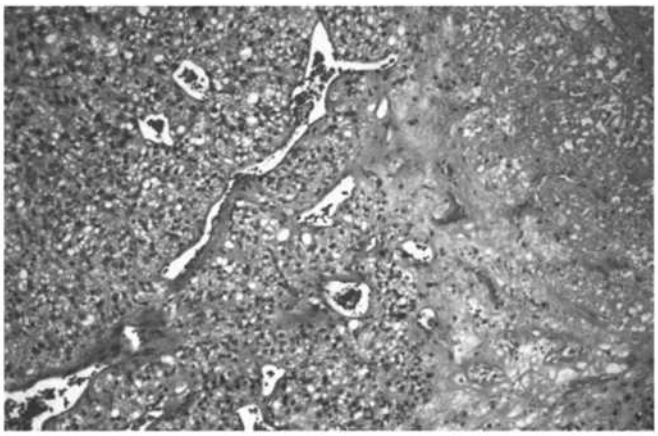


Fig. 94. Adrenal cortical carcinoma. Zone of necrosis in a background of relatively uniform cells with mostly clear cytoplasm.

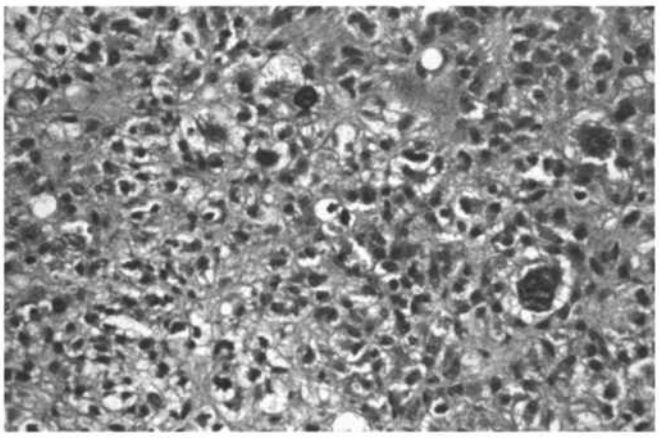


Fig. 95. Adrenal cortical carcinoma. Scattered atypical nuclei are present.

Macroscopic ***(Figure 92)***

- Large cortical masses (usually >100 g in adults and >500 g in children); usually >6 cm and only rarely <3 cm
- Cut section pink to tan to yellow, depending on lipid content of tumor cells
- Commonly lobulated with areas of fibrosis, necrosis, hemorrhage, or calcification
- Invasion of adjacent structures

Microscopic ***(Figures 93–95)***

- Varied cellular appearance depending on lipid content: small cells with eosinophilic cytoplasm (lipid-depleted) to large and vacuolated (lipid-laden) ones
- Growth patterns may be alveolar, trabecular, or diffuse
- Features strongly suggesting malignancy include:
  - High-grade nuclear pleomorphism
  - Frequent mitoses (>5 per 50 HPF), especially atypical forms
  - Broad fibrous bands
  - Necrosis (>2 HPF in diameter)
  - Diffuse growth pattern (comprising >30% of tumor)
  - Capsular or venous invasion
  - Predominantly lipid-depleted (non-clear) cells (<25% clear cells)
- Benign cortical adenomas in pediatric patients more commonly demonstrate high mitotic rate, necrosis, fibrous bands, and nuclear pleomorphism than their adult counterparts

Immunohistochemistry

- Immunoreactive for vimentin, but – for LMWK (*see* **Table 2**)
- May occasionally show immunoreactivity for neurofilament, S-100, synaptophysin, and neuron-specific enolase

Differential Diagnosis

- Cortical adenoma:
  - Smaller in size (usually 3–6 cm in adults)
  - Well-circumscribed, often encapsulated
  - May show some nuclear pleomorphism
  - No necrosis, increased mitoses, or invasion of capsule or vessels
- Metastatic carcinoma:
  - Common primary sites include lung, breast, gastrointestinal tract, thyroid, and kidney
  - Growth pattern usually solid rather than alveolar or trabecular
  - Immunohistochemistry: immunoreactive for cyto-keratin, epithelial membrane antigen, and/or carcino-embryonic antigen
- Melanoma:
  - Exceptionally primary, more commonly metastasis from an occult primary
  - Melanin pigment
  - Immunohistochemistry: immunoreactive for S-100 protein and HMB-45
- Pheochromocytoma:
  - Arising from adrenal medulla with normal adrenal cortex stretched out over its surface
  - Red-brown in color with areas of hemorrhage or cystic degeneration if large
  - Organoid growth pattern with nests of cells ("zell-ballen") and delicate vascular septa
  - Immunohistochemistry: immunoreactive for neuro-filament, chromogranin, synaptophysin, and S-100 (in sustentacular cell staining pattern); – for vimentin
- Liposarcoma:
  - Gross appearance white to yellow, poorly circumscribed, with infiltrating edges
  - Malignant cells with spindled to epithelioid appearance
  - Lipoblasts
  - Immunohistochemistry: immunoreactive for vimentin and S-100

Neuroblastoma (Stroma-Poor Neuroblastoma)

Clinical

- Malignant neurogenic tumor composed of immature neuroblasts
- 1 in 7,000–10,000 live births
- 50% of patients are <2 years old, 90% <8 years old; median age = 21 months
- Patients usually present with intraabdominal mass; may rarely be associated with hormonal (catecholamines, vasoactive intestinal peptide) or other para-neoplastic syndromes
- Infants at increased risk include those with fetal alcohol syndrome or fetal hydantoin syndrome



Fig. 96. Neuroblastoma. Circumscribed tumor with large red and yellow nodules.

- Prognosis related to number of factors:
  - Good prognostic signs: low stage (I–II), young age (<1 year), favorable histology, aneuploid tumors, <3 N-myc copies per cell, extra-adrenal location
  - Poor prognostic signs: higher stage (III–IV), older age, unfavorable histology, diploid tumor, >10 N-myc copies per cell, adrenal location
- 70% occur in retroperitoneum, usually adrenal gland
- Other sites include mediastinum, head and neck region, and pelvic region
- Common cytogenetic abnormalities include 1p deletions and amplification of N-myc oncogene (associated with poorer prognosis); tumor ploidy affects prognosis
- Associated with Beckman-Wiedemann syndrome and neurofibromatosis

*Macroscopic (**Figure 96**)*

- Solitary, soft gray, well-circumscribed masses
- Areas of hemorrhage, necrosis, calcification, or cystic degeneration often seen in large tumors

*Microscopic (**Figure 97**)*

- Cells small and uniform, with little cytoplasm and round, hyperchromatic nuclei with small nucleoli
- Individual cells separated by fine fibrillar eosinophilic matrix
- Cells arranged in sheets, which form vague lobules divided by thin fibrovascular septa
- Homer-Wright pseudorosettes (rings of neuroblasts, 1–2 layers thick, surrounding central area filled with eosinophilic fibrillary material) in 30% of cases
- Necrosis, hemorrhage, and calcifications common findings
- Tumors may show varying degrees of differentiation toward ganglioneuroma, with cellular and nuclear enlargement, prominent nucleoli, and stroma resembling neurofibroma (**Figures 98,99**)

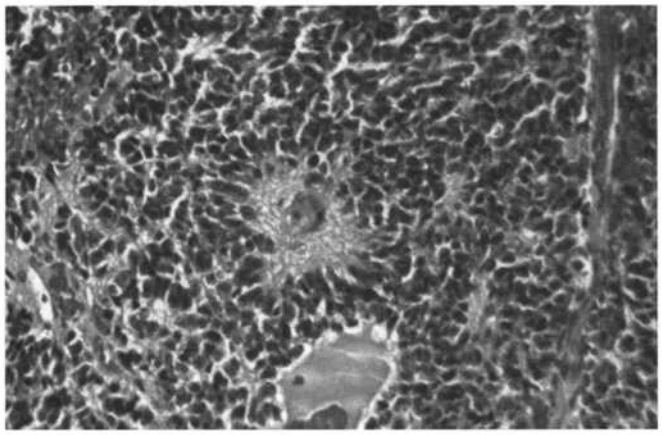


Fig. 97. Neuroblastoma. Population of small cells interspersed with pseudorosettes.

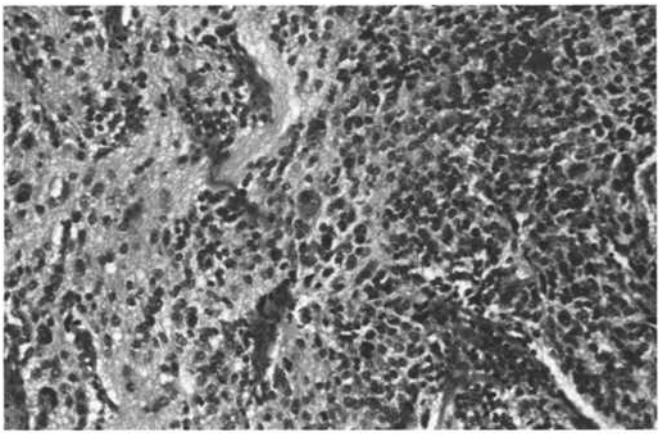


Fig. 98. Maturing neuroblastoma. Sheet of small cells (neuroblasts) merges into zone with accumulating glial fibrils.

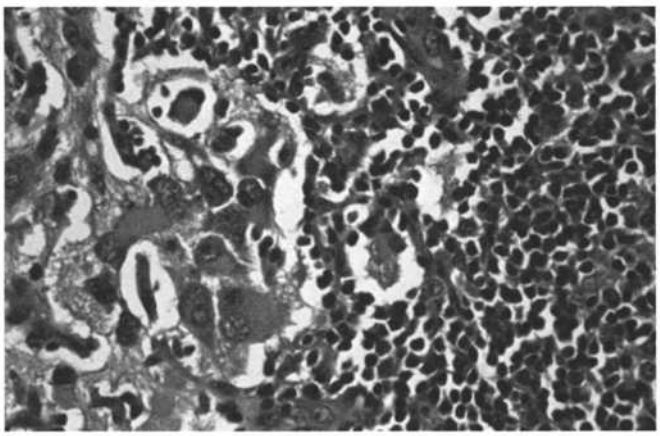


Fig. 99. Maturing neuroblastoma. Sheet of justapposed small cells (neuroblasts) and cells with ganglionic differentiation.

Immunohistochemistry

- Tumor cells immunoreactive for neuron-specific enolase, chromogranin, synaptophysin, microtubule-associated proteins, neurofilaments, alpha-internexin, secretogranin II, and vasoactive intestinal peptide (*see* **Table 2**)
- Stromal cells immunoreactive for S-100 protein, glial fibrillary acidic protein, and myelin basic protein

Electron Microscopy

- Neurosecretory granules (50–200 μm)
- Cell processes with microtubules
- Cytoplasmic filaments (100 μm)
- Synapse-like cell junctions

Variants

- Undifferentiated:
  - Contain <5% differentiating cells
  - 5-year survival = 36%
- Differentiating:
  - Contain >5% differentiating cells
  - 5-year survival = 72%
- Neuroblastoma, stroma-rich (*see* ganglioneuroblastoma)

Differential Diagnosis

- Ewing's sarcoma (extraskeletal):
  - Usually older patients (>5 years)
  - Histology very similar to neuroblastoma (may even have pseudorosettes rarely)
  - Immunohistochemistry: cytoplasmic staining with periodic acid-Schiff reaction
  - Electron microscopy: glycogen deposits, no neurosecretory granules
  - Cytogenetics: characteristic t(11;22) translocation
- Nephroblastoma (Wilm's tumor):
  - Microscopically composed of three elements: undifferentiated blastema, mesenchyme, and epithelium
  - Tumors composed largely of blastema may resemble neuroblastoma; need to look carefully for other elements
  - Immunohistochemistry: blastema stains only for vimentin, no reactivity with neuroendocrine markers
- Rhabdomyosarcoma:
  - Areas of hypo- and hypercellularity, characteristic "strap cells"
  - Immunohistochemistry: immunoreactive for actin and desmin
  - Electron microscopy: actin and myosin filaments, no neurosecretory granules or cytoplasmic processes
- Lymphoma:
  - Sheets of poorly cohesive cells with lymphocytic to epithelioid appearance; irregular nuclear borders
  - Immunohistochemisty: immunoreactive for T- and B-cell markers (CD3, CD20, leukocyte common

antigen); - for neuroendocrine markers (synaptophysin, chromogranin, etc.)
- Electron microscopy: no cytoplasmic filaments or cell junctions

Ganglioneuroblastoma (Stroma-Rich Neuroblastoma)

Clinical

- Combination tumor representing maturational intermediate between neuroblastoma and ganglioneuroma
- Usually seen in children <10 years, can occur in adults
- Presents as intraabdominal or intrathoracic mass; rarely seen with hormonal syndromes similar to neuroblastoma
- May occur in adrenal gland; more common in extra-adrenal retroperitoneum and mediastinum
- Cytogenetic findings similar to neuroblastoma

Macroscopic

- Varied, depending on relative proportion of fully differentiated and undifferentiated (or differentiating) elements:
- Differentiated variants tend to resemble typical ganglioneuromas (circumscribed firm white-gray masses)
- Undifferentiated variants show large nodular areas grossly resembling neuroblastoma (soft white-gray with areas of necrosis and hemorrhage

Microscopic

- Differentiated and undifferentiated areas with morphologic features of ganglioneuroma and neuroblastoma, respectively:
- Differentiated: collagenous stroma with scattered atypical ganglion cells
- Undifferentiated: sheets or nodules of small regular cells with hyperchromatic nuclei

Immunohistochemistry

- Typical for respective elements (*see* neuroblastoma and ganglioneuroma)

Electron Microscopy

- Typical for respective elements (*see* neuroblastoma and ganglioneuroma)

Variants

- Nodular (stroma-rich neuroblastoma, nodular):
  - Ganglioneuroma with one or more nodular masses of neuroblastoma
  - Poor prognosis (5-year survival = 18%)
- Intermixed (stroma-rich neuroblastoma, intermixed):
  - Ganglioneuroma with microscopic nests of neuroblasts
  - Good prognosis (5-year survival = 92%)
- Borderline (stroma-rich neuroblastoma, well differentiated):
  - Ganglioneuroma with scattered individual neuroblasts
  - Excellent prognosis (5-year survival = 100%)

Differential Diagnosis

- Neuroblastoma:
  - Similar to ganglioneuroblastoma, but neuroblasto-matous component usually composes >50% of tumor mass
- Ganglioneuroma:
  - No undifferentiated elements seen
  - Lymphocytes within stroma may mimic neuroblasts

TNM CLASSIFICATION OF THYROID CARCINOMAS (2002 REVISION)

- Primary tumor (T)*:
  - Each category may be subdivided into solitary tumor or multifocal tumor (the largest determine the classification)
  - TX: primary tumor cannot be assessed
  - T0: no evidence of primary tumor
  - T1: tumor = 2 cm in greatest dimension limited to thyroid
  - T2: tumor >2 cm but <4 cm in greatest dimension limited to thyroid
  - T3: tumor >4 cm in greatest dimension limited to thyroid or any tumor with minimal extrthyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissue)
- T4a: tumor of any size extending beyond capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
- T4b: Tumor invades prevertebral fascia or encase carotid artery or mediastinal vessels

*All anaplastic carcinomas are considered T4, which is subdivided into T4a (intrathyroid anaplastic carcinoma) and T4b (extrathyroidal anaplastic carcinoma)

- Regional lymph nodes (N):
  - Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes
  - NX: regional lymph nodes cannot be assessed
  - N0: no regional lymph node metastases
  - N1: regional lymph node metastases
  - N1a: metastasis to Level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes)
  - N1b: metastasis to unilateral, bilateral, or contralateral cervical or superior mediastinal lymph nodes
- Distant metastasis (M):
  - MX: distant metastasis cannot be assessed
  - M0: no distant metastasis
  - M1: distant metastasis

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15

Bone and Joints

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CONTENTS

I. Skeletal Trauma and Other Common Conditions 15-3
Heterotopic Ossification 15-3
Myositis Ossificans ("Traumatica") 15-3
Reflex Sympathetic Dystrophy (Algodystrophy) 15-4
Osteonecrosis (Avascular, Aseptic, Ischemic Necrosis) 15-4
Osteochondritis "Juvenilis" 15-5

II. Bone Infections 15-5
Pyogenic Osteomyelitis 15-5
Acute Osteomyelitis 15-5
Chronic Osteomyelitis 15-5
Sclerosing Osteitis (Sclerosing Osteomyelitis) 15-6
Chronic Multifocal Recurrent Osteomyelitis 15-6
Tubercular Osteomyelitis 15-6
Fungal Osteomyelitis 15-7

III. Arthritides 15-7
Osteoarthritis (OA) 15-7
Neuropathic Arthropathy (Charcot's Joints) 15-8
Crystal Arthropathies 15-8
Gout and Gouty Arthritis 15-8
Calcium Pyrophosphate Crystal Deposition Disease (Pseudogout, Chondrocalcinosis) 15-8
Rheumatoid Arthritis (RA) 15-9

IV. Metabolic Bone Diseases 15-9
Osteoporosis 15-9
Rickets and Osteomalacia 15-10
Primary Hyperparathyroidism 15-10
Paget's Disease (Osteitis Deformans) 15-11
Osteopetrosis (Albers-Schönberg Marble Bone Disease) 15-12
Osteogenesis Imperfecta (OI) 15-12
Mucopolysacharidoses 15-13
Gaucher's Disease 15-13

V. Musculoskeletal Neoplasms 15-13
Bone Cysts 15-13
Simple (Unicameral) Bone Cyst (UBC) 15-13
Intraosseous Ganglion 15-13
Aneurysmal Bone Cyst (ABC) 15-14
Bone-Forming Lesions 15-15
Osteoid Osteoma 15-15
Osteoblastoma 15-15
Osteosarcoma and Its Variants 15-16
Cartilagenous Lesions 15-20
Osteochondroma (Osteocartilaginous Exostosis) 15-20
Bizarre Parosteal Osteochondromatous Proliferation (Nora's Lesion) 15-21
Chondroma 15-21
Chondroblastoma 15-22
Chondromyxoid Fibroma 15-23
Chondrosarcoma and Its Variants 15-24

Vascular Lesions....15-25
Solitary Lymphangioma, Hemangioma and Skeletal Angiomatosis....15-25
Gorham's Disease (Massive Osteolysis)....15-26
Hemophilic Pseudotumor....15-26
Epithelioid (Histiocytoid) Hemangioethelioma....15-26
Angiosarcoma....15-26
Hemangiopericytoma....15-26
Glomus Tumor....15-26
Vascular Tumors in Immunocompromised Patients....15-27
Giant Cell Lesions....15-27
Giant Cell Tumor (Osteoclastoma)....15-27
Giant Cell Reparative Granuloma....15-28
Fibrous Lesions....15-28
Desmoplastic Fibroma....15-28
Fibrosarcoma....15-28
Fibro-Histiocytic Lesions....15-28
Benign and Atypical Fibrous Histiocytoma....15-28
Malignant Fibrous Histiocytoma (MFH)....15-28
Other Mesenchymal Lesions....15-29
Metaphyseal Fibrous Defect (Non-Ossifying Fibroma)....15-29
Fibrous Dysplasia (FD, Jaffe-Lichtenstein Syndrome)....15-29
Campanacci's Disease (Osteofibrous Dysplasia)....15-30
Fibrocartilaginous Mesenchymoma....15-30
Adamantinoma....15-30
Ewing's Sarcoma....15-30
Conventional Chordoma....15-31
Chondroid Chordoma....15-31
Plasma Cell Dyscrasias (Plasmacytoma/Multiple Myeloma)....15-32
Non-Hodgkin's Lymphoma....15-32
Langerhans' Cell Histiocytosis (LCH)....15-32
Erdheim-Chester Disease....15-32
Metastatic Bone Disease....15-33

VI. Staging of Musculoskeletal Neoplasms....15-33

VII. Suggested Reading....15-33

SKELETAL TRAUMA AND OTHER COMMON CONDITIONS

Heterotopic Ossification

Definition

- The term "heterotopic ossification" refers to bone formation within soft tissues
- By definition there is no history of trauma and no known underlying metabolic condition

Clinical

- The most common clinical situation is post-operative ossification in the hip following arthroplasty (although strictly speaking this is following surgical trauma)
- Prevalence: 2–90%, depending on the population studied and the criteria used
- Two types:
  - Central:
    - Around the neck of the femur
    - Individual-specific and is unrelated to prosthesis type, cement, or the mobilization regime
    - Strong genetic predisposition in certain populations
    - Radiation and anti-inflammatory drugs have been used to reduce the incidence
  - Lateral:
    - Around the trochanter
    - Follows surgery using the lateral (McFarland) approach
    - A misnomer; since it represents a form of traumatic ossification (myositis ossificans)

Differential Diagnosis

- Metastatic calcification in hyperparathyroidism
- Traumatic ossification (myositis ossificans)

Myositis Ossificans ("Traumatica")

Definition

- Reaction to trauma; seen most often in soft tissues, but also in a subperiosteal location (subperiosteal hematoma)
- This is a time-honored term, and is considered acceptable despite being neither a muscle nor an inflammatory disorder

Clinical

- Most often represents a localized tissue disruption, followed by a hematoma
- The hematoma is organized in a fashion similar to a healing fracture
- Clinically, may present as a painful mass or soft tissue tumor

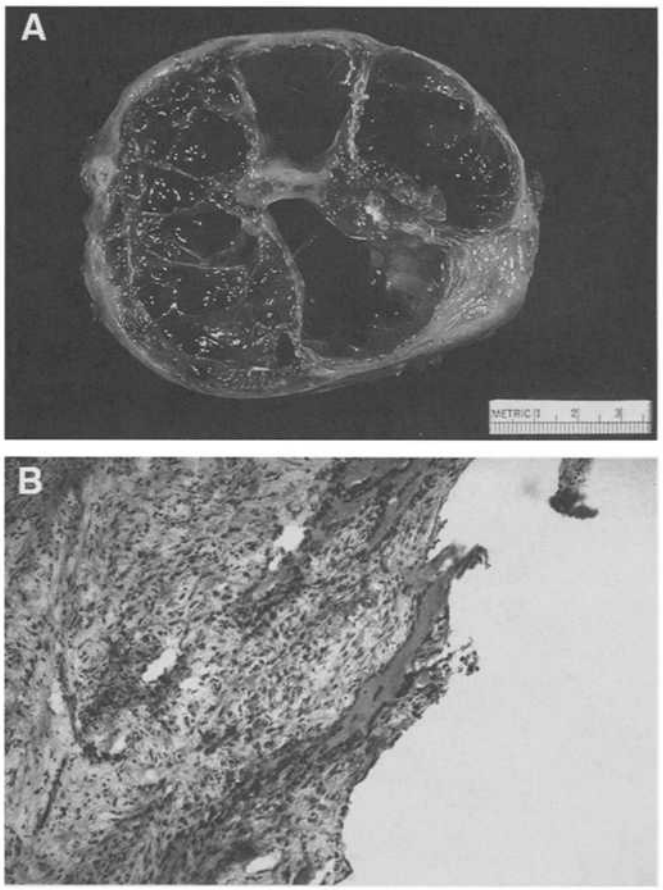


Fig. 1. Myositis ossificans (gross) forming a circumscribed mass with a bony shell and a hemorrhagic fibrous center **(A)**. Myositis ossificans (micro) at frozen section a well developed "zonation" is identified **(B)**.

Microscopic

- Ossification commences from the outside to within; in late stages, the entire mass may become ossified **(Figure 1A)**
- Zonation is present (maturation at periphery and immature fibroblasts located more centrally)
- The central fibroblastic repair reaction can be alarming **(Figure 1B)**

Differential Diagnosis

- Fibrodysplasia progressiva (previously called myositis ossificans progressiva): this is an entirely different and progressive condition that is genetic
- Bone forming tumors (such as osteosarcoma): can be differentiated since there is no peripheral maturation (zonation) in tumors. Additionally, osteosarcoma has a hypercellular spindle cell proliferation with considerable cytological atypia and sometimes sheets of atypical osteoblasts

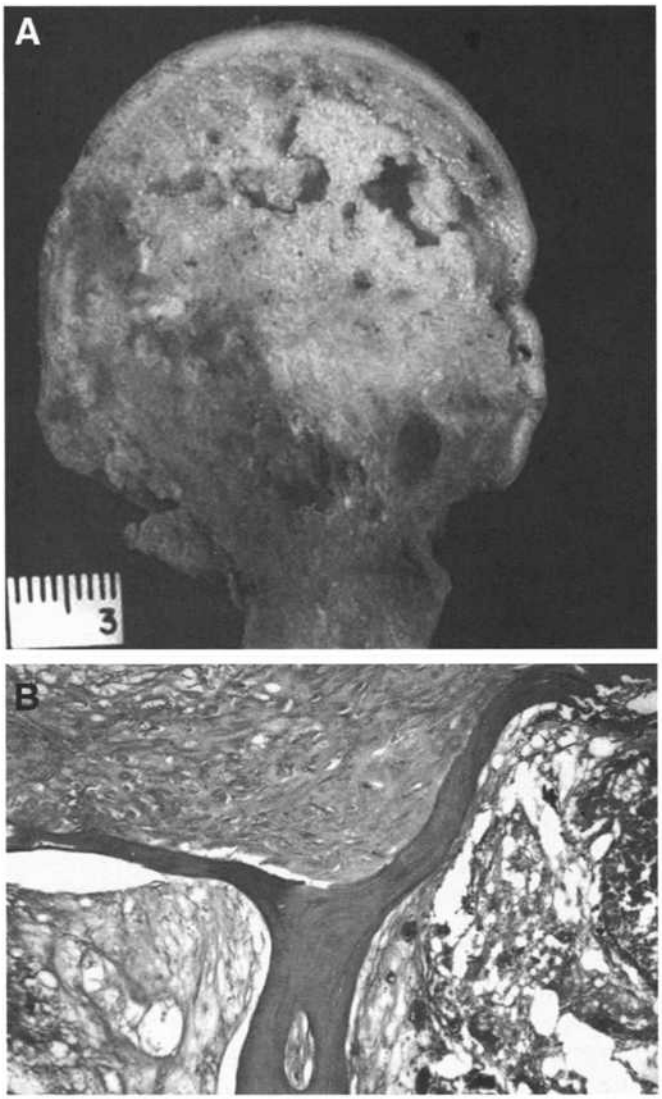


Fig. 2. Avascular necrosis of the femoral head (gross) **(A)**. The photograph shows the infarcted bone is beginning to separate from the adjacent bone and the overlying cartilage **(A)**. The trabeculae are anucleate and the adjacent marrow shows necrosis and fibrosis **(B)**.

Reflex Sympathetic Dystrophy (Algodystrophy)

Definition

- A condition of severe regional, patchy osteopenia and often pain, following trauma

Clinical

- Associated with trophic skin changes, edema of the extremity, and psychological disturbances
- Must be differentiated from other forms of osteopenia such as bone marrow edema, transient osteoporosis, migratory osteolysis, and idiopathic regional osteoporosis

Microscopic

- Proliferation of fibroblasts within the marrow space
- Bone necrosis and new bone formation may be seen

Osteonecrosis (Avascular, Aseptic, Ischemic Necrosis)

Definition

- The in situ death of bone, presumably from one or more vascular insults. By definition necrosis of bone occurring as a result of infection is excluded **(Figure 2A)**

Clinical

- Two main forms:
  - Medullary infarction (marrow cavity and trabecular bone):
    - Usually silent
  - Cortico-medullary infarction (cortex also involved):
    - May be painful and progressive
- Conditions predisposing to osteonecrosis:
  - Trauma, infection, fatigue fractures
  - Alcohol abuse
  - Dysbarism
  - Gaucher's disease
  - Connective tissue disorders
  - Vasculitis
  - Hemoglobinopathies, coagulopathies
  - Radiation injury
  - Corticosteroid therapy
  - Pregnancy
  - Aging
  - Gout
  - Pancreatitis
  - Childhood osteochondritides such as Perthe's, Keinbock's, Sever's, Kohler's, Larsen's, Blount's, or Panner's disease
- The pathogenesis remains uncertain
- The condition is suspected on the basis of clinical history, physical findings, X-rays, and scanning techniques
- MRI is especially sensitive for detection
- Diagnosis is confirmed by biopsy

Microscopic

- Anucleate bone (with empty lacunae) is the most prominent finding. Surrounding this is reactive hyperemia in the early course **(Figure 2B)**
- Fibrovascular proliferation adjacent to the bone
- The necrotic bone is walled off, in a fashion similar to sequestrum formation in osteomyelitis
- Revascularization of dead bone occurs in a few weeks
- "Cutting cones" of osteocasts carrying blood vessels enter the dead bone, removing it by osteoclastic resorption

- At the same time, osteoblasts lay down bone on top of this necrotic fragment
- The next stage is unpredictable, depending on the site and extent of damage:
  - May culminate in restitution (complete healing)
  - May lead to the relentless continuation of the repair process that damages the integrity of bone
  - This second course leads to fatigue fractures, collapse of the subchondral bone, cartilage disintegration, and joint deformity

Osteochondritis "Juvenilis"

- Refers to the earlier set of eponymic names for avascular necrosis occurring in certain bones
- Includes conditions such as Perthe's, Keinbock's, Sever's, Kohler's, Larsen's, Blount's, or Panner's diseases
- With the exception of Perthe's disease (which may be associated with constitutional skeletal abnormalities), these conditions are similar to the osteonecrosis occurring in the noneponymic locations

BONE INFECTIONS

Pyogenic Osteomyelitis

Acute Osteomyelitis

Clinical

- Infections can reach the bone by:
  - Hematogenous route:
    - This is the most common way, and may be associated with an antecedent focus of infection elsewhere
    - Most cases of hematogenous osteomyelitis occur in the metaphyses of long tubular bones in children
  - Direct extension:
    - Usually in association with trauma. It has no predisposition to children
- Commonly encountered organisms:
  - Staphylococcus aureus (most common)
  - Escherichia coli, Klebsiella and Pseudomonas species
  - Salmonella (in patients with sickle cell anemia):
    - Results in a cortically based osteomyelitis
  - Treponema, gram-rods, streptococci, Hemophilus influenzae and Listeria species (occur in neonates)
  - Pseudomonas infections (addicts abusing intravenous street drugs)

Macroscopic

- Region is often intensely hyperemic
- The pressure exerted by the pus may compress smaller vessels, which may result in additional ischemic damage to the bone
- The exudate follows the path of least resistance and exits through the Volkmann canals into the subperiosteal space
- In the neonatal age group, the Sharpey's fibers are less well-developed; thus, considerable subperiosteal spread may occur
- Medullary spread may cause additional damage
- In severe cases, the combination of subperiosteal and intramedullary spread can cause the entire diaphysis to become necrotic, forming a "ring sequestrum"

Microscopic

- Bone destruction (anucleate bone) surrounded by polymorphonuclear leukocytes, and cell debris

Chronic Osteomyelitis

Clinical

- Although de novo cases also occur, the majorities are a result of unresolved acute osteomyelitis
- A protracted course, interspersed with acute exacerbations
- Because of the low levels of causative organisms, cultures are often negative
- Common organisms include:
  - *Staphylococcus aureus*
  - *Streptococci* (group A is more frequent)
  - *Klebsiella* (may cause extensive bone damage)
  - *Aerobacter, Proteus, Brucella, Staphylococcus epidermidis*, and *Bacteroides*

Microscopic

- Necrotic bone in an chronic inflammatory background
- When the necrotic fragment separates from the adjacent tissue, it is known as a sequestrum:
  - Separation of the sequestrum generally takes months to complete
  - The bone is often of cortical origin
- The bone surrounding a focus of chronic osteomyelitis is often dense, and is referred to as the "involucrum":
  - The involucrum is often of periosteal origin
  - The involucrum frequently has several openings of "cloacae" through which exudate, bone debris, and sequestra exit and pass through sinus tracts to the surface **(Figure 3A)**
  - Constant destruction of the neighboring soft tissues leads to scarring and squamous metaplasia of the sinus tract
- The microscopic diagnosis of chronic osteomyelitis can be difficult

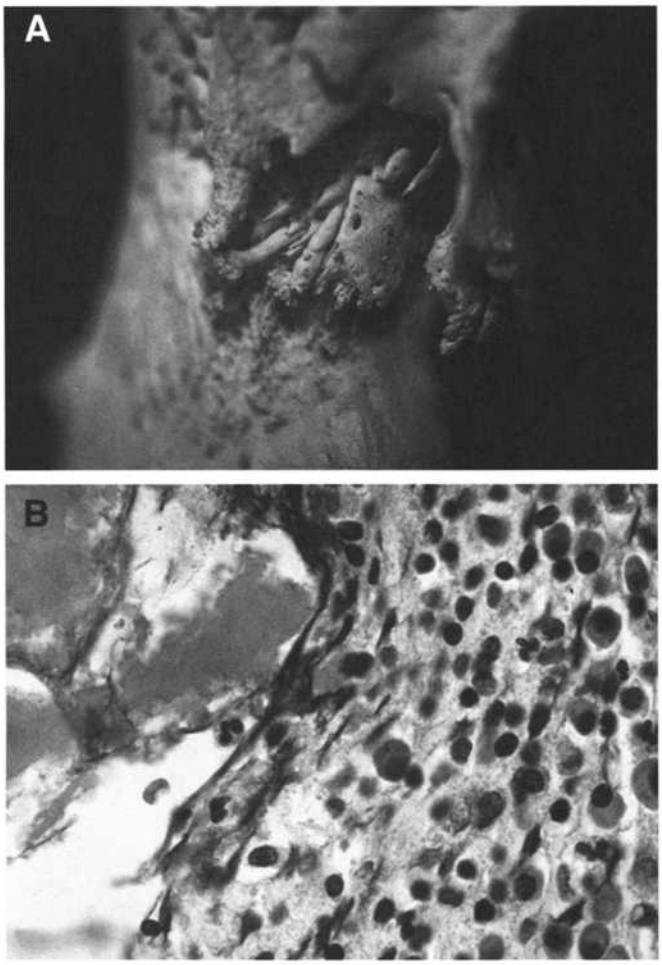


Fig. 3. Chronic osteomyelitis showing bone thickening and colaca/sinus formation **(A)**. Chronic osteomyelitis may show several plasma cells and have to be differentiated from a plasma cell dyscrasia or myeloma **(B)**.

- The inflammatory infiltrate is often sparse and may mimic the normal elements of the marrow space and sometimes be mistaken for a hematological malignancy **(Figure 3B)**
- Microscopic recognition of the sequestrum is helpful for the diagnosis of infection:
  - The sequestrum is recognized by virtue of its anucleate nature; often the edges are jagged (because of the action of proteolytic enzymes and osteoclastic action)
  - Overdecalcification of bone during processing can cause the bone to become artificially "anucleate," making the recognition of dead bone particularly difficult

Differential Diagnosis

- Normal marrow:
  - Preservation of normal fat pattern of marrow
  - Lack of fibrous background

Sclerosing Osteitis (Sclerosing Osteomyelitis)

Definition

- The condition of gradual, usually unilateral bony sclerosis, often associated with pain

Clinical

- Usually affects children
- Most frequent sites include the tibia, jaw, and clavicle (and pubis in adults)
- Constitutional symptoms are infrequent

Microscopic

- Non-specific
- Biopsy fails to show inflammation
- Culture results often negative

Chronic Multifocal Recurrent Osteomyelitis

Clinical

- Recurrent episodes of bone pain, erythema, and swelling
- X-rays and bone scans are consistent with osteomyelitis
- Antimicrobial therapy is not helpful
- Usually resolves with time

Microscopic

- Bone biopsies confirm the suspicion of osteomyelitis
- Organisms are usually not isolated
- May be related to the sero-negative spondyloarthropathies

Tubercular Osteomyelitis

Clinical

- Occurs frequently in children
- Occurs in vertebrae, or in long tubular bones in a metaphyseal location
- In adults, vertebrae or epiphyses of the long bones may be involved

Pathology

- May affect the bone, the joints, or (frequently) both **(Figure 4A)**
- Often occurs by hematogenous spread
- Usually is associated with a reactivation of a preexisting primary focus in the lung
- The emergence of multi-drug-resistant tuberculosis and the AIDS epidemic have reemphasized the importance of mycobacterial infections

Microscopic

- The disease has traditionally been divided into the "dry or granular" and the "exudative" types **(Figure 4B)**
- Granulomatous inflammation, often with Langerhans'-type giant cells **(Figure 4C)**
- Special stains often (but not always) reveal acid-fast organisms

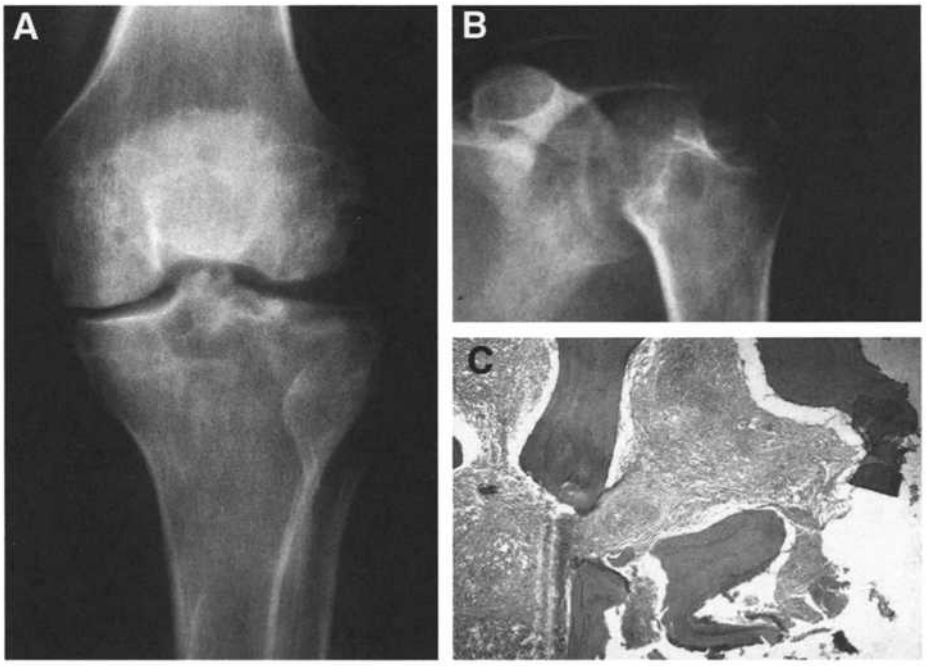


Fig. 4. Tuberculosis of the knee showing multiple lucencies and an erosion of the femoral condyle **(A)**. Caries sicca – a "dry or non-exudative" form of tuberculosis involving the shoulder joint **(B)**. Granulomatous inflammation in the inter-trabecular spaces **(C)**.

Fungal Osteomyelitis

- Fungal infection of bone is uncommon
- More common infections include:
  - Blastomycosis
  - Coccidiodomycosis
  - Actinomycosis
  - Maduramycosis
  - Sporotrichosis
- These infections often involve the hands, feet, or craniofacial skeleton

ARTHRITIDES

Osteoarthritis (OA)

- Also termed degenerative joint disease
- Generally refers to a failure of diarthrodial (movable, synovial lined) joint
- Two forms:
  - Idiopathic (primary) OA:
    - Most common
    - No known predisposing factor
  - Secondary OA:
    - Attributed to an underlying cause (developmental disorders, metabolic or endocrine conditions, crystal deposition, trauma, infection, avascular necrosis, neuropathic disease, etc.)
    - Pathologically indistinguishable from idiopathic form

Microscopic

- The most striking changes are seen in load-bearing areas of the articular cartilage
- In the very early stage, the cartilage is thicker than normal
- The joint surface thins and the cartilage softens with progression
- The integrity of the surface is breached and vertical clefts develop with fibrillation **(Figure 5)**
- Areas of fibrocartilaginous repair may develop
- The articular cartilage is metabolically active and the chondrocytes replicate, forming clusters (termed "cloning")
- Later, the cartilage becomes hypocellular
- Remodeling and hypertrophy of bone are also major features:
  - Appositional bone growth occurs in the subchondral region
  - The abraded bone under a cartilage ulcer may resemble ivory wood (termed "eburnation")
- Growth of cartilage and bone at the joint margin leads to osteophytes (spurs)

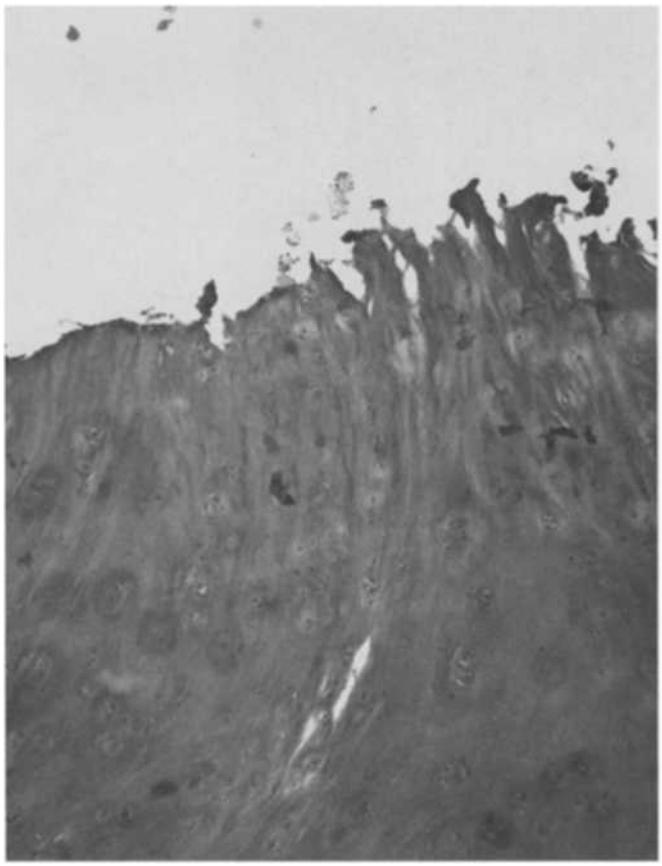


Fig. 5. Osteoarthritis with clefting of the articular cartilage.

- Osteophytes alter the contour of the joint, restricting movement
- Thickening of the joint capsule along with chronic synovitis further restricts joint movement

Neuropathic Arthropathy (Charcot's Joints)

Clinical

- Extremely destructive joint disorder in patients with neurosyphilis, diabetes or other causes of damaged sensory innervation to the joint
- With the decline of tertiary syphilis, other causes of neuropathic joints have now become more important, such as:
  - Diabetes
  - Syringomyelia
  - Amyloidosis
  - Alcoholic neuropathy
  - Leprosy

Microscopic

- Fragmentation of the joint surface with extensive detritic synovitis resulting from particles of bone and cartilage embedded in the synovium

Crystal Arthropathies

Pathogenesis

- Crystal arthropathy can be caused by endogenous (monosodium urate [MSU], calcium pyrophosphate [hydroxyapatite]) and exogenous (corticosteroid ester crystals, talc, polyethylene, methylmethacrylate) crystal deposition producing disease by triggering a cascade that results in cytokine-mediated cartilage destruction

Gout and Gouty Arthritis

Clinical

- Gout is the common end point of a group of disorders that produce hyperuricemia
- Marked by transient attacks of acute arthritis initiated by the crystallization of urates within and around joints
- Deposition of masses of urates in joints and other sites, creating tophi
- Factors that may result in the conversion of hyperuricemia into primary gout:
  - Age (gout rarely appears before age 20–30)
  - Duration of the hyperuricemia
  - Genetic predisposition:
    - X-linked abnormalities of hypoxanthine-guanine phosphoribosyl transferase (HGPRT)
    - Multifactorial inheritance
  - Heavy alcohol consumption
  - Obesity
  - Thiazide diuretics
- Gout can result in:
  - Acute arthritis
  - Chronic tophaceous arthritis
  - Gouty nephropathy
  - Tophi in various sites

Microscopic

- Characteristic needle-like crystals that are negatively birefregent under polarized light

Calcium Pyrophosphate Crystal Deposition Disease (Pseudogout, Chondrocalcinosis)

- Three types:
  - Sporadic
  - Hereditary
  - Secondary types linked to:
    - Hyperparathyroidism
    - Hemochromatosis
    - Hypomagnesemia
    - Hypothyroidism
    - Ochronosis
    - Diabetes

- More common at age 50 or older
- Joint involvement may mimic OA or rheumatoid arthritis (RA)
- Pathogenesis is uncertain:
  - Altered activity of the cartilage matrix enzyme produces and degrades pyrophosphate, resulting in its accumulation and eventual crystallization
  - The crystals first develop in the articular matrix, menisci, and intervertebral discs

Rheumatoid Arthritis (RA)

Clinical

- A systemic disease that manifests in the joints as a synovial lesion
- Autoimmune inflammatory process that targets primarily the synovial tissue
- Humoral and cellular immune response is involved

Microscopic

- Nonsuppurative chronic inflammation in the capsule of the joint:
  - Hypertrophy and hyperplasia of the synovial cells resulting grossly in a papillary pattern on the surface of the synovium
  - Later, a pannus forms:
    - Combination of proliferating mesenchymal cells and granulation tissue starting at the periphery of a joint and subsequently destroying articular cartilage

METABOLIC BONE DISEASES

Osteoporosis

Definition

- A condition characterized by a reduced amount of normally mineralized bone

Classification

- Postmenopausal (type I)
- Age related (type II)
- Secondary (accounts for ~5% of cases):
  - Can be seen in a variety of conditions:
    - Osteogenesis imperfecta
    - Turner syndrome
    - RA
    - Systemic mastocytosis
    - Hyperthyroidism
    - Adrenal disease
    - Steroid or heparin therapy
    - Chronic alcoholism
    - Space travel

Clinical

- Higher incidence associated with:
  - Race (Caucasians > African Americans)
  - Sex (F > M)
  - Physical inactivity
  - Slender body builds
  - Smoking
  - Nulliparity
  - Early menopause
- The major clinical symptoms are those of fractures
- Common sites include:
  - Spinal vertebral crush fractures
  - Hip fractures
  - Colle's or other fractures of the distal radius
- Laboratory investigations include the exclusion of other metabolic diseases by assessing:
  - Serum calcium
  - Serum phosphate
  - Alkaline phosphatase
  - 25-hydroxy and 1,25-dihydroxy-vitamin D
  - Urinary calcium
- Biologic markers that may be useful for assessing bone turnover:
  - Bone-specific alkaline phosphatase
  - Serum/urinary osteocalcin
  - Serum Type I collagen extension peptides
  - Plasma tartrate resistant acid phosphatase
  - Urinary levels of hydroxyproline
  - Urinary pyridinoline crosslinks of type I collagen
- Pathogenesis:
  - Postmenopausal osteoporosis:
    - Associated with increased osteoclastic activity
    - May be initiated or maintained by a variety of bone cytokines, perhaps initiated by RANK and RANK-ligand interaction
    - May be genetically predetermined by the polymorphisms of the Vitamin D receptor gene
  - Age-related osteoporosis:
    - Inefficiency of bone formation in a normal remodeling cycle

- Less bone is formed than is resorbed with each remodeling cycle throughout life

Microscopic

♦ Cortex:
- Enlarged Haversian and Volkmann's canals tunneled by osteoclasts
- The cortex is thinned:
  - Caused by resorption of the subperiosteal and endosteal surfaces
  - Endosteal resorption results in a blurring of the cortical-cancellous border, referred to as "trabeculization" of the cortex

♦ Trabecular bone:
- Thinning and perforation of the trabeculae:
  - Perforation is an irreversible process, which occurs when an osteoclast resorbs bone all the way through a trabeculum or when two osteoclasts fortuitously located at opposite ends of the trabeculum meet midway
- These thin trabeculae seem to "float" in the marrow space
- Increased osteoclastic activity may be seen in "high turnover" (postmenopausal) osteoporosis

Rickets and Osteomalacia

Definition

♦ Syndromes (rather than specific disease entities) characterized by a failure of normal mineralization of bone and epiphyseal cartilage

♦ Clinically characterized by bone deformities

♦ In Rickets (which occurs in children), bone and epiphyseal cartilage is involved

Causes of Rickets and Osteomalacia

♦ Deficiency states: diet; lack of sunlight

♦ Gastrointestinal causes: gastric resections; biliary and enteric causes

♦ Renal tubular causes:
- Hypophosphatemic states
- Fanconi syndromes
- End organ defect
- Renal tubular acidosis

♦ Unusual causes:
- Phosphaturic tumors **(Figure 6)**
- Anticonvulsant therapy

♦ Renal osteodystrophy: renal failure

Pathology

♦ Rickets:
- A disease of the growing skeleton
- Affects the epiphyseal plate and bones of children

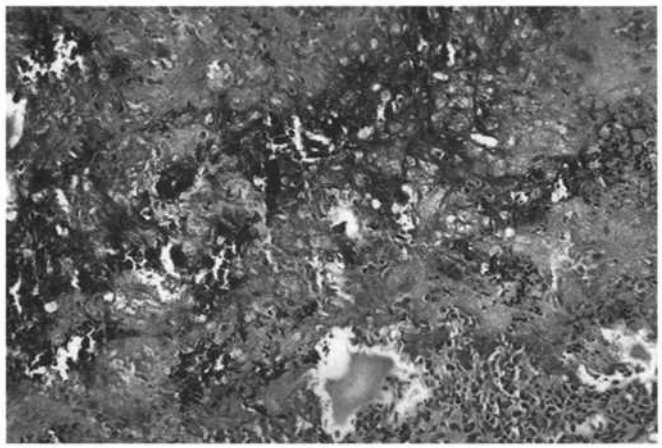


Fig. 6. Mesenchymal phosphaturic tumor (initially called a cartilaginous neoplasm) that caused oncogenic osteomalacia. The tumors are thought to produce phosphatonin, a hormone (possibly fibroblast growth factor 23) that causes phosphaturia.

♦ Osteomalacia:
- Occurs in adults, after the growth cartilage has fused and the epiphysis is obliterated

♦ In both instances, there is insufficient ionized calcium or inorganic phosphate (or both) to mineralize the skeleton, leading to less mineralized bone per unit volume of bone

♦ There may be less bone overall, but more strikingly, the bone that is present fails to mineralize properly

♦ Trabeculae are surrounded by unmineralized osteoid, called "osteoid seams":
- Osteoid seams >12.5 μm are virtually diagnostic
- Bone histomorphometry has shown that the mineralization lag time is >100 days in rickets/osteomalacia (normal = 80–90 days)

♦ All rachitic syndromes have similar histology and the individual diagnosis cannot be made on the basis of a bone biopsy

♦ Stains for aluminum may be considered in renal osteodystrophy

♦ In rickets, pressure effects cause deformity at the epiphysis-metaphysis junction, resulting in metaphyseal flaring and a disordered physis

Primary Hyperparathyroidism

♦ This entity was defined in part by Von Recklinghausen under the term osteitis fibrosa cystica generalisata

♦ Most often results from a hyperplasia or adenoma (and rarely a carcinoma) of the parathyroid glands:
- The diseased gland does not recognize the signal of high serum calcium concentration
- There is increased production of 1,25-dihydroxyvitamin D and parathyroid hormone, increasing absorption of

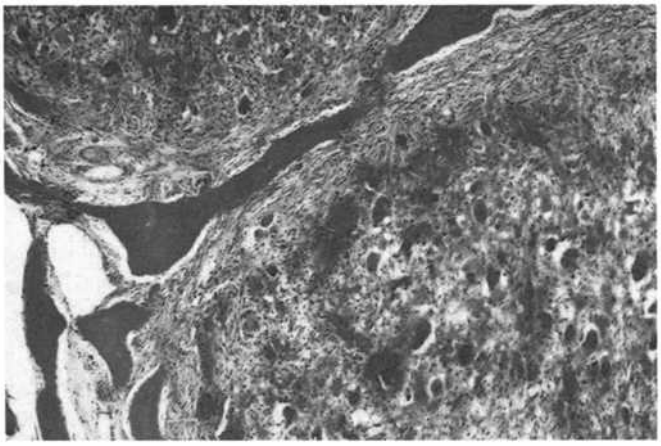


Fig. 7. Brown tumor. There is fibrosis, hemorrhage and a cluster of osteoclast giant cells.

calcium from the gut and bone and preventing its excretion in the kidney
- Simultaneously, there is hyperphosphaturia
- Serum levels of alkaline phosphatase are frequently high

Microscopic

- The bones are characterized by:
  - Fibrosis of the marrow
  - Osteoclastic resorption
  - Osteoblastic rimming on new and often incompletely mineralized lamellar bone trabeculae (narrow osteoid seams)
  - "Brown tumors" (**Figure 7**):
    - These represent granulation tissue, inflammatory cells, and macrophages containing hemosiderin and giant cell formation
    - There is virtually no bone present in these areas
- Occasionally, cystic change may supervene
- Increased osteoclastic activity is seen in subperiosteal, intracortical, endosteal, subchondral, and trabecular surfaces:
  - Intracortical resorption is characterized by groups of osteoclasts (known as cutting cones) that tunnel through the cortex, enlarging the Haversian and Volkmann's canals:
    - These channels are often expanded to 1 mm or more in some cases, and may be seen radiographically as lucent lines within the cortex
  - Endosteal resorption is also visible radiographically as "scalloping" of the cortex at its marrow interface
  - Subchondral resorption is best seen histologically (and radiographically) at the sacroiliac joint

Paget's Disease (Osteitis Deformans)

Clinical

- Patients above the 4th decade
- Slight male predominance
- Common among the white population of England, France, Austria, Germany, Australia, New Zealand, and the United States
- Rare in Scandinavia, China, Japan, and Africa
- May be uni- or multi-focal
- Most frequent involvement in the axial and the proximal appendicular skeleton
- Less frequent involvement in the ribs, fibulae, and bones of the hands and feet
- Presenting symptoms:
  - Pain
  - Increased width of bone
  - Weight-bearing bones may be bowed or deformed
  - May be asymptomatic and discovered incidentally
  - Hyperdynamic circulation may lead to high output cardiac failure
  - The most common secondary malignancy is osteosarcoma
- Radiographically, three phases can be discerned: lytic, mixed, and blastic:
  - Eventually, the disease "burns itself out" in that particular site
- Laboratory investigations reflect this increased bone turnover through increased levels of serum alkaline phosphatase and urinary hydroxyproline

Etiology

- Possibly related to an infection by a paramyxovirus, similar to measles or respiratory syncitial virus:
  - In situ hybridization studies have localized canine distemper virus (a paramyxovirus) in Pagetic osteoblasts, osteoclasts, and osteocytes
  - The target of the virus is probably the osteoblast; however, the cell-associated virus particles have only been found in the osteoclasts
  - Retroviruses can induce the secretion of IL-6 from fibroblasts and macrophages
  - IL-6 is thought to be important in the pathogenesis of Paget's disease and is implicated in the recruitment and activation of osteoclasts

Microscopic

- Paget's disease is a focal process
- The histologic hallmark is mosaic lamellar bone:
  - characterized by haphazard cement lines (jigsaw-like pattern) (**Figure 8**)
- Lytic phase:
  - Waves of osteoclastic activity
  - Numerous resorptive pits
- Mixed phase:
  - The osteoclasts are admixed with osteoblasts, which line the bone surfaces

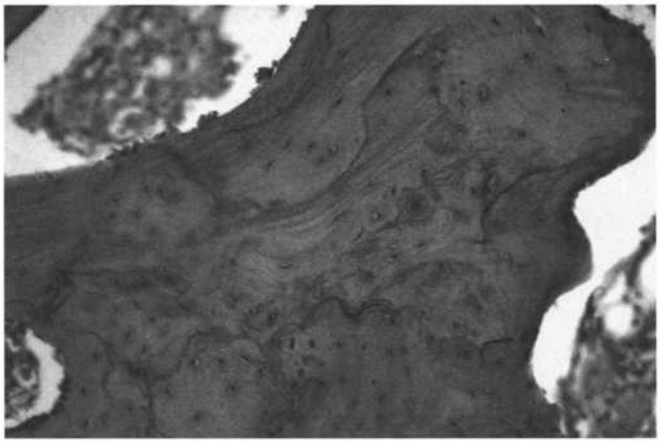


Fig. 8. Mosaic bone of Paget's disease.

- The marrow adjacent to the bone becomes replaced by loose, vascularized, connective tissue
- The newly formed bone is initially woven bone, and is later remodeled into lamellar bone
- As the mosaic pattern becomes prominent, cell activity ceases
- The fibrovascular tissue is replaced by normal marrow (burnt out phase)
- Eventually, the bone becomes larger, with thick, irregular trabeculae and porous corticies

♦ Blastic phase:
- Characterized by reactive and lamellar bone

Osteopetrosis (Albers-Schönberg Marble Bone Disease)

Definition

♦ A group of hereditary diseases characterized by osteoclast dysfunction resulting in diffuse, symmetric, stone-like, skeletal sclerosis and abnormally brittle bone

♦ Bisphosphonate—induced osteopetrosis has been reported

Clinical

♦ Several clinical variants are distinguished:
- Autosomal recessive form ("malignant") (ARO):
  - 50% of patients harbor mutations of the ATP 6i gene (TCIRG 1) encoding the osteoclast-specific a3 subunit of the vacuolar H^+-ATP-ase
- Autosomal dominant form types I and II:
  - ClCN7 gene mutations underlie type II ADO. This gene encodes for the type 7 chloride channel located in the osteoclast border membrane

♦ Other genetic abnormalities have been described:
- Deficiency of osteoclast carbonic anhydrase II, deletions of c-src gene, macrophage colony stimulating factor, etc.

♦ Patients have a high postnatal mortality

♦ Survivors have anemia, fractures, and hydrocephalus

♦ Later in life, patients are prone to cranial nerve problems and recurrent infections

♦ Extramedullary hematopoisis results in hepatosplenomegaly

Microscopic

♦ Bones lack a medullary cavity

♦ The ends of the bones are bulbous (Erlenmeyer flask deformity)

♦ Neural foramina are small, compressing the exiting nerves

♦ Primary spongiosa consisting of ossifying cartilage persists

♦ Medullary cavity contains little or no hematopoietic elements due to overgrowth and accumulation of the primary spongiosa

♦ Bone is mainly woven and lacks remodeling

♦ The numbers of osteoclasts may be normal, increased, or decreased

Osteogenesis Imperfecta (OI)

Definition

A heterogeneous group of conditions characterized by bone fragility and mutations in the loci coding for the pro-α1 and pro-α2 collagen chains (COL1A1 on 17q21 and COL1A2 on 7q22.1)

Classification

♦ Type I:
- Autosomal dominant
- The less severe form
- Loose joints and low muscle tone
- Bone predisposed to fractures
- Blue/purple tint of the sclera

♦ Type II:
- Autosomal dominant with new mutation
- The most severe form
- Lethal at or shortly after birth due to respiratory failure
- Numerous fractures, severe bone deformity

♦ Type III:
- Autosomal dominant with new mutation. Rarely, autosomal recessive forms are observed
- Bone fracture easily, with fractures often present at birth
- Bone deformity, frequent severe
- Associated respiratory problems

♦ Type IV:
- Autosomal dominant
- Severity between types I and III

Microscopic

♦ Amount of osseous tissue is decreased

- There may be fibromembranous tissue with foci of bone, especially in the severe forms (this finding is more common in the skull)
- In the long bones, the cortices are thin, except at the site of a fracture
- Sparse trabeculae in the medullary cavity
- The inner (cambium) layer of the periosteum may be prominent
- The osteoblasts lining the bone trabeculae tend to be less plump, and more spindled than is normal
- Osteoclasts are sparse
- The growth plates are normal and ossification is not delayed
- The ossification centers may be smaller than normal
- The chondrocytes and cartilage matrix appear normal by light microscopy
- The teeth are abnormal:
  - The mesodermal component is severely affected and may be deficient
  - The ectodermal component is usually normal

Mucopolysacharidoses

Definition

- A heterogeneous group of lysosomal storage disorders, associated with glycosaminoglycan excretion in the urine and accumulation in the tissues
- Deficiencies in enzymes (acid hydrolases) that degrade the glycosaminoglycans
- Cartilage tends to be severely affected

Classification (several types, common ones are)

- Type I (Hurler syndrome):
  - Associated with defects in α-L-iduronidase
  - Results in accumulation of dermatan sulfate
- Type II (Hunter syndrome):
  - Associated with defects in L-iduronosulfate sulfatase
  - Results in accumulation of heparan sulfate

Gaucher's Disease

Definition

- A group of conditions resulting from different allelic mutations in the structural gene of the enzyme glucocerobrosidase

Biochemical Basis

- The gene of glucocerebrosidase is located on chromosome 1q21
- The enzyme cleaves glucose from ceramide

Clinical

- Glucocerobroside accumulates in the phagocytic cells and in the cells of the central nervous system
- Skeletal manifestations include the Erlenmeyer flask deformity of the femur, osteonecrosis of the femoral head, bone infarcts, and pathologic fractures

MUSCULOSKELETAL NEOPLASMS

Bone Cysts

Simple (Unicameral) Bone Cyst (UBC)

Clinical

- Most patients are within the first two decades of life, with male predominance
- Sudden onset of pain from pathologic fracture
- ~80% of cases are seen in either the humerus or femur
- May occur in the ilium and calcaneus in older patients
- Hemodynamic data may help the differential diagnosis from aneurysmal bone cysts and giant cell tumor

X-rays and Imaging Findings

- Geographic, lytic, and cystic lesions, often metaphyseal
- May encroach the epiphysis in skeletally immature individuals
- As the bone lengthens at the physeal end, the cyst may appear to "move" into a diaphyseal location

Microscopic

- An intramedullary cystic cavity, often unilocular, and filled with clear or straw-colored fluid
- Cyst lined by a thin, fibrovascular membrane
- Irregular fragments of membranous, fibrovascular tissue
- Hemosiderin, granulation tissue or mild focal chronic inflammatory cells
- Pink, cementum-like, rounded material may be seen:
  - These may be examples of the Liesegang phenomenon, forming from diffusion and precipitation of supersaturated solutions

Intraosseous Ganglion

Definition

- An intramedullary, mucin-filled, fibrous-lined lesion

Clinical

- Wide age range, often with pain; incidental finding

- The distal and proximal tibia, femur, ulna, and the hands and feet are commonly involved

X-rays and Imaging Findings

- Geographic lesions that are epiphyseally located and show sclerotic margins
- The joint articular surface is usually normal (as opposed to subchondral cysts)

Microscopic

- Mainly myxoid tissue mixed with fibroblasts
- Fibrous tissue may be haphazardly interspersed or be arranged in the form of septa
- The outer layer is often heavily collagenized

Differential Diagnosis

- Extragnathic fibromyxoma
- Chondromyxoid fibromas
- Subchondral cysts of degeneration joint disease

Aneurysmal Bone Cyst (ABC)

Clinical

- Wide age range, but mostly occurs between ages 5–25 years
- Pain of a few weeks duration is most common
- Most primary ABCs of long bones are metaphyseal in location
- Secondary ABCs follow the site of predilection of their primary lesions
- May represent a change secondary to an arterio-venous malformation or to a variety of different bone neoplasms, including:
  - Giant cell tumor
  - Non-ossifying fibroma
  - Giant cell reparative granuloma
  - Fibrous dysplasia
  - Chondromyxoid fibroma
  - Chondroblastoma
  - Osteoblastoma
  - UBC
  - Hemangioma
  - Osteosarcoma
- The diagnosis of ABC is essentially that of exclusion
- Some of these lesions spontaneously regress

X-rays and Imaging Findings

- A benign (and probably non-neoplastic) lesion that is often multicystic, rapidly expansile, and locally destructive
- The ABCs of long bones may be eccentric, parosteal (an uncommon location), and central
- In the initial (or incipient) phase, there is a small lytic lesion that does not expand the bone

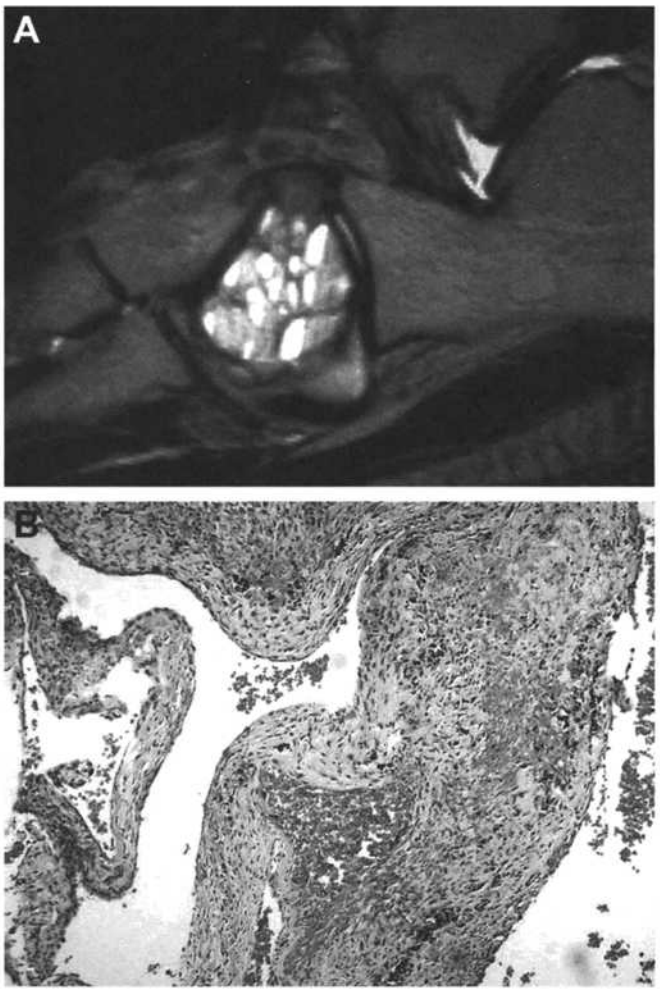


Fig. 9. Aneurysmal bone cyst—MRI showing fluid levels within a well-delineated lesion limited to the cuboid **(A)**. Microscopic examination showed hypocellular fibrous septae with some reactive osteoid and hemosiderin **(B)**.

- In the stable phase, the X-rays have a characteristic picture with expanded bone and a "shell" around the lesion, along with trabeculations coursing within it
- In the healing phase, progressive ossification results in a coarsely trabeculated bony mass
- Fluid/fluid levels on CT scan or MRI are characteristic **(Figure 9A)**

Macroscopic

- Grossly (if intact), the lesions have a thin osseous bony shell surrounding a honeycombed mass with cavernous vascular spaces that "ooze" blood like a veritable sponge
- Older cysts may contain sero-sanguinous fluid rather than blood
- A careful search should be made for solid areas that may represent the precursor lesion

Microscopic

- Fibrous walls that contain varying proportions of osteoid, chondroid, giant cells, and inflammation **(Figure 9B)**
- Cavernous spaces that are filled with blood
- Lack the smooth muscle wall and endothelial cells of blood vessels
- The mineralizing component may have a chondroid aura, unusual in any other lesion
- The chondroid usually has a fibrillary or chondro-myxoid quality and may be focally calcified
- Mitotic figures may be numerous, particularly in the areas of osteoid formation
- The stromal cells lack anaplasia
- A solid variant of ABC has been described that may be related (if not identical) to a reparative giant cell granuloma

Differential Diagnosis

- Telangiectatic osteosarcoma:
  - The radiographic appearance can occasionally be misleading
  - Presence of cellular anaplasia and atypical mitotic figures
  - Irregular lace-like deposition of osteoid
- Ossifying hematoma and pseudotumor of hemophilia:
  - Subperiosteal hematomas
  - Radiographically, may mimic a parosteal ABC
  - Hemosiderin, zonation, and organized appearance of bone
- Giant cell tumor with ABC component:
  - Older patients
  - Sheets of giant cells
  - No marked osteoblastic change

Bone-Forming Lesions

Osteoid Osteoma

Clinical

- Majority found within the first 3 decades
- Presentation:
  - Severe, unremitting pain
  - Relief of pain by aspirin is seen in the majority of patients

X-rays and Imaging Findings

- Classic location: long bones
- The lesion has sclerotic borders on X-rays
- The nidus is lucent or may have a small central radiodense spot of calcification
- Demonstration of the nidus may require tomograms or CT scans
- Osteoid osteomas of the joints can be difficult to detect by plain films
- Technetium pyrophosphate bone scans: "hot" lesion

Macroscopic

- The nidus is red, spherical, and gritty
- Usually can be "shelled" out from the surrounding bone

Microscopic

- A benign neoplasm consisting of a nidus and surrounding reactive, sclerotic bone
- The nidus is a highly vascular, sharply defined osteoblastic proliferation usually <1.5 cm
- Sharp demarcation of the nidus from the surrounding sclerotic bone
- Nidus may be poorly ossified with a richly vascularized stroma
- Nidus may be ossified, with calcific or lacy osteoid composed of osteoid rimmed with plump osteoblasts
- Lacks atypical mitotic figures
- The woven bone shows prominent osteoblastic rimming
- 0.1–0.2 cm zone of less trabeculated fibrovascular tissue around the nidus
- Sclerotic compact or spongy lamellar bone surrounds the fibrovascular tissue

Differential Diagnosis

- Clinical and radiologic mimics:
  - Intracortical abscess (such as Salmonella infection)
  - Sclerosing osteomyelitis (of Garre)
  - Enostosis
  - Aseptic necrosis
  - Stress fracture
  - Langerhans' cell histiocytosis
  - Metastasis
- Histologic mimics:
  - Osteoblastoma:
    - Osteoid osteomas are always <2 cm
    - The previously termed "giant" osteoid osteomas (>2cm) were probably examples of osteoblastomas
    - Lack zonation and uniformity of maturation
  - Osteosarcoma:
    - Lack osteoblastic rimming
    - Infiltrative permeative margin with entrapped cortical bones
    - Cytologic atypia or atypical mitotic figures
    - Cartilage may be present

Osteoblastoma

Clinical

- Most seen in patients <30 years old, with male predilection

- Pain, but often less intense than that of osteoid osteoma; not relieved by aspirin
- Predilection for the axial skeleton, with the majority of cases affecting the posterior elements of the spine
- Metaphyseal or diaphyseal location

X-rays and Imaging Findings

- Most lesions measure between 4–6 cm
- Uniform, geographic, expansile lucent lesions
- Most lesions are cortical; ~1/3 may be intramedullary
- There may be a stippled calcification in the matrix of the lesion

Macroscopic

- Circumscribed, 2–10 cm
- A secondary cystic change (aneurysmal bone cyst) may supervene

Microscopic

- Benign or sometimes locally aggressive osseous lesions, with microscopic similarity to the osteoid osteomas
- Anastomosing bony trabeculae in a fibrovascular stroma; well-circumscribed
- The edges of the lesion merge into the adjacent bone, imparting an appearance of maturation
- The bony trabeculae are variably calcified:
  - Some lesions are heavily mineralized, whereas others may be made of just osteoid
  - Considerable intralesional variations in trabeculum size exist:
    - In the majority of cases, the trabeculae are thick
    - Plump, mitotically active osteoblasts line these trabeculae
- Early lesions may be rich in giant cells
- Chondroid differentiation can occur, but is unusual in the absence of fracture
- Bizarre pleomorphic nuclei (thought to represent a secondary degenerative change) may be present
- Secondary aneurysmal bone cyst-like change occurs in 10% of cases

Variant

- "Aggressive" osteoblastomas:
  - Larger lesions occur in a wider age range
  - A subgroup also termed "malignant" osteoblastomas or "low-grade osteosarcomas" by some authors
  - In a variety of bones
  - Tend to recur
  - Wider and more irregular forms of trabecular pattern of osteoid:
    - Occasional areas of non-trabecular (lace-like) osteoid
    - The osteoblasts are large (almost twice the size of normal osteoblasts) with an epithelioid quality
    - The nuclei may have a vesicular "histiocyte-like" appearance

Differential Diagnosis

- Osteoid osteomas
- Low-grade osteosarcoma:
  - The relationship between these two lesions is still unclear
  - The distinction between osteoblastoma and osteosarcoma may be impossible in limited material
  - Lacks sharp circumscription and osteoblastic rimming of the trabeculae
  - Permeation and inflitrative margin
  - Cellular anaplasia and atypical mitotic figures

Osteosarcoma and Its Variants

Clinical

- Osteosarcomas may arise:
  - De-novo (see below)
  - Secondarily on other lesions:
    - Paget's disease
    - Osteogenesis imperfecta
    - Bone infarct
    - Chronic osteomyelitis
    - Fibrous dysplasia
    - Giant cell tumor
    - Osteoblastoma
  - Traditionally, osteosarcomas that arise on an underlying low-grade chondrosarcoma have been termed dedifferentiated chondrosarcoma
  - Secondary osteosarcoma has much higher incidence of flat bone and diaphyseal involvement
- Associated with:
  - Prior radiation therapy
  - Possibly metallic or other orthopedic implants
  - The relationship with trauma is poorly documented and understood
- Some cases of osteosarcoma may be familial:
  - Children with bilateral retinoblastomas
  - Li Fraumeni Syndrome (*see* Chapter 2)

De-novo Osteosarcoma

Clinical

- >85% of patients are <30 years of age
- The long tubular bones, in the active growth phase (2nd decade) (~3/4 of all tumors)
- The metaphyseal region is the site of >85% of these tumors; the diaphysis is the primary site in ~10%
- Epiphyseal location is rare

- Very low incidence of osteosarcoma (in fact of all malignant bone tumors) in the distal appendicular skeleton, such as the hands and feet
- Clinical presentations:
  - Pain is the most frequent presenting symptom, followed by swelling
  - The duration of the symptoms is a few weeks to months
  - Pathologic fractures (5% of cases)

Laboratory

- The serum alkaline phosphatase may be raised in the heavily osteoblastic tumors, but is often normal in the lytic cases
- A rise in alkaline phosphatase following excision may herald a recurrence

X-rays and Imaging Findings

- Radiographic appearances are diagnostic in ~2/3 of all cases
- Intramedullary lytic and sclerotic lesion with cortical breakthrough and associated matrix bone formation
- Some lesions may be purely lytic or sclerotic
- The margins vary from focally circumscribed to permeative
- The periosteum is often lifted to form a Codman's angle, "Codman's triangle"
- Rapid growth may result in an "onion skinning" appearance

Macroscopic

- Penetration of the cortex with an extraosseous soft tissue extension
- The intramedullary extension can be extensive and may be underestimated by radiologic studies
- Distant foci, within the marrow cavity of the same bone ("skip" lesions or skip-metastases) are important potential causes of recurrent disease
- Foci of hemorrhage and necrosis are common
- Large blood-filled areas may represent a telangiectatic component
- The periosteal reaction is frequently visible as spicules or lamellae of bone
- Epiphyseal penetration is an uncommon gross finding
- Joint extension may occur along the intra-articular ligaments (ligamentum teres in the femoral head, or the cruciate ligaments in the knee)

Microscopic

- Malignant, high-grade neoplasms of bone composed of proliferating cells that produce osteoid, at least focally **(Figure 10)**
- Osteoblastic, chondroblastic, and fibroblastic differentiation is common
- The amount of osteoid production can be minimal or absent in otherwise typical osteosarcomas:
  - Such lesions may be arbitrarily designated as osteosarcomas as opposed to malignant fibrous histiocytomas
  - Such lesions may produce heavily ossified metastases

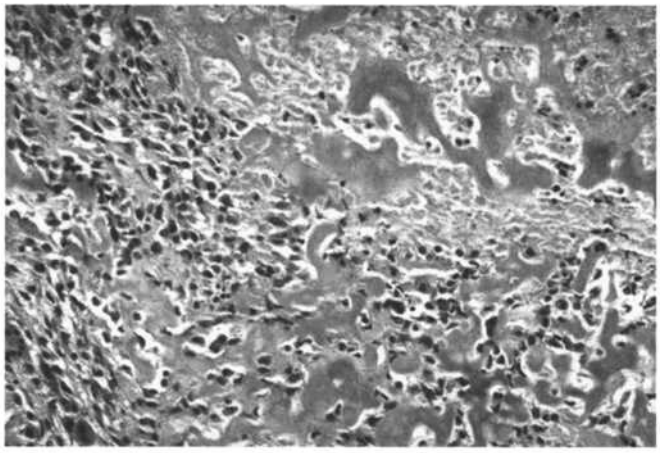


Fig. 10. Osteosarcoma showing delicate lacy osteoid and a high-grade sarcomatous stroma.

- Spindle or oval anaplastic cells with atypical mitotic figures
- "Normalization" is the tendency of the osteoblasts to become smaller and less pleomorphic as they get incorporated into the osteoid
- Osteoid may have variable thickness and degrees of mineralization
- A thin, highly mineralized pattern (filigreed pattern) without osteoblastic rimming is suggestive of neoplastic osteoid
- Some osteosarcomas are composed of epithelioid-appearing cells:
  - Rosette formation may give the appearance of gland formation
  - Immunohistochemical stains may be + for epithelial differentiation markers
  - Such osteosarcomas can be also seen as part of the sarcomatous component of a dedifferentiated chondrosarcoma
- Chemonecrosis of the tumor (following neo-adjuvant therapy):
  - Important to recognize and quantitate
  - The appearance of the tumor after chemotherapy depends on its original morphology:
    - Chondroblastic foci appear as acellular chondroid, often with ghost cells in the lacunae
    - Telangiectatic foci appear as acellular blood-filled cysts
    - Osteoblastic foci appear as acellular osteoid matrix
    - Atypical stromal cells may be scattered in all of these foci

Variants

- Osteosarcoma with prominent giant cells:
  - Proliferation of uniform giant cells amidst a sarcomatous stoma

- Osteoid production is usually sparse, encircling mononuclear pleomorphic stomal cells

♦ Osteosarcomas of the jaw bones (gnathic osteosarcomas):
- Frequently chondroblastic
- Thought to have a somewhat better outcome
- The average age of patients is usually higher
- The tumors tend to have less anaplasia and are often of a lower grade
- The differentiation from benign lesions may be difficult in many cases
- Cartilage differentiation in the jaw should always be viewed with suspicion

Differential Diagnosis

♦ Osteoblastoma:
- ~10% of osteosarcomas may appear radiologically benign
- Conversely, ~1/4 of osteoblastomas may be worrisome on X-rays
- Osteoblastic rimming favors osteoblastomas
- Lacks infiltration; cellular anaplasia, atypical mitotic figures
- Lacks cartilage

♦ Fracture callus:
- Callus can be extremely hypercellular, forming compact masses of osteoid in a mitotically active stroma
- Zonation (a pattern of peripheral ossification with a fibrous or less ossified center)
- Osteoblastic rimming
- Lack atypical mitotic figures or significant atypia
- Lack atypical or frankly malignant cartilage

Multifocal Osteosarcoma

♦ A small but distinct subgroup of osteosarcomas , divided traditionally into synchronous and metachronous types:

♦ Synchronous lesions:
- Arise (or are discovered) simultaneously (within 6 months)
- May represent multifocal primary osteosarcomas
- Subdivided into the "juvenile" and "adult" types:
  - Juvenile (or childhood-adolescent) form:
    - Typically found in the age group 5–17 years
    - Lesions are osteoblastic and of high grade
  - Adult form:
    - Mean age 37 years
    - The tumors are better differentiated (resemble the low-grade intraosseous osteosarcoma)

♦ Metachronous (asynchronous) lesions:
- More common than the synchronous variant
- Several long-term survivors are known

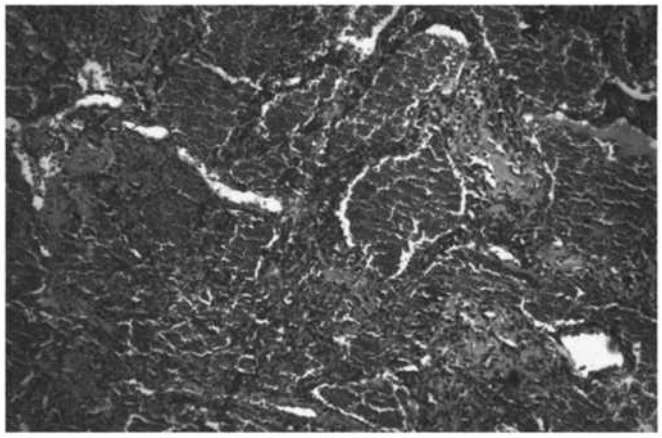


Fig. 11. Telangiactetic osteosarcoma with several blood filled spaces lined by a high-grade sarcoma.

Telangiectatic Osteosarcoma

♦ Diagnostic criteria for this entity have been varied

♦ The incidence is low (<10%)

♦ Radiologically:
- Purely lytic with features of rapid growth
- Permeative margins, cortical destruction, and soft tissue extension
- ABC-like appearance may be seen

Macroscopic

♦ Hemorrhagic-necrotic mass

♦ Multicystic with blood-filled spaces

Microscopic

♦ Two variants are described, corresponding to the gross appearances:
- Hemorrhagic-necrotic variant **(Figure 11)**
- ABC-like variant

Small Cell Osteosarcoma

♦ A microscopically distinct variant of a high-grade intra-medullary osteosarcoma

♦ May contain hemangiopericytotoma-like pattern

♦ Hypocellular uniform spindle cells

♦ Islands of long parallel arranged trabecular bone without osteoblastic rimming

♦ Small round cells with delicate lace-like osteoid deposition

♦ Relationship with Ewings sarcoma is unclear

♦ Glycogen + and may share the t(11;22) chromosomal translocation

Intraosseous Well-Differentiated Osteosarcoma

♦ An intramedullary variant of osteosarcoma with better prognosis

- Low-grade fibrous and osseous tissue with only minimal cytologic atypia. It has a permeative growth pattern

Differential Diagnosis

- Desmoplastic fibroma: lacks osteoid production
- Osteoblastoma:
  - Fibrovascular stroma and osteoblastic rimming
- Fibrous dysplasia:
  - Haphazard arrangement of short trabecullae ("Chinese letters")
  - No permeative growth pattern

Intracortical Osteosarcoma

- Rare variant
- Arises within and is confined to the cortex of a long bone (diaphysis of tibia and femur)

Periosteal Osteosarcoma

- Formerly called juxtacortical chondrosarcoma
- Predilection for the diaphysis of long bones in young patients (20s–30s)
- Radiographic:
  - Located on the external surface of the cortex and extends into the surrounding soft tissues
  - Predominantly lucent lesions
  - Mineralization, if any, is confined to the base of the tumor adjacent to the cortex
  - Characteristic spiculated (radiating) pattern of calcification (oriented perpendicular to the cortex)
  - Intramedullary extension is absent
- Macroscopic:
  - Sharply demarcated, lobulated, and cartilaginous tumor
- Microscopic:
  - Dominant chondrosarcomatous areas (Grade 2–3) with at least focal osteoid formation

High-Grade Surface Osteosarcoma

- A rare variant of osteosarcoma arising from the outer cortex of the bone
- Intramedullary extension is absent or minimal
- The lesions are often diaphyseal
- Presentation is similar to the high-grade, conventional intramedullary osteosarcoma
- Microscopically similar to conventional high-grade osteosarcoma

Parosteal Osteosarcoma

Clinical

- A well-differentiated, low-grade, fibro-osseous variant of juxtacortical osteosarcoma
- The prognosis is often much better compared to the conventional type

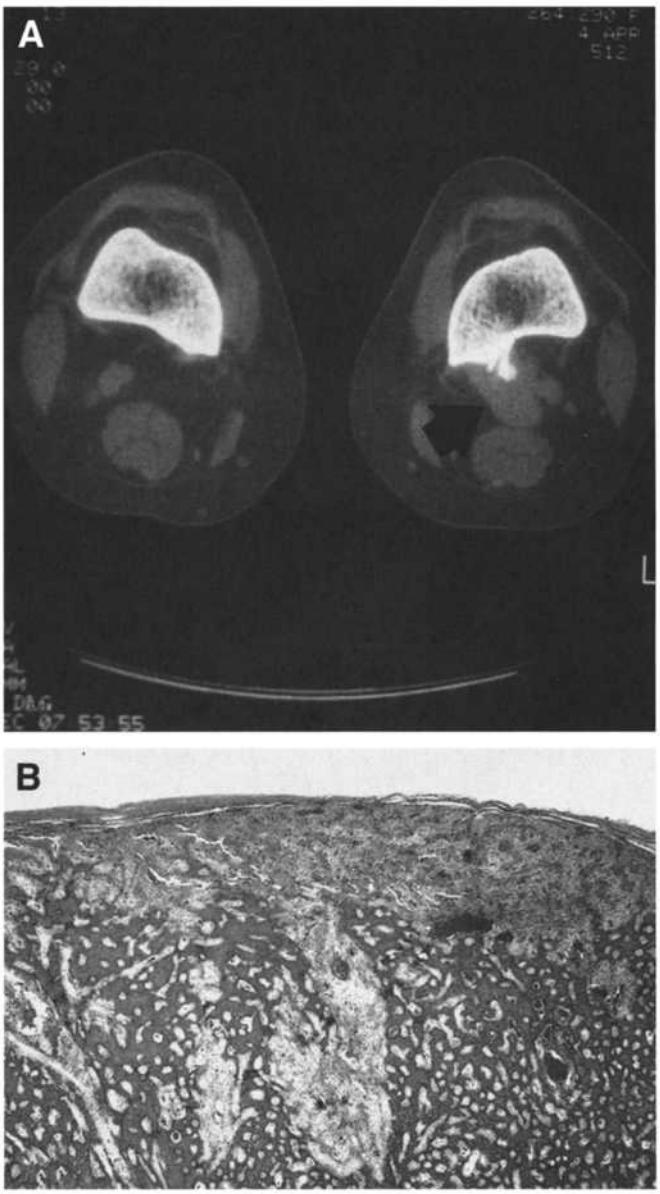


Fig. 12. Parosteal osteosarcoma is seen as a distal femoral exophytic mass mimicking an osteochondroma. Microscopic examination showed a well differentiated tumor with well developed bone and cellular stroma.

- Presentation:
  - Painless mass in female (usually around 40 years)
  - Most commonly situated in the posterior metaphysis of the distal femur (>2/3 of cases)
  - Other common sites include the tibia humerus

X-rays and Imaging Findings

- A dense mass of bone attached to the outer metaphyseal cortex by a broad base **(Figure 12A)**
- Plain X-ray has often underdiagnosed these lesions as osteochondromas

- There is dense mineralization, which is often less prominent peripherally
- The tumor tends to encircle the parent bone, a feature demonstrable by CT scanning
- A lucent line between the mass and the bone (string sign)
- Periosteal new bone is usually absent
- Intralesional lucencies are uncommon, suggesting dedifferentiation
- In dedifferentiated tumors, CT scan may demonstrate satellite lesions and intramedullary extension

Macroscopic

- Large, ossified exophytic mass with a broad base
- Less often, the tumor encircles the bone
- Resemblance to an osteochondroma may be considerable, including the presence of a cartilaginous cap
- The lesions are heavily ossified and may be lobulated

Microscopic

- Long, narrow trabeculae, or ill-defined areas of osteoid and woven bone separated by a fibrous stroma
- The trabeculae may show maturation (normalization), which may result in lamellar bone **(Figure 12B)**
- The spaces between the trabeculae are often filled with spindled fibroblastic tissue showing only minimal cytologic atypia
- Most lesions are grade 1
- High-grade areas resembling conventional osteosarcomas should be interpreted as evidence of dedifferentiation

Differential Diagnosis

- High-grade surface osteosarcomas
- Conventional osteosarcomas with a prominent extra-osseous component
- Periosteal osteosarcoma
- Osteochondromas:
  - The extension of the medullary cavity into the extracortical mass
  - Lack an atypical fibrous stroma/osteoid
  - Fat or hematopoietic marrow between trabeculae in continuity with involved parent bone
- Reactive soft tissue and periosteal processes:
  - May be difficult to differentiate on radiologic grounds
  - Such conditions include myositis ossificans and reactive periostitis
  - Evidence of zonation is helpful in diagnosing these conditions as benign

Cartilagenous Lesions

Osteochondroma (Osteocartilaginous Exostosis)

Clinical

- An outgrowth of bone with the combination of medullary and cortical bone
- Projects from the cortical surface and is covered with a cartilage cap
- Most often seen in the first 2 decades of life
- No predilection for gender
- Mostly long bones formed by enchondral ossification
- May originate from a displaced epihyseal cartilage that herniates through a periosteal defect
- Often asymptomatic and incidental findings
- Multiple osteochondromas:
  - Sporadic
  - Familial:
    - Termed (multiple) hereditary exostoses or diaphyseal (or metaphyseal) aclasis
    - Autosomal dominant inheritance
    - Associated with a generalized osseous modeling defect
    - Associated with limb growth asymmetry
- Malignant transformation:
  - Long-standing osteochondromas rarely show an aggressive (invasive or malignant) change
  - The incidence is probably <1% for solitary osteochondromas and slightly more for multiple osteochondromas

X-rays and Imaging Findings

- Located in the meta-diaphyseal region
- MRI scan is useful for measuring the thickness of the cartilage cap and locating the presence of wide fibrous septae within the osteochondroma
- MRI or CT scan can be used for establishing the continuation of the native medullary cavity into the marrow cavity of the osteochondroma

Macroscopic

- Entirely (extraperiosteally) resected lesions are covered by periosteum
- Well-defined bony stalk, capped by cartilage
- The marrow cavity of the parent bone continues into the osteochondroma
- Cartilage cap >2.0 cm in an adult is suspicious for a chondrosarcoma

Microscopic

- Presence of periosteum over the cartilage cap
- Linear cartilage bar with enchondral calcification
- The chondrocytes:
  - The cells occur in clusters and in lacunae in the superficial portion of the cap
  - Toward the base, the chondrocytes line up, simulating a growth plate
  - Below this, enchondral ossification is often seen
- A spindle cell proliferation occurring within an osteochondroma may be the result of a repair reaction from trauma

Differential Diagnosis

- Chondrosarcoma developing in an osteochondroma
- Parosteal osteosarcoma

Bizarre Parosteal Osteochondromatous Proliferation (Nora's Lesion)

Clinical

- An exophytic outgrowth from the cortex, consisting of a mixture of cartilage, fibrous tissue, and bone
- Occurs in patients 20–35 years of age, without gender predilection
- Predilection for the bones of the hands and feet, especially proximal phalanges of the hand
- Long bone involvement is less common

Macroscopic

- The lesions have a stalk and may have a well-defined cartilage cap
- The mass may sometimes show lobulations

Microscopic

- A triad of cartilage, bone, and a spindle cell element is seen
- The cartilage may form a cap and is often very cellular, with enlarged, bizarre nuclei at the peripheral of the lesion
- The chondrocytes often show bi- or multinucleation
- The interface with the underlying bone is irregular, with admixtures of bone and cartilage
- Occasionally, no cap is seen and the cartilage is admixed with bone and spindle cells
- The bone may show considerable osteoblastic prominence and is more irregular than is typically seen in osteochondromas
- A helpful clue is the blue tinctorial quality of the bone in routine Hematoxylin and Eosin sections
- Fibrous tissue and osteoclast-type giant cells may be intermixed within the lesion

Chondroma

Clinical

- Benign cartilaginous neoplasms occurring in either a central location within the bone (enchondroma) or on the surface (periosteal chondroma)
- There are lesions with overlapping features (enchondroma protruberans)
- The most frequent locations are the metaphysis or diaphysis of the hand and foot bones
- Periosteal chondromas are more frequent in the appendicular skeleton
- Flat bones are less often involved
- Ollier's disease:
  - Multiple enchondromas generally confined to one limb (unilateral)
  - 1/3 has malignant transformation
  - Often accompanied by parosteal chondroma
  - Associated with ovarian sex-cord stromal tumor
  - Histologically more cellular, more atypia, and more myxoid
- Maffuci's syndrome:
  - Multiple unilateral enchondromas associated with soft tissue hemangiomas
  - Increased risk of astrocytoma and ovarian cancer (juvenile granulosa cell tumor of ovary)

X-rays and Imaging Findings

- Small lesions with well-defined margins, sometimes with lobulated edges
- Mineralization in the form of semicircles and circles ("Cs" and "Os")
- Often "hot" on technetium bone scans

Macroscopic

- Well-circumscribed, small (3–5 cm) cartilaginous lesions

Microscopic

- Lobules and islands of hyaline cartilage intermixed with normal bone trabeculae and marrow
- The lobular configuration of cartilage is characteristic:
  - The lobules are separated by fibrous or lamellar bony septae
  - These may be rimmed by reactive woven bone or calcification
- Enchondromas in the tubular long bones (excluding the hands and feet):
  - Small chondrocytes lying in lacunae
  - Round, regular nuclei, which are barely visible at low magnification
- Enchondromas of the hands and feet:
  - Can be alarmingly cellular
  - Chondrocytes may be present in clusters or even in sheets
  - Nucleomegaly, binucleation, and slight myxoid change of cartilage
  - Permeation of the cortex of the phalanges, however, is diagnostic of a chondrosarcoma
  - Extreme hypercellularity, nuclear pleomorphism, and extensive myxoid change are suggestive of malignancy
- Periosteal chondromas:
  - Well-demarcated lesions with no tendency to permeation
  - May also show cytologic atypia
  - Myxoid change is unusual
  - Lobules of hyaline cartilage in a fibrous stroma
- Multiple enchondromas:
  - Can also be cellular with spindle-shaped chondrocytes
  - Atypia and myxoid change are worrisome for chondrosarcoma

Differential Diagnosis

- Juxtacortical chondrosarcoma
- Periosteal osteosarcoma

Chondroblastoma

Clinical

- A benign cartilaginous neoplasm with predilection for the epiphysis (giant cell tumor, clear cell chondrosarcoma, osteomyelitis, and eosinophilic granuloma also show epiphysis predilection)
- The majority occur in patients <25 years of age
- Chondroblastomas in unusual locations may occur in older patients
- 20–30% of chondroblastomas occur in flat bones or the short tubular bones
- The most common benign tumor of the foot (in the talus or the calcaneus)
- Occasionally, lesions occur in the cranio-facial skeleton, especially the temporal bone
- Treatment = curettage and packing

X-rays and Imaging Findings

- Lytic geographic lesions, with sclerotic or well-defined margins
- Centered in the epiphysis but may grow into the metaphysis **(Figure 13)**
- No matrix production in the majority of cases:
  - Fine matrix calcifications or trabeculations may be seen in ~1/3 of cases

Macroscopic

- Circumscribed, variegated lesions
- A secondary ABC component may be seen

Microscopic

- A spectrum of histologic appearances due to the inconstant amounts of matrix, ABC-like secondary changes and cytological variability
- The chondroblast:
  - Typically, a polygonal to oval cell with a sharp cytoplasmic border and lightly staining or clear cytoplasm
  - Some chondroblastomas lack this feature and may be referred to as the syncitial variant
  - The nucleus is round to oval, often with prominent grooves
  - Reticulin fibers surround individual chondroblasts
  - Mitotic figures may be seen, but are not frequent
  - Epithelioid variants of chondroblastomas are comprised of cells with abundant pink cytoplasm
  - Focal aggregates of spindle cells may be seen
  - Scattered osteoclast-type giant cells may be seen
  - ~1/4 of chondroblastomas show a small number of cells with enlarged, hyperchromatic nuclei:
    - Not related to an adverse outcome
  - Pigment is often prominent in lesions occurring in the cranio-facial and skull bones
- The matrix:
  - Has an eosinophillic quality in most cases
  - Calcification may be found focally, or more typically surrounding the chondroblast, especially in foci of necrotic chondroblasts
  - A characteristic "chicken wire" pattern of calcium deposition
- Mature chondrocytes are unusual
- Features suggestive of a chondromyxoid fibroma may be seen
- Focal cellular atypia or necrosis can be seen in up to 10% of cases
- Vascular invasion may be present, especially in lesions of the skull bones



Fig. 13. Chondroblastoma forming a well-delineated radiolucency with sclerotic margins involving the epiphyseal end of the humerus.

Differential Diagnosis

- Giant cell tumor:

- Generally occurs after the epiphyseal plate closes
- Mononuclear stromal cells with folded nuclei

♦ Clear cell chondrosarcomas:
- Broad sheets of cells with a voluminous clear cytoplasm

Chondromyxoid Fibroma

Clinical

♦ A benign, but locally aggressive cartilaginous tumor characterized by lobules of spindle-shaped or stellate cells in a myxoid (or chondroid) stroma
♦ The majority of the patients are <30 years of age
♦ Mild, transient, often long-standing pain
♦ Most cases occur in the long bones of the appendicular skeleton, especially the tibia
♦ 1/4 of cases are seen in the flat bones, especially the ilium
♦ Involvement of the short tubular bones of the hands and feet is not infrequent

X-rays and Imaging Findings

♦ Geographic and well-demarcated lesions
♦ Often eccentric and centered around the metaphysis
♦ Epiphyseal extension may be seen
♦ Chondro-myxoid fibromas of the hands and feet are often central and cause expansion of the short tubular bones
♦ Tumors of the flat bones are often irregularly lobulated
♦ Matrix calcification in any site should raise suspicion of a chondrosarcoma
♦ Surface lesions may be heavily mineralized

Macroscopic

♦ Small, circumscribed, and lobulated lesion with a semitranslucent quality

Microscopic

♦ Variable and may show several different components in varying proportions
♦ The chondroid lobules have hypercellular septae surrounding a hypocellular myxoid matrix **(Figure 14)**
♦ The fibrous component is usually small, and often confined to the septae separating the lobules
♦ The septae occasionally contain blood vessels, osteoclast type giant cells, and osteoid
♦ The cells in the septae may be spindle or stellate
♦ Features suggestive of chondroblastomas may be seen
♦ The myxoid component within and between the lobules is variably cellular
♦ Pleomorphic cells are frequent and should not be overinterpreted
♦ Absence of cellularity in the center of the lobules
♦ Lack atypical mitotic figures
♦ Either chunky or fine, lace-like calcification and necrotic foci may be seen

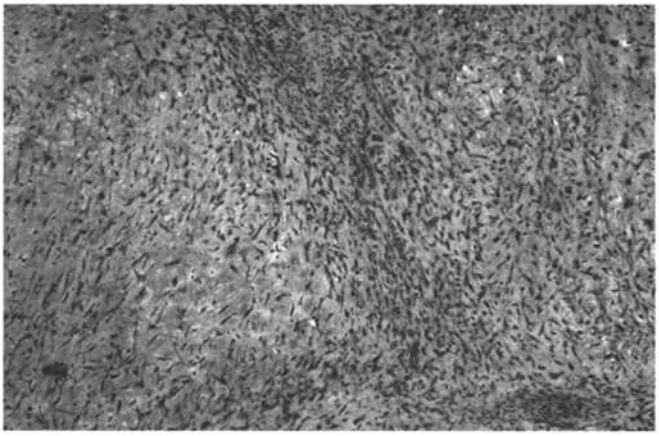


Fig. 14. Chondromyxoid fibroma showing the typical hypocellular and hypocellular areas.

Differential Diagnosis

♦ Chondrosarcoma:
- Differentiation may be difficult on morphological ground
- Both tumors can have a lobular growth pattern, peripheral cellularity, atypical cells, and a myxoid stroma
- Reactive osteoid can be seen along the edges of the lobules in both lesions
- Extreme hypercellularity in the central portion of the lobules is a feature of chondrosarcoma
- Radiographic and clinical features are of utmost importance in differentiating the lesions
- Features indicative of malignancy:
  - Infiltrative margin or radiologic appearance with permeation of the cortex
  - Entrapment of (necrotic) bone
  - Infiltration of the Haversian system
- Atypical mitotic figures and marked cytologic atypia
- Invasion into soft tissue

Osteochondromyxoma

♦ Associated with Carney complex (pigmented skin spots, myxomas, endocrine overactivity and schwannomas)
♦ Clinically—painless masses in distal long bones and small flat bones

Macroscopic

♦ Circumscribed but not encapsulated tumors
♦ Cause erosion of bone and extended into soft tissue

Microscopic

♦ Solid sheets with a macrolobular and microlobular pattern
♦ Myxomatous mesenchyme, cartilage, bone (formed *de novo* and from cartilage) and myxomatous tissue

- Hypodense to moderately dense polymorphic cell population with uniformly bland nuclei and few mitotic figures

Chondrosarcoma and Its Variants

Conventional Chondrosarcoma

Classification

- Primary:
  - Arising in a previously normal bone
- Secondary:
  - Arising in an underlying benign, usually cartilaginous neoplasm, such as osteochondroma
- According to location within the bone:
  - Central or intramedullary
  - Peripheral (must be differentiated from periosteal osteosarcomas)
- Genetic abnormalities—loss of heterozygosity (LOH) at 9p21 = constant genetic alteration found in conventional chondrosarcoma

Clinical

- A malignant tumor in which the neoplastic cells differentiate to form chondroid but not osteoid
- Occurs in age groups older than de-novo osteosarcomas
- Primary chondrosarcomas have a peak incidence in the 5th to 7th decades
- <2% chondrosarcomas occur in patients <20 years of age
- Presentation:
  - Central chondrosarcomas:
    - Pain with or without a mass
  - Peripheral chondrosarcomas:
    - Mass with or without pain
- Most frequent involvement seen in the bones of the pelvis and long tubular bones of the appendicular skeleton
- Involvement of the bones of the hands and feet is rare
- Chondrosarcomas are often centered around the trunk and proximal limbs
- ~2/3 of chondrosarcomas occur in the limb-girdles, femora, and humeri
- Chondrosarcomas have a slow biologic evolution, compared to dedifferentiated osteosarcomas
- A minority of chondrosarcomas give rise to highly malignant tumors, such as osteosarcomas, malignant fibrous histiocytomas, fibrosarcomas, etc. (dedifferentiation)
- Cartilagenous tumors of the sternum are almost always malignant, regardless of the histologic appearance
- Chondromas of the hands and feet, perosteal chondromas, enchondromas of Ollier's disease and Maffuci's syndrome, synovial chondromatosis, and soft tissue chondromas of the hands and feet are most often benign, in spite of sometimes alarming cellularity

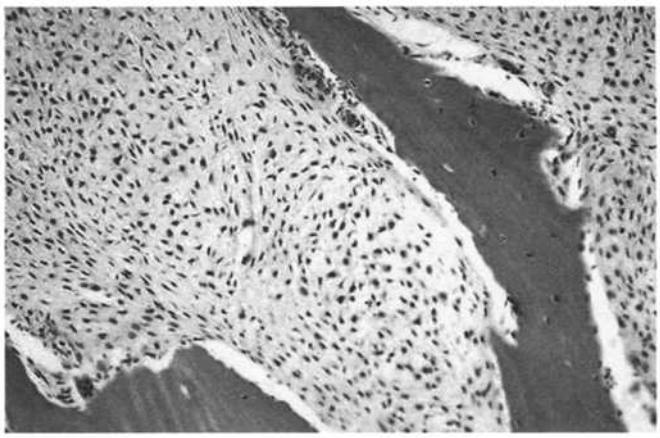


Fig. 15. Grade 2 (of 3) chondrosarcoma showing a permeative growth pattern.

- Genetic abnormalities—numerous have been described; constantly described = loss of heterozygosity (LOH) at chromosomal band 9p21

X-rays and Imaging Findings

- Central chondrosarcomas arise in either the diaphysis or the metaphysis
- Epiphyseal origin and joint involvement is rare, except in the clear cell variant of chondrosarcoma
- Intramedullary spread is common and can be extensive
- Peripheral chondrosarcomas appear as masses protruding from the bone
- Matrix calcifications in the form of "Cs" and "Os" are common in tumors of cartilage origin
- The margins of the lesion can vary from irregular geographic to permeative
- Areas of increased lucency or inhomogeneity within the lesion should raise suspicion of dedifferentiation

Macroscopic

- A lobular large lesion with a hyaline quality
- Foci of hemorrhage, necrosis, and cystic or myxoid change may be present
- The matrix can vary in consistency from firm hyaline cartilage to thin mucus-like cartilage

Microscopic

- Lobules of neoplastic cartilage in a chondromyxoid stroma
- Myxoid cystic change is common
- Necrotic foci can later calcify
- Marked myxoid change, extensive necrosis, or cellularity suggests malignancy
- A low power view suggestive of infiltration or entrapment of native bone is one of the most helpful clues suggesting malignancy **(Figure 15):**

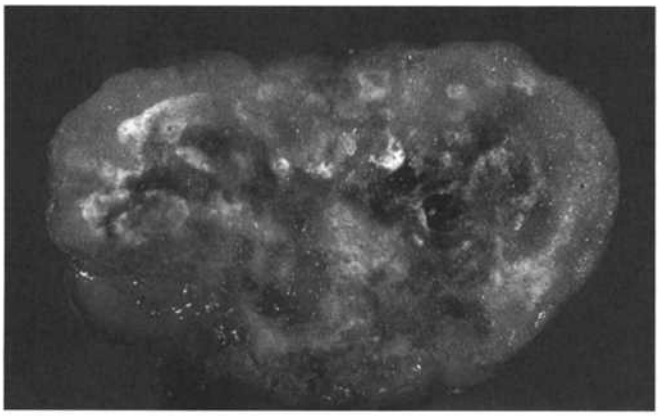


Fig. 16. Chondrosarcoma arising in an osteochondroma. The cartilage cap was 2 cm. thick. The lesion had grown over the past three months (as demonstrated by repeated MR scans).

  - The entrapped bone can also appear as islands of (usually necrotic) bone
- Peripheral/secondary chondrosarcomas often lack an infiltrative quality and frequently demonstrate a "pushing" border
- Chondrosarcomas tend to be more cellular than chondromas
- Soft tissue involvement (in the absence of fracture or previous surgery) is a definite sign of malignancy
- Calcification can be present, often around the lobules of cartilage
- Reactive woven bone may be present; however, malignant osteoid is a feature of an osteosarcoma
- When chondrosarcomas supervene on a previous osteochondroma:
  - The thickness of the cartilage cap increases **(Figure 16)**
  - The normal columnar arrangement of chondrocyte columns is lost
  - Nodules of cartilage can sometimes be found in the adjacent soft tissues

Differential Diagnosis

- Chondroblastic osteosarcoma:
  - Identification of malignant osteoid is required for this distinction
  - The woven bone that surrounds chondrosarcoma lobules should not be overinterpreted
  - Osseous metaplasia is not diagnostic of an osteosarcoma
- Tophaceous pseudogout:
  - Finding of polarizable crystals and the presence of a granulomatous response
  - Tissue processing for regular histology may dissolve the crystals

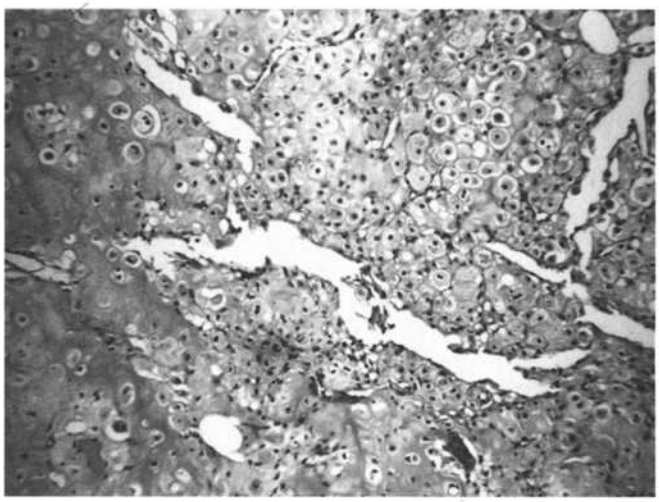


Fig. 17. Clear cell chondrosarcoma showing sheets of chondrocytes with clear cytoplasm.

Variants

- Dedifferentiated chondrosarcoma:
  - Refers to chondrosarcomas with a high-grade, non-chondromatous sarcoma component presumably arising from a low-grade cartilaginous neoplasm
  - The non-chondromatous component may be:
    - Osteosarcoma
    - Malignant fibrous histiocytoma (MFH)
    - Rhabdomyosarcoma
- Clear cell chondrosarcoma:
  - Malignant, but slow-growing tumors composed of neoplastic chondrocytes with abundant clear cytoplasm and a sparse intercellular matrix **(Figure 17)**
  - Foci of conventional chondrosarcoma may also be present
  - Often mistaken clinically as well as histologically for chondroblastomas and osteoblastomas
- Mesenchymal chondrosarcoma:
  - Often occurs in young adults; jaw bone and ribs
  - Prognosis is good
  - Malignant, cartilage-forming tumors that are primarily composed of small, round to oval cells arranged in a hemangiopericytoma-like pattern
  - Small areas of osteoid may be present
  - Abrupt transition to low-grade cartilage from these small round cell areas **(Figure 18)**

Vascular Lesions

Solitary Lymphangioma, Hemangioma, and Skeletal Angiomatosis

- Lymphangiomas and hemangiomas are benign proliferations of lymphatic or vascular channels that occur in and replace bone **(Figure 19)**

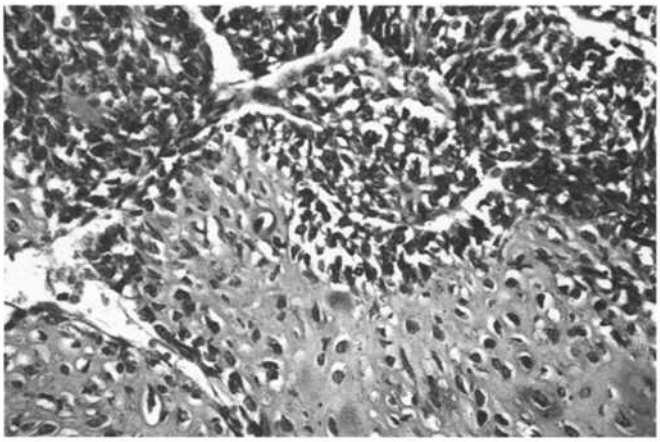


Fig. 18. Mesenchymal chondrosarcoma showing a very sharp junction between the small cell component and the cartilage.

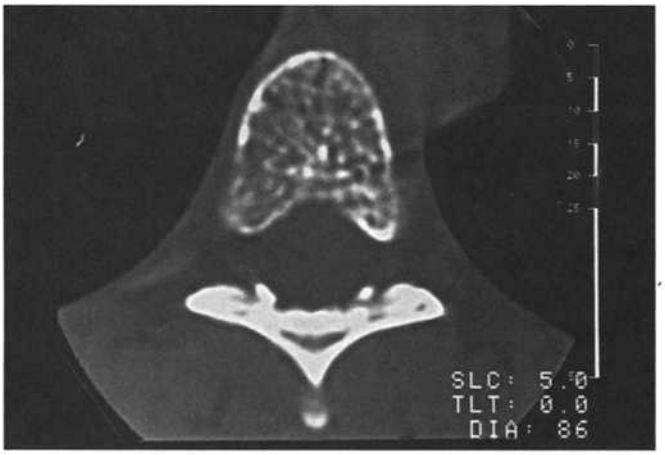


Fig. 19. Hemangioma of the vertebra—the "dot-like" pattern on CT scan is characteristic.

- Angiomatosis is a multifocal or diffuse intra-osseous proliferation of benign hemangiomatous or lymphangiomatous channels
- There may be associated extra-osseous vascular malformations or combined "skeletal-extraskeletal" angiomatosis in continuity

Gorham's Disease (Massive Osteolysis)

- Predilection for mandible and rib
- A vanishing or disappearing bone disease resulting in massive osseous resorption
- Characterized by resorption of most or almost all of the bone associated with a proliferation of benign vascular channels
- The difference with skeletal angiomatosis is the extent of involvement
- Involves one or more contiguous bones in contrast to the multifocal nature of skeletal angiomatosis

Hemophilic Pseudotumor

- A tumor-like lesion that may mimic several aggressive bone neoplasms
- May cause massive bone destruction
- Not strictly a vascular proliferation; arise secondary to the large amounts of hemorrhage that occurs in bleeding disorders
- The hemorrhage is often intra-articular and associated with reactive synovitis and degenerative joint disease

Epithelioid (Histiocytoid) Hemangioendothelioma

- A low-grade malignant neoplasm composed of endothelial cells with conspicuous cytoplasm
- A variable degree of vasoformative features varying from vacuolization of cells to well-formed vascular channels
- Patients often have concomitant cutaneous, systemic, or soft tissue disease
- Multifocal disease is not uncommon
- Soft tissue or lung "metastases" should raise the question of possible multifocal primary tumors

Angiosarcoma

- A high-grade (sometimes surface) sarcoma of bone composed of cytological malignant endothelial cells
- Multifocality is common
- Lytic, destructive, permeated lesions with frequent soft tissue extension
- Areas of well-formed anastomosing vascular channels lined by atypical endothelial cells, with large vesicular or hyperchromatic nuclei
- The vasoformative nature may not be evident in other solid, poorly differentiated areas

Hemangiopericytoma

- A potentially low-grade malignant vascular tumor consisting of pericyte-like cells with a prominent vascular pattern
- Occasionally, a paraneoplastic syndrome of hypophosphatemic osteomalacia may be present
- A variety of tumors can exhibit hemangiopericytoma-like areas:
  - Synovial sarcoma
  - Mesenchymal chondrosarcomas
  - MFH
  - Small cell osteosarcoma
  - Solitary fibrous tumor

Glomus Tumor

- A benign, highly vascular tumor composed of small, uniform, specialized smooth muscle cells resembling those of the glomus body
- Osseous glomus tumors are less frequent than their soft tissue counterparts
- Most commonly occur in the distal phalanges

Vascular Tumors in Immunocompromised Patients

- Both Kaposi's sarcoma and Bacillary angiomatosis have been described in bone

Giant Cell Lesions

Giant Cell Tumor (Osteoclastoma)

Clinical

- Giant cell tumors are more common in the skeletally mature adult population
- Peak incidence in the 3rd decade; occur in the region of the epiphysis
- Complaints are usually non-specific; there may be pain or a mass
- ~10% of patients present with a pathologic fracture

Laboratory

- Serum chemistries are generally normal
- Elevated serum calcium should raise the possibility of hyperparathyroidism
- Elevated serum alkaline phosphatase should raise the possibility of Paget's disease

Location

- ~1/2 of all giant cell tumors arise around the knee:
  - Other common sites include the distal radius, proximal femur, proximal humerus, and distal tibia
  - The flat bones most commonly involved are the sacrum and pelvic bones
- Most giant cell lesions of the gnathic skeleton are thought to be giant cell reparative granulomas rather than true giant cell tumors

X-rays and Imaging Findings

- Most lesions are epiphyseal, with frequent metaphyseal extensions **(Figure 20)**
- 15% of patients are <20 years of age
- The tumors occur (for this age group) in a metaphysical or epi-metaphysical location
- Lytic usually geographic lesions with well-defined (but not always sclerotic) margins
- May show lesional trabeculations
- Aggressive periosteal reactions and calcifications (sunburst, onion-skinning or Codman's angles) are not features of the giant cell tumor
- Lesions extending into the soft tissue often have a thin rim of bone ("egg-shell")
- Enneking's system
- Three stages of tumor:
  - Benign latent tumors:
    - Devoid of features of local aggressiveness
  - Benign active tumors:
    - Symptomatic
    - Show bone expansion on imaging studies
  - Aggressive tumors:
    - Correspond to the hypervascular lesions that erode into the soft tissues
    - May have an associated pathologic fracture

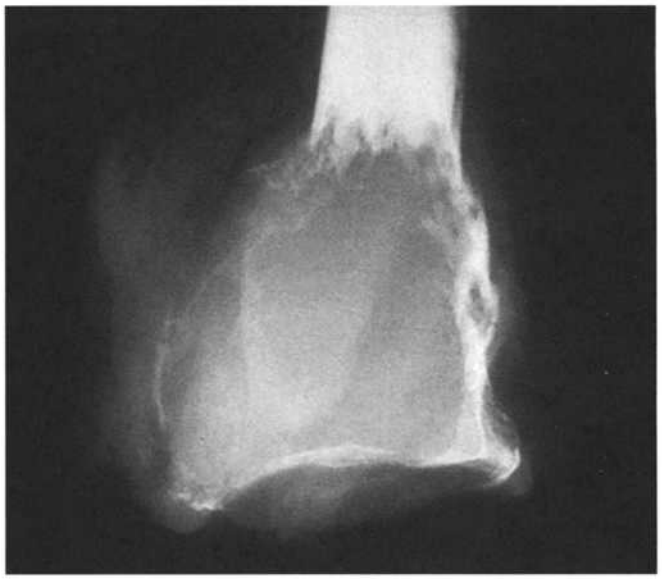


Fig. 20. Giant cell tumor involving the distal radius. The epiphyseal location is usual in this tumor.

Macroscopic

- Hemorrhagic with focal aneurysmal bone cyst-like areas

Microscopic

- A locally aggressive neoplasm characterized by large numbers of osteoclast-type giant cells uniformly distributed in a population of plump, epithelioid, or spindle cells
- The diagnosis is made on the background population of stromal cells:
  - Stromal cells are round to oval, occasionally spindled, with storiform pattern
  - Nuclei resembling those of the giant cells
  - Mitotic figures may be abundant (2–3 per high power field)
  - No cytologic features of malignancy
- Giant cells are numerous and diffusely distributed with a few to hundreds of nuclei
- Occasional cases may have broad bands of collagen coursing throughout, especially in recurrent tumors

"Malignant Giant Cell Tumor"

- The term has been used:
  - To designate true bone sarcomas rich in giant cells
  - To describe a "dedifferentiated" giant cell tumor
  - To describe giant cell tumors that have metastasized
- The term is confusing and it is best to avoid its use

Differential Diagnosis

- Giant cell reparative granulomas:
  - Giant cells tend to be aggregated, mostly around areas of hemorrhage with less nuclei
  - The stroma is fibrotic, with hemorrhage and hemosiderin deposition
  - Foci of reactive bone are more common
- Non-ossifying fibroma:
  - Spindled stromal cells, stromal fibrosis, and xanthomatous foamy macrophages are more prominent
  - Occur in metaphysis of pediatric patients (rather than epiphysis)
- Benign fibrous histiocytomas:
  - A diagnosis of exclusion
  - Lack sheets of mononuclear stromal cells
- Aneurysmal bone cysts:
  - Non-epiphyseal tumor
  - Differentiation from a true ABC may be difficult in the spine
  - The Armed Forces Institute of Pathology tends to interpret most such cases as giant cell tumors with secondary ABC formation
- Osteosarcoma with prominent giant cells:
  - Osteoid production may be minimal, limited to thin strands encircling mononuclear pleomorphic stromal cells
  - The stromal cells usually have hyperchromatic nuclei, often with numerous atypical mitotic figures
  - The radiographic pattern suggests a permeative growth, not extending into the epiphyses
- Metastatic carcinoma:
  - Cytokeratin +

Giant Cell Reparative Granuloma

- A benign, reactive intraosseous proliferation characterized by granuloma-like aggregates of giant cells in a fibrovascular stroma
- The lesion is commonly seen in the gnathic skeleton
- Cherubism occurring bilaterally in the jaws of children, as well as the "solid" aneurysmal bone cyst may be other entities that are related to the giant cell reparative granuloma

Differential Diagnosis

- Giant cell tumor:
  - More uniform distribution of giant cells with more nuclei
  - Characteristic stromal mononuclear cells
  - Less stromal fibrosis and hemorrhage

Fibrous Lesions

Desmoplastic Fibroma

- Considered to be the bone counterpart of the soft tissue aggressive fibromatosis
- A non-metastasizing, but locally aggressive lesion
- Composed of cytologically typical fibroblasts in an abundantly collagenized stroma

Liposclerosing myxofibrous tumor (LSMTF)

- Benign myxofibrous tumor with predilection for the proximal femur
- Complex mixture of histologic elements which may include lipoma, fibroxanthoma, myxoma, myxofibroma, fibrous dysplasia-like features, cyst formation, fat necrosis, ischemic ossification and rarely cartilage
- Radiologic—well-defined, geographic lytic lesion with sclerotic margin
- Potential risk for malignant transformation—osteosarcoma, MFH

Fibrosarcoma

- A malignant spindle cell lesion that exclusively exhibits fibrous differentiation
- Lacks osteoid and chondroid matrices
- The skeletal site distribution is similar to osteosarcoma
- The age of the patients is more evenly distributed from the 2nd to the 7th decades

Fibro-Histiocytic Lesions

Benign and Atypical Fibrous Histiocytoma

- Several lesions show common histologic features of a storiform pattern, histiocyte-like giant cells, foam cells, and a polymorphic infiltrate
- Such lesions are often grouped together under the general heading of benign fibrous histiocytomas
- These lesions may be unrelated to each other or to histiocytes

Malignant Fibrous Histiocytoma (MFH)

Clinical

- Wide age range with no predilection for gender
- Presentation: pain or a mass
- Some lesions arise in the setting of orthopedic implants, Paget's disease, fibrous dysplasia, and bone infarcts
- Associated with a pathologic fracture in up to 25% of cases

X-rays and Imaging Findings

- The metaphyseal regions of long bones are the most frequently involved
- Ill-defined, lytic lesions
- Cortical expansion and breakthrough with minimal periosteal reaction

Macroscopic

- A variegated tumor with hemorrhage and necrosis
- Margins are frequently permeative

Microscopic

- May exhibit a variety of patterns similar to soft tissue MFH
- Multinucleated malignant giant cells are present in most cases
- Histiocytic cells with grooved nuclei are frequent
- Fibrosis is variable
- Spindle cell areas with a storiform arrangement are common
- Chronic inflammatory cells are often seen
- Lack malignant osteoid or low-grade areas

Immunohistochemistry

- S100 protein±, cytokeratin– (or focal+)

Differential Diagnosis

- Fibrosarcomas:
  - The fasicular arrangement or herringbone pattern
- Osteosarcoma:
  - Areas of malignant osteoid
- Metastatic spindle cell carcinoma and melanoma:
  - Immunohistochemistry is useful

Other Mesenchymal Lesions

Metaphyseal Fibrous Defect (Non-Ossifying Fibroma)

Clinical

- The incidence of these lesions may be age related
- Up to 35% of all children (if screened) are thought to have these lesions; most common between the ages of 4–8 years
- The majority of the lesions in this group are <0.5 cm in size
- The vast majority of lesions occur in the distal femur, distal and proximal tibia, and fibula

X-rays and Imaging Findings

- Most lesions are geographic, lytic lesions with sclerotic margins
- Varying amounts of sclerosis within the lesion in the healing phase

Microscopic

- Intracortical proliferation of fibrous tissue and histiocytes
- Predominantly fibrous lesions, often with a storiform arrangement
- Foamy histiocytes (xanthoma cells), hemosiderin-laden macrophages, and multinucleated giant cells
- Reactive woven bone may be present in the presence of fracture or in the healing phase

Differential Diagnosis

- Benign fibrous histiocytoma:
  - Intramedullary location, adult

Fibrous Dysplasia (FD, Jaffe-Lichtenstein Syndrome)

Clinical

- Mono-ostotic FD (80%):
  - May be seen at any age (usually <30 years old)
- Poly-ostotic FD (20%):
  - Generally presents before the age of puberty
- Presentation:
  - Pain, pathologic fracture, deformity (especially gnathic or upper femoral FD)
  - May be asymptomatic
  - Secondary sarcomas rarely develop
- Associated syndromes:
  - McCune-Albright syndrome:
    - Poly-ostotic FD with macular skin lesions, precocious puberty, with or without fibromyxomatous soft tissue tumors
  - Hyperphosphaturic hypophosphatemic rickets or osteomalacia has been associated
  - Mazabraud syndrome:
    - Associated with a soft tissue or intramuscular myxoma
- Location:
  - Mono-ostotic:
    - 33% involve the crani-facial bones
    - 33% involve the tibia and femur
    - 20% involve the ribs
  - Poly-ostotic:
    - Femur, tibia, and pelvis are commonly involved
    - Small bones of the hands and feet, the ribs, and the skull may also be involved
- Pathogenesis:
  - Somatic mutation in the gene that encodes the α subunit of the GTP binding protein leading to the substitution of His or Cys for Arg at aminoacid 201 of the alpha-subunit of Gs.

X-rays and Imaging Findings

- Intramedullary, geographic lesions with sclerotic or well defined margins and a "ground-glass" matrix
- The lesions are intensely hot on bone scans

Microscopic

- Trabeculae of woven bone in a background of moderately cellular fibrous tissue **(Figure 21)**
- The trabeculae often obtain a variety of shapes (Cs, circles, etc.) ("Chinese-letters")
- Osteoid tends to merge into the background ("metaplastic")

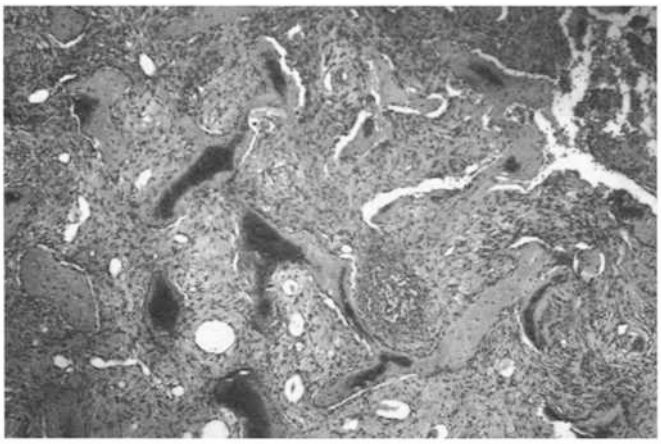


Fig. 21. Fibrous dysplasia—emerging trabeculae of metaplastic bone within a fibrous stroma.

- Osteoblasts are interspersed in the woven bone, but are not conspicuous around the trabeculae
- Small foci of lamellar bone may be seen
- The fibro-osseous proliferation may show an infiltrative pattern at the junction with non-lesional bone
- The fibrous stroma may be highly or sparsely cellular, myxomatous, or show considerable collagenization
- The fibroblasts usually have plump, ovoid nuclei
- Multinucleated osteoclast type giant cells may be present
- Cartilage with peripheral enchondral ossification may be present
- Collections of foam cells are common

Differential Diagnosis

- Osteofibrous dysplasia:
  - A cortically based lesion
  - Most often affects the tibia or fibula in children (often <5 years)
  - Reactive woven bone
  - Osteoblastic rimming is more prominent
- Well-differentiated intraosseous osteosarcoma:
  - The stromal cells have larger nuclei with cytologic atypia and atypical mitotic figures
- Desmoplastic fibroma:
  - Usually heavily collagenized with prominent osteoblast rimming

Campanacci's Disease (Osteofibrous Dysplasia)

- A cortically based fibro-osseous proliferation
- Predilection for the tibia (and less frequently fibula) in children and infants

Fibrocartilaginous Mesenchymoma

- Consists of a combination of bone, spindle cells, and cartilage, predominantly in the chest wall
- The cartilage has a characteristic appearance of epiphyseal plate formation

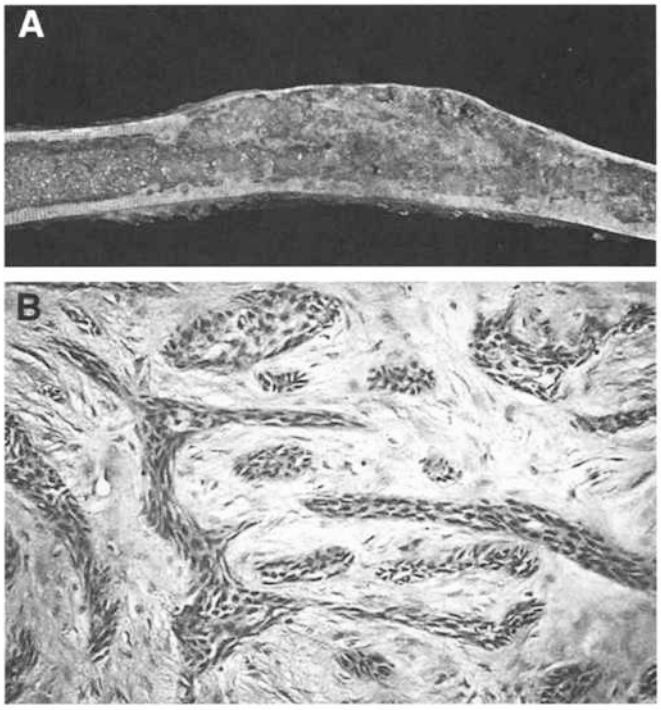


Fig. 22. Adamantinoma (gross) involving the tibia causing a prominent bowing deformity **(A)**. Microscopic examination showed groups of epithelial cells within a fibrous background **(B)**.

- A dense, spindle cell proliferation is seen between well-formed bony trabeculae
- No or little collagen

Adamantinoma

- Shows marked predilection for the tibia **(Figure 22A)**
- A low-grade malignant neoplasm with epithelial differentiation **(Figure 22B)**
- Controversial relationship with Campanacci's disease or osteofibrous dysplasia

Ewing's Sarcoma

Clinical

- Affects patients in the first 2 decades of life
- Localized pain and a mass with fever, leukocytosis, and a raised sedimentation rate
- Up to 10% of patients may have skeletal metastases at the time of presentation
- Most often involves the diaphysis of long tubular bones (femur) as well as some flat bones (pelvis and ribs)
- Characteristic chromosomal translocation: t(11;22) (also seen in primitive neuroectodermal tumor [PNET] and ASKIN tumor of chest):
  - Occurs in 85% of patients
  - The EWS gene (located on chromosome 22q12) is translocated to the FL1 (a gene of the ETS family

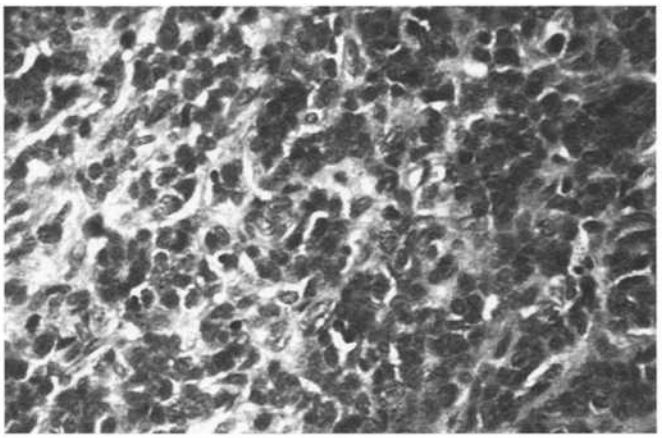


Fig. 23. Ewing's sarcoma—sheets of small blue cells are identified with no matrix production.

located on chromosome 11), resulting in the formation of a chimeric protein product

- A second, t(21;22), translocation has been identified in 15% of patients:
  - Fusion of the EWS gene with a different member of the ETS family, the ERG gene located at chromosome 21q22, resulting in a chimeric EWS/ERG protein product

X-rays and Imaging Findings

- Ill-defined, lytic lesions with permeative margins
- A periosteal reaction of the onion-skin, sunburst, or other rapidly growing type
- A soft tissue component is detected by CT or MR scans

Microscopic

- Classic form:
  - Sheets and large nests of uniform, small, round to polygonal cells with scanty cytoplasm **(Figure 23)**
  - The chromatin is finely dispersed, usually with no nucleoli
  - Variable number of mitotic figures
  - Perivascular cuffing may be evident in areas of necrosis
  - Cytoplasmic glycogen, demonstrated by the PAS stain, is evident

Variants

- Large-cell type pattern:
  - Cells may be larger and may have nucleoli
- Filigree pattern:
  - Bi-cellular architecture, separated by stroma

Immunohistochemistry

- Mic-2 (CD99 or HBA 71) + (+ in PNETs, some rhabdomyosarcomas, acute lymphoblastic leukemia, pancreatic islets, and ependymoma)
- Vimentin+, CK–/+, neurofilament+, synaptophysin–/+, NSE±

Electron Microscopy

- Nuclei with euchromatic pattern
- Scant cytoplasmic organelles and glycogen lake

Differential Diagnosis

- Small cell osteosarcoma and mesenchymal chondrosarcoma:
  - Production of malignant osteoid or cartilage matrices
- Lymphoma:
  - LCA+
- Metastatic neuroblastoma:
  - More common than Ewing's sarcoma
  - Patients are usually <5 years of age
  - Homer-Wright pseudo-rosettes, pink fibrillary background, ganglion cell differentiation
  - Neuritic cell processes containing neurofilaments, neural tubules, and dense core granules by electron microscopy
  - Increased catecholamine metabolite levels in neuroblastoma
  - Demonstration of an adrenal mass on CT scan
- Primitive neuroectodermal tumor (PNET):
  - An entity closely related to Ewing's sarcoma, with neuroectodermal differentiation
  - Homer-Wright rosettes
  - Immunohistochemistry:
    - NSE+, synaptophysin+, neurofilament+, Mic-2+
  - Ultrastructural evidence of dense core granules
  - Age/sex distribution and radiologic features are similar to Ewing's sarcoma

Conventional Chordoma

Clinical

- A low-grade malignant tumor occurring predominantly in the axial skeleton in the region of the embryonic notochord
- Particular predilection to the caudal and cranial extremes
- The clivus and the sacrum are the most common sites
- Vestigial rests of notochord-like tissue located in the spheno-occipital region are sometimes found and termed ecchordosis physaliphora

Microscopic

- Lobulated lesions with a myxoid background
- Cords, sheets, or occasionally haphazardly arranged cells
- Vacuolated cytoplasm (physaliphorous cells)
- Some cells may have abundant eosinophillic cytoplasm or may mimic signet ring cells
- Nuclear pleomorphism is mild and mitotic activity low to absent

Chondroid Chordoma

- A variant of conventional chordoma with foci of cartilaginous differentiation

Plasma Cell Dyscrasias (Plasmacytoma/Multiple Myeloma)

Clinical

- Most common tumor of the bone
- Pathogenesis involves osteoclastic activation by IL-6
- Multiple myeloma:
  - There may be bone lesions, marrow plasmacytosis, or foci of collections of plasma cells
  - Secretion of monoclonal immunoglobulin chains into the blood
  - Anemia, bone pain, pathologic fracture, neurologic abnormalities, renal failure, and amyloid deposits are some other features
- Plasmacytoma:
  - Frequently, only a single deposit of clonally proliferating plasma cells
  - With or without secretion of immunoglobulins into the blood
- POEMS syndrome:
  - A variant consisting of sclerotic bone lesions along with polyneuropathies, endocrine abnormalities, and skin changes

X-rays and Imaging Findings

- Lytic (punched out) lesions in the diaphysis or metaphysis
- The radiological differential diagnosis:
  - Metastatic carcinoma
  - Malignant lymphoma
  - Hyperparathyroidism

Microscopic

- Sheets or aggregates of atypical plasma cells with a pink cytoplasm
- Multinucleated nuclei and prominent nucleoli may be present
- Amyloid deposits may be seen

Differential Diagnosis

- Osteomyelitis
- Malignant lymphoma

Non-Hodgkin's Lymphoma

- Bone lymphomas are very uncommon before the second decade
- Osseous lymphoma lesions are far more common as a secondary rather than a primary form of involvement

Langerhans' Cell Histiocytosis (LCH)

Clinical

- Terms such as histiocytosis X, eosinophilic granuloma, Letterer-Siewe disease, Hand-Schuller-Christian disease, etc. have been used
- The cells bear ultrastructural resemblance to Langerhan's cells of the skin, with the characteristic "Birbeck" granules
- Members of the group of the monocyte, phagocyte, and immune-regulator effector cell system (M-PIRE system)
- A clonal, (possibly neoplastic rather than a reactive) process
- More common in the first three decades of life, although no age is completely exempt
- Pain and swelling are the most frequent presentations
- Systemic symptoms include diabetes insipidus, exophthalmos, skin lesions, and mastoiditis

X-rays and Imaging Findings

- Lytic, geographic lesions occasionally showing bony expansion
- Multiple punch out lesions

Microscopic

- Proliferation of histiocytoid cells with variable amounts of cytoplasm
- The cell borders may be well defined or syncytium-like
- The nuclei have characteristic "grooves" and may be reniform or coffee bean like
- Multinucleated giant cells may be present
- A variable number of mitotic figures may be seen
- Associated inflammatory response, often rich in eosinophils
- Lipid-laden histiocytes are sometimes seen

Immunohistochemistry

- S-100 protein+, CD1a+

Differential Diagnosis

- Granulomatous inflammation
- Osteomyelitis:
  - May be particularly difficult to distinguish on X-rays
  - Necrotic bone trabeculae
  - Predominantly neutrophils with less eosinophils
  - Rarely involves the skull
  - S-100 protein–, CD1a–
- Hodgkin's disease:
  - The diagnostic Reed-Sternberg cells
  - Distinct immunohistochemical profile

Erdheim-Chester Disease

- A condition of unknown cause that may be related to Langerhan's cell histiocytosis
- Most patients are male
- Presentation: weight loss and bone pain; may be asymptomatic
- Bilateral, symmetric sclerosis of the meta-diaphyseal regions of the long bones

Metastatic Bone Disease

Clinical

- Young children:
  - Neuroblastoma is most common
- Older adults:
  - Metastatic carcinoma predominates
- Most frequent primary sites:
  - Lytic lesions (majority of lesions):
    - Kidney
    - Thyroid
    - Gastrointestinal tract
  - Blastic lesions:
    - Prostate
    - Carcinoid tumors
    - Medulloblastoma
  - Blastic and/or lytic:
    - Breast
- Adult patients commonly present with pain, swelling, tenderness, or pathologic fracture
- The bones of the axial skeleton and proximal appendicular skeleton are more frequently affected
- IL-1, IL-6, TGF-β, PDGF, plasminogen activator, and bone morphogenetic proteins (BMPs) may be involved

X-rays and Imaging Findings

- Blastic, lytic, or mixed lesions
- Periosteal reactions are infrequent
- Lesions are often geographic and occasionally expansile

Macroscopic

- Metastatic lytic tumors tend to be more sharply demarcated
- Other metastatic tumors tend to be exquisitely vascular (kidney and thyroid tumors)
- Tumors can vary from hard, bony tumors to soft, fleshy, or friable

Microscopic

- Well-differentiated metastatic tumors do not pose a problem
- Renal cell or thyroid carcinomas can often be diagnosed without immunohistochemical stains
- Mucicarmine or immunostains for epithelial markers are helpful
- Reactive bone formation may mimic osteosarcoma
- Some sarcomas can be ± for epithelial markers such as cytokeratin (leiomyosarcomas, MFH, epithelioid osteosarcomas, epithelioid hemangioendotheliomas, etc.)

STAGING OF MUSCULOSKELETAL NEOPLASMS

The system uses the GTM approach (Grade, SiTe, Metastasis or the Enneking system)

- Grade:
  - G0: Benign
  - G1: Low grade
  - G2: High grade
- Tumor site:
  - T1: Intracompartmental locations, including:
    - Intraosseous
    - Intraarticular
    - Intrafascial (ray of hand, volar compartment of forearm, etc.)
  - T2: Extracompartmental locations:
    - Evidence of soft tissue or fascial extension
    - Certain anatomic locations are always considered to be T2 locations:
      - Popliteal and antecubital fossa
      - Femoral triangle
      - Mid and hind foot
      - Mid hand
      - Intrapelvic locations
      - Axilla
- Metastasis:
  - M0: Absent
  - M1: Present

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16

Soft Tissue Tumors

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CONTENTS

I. Fibrous Tumors 16-4
- Classification of Fibrous Tumors 16-4
- Benign 16-4
  - Nodular Fasciitis 16-4
  - Proliferative Fasciitis 16-4
  - Proliferative Myositis 16-5
  - Ischemic Fasciitis (Atypical Decubital Fibroplasia) 16-5
  - Elastofibroma 16-6
  - Fibroma of Tendon Sheath 16-6
  - Nuchal Fibroma 16-7
  - Solitary Fibrous Tumor 16-7
  - Keloid Scar 16-7
- Pediatric Fibrous Tumors 16-7
  - Fibrous Hamartoma of Infancy 16-7
  - Infantile Myofibromatosis 16-8
  - Fibromatosis Colli 16-8
  - Juvenile Hyaline Fibromatosis 16-8
  - Inclusion Body Fibromatosis (Infantile Digital Fibromatosis) 16-8
  - Infantile Fibromatosis (Desmoid-Type) 16-8
  - Calcifying Aponeurotic Fibroma 16-9
- Fibromatoses 16-9
  - Superficial Fibromatoses 16-9
  - Deep (Desmoid) Fibromatoses 16-10
- Inflammatory myofibroblastic tumor 16-11
- Malignant 16-11
  - Low grade myofibroblastic sarcoma 16-11
  - Fibrosarcoma 16-11

II. Fibrohistiocytic Tumors 16-12
- Classification of Fibrohistiocytic Tumors 16-12
- Benign 16-12
  - Benign Fibrous Histiocytoma 16-12
  - Juvenile Xanthogranuloma 16-13
  - Reticulohistiocytoma 16-13
  - Xanthoma 16-14
- Low-Grade Malignant 16-14
- Dermatofibrosarcoma Protuberans (DFSP) 16-14
  - Giant Cell Fibroblastoma 16-15
  - Plexiform Fibrohistiocytic Tumor 16-15
  - Atypical Fibroxanthoma 16-16
  - Angiomatoid MFH 16-16
- Malignant 16-16
  - "Malignant Fibrous Histiocytoma" (MFH) 16-16

III. Lipomatous Tumors 16-17
- Classification of Lipomatous Tumor 16-17
- Benign 16-17
  - Lipoma 16-17
  - Angiolipoma 16-19
  - Spindle Cell Lipoma 16-19
  - Pleomorphic Lipoma 16-20
  - Lipoblastoma 16-20
  - Hibernoma 16-20
  - Lipomatosis 16-20
- Malignant 16-21
  - Liposarcoma 16-21
  - Well-Differentiated Liposarcoma (WDLS)/Alypical Lipomatous Dedifferentiated Liposarcoma 16-21

Myxoid Liposarcoma 16-22
Pleomorphic Liposarcoma 16-22

IV. Smooth Muscle Tumors 16-22
Classification of Smooth Muscle Tumors 16-22
Benign 16-22
Leiomyoma 16-22
Intravenous Leiomyomatosis 16-23
Peritoneal Leiomyomatosis (Leiomyomatosis peritonealis Disseminata) 16-23
Palisaded Myofibroblastoma of Lymph Node 16-23
Malignant 16-24
Leiomyosarcoma 16-24

V. Skeletal Muscle Tumors 16-24
Classification of Skeletal Muscle Tumors 16-24
Benign 16-24
Rhabdomyomatous Mesenchymal Hamartoma 16-24
Cardiac Rhabdomyoma 16-24
Adult Rhabdomyoma 16-25
Fetal Rhabdomyoma 16-25
Genital Rhabdomyoma 16-25
Malignant 16-25
Rhabdomyosarcoma 16-25
Malignant Triton Tumor 16-27
Ectomesenchymoma 16-27

VI. Vascular Tumors....16-27
Classification of Vascular Tumors 16-27
Benign 16-27
Low-Grade Malignant 16-29
Kaposiform Hemangioendothelioma (Kaposi-Like Hemangioendothelioma) 16-29
Kaposi's Sarcoma 16-30
Malignant 16-30
Epithelioid Hemangioendothelioma 16-30
Angiosarcoma 16-31
Perivascular Tumors 16-32
Glomus Tumor 16-32
Hemangiopericytoma 16-32

VII. Synovial Tumors....16-33
Classification of Synovial Tumors 16-33
Benign 16-33
Giant Cell Tumor of Tendon Sheath (Localized Type) 16-33
Malignant 16-33
Synovial Sarcoma 16-33

VIII. Peripheral Neural Tumors 16-34
Classification of Peripheral Neural Tumors 16-34
Benign 16-34
Traumatic Neuroma (Amputation Neuroma) 16-34
Morton's Neuroma (Localized Interdigital Neuritis) 16-35
Digital Pacinian Neuroma 16-35
Mucosal Neuroma 16-35
Solitary Circumscribed Neuroma (Palisaded Encapsulated Neuroma) 16-35
Schwannoma (Neurilemmoma) 16-35
Solitary Neurofibroma 16-36
Diffuse Neurofibroma 16-37
Plexiform Neurofibroma 16-37
Perineurioma 16-37
Cellular Neurothekeoma 16-38
Dermal Nerve Sheath Myxoma 16-38
Ganglioneuroma 16-38
Granular Cell Tumor 16-38
Heterotopic Meningeal Lesion (Ectopic Meningioma) 16-39
Heterotopic Glial Nodules (Nasal Gliomas) 16-39
Malignant 16-39
Malignant Peripheral Nerve Sheath Tumor (Maligant Schwannoma or Neurofibrosarcoma) 16-39
Clear Cell Sarcoma (Malignant Melanoma of Soft Parts) 16-40
Extraspinal (Soft Tissue) Ependymoma 16-41

IX. Chondro-Osseous Tumors 16-42
Classification of Chondro-Osseous Tumors 16-42
Benign 16-42
Osteoma Cutis 16-42
Myositis Ossificans 16-42
Soft Tissue Chondroma 16-42
Malignant 16-42
Extraskeletal Myxoid Chondrosarcoma (Chordoid Sarcoma) 16-42
Extraskeletal Mesenchymal Chondro– sarcoma 16-43
Extraskeletal Osteosarcoma 16-43

X. Miscellaneous Tumors 16-43
Classification of Tumors of Uncertain Histogenesis 16-43

Benign 16-43
Tumoral Calcinosis 16-43
Amyloidoma 16-43
Myxoma 16-44
Ossifying Fibromyxoid Tumor 16-45
Malignant 16-45
Alveolar Soft Part Sarcoma 16-45
Epithelioid Sarcoma 16-46
Primitive Neuroectodermal Tumor 16-46
Extrarenal Rhabdoid Tumor 16-47
Desmoplastic Small Round Cell Tumor 16-47

XI. Suggested Reading 16-48

FIBROUS TUMORS

♦ Classification: *see* **Table 1**

Benign

Nodular Fasciitis (Figure 1)

♦ Common, self-limiting, reactive proliferation of fibroblasts

♦ Histologically often mistaken for sarcoma

Clinical

♦ Typically, rapidly growing, often painful or tender subcutaneous nodule

♦ Duration: variable, most <10–12 weeks

♦ Most common in adults, 20–40 years; no sex predilection

♦ Common sites: upper extremities and trunk; head and neck in children

♦ 10% are intramuscular

♦ Self-limiting, usually regress spontaneously (if untreated); 2% local recurrence

Macroscopic

♦ Well-circumscribed or stellate mass, usually <3 cm in diameter; unencapsulated

♦ Cut surface: myxoid, centrally cystic or fibrous (depending on duration)

Microscopic

♦ Cellular myofibroblastic proliferation in short interweaving fascicles

♦ Loose, myxoid collagenous stroma (feathery appearance)

♦ Plump nuclei with occasional prominent nucleoli, no atypia

♦ Normal mitoses may be numerous

♦ Delicate thin-walled vessels (granulation tissue-like)

♦ Extravasated red blood cells and scattered inflammatory cells

♦ Hyalinized (sometimes keloidal) stroma (variable)

♦ Multinucleated giant cells (osteoclastic type) and reactive new bone formation (rare)

Immunohistochemistry

♦ Vimentin+, muscle-specific actin+, smooth muscle actin+

♦ Desmin–, S-100 protein–

♦ CD 68± (controversial)

Variants

♦ Ossifying fasciitis (fasciitis ossificans):
- Periosteal location
- Show reactive bone formation
- Features of both nodular fasciitis and myositis ossificans

♦ Intravascular fasciitis:
- Involves small or medium-sized veins (mainly) or arteries
- Predominant or focal intravascular growth
- Upper limbs or head and neck regions

♦ Cranial fasciitis:
- Occurs predominantly in infants
- Involves soft tissue of the scalp and underlying skull
- Show bone erosion

Differential Diagnosis

♦ Sarcomas:
- Rarely grow as rapidly, larger size and deep location
- More cellular, densely packed, more nuclear atypia, hyperchromasia +/– necrosis

♦ Fibromatosis:
- Larger, more infiltrative growth, usually involve skeletal muscle
- May have areas of fasciitis-like architecture (especially intra-abdominal and breast desmoid tumors)
- Fascicular pattern with abundant collagen, slender fibroblasts
- Less frequent mitoses

♦ Benign fibrous histiocytoma:
- Whorled or storiform growth pattern, more polymorphous
- Usually actin only focally +

Proliferative Fasciitis

Clinical

♦ Peak incidence: 40–70 years (6th decade); M : F equal

♦ Common sites: extremities, especially forearm and thigh

♦ Like nodular fasciitis grows rapidly within two or three weeks

♦ Rarely recurs

Macroscopic

♦ Poorly circumscribed, subcutaneous, gray-white mass; 1–5 cm

Microscopic

♦ Similar to nodular fasciitis

♦ Numerous basophilic polygonal large cells with one or more nuclei with prominent nucleoli (ganglion cell-like)

♦ Prominent vessels (resembling granulation tissue)

♦ Poorly defined margins

♦ Septal distribution in subcutis

Immunohistochemistry

♦ Ganglion-like cells are actin negative

Table 1. Classification of Fibrous Tumors

Benign	Fibromatosis colli
Nodular fasciitis	Juvenile hyaline fibromatosis
Variants:	Infantile digital fibromatosis (inclusion body fibromatosis)
Ossifying fasciitis	Infantile fibromatosis (desmoid-type)
Intravascular fasciitis	Gingival fibromatosis
Cranial fasciitis	Calcifying aponeurotic fibroma
Proliferative fasciitis	Calcifying fibrous pseudotumor
Proliferative myositis	**Fibromatoses**
Ischemic fasciitis (atypical decubital fibroplasia)	Superficial fibromatoses
Keloid scar	Palmar fibromatosis (Dupuytren's contracture).
Elastofibroma	Plantar fibromatosis (Ledderhose's disease)
Fibroma of tendon sheath	Penile fibromatosis (Peyronie's disease)
Nuchal fibroma	Knuckle pads
Nasopharyngeal angiofibroma (see Head and Neck tumors)	Deep fibromatoses (desmoid tumors)
Dermatofibroma (see Skin tumors)	Extra-abdominal fibromatosis (extra-abdominal desmoid)
Angiomyofibroblastoma (see Vulval tumors)	Abdominal fibromatosis (abdominal desmoid)
Myofibroblastoma (see Breast tumors)	Intra-abdominal fibromatosis (intra-abdominal desmoid)
Solitary fibrous tumor	**Malignant**
Pediatric	Fibrosarcoma
Fibrous hamartoma of infancy	Variant: Infantile fibrosarcoma
Infantile myofibromatosis	
Variant: Solitary myofibroma	

Differential Diagnosis

Pleomorphic Rhabdomyosarcoma

- Rarely subcutaneous; more cytological atypia; atypical mitoses
- Desmin+, actin+, Myf-4 (myogenin) +

Proliferative Myositis

Definition

- Deep or intramuscular counterpart of proliferative fasciitis

Clinical

- Peak: 5th and 6th decades; M = F
- Solitary, rapidly growing lesion, <4 weeks duration
- Mainly involves flat muscles of trunk and shoulder girdle
- Outcome is excellent; recur rarely

Macroscopic

- Poorly demarcated; 1–6 cm in diameter
- Scar-like induration involving muscle and overlying fascia

Microscopic

- Similar to proliferative fasciitis
- Along fibrous septa and between individual muscle fibers (uninvolved)
- "Checkerboard" appearance with atrophy, but preservation, of muscle fibers
- Foci of metaplastic bone or cartilage (10%)

Differential Diagnosis

Sarcoma

- More localized and does not preserve muscle fibers
- More cytological atypia and pleomorphism

Ischemic Fasciitis (Atypical Decubital Fibroplasia)

Clinical

- Occurs in debilitated, immobilized or bedridden patients
- Result of prolonged pressure and impaired circulation
- Chiefly in subcutaneous areas over bony prominences: shoulder, sacrum and hip



Fig. 1. Nodular fasciitis: intervening short fascicles of spindle cells with a "tissue culture" appearance and extravazated red blood cells.

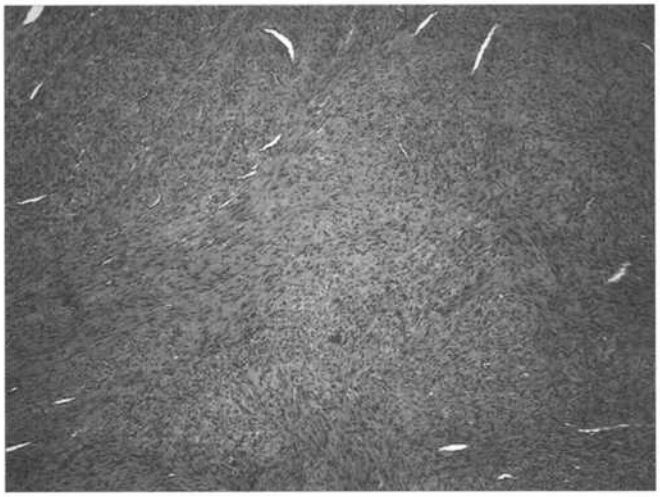


Fig. 2. Fibroma of tendon sheath: bland fibroblastic/myofibroblastic proliferation with slit-like vessels.

- Painless soft tissue mass, mistaken for a neoplasm
- Slight female predilection; peak age: 70–90 years
- Local recurrence after excision may occur

Macroscopic

- Poorly circumscribed mass in deep subcutis, may extend into muscle

Microscopic

- Lobular or zonal growth pattern
- Vascular, inflamed granulation tissue with plump, atypical fibroblasts
- Prominent myxoid stroma and cystic changes
- Diffuse fibrinoid necrosis
- Fibrosis (variable, usually in older lesions)

Elastofibroma

Clinical

- Uncommon distinct lesion
- Believed to be reactive; however, reports of clonal abnormalities raise the possibility of neoplasia
- Usually subscapular location, 10% bilateral
- Elderly, marked female predilection
- Slow-growing, ill-defined mass attached to periosteum of ribs
- No tendency for local recurrence
- Clustering of cases suggest genetic predisposition

Macroscopic

- Ill-defined margins; range 5–10 cm in size
- Cut surface looks like dense fibroadipose tissue

Microscopic

- Irregular bands of dense, hypocellular hyalinized collagenous fibrous tissue
- Numerous thick, serrated, eosinophilic elastic fibers, highlighted by elastic stain (diagnostic)
- Entrapped mature adipose tissue
- Myxoid matrix (variable)

Fibroma of Tendon Sheath (Figure 2)

Clinical

- Relatively common in adults, peak: 20–50 years; M : F = 2 : 1
- Slow-growing, painless, hard nodule attached to tendon
- Mostly hands (mainly fingers) and feet
- Up to 25% recur after local excision

Macroscopic

- Well-circumscribed, firm and rubbery, attached to tendon
- Range: 1–2 cm in size

Microscopic

- Lobulated configuration
- Bland fibroblasts and myofibroblasts
- Densely collagenized stroma
- Thin, slit-like vessels between lobules
- Cellularity and mitosis (vary with duration)

Differential Diagnosis

- Giant cell tumor of tendon sheath:
  - Possibly a spectrum, more cellular and less hyalinized
- Nodular fasciitis:
  - Not attached to tendon, more cellular and zonation pattern
- Fibromatosis and Fibrosarcoma:
  - Not circumscribed or lobulated, no slit-like vessels

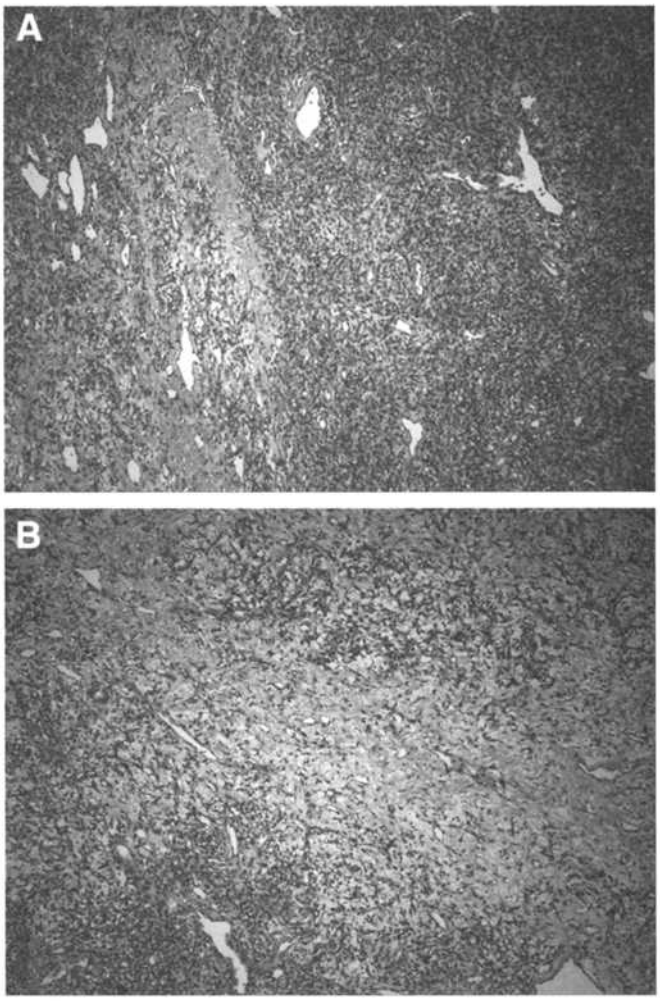


Fig. 3. Solitary fibrous tumor: "patternless" spindle cell neoplasm with alternating hypercellular **(A)** and hypocellular **(B)** areas, and "HPC-like" vessels.

Nuchal Fibroma

- Association with Gardner's syndrome (APC gene) and diabetes mellitus (30–40% cases)
- Rare, ill-circumscribed, subcutaneous fibrous growth
- Usually back of neck, interscapular and paraspinal regions of adults
- Dense hypocellular, haphazardly arranged collagen bandles
- Entrapment of normal tissues (adipose tissue and small peripheral nerves)
- May recur if incompletely excised

Solitary Fibrous Tumor (Figure 3)

Clinical

- May occur in many sites other than pleura, including: peritoneum, retroperitoneum, mediastinum, and head and neck
- Usually adults, no sex predilection
- Slowly enlarging mass, located in deep soft tissues
- Associated with systemic symptoms (rarely): hypoglycemia and finger clubbing
- Usually benign clinical course, rare malignant transformation

Microscopic

- Large, well-circumscribed and lobulated
- "Patternless" growth pattern with marked variation in cellularity
- Spindle fibroblast-like cells with intervening collagen bundles
- Dense hyalinized stroma (variable)
- Hemangiopericytoma-like vascular pattern
- Malignant SFT: >4 mitoses/10 high-power fields, necrosis, pleomorphism
- Lipomatous STF: prominent adipocytic component

Immunohistochemistry

- CD34+, CD99+, bcl-2+
- Actin–, S-100 protein–, desmin–

Keloid Scar

Clinical

- Reactive fibrous proliferation following local trauma or surgery
- Peak: 15–45 years; blacks > whites; may be familial
- Any anatomic location, especially head and neck region
- Treatment is difficult and up to 50% recur locally after excision

Macroscopic

- Excessive scar tissue
- Extends beyond the boundaries of the site of initial tissue damage

Microscopic

- Hypocellular, thick, glassy, hyalinized, eosinophilic collagen fibers
- Haphazardly arranged into broad bands or nodules
- Calcification (variable)

Differential Diagnosis

- Hypertrophic scar:
  - Less common, confined to the original site of tissue damage
  - More cellular scar tissue with nodular configuration
  - Less prone to local recurrence

Pediatric Fibrous Tumors

Fibrous Hamartoma of Infancy

Clinical

- First 2 years of life, usually <1 year; marked male predilection

- Usually solitary; involves dermis and subcutis; freely movable
- Commonly in axillary, upper arm and shoulder regions
- Cured by local excision; rarely recur

Macroscopic

- Poorly circumscribed; on average 3–5 cm in size

Microscopic

- Organoid growth pattern
- Composed of 4 components in varying proportions:
  - Myxoid foci with small round nests of undifferentiated spindle cells
  - Fascicles of myofibroblasts with wavy, tapering nuclei
  - Irregular fibrous trabeculae or septa with inflammatory cells
  - Islands of mature adipose tissue

Differential Diagnosis

- No real differential at this age and location

Infantile Myofibromatosis

- In the spectrum of myopericytic (perivascular contractile cells) proliferations

Clinical

- Usually <2 years, 30% congenital; M > F
- Solitary or multicentric (25%)
- Most involve skin and superficial soft tissue, or bone
- Common sites: head and neck and trunk, bone
- Multicentric cases may involve viscera, mainly gut or lungs
- Soft tissue and bone lesions are benign and may regress spontaneously
- Multiple visceral lesions may have fatal outcome (rare)

Microscopic

- Most <3 cm, well-circumscribed, unencapsulated
- Lobulated or multinodular pattern
- Peripherally, fascicles of bland eosinophilic myofibroblasts
- Centrally, primitive round cells around prominent hemangiopericytoma-like vessels
- Hyalinized and myxoid stroma (at periphery)
- Mitoses (few and typical)
- Necrosis (frequent)
- Subendothelial proliferation of spindle cells with projection into vessel (frequent)

Variant

- Solitary myofibroma:
  - Usually in head and neck region of adults
  - No gender predilection
  - Firm, cutaneous, painful nodule
  - No tendency to local recurrence
  - Similar histologic appearance but with less conspicuous primitive hemangiopericytoma-like areas

Fibromatosis Colli

- Diffuse fibrous replacement of sternocleidomastoid muscle
- Usually neonates, 2–4 weeks; M = F; R > L
- Often associated with breech or forceps delivery
- Many resolve spontaneously, 10% develop torticollis (wry neck deformity)
- Muscle atrophy and degeneration

Juvenile Hyaline Fibromatosis

- Exceedingly rare, hereditary disorder of infants and children
- Autosomal recessive inheritance
- Head and neck tumors associated with gingival hypertrophy, joint contractures and bone lesions
- Accumulation of amorphous hyaline material of unknown origin
- Mutations of gene encoding capillary morphogenesis protein 2 (CMG2) on chromosome 4q21

Inclusion Body Fibromatosis (Infantile Digital Fibromatosis)

- Distinct fibrous tumor in fingers and toes of infants
- Small digital nodule <2 cm, in dermis and subcutis
- 30% congenital, rarely in older children
- 60% recur following local excision; most regress spontaneously
- Ill-defined nodule composed of fascicles of myofibroblasts
- Intracytoplasmic rounded eosinophilic inclusions, close to nucleus (trichrome+, actin+)

Infantile Fibromatosis (Desmoid-Type)

- Childhood counterpart of the desmoid-type fibromatosis

Clinical

- Usually deep, poorly-circumscribed, solitary mass
- Involves skeletal muscle or fascia
- Mostly <8 years; M > F
- Common sites: head and neck, shoulder, upper arm and thigh
- Locally aggressive: tend to recur locally, do not metastasize

Macroscopic

- Ill-defined, dense fibrous tissue, range: 1–10 cm in size

Microscopic

- Diffuse or mesenchymal form:
  - Infants, few months old
  - Haphazard arrangement of small cells
  - Primitive fibroblast-like cells in myxoid background

- Diffuse infiltration of skeletal muscle
- Atrophic muscle with fat replacement

♦ Fibroblastic form:
- Cellular with bundles and fascicles
- Plump spindle-shaped fibroblasts
- Diffuse infiltration of skeletal muscle

♦ Desmoid form (like adult-type):
- Less cellular and more collagenous
- Usually children > 5 years
- Behaves like adult-type

Differential Diagnosis

♦ Myxoid liposarcoma:
- Rare in < 5 years, plexiform capillary pattern, presence of lipoblasts

♦ Lipoblastomatosis:
- Lobular pattern, presence of lipoblasts

♦ Infantile fibrosarcoma:
- Pushing margin, uniform cellularity, rapidly growing, mitotic activity and destructive behavior

Calcifying Aponeurotic Fibroma

Clinical

♦ Rare, slowly growing fibroblastic proliferation in extremities

♦ Mainly children and adolescents (median age 9 years); M > F (slight)

♦ Poorly defined, painless mass involving aponeuroses and tendons

♦ Recur locally

Microscopic

♦ Usually <3 cm; infiltrative growth pattern

♦ Central calcified foci surrounded by chondroid-like areas (variable)

♦ Plump myofibroblasts, may show cord-like orientation

♦ Osteoclast-like giant cells around calcification (variable)

Fibromatoses

♦ Locally aggressive neoplasms, commonly recur but do not metastasize

♦ Subclassified into superficial and deep types

Superficial Fibromatoses (Figure 4)

Clinical

♦ Small, slow growing, bland myofibroblastic proliferations

♦ Usually in adults; 50% are bilateral

♦ Involve the superficial fascia or aponeurosis

♦ May cause flexion contractures

♦ May be associated with epilepsy, diabetes, alcohol abuse

♦ Local excision, usually fasciectomy; may recur



Fig. 4. Plantar fibromatosis: long fascicles of myofibroblasts with tapered nuclei.

Microscopic

♦ Variable cellularity and collagenization

♦ Early active growth phase with plump myofibroblasts and increased numbers of mitoses

♦ More hyalinized in later stage lesions with uniform mitotically inactive myofibroblasts

♦ Myxoid matrix and mitoses (variable, usually early lesions)

♦ Cartilaginous or osseous metaplasia (rare)

Variants

♦ Palmar fibromatosis *(Dupuytren's contracture)*:
- Involve hand or fingers, adults, M > F
- Cytogenetics: trisomies 7, 8 and 14

♦ Plantar fibromatosis *(Ledderhose's disease)*:
- Involves feet, may occur between 5–15 years; more common
- No contraction deformities
- Common local recurrence after surgery
- Similar cytogenetic abnormalities

♦ Knuckle pad:
- Bland cellular fibrous tissue in dermis with overlying hyperkeratosis, no treatment required

♦ Penile fibromatosis *(Peyronie's disease)*:
- Involves shaft of the penis with pain and curvature
- Mainly between 40–60 years, slow growing
- Hypocellular scar tissue with chronic inflammation +/– metaplastic ossification
- No effective treatment except surgical excision

Differential Diagnosis

♦ No realistic differential diagnosis in the right clinical setting

Deep (Desmoid) Fibromatoses (Figure 5)

Clinical

- Three clinical settings: sporadic, associated with familial adenomatous polyposis (FAP), multicentric or familial
- Three anatomic locations: extraabdominal, abdominal wall and intra-abdominal
- Peak incidence: 15–35 years; M : F = 1 : 2
- Usually large, infiltrative masses involving deep musculature
- Wide complete excision +/– radiotherapy
- Recurrence rate range: 25–80%
- Mutations in the APC gene (chromosome 5q)

Macroscopic

- Irregular large lesions (>5 cm), depending on location
- Cut surface: pale, whorled and fibrous
- Poorly-defined, infiltrative margins

Microscopic

- Usually hypocellular, fascicular or broad storiform growth pattern
- Pale eosinophilic fibroblasts and myofibroblasts
- Cellularity and mitotic activity (variable but usually low)
- Variably collagenous stroma, focally myxoid (variable)
- Thick-walled, elongated, compressed blood vessels
- Focal fasciitis-like areas (especially in intra-abdominal desmoid tumors)
- May show keloidal hyalinization
- Lymphoid aggregates, usually at the periphery
- Cartilaginous or osseous metaplasia (rare)

Subtypes

- Extraabdominal fibromatosis (desmoid)—60%:
  - Common sites: limb girdles, proximal extremities
- Abdominal fibromatosis (desmoid)—25%:
  - Usually anterior abdominal wall
  - Usually females, frequently during or soon after pregnancy
  - May arise in a preceding scar (e.g., cesarean section)
- Intra-abdominal fibromatosis (desmoid)—15%:
  - Usually involves mesentery, often after prior surgery
  - May be associated with FAP

Immunohistochemistry

- β-catenin+ (nuclear positivity)
- Actin+, Desmin–, S-100 protein+ (focal)

Differential Diagnosis

- Nodular fasciitis:
  - Loose arrangement with microcystic stromal degeneration, zonation pattern, inflammation and hemorrhage

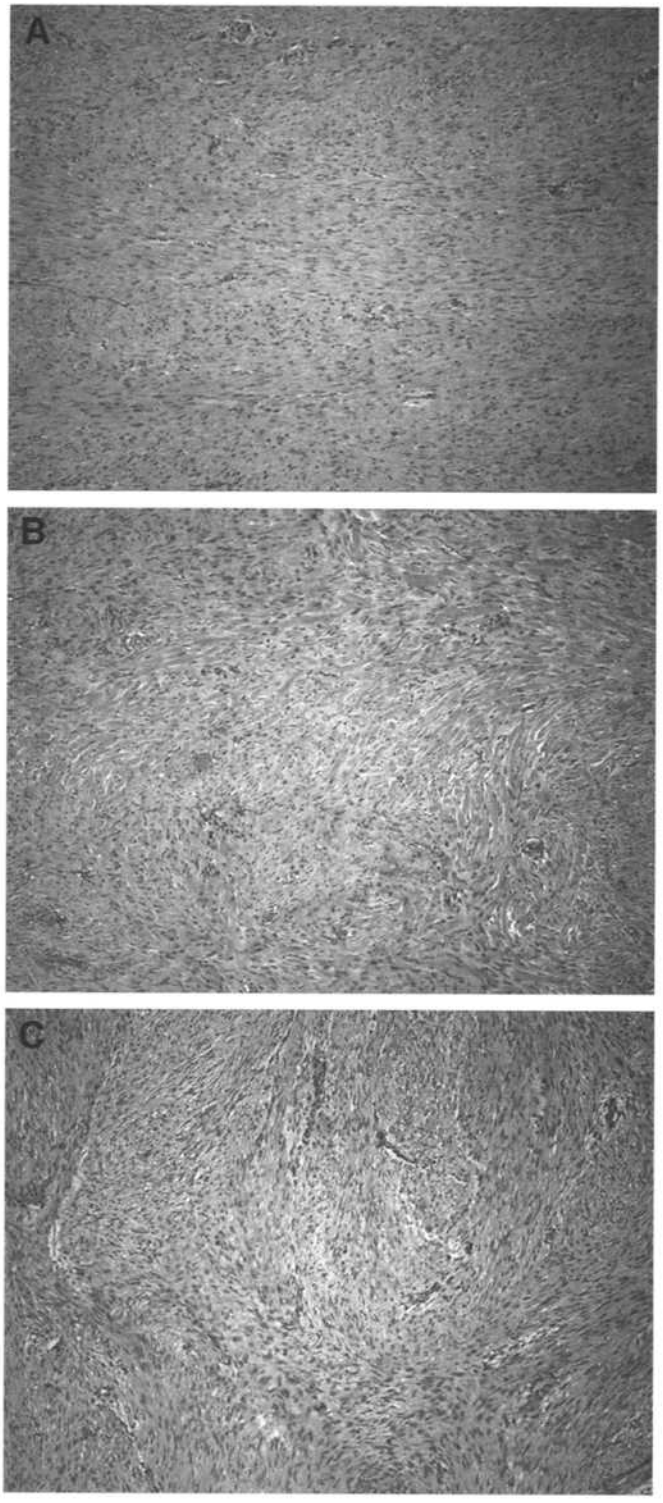


Fig. 5. Desmoid fibromatosis: long fascicles of fibroblasts/myofibroblasts **(A)** Occasionally, keloidal hyalinization is noted **(B)**. Intra-abdominal desmoid fibromatosis often shows "fasciitis-like" features in some areas **(C)**.

- Cellular neurofibroma and low grade malignant nerve sheath tumor:
  - Wavy, elongated nuclei and S-100+ (diffuse)
- Fibrosarcoma:
  - More cellular, less collagenous, herringbone pattern and nuclear atypia

Inflammatory Myofibroblastic Tumor

Clinical

- Childhood and adolescence; slight female predominance
- Occurs most commonly in the abdominal cavity
- Systemic symptoms in 20% cases
- May recur locally
- May metastasize (rare)

Microscopy

- Fascicular spindle cell proliferation of myofibroblasts + prominent inflammatory infiltrate
- Lymphocytes and plasma cells
- Variable mitotic rate, necrosis, calcification

Immunohistochemistry

- Actin+, desmin+/–, keratin+/–
- ALK-1 protein+

Cytogenetics

- Rearrangement of ALK gene on chromosome 2p

Malignant

Low Grade Myofibroblastic Sarcoma

Clinical

- Young to middle-aged adults, M = F
- Wide anatomic distribution, deep-seated
- Commonly recurs and metastasize

Microscopy

- Fascicular, hypercellular neoplasm composed of elongated myofibroblasts
- Nuclear atypia
- Diffuse infiltration of skeletal muscle

Fibrosarcoma (Figure 6)

Clinical

- Uncommon tumor, adult and infantile types

Adult fibrosarcoma

- Usually 4th to 6th decades, male predominance
- Deep-seated, painful, slow-growing mass
- Common sites: thigh, trunk
- 40% 5-year survival, depends on histologic grade and resectability

Macroscopic

- Usually well-circumscribed, <10 cm in diameter

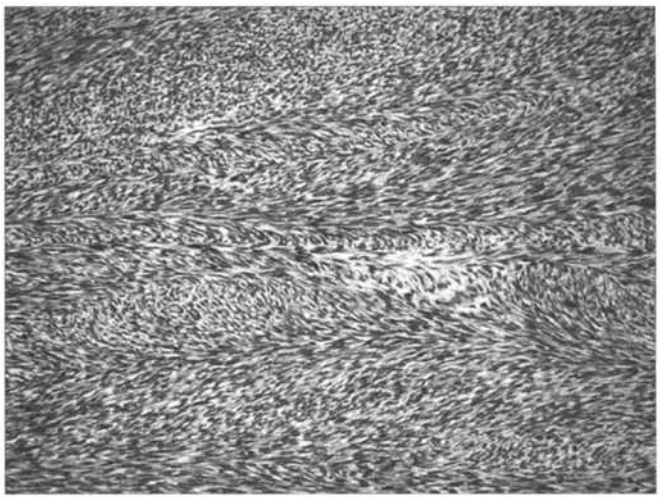


Fig. 6. Fibrosarcoma: note the herringbone pattern of the long fascicles of spindle cells.

Microscopic

- Typically cellular with herringbone fascicular pattern
- Monomorphic spindle cells with indistinct cell borders and elongated, tapering nuclei
- Variable mitotic rate and minimal pleomorphism
- Limited collagen production
- Rare primitive, round, uniform cells (some childhood cases)
- Branching hemangiopericytoma-like vascular pattern (variable)

Immunohistochemistry

- S-100 protein–, EMA–, keratin– and desmin–
- Focally actin+ (some childhood cases)

Variants

- Sclerosing epithelioid fibrosarcoma
- Low grade fibromyxoid sarcoma:
  - Mostly adults; peak age: 30–60 years
  - Any location, usually superficial, most often around limb girdles
  - Whorled growth pattern
  - Variable dense fibrous and myxoid stroma
  - Bland, uniform fibroblasts, no pleomorphism
  - Hypovascular and rare mitoses
  - May have giant hyalinized rosettes
  - Vimentin+, actin–, desmin–, CD34– and S100–
  - Recurs frequently and metastasize in 50% of cases (lung)

Infantile Fibrosarcoma

- Within first two years of life, often congenital; M>F
- Large painless mass, may involve subcutis
- Predilection for distal extremities
- 5-year survival >80%
- Similar morphologic appearances

- Cytogenetics: t(12;15)(p13;q25) (also seen in mesoblastic nephroma) and multiple trisomies

Differential Diagnosis

- Desmoid fibromatosis: less cellular
- Low grade myofibroblastic sarcoma
- Malignant peripheral nerve sheath tumor
- Synovial sarcoma: more stromal collagen; t(X;18)
- Usually a diagnosis of exclusion

FIBROHISTIOCYTIC TUMORS

- Classification: *see* **Table 2**

Benign

Benign Fibrous Histiocytoma (Figure 7)

Clinical

- May be subdivided into:
  - cutaneous form (dermatofibroma—see skin chapter)
  - deep (<5%) within subcutis, skeletal muscle or abdominal cavity
- Principally adults, 20–40 years of age; M > F
- Commonest sites: lower limb and head and neck region
- 20–30% may recur after local excision

Macroscopic

- Well-circumscribed and pseudoencapsulated
- Usually >4 cm in diameter
- Central hemorrhage or cystic change (occasional)

Microscopic

- Storiform growth pattern with short fascicles
- Eosinophilic spindle cells with elongated or plump vesicular nuclei
- Foamy cells and giant cells (infrequent)
- Mitoses common, usually <5/10 HPF
- Foci of necrosis (occasional)
- Focal hyalinized or myxoid stroma
- Perivascular hyalinization or hemangiopericytoma-like vessels
- Hemorrhage; hemosiderin deposition
- Admixed inflammatory cells

Variants

- Aneurysmal Fibrous Histiocytoma:
  - Mainly in young and middle aged adults; slight female predominance
  - May grow rapidly to a large size
  - Numerous blood-filled cavernous cavities, no endothelial lining
  - Background of cellular fibrous histiocytoma
  - Abundant hemosiderin deposition and giant cells
  - May recur locally
- Atypical Fibrous Histiocytoma (dermatofibroma with monster cells):
  - Clinically non-distinct variant with atypical cytological features
  - Bizarre hyperchromatic giant cells and histiocytes
  - Mainly demal, occasional extension into subcutis
  - Increased numbers of mitoses, including atypical forms
  - May recur locally, rarely metastasize
- Epithelioid Fibrous Histiocytoma:
  - Epithelioid cells with ample eosinophilic cytoplasm
  - Resembles Spitz nevi, however S-100 protein–
- Cellular variant of Benign Fibrous Histiocytoma:
  - Accounts for 5% of cases; may be mistaken for malignancy
  - Relatively monomorphic and fascicular
  - Recurs in up to 30% of cases

Immunohistochemistry

- Usually not helpful
- Scattered Factor XIIIa+ cells (controversial)
- CD34+ (deep benign fibrous histiocytoma)

Differential Diagnosis

- Nodular fasciitis:
  - Loosely arranged bundles with zonation pattern
- Neurofibroma:
  - More uniform bundles, slender wavy nuclei, thick wavy collagen bundles, S100 protein+
- Leiomyoma:
  - More distinct fascicular pattern, blunt-ended plumper nuclei
  - Actin+, desmin+
- Dermatofibrosarcoma protuberans:
  - More extensive subcutaneous involvement
  - Uniform cellular population
  - Lacks giant cells, inflammatory cells and xanthoma cells
  - More infiltrative growth pattern
  - CD34+, Factor XIIIa–
- "Malignant fibrous histiocytoma":
  - Deeper situated tumor

Table 2. Classification of Fibrohistiocytic Tumors

Benign	**Low-Grade Malignant**
Fibrous histiocytoma	Dermatofibrosarcoma protuberans (DFSP)
Variants:	Giant cell fibroblastoma
Dermatofibroma (cutaneous form—see Skin tumors)	Plexiform fibrohistiocytic tumor
Aneurysmal fibrous histiocytoma	Atypical fibroxanthoma (AFX)
Atypical fibrous histiocytoma	Angiomatoid malignant fibrous histiocytoma
Epithelioid fibrous histiocytoma	**Malignant**
Cellular variant of benign fibrous histiocytoma	Malignant fibrous histiocytoma (MFH)
Juvenile xanthogranuloma	Storiform/Pleomorphic MFH
Reticulohistiocytoma	Myxoid MFH (myxofibrosarcoma)
Xanthoma	Giant cell MFH
	Inflammatory MFH

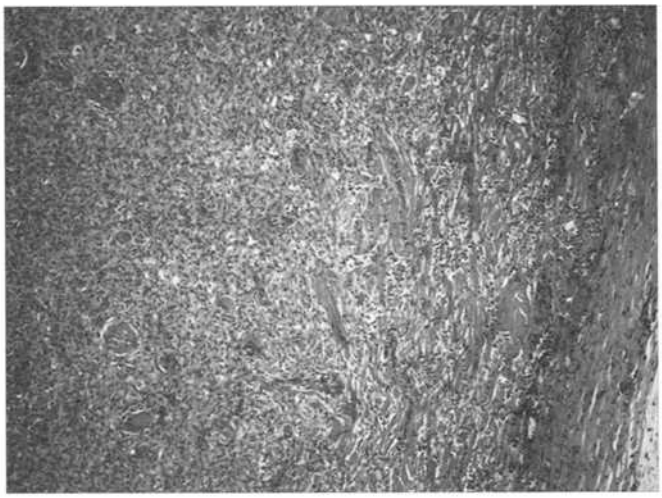


Fig. 7. Benign fibrous histiocytoma: polymorphous storiform spindle cell proliferation with peripheral entrapment of collagen fibers.

- More cytological atypia, pleomorphism and abnormal mitoses

Juvenile Xanthogranuloma

Clinical

- 20% congenital; usually develop between 6–24 months; 15% in adults
- No sex predilection; solitary : multiple = 2 : 1
- Head and neck region is commonly affected
- Usually cutaneous, 5% deep soft tissue or other organs (e.g., eye)
- Usually self-limited, occasionally spontaneous involution

Macroscopic

- Usually <1 cm
- Unencapsulated but well-defined margins

Microscopic

- Diffuse, uniform population of histiocytes
- Eosinophilic, vacuolated or xanthomatous (lipidized) cytoplasm
- Mitotic figures common, sometimes frequent
- Touton giant cells, lymphocytes, eosinophils, and plasma cells (all variable)
- Sclerosis with regression
- Overlying atrophic epidermis, usually uninvolved, rarely ulcerated

Differential Diagnosis

- Langerhans cell histiocytosis:
  - Less cellular cohesion, no Touton giant cells, S-100+, CD1a+
- Benign fibrous histiocytoma:
  - Storiform growth pattern, more polymorphous cell population
- Xanthoma:
  - More uniform foamy cell population, no Touton giant cells

Reticulohistiocytoma

Clinical

- Uncommon cutaneous lesion
- Usually young or middle age adults; F > M
- Usually slowly-growing, solitary nodule (<1cm) on upper body or head and neck region

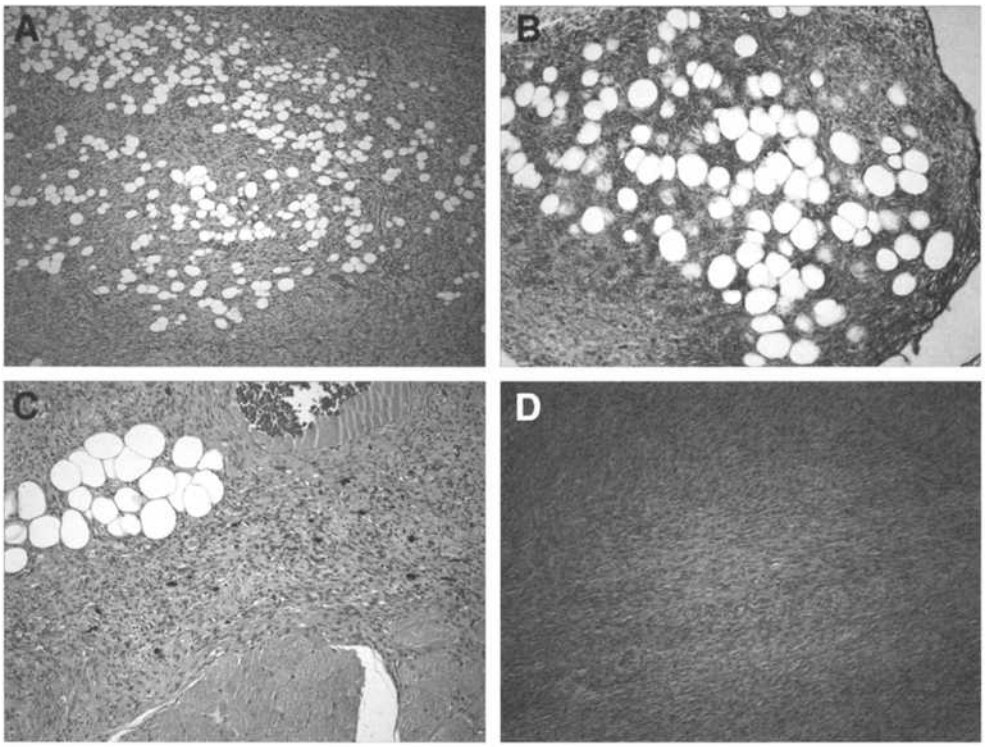


Fig. 8. Dermatofibrosarcoma protuberans: monomorphic storiform proliferation with diffuse infiltration ("honeycombing") of subcutaneous adipose tissue (**A,** H&E stain; **B,** CD34 stain). Occasionally, admixed pigmented dendritic cells are noted (**C,** Bednář tumor). Fibrosarcomatous, or higher grade, areas show herringbone pattern, reminiscent of fibrosarcoma **(D)**.

- ♦ May be multiple (20% associated with destructive arthritis)
- ♦ 30% of patients have associated malignancy and/or vasculitis
- ♦ Benign or self-limiting course

Microscopic

- ♦ Well-circumscribed, uniform population of histiocytes within the dermis
- ♦ Abundant, ground-glass, eosinophilic cytoplasm with peripheral nuclei
- ♦ Multinucleated histiocytes, epithelioid cells and mixed inflammatory cells
- ♦ Diastase-resistant PAS-positive material in cytoplasm of giant cells

Differential Diagnosis

- ♦ "Malignant fibrous histiocytoma":
  - More cytological atypia and pleomorphism with abnormal mitoses
- ♦ Malignant melanoma:
  - More cytological atypia and pleomorphism
  - S-100 protein+ and HMB-45+

Xanthoma

- ♦ A reactive proliferation of histiocytes that contain intracytoplasmic lipid
- ♦ Frequently associated with hyperlipidemia
- ♦ Usually occur in skin and subcutis, may involve tendons or synovium
- ♦ The various types are related to type of lipid disorder and anatomic location: eruptive, tuberous, tendinous, plain xanthomas and xanthelasmas

Low-Grade Malignant

Dermatofibrosarcoma Protuberance (DFSP) (Figure 8)

Clinical

- ♦ Involves dermis and subcutis of adults, between 20–50 years
- ♦ No sex or racial predilection
- ♦ Most occur on trunk, groin, head and neck and lower extremity
- ♦ Slow-growing, commonly diagnosed after 5 years or more
- ♦ Local recurrences: 30–60%; complete local excision is required
- ♦ Metastasis is very rare
- ♦ May transform to fibrosarcoma or MFH

Macroscopic

- ♦ Usually biopsied at nodular stage—solitary, protuberant, whitish mass
- ♦ Average size: 5 cm, occasionally >20 cm

- Overlying skin may be ulcerated
- Skeletal muscle extension is uncommon

Microscopic

- Poorly circumscribed with diffusely infiltrative margins
- Uniform population of spindle cells with monomorphous storiform pattern
- Extends into subcutis with infiltration and isolation of fat lobules
- Overlying epidermis separated by a Grenz zone
- Spindled fibroblast-like cells with amphophilic or pale cytoplasm
- Minimal cellular heterogeneity or hyperchromatism
- Rare foam cells, Touton giant cells and/or granular cells
- Low mitotic index, usually <5/10 HPF
- Myxoid or giant cell fibroblastoma-like (variable)

Variants

- Bednář tumor (5% of cases):
  - DFSP with heavy melanin-pigmented dendritic spindle cells
  - More common in black patients
- Fibrosarcomatous variant:
  - Foci of herringbone growth pattern, similar to fibrosarcoma
  - Increased mitotic rate
  - Increased risk of metastasis (15%)
- DFSP with myofibroblastic differentiation (myoid variant):
  - DFSP with nodules and bundles of myofibroblasts

Cytogenetics

- Ring chromosome derived from portions of chromosomes 17 and 22
- Constitutively active platelet derived growth factor (PDGF) β-chain (tyrosine kinase)

Immunohistochemistry

- Vimentin+, CD 34+, Desmin–
- Actin– (except for myofibroblasts in myoid variant)
- S-100– (except in dendritic cells of Bednář tumor)

Differential Diagnosis

- Benign fibrous histiocytoma:
  - Usually smaller size, CD34–
  - More heterogeneous cell population with lipid and hemosiderin
- Atypical fibroxanthoma and "MFH":
  - Prominent cytological pleomorphism and abnormal mitoses
- Fibrosarcoma:
  - Deeply-seated tumor, greater mitotic activity
- Myxoid liposarcoma:
  - Plexiform vascular network and presence of small univacuolated lipoblast
  - Cytogenetics: t(12;16)

Giant Cell Fibroblastoma

Clinical

- Primarily but not exclusively in children (1st decade of life), usually boys
- Slowly growing painless mass in dermis and subcutis
- Frequently trunk
- Excision is often curative, but up to 50% may recur
- May be related closely to DFSP and shares similar clinicopathological and immunohistochemical features

Macroscopic

- Approximately 1–8 cm in diameter
- Overlying skin uninvolved

Microscopic

- Poorly circumscribed with a diffuse and/or fascicular pattern
- Classic pseudosinusoidal "angiectoid" spaces, lined by giant cells
- Cellularity (variable) diffuse, homogenous, spindle cells
- Multinucleated giant cells (frequently lining spaces)
- Fibrous to myxoid matrix
- Low mitotic index (<1/10 HPF)
- Occasionally seen in association with DFSP

Cytogenetics

- Same aberrations seen in DFSP: ring chromosome derived from chromosomes 17 and 22

Plexiform Fibrohistiocytic Tumor

Clinical

- Rare mesenchymal neoplasm occurring in children and young adults
- Female predominance; usually in upper extremities
- Involves the subcutis and may extend to dermis and/or skeletal muscle
- Wide local excision; prone to recur locally and may metastasize (especially to lungs)

Macroscopic

- Firm, fibrous, poorly circumscribed tumors
- Range: 0.5–8 cm in size, median 2 cm

Microscopic

- Plexiform proliferation of fibroblast-like, histiocyte-like and multinucleated giant cells (all variable)
- Usually mild cellular atypia without significant pleomorphism

- Mitotic activity (usually 3/10 HPF), occasional atypical mitoses
- Collagenous stroma between nodules
- Vascular invasion (rare)

Atypical Fibroxanthoma

Clinical

- Superficial (cutaneous) variant of MFH with an indolent course
- Usually rapidly enlarging, solitary nodule; ulceration is common
- Occurs in actinically damaged skin of head and neck in older adults
- Complete surgical excision with a uniformly good prognosis

Microscopic

- Usually 1–2 cm; often circumscribed, may be infiltrative
- Polypoid lesion in dermis with epidermal collarette
- Usually abut epidermis without a Grenz zone
- May extend focally (but not extensively) into superficial subcutis
- Haphazard, storiform or fascicular growth pattern
- Variably sized tumor cells with pleomorphic bizarre cells
- Abundant eosinophilic or amphophilic cytoplasm
- Frequent typical and atypical mitotic figures
- Touton giant cells (occasional)
- Collagenized and/or myxoid matrix (variable)
- Necrosis (rare)
- No vascular or perineural invasion

Immunohistochemistry

- Vimentin+, S-100 protein–, HMB-45–, Desmin–, Cytokeratins–

Differential Diagnosis

- Spindle cell squamous cell carcinoma:
  - Cytokeratins+
- Malignant melanoma:
  - S-100 protein+ and HMB-45+
- Leiomyosarcoma:
  - Desmin+ and smooth muscle actin+
  - Clinical setting: usually deep-seated large masses with necrosis
- "Malignant fibrous histiocytoma":
  - Extensive involvement of subcutis, penetrates fascia and muscle
  - Necrosis and vascular invasion

Angiomatoid MFH

Clinical

- Most often in children or adolescents; no sex predilection
- Occurs in subcutis and deep dermis of upper extremities
- May be associated with systemic features including pyrexia, anemia, weight loss or paraproteinemia
- Slowly growing, fluctuant, subcutaneous mass
- Excellent prognosis, provided lesion is completely excised
- 10–15% local recurrence rate
- <1% metastasize to lungs and lymph nodes

Macroscopic

- Well-circumscribed, multinodular, cystic masses
- Generally <3–4 cm in size

Microscopic

- Multiple nodules and sheets of uniform cells
- Collagenous stroma with fibrous pseudocapsule
- Large blood-filled pseudovascular spaces (no endothelial lining) with cystic hemorrhage
- Histiocytoid cells with vesicular, spindled nuclei
- Infrequent mitoses and mild pleomorphism
- Giant cells (rare)
- Prominent lymphoid hyperplasia (peripheral) simulating lymph node
- Extensive hemosiderin deposition
- Focal myxoid change (variable)

Immunohistochemistry

- Desmin+, HHF-35+, Smooth muscle actin+/–

Differential Diagnosis

- Aneurysmal benign fibrous histiocytoma:
  - More superficial, more polymorphous cell population, desmin–
- "Malignant fibrous histiocytoma":
  - More cytological atypia and pleomorphism with abnormal mitoses
- Metastatic melanoma:
  - S-100+ and HMB-45+

Malignant

"Malignant Fibrous Histiocytoma" (MFH) (Figure 9)

Clinical

- Controversial entity: most tumors with this label can be further classified into well-defined entities with the help of ancillary studies (immunohistochemistry, EM, cytogenetics and molecular biology)
- Arguably the most common sarcoma of adults
- If extensive work-up cannot classify the lesion: best regarded as "unclassified sarcoma"

Variants

- Pleomorphic "MFH":
  - Most common variant, may not be a cohesive entity
  - Deep soft tissues of adults

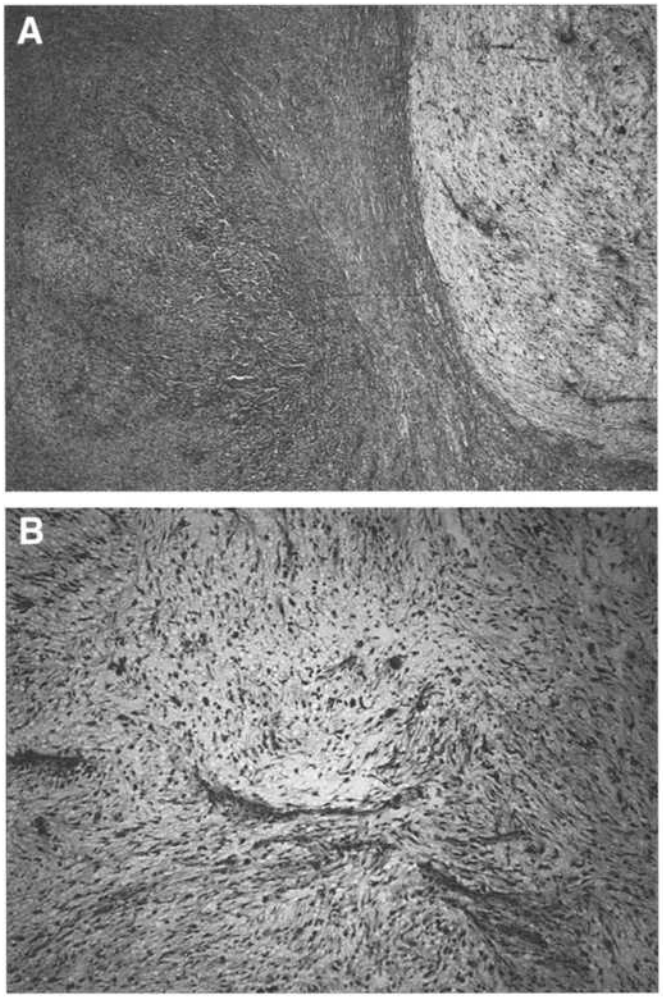


Fig. 9. Myxofibrosarcoma (Myxoid "MFH"): alternation of hypercellular and myxoid areas **(A)** and presence of curvilinear vessels **(B)** are diagnostic of this entity.

- Storiform pattern with short fascicles of fibroblasts
- Bizarre pleomorphic cells with atypical mitosis
- Include pleomorphic variants of liposarcoma, leiomyosarcoma and rhabdomyosarcoma, sarcomatoid carcinoma, melanoma, anaplastic lymphoma
- Treatment and prognosis is highly dependent on the correct classification of the tumor

♦ Myxofibrosarcoma (Myxoid "MFH"):
- Distinct entity, range from low to high grade histological features
- Older adults, mainly in extremities; usually subcutaneous
- Survival depends on grade; overall 60–70% 5-yr survival
- 10–20% hypocellular myxoid areas with prominent thin-walled, curvilinear vessels
- Perivascular tumor growth; vacuolated, mucin-filled cells (pseudolipoblasts)
- Areas of unclassified sarcoma

♦ *Differential Diagnosis:*
- Intramuscular myxoma: hypocellular, hypovascular and no nuclear atypia
- Myxoid neurofibroma: less pleomorphic and S100+
- Myxoid liposarcoma: plexiform vascular pattern, lipoblasts, less nuclear atypia
- Low-grade fibromyxoid sarcoma: less vascular, more collagen, less nuclear pleomorphism

♦ Giant Cell "MFH":
- Heterogeneous group: includes entities such as giant cell-rich osteosarcoma, leiomyosarcoma, giant cell tumor, carcinoma
- Affect mainly older patients, lower extremities
- Multinodular growth pattern with osteoclast-like giant cells
- Conventional MFH areas
- Deep lesions have a poor prognosis

♦ Inflammatory "MFH":
- Uncommon variant; predilection for retroperitoneum
- Includes: T cell lymphomas, dedifferentiated liposarcoma, xanthogranuloma pyelonephritis
- Behaves in a very aggressive fashion
- Large xanthomatous cells with atypical nuclei
- Prominent inflammatory component, especially neutrophils
- Conventional MFH areas

LIPOMATOUS TUMORS

♦ Classification: *see* **Table 3**

Benign

Lipoma (Figure 10)

Clinical

♦ Composed of mature adipose tissue and usually arises in subcutis

♦ Most common mesenchymal neoplasm

♦ Adults >30 years of age, no sex predilection

♦ May occur anywhere, most frequently trunk and proximal limbs

♦ Rare in abdomen and retroperitoneum

♦ Most are solitary, 2–3% are multiple

♦ Local recurrence after excision is rare (1–2%)

Table 3. Classification of Lipomatous Tumors

Benign
- Lipoma
  - Variants
    - Intramuscular and intermuscular lipoma
    - Lipoma of tendon sheath
    - Synovial lipoma
    - Lumbosacral lipoma
    - Fibrolipomatous hamartoma of nerve (neural fibrolipoma)
    - Myolipoma
    - Chondroid lipoma
    - Myelolipoma
    - Angiomyolipoma
    - Angiolipoma
    - Spindle cell lipoma
    - Pleomorphic lipoma
    - Lipoblastoma
- Lipomatosis
- Hibernoma

Malignant
- Liposarcoma
  - Well-differentiated liposarcoma:
    - Lipoma-like type ('atypical lipoma')
    - Sclerosing type
    - Inflammatory type
      - High grade variant: Dedifferentiated liposarcoma
  - Myxoid liposarcoma
    - High grade variant: Round cell liposarcoma
  - Pleomorphic liposarcoma

Macroscopic
- Well-circumscribed, thinly encapsulated and lobulated
- Variable size, rarely >10cm

Microscopic
- Mature adipocytes with thin fibrous septa
- Minimal variation in adipocytes size and shape
- Myxoid change (variable, when prominent—myxolipoma)
- Fibrosis (variable, when prominent—fibrolipoma)
- Secondary microscopic fat necrosis and hemorrhage

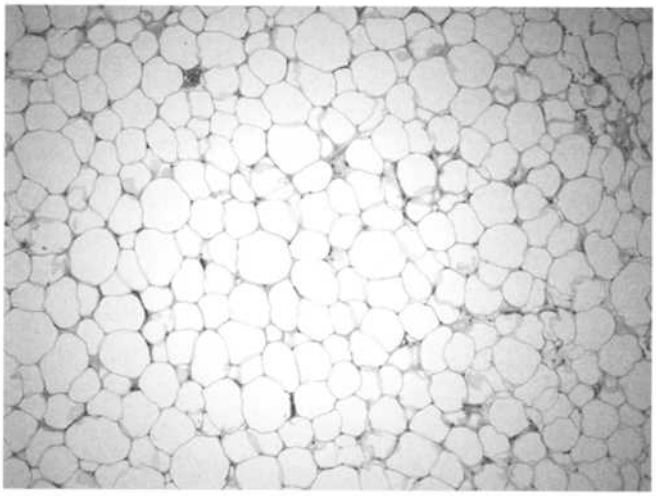


Fig. 10. Lipoma: neoplasm composed of mature adipose tissue.

Cytogenetics
- 12q13-15 abnormalities

Variants
- Intramuscular lipoma:
  - Infiltrates skeletal muscle and fascia in the extremities
  - Tend to recur if incompletely excised
- Lipoma of tendon sheath:
  - Young adults; distal extremities; 50% bilateral
- Synovial lipoma (lipoma arborescens):
  - Older adults; associated with chronic arthritis
- Lumbosacral lipoma:
  - Children <10 years; associated with spina bifida
- Fibrolipomatous hamartoma of nerve (neural fibrolipoma):
  - Mainly children and adolescents
  - Infiltrate large peripheral nerves and their branches
  - Primarily in hands and feet
- Myolipoma:
  - Rare, benign fat and smooth muscle
  - Common sites: trunk, inguinal region and pelvis
- Chondroid lipoma:
  - Uncommon, benign, females are more affected
  - Mature and immature adipocytes with lipoblasts
  - Myxohyaline, pseudochondroid matrix

Differential Diagnosis
- Myxoma:
  - Hypocellular without adipose tissue
- Intramuscular hemangioma:
  - Presence of intramuscular irregular vascular proliferation

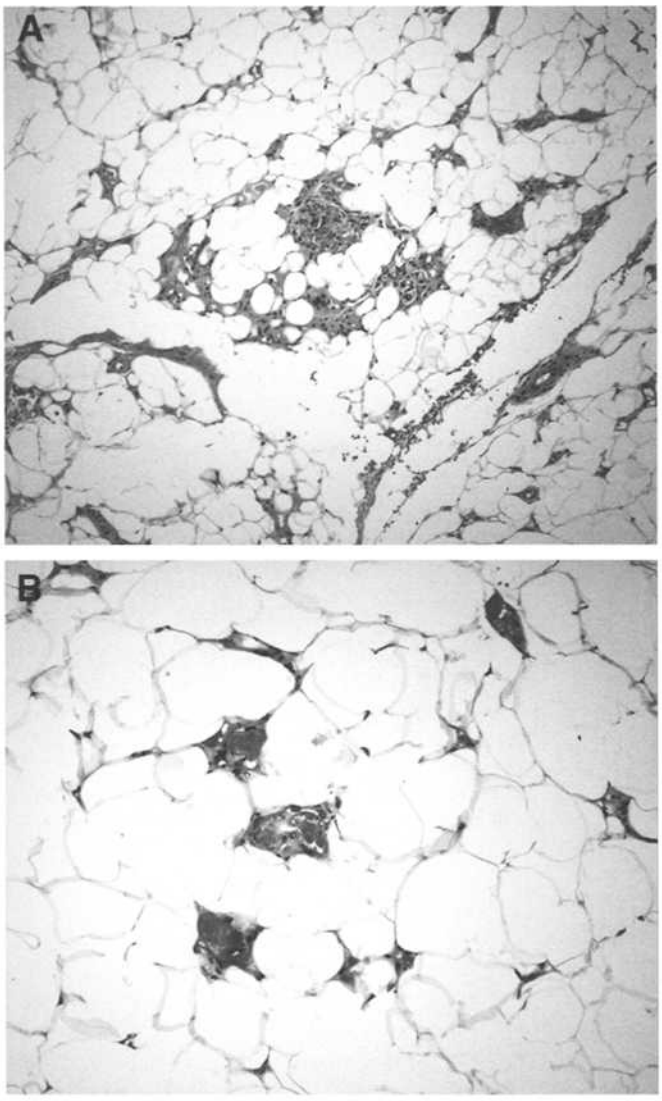


Fig. 11. Angiolipoma: mature adipose tissue with a vascular component of small vessels containing fibrin thrombi **(A&B).**

- Atypical lipomatou tumor (*see* below):
  - Scattering of lipoblasts and atypical, hyperchromatic nuclei, distinct cytogenetics
- Well-differentiated liposarcoma (*see* below):
  - Deep soft tissue: extremities, groin and retroperitoneum
  - Scattering of lipoblasts and atypical, hyperchromatic nuclei, distinct cytogenetics
- Myxoid liposarcoma (*see* below):
  - Presence of lipoblasts and plexiform capillary pattern
  - Distinct cytogenetics

Angiolipoma (Figure 11)

Clinical

- Common, painful, subcutaneous lesion in young adults
- Male predominance

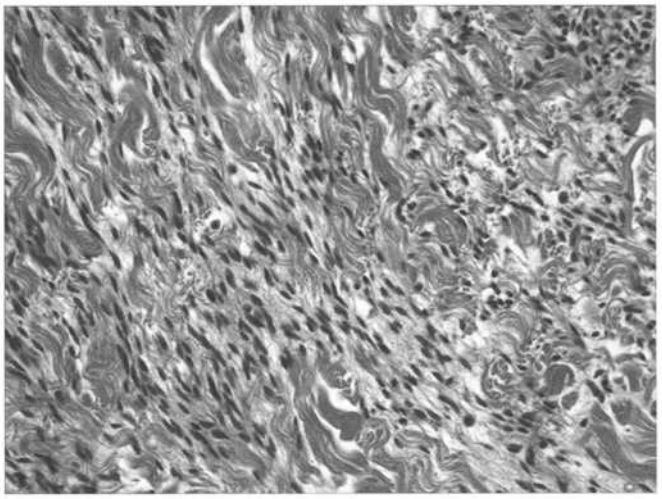


Fig. 12. Spindle cell lipoma: small primitive appearing spindle cells with admixed mast cells and hyaline collagen.

- Commonly in forearm, followed by trunk and upper arm
- Multiple in 60% of cases, <5% familial
- No tendency to local recurrence or malignant transformation

Macroscopic

- Encapsulated, usually <2 cm

Microscopic

- Mature adipose tissue with subcapsular vascular proliferation
- Prominent, small branching vessels with fibrin thrombi (diagnostic)
- Vessels may dominate histologic picture, simulating a vascular neoplasm
- Perivascular fibrosis (variable)

Differential Diagnosis

- Lipoma:
  - Lack of prominent, small, branching vessels with fibrin thrombi
- Intramuscular hemangioma:
  - Intramuscular location and poorly circumscribed
- Kaposi's sarcoma and angiosarcoma:
  - Larger, not encapsulated, no adipocytes or microthrombi

Spindle Cell Lipoma (Figure 12)

Clinical

- Painless, slow-growing, well-defined, solitary mass
- Usually males, between 45–65 years
- Chiefly posterior neck and shoulder, in subcutis
- Local excision, recurrence uncommon

Macroscopic

- Average 3–5 cm in size
- Well-circumscribed, thinly encapsulated

Microscopic

- Admixture of mature fat and uniform, small, slender spindle cells (variable amounts)
- Myxoid matrix (variable) and mast cells
- Birefringent, eosinophilic, hyaline collagen fibers

Cytogenetics

- 13q and 16q abnormalities

Differential Diagnosis

- Myxoma:
  - Hypocellular, less vascular and no adipocytes
- Schwannoma:
  - No adipocytes and S100+ spindle cells
- Myxoid liposarcoma:
  - Location, more vascular and lipoblasts

Pleomorphic Lipoma

Clinical

- Closely related or variant of spindle cell lipoma
- Same clinical features as spindle cell lipoma

Macroscopic

- Same as spindle cell lipoma

Microscopic

- Mature adipocytes
- Variable number of multinucleated giant cells (floret cells)
- Collagen and sclerosis (hybrid appearance with spindle cell lipoma)
- Rare mitoses and lipoblasts
- Myxoid change (variable)
- Chronic inflammation

Differential Diagnosis

- Atypical lipoma and well-differentiated liposarcoma:
  - Deeper location, larger size and more adipocytic nuclear atypia

Lipoblastoma

Clinical

- Tumor of infancy, usually <3 years; M : F = 2 : 1
- Usually superficial, circumscribed, slowly-growing mass
- Involves limbs; approximately 5 cm in size
- Deeper lesions are larger and diffusely infiltrative (lipoblastomatosis)
- Infrequent local recurrence following excision

Microscopic

- Distinct lobular architecture with fibrous septa
- Variable admixture of mature and immature fat cells
- Immature cells range from primitive mesenchymal cells to univacuolated and multivacuolated cells
- Myxoid matrix and mast cells (variable)
- No cellular atypia
- Foci of extramedullary hematopoiesis

Cytogenetics

- Deletions of chromosome 8

Differential Diagnosis

- Lipoma:
  - Absence of immature fat cells and lipoblasts
- Myxoid liposarcoma:
  - Very rare in children
  - May be impossible to distinguish on histological grounds

Hibernoma

Clinical

- Uncommon, usually young adults
- Interscapular region and back of neck
- Slowly-growing, painless, subcutaneous mass, rarely intramuscular
- Cured by complete excision

Macroscopic

- Encapsulated, usually 5–10 cm diameter
- Tan-brown cut surface

Microscopic

- Distinct lobular pattern with a variable admixture of cells
- Large round cells with centrally located nuclei and granular cytoplasm
- Multivacuolated (lipoblast-like) eosinophilic cytoplasm
- Mature univacuolated adipocytes

Cytogenetics

- 11q13 rearrangements

Differential Diagnosis

- Adult rhabdomyoma:
  - Larger cells containing glycogen
- Granular cell tumor:
  - Absence of intracellular lipid vacuoles
- Myxoid and Round Cell Liposarcoma:
  - More cytological atypia and plexiform capillary pattern

Lipomatosis

- Rare condition, usually affects adult males, as different clinical forms
- Diffuse overgrowth of mature adipose tissue

Malignant

Liposarcoma

- One of the most common soft tissue sarcoma of adults
- Three major histologic subtypes:
  - Well-differentiated
  - Myxoid
  - Pleomorphic
- Subclassification is mandatory due to prognostic significance

Clinical

- Tumor of adulthood; M > F
- Peak age: 40–60 years, extremely rare in children
- Usually deep-seated
- Major sites: extremities, especially thigh and retroperitoneum
- Well-differentiated and myxoid types are low grade with multiple local recurrences and low metastatic rate
- High grade liposarcomas (dedifferentiated, pleomorphic and round cell types) behave more aggressively with short survival and metastases
- Recurrence rates depend on location and resectability

Well-Differentiated Liposarcoma (WDLS) / Atypical Lipomatous Tumor (ALT) (Figure 13)

- Nomenclature depends on surgical amenability:
  - WDLS: retroperitoneum, spermatic cord and mediastinum
  - ALT: other sites

Macroscopic

- Usually large, well-circumscribed and coarsely lobulated

Microscopic

- Mature adipocytes with variation in cell size and shape
- Atypical, hyperchromatic nuclei
- Variable number of lipoblasts
- Multinucleated stromal cells
- Variable prominent fibrous septa with occasional bizarre hyperchromatic cells
- Myxoid stroma (variable)
- Foci of metaplastic bone or smooth muscle differentiation (rare)

Variants

- Sclerosing liposarcoma:
  - Collagenous, hypocellular fibrous tissue with scattered mature adipocytes and bizarre hyperchromatic stromal cells
- Inflammatory type:
  - Numerous prominent lymphoplasmacytic aggregates
  - May simulate inflammatory pseudotumor or lymphoma

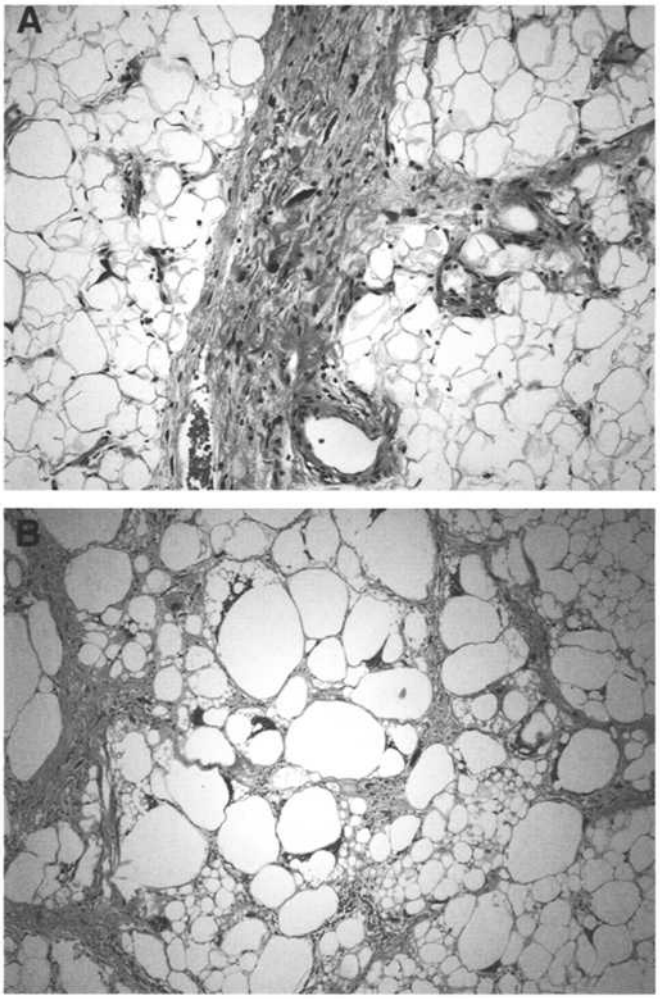


Fig. 13. Well-differentiated liposarcoma: variation of adipocyte size and shape with prominent fibrous septa containing atypical cells **(A)**. Occasionally, lipoblasts are quite prominent **(B)**.

- Spindle cell type:
  - Usually located in the subcutis

Cytogenetics

- Ring or long marker derived from 12q chromosomes

Dedifferentiated Liposarcoma (Figure 14)

- Abrupt transition from well-differentiated liposarcoma to unclassifiable non-lipogenic sarcoma either in the primary tumor or in a recurrence
- 90% of cases occur de novo, 10% in recurrences
- Most often in retroperitoneum and groin

Macroscopic

- Both components are often easily distinguished
- Well-differentiated component has to be sampled for diagnosis in a primary tumor

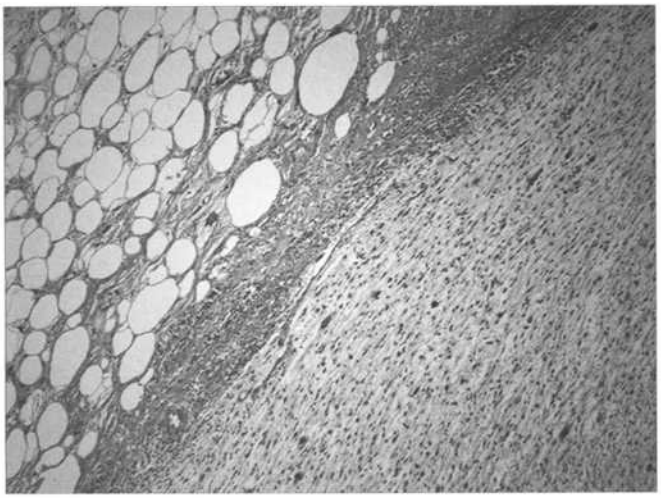


Fig. 14. Dedifferentiated liposarcoma: abrupt transition between well-differentiated liposarcoma (left) and non-lipogenic sarcoma (right).

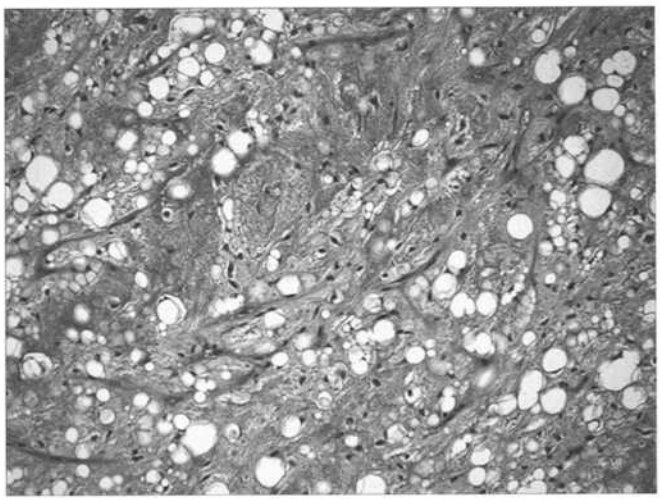


Fig. 15. Myxoid liposarcoma: small round to ovoid cells in a myxoid background with thin-walled vessels and small uni- or bivacuolated lipoblasts.

Microscopic

- Dedifferentiated component usually looks like "MFH" (high or low grade)
- Heterologous differentiation: rhabdomyosarcomatous, leiomyosarcomatous, osteosarcomatous

Cytogenetics

- Ring or long marker derived from 12q chromosomes

Myxoid Liposarcoma (Figure 15)

- Specific reciprocal chromosomal translocation t(12;16)(q13;p11)

Microscopic

- Multilobular architecture
- Prominent, delicate plexiform capillary pattern ("chicken-wire")
- Copious myxoid matrix with pooling of mucin
- Univacuolated and multivacuolated small lipoblasts
- Primitive round to angulated cells (variable)
- Mature adipocytes, variable, multinucleated giant cells (rare)
- Focal chondroid, smooth muscle or osseous metaplasia (rare)
- "Round cell liposarcoma": hypercellularity dictates tumor grade of myxoid liposarcoma; increased metastatic potential

Differential Diagnosis

- Intramuscular myxoma:
  - Less vascular, no lipoblasts
- Myxofibrosarcoma:
  - More nuclear pleomorphism, curvilinear vessels
- Anaplastic round cell malignancy (from round cell liposarcoma):
  - Lack of plexiform capillary network, mucin pooling and no lipoblasts

Pleomorphic Liposarcoma

- High grade liposarcoma with metastatic potential
- Accounts for 5% of liposarcomas
- High grade pleomorphic sarcoma with multivacuolated lipoblasts
- Marked cytological pleomorphism with numerous intracytoplasmic eosinophilic globules or droplets
- Cytogenetics: non-unique and very complex abnormalities

SMOOTH MUSCLE TUMORS

- Classification: *see* **Table 4**

Benign

Leiomyoma (Figure 16)

Microscopic

- Usually well-circumscribed
- Interlacing bundles and fascicles of smooth muscle cells
- Blunt-ended cigar-shaped nuclei with eosinophilic cytoplasm
- Mitoses absent/very rare
- Degenerative pleomorphism (variable): "smudged" nuclei
- Fibrosis and calcification (variable)
- Immunoperoxidase: actin+, desmin+, h-caldesmon+

Table 4. Classification of Smooth Muscle Tumors

Benign	Malignant
Leiomyoma	Leiomyosarcoma
Variants:	Variants:
Pilar leiomyoma	Intra-abdominal leiomyosarcoma
Genital leiomyoma	Subcutaneous leiomyosarcoma
Deep leiomyoma	Cutaneous leiomyosarcoma
Angiomyoma (angioleiomyoma, vascular leiomyoma)	Vascular leiomyosarcoma
Epithelioid leiomyoma (leiomyoblastoma)	Epithelioid leiomyosarcoma (malignant leiomyoblastoma)
Intravenous leiomyomatosis	
Peritoneal leiomyomatosis	
Palisaded Myofibroblastoma of Lymph Node	

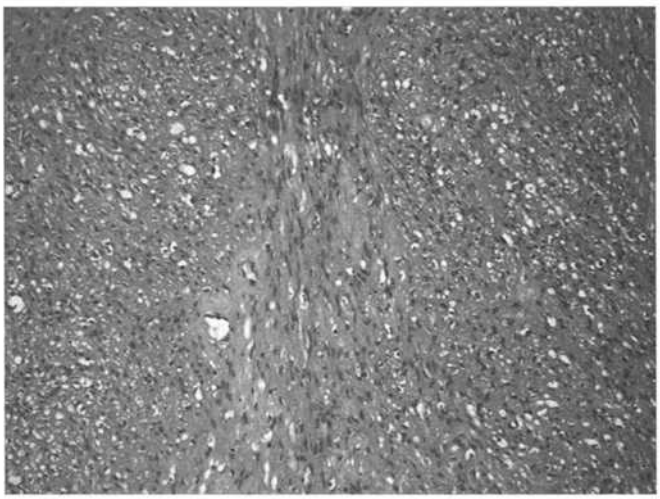


Fig. 16. Leiomyoma: long fascicles composed of elongated spindle cells.

Variants

- Pilar leiomyoma:
  - Multiple, slow-growing, painful, cutaneous nodules
  - Mainly limbs and trunk of young adults; M = F
  - Irregular, ill-defined margins in the dermis
  - Associated with hair follicle
- Genital leiomyoma:
  - Involve nipple, vulva and scrotum
  - Nipple lesions—similar to pilar leiomyomas
  - Vulvar lesions—circumscribed with myxohyaline degeneration
  - Scrotal lesions—large, cellular and focally infiltrative
- Deep leiomyoma:
  - Uncommon, solitary, painless, slow-growing tumors
  - Peak age: middle-aged adults
  - Usually extremities, abdominal cavity and retroperitoneum
  - Well-circumscribed and typically >5 cm
  - Females: <10 mitoses/50hpf; males: no mitotic activity accepted
- Angioleiomyoma:
  - Solitary, painful, usually subcutaneous
  - Usually women, 40–60 years; extremities especially lower leg
  - Well-circumscribed; <3 cm in diameter
  - Mature smooth muscle cells around thick-walled blood vessels
  - Vessels lack elastic laminae
- Epithelioid leiomyoma (leiomyoblastoma):
  - Most arise in stomach, small intestine and mesentery
  - See gastrointestinal stromal tumors

Intravenous Leiomyomatosis (see Uterine Tumors)

- Intravascular growth of benign smooth muscle in uterine or pelvic veins

Peritoneal Leiomyomatosis (Leiomyomatosis Peritonealis Disseminata)

- Multiple peritoneal nodules of benign smooth muscle cells
- Rare, usually incidental finding
- Usually premenopausal women, especially pregnant and black women
- Lesions regress with removal of estrogen and progesterone source

Palisaded Myofibroblastoma of Lymph Node

- Benign myofibroblastic proliferation in lymph nodes, usually groin
- Simulate schwannoma, due to palisading pattern
- Amianthoid fibers or thick collagen mats (distinctive)

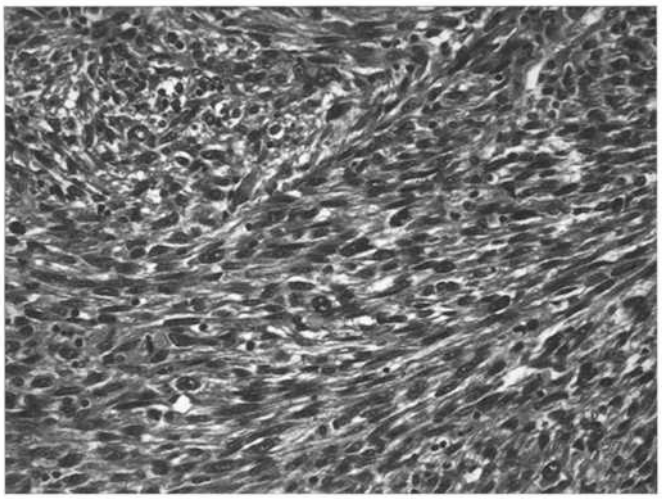


Fig. 17. Leiomyosarcoma: cells with cigar-shaped nuclei, pleomorphism and frequent necrosis, including atypical forms.

Malignant

Leiomyosarcoma (Figure 17)

Clinical

- Depends on location, see variants

Microscopic

- Usually well-circumscribed, except for cutaneous lesions
- Deep-seated types are larger with more necrosis
- Appearance varies with degree of differentiation or grade
- Interlacing fascicles and bundles of spindle cells
- Vesicular, ovoid to cigar-shaped nuclei with eosinophilic cytoplasm
- Nuclear pleomorphism and mitoses (variable)
- Epithelioid or round cells (rare)
- Hyalinization, myxoid change and necrosis (all variable)
- Multinucleated, osteoclast-like giant cells (rare)
- "MFH"-like areas (variable)

Immunohistochemistry

- Muscle specific actin+
- Smooth muscle actin+
- Desmin+
- S-100 protein+
- Keratin+/–
- EMA+/–

Variants

- Intra-abdominal leiomyosarcoma:
  - Retroperitoneum, mesentery or omentum
  - Peak: 50–70 years, M < F
  - Range: 7–35 cm; wide excision not possible
  - Metastasize to lungs and liver
  - 20–30% 5 year survival
- Subcutaneous leiomyosarcoma (deep soft tissue of limbs):
  - Most common in thigh
  - 50–70 years; slight male predominance
  - 50% metastasize; 60% 5 year survival
- Cutaneous leiomyosarcoma:
  - Usually limbs, especially lower leg, often painful
  - Mainly younger adults; male predilection
  - Commonly recur locally, rarely metastasize
- Vascular leiomyosarcoma:
  - Usually arise from inferior vena cava or large leg veins
  - Older adults; IVC tumors occur in women
  - Frequent metastases to liver, lymph nodes and lungs
  - 20% 5 year survival, depends on location and resectability

Cytogenetics

- Complex karyotype with numerous copies of entire or parts of chromosomes

Differential Diagnosis

- Leiomyoma:
  - Smaller, less pleomorphism, rare mitoses and no necrosis, simple karyotype
- Postoperative (reactive) myofibroblastic nodules:
  - Haphazard arrangement of cells, basophilic cytoplasm and lack of linear striations
- Malignant peripheral nerve sheath tumor:
  - Wavy, buckled, asymmetrical nuclei
  - S-100+ (variable), actin– and desmin–
- Fibrosarcoma:
  - Tapered nuclei, actin– and desmin–

SKELETAL MUSCLE TUMORS

- Classification: *see* **Table 5**

Benign

Rhabdomyomatous Mesenchymal Hamartoma

- Extremely rare, peculiar striated muscle proliferation
- Cutaneous nodules in head and neck of neonates and infants

Cardiac Rhabdomyoma (see Chapter 16)

- Hamartomatous process often associated with tuberous sclerosis

Table 5. Classification of Skeletal Muscle Tumors

Benign	Malignant
Rhabdomyoma	Rhabdomyosarcoma
Rhabdomyomatous mesenchymal hamartoma	Embryonal rhabdomyosarcoma
Cardiac rhabdomyoma	Alveolar rhabdomyosarcoma
Adult rhabdomyoma	Pleomorphic rhabdomyosarcoma
Fetal rhabdomyoma	
Genital rhabdomyoma	

Adult Rhabdomyoma

- Rare, slow-growing lesion in head and neck region
- Middle-aged adults; M > F
- 10% multifocal
- Occasionally recur after local excision
- Encapsulated, usually <5 cm
- Large, polygonal, eosinophilic cells with peripheral small nuclei
- Granular or vacuolated cytoplasm
- Cytoplasmic cross-striations (variable)
- Desmin+ and myoglobin+

Fetal Rhabdomyoma

- Rarer entity, presumable hamartomatous
- Any age, peak: <3 years
- Subcutis and submucosa of head and neck, especially behind ear
- Solitary, usually <5 cm
- Do not recur
- Zonation pattern with central primitive spindle cells in myxoid matrix
- More mature eosinophilic rhabdomyoblasts at periphery
- No nuclear atypia and rare mitoses (unlike rhabdomyosarcoma)

Genital Rhabdomyoma

- Solitary, polypoid mass in vagina, vulva or cervix
- Young or middle-aged women; usually asymptomatic
- Slow-growing, usually <3 cm
- Do not recur
- Submucosal proliferation of elongated, eosinophilic rhabdomyoblasts
- Cytoplasmic cross-striations
- Mitoses absent
- Desmin+ and myoglobin+
- Differential diagnosis: Botyroid rhabdomyosarcoma

Malignant

Rhabdomyosarcoma

- Malignant neoplasms which show evidence of skeletal muscle differentiation, in the absence of other differentiation
- Most common sarcoma of children and adolescents
- Three basic types:
  - Embryonal
  - Alveolar
  - Pleomorphic

Embryonal Rhabdomyosarcoma (Figure 18)

Clinical

- Infants and children <15 years, peak: 4 years
- Male predominance
- Common sites: head and neck, paratesticular regions

Microscopic

- Infiltrative and haphazardly arranged
- Varying cellularity with alternating hypercellular and loose myxoid areas
- Undifferentiated, hyperchromatic, round or spindle-shaped cells
- Rhabdomyoblasts with eosinophilic, fibrillary cytoplasm
- Minimal collagen and myxoid matrix (variable)
- Cross-striations (in 30–60%)
- Mitoses and glycogen; nuclear pleomorphism (variable)

Cytogenetics

- 11p deletions

Variants

- Botyroid rhabdomyosarcoma:
  - Submucosal variant forming a polypoid (grape-like) mass
  - Hypocellular, myxoid areas with a cambium-layer (>50%)
- Spindle cell rhabdomyosarcoma:
  - Subtype with favorable clinical outcome; 90% 5-year survival

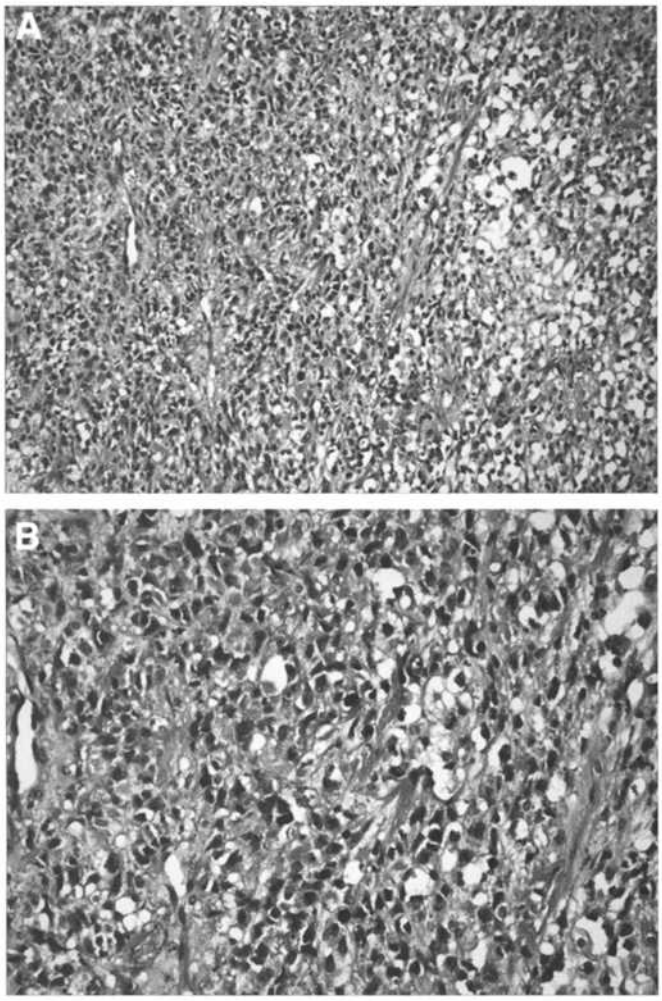


Fig. 18. Embryonal Rhabdomyosarcoma: small round blue cell tumor with evidence of myogenic differentiation **(A,B)**.

- Usually paratesticular and head and neck region
- Fascicular or storiform growth pattern
- Eosinophilic, spindle rhabdomyoblasts
- Few mitoses and collagenized stroma

Alveolar Rhabdomyosarcoma (Figure 19)

Clinical

- Mainly adolescents and young adults
- Usually deep-seated mass involving limbs
- Worse prognosis

Microscopic

- Circumscribed or infiltrative margins
- Ill-defined aggregates of round cells
- Fibrous septa with dyscohesive alveolar pattern
- Multinucleated giant cells with peripheral wreath-like nuclei
- Cross-striations (in 16–30% of cases)

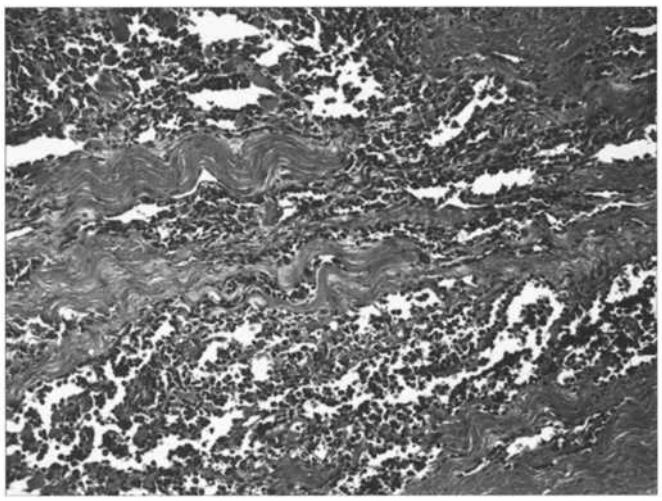


Fig. 19. Alveolar Rhabdomyosarcoma: larger cells with dyscohesive pattern, producing alveolar appearance. Note the presence of prominent rhabdomyoblasts (top).

Cytogenetics

- t(2;13)(q35;q14)

Variant

- Solid variant of alveolar RMS:
  - Densely packed tumor cells without alveolar pattern
  - Resemble embryonal RMS, however cells are larger

Pleomorphic Rhabdomyosarcoma

Clinical

- Rarest type; older patients >45 years

Microscopic

- Infiltrative growth pattern
- Haphazard, loose arrangement of cells
- Large, pleomorphic or spindle-shaped eosinophilic rhabdomyoblasts
- Collagenous stroma (variable)
- Cross-striations (rare)

Immunohistochemistry of RMS (All Types)

- Desmin+, muscle-specific actin+
- Myogenin (Myf-4)+, MyoD1+
- Vimentin+, cytokeratin±
- S-100 protein±, CD99 (MIC-2)+ (15%)

Differential Diagnosis of RMS

- Ewings's sarcoma/primitive neuroectodermal tumor (PNET): CD99+
- Neuroblastoma: Chromogranin and synaptophysin+
- Angiosarcoma: CD31 and Factor VIII+
- Synovial sarcoma: Cytokeratin and EMA+
- Malignant melanoma: S-100 and HMB-45+

- Granulocytic sarcoma: CD45, myeloperoxidase, CD43 and CD68+
- Malignant lymphoma: CD45+
- Small cell carcinoma:
  - Low molecular weight cytokeratin (Cam 5.2)+
  - Location, age, lack of rhabdomyoblasts
- Rhabdoid tumor:
  - Cytokeratin+, desmin and myoglobin–
- Alveolar soft part sarcoma:
  - Alveolar pattern with intervening thin-walled vessels
  - Intracellular PAS with diastase-positive crystalline material
- Proliferative fasciitis/myositis
- Inflammatory reactive pseudotumor
- Granular cell tumor
- Myxoma:
  - Age and location usually provide correct diagnosis

Malignant Triton Tumor

- Malignant peripheral nerve sheath tumor with rhabdomyoblastic differentiation
- Worse prognosis

Ectomesenchymoma

- Ganglioneuroblastoma with rhabdomyoblastic differentiation

VASCULAR TUMORS

- Classification: *see* **Table 6**

Benign

Papillary Endothelial Hyperplasia (Masson's tumor)

- Reactive lesion—unusual form of an organizing thrombus
- May arise in a dilated blood vessel or underlying vascular lesion
- Usually head and neck or fingers of young adults
- Commonly <2 cm and do not recur
- Well-circumscribed and commonly intravascular
- Papillary configuration with anastomosing endothelial-lined channels
- Associated with thrombosis and fibrosis

Bacillary Angiomatosis

- Reactive epithelioid vascular proliferation
- Associated with neutrophilic infiltrate
- Usually in immunocompromised hosts
- Caused by *Rochalimae henselae* (rickettsial organism)

Capillary Hemangioma (Infantile Hemangioendothelioma)

- Most common benign vascular tumor of childhood
- Usually involves superficial soft tissue of head and neck region
- Usually presents soon after birth, grows rapidly
- 70% regress spontaneously
- Multilobulated architecture, cellular, closely packed capillaries
- Plump endothelial cells with mitoses
- Interstitial fibrosis (variable)

Variants

- Tufted angioma
- Verrucous hemangioma
- Cherry angioma (senile angioma)

Lobular Capillary Hemangioma (Pyogenic Granuloma) (Figure 20)

- Common variant of capillary hemangioma
- Usually solitary, ulcerated, polypoid nodule <2 cm
- Typically skin of fingers and skin and mucosa of head and neck; any age
- Do not regress and 10–15% may recur (including satellitosis)
- Well-circumscribed, lobular proliferation of capillaries
- Inflamed granulation tissue-like stroma
- Epithelial collarette and ulceration (variable)

Variants

- Intravascular pyogenic granuloma:
  - Rare variant, usually adults
- Granuloma gravidarum:
  - Usually gingivae of pregnant women; regress postpartum

Cavernous Hemangioma

- Less common than capillary hemangioma
- Usually larger and more deep-seated and do not regress
- Any organ may be involved
- May be associated with:
  - Mafucci's syndrome (multiple enchondromas, lymphangiomas and spindle cell hemangiomas)
  - Kasabach-Merritt syndrome (consumption coagulopathy)
  - Blue Rubber Bleb Nevus syndrome (skin and GI hemangiomas)
- Poorly-circumscribed, dilated, thin-walled blood vessels
- Areas of capillary hemangioma (variable)
- Thrombosis and secondary dystrophic calcification (variable)

Table 6. Classification of Vascular Tumors

Blood Vessel Tumors

Benign Tumors and Tumor-Like Conditions

- Reactive
  - Papillary endothelial hyperplasia (Masson's tumor)
  - Vascular transformation of lymph node (nodal angiomatosis)
  - Glomeruloid hemangioma
  - Bacillary angiomatosis
- Vascular ectasia
  - Nevus flammeus (nevus telangiectaticus)
  - Arterial spider (nevus araneus)
  - Hereditary hemorrhagic telangiectasia (Osler- Weber-Rendu disease)
- Superficial hemangiomas
  - Capillary hemangioma
    - Variants:
      - Cellular hemangioma of infancy (strawberry nevus)
      - Tufted angioma
      - Verrucous hemangioma
      - Cherry angioma (senile angioma)
      - Lobular hemangioma (pyogenic granuloma)
  - Cavernous hemangioma
    - Variants:
      - Sinusoidal hemangioma
  - Arteriovenous hemangioma
  - Venous hemangioma
  - Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia)
- Deep hemangiomas
  - Intramuscular hemangioma
  - Synovial hemangioma
  - Hemangioma of peripheral nerve
  - Intranodal hemangioma
  - Angiomatosis (Diffuse hemangioma)
  - Spindle cell hemangioendothelioma

Low Grade Malignant Tumor

- Epithelioid hemangioendothelioma
- Kaposiform hemangioendothelioma
- Malignant endovascular papillary angioendothelioma (Dabska's tumor)
- Kaposi's sarcoma

Malignant Vascular Tumors

- Angiosarcoma
  - Idiopathic superficial (head and neck)
  - Associated with lymphedema (Stewart-Trevers syndrome)
  - Angiosarcoma of breast
  - Radiation-induced
  - Angiosarcoma of deep soft tissues

Perivascular Tumors

- Glomus tumor
  - Variants:
    - Glomangiosarcoma
    - Glomangiomyoma
- Glomangiosarcoma
- Hemangiopericytoma

Lymph Vessel Tumors

- Lymphangioma
  - Variants:
    - Cavernous lymphangioma (cystic hygroma)
- Lymphangioma circumscriptum (cutaneous)
- Lymphangiomatosis
- Lymphangiomyoma
- Lymphangiomyomatosis

Variant

- Sinusoidal hemangioma

Epithelioid Hemangioma (Angiolymphoid Hyperplasia with Eosinophilia)

- Usually cutaneous red lesions in head and neck region
- Peak age: 30–60 years
- Solitary or multiple and involve dermis and subcutis
- Approximately 30% of cases recur
- Relatively circumscribed proliferation of small and medium-sized vessels
- Plump epithelioid endothelial cells with eosinophilic cytoplasm
- "Tombstone" appearance of nuclei
- Prominent lymphoid follicles with germinal centers, plasma cells and mast cells

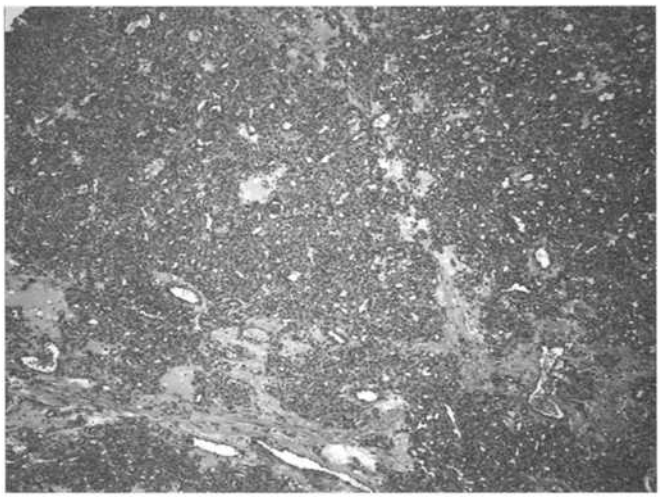


Fig. 20. Lobular capillary hemangioma: lobular proliferation of small capillaries.



Fig. 21. Spindle cell hemangioma: spindle cell proliferation with evidence of vascular differentiation.

Differential Diagnosis

- Kimura's disease:
  - Involves lymph nodes, associated with eosinophilia and flat endothelial lining

Intramuscular Hemangioma

- Any age, usually <30 years, M = F
- Commonly lower limbs especially thigh
- Slowly growing mass, may be painful
- Radiographs: frequently calcified, probably phlebolith
- Recurrence common (up to 50%)
- Mixed capillary and cavernous vessels (variable)
- Ill-defined and admixed with adipose tissue

Differential Diagnosis

- Intramuscular lipoma—no vascular component, more indolent
- Angiosarcoma—no lobular architecture, more endothelial atypia

Angiomatosis (Diffuse Hemangioma)

- Rare lesion, childhood or adolescence
- Probably malformation with a diffuse proliferation of blood vessels
- Involves large areas, usually limbs or visceral organs
- Clinically extensive, surgical treatment is difficult; common recurrences
- Diffuse infiltration of dermis, subcutis, skeletal muscle and bone
- Mixture of veins, capillaries and cavernous vascular spaces
- Mature adipose tissue (variable)

Differential Diagnosis

- Intramuscular hemangioma—usually involves one muscle group
- Arteriovenous hemangioma—shunting, mixture of arteries and veins

Spindle Cell Hemangioma (Figure 21)

- Initially described as low grade malignant, but probably non-neoplastic
- Solitary or multiple red nodules on distal extremities, especially hands
- Usually adolescents and young adults; M : F equal
- Indolent clinical course, may develop new lesions over many years
- Ill-defined lesion involving dermis and subcutis
- Irregular cavernous vascular spaces with flat endothelial lining, containing organizing thrombi
- Solid areas of bland spindle cells with eosinophilic cytoplasm
- Epithelioid endothelial cells with intracytoplasmic vacuoles
- May be an intravascular lesion
- Vascular lining and epithelioid cells: CD34 and CD31+
- Spindle cells: Vimentin+, CD34 and CD31–

Differential Diagnosis

- Kaposi's sarcoma:
  - No cavernous spaces, no epithelioid endothelial cells
  - CD34, CD31 and HHV-8+

Low Grade Malignant

Kaposiform Hemangioendothelioma (Kaposi-Like Hemangioendothelioma)

- Rare tumor of childhood
- Usually retroperitoneum, upper limbs, chest wall and head and neck
- Mortality and morbidity associated with infiltrative growth

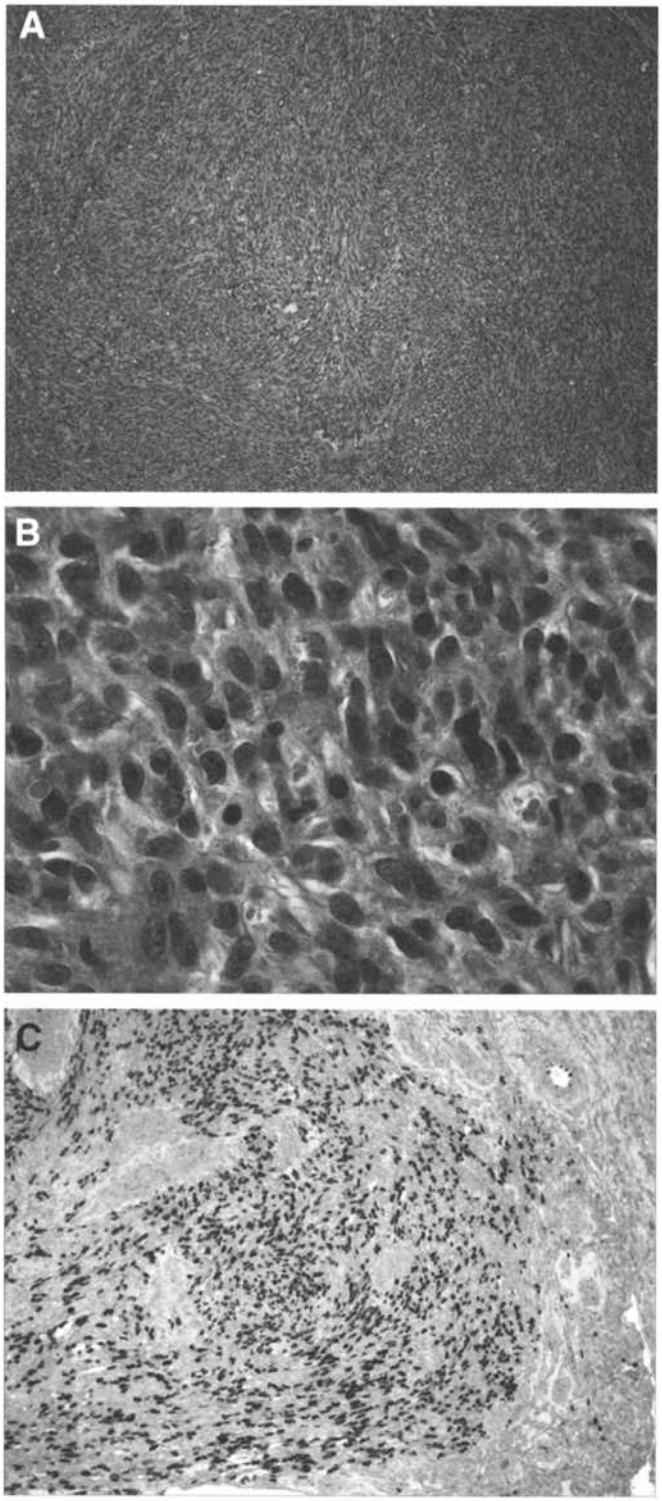


Fig. 22. Kaposi's sarcoma: spindle cell vascular neoplasm that shows close relationship to HHV-8. Note intracytoplasmic hyaline globules (**A,B,** H&E stain; **C,** HHV-8 stain).

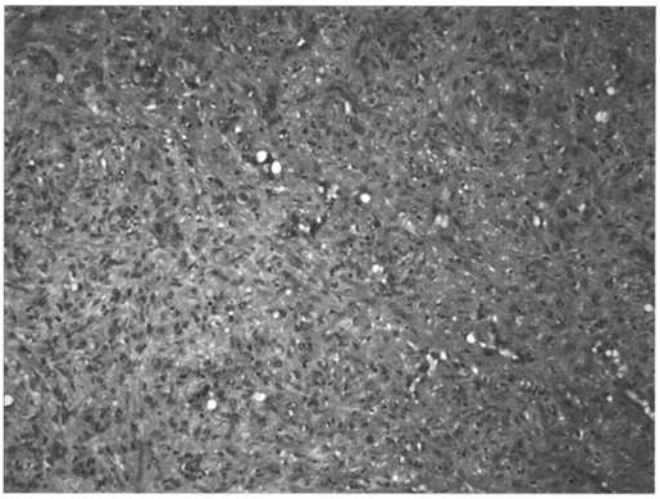


Fig. 23. Epithelioid hemangioendothelioma: epithelioid cells with intracytoplasmic vacuoles.

- Commonly associated with Kasabach-Merritt syndrome (consumption coagulopathy)
- Ill-defined nodules bland spindled cells, slit-like vascular spaces, proliferation of capillaries
- Scattered epithelioid endothelial cells
- Hemosiderin and hyaline globules (variable)

Differential Diagnosis

- Kaposi's sarcoma:
  - Rare in children, multicentric, not lobular
  - Prominent inflammatory infiltrate
- Capillary hemangioma:
  - Solid nodules of capillary proliferations
  - No spindle cell component

Kaposi's Sarcoma (see Skin Tumors) (Figure 22)

- Probably represents a reactive, multifocal vascular proliferation
- Related to Human Herpes Virus 8 (HHV-8)
- 4 distinct clinical groups, where AIDS-related form is commonest
- All groups have similar histologic features with 3 stages

Malignant

Epithelioid Hemangioendothelioma (Figure 23)

Clinical

- Low grade malignant vascular tumor that may involve any organ
- Usually solitary mass in soft tissue, associated with a blood vessel
- Commonly multiple in lung, liver and bone
- Wide range, usually adults; M : F equal (soft tissue), F > M (lungs and liver)
- Local recurrence >15%

♦ Metastatic rate >30%, usually to lymph nodes, lung, liver and bone

Microscopic

♦ Ill-defined and infiltrative
♦ Prominent myxoid to hyaline stroma (chondroid-like)
♦ Nests and trabeculae of epithelioid or spindle cells
♦ Eosinophilic cytoplasm with vesicular nuclei
♦ Intracytoplasmic vacuoles containing red blood cells
♦ Cytological atypia and mitosis usually not prominent
♦ May arise in a vessel with perivascular extension

Immunohistochemistry

♦ CD31+
♦ Cytokeratin+ (50%)
♦ Factor VIII+
♦ EMA–

Differential Diagnosis

♦ Metastatic carcinoma:
  – More nuclear atypia and mitosis, usually not angiocentric
  – CD31–, EMA+
♦ Melanoma:
  – More nuclear atypia and mitoses, usually not angiocentric
  – CD31–, S100+ and HMB 45+
♦ Epithelioid angiosarcoma:
  – More nuclear atypia and mitoses, necrosis
  – Irregular anastomosing channels
♦ Epithelioid sarcoma:
  – Usual distal extremity of young patients
  – Nodular growth pattern with central necrosis
  – Dense collagenous stroma which blends with epithelioid cells

Angiosarcoma (Figure 24)

Clinical

♦ May arise as part of MPNST or germ cell tumors
♦ Primary angiosarcoma may be divided into 5 clinical groups:
  – Idiopathic Cutaneous Angiosarcoma:
    • Usually head and neck of elderly, M > F
    • Multiple erythematous plaques and nodules
    • Poor prognosis with disseminated, aggressive course
  – Lymphedemaassociated angiosarcoma:
    • Also known as lymphangiosarcoma of Stewart-Treves
    • Usually arm of females (outside radiation field); 1–30 years post-radical mastectomy +/– radiation
    • Poor prognosis

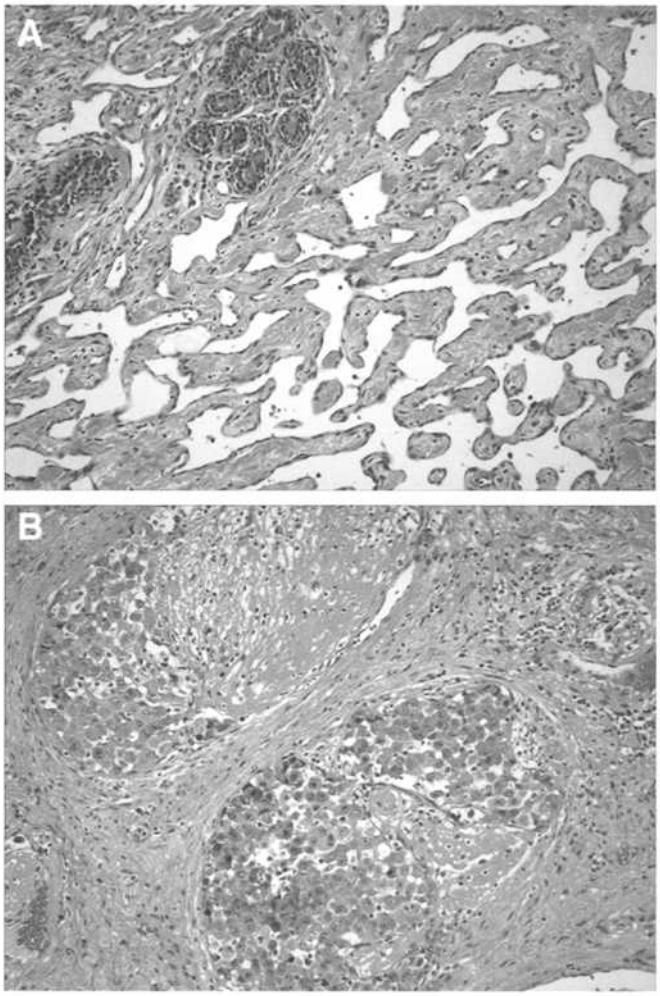


Fig. 24. Angiosarcoma: low grade breast angiosarcoma may be low-grade with a prominent dissecting pattern **(A)**. Epithelioid morphology may mimic carcinoma and melanoma **(B)**.

  – Radiation-induced angiosarcoma:
    • Rare, usually often a mean of 5 years after therapy
    • Commonest on skin and/or parenchyma of breast after radiation for breast cancer
    • Poor prognosis
  – Angiosarcoma of breast parenchyma:
    • Rare, usually females; peak: 20–40 years
    • May be low grade, survival rate depends on tumor grade
  – Angiosarcoma of deep soft tissue:
    • Rare, many extend from cutaneous forms
    • Older adults, M > F, lower limbs and retroperitoneum
    • Poor prognosis

Microscopic

♦ All forms have similar histologic features
♦ Infiltrative tumors, usually multifocal

- Numerous, irregular, anastomosing vascular channels
- Dissecting pattern between collagen bundles (cutaneous)
- Endothelial multilayering, pleomorphism and hyperchromasia (variable)
- Tufting and papillary formation
- Mitoses and necrosis (variable)
- Solid areas without vascular architecture (variable)

Immunohistochemistry

- CD31+
- CD34+
- Factor VIII+/–

Electron Microscopy

- Weibel-Palade bodies

Differential Diagnosis

- Hemangioma
- Angiomatosis
- Angiolipoma
- Bacillary angiomatosis
- Epithelioid sarcoma
- Malignant melanoma
- Spindle cell sarcoma
- Sarcomatoid carcinoma

Variants

- Epithelioid angiosarcoma:
  - Composed exclusively of epithelioid cells
  - Necrosis and hemorrhage
  - Differential diagnosis: carcinoma and melanoma
  - Aggressive clinical course with systemic metastases and death

Perivascular Tumors

Glomus Tumor

Clinical

- Common and usually adults 30–50 years
- M : F equal, except for subungual types (usually in women)
- Usually solitary, painful, <1 cm mass in dermis or subcutis of fingers
- 10% may recur after excision
- Rare malignant transformation (Glomangiosarcoma)

Microscopic

- Well-circumscribed and cellular (variable)
- Solid sheets or nests of round, uniform cells
- Pale, eosinophilic cytoplasm and central, round hyperchromatic nuclei
- Well-defined cell margins (PAS-positive cytoplasmic membranes)
- Edematous stroma with myxoid change

Variants

- Glomangioma:
  - Cavernous vascular spaces with clusters of glomus cells around and lining vessels
  - Thrombi (variable)
- Glomangiomyoma:
  - Features of glomangioma and glomus tumor with smooth muscle proliferation

Immunohistochemistry

- Smooth muscle actin+
- Muscle specific actin+
- Desmin +/–

Differential Diagnosis

- Adnexal tumor:
  - Focal ductal differentiation, cytokeratin+
- Intradermal nevus:
  - Focal nesting pattern, maturation, S-100+

Hemangiopericytoma

Clinical

- Wastebasket diagnosis: most tumors can be reclassified as synovial sarcoma, solitary fibrous tumor, endometrial stromal sarcoma, infantile myofibromatosis
- Rare neoplasm, usually slowly growing, deep-seated mass
- Adults; M = F
- Commonly lower limb and retroperitoneum
- Also orbit, nose, paranasal sinuses and meninges
- Clinical behavior is difficult to predict based on histology

Microscopic

- Well circumscribed; lobulated appearance
- Numerous, thin-walled, branching vessels (staghorn configuration)
- Perivascular sheets or clusters of uniform cells
- Small, spindle cells with oval nuclei and ill-defined cytoplasm
- Myxoid stroma and fibrosis (variable)
- Features of malignancy:
  - Hypercellularity and nuclear atypia
  - Necrosis and hemorrhage
  - Mitoses >4/10 high power fields

Immunohistochemistry
- Vimentin+
- CD34+ (variable, usually focal)
- Factor XIIIa+
- HLA-DR+

Differential Diagnosis
- Fibrous histiocytoma:
  - More prominent spindle cell pattern, storiform arrangement
  - More polymorphic cell population
- Synovial sarcoma:
  - Focal biphasic pattern, more spindling, calcifications
  - Cytokeratin+, EMA+
- Mesenchymal chondrosarcoma:
  - Islands of well-differentiated cartilage
- Solitary fibrous pseudotumor (see fibrous tumors)
- Infantile fibrosarcoma (see fibrous tumors)
- Metastatic endometrial stromal sarcoma:
  - Location and clinical history

"SYNOVIAL TUMORS"

- Classification: *see* **Table 7**

Benign

Giant Cell Tumor of Tendon Sheath (Localized Type) (Figure 25)

Clinical
- Very common; predominantly digits, mostly hand
- Painless, slow-growing and fixed to underlying tendon
- Peak age: 20–40 years; M : F = 1 : 2
- 10–20% recur after local excision

Macroscopic
- Multinodular, lobulated and well-circumscribed
- Usually 2–3 cm in diameter

Microscopic
- Sheets and nests of round, mononuclear stromal cells
- Multinucleated giant cells
- Foamy histiocytes and hemosiderin-laden cells
- Chronic inflammation
- Collagenous stroma and hyalinization (variable)
- Cellularity and mitoses (variable)

Cytogenetics
- Clonal abnormalities involving chromosome 1p

Malignant

Synovial Sarcoma (Figure 26)

Clinical
- Initially believed to originate from synoviocytes, but show no relationship with synovium
- Any age; peak: 10–35 years; slight male predominance
- Deep-seated painful, slow-growing; usually close to large joint
- Common sites: lower limbs, abdomen, head and neck
- 20% involve bone; 30% are calcified
- 50% 5 year survival
- Late recurrences and metastases to lungs, lymph nodes, bone marrow
- Good prognostic signs: <5 cm, early clinical stage and <10 years of age

Macroscopic
- Well-circumscribed, multilobular with pseudocapsule
- Variable size

Microscopic
- Two histologic groups: biphasic and monophasic
- Hypercellular, monomorphic spindle cells arranged in fascicles and whorls
- High nuclear to cytoplasmic ratio with tapering nuclei
- Mitoses (variable)
- Collagenous stroma (variable)
- Focal stromal calcification or ossification
- Stromal mast cells
- Branching, hemangiopericytoma-like vascular pattern
- Biphasic: glandular structures lined by cuboidal to columnar epithelium
- Round cell morphology: poorly differentiated synovial sarcoma, worse prognosis

Immunohistochemistry
- Cytokeratin+, EMA+
- S-100+, CD99+ (non specific)

Cytogenetics
- t(X;18)(p11.2; q11.2)
- Two fusion genes:
  - SYT-SSX1: biphasic and monophasic tumors, worse prognosis
  - SYT-SSX2: monophasic tumors

Table 7. Classification of Synovial Tumors

Benign
Giant Cell Tumor of Tendon Sheath (Localized type)
Variant: Diffuse type (pigmented Villonodular synovitis)
Malignant
Synovial sarcoma

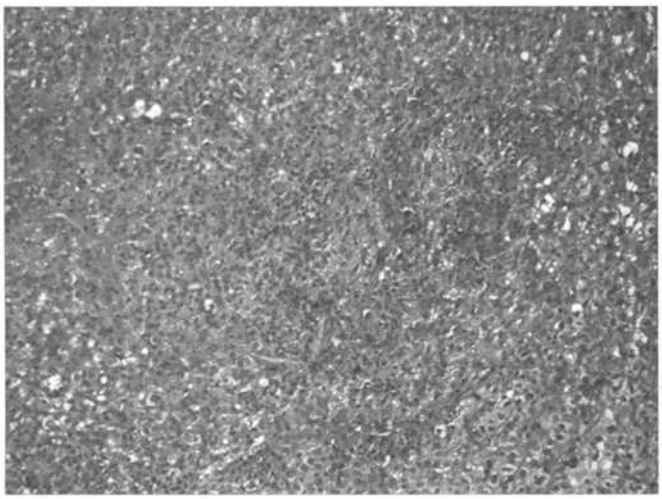


Fig. 25. Giant cell tumor of tendon sheath: mononuclear and rare multinucleated cells show similar nuclear morphology, and are admixed with chronic inflammatory cells and foamy macrophages.

Differential Diagnosis

- Epithelioid sarcoma:
  - Superficial location, upper limb, multinodular with central necrosis
- Clear cell sarcoma (melanoma of soft parts):
  - Nesting pattern, pale nuclei with macronucleoli, intracellular glycogen
  - Cytokeratin– and S-100 protein+
- Malignant peripheral nerve sheath tumor:
  - Usually associated with large nerve, neurofibroma or NF-1

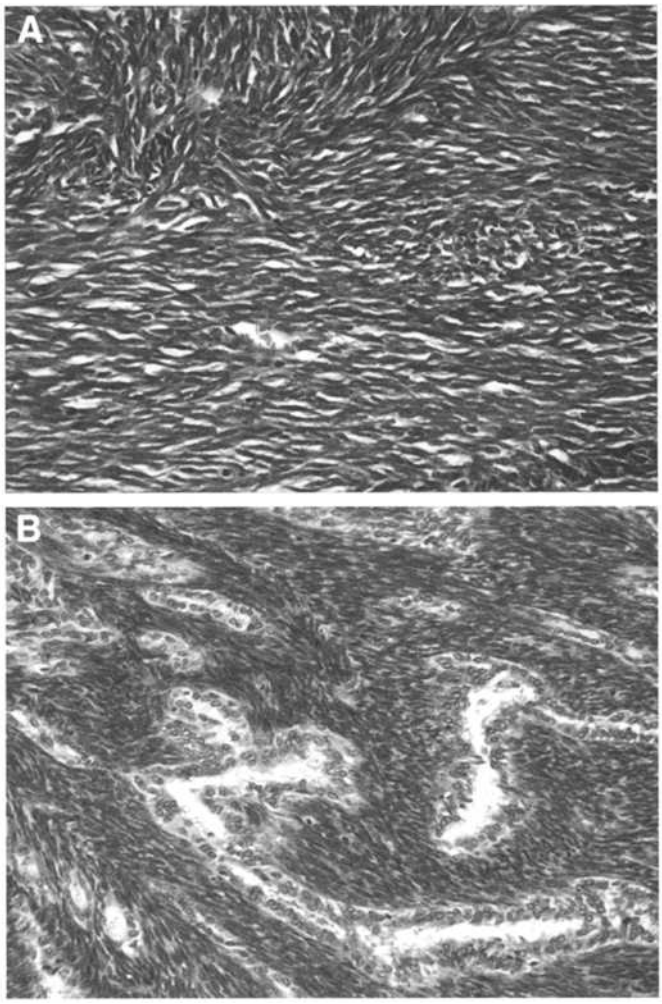


Fig. 26. Synovial sarcoma: monophasic **(A)** and biphasic **(B)**.

- Fibrosarcoma:
  - Not near joint, not multilobular, slender nuclei, no whorling
  - No mast cells or calcifications
- Carcinoma, especially adnexal origin:
  - No spindle cell component
- Carcinosarcoma:
  - Epithelial sarcomatous components are higher grade

PERIPHERAL NEURAL TUMORS

- Classification: *see* **Table 8**

Benign

Traumatic Neuroma (Amputation Neuroma)

- Reparative process arising from the proximal end of a nerve

Clinical

- Any location where peripheral nerve is severed without healing
- Usually trauma or surgery, especially amputation
- Small, painful nodule in superficial soft tissue

Table 8. Classification of Peripheral Neural Tumors

Benign	Perineurioma
Traumatic neuroma (Amputation Neuroma)	Neurothekeoma
Morton's neuroma (Localized interdigital neuritis)	Nerve sheath myxoma
Digital pacinian neuroma	Ganglioneuroma
Mucosal neuroma	Granular cell tumor
Neuromuscular hamartoma (Benign Triton tumor)	Variant: Malignant granular cell tumor
Solitary circumscribed neuroma (Palisaded encapsulated neuroma)	Heterotopic meningeal lesion (Ectopic meningioma)
Neurilemmoma (Schwannoma)	Heterotopic glial nodules (Nasal gliomas)
Variants: Ancient (degenerated)	**Malignant**
Cellular schwannoma	Malignant Peripheral Nerve Sheath Tumor (MPNST)
Plexiform schwannoma	Variants: Epithelioid MPNST
Melanotic schwannoma	Pigmented (melanotic) MPNST
Solitary neurofibroma	Malignant Triton tumor
Variants: Epithelioid neurofibroma schwannoma	Neuroblastoma and Ganglioneuroblastoma (See Adrenal Tumors)
Pacinian neurofibroma	Clear cell sarcoma (Malignant melanoma of soft parts)
Diffuse neurofibroma	Extraspinal (soft tissue) ependymoma
Plexiform neurofibroma	

Microscopic

- Poorly circumscribed with disorderly arrangement of nerve fascicles
- Mixture of fibroblasts, Schwann cells and axons
- Collagenous stroma with myxoid change (variable)

Morton's Neuroma (Localized Interdigital Neuritis)

Clinical

- Severe lancinating pain in region of metatarsal heads
- Adults, with female predilection
- Reactive, sclerosing process involving peripheral nerves
- Resection is curative

Microscopic

- Irregular margins
- Marked endoneurial, perineurial and epineurial fibrosis with loss of axons
- Extension of fibrosis to adjacent fat and vessel walls

Digital Pacinian Neuroma

- Uncommon type of Pacinian neuroma
- Unencapsulated collection of hyperplastic Pacinian corpuscles

Mucosal Neuroma

- Rare, almost always part of MEN type IIb (Gorlin's Syndrome)
- Haphazardly arranged hyperplastic nerve fibers

Solitary Circumscribed Neuroma (Palisaded Encapsulated Neuroma)

Clinical

- Long-standing, solitary, painless nodule; most 3 mm in size
- Usually on the face; peak age: 30–60 years

Microscopic

- Circumscribed, usually in the dermis
- Bland, spindle cells with small, wavy nuclei
- Fascicular growth in a fibrous stroma
- Artefactual clefts
- No nuclear palisading or zonation

Immunohistochemistry

- Schwann cells: S-100 protein+
- Axons: neurofilament+
- Capsule: EMA+

Schwannoma (Neurilemmoma) (Figure 27)

- Benign, encapsulated nerve sheath tumor composed of Schwann cells

Clinical

- Peak: 20–50 years; M : F equal
- Usually, superficial or deep solitary, slow-growing mass; asymptomatic

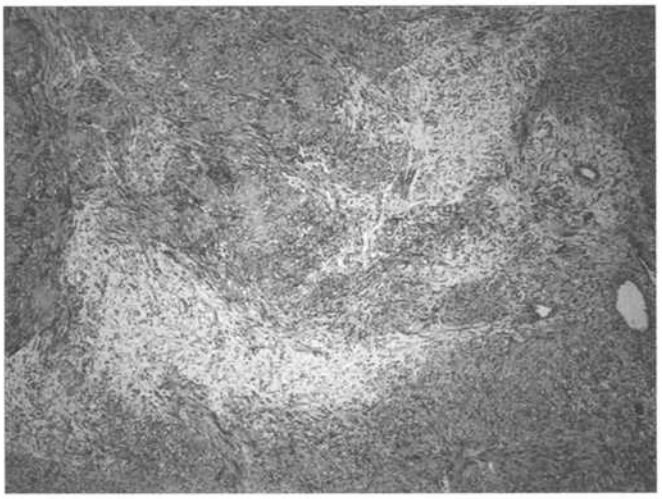


Fig. 27. Schwannoma: alternating Antoni A and B zones with hyalinized blood vessels. Occasional Verocay bodies may be seen.

- Common sites: head and neck and extremities
- Most solitary (unless NF-2)
- Usually do not recur after excision

Macroscopic

- Arise from nerve but usually easily separated at surgery
- Majority <5 cm in diameter; encapsulated

Microscopic

- Variable cellularity with fascicular or swirling pattern
- 2 components: Antoni A and B in varying proportions
- Antoni A:
  - Compact, cellular area with monomorphic eosinophilic spindle cells
  - Nuclear palisading around Verocay bodies
  - Collagenous stroma
- Antoni B:
  - Hypocellular, spindle cells in copious myxoid stroma
  - Blood vessels with thick hyalinized walls
- Mitoses (variable, usually few and not atypical)
- Nuclear hyperchromasia and mild pleomorphism
- Degenerative changes including hyalinization and stromal hemorrhage
- Infrequent microfoci of necrosis (not geographic like MPNST)

Immunohistochemistry

- S-100 strongly+
- EMA+ (capsule)
- Neurofilament– (absence of axons)

Variants

- Ancient (degenerated) schwannoma:
  - Benign schwannoma with prominent degenerative changes
  - Significant nuclear atypia; no mitoses
- Cellular schwannoma:
  - May be mistaken for sarcoma; large deep tumors
  - Usually retroperitoneum or mediastinum
  - Hypercellular, fascicular pattern (predominant Antoni A)
  - Nuclear pleomorphism usually degenerative
  - Mitoses <10/10 HPF
  - Infrequent microfoci of necrosis (not geographic like MPNST)
  - S-100+; desmin– (unlike leiomyosarcoma)
- Plexiform schwannoma:
  - Uncommon type; usually not associated with neurofibromatosis
- Melanotic schwannoma—rare variant

Solitary Neurofibroma (Figure 28)

- Benign nerve sheath tumor composed of mixture of Schwann cells, perineurial-like cells and fibroblasts

Clinical

- Solitary localized, painless, nodular, skin lesions
- Not associated with neurofibromatosis (NF-1)
- Peak age: 20–30 years
- Wide distribution, usually in dermis and subcutis
- Deeper lesions may be associated with NF-1 and may undergo malignant change (rare)
- Arise within nerve; no tendency for local recurrence

Microscopic

- Circumscribed but not encapsulated
- Fusiform expansion of nerve trunk (variable)
- Uniform cellularity (variable) in a variable fibromyxoid stroma
- Elongated spindle cells with eosinophilic processes
- Tapering or wavy, hyperchromatic nuclei
- Small nerve fibers and mast cells
- May show degenerative changes
- Hyalinized stroma (variable)
- Mitoses are not accepted
- S-100+ in 30–50% of cells, Neurofilament+

Variants

- Epithelioid neurofibroma (rare)
- Pigmented neurofibroma (rare
- Pacinian neurofibroma—possibly variant of schwannoma

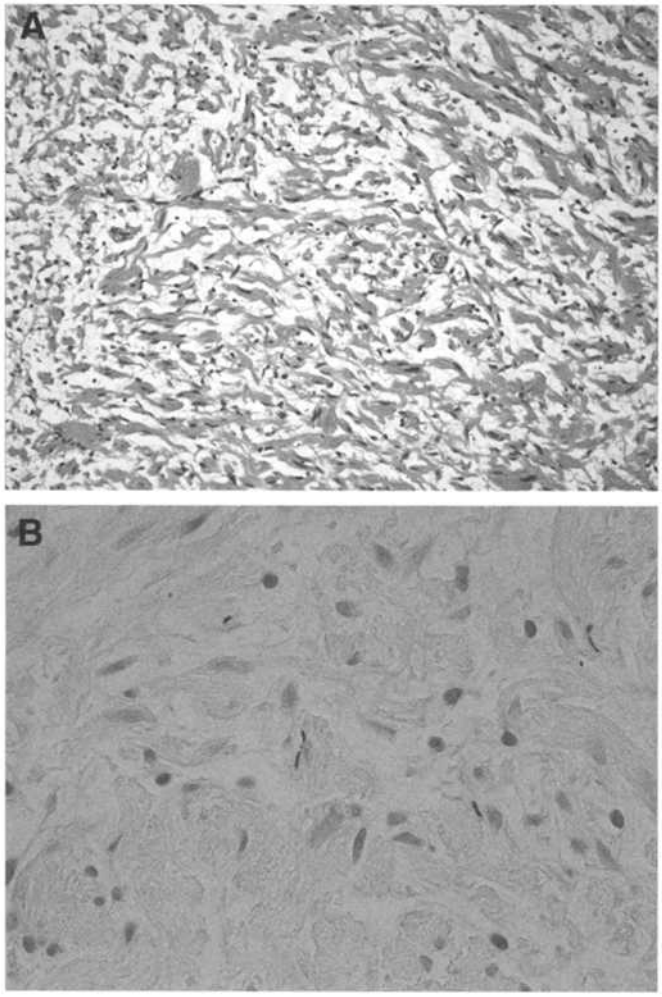


Fig. 28. Solitary neurofibroma: small spindly cells with tapered nuclei **(A)**. Immunostain for neurofilament protein highlight admixed axons **(B)**.

Diffuse Neurofibroma

- Superficial variant of neurofibroma with ill-defined, infiltrative margins
- Peak age: 10–30 years
- 10% are associated with NF-1
- No tendency to undergo malignant transformation
- Meissnerian differentiation is frequently identified

Plexiform Neurofibroma

- Children, M = F
- Diffuse enlargement and distortion of nerves by neurofibromatous tissue
- Pathognomonic for NF-1; may be large and disfiguring
- Usually superficially and most common in head and neck region
- Large and deep-seated lesions have risk of malignant change

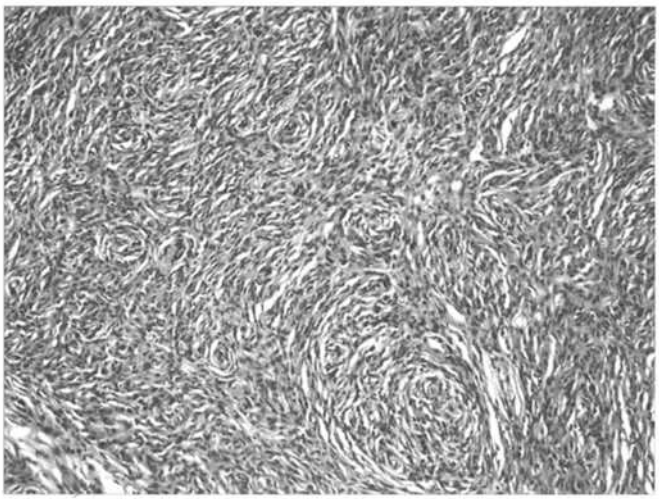


Fig. 29. Soft tissue perineurioma: note the whorled growth pattern of the neoplastic cells, closely resembling meningioma.

Perineurioma (Figure 29)

- Neoplasm composed of differentiated perineurial cells

Clinical

- Soft tissue perineurioma:
  - Limbs and trunk: painless subcutaneous mass
  - Adults
  - F > M
  - No association with NF-1
- Intraneural perineurioma:
  - Young adults
  - Associated with motor deficit
- Sclerosing perineurioma:
  - Solitary small nodules on fingers and palms
  - Young adults
- Complete excision is curative, without recurrence

Microscopic (Soft Tissue Perineurioma)

- Demarcated and unassociated with identifiable nerve
- Well-circumscribed, nodular or ovoid lesions; 1.5–20 cm in size
- Variable histology: elongated bundles, interweaving fascicles, loose whorls or storiform pattern
- "Cracking" artefact
- Wavy spindle cells dissecting collagenous stroma
- Mild nuclear hyperchromasia but no degenerative atypia
- Mitoses (rare)
- Myxoid change (infrequent)

Immunohistochemistry (all types)

- EMA+ (membranous staining)



Fig. 30. Cellular neurothekeoma: dermal nests of short spindle cells.

- S100+ (axons and Schwann cells)
- Neurofilament+ (axons)

Cytogenetics (all types)

- Rearrangement of chromosome 22

Cellular Neurothekeoma (Figure 30)

Clinical

- Usually solitary, cutaneous lesion in children and young adults
- Common sites: face, arm and shoulder
- No association with NF; local recurrence is uncommon

Microscopic

- Multilobular growth pattern; 0.5–3 cm in size
- Hypercellular with focal myxoid stroma
- Fascicles and whorls of spindle or epithelioid cells
- Multinucleated cells and mitoses (frequent)

Immunohistochemistry

- S-100 protein–
- NKI-C3+
- NSE+
- SMA+

Dermal Nerve Sheath Myxoma

Clinical

- Slow-growing, solitary, painless, lesions in young adults, F > M
- Common sites: hands, back, arm, face and neck
- No association with NF-1; local recurrence is uncommon

Microscopic

- Circumscribed with multilobular growth pattern; 0.5–3 cm in size
- Loose network of stellate, spindle and epithelioid cells
- Abundant myxoid stroma
- Eosinophilic, thin cytoplasmic processes
- Intranuclear and cytoplasmic vacuoles
- Mitoses (rare)
- S-100 protein+

Ganglioneuroma

- Benign neoplasm composed of mature autonomic ganglion cells and numerous axons with Schwann cells in a fibrous stroma

Clinical

- Peak age: 10–20 years; female predilection
- Most occur in the mediastinum, retroperitoneum and adrenal medulla
- Symptomatic due to mass effect and rarely due to endocrine activity
- Most arise de novo, a few may represent matured neuroblastoma/ganglioneuroblastoma
- May arise in association with schwannoma or pheochromocytoma
- Resection is curative

Microscopic

- Well-circumscribed mass with a fibrous capsule; most <15 cm
- Loose network with bundles of axonal processes with Schwann cells, resembling neurofibroma
- Nests or scattered mature ganglion cells
- Multinucleated cells, pleomorphism and vacuolation (all variable)
- Degenerative changes (variable)
- Adequate sampling to rule out ganglioneuroblastoma

Granular Cell Tumor (Figure 31)

Clinical

- Common lesion; usually skin or subcutis
- Peak age: 40–70 years; slight female predominance
- Any anatomic site; commonly trunk, tongue and arms
- Usually solitary, 10% multiple
- Majority are benign and local recurrence is rare

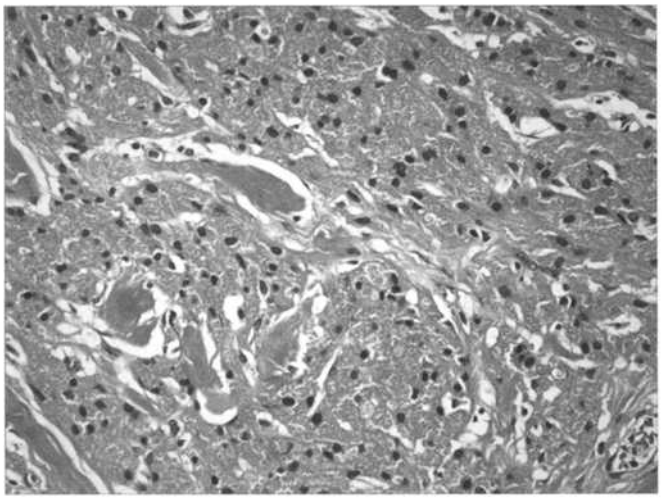


Fig. 31. Granular cell tumor: large eosinophilic cells with small centrally located nuclei.

Microscopic

- Usually <3 cm
- Poorly circumscribed or infiltrative margins
- Uniform appearance at any location
- Nests, trabecular or sheets of round to polygonal cells
- Copious granular, eosinophilic cytoplasm
- PAS with diastase + intracytoplasmic granules (30% of cases)
- Uniform, central, pyknotic nuclei
- Minimal nuclear pleomorphism and scattered mitoses
- Fibrosis (variable)
- Pseudoepitheliomatous hyperplasia of overlying squamous epithelium
- S-100+, neuron-specific enolase (NSE)+ and NKI-C3+

Variant

- Gingival granular cell tumor of newborn infants (congenital epulis):
  - Maxilla
  - F>>>M
  - Similar histology with prominent vessels, inflammatory cells and entrapped nests of odontogenic epithelium
- Malignant granular cell tumor:
  - 2–3% of all cases; usually occur in deep soft tissue
  - 50% have a metastasizing, fatal clinical course
  - Similar morphologic features, usually infiltrative margins
  - Prominent nucleoli and frequent mitoses

Differential Diagnosis

- Adult rhabdomyoma:
  - No cytoplasmic granules; cross-striations and cytoplasmic glycogen
- Hibernoma and fibroxanthoma:
  - Presence of lipid droplets
- Reactive processes:
  - No nested or trabecular arrangement, inflammatory cells and necrosis
- Squamous cell carcinoma (vs pseudoepitheliomatous hyperplasia):
  - No underlying granular cells and more nuclear atypia

Heterotopic Meningeal Lesions (Ectopic Meningioma)

- Consists of three types:
  - Ectopic meningothelial hamartoma—usually over scalp and spinal column; present in childhood; pseudoangimatous appearance
  - Cutaneous meningioma—usually adults, mostly head
  - Type III—spread of central nervous system meningioma to overlying skin or subcutis

Heterotopic Glial Nodules (Nasal Gliomas)

- Usually result of misplaced glial tissue in subcutis in head and neck (most common in the nose)
- Circumscribed mass of mature glial tissue; neurons are absent
- GFAP+

Malignant

Malignant Peripheral Nerve Sheath Tumor (Malignant Schwannoma or Neurofibrosarcoma) (Figure 32)

Clinical

- 3 principal forms: sporadic, radiotherapy-induced (10%) and associated with NF-1 (30–50%)
- Peak age: 20–50 years; 10–15 years younger in patients with NF-1
- Sporadic form: M : F equal; NF-1patients: M : F = 4 : 1
- Common sites: proximal limbs and trunk
- May arise in a neurofibroma (NF-1) and rarely post-radiation
- 50% 5 year survival in sporadics and 20–25% in NF-1
- Metastases are usually to lung, liver, subcutis and bone

Macroscopic

- Usually large, fusiform, eccentric mass within a nerve
- Most >10 cm in diameter
- Fleshy, whitish cut surface with areas of hemorrhage and necrosis

Microscopic

- Fascicular spindle cell pattern (fibrosarcoma-like)
- Abrupt transition between cellular and myxoid areas
- Perivascular whorling of tumor cells
- Elongated cells with tapering or wavy, hyperchromatic nuclei

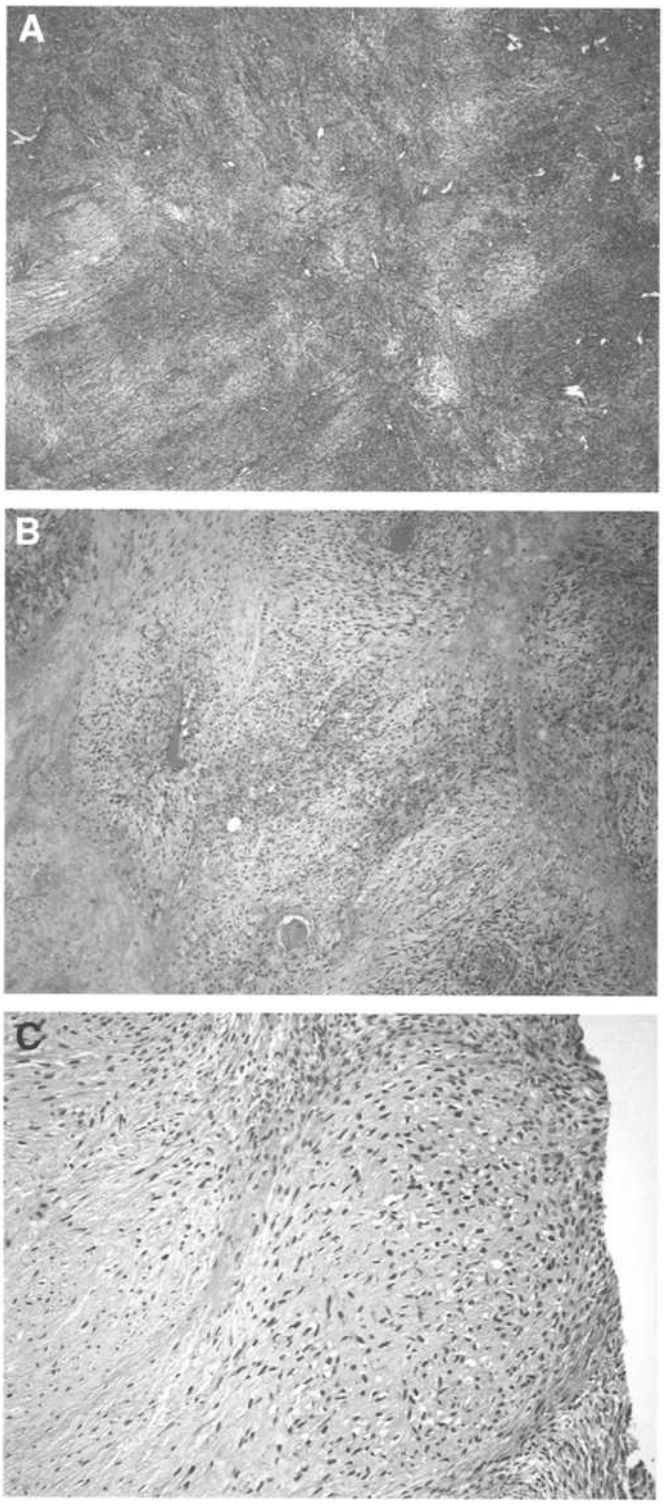


Fig. 32. Malignant peripheral nerve sheath tumor: alternating hypercellular and myxoid areas composed of spindle cells with tapered nuclei (**A**). Perivascular accentuation of tumor cells is a frequent features seen in MPNST (**B**). Occasionally, heterologous differentiation, such as chondrosarcomatous may be seen (**C**).

- Pale, ill-defined cytoplasm:
  - Mild nuclear pleomorphism and mitoses
  - Nuclear palisading (uncommon)
- Myxoid stroma and fibrosis (variable)
- Geographic necrosis (variable)
- Heterologous differentiation (10–15%):
  - Rhabdomyosarcoma (Malignant Triton tumor): worse prognosis
  - Osteosarcoma or chondrosarcoma
  - Angiosarcoma
  - Glandular differentiation

Immunohistochemistry

- S-100+ (50% of cases) and usually 20–30% of cells
- GFAP+

Variants

- Epithelioid MPNST:
  - 5% of MPNSTs; 50% are superficial with better prognosis
  - Difficult differential diagnosis from carcinoma or melanoma
  - Usually S-100+, HMB 45– and keratin–
- Pigmented (melanotic) MPNST
- Malignant Triton tumor:
  - MPNST with rhabdomyoblastic differentiation

Differential Diagnosis

- Fibrosarcoma:
  - Uniform fascicular pattern, no neural differentiation, S-100–, diagnosis of exclusion
- Synovial sarcoma:
  - Uniform fascicular pattern, no neural differentiation, calcification
  - Cytokeratin+, EMA+
- Leiomyosarcoma:
  - Eosinophilic cytoplasm, central blunt-ended nuclei
  - S-100–, actin+, desmin+
- Cellular neurofibroma (especially in NF-1):
  - No mitoses
- Cellular schwannoma:
  - Location, Antoni A and B pattern, perivascular hyalinization, encapsulation, strong and diffuse S-100 protein+

Clear Cell Sarcoma (Malignant Melanoma of Soft Parts) (Figure 33)

Clinical

- Intimately associated with tendons and aponeuroses
- Peak age: 20–40 years; slight female predominance

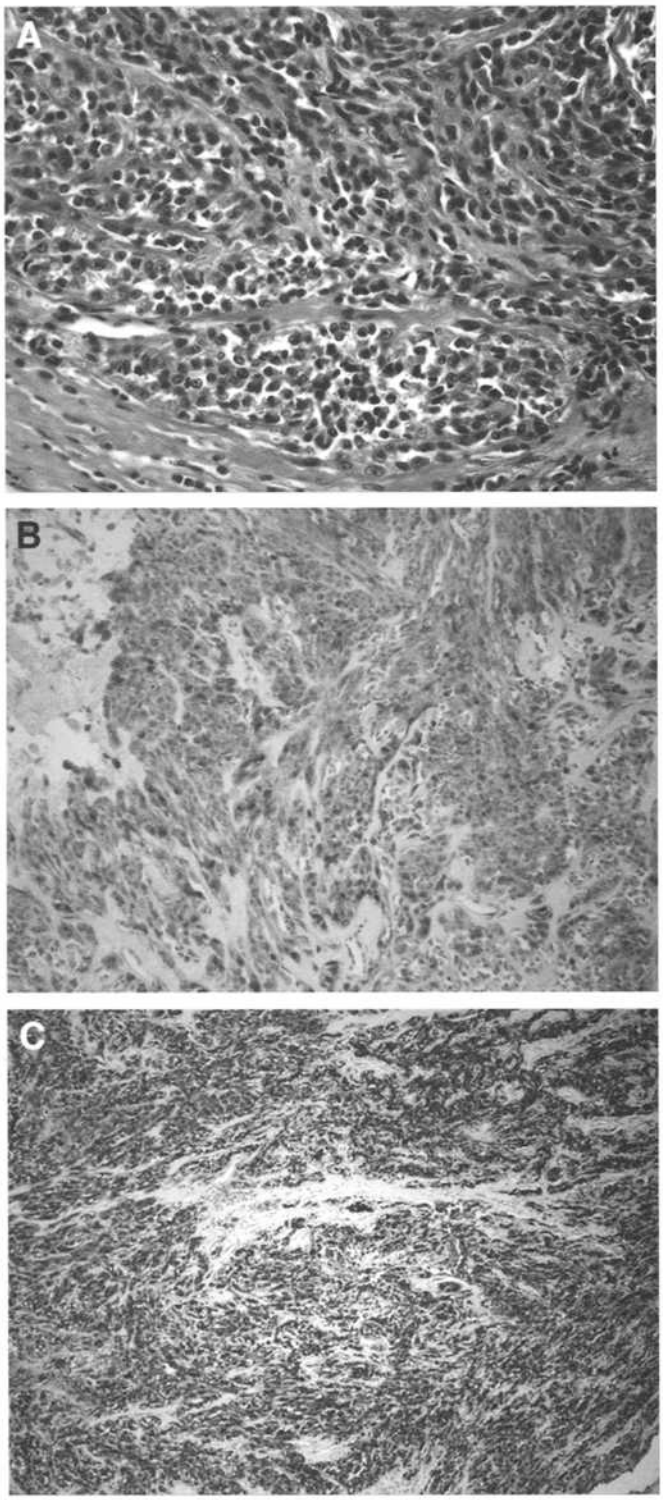


Fig. 33. Clear cell sarcoma: small spindled cells with monotonous cytomorphology and prominent nucleoli, similar to malignant melanoma (**A**). These tumors show positivity for S-100 protein (**B**) and HMB-45 (**C**).

- Common sites: distal extremities, especially foot and ankle
- Slowly growing, painful mass
- Repeated local recurrences due to incomplete excision
- 50% develop late metastases to lungs, lymph nodes or bone
- Poor long-term prognosis despite adjuvant therapy

Microscopic

- Usually <5 cm, associated with fascia and tendons
- Nests or fascicles of cells separated by fibrous septa
- Infiltrate into fibrotendinous tissue, subcutis or deep dermis
- Uniform cells with pale eosinophilic to clear cytoplasm
- Intracytoplasmic glycogen
- Round, polygonal to spindle cells
- Vesicular nuclei with prominent nucleoli
- Multinucleated giant cells (wreath-like nuclei)
- Fibrosis (variable)

Immunohistochemistry

- S-100+
- HMB 45+
- Neuron specific enolase (NSE)+

Cytogenetics

- t(12; 22) (q13; q13)

Differential Diagnosis

- Cutaneous melanoma:
  - Junctional activity; irregular growth pattern, more pleomorphism
- Fibrosarcoma:
  - No cellular aggregates, no intracytoplasmic glycogen
  - S-100–, HMB 45–
- MPNST:
  - Association with peripheral nerve or NF-1
  - No glycogen, more hyperchromatic nuclei and more mitoses
  - HMB 45–
- Metastatic renal cell carcinoma:
  - Less prominent nucleoli, no fusiform appearance
  - Cytokeratin (low molecular weight) and EMA+

Extraspinal (Soft Tissue) Ependymoma (see CNS tumors)

- Rare tumors; occur in subcutis dorsal to sacrum and coccyx
- Usually are of the myxopapillary type
- Greater tendency to metastasize than intraspinal counterpart
- Usually late metastasis (>10 years) to lung

CHONDRO-OSSEOUS TUMORS

♦ Classification: *see* **Table 9**

Benign

Osteoma Cutis

♦ Rare, usually multiple cutaneous nodules of mature bone
♦ Majority of bony nodules in skin are due to secondary ossification

Myositis Ossificans

Clinical

♦ Solitary, self-limiting, reactive, related to trauma (30%)
♦ Young adults with male predominance; uncommon in children
♦ Common sites: quadriceps and brachialis muscles
♦ Radiographs: well-circumscribed lesion with peripheral calcification and central lucency (variable with duration)

Macroscopic

♦ Well-circumscribed with edematous muscle at the periphery

Microscopic

♦ Zonation pattern
♦ Central zone—myofibroblastic proliferation (nodular fasciitis-like)
♦ Maturation towards periphery with osteoid production
♦ Mild nuclear atypia and mitoses
♦ Hemorrhage (variable)
♦ Endochrondral calcification (variable)
♦ Entrapped, atrophic skeletal muscle fibers

Variants

♦ Panniculitis Ossificans:
  – Myositis ossificans in subcutis; usually upper limbs of women
♦ Fibro-osseous pseudotumor of the digits (florid reactive periostitis):
  – Rare heterotopic ossification in subcutis of digits
  – Young adults; M < F
  – Resembles myositis ossificans without zonation
♦ Fibrodysplasia (myositis) ossificans progressive:
  – Disseminated myositis ossificans
  – Rare, hereditary disease effecting children <10 years
  – Associated with skeletal abnormalities
  – Slowly progressive with poor long-term prognosis

Differential Diagnosis

♦ Extraskeletal osteosarcoma:
  – No zonation phenomenon or 'reversed' zonation
  – Marked nuclear pleomorphism and necrosis

Table 9. Classification of Chondro-Osseous Tumors

Benign
Osteoma cutis
Myositis ossificans
Variants:
Panniculitis ossificans
Fibro-osseous pseudotumor of digits (florid reactive periostitis)
Fibrodysplasia (myositis) ossificans progressive
Soft tissue chondroma (Extraskeletal chondroma)
Malignant
Extraskeletal myxoid chondrosarcoma (chordoid sarcoma)
Extraskeletal mesenchymal chondrosarcoma
Extraskeletal osteosarcoma

Soft Tissue Chondroma (see Bone Tumors)

♦ Soft tissue counterpart of osseous tumors
♦ Exclusively hands and feet, usually fingers in adults
♦ Usually solitary and often associated with tendon

Malignant

Extraskeletal Myxoid Chondrosarcoma (Chordoid Sarcoma) (Figure 34)

Clinical

♦ Painless, slow-growing, deep-seated mass
♦ Adults, peak age: 30–60 years; slight male predominance
♦ Common sites: lower limb (70%), trunk (20%) and upper limb (10%)
♦ Low grade tumor prone to local recurrences and metastases (40–50% of cases)
♦ Metastasize to lungs, lymph nodes, bone and brain
♦ Bad prognostic factors: advanced age at presentation and >10 cm

Microscopic

♦ Well-circumscribed, multilobular, usually 5–15 cm
♦ Lobular growth pattern with fibrous septa
♦ Anastomosing cords, strands of small uniform ovoid cells
♦ Copious myxoid matrix
♦ More cellular at periphery of lobules
♦ Cartilaginous differentiation (rare)

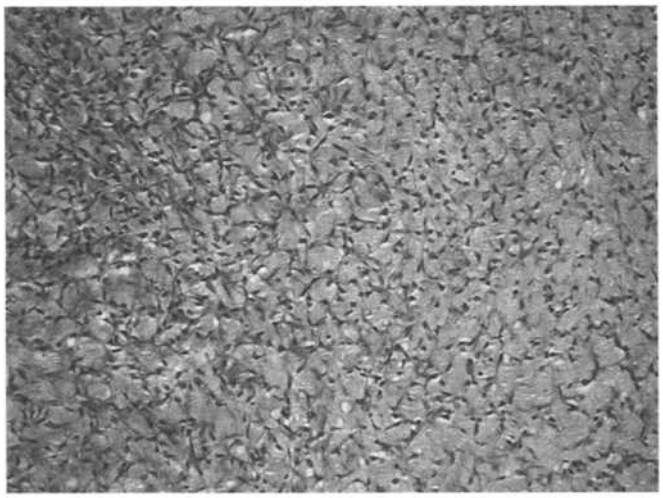


Fig. 34. Extraskeletal myxoid chondrosarcoma: anastomosing cords of small ovoid cells in a prominent myxoid background.

- Cytoplasmic hyaline (rhabdoid) inclusions (variable)
- Mitoses and necrosis (variable)
- Intracytoplasmic glycogen (PAS+)

Immunohistochemistry

- S-100+ (focal, 20% of cases)

Cytogenetics

- t(9;22)(q22;q12)

Differential Diagnosis

- Myoepithelioma of soft tissue:
  - More superficial location, epithelial differentiation
  - Keratin, actin and S-100 protein+

Extraskeletal Mesenchymal Chondrosarcoma (see Bone Tumors)

- Highly malignant neoplasm, more common in bone
- Head and neck lesions in 25 year olds
- Deep musculature, especially thigh in >45 year olds
- Aggressive clinical course with metastases to lungs and lymph nodes

Extraskeletal Osteosarcoma

- 5% of all osteosarcomas arise in soft tissue
- Adults: 60–90 years; M > F
- Common sites: limbs, especially thigh and retroperitoneum
- May be radiation-induced
- Poor prognosis with aggressive, metastasizing clinical course
- Overall mortality: 60–70%
- Histology similar to bone tumors, commonest pattern is MFH-like

MISCELLANEOUS TUMORS

- Classification: *see* **Table 10**

Benign

Tumoral Calcinosis

- Idiopathic disorder with tumor-like calcium deposition in periarticular soft tissue
- Unassociated with chronic renal failure or collagen vascular disorder

Clinical

- Peak age: 10–30 years: M > F
- 2/3 of cases involve blacks; siblings in 50%
- Usually around large joints: hip, shoulder and elbow
- Slow-growing, firm, subcutaneous mass
- 2/3 are multiple and bilateral

Microscopic

- Unencapsulated, firm, rubbery mass; range: 5–15 cm in diameter
- Cut surface: calcified, chalky masses with dense fibrous tissue
- Proliferation of multinucleated and osteoclast-like giant cells and macrophages
- Dense fibrous tissue around calcified material
- Psammomatous calcifications (rare)

Differential Diagnosis

- Metastatic calcifications:
  - Associated with chronic renal failure and secondary hyperparathyroidism
  - Hyperphosphatemia with uremia on hemodialysis
  - Hypercalcemia in hypervitaminosis D, hyperparathyroidism
- Calcinosis universalis and calcinosis circumscripta:
  - Associated with collagen vascular disease
- Dystrophic calcifications:
  - Smaller, usually in damaged tissue e.g.: injury or infection

Amyloidoma

- Rare in soft tissue; solitary or multiple
- May be primary or secondary

Table 10. Classification of Tumors of Uncertain Histogenesis

Benign
Tumoral calcinosis
Amyloidoma
Myxoma
Intramuscular myxoma
Juxta-articular myxoma
Dermal myxoma (cutaneous myxoid cyst)
Myxoma of the jaw
Cutaneous myxoma (superficial angiomyoma)
Ganglion
Aggressive angiomyxoma
Ossifying Fibromyxoid Tumor
Malignant
Alveolar Soft Part Sarcoma
Epithelioid Sarcoma
Primitive Neuroectodermal Tumor (Extraskeletal Ewing's sarcoma)
Extrarenal Rhabdoid Tumor
Desmoplastic Small Round Cell Tumor

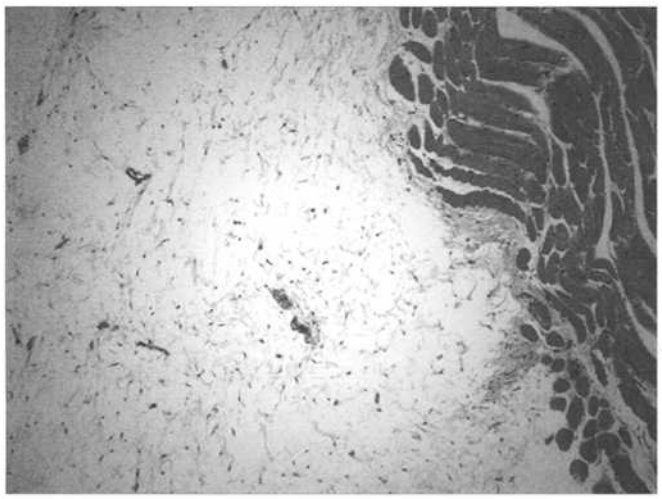


Fig. 35. Intramuscular myxoma: hypocellular spindle cell neoplasm with small spindle cells.

MYXOMA (FIGURES 35,36)

Intramuscular Myxoma

Clinical

- Peak age: 30–70 years; female predominance
- Involve large muscles, usually thigh and limb girdles
- Slowly growing, painless mass in lower limbs
- 5% multiple and associated with fibrous dysplasia (Mazabraud's syndrome)
- Local recurrences are rare

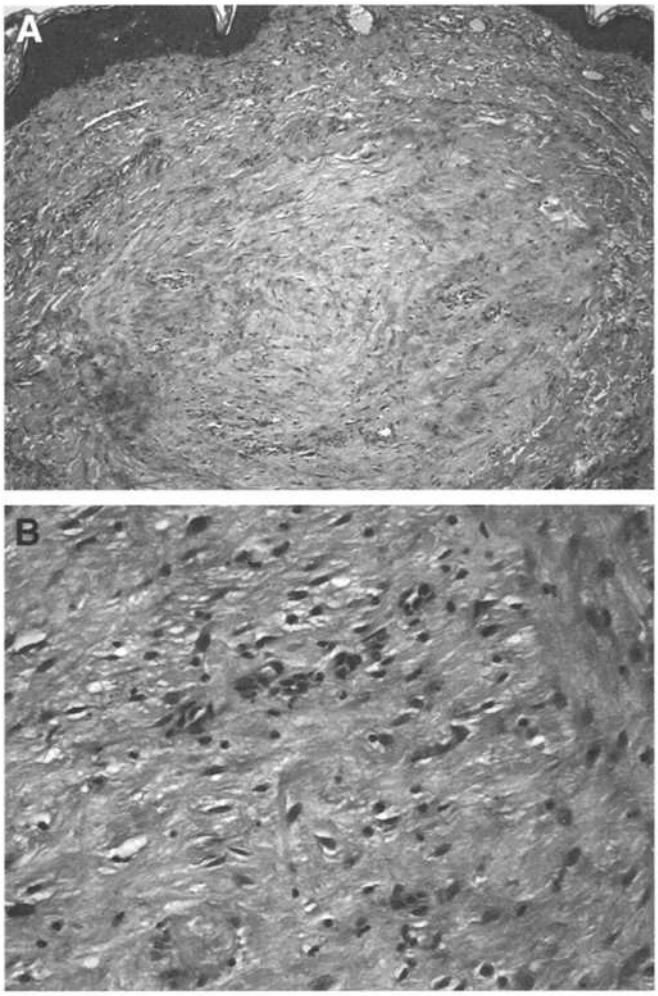


Fig. 36. Superficial angiomyxoma: similar morphology with scattered neutrophils and no association with necrosis or ulceration **(A,B).**

Microscopic

- Circumscribed to ill-defined margins extending between muscle fibers
- Paucicellular and minimal vascularity
- Small, bland, spindle or stellate cells with hyperchromatic nuclei
- No pleomorphism or mitotic activity

Differential Diagnosis

- Myxoid liposarcoma:
  - Plexiform capillary network and lipoblasts

- Myxoid MFH (myxofibrosarcoma):
  - Hypercellularity, nuclear pleomorphism and mitoses

Juxtaarticular Myxoma

- Uncommon variant
- Adjacent to large joints, usually knee, shoulder, elbow and hip
- Mainly males; peak age: 30–70 years
- Associated with cysts and degenerative joint disease
- May involve subcutis, tendons and joints
- Often recur locally
- Poorly marginated and may be more cellular

Digital Myxoma (Cutaneous Myxoid Cyst)

- Uncommon lesion on the finger of adults; marked female predominance
- Frequent local recurrence

Superficial Angiomyxoma

- Usually sporadic, may be associated with Carney's complex
- Affects adults; usually head and neck or trunk
- Superficial nodule involving dermis and subcutis, <3–4 cm
- Commonly recur locally
- Multiple, poorly-defined myxoid nodules
- Numerous thin-walled vessels:
  - Entrapped epithelial elements
  - Neutrophilic infiltrate with no association with necrosis or ulceration

Ganglion

- Common, usually dorsum of wrist in young adults
- Frequently attached to joint capsule and tendon sheath

Aggressive Angiomyxoma

- (*see* Vulvar tumors)
- Involves vulva or pelvis of adult female
- Commonly recurs

Ossifying Fibromyxoid Tumor

Clinical

- Usually subcutaneous nodule involving extremities
- Adults; M > F
- May recur locally

Microscopic

- Well circumscribed, multinodular; <5 cm in diameter
- Fibrous capsule and fibrous septa
- Shell of mature lamellar bone (90%)
- Nests and cords of cells
- Round cells with pale cytoplasm uniform, vesicular nuclei

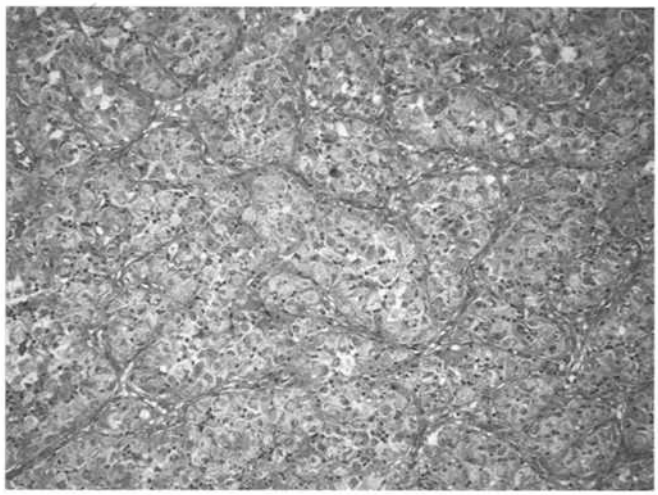


Fig. 37. Alveolar soft part sarcoma: large polygonal cells with central degeneration and alveolar pattern.

- Minimal pleomorphism and scarce mitoses
- Abundant fibromyxoid stroma
- Chondroid metaplasia (variable)
- Atypical OFMT: irregular bone distribution, increased cellularity and mitosis, common recurrence, rare metastasis (lung)

Immunohistochemistry

- S-100 protein+
- Desmin+/–
- Actin+/–

Malignant

Alveolar Soft Part Sarcoma

Clinical

- Uncommon; <1% of all sarcomas
- Occurs in adolescents or young adults; F > M
- Lower extremities (adults); head and neck region (children)
- Slow-growing and painless
- May present with metastases to lungs or brain
- Indolent but bleak prognosis
- Children seem to have a better prognosis

Microscopic ***(Figure 37)***

- Well-circumscribed and lobulated
- Organoid pattern with nests and sheets of large cells
- Alveolar pattern due to central dyscohesion
- Fibrovascular septa
- Large, round cells with clear to eosinophilic granular cytoplasm
- Eccentric round nuclei with prominent nuclei
- PAS-diastase + intracytoplasmic crystals and granules

- Intracytoplasmic glycogen
- Necrosis and hemorrhage (variable)
- Mild nuclear pleomorphism and rare mitoses
- Vascular invasion, especially of dilated periphery veins

Differential Diagnosis

- Metastatic renal cell carcinoma:
  - More pleomorphism, lack intracytoplasmic crystals
  - Cytokeratin+
- Melanoma:
  - More pleomorphism, HMB-45 and S-100 protein+
- Paraganglioma:
  - No glycogen, chromogranin and synaptophysin+
- Granular cell tumor:
  - Not lobulated, less well-defined cells, less vascular, more granular cytoplasm, S-100 protein+

Epithelioid Sarcoma

Clinical

- Usually adolescents and young adults; male predominance
- Typically distal extremities, especially hand and wrist
- Solitary or multinodular, slow-growing, superficial mass
- Involve dermis, subcutis, fascia or tendons
- Pain and ulceration (common)
- Spreads along fascial planes or neurovascular bundles
- Treatment: radical surgery/limb amputation
- Slow, relentless course with multiple local recurrences
- Eventual metastases and death despite treatment
- 50% metastasize to lymph nodes, lung and soft tissue
- Tumor <5 cm have a better prognosis

Microscopic

- Ill-defined, multinodular firm mass with geographic necrotic foci
- Usually <5 cm
- Diffusely infiltrative margins
- Nodules of monomorphic, eosinophilic, epithelioid to spindle-shaped cells
- Dense fibrous stroma
- Minimal nuclear pleomorphism
- Mitoses (variable)
- Central necrosis or myxohyaline degeneration
- Perineural and vascular invasion
- Cytoplasmic vacuolation (variable)
- Chondroid or osseous metaplasia (rare)

Immunohistochemistry

- Cytokeratin+
- EMA+
- CD34+ (50% of cases)

Differential Diagnosis

- Infections or necrobiotic granuloma:
  - No nuclear pleomorphism, no vascular and perineural invasion
  - Keratin and EMA–, CD68+
- Nodular fasciitis, fibrous histiocytoma and fibromatosis:
  - No epithelioid features, no nodularity, cytokeratin –
- Squamous cell carcinoma:
  - Epidermal involvement, dyskeratosis, keratin pearls
  - More cytological pleomorphism
  - CD34–
- Malignant melanoma:
  - More pleomorphism, S100+, HMB45+, cytokeratin –
- Synovial sarcoma:
  - Location, no dermal involvement and ulceration
  - Biphasic pattern, intracellular mucin, small cells not eosinophilic

Peripheral Primitive Neuroectodermal Tumor (Peripheral Neuroepithelioma, Askin Tumor, Extraosseous Ewing's Sarcoma) (Figure 38)

- Family of lesions with specific and reproducible translocation t(11; 22)(q24;q12) and variable neuroectodermal differentiation

Clinical

- Wide age range; peak: 10–30 years; M = F
- Common sites: trunk and lower limbs
- Occasionally arise in association with nerve trunk
- Usually rapidly enlarging, deep-seated mass (unresectable)
- Susceptible to chemotherapy, the more primitive (Ewing's) respond well
- Overall 5-year survival is 20–30%
- Metastases occur to lungs and lymph nodes

Microscopic

- Variable depending on degree of neuroectodermal differentiation
- Lobules, trabecular and sheets of cells
- Prominent capillary network and scant stroma
- Necrosis (common)
- Primitive cells with round open to hyperchromatic nuclei
- Nucleoli (variable)
- Mitoses (variable)
- Pale, scanty to eosinophilic cytoplasm
- Intracytoplasmic glycogen (variable, typical in Ewing's)
- Homer-Wright rosettes and pseudorosettes (variable)

Immunohistochemistry

- MIC-2 (CD99)+ (membranous, "Olympic ring" pattern)

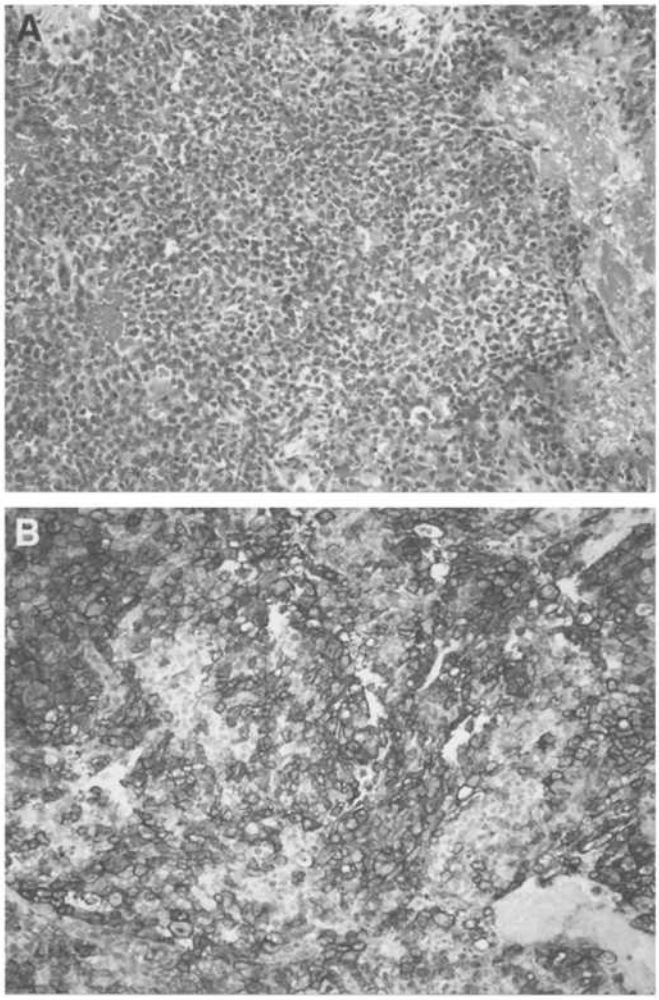


Fig. 38. Ewing's sarcoma: small round cell neoplasm with primitive appearance **(A)** and characterized by membranous positivity for CD99 **(B)**.

- LEU-7+
- Neuron-specific enolase (NSE)+
- Synaptophysin+
- Neurofilament+
- Chromogranin+
- S-100 protein+

Cytogenetics

- t(11;22)(q24;q12)

Molecular Genetics

- EWS-FLI-1 fusion protein

Differential Diagnosis

- Neuroblastoma:
  - Presence of neuropil, ganglionic differentiation, calcification
  - MIC-2–

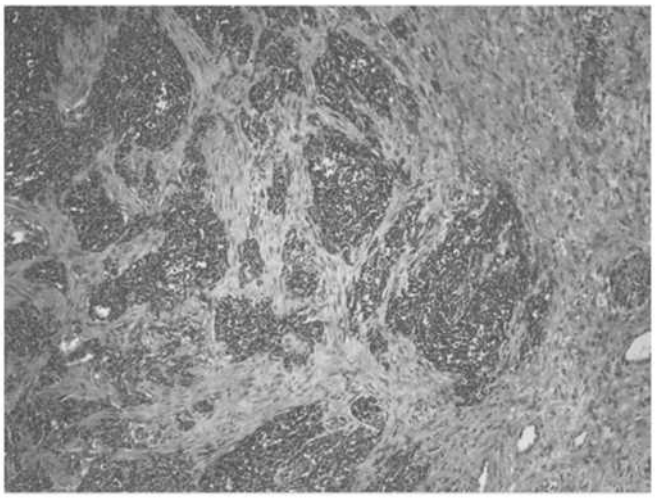


Fig. 39. Desmoplastic small round cell tumor: nests of small spindle cells with intervening desmoplastic stroma.

- Rhabdomyosarcoma:
  - Actin and desmin+, synaptophysin–
- Lymphoma:
  - No specific growth pattern, CD45+
- Neuroendocrine carcinoma:
  - Location, cytokeratin+, MIC-2–

Extrarenal Rhabdoid Tumor

- Rare, ill-defined entity (possibly a heterogeneous group)
- Usually infancy, wide age range
- Any location, usually trunk and proximal extremities
- Very aggressive clinical course with median survival of 6 months
- Metastases to lungs, liver, lymph nodes and soft tissue
- Hyaline globular cytoplasmic inclusions and large nucleoli
- Cytokeratin+, EMA+, vimentin+
- EM: Abundant paranuclear whorls of intermediate filaments
- Remember: a variety of neoplasms may show "rhabdoid" cytoplasmic inclusions; immunohistochemistry is helpful in the differential diagnosis

Desmoplastic Small Round Cell Tumor (Figure 39)

Clinical

- Usually adolescents and young adults; marked male predominance
- Common sites: abdomen, pelvis, and omentum
- May be associated with widespread peritoneal implants
- Usually palpable, often painful mass
- Associated with distension, constipation, obstruction or ascites

- Highly aggressive neoplasm with a poor prognosis
- Widespread metastases (common)
- Normally not amenable to surgical excision
- Death despite treatment within a few years

Microscopic

- Solid, large multilobulated mass ± areas of necrosis
- Nests or masses of small rounded cells
- May have a trabecular or cord-like arrangement
- Intervening abundant fibrous, desmoplastic stroma
- Hyperchromatic nuclei and scanty cytoplasm
- Cells may be vacuolated or contain PAS + eosinophilic inclusions

Immunohistochemistry

- Cytokeratin+
- EMA+
- Desmin+ (usually paranuclear dot-like)
- polyclonal WT-1+
- S-100 protein±
- CEA–

Cytogenetics

- t(11;22)(q13;q12)

Differential Diagnosis

- Primitive neuroectodermal tumor (Ewing's sarcoma)
- Neuroblastoma
- Rhabdomyosarcoma
- Neuroendocrine carcinoma
- Seminoma
- Lymphoma

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17

Tumors of the Salivary Glands

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CONTENTS

I. Introduction to Salivary Gland Tumors 17-3
General features 17-3

II. Benign Epithelial Tumors 17-3
Pleomorphic Adenoma (Mixed Tumor) 17-3
Recurrent Mixed Tumor 17-3
Myoepithelioma 17-3
Oncocytoma 17-3
Warthin's Tumor (Adenolymphoma) 17-7
Sebaceous Lymphadenoma 17-7
Sebaceous Adenoma 17-7
Basal Cell Adenoma 17-8
Dermal Analogue Tumor (Membranous Adenoma) 17-8
Canalicular Adenoma 17-8

III. Malignant Epithelial Tumors 17-9
Malignant Mixed Tumor 17-9
Carcinoma Ex-Pleomorphic Adenoma 17-9
Carcinosarcoma (Concomitant Epithelial and Mesenchymal Malignancy) 17-10
Metastasizing Pleomorphic Adenoma 17-11
Myoepithelial Carcinoma 17-11
Oncocytic Carcinoma 17-12
Carcinoma in Warthin's Tumors 17-12
Sebaceous Carcinoma 17-13
Basal Cell Adenocarcinoma 17-13
Acinic Cell Carcinoma 17-14
Adenoid Cystic Carcinoma 17-15
Mucoepidermoid Carcinoma 17-17
Salivary Duct Carcinoma 17-18
Epithelial-Myoepithelial Carcinoma 17-19
Terminal Duct Carcinoma (Polymorphous Low-Grade Adenocarcinoma) 17-20
Primary Squamous Cell Carcinoma 17-21
Undifferentiated Carcinoma 17-21
Small Cell Carcinoma 17-21
Large Cell Carcinoma 17-22
Lymphoepithelial Carcinoma 17-22
Clinicopathologic Factors 17-23

IV. Immunohistochemistry 17-23

V. Other Tumors 17-24
Salivary Gland Lymphoma 17-24
Primary Lymphomas 17-24
Mesenchymal Tumors of the Salivary Glands 17-24
Salivary Gland Tumors in Children 17-25
General Features 17-25
Hemangioma 17-25
Sialoblastoma (Embryoma) 17-25
Malignant Epithelial Tumors 17-27
Metastasis to Salivary Glands 17-27

VI. Tumor-like and Cystic Lesions 17-27
Tumor-Like Lesions
Sialolithiasis 17-27
Sialadenitis 17-28
Sialadenosis 17-28
Oncocytosis 17-28
Necrotizing Sialmetaplasia 17-28
Benign Lymphoepithelial Lesions 17-29
Sjögrens Syndrome 17-29

Chronic Sclerosing Sialadenitis of Submandibular Gland (Kuttner's Tumor) 17-29
Cystic Lymphoid Hyperplasia (HIV + Subjects) 17-29
Inflammatory Pseudotumors....17-30
Cystic Lesions
Benign Cysts of Salivary gland: An Overview 17-30
Cystic Neoplasms 17-30
Inflammatory, Specific and Non-specific 17-30
Dysgenetic Cysts....17-30
Secondary Cysts 17-31
Mucoceles, Retension and Extravasation (Ranula)....17-31
Benign Cystic Lesions of Neck 17-32

VII. TNM Classification of Major Salivary Gland Tumors (2002 Revision) 17-32

VIII. Suggested Reading....17-32

INTRODUCTION TO SALIVARY GLANDS

- Salivary gland tumors are predominantly epithelial (**Tables 1** and **2**). Mesenchymal tumors most often involve glands by extension rather than arising within the gland. The latter are also found predominantly in children and adolescents. The most commonly encountered tumors in surgical pathology will be highlighted in this chapter.

The non-pleomorphic salivary adenomas can be placed under the domain of monomorphic adenoma. These, in turn, can be divided into basaloid and non-basaloid tumors (**Tables 3** and **4**). There is also an inverse relationship between site of the affected salivary gland and the frequency of malignancy (**Table 5**)

BENIGN EPITHELIAL TUMORS

Pleomorphic Adenoma (Mixed Tumor)

Clinical

- Comprised of 55% to 70% of all salivary neoplasms
- More in females in 4th decade
- Painless, slow growing mass
- In parotid: 90% superficial lobe, 10% deep lobe

Macroscopic

- Well-defined, lobulated mass
- Multifocal in 0.5% of cases
- Variegated appearance, cartilaginous

*Microscopic (**Figures 1–3**)*

- Biphasic epithelial and mesenchymal elements
- Epithelial cells:
  - Tubules, nests, ribbons, and files with occasional squamous, oncocytic, or sebaceous differentiation
- Myoepithelial cells:
  - Spindle or plasmacytoid cells
- Stroma: mucoid, myxoid, hyaline, or chondroid; rarely adipose tissue and bone
- Crystals: tyrosine-calcium oxyalate, collagenous spherules

Immunohistochemistry

- Generally non-contributory
- S-100 protein and smooth muscle actin (SMA)+ in stromal and myoepithelial cells

Cytogenetics and Molecular Genetics

- Alteration, rearrangements, and LOH at 8q21 and 12q 14–15 regions

Differential Diagnosis

- Adenoid cystic carcinoma:
  - Lacks mesenchymal elements; clear demarcation between collagenous, epithelial, and mucoid materials
  - Propensity for perineural invasion
- Myoepithelioma:
  - Lacks ductal and mesenchymal elements
- Terminal duct carcinoma:
  - Variegated epithelial patterns; lacks mesenchymal features

Recurrent Mixed Tumor

- Histologically similar to original tumor
- Multiple nodules
- Extension to surrounding tissue

Myoepithelioma

Clinical

- Uncommon, 1.5% of all salivary tumors
- 2.2% to 5.7% of all benign tumors
- Male : female ratio = 1 : 1
- Most common sites: palate and parotid

Macroscopic

- Well-demarcated mass; tan, homogenous, and solid

*Microscopic (**Figures 4–6**)*

- Comprised of >90% myoepithelial cells
- Cellular, mucoid, or hyalinized stroma may be present
- Lacks ductal differentiation
- Cell types: spindle, plasmacytoid, epithelioid, clear cells

Immunohistochemistry

- Keratin+, Muscle specific antigen (MSA)+, S-100 protein+, desmin–

Electron Microscopy

- Microfilaments, 50 to 100 Å in size; pinocytic vesicles

Differential Diagnosis

- Spindle cell myoepithelioma:
  - Leiomyoma, nerve sheath tumors, synovial sarcoma, nodular fasciitis
  - Strong positive immunoreactivity for keratin excludes these mesenchymal tumors
- Plasmacytoid myoepithelioma:
  - Plasmacytoma: + for monoclonal light chain reaction, keratin–

Table 1. Salivary Gland Tumors

Benign		*Malignant*	
Epithelial	*Mesenchymal*	*Epithelial*	*Non-Epithelial/ Mesenchymal*
Pleomorphic adenoma (benign mixed tumor)	Angioma	Mucoepidermoid carcinoma	Sarcomas
Basal cell adenoma	Lipoma	Adenoid cystic carcinoma	Lymphomas
Canalicular adenoma	Fibrous histiocytoma	Acinic cell carcinoma	
Warthin's tumor	Neurofibroma and neurilemmoma	Terminal duct carcinoma (polymorphous low-grade adenocarcinoma)	
Oncocytoma	Hemangioma	Epithelial-myoepithelial carcinoma	
Myoepithelioma		Salivary duct carcinoma	
Sebaceous lymphadenoma and adenoma		Basal cell adenocarcinoma	
Ductal papillomas		Sebaceous carcinoma	
Cystadenoma		Oncocytic carcinoma	
		Adenocarcinoma, NOS (not otherwise specified)	
		Squamous cell carcinoma	
		Carcinoma ex-pleomorphic adenoma	
		Carcinosarcoma (sarcomatoid carcinoma)	
		Myoepithelial carcinoma (malignant myoepithelioma)	
		Undifferentiated carcinoma (small and large cell)	
		Nasopharyngeal-like carcinoma (undifferentiated carcinoma with lymphoid stroma)	

Table 2. Incidence of Primary Epithelial Salivary Gland Tumors in Different Sites (%)

Diagnosis	*Parotid*	*Submandibular*	*Sublingual*	*Minor*
Benign				
Pleomorphic adenoma	63.3	59.5	0	42.9
Warthin's tumor	14.0	0.8	0	0
Monomorphic adenoma	8.0	2.3	14	11
Malignant				
Mucoepidermoid carcinoma	1.5	1.6	0	8.9
Acinic cell carcinoma	2.5	0.4	0	1.8
Adenoid cystic carcinoma	2.0	16.8	28.6	13.1
Adenocarcinoma (NOS)	2.6	5.0	14.2	12.2
Squamous carcinoma	1.1	1.9	0	1.2
Undifferentiated carcinoma	1.8	3.9	14.2	2.1
Carcinoma ex pleomorphic adenoma	3.2	7.8	28.6	7.1

Table 3. Types of Monomorphic Adenomas

Basaloid	*Non-Basaloid*
Basal Cell	Warthin's tumor
Tubulotrabecular	Oncocytoma
Solid	Sebaceous lymphadenoma
Canalicular	Sebaceous adenoma
Dermal analogue (membranous)	Ductal adenoma
	Myoepithelioma

Table 4. Differential Characteristics Between Basaloid Adenomas and Canalicular Adenoma

Feature	*Basaloid*		*Canalicular*
	Dermal analogue	*Other types*	
Sex			
Male : Female	10:1	1:1	1:1.7
Age (years)			
Range	34–74	1–83	34–88
Mean	58.1	58.6	65.1
Synchronous dermal lesions (%)	37.7	0	0
Site (%)			
Parotid	86.2	90.1	1.6
Submandibular	6.8	4.9	0
Upper lip	0	4.9	87.2
Other minor sites	6.8	0	24.7
Multicentricity (%)	48	0.9	24
Recurrences (%)	24	0	0
Malignant transformation (%)	28	3.9	0

Modified from Eveson & Caswon, 1985

- Clear cell myoepithelioma:
  - Metastatic renal cell carcinoma: vascular, cellular atypia, hemorrhage, clinical history
  - Myoepithelial carcinoma: cellular atypia, infiltrative growth

Table 5. Frequency of Epithelial Malignancy in Different Salivary Gland Sites (%)

Site	*Malignant*
Parotid	14.7
Submanidublar	37.0
Sublingual	85.7
Minor	46.1

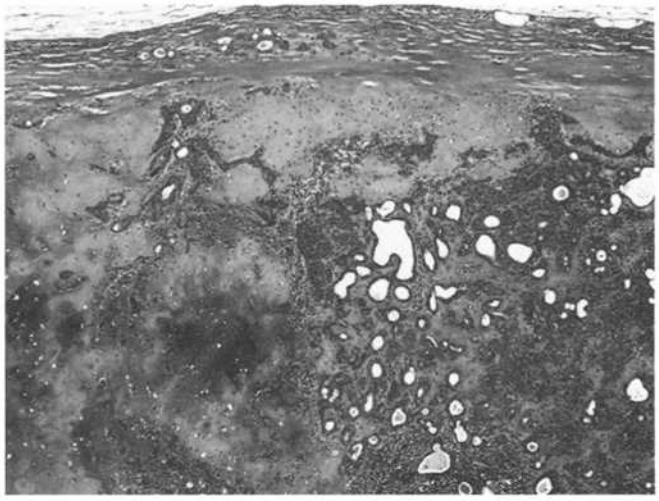


Fig. 1. Pleomorphic adenoma (cartilaginous and ductal structures).

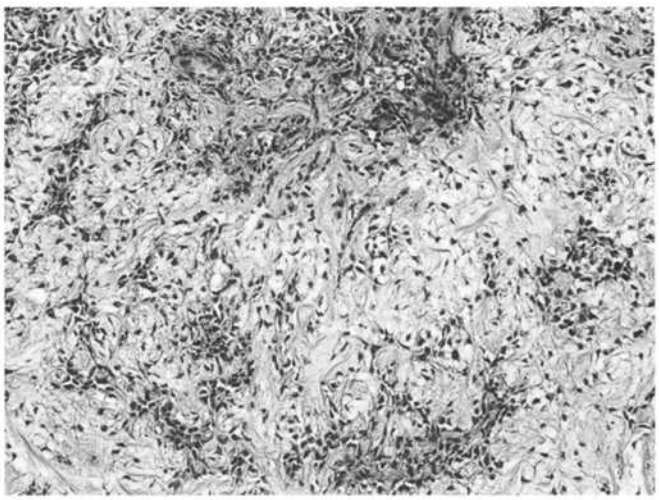


Fig. 2. Pleomorphic adenoma, myxoid stroma.

Oncocytoma

Clinical

- Rare, 1% of all salivary tumors
- Women slightly more than men

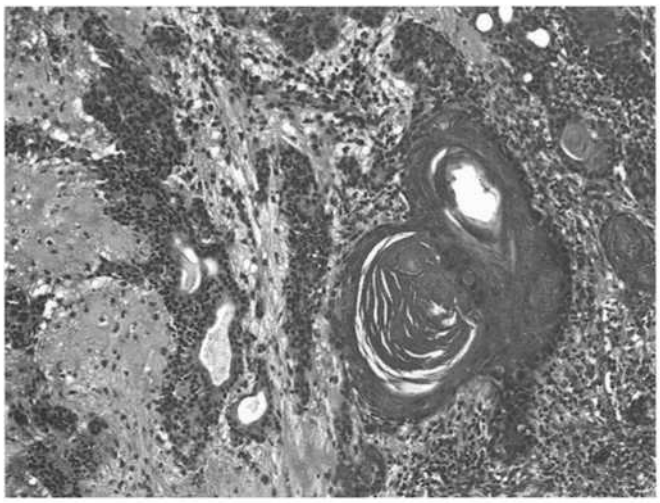


Fig. 3. Pleomorphic adenoma, squamous metaplasia.

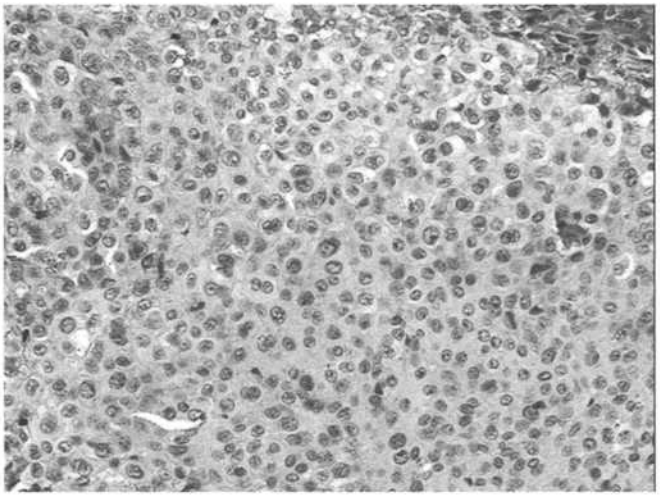


Fig. 4. Myoepithelioma, plasmacytoid type.

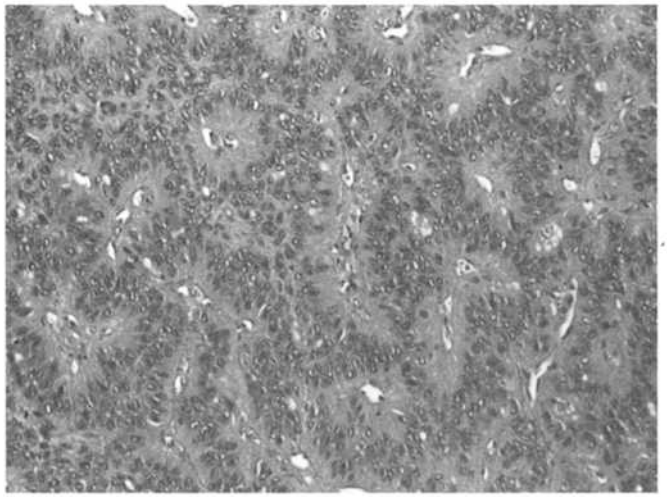


Fig. 5. Myoepithelioma, organoid pattern.

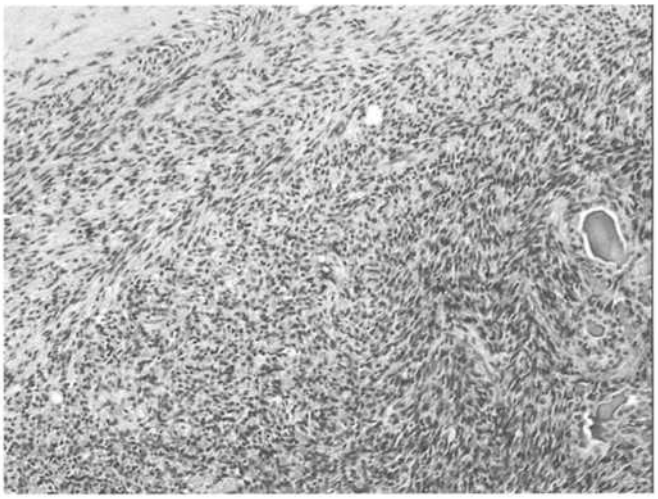


Fig. 6. Myoepithelioma, spindle cell type.

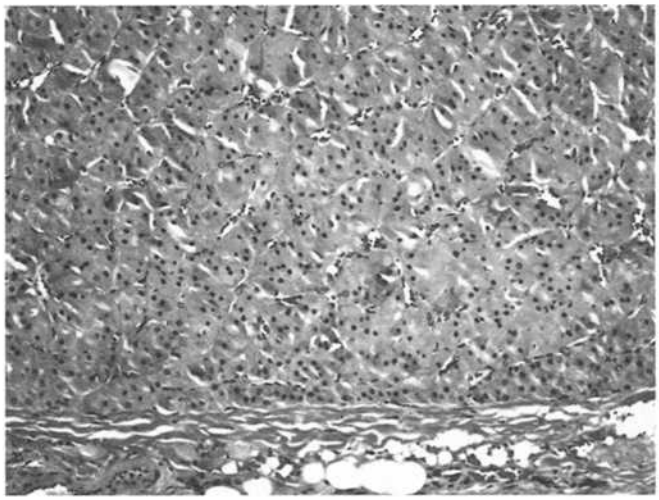


Fig. 7. Oncocytoma.

- Bilateral in 7% of cases
- Main presentation is swelling

Macroscopic

- Solitary, encapsulated
- Reddish brown, smooth, and homogenous cut surface

*Microscopic (**Figure 7**)*

- Large polygonal eosinophilic cells with central round nuclei
- Cord, ribbon, and acinar formation
- Focal mucinous or squamous metaplasia may be present
- Clear cell variant (clear cell oncocytoma)
- Oncocytic hyperplasia may occasionally be found at periphery

Immunohistochemistry

- Non-contributory

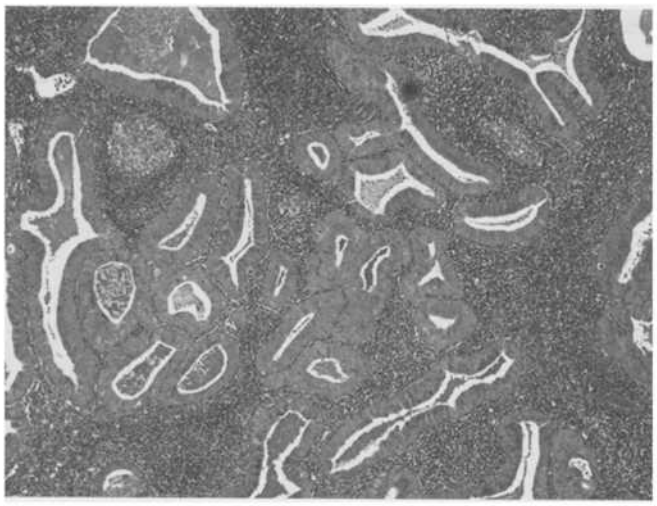


Fig. 8. Warthin's tumor, oncocytic ducts with lymphoid stroma.

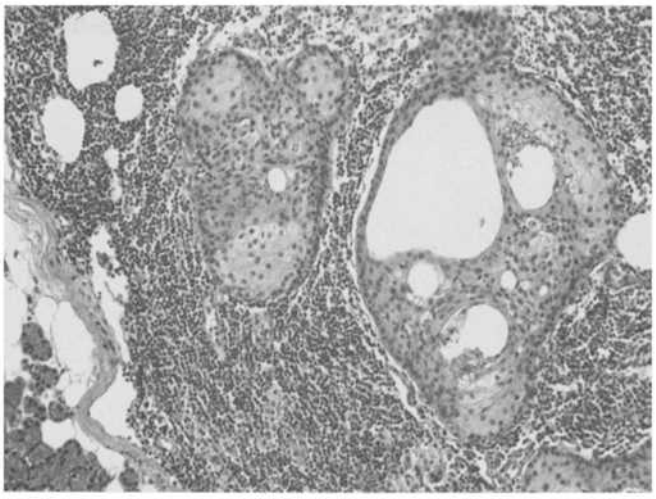


Fig. 9. Sebaceous lymph-adenoma, squamous islands with clear cells.

Electron Microscopy

- Large accumulation of mitochondria with lamellar structure
- Occasionally large glycogen particles

Special Stains

- Phosphotangestic acid hematoxylin stain (PTAH)+

Differential Diagnosis

- Conventional oncocytoma:
  - Pleomorphic adenoma with oncocytic metaplasia: features of pleomorphic adenoma
  - Mucoepidermoid carcinoma: PTAH–; mucinous, intermediate, and squamous differentiation
  - Acinic cell carcinoma: acinar differentiation, PTAH–, granules
  - Oncocytosis and oncocytic hyperplasia: diffuse, lacks fibrous encapsulation, retains architecture
- Clear cell oncocytoma:
  - Epimyoepithelial carcinoma: dual cellular differentiation (myoepithelial and ductal)
  - Metastatic renal cell carcinoma: high vascularity, history of renal cell carcinoma

Warthin's Tumor (Adenolymphoma)

Clinical

- Second most common benign tumor
- Superficial, slow-growing mass
- Exclusively parotid, 2% to 15% of all parotid tumors
- Bilaterality not uncommon
- Male : female ratio = 8 : 1

Macroscopic

- Well-circumscribed and cystic
- Brownish, creamy materials

*Microscopic (**Figure 8**)*

- Oncocytic epithelial lined spaces with occasional papillary formation
- Lymphoid stroma, with germinal centers
- Occasional globlet, squamous, and sebaceous cells

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Enlarged mitochondria in oncocytes

Cytogenetics

- Structural alteration in chromosome 7

Differential Diagnosis

- Oncocytoma (to differentiate from stroma-deficient Warthin's tumor):
  - Lack cystic formation
- Sebaceous adenoma, squamous carcinoma, and mucoepidermoid carcinoma:
  - Lack lymphoid stroma; minimal oncocytic features

Sebaceous Lymphadenoma

Clinical

- Rare, 0.1% of all adenomas
- Parotid is the most common site
- Male : female ratio = 1 : 1
- Painless mass

Macroscopic

- Circumscribed and encapsulated mass

*Microscopic (**Figure 9**)*

- Solid sebaceous or cystic nests and metaplastic ducts in lymphoid stroma
- Giant cell reaction to extravasated cystic content

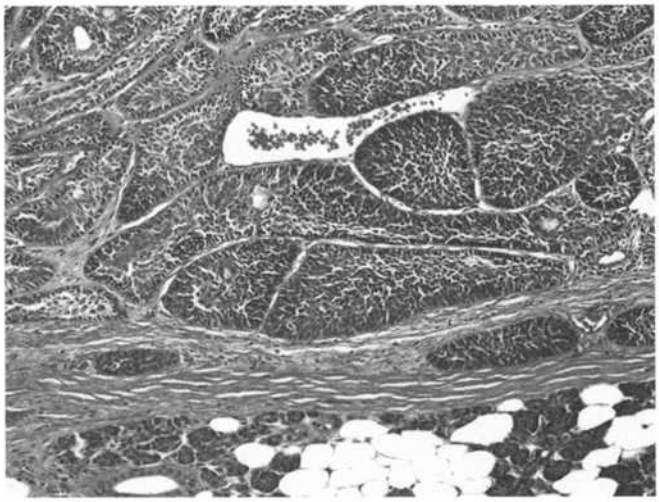


Fig. 10. Basaloid adenoma, dermal analogue tumor.

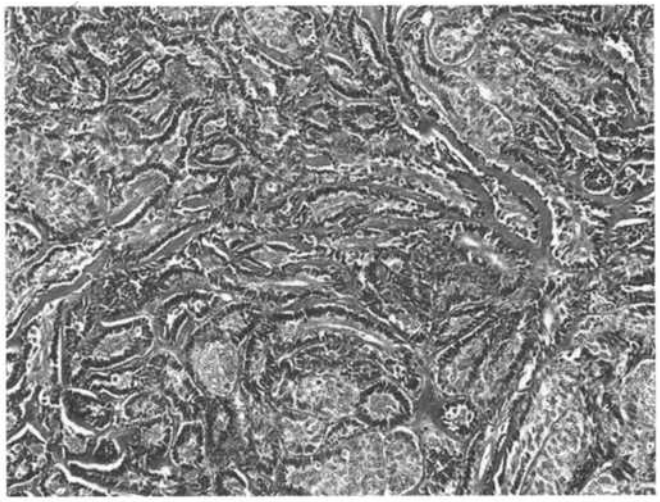


Fig. 11. Basaloid adenoma, peripheral palisading.

Sebaceous Adenoma

Clinical

- Rare, 0.1% of all salivary gland tumors
- Males slightly more than females
- Parotid, submandibular, and oral cavity glands are most common sites

Macroscopic

- Solid, gray, well-circumscribed mass

Microscopic

- Benign, irregular, sebaceous, cellular nests in lymphoid stroma
- Large cystic formation

Basal Cell Adenoma

Clinical

- 1% to 3% of all major salivary gland tumors
- Mostly in women
- Parotid is most common site
- May present within cervical lymph node

Macroscopic

- Encapsulated, round, or oval mass
- Grayish or white homogenous cut surface
- Average size 2 cm
- Occasional cystic formation

Microscopic ***(Figure 10)***

- Trabecular, solid, mixed, and membranous cellular patterns
- Mixed variant common
- Monotonous, small, dark nuclei with scant basophilic cytoplasm
- Cords and nests with peripheral palisading
- Tubular pattern in minor glands
- Basement membrane materials between cell nests and stroma, marked in membranous type

Dermal Analogue Tumor (Membranous Adenoma)

Clinical

- Mainly parotid and peri- or intra-parotid lymph nodes
- High recurrence rate
- Synchronous or metachronous skin adnexal tumors (e.g., dermal cylindromas, trichoepitheliomas, eccrine spiradenomas) not uncommon

Macroscopic

- Multicentric
- Unencapsulated nodule

Microscopic ***(Figure 11)***

- Hyaline materials between cellular nests
- Morula-like structure with keratinization

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Reduplicated basal laminae
- Ductal, myoepithelial, and basal cells features

Differential Diagnosis

- Adenoid cystic carcinoma:
  - Manifests invasive pattern; lacks vascularity
- Basal cell adenocarcinoma:
  - Similar cytomorphology, but shows invasive features

Canalicular Adenoma

Clinical

- 1% of all salivary gland tumors, 4% of all minor glands
- >73% in upper lip and buccal mucosa

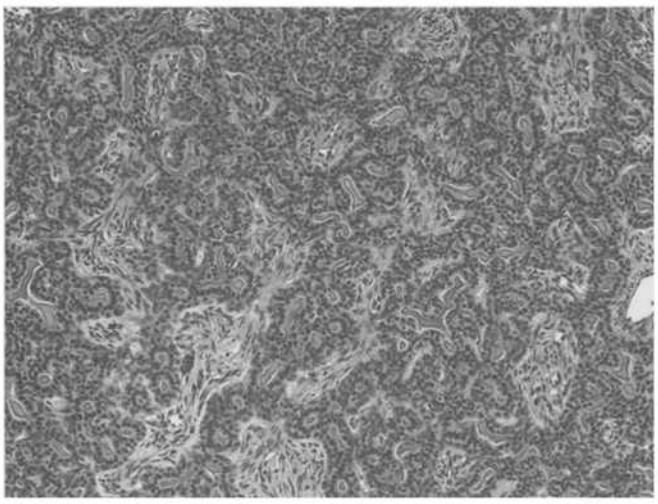


Fig. 12. Canalicular adenoma.

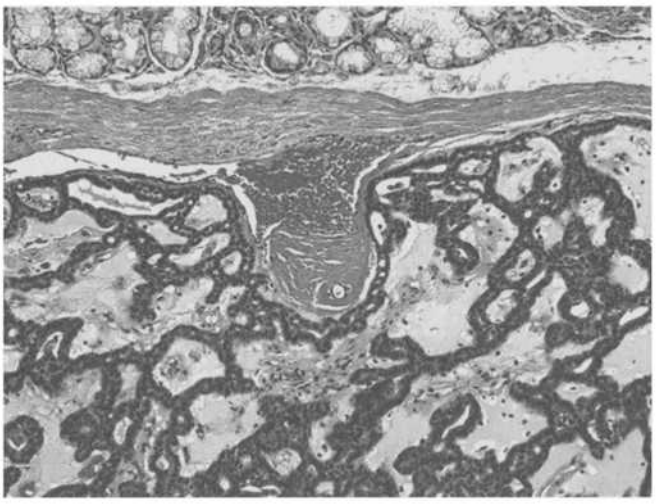


Fig. 13. Canalicular adenoma.

- Male : female ratio = 1.0 : 1.7
- Painless swelling

Macroscopic

- Circumscribed and encapsulated nodules (0.5 to 2 cm in size, mean 1.7 cm)
- Occasionally multinodular and multicentric
- Homogenous, tan, soft mass

*Microscopic (**Figures 12,13**)*

- Cords of columnar cells with abundant cytoplasm
- Loose vascular stroma
- Cystic and papillary projection

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Non-diagnostic
- Desmosomes, polysomes, and endoplasmic reticulum

Differential Diagnosis

- Basal cell adenoma: lacks columnar cell features
- Adenoid cystic carcinoma: lacks circumscription and vascularity
- Other benign adenomas
- Mucinous cystadenoma: mucin-lined cells

MALIGNANT EPITHELIAL TUMORS

Malignant Mixed Tumor

- "Malignant mixed tumor" is a generic term for malignancy associated with mixed tumors. The carcinoma ex pleomorphic adenoma is, by far, the most frequent. Carcinosarcoma, on the other hand, are few in number. Metastasizing pleomorphic adenoma is a disputed case
- Incidence: 3% to 12% of all malignancy and 2% of all salivary tumors

Carcinoma Ex-Pleomorphic Adenoma

Clinical

- Painless, rapidly growing mass
- 5% to 10% of pleomorphic adenomas, 11.6% of all malignant tumors
- Mainly major salivary glands: parotid (82%), submandibular (18%), sublingual (0.3%)
- Minor glands: palate, sinonasal tract
- Facial nerve paralysis (38%)
- Fixation to surrounding structure is common

Macroscopic

- Poorly circumscribed and infiltrative mass
- Variegated cut surface, soft to firm
- Hemorrhage and necrosis

*Microscopic (**Figures 14–16**)*

- Malignant features:
  - Cellular atypia, infiltrative growth, necrosis, hemorrhage, hyalinization, and calcification

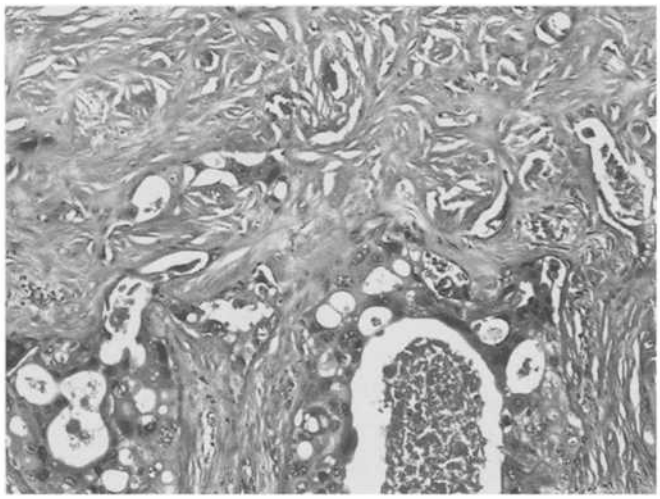


Fig. 14. Carcinoma Ex-Pa with salivary duct type comedonecrosis.

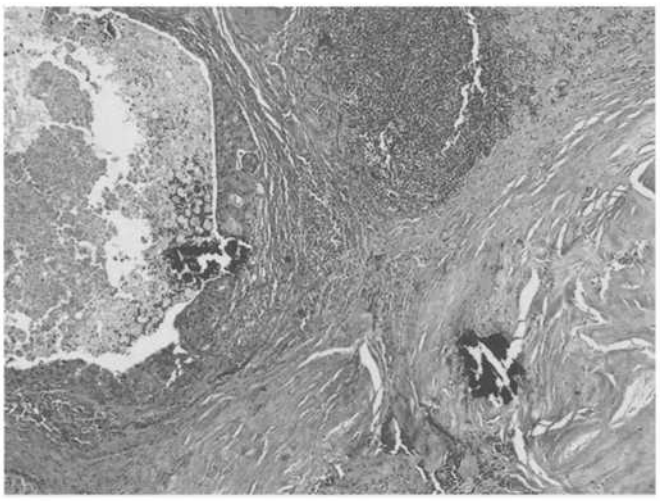


Fig. 15. Carcinoma Ex-PA, salivary duct phenotype.

Histologic Types

- Adenocarcinoma, NOS
- Squamous carcinoma
- Terminal duct carcinoma
- Undifferentiated carcinoma
- Mucoepidermoid carcinoma
- Salivary duct carcinoma

Subtypes

- Non-invasive (intratumoral carcinoma)
- Invasive

Immunohistochemistry

- Non-contributory

Differential Diagnosis

- Benign mixed tumors
- Carcinosarcoma

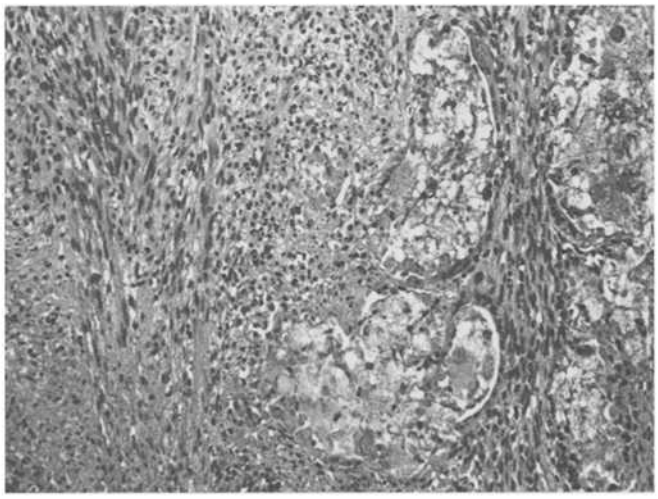


Fig. 16. Carcinoma Ex-PA, poorly differentiated.

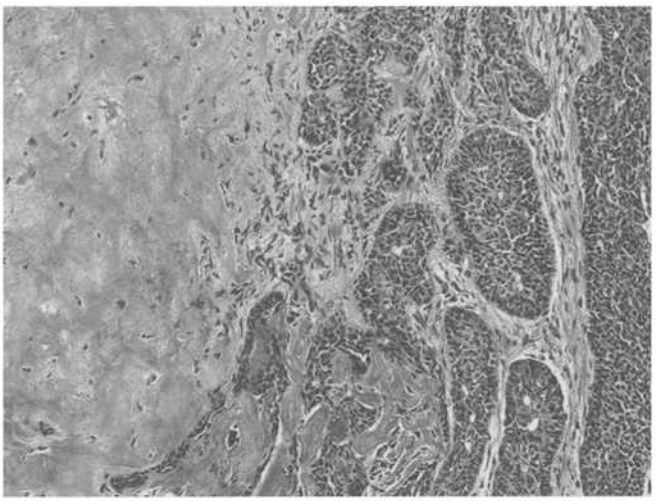


Fig. 17. Carcinosarcoma, anaplastic carcinoma and high grade sarcoma.

Carcinosarcoma (Concomitant Epithelial and Mesenchymal Malignancy)

Clinical

- Rapid onset
- Parotid is most common site
- Rare, 0.06% of salivary neoplasms and 0.16% of malignant tumors

Macroscopic

- Large mass, unencapsulated

Microscopic ***(Figure 17,18)***

- Infiltrative borders
- Biphasic epithelial and mesenchymal cells
- Malignant cellular features in both mesenchymal and epithelial components

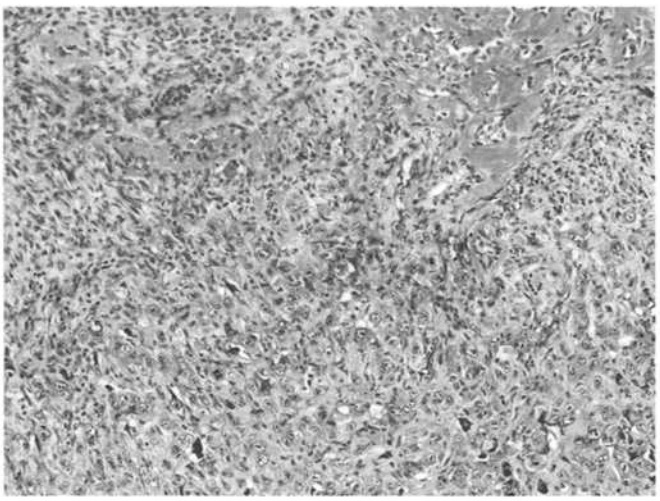


Fig. 18. Carcinosarcoma with osteoid formation.

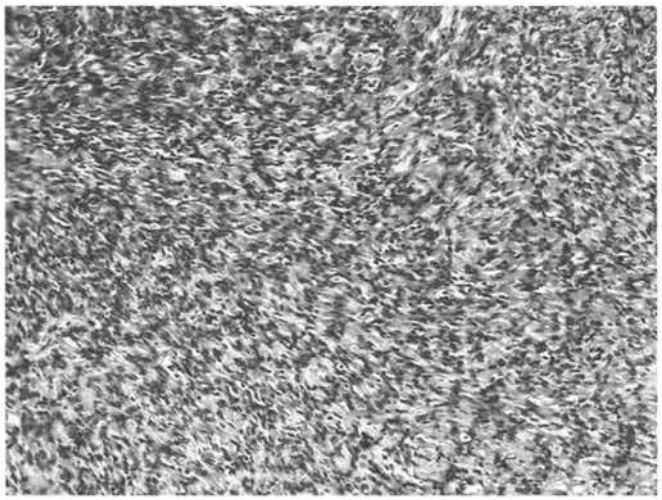


Fig. 19. Myoepithelial carcinoma with palisading features.

- Cellular pleomorphism and mitosis
- Adenocarcinoma, chondrosarcoma, osteosarcoma, malignant fibrous histiocytoma, and unclassified sarcoma may be seen

Immunohistochemistry

- Keratin+, EMA+, desmin+, SMA+

DNA Content

- High proliferation and DNA aneuploidy

Differential Diagnosis

- Spindle cell carcinoma: keratin+, desmin–, and SMA–
- Primary sarcoma: keratin–
- Synovial sarcoma: uniform spindle and glandular components

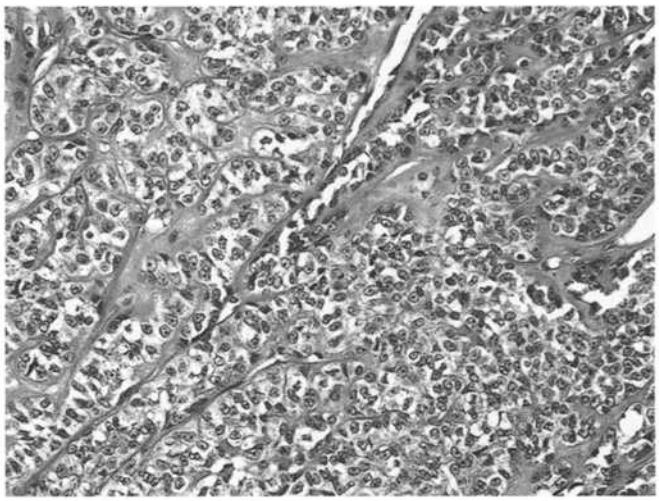


Fig. 20. Myoepithelial carcinoma, clear cell/epithelioid type.

Metastasizing Pleomorphic Adenoma

Clinical

- History of multiple recurrent pleomorphic adenoma
- Latent, average 16 years after primary excision

Microscopic

- Similar to benign mixed tumor

Macroscopic

- Non-encapsulated nodules

Differential Diagnosis

- Chrondroid hamartomas of lung: lacks myoepithelial cells
- Chondroid chordoma: usually afflicts vertebra; lacks duct component

Flow Cytometry

- Diploid with low proliferative activity

Myoepithelial Carcinoma

Clinical

- 0.2% of all epithelial neoplasms
- Parotid is most common site
- Male : female ratio = 1 : 1

Macroscopic

- Unencapsulated
- Hemorrhage, necrosis, and cystic degeneration

Microscopic ***(Figures 19–21)***

- Malignant spindle, plasmacytoid, clear, and epithelioid cells

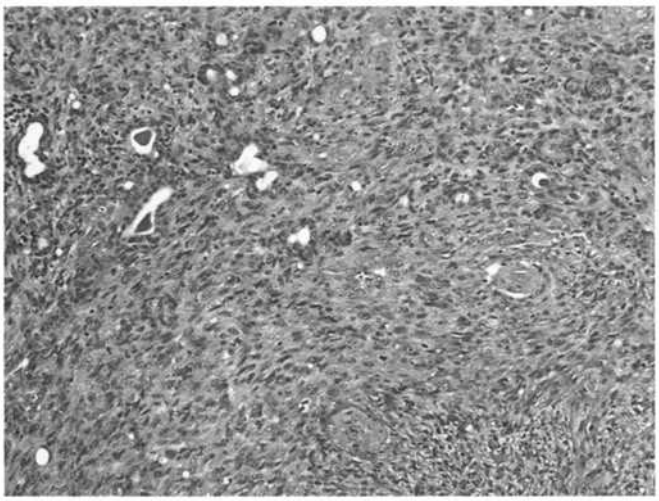


Fig. 21. Myoepithelial carcinoma with sarcomatoid features.

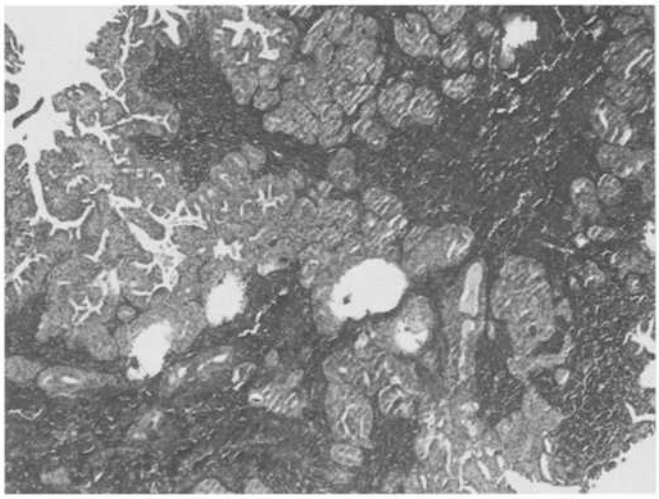


Fig. 22. Warthin's tumor with malignant transformation (upper left).

- Marked pheomorphism, mitosis, and necrosis
- Invasive borders

Immunohistochemistry

- S-100 protein and actin+, keratin+/–

Electron Microscopy

- Microfilaments with focal dense bodies
- Desmosomes and pinocytic vesicles

Flow Cytometry

- Abnormal DNA content (aneuploidy)

Differential Diagnosis

- Leiomyosarcoma: Keratin–, SMA+
- Nerve sheath tumor: S-100 protein+, keratin–
- Spindle cell carcinoma: keratin +, S-100 protein–
- Metastatic melanoma: HMB 45+, keratin–
- Synovial sarcoma: biphasic features

Oncocytic Carcinoma

Clinical

- Rare, 5% of all oncocytic tumors
- 0.005% of all epithelial neoplasms
- Major salivary glands; parotid is most common site
- Male : female ratio = 1 : 1; elderly patients
- Pain, paralysis ($^1/_3$ of patients)

Macroscopic

- Ill-defined, infiltrative mass; necrosis, hemorrhage

Microscopic

- Large cells with oncocytic cytoplasm
- Nuclear and cellular aytpia with pheomorphism, mitosis
- Vascular and soft tissue invasion

Immunohistochemistry

- Non-contributory

Special Stains

- Phosphotangestic acid hematoxylin stain (PTAH)+

Differential Diagnosis

- Oncocytoma:
  - Lacks invasion or cellular atypia
- Salivary duct carcinoma:
  - Cribriform and apocrine features; PTAH–

Carcinoma in Warthin's Tumors

Clinical

- Extremely rare
- Typically parotid or intraparotid lymph nodes
- Male : female ratio = 4.5 : 1
- Middle- and old-age individuals
- History of prior irradiation not uncommon

Macroscopic

- Solid, cystic, ill-defined mass; gray to light pink

Microscopic ***(Figure 22)***

- Oncocytic carcinoma, most common
- Squamous and adenocarcinoma, occasionally
- Undifferentiated carcinoma is rare

Immunohistochemistry

- Non-contributory

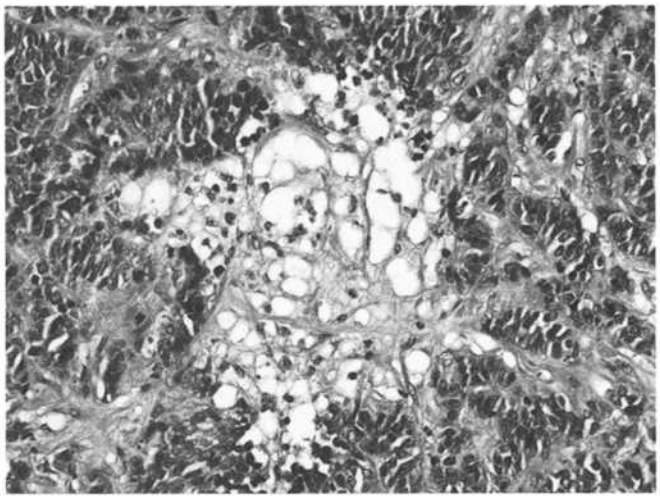


Fig. 23. Sebaceous carcinoma.

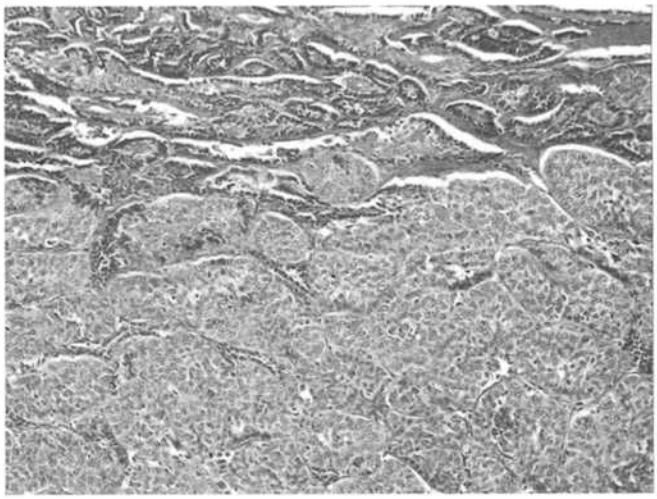


Fig. 24. Basal cell salivary adenocarcinoma Ex-monomorphic adenoma (low-power).

Differential Diagnosis

- Metastatic carcinoma:
  - History of primary tumor elsewhere
- Concomitant primary salivary gland tumor

Sebaceous Carcinoma

Types

- Sebaceous carcinoma
- Sebaceous lymphadenocarcinoma

Clinical

- Very rare; exclusively parotid
- Male : female ratio = 1 : 1
- Occasionally painful mass

Macroscopic

- Infiltrative, ill-defined mass
- Necrosis and hemorrhage

*Microscopic **(Figure 23)***

- Undifferentiated malignant cells with evidence of sebaceous differentiation
- Nerve invasion and soft tissue extension not infrequent

Special Studies

- Immunohistochemstry:
  - Lactoferrin+
- Electron microscopy:
  - Lipid vacuoles and glandular features

Differential Diagnosis

- High-grade salivary gland carcinoma:
  - Lacks any sebaceous features
- Adnexal skin tumors

Basal Cell Adenocarcinoma

Types

- De novo
- Carcinoma ex-basal cell adenoma

Clinical

- 2% of malignant epithelial tumors, 1.6% of all salivary tumors
- Mainly parotid, occasionally in submandibular and minor glands
- Male : female ratio = 1 : 1
- Adults average 60 years
- Swelling, occasional pain and tenderness

Macroscopic

- Unencapsulated but well-circumscribed mass
- Occasionally infiltrative
- Homogenous mass with tan, cut surface, rarely cystic

*Microscopic **(Figures 24,25)***

- Small, round-to-ovoid cells with dark hyperchromatic nuclei and scant cytoplasm
- Peripheral palisading
- Minimal nuclear atypia
- Mitotic figures: 1 to 10/10 HPF
- Focal squamous metaplasia (25%)
- Infiltrative growth
- Perineural invasion (30%), vascular invasion (20%)

Special Studies

- Non-contributory

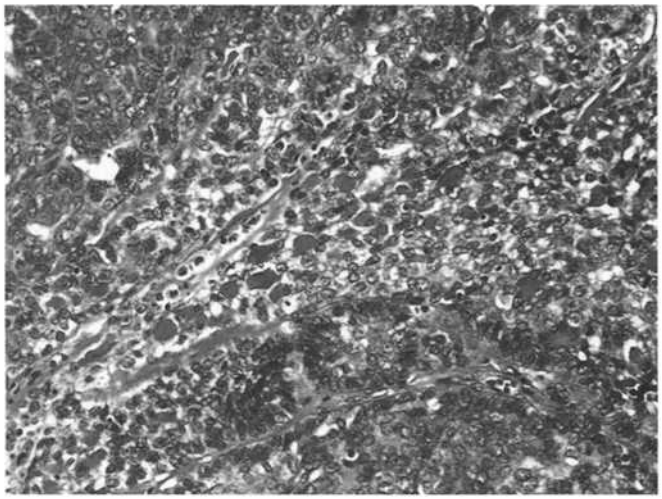


Fig. 25. Basal cell salivary adenocarcinoma.

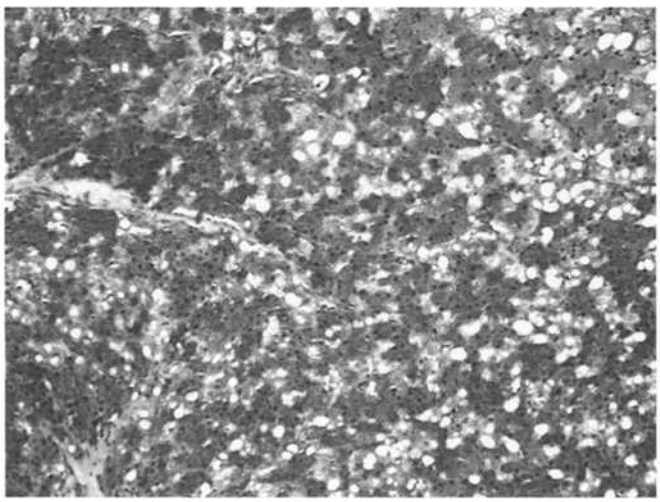


Fig. 26. Acinic cell carcinoma, classic form.

Differential Diagnosis

- Basal cell adenoma:
  - Lacks invasive features
- Basal cell carcinoma of skin:
  - History of BCC
- Solid adenoid cystic carcinoma:
  - High-grade solid areas with foci of cribriform and tubular patterns
- Undifferentiated small cell carcinoma:
  - Neuroendocrine markers+
- Basaloid squamous carcinoma:
  - Comedo-necrosis, origin from dysplastic squamous epithelium

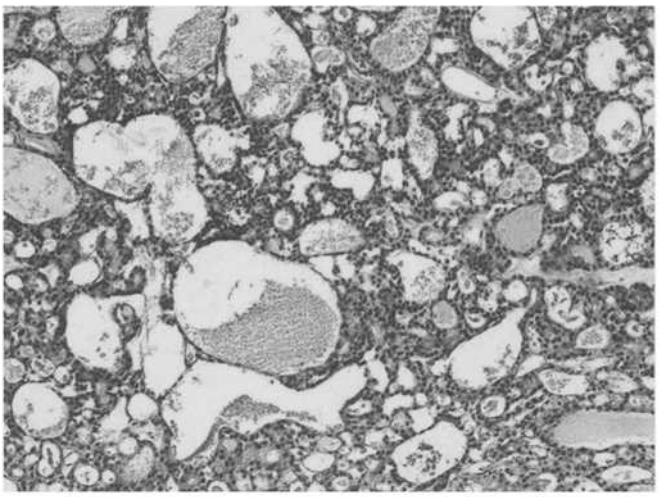


Fig. 27. Acinic cell carcinoma, microcystic form.

Acinic Cell Carcinoma (Table 6)

Clinical

- Parotid 99%, rarely in submandibular and oral cavity
- Ectopic: may present in middle and lower cervical lymph nodes

Macroscopic

- Circumscribed or infiltrative
- Homogenous mass with gray cut surface
- Multinodular

Microscopic ***(Figures 26–28)***

- Large cells with small, central nuclei
- Abundant basophilic cytoplasm with coarse granules
- Vacuolation and clear cytoplasm not uncommon
- Lymphoid infiltrate with germinal center

Electron Microscopy

- Three types of cells:
  - Ductal with few organelles and luminal microvilli
  - Serous with abundant granules
  - Undifferentiated

Special Stains

- Periodic acid schiff-diastase resistant granules

Immunohistochemstry

- Non-contributory

Differential Diagnosis

- Terminal duct carcinoma:
  - Most common in minor salivary glands
  - Perineural invasion

Table 6. Characteristics of Acinic Cell Carcinoma

Feature	*Frequency (%)*
Pattern	
Solid	50
Microcystic	30
Follicular	15
Papillary-cystic	5
Cell type	
Serous-acinar	75
Ductal	20
Vacuolated, clear	5
Male : Female	1:2
Incidence	
All parotid tumors	2–4
All parotid malignancies	12–17
Bilaterality	3
Local recurrence	45
Metastasis	20

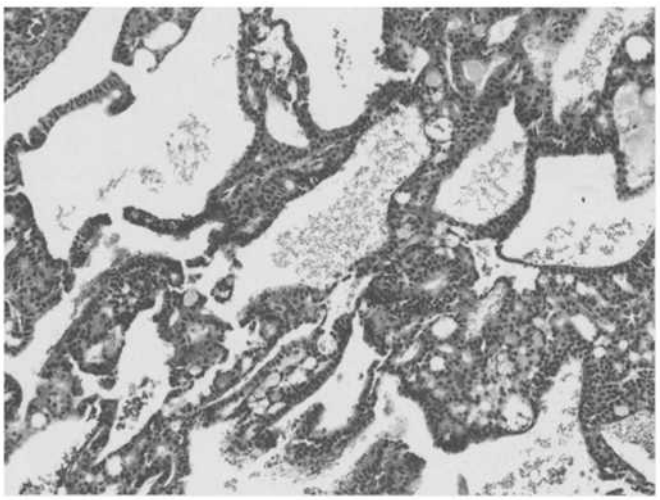


Fig. 28. Acinic cell carcinoma, macrocytic form.

- Variegated patterns
- Uniform cell populations

♦ Tumors with clear cell features:

- Mucoepidermoid carcinoma: epidermoid features, mucinous and intermediate cells, and glandular formation

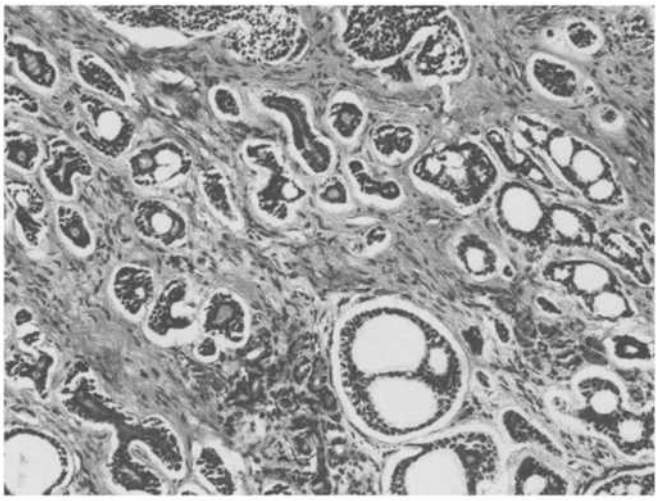


Fig. 29. Adenoid cystic carcinoma, predominantly tubular type.

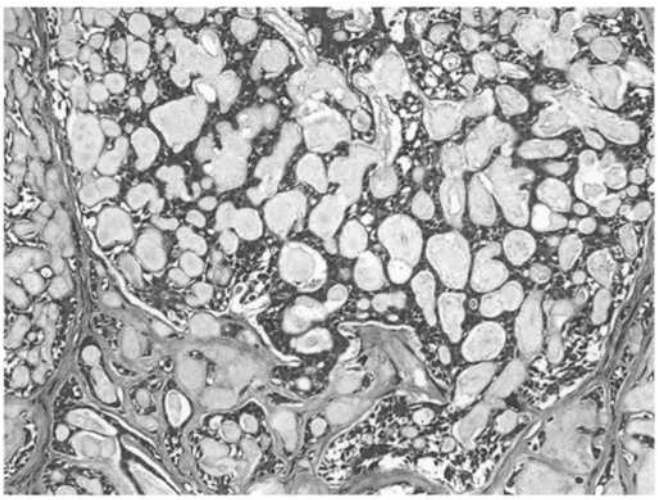


Fig. 30. Adenoid cystic carcinoma, cribriform-type.

- Metastatic renal cell carcinoma: vascular, history of RCC
- Epi-myoepithelial carcinoma: ductal and myoepithelial cells, S-100 protein+

♦ Tumors with papillary features:

- Cystadenocarcinoma: mucin+
- Metastatic papillary thyroid carcinoma: thyroglobulin+, nuclear inclusion

Adenoid Cystic Carcinoma

Clinical

♦ 6.5% to 10% of all epithelial salivary gland tumors, 2% to 4% of parotid tumors, 15% of submandibular tumors, and 30% of minor gland tumors

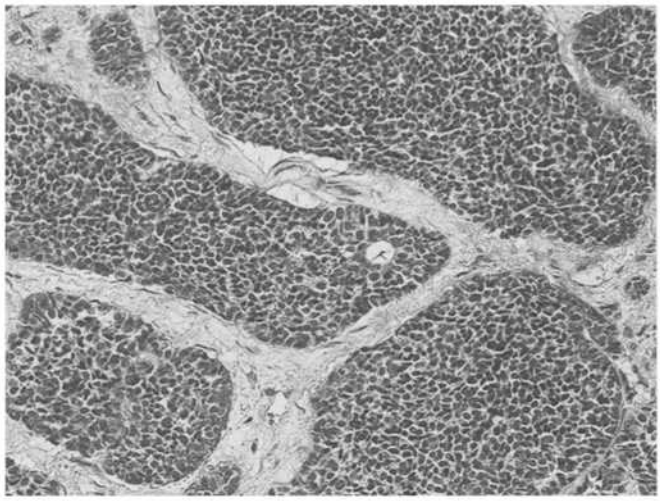


Fig. 31. Adenoid cystic carcinoma, solid type.

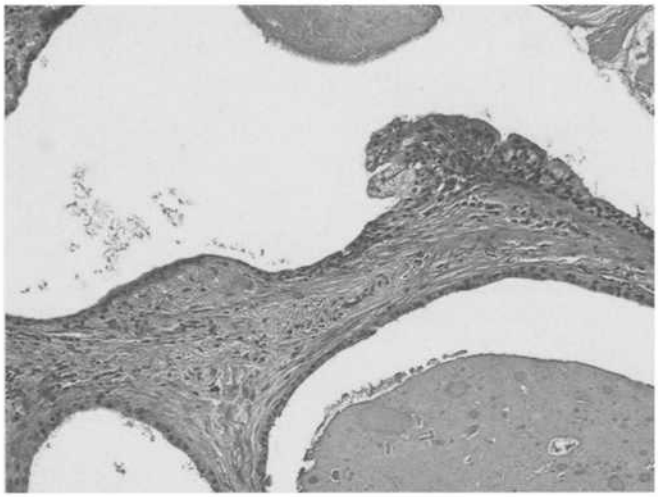


Fig. 32. Mucoepidermoid carcinoma, low-grade cystic.

- Slightly more in women, in submandibular gland
- Slowly growing mass
- Pain in approximately 18% of patients
- Facial nerve paralysis in 4% of cases

Macroscopic

- Circumscribed, but uncapsulated, size 1.5 to 4 cm
- Firm, monolobular mass
- Gray and homogenous cut surface

Microscopic

- Features and grades:
  - Tubular form **(Figure 29)**:
    - Low grade
    - Monotonous cellular features, two cell types
  - Cribriform, cylindromatous **(Figure 30)**:
    - Intermediate grade
    - Tumor nests with "sieve-like" or "Swiss cheese" configuration
    - Pseudoglandular spaces with hyaline materials
  - Solid **(Figure 31)**:
    - Nests of basaloid high-grade tumor cells
    - Focal areas of tubular and cribriform patterns
    - Hyalized stroma, mucinous, and myxoid forms may be present

Immunohistochemistry

- Ductal cells: CEA, EMA, and keratin+; S-100 protein and SMA–
- Myoepithelial cells: SMA+, S-100 protein and keratin+

Flow Cytometry

- DNA aneuploid and high S-phase tumors, aggressive



Fig. 33. Mucoepidermoid carcinoma, sclerotic type.

Cytogenetics

- Translocation of t(6;9) chromosomes

Differential Diagnosis

- Terminal duct carcinoma:
  - Variegated patterns, but no high-grade solid type
- Basal cell adenoma:
  - One cell type, lacks infiltration
- Basaloid squamous carcinoma:
  - Squamous differentiation, necrosis, origin from squamous dysplasia
- Small-cell undifferentiated carcinoma:
  - Immunostaining positivity to neuroendocrine markers and EM granules

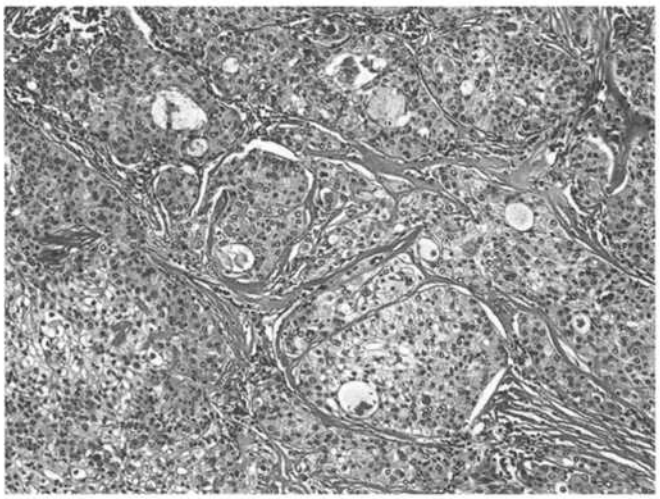


Fig. 34. Mucoepidermoid carcinoma, intermediate-grade.

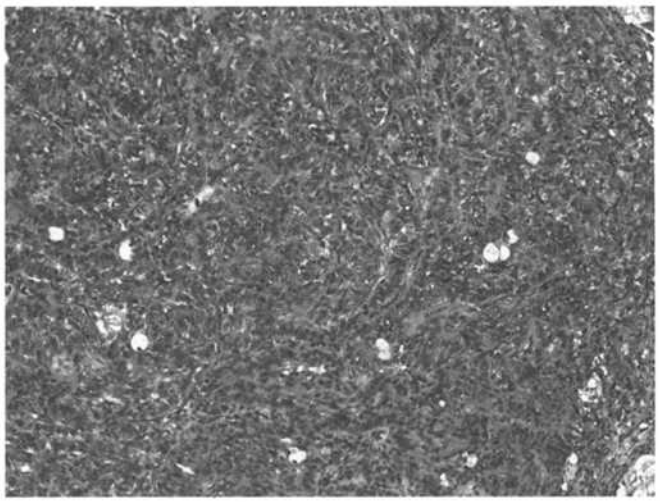


Fig. 35. Mucoepidermoid carcinoma, high grade.

- Poorly differentiated mucoepidermoid carcinoma:
  - Mucin +, epidermoid features

Mucoepidermoid Carcinoma

Clinical

- Most common malignant tumor, 15.5% of all salivary tumors
- Parotid 60% to 70%, oval cavity 15% to 20%, submandibular 6% to 10%
- Most common malignancy in children
- May present in mandible and paraparotid lymph node
- Average time to diagnosis: 6.8 years in low-grade tumors, 1.5 years in high-grade tumors

Macroscopic

- Low grade: well-circumscribed, cystic, and mucoid, rarely exceed 3.0 cm
- Intermediate and high grades: poorly circumscribed, infiltrative, and solid

Microscopic

- Grade I **(Figure 32)**:
  - Macro- or microcystic
  - Mucin-producing cells abundant
  - Lack of pleomorphism and mitosis
  - Broad borders
  - Mucin pools
  - Sclerotic form **(Figure 33)**
- Grade II **(Figures 34,35)**:
  - No cyst formation
  - Intermediate cells with or without epidermoid features
  - Moderate nuclear pleomorphism
  - Invasive borders
  - Inflammation and fibrosis
- Grade III:
  - Rare mucin cells
  - Poorly differentiated epidermoid and glandular components
  - Cellular pleomorphism
  - Invasive border

Immunohistochemistry

- Rarely required
- Proliferation markers, elevated in high grade

Cytogenetics

- Deletion of -5q

Differential Diagnosis

- Benign mixed tumors with squamous differentiation:
  - Stroma of mixed tumor and myoepithelial cells
- Squamous cell carcinoma:
  - Keratinization; lacks intermediate and mucinous cells
- Necrotizing sialometaplasia:
  - Preservation of lobular pattern; lacks malignant cellular features

Salivary Duct Carcinoma (Tables 7,8)

Clinical

- Swelling and mass formation is common presentation

Macroscopic

- Poorly demarcated and infiltrative
- Light tan and firm

Table 7. Clinicopathologic Characteristics of Salivary Duct Carcinoma

Feature	*Frequency (%)*
Percent of:	
All epithelial neoplasms	0.2
All malignant tumors	0.5
Parotid malignancy	1–6
Male : Female	4:1
Age	27–83 (Median 63 y)
Site	
Parotid	83
Submandibular	12
Minor glands	5
Lymph node metastasis	57
Died of Disease	53

Table 8. Differential Clinicopathologic Characteristics Between Terminal Duct Carcinoma (TDC) and Salivary Duct Carcinoma (SDC)

Category	*TDC*	*SDC*
Sex		
Male : Female	1:2	4:1
Age		
Range	23–79	27–83
Mean	(49)	(64)
Salivary Gland Site	Palate (65.5%)	Parotid (83.3%)
Behavior		
Recurrence	(12%)	55%
Cervical node metastasis	(10%)	66%
Distant metastasis	0	66%
	1.4%	70%

Modified from Batsakis & Luna, 1989

*Microscopic **(Figures 36–38)***

- Intraductal and infiltrative features, mimics mammary duct carcinoma:
  - Intraductal: comedo, cribriform, and solid forms

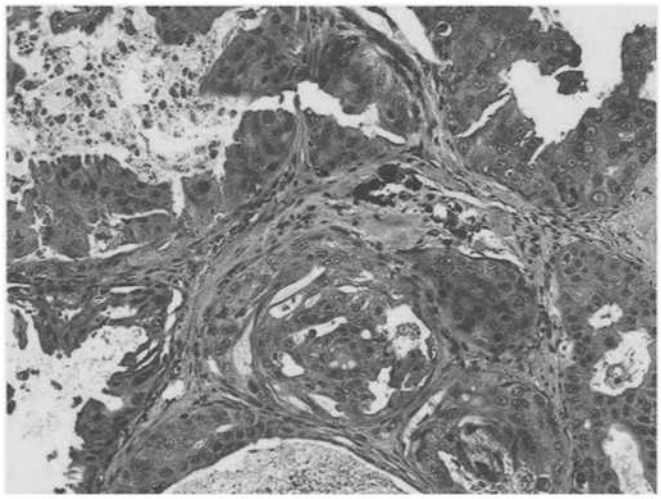


Fig. 36. Salivary duct carcinoma, cystic with roman bridge features.

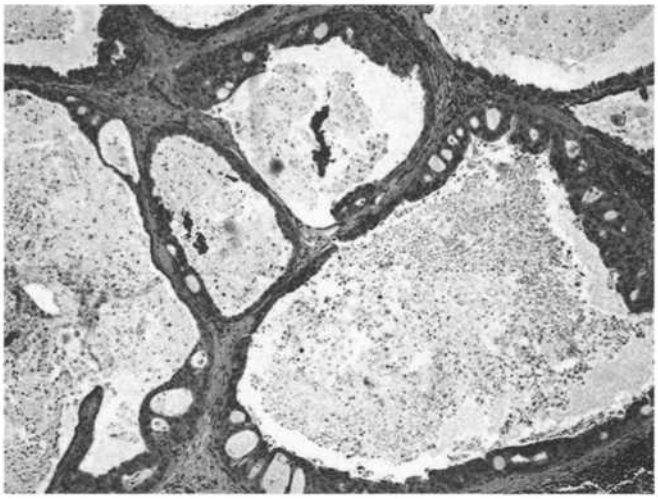


Fig. 37. Salivary duct carcinoma, ductal with comedo-formation.

- Desmoplasia and hyalinization in invasive tumors
- Lacks myoepithelial and epidermoid cells
- Vascular and neural permeation not uncommon
- Goblet cells may be seen

Special Studies

- Mucin: generally negative
- Immunostaining: non-contributory
- Ki-67: high-growth fraction
- Estrogen receptor: typically negative
- Progesterone receptor: occasionally positive
- Flow cytometry: predominantly DNA aneuploid with elevated S-phase

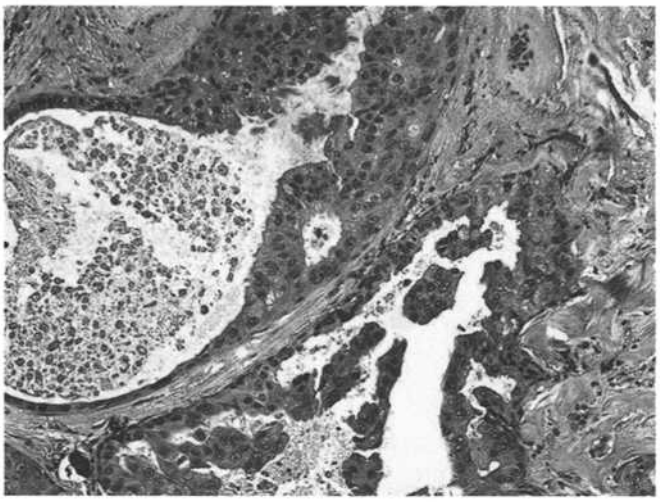


Fig. 38. Salivary duct carcinoma, papillary formation.

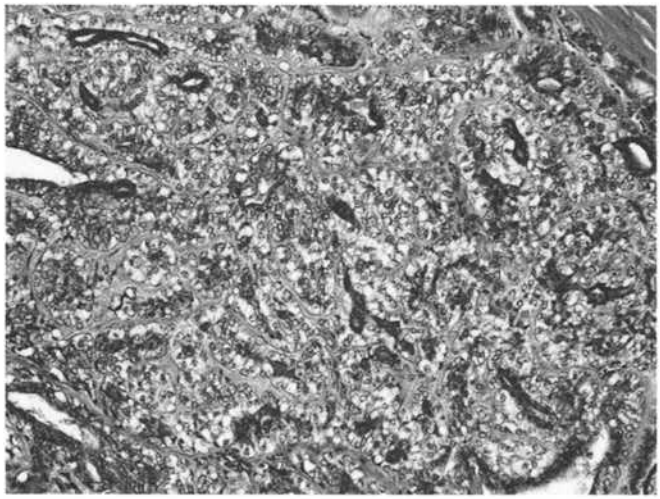


Fig. 39. Epi-myoepithelial carcinoma, low-power.

Differential Diagnosis

- Mucoepidermoid carcinoma:
  - Lacks cribriform and intraductal component
  - Shows intermediate and epidermoid cells, contains goblet cells
- Acinic cell carcinoma:
  - Monotonous cells, no intraductal features
  - Lacks comedo-necrosis, characteristic granules
- Oncocytic carcinoma:
  - Large cells with granular cytoplasm, no papillary or cribriform features
- Mucin-producing adenopapillary carcinoma:
  - Columnar, goblet, and signet-ring cells
  - Lacks comedo-necrosis and intraductal component

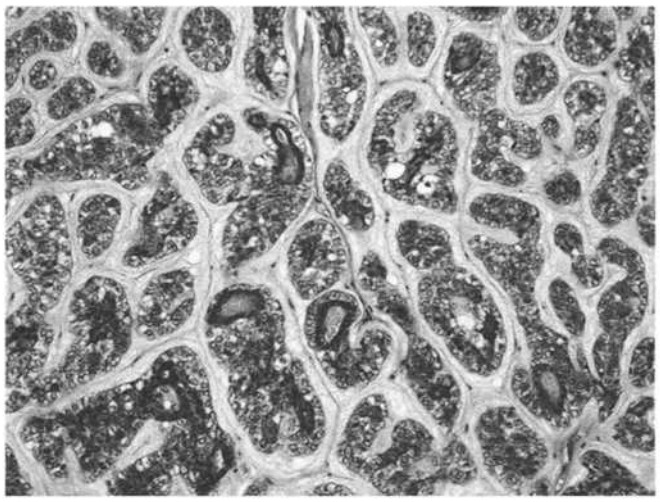


Fig. 40. Epi-myoepithelial carcinoma, high-power.

- Metastatic breast carcinoma:
  - Most challenging differential diagnosis:
    - Female predominance
    - History of breast carcinoma

Epithelial-Myoepithelial Carcinoma

Clinical

- 1% of all salivary tumors
- Predominantly major glands: parotid 75%, submandibular and minor glands 25%
- Male : female ratio = 1 : 2
- Painless mass

Gross Findings

- Solitary, well-defined, circumscribed or lobulated, gray mass
- Size ranges from 2 to 8 cm
- Recurrent tumors: lobulated, ill-defined borders with necrosis

Microscopic ***(Figures 39,40)***

- Variable intra- and intertumoral patterns
- Dual cell layers: inner ductal and outer myoepithelial cells
- Ductal cells: cuboidal or columnar with eosinophilic cytoplasm
- Myoepithelial cells: ovoid with abundant clear cytoplasm surrounded by basal materials

Special Stains

- Mucin–
- PAS diastase resistant+

Immunohistochemistry

- Myoepithelial cells: SMA+, S-100 protein+, keratin weakly–
- Ductal: keratin+

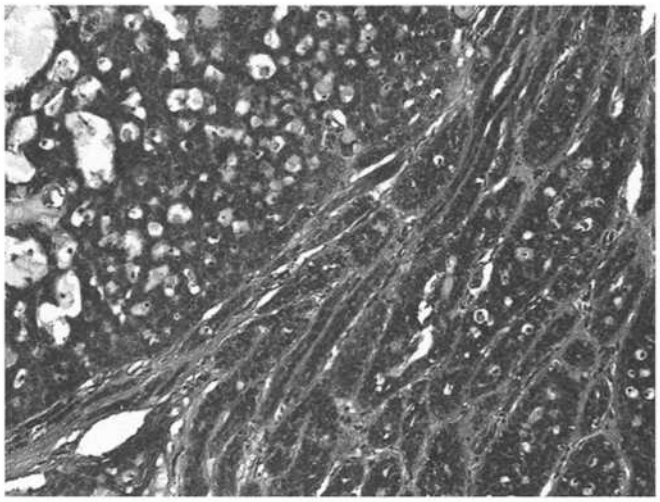


Fig. 41. Polymorphous low-grade adenocarcinoma, tubular and cribriform patterns.

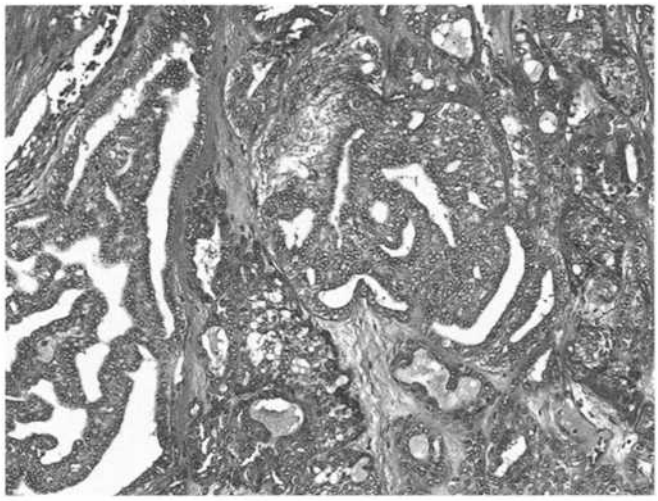


Fig. 42. Polymorphous low-grade adenocarcinoma, cystic and tubular form.

Differential Diagnosis

- Mucoepidermoid carcinoma:
  - Lacks dual cellular composition; cystic features in low grade
- Acinic cell carcinoma:
  - Clear cell type, PAS+, diastase+, characteristic basophilic granules
- Sebaceous carcinoma:
  - Fat stain+, occasional squamous differentiation
- Metastatic renal cell carcinoma:
  - High vascularity, necrosis, history of renal cell carcinoma

Terminal Duct Carcinoma (Polymorphous Low-Grade Adenocarcinoma)

Clinical

- Incidence: 7.4% of all minor salivary gland tumors, 19.6% of malignant tumors
- Hard palate is most common site **(Table 8)**
- Occurs occasionally in major salivary gland

Macroscopic

- Small, lobulated mass
- Yellow-tan and firm

*Microscopic **(Figures 41–43)***

- Uniform cytology, but heterogeneous patterns
- Patterns: tubular, cribriform, papillary, solid, and fascicular features
- Mitosis, low; necrosis, rare
- Mucoid, hyaline, and mucohyaline stroma
- Perineural invasion common

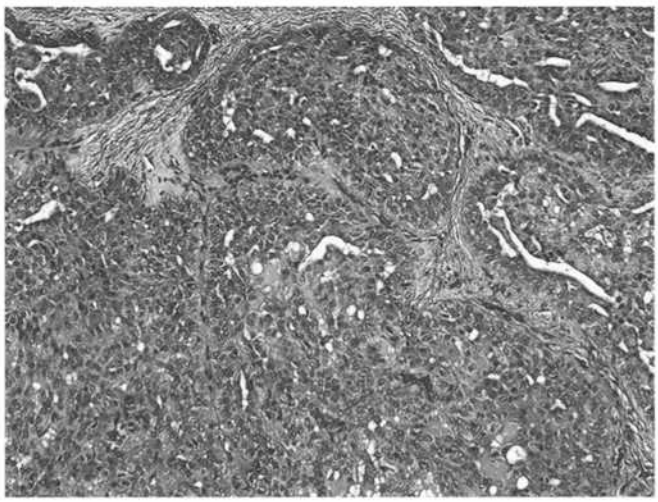


Fig. 43. Polymorphous low-grade adenocarcinoma, solid pattern.

Immunohistochemistry

- Non-contributory

Differential Diagnosis

- Pleomorphic adenoma:
  - Epithelial and stromal elements
- Basal and canalicular adenomas:
  - Well-circumscribed
  - Uniform basal or columnar cellular pattern
- Adenoid cystic carcinoma:
  - Most difficult differential diagnosis, especially in low-grade tumors
  - Lacks varied patterns of terminal duct carcinoma
  - Manifests cribriform and solid features
- Salivary duct carcinoma: see **Table 8**

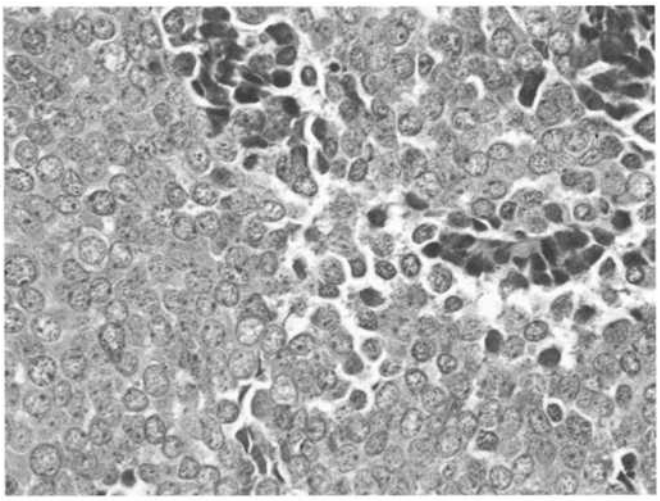


Fig. 44. Small cell neuroendocrine carcinoma.

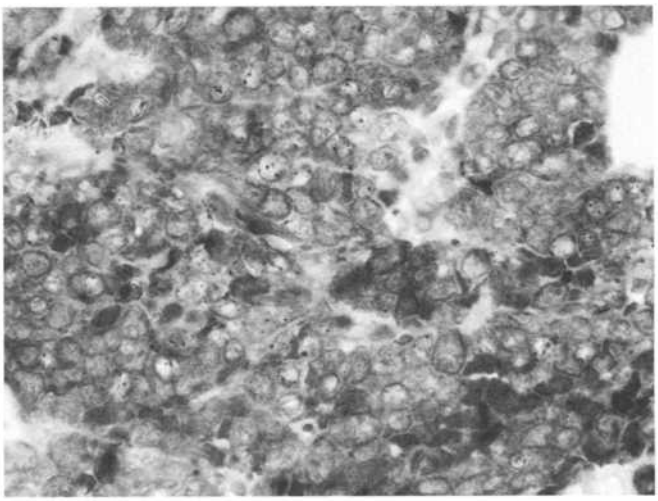


Fig. 45. Positive synaptophysin staining in small-cell carcinoma.

Primary Squamous Cell Carcinoma

Clinical

- 0.9% to 4.7% of all malignancies; parotid gland 0.3% to 1.5% and submandibular 2.4% to 7.0%
- Male : female ratio = 3 : 1
- Symptoms: Mass (50%), pain (33%), nerve paralysis (17%)

Macroscopic

- Infiltrative, ill-defined, and firm mass
- Necrosis not uncommon

Microscopic

- Well to poorly differentiated squamous cells with keratinization
- Dysplastic ductal epithelium may be found

Differential Diagnosis

- Metastatic squamous cell carcinoma:
  - Circumscribed nodule within gland
  - History of squamous carcinoma
- Mucoepidermoid carcinoma:
  - Mucin-producing cells
  - Lacks keratinization
- Necrotizing sialometaplasia:
  - Lobular preservation of salivary structure
  - Lacks atypia and keratinization

Undifferentiated Carcinoma

- 1% to 30% of epithelial malignancy

Types

- Small cell, neuroendocrine
- Large cell, neuroendocrine
- Undifferentiated carcinoma with lymphoid stroma (lymphoepithelial carcinoma)

Differential Diagnosis

- Metastasis:
  - Merkel cell carcinoma: history of Merkel cell carcinoma, keratin nodular+, CK20+
  - Basal cell carcinoma: history of skin lesions
  - Solid adenoid cystic carcinoma: focal tubular and cribriform patterns

Small Cell Carcinoma

Clinical

- Very rare: 1.7% of malignant parotid tumors, 2.2% of malignant submandibular tumors
- Mainly parotid; male : female ratio = 6 : 1

Macroscopic

- Light tan and soft nodule

Microscopic ***(Figures 44–46)***

- Identical to small cell carcinoma of lung

Immunohistochemistry

- Keratin (dot-like), synaptophysin, and chromogranin+

Electron Microscopy

- Rare neurosecretory granules

Differential Diagnosis

- Lymphoma:
  - Keratin–, leukocyte common antigen (LCA)+
- Adenoid cystic carcinoma, solid type:
  - Tubular and cribriform components may be present
  - Negative staining for neuroendocrine markers
- Merkel cell carcinoma:
  - History of primary tumor
  - Keratin immunostaining (CK 20+)

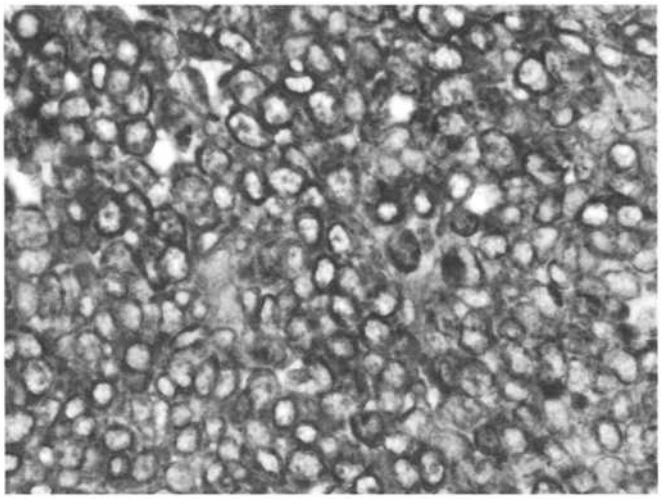


Fig. 46. Pan-keratin cytoplasmic staining in small cell carcinoma.

Large Cell Carcinoma

Clinical

- Predominantly parotid

Microscopic

- Cells larger than small cell carcinoma
- Abundant cytoplasm
- Cords and nests may be seen

Immunohistochemistry

- Keratin+, LCA–
- Neural markers occasionally+

Differential Diagnosis

- Melanoma:
  - S-100 protein and HMB-45+, keratin–
- Undifferentiated carcinoma:
  - Neuroendocrine markers+, keratin+

Lymphoepithelial Carcinoma (Table 9)

Clinical

- 0.4% of all salivary gland tumors
- Male : female ratio = 1.5 : 1
- Evidence of familial clustering
- Evidence of EBV-association

*Microscopic (**Figure 47**)*

- Indistinguishable from nasopharyngeal lymphoepithelial carcinoma
- Lymphoid content varies
- Occasional squamous differentiation
- Carcinoma demarcated from surrounding non-epithelial elements, epi-myoepithelial islands of lympho-epithelial lesions

Table 9. Site and Ethnic Distribution of Lymphoepithelial Carcinoma of Major Salivary Glands

Feature	*Incidence (%)*
Site	
Parotid	83.70
Submandibular	15.00
Unstated	1.25
Ethnicity	
Eskimo-Greenlander	52.50
Southern Chinese	20.00
White	11.25
Indian	2.50
Japanese	2.50
Black	2.50
Others	8.75

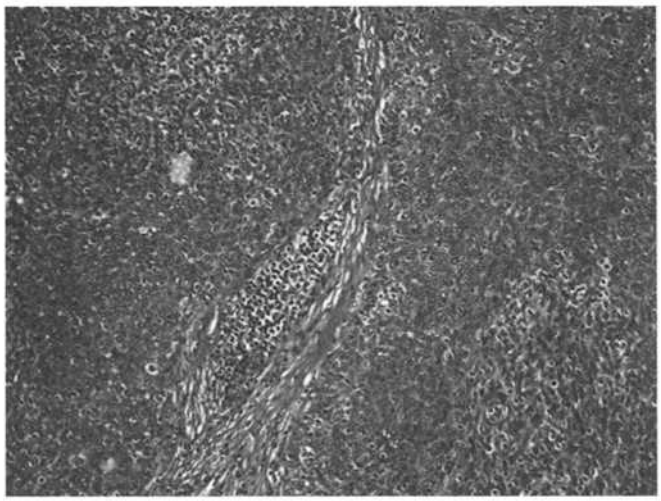


Fig. 47. Lymphoepithial carcinoma, undifferentiated carcinoma with lymphoid stroma.

Differential Diagnosis

- Metastasis from conventional sites

Rare Types of Adenocarcinoma

- Adenopapillary carcinoma
- Cystadenocarcinoma
- Adenosquamous carcinoma

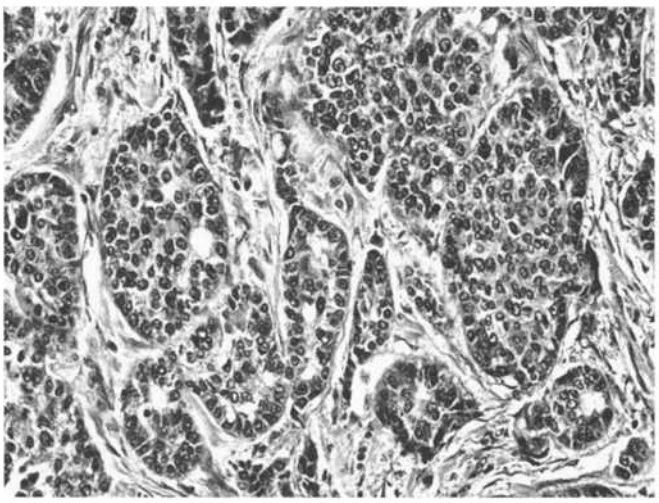


Fig. 48. Adenocarcinoma, not otherwise classified.

Table 10. Prognostic Factors in Salivary Gland Carcinomas

Favorable features	*Unfavorable features*
Low-grade histology	High-grade
Low stage	High stage
Parotid location	Submandibular gland site
	Cervical node metastasis
	Facial nerve paralysis
	Skin involvement
	Recurrence
	Radio- and chemoresistant

- Adenocarcinoma (NOS) not other wise classified (**Figure 48**):
  - Moderately differentiated adenocarcinoma
  - Lack any resemblance to know salivary gland carcinomas

Clinicopathologic Factors

- A number of clinicopathologic factors related to salivary gland carcinomas impact on the therapeutic outcome in patient prognosis. Clinical stage is probably the most important. Other factors are listed in **Table 10**. **Table 11 through 13** present recurrence, cervical lymph node metastases, and distant spread data for selected malignant salivary gland tumors

Table 11. Frequency of Local Recurrence in Salivary Gland Carcinomas

Diagnosis	*Recurrence (%)*
Squamous cell carcinoma	64
Undifferentiated carcinoma	64
Adenoid cystic carcinoma	61
Carcinoma ex-pleomorphic adenoma	60
Adenocarcinoma, NOS	48
Acinic cell carcinoma	15
Mucoepidermoid carcinoma	5

Table 12. Frequency of Lymph Node Metastasis by Diagnosis of Salivary Gland Carcinomas

Histology	*Metastasis (%)*
Mucoepidermoid carcinoma	44
Adenocarcinoma, NOS	36
Undifferentiated carcinoma	23
Carcinoma ex pleomorphic adenoma	21
Acinic cell carcinoma	13
Adenoid cystic carcinoma	5

Johns, 1989

Table 13. Frequency of Distant Metastasis by Diagnosis of Salivary Gland Carcinomas

Histology	*Metastasis (%)*
Adenoid cystic carcinoma	42
Undifferentiated carcinoma	36
Adenocarcinoma, NOS	27
Carcinoma ex pleomorphic adenoma	21
Squamous cell carcinoma	15
Acinic cell carcinoma	14
Mucoepidermoid carcinoma	9

IMMUNOHISTOCHEMISTRY

See **Tables 14, 15,** and **16**

Table 14. Immunohistochemical Analysis of Tumors with Myxohyalinized Stroma

Marker	*PA*	*ADCC*	*BCA*
GFAP	+	–	–
S-100	+	±	–
Keratin	±	+	+
SMA	±	+	+
Desmin	–	–	–

PA = Pleomorphic adenoma, ADCC = Adenoid cystic carcinoma, BCA = Basal cell adenoma

Table 15. Carcinoma with Basaloid Features

Markers	*Small cell*	*Adenoid cystic*	*Basaloid*
Keratin +	+	+	–
S-100	±	±	–
Chromogranin	+	–	–
SMA	–	±	–

SMA = Smooth muscleactin

Table 16. Immunohistochemistry in Differential Diagnosis of Salivary Gland Tumors with Clear Cell Features

Marker	*CCC*	*ME/MC*	*EMC*
CK	+	+	+
CK-CAM	+	+	+
CEA	±	–	+
EMA	+	±	+
S-100	–	+	+
SMA	–	+	+
MSA	–	+	+

CCC = Clear cell carcinoma, ME = Myoepithelioma, MC = Myoepithelial carcinoma, EMC = Epithelial-Myoepithelial Carcinoma, CK = Cytokeratin; CEA = Carcinoembryonic antigen, EMA = Epithelial membrane antigen, SMA = Smooth muscle actin, MSA = Muscle specific antigen

OTHER TUMORS

Primary Lymphomas of Salivary Gland (also see Chapter 9)

Clinical

- Rare (**Table 17**)
- Parotid:submandibular glands = 8 : 1
- Mainly older patients, 6th to 7th decade of life
- Intraparotid lymph node involvement staged as in cervical lymphoma

Microscopic

- Sclerosis, common in large type
- Small cell type arise in a background of benign lymphoepithelial lesions
- Plasmacytoma, very rare

Mesenchymal Tumors of Salivary Glands

- 5% of all tumors
- Both benign and malignant mesenchymal tumors affect children and adolescents (**Tables 18,19**)
- Location: mainly major salivary gland, especially the parotid glands
- Benign:
  - Types: angiomas, lipomas, neurofibromas, and hemangiopericytomas (**Figure 49**)
  - Incidence less than 5%
  - Except for neurofibroma, exclusively parotid in origin
  - Usually ill-defined lesions
  - Histologically identical to soft tissue counterpart

Table 17. Characteristics of Primary Salivary Gland Lymphoma

5% of all extranodal lymphomas
40% of all head and neck lymphomas
85% non-Hodgkin's B-cell origin ($^2/_3$ well-differentiated)
15% Hodgkin lymphoma, majority extranodal and parenchymal (MALT)

- Sarcoma:
  - Rare, infiltrative mass
  - Comparable microscopic characteristics to soft tissue counterparts

Salivary Gland Tumors in Children (Table 19)

General Features

- Comprise 5% of childhood tumors
- High incidence of benign non-epithelial tumors
- High incidence of epithelial malignancy
- Predominantly in parotid
- Vasoformative tumors, most common in neonates and infants
- Pleomorphic adenoma, mucoepidermoid, and acinic cell carcinomas in children between 10 and 16 years

Hemangioma

Clinical

- Most common postnatal tumor
- Commonly in girls with a left-side predilection
- Spontaneous involution not uncommon
- Angle of mandible common
- Recurrence uncommon
- 50% undergo spontaneous involution

Macroscopic

- Enlarged gland, purple-red and spongy

Microscopic

- Similar to other sites

Sialoblastoma (Embryoma)

Clinical

- Congenital or prenatal
- Newborn and first year of life
- Low-grade malignancy
- Major salivary glands
- 1.5 to 15 cm in size
- No gender preference
- Typically asymptomatic

Table 18. Primary Sarcomas of Major Salivary Glands

Characteristic		*Incidence*
Sex	Male : Female	12 : 1
Age	Range	10-91 years
	Mean	36 years
Site	Parotid	91.8
	Submandibular	8.2
Most frequent subtypes	Rhabdomyosarcoma	21.6
	MFH	16.2
	Fibrosarcoma	12.1
	Neurosarcoma	9.4
	Angiosarcoma	6.7
Recurrence		22.9
Metastasis		32.4
Died of disease (DOD)		36.4

Modified from Luna, et al., 1991

Macroscopic

- Well-circumscribed, encapsulated, and lobulated mass
- Yellowish, tan and firm

Microscopic ***(Figures 50,51)***

- Primitive basaloid cells, resembling primitive epithelium
- Focal sebaceous differentiation occasionally
- Peripheral palisading is common
- Necrosis, perineural, or vascular invasions are not uncommon

Immunohistochemistry

- Non-contributory

Electron Microscopy

- Primitive features, free ribosomes, sparse endoplasmic reticulum

Differential Diagnosis

- Basal cell adenoma:
  - Less primitive cells, less mitotic activities, and primitive stroma
- Adenoid cystic carcinoma and basal cell adenocarcinoma are very rare in this age

Table 19. Histologic Types of Salivary Gland in Children Under 16 years of Age

Epithelial (Total #394)	*Incidence (%)*	*Mesenchymal (Total #274)*	*Incidence (%)*
Benign (50%)		**Benign (93.8%)**	
Pleomorphic adenoma	46	Hemangioma	69.7
Embryoma	2	Lymphangioma	17.5
Warthin's tumor	0.70	Neurogenic	4
Cystadenoma	0.70	Lipoma	1.5
Lymphoepithelial lesions	0.70	Xanthoma	0.7
Monomorphic adenoma	0.25	Fibromatosis	0.7
Malignant (50%)		**Malignant (6.2%)**	
Mucoepidermoid carcinoma	27.3	Sarcoma	5.5
Acinic cell carcinoma	6.8	Ganglioneuroblastoma	0.4
Adenocarcinoma	5.6		
Undifferentiated carcinoma	3.8		
Adenoid cystic carcinoma	2.8		
Carcinoma	2.3		
Ex-pleomorphic adenoma	1		
Squamous cell carcinoma	0.25		
Unclassified carcinoma			

Modified from Luna et al., 1998

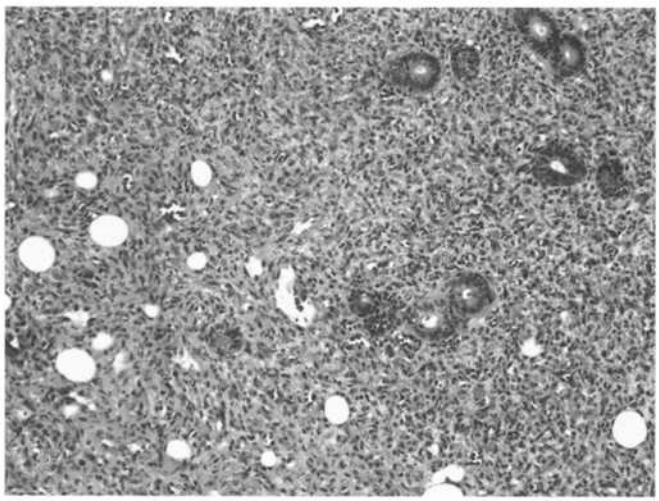


Fig. 49. Hemangiopericytoma.

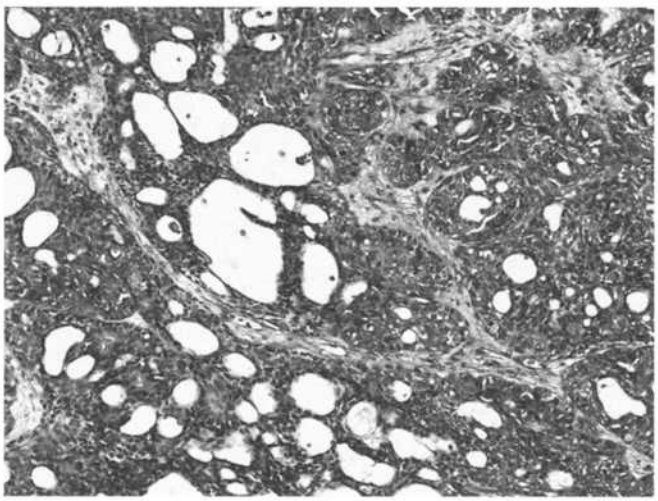


Fig. 50. Sialobastoma.

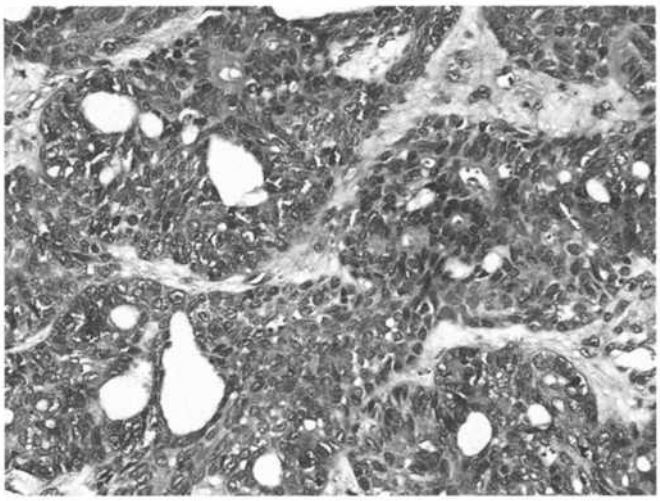


Fig. 51. Sialoblastoma.

Table 20. Infraclavicular Primary Malignancy and Parotid and Parotid Node Metastasis

Primary	*Incidence (%)*
Lung	34.3
Kidney	31.4
Breast	11.4
Colorectal	11.4
Others	11.4

Malignant Epithelial Tumors

- Mucoepidermoid and acinic cell carcinomas account for 60% of salivary gland malignancy in children
- Adenoid cystic carcinoma, adenocarcinoma, and undifferentiated carcinomas are very rare in this age

Metastasis to Salivary Gland (Tables 20–23)

- Routes: lymphatic, hematogenous, local spread (sarcomas of the facial bones or soft tissue and skin cancer)

Table 21. Metastasis to Major and Minor Salivary Glands

Site	*Incidence (%)*
Intraoral Minor	85.7
Parotid	7.1
Submandibular	8.7
Submandibular space	1.5

Table 22. Supraclavicular Primary Tumors with Metastasis to Parotid Gland and Intraparotid Lymph Nodes

Site	*Diagnosis*	*Incidence (%)*
Skin & mucous membrane	Squamous carcinoma	68.9
	Melanoma	25.3
Nasopharynx	Carcinoma	4.9

Table 23. Metastatic Malignancy From Infraclavicular Primary to Submandibular Gland

Primary	*Incidence (%)*
Breast	38.9
Lung	27.7
Kidney	22.3
Other	11.1

- Parotid metastasis: lymphatic and hematogenous
- Submandibular gland metastasis rare
- Parotid is the most common site because of lymphatic content

TUMOR-LIKE AND CYSTIC LESIONS

Tumor-Like Lesions (Table 24)

Sialolithiasis

- Predominantly in submandibular gland
- Undulant and tender swelling
- Parotid less frequent and difficult to diagnose clinically

Table 24. Tumor-Like Lesions of Salivary Glands

Sialolithiasis	Salivary gland cysts (Table 14–27)
Sialadenitis	Chronic sclerosing sialadenitis of submandibular gland (Küttner tumor)
Sialadenosis	Cystic lymphoid hyperplasia in AIDS
Oncocytosis	Inflammatory pseudotumors
Necrotizing sialometaplasia	Others, nodular fasciitis, sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), Wegener's granulomatosis
Benign lymphoepithelial lesions and Sjögrens Syndrome	

Modified from WHO Classification

Microscopic

- Dilated ducts
- Squamous metaplasia
- Acinar atrophy and inflammation

Sialadenitis

- Acute and chronic non-specific inflammation:
  - Bacterial: Staphylococcus aureus
  - Viral: cytomegalovirus, paramyxovirus, Epstein-Barr virus, para and influenza viruses, and coxackievirus
- Granulomatous:
  - Obstructive sialadenopathy:
    - Ruptured mucoceles
    - Extravasated mucin
  - Infectious:
    - Myobacterial, cat-scratch, disease, tularemia, fungal, toxoplasmosis, and other
  - Sarcoidosis
  - Associated with systemic disease:
    - Wegener's granulomatosis, Crohn's disease, and others
  - Associated with salivary gland tumor:
    - Acinic cell carcinoma
    - Mucoepidermoid carcinoma
    - Warthin's tumor
    - Lymphoepithelial lesions
  - Foreign body granulomas:
    - Iatrogenic (sialography)

Sialadenosis

- Hypertrophy and hyperplasia of acini
- Associated with systemic and neural disorders
- Presents as bilateral painless and recurrent swelling
- Etiology: neurogenic, metabolic, or hormonal

Oncocytosis (Figure 52)

- Oncocytic hyperplasia of ductal and acinar structure
- Unilateral or bilateral enlargement
- Preservations of lobular architecture
- Old age

Necrotizing Sialometaplasia

Clinical

- Benign self-limiting reactive inflammatory process
- Sites: palate, 81.7%; other oral sites, 7.0%; major glands 7.8%; and other. 3.5%
- Age: 40–60 years
- More men than women
- Uncertain etiology (vascular orgin?)

Macroscopic

- Mucosal site, ulceration, and painful swelling
- Non-ulcerated: $^1/_3$ of lesions

Microscopic (Figure 53)

- Lobular distribution
- Central ductal squamous metaplasia
- Peripheral necrotic and inflamed acini

Differential Diagnosis

- Squamous carcinoma:
  - Infiltrative, keratinization, cellular features of malignancy
  - Lacks lobular preservation
- Mucoepidermoid carcinoma:
  - Mucinous cells, infiltrative intermediate cells, and cystic formations

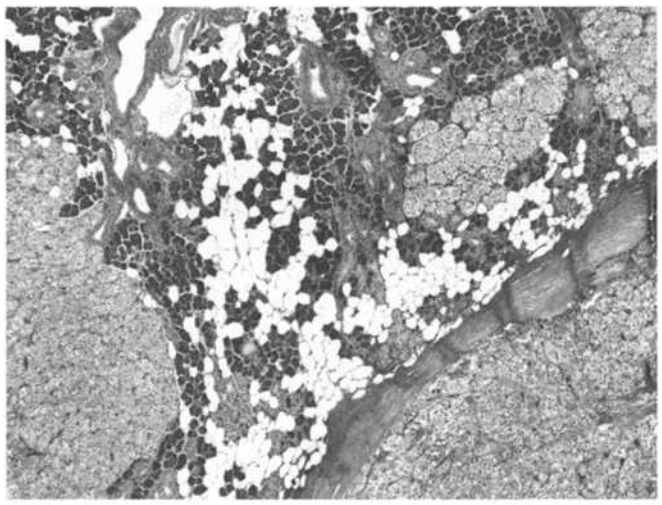


Fig. 52. Oncocytosis, multifocal ococytic hyperplasia.

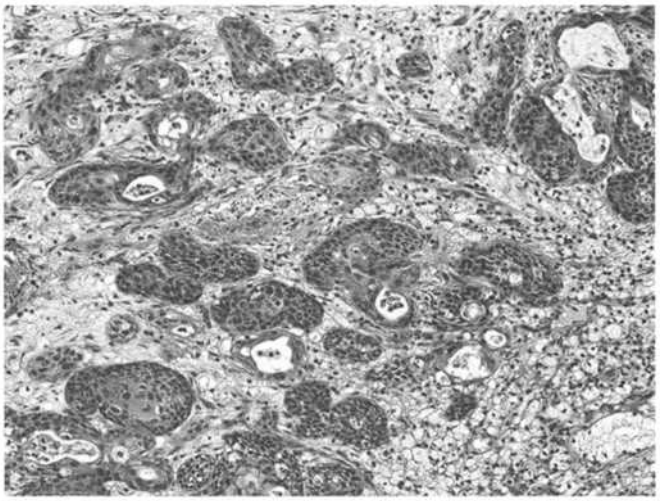


Fig. 53. Necrotizing sialometaplasia.

Benign Lymphoepithelial Lesions and Sjögren's Syndrome

Clinical

- Idiopathic, autoimmune disease, HIV infection
- Localized, systemic
- Older women
- Recurrent painful swelling
- The minor salivary glands rarely affected

Microscopic ***(Figure 54)***

- Focal periductal lymphoid proliferation
- Partial or total obliteration of acinar structure
- The lobular architecture is retained

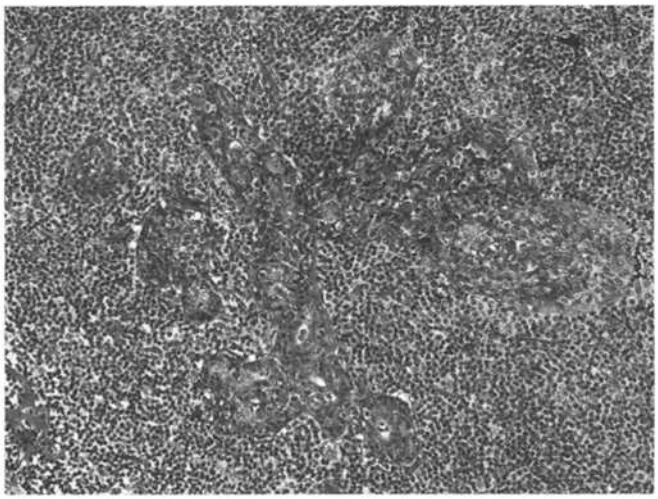


Fig. 54. Lymphoepithial lesions.

- Epi-myoepithelial islands
- Marked lymphoreticular infiltrate with germinal centers
- Hyaline-like material deposits

Sjögren's Syndrome

Clinical

- High incidence of non-Hodgkin's lymphoma in women
- Associated with:
  - Keratoconjunctivitis sicca
  - Xerostomia
  - Connective tissue disease
- Assessed by labial minor salivary gland biopsy:
  - Focus score: number of inflammatory foci/4 mm of gland (focus is defined as >50 lymphocytes)

Differential Diagnosis

- Lymphoepithelial carcinoma
- Lymphoma (MALT):
  - Both tumors may arise in this setting

Chronic Sclerosing Sialadenitis of Submandibular Gland (Küttner's Tumor)

- Unilateral
- Lympho-plasmacytic periductal infiltrate with fibrosis
- Clinically tumor-like

Cystic Lymphoid Hyperplasia (HIV+ Subjects)

Clinical

- HIV-infected patients
- Hodular or diffuse enlargement of salivary glands

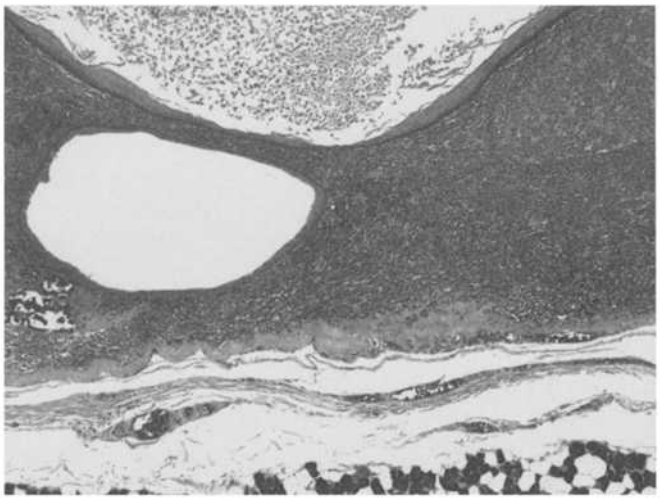


Fig. 55. Cystic lymphoid hyperplasia.

Table 25. Frequency and Location of Non-Neoplastic Salivary Gland Cysts

Type	*Site*	*Frequency (%)*
Mucocele	Minor glands	76
Salivary duct	Parotid	9
Lymphoepithelial	Parotid and oral cavity	7
Ranula	Sublingual gland	5
Congenital sialectasis	Parotid	1.5
Polycystic (dysgenetic)	Parotid	2

Batsakis & Raymond, 1989

- Unknown pathogenesis
- Antigen infection

Microscopic ***(Figure 55)***

- Glandular atrophy
- Intense lymphocytic proliferation with follicular hyperplasia
- Cystic formation with epithelial lining from ductal inclusion
- Epimyoepithelial islands

Inflammatory Pseudotumors

Clinical

- Firm, nodular swelling in the parotid

Microscopic

- Myofibroblastic proliferation and chronic inflammatory cells

Immunohistochemstry

- SMA, MSA, and KPI CD68+

Cystic Lesions

Salivary Gland Cysts

Benign Cysts of Salivary Gland: An Overview

- Types **(Table 25)**
- Congenital (dysgenetic) cyst: rare (2%) **(Figure 56)**
- Most of secondary pseudocysts are mucocele, followed by salivary duct cyst, lymphoepithelial cyst, and ranulas:
  - Two subtypes of mucoceles: the retention type and the extravasation type (Ranulas)

Cystic Neoplasms

- Cystic mucoepidermoid carcinoma

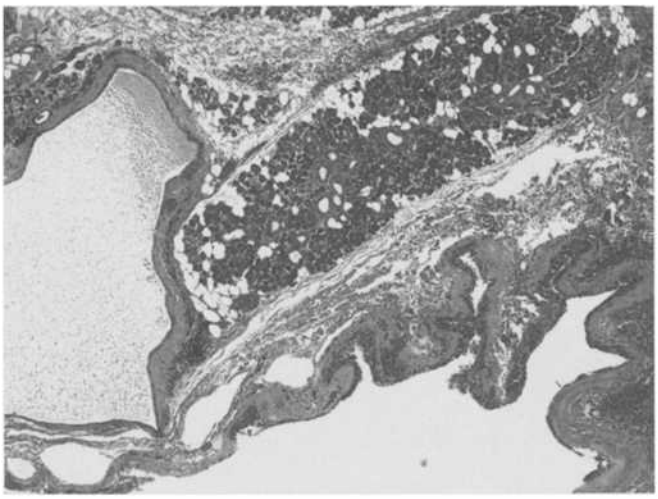


Fig. 56. Congenital cyst.

- Warthin's tumor
- Cystadenocarcinoma
- Sebaceous lymphadenoma

Inflammatory, Specific and Non-Specific

Dysgenetic Cysts

- Polycystic dysgenetic lesions **(Figure 57)**:
  - Rare, mainly parotid
  - Multiple cysts lined by simple epithelial lining
  - Female predominance, bilateral
  - Delayed clinical manifestation
  - Fluctuating, non-tender parotid swelling

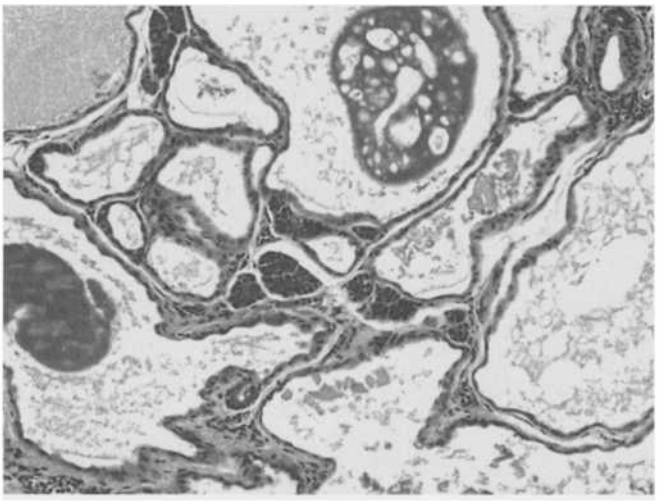


Fig. 57. Dysgenetic polycystic lesion.

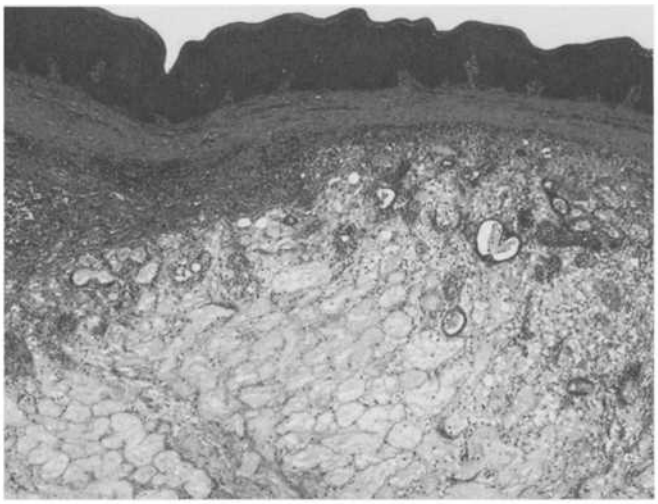


Fig. 58. Sub-epithelial mucin leakage (ranula).

Table 26. Frequency of Mucoceles by Site

Site	*Frequency (%)*
Lower lip	23.5
Cheek	13.2
Floor of mouth	12.6
Upper lip	15.4
Palate	8.8
Tongue	4.4
Other areas	16.1
No information	5.9

Modified from G. Seifert, 1991

- Diagnosis: sialogram, typically spare main salivary duct
- Surgical excision for diagnosis and treatment
- Etiology: most likely developmental

♦ Cyst of submandibular gland:
- Benign cyst lined by flattened epithelium
- Etiology: duct segmentation

Secondary Cysts

♦ Salivary duct cysts:
- 10% of all non-neoplastic cysts, mainly parotid
- More than $^2/_3$ male in 2nd decade of life
- Multilayered, cuboidal epithelial lining
- Occasional oncocytic and squamous metaplastic changes
- Cystic contents, spheroliths or crystalline precipitate
- Pathogenesis: ductal obstruction

♦ Lymphoepithelial cysts:
- Locations: parotid, intraparotid lymph nodes, floor of mouth
- Lining: flattened or multilayered epithelium surrounded by lymphocytes and lymphoid follides
- Sebaceous glands and goblet cells may be present
- Pathogenesis: displacement of epithelium into lymphoid tissue or proliferation of bronchial pouch epithelium
- Related to benign lymphoepithelial lesions, chronic myoepithelial sialadenitis, and HIV-related cystic lymphoid hyperplasia

Mucoceles, Retension and Extravasation (Ranula) (Table 26)

♦ Retention mucocele:
- Less common, 15%
- Older age, >20 years
- Site: minor salivary glands
- Cyst lined by flat, cuboidal, or multilayered epithelium surrounded by thick fibrous capsule
- Pathogenesis: obstruction

♦ Extravasation (Ranulas) (**Figure 58**):
- Most common, 85%
- Sites: lip, cheek, and floor of mouth
- More in men (60%)

Table 27. Benign Cystic Lesions of Neck

Type	*Characteristics*
Thyroglossal duct cyst	Midline, 2/3 below hyoid bone, 1/3 off midline, anteromedial to carotid artery and jugular vein
Bronchial cyst	Lateral neck, unrelated to hyoid, majority near angle of mandible; if small, anterior to sternomastoid, lateral to carotid artery and internal jugular vein
Parathyroid cyst	95% near inferior thyroid margin, off midline; anterior to carotid artery and internal jugular vein
Cervical thymic cyst	Off midline; low neck; anterior to carotid artery and internal jugular vein
Cystic hygroma	Off midline, usually posterior to carotid artery and internal jugular vein, may involve floor of mouth
Dermoid cyst	Near midline, usually upper neck
Benign teratoma	Usually near thyroid gland
Cervical ranula	Off midline and suprahyoid in submental and submandibular triangle

- Peak incidence: 2nd decade
- Initially ill-defined mucus lakes, followed by granuloma formation and muciphages, finally mucin-filled pseudocysts (no epithelial lining)

Benign Cystic Lesion of the Neck (see Table 27)

TNM CLASSIFICATION OF MAJOR SALIVARY GLAND (2002 REVISION)

- T: Primary Tumor:
  - T1: Tumor = 2 cm in greatest dimension without extraparenchymal extension
  - T2: Tumor > 2 cm but < 4 cm in greatest dimension. No extraparenchymal extension
  - T3: Tumor having extraparenchymal extension and/or > 4 cm in greatest dimension
  - T4a: Tumor invades skin, mandible, ear canal, and/or facial nerve
  - T4b: Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
- N: Regional Lymph Nodes:
  - N0: No regional lymph node metastasis
  - N1: Metastasis in a single ipsilateral node, = 3 cm in greatest dimesnion
  - N2: Metastasis in a single ipsilateral lymph node, > 3 cm but < 6 cm in geratest dimension, or in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension, or in bilateral or contra-lateral lymph nodes, none > 6 cm in greatest dimension:
    - N2a: Metastasis in a single ipsilateral lmph node > 3 cm but < 6 cm in greatest dimension
    - N2b: Metastasis in multiple ipsilateral lymph nodes, none > 6 cm in greatest dimension
    - N2c: Metastasis in bilateral or contraleteral lymph nodes, none > 6 cm in greatest dimension
  - N3: Metastasis in lymph node > 6 cm in greatest dimension
- M: Distant Metastasis:
  - M0: No distant metastasis
  - M1: Distant Metastasis

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18

Head and Neck

John D. Henley, MD and
Don-John Summerlin, DMD, MS

CONTENTS

I. Oral Cavity 18-4
Infection 18-4
Candidiasis 18-4
Herpes Simplex Virus 18-4
Oral Hairy Leukoplakia 18-4
Human Papillomavirus 18-4
Disseminated Fungal Infection 18-4
Immune-Mediated Disease 18-5
Lichen Planus 18-5
Benign Mucous Membrane (Cicatricial) Pemphigoid 18-6
Pemphigus Vulgaris 18-6
Inflammatory/Non-Neoplastic Lesions 18-6
Peripheral Ossifying Fibroma 18-6
Peripheral Giant Cell Granuloma 18-6
Verruciform Xanthoma 18-7
Traumatic Ulcerative Granuloma with Stromal Eosinophilia 18-7
Mucous Extravasation Phenomena (Mucocele/Ranula) 18-7
Necrotizing Sialometaplasia 18-7
Benign Neoplasms 18-8
Granular Cell Tumor 18-8
Congenital Gingival Granular Cell Tumor 18-8
Premalignant/Malignant Neoplasms 18-8
"Leukoplakia" 18-8
Squamous Dysplasia/Carcinoma *in situ* 18-8
Proliferative Verrucous Leukoplakia 18-9
Squamous Cell Carcinoma 18-9
Verrucous Carcinoma 18-9
Sarcomatoid (Spindle Cell) Carcinoma 18-10
Papillary Squamous Cell Carcinoma 18-10
Malignant Melanoma 18-10
Miscellaneous Lesions 18-11
Adenomatoid Hyperplasia 18-11
Amalgam Tattoo 18-11
Aphthous Stomatitis 18-11
Dermoid Cyst 18-11
Geographic Tongue (Erythema Migrans) 18-11
Lingual Thyroid 18-11
Lymphoepithelial Cyst 18-11
Melanoacanthoma 18-12
Nicotine Stomatitis 18-12
Oral Focal Mucinosis 18-12
Palisaded, Encapsulated (Solitary, Circumscribed) Neuroma 18-12
Salivary Duct Cyst 18-12
Smokeless Tobacco-induced Keratosis 18-12

II. Jaws 18-12
Non-Odontogenic Cysts/Pseudocysts 18-12
Nasopalatine Cyst 18-12
Traumatic Bone Cavity 18-12
Odontogenic Cysts 18-13
Dentigerous Cyst 18-13
Odontogenic Keratocyst 18-13
Apical Periodontal Cyst 18-13

Calcifying Odontogenic Cyst (Gorlin Cyst) 18-13
Dentinogenic Ghost Cell Tumor....18-14
Reactive/Non-Neoplastic Lesions 18-14
Cemento-Osseous Dysplasia 18-14
Odontoma 18-14
'Giant Cell' and Giant Cell-rich Lesions 18-14
Giant Cell Granuloma....18-14
Giant Cell Tumor 18-14
Aneurysmal Bone Cyst....18-14
Cherubism....18-15
Benign Neoplasms 18-15
Ameloblastoma....18-15
Adenomatoid Odontogenic Tumor....18-16
Calcifying Epithelial Odontogenic Tumor (Pindborg Tumor)....18-16
Squamous Odontogenic Tumor 18-16
Ameloblastic Fibroma 18-16
Cementoblastoma 18-16
Central Cemento-Ossifying Fibroma ..18-17
Odontogenic Fibroma....18-17
Malignant Neoplasms....18-17
Ameloblastic Carcinoma 18-17
Squamous Cell Carcinoma 18-17
Clear Cell Odontogenic Carcinoma 18-17
Osteosarcoma 18-18
Chondrosarcoma....18-18
Mesenchymal Chondrosarcoma 18-18
Metastatic Disease 18-18
Melanotic Neuroectodermal Tumor of Infancy....18-18
Miscellaneous Lesions 18-19
Stafne Defect 18-19
Tori 18-19
Gingival Cyst/Lateral Periodontal cyst 18-19
Central Mucoepidermoid Carcinoma ..18-19

III. Oro/Hypopharynx 18-19
Malignant Neoplasms....18-19
Squamous Cell Carcinoma 18-19
Lymphoepithelial Carcinoma 18-19
Basaloid Squamous Cell Carcinoma ..18-19
Papillary Squamous Cell Carcinoma ..18-20

IV. Nasal Cavity, Paranasal Sinuses, & Nasopharynx 18-20
Infection 18-20
Sinusitis....18-20
Allergic Fungal Sinusitis....18-20
Invasive Fungal Sinusitis....18-21
Other Forms of Infectious Sinusitis 18-21
Scleroma (Rhinoscleroma) 18-21
Rhinosporidiosis 18-21
Mycobacterial Infection 18-21
Leprosy 18-21
Syphilis 18-21
Inflammatory/Non-Neoplastic Lesions 18-22
Mucocele....18-22
Wegener's Granulomatosis 18-22
Sarcoidosis 18-22
Myospherulosis....18-22
Polyps 18-22
Variants....18-23
Choanal Polyp....18-23
Angiomatous Polyp....18-23
Polyp with Stomal Atypia....18-23
Benign Neoplasms 18-23
Lobular Capillary Hemangioma (Granuloma Pyogenicums) 18-23
Hyperkeratotic Squamous Papilloma....18-24
Sinonasal Papilloma (Inverted Papilloma, Schneiderian Papilloma) 18-24
Hemangiopericytoma-Like Tumor of the Nasal Cavity 18-24
Nasopharyngeal Angiofibroma....18-25
Malignant Neoplasms....18-25
Squamous Cell Carcinoma 18-25
Verrucous Carcinoma 18-25
Basaloid Squamous Cell Carcinoma ..18-25
Papillary Squamous Cell Carcinoma ..18-25
Malignant Lymphoma....18-25
NK/T-Cell Lymphoma 18-25
B-cell Lymphoma 18-25
Adenoid Cystic Carcinoma....18-26
Olfactory Neuroblastoma (Esthesioneuroblastoma) 18-27
Sinonasal Undifferentiated Carcinoma (SNUC) 18-27
Malignant Melanoma (Sinonasal Melanoma)....18-27
Neuroendocrine Carcinoma 18-28
Adenocarcinoma....18-28
Rhabdomyosarcoma 18-28
Nasopharyngeal Carcinoma 18-29
Miscellaneous Lesions 18-29
Respiratory Epithelial Adenomatoid Hamartoma....18-29
Necrotizing Sialometaplasia....18-29
Cholesterol Granuloma....18-30
Chondromesenchymal Hamartoma 18-30
Extranodal Sinus Histiocytosis (Sinus Histiocytosis with Massive Lymphadenopathy, Rosai-Dorfman Disease) 18-30
Fibromatosis 18-30

Hemangioma of Nasofacial Bones 18-30
Meningioma 18-30
Mesenchymal Chondrosarcoma 18-30
Osteoma 18-30
Metastatic Tumors 18-30
Pituitary Adenoma 18-30
Salivary Gland Tumors 18-30
Sarcoma 18-30
Solitary Fibrous Tumor 18-30
Teratocarcinosarcoma 18-30

V. Larynx and Trachea 18-31

Infection 18-31
Disseminated Fungal Infection 18-31
Inflammatory/Non-Neoplastic Lesions 18-31
Laryngocele 18-31
Oncocytic Cyst 18-31
Laryngeal Nodule/Polyp 18-31
Contact Ulcer 18-31
Benign Neoplasms 18-32
Laryngeal Papillomatosis (Squamous Papillomas) 18-32
Premalignant/Malignant Neoplasms 18-32
Hyperkeratosis 18-32
Squamous Dysplasia/Carcinoma *in-situ* 18-32
Squamous Cell Carcinoma 18-33
Verrucous Carcinoma 18-33
Basaloid Squamous Cell Carcinoma 18-33
Sarcomatoid Carcinoma (Spindle Cell Carcinoma) 18-33
Papillary Squamous Cell Carcinoma ..18-34
Lymphoepithelioma-like Carcinoma ..18-34
Small Cell (Neuroendocrine) Carcinoma 18-34
Large Cell Neuroendocrine Carcinoma 18-34
Adenoid Cystic Carcinoma 18-34
Chondrosarcoma 18-34
Mesenchymal/Soft Tissue Tumors 18-35

VI. TNM Classifications 18-35

ORAL CAVITY

Infection

Candidiasis

Clinical

- Most common opportunistic infection in the oral cavity
- Caused by a variety of species, most commonly Candida albicans
- Seen at any age, including infancy
- Usually secondary to underlying disease (immunosuppression) or local factors (ill-fitting dentures)
- May appear as a curd-like pseudomembrane, tissue hyperplasia or erythema

Microscopic

- Perpendicularly oriented (relative to mucosa) pseudohyphae and spores located in the superficial parakeratin
- Neutrophilic exocytosis
- Visualization aided by GMS and PAS stains

Herpes Simplex Virus

Clinical

- Most herpetic lesions of the oral cavity caused by Herpes simplex virus, types I or II
- Presents as localized vesicle or ulcer on keratinized mucosa or lip vermilion
- Mucosal eruptions can be widespread in children not previously exposed (gingivostomatitis)

Microscopic

- Vesicles with acantholytic cells (Tzanck cells)
- If ulcerated, cells on margin of ulceration often demonstrate viral cytopathic effect (multinucleate cells with 'ground glass' chromatin and intranuclear eosinophilic inclusions) (**Figure 1**)

Oral Hairy Leukoplakia

Clinical

- Peculiar manifestation of Epstein-Barr virus, mostly in immunosuppressed hosts
- Usually bilateral linear striation on lateral border of tongue
- May be seen in AIDS, organ transplant patients, diabetics and cancer patients
- Rarely in immunocompetent hosts

Microscopic

- Hyperkeratosis with a linear band of cells with edematous cytoplasm and nuclei that demonstrate chromatin margination **(Figures 2A,B)**
- Superimposed candidiasis in most cases

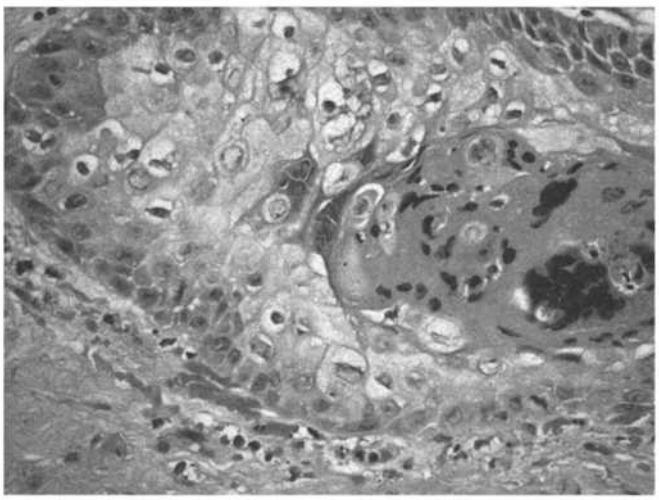


Fig. 1. Multinucleate cells with ground glass nuclear change characterize infection with Herpes simplex virus.

Differential Diagnosis

- Morsicatio linguarum (tongue chewing):
  - Thickened parakeratin with ragged surface and adherent bacterial colonies
  - lacks candidal infection and EBV

Human Papillomavirus

Clinical

- Induce papillary lesions of the oral cavity—papillomas, condylomas and verrucae
- Usually seen in young patients on tongue, gingival, soft palate complex
- Papillary growth pattern, localized

Microscopic

- Papillary epithelial proliferations arising from stalk
- Verrucae demonstrate coarse keratohyaline granules, hyperkeratosis, and axial inclination of rete ridges
- Condylomas demonstrate koilocytes and broader papillations and branching
- Presence of condylomas in children may suggest child abuse
- HPV types 16 & 18 associated with squamous cell carcinomas of tonsil/oropharynx

Disseminated Fungal Infection

Clinical

- A variety of disseminated fungal infections may have oral manifestations, including histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis
- Most, but not all, patients with definable immunodeficient state (i.e., HIV, diabetes, status post organ transplantation, malignancy)

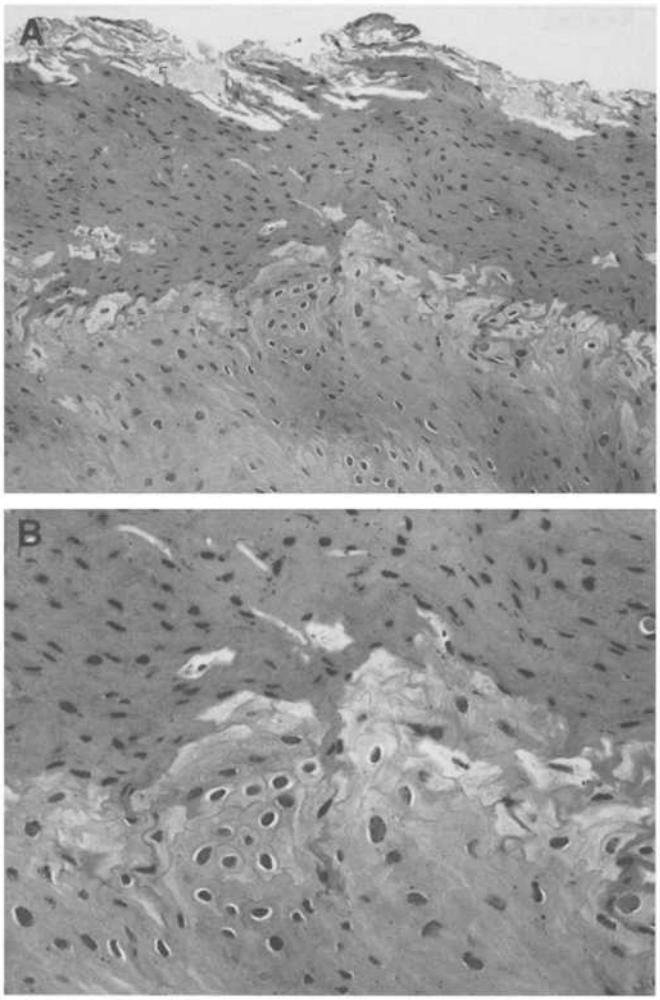


Fig. 2. The hyperkeratotic lesions of oral hairy leukoplakia usually present on the lateral border of the tongue in immunosuppressed patients **(A)**. Cellular changes characterized by edematous cytoplasm and nuclei that demonstrate chromatin margination are secondary to Epstein-Barr virus **(B)**.

- Oral ulceration, weight loss, fevers
- Oral lesions preceded by pulmonary infection

Microscopic

- Typically granulomatous inflammatory response, including histiocytes, giant cells, and necrosis **(Figure 3)**
- Neutophilic infiltration with giant cells characteristic of blastomycosis
- Blastomycosis notorious for associated pseudoepitheliomatous hyperplasia, simulating squamous cell carcinoma
- Granulomas may be absent (i.e., bug-laden, foamy histiocytes with necrosis and non-specific inflammation common appearance of histoplasmosis)
- Fungal stains aid identification of micro-organisms

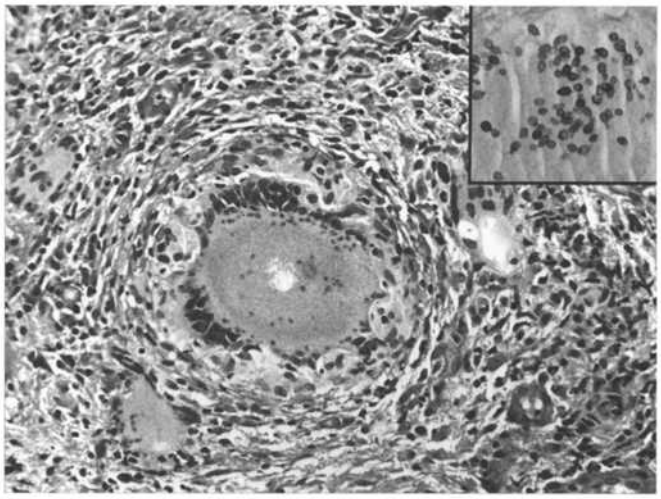


Fig. 3. Oral manifestations of histoplasmosis reflect disseminated disease. (inset) GMS stain highlights yeast.



Fig. 4. Band-like inflammatory infiltrates and spike-shaped rete ridges characterize lichen planus.

Immune-Mediated Disease

Lichen Planus

Clinical

- Bilateral, symmetrical white striations (striae of Wickham) superimposed on erythematous background
- Perimenopausal females
- Buccal mucosa, tongue, gingival
- Erosive form–erythematous with faint peripheral striations

Microscopic

- Band-like infiltrate of lymphocytes obscuring epithelial/connective tissue junction **(Figure 4)**

- Spike-shaped rete ridges
- Dissolution of basal epithelial layer

Immunofluorescence

- Granular deposition of fibrinogen at basement membrane level

Differential Diagnosis

- Lichenoid mucositis:
  - Histologically similar to lichen planus, but typically not symmetrical
  - Due to a variety of stimuli–dental products, dental materials, systemic medication
- Epithelial dysplasia with lichenoid inflammation:
  - Epithelial alterations consistent with irreversible change, probably accounts for most cases of "malignant transformation" of lichen planus

Benign Mucous Membrane (Cicatricial) Pemphigoid

Clinical

- Generalized sloughing of epithelium leaving bleeding erythematous base
- Peri/postmenopausal females
- Often sloughing can be elicited with gauze or gloved finger
- Ocular and genital mucosal involvement also seen

Microscopic

- Subbasilar separation of the epithelium
- Chronic inflammation of lymphocytes with smattering of eosinophils

Immunofluorescence

- Linear deposition of C3 and IgG along basement membrane zone

Differential Diagnosis

- Lichen planus:
  - Can demonstrate separation, but basal layer lost
- Pemphigus vulgaris:
  - Separation above basal layer

Pemphigus Vulgaris

Clinical

- Widespread sloughing and ulceration of mucosa
- Young adult males and females
- Can manifest as gingival desquamation

Microscopic

- Suprabasilar separation of the epithelium
- Infiltrate of lymphocytes seen

Immunofluorescence

- Intraepithelial (desmosomal) deposition of C3 and IgG in a spider web pattern

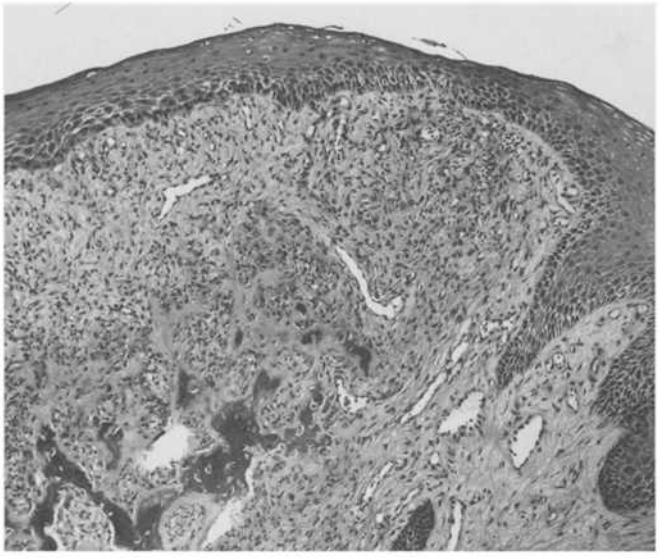


Fig. 5. Peripheral ossifying fibroma is a gingival-based nodule exhibiting matrix (i.e., bone or cementum) production.

Differential Diagnosis

- Lichen planus, see above
- Cicatricial pemphigoid, see above
- Drug-induced pemphigus:
  - Seen in particular with penicillamine
- Paraneoplastic pemphigus:
  - Supra and subbasilar splits seen in patients with lymphoma and leukemia

Inflammatory/Non-Neoplastic Lesions

Peripheral Ossifying Fibroma

Clinical

- Reactive proliferation of periodontal ligament origin
- Second to third decade
- Female predilection
- Seen on the gingiva, mostly anteriorly as a broad based nodule
- Typically ulcerated

Microscopic

- Cellular mesenchymal tissue with intermixed calcifications that can resemble bone or cementum **(Figure 5)**
- Extends to base because of origin, often resulting in recurrence

Peripheral Giant Cell Granuloma

Clinical

- Reactive proliferation of vascular mesenchymal tissue with intermixed osteoclasts
- Older adults, fourth to sixth decades
- Lobular, blue to purple mass on the gingiva/alveolar ridge
- May erode bone superficially

Microscopic

- Exuberant mass of spindle-shaped cells with numerous extravasated erythrocytes, hemosiderin pigment (especially at periphery) and multinucleated giant cells
- Can recur

Verruciform Xanthoma

Clinical

- Peculiar reactive proliferation of lipid-laden macrophages
- Typically on the gingiva or palatal mucosa in adults
- Red to yellow in coloration with a granular surface and a crater form

Microscopic

- Papillary proliferations of epithelium with brightly eosinophilic keratin
- Connective tissue papillae filled with lipid-laden macrophages
- Lesional cells confined to papillary lamina propria

Traumatic Ulcerative Granuloma with Stromal Eosinophilia

Clinical

- Peculiar exuberant reactive process that mimics carcinoma clinically
- Typically on dorsolateral tongue in adults
- Exophytic ulcerative mass usually of several weeks duration
- Painful
- May persist even after multiple surgeries

Microscopic

- Surface ulceration overlying proliferation of inflamed granulation tissue with prominent, reactive endothelial cells **(Figure 6)**
- Eosinophils and macrophages prominent in the deeper aspects approximating and involving muscle

Differential Diagnosis

- Clinical mimic of squamous cell carcinoma
- Lymphoma:
  - Atypical lymphoid cells, clonal
  - Aside from NK/T cell lymphomas, which may be polymorphous, most lymphomas are monomorphic infiltrates relative to mixed infiltrate of traumatic ulcerative granuloma
  - Generally lack prominent eosinophils

Mucous Extravasation Phenomena (Mucocele/Ranula)

Clinical

- Reactive lesion representing spillage of mucin into tissue due to duct damage
- Typically young patients, first to second decade
- Mucoceles seen on lower lip, ranulae in floor of mouth

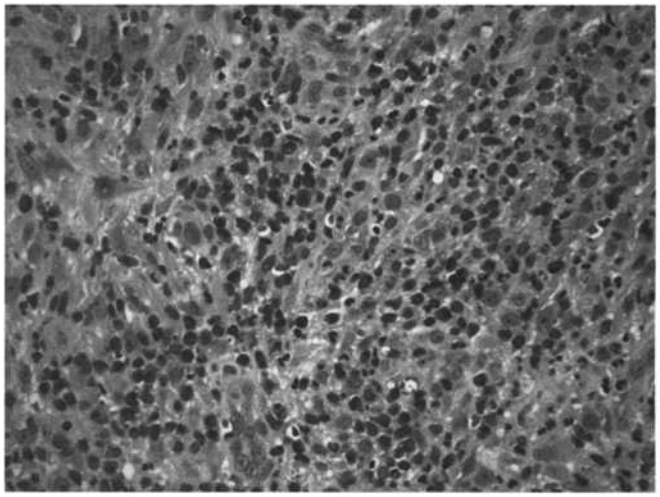


Fig. 6. The ulcer bed in traumatic ulcerative granuloma with stromal eosinophilia can be extremely cellular and mistaken for a neoplastic process.



Fig. 7. Disruption of salivary gland ducts results in mucin extravasation into connective tissue.

- Dome-shaped, fluid-filled lesions that may wax and wane with rupture
- "Plunging ranula" presents as neck mass

Microscopic

- Pseudocystic accumulations of mucin surrounded by a wall of compressed granulation tissue and inflammation **(Figure 7)**

Necrotizing Sialometaplasia

Clinical

- Ulcerative lesion involving salivary gland that can mimic malignancy
- Possibly due to underlying ischemic event
- Younger adults

- Palate most common site
- Swelling with pain, followed by sharply demarcated ulceration over two week period

Microscopic

- Coagulative necrosis with surface ulceration and squamous metaplasia of salivary ducts
- Typical maintenance of lobular architecture of salivary gland
- Can mimic squamous cell carcinoma or mucoepidermoid carcinoma

Differential Diagnosis

- Squamous cell carcinoma:
  - Infiltrative growth, cytologic atypia
- Mucoepidermoid carcinoma:
  - Infiltrative growth, prominent-proliferative appearance to goblet cells

Benign Neoplasms

Granular Cell Tumor

Clinical

- Benign, non-neoplastic proliferation of probable perineural sheath cells
- 70% occur on tongue, primarily dorsum
- Deep mass with maintenance of surface architecture
- Often long standing

Microscopic

- Ill-defined collections of cells with granular cytoplasm, eccentric nuclei and indistinct cytoplasmic boundaries **(Figure 8)**
- Many cases have superimposed pseudoepitheliomatous hyperplasia, mimicking squamous cell carcinoma
- Tend not to recur, even with incomplete removal

Immunohistochemistry

- S-100 protein+

Differential Diagnosis

- Squamous cell carcinoma:
  - Lack the subepithelial granular cells that accompany pseudoepitheliomatous hyperplasia
  - Rare on the dorsum of the tongue where granular cell tumor is common

Congenital Gingival Granular Cell Tumor

Clinical

- Benign proliferation of granular cells on the alveolar ridge in newborns
- Exophytic mass, often large (greater than five cm), on the maxillary alveolar ridge most commonly
- As name implies, typically present at birth

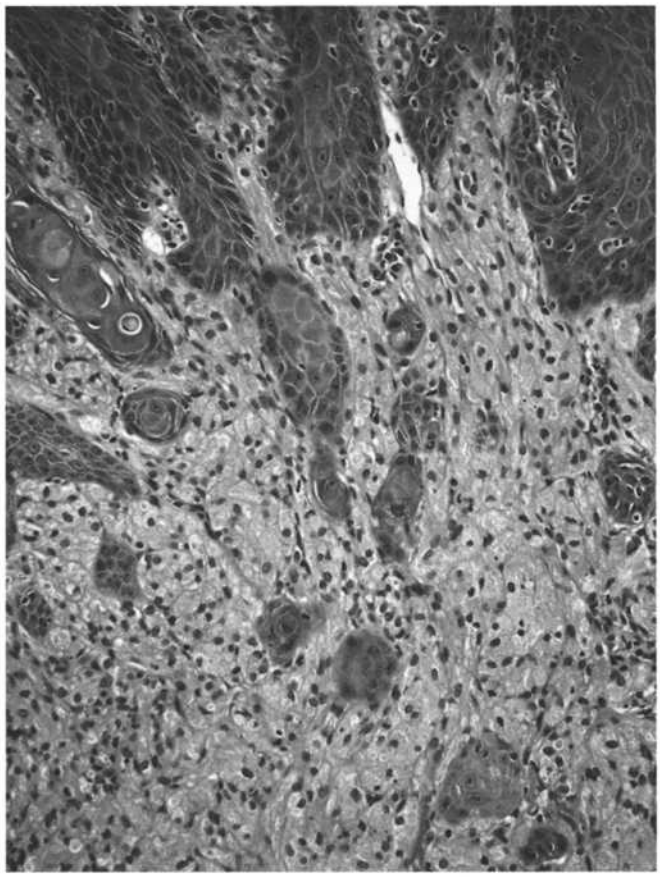


Fig. 8. Granular cell tumors are notorious for inducing pseudoepitheliomatous hyperplasia of the overlying epithelium.

Microscopic

- Mass of cells with granular cytoplasm, often distinct boundaries
- Overlying epithelium typically atrophic

Immunohistochemistry

- S-100–

Premalignant/Malignant Neoplasms

"Leukoplakia"

- Strictly a clinical term, should never be used as a microscopic diagnosis
- Just means white patch and, as such, carries no histologic implications
- Clinical location, symptoms and risk factors more important in assessing risk of preneoplasia/carcinoma
- Microscopic diagnosis ranges from hyperkeratosis to squamous cell carcinoma
- Use of the term is to be discouraged

Squamous Dysplasia/Carcinoma in situ

Clinical

- As with other sites, the oral epithelium tends to demonstrate precursor lesions prior to frank invasion

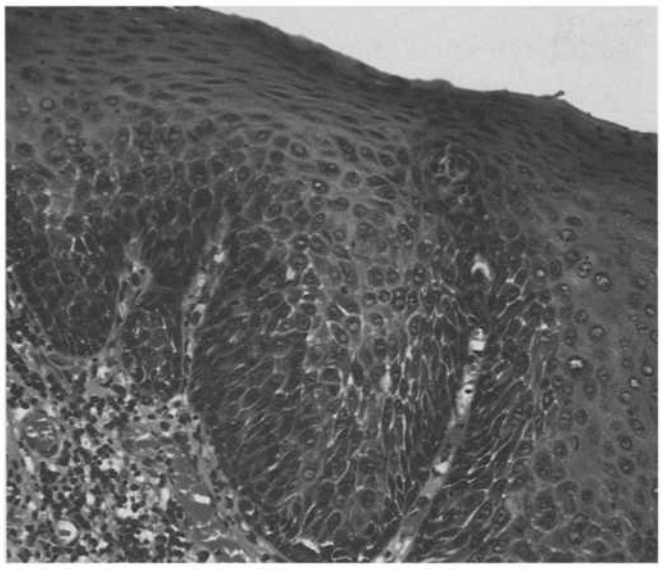


Fig. 9. The most apparent atypical changes of severely dysplastic epithelium in the oral cavity may be limited to lower aspect of the epithelium.

- Most classifications grade squamous dysplasia to carcinoma *in situ* dependent upon degree and thickness of epithelial involvement
- Presents as white patch, red patch (erythroplasia) or ulcer
- Typically seen in patients over 40, smokers and drinkers
- Females now represent approximately 50% of cases
- Ventrolateral tongue, floor of mouth and soft palate complex high risk sites

Microscopic

- Nuclear enlargement, hyperchromatism, pleomorphism, loss of polarity, and architectural changes (i.e., formation of bulbous rete ridges) **(Figure 9)**
- WHO Classification of oral dysplasia:
  - *Mild*—lower third abnormalities
  - *Moderate*—lower half abnormalities
  - *Severe*—lower two thirds abnormalities
  - *Carcinoma in-situ*—full thickness abnormalities
- Grade of dysplasia does correlate with risk of squamous cell carcinoma
- Reproducibility of grading oral dysplasia generally poor

Proliferative Verrucous Leukoplakia

Clinical

- A progressive condition involving multiple sites in the oral cavity
- Fifth decade or later
- Female predilection
- No strong tobacco association
- Multiple white patches that tend to enlarge, become verrucous and coalesce over time
- Progresses to squamous cell carcinoma in less than a decade
- Has yet to be successfully managed with consistency

Microscopic

- Varies site to site in the oral cavity from verrucous hyperkeratosis to epithelial dysplasia to verrucous carcinoma to squamous cell carcinoma

Squamous Cell Carcinoma

Clinical

- Most common malignancy in the oral cavity
- Ventrolateral tongue, floor of mouth and gingival
- Mostly in smokers and/or drinkers over age of 40
- Females increasing in incidence to 50% of cases
- Manifest as white patch, red patch, ulcer or exophytic mass

Microscopic

- Invasive and proliferative squamous epithelium demonstrating cytologic and morphologic alterations described above with keratin pearls
- Level of differentiation graded as *well, moderately,* or *poorly differentiated*
- Histologic grade does correlate with disease aggressiveness, although not as directly as clinical stage
- Depth of invasion (>4 mm), perineural invasion negative predictors
- ~50% five year survival

Differential Diagnosis

- *See* **Table 1**

Verrucous Carcinoma

Clinical

- Low-grade, well-differentiated variant of squamous cell carcinoma
- Usually over the age of 60
- More commonly seen in smokeless tobacco users
- Large (>4 cm) papillary mass with broad base, often snow white due to hyperkeratosis
- Typically seen on tongue, alveolar mucosa, buccal mucosa
- Often long standing duration
- Non-metastazing, neck dissection not indicated

Microscopic

- Broad papillations ('church spires') of squamous epithelium exhibiting minimal atypia with deeply invaginated folds of parakeratin ('parakeratin plugging') **(Figure 10)**
- Enlarge keratinocytes, especially of acanthotic stratum spinosum
- If cytologic atypia present the diagnosis of 'verrucous' type carcinoma should be doubted
- 95% five year survival

Table 1. Differential Diagnosis of the Poorly/Undifferentiated Sinonasal Neoplasm

Squamous cell carcinoma	– squamous differentiation: keratin, intercellular bridges and/or dyskeratotic cells
Lymphoma – NK/T lymphoma: midline – B cell lymphoma: paranasal sinuses	– lymphoid markers+ (CD45RO, CD56, CD3, CD20) – cytokeratin–
Sinonasal undifferentiated carcinoma (SNUC)	– cytokeratin+, neuroendocrine markers– prominent nucleoli – scant cytoplasm – prominent mitotic figures
Malignant melanoma	– S-100 protein+, cytokeratin– – melanoma markers+ (HMB-45, MelanA)
Olfactory neuroblastoma	– synaptophysin+, chromogranin+ S-100 protein+ sustentacular cells cytokeratin–
Basaloid squamous cell carcinoma	– undifferentiated basaloid cells – squamous differentiation, 'mosaic pattern' of keratinization
Lymphoepithelioma-like carcinoma	– cytokeratin+ – lymphoma and melanoma markers– – histologically indistinguishable from nasopharyngeal carcinoma
Adenoid cystic carcinoma, solid pattern or so-called 'dedifferentiated'	– evidence of glandular differentiation as tubular and/or cribriform structures – myoepithelial differentiation (S100, actin+)
Pituitary adenoma	– synaptophysin+ – cytokeratin+/– – no (rare) mitotic figures
Rhabdomyosarcoma	– MyoD1+, myogenin+, desmin+, muscle-specific actin+ – CD99– – children

Differential Diagnosis

- Papillomas:
  - Typically smaller, well confined lesions

Sarcomatoid (Spindle Cell) Carcinoma

Clinical

- Poorly differentiated variant of squamous cell carcinoma
- Usually manifests after age of 40
- Can occur in a history of radiation or burns, particularly electrical
- Usually a polypoid, ulcerated mass on posterior tongue or in oropharynx

Microscopic

- Exuberant proliferation of anaplastic spindle-shaped cells that appear to 'drop off' from atypical surface epithelium (**Figure 11**)

Immunohistochemistry

- Cytokeratin+

Differential Diagnosis

- Spindle cell sarcomas:
  - Cytokeratin–
  - Most superficial spindle cell malignancies in the oral cavity are carcinomas

Papillary Squamous Cell Carcinoma

Clinical

- Exophytic variant of squamous cell carcinoma
- Associated with HPV types 16 & 18
- Predilection for tonsil-oropharynx, hypopharynx
- Prognosis generally more favorable and probably relates to depth of stromal invasion more than size of exophytic component

Microscopic

- Branching papillary architecture (**Figure 12**):
  - Little tendency to keratinize
  - Brisk mitotic activity and notable cytologic atypia

Differential Diagnosis

- Squamous papilloma:
  - Lacks the cytologic atypia and architectural complexity of papillary squamous cell carcinomas

Malignant Melanoma

Clinical

- Rare malignancy of melanocytes arising from mucosa
- Typically seen in adults throughout the mucosa
- May be a lesion of long standing duration presenting as widespread discoloration
- Also can occur as exophytic pigmented mass



Fig. 10. Verrucous carcinoma is a broad-based, hyperkeratotic tumor that infiltrates in a 'pushing' fashion.

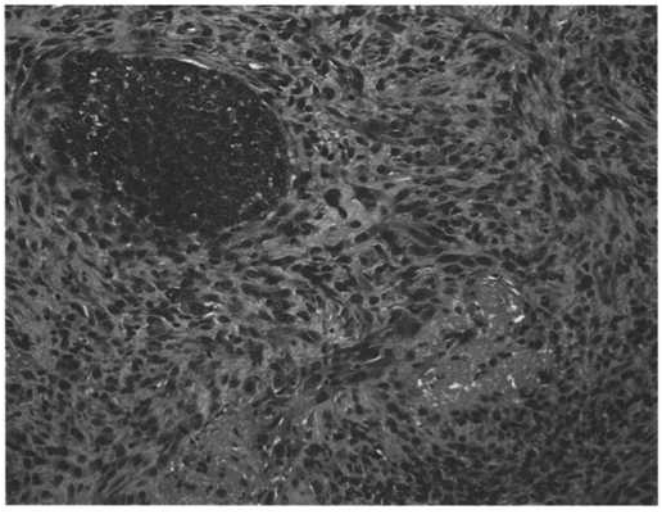


Fig. 11. Spindle cell carcinoma, surrounding a focus of malignant basaloid cells, simulates sarcoma.

Microscopic

- Cells typically large with prominent nucleoli, abundant cytoplasm
- Often amelanotic
- Must determine whether primary or metastatic, usually atypical cells within epithelium
- Poor prognosis due to nature and delay in diagnosis

Miscellaneous Lesions

Adenomatoid Hyperplasia

- Enlarged mucous glands in a tumor-like pattern seen in the palate
- May actually represent normal glands overlying a neoplasm

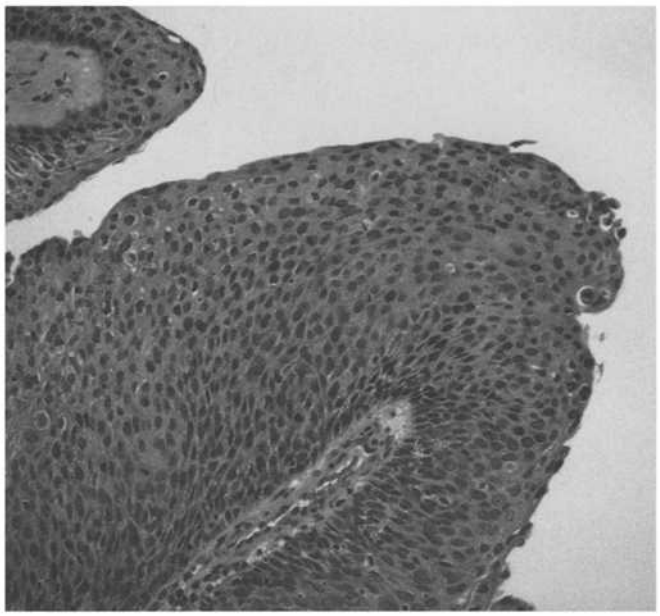


Fig. 12. Papillary squamous cell carcinoma has a predilection for the oropharynx, including the tonsil, and is associated with human papillomavirus.

Amalgam Tattoo

- Localized discolored area demonstrating granular, black foreign material aligned along collagen fibers and staining basement membrane
- Seen in area of dental restorations

Aphthous Stomatitis

- Ulcerations seen primarily in the lining mucosa in a variety of patterns–minor–less than 1 cm ulcers with fibrinous membrane and halo of erythema—herpetiform–multiple punctate erythematous ulcerations–major–large greater than 2 cm ulcerations with significant pain
- No distinctive histopathology

Dermoid Cyst

- Developmental anomaly seen in the midline floor of mouth exhibiting keratinized lining with adnexal structures–true teratomas rarely seen

Geographic Tongue (Erythema Migrans)

- Inflammatory condition of the tongue primarily characterized by superficial microabscesses
- May represent form of psoriasis

Lingual Thyroid

- Residual thyroid remaining on posterior dorsum or within the substance of the tongue

Lymphoepithelial Cyst

- Cavity lined by epithelium and surrounded by lymphoid follicles seen in floor of mouth, posterior/lateral tongue and tonsillar region

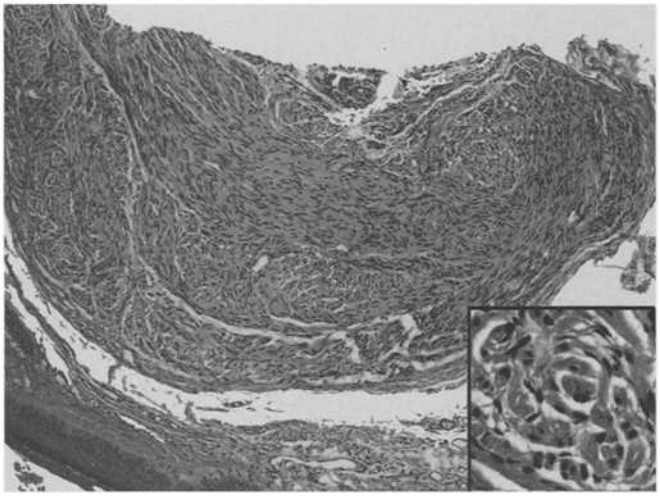


Fig. 13. Palisaded encapsulated neuroma is a circumscribed neural lesion and, thus, may be mistaken for schwannoma. (inset) Axonal proliferation distinguishes neuroma from nerve sheath tumor.

Melanoacanthoma

- Suddenly progressing and regressing pigmented lesion of the buccal mucosa in African-Americans—histologically demonstrates the presence of dendritic melanocytes within the spinous layer of epithelium

Nicotine Stomatitis

- Punctate erythematous areas surrounded by white zones on palate of primarily pipe smokers–microscopic demonstrates proliferation of squamous epithelium around central salivary duct with associated inflammation

Oral Focal Mucinosis

- Localized mass seen at any site in the mucosa characterized by the presence of abundant ground substance and flattening of the rete ridges of the epithelium

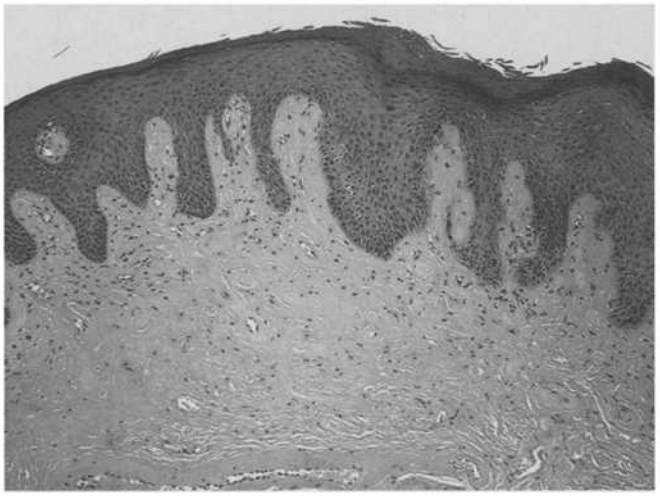


Fig. 14. Smokeless tobacco-induced keratosis is notable for acellular, subepithelial hyalinization.

Palisaded, Encapsulated (Solitary, Circumscribed) Neuroma

- Discrete nodule usually less than 1 cm seen most frequently on lip vermilion and hard palate
- Characterized by well-demarcated proliferation of Schwann cells with faint palisaded arrangements—axons present (**Figure 13**)

Salivary Duct Cyst

- Focal, small cystic lesion lined by salivary ductal epithelium seen most commonly in upper lip, buccal mucosa and palate

Smokeless Tobacco-Induced Keratosis

- Corrugated white patch seen in the location of placement of tobacco–demonstrates superficial epithelial necrosis and an amorphous hyalinized material histologically (**Figure 14**)

JAWS

Non-Odontogenic Cysts/Pseudocysts

Nasopalatine Cyst

Clinical

- Cystic degeneration of epithelial remnants of the nasopalatine duct
- Anterior maxilla, midline between maxillary central incisors
- Adults
- Possible swelling in the anterior hard palate

Radiograph

- Pear or heart shaped well-demarcated radiolucency between the roots of the central incisors

Microscopic

- Lining simple cuboidal, respiratory or stratified squamous epithelium
- Prominent neurovascular bundles

Traumatic Bone Cavity

Clinical

- Cavity in bone possibly due to trauma with subsequent lysis of clot
- Posterior mandibular body with possible expansion
- Young adults
- Male predilection
- Often filled with serosanguinous fluid

Radiograph

- Demarcated lucency with scalloping between tooth roots

Microscopic

- Thin fibrous connective tissue wall with or without inflammation

Odontogenic Cysts

Dentigerous Cyst

Clinical

- Cyst occurring around the crown of impacted tooth
- Most commonly mandibular third molar region
- Lining can give rise to ameloblastoma, squamous cell carcinoma or intraosseous mucoepidermoid carcinoma

Radiograph

- Unilocular radiolucency around the crown of impacted tooth

Microscopic

- Bilayer of cuboidal cells or stratified squamous lining with myxomatous connective tissue containing small islands of odontogenic epithelium

Odontogenic Keratocyst

Clinical

- Peculiar keratinized odontogenic cyst arising from prefunctional dental lamina
- Most common in the second to third decades
- Posterior mandible
- Can be multiple
- Often form "daughter" cysts, making complete removal more difficult
- Recurrence ~30%
- Associated with the *Nevoid basal cell carcinoma syndrome* (Gorlin-Goltz syndrome):
  - Autosomal dominant, defect in ptch gene (chromosome 9)
  - Multiple basal cell carcinomas on non- or minimally-sun exposed skin
  - Palmar and plantar pits
  - Skeletal anomalies—bifid ribs, brachymetacarpalism, kyphoscoliosis, calcified falx cerebri
  - Other tumors including medulloblastoma

Radiograph

- Most commonly multilocular radiolucency with possible expansion
- May be unilocular
- Tend to demonstrate linear growth pattern within the jaw

Microscopic

- Squamoid epithelium with luminal layer of corrugated parakeratin (**Figure 15**)



Fig. 15. Odontogenic keratocysts are cytologically bland, locally aggressive cystic lesions.

- Uniform thickness of 6-8 cell layers
- Basal layer prominent with palisading nuclei

Differential diagnosis

- Keratinizing odontogenic cyst:
  - Luminal layer orthokeratin, an indistinct basal layer and no association with the *nevoid basal cell carcinoma syndrome*

Apical Periodontal Cyst

Clinical

- Inflammatory cyst due to pulpally infected tooth
- Seen at the apex of a non-vital tooth

Radiograph

- Unilocular lucency at the apex of tooth

Microscopic

- Proliferative squamous epithelial lining with a wall of inflamed granulation tissue

Calcifying Odontogenic Cyst (Gorlin Cyst)

Clinical

- Developmental odontogenic cyst with questionable neoplastic potential
- Second to third decade
- Anterior aspects of the jaws
- May occur in an extraosseous fashion on the gingiva
- Recurrence ~10%
- May be associated with ameloblastoma

Radiograph

- Unilocular or multilocular expansile radiolucency with intermixed calcifications
- May be associated with an odontoma

Microscopic

- Lining of odontogenic epithelium with a basal layer of columnar cells with palisading nuclei
- Presence of "ghost" cells, squamous cells with abundant cytoplasm and central voids lacking nuclei
- Variable amounts of odontogenic product "dentinoid"

Dentinogenic Ghost Cell Tumor (Included Here Given Similarity to Gorlin Cyst)

- Represents a non-cystic neoplasm with microscopic characteristics similar to Gorlin cyst
- More aggressive lesions
- Rare malignant counterparts have been reported

Reactive/Non-Neoplastic Disease

Cemento-Osseous Dysplasia

Clinical

- Non-neoplastic proliferations of periodontal ligament origin
- Typically asymptomatic, found on routine radiographic survey
- Predilection for African-American females
- Third to fifth decade
- Periapical–seen around apices of mandibular anterior teeth
- Focal–single lesion seen in the posterior mandible
- Florid–multiple lesions seen in at least two quadrants
- Does not require removal, only identification
- Patients at risk for osteomyelitis as the lesions calcify and become avascular

Radiograph

- Appear as relatively well demarcated, mixed radiolucent/radiopaque lesions

Microscopic

- Typically curetted fragments with high cellularity of spindle-shaped mesenchymal cells
- Mixed with calcified product, often small sphericals of cementum and/or bone

Differential Diagnosis

- Central cemento-ossifying fibroma:
  - Field for field histologically identical
  - Distinguished by radiograph (well-demarcated, expansile lucency) and surgical findings (avascular, delineated solid mass)

Odontoma

Clinical

- Hamartomatous process of the odontogenic apparatus
- Seen primarily in the first two decades of life
- Compound–forms tooth-like structures most commonly in the anterior maxilla
- Complex–forms a mass of calcified product in the posterior jaws

Radiograph

- Compound–Multiple tooth-like structures with radiolucent rim
- Complex–Central mass of opaque material surrounded by radiolucent rim

Microscopic

- Mixture of enamel, enamel matrix, dentin, pulp and follicular tissue, either in appropriate context or haphazardly arranged

'Giant Cell' and Giant Cell-Rich Lesions

Giant Cell Granuloma

Clinical

- Central lesion (?neoplasm) seen most commonly early second decade
- Female predilection
- Anterior mandible crossing the midline
- Etiology unknown
- Recurrence rate 15%
- *Peripheral variant*: seen most commonly on mandibular gingiva or alveolar mucosa as purplish, exophytic mass

Radiograph

- Typically multilocular radiolucency, can be unilocular
- Expansion, tooth movement and resorption possible

Microscopic

- Cellular spindle-cell framework with clusters of multinucleated giant cells (osteoclasts), extravasated erythrocytes and hemosiderin

Differential Diagnosis

- Giant cell lesions of the jaws constitute an area of confusion:
  - Much has been written as to whether giant cell granulomas, giant cell tumors and aneurysmal bone cysts represent the same lesion, entities on a continuum or separate and distinct conditions
- Brown tumor of hyperparathyroidism is indistinguishable from the central giant cell granuloma and, accordingly, this systemic disease must be excluded (**Figure 16**)

Giant Cell Tumor

- True neoplasm that rarely occurs in the oral cavity
- *See* Bone and Soft Tissue section

Aneurysmal Bone Cyst

Clinical

- Age at diagnosis ~20 years; no gender predilection
- Mandible more common
- Often rapidly expansile

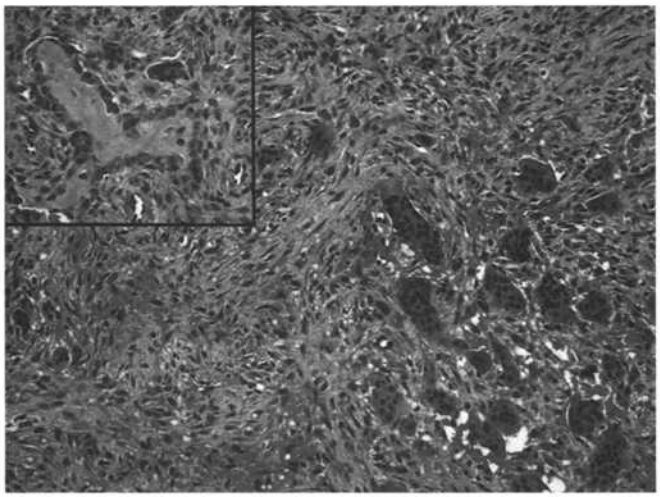


Fig. 16. Osteitis fibrosa cystica ('brown tumor') results from hyperparathyroidism and is histologically indistinguishable from giant cell reparative granuloma. (inset) Reactive osteoid may be prominent.

- Often substantial recurrence due to incomplete removal
- May occur in concert with other pathologic entities including fibro-osseous lesions and osseous neoplasms
- Etiology unknown, although trauma suspected

Radiograph

- Symmetrically expansile, unilocular radiolucency
- Can be multilocular

Microscopic

- Large pools of extravasated erythrocytes surrounded by cellular mesenchymal tissue with giant cells bordering the cavities
- Not endothelially lined

Cherubism

Clinical

- Inherited disease, autosomal dominant, chromosome 4p16, complete penetrance in males, incomplete in females
- Age at diagnosis ~5 years
- Bilateral expansion of the maxilla and mandible, producing chubby cheeks, hence the name
- Typically regress at puberty without surgery
- May require surgical intervention if grossly deforming

Radiograph

- Bilateral, expansile multilocular radiolucencies in the posterior mandible and maxilla

Microscopic

- Cellular, myxomatous mesenchymal tissue with intermixed giant cells
- Perivascular cuffing of hyaline material represents a useful clue

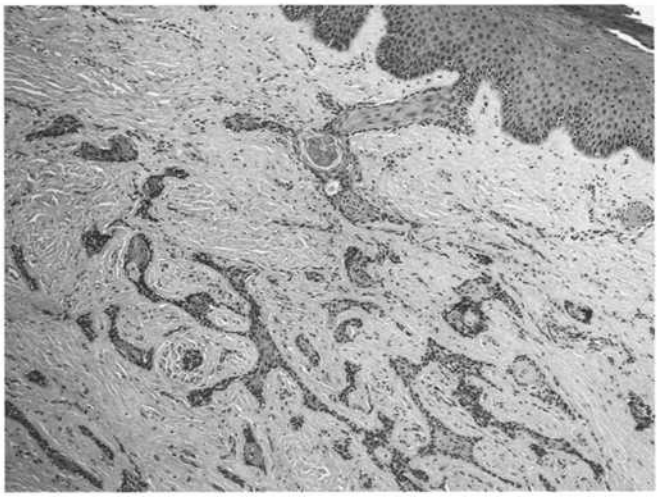


Fig. 17. Peripheral ameloblastoma resembles its intra-osseous counterpart. Note overlying mucosa.

Benign Neoplasms

Ameloblastoma

Clinical

- Most common epithelial odontogenic neoplasm, recapitulates enamel organ
- Third to fifth decade of life
- Presents as painless expansion
- Most common in posterior mandible
- Typically aggressive
- Up to 90% recurrence rate with curettage
- 15–20% recurrence rate with resection
- Rare examples of metastasis reported (malignant ameloblastoma)
- *Peripheral variant*: extraosseous location (**Figure 17**)

Radiograph

- Either expansile unilocular or multilocular (soap bubble) radiolucency
- Often perforates cortical plate

Microscopic

- Unicystic ameloblastoma–cystic with luminal proliferation of plexiform pattern of ameloblastoma
- Conventional ameloblatoma–variety of patterns including: follicular, plexiform, acanthomatous, granular cell, basal cell, desmoplastic (**Figure 18**)
- Typically characterized by peripheral layer of columnar cells with reverse polarization and nuclear palisading
- Central zones of stellate cells with exaggerated intercellular spacing
- Can be predominantly cystic

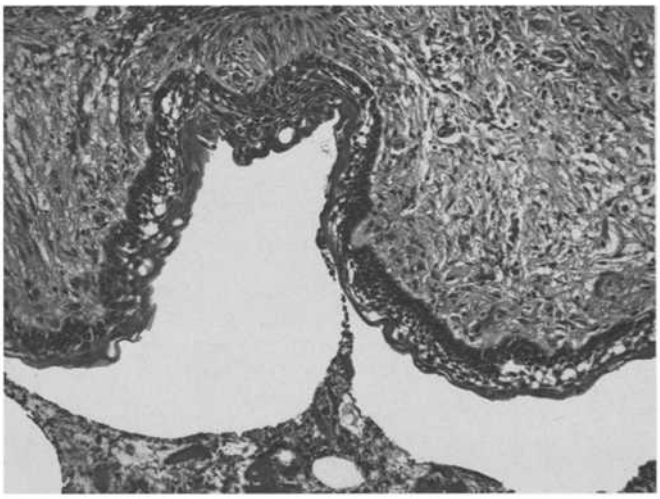


Fig. 18. Ameloblastoma may show prominent cystic change. Peripheral cells exhibit nuclear palisading with reverse polarization; the latter is not conspicuous in this example.

Adenomatoid Odontogenic Tumor

Clinical

- Benign neoplasm of odontogenic apparatus forming gland-like spaces
- Most commonly in the anterior maxilla associated with an impacted canine tooth
- 67% female
- Enucleation tends to be curative

Radiograph

- Pericoronal lucency with or without calcification

Microscopic

- Cystic lesion with proliferation of epithelial cells demonstrating whorls and focal gland-like spaces lined by columnar cells
- Dentinoid and amyloid may also be present

Calcifying Epithelial Odontogenic Tumor (Pindborg Tumor)

Clinical

- Benign epithelial odontogenic neoplasm that can mimic malignancy due to cellular pleomorphism
- Fourth to sixth decade
- Posterior mandible most common
- Slowly progressing expansile mass
- 15% recurrence after removal

Radiograph

- Well-demarcated multilocular radiolucency with calcifications ('driven snow' appearance)

Microscopic

- Sheets of polygonal epithelial cells with prominent intercellular bridging
- Marked pleomorphism without mitotic activity
- Spherical laminated calcifications (Liesegang rings)
- Amyloid present

Differential Diagnosis

- Squamous cell carcinoma:
  - Mitoses, invasive growth, ill-defined radiographically

Squamous Odontogenic Tumor

Clinical

- Benign epithelial odontogenic neoplasm that can mimic squamous cell carcinoma
- Third to fourth decade
- Posterior jaws
- Expansion
- Rarely recurs

Radiograph

- Semilunar radiolucency arising in alveolar bone

Microscopic

- Islands of squamous epithelial cells without remarkable basal layer
- No atypia or mitotic figures
- Islands may demonstrate central cystic degeneration

Differential Diagnosis

- Ameloblastoma, acanthomatous type:
  - Prominent palisading arrangement of basal cell layer

Ameloblastic Fibroma

Clinical

- Benign odontogenic neoplasm with coexistent epithelial and mesenchymal components
- First and second decade
- Majority in posterior mandible impeding eruption of 1st molar
- 10–20% recurrence rate

Radiograph

- Unilocular or multilocular radiolucency associated with impacted tooth

Microscopic

- Bilayer strands of odontogenic epithelium embedded within cellular myxomatous mesenchymal tissue

Cementoblastoma

Clinical

- Benign odontogenic counterpart to the osteoblastoma
- First two decades
- Mandibular first molar
- Pain and swelling
- Can recur if incompletely removed

Radiograph

- Opaque symmetrical mass merging imperceptibly with the root of the tooth
- Radiolucent peripheral rim

Microscopic

- Peripheral radiation of cemental product punctuated by prominent cementoblasts, cementoclasts and vascularity
- Odontogenic analogue of osteoblastoma

Central Cemento-Ossifying Fibroma

Clinical

- Benign product forming neoplasm of periodontal ligament origin
- Second to fourth decades
- Female predilection
- Posterior mandibular swelling, slowly progressing
- Rarely recurs

Radiograph

- Typically well-demarcated unilocular radiolucency with characteristic bowing of the inferior border of the mandible
- Usually only small flecks of calcification

Microscopic

- Avascular, well-delineated mass of cellular mesenchymal tissue
- Spindle-shaped cells arranged in whorls and fascicles
- Usually only limited punctate calcifications

Odontogenic Fibroma

Clinical

- Benign odontogenic mesenchymal neoplasm with variable epithelium and calcification
- Can be central or peripheral
- Average age of 40 with wide range
- Prominent female propensity
- Posterior maxilla most common
- May be associated with peculiar cleft defect in maxilla
- Rare recurrence

Radiograph

- Unilocular or multilocular radiolucency

Microscopic

- Simple type–collagenous stroma with evenly-dispersed bland spindle cells
- WHO type–cellular mesenchymal tissue with strands of odontogenic epithelium and variable calcified product

Malignant Neoplasms

Ameloblastic Carcinoma

Clinical

- Epithelial malignancy with ameloblastic differentiation

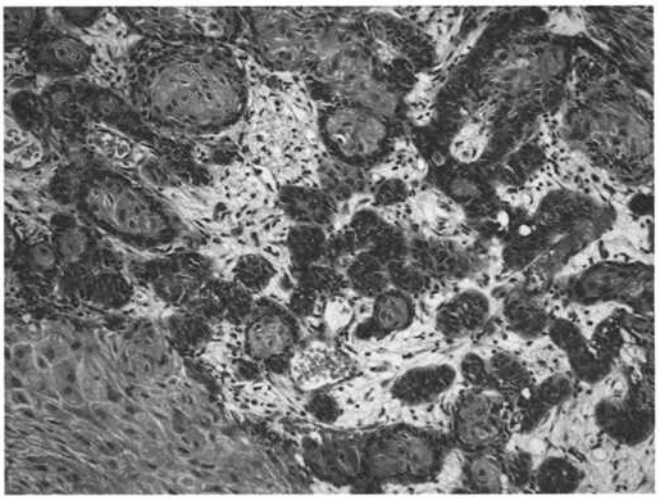


Fig. 19. Cellular pleomorphism, as seen here, distinguishes ameloblastic carcinoma from ameloblastoma.

- Fourth decade
- Mandibular predilection
- Metastasis to lungs
- <50% five year survival

Radiograph

- Ill-defined, lytic lesion

Microscopic

- Epithelial proliferation with peripheral cells demonstrating columnar appearance with reverse polarization (**Figure 19**)
- Prominent pleomorphism and mitotic activity

Squamous Cell Carcinoma

Clinical

- Odontogenic carcinoma demonstrating squamous differentiation
- Adults
- Mandibular predilection
- Dependent on grade and stage
- Most are local disease amenable to surgery

Radiograph

- May be poorly defined lytic lesion or arising from pre-existing odontogenic cyst

Microscopic

- Epithelial malignancy with squamous differentiation
- Must rule out metastasis or antral primary

Clear Cell Odontogenic Carcinoma

Clinical

- Malignancy composed of odontogenic epithelium with prominent cytoplasmic clearing
- Sixth decade or later

- Mandible
- Metastasis known, but not common
- Multiple recurrences with locally aggressive behavior

Radiograph

- Ill-defined lucency

Microscopic

- Strands and sheets of cells with odontogenic differentiation and cytoplasmic clearing
- May or may not demonstrate glycogen
- Stroma often cellular with hyalinization around the epithelium

Differential Diagnosis

- Metastatic renal cell carcinoma:
  - Prominent vascular stroma without the stromal cellularity

Osteosarcoma

- Relative to osteosarcoma of the long bones:
  - Tend to occur at a later age, average ~33 years
  - Tend to be lower grade
  - Tend to be chondroblastic
- Survival rate relatively unchanged even with newer modalities of treatment
- Mandible: 40% five year survival
- Maxilla: 25% five year survival

Chondrosarcoma

- Although some have speculated otherwise, these do occur in the jaws
- Average age ~30 years
- Tend to be slow growing lesions
- Tend to be low grade

Mesenchymal Chondrosarcomas

Clinical

- Mandible and maxilla most frequent sites, respectively
- May arise in soft tissue
- Second and third decades

Microscopic

- Undifferentiated stromal cells with islands of cartilage
- Stromal component may resemble 'small blue cell tumor' and/or hemangiopericytoma ('staghorn' vascular pattern)
- Mitotic figures scare to frequent
- Cartilaginous foci vary from prominent to scarce

Differential Diagnosis

- Distinction from Ewing's sarcoma, hemangiopericytoma and others relies upon recognition of cartilaginous foci

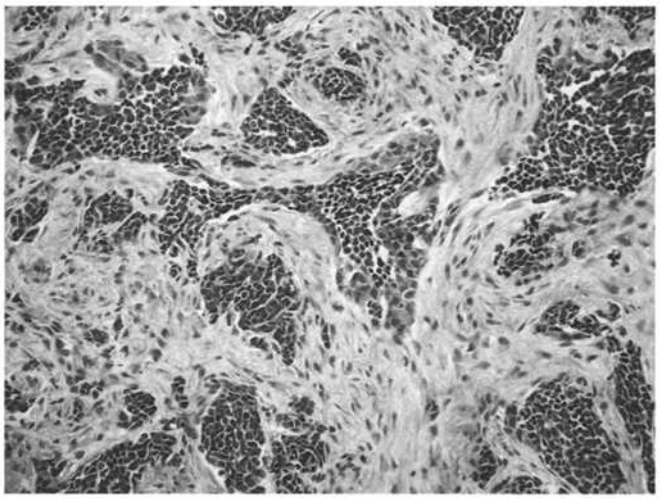


Fig. 20. Larger pigmented cells surround small blue cells in the melanotic neuroectodermal tumor of infancy.

Metastatic disease

Clinical

- Carcinomas of breast, lung, prostate, renal origin most common
- Fully 1/3 of patients unaware of primary tumor at time of diagnosis
- Often present with pain and/or paresthesia

Radiographic

- Lytic, ill-defined lesions
- Prostatic and breast metastases can be dramatically osteoblastic

Melanotic Neuroectodermal Tumor of Infancy

Clinical

- Neoplastic process of neuroectodermal origin
- Usually manifest in first year of life as expansile lesion in the anterior maxilla
- Elevated levels of urinary vanillylmandelic acid
- 15% recurrence
- 6% malignant behavior

Radiograph

- Demarcated radiolucency of the anterior maxilla with a primary tooth "floating in space"

Microscopic

- Epithelial lesion with two cell types: a small cell with hyperchromatic nucleus and scant cytoplasm and a large cell with vesicular nucleus, abundant cytoplasm and melanin pigment (**Figure 20**)
- Arranged in small islands and cords

Miscellaneous Lesions

Stafne Defect

- Bony defect at the posterior inferior margin of the mandible occupied by the submandibular gland—should be recognized radiographically, no surgery necessary

Tori

- Bony outcroppings seen in midline of hard palate and bilateral medial mandible—variations of anatomic normal

Gingival Cyst/Lateral Periodontal Cyst

- Cystic lesions of odontogenic apparatus
- Lined by bilayer of cuboidal to flattened epithelium with focal plaque-like thickenings and a single cavity—gingival cyst on mucosa, lateral periodontal cyst in bone
- *Botryoid odontogenic cyst* represents a multiple compartmented cyst in bone with similar histology but more aggressive clinical course
- *Glandular odontogenic cyst* demonstrates luminal layer of cuboidal cells and duct-like structures–behavior much like ameloblastoma with high recurrence rate and significant expansion

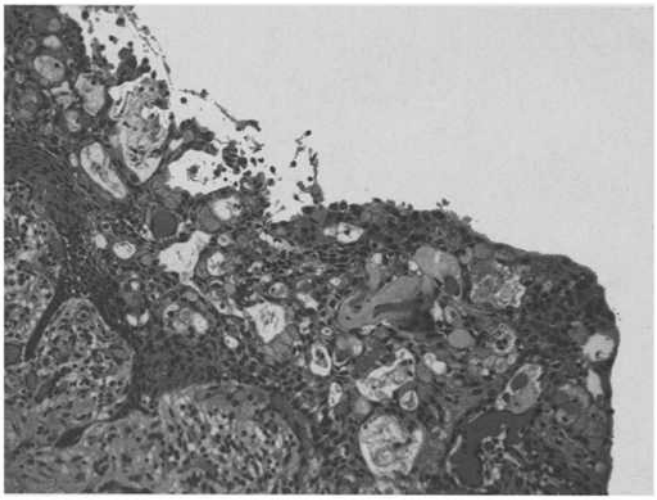


Fig. 21. Cental mucoepidermoid carcinoma arises within the mandible and resembles a salivary gland primary.

Central Mucoepidermoid Carcinoma

- Mucoepidermoid carcinoma arising within the mandible primarily, probably from pluripotential odontogenic epithelium (**Figure 21**)
- Usually low-grade with good prognosis

ORO/HYPOPHARYNX

Malignant Neoplasms

Squamous Cell Carcinoma

Clinical

- Most commonly seen in the base of tongue and tonsil
- Typically large (T3-T4) by time of diagnosis
- Dysphagia, exophytic mass, otalgia presenting complaints
- Stage III and IV disease have 5 yr survival rates below 30%

Microscopic

- Typically less differentiated with limited to no keratin production

Lymphoepithelial Carcinoma

Clinical

- Malignant epithelial neoplasm that is essentially undifferentiated with prominent lymphoid component (evidence of squamous differentiation may be by seen via electron microscopy)
- Probably related to Epstein-Barr virus, although evidence somewhat equivocal
- Adults
- Rarely occurs in the tonsil and base of tongue
- Less than 50% five year survival

Microscopic

- Sheets of undifferentiated epithelial cells embedded within lymphoid stroma
- Nuclei vesicular and large with prominent nucleoli

Basaloid Squamous Carcinoma

Clinical

- Peculiar high grade variant of squamous cell carcinoma demonstrating both basaloid and squamous components
- Sixth to eighth decades
- Male predilection
- Seen primarily in the base of tongue when occurring in the oropharynx
- Poor, less than 30% five year survival
- *See* section Larynx

Microscopic

- Biphasic tumor ('mosaic pattern' of cells) with lobules and cords of cells with hyperchromatic nuclei and scanty cytoplasm, often surrounded by prominent hyalinization (**Figure 22**)

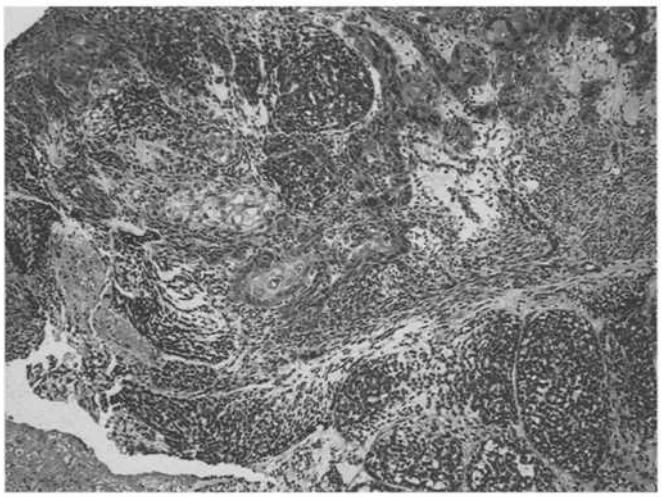


Fig. 22. Basaloid squamous carcinoma is an aggressive malignancy with a predilection for the base of tongue and larynx.

- Peripheral palisading and central necrosis common
- Often merges with typical squamous cell carcinoma
- Surface epithelial alterations may be evident

*Differential diagnosis (see **Table 1**)*

- Adenoid cystic carcinoma:
  - Lacks squamous differentiation and surface epithelial involvement

Papillary squamous cell carcinoma

Clinical

- Exophytic HPV-associated variants of squamous cell carcinoma
- Preferentially involve tonsil/oropharynx, larynx, and sinonasal tract
- Prognosis likely relates to extent of invasion

Microscopic

- Papillary condylomatous-like architecture (**Figure 12**)
- Cytologic atypia exceeds that seen in papillomas/condylomas

Differential Diagnosis

- Squamous papillomas with or without dysplasia:
  - Exhibit less cytologic atypia
  - Koilocytes present

NASAL CAVITY, PARANASAL SINUSES, & NASOPHARYNX

Infection

Sinusitis

Clinical

- *Chronic rhinosinusitis* defined as the presence of paranasal sinus inflammation for greater than 12 weeks
- Most commonly reported chronic disease in the United States
- Maxillary sinus most common site
- Bacteria infection implicated in *purulent sinusitis*
- Decrease in ostial size, retention of secretions, and decrease in mucociliary action contribute to the pathogenesis
- Limited coronal computed tomography the most definitive technique for the diagnosis

Microscopic

- Edema, hyperplastic seromucinous glands, thickened basement membrane, inflammatory cells (neutrophils, lymphocytes, plasma cells, and eosinophils)
- Retention cysts (**Figure 23**)
- Obstruction may lead to mucocele (frontal and ethmoid sinuses most commonly affected)

Differential Diagnosis

- Lymphoma:
  - Lacks the mature appearance of sinusitis (sinusitis rich with plasma cells, Russell bodies present)
  - Atypical lymphoid cells often with angiotropic growth accompanied by thrombosis and necrosis
- Allergic fungal sinusitis:
  - Dense eosinophil-rich exudate with fungal elements visible on GMS stain
- Wegener's granulomatosis:
  - Necrosis, granulomatous inflammation, and vasculitis
  - Histopathology non-specific, and typically incompletely developed, requiring serologic support (c-ANCA) for diagnosis

Allergic Fungal Sinusitis

Clinical

- Noninvasive sinonasal mycosis
- Most common form of fungal rhinosinusitis
- Patients often young and asthmatic and lack immunodeficiency or diabetes
- Bony erosion, rupture of the sinus walls and/or orbital extension not uncommon
- Offending organisms are ubiquitous, dematiacious family common (i.e., Curvularia and Bipolaris species)
- Eradication difficult, recurrence common

Microscopic

- Hallmark is 'allergic mucin': dense, thick eosinophil-rich mucin with fungal hyphae evident on GMS stain

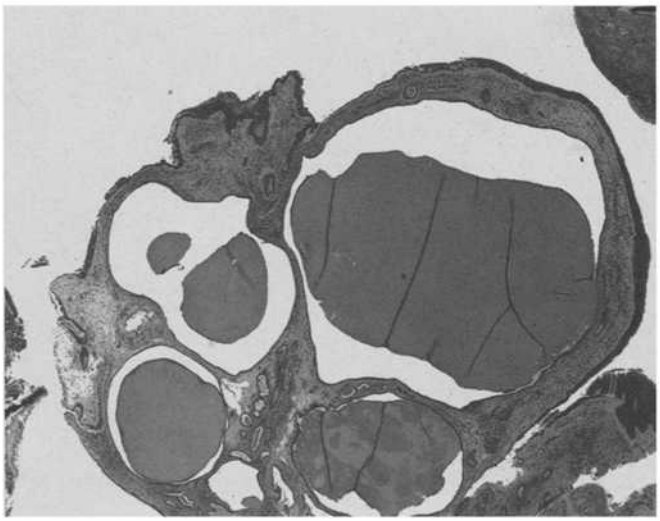


Fig. 23. Retention cysts are a common finding in the mucosa of individuals with chronic sinusitis.

- Charcot-Leyden crystals
- Mucosal changes of sinusitis with or without polyps

Differential Diagnosis

- Invasive fungal sinusitis:
  - Diabetic or immunodeficient patients
  - Angiotropic growth of fungus with thrombosis and necrosis
  - Fungus present in viable and/or necrotic tissue, not confined to exudate
- Sinus mycetoma ("fungal ball"):
  - Rare, non-invasive
  - Lacks the eosinophilic rich infiltrate

Invasive Fungal Sinusitis

- Rhinocerebral disease due to Zygomycetes (*Rhizopus-Mucor-Absidia*):
  - Headache, pain, fever
  - Patients with diabetic ketoacidosis experience rapidly progressive disease with extension into CNS
  - Turbinates appear necrotic
  - Angioinvasive growth with thrombosis, hemorrhage and infarction
  - GMS staining shows irregular ribbon-like hyphae (up to 50 micron) devoid of septa
- Nasoorbital disease due to *Aspergillus* species:
  - Immunocompromised patients: AIDS, neutropenia, hematologic malignancies
  - Angioinvasive growth with thrombosis, hemorrhage and infarction
  - GMS staining shows small hyphae (3–6 micron), 45 degree branching, distinct cross-septa

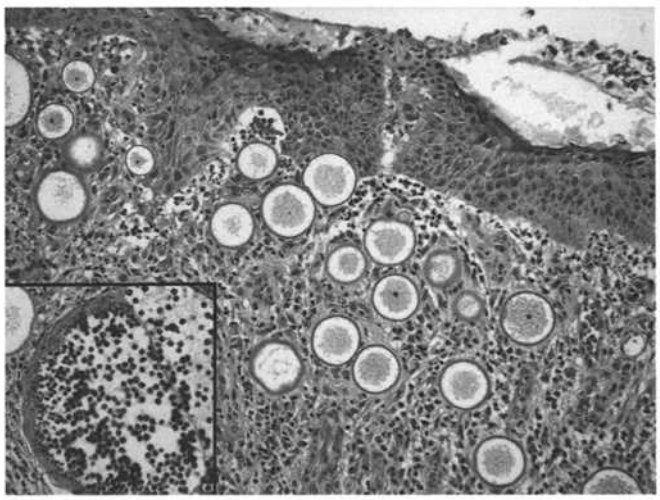


Fig. 24. Sporangia are numerous in the mucosal lesions of Rhinosporidiosis. (inset) Sporganium containing spores.

Other Forms of Infectious Sinusitis

- Scleroma (rhinoscleroma):
  - Etiology: bacterium-*Klebsiella rhinoscleromatis*
  - Microscopic: histocytic/'foamy cell' (Mikulicz cell) containing coccobacilli evident by Warthin-Starry, Giemsa stains, plasma cells with Russell bodies
  - Differential diagnosis: Rosai-Dorfman disease, leprosy, metabolic storage disease
- Rhinosporidiosis:
  - Etiology: fungus-*Rhinosporidium seeberi*, endemic to India
  - Microscopic: polypoid mucosal lesions, large sporangia (100–400 microns) resemble *Coccidioides immitis* though bigger (**Figure 24**)
  - Differential diagnosis: can simulate angiomatous nasal polyp
- Mycobacterial infection:
  - Etiology: bacterium-*Mycobacterium tuberculosis*, atypical mycobacteria-rare (HIV pts.)
  - Microscopic: caseating granulomas, ulceration, histiocytic inflammation, destruction of septal cartilage
- Leprosy:
  - Etiology: bacterium-*Mycobacterium leprae*
  - Microscopic: ulceration, macrophages, perivascular histiocytes with acid-fast bacilli
  - Involvement of paranasal sinuses is common and of epidemiological significance in lepromatous-type leprosy
- Syphilis:
  - Etiology: bacterium-*Treponema pallidum*
  - Microscopic: plasma cell endarteritis, ulceration, septal perforation
  - Primary, secondary, and tertiary syphilis can all cause intranasal pathology

Inflammatory/Non-Neoplastic Lesions

Mucocele

Clinical

- Predilection for mastoid, frontal and ethmoid sinuses
- Due to ostial obstruction and impaired lymphatic drainage, potential complication of sinusitis
- Can simulate neoplasm with progressive expansion

Microscopic

- Epithelial lining may or may not be apparent
- Goblet cells may be hyperplastic
- Degenerating debris, mucous, muciphages

Wegener's Granulomatosis

Clinical

- Sinonasal tract involved in 60 to 95% of patients
- Ulceration of the nasal septum, sinus mucosa, oral mucosa or destruction of the vocal cord
- Histological confirmation by nasal biopsy, though multiple biopsies often required
- C-ANCA positive in most of patients (c-ANCA negative cases occur)
- From a histopathologic perspective: largely, a disease of exclusion, other causes of granulomas and necrosis must be ruled out

Microscopic

- Histologic spectrum: from neutrophilic microabscesses to the signature triad of necrosis, granulomatous inflammation, and vasculitis (**Figure 25**)
- Typically triad is incomplete, histologic specificity for Wegener's decreases as fewer elements of triad present

Differential Diagnosis

- Malignant lymphoma
- Infection

Sarcoidosis

Clinical

- ~5% of patients have sinonasal involvement, septal and inferior turbinates
- Nasal obstruction and chronic sinusitis
- Mucosal crusting, studding, plaque-like changes, or polyps in the nose
- Radiologic studies may simulate diffuse polyposis and/or chronic bacterial/fungal sinusitis.

Microscopic

- Noncaseating granulomas (can have small foci of central caseation)
- Negative stains for fungus and acid-fast bacilli

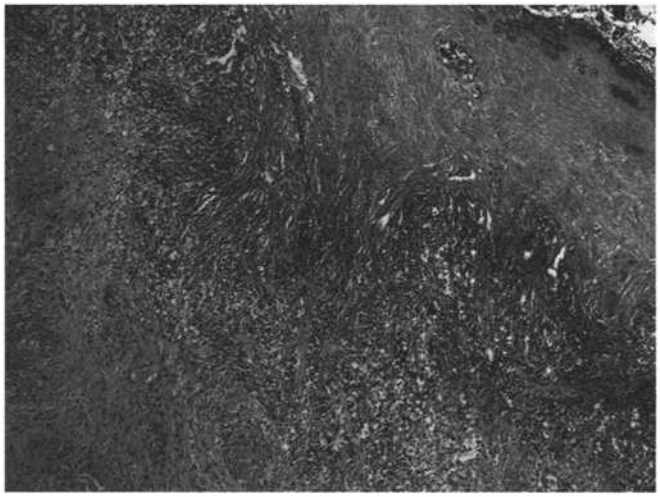


Fig. 25. Consider the possibility of Wegener's granulomatsis, lymphoma, and fungal infection in sinonasal specimens with prominent necrosis.

Differential Diagnosis

- Negative serologies for syphilis and vasculitis (i.e., c-ANCA)

Myospherulosis

Clinical

- Iatrogenic origin: foreign body/granulomatous reaction to petrolatum-based material used for nasal packing

Microscopic

- Large spherules simulating fungi containing altered erythrocytes

Differential Diagnosis

- Fungal infection:
  - Positive fungal stains (i.e., GMS)

Polyps

Clinical

- Common, ~1 to 4% of the population
- Bilateral, multiple
- Pathogenesis poorly understood; associated with sinusitis, allergy, immune deficiency, cystic fibrosis, ciliary dyskinesia and aspirin hypersensitivity, ? role of *S. aureus* superantigens
- Soft, edematous, semitranslucent

Microscopic

- Large quantities of extracellular fluid-edema separates bland stromal cells (**Figure 26**)
- Eosinophil rich in most cases
- Seromucinous glands may be hyperplastic or inapparent

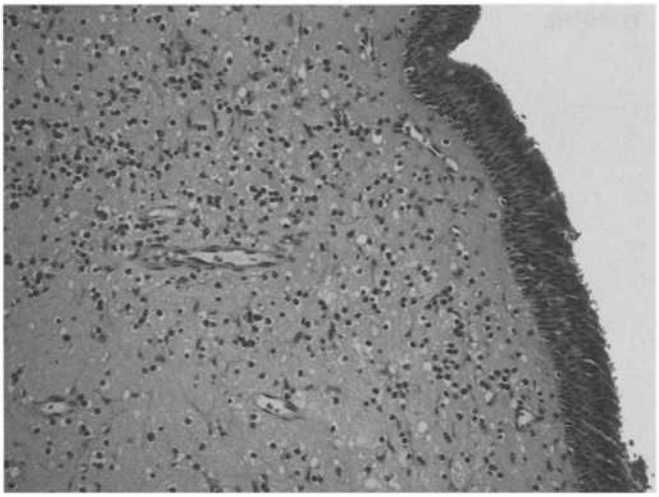


Fig. 26. Extracellular fluid and inflammation, particularly eosinophils, are features of nasal polyps.

- Retention cysts common
- Minority develop extensive vascular proliferation and ectasia with deposition of pseudoamyloid

Variants

- Choanal polyp:
  - Clinically defined variant originating in parasinus
  - Histologically indistinguishable from typical polyps
  - More prevalent in children
  - Solitary
  - May undergo torsion/infarction
- Angiomatous polyp:
  - Repeated vascular compromise/insult with subsequent repair can lead to prominent angiomatous changes-choanal polyps at particularly predisposed to such change
  - May undergo complete infarction
- Polyp with stomal atypia:
  - Atypical stromal cells, similar cells encountered in benign polyps of the vagina, esophagus, and mouth

Differential Diagnosis

- Lobular capillary hemangioma:
  - Densely packed capillary-sized vessels with lobular or 'organized' configuration
- Sinonasal papilloma:
  - True neoplasms with proliferative epithelial lining
- Juvenile angiofibroma:
  - Characteristic clinicopathologic features: young males, nasopharynx
  - Collagenous stroma

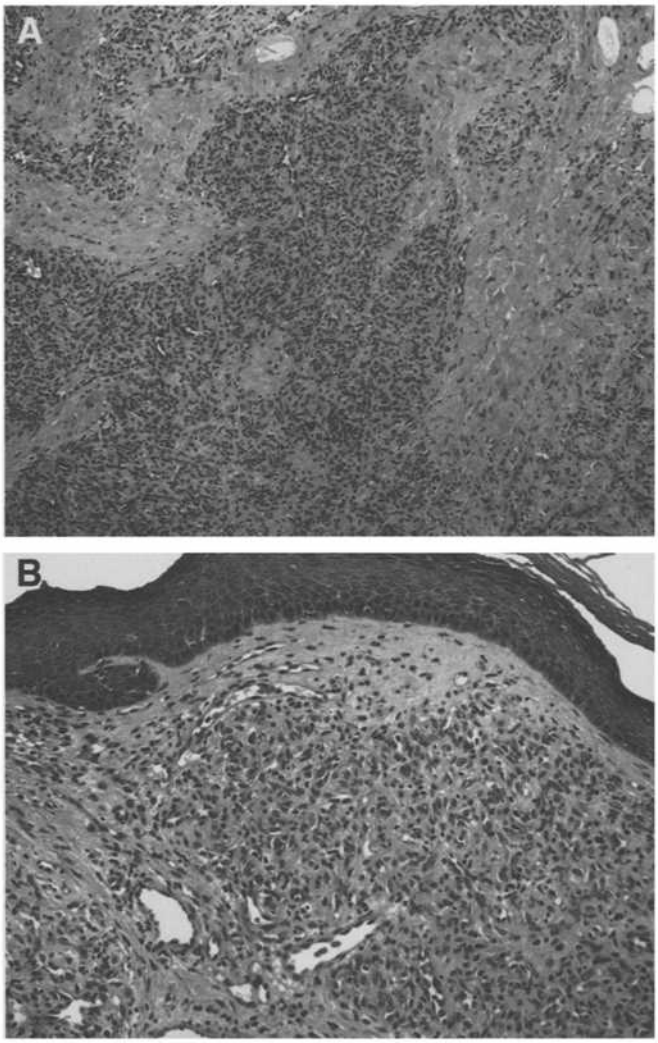


Fig. 27. A lobular distribution of cells is extremely useful in recognizing lobular capillary hemangioma of the nasal cavity (**A**). Lobular capillary hemangioma is uncapsulated, abuts the mucosa, and often ulcerates (**B**).

Benign Neoplasms

Lobular Capillary Hemangioma (Granuloma Pyogenicums)

Clinical

- Benign, though can grow rapidly
- Associated with microtrauma, pregnancy

Microscopic

- Lobular proliferation of small capillaries (**Figure 27A,B**)
- Mucosa often shows erosion/ulceration with superimposed repair

Differential Diagnosis

- Juvenile nasopharyngeal angiofibroma:
  - Young males, uniformly fibrous stroma, characteristic site of origin

- Angiomatous polyp:
  - Congested, often ectatic vessels
  - Lacks uniformity and organization of hemangioma

Hyperkeratotic Squamous Papilloma

Clinical

- Arise from nasal vestibule
- Benign, cytologically bland papillary squamous proliferation
- Analogous to counterpart arising elsewhere on the skin

Microscopic

- Keratinizing squamous proliferation with fibrovascular cores
- No dysplasia

Sinonasal Papilloma (Inverted Papilloma, Schneiderian Papilloma)

Clinical

- Nasal obstruction
- Locally aggressive, progressive tumors
- Require surgical removal
- Marked tendency for recurrence
- Association with carcinoma in less than 5% of cases
- Septal tumors tend to be fungiform; lateral nasal/paranasal lesions inverted in growth
- Papillomavirus detected in some sinonasal papillomas

Microscopic

- Inverted and fungiform growth patterns, both often present in a given lesion (**Figure 28A,B**)
- Proliferating squamous, transitional and columnar cells with interspersed mucinous cells
- Microcytic change with neutrophils
- May have parakeratin
- Koilocytic-like changes may be observed
- Dysplasia less common

Differential Diagnosis

- Squamous cell carcinoma:
  - Generally, greater cytologic atypia than papilloma

Hemangiopericytoma-Like Tumor of the Nasal Cavity

Clinical

- Mean age ~60 years
- Obstruction, epistaxis
- Vast majority behave benignly

Microscopic

- Submucosal and unencapsulated (**Figure 29**)
- Fascicular, solid to focally whorled patterns of plump spindle cells

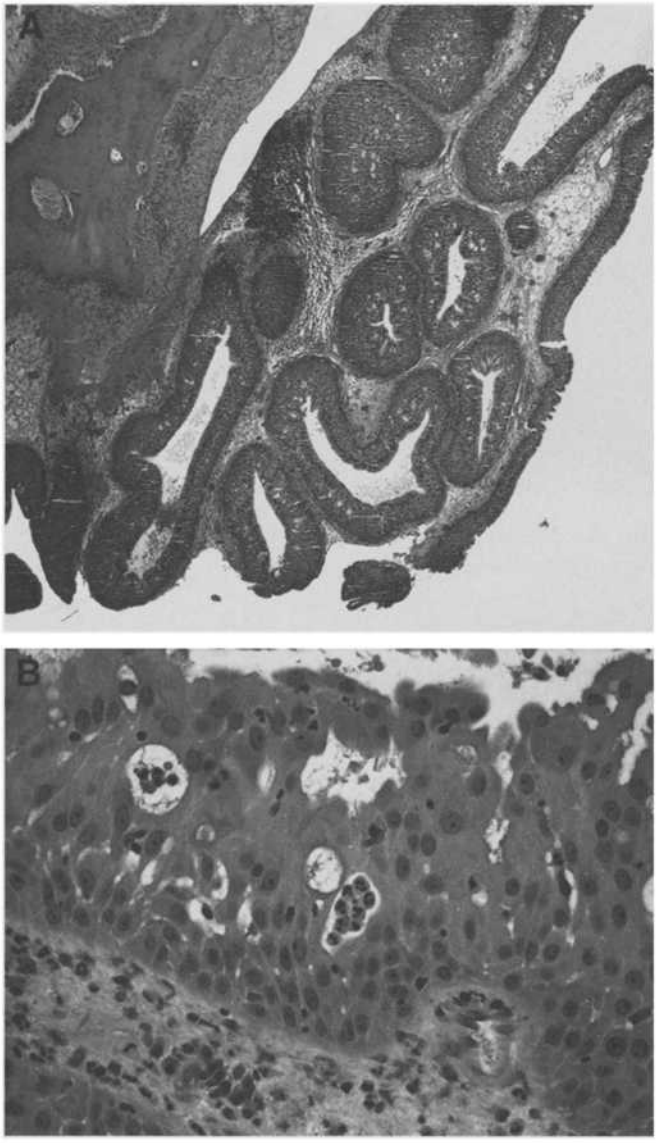


Fig. 28. Inverted papilloma derives its name from its 'inverted' pattern of growth; although, both inverted and exophytic growth patterns are often present in a given lesion **(A)**. Intraepithelial cysts with clusters of neutrophils are common in inverted papilloma **(B)**.

- Indistinct cell borders
- Spindle-shaped to round/oval nuclei with vesicular to hyperchromatic chromatin
- Minimal pleomorphism
- Staghorn-pattern vasculature

Immunohistochemistry

- Only vimentin consistently+, CD34–

Differential Diagnosis

- Solitary fibrous tumor:
  - CD34+

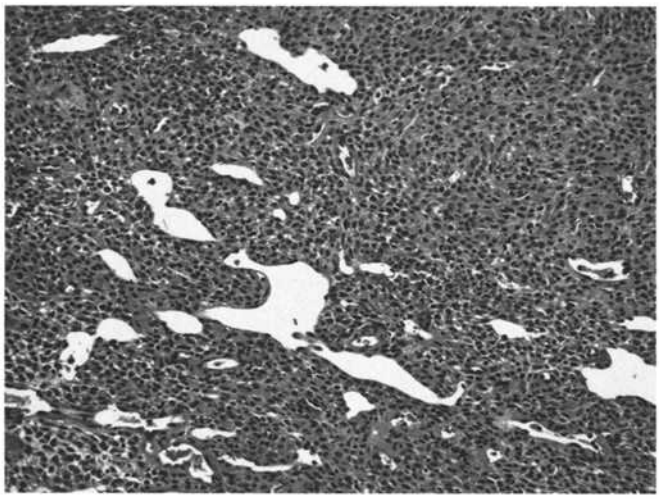


Fig. 29. Hemangiopericytoma-like tumor is biologically indolent and composed of isomorphic cells with no consistent pattern of immunohistochemical staining, aside from vimentin positivity.

- Hemangioma:
  - Tends to be less cellular, though distinction may be difficult

Nasopharyngeal Angiofibroma

Clinical

- Occurs exclusively in males in second and third decades (mean age 16 yrs, range 10 to 26)
- Rare, histologically benign tumor
- Origin in the pterygo-palatine fossa
- High recurrence rate with incomplete surgical excision
- Notoriously for profuse bleeding intraoperatively, preoperative embolization desirable

Microscopic

- Thin walled vessels, stellate stromal cells with scant cytoplasm, collagenous stroma
- No mitoses in stromal cells
- Vascular component may be inconspicuous on biopsy material, diagnosis aided by clinicopathologic correlation

Immunohistochemistry

- Vimentin–, CD34+, androgen receptor+

Differential Diagnosis

- Hemangioma:
  - Typically more cellular, with more densely packed vessels and less fibrous
- Angiomatous polyp:
  - Clinicopathologic features aid distinction

Malignant Neoplasms

Squamous Cell Carcinoma

Clinical

- Most common malignancy of nasal cavity and paranasal sinuses
- Adults, elderly
- Associations: smoking, human papillomavirus, chromium exposure

Microscopic

- Keratin production, intracellular bridges, and/or dyskeratotic cells
- Graded as well, moderately or poorly differentiated
- Exophytic/papillary growth may occur
- Rarely spindle cell or sarcomatoid morphology

Variants

- Verrucous carcinoma:
  - Rare
  - Non-metastasizing, progressive tumor
  - 'Pushing' margin of invasion with minimal cytologic atypia
- Basaloid squamous cell carcinoma:

See Oropharyx and Larynx sections

  - Biologically aggressive
  - Rare in sinuses, predilection for the larynx, hypopharynx, tonsils, and base of the tongue
- Papillary squamous cell carcinoma:
  - HPV-associated variant of squamous cell carcinoma
  - Sinonasal tract primaries have poorest prognosis, relative to papillary squamous cell carcinoma arising elsewhere

Malignant Lymphoma

- Majority represented by Natural killer (NK)/T-cell, B-cell type, and peripheral T-cell-type lymphomas
- Hodgkin's disease vanishing rare in nasal cavity, paranasal sinuses

See Lymphoma Chapter

- NK/T-cell lymphoma:
  - Midline/nasal cavity
  - Associated with Epstein-Barr virus
  - Histologic spectrum: small to large cells, irregular nuclei, often with clear/pale cytoplasm (**Figure 30**)
  - Angiocentric growth with thrombosis and necrosis
  - CD45RO+, CD2+, CD56+
  - Historically represented by 'lethal midline granuloma' among others
- B-cell lymphoma:
  - More common in paranasal sinuses, in distinction to NK/T-cell lymphoma

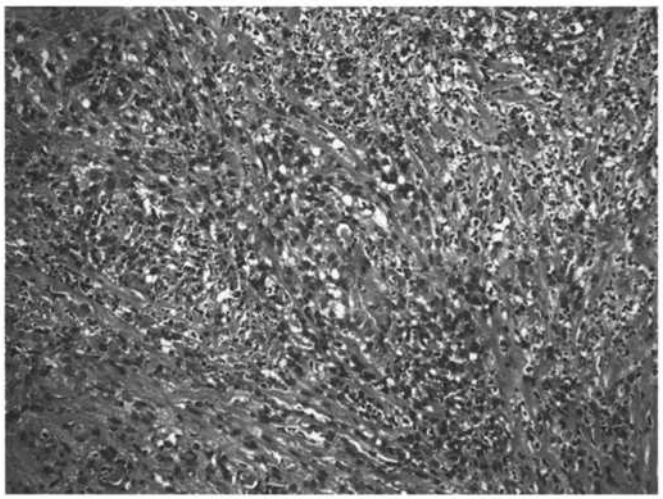


Fig. 30. NK/T cell lymphomas exhibit angiotropic growth, thrombosis, and necrosis. These tumors are typically polymorphous; malignant cells may have clear cytoplasm.

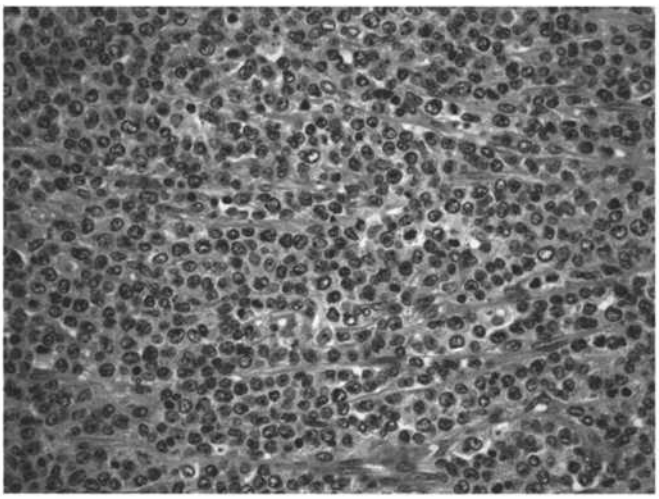


Fig. 31. Diffuse large cell lymphoma shows sheets of atypical lymphoid cells with conspicuous mitotic figures.

- CD45RO+, CD 20+
- Typically diffuse growth of large B cells (**Figure 31**)
- More monomorphic in appearance than NK/T cell lymphoma

Adenoid Cystic Carcinoma

Clinical

- Second most common malignancy of paranasal sinuses
- Aggressive tumor with high incidence of local recurrence and distant metastasis
- CNS extension common
- Most cases are ultimately fatal
- Solid pattern tumors progress more quickly

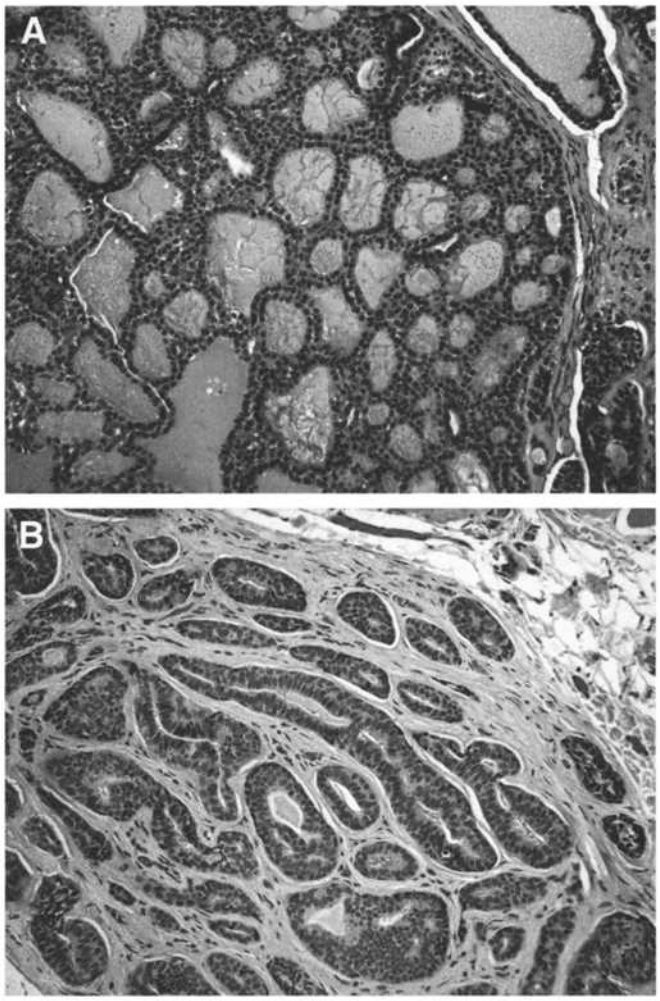


Fig. 32. Adenoid cystic carcinoma is the most common malignant gland forming tumor of the nasal cavity and paranasal sinuses. The cribriform pattern of adenoid cystic carcinoma is well recognized **(A)**. Predominant tubular patterns of adenoid cystic carcinoma can be challenging diagnostically **(B)**.

Microscopic

- Cribriform, tubular, and solid patterns **(Figure 32A,B)**
- Small basophilic cells with scant cytoplasm and inconspicuous nucleoli
- Predilection for perineural spread
- Mitotic figures, nucleoli, and necrosis common in solid pattern
- Tubular pattern shows bilayer profiles

Immunohistochemistry

- Cytokeratin+
- Peripheral myoepithelial immunophenotype present: actin+, S-100 protein+, calponin+
- c-KIT+

*Differential Diagnosis (see **Table 1**)*

- Adenocarcinoma-NOS:
  - Lacks the myoepithelial differentiation (actin–, calponin–) seen in adenoid cystic carcinoma
- Polymorphous low-grade adenocarcinoma:
  - Very unusual in nasal cavity/paranasal sinus

Olfactory Neuroblastoma (Esthesioneuroblastoma)

Clinical

- Rare neuroectodermal tumor, ~1 to 5% of the malignant nasal cavity neoplasms
- Mean age ~50 years
- Obstruction, bleeding, pain, optic disorder, impaired sense of smell
- Paraneoplastic syndromes (i.e., Cushing's syndrome, SIADH, etc.)
- Arises near the cribriform plate with risk of intracranial spread

Microscopic

- Histologic spectrum from nested, uniform cells embedded in fibrillary matrix to more epithelioid-appearing polygonal cells (paraganglioma-like appearance) **(Figure 33A,B)**

Variable mitotic rate: mitotic figures often inconspicuous

- Homer Wright pseudo-rosettes
- Often accompanied by prominent vascular proliferation
- Histologic diagnosis warrants immunohistochemical corroboration
- Melanin can be present

Immunohistochemistry

- Synaptophysin+, chromogranin+, cytokeratin–
- S-100 protein + sustentacular cells present peripherally in tumor cell nests

*Differential Diagnosis (see **Table 1**)*

- Neuroendocrine carcinoma: cytokeratin+, lacks S-100 protein+ sustentacular cells
- Other 'small blue cell tumors'

Sinonasal Undifferentiated Carcinoma (SNUC)

Clinical

- Pain, obstruction, epistaxis, features of advanced-stage disease such as diplopia, proptosis
- Very aggressive

Microscopic

- Nests, trabeculae, and sheets of medium-sized cells with hyperchromatic nuclei and a high nuclear to cytoplasmic ratios (**Figure 34**)
- Small to moderate amounts of eosinophilic cytoplasm
- High mitotic rate, necrosis, and prominent vascular invasion

Immunohistochemistry

- Cytokeratin+, neuroendocrine markers–

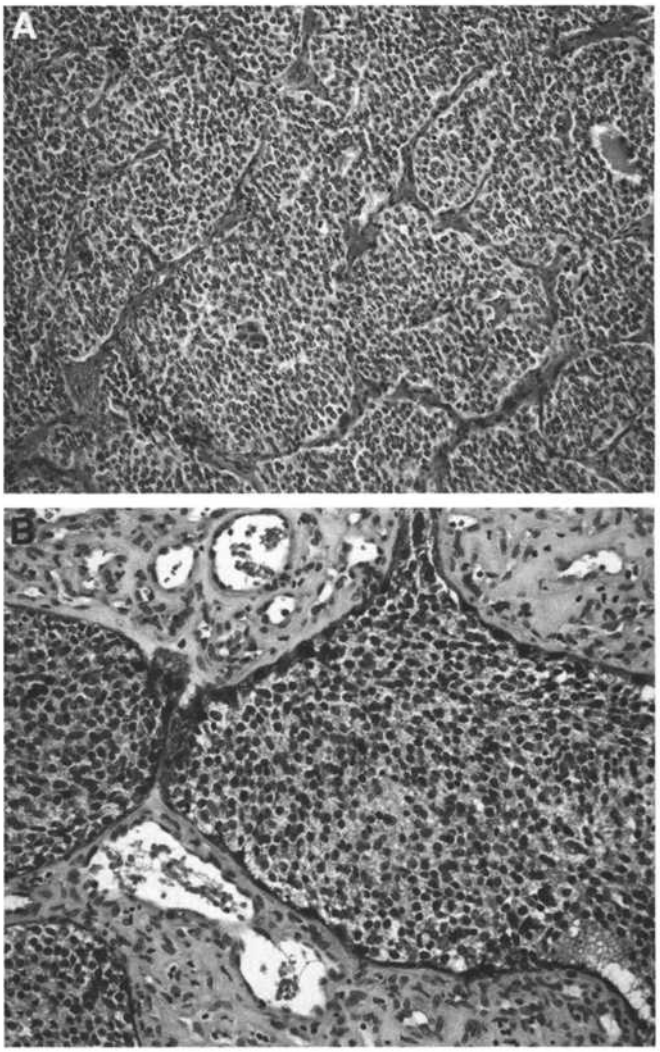


Fig. 33. A nested pattern of growth, isomorphic cells, and a prominent vasculature are features of olfactory neuroblastoma **(A)**. S-100 protein positive sustentacular cells are a signature feature of olfactory neuroblastoma **(B)**.

Differential Diagnosis

- Olfactory neuroblastoma: S-100 protein+ sustentacular cells, synaptophysin+, chromogranin+
- Neuroendocrine carcinoma: synaptophysin+, chromogranin+/–
- Rhabdomyosarcoma: desmin+, muscle specific actin+, myogenin+, MyoD1+
- Malignant lymphoma: lymphoid markers+
- Malignant melanoma: S-100 protein+, cytokeratin–

Malignant Melanoma (Sinonasal Melanoma)

Clinical

- Mean age ~70 years
- Epistaxis, obstruction, mass
- 5-year survival rate: nasal cavity-poor; paranasal sinus-worse

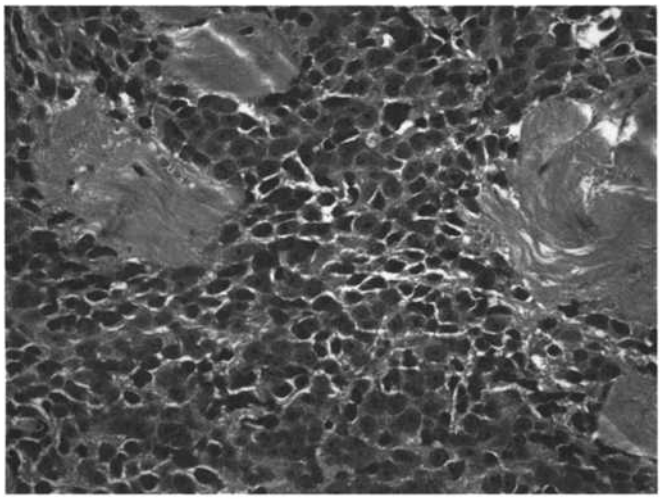


Fig. 34. This sinonasal undifferentiated carcinoma was metastatic to the skin of the neck and negative for neuroendocrine markers.

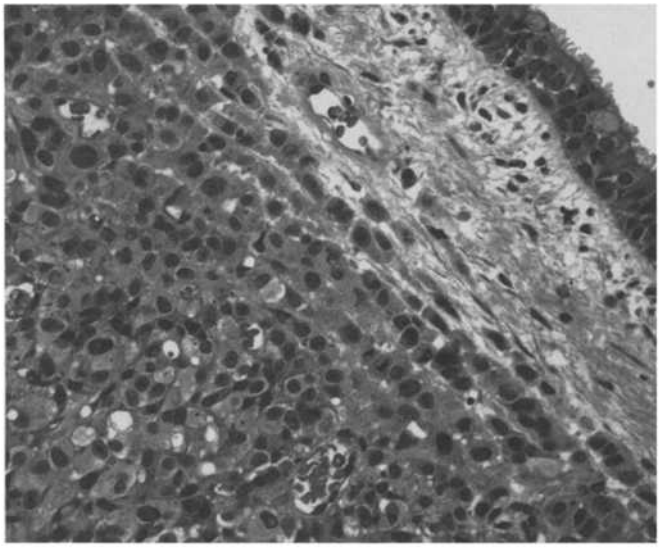


Fig. 35. Malignant melanoma. Cytokeratin and S-100 immunohistochemistry is crucial in the work-up of any undifferentiated sinonasal tumor in which melanoma is a diagnostic consideration.

Microscopic

- Epithelioid and/or spindle cells (**Figure 35**)
- Small and pleomorphic cell types less common
- Frequently arranged in a peritheliomatous distribution
- Prominent eosinophilic nucleoli
- Often amelanotic

Immunohistochemistry

- S-100 protein+, HMB45+, Melan A+, tyrosinase+, microphthalmia transcription factor+, vimentin+, cytokeratin–, LCA–

Differential Diagnosis

- Carcinoma: cytokeratin+, vimentin–
- Olfactory neuroblastoma: synaptophysin+, chromogranin+/–, S-100 protein+ sustentacular cells
- Lymphoma: lymphoid cell markers+, S-100 protein–

Neuroendocrine carcinoma

Clinical

- Mean age ~50 years
- Recurrences and metastasis in 70%, occurred later than the third year

Microscopic

- Small to intermediate sized cells, scanty cytoplasm
- Nuclei oval or round, hyperchromatic with inconspicuous nucleoli
- Nested, cord-like, and trabeculae growth
- Necrosis and hemorrhage
- Nuclear molding and crush artefact
- Ultrastructurally: dense core granules

Immunohistochemistry

- Cytokeratin+, synaptophysin+, chromogranin+/–

Differential Diagnosis

- Olfactory neuroblastoma
  - S-100 protein+ sustentacular cells, cytokeratin–, younger pt
- Melanoma
  - S-100 protein+, HMB45+, Melan A+, tyrosinase+, microphthalmia transcription factor+, cytokeratin–
- Sinonasal undifferentiated carcinoma
  - Synaptophysin–, chromogranin–

Adenocarcinoma

Clinical

- Relatively rare
- Woodworkers have a higher incidence of nasal vault enteric-type tumors

Microscopic

- Enteric-type: cytologically high grade simulates colonic carcinoma histologically
- Low-grade: tubulopapillary most common pattern, variety of others; cytologically bland, unencapulated

Differential Diagnosis

- Metastatic adenocarcinoma of colonic origin
- Adenoma of salivary gland type-very unusual

Rhabdomyosarcoma

Clinical

- Generally tumor of childhood, mean age 4 yrs

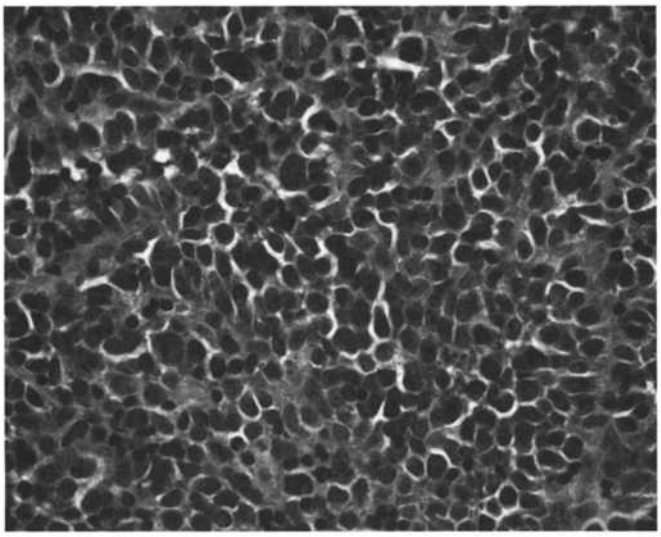


Fig. 36. Immunohistochemistry is fundamental in the diagnosis of small blue cell tumors. This rhabdomyosarcoma of the head and neck was metastatic to lymph node.

- Nasopharynx second most common site in head and neck after orbit
- Embryonal is the most common subtype

Microscopic

- 'Small blue cell tumor', primitive cells, variably spindled with hyperchromatic nuclei and high mitotic rate (**Figure 36**)
- Ultrastructurally z-bands and myofilaments

Immunohistochemistry

- MyoD1+, myogenin+, desmin+, muscle-specific actin+, CD99–

Differential Diagnosis

- Other small round blue cell tumors of childhood, *see* Soft tissue chapter

Nasopharyngeal Carcinoma

Subtypes

- Keratinizing differentiated carcinoma (WHO type I)
- Non-keratinizing differentiated carcinoma (WHO type II)
- Undifferentiated carcinoma (WHO type III)

Clinical

- Types II and III:
  - Strong EBV association
  - Most common head and neck malignancy in southeastern China and Taiwan
  - High risk populations include southern Chinese, Eskimos and other natives of the Arctic region
  - HLA-A2 and HLA-B-Sin 2 histocompatibility loci have been identified as possible markers for genetic susceptibility
  - Bimodal age incidence with peaks occurring near 20 and 65 yrs of age
  - Otitis media, hearing loss
  - Metastatic disease is first presentation of disease (i.e., neck mass) in ~50%
  - All subtypes considered variants of squamous cell carcinoma
  - High radiosensitivity
  - 5 year survival >60%
- Type I:
  - Weaker association with EBV
  - Older patients
  - 5 year survival <40%
  - Larger tumors

Microscopic

- WHO type I:
  - Keratinizing squamous cell carcinoma, as seen elsewhere
- WHO type II:
  - Nests and sheets of epidermoid appearing cells lacking keratinization
  - Large, oval, vesicular nuclei with prominent nucleoli
  - Robust lymphoplasmatic inflammation accompanies the tumor
- WHO type III:
  - Polygonal cells with indistinct cytoplasmic membranes imparting a syncytial appearance
  - Dense lymphoplasmatic inflammation which may obscure tumor cells
  - Vesicular nuclei with little chromatin and distinct nuclei membranes
  - No keratinization

Immunohistochemistry

- Cytokeratin+

Differential Diagnosis

- Lymphoma:
  - Lymphoid markers+, cytokeratin–
- Melanoma:
  - S-100 protein+, cytokeratin–

Miscellaneous Lesions

Respiratory Epithelial Adenomatoid Hamartoma

- Polypoid proliferation of respiratory ciliated cells, that must be distinguished from well differentiated adenocarcinoma

Necrotizing Sialometaplasia

- May involve seromucinous glands at any site including upper aerodigestive tract common following chemoradiation therapy
- Histological mimic of squamous cell carcinoma

Cholesterol Granuloma

- Cholesterol debris, giant cells, hemosiderin
- Etiology-? resorbing hemorrhage

Chondromesenchymal Hamartoma

- Intranasal/paranasal mass in infants
- Foci of cartilage within bland spindle cells with fibrosis stroma, aneurysmal bone cyst-like change with giant cells may be present

Extranodal Sinus Histiocytosis (Sinus Histiocytosis with Massive Lymphadenopathy, Rosai-Dorfman Disease)

- Self-limited mixed inflammatory disease; lesion defining cells are foamy histiocytes that often contain intracytoplasmic lymphocytes

Fibromatosis

- Rare, histologically similar to fibromatosis occuring elsewhere
- Differential diagnosis: solitary fibrous tumor, low-grade sarcomas

Hemangioma of Nasofacial Bones

- Grossly produces bony irregularities
- Easily overlooked on microscopic examination; cavernous thin walled vessels fill and expand marrow space

Meningioma

- Histology similar to those of conventional intracranial lesions, including nuclear pseudoinclusions, psammoma bodies

Mesenchymal Chondrosarcoma

- Primitive appear spindle cell tumor, hemangiopericytoma-like pattern common, with foci of cartilaginous matrix
- Paucity of cartilaginous matrix may obscure diagnosis

Osteoma

- Dense tumor-like lesion of lamellar bone
- Gardner's syndrome: craniofacial osteomas, gastrointestinal adenomas, fibromatosis, keratinous cysts

Metastatic Tumors

- Most common is renal cell carcinoma followed by lung, breast, thyroid and prostate primaries

Pituitary Adenoma

- Sinus involvement via extension from an intrasellar lesion or as primary ectopic tumor (**Figure 37**)

Salivary Gland Tumors

- Rare, aside from adenoid cystic carcinoma
- Unusual reports of most types exist

Sarcoma

- Wide array including: osteosarcoma, chondrosarcoma, Ewing's sarcoma/PNET, soft tissue sarcomas

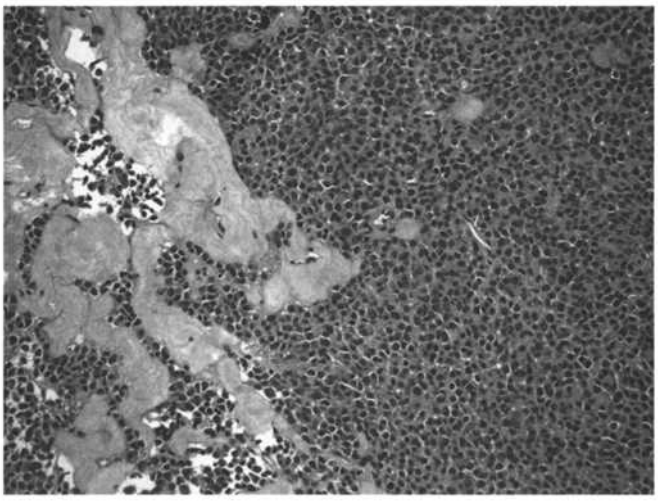


Fig. 37. Pituitary adenoma may rarely present as a sinus tumor as in this case.

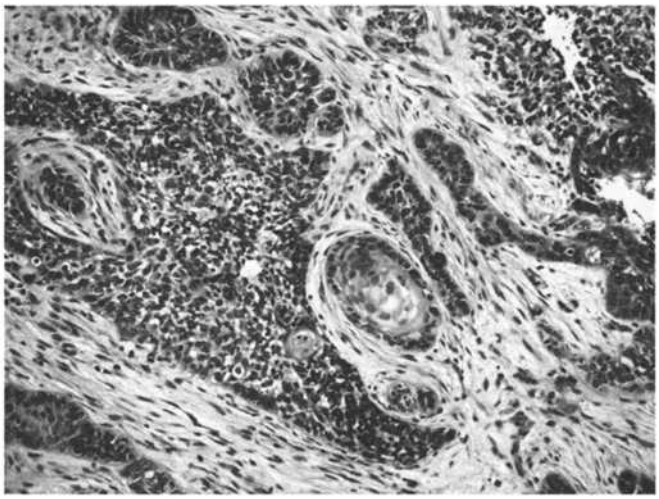


Fig. 38. Teratocarcinosarcoma is an unusual sinus tumor that is reminiscent of germ cell neoplasia. Primitive or blastema-like elements are common and may accompany malignant squamous and/or glandular components.

- Chondrosarcoma is rare though most occur in sinuses, opposed to nasal septum

Solitary Fibrous Tumor

- Many recent reports of sinonasal solitary fibrous tumor
- CD34+, vimentin+, S-100 protein–
- Differential diagnosis: hemangiopericytoma, angiofibroma, and fibrous histiocytoma

Teratocarcinosarcoma

- Histologically complex: features of an immature teratoma mixed with carcinoma, neuroectodermal/rosette-like structures typical (**Figure 38**)
- Differential diagnosis: sarcomatoid carcinomas, sarcomas, and olfactory neuroblastoma

LARYNX AND TRACHEA

Infection

Disseminated Fungal Infection

Clinical

- A variety of disseminated fungal infections may have laryngeal manifestations, including histoplasmosis, blastomycosis, cryptococcosis, coccidioidomycosis (*see* above under Oral Section)
- Preceded by pulmonary infection
- Clinical impression is often laryngeal carcinoma or tuberculosis

Microscopic

- Typically granulomatous inflammatory response, including histiocytes, giant cells, and necrosis
- Neutophilic infiltration with giant cells characteristic of blastomycosis (**Figure 39**)
- Blastomycosis notorious for associated pseudo-epitheliomatous hyperplasia, simulating squamous cell carcinoma
- Granulomas may be absent (i.e., bug-laden, foamy histiocytes with necrosis and non-specific inflammation common appearance of histoplasmosis)

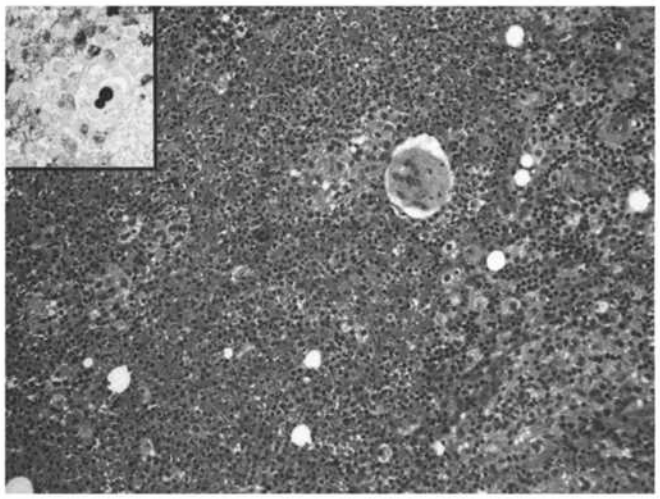


Fig. 39. In Blastomycosis granulomatous inflammation is typically rich with neutrophils. (inset) GMS stain showing broad-based budding yeast.

Inflammatory/Non-Neoplastic Lesions

Laryngocele

Clinical

- Congenital or acquired air-filled (can accumulate fluid) dilation of the laryngeal saccule

Microscopic

- Lined by respiratory type epithelium, may undergo oncocytic metaplasia
- Chronic inflammation
- Neutrophils indication secondary infection-laryngopyocele

Oncocytic Cyst

Clinical

- Hoarseness
- Elderly
- Most common within the ventricle

Microscopic

- Cystic change involving seromucinous glands of larynx (**Figure 40**)
- Cysts and papillary infoldings lined by large oncocytic cells
- Resemble Warthin's tumor, though lack prominent lymphoid component

Laryngeal Nodule/Polyp

Clinical

- Polyp or nodule(s) on true vocal cord
- Associated with voice overuse

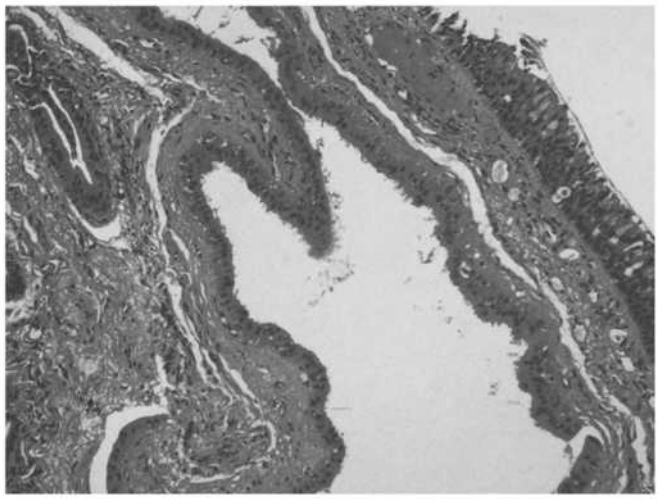


Fig. 40. Oncocytic cysts larygneal cysts are non-neoplastic lesions that occur with increasing frequency in the elderly.

Microscopic

- Varying degrees of stomal hyaline and myxoid change/degeneration (**Figure 41**)
- Perivascular hyalinization
- Congestion/hemorrhage and thrombosis
- Increased stromal cellularity may simulate neoplasm
- Overlying mild squamous atypia may be present

Contact Ulcer

Clinical

- Posterior commissure
- Often recurs
- Gastric reflux implicated in pathogenesis

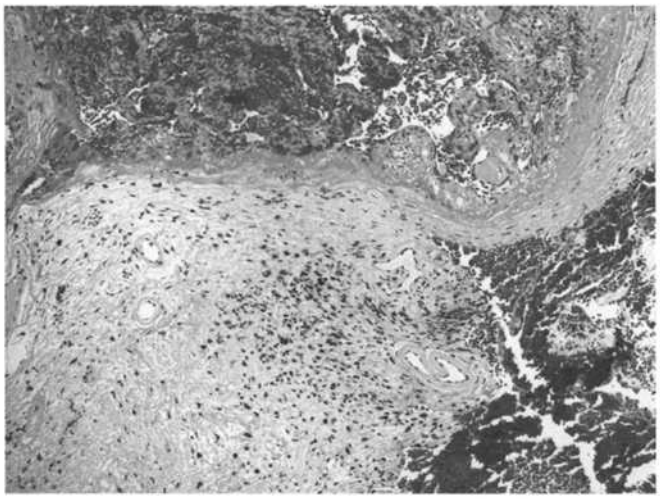


Fig. 41. Laryngeal polyps are characterized by myxoid stroma and are often exhibit hemorrhage and thrombosis as seen in this case.

Microscopic

- Markedly inflamed stroma with ulceration
- May appear polypoid
- Adjacent epithelial hyperplasia

Differential Diagnosis

- Characteristic location/clinical features aids distinction from potential mimics such as hemangioma, spindle cell carcinoma, and granulomatous infectious disease

Benign Neoplasms

Laryngeal Papillomatosis (Squamous Papillomas)

Clinical

- Juvenile laryngeal papillomas-onset in childhood/adolescence
- Centered upon true cords, extension to false cords, vestibule and subglottis not uncommon, rarely involves trachea and bronchi
- Multiple recurrences typical, most cases eventually regress
- Progressive disease leading to death can occur
- Results from vertically transmission of human papillomavirus infection, HPV types 6 & 11
- Adult laryngeal papillomas tend to be solitary, recur less often, same HPV association

Microscopic

- Branching papillary proliferations of squamous epithelium (**Figure 42**)
- Basal cell hyperplasia, koilocytosis, binucleated epithelial cells
- Nuclear atypia
- Increase mitotic activity
- Parakeratin

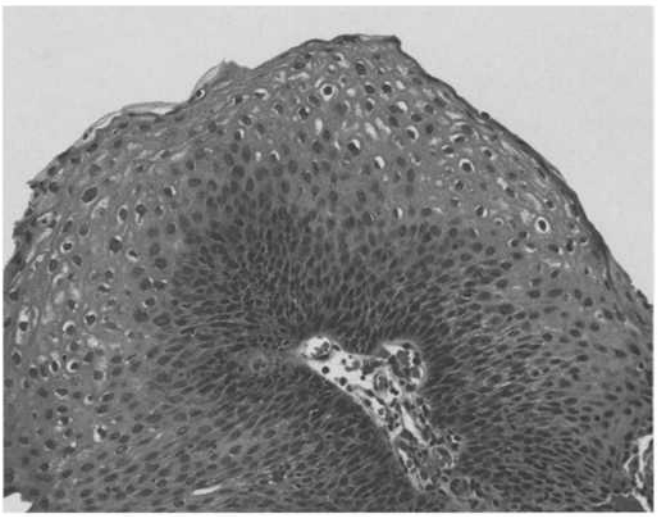


Fig. 42. Numerous HPV-induced squamous papillomas are encountered in laryngeal papillomatosis.

Immunohistochemistry

- HPV antigen+
- HPV 6/11+ (*in-situ* hybridization)

Differential Diagnosis

- Invasive papillomatosis:
  - Histologically identical to typical papillomas, though exhibits invasive growth pattern into adjacent soft tissues of larynx
- Squamous cell carcinoma, papillary type:
  - Greater cytologic atypia than papilloma
  - Lacks koilocytic features of papilloma

Premalignant/Malignant Neoplasms

Hyperkeratosis

Clinical

- True cords/interarytenoid area
- Associated with hoarseness
- Smokers, voice abusers

Microscopic

- Acanthotic cytologically bland squamous epithelium with hyperkeratosis

Variant

- Verrucous hyperkeratosis:
  - Hyperkeratosis with verrucoid or papillary architecture
  - Lacks the papillary branching of papilloma
  - Lacks the invasion seen verrucous carcinoma

Squamous Dysplasia/Carcinoma In-Situ

- Keratotic lesions showing spectrum of dysplasia to squamous cell carcinoma *in-situ*

- WHO grades dysplasia into mild, moderate, severe, and carcinoma *in-situ*
- Correlation between degree of dysplasia and progression to invasive carcinoma
- Progression to invasion may take years
- Reproducibility of dysplasia grading poor
- Atypia induced by previous radiation therapy may simulate dysplasia/carcinoma *in-situ*

Squamous Cell Carcinoma

Clinical

- Most common neoplasm of the larynx
- Separated into glottic (65%), supraglottic (35%), and infraglottic (<5%) tumors
- Smoking dominant risk factor for all types, including variants
- Mean age = 60 years
- Over 90% of carcinomas squamous type
- Most common site is anterior part of the true cord
- Lung most common site of blood borne metastases

Microscopic

- Keratin production, intracellular bridges, and/or dyskeratotic cells
- Graded as well, moderately or poorly differentiated
- Varying degrees of exophytic/papillary growth may occur in a given tumor

Verrucous Carcinoma

Clinical

- Low grade variant of squamous cell carcinoma occurring most frequently in the oral cavity
- Clinicopathologic features similar to those occuring elsewhere (i.e., non-metastasizing)
- Grossly gray-white warty broadly implanted mucosal growth
- ~2% of glottic carcinomas
- Cooperation between the pathologist and the clinician typically necessary to establish diagnosis of biopsy material

Microscopic

- *See* above, Oral cavity section
- No to little cytologic atypia

Differential Diagnosis

- Verrucous hyperkeratosis (verrucous squamous hyperplasia):
  - Lacks pushing border of invasion
  - Broadly implanted lesion raises suspicion for carcinoma, requires clinical input

Basaloid Squamous Cell Carcinoma

Clinical

- High grade variant of squamous cell carcinoma with predilection for the supraglottic larynx, hypopharynx, and tongue base
- Often exophytic
- Biologically high-grade tumor with a propensity for nodal as well as systemic metastases
- 5 year survival rate ~18%

Microscopic

- Lobular, solid, trabecular, and cribriform patterns
- Pleomorphic basaloid-appearing cells with hyperchromatic nuclei, inconspicuous to prominent nucleoli, and variable cytoplasm
- Peripheral nuclear palisading, squamous differentiation centrally
- Brisk mitotic activity, necrosis
- Intercellular stromal hyalinization (simulating salivary gland tumor)
- Neural-type rosettes may be found

Immunohistochemical

- Cytokeratin+, EMA+/–, CEA+/–

Differential Diagnosis

- Adenoid cystic carcinoma:
  - Lacks squamous differentiation
  - Tends to lack the pleomorphism seen in basaloid squamous cell carcinoma
- Small cell neuroendocrine carcinoma:
  - Synaptophysin+, HMW cytokeratin–

Sarcomatoid Carcinoma (Spindle Cell Carcinoma)

Clinical

- Variant of squamous cell carcinoma
- Larynx most common site for spindle cell carcinoma, although also occurs in oral and nasal cavities, paranasal sinus, hypopharynx, esophagus
- Average age = 66 years
- Most tumors are glottic
- Mean tumor size >2 cm
- May simulate benign polyp
- Recurrences may develop in up to ~50% of patients
- Survival related to depth of invasion

Microscopic

- Component of squamous cell carcinoma or in-situ carcinoma coexists with malignant spindle cell component may be cytologically bland or markedly atypical
- Foci of benign or malignant-appearing cartilage and/or bone may be present (so-called 'carcinosarcoma')
- Giant cells may be present

Immunohistochemistry

- Spindle cells: cytokeratin+, vimentin+

Differential Diagnosis

- Reactive lesions:
  - Cytologically bland appearance of spindle cell carcinoma can belie its malignant nature
  - Cytokeratin–
- Mesenchymal malignancies:
  - Lack associated carcinoma in-situ and/or invasive epithelial component
  - Cytokeratin–

Papillary Squamous Cell Carcinoma

Clinical

- Exophytic HPV-associated variants of squamous cell carcinoma, *see* Oropharyx section
- Laryngeal primary tumors have the best prognosis relative to papillary squamous cell carcinoma arising elsewhere

Microscopic

- Papillary condylomatous-like architecture
- Cytologic atypia exceeds that seen in papillomas/condylomas

Differential Diagnosis

- Squamous papillomas with or without dysplasia:
  - Exhibit less cytologic atypia
  - Koilocytes present

Lymphoepithelioma-Like Carcinoma

Clinical

- Most cases have not been associated with EBV
- Behaves similar to nasopharyngeal carcinoma-lymph node metastasis occurs in most patients
- Visceral dissemination occurs in ~25%

Microscopic

- Similar to counterpart occurring in the nasopharynx.
- Large, poorly differentiated, nonkeratinized cells intermingled with small nonneoplastic lymphocytes and plasma cells.

Immunohistochemical

- *Cytokeratin+*

Differential Diagnosis (see **Table 1***)*

- Lymphoma
  - Lymphoid markers+, cytokeratin–
- Malignant melanoma
  - S-100 protein+, cytokeratin–

Small Cell (Neuroendocrine) Carcinoma

Clinical

- Histologically identical to it pulmonary counterpart
- Early development of metastatic disease
- Mean survival 11 months
- Strong association with smoking

Microscopic

- Hyperchromatic cells with scant cytoplasm
- Nuclear molding with crush artefact
- Inconspicuous nucleoli

Immunohistochemical

- Synaptophysin+, chromogranin+/–, cytokeratin+, NSE+

Differential Diagnosis

- Lymphoma
  - Lymphoid markers+, cytokeratin–

Large Cell Neuroendocrine Carcinoma

Clinical

- Most arise in supraglottis
- Mean survival 36 months
- Strong association with smoking
- Lymph node and systemic metastasis

Microscopic

- Nested, trabecular growth
- Pleomorphism, mitotic figures, necrosis
- Hyperchromatic nuclei with variable chromatin
- Ultrastructurally: dense core neurosecretory granules

Immunohistochemical

- Cytokeratin+, synaptophysin+, chromogranin+

Differential Diagnosis

- Paraganglioma
  - S-100 protein+ sustentacular cells
  - Lacks mitotic activity
  - Cytokeratin–

Adenoid Cystic Carcinoma

Clinical

- Second most common malignant tumor of trachea after squamous cell carcinoma
- Slow but relentless course with poor prognosis

Microscopic

- Similar to those occuring elsewhere
- Cribriform, tubular, and solid patterns

Chondrosarcoma

Clinical

- Most common malignant mesenchymal tumor of the larynx in adults
- Hoarseness
- Involved the cricoid cartilage
- Mean size = 3.5 cm
- Majority low-grade (grade 1 or 2 chondrosarcoma)

- ♦ May be associated with benign chondroma
- ♦ Conservative resection advocated for low-grade tumors

Microscopic

- ♦ Lobules of well-differentiated cartilage
- ♦ Increased cellularity
- ♦ Chondrocyte atypia including nucleoli, binucleation, pleomorphism

Differential Diagnosis

- ♦ Chondroma:
  - – Distinction can be difficult as is the case for cartilaginous tumors occurring elsewhere
  - – Some have advocated considering all symptomatic lesions as representing chondrosarcoma - nomenclature aside, surgeons must be informed that conservative resection is the treatment of choice for low-grade tumors

Mesenchymal/Soft Tissue Tumors

- ♦ Unusual reports described a wide spectrum of benign and malignant mesenchymal neoplasms arising in the larynx (*see* soft tissue chapter)
- ♦ The most frequent malignant laryngeal neoplasm in children and adolescents is the embryonal variant of rhabdomyosarcoma

TNM CLASSIFICATIONS

TNM Classifications for the Lip and Oral Cavity

Rules for Classification

- ♦ The classification applies only to carcinomas. There should be histologic confirmation of the disease.
- ♦ The following are the procedures for assessing T, N, and M categories:
  - – T categories: Physical examination, laryngoscopy, and imaging
  - – N categories: Physical examination and imaging
  - – M categories: Physical examination and imaging

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 2 cm of less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4 (lip)	Tumor invades adjacent structures (e.g., through cortical bone, inferior alveolar nerve, floor of mouth, skin of face)
T4 (oral cavity)	Tumor invades adjacent structures (e.g., through cortical bone, into deep [extrinsic] muscle of tongue, maxillary sinus, skin; superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify as T4)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension:
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

TNM Classifications for the Larynx

Definition of TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ

Supraglottis

T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic tissues
T4	Tumor invades through the thyroid cartilage, and/or extends into soft tissue of the neck, thyroid, and/or esophagus

Glottis

T1	Tumor limited to the true vocal cords (may involve anterior or posterior commissure) with normal mobility:
	T1a: Tumor limited to one true vocal cord
	T1b: Tumor involves both true vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired true vocal cord mobility
T3	Tumor limited to the larynx with true vocal cord fixation
T4	Tumor invades through the thyroid cartilage and/or to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including tyroid, pharynx)

Subglottis

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cords with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4	Tumor invades through cricoid or thyroid cartilage and/or extends to other tissues beyond the larynx (e.g., trachea, soft tissues of neck, including thyroid, esophagus)

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension:
N2a:	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b:	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c:	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

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19

Eye and Ocular Adnexa

Jose M. Bonnin, MD

CONTENTS

I. Basic Anatomy of the Eye 19-3

II. Diseases That Affect Multiple Structures in the Eye 19-3

Glaucoma 19-3
Retinopathy of Prematurity 19-3
Persistent Hyperplastic Primary Vitreous 19-3
Inflammations of eye 19-4
Acute Inflammation 19-5
Endopthalmitis 19-5
Panophthalmitis 19-5
Chronic Nongranulomatous Inflammation 19-5
Chronic Granulomatous Inflammation 19-6
Sympathetic Ophthalmia (Sympathetic Uveitis) 19-6
Phacoantigenic Endophthalmitis 19-7
Diabetes 19-7
Coat's Disease 19-8
Massive Retinal Gliosis 19-8
Phthisis Bulbi 19-8

III. Cornea 19-8

Basic Anatomy of the Cornea 19-8
Corneal Edema and Bullous Keratopathy 19-8
Stromal Scarring and Vascularization 19-9
Corneal Opacifications 19-9
Keratitis and Corneal Ulcers 19-10
Syphilitic Keratitis 19-10
Orchocerciasis 19-10
Peripheral Corneal Ulcers 19-10
Ring Ulcer and Ring Abscess 19-10
Central Corneal Ulcers 19-10
Herpes Simplex Keratitis 19-11
Bacterial Ulcers 19-11
Mycotic Ulcers 19-11
Acanthamoeba Corneal Ulcer 19-11
Complications of Corneal Ulcers 19-11
Failed Corneal Graft 19-11
Corneal Degenerations and Dystrophies 19-12
Fuchs' Dystrophy 19-12
Granular Dystrophy 19-12
Macular Dystrophy 19-13
Lattice Dystrophy 19-13
Lipid Degeneration 19-13
Keratoconus 19-13

IV. Conjunctiva 19-14

Limbal Dermoids 19-14
Complex Choristomas 19-14
Degenerations 19-14
Pinguecula 19-14
Pterygium 19-14
Conjunctival Cysts 19-14
Conjunctival Inclusion Cysts 19-14
Ductal Cysts 19-15
Conjunctival Inflammations 19-15
Acute Conjunctivitis 19-15
Superior Limbal Keratoconjunctivitis 19-15
Chronic Follicular Conjunctivitis 19-15
Chronic Papillary Conjunctivitis 19-16
Ligneous Conjunctivitis 19-16
Sarcoidosis 19-17
Rhinosporidiosis 19-17

V. Tumors and Mass Lesions of Conjunctiva 19-17
Conjunctival Papillomas.....19-17
Conjunctival Intraepithelial Carcinoma (Squamous Cell Carcinoma In Situ) 19-17
Invasive Squamous Cell Carcinoma.....19-17
TNM Classification of Carcinoma of the Conjunctiva 19-17
Melanocytic Lesions of the Conjunctiva 19-18
Congenital and Acquired Melanosis 19-18
Congenital Melanosis Oculi 19-18
Primary Acquired Melanosis.....19-18
Secondary Acquired Melanosis 19-18
Nevi 19-18
Malignant Melanoma 19-18
TNM Classification of Malignant Melanoma of the Conjunctiva 19-19
Lymphoid Tumors 19-19

VI. Tumors of the Eye 19-19
Malignant Melanoma 19-19
TNM Classification of Melanoma of the Uvea.....19-20
Retinoblastoma.....19-22
TNM Classification of Retinoblastoma 19-23
Other Tumors of the Eye 19-25
Malignant Lymphoma.....19-25
Fuchs' Adenoma 19-25
Medulloepithelioma 19-25
Leiomyoma.....19-25
Vascular Anomalies and Hemangioblastoma 19-25
Glial Tumors of the Retina.....19-25
Metastatic Tumors 19-25

VII. Eyelids 19-25
Anatomical Components 19-25
Inflammations.....19-25
Chalazion 19-25
Hordeolum 19-26
Cystic Lesions of the Eyelid 19-26
Hydrocystomas 19-26
Apocrine Hydrocytstomas.....19-26
Eccrine Hydrocytstomas 19-26
Amyloidosis 19-26
Tumors and Other Mass Lesions 19-27
Squamous Papilloma 19-27
Xanthelasma 19-27
Squamous Cell Carcinoma 19-27
Sebaceous Carcinoma.....19-28
TNM Classification of Carcinoma of the Eyelid.....19-28

VIII. Lacrimal Apparatus 19-29
Dacryocystitis.....19-29
Dacryolithiasis 19-29
Tumors of the Lacrimal Sac. 19-30
Tumors of the Lacrimal Gland.....19-30
TNM Classification of Carcinoma of the Lacrimal Gland 19-30

IX. Orbit 19-30
Tumors and Mass Lesions of the Orbit 19-30
Inflammatory Pseudotumors.....19-30
Graves' Disease.....19-32
Rhabdomyosarcoma of the Orbit 19-32
TNM Classification of Sarcoma of the Orbit.....19-33
Glioma of the Optic Nerve 19-33
Meningioma of the Optic Nerve.....19-33
Lymphoid Tumors.....19-34

X. Suggested Reading.....19-34

BASIC ANATOMY OF THE EYE

- Histopathological evaluation of ophthalmic lesions requires some basic knowledge of the normal anatomy and histology of the eye and its adnexa
- Ocular lesions may affect one or more structures in the eye
- The basic structure of the eye consists of concentric layers or coats and the transparent media:
  - Fibrous coat:
    - Cornea
    - Sclera
  - Uveal tract or vascular coat:
    - Iris
    - Ciliary body
    - Choroid
  - Neural coat:
    - Retina
  - Transparent media:
    - Cornea
    - Anterior chamber
    - Lens
    - Vitreous body
  - Optic nerve

DISEASES THAT AFFECT MULTIPLE STRUCTURES IN THE EYE

Glaucoma

- An optic neuropathy associated with excavation of the optic nerve disc and progressive visual loss due to loss of ganglion cells and optic nerve fibers in the inner layers of the retina
- Often, but not always, associated with elevated intraocular pressure
- Aqueous humor is produced in ciliary body processes, flows through the pupil into the anterior chamber and is largely resorbed in the trabecular meshwork in the angle of the anterior chamber

Congenital Glaucoma

- Etiology: malformations involving iris and angle of anterior chamber (*see* **Table 1**)

Clinical

- Elevated intraocular pressure
- Corneal edema
- Generalized enlargement of the eye (buphthalmos)

Microscopic

- Degeneration an atrophy of inner layers of retina, mainly ganglion cell layer and optic nerve fiber layer
- Optic nerve atrophy with excavation ("cupping") of optic nerve head
- Corneal edema
- Rupture of corneal Descemet's membrane and Haab's striae
- Atrophy of iris and ciliary body

Acquired Glaucoma

Types

- Primary:
  - Open-angle glaucoma or simple
  - Closed-angle glaucoma
  - Secondary (*see* **Table 2**) **(Figure 1)**

Microscopic

- Degeneration and atrophy of inner layers of retina, mainly ganglion cell layer and optic nerve fiber layer
- Optic nerve atrophy with excavation ("cupping") of optic nerve head
- Corneal edema
- Atrophy and fibrosis of anterior uvea (iris and ciliary body)
- Histological changes associated with coexisting lesions (*see* **Table 2**)

Retinopathy of Prematurity (Retrolental Fibroplasia)

Clinical

- Usually develops in premature infants after birth
- Usually received supplemental oxygen therapy in early postnatal period
- May present with "white pupil" or "leukocoria"
- Often bilateral

Microscopic

- Capillary proliferation in retina
- Hemorrhages and fibrosis
- Fibrous membranes with tractional detachment of the retina:
  - Fibrous mass behind the lens may simulate retinoblastoma

Persistent Hyperplastic Primary Vitreous

Clinical

- Congenital anomaly present at birth
- Often associated with microophthalmia
- Usually unilateral
- May present with "white pupil" or "leukocoria"

Table 1. Diseases Associated With Congenital Glaucoma
Iris Anomalies
Iridocorneal Synechiae and Other Anomalies
Peter's Anomaly
Axenfeld's Anomaly
Rieger's Anomaly
Phacomatoses
Neurofibromatosis
Sturge-Weber Syndrome
Rubella
Marfan's Syndrome
Persistent Hyperplastic Primary Vitreous
Retinopathy of Prematurity
Retinoblastoma
Juvenile Xanthogranuloma

Table 2. Conditions Associated With Secondary Glaucoma
Abnormalities of the Native Lens
Lens Dislocation
Persistent Flat Anterior Chamber (Post Eye Trauma)
Iridocorneal Endothelial Syndrome
Anterior Uveitis (Iritis)
Retinopathy of Prematurity
Persistent Hyperplastic Primary Vitreous
Iris Neovascularization
Cysts of Ciliary Body and Iris
Juvenile Xanthogranuloma
Intraocular Neoplasias
Hemorrhage in Anterior Chamber
Hemolysis

Microscopic

- Loose fibrovascular tissue in vitreous cavity **(Figure 2)**
- Persistence of hyaloid vessels
- Adipose tissue, muscle fibers and islands of cartilage
- Elongation of ciliary processes
- Retinal dysplasia

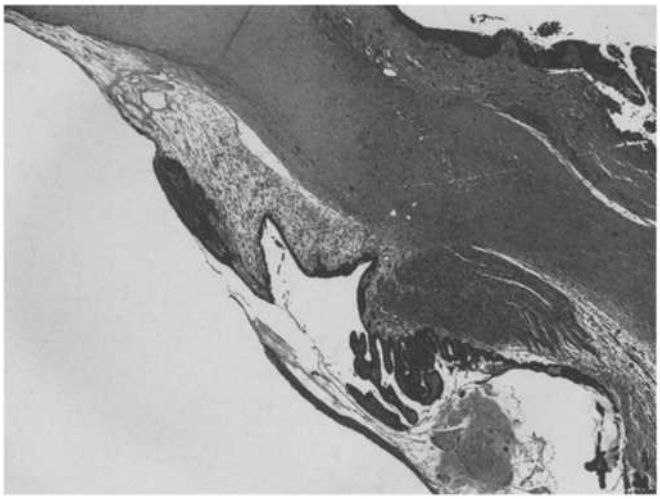


Fig. 1. Glaucoma. Closed-angle glaucoma due to extensive iridocorneal synechiae and obliteration of angle of anterior chamber in a patient with previous cataract surgery.



Fig. 2. Persistent hyperplastic primary vitreous. The vitreous cavity is occupied with a loose fibroconnective and adipose tissues and remnants of the hyaloid vessels. The vitreous contents are firmly adherent to the retina, which is detached and is dysplastic.

Inflammations of the Eye

- As in any other organ, inflammations may be acute or chronic
- May affect one or more coat of the eye or the transparent media
- Viruses, bacteria, fungi and parasites may affect the eye. **(Figure 3)**
- Infection occurs mainly by direct penetration of the infectious agent through a wound, traumatic or surgical

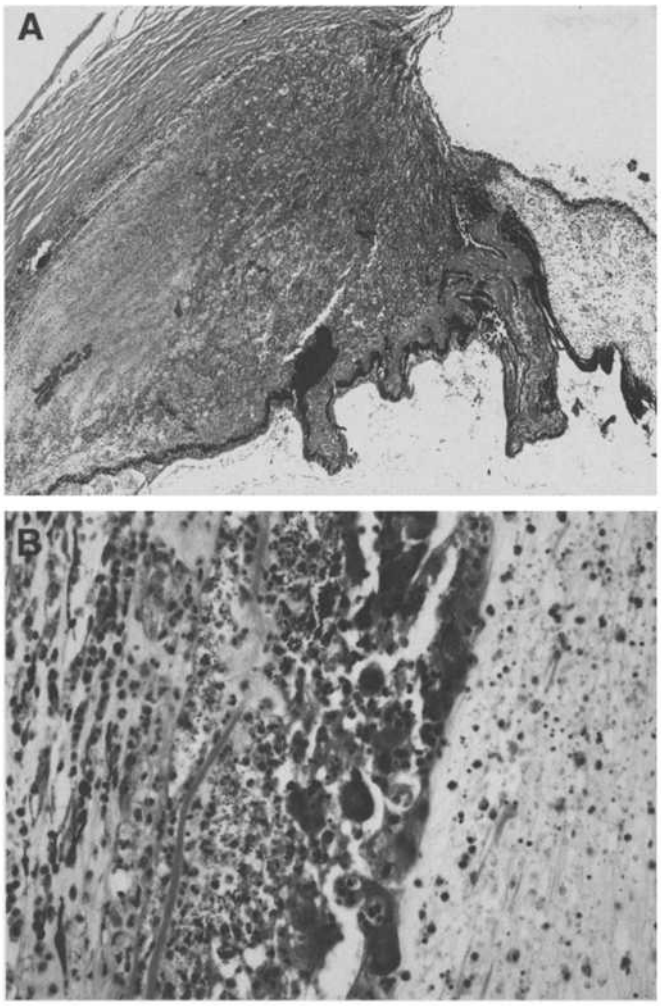


Fig. 3. Viral infection. **(A)** Marked inflammation of the ciliary body due to CMV uveitis and retinitis in an HIV positive patient. **(B)** CMV inclusions in necrotic retinal pigment epithelium.

- Agents may reach the eye by extension of infectious processes from adjacent structures (i.e. paranasal sinuses) or hematogenous dissemination

Acute Inflammation

Endopthalmitis

Clinical

- Inflammation of the vitreous and inner coats of the eye
- Etiology: bacteria, fungi, virus (herpes virus, cytomegalovirus, measles)
- Tumors with extensive necrosis (melanoma and retinoblastoma) may present as endophthalmitis

Microscopic

- Suppurative inflammation in anterior chamber and vitreous cavity **(Figure 4)**
- Variable degress of necrosis of uvea and retina

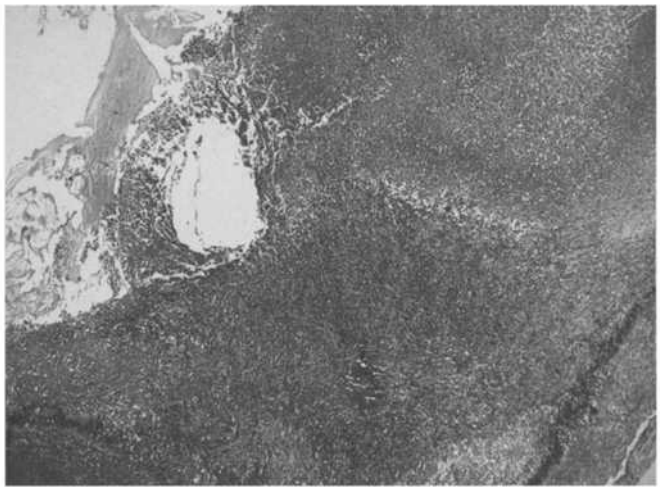


Fig. 4. Acute suppurative endophthalmitis with inflammation and necrosis of all intraocular structure.

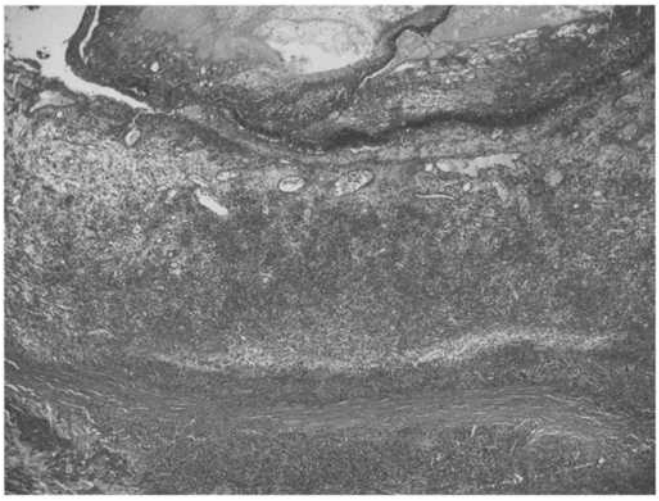


Fig. 5. Acute suppurative panophthalmitis. Purulent exudate extents beyond the cavities of the eye with almost complete necrosis of the sclera.

Panophthalmitis

Clinical

- Inflammation involving all coats of the eye, including the sclera:
  - Etiology is similar to endophthalmitis but viruses rarely affect the sclera

Microscopic

- Suppurative inflammation involving all chambers and coats of the eye
- Process may extend to adjacent orbital soft tissues **(Figure 5)**

Chronic Nongranulomatous Inflammation

- Usually affects of uveal tract (uveitis)

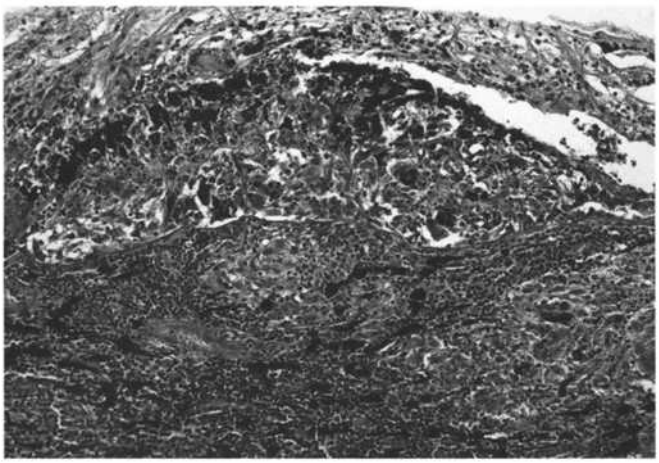


Fig. 6. Sympathetic ophthalmia. Ill-defined granulomas with multinucleated giant cells and marked lymphoplasmacytic infiltration in choroid. Noted the large group of epithelioid cells and pigment epithelium in the subretinal space, the Dalén-Fuchs' nodule, characteristic of sympathetic ophthalmia.

Etiology

- Infectious agents
- Noninfectious:
  - Physical and chemical injury
  - Allergic
- Affects one or more uveal structures:
  - Iritis
  - Cyclitis
  - Iridocyclitis
  - Choroiditis
- Uveitis may be associated with numerous syndromes:
  - Ankylosing spondylitis
  - Reiter's syndrome
  - Inflammatory bowel disease
  - Psoriasis

Microscopic

- Focal of diffuse small mononuclear cell infiltration
- Plasma cells may be the predominant elements in the infiltrate
- Iridocorneal synechiae, iris-lens synechiae and glaucoma may follow repeated episodes of inflammation in the iris
- In late stages of the disease, phthisis bulbi may develop

Chronic Granulomatous Inflammation

Sympathetic Uveitis (Sympathetic Ophthalmia)

Clinical

- Diffuse bilateral inflammation of the uveal tract following eye trauma or surgery

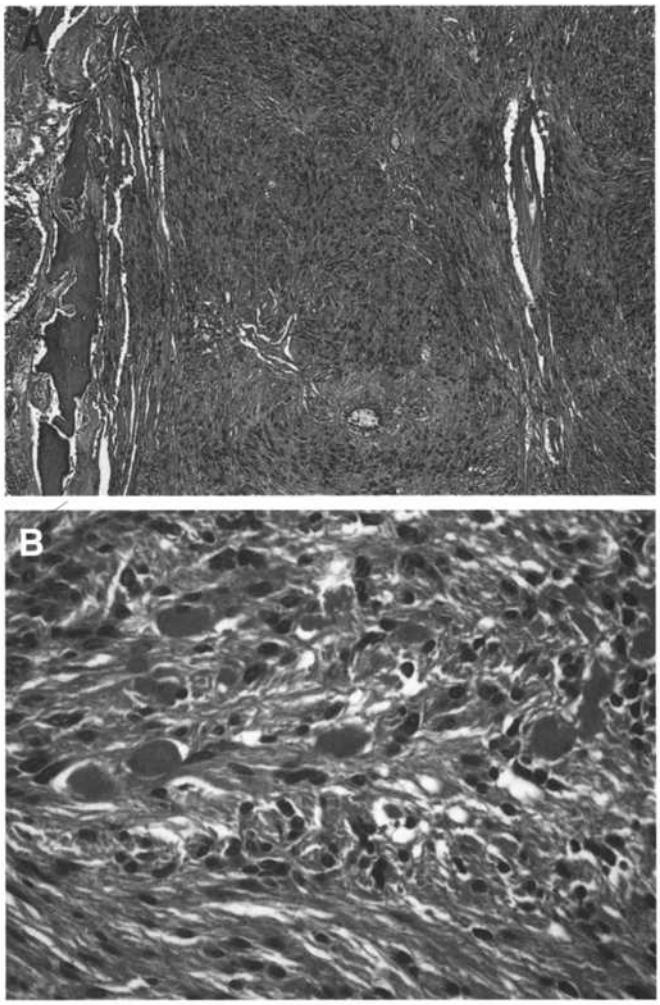
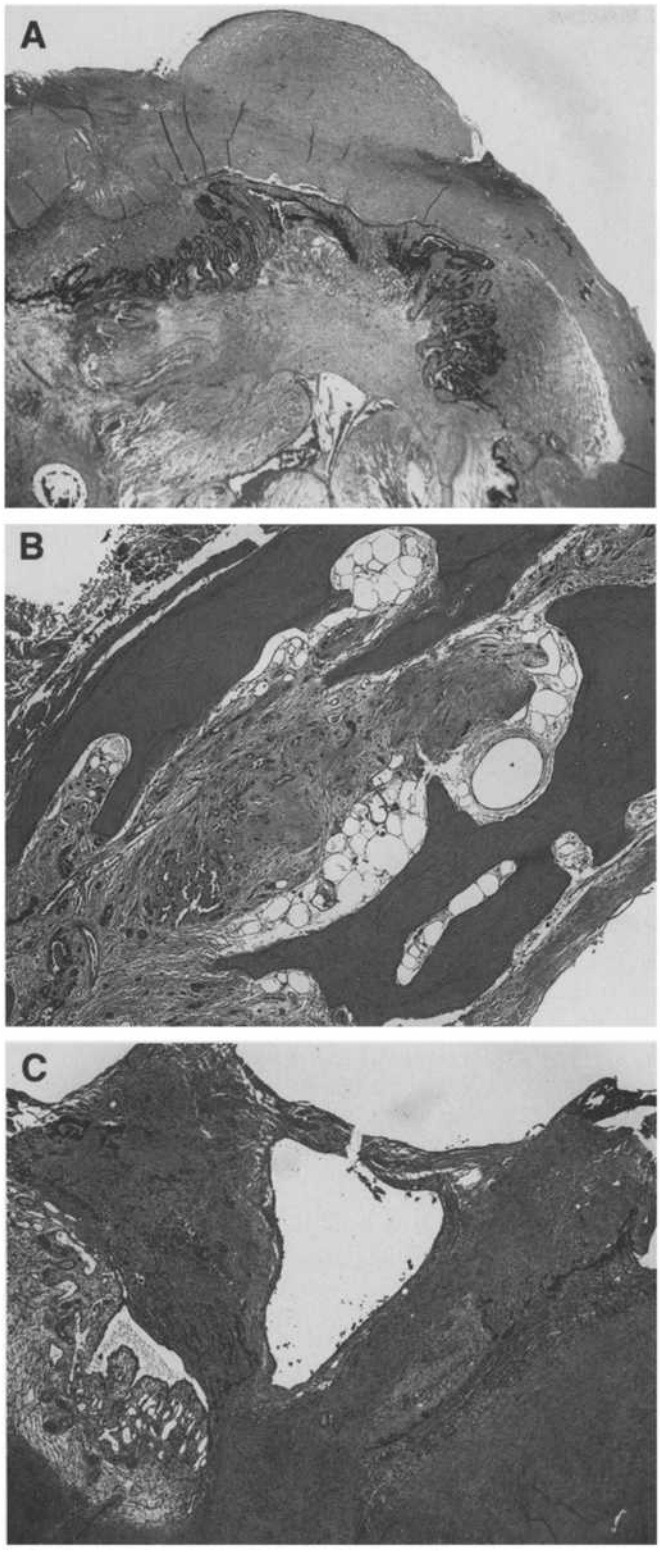


Fig. 7. **(A)** Massive gliosis of the retina in an eye enucleted several years after severe ocular trauma follow by phthisis bulbi. Note the focus of ossification. **(B)** Rosenthal fibers in densely reactive glial proliferation.

- Delayed hypersensitivity reaction to antigen released at the time of injury
- Develops 2 weeks to years after a penetrating or perforating trauma to the eye
- The contralateral eye (sympathizing eye) develops lesions similar to those present in the affected, previously injured eye (exciting eye)
- Uveal incarceration or prolapse into the wound is usually observed
- Initial presentation characterized by blurred vision, photophobia and muton-fat keratic deposits

Microscopic

- Diffuse granulomatous inflammation involving iris, ciliary body and choroid
- In the choroid, the choriocapillary layer is usually spared



- Epithelioid cells and multinucleated giant cells may contain phagocytized pigment granules in their cytoplasm
- Nodules of epithelioid cells and pigment laden cells (Dalén-Fuchs' nodules) in the subretinal space are characteristic **(Figure 6)**

Phacoantigenic Endophthalmitis

Clinical

- Rare severe granulomatous inflammation of the eye
- It is an immune complex disease with loss of immune tolerance
- Secondary to traumatic rupture of the lens capsule and release of lens proteins
- It may coexist with sympathetic ophthalmia

Microscopic

- Zonal granulomatous inflammation around lens with ruptured capsule
- First zone: Prominent polymorphonuclear cell infiltration
- Second zone: Layer of histiocytes and multinucleated giant cells
- Third zone: In the periphery, there is a layer of granulation tissue with lymphoplasmacytic infiltration

Diabetes

Clinical

- Major cause of blindness in the United States and other Western countries
- Women are more commonly affected
- Diabetes and its complications may involve:
  - All coats and transparent media in the eye
  - Optic nerve and intracranial visual pathways
  - Ocular adnexa
  - Orbit

Microscopic

- Conjunctival microaneurysms
- Recurrent erosions and corneal ulcers (in patients with diabetic neuropathy)
- Neovascularization of the iris (rubeosis iridis)
- Cataracts
- Glaucoma
- Proliferative retinopathy with retinal detachments
- Retinal hemorrhages
- Ischemic optic neuropathy

Fig. 8. Phthisis bulbi. **(A)** Marked shrinkage of entire globe with disorganization and atrophy of old intraocular structures. Note the scarring of the cornea, the atrophy and gliosis of the retina and the extensive syneachiae of the iris and ciliary body to the cornea. **(B)** Hyperplasia and metaplasia of the retinal pigment epithelium and foci of ossification. **(C)** Posterior aspect of the globe. Old retinal detachment with atrophy and gliosis of retina and reactive proliferation of the retinal pigment epithelium.

Coats' Disease

Clinical

- Exudative retinal detachment
- Usually unilateral
- Mainly affects male children up to 18 years of age
- Clinically, it mimics retinoblastoma

Microscopic

- Telangiectatic dilatation of retinal vessels, microaneurysms and areas of ischemia
- Protein and lipid rich transudate in outer retinal layers
- Subretinal exudates containing foamy macrophages and cholesterol crystals
- Retinal detachment

Massive Retinal Gliosis

Clinical

- Segmental or total replacement of neural retina by glial tissue
- Usually follows penetrating trauma to the eye
- Chronic inflammatory processes, congenital malformations and retinal vascular disorders may also develop massive retinal gliosis

Microscopic

- Large mass of glial cells that partially or totally fills the cavities of the eye
- Glial cells are elongated pilocytic and have long pale eosinophilic processes
- Rosenthal fibers and foci of calcification may occur within the mass **(Figure 7)**
- Blood vessels are usually dilated and have thin walls
- Degenerative changes in intraocular tissue and foci of ossification may be observed
  - Cells forming the mass are positive for glial fibrillary acidic protein (GFAP)

Phthisis Bulbi

Clinical

- End stage of many diffuse ocular diseases
- Usually submitted by the ophthalmologists with the diagnosis of "blind painful eye"
- Marked atrophy and shrinkage of the eye ball

Microscopic

- Marked shrinkage and disorganization of eye **(Figure 8)**
- Corneal scarring with or without vascularization
- Thickened sclera
- Profound disorganization of intraocular tissues
- Foci of calcification and ossification are usually observed

CORNEA

Basic Anatomy of the Cornea

- The normal cornea is 9 to 13 mm in diameter
- It is 0.8 to 0.9 mm thick in the center and 1.1 mm in the periphery
- The cornea has six anatomic layers:
  - Anterior corneal epithelium, five layers of non keratinizing squamous cells
  - Basement membrane of the anterior corneal epithelium
  - Bowman's membrane, thick layer of collagen fibrils
  - Stroma, represents 90% of the entire thickness of the cornea. It is made up of multiple lamellae of collagen and fibroblasts (keratocytes)
  - Descemet's membrane, thick basement membrane of the corneal endothelium
  - Corneal endothelium
- Blood vessels are not observed in the normal cornea
- There is a rich innervation (ophthalmic division of the trigeminal nerve)
- Mitoses are not observed in the anterior corneal epithelium except in the periphery (stem cell region). Cells are continuously replaced by sliding of cells from the periphery towards the center

Corneal Edema and Bullous Keratopathy

Clinical

- Corneal edema and bullous keratopathy are major indications for corneal transplantation
- Many clinical conditions are associated with corneal edema
- It may occur sometimes after intraocular surgery (i.e cataract extraction)
- It is usually secondary to dysfunction of the corneal endothelium (*"Endothelial decompensation"*)
- Edema may be bilateral but is often asymmetric
- Chronic corneal edema may result in the formation of bullae in the anterior corneal epithelium
- Rupture of the bullae is associated with severe pain and may lead to complications

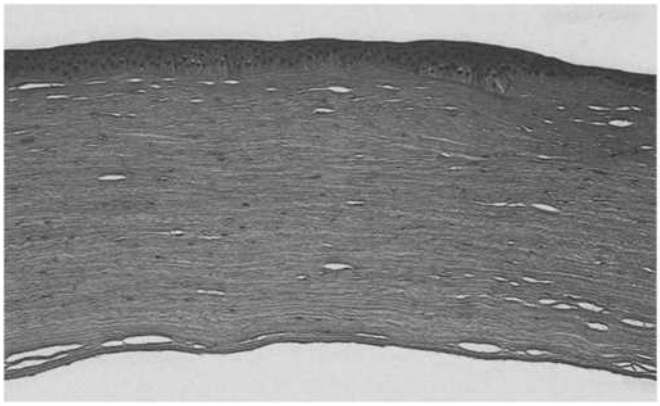


Fig. 9. Cornea. Edema in anterior corneal epithelium overlying a focus of post-traumatic stromal scarring.

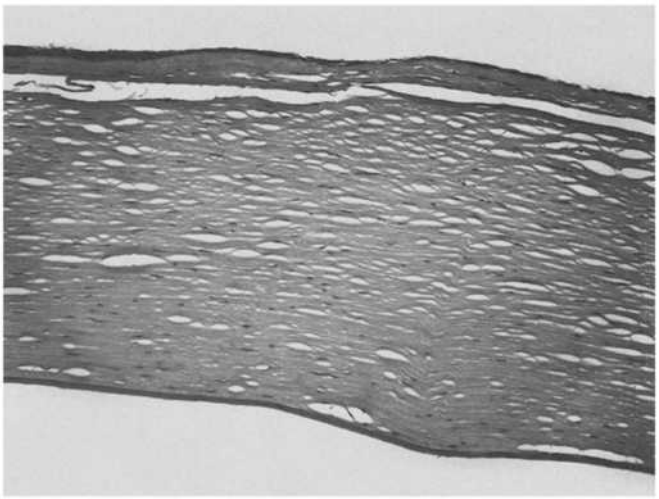


Fig. 10. Chronic corneal edema. Atrophy of anterior corneal epithelium and dense subepithelial fibrous pannus.

- In late stages, spindle cells from the stroma may migrate into the subepithelial space and form a dense fibrous layer ("fibrous pannus")

Microscopic

- Increased fluid in corneal stroma is difficult to document histologically because it causes separation of the lamellae (which is also a common artifact of histological processing)
- Edema of the anterior corneal epithelium is the most reliable diagnostic feature **(Figure 9)**
- The number of endothelial cells may be reduced
- Thickening and lamination of the Descemet's membrane suggest dysfunction of the endothelial cells
- Wart-like protrusions on the posterior surface of the Descemet's membrane ("guttae") may develop. They are best demonstrated with the PAS stain
- Epithelial bullae and fibrous pannus are seen late in the course of the disease **(Figure 10)**

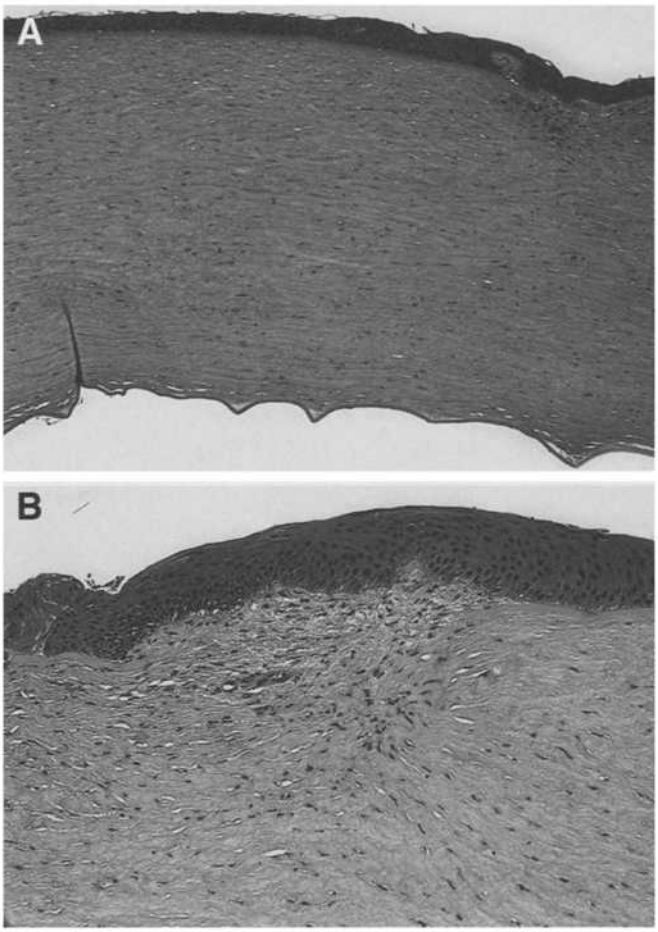


Fig. 11. Cornea. **(A)** Scar in anterior corneal stroma following penetrating injury. **(B)** Scarring and vascularization of anterior corneal stroma.

Stromal Scarring and Vascularization

- Scarring and vascularization of the corneal stroma are non-specific
- They may occur as complication of trauma, inflammatory processes, ulcers, chemical burns, irradiation and other conditions
- Scars may be focal or diffuse, depending on the cause of the injury
- The Bowman's membrane and corneal stroma do not regenerate after an injury but are replaced by scar tissue. **(Figure 11)**

Corneal Opacification. Facette, Nebula, Macula and Leukoma

Facette

- Small foci of thickening of the anterior corneal epithelium filling superficial defects with loss of Bowman's membrane and superficial corneal stroma
- The normal curvature of the anterior surface of the cornea is preserved

Nebula

- Small delicate opacities in corneal stroma
- Histologically, they appear as small superficial scars

Macula

- Larger opacities due to more extensive scarring, usually deeper in the stroma

Leukoma

- Focus of scarring involving almost the entire thickness of the corneal stroma

Keratitis (Corneal Inflammations) and Corneal Ulcers

- Corneal erosions: limited damage to epithelium, best seen clinically after fluorescein staining
- Keratitis: more extensive epithelial damage with variable depths of stromal involvement. It is seen on macroscopic examination

Etiology

- Trauma
- Toxic
- Radiation induced
- Infectious:
  - Viral:
    - Adenovirus (several types, mainly type 8)
    - Herpes simplex virus
    - Herpes zoster virus
    - Epstein-Barr virus
  - Bacterial:
    - Pyogenic bacteria
    - Syphilis
    - Trachoma
    - Lyme disease
    - Tuberculosis
    - Leprosy
  - Parasitic:
    - Protozoal:
      - Leishmaniasis
      - Trypanosomiasis
  - Nematodes:
    - Onchocerciasis
- Other causes:
  - Sarcoidosis
  - Lymphogranuloma venereum
  - Atopic keratoconjunctivitis
  - Lymphoproliferative disorders (mycosis fungoides, Hodgkin lymphoma)
  - Rosacea
  - Crohn's disease

Syphilitic Keratitis

- Extensive stromal involvement
- Anterior uveitis present in early stages:
  - Congenital form:
    - Usually bilateral
    - May be present at birth
    - Cloudy cornea due to inflammation
    - and vascularization of deep stroma
    - It is part of the Hutchinson's triad
  - Acquired form:
    - Late manifestation—10 years after primary infection
    - Usually unilateral, sector shape lesion

Onchocerciasis

- Leading cause of blindness in the world; Africa, Central and South America (18 million children and young adults)
- Causes the *River blindness*
- Acute phase: nummular or snowflake corneal opacities
- Late phase: dense stromal scarring
- Microfilariae migrate through skin and subcutaneous tissue
- Small, black fly, *Simuliam sp.* Transmits parasite from human to
- Human

Peripheral Corneal Ulcers

Ring Ulcer and Ring Abscess

- Linear stromal ulcerated lesion that involves most of the entire circumference of the cornea:
  - Usually follows accidental or surgical trauma
  - Starts at 1–2 mm from the limbus into the clear portion of the cornea
  - Rim of clear cornea always remains
  - Central cornea rapidly undergoes necrosis
  - Panophthalmitis follows
  - The eye is lost
  - Usually infectious; collagen diseases may be the cause

Central Corneal Ulcers

Etiology

- Viral
- Bacterial
- Mycotic
- Parasitic

Herpes Simplex Keratitis

- Most common cause of central corneal ulcer
- Initially involves the epithelium with a dendritic pattern
- Patients with atopic dermatitis—susceptible to dissemination
- The virus spreads from ganglion cells along branches of the ophthalmic division of the trigeminal nerve

Bacterial Ulcers

- They are associated with severe inflammation of the corneal epithelium and stroma
- Cause purulent infiltrate

Etiology

- Organisms that may cause corneal ulcers:
  - Pneumococcus
  - Streptococcus
  - Pseudomonas
  - Klebsiella
  - Staphylococcus
  - Other less virulent bacteria

Mycotic Ulcers

- Usually present with a "dry" main lesion and smaller satellite lesions
- Hypopyon (purulent exudates in anterior chamber) is common
- Fungus may be isolated by scraping margins and depth of ulcer
- Agents isolated from ulcers may be in mycelial form (i.e. *Aspergillus*) or yeasts (i.e. *Candida*)
- Generally, they are secondary to trauma and contamination with plant or animal matter

Acanthamoeba Corneal Ulcer

- Agent is a free living protozoon found in soil, fresh water, and human oral cavity
- Most cases occur in patients who wear contact lenses
- The lesion is usually a painful, central or paracentral ulcer
- The inflammatory infiltrate predominates in the anterior and mid section of the stroma
- The process has a waxing and waning course
- An associated scleral infection may occur
- The diagnosis is confirmed by identification of the cysts in H&E stained sections. Cyst walls stain with PAS, GMS and Giemsa
- Trophozoites are better identified in cultures

Complications of Corneal Ulcers

- **Vascularization** of the corneal stroma
- **Scarring of the Stroma** may be focal or extensive and may involve only part of the entire thickness of the cornea

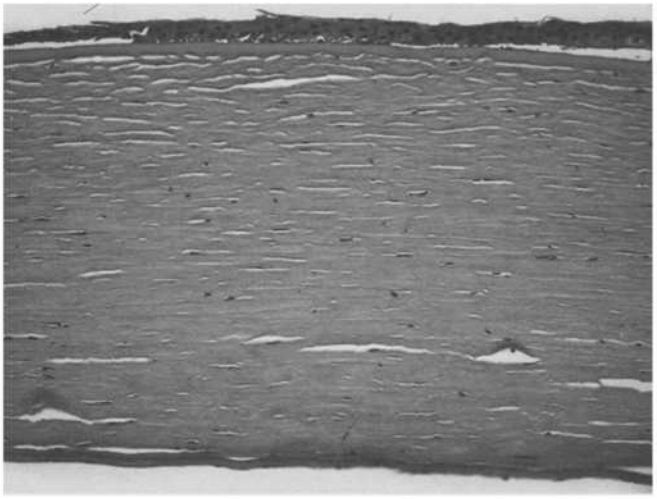


Fig. 12. Failed corneal graft. Atrophy and partial disorganization of epithelial cells. The anterior corneal epithelium is partly detached from the underlying Bowman's membrane. The inflammatory infiltration and vascularization of graft rejection are not observed.

- **Descemetocele** is a herniation of the Descemet's membrane through a defect of the corneal stroma secondary of a deep penetrating ulcer
- **Ectasia,** partial or diffuse protrusion of a thin cornea secondary to the inflammatory process
- **Staphyloma**. Lesion is a corneal ectasia with a bluish color given by the pigmented uveal tissue behind the cornea
- **Xerosis.** Dryness and secondary keratinization of the cornea is secondary to destruction of conjunctival goblet cells and lacrimal glands by the inflammatory process

Failed Corneal Graft

- Corneal transplants or penetrating keratoplasty is usually performed without providing any immunosupression
- Success rate is markedly diminished if the cornea is vascularized
- Failed corneal grafts are usually secondary to endothelial damage

Microscopic

- Changes are similar to those seen in chronic corneal edema and bullous keratopathy **(Figure 12)**
- A layer of fibrous tissue may develop on the posterior surface of the cornea ("retrocorneal fibrous plaque"). It usually starts in the area of the surgical wound
- Immune rejection of a corneal graft may occur. It causes marked vascular proliferation and inflammatory cell infiltration in the periphery of the corneal button

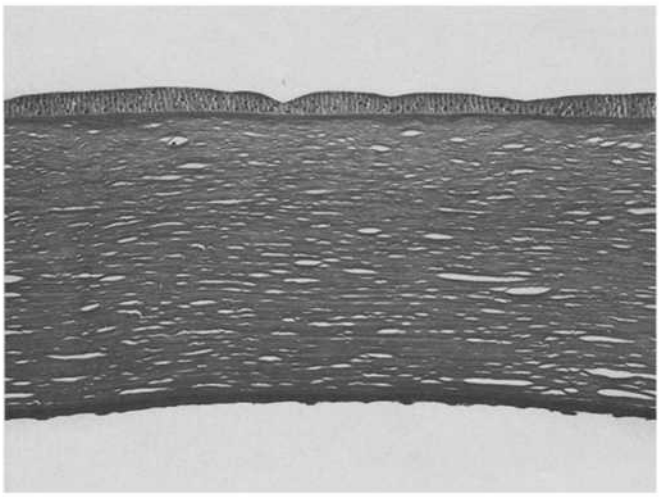


Fig. 13. Fuchs' dystrophy. The thickened Descemet's membrane is studded with wart-like protrusions ("guttate") on its posterior surface. PAS stain.

Corneal Degenerations and Dystrophies

Fuchs' Dystrophy (Fuchs' Endothelial Dystrophy, Cornea Guttata)

Clinical

- The most common corneal dystrophy
- Etiology: primary defect of corneal endothelium
- Usually develops in late adult life
- Patients present with chronic corneal edema and bullous keratopathy
- Defects on posterior surface of Descemet's membrane are easily observed on slit lamp examination

Microscopic

- Thickened Descemet's membrane, best demonstrated in PAS stained sections
- Descemet's membrane may have a laminated appearance
- Numerous wart-like or mushroom-like protrusions on posterior surface of Descemet's membrane ("guttae") due to abnormal deposition of basement membrane material by dysfunctional corneal endothelium **(Figure 13)**
- Number of endothelial cells is decreased
- Melanin pigment granules from the iris may be observed in the cytoplasm of endothelial cells
- Changes due to chronic corneal edema and bullous keratopathy are usually observed

Granular Dystrophy

Clinical

- One of the classical dystrophies of the corneal stroma
- It is a hereditary condition transmitted as an autosomal dominant trait

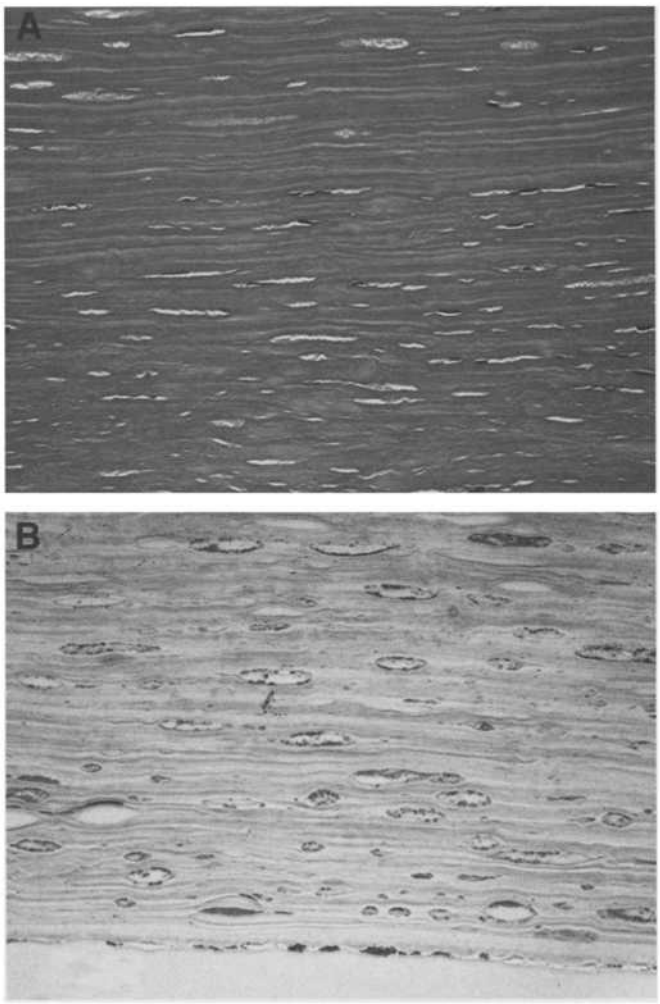


Fig. 14. Macular corneal dystrophy. **(A)** Granular deposits of abnormal mucopolysaccharides in extracellular spaces and keratocytes. **(B)** Mucopolysaccharide deposits in extracellular spaces, cytoplasm of keratocytes and endothelial cells. Alcian blue stain.

- Usually develops older adults
- Presents as multiple superficial opacities in the stroma of the cornea
- Visual acuity is minimally impaired
- The lesion recurs after corneal transplantation

Microscopic

- Multiple irregular deposits of a pale eosinophilic material in stroma
- Deposits stain bright red with the Masson's trichrome and are negative with Congo red
- Ultrastructurally, the deposits appear as dense crystalloids, occasionally with vague periodicity

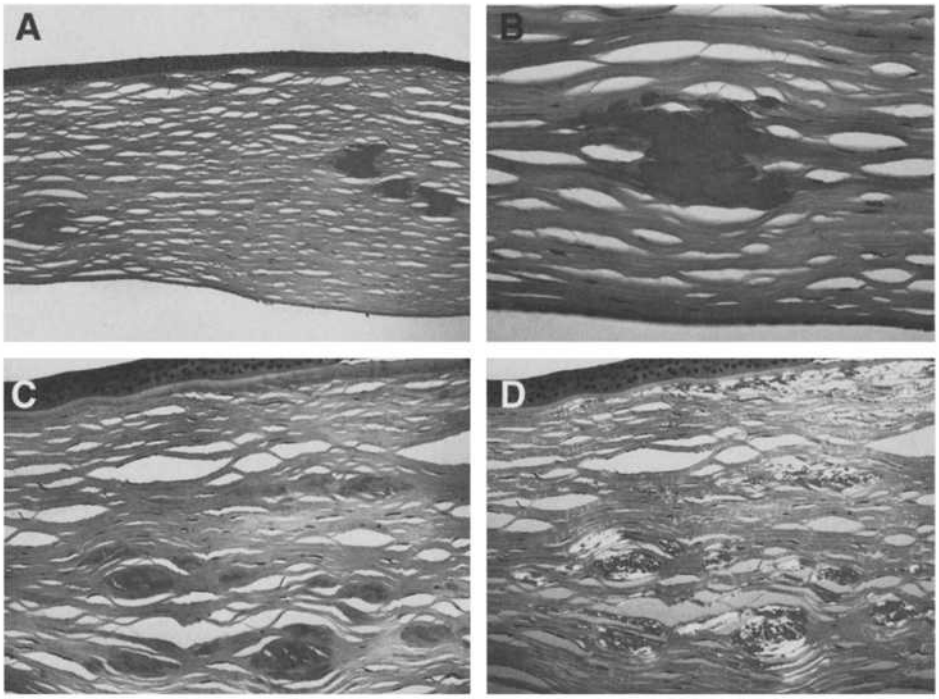


Fig. 15. Lattice corneal dystrophy. **(A)** and **(B)** Deposits of amyloid in corneal stroma. **(C)** Amyloid deposits in stroma are Congo red positive. **(D)** Birefringent amyloid deposits examined with polarization microscopic.

Macular Dystrophy

Clinical

- Conditions is inherited as an autosomal recessive trait
- Leads to more severe visual impairment requiring corneal transplantation in the second of third decades of life
- Relatively uncommon in the United States
- It is a form of localized corneal mucopolysaccharidosis

Microscopic

- The cornea may be thinner than normally
- Multiple delicate granules are observed within the keratocytes and interlamelar spaces in the stroma
- Endothelial cells are also affected
- The granular material is PAS positive
- Staining with colloidal iron or Alcian blue for acid mucopolysaccharides confirms the diagnosis **(Figure 14)**

Lattice Dystrophy

Clinical

- It is a localized form of corneal amyloidosis
- The defect is transmitted as an autosomal dominant trait
- The lesion usually manifests before adolescence, progresses slowly and may require corneal transplantation by the fifth decade
- On clinical examination, the deposits of amyloid appear as irregularly branched lines criss-crossing the cornea

Microscopic

- Irregular, round or oval deposits of amyloid in the corneal stroma
- Deposits also accumulate in the subepithelial and pre-Descemet's regions of the stroma **(Figure 15)**
- The material is eosinophilic and stains positively with Congo red and crystal violet, is fluorescent in thioflavin T stained sections and shows the characteristic features of amyloid when examined with polarization microscopy

Lipid Degeneration

- **Arcus senilis,** is a deposition of lipids in the stroma of the peripheral, paralimbal cornea:
  - It is not necessarily associated with abnormalities in lipid metabolism
- **Primary Lipid Degeneration**, appears as an exaggeration of *arcus senilis*, with extensive lipid deposits towards the center of the cornea
- **Secondary Lipid Degeneration:**
  - Usually follows some form of corneal trauma, including surgical injury
  - The lipid deposition occurs within a thick subepithelial fibrous pannus

Keratoconus

Clinical

- Thinning and ectasia of central or paracentral cornea
- Appears in early in adolescence and progresses until the fifth decade

- It is bilateral in 90 per cent of the cases
- Females are more often affected
- Clinically, if produces irregular astigmatism
- It may be associated with multiple systemic diseases
- Corneal opacities may develop due to stromal scarring
- Rupture of the Descemet's membrane results is severe acute corneal edema ("acute hydrops")

Microscopic

- The central corneal stroma is markedly thinner than the periphery
- Ruptures of the Bowman's membrane are common and are sometimes associated with superficial stromal scarring
- The anterior corneal epithelium overlying the cone may be atrophic
- If the Descemet's membrane ruptures, the coiled edges of the membrane appear as well defined lines on clinical examination ("Haab's striae")
- Following rupture of the Descemet's membrane, the stroma becomes markedly edematous ("acute hydrops"). **(Figure 16)**

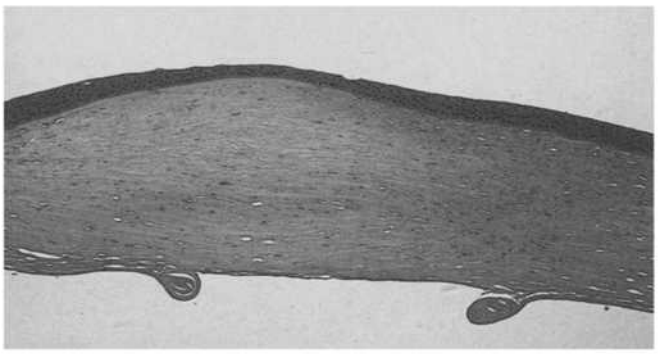


Fig. 16. Keratoconus. Extreme thinning of cornea led to rupture of Descemet's membrane with massive edema of stroma ("acute hydrops"). The curled edges of the ruptured membrane are seen clinically as lines or striae crossing the cornea ("Haab's striae").

- The defect is usually covered by a newly deposited thin Descemet's membrane
- Prussian blue staining may show a ring of iron deposition around the cone (Fleischer ring)

CONJUNCTIVA

Limbal (Epibulbar) Dermoids

Clinical

- Congenital lesions occurring in the temporal limbus (corneal/conjunctival interface)
- Elevated plaques of skin with or without subcutaneous fat
- Some epibulbar dermoids are cystic

Microscopic

- Island of skin with skin adnexa and adipose tissue **(Figure 17)**
- Surface epidermis may be replaced by corneal or conjunctival epithelium
- Similar lesions, without skin adnexa, are designated as **dermolipomas** or **lipodermoids**
- Goldenhar syndrome: limbal dermoids, preauricular skin tags, aural fistulas and vertebral anomalies

Complex Choristomas

- Limbal dermoids containing heterologous tissues:
- Cartilage
- Lacrimal gland **(Figure 18)**
- Smooth or striate muscle fibers
- Teeth
- Bone
- Nervous tissue

Degenerations

Pinguecula

Clinical

- Focal elevation in bulbar conjunctival mucosa
- Involves area corresponding to the interpalpebral fissure
- Reactive proliferative response in conjunctival mucosa
- Due to environmental irritants, dust, wind, particulate and chemical air pollution, solar irradiation

Microscopic

- Atrophy or hyperplasia of surface epithelium
- Increased fibrovascular tissue in conjunctival stroma
- Elastotic degeneration (solar elastosis). It may be minimal in some cases

Pterygium

- Similar etiology to pinguecula
- Involves paralimbal conjunctiva and encroaches on the cornea
- The underlying Bowman's membrane is absent
- Squamous cell carcinoma and amelanotic melanoma of conjunctiva may mimic pterygia

Conjunctival Cysts

Conjunctival Inclusion Cysts

Clinical

- May be congenital

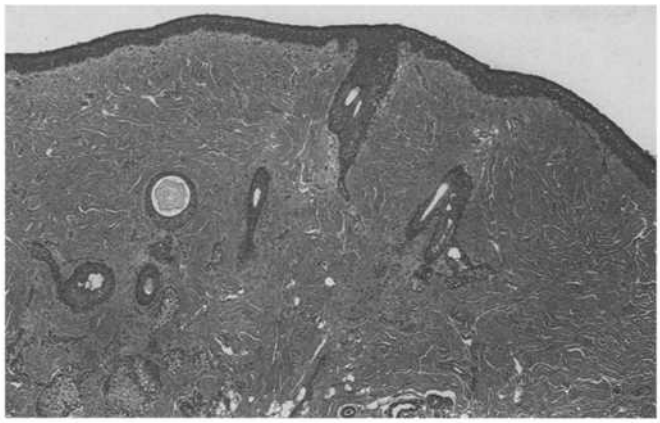


Fig. 17. Limbal dermoid. Island of skin and skin adnexa in limbal conjunctiva.

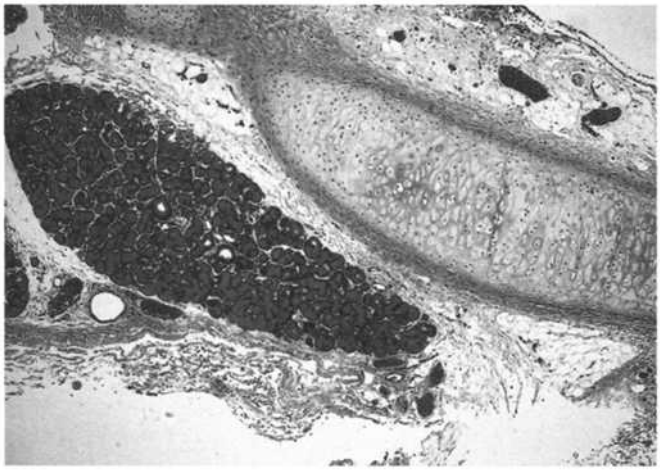


Fig. 18. Heterologous tissues (ectopic lacrimal gland and cartilage) in complex choristoma of conjunctiva.

- Or secondary to post surgical or post-traumatic implantation of conjunctival epithelium or epithelial inclusions in conjunctivitis

Microscopic

- Lining made up of conjunctival epithelium with goblet cells
- Contents may be mucinous, proteinaceous or both **(Figure 19)**
- Focal calcification occurs in some cases

Ductal Cysts

Clinical

- Cystic lesions secondary to blockage of accessory lacrimal gland ducts

Microscopic

- Cyst lining is made up of a double layer ductal epithelium
- Lumen contains clear fluid

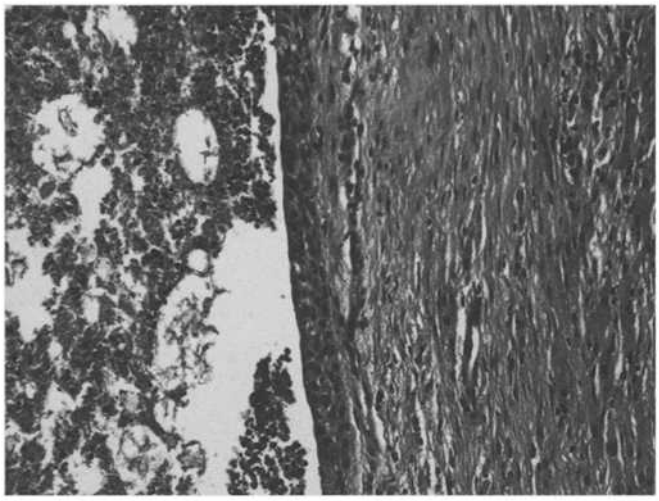


Fig. 19. Wall of a conjunctival inclusion cysts with rupture and secondary inflammation. Note the goblet cells in the lining epithelium of the cyst.

Conjunctival Inflammations

Acute Conjunctivitis

- Rarely examined pathologically except in scrapings and smears
- Etiology: viruses, bacteria, fungi and parasites
- Clinical presentation: redness and chemosis
- Exudates may be purulent

Superior Limbic Keratoconjunctivitis

- Marked inflammation of palpebral conjunctiva of superior eyelid or upper bulbar conjunctiva
- Etiology is unknown
- Microscopically, keratinization of surface epithelium with dyskeratosis, acanthosis and mixed inflammatory cell infiltration

Chronic Follicular Conjunctivitis

- Common pattern of chronic conjunctival inflammation
- Etiology:
  - Viruses:
    - Herpes simplex
    - Adenovirus
    - Enterovirus
    - Newcastle virus
  - Chlamydia:
    - Trachoma; one of most important causes of blindness worlwide
  - Cosmetics
  - Topical medications
  - Environmental irritants



Fig. 20. Papillary conjunctivitis with numerous inclusions of conjunctival epithelium.



Fig. 21. Ligneous conjunctivitis. Granulation tissue and fibrinous material. Lesion bleeds easily when overlying pseudomembranes are removed.

- Clinically, multiple gray-white rounded or oval elevations in conjunctival surface and marked congestion of conjunctival mucosa
- Microscopically, marked follicular lymphoid hyperplasia in substantia propria

Chronic Papillary Conjunctivitis

Clinical

- Common nonspecific reaction of conjunctiva in chronic inflammation
- Occurs mainly in palpebral conjunctiva
- Gives the conjunctiva a "cobblestone" appearance
- Appears in late stages of chronic conjunctivitis of various etiologies

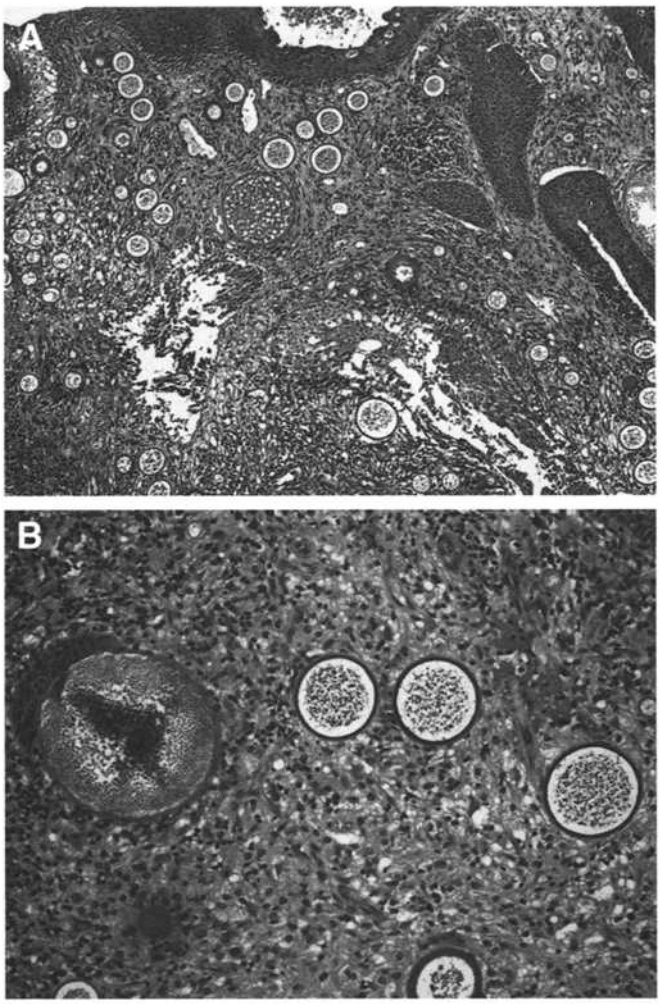


Fig. 22. **(A,B)**. Rhinosporidiosis of eyelid.

- Often seen in vernal conjunctivitis, a form of recurrent atopic conjunctivitis

Microscopic

- Papillary hypertrophy of mucosa with deep infoldings of epithelium **(Figure 20)**
- Fibrovascular cores may contain a prominent mixed inflammatory infiltration
- The surface of the papillae may undergo squamous metaplasia
- Hyperplasia of goblet cells occurs in the "valleys" between papillae

Ligneous Conjunctivitis

Clinical

- Rare form of chronic conjunctivitis
- Recurrent disease
- Affects mainly young girls
- Characteristic psedomemebranes with woody consistency

- Removal of pseudomembranes causes bleeding and is rapidly replaced by another pseudomembrane

Microscopic

- Pseudomembranes containing inflammatory cells, cell debris and fibrinous material
- Granulation tissue with mixed inflammatory cell infiltration **(Figure 21)**
- Variable degrees of fibrosis

Sarcoidosis

- Sarcoidosis may affect multiple structures in the eye including retina and optic nerve
- Conjunctival biopsies are sometimes obtained for diagnosis
- Approximately one fifth of blind conjunctival biopsies show the classical sarcoid granulomas
- As in other sites, an infectious etiology should be ruled out

Rhinosporiosis

- Rhinosporidium seeberi may affect conjunctiva and nasal mucosae
- Rarely seen in the United States but it is common in India and other developing countries

Clinical

- Coarse, fleshy papillary lesions
- Numerous endosporulating and encapsulated organisms are seen in the lesion **(Figure 22)**
- Recurrence is common after removal
- Large lesions may lead to scleral perforation

TUMORS AND MASS LESIONS OF THE CONJUNCTIVA

Conjunctival Papillomas

Clinical

- Multiple papillary fronds on conjunctival surface
- Multiple lesions may occur in children
- Recurrence is common
- May be associated with human papillomavirus types 16 and 18

Microscopic

- Papilomatous processes of variable complexity
- Papillae are covered with conjunctival epithelium with a variable number of Goblet cells **(Figure 23)**
- Delicate fibrovascular cores may contain inflammatory cells

Conjunctival Intraepithelial Carcinoma (Squamous Cell Carcinoma In Situ)

Clinical

- Plaque or slightly elevated lesions
- White a pale pink color

Microscopic

- Thickned conjunctival epithelium
- Epithelial cell atypia with loss of polarity, nuclear hyperchromatism and increased number of mitoses
- Keratinization may be observed in lesions with a white color
- Basement membrane is intact
- Marked inflammatory cell infiltration in superficial conjunctival stroma may be present

Invasive Squamous Cell Carcinoma

- Is observed less often than conjunctival intraepithelial neoplasia
- Generally invades locally
- Early invasive lesions are clinically similar to non-invasive carcinoma
- Invasion of sclera and orbital soft tissues may occur if not treated
- Preauricular and submadibular lymph nodes may contain metastatic foci

Microscopic

- Similar features of invasive squamous cell carcinomas of the skin

TNM Classification of Carcinoma of the Conjunctiva (2002 Revision)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor 5 mm or less in greatest dimension
T2	Tumor more than 5 mm in greatest dimension, without invasion of adjacent structures
T3	Tumor invades adjacent structures, excluding the orbit
T4	Tumor invades the orbit with or without further extension
T4a	Tumor invades orbital soft tissues, without bone invasion
T4b	Tumor invades bone
T4c	Tumor invades adjacent paranasal sinuses
T4d	Tumor invades brain

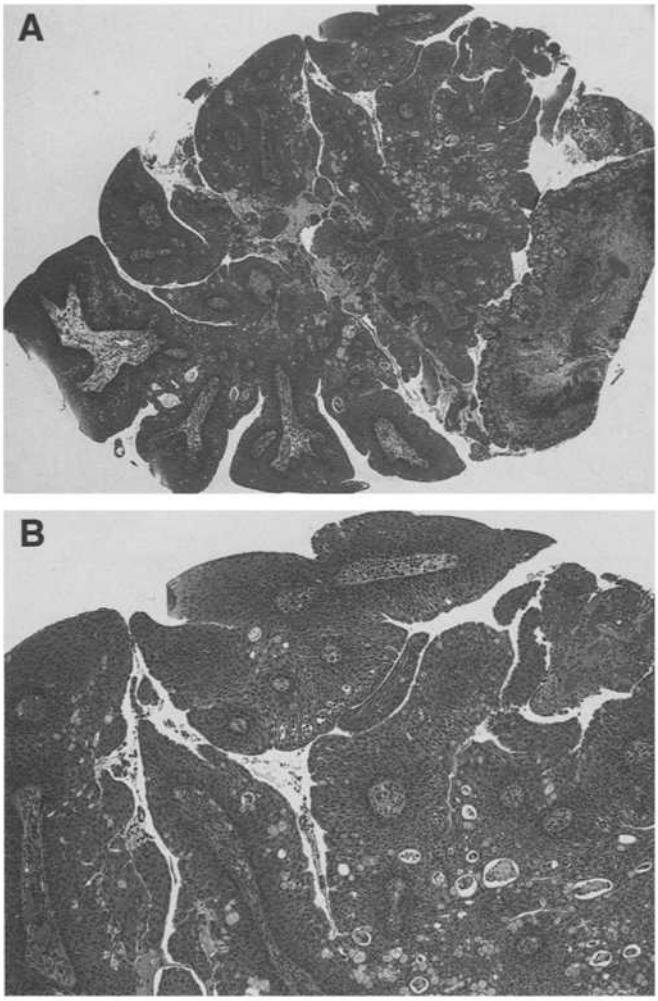


Fig. 23. **(A)** Conjunctival papilloma. **(B)** The presence of goblet cells in the non-keratized epithelium differentiates this lesion from squamous papillomas.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Melanotic Lesions of the Conjunctiva

Congenital and Acquired Melanosis

Congenital Melanosis Oculi

- Diffuse increased number of melanocytes in conjunctival substantia prorpria, episcleral and scleral tissue

Clinical

- Broad patches of brown to light blue pigmentation
- **Nevus of Ota:**
  - Heavily pigmented melanocytes with diffuse infiltration of:
    - Conjunctiva
    - Sclera
    - Episcleral soft tissues
    - Uvea
    - Eyelids
    - Facial skin

Primary Acquired Melanosis Oculi

- Minimal to marked junctional melanocytic proliferation in basal layer of conjuntival eptielium
- Diffuse pigmentation of conjunctiva that moves easily and is not adherent to sclera
- Variable degrees of melanocytic atypia
- Lesion is analogous to lentigo maligna of the skin
- Approximately 20% becomes malignant
- Enlarges slowly over a period of years

Secondary Acquired Melanosis Oculi

- Diffuse conjunctival pigmentation secondary to:
  - Radiation
  - Pregnancy
  - Addison's disease
  - Chemical and drug induced
  - Chronic conjunctival lesions
  - Trachoma
  - Vernal conjunctivitis
  - Keratomalacia

Nevi

- Common conjunctival lesions
- Types:
  - Junctional
  - Compound
  - Stromal or subepithelial, analogous to dermal nevi of the skin
- Architectural and cytological features similar to cutaneous nevi
- Often associated with numerous small conjunctival inclusion cysts
- Large number of cysts and lymphocytic infiltration may obscure the nevus cell component
- Junctional component may occur in the wall of the inclusion cysts

Malignant Melanoma

- May arise from:
  - Pre-existing nevi
  - Primary acquired melanosis oculi

- Direct extension of intraocular melanoma
- *de novo*

- Most frequently located in the limbal or paralimbal region
- It is usually locally invasive
- Clinically less aggressive than melanomas of the eyelid skin
- Microscopically, similar to malignant melanomas of the skin

TNM Classification of Malignant Melanoma of the Conjunctiva (2002 Revision)

Primary Tumor (pT)

pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor of the bulbar conjunctiva confined to the epithelium
pT2	Tumor of the bulbar conjunctiva not more than 0.8 mm in thickness with invasion of the substantia propria
pT3	Tumor of the bulbar conjunctiva more than 0.8 mm in thickness with invasion of the substantia propria or tumors involving the palpebral or caruncular conjunctiva
pT4	Tumor invades the eyelid, globe, orbit, sinuses, or central nervous system

Regional Lymph Nodes (pN)

pNX	Regional lymphnodes cannot be assessed
pN0	No regional lymph node metastasis
pNX	Regional lymph node metastasis present

Distant Metastasis (pM)

pMX	Distant metastasis cannot be assessed
pM0	No distant metastasis
pM1	Distant metastasis

Lymphoid Lesions

- Conjunctival lymphoid lesions include the entire spectrum, from benign lymphoid follicular hyperplasia to malignant lymphoma
- Lymphomas may be primary in the conjunctiva, direct extension from an orbital lymphoma or metastatic from a systemic lymphoma
- Clinically, "salmon pink" patch in conjunctival mucosa
- Microscopically, similar to malignant lymphomas elsewhere
- Immunophenotyping is necessary for final classification of tumor type
- If biopsy is not very small, part of the sample should be saved for flow cytometry

TUMORS OF THE EYE

Malignant Melanoma

Clincal

- Malignant melanocytic tumors of the uvea are the most frequent intraocular tumors in adults
- Malignant melanomas of the uvea may occur at any age but they are most frequent in older adults
- Tumors arising in the choroid are more frequent than those originating in the ciliary body or iris
- Iris tumors are diagnose earlier and tend to be smaller
- Choroidal melanomas usually are identified after they produce significant visual disturbances because of retinal detachment or because the mass reaches the visual axis

Macroscopic

- Their color varies from light tan to heavily pigmented lesions
- Iris melanomas are usually small elevated masses
- Choroidal melanomas tend to be large nodules and are often associated with detachment of the retina and accumulation of serous fluid in the subretinal space
- Mushroom-shaped lesions are frequent **(Figure 24)**
- Ciliary body tumors usually extend anteriorly and infiltrate the root of the iris. They may be seen in the angle through the transparent cornea **(Figure 25)**

Microscopic

- There are three main cytological variants:
- *Spindle cell melanomas,* with elongated nuclei, moderately nuclear pleomorphism and distinct nucleoli
- *Epithelioid melanomas* made up of large cells, with vesicular nuclei, prominent nucleoli and abundant eosinophilic cytoplasm
- *Mixed cell melanomas* contain a variable amount of both spindle and epithelioid cell components **(Figure 26)**
- The degree of pigmentation in tumor cells is variable. In some lesion, the pigment is present mainly in numerous melanophages. Amelanotic lesions do occur
- Immunohistochemical features of the tumor cells are similar to cutaneous malignant melanomas
- The vascularity of the tumor may be prominent
- Necrosis may be present but it usually not extensive
- Some tumors show massive necrosis and hemorrhage at the time of the initial presentation

Tumor extension

- Choroidal melanomas:
  - Optic nerve extensions may occur but they are less frequent than in retinoblastoma

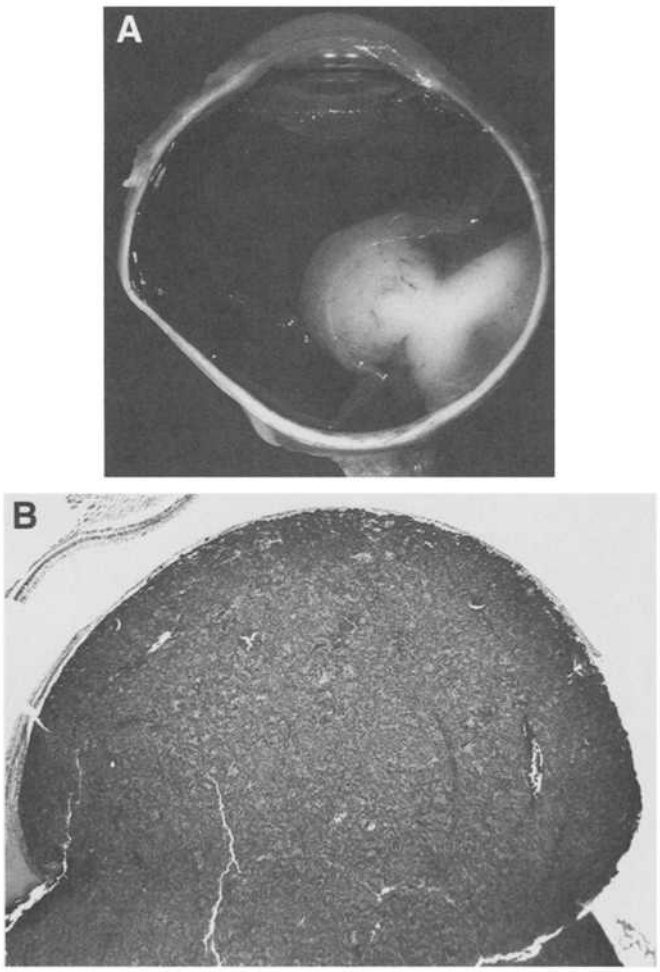


Fig. 24. **(A)** Malignant melanoma of choroid extending into subretinal space through a defect of Bruch's membrane. The mushrooming head of the tumor detaches the retina. **(B)** Malignant melanoma of choroid.

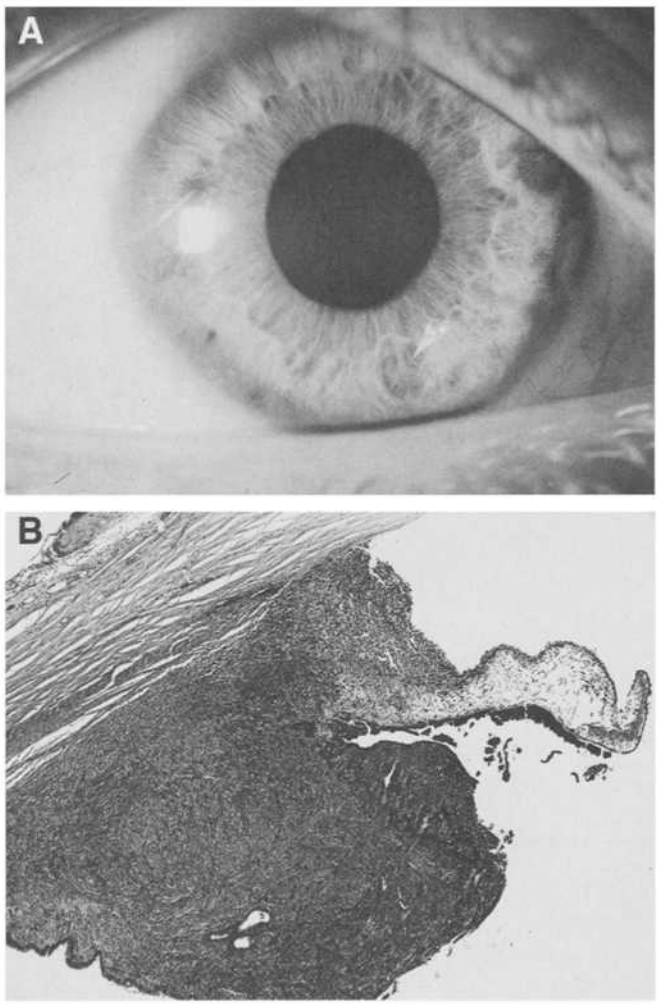


Fig. 25. **(A)** Malignant melanoma of ciliary body with invasion of iris and angle of anterior chamber. **(B)** Malignant melanoma of ciliary body.

  - The tumor may invade scleral channels and extend to the orbit along perivascular spaces and nerves **(Figure 27)**
  - Anterior extension and rupture through the sclera or cornea is rare **(Figure 28)**
- Ciliary body melanomas:
  - Usually grow anteriorly to involve the iris root, the angle of the anterior chamber and the trabecular meshwork
  - The tumor may also invade scleral channels
- Distant metastases usually occur in the liver, lung, bone and skin

Morphological features

The following have prognostic implications and should appear in the surgical pathology report:

- Tumor size, large tumors have a poorer outcome
- Cell type. Epithelioid melanomas are associated with a lower survival rate than mixed and spindle cell tumors
- Location. Iris tumors have a better prognosis since they are diagnosed and treated earlier
- Extrascleral extension
- Necrosis
- Other features such as neovascularization, lymphocytic infiltratin, degree of pigmentation, deposition of reticulin fibers, and others may be mentioned in the report but are not known to affect the patient's outcome

TNM Classification of Melignant Melanoma of the Uvea (2002 Revision)

Primary Tumor (T)

All Uveal Melanomas

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor

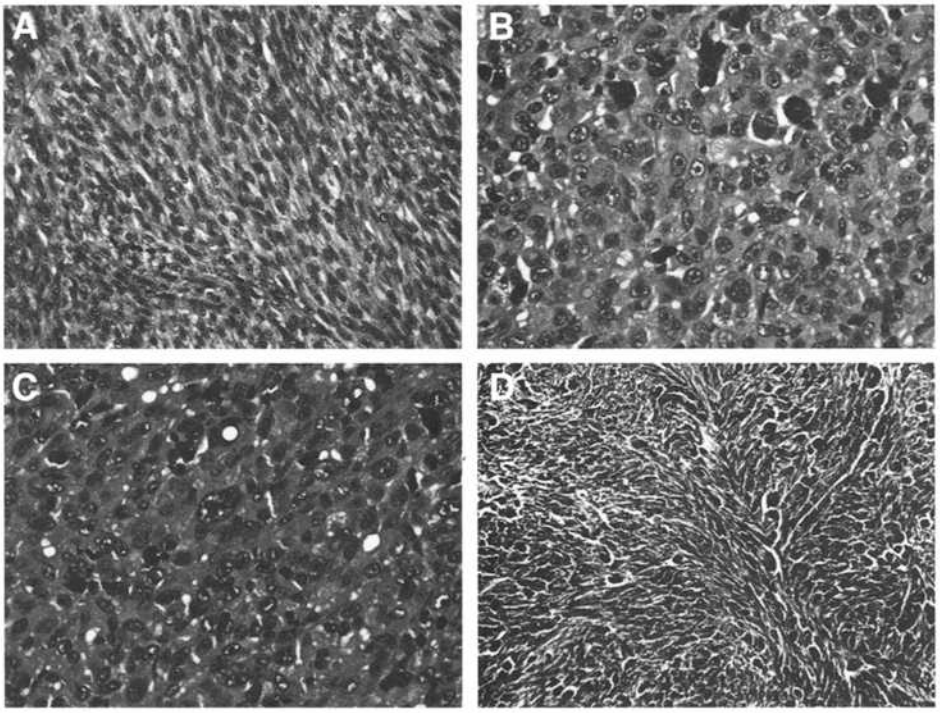


Fig. 26. Malignant melanoma. **(A)** Spindle cell melanoma. **(B)** and **(C)** Epithelioid melanoma. **(D)** Heavily pigmented tumors require bleaching to evaluate cytological details.

Iris

T1	Tumor limited to the iris
T1a	Tumor limited to the iris not more than 3 clock hours in size
T1b	Tumor limited to the iris more than 3 clock hours in size
T1c	Tumor limited to the iris with melanomalytic glaucoma
T2	Tumor confluent with or extending into the ciliary body and/or choroid
T2a	Tumor confluent with or extending into ciliary body and/or choroid with melanomalytic glaucoma
T3	Tumor confluent with or extending into the ciliary body and/or choroid with scleral extension
T3a	Tumor confluent with or extending into the ciliary body with scleral extension and melanomalytic glaucoma
T4	Tumor with extraocular extension

Ciliary Body and Choroid

T1	Tumor 10 mm or less in greatest diameter and 2.5 mm or less ingreatest height (thickness)
T1a	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) without microscopic extraocular extension
T1b	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with microscopic extraocular extension
T1c	Tumor 10 mm or less in greatest diameter and 2.5 mm or less in greatest height (thickness) with macroscopic extraocular extension
T2	Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness)
T2a	Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) without microscopic extraocular extension
T2b	Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with microscopic extraocular extension
T2c	Tumor greater than 10 mm but not more than 16 mm in greatest basal diameter and between 2.5 and 10 mm in maximum height (thickness) with macroscopic extraocular extension
T3	Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) without extraocular extension
T4	Tumor more than 16 mm in greatest diameter and/or greater than 10 mm in maximum height (thickness) with extraocular extension

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

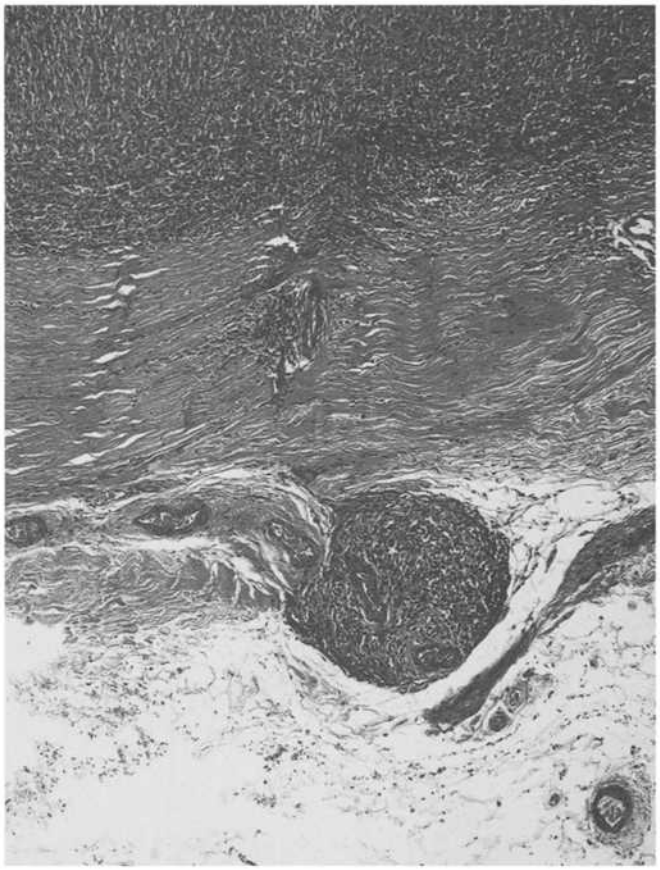


Fig. 27. Malignant melanoma of choroid extending to orbital soft tissues through a scleral channel.

Retinoblastoma

Clinical

- The most common intraocular tumor in children
- Most tumors are probably congenital
- The tumor may be sporadic or familial
- The retinoblastoma gene (Rb) has been identified in chromosome 13q14
- Retinoblastomas may be bilateral, especially in familial cases
- "Trilateral" retinoblastomas, bilateral retinoblastomas and a morphologically identical pineoblastoma may occur
- A large number of intraocular diseases may mimic retinoblastoma:
  - Retinal detachment
  - Coats' disease
  - Glial tumors of the retina
  - Persistent hyperplastic primary vitreous
  - Retrolental fibroplasias

Clinical presentation

- Leukocoria (white papillary reflex) is the most frequent sign at presentation

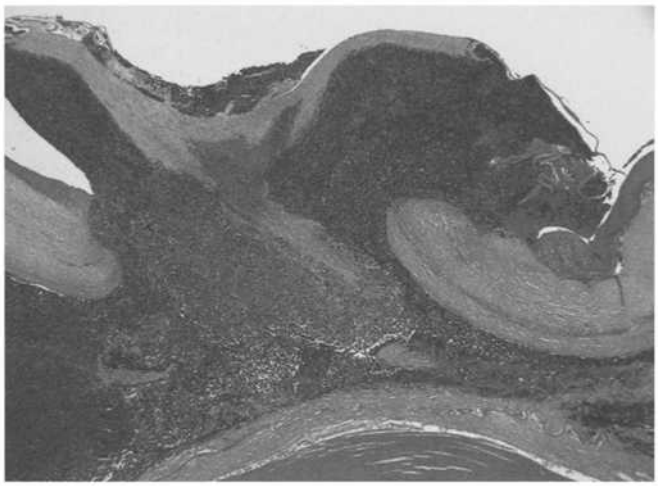


Fig. 28. Massive epithelioid malignant melanoma protruding onto the anterior surface of the eye through a corneal defect.

- Strabismus may occur
- Proptosis due to orbital extension of the tumor is rare

Macroscopic

- Large masses with masses partially or completely filling the vitreous cavity
- Necrosis and calcifications may be present
- Extensive retinal detachment
- The lens may be displaced forward

Microscopic

- Sheets and cords of small round cells with hyperchromatic nuclei and scanty cytoplasm
- Small Flexner-Wintersteiner rosettes (with a central lumen) and Homer Wright rosettes (with a fibrillary center) are often encountered. **(Figure 29)**
- Fluerettes, small groups of abortive photoreceptors mimicking the petals of a flower, may occur in some tumors
- The tumor cells massively expand the retina and extend into the subretinal space (exophytic tumors), the vitreous cavity (endophytic tumors), or both
- Mitoses are numerous
- Necrosis is usually extensive with the viable component of the tumor remaining only around blood vessels
- A basophilic granular material may be deposited on the outer surface of blood vessels. They are debris from necrotic tumor cells
- Granular calcification tends to be prominent in areas of necrosis
- Extension into optic nerve, choroid or beyond the vitreous base, into the posterior or anterior chambers, may occur. These findings have prognostic and therapeutic implications and should always be mentioned in the pathology report **(Figure 30).**

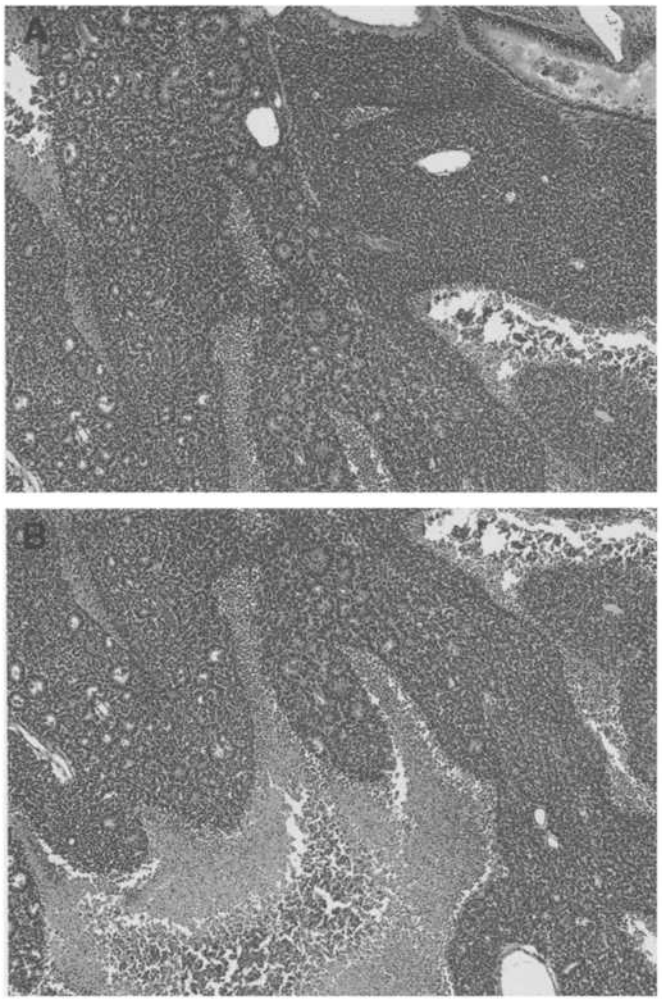


Fig. 29. Retinoblastoma. **(A)** Sheets of retinoblasts with numerous Flexner-Wintersteiner rosettes and Homer Wright rosettes. **(B)** Large areas of necrosis and calcification.

- Tumor cells in the anterior chamber may mimic a purulent exudates (pseudohypopyon)
- Immunohistochemistry and electron microscopic are usually not needed for diagnosis

TNM Classification of Retinoblastoma (2002 Revision)

Primary tumor (T)

pTX	Primary tumor cannot be assessed
pT0	No evidence of primary tumor
pT1	Tumor confined to the retina, vitreous, or subretinal space. No optic nerve or choroidal invasion
pT2	Minimal invasion of the optic nerve and/or optic coats
pT2a	Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa
pT2b	Tumor invades the choroid focally

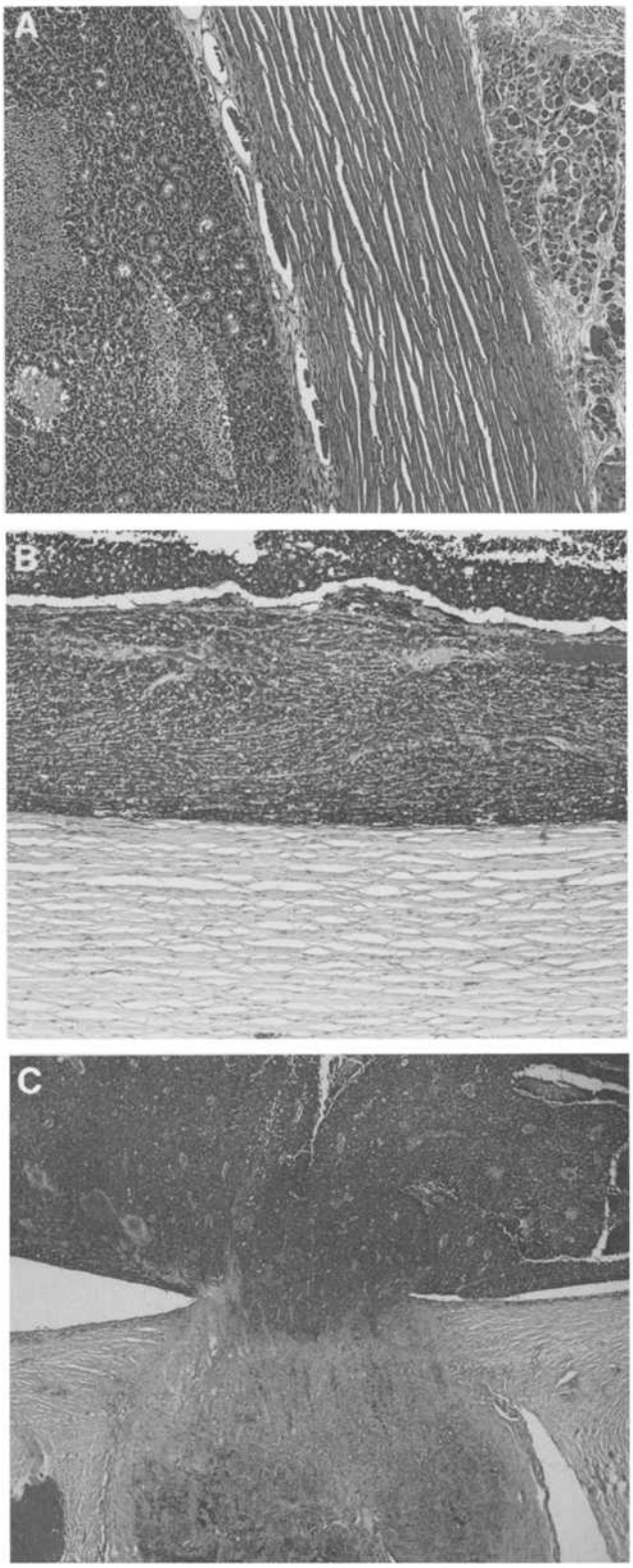


Fig. 30. Retinoblastoma. **(A)** Exophytic component of tumor extends to Bruch's membrane, without involving choroid. **(B)** Massive tumor infiltration in choroid. **(C)** Tumor extension into optic nerve beyond the lamina cribrosa.

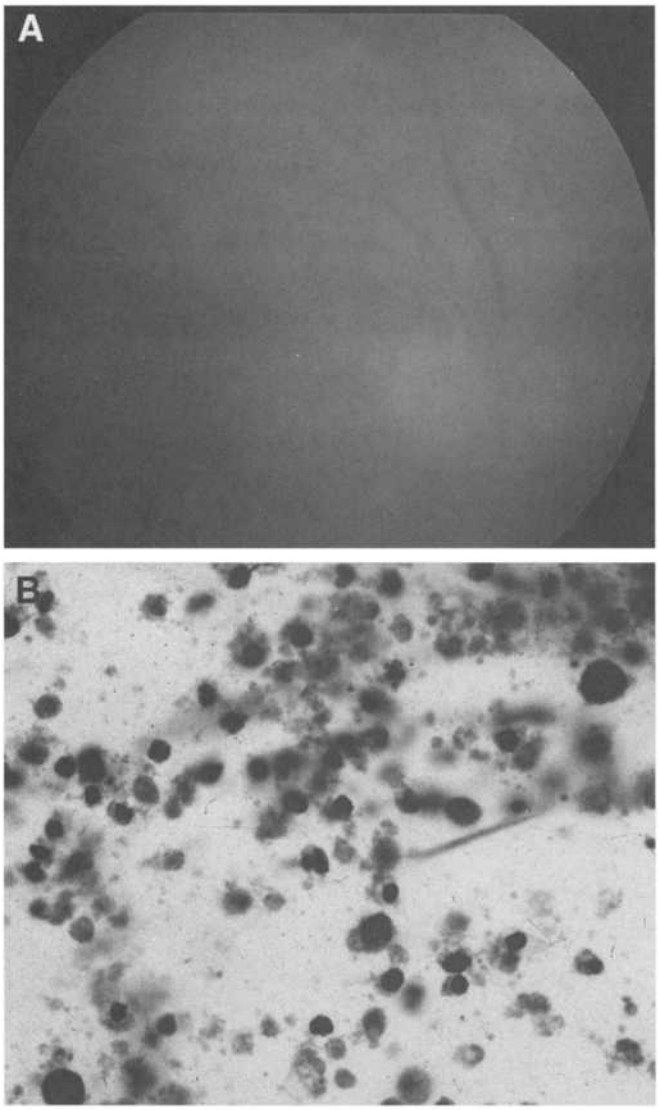


Fig. 31. **(A)** Vitreous opacification in a patient with intraocular malignant lymphoma. **(B)** Lymphoma cells in vitrectomy specimen.

pT2c	Tumor invades optic nerve up to, but not through, the level of the lamina cribrosa **and** invades the choroid focally
pT3	Significant invasion of the optic nerve and/or optic coats
pT3a	Tumor invades optic nerve through the level of the lamina cribrosa but not to the line of resection
pT3b	Tumor massively invades the choroid
pT3c	Tumor invades optic nerve through the level of the lamina cribrosa but not to the line of resection **and** massively invades the choroid
T4	Extraocular tumor extension that includes:
	Invasion of the optic nerve to the line of resection
	Invasion of the orbit through the sclera
	Extension both anteriorly and posteriorly to the orbit

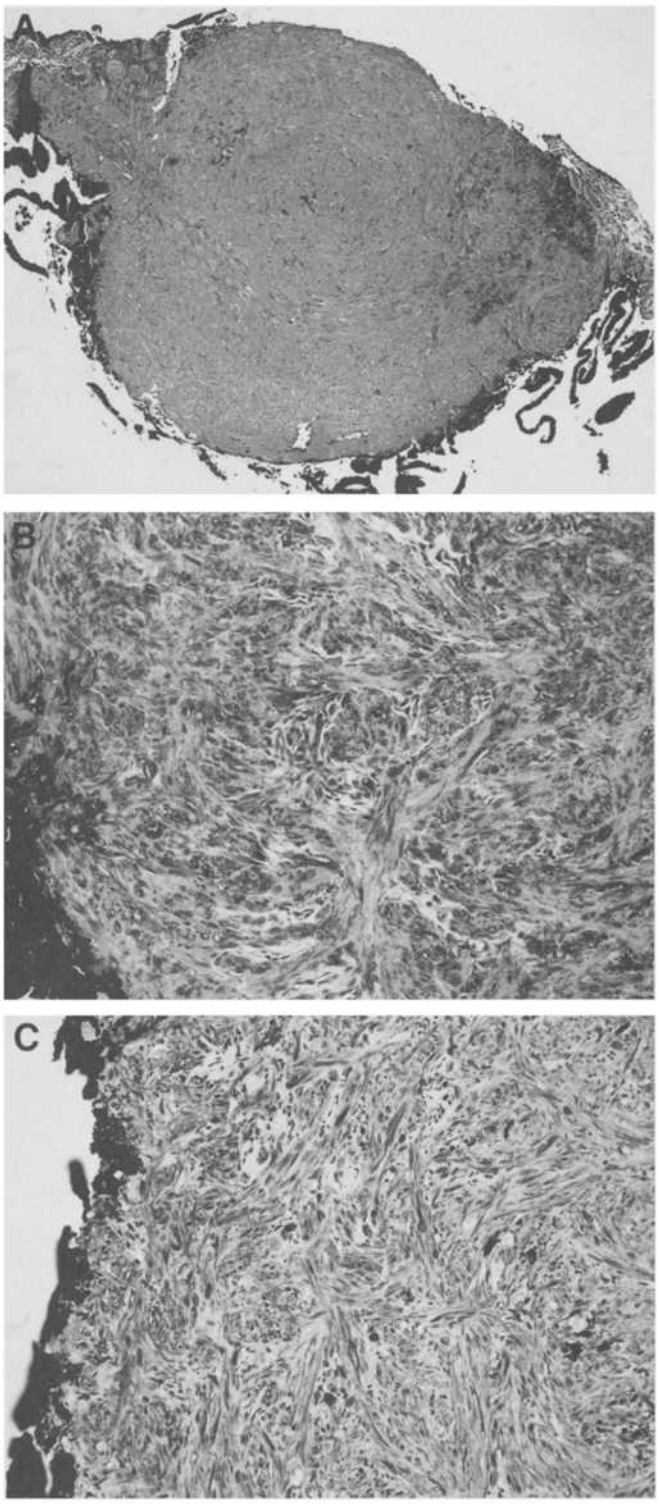


Fig. 32. **(A)** Leiomyoma of iris. Clinically, the lesion appeared heavily pigmented. **(B)** Tumor stained for smooth muscle-specific actin, and **(C)** desmin.

Extension into the brain
Extension into the subarachnoidal space of the optic nerve
Extension to the apex of the orbit
Extension to, but not through, the chiasm
Extension into the brain beyond the chiasm

Regional Lymph Nodes (N)

pNX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Regional lymph node metastasis

Distant Metastasis (M)

pMX Distant metastsis cannot be assessed
pM0 No distant metastasis
pM1 Distant metastasis
pM1a Bone marrow
pM1b Other sites

Other Tumors of the Eye

Malignant Lymphoma

- Intraocular lymphomas do not differ morphologically from their systemic counterparts (**Figure 31**)
- Lymphomas involving the vitreous body are usually associated with a central nervous system lymphoma while lymphomas of the uvea are generally seen in patients with systemic lymhomas

Fuchs' Adenoma

- Benign epithelial tumor of the ciliary body
- It rarely becomes clinically evident

Microscopic

- Interlacing cords of monomorphic cells with features similar to the non-pigment layer of the ciliary epithelium
- A PAS positive material is usually associated with the cellular proliferation

Medulloepithelioma

Leiomyomas

- May occur in the ciliary body or iris (**Figure 32**)

Vascular tumors

- Hemngiomas
- Hemangioblastomas

Glial Tumors of the Retina (Astrocytoma)

Metastatic Tumors

- Intraocular metastatic tumors usually involve the choroid
- Their distribution is similar to metastases to the central nervous system
- Most frequent tumors that metastasize to the eye are breast (in females), lung (in males), gastrointestinal tract, the genitourinary tract and cutaneous malignant melanomas
- May mimic primary malignant melanomas of the eye

EYELIDS

Anatomical Components

- Skin with delicate hair follicles and small skin adnexa
- Skeletal muscle fibers of the orbicularis oculi and tendinous fibers of levator
- Tarsus, a dense lamina of fibrous tissue that invests the meibomian glands, long branched sebaceous glands that are more numerous in the upper than in the lower eyelids
- Palpebral conjunctiva
- Structures present in the eyelid margin:
  - Large hair follicles, the cilia or eyelashes
  - Glands of Zeis, small sebaceous glands attached to the follicles of the cilia
  - Glands of Moll, small apocrine sweat glands
- Other glands in the eyelids:
  - Glands of Wolfring: small accessory lacrimal glands that empty their secretion on the palpeblral conjunctiva, just above the tarsus
  - Glands of Krause: small accessory lacrimal glands in the fornix of the conjunctiva

Inflammations

CHALAZION

Clinical

- Lipogranulomatous inflammation resulting from the release of lipids by the meibomian glands or the glands of Zeis
- Firm painless nodules in the eyelid
- Its rupture may lead to a rapidly enlarging pyogenic granuloma
- Sebaceous carcinoma may mimic chalazion
- Recurrent chalazia should be examined histologically

Microscopic

- Early stages: small abscess centered around a meibomian gland or a gland of Zeis

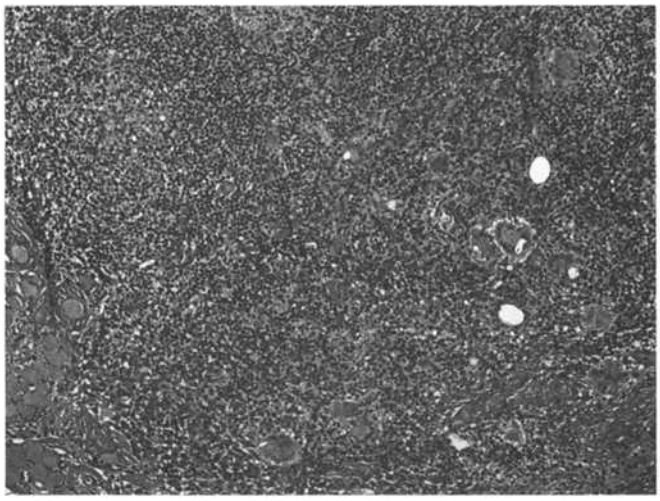


Fig. 33. Chalazion. Lipogranulomatous inflammation of eyelid glands. Clnically recurrent chalazia should be examined histopathologically to rule out malignant processes such as sebaceous carcinoma.

- Granulomatous inflammation with multinucleated giant cell reaction and empty vacuoles of released lipid from the sebaceous glands **(Figure 33)**

HORDEOLUM

External Hordeolum or Stye

Definiton

- Acute suppurative inflammation of the superficial glands and hair follicles in the eyelids

Clinical

- Superficial elevation of skin of eyelid with signs of acute inflammation
- Usually is located at the eyelid margin or adjacent to it

Microscopic

- Polymorphonuclear cell infiltration involving a hair follicle and adjacent soft tissues and adnexal glands

Internal Hordeolum

- Acute suppurative inflammation of meibomian gland
- Diffuse, tender erythematous lesion affecting most of the eyelid

Cystic Lesions of the Eyelid

- Epidermoid cysts
- Dermoid cysts

Hydrocystomas ("water cysts")

- Develop after occlusion of eccrine or apocrine sweat glands
- Hydrocystomas may be solitary or multiple

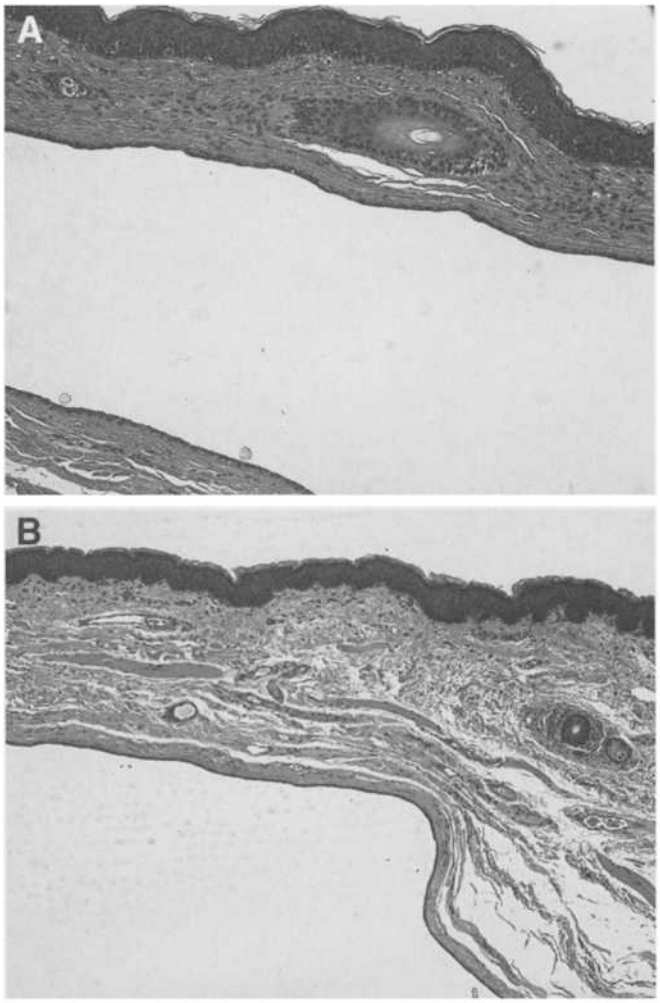


Fig. 34. **(A)** Eccrine hydrocystoma of the eyelid. **(B)** Lining of eccrine hydrocystoma with double layer of cuboidal cells.

Apocrine Hydrocytstomas

- Derived from the gland of Moll
- Usually occur ing adults, near the eyelid margin **(Figure 35)**
- The surface may have a vague bluish discoloration

Eccrine Hydrocystomas

- Similar appearance to apocrine hydrocystomas
- Microscopically, two layers of cuboidal cells, similar to those observed in the secretory portion of the gland of origin. **(Figure 34)**

Amyloidosis

- Primary Amyloidosis:
  - In **Systemic Amyloidosis**, abnormal deposits may occur around blood vessels in the eyelids and conjunctiva but are of lesser clinical importance than the retinal, uveal and orbital lesions

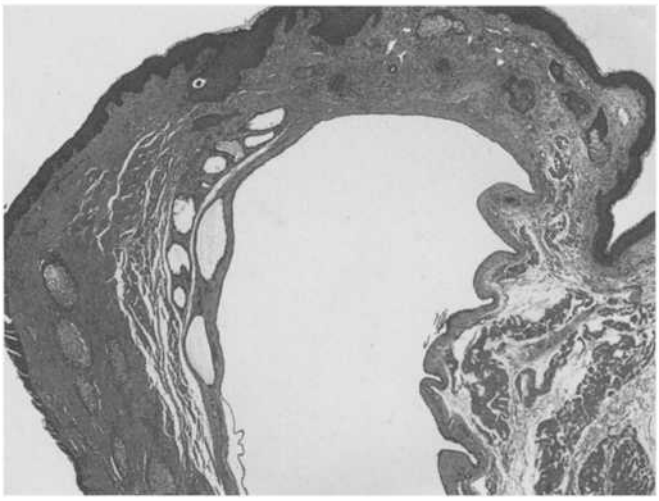


Fig. 35. Apocrine hydrocystoma arising from the gland of Moll (apocrine sweat gland).

- **Localized Nodular Amyloidosis:**
  - Nodules of red-brown color and variable size may develop in the eyelids and conjunctiva
  - No other ocular structures are affected

♦ Secondary Amyloidosis:
- Multiple small nodules of amyloid deposition may occur in the eyelid of patients with chronic inflammatory disease such as osteomyelitis, rheumatoid arthritis, leprosy and myltiple myeloma
- **Secondary Localized Amyloidosis** may develop in patients with chronic inflammatory lesions in the conjunctivaa and eyelid

Microscopic

♦ Pale eosinophilic and amorphous deposits in the connective tissue and in blood vessel walls

♦ Deposits are positive when stained with Congo red, show fluorescence with thioflavine-T and display birefringence when examined with polarized light

Tumors and Other Mass Lesions of the Eyelid

♦ Benign and malignant tumors of the eyelid skin do not differ from those occurring elsewhere in the skin and soft tissues (**Figures 36–38;** *see* Chapter 12)

Squamous Papilloma

♦ Lesions may be sessile or pedunculated

♦ They may occur anywhere in the skin of the eyelids

Microscopic

♦ Finger-like projections of the dermis covered by normal epidermis

♦ Trauma may led to epidermal erosions and inflammatory cell infiltration



Fig. 36. Dermal blue nevus in eyelid margin. Note the dilated glands of Moll. There is also atrophy of the meibomian gland and dilatation of its main duct.

Xanthelasma

♦ Middle aged and elderly patients are usually affected

♦ Xanthelasma develops in patients with hypercholesterolemia but it is more common in persons with normal serum cholesterol

Clinical

♦ Irregular elevated soft, yellow plaques

♦ Both eyelids may be affected

♦ The inner aspect of the eyelids are usually involved

♦ Bilateral and multiple lesions are not uncommon

♦ They may recur after excision

Microscopic

♦ Multiple clusters of xanthoma cells in the dermis **(Figure 39)**

Basal Cell Carcinoma

♦ *See* Chapter 12

Squamous Cell Carcinoma

♦ *See* Chapter 12



Fig. 37. Plexiform neurofibroma of eyelid extending into orbit in a patient with neurofibromatosis I.

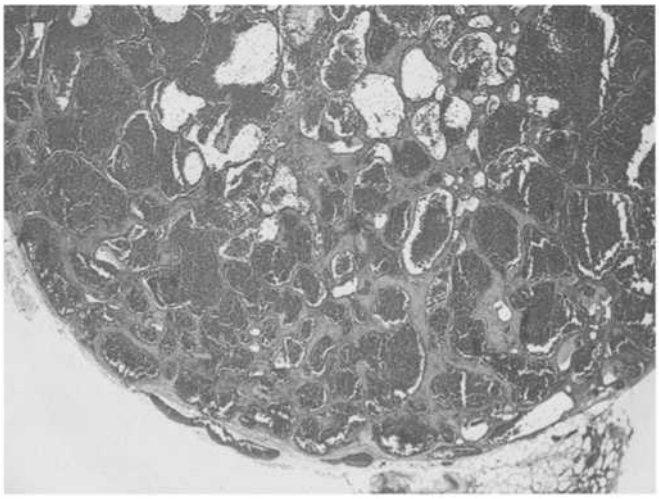


Fig. 38. Cavernous hemangioma. The fibrous septa separating the vessels may contain smooth muscle.

Sebaceous Carcinoma

Clinical

- The large majority of sebaceous carcinomas develop in the eyelids
- In the eyelids, they are second in frequency to basal cell carcinomas
- Most tumors originate from the meibomian glands
- Clinically, sebaceous carcinomas may resemble chalazia and other eyelid lesions
- They are more frequent in the upper eyelid. Occasionally they develop in the caruncle and in the eyebrow
- Typically, it affects elderly patients
- It is more frequent in women



Fig. 39. Xanthelasma. Clusters of foamy, lipid-laden histiocytes that tend to aggregate around blood vessels.

- Treatment:
  - Early detection and treatment improves prognosis
  - Wide local excision with clear margins, whenever feasible, is the treatment of choice
  - Particular attention should be given to the presence or absence of pagetoid spread
  - Orbital exenteration is often performed when there is extension into the orbit
  - Radiation is reserved for advanced cases

Microscopic

- Lobular masses of neoplastic cells **(Figure 40)**
- Cellular anaplasia may be extreme
- Cytoplasmic lipid vacuoles are observed in well and moderately differentiated tumors
- Mitoses are frequent
- Pagetoid spread along the epidermis and conjunctival epithelium is common
- Can be extensive, even in small tumors
- Foci of necrosis, sometimes with a comedo pattern, are often observed
- Direct extension into orbital soft tissues and metastases to lymph nodes, lung, liver, bone and brain may occur

TNM Classification of Carcinoma of the Eyelid (2002 Revision)

Primary tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
T1	Tumor of any size, not invading the tarsal plate or, at the eyelid margin, 5 mm or less in greatest dimension

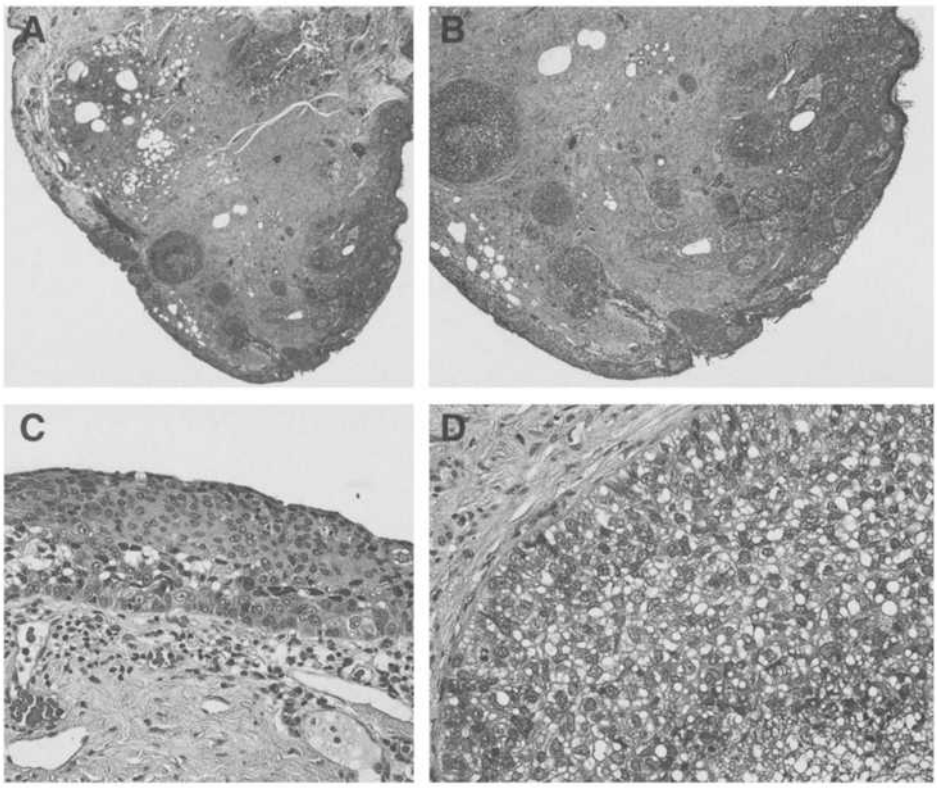


Fig. 40. Sebaceous carcinoma arising in eyelid margin. **(A)** and **(B)** Tumor involves both skin and conjunctival surfaces. **(C)** Pagetoid spread of tumor cells into conjunctival epithelium. **(D)** Marked cytoplasmic vacuolation in tumor cells.

T2	Tumor invades tarsal plate or, at the eyelid margin, more than 5 mm but not more than10 mm in greatest dimension
T3	Tumor involves full eyelid thickness or, at the eyelid margin, more than 10 mm in greatest dimension
T4	Tumor invades adjacent structures, which include bulbar conjunctiva, sclera and globe, soft sissues of the orbit, perineural space, bone and periosteum of the orbit, nasal cavity and paranasal sinuses, and central nervous system

Regional Lymph nodes (N)

MX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

LESIONS OF THE LACRIMAL DRAINAGE SYSTEM AND LACRIMAL GLANDS

- The lacrimal fluid drains from the inner canthus into the nasal cavity through the canaliculi, lacrimal sac and nasolacrimal duct
- Their epithelial lining varies:
  - Canaliculi, stratified squamous epithelium without keratinization
  - Lacrimal sac, stratified squamous epithelium, numerous goblet cells and islands of respiratory epithelium
  - Nasolacrimal duct, respiratory epithelium similar to the one in the nasal cavity

Dacryocystitis

- Inflammation of the lacrimal sac
- May be acute or chronic
- Specimens obtained at dacryocystorhinostomy usually show a variable chronic lymphoplasmacytic infiltration

Dacryolithiasis

- Concretions with a vague laminated pattern and made up of proteinaceous material
- They may contain fungal structures

- Sulphur granules of *Actinomyces sp* may also occlude the lacrimal drainage

Tumors of the Lacrimal Sac

- Squamous papilloma
- Inverted papilloma
- Oncocytoma
- Squamous cell carcinoma
- Adenocarcinoma
- Adenoid cystic carcinoma
- Malignant melanoma

Tumors of the Lacrimal Glands

- The main lacrimal gland is located in the superior temporal aspect of the orbit, in a shallow depression of the frontal bone
- The accessory lacrimal glands of Krause drain into the conjunctival sac at the level of the fornix
- The accessory lacrimal glands of Wolfring are in the posterior aspect of the eyelid and their ducts open on the palpebral conjunctiva, just above the tarsal plate
- All lacrimal glands are considered to be minor salivary glands
- They contain serous acini exclusively
- Tumors of the lacrimal glands are morphologically identical to tumors of the salivary glands (*See* chapter 17)
- Tumors of the lacrimal glands show less variation than those in the salivary glands:
  - Pleomorphic adenoma is the most frequent benign tumor of the lacrimal gland
  - Warthin's tumor is extremely rare
  - Oncocytoma
- Malignant tumors in the lacrimal gland are more frequent than in the major salivary glands:
  - Adenoid cystic carcinoma is the second most common lacrimal gland tumor after pleomorphic adenoma
  - Adenocarcinoma
  - Carcinoma ex pleomorphic adenoma
  - Mucoepidermoid carcinomas and acinic cell carcinomas are rare in the lacrimal glands
- Orbital malignancies often involve the lacrimal gland

TNM Classification of Carcinoma of the Lacrimal Gland

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2.5 cm or less in greatest dimension, limited to the lacrimal gland
T2	Tumor more than 2.5 cm but not more than 5 cm in greatest dimension, limited to the lacrimal gland
T3	Tumor invades the periosteum
T3a	Tumor no more than 5 cm invades the periosteum of the lacrimal gland fossa
T3b	Tumor more than 5 cm in greatest dimension with periosteum
T4	Tumor invades the orbital soft tissues, optic nerve, or globe with or without bone invasion; tumor extends beyond the orbit to adjacent structures, including brain

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

ORBIT

See **Tables 3–5** for additional considerations.

Tumors and Mass Lesions in the Orbit

Inflammatory Pseudotumor of the Orbit

Clinical

- Relatively common orbital disease
- Generally affects adults but it can occur in children and the elderly
- Abrupt onset with diffuse or localizaed orbital pain
- Double vision (diplopia)
- Restriction of eye movements
- Swelling and reddening of the eye
- May be chronic or recurrent

Diagnosis

- Usually not biopsied unless it becomes recurrent
- Clinical presentation and radiological findings may suffice for diagnosis

Microscopic

- Multiple variants: granulomatous, sclerosing, vasculitic, eosinophilic

Table 3. Orbital Tumors

Benign	Malignant
Cartilaginous and Osseus Tumors	Hemangiopericytoma
Dermoid Cysts	Langerhans Cell Hystiocytosis
Fibrous Dysplasia	Lymphoma
Granular Cell Tumor	Malignant Fibrous Histiocytoma
Hemangiomas	Osteosarcoma
Leiomyoma	Rhabdomyosarcoma
Lipoma	Other Soft Tissue Sarcomas
Lymphangiomas	Teratomas
Neurofibroma	Alveolar Soft Part Sarcoma
Reactive Lymphoid Hyperplasias	Germ Cell Tumors
Schwannoma	Paraganglioma, Primary
Solitary Fibrous Tumor	Orbital Carcinoid
Rare	Primary Orbital Melanoma
Aneurysmal Bone Cysts	Malignant Rhabdoid Tumor
Giant Cell Reparative Granuloma	Primitive Neuroectodermal Tumor
Giant Cell Tumor	
Eosinophilic Granuloma	

Table 4. Most Frequent Metastatic Tumors to the Orbit

Breast
Lung
Prostate
Gastrointestinal Tract
Neuroblastoma
Ewing Sarcoma

Table 5. Direct Tumor Extension From Adjacent Structures to the Orbit

Tumors of the Skin of Eyelids
Tumors of the Nasal Cavity and Paranasal Sinuses
Tumors of the Eye
Tumors of the Lacrimal Gland
Tumors of the Base of the Skull
Tumors of the Meninges

- Fibrovascular tissue proliferation with an inflammatory infiltrate that includes polymorphonuclear leukocytes, lymphocytes, plasma cells, eosinophils, histiocytes and sometimes multinucleated giant cells. **(Figure 41)**
- Lymphoid follicles with or without germinal centers
- The inflammatory process involves the soft tissue of the orbit as well as extraocular muscles, lacrimal gland

Differential diagnosis

- Malignant lymphoma
- Graves' disease
- Dacryoadenitis
- Sjogren's syndrome
- Orbital cellulitis

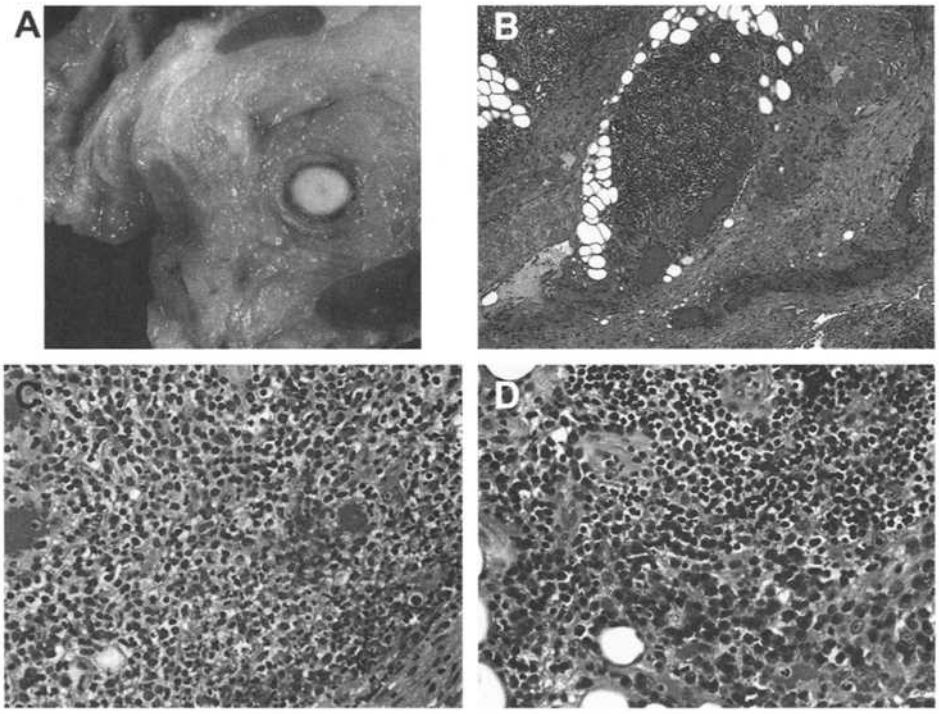


Fig. 41. Idiopathic orbital inflammation. **(A)** Cross section of posterior aspect of orbit. The lesion surrounds the extraocular muscle above the optic nerve. **(B)** The orbital fat contains islands of chronic inflammatory cells ad variable degrees of fibrosis. **(C)** The inflammatory infiltrate may contain numerous eosinophils. **(D)** Prominent lymphocytic and plasma cell infiltration.

- Sarcoidosis
- Wegener's granulomatosis
- Orbital amyloidosis

Treatment

- Steroid therapy is usually given. The inflammation often recurs when treatment is discontinued
- Sclerosing variant responds poorly to steroids
- Radiation therapy and chemotherapy may be added for recurrent pseudotumors

Graves' Disease (Thyroid Ophthalmopathy)

Clinical

- Most common cause of unilateral or bilateral exophthalmos
- Visual loss due to optic nerve compression by swollen extraocular muscles
- Exposure keratopathy
- Coexist with signs of thyroid gland dysfunction
- Thyroid function test may be low, high or normal
- Diagnosis is apparent in CT or MRI scans

Macroscopic

- Enlargement of extraocular muscles

Microscopic

- Chronic lymphoplasmacytic infiltration in extraocular muscles
- Tendinous tissue and soft tissues of the orbit are spared
- Biopsy is rarely performed for diagnosis

Rhabdomyosarcoma of the Orbit

Clinical

- Rhabdomyosaroma is the most frequent malignant tumor of the orbit in children
- It is always in the differential diagnosis of pediatric orbital lesions
- The tumor affects boys more often than girls and usually occurs in the first decade of life
- Patients often present with a rapidly developing proptosis
- Prompt diagnosis and treatment are associated with improved survival

Macroscopic

- They often involve the superior orbit
- The tumor is usually soft, with a yellow or red-tan color

Microscopic

- Most pediatric orbital rhabdomyosarcomas are poorly differentiated embryonal tumors
- Spindle cells and strap-like cells may be the predominant component
- Large rhabdomyoblasts with abundant eosinophilic cytoplasms are sometimes observed

- Cross striations may be difficult to identified
- Some tumors have an abundant myxoid matrix
- Immunohistochemical stainings for muscle markers and electron microscopic are often needed to confirm the diagnosis
- Other variants include botryoid and alveolar rhabdomyosarcomas

TNM Classification of Sarcoma of the Orbit (2002 revision)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 15 mm or less in greatest dimension
T2	Tumor more than 15 mm in greatest dimension without invasion of globe or bony wall
T3	Tumor of any size with invasion of orbital tissues and/or bony wall
T4	Tumor invasion of globe or periorbital structure, such as eyelids, temporal fossa, nasal cavity and paranasal sinues, and/or central nervous system

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Regional lymph node metastasis

Distant Metastasis (M)

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Glioma of the Optic Nerve (Pilocytic Astrocytoma of the Optic Nerve)

Clinical

- It most often affects children before the age of 10
- The initial manifestations are usually strabismus, unilateral proptosis and visual loss
- The patient may have signs of neurofibromatosis type I
- The tumor is readily diagnose with CT or MRI scans

Macroscopic

- Resection is often accomplished without eye enucleation
- The lesion appears as a large fusiform enlargement of the optic nerve
- Tumor is usually contained within the optic nerve sheath
- The resection margin (the intracranial end, in tumors removed without eye enucleation) should be sampled for histological examination

Microscopic

- Elongated, "piloid" astrocytes invade the optic nerve along its fibers

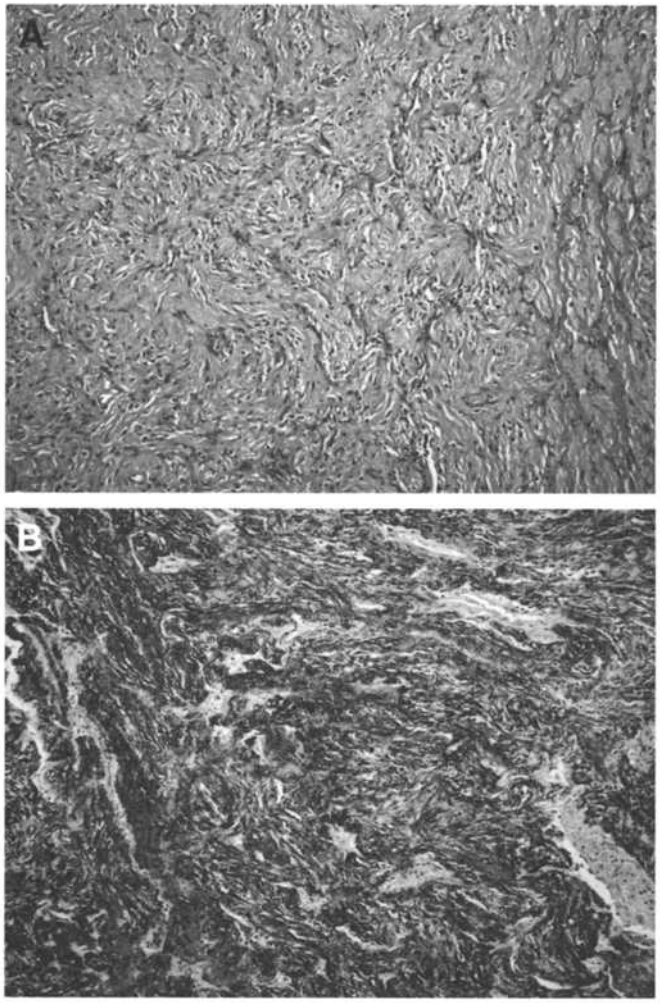


Fig. 42. Glioma of the optic nerve. **(A)** Hematoxylin and eosin. **(B)** Tumor stained for glial fibrillary acidic protein.

- The cells are GFAP positive **(Figure 42)**
- Rosenthal fibers, thick bright eosinophilic fibers, may be observed
- The tumor does not extend beyond the optic nerve sheath but it often invades the subarachnoid space ("subarachnoid gliomatosis")
- The optic nerve meninges may show a remarkable hyperplasia of the meningothelial cells which may be misinterpreted as "optic nerve meningioma" in superficial biopsies of the nerve

Meningioma of the Optic Nerve

Clinical

- The tumor may affect patients of all ages
- Patients usually complain of visual loss
- Clinical examination reveals optic nerve atrophy and abnormal vascular patterns in the optic disc

- Lesions developing in children tend to behave more aggressively
- Primary orbital meningiomas and meningiomas extending into the orbit from the intracranial compartment may also occur

Microscopic

- Sheaths or nodules of proliferating cells with meningothelial, fibroblastic or mixed patterns
- Cellular whorls and psammoma bodies may be numerous
- The vascular component of the tumor is sometimes very prominent and occasionally mimics an angiomatous lesion
- Mitoses are rare except in malignant tumors with aggressive biological behaviour
- Atypical cells may occur but have no prognostic implications unless they are associated with other signs of malignancy

Lymphoid Tumors

Clinical

- Benign and malignant lymphoid tumors of the orbit are relatively common
- Primary orbital lymphomas usually develop in older adults
- Clinically, they usually become manifested with proptosis
- They are rarely associated with pain
- A salmon pink conjunctival mass may be the only manifestation of a large orbital tumor
- Most lymphomas involve the superior aspect of the orbit and the lacrimal gland is often involved
- Their diagnosis and treatment do not differ from lymphomas involving other organ systems

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20

Mediastinum and Thymus

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CONTENTS

I. Classification of Diseases 20-2

II. Non-Neoplastic Disorders 20-3
- Inflammatory/Infectious 20-3
  - Acute Mediastinitis 20-3
  - Granulomatous Mediastinitis 20-3
  - Fibrosing Mediastinitis 20-4
- Cystic Lesions 20-4
  - Brochogenic Cyst 20-4
  - Esophageal Cyst 20-4
  - Gastroenteric Cyst 20-5
  - Pericardial Cyst (Coelomic Cyst) 20-5
  - Thymic Cyst 20-5
- Non-Neoplastic Lesions of Thymus 20-6
  - Thymic Dysplasia 20-6
  - Thymic Aplasia 20-6
  - True Thymic Hyperplasia 20-6
  - Lymphoid Hyperplasia 20-6
- Lesions Mimicking Mediastinal Tumors 20-7
  - Substernal Thyroid (Mediastinal Goiter) 20-7
  - Mediastinal Parathyroid Lesions 20-7
- Other Conditions 20-8
  - Pneumomediastinum 20-8

III. Neoplasms of the Thymus 20-8
- Histologic Features of Thymus 20-8
- Thymoma 20-8
- Thymic Carcinoma 20-13
- Thymic Carcinoid (Including Atypical Carcinoid) 20-14
- Thymic Stromal Tumors 20-15

IV. Neoplasms Not Limited to Thymus 20-16
- Neurogenic Tumors 20-16
- Paraganglioma 20-16
- Germ Cell Tumors 20-17
- Lymphoproliferative Disorders 20-18
- Mesenchymal Tumors 20-24
- Metastatic Tumors 20-24

V. TNM Classification of Thymoma 20-25

VI. The Definition of WHO Classification of Thymic Epithelial Tumors 20-25

VII. Suggested Reading 20-25

CLASSIFICATION OF DISEASES

Table 1. Classification of Diseases

Non-Neoplastic Disorders

Inflammatory/infectious

- ♦ Acute mediastinitis
- ♦ Granulomatous mediastinitis
- ♦ Fibrosing mediastinitis

Cystic lesions

- ♦ Bronchogenic cyst
- ♦ Esophageal cyst
- ♦ Gastroenteric cyst
- ♦ Pericardial cyst
- ♦ Thymic cyst
  - – Unilocular
  - – Multilocular

Non-neoplastic lesions of thymus

- ♦ Thymic dysplasia
- ♦ Thymic aplasia
- ♦ Thymic hyperplasia
- ♦ Lymphoid hyperplasia

Lesions mimicking mediastinal tumors

- ♦ Substernal thyroid (mediastinal goiter)
- ♦ Mediastinal parathyroid lesions
- ♦ Cystic hygroma
- ♦ Thoracic skeletal lesions
  - – Chordoma
  - – Osseous tumors of thoracic spine
  - – Paravertebral abscess
  - – Myelomeningocele
- ♦ Extramedullary hematopoiesis
- ♦ Vascular lesions
  - – Aortic aneurysm
  - – Venous lesions
- ♦ Esophageal lesions
  - – Diverticula
  - – Leiomyoma
  - – Achalasia
  - – Carcinoma
- ♦ Pulmonary lesions
  - – Extralobar sequestration
  - – Hilar/mediastinal lymphadenopathy
  - – Lung cancer
- ♦ Subdiaphragmatic lesions
  - – Pancreatic pseudocyst
  - – Hiatal hernia

Other conditions

- ♦ Pneumomediastinum

Neoplasms

Thymus

- ♦ Thymoma (tumor of thymic epithelium)
  - – Circumscribed (usually benign) thymoma
  - – Invasive (malignant) thymoma
- ♦ Thymic carcinoma (cytologically malignant, tumor of thymic epithelium)
- ♦ Thymic carcinoid
- ♦ Thymic stromal tumors
  - – Thymolipoma
  - – Thymic stromal sarcomas

Neoplasms not limited to thymus

- ♦ Neurogenic tumors
  - – Peripheral nerve sheath tumors
    - • Schwannoma
    - • Neurofibroma
    - • Malignant peripheral nerve sheath tumor
  - – Tumors of sympathetic nervous system
    - • Neuroblastoma
    - • Ganglioneuroblastoma
    - • Ganglioneuroma
  - – Other (rare)
    - • Ependymoma
    - • Meningioma
- ♦ Paraganglioma
- ♦ Germ cell tumors
- ♦ Lymphoproliferative disorders
- ♦ Mesenchymal tumors
- ♦ Metastatic tumor

NON-NEOPLASTIC DISORDERS

Inflammatory/Infectious

Acute Mediastinitis

Clinical

- Life-threatening acute infection
- Most common causes by compartment:
  - Anterior: post-sternotomy after cardiac surgery
  - Middle: esophageal perforation, Boerhaave's syndrome (post-emetic rupture of esophagus)
  - Posterior: direct extension from lung or spinal infection
- Descending necrotizing mediastinitis:
  - Tracks through fascial planes from deep cervical infections originating in oropharynx
  - Mixed aerobic and anaerobic organisms

Macroscopic

- Purulent exudate layered on mediastinal structures
- Abscess formation
- Hemorrhage and necrosis (inhalational anthrax)
- Air crepitance secondary to pneumomediastinum (occasional)

Microscopic

- Acute fibrinopurulent inflammation
- Infectious agents identified by appropriate stains for fungi and bacteria

Differential Diagnosis

- Determine underlying etiology:
  - Variable potential organisms (Gram, GMS stains, microbiologic cultures) depending on underlying etiology and immune status of patient

Granulomatous Mediastinitis (Localized Fibrosing Mediastinitis)

Clinical

- Disease of mediastinal lymph nodes
- Most common cause is Histoplasma capsulatum; less frequently, tuberculosis
- Complications: perforation and fistula formation, esophageal diverticula, erosion into bronchus and broncho-lithiasis

Macroscopic

- Frequently large, calcified, fibrocaseous mass of coalesced lymph nodes (mediastinal granuloma) (*See* **Figure 1**)

Microscopic

- Necrotizing granulomatous inflammation, fibrosis, and calcified caseonecrotic debris
- Acid fast bacilli (AFB) or yeast forms of H. capsulatum by special stains (*See* **Figure 2**)

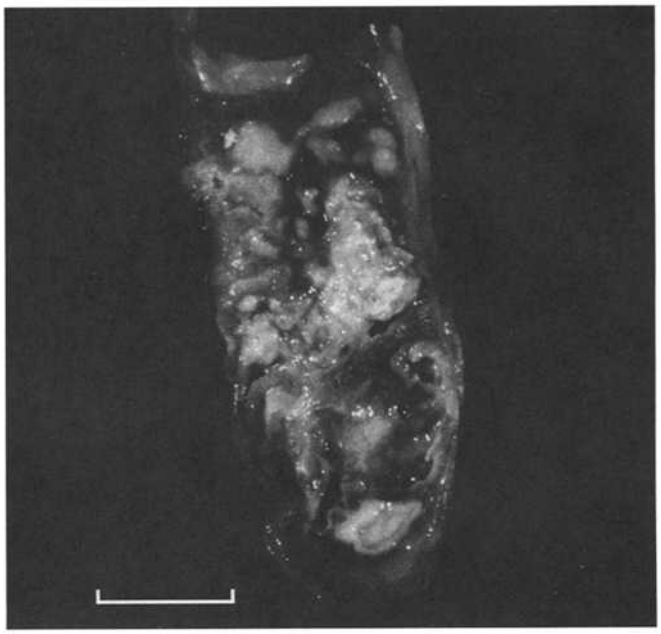


Fig. 1. Mediastinal Granuloma. Enlarged, matted lymph nodes replaced by fibrocaseous granulomas. (Scale = 1cm.)

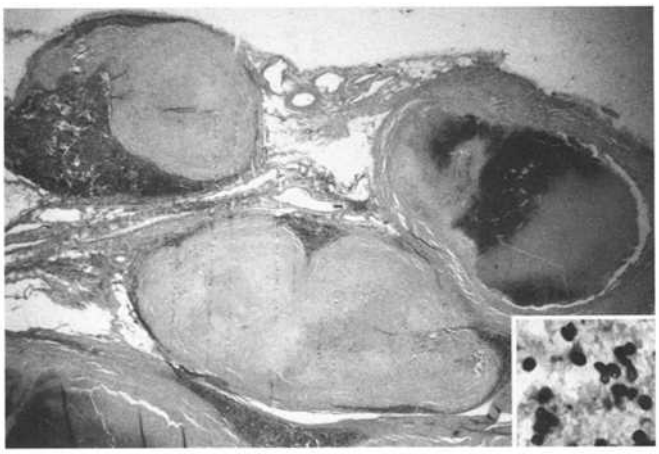


Fig. 2. Fibrocaseous, partially calcified granulomas within lymph nodes. Insert. Budding yeast-like organisms consistent with Histoplasma capsulatum.

Differential Diagnosis

- Histoplasmosis:
  - Thick fibrous capsule; yeast forms (GMS)
- Tuberculosis:
  - Thin fibrous capsule; acid-fast organisms
- Sarcoidosis:
  - Non-necrotizing granulomas; stains for microorganisms are negative

- Infected teratoma or bronchogenic cyst:
  - Necrosis may obscure typical identifying features
- Fibrosing mediastinitis:
  - Usually no caseous necrosis; ropy collagen present; superior vena caval obstruction; extension of fibrosis beyond lymph nodes

Fibrosing Mediastinitis

Clinical

- Young adults, female predominance
- Variety of compression syndromes due to involvement of mediastinal structures:
  - Superior vena caval syndrome
  - Tracheobronchial compression (hilar fibrosis)
  - Pulmonary artery or venous obstruction
- Associated with collagen vascular disease, pseudotumor of orbit, Riedel's struma, retroperitoneal fibrosis, and pulmonary hyalinizing granuloma
- May be idiopathic, or secondary reaction to documented fungal (histoplasma) or mycobacterial (rarely) infection

Macroscopic

- Firm gray fibrous tissue forms an ill-defined mass invading and compressing the mediastinal structures

Microscopic

- Dense hyalinized collagenous tissue (ropy collagen) (*See* **Figure 3**)
- Scant lymphocytic and plasmacytic inflammation
- Rare granulomas
- Fibromyxoid granulation tissue may represent early stage fibrosing mediastinitis

Immunohistochemistry

- CD45, CD3, Vimentin, Muscle actin:
  - Immunomarkers positive in early cellular lesions
  - Few reactive cells in sclerotic lesions

Differential Diagnosis

- Nodular sclerosis Hodgkin's disease; other lymphomas with sclerosis:
  - Reed-Sternberg cells positive for CD30, CD15
- Fungal/mycobacterial infection:
  - *See* granulomatous mediastinitis
- Secondary effects seen in open lung biopsy:
  - Hyalinizing granuloma, pulmonary hemosiderosis, venous infarcts, and venous and arterial sclerosis (simulates pulmonary veno-occlusive disease or pulmonary venous hypertension)
- Amyloidosis:
  - Confirm with congo red or crystal violet stain
- Progressive massive fibrosis:
  - Due to coal or silica exposure

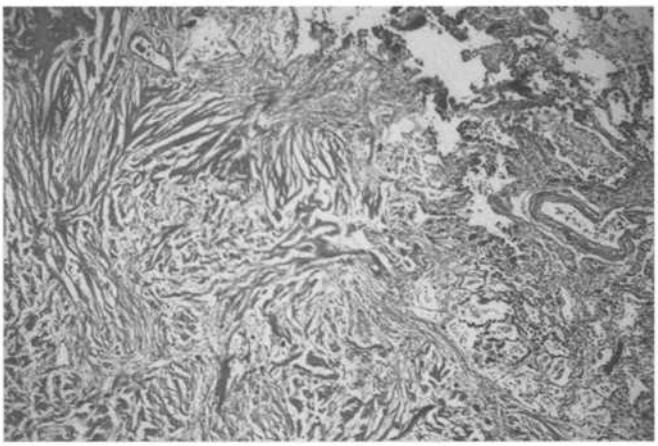


Fig. 3. Fibrosing Mediastinitis. Dense, ropy, collagenous fibrosis infiltrates adjacent lung tissue (right upper).

  - Usually within lung parenchyma; may extend to hilar or mediastinal structures
  - Associated pigment deposition
- Desmoplastic mesothelioma (rare)

Cystic Lesions

Bronchogenic Cyst

Clinical

- Most common congenital cyst of mediastinum
- Young adults
- Usual location is middle mediastinum

Macroscopic

- Spherical, unilocular or multilocular, clear or gelatinous fluid (*See* **Figure 4**)

Microscopic

- Respiratory epithelium, squamous epithelium; bronchial glands, smooth muscle, and cartilage may be present (*See* **Figure 5**)

Differential Diagnosis

- Esophageal cyst:
  - Absence of cartilage; double muscle layer+

Esophageal Cyst

Clinical

- Close association with esophageal wall in middle or posterior mediastinum

Macroscopic

- Spherical, unilocular

Microscopic

- Squamous and/or ciliated epithelium
- Esophageal glands

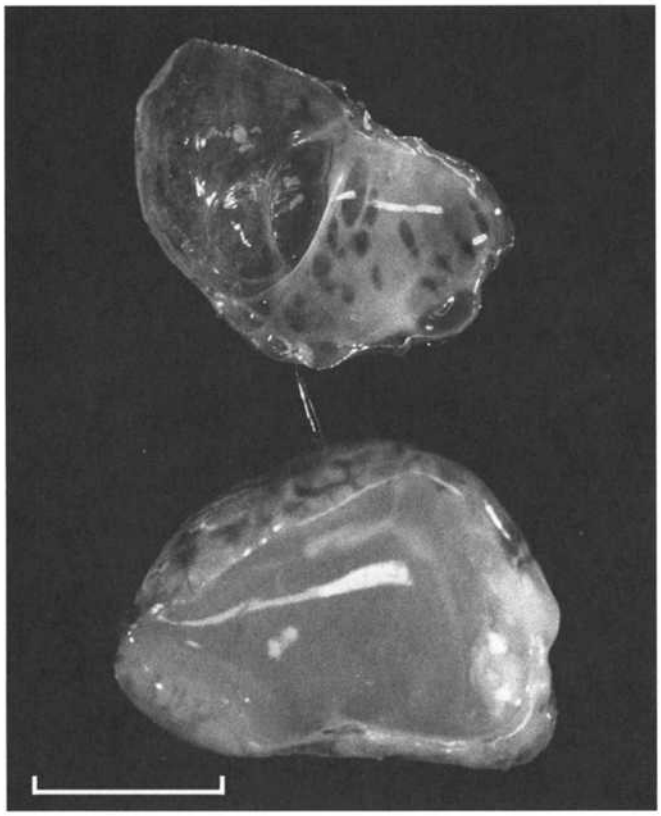


Fig. 4. Bisected bronchogenic cyst showing inner trabeculations of cyst wall and mucoid content. (Scale = 1cm.)

- Cartilage absent
- Double layer of muscle

Differential Diagnosis

- Bronchogenic cyst:
  - Presence of cartilage, no double muscular layer

Gastroenteric Cyst

Clinical

- Located in posterior mediastinum
- Often connected to vertebral column
- Associated with malformations of thoracic vertebrae (neuroenteric cyst)
- Symptoms related to nerve compression, peptic ulceration, and perforation

Macroscopic

- Unilocular cyst attached to or within esophageal wall

Microscopic

- Inner lining variable: gastric, duodenal, small intestinal, large intestinal, squamous, or respiratory epithelium
- Usually includes well-developed muscularis propria

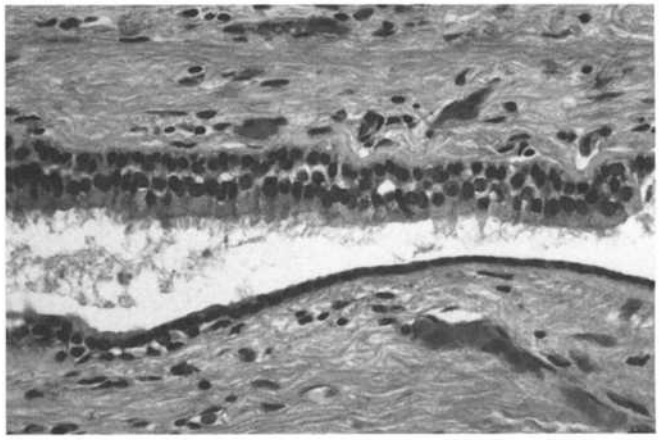


Fig. 5. Epithelial lining of bronchogenic cyst consists of ciliated respiratory epithelium.

Differential Diagnosis

- Differentiated from bronchogenic and esophageal cysts by location and gastric or intestinal epithelium

Pericardial Cyst (Coelomic Cyst)

Clinical

- Usual location in right cardiophrenic angle
- Rare in children

Macroscopic

- Spherical, unilocular, thin-walled cyst
- Usually no communication with pericardium
- Clear or straw-colored fluid

Microscopic

- Single layer of mesothelial cells overlying loose connective tissue

Immunohistochemistry

- Mesothelial cells strongly keratin+

Differential Diagnosis

- *See* bronchogenic, esophageal, and gastroenteric cysts
- Thymic cyst:
  - Located in superior mediastinum, thymic tissue in wall

Thymic Cyst

Unilocular Thymic Cyst (Developmental Origin)

Clinical

- Small; located in lateral neck more often than in mediastinum

Macroscopic

- Unilocular with thin and translucent wall

Microscopic

- Flat, cuboidal, columnar, or (rarely) squamous epithelial lining
- Thymic tissue present in wall
- Usually lack of inflammation

Multilocular Thymic Cyst (Acquired [Reactive] Process)

Clinical

- Asymptomatic large tumor-like mass in anterosuperior mediastinum:
  - Incidental finding on chest X-ray
  - Frequently associated with thymic neoplasms
  - May arise in setting of HIV infection

Macroscopic

- Multilocular with thick fibrous septa containing cloudy to blood-tinged fluid

Microscopic

- Squamous (often), flat cuboidal, ciliated columnar, either single or stratified epithelial lining
- Acute and chronic inflammation with fibrovascular proliferation, necrosis, hemorrhage, cholesterol granulomas, and reactive lymphoid hyperplasia
- Thymic tissue present in wall

Differential Diagnosis

- Cystic thymoma:
  - Maintains features of thymoma with nodular proliferation of thymic epithelial cells in addition to prominent cystic changes
- Cystic teratoma (*see* germ cell tumors later)
- Cystic lymphangioma:
  - Prominent ectatic lymphatic channels
- Nodular sclerosis Hodgkin's disease and large cell lymphoma with cystic changes (*see* lymphoproliferative disorders later)
- Seminoma (germinoma) with cystic changes (*see* germ cell tumors later)
- Thymic carcinoma:
  - Invasive growth, malignant cytology

Non-Neoplastic Lesions of Thymus

Thymic Dysplasia

Clinical

- Present at birth
- Associated disease: usual X-linked or autosomal recessive form of severe combined immunodeficiency, ataxia telangiectasia, and related chromosomal instability syndromes; Nezelof syndrome; and incomplete form of DiGeorge syndrome (usually located ectopically)

Macroscopic

- Very small size (<5g)

Microscopic

- Primitive-appearing epithelium without segregation into cortical and medullary regions
- Absence of Hassall's corpuscles
- Almost total absence of lymphocytes
- Small-sized vessels

Differential Diagnosis

- Acute thymic involution often seen at autopsy:
  - Results from stress and superimposed infections
  - Marked lymphocytic depletion with preservation of lobular architecture and of Hassall's corpuscles
  - Disproportionately large vessels compared to size of lobules
  - Scattering of inflammatory cells (particularly plasma cells) within interlobular and perilobular tissue

Thymic Aplasia

Clinical

- Present at birth
- Associated with complete form of DiGeorge syndrome

Macroscopic and Microscopic

- Complete absence of thymus gland

True Thymic Hyperplasia

- Enlargement of thymus gland (by weight and volume) beyond upper limit of normal for age

Clinical

- Unknown clinical significance; questionable immunologic rebound phenomenon (post cessation of chemotherapy
- Associated diseases: Thyromegaly, Graves' disease, acromegaly

Macroscopic

- Enlarged thymus gland

Microscopic

- Normal thymic architecture
- Diagnosis made by increased size and weight

Differential Diagnosis

- Thymoma:
  - Preservation of thymic architecture in hyperplasia

Lymphoid Hyperplasia

Clinical

- Associated diseases: myasthenia gravis (most common), systemic lupus erythematosus, rheumatoid arthritis, scleroderma, allergic vasculitis, and thyrotoxicosis

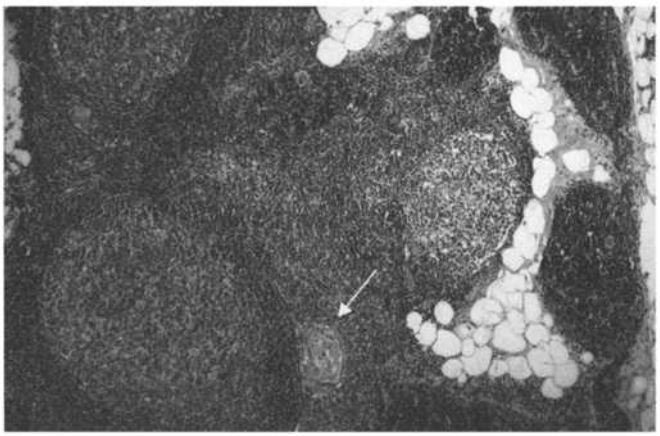


Fig. 6. Thymic lymphoid hyperplasia. Prominent lymphoid follicles are present in thymus gland. Note adjacent Hassall's corpuscle (arrow).

Macroscopic

- Normal size and weight of thymus gland for age

Microscopic

- Increased number of lymphoid follicles with prominent germinal centers (*See* **Figure 6**)

Differential Diagnosis

- Thymoma:
  - Preservation of thymic architecture in lymphoid hyperplasia
- Reactive lymph node hyperplasia or lymphoproliferative lesions:
  - Reactive germinal centers with preserved thymic architecture in lymphoid hyperplasia

Lesions Mimicking Primary Mediastinal Neoplasms Substernal Thyroid (Mediastinal Goiter)

Clinical

- Located in superior mediastinum, usually connected to cervical goiter
- Can usually be excised via neck incision
- Compressive symptoms
- Radioactive iodine scanning+ in half of cases

Macroscopic

- Features of adenomatous goiter, frequently extends from inferior pole of thyroid in neck (*see* **Figure 7**) (*see* Chapter 11)

Microscopic

- Nodular hyperplasia of thyroid tissue (*see* Chapter 11)



Fig. 7. Large substernal goiter arising from the lower pole of the left lobe of the thyroid gland. (Scale = 1 cm.)

Differential Diagnosis

- Other thyroid lesions are less frequent (e.g., adenoma, carcinoma)

Mediastinal Parathyroid Lesions

Clinical

- Arise from ectopic parathyroid tissue in superior mediastinum
- Clinically associated with hyperparathyroidism and hypercalcemia

Macroscopic

- Enlarged parathyroid tissue
- Parathyroid cysts (rare)

Microscopic

- Features of parathyroid adenoma or hyperplasia (Chapter 11)
- Simple cyst with parathyroid tissue in wall

Differential Diagnosis

- Paraganglioma or carcinoid tumor:
  - Not associated with hypercalcemia
  - Histologically chief cells and/or water clear cells in parathyroid lesions

Other Conditions

Pneumomediastinum

Clinical

- Air within fascial planes of mediastinum, often in association with pulmonary interstitial emphysema, pneumopericardium, pneumothorax, and subcutaneous emphysema
- Major causes are mechanical ventilation (barotrauma), esophageal perforation, acute mediastinitis, and increased intrathoracic pressure (straining, valsalva maneuver)
- Chest X-ray and CT scan show mediastinal air outlining aorta, esophagus, and left heart border

Macroscopic

- Air bubbles and crepitance in mediastinal tissue at autopsy
- Tension pneumothorax often also seen in patients receiving mechanical ventilation

Microscopic

- Widened, empty interstitial spaces in mediastinal fat. (*See* **Figure 8**)

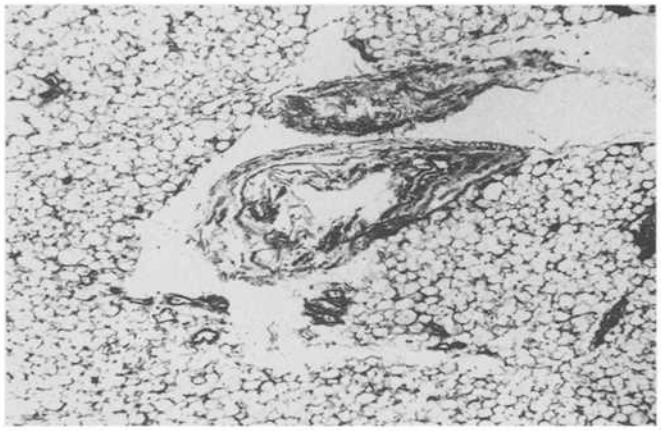


Fig. 8. Pneumomediastinum. Empty-appearing cystic spaces displace mediastinal fat and fibrovascular tissue.

- Interstitial pulmonary emphysema tracks along broncho-vascular sheaths in lung

Differential Diagnosis

- Lymphangiectasia:
  - Same distribution as interstitial air dissection
  - Look for endothelial lining in lymphangiectasia vs. acute hemorrhage and empty spaces in air dissection
- Determine underlying cause (*see* clinical, above)

NEOPLASMS OF THE THYMUS

Histologic Features of Thymus

- Lobulated; encapsulated; subdivided into cortex and medulla
- Cell types:
  - Epithelial cell:
    - Endodermally derived
    - Modulates differentiation of T lymphocytes
    - Keratin+, HLA-DR+
    - Subtypes:
      - Cortical: medium to large, round or polygonal, clear nuclei with nucleoli
      - Medullary: spindle nuclei
      - Epithelium forming Hassall's corpuscle
  - Lymphocytes (traditionally known as thymocytes):
    - Bone-marrow derived
    - Subtypes:
      - Cortical: immature T cells (immuno-phenotyping: cytoplasmic CD3+, CD1a+, terminal deoxynucleotidyl transferase (TdT)+, coexpresses CD4/8)
      - Medullary: mature T lymphocytes (immuno-phenotyping: surface CD3+, either CD4+ or CD8+)
  - Other (minor) cell types:
    - Interdigitating reticulum cells
    - Langerhans' cells
    - Mast cells
    - Eosinophils (especially in neonates)
    - Mesenchymal stromal cells

Thymoma (*see* Figures 9–18)

- Tumor of thymic epithelium; cytologically bland, with associated cortical-type T cells
- WHO; *see* table at the end of the chapter
- Major subtypes: Circumscribed (usually benign) thymoma and Invasive

Circumscribed (Usually Benign) Thymoma (Histologic Classification) (See Figure 18)

- Lattes-Bernatz (L-B):
  - Predominantly spindle cell
  - Predominantly lymphoid

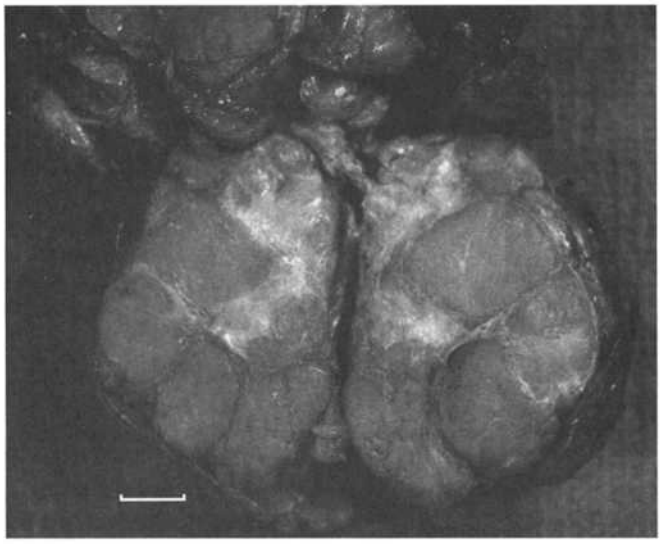


Fig. 9. Circumscribed thymoma (mixed type). Note lobules of tumor separated by bands of connective tissue and central scar.

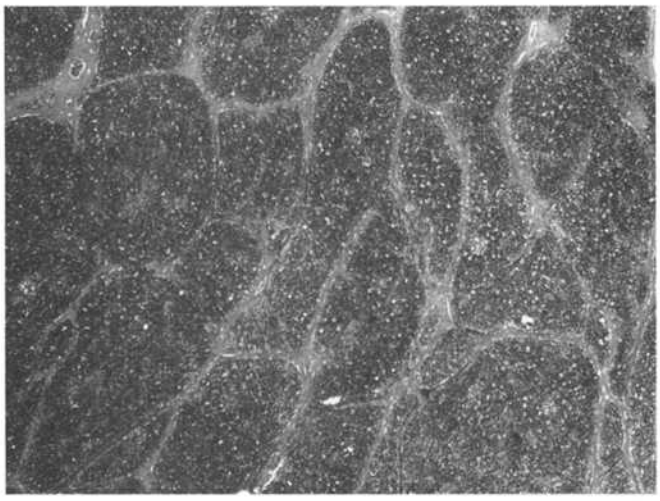


Fig. 10. Thymoma, general features. Cellular lobules separated by fibrous septa.

- Predominantly mixed
- Predominantly epithelial

♦ Muller-Hermelink (M-H):
- Medullary
- Non-medullary:
  - Predominantly cortical (organoid)
  - Mixed
  - Cortical
  - Well-differentiated thymic carcinoma

Invasive (Malignant) Thymoma

♦ Any of the histologic subtypes (*see* Microscopic, following) with evidence of invasion (*see* **Figure 18**)

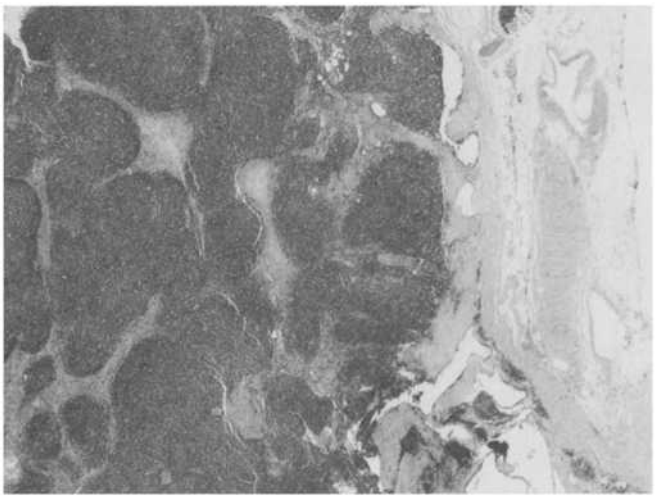


Fig. 11. Thymoma, general features.

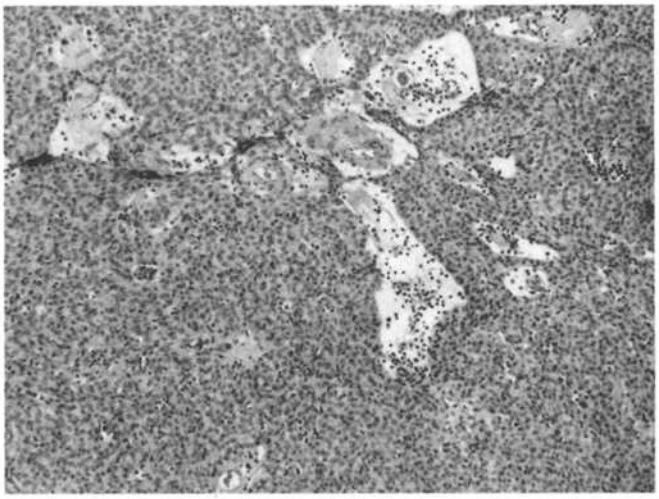


Fig. 12. Thymoma, general features. Perivascular spaces (serum lakes) containing lymphocytes, proteinaceous fluid, red blood cells, foamy macrophages.

Clinical

♦ Mainly adults

♦ Usually located in anterosuperior mediastinum

♦ Lobulated mediastinal mass on chest X-ray, CT, and MRI

♦ Associated diseases:
- Myasthenia gravis (almost exclusively associated with non-medullary thymoma or Type B thymoma by WHO classification)
- Hypogammaglobulinemia (mainly associated with medullary thymoma)
- Erythroid hyperplasia (mainly associated with medullary thymoma)

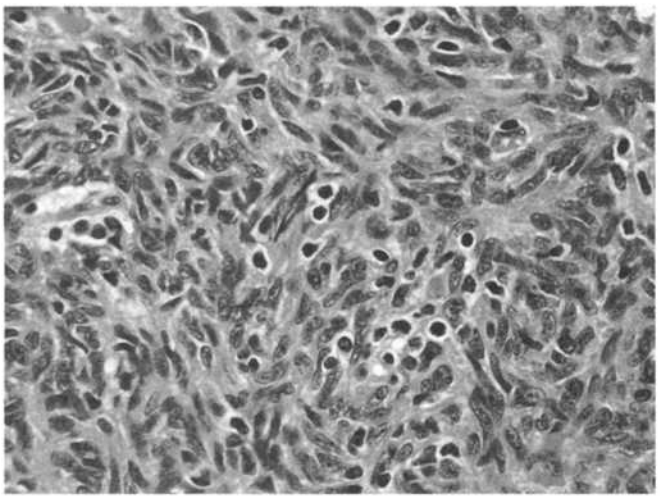


Fig. 13. Thymoma, predominantly spindle cell (medullary [M-H], Type A [WHO]).

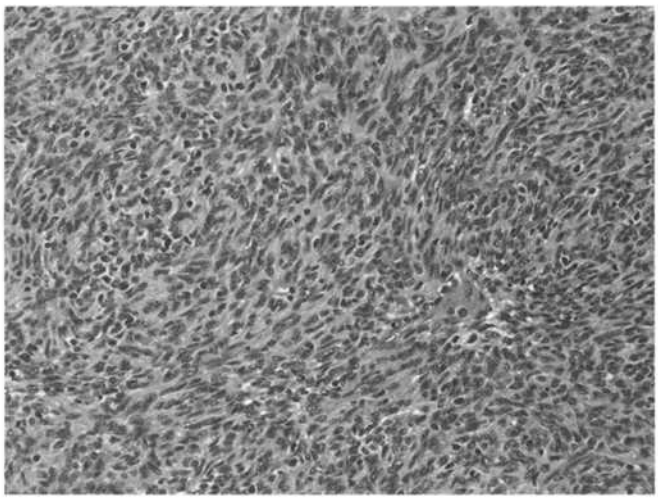


Fig. 14. Thymoma, predominantly spindle cell (medullary [M-H], Type A [WHO]).

Treatment:

- Surgery alone for entirely encapsulated (benign) thymoma (2% to 10% recurrence)
- Surgery with radiation for invasive thymoma
- Chemotherapy for metastatic disease

Prognosis

- Degree of tumor invasion (stage of disease) best prognostic factor
- WHO histologic subtype may be an independent prognostic factor, particularly in Stage I and II thymomas, among which WHO Type A, AB, and B1 thymomas form a low-risk group
- The proportion of invasive tumors increased by type—from A to AB, B1, B2, and B3.
- Myasthenia gravis has no prognostic significance

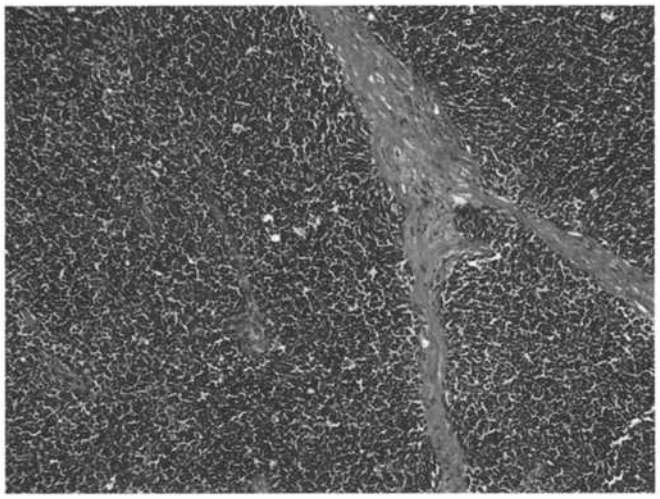


Fig. 15. Thymoma, predominantly lymphoid (predominantly cortical [M-H], and B1 [WHO]).

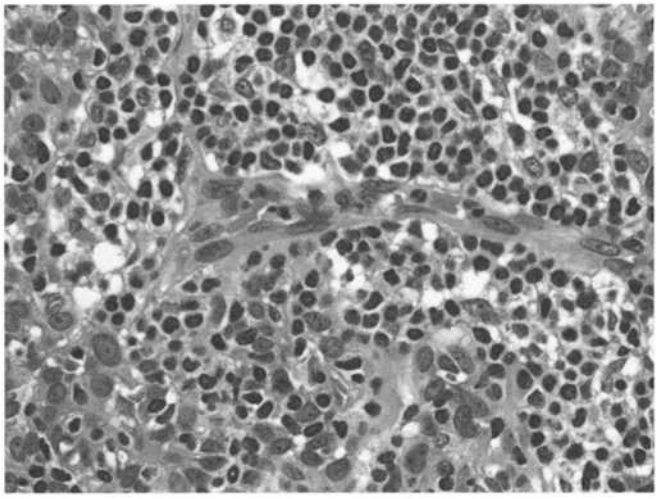


Fig. 16. Thymoma, predominantly mixed (mixed or cortical [M-H], Type AB or B2 [WHO]).

Macroscopic

- Circumscribed thymoma:
  - 2–20 cm
  - Predominantly solid, yellowish gray, lobulated by connective tissue septa, encapsulated (*See* **Figure 9**)
  - Cystic degeneration in larger tumors
- Invasive thymoma:
  - Similar to circumscribed thymoma in addition to infiltration of surrounding structures

Microscopic

- General (applies to all histologic subtypes):
  - Cellular lobules separated by fibrous septa (*See* **Figure 10,11**)
  - Fibrous capsule complete in circumscribed thymoma, incomplete with capsular invasion in invasive thymoma

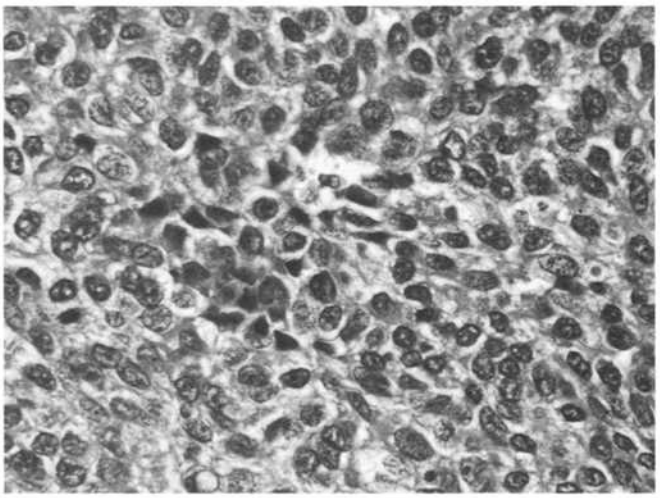


Fig. 17. Thymoma, predominantly epithelial (well-differentiated thymic carcinoma [M-H], Type B3 [WHO]).

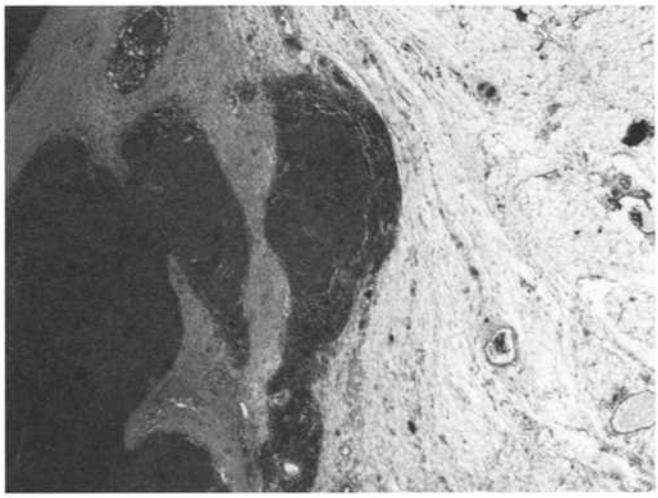


Fig. 18. Invasive thymoma. The thymoma breaks through the capsule and invades the lung parenchyma.

- Varying proportion of lymphocytes and neoplastic epithelial cells
- Perivascular spaces containing lymphocytes, proteinaceous fluid, red blood cells, foamy macrophages, or fibrous tissue (*See* **Figure 12**)
- Occasional gland or pseudogland structures
- Hassall's corpuscle-like structure

♦ Histologic subtypes:

- Predominantly spindle cell (medullary [M-H], Type A [WHO]) (*See* **Figure 13, 14**):
- Predominantly spindle-shaped epithelial cells with few mature lymphocytes
- Variable patterns: storiform, hemangiopericytoma-like, rosette-like (without central lumen), glandular formation
- Capsular invasion rare
- Predominantly lymphoid (<33% epithelial cells, predominantly cortical [M-H], Type B1 [WHO]) (*See* **Figure 15**):
- Scattered large polygonal epithelial cells in diffuse, small, round lymphocytic background (CD1a+, coexpress CD4/8)
- Sparse foci of medullary differentiation containing tingible body macrophages ("starry sky" pattern)
- Capsular invasion rare
- Predominantly mixed (34% to 66% epithelial cells, mixed or cortical [M-H], Type AB or B2 [WHO]) (*See* **Figure 16**):
  - Mixed type (M-H)/Type AB (WHO):
    - Mixture of medullary and predominantly lymphoid pattern
    - Capsular invasion rare
  - Cortical type (M-H)/Type B2 (WHO):
    - Sheets of polygonal epithelial cells (large nuclei and prominent nucleoli) intermixed with lymphocytes
    - Minimal medullary differentiation
    - Capsular invasion may be present
- Predominantly epithelial (well-differentiated thymic carcinoma [M-H], Type B3 [WHO]) (*See* **Figure 17**)):
  - Sheets of polygonal epidermoid cells with large vesicular, hyperchromatic granular nuclei, nucleoli
  - Slight to moderate cellular atypia
  - Mitosis (up to 10/10 HPF)
  - Usually invasive growth
  - Considered to be variant of cortical thymoma

Electron Microscopic

♦ Neoplastic epithelial cells: branching tonofilaments; complete desmosomes; elongated cell processes and basal lamina

*Immunohistochemistry (see **Table 2**)*

♦ Neoplastic epithelial cells: keratin +, epithelial membrane antigen (EMA)+

♦ Non-neoplastic lymphocytes:

- Medullary: mature lymphocytes with features of medullary thymocytes (CD1a–, either CD4+ or CD8+)
- Non-medullary: immature lymphocytes with features of cortical thymocyte (TdT+, CD1a+, coexpress both CD4 and CD8)

Differential Diagnosis

♦ Thymic carcinoma:

- Cytologically malignant; high mitotic rate with atypical mitoses, invasive growth, sclerosis in center of tumor, and coagulative necrosis

Table 2. Immunohistochemistry Stain Profile of Mediastinal Tumors

	Thymoma		*Metastatic carcinoma*	*Thymic carcinoma*		*Thymic carcinoid*	*Germ cell tumor*	*HD nodular sclerosing type*	*LL*	*DLCL with sclerosis*
	Neoplastic epithelial cells	*Nonneoplastic lymphoid cells*		*Neoplastic epithelial cells*	*Nonneoplastic lymphoid cells*					
Keratin	+	−	+	+	−	±	+ except seminoma	−	−	−
EMA	+	−	+	+	−	±	−	−	−	−
LCA (CD45)	−	+	−	−	+	−	−	−	+	+
CD1a, TdT	−	+ except medullary	−	−	−	−	−	−	−	−
CD5	−	+	−	+	+	−	−	− (+ in background T cells)	+ (− in B-LL)	−
CD15, CD30	−	−	−	−	−	−	− embryonal Ca CD30 ±	+ (in R-S cells and variants)	−	−
PLAP	−	−	−	−	−	−	+	−	−	−
CEA	−	−	±	±	−	±	−	−	−	−
B72.3	−	−	±	±	−	±	−	−	−	−
Neuroendocrine marker	−	−	− (+ in small cell undifferentiated carcinoma)	−	−	+	−	−	−	−

Abbreviations: HD = Hodgkin's disease; LL = Lymphoblastic lymphoma; DLCL = Diffuse large cell lymphoma; B-LL = B-cell LL; R-S = Reed-Sternberg

- CEA and B72.3+ in thymic carcinoma, but – in thymoma
- Infiltrating lymphocytes are mature lymphocytes and negative for CD1a (very useful criteria in needle biopsy)
- Usually not associated with myasthenia gravis

♦ Carcinoid:
- Unencapsulated; monomorphous cell population with true rosettes, ribbons, or festoons
- Positive staining for neuroendocrine markers
- Some associated with Cushing's syndrome

♦ Thymic Hodgkin's disease:
- Extensive fibrosis with rounded (as opposed to angulated) lobules
- Prominent cysts
- Reed-Sternberg cells or lacunar cells (CD15+, CD30+)
- Mixed inflammatory cells

♦ Lymphoblastic lymphoma:
- Diffuse growth or thin, separated lobules
- Numerous mitoses in lymphoid cells
- Positive for T-cell receptor or immunoglobulin chain gene rearrangement

♦ Diffuse large B-cell lymphoma with sclerosis:
- Diffuse growth
- Variable fibrosis with occasional compartmentalization
- Residual cystic thymus
- Lymphocytes with vesicular nuclei, prominent nucleoli, and variable cytoplasm
- Positive for B-cell markers (CD20)

♦ Thymic seminoma:
- Subdivided by fine fibrous trabeculae into variable-sized compartments
- Placental-like alkaline phosphatase (PLAP)+, keratin–

♦ Localized lymphoid hyperplasia (vs thymoma, predominantly lymphoid subtype):
- Retention of normal cortical and medullary structure
- Presence of lymphoid follicles with germinal centers

♦ Fibrous histiocytoma and hemangiopericytoma (vs. predominantly epithelial or predominantly spindle-cell thymoma with storiform and hemangiopericytoma-like growth pattern):
- Keratin–

♦ Spindle epithelial tumor with thymus-like elements (SETTLE):
- Young age
- Occurrence in thyroid gland
- Mucous glands frequently present
- Lymphocytes lacking

Thymic Carcinoma (Type C of Thymic Epithelial Tumors by WHO Classification)

♦ Tumors of thymic epithelium, cytologically malignant, not associated with cortical-type immature T cells

Clinical

♦ Rarely associated with myasthenia gravis or other thymoma-related paraneoplastic syndromes

♦ Asymptomatic or nonspecific symptoms found by routine chest X-ray

♦ Superior vena cava syndrome (occasional)

♦ Metastatic sites:
- Lymph nodes (mediastinal, cervical, and axillary), bone, lung, liver, and brain

♦ Treatment: surgery and radiation with or without chemotherapy

♦ Prognosis depends on histologic subtype:
- Very aggressive: non-keratinizing carcinoma (including lymphoepithelioma-like tumors), sarcomatoid carcinoma, clear cell carcinoma, and undifferentiated (anaplastic) carcinoma
- Intermediate: squamous cell carcinoma (SCC)
- Relatively indolent: mucoepidermoid and basaloid carcinoma

Macroscopic

♦ Homogeneous, yellow to gray cut surface with hemorrhage, necrosis, and infiltrating borders

Microscopic

♦ Morphologically similar to carcinoma in other organ systems

♦ Cytologic features of malignancy; displays none of characteristic features of thymoma

♦ Lacks cortical-type T lymphocytes

♦ Subtypes:
- Common:
  - Keratinizing SCC
  - Lymphoepithelioma-like (non-keratinizing) SCC (*See* **Figure 19**):
    - Epstein-Barr virus associated (some cases)
- Rare:
  - Mucoepidermoid carcinoma
  - Adenosquamous carcinoma
  - Basaloid carcinoma
  - Small cell undifferentiated carcinoma
  - Large cell undifferentiated (anaplastic) carcinoma
  - Sarcomatoid carcinoma
  - Clear cell carcinoma

Immunohistochemistry

♦ Neoplastic epithelial cells: keratin+, EMA+, CEA+, B72.3+, and infrequently Leu-7 (CD57)+

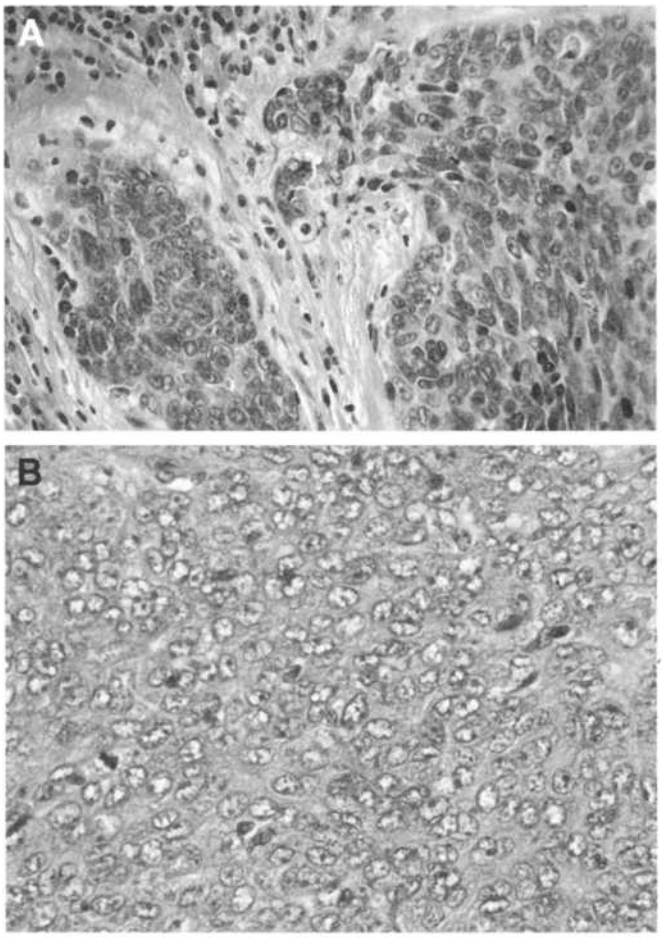


Fig. 19. Thymic carcinoma (non-keratinizing type) **(A,B)**. Note infiltrative malignant cells with prominent nucleoli and mitotic figures.

- Thymic carcinoma cells are usually CD5+ (CD5 usually – in carcinomas other than thymic primary)
- Infiltrating lymphocytes: CD1a–

Differential Diagnosis

- Thymoma:
  - *See* above thymoma
- Carcinoma metastatic to or invading anterior mediastinum (particularly carcinoma of lung) and malignant mesothelioma:
  - Thymic squamous carcinoma often exhibits lobulated growth pattern, central sclerosis, and abrupt keratinization simulating Hassall's corpuscles
  - Other subtypes of thymic carcinoma cannot be differentiated based solely on histology (thymic carcinoma is a diagnosis of exclusion: in presence of malignant epithelial tumor located in thymic region in absence of known primary)
  - CD5+ for tumor cells supports diagnosis of primary thymic carcinoma
- Germ cell tumors:
  - PLAP+, human chorionic gonadotropin (HCG)± (*see* section on germ cell tumors)
- Diffuse large cell lymphoma with sclerosis:
  - leuokocyte common antigen (LCA)+, CD20 (B cell marker)+, keratin–, EMA–
- Carcinoma with thymus-like elements (CASTLE):
  - Tumor of thyroid gland or soft tissues of neck of middle-aged adult
  - Histologically identical to thymic lymphoepithelioma-like carcinoma with better prognosis and more indolent course

Thymic Carcinoid (Including Atypical Carcinoid)

Clinical

- Adults
- Radiology:
  - Nonfunctional carcinoid:
    - Large, radiopaque, noncystic anterior mediastinal mass with/without fine calcification
  - Functional carcinoid (associated with Cushing's syndrome):
    - Usually of small size, detected by CT scan
- No reported cases of carcinoid syndrome
- Functional tumors have more aggressive course, invade locally, and metastasize infrequently
- Occasionally associated with multiple endocrine neoplasia syndrome (MEN) Types I or IIa or carcinoid tumors of other sites, such as bronchus and ileum
- Usually cured by excision
- Atypical carcinoids have increased metastatic potential and worse prognosis

Macroscopic

- Solid, well-circumscribed, but not encapsulated (*See* **Figure 20**)
- Lobulated, yellow-tan mass

Microscopic

- Typical carcinoid:
  - Rosette-like glands with central lumina, ribbon, and festoon formation (*See* **Figure 21**)
  - Uniform nuclei with low mitotic rate
  - Marked vascularization
- Atypical carcinoid (majority of tumors):
  - Nuclear pleomorphism
  - Increased mitotic rate and necrosis

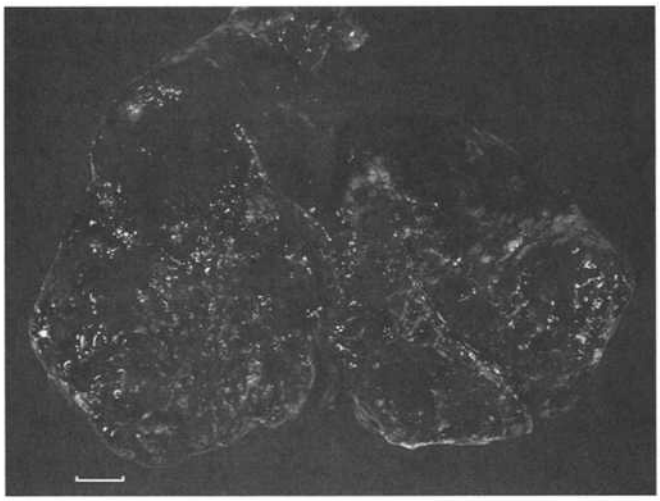


Fig. 20. Thymic carcinoid tumor. The hemorrhagic appearance denotes prominent tumor vascularity. (Scale = 1 cm.)

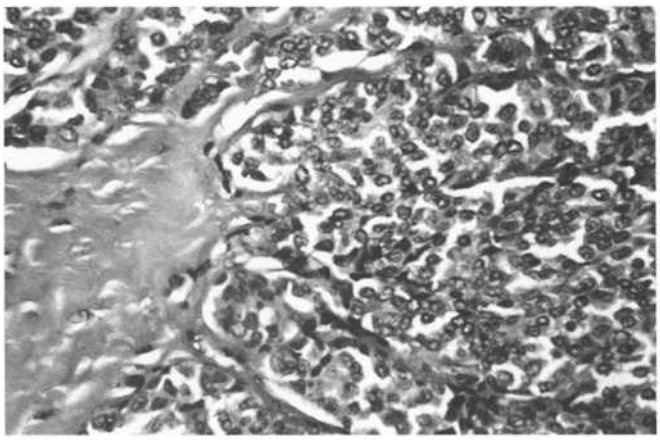


Fig. 21. Typical carcinoid tumor. Note uniform appearance of cells in a neuroendocrine nesting pattern.

Electron Microscopic

- Dense core neuroendocrine granules

Immunohistochemistry Stain

- Keratin+, neuron-specific enolase+, chromogranin+, adrenocorticotropic hormone (ACTH)+ (for cases associated with Cushing's syndrome)

Differential Diagnosis

- Small cell undifferentiated carcinoma (vs. atypical carcinoid):
  - High mitotic rate; small nuclear size, with homogenous chromatin pattern
- Epithelial cell predominant thymoma with rosette-like structures:
  - Rosette-like structures frequently associated with lymphocytes, negative for neuroendocrine markers

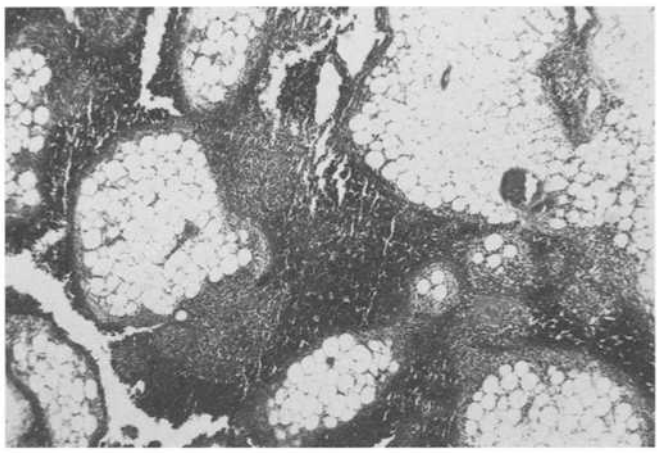


Fig. 22. Thymolipoma. Thymic tissue is separated by lobules of mature adipose tissue.

Thymic Stromal Tumors

Thymolipoma

Clinical

- M : F = 2.3: 1, young adult (mean age = 20–30 years)
- Benign, large, asymptomatic mass (>500 gm) of anterior mediastinum
- Association: myasthenia gravis, aplastic anemia, and Graves' disease
- Radiographically resembles cardiomegaly or pulmonary sequestration

Macroscopic

- Encapsulated, can be huge
- Appearance of lipoma with focal presence of whitish solid areas

Microscopic

- Admixture in various proportions of mature adipose tissue and unremarkable thymic tissue being in excess of that normally expected for age (*See* **Figure 22**)

Differential Diagnosis

- Lipoma:
  - Lacks thymic component
- Lymphoid hyperplasia:
  - Smaller size, less adipose tissue, prominent germinal centers

Thymic Stromal Sarcomas

- Rare, low-grade malignant mesenchymal tumors arising from thymic stroma, well-differentiated liposarcoma being the predominant component ("thymoliposarcoma")

NEOPLASMS NOT LIMITED TO THYMUS

Neurogenic Tumors

- Account for ~19% of primary mediastinal masses; majority occur in posterior mediastinum

Peripheral Nerve Sheath Tumors

Schwannoma

Clinical

- Typically in young adults
- Most common neurogenic tumor of mediastinum
- Usually asymptomatic, occasionally presenting as "dumbbell" tumor with extension through intervertebral foramen causing nerve root and spinal cord compression
- Radiography:
  - Well-circumscribed posterior mediastinal mass, usually single
- Multiple tumors associated with von Recklinghausen's disease
- Good prognosis, recurrence rare

Macroscopic, Microscopic, and Differential Diagnosis

- See Chapter 13 Mediastinal schwannomas frequently attain large size and are associated with degerative changes including sclerosis, fatty degeneration, hemorrhage, and cyst formation

Neurofibroma

Clinical

- Similar to schwannoma, second to schwannoma in frequency

Macroscopic, Microscopic, and Differential Diagnosis

- *See* Chapter 13
- Mediastinal neurofibroma is often enclosed by a complete fibrous capsule

Malignant Peripheral Nerve Sheath Tumor (MPNST)

Clinical

- Age range = 20–50 years
- Rare in mediastinum (<10% of thoracic neurogenic tumors)
- Poor prognosis: local invasion, recurrence, and metastasis
- Associated with von Recklinghausen's disease and prior radiation

Macroscopic, Microscopic, and Differential Diagnosis

- *See* Chapter 13

Tumors of Sympathetic Nervous System

Neuroblastoma

Clinical

- Most common mediastinal neurogenic neoplasm in children, particularly <1 year of age
- Usually symptomatic:
  - Esophageal or spinal nerve root compression, some with paraneoplastic neurologic syndrome known as opsoclonus myoclonus ("dancing feet and dancing eyes"); erosion of contiguous vertebral bones; failure to thrive; elevated level of catecholamine metabolites in urine or blood
- More than half with metastasis at time of diagnosis
- Frequent sites of metastasis: brain, liver, bone, or regional lymph nodes

Macroscopic, Microscopic, and Differential Diagnosis

- *See* Chapter 11

Ganglioneuroblastoma

Clinical

- Occurs in older infants and children
- Less aggressive than neuroblastoma

Macroscopic, Microscopic, and Differential Diagnosis

- *See* Chapter 11

Ganglioneuroma

Clinical

- Occurs in older children and young adults
- Usually asymptomatic, occasionally with spinal nerve root compression
- Usually good prognosis

Macroscopic, Microscopic, and Differential Diagnosis

- *See* Chapter 11

Paraganglioma

Clinical

- Two major types by location:
  - Anterosuperior mediastinum:
    - Associated with aorticopulmonary paraganglia
    - Average age = 49 years
    - Slight predilection for women
    - 3% of cases synthesize catecholamines
  - Posterior mediastinum:
    - Paravertebral location
    - Average age = 29 years
    - Men dominant

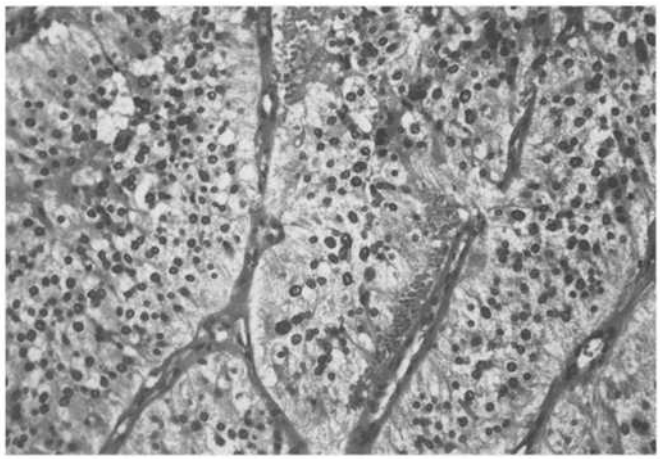


Fig. 23. Paraganglioma. Uniform neuroendocrine cells in a zelballen pattern.

  - 50% of cases synthesize catecholamines
  - Secretory paragangliomas produce clinical symptoms similar to those of pheochromocytoma
- Carney triad:
  - Functional paragangliomas, pulmonary hamartomas, and gastrointestinal malignant stromal tumors
  - Most common in young women
- 50% of cases are fatal due to infiltrative growth and unresectability due to close association with great vessels

*Macroscopic, Microscopic, and Differential Diagnosis (See **Figure 23**)*

- *See* Chapter 11

Germ Cell Tumors / Teratomas

- Located in anterior and superior mediastinum
- Intimately associated with thymus
- Except for benign mature teratoma, almost exclusively occur in males
- Association with Klinefelter's syndrome
- Association with hematologic neoplasia [leukemia, anaplastic large cell (Ki-1) lymphoma]
- Symptoms due to compression or asymptomatic mass

Benign Mature Teratoma

Clinical

- Most common mediastinal germ cell tumor
- Affects adolescents and young adults:
  - Equal sex distribution
  - Often asymptomatic
  - Rarely erodes bronchus with expectoration of tumor content
  - Surgical excision is curative

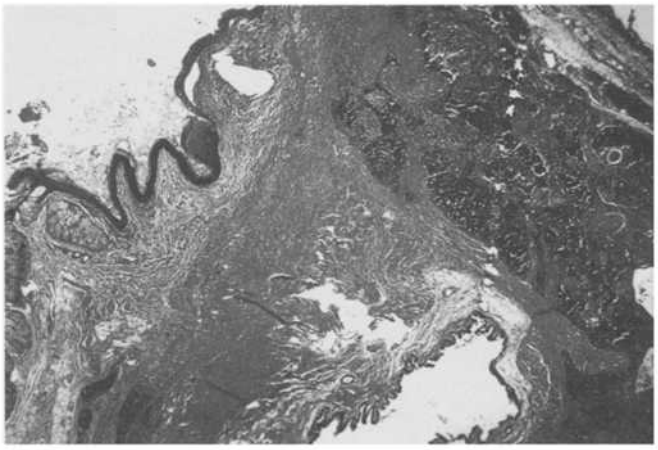


Fig. 24. Mature cystic teratoma of thymus. Note teratomatous elements alternating with thymic tissue (right). A keratinous cyst with adjacent sebaceous glands is a major component of the neoplasm.

Macroscopic

- Cystic, well-circumscribed, fibrous encapsulation; may contain fat, oily liquid, and hair

Microscopic

- Similar to gonadal teratoma (*See* **Figure 24**)
- Pancreatic and gastric tissue more common

Differential Diagnosis

- Metastatic teratoma
- Immature teratoma:
  - Embryonic tissue components
- Teratoma with additional malignant components:
  - Mixed germ cell or non-germ cell malignant components

Immature Teratoma

Clinical

- Male predominance, rarely affects women
- Benign

Macroscopic

- Large, solid, adherent to mediastinal structures
- Cut surface variegated

Microscopic

- Contains immature epithelial, mesenchymal, or neural elements with or without elements of mature teratoma

Differential Diagnosis

- *See* mature teratoma

Teratoma with Additional Malignant Components

Clinical

- Aggressive course with invasion of adjacent structures

Macroscopic

- Solid with areas of hemorrhage and necrosis

Microscopic

- Teratoma with components of other germ cell tumors (mixed germ cell tumor)
- Teratoma with malignant non-germ cell components (carcinoma, sarcoma)

Seminoma (Germinoma)

Clinical

- Males predominant, rare in females
- Second to fourth decades:
  - Responsive to radiation therapy (up to 100% 5-year survival)
  - Serum HCG may be positive, serum alpha-fetoprotein negative

Macroscopic

- Solid, lobulated, homogeneous mass

Microscopic, Immunohistochemistry

- Similar to testicular seminoma
- dot-like positivity for CAM 5.2

Differential Diagnosis

- Lymphoepithelioma-like carcinoma of thymus:
  - EMA+, cytokeratin+, PLAP–
- Diffuse large cell lymphoma:
  - Leukocytic common antigen+
- Hodgkin Disease:
  - Reed-Sternberg cells present PLAP–

Embryonal Carcinoma

Clinical

- Rare, highly malignant
- Affects males

Macroscopic

- Large, solid, hemorrhagic, and necrotic mass

Microscopic

- Poorly differentiated, with necrosis (identical to gonadal embryonal carcinoma)
- Usually mixed with other germ cell tumor components (mixed germ cell tumor)

Differential Diagnosis

- Metastatic adenocarcinoma:
  - PLAP–, alpha fetoprotein–, CD30–
- Yolk sac tumor:
  - Presence of Schiller-Duval bodies and reticular pattern

Yolk Sac Tumor

Clinical

- Affects males in third and fourth decades:
  - High levels of serum alpha fetoprotein
  - Associated with hematologic neoplasia
- Poor prognosis

Macroscopic

- Large, necrotic, invasive mass

Microscopic

- Identical to gonadal yolk sac tumor
- Usually mixed with teratoma or other germ cell tumor elements

Differential Diagnosis

- Embryonal carcinoma:
  - Absence of Schiller-Duval bodies and reticular growth pattern; CD30+

Choriocarcinoma

Clinical

- Affects males in third decade
- Must exclude metastasis from occult testicular primary
- Elevated serum HCG
- Gynecomastia
- Poor prognosis; may be responsive to combination chemotherapy

Macroscopic

- Hemorrhagic mass

Microscopic

- Identical to gonadal choriocarcinoma

Differential Diagnosis

- Metastatic choriocarcinoma
- Mixed germ cell tumor
- Anaplastic carcinoma: HCG–

Lymphoproliferative Disorders (*see* Chapter 7)

- Occur in all mediastinal compartments
- Malignant lymphoma: most common primary neoplasm of middle portion of mediastinum
- Lymphoma may be primary mediastinal process or manifestation of disseminated disease (*see* Chapter 7)

Hodgkin's Disease (HD)

Clinical

- Involves thymus and/or lymph nodes
- Young adults, female predominant:
  - Local pressure symptoms (dyspnea, cough or chest pain) or an incidental finding on chest X-ray

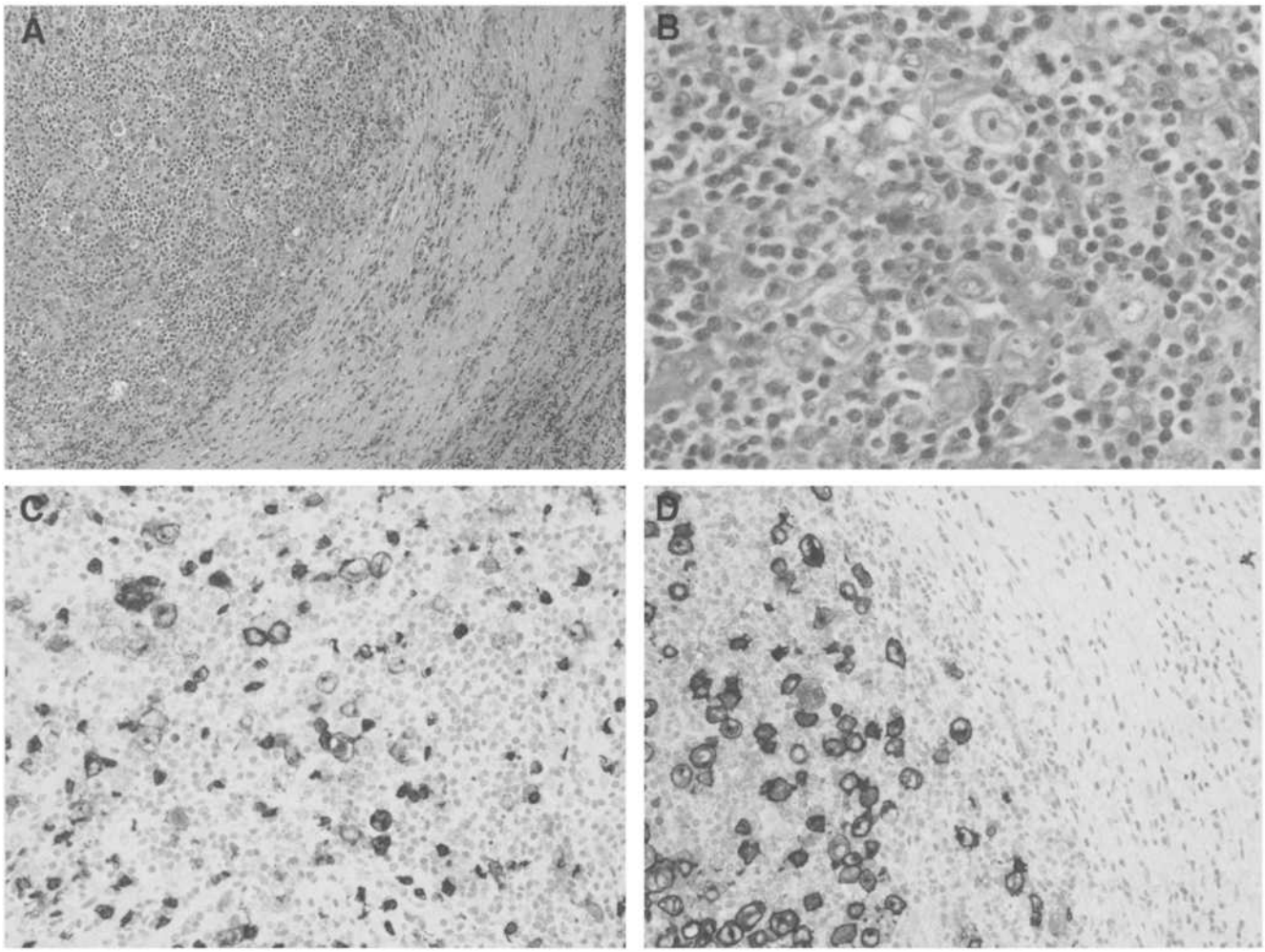


Fig. 25. Hodgkin's disease. **(A)** Cellular nodules surrounded by fibrous bands. **(B)** Polymorphic cell population with diagnostic lacunar cells. **(C)** CD15 stain. **(D)** CD30 stain. Note targetoid staining pattern in large neoplastic cells in C and D.

- Nearly always nodular sclerosis type; cervical lymph nodes also frequently involved

Macroscopic

- Well-circumscribed with thick capsule; mimics thymoma
- Composed of single or multiple hard nodules with lobulated pattern
- Occasionally cystic (within thymus)

Microscopic

- Cellular nodules surrounded by fibrous bands (*See* **Figure 25A**)
- Polymorphic cell population with diagnostic lacunar cells (*See* **Figure 25B**), Reed-Sternberg (R-S) cells with mixed inflammatory background

Immunophenotyping

- R-S cells and lacunar cells: CD15 + (*See* **Figure 25C**), CD30+ (*See* **Figure 25D**)

Differential Diagnosis

- Thymoma: *see* thymoma earlier
- Thymic cysts: *see* thymic cyst earlier

Lymphoblastic Lymphoma (LBL)

Clinical

- Predilection for thymic region
- Presents with acute respiratory distress in children and adolescents due to large mediastinal mass
- Male predominant
- Bone marrow, lymph node, central nervous system, and gonadal involvement

Macroscopic

- Solid, soft, and nonencapsulated mass

Microscopic

- Diffuse and infiltrative pattern of atypical lymphocytic growth involving thymic parenchyma

- Neoplastic lymphocytes: medium-sized, very fine chromatin pattern with frequent nuclear convolutions (*See* **Figure 26A**)
- Numerous mitotic figures and necrotic cells Starry sky pattern similar to that *seen* in Burkitt's lymphoma
- Neoplastic lymphocytes extending into perithymic fat and blood vessels

Immunophenotyping and Genotyping

- T cells (80% of cases):
  - Immunophenotyping similar to cortical thymocytes (TdT+ (*See* **Figure 26B**), CD1a+, coexpression of CD4/CD8)
  - Positive T-cell receptor gene rearrangement
- B cells (20% of cases):
  - TdT and B-cell marker (CD20)+
  - Positive immunoglobulin heavy chain and light chain gene rearrangement
- Rarely NK cell

Differential Diagnosis

- Thymoma, predominantly lymphoid:
  - Residual thymic lobules and Hassall's corpuscles in lymphoblastic lymphoma can mimic thymoma
  - Lymphocytes not atypical in thymoma
  - Presence of other features of thymoma such as perivascular spaces in thymoma
  - True thymoma rare in children
- Other lymphomas

Diffuse Large Cell Lymphoma with Sclerosis

Clinical

- Mass in thymus with or without lymph node involvement
- Young adult females (<35 years old)
- Presents with superior vena cava syndrome
- Radiology: large mass in anterior mediastinum
- Frequently invading large vessels, pericardium, pleura, lung, and chest wall
- Frequently recurs (usually involving kidney) after initial good response to chemotherapy and radiotherapy

Macroscopic

- Large (>10 cm), grossly invasive features; extension into pericardium, pleura, lung, sternum, and chest wall
- Firm with lobulation and foci of necrosis

Microscopic

- Lobules separated by wide fibrous bands (*See* **Figure 27A**)
- Neoplastic lymphocytes with large, vesicular, irregularly shaped nuclei (indented, kidney-shaped, poly-lobated) and abundant pale to basophilic cytoplasm (*See* **Figure 27B**)
- Frequent mitoses
- Entrapment of intrathymic and perithymic fat
- Invasion of blood vessel wall, pleura, or lung
- Sometimes abundant reactive histiocytic cells

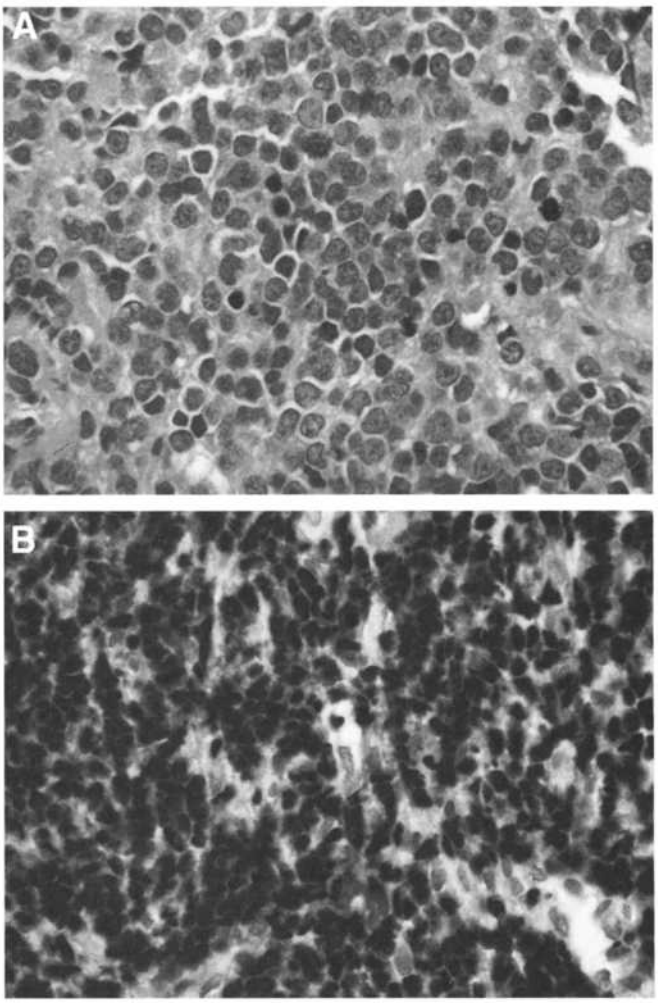


Fig. 26. Lymphoblastic lymphoma. **(A)** Neoplastic lymphocytes with medium-sized, very fine chromatin pattern with frequent nuclear convolutions. Frequent mitotic figures are present. **(B)** TdT stain. Note the nuclear stain pattern.

Immunophenotyping and Genotyping

- Majority with B-cell phenotype (CD19+, CD20+ (*See* **Figure 27C**), CD5–, CD21–, CD10+/–, Bcl-6+/–, MUM1+/–)
- Surface immunoglobulins are often negative; when positive, are of IgG or IgA type, in contrast to other large cell lymphomas of nodal origin (IgM or D type)

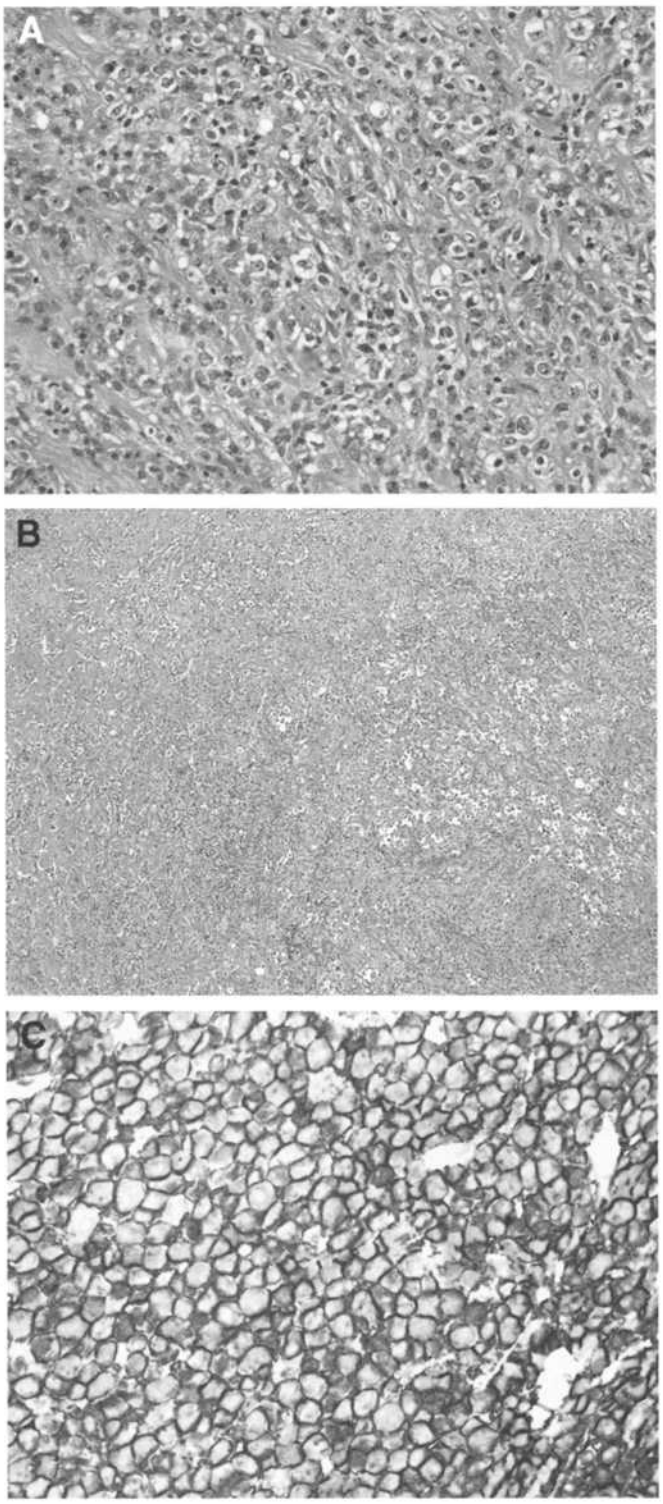


Fig. 27. Diffuse large B-cell lymphoma with sclerosis. **(A)** CD20 stain. **(B)** Neoplastic lymphocytes with large, vesicular, irregularly shaped nuclei (indented, kidney-shaped, poly-lobated) and abundant pale to basophilic cytoplasm. **(C)** Lobules separated by wide fibrous bands.

- Positive for heavy chain and light chain gene rearrangements

Immunophenotype and genotype suggesting a germinal center or post germinal center B-cell origin

Variants

- Anaplastic large cell lymphoma with T-cell phenotype (CD3+)
- Clear cell lymphoma of B-cell type
- Pleomorphic large cell lymphoma of B-cell type

Differential Diagnosis

- Malignant thymoma: keratin+
- Germinoma: PLAP+
- Hodgkin's disease: CD15+, CD30+
- Metastatic undifferentiated carcinoma: keratin+
- Metastatic amelanotic melanoma: S-100 protein+, HMB45+
- Other systemic lymphomas

Low-Grade B-Cell Lymphoma of MALT Type

Clinical

- Localized at diagnosis; cured by excision; indolent clinical course; some associated with Sjogren's syndrome

Macroscopic

- Encapsulated large masses (9–12 cm)
- Pale, tan, homogenous cut surface studded with fluid-filled cysts

Microscopic

- Normal architecture of thymus obscured by lymphoid infiltrate, in which Hassall's corpuscles remain
- Lymphoid infiltrate consists of reactive type of follicles and diffuse growth of predominantly "centrocyte-like lymphocytes" (monocytoid B cells), with abundant, clear, faintly granular cytoplasm, and sharp cell borders, admixed with scattered large transformed lymphocytes and scattered plasma cells
- Scattered cysts lined by attenuated epithelium or Hassall's corpuscles infiltrated by neoplastic lymphocytes

Immunophenotyping

- CD20+, CD22+, CD5–, CD10–

Granulocytic Sarcoma (Myeloblastoma, Chloroma)

Clinical

- Occurs de novo, as manifestation of acute myeloid leukemias at presentation or relapse, or as manifestation of blastic transformation of myeloproliferative disorder such as chronic myeloid leukemia
- Most common in pediatric patients
- Rarely presents in mediastinum

Macroscopic

- Greenish hue on cut surface

Microscopic

- Blastic lesions: composed of predominantly myeloblasts
- Immature lesions: composed of myeloblasts and promyelocytes
- Differentiated lesions: composed of promyelocytes and cells at later stages of maturation

Immunophenotyping and Enzyme Histochemical Stains

- CD43+, myeloperoxidase+, lysozyme+, chloroacetate esterase+

Differential Diagnosis

- Large cell lymphoma, lymphoblastic lymphoma, and small non-cleaved cell lymphoma: *see* above lymphoproliferative disorders and Chapter 7
- Undifferentiated carcinoma: keratin+

Extramedullary Plasmacytoma

Clinical

- Rarely involves mediastinum (more commonly occurs in head and neck, primarily in mucosa-associated sites)

Macroscopic, Microscopic, and Differential Diagnosis

- *See* Chapter 7

Castleman's Disease (Angiofollicular Lymphoid Hyperplasia)

Localized Form—Hyaline-Vascular Type (90%)

Clinical

- Asymptomatic
- Children and adults of middle age
- Common in anterosuperior mediastinal lymph nodes
- Rarely centered in thymus

Macroscopic

- Single encapsulated mass; solid; homogenous; gray nodular and sometimes hemorrhagic

Microscopic

- Abnormal follicles and striking interfollicular vasculature (Inset **Figure 28A**)
- Follicles with expanded mantle zones with atrophic germinal centers
- One or more small blood vessels entering from perifollicular tissue into follicles (Inset **Figure 28B**)
- Vessels having hyalinized and thickened walls
- More than one small germinal center within single follicle

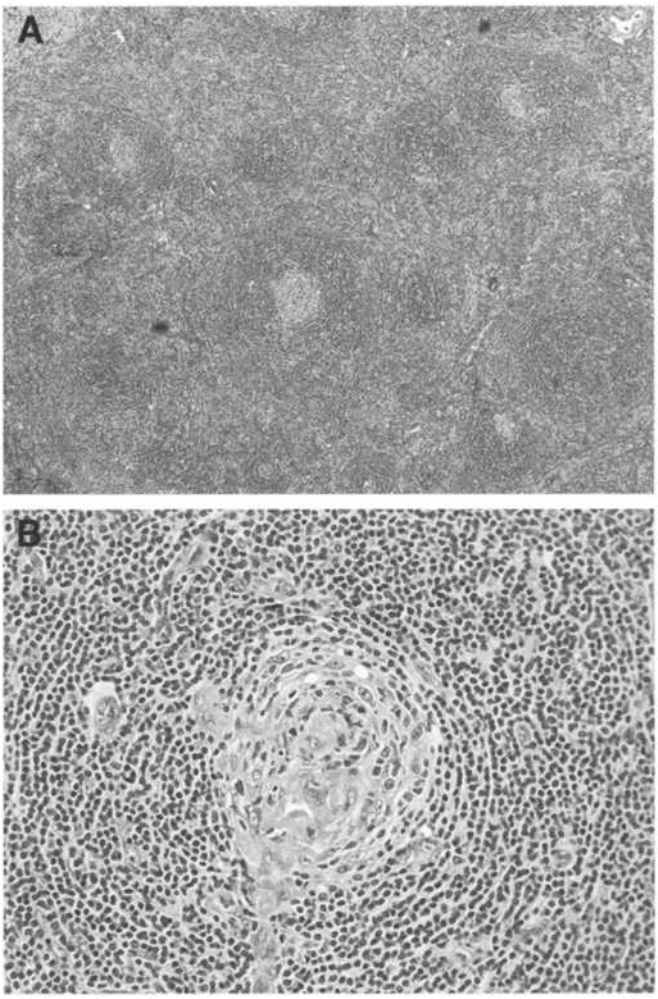


Fig. 28. Castleman's Disease (angiofollicular lymphoid hyperplasia), hyaline-vascular type. **(A)** Abnormal follicles with atrophic germinal centers and expanded mantle zones and striking interfollicular vasculature. **(B)** One or more small blood vessels entering from perifollicular tissue into follicles.

Localized form—plasma Cell Type

Clinical

- Similar to above type in addition to systemic manifestations:
  - Anemia, polyclonal gammopathy, elevated ESR, bone marrow plasmacytosis, and thrombocytosis
- Systemic manifestations disappear following excision of the mass

Macroscopic

- Several discrete matted nodes or a mass with adjacent smaller nodes

Microscopic

- Relatively well-preserved nodal architecture

- Interfollicular areas are densely infiltrated by polyclonal plasma cells (Inset **Figure 29A**)
- Central region of follicle shows abundance of dendritic reticulum cells

Multicentric Form—Plasma Cell Type

- Occurs in older patients
- Frequently associated with HHV-8 infection in HIV infected patients
- Peripheral nodal disease
- Plasma cell type dominant, plasma cells frequently lambda light chain restricted, plasma cells around the mantle zone with blastic morphology (*See* **Figure 29B**)
- More aggressive clinical course with development of malignancies such as Kaposi's sarcoma or lymphomas
- Some associated with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes)

Differential Diagnosis

- For hyaline-vascular type:
  - Other lymphomas including mantle cell lymphoma, follicle center lymphoma, and angioimmunoblastic T-cell lymphoma discussionThymoma: *see* earlier
- For plasma cell type:
  - Lymphadenopathy in patients with rheumatoid arthritis:
    - Clinical correlation
  - Lymphadenopathy in patients with syphilis:
    - Sarcoidal or necrotizing granulomas, spirochetes may be found
  - Lymphoplasmacytic lymphoma
- For both types:
  - Lymphadenopathy in patients with HIV infections

Mesenchymal Tumors

- Account for <2% of primary tumors of mediastinum
- Many types of mesenchymal tumor have been described:
  - All have similar clinical findings, including mediastinal mass and/or compressive symptoms

Benign (Low-Grade) Mesenchymal Tumors

Lipoma

Clinical

- Usually located in anterior compartment
- Tends to be bulky with extension to bilateral pleural cavities

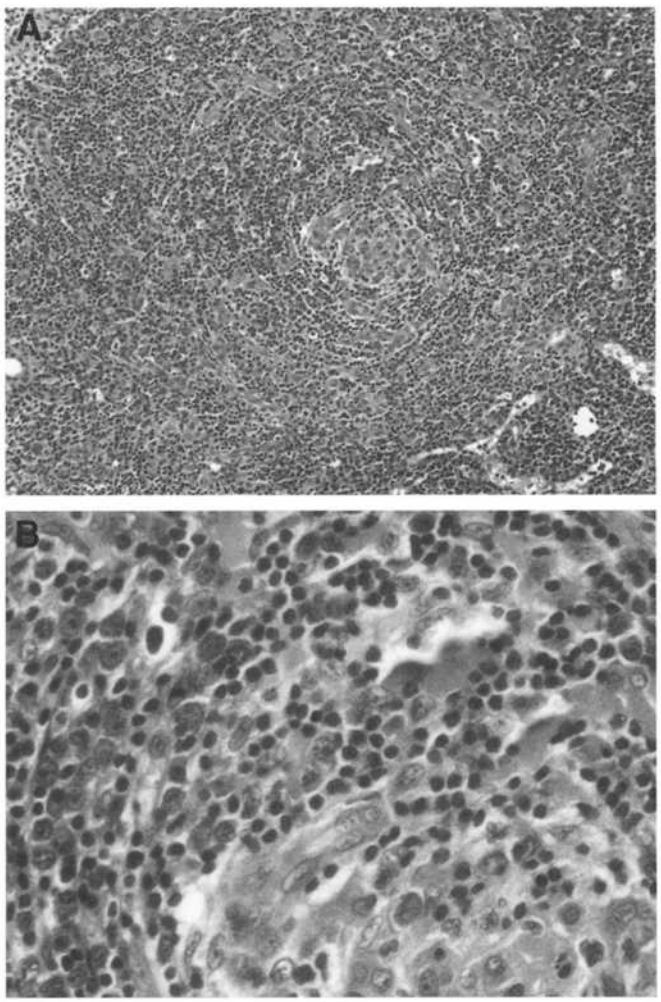


Fig. 29. Castleman's Disease (angiofollicular lymphoid hyperplasia), plasma cell type. (A) Interfollicular areas are densely infiltrated by polyclonal plasma cells (localized form). (B) Some plasma cells with blastic (prominent nucleoli) morphology.

Differential Diagnosis

- Thymolipoma:
  - Presence of thymic tissue in addition to adipose tissue
- Lipomatosis:
  - Diffuse accumulation of adipose tissue *seen* in association with obesity, Cushing's syndrome, and steroid therapy
  - Associated with "sabre-sheath" tracheal deformity
- Other benign adipose tissue tumors and low-grade liposarcoma (*see* Chapter 13)

Lymphangioma

Clinical

- Anterosuperior mediastinum most frequent
- Usually in children, often includes cervical component

Macroscopic

- Circumscribed mass with large, cystic, smooth-walled spaces

Microscopic

- Endothelial-lined channels, lymphocytic infiltrate

Differential Diagnosis

- Hemangioma:
  - Blood-filled spaces
- Lymphangiomyomatosis:
  - Prominent smooth muscle component (HMB45+) infiltrative; occurs exclusively in females

Hemangioma

Macroscopic

- Poor circumscription, large cystic spaces filled with blood

Microscopic

- Cavernous hemangioma more common in adults
- Thrombosis, calcification, and cholesterol granulomas common
- Cellular hemangiomas more common in children

Differential Diagnosis

- Lymphangioma (*see* earlier)
- Other vascular tumors include hemangiopericytoma, epithelioid hemangioendothelioma, and angiosarcoma (*see* Chapter 13)

Localized Fibrous Tumor

Clinical

- Anterior mediastinum
- May run aggressive course
- Some associated with hyperglycemia

Macroscopic

- Large, tan, firm, and well-circumscribed

Microscopic

- Bland-appearing short spindle cells and fibrous stroma with ropy collagen
- CD34+

Differential Diagnosis

- Thymoma (hemangiopericytoma-like): keratin+, CD34–
- Hemangiopericytoma: CD34–
- Malignant mesothelioma: malignant appearing spindle cells, keratin+, CD34–
- Fibromatosis: poor circumscription, CD34–

Malignant Mesenchymal Tumors

Liposarcoma

Clinical

- Most common malignant mesenchymal tumor of mediastinum; may be associated with liposarcoma at other body sites

Differential Diagnosis

- Lipoma:
  - Absence of lipoblasts
- Thymic liposarcoma or thymolipoma:
  - Remnants of thymus gland

Synovial Sarcoma

Clinical

- Occurs in superior and middle mediastinum

Macroscopic, Microscopic

- Similar to soft tissue counterparts

Differential Diagnosis

- Biphasic malignant mesothelioma
- Fibrosarcoma (when monophasic)

Metastatic Tumors

Small Cell Undifferentiated Carcinoma of Lung

Clinical

- Frequently presents with mediastinal widening that overshadows lung involvement

Differential Diagnosis

- Thymic small cell undifferentiated carcinoma:
  - Absence of recognizable lung primary; more solid mass (as opposed to lymph node involvement); lobulated appearance
- Lymphoma: LCA+, keratin–

Metastases from Distal Sites

- Direct extension of tumors from esophagus, chest wall, vertebrae, pleura, and trachea

Clinical

- Especially problematic: metastatic germ cell tumor, melanoma, and prostatic carcinoma

Macroscopic

- Lymph node involvement often predominates with lesser degree of extranodal soft tissue spread

Differential Diagnosis

- Thymic carcinoma and primary germ cell tumors: must always rule out metastases

TNM CLASSIFICATION OF THYMOMA

TNM System Staging for Thymoma

- T: Primary tumor:
  - T1: macroscopically completely encapsulated and microscopically no capsular invasion
  - T2: macroscopic adhesion or invasion into surrounding fatty tissue or mediastinal pleura, or microscopic invasion into capsule
  - T3: invasion into neighboring organs, such as pericardium, great vessels, and lung
  - T4: pleural or pericardial dissemination
- N: Regional lymph node:
  - N0: no lymph node metastasis
  - N1: metastasis to anterior mediastinal lymph nodes
  - N2: metastasis to intrathoracic lymph nodes other than anterior mediastinal lymph nodes
  - N3: metastasis to extrathoracic lymph nodes
- M: Distant metastasis:
  - M0: no distal metastasis
  - M1: distal metastasis

Clinical Staging

Stage I

- Completely encapsulated without microscopic capsular invasion (benign thymoma)

Stage II

- Macroscopic invasion into surrounding fatty tissue or mediastinal pleura or microscopic invasion into capsule

Stage III

- Macroscopic invasion into neighboring organs (i.e., pericardium, great vessels, or lung)

Stage IVa

- Diffuse pleural or pericardial involvement

Stage IVb

- Distal metastasis

THE DEFINITION OF WHO CLASSIFICATION OF THYMIC EPITHELIAL TUMORS

Type A: A tumor composed of homogeneous population of neoplastic eptithelial cells having spindle/oval shape, lacking nuclear atypia, and accompanied by few or no non-neoplastic lymphocytes.

Type AB: A tumor in which foci having the features of type A thymoma are admixed with foci rich in lymphocytes; the segregation of the two patterns can be sharp or indistinct.

Type B1: A tumor which resembles the normal functional thymus in that it combines large expanses having an appearance practically indistinguishable from normal thymic cortex with areas resembling thymic medulla.

Type B2: A tumor in which the neoplastic epithelial component appears as scattered plump cells with vesicular nuclei and distinct nucleoli among a heavy population of lymphocytes; foci of squamous metaplasia and perivascular spaces are common.

Type B3: A tumor predominantly composed of epithelial cells having a round or polygonal shape and exhibiting mild atypia, admixed with a minor component of lymphocytes; foci of squamous metaplasia and perivascular spaces are common.

Type C: Thymic carcinoma

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21

Cardiovascular Pathology

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CONTENTS

I. Pathology of the Heart 21-3

Congenital Heart Disease 21-3
Aortic Stenosis 21-3
Atrial Septal Defect (ASD) 21-3
Coarctation of Aorta 21-3
Patent Ductal Artery (Patent ductus arteriosis, PDA) 21-3
Pulmonary Stenosis 21-3
Tetrology of Fallot 21-3
Transposition of Great Arteries 21-3
Ventricular Septal Defect (VSD) 21-3
Myocardium 21-4
Ischemic Heart Disease 21-4
Cardiomyopathy (Heart Muscle Disease of Unknown Cause) 21-4
Idiopathic Hypertrophic Cardiomyopathy 21-4
Idiopathic Dilated Cardiomyopathy 21-4
Arrythmogenic Right Ventricular Cardiomyopathy [Arrythmogenic Right Ventricular Dysplasia (ARVD)] 21-5
Hypertensive Heart Disease 21-5
Infiltrative Diseases 21-5
Myocarditis 21-6
Antracycline Cardiotoxicity 21-6
Angiokeratoma Corporis Diffusum Universale 21-7
Pericardium 21-7
Pericardial Effusion and Hemopericardium 21-7
Pericarditis 21-7
Valves and Endocardium 21-7
Acute and Chronic Rheumatic Heart Disease 21-7
Aortic Valve Stenosis 21-8
Aortic Valve Insufficiency 21-8
Carcinoid Heart Disease (CHD) 21-8
Endocarditis 21-8
Mitral Regurgitation 21-9
Mitral Stenosis 21-9
Prosthetic Valves 21-9
Cardiac Transplantation 21-9
Acute Humoral Rejection (Hyperacute Rejection) 21-9
Acute Cellular Rejection 21-10
Humoral ("Vascular") Rejection 21-10
Chronic Rejection 21-11
Quilty Effect 21-11
Epstein-Barr Virus (EBV)-Associated Post-transplant Lymphoproliferative Disorder 21-11
Post-transplantation Infection 21-11
Cardiac Neoplasms 21-11
Benign 21-11
Myxoma 21-11
Papillary Fibroelastoma 21-12
Fibroma 21-12
Rhabdomyoma 21-13
Lipomatous Hypertrophy of the Interatrial Septum 21-13
Cystic Tumor of the Atrioventricular Node 21-13
Paraganglioma (Extra-adrenal Pheochromocytoma) 21-13
Malignant 21-13

Angiosarcoma 21-14
Lymphoma.....21-14
Neoplasms Metastatic to Heart....21-14
Others 21-14

II. Pathology of Blood Vessels.....21-14

Arteriosclerosis.....21-14
Atherosclerosis 21-14
Hypertensive Vascular Disease.....21-14
Mönckeberg's Calcific Medial Sclerosis 21-15
Fibromuscular Dysplasia 21-15
Myxoid Medial Degeneration (Cystic Medical Necrosis) of Aorta.....21-15
Aneurysms 21-15
Atherosclerotic Aneurysm of Abdominal Aorta 21-15
Berry Aneurysms of the Cerebral Arteries 21-16
Infectious (Mycotic) Aneurysms 21-16
Syphilitic Aneurysms 21-16
Dissection.....21-16
Vasculitis 21-17
Infectious Vasculitis 21-17
Non-infectious Vasculitis: Medium to Large Sized Vessels 21-17
Giant Cell Arteritis/Aoritis 21-17
Kawasaki's Disease (Mucocutaneous Lymph Node Syndrome) 21-17
Takayasu's Disease 21-17
Non-infectious Vasculitis: Small to Medium Sized Vessels.....21-18
Churg-Strauss Syndrome 21-18
Polyarteritis Nodosa (PAN).....21-18
Microscopic Polyarteritis 21-18
Temporal Arteritis (Giant Cell Arteritis) 21-18
Thromboangiitis Obliterans (Buerger's Disease) 21-19
Wegener's Granulomatosis 21-19
Other 21-19

III. Suggested Reading.....21-19

PATHOLOGY OF HEART

Congenital Heart Disease

- General information:
  - 0.6 to 0.8% of live births
  - No identifiable cause in most cases
  - Approximately 5% associated with chromosomal abnormality
  - First trimester rubella infection can lead to patent ductal artery, pulmonary stenosis
  - Down syndrome associated with septal defects (atrial and ventricular), defects of atrioventricular valves
  - Turner syndrome associated with coarctation of aorta
  - Drugs, such as alcohol and thalidomide, can also lead to congenital heart abnormalities

Aortic Stenosis

- Approximately 6% of congenital heart abnormalities
- May assume valvular and subvalvular forms
- Most common cause is bicuspid aortic valve

Atrial Septal Defect (ASD)

- Approximately 10% of congenital abnormalities
- Ostium secundum (OS) defect much more common than ostium primum (OP) defect
- Diagnosis was usually made clinically in both cases
- Often not detected in childhood, presenting in adult
- Results in increased pulmonary blood flow, systolic ejection murmur, widely split second heart sound, eventual right ventricular hypertrophy
- Most important complication is pulmonary hypertension; others include right heart failure, paradoxical embolization
- OP ASD presents in childhood, associated with mitral valve defects and mitral incompetence

Coarctation of Aorta

- Approximately 7% of congenital heart abnormalities
- More common in males
- Common in Turner's syndrome
- Approximately 60% will die (frequently of aortic rupture) by age 40 if not corrected
- 50% of cases associated with other congenital heart defects
- Coarctation located usually just distal to ductus arteriosus (adult type), but may occur just proximal to this structure in infantile type

Patent Ductal Artery (Patent Ductus Arteriosis, PDA)

- Manifestations depend on size of communication between aorta and pulmonary artery
- Indomethacin induce closure by inhibiting prostaglandin E (PGE) synthesis
- Small PDA results in small left-to right shunt, with "machinery" murmur
- Very mild symptoms in patients with small PDA
- Large PDA results in large shunt, with pulmonary hypertension, eventuating in shunt reversal with cyanosis

Pulmonary Stenosis

- Approximately 7% of congenital heart abnormalities
- Caused usually by valve cusp fusion
- In case of pulmonary atresia, right ventricle will be hypoplastic

Tetralogy of Fallot

- Most common cyanotic congenital anomaly
- Presents at birth with severe cyanosis
- Poor prognosis if not corrected surgically
- Four classic anatomical findings:
  - Ventricular septal defect (VSD)
  - Dextroposed aorta which overrides right ventricular outflow tract, and leads to
  - Pulmonary stenosis, which leads to
  - Right ventricular hypertrophy

Transposition of Great Arteries

- Approximately 4% of congenital heart defects
- Cyanosis at birth
- Child doesn't survive without some interatrial communication (PDA, VSD)
- Can be corrected surgically
- Grossly, aorta arises from morphologic right ventricle and is anterior and to right of pulmonary artery (normal lie posterior and to right of pulmonary artery)

Ventricular Septal Defect (VSD)

- Most common cardiac defect seen in children
- Classified according to size of defect, e.g., large, small (<5 mm)
- Most occur in membranous portion of interventricular septum
- May predispose to infective endocarditis
- Small VSD:
  - Infrequent, minor symptoms usually
  - Systolic murmur with mild shunt
  - Pansystolic murmur
  - May close spontaneously as patient gets older
- Large VSD:
  - More serious than small VSDs
  - Large left-to-right shunts producing:
    - Volume overload
    - Biventricular hypertrophy
    - Pulmonary hypertension
    - Eventual reversal of shunt with cyanosis (Eisenmenger's syndrome)

Table 1. Sequence of Certain Microscopic Changes in Acute Myocardial Ischemia (Approximate)

Time After Event	*Gross Findings*	*Histopathologic Findings*
1 day	Softening, pallor, and edema	Eosinophilic necrosis, edema, interstitial hemorraghe, contaction band change, nuclear pyknosis, beginning neutrophil infiltration
2–3 days	Opaque with grey-yellow center and hemorrhagic border	Marked neutrophil infiltrate, loss of nuclei and striations
3 days to 1 week	Rubbery center with shrinkage	Beginning macrophage infiltration, with phagocytosis and early fibroblastic response
10 days	Thinning of myocardium with red-brown discoloration.	Extensive phagocytosis, granulation tissue formation
2 months	Cicatrization	Cicatrization

Myocardium

Ischemic Heart Disease

Clinical

- Most often due to coronary artery atherosclerosis
- Sometimes with demonstrable complication (plaque rupture, thrombosis, etc.) in acute setting
- May manifest as angina pectoris, myocardial infarct (MI), congestive heart failure, arrythmias, sudden death
- Complications include:
  - Arrythmia
  - Congestive heart failure
  - Hypotension
  - Post MI ventricular and/or papillary muscle dysfunction rupture
  - Extension of infarct
  - Pericarditis
  - Microbial colonization
  - Mural thrombosis/embolism
  - Ventricular aneurysm/rupture

Macroscopic

- Myocardial necrosis in an acute MI
- May be either transmural (most common), or subendocardial
- Usually no grossly detectable changes in first 6–12 hours
- After 18–24 hours, there may be either myocardial pallor, or a red-blue discoloration
- The infarcted zone begins to appear yellow as polymorphonuclear neutrophils move in (2–3 days)
- By 7–8 weeks cicatrization may be complete
- "Old" ischemic heart disease may manifest as an old MI, interstitial myocardial fibrosis, chamber dilation and compensatory hypertrophy

Microscopic

- Acute myocardial ischemia (see **Table 1**, **Figures 1,2**)
- Old myocardial ischemia (as interstitial fibrosis, **Figure 3**, vacuolar change in cardiac myocytes)
- Compensatory myocyte hypertrophy

Cardiomyopathy (Heart Muscle Disease of Unknown Cause)

Idiopathic Hypertrophic Cardiomyopathy

Clinical

- 50% familial (autosomal dominant), myosin heavy chain defect
- HLA linkage to chromosome 6
- Clinical evaluation needed to make diagnosis
- Symptoms of left ventricular outflow obstruction
- Cause of sudden death during exercise
- Treated by beta adrenergic blockage, septal myotomy or myomectomy

Macroscopic

- Asymmetric septal hypertrophy
- Plaque in the left ventricular
- Mitral valve thickening and enlarged left atrium

Microscopic

- Nonspecific myofiber disarray, hypertrophy, interstitial fibrosis

Differential Diagnosis

- Hypertensive disease:
  - Shows concentric left ventricular hypertrophy

Idiopathic Dilated Cardiomyopathy

- Clinical evaluation needed to make diagnosis
- Often severe 4-chamber dilation grossly
- Biopsy may show non-specific hypertrophy, interstitial fibrosis

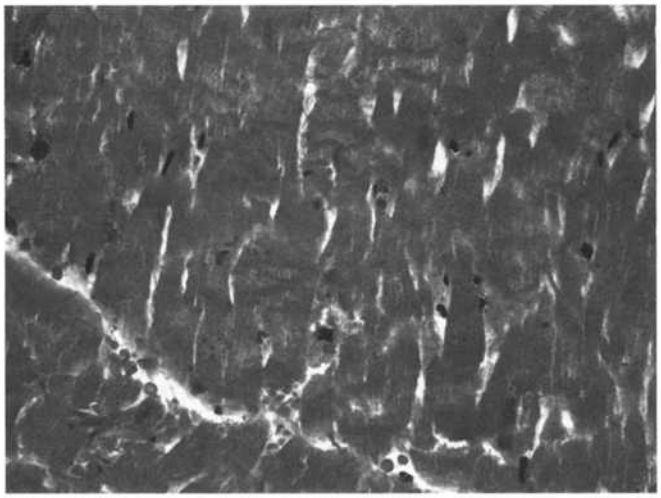


Fig. 1. Acute myocardial contraction band necrosis.

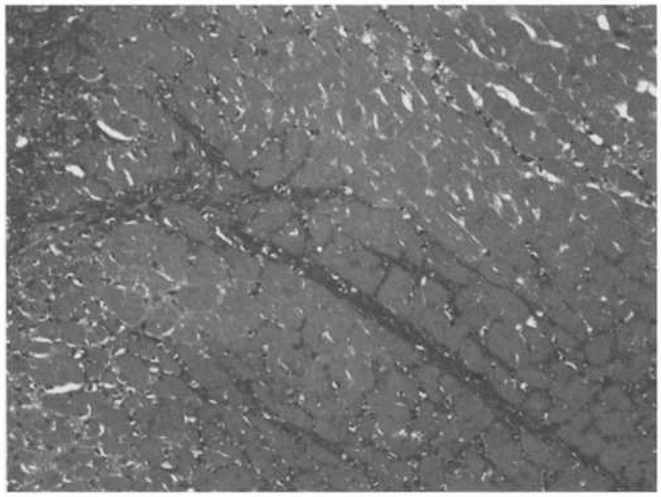


Fig. 2. Acute myocardial infarction.

Differential Diagnosis

- Rule out ischemia, other causes

Arrythmogenic Right Ventricular Cardiomyopathy [Arrythmogenic Right Ventricular Dysplasia (ARVD)] (Figure 4)

- Asymptomatic, arrythmias, sudden death
- Can be familial
- Gross infiltration of right ventricular free wall by fat and/or fibrous tissue, with dilation and wall thinning
- Left ventricle may be involved also
- Myocyte loss, with presence of admixed myocytes, adipose and/or fibrous tissue
- Myocarditis may be present

Differential Diagnosis

- Normal fat infiltration of right ventricle, especially in obese persons

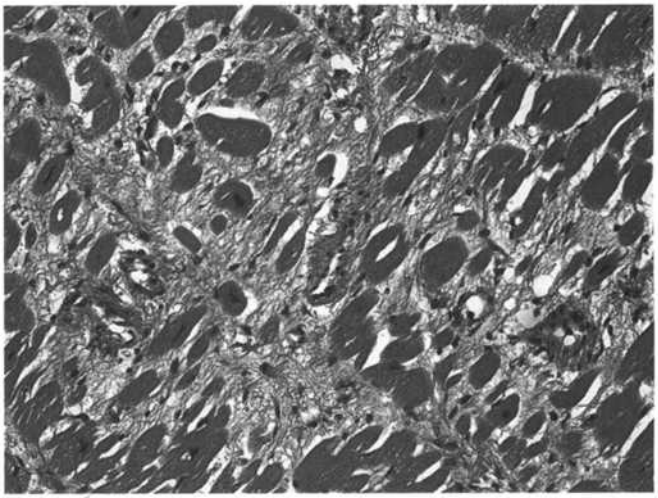


Fig. 3. Interstitial fibrosis.

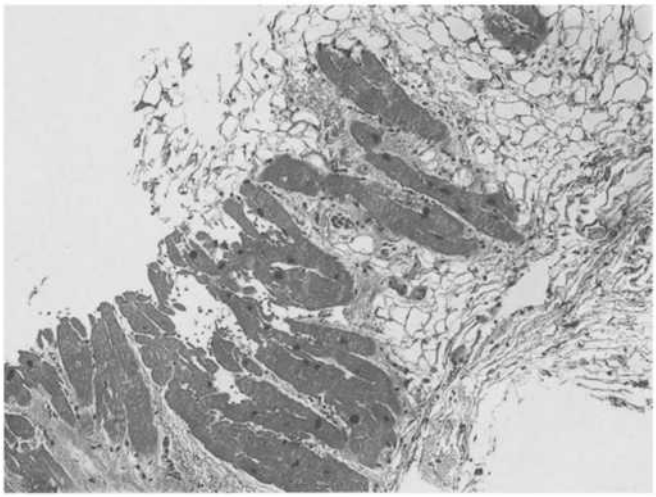


Fig. 4. Biopsy of patient with arrhythmogenic right ventricular cardiomyopathy.

Hypertensive Heart Disease

- Secondary to long standing systemic hypertension
- Grossly, concentric left ventricular hypertrophy

Infiltrative Diseases

Amyloidosis

Clinical

- Depending upon type and degree of involvement
- May be asymptomatic or present with congestive heart failure, arrythmias, valve disease, ischemic disease, sudden death
- Amyloid in heart, which may be deposited in most types of amyloidosis, may be further characterized by identifying protein subclass, using immunohistochemical techniques
- In senile systemic amyloidosis with cardiac involvement, amyloid is composed of transthyretin

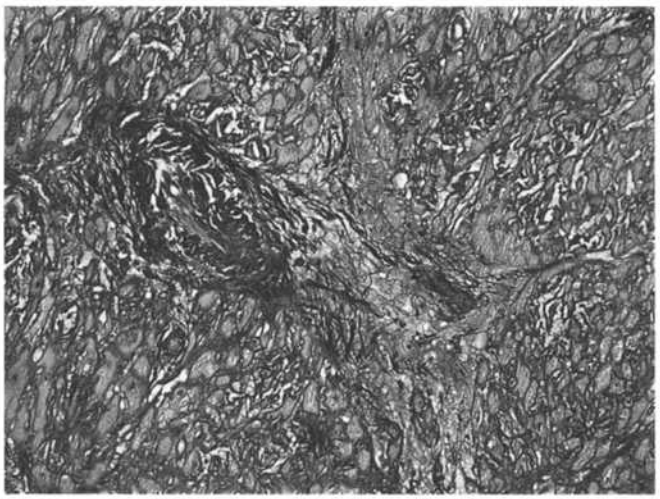


Fig. 5. Amyloidosis. Congo red staining showed apple green interstitial and vascular amyloid deposits.

- In isolated atrial amyloid, it is composed of atrial natriuretic factor

Macroscopic

- Extensive deposits may lead to pale, firm and rubbery myocardium
- Valvular deposits may appear waxy and shiny

Microscopic

- Amorphous, extracellular, pink material on H&E section
- Deposits can be interstitial and/or intravascular, and may cause vessel stenosis
- By definition, deposits are Congo-red positive, with apple-green birefringence with polarized light **(Figure 5)**
- Electron microscopy also definitive, but rarely necessary

Glycogen Storage Diseases

- Excess sequestration of various glycogen storage products lead to heart failure

Hemochromatosis/Hemosiderosis

- Systemic iron deposition with organ damage (usually in hemochromatosis)
- Iron stain to demonstrate reticuloendothelial iron in hemosiderosis, parenchymal iron in hemochromatosis

Myocarditis

- "Dallas criteria": leukocytic infiltrate (usually lymphocytic) with myocyte degeneration/necrosis

Clinical

- Viral (most often coxsackievirus B), bacterial, fungal, para-sitic, collagen-vascular disease, drug reaction, radiation
- Complications include congestive heart failure, conduction defects, arrythmias, and sudden death

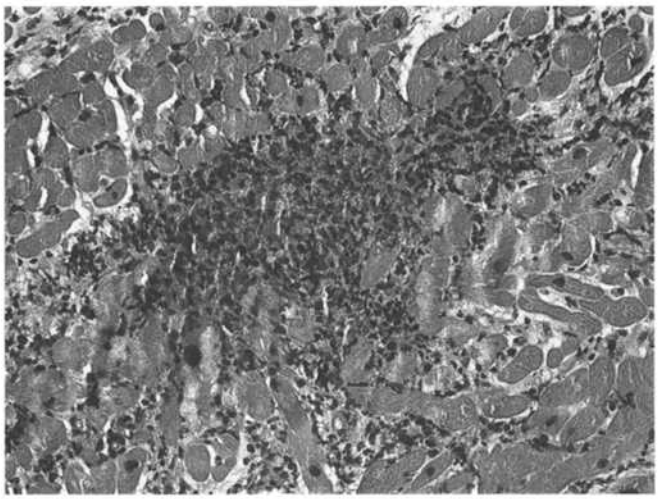


Fig. 6. Acute myocarditis.

Macroscopic

- Range from normal to biventricular dilation/hypertrophy with pale "flappy" myocardium or fibrosis

Microscopic

- In most cases, a T-cell lymphocytic infiltrate admixed with histiocytes **(Figure 6)**
- Occasionally with eosinophils, necessarily with myocyte damage
- Giant cells are seen in giant cell or Fiedler's myocarditis (idiopathic), as well as sarcoidosis
- Distinction between these two entities may be difficult

Variant: Giant Cell Myocarditis

- Occur in young and middle aged adults
- Present with arrythmias, conduction defects, cardiac failure, and sudden death (50%)
- Rapidly progressive and fatal, heart transplantation may be indicated
- Association: thymoma, SLE, thyrotoxicosis
- Microscopically, lymphohistiocytic infiltration and geographic myocyte necrosis **(Figure 7)**
- Lack discrete granulomas or epithelioid histiocytes
- Giant cells are of both macrophage and myocyte origin

Differential Diagnosis: Cardiac sarcoidosis

- Myocardial necrosis associated with discrete non-necrotizing epithelioid granuloma
- Giant cells are exclusively of macrophage origin Microscopically, myocyte hypertrophy and interstitial fibrosis (not due to coronary ischemia)

Antracycline Cardiotoxicity

- Including doxorubicin (adriamycin) and daunorubicin
- Etiology unknown, may be due to lipid peroxidation of myofiber membrane

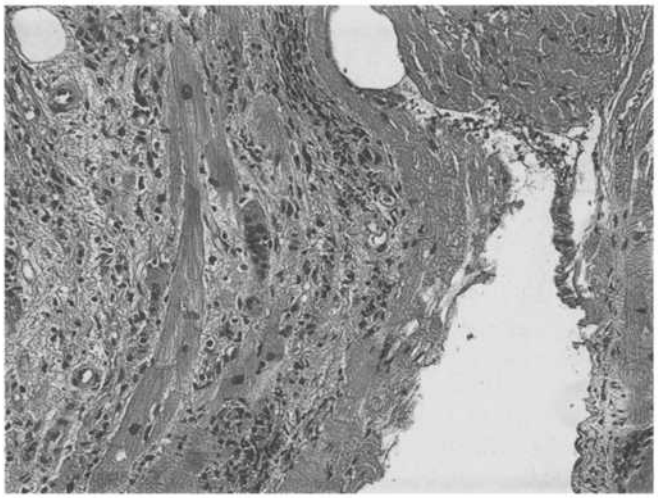


Fig. 7. Giant cell myocarditis.

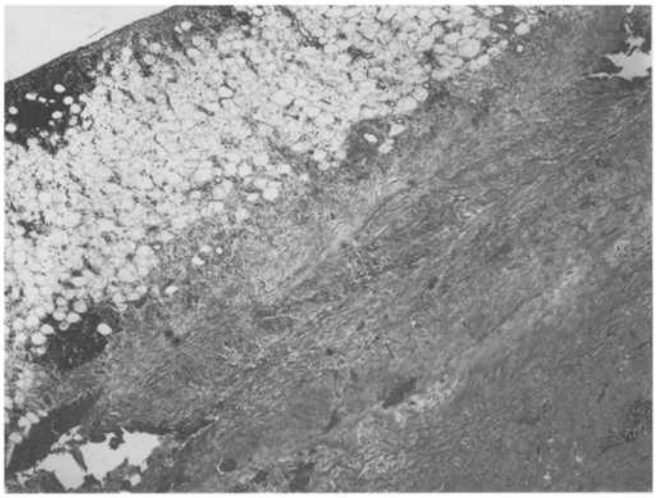


Fig. 8. Chronic fibrosing pericarditis.

- Earliest changes include myocyte vacuolization secondary to sarcotubular system dilation
- Adria cells: myocyte with loss of cross striation and homogenous basophilic staining
- EM findings include cytoplasmic vacuolization, sarcotubular system dilation, and lysis of myofibrils
- Grading (0–3) based on the percentage of cells affected in 10 plastic embedded blocks of tissue

Angiokeratoma Corporis Diffusum Universale

- X-linked recessive inheritance
- Deficiency of lysosomal alpha-galactodase leading to ceramide trihexoside accumulation
- Skin, cornea, kidney, and heart affected
- Microscopically, myocyte vacuolization seen
- Intralysosomal concentric or parallel lamellae by electron microscope

Pericardium

Pericardial Effusion and Hemopericardium

Clinical

- Accumulation of fluid (serous, chylous, serosanguinous) and/or pure blood in pericardial sac, respectively
- If volume is rapidly increasing, cardiac tamponade may result

Macroscopic

- Excess fluid/blood in sac (>50 or so mL)
- Fibrinous exudate in fibrinous pericarditis (see below)
- Hemopericardium usually due to ruptured myocardial infarction, trauma, aortic rupture
- Serosanguinous exudate most often due to malignancy, but infection and renal failure need to be considered

Acute Pericarditis

Clinical

- Fever, friction rub, heart failure, pain

Macroscopic

- Serous exudate: usually non-infectious
- Fibrinous: acute MI, post MI (Dressler's syndrome), uremia, radiation, trauma, lupus, rheumatic fever
- Purulent: usually infections
- Hemorrhagic: usually due to malignancy in pericardium, also tuberculosis in other countries
- Caseous: TB until proven otherwise, infrequently fungi

Chronic Pericarditis

- Healed phase of acute pericarditis
- May result in constrictive pericarditis
- Fibrosis, sometimes residual collections of lymphocytes **(Figure 8)**

Valves and Endocardium

Acute and Chronic Rheumatic Heart Disease

- Included here, although effects valves as well as myocardium and/or pericardium, because long-term effects in survivors are predominantly valvular

Clinical

- Recurrent acute febrile disease of children following *Steptococcal* (group A) *pharyngitis*
- Etiology is due to an autoimmune mechanism
- Most common cause of mitral stenosis

Gross

- Subendocardial/perivascular areas of fibrinoid necrosis in acute form
- Later, lymphocytic then macrophage infiltrates which may become granulomatous

Table 2. Helpful Distinguishing Features of Congenital and Bicuspid Aortic Valves

Acquired Commisural Fusion	*Congenital Bicuspid Valve*
Intercomissural diatances are nearly equal in three cusps	Intercommisural diatance of each fused cusp is smaller than unfused cusp
Cephalad height of raphe is equal to height of unfused commisures	Cephalad height of raphe is lower than height of unfused commisures
Raphe is wide and extends to cusp margin	Raphe is narrow and does not extend to cusp margin

- These are called Aschoff's bodie, and they may contain characteristic "caterpillar cell"
- Small valvular vegetations may be present
- In chronic form, one may see (especially mitral) valvular fibrosis and thickening, calcification, with thickened and shortened chordae (see Mitral stenosis, below)

Aortic Valve Stenosis

Clinical

- Most common cause of left ventricular outflow obstruction
- Patients may develop concentric left ventricular hypertrophy, pulmonary hypertension, infective endocarditis, systemic embolization
- Associated with sudden death
- Most commonly a consequence of congenital bicuspid aortic valve (in persons younger than 70), and degenerative fibrosis and calcification (senile-type) in persons older than 70
- Other etiologies of aortic valve stenosis include congenital unicuspid valve, post-inflammatory (rheumatic) state, which occurs usually in association with mital valve involvement
- A small percentage of cases may preclude definitive assessment
- Congenital bicuspid aortic valves:
  - Rarely stenotic at birth
  - Tend to develop fibrosis and calcification with increasing age, resulting in stenosis
  - Prevalence of stenosis is proportional with age
  - Gross cusps are oriented either anterior-posterior, or right-left
  - A raphe may be seen in either right or anterior cusp, depending on orientation
  - Calcification and fibrosis may be severe
- Degenerative fibrosis and calcification (senile-type):
  - Occurs in three-cusped aortic valves
  - Usually affects patients older than 60 years
  - Gross calcification and fibrosis of valve cusps, with calcific deposits that may fill sinuses of Valsalva
  - Senile-type calcification and fibrosis may be associated with fusion of one or more commisures, making distinction from congenital bicuspid valve difficult
  - Helpful features are summarized in **Table 2**

Aortic Valve Insufficiency

- May result from a lesion of valvular cusps or dilation of aortic root itself
- Cusp lesions may include post-inflammatory (rheumatic) changes (the most common cause), infectious endocarditis, congenital bicuspid valve, and others

Carcinoid Heart Disease (CHD)

Clinical

- Occurs in setting of metastatic carcinoid tumor, in patients with the carcinoid syndrome
- Left sided lesions are associated with carcinoid tumors in lung
- The valvular lesions may cause pulmonary stenosis, tricuspid regurgitation, but rarely pure tricuspid stenosis

Macroscopic

- White endocardial or valvular plaques, usually of right atrium and/or ventricle

Microscopic

- Smooth muscle proliferation in proteoglycan-rich matrix

Differential Diagnosis

- Endocardial fibroelastosis:
  - Unlike CHD, occurs in infants and children (not adults)
  - Contains prominent elastin
  - Irraditation
  - History helpful here
  - Pericardial fibrosis may also be present

Endocarditis: Infectious (Figure 9)

- Usually due to hematogenously transmitted infections by bacteria:
  - Most commonly Streptococcus (viridans, bovis, fecalis), which is less virulent than Staphylococcus aureus

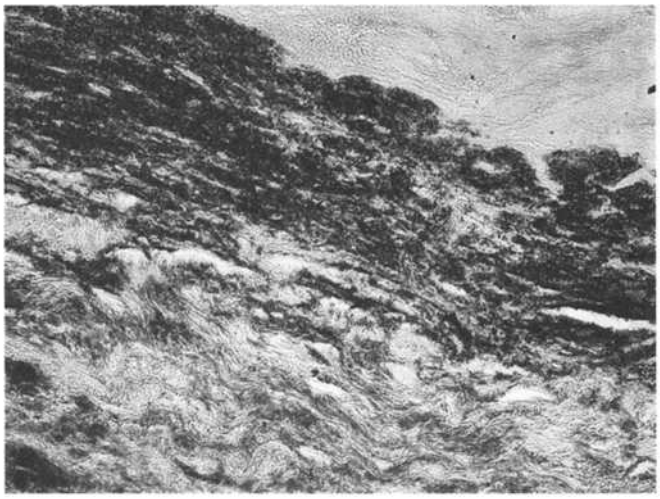


Fig. 9. Acute bacterial endocarditits, gram staining.

- Approximately 30% occur on normal valves
- Usually there is some predisposition, such as:
  - Cardiac abnormality which creates turbulence, and presumably endothelial injury, such as valve stenosis/regurgitation, prosthesis, septal defects)
  - Clinical circumstance, such as immune suppression, cancers
  - IV drug use may lead to infectious endocarditis, usually of right sided valves
- Complications of infectious endocarditis include valve insufficiency (or stenosis less commonly), septic systemic embolization
- Grossly, friable vegetaions on side of direct flow, often near free edge, composed of thrombus material and bacteria (or fungi, etc.)

Endocarditis: Non-Infectious

- Non-bacterial thombotic endocarditis (marantic endocarditis):
  - Occurs in setting of cancer (especially mucinous adenocarcinoma) or other systemic wasting illness
  - May embolize
  - Grossly, small or large fibrin masses, without organisms, present at lines of closure on the aortic or mitral valves
  - Microscopically, fibrin and entrapped red blood cells, no inflammation
- Libman-Sacks disease (verrucous endocarditis):
  - Seen in systemic lupus erythematosus (SLE)
  - Multiple small leaflet vegetations, usually on non-flow side (ventricular surface) of mitral and/or tricuspid valves
  - Microscopically, fibrin intermixed with cellular debris and scattered inflammatory cells

Mitral Regurgitation: Floppy Mitral Valve

Clinical

- Most common cause of mitral regurgitation in one series
- Risk of developing severe regurgitation due to floppy valve increases with age, especially over 50
- Complications include ruptured chordae, infective endocarditis, thromboembolism, arrhythmias, and sudden death

Gross/Microscopic

- Excess valve cusp material, which is thick and hooded, with thickening or thinning of chordae
- Loose myxoid connective tissue expanding spongiosa layer, which may extend into the chordae

Mitral Regurgitation: Other Causes

- Papillary muscle dysfunction
- Infective endocarditis
- Chronic rheumatic valvular disease

Mitral Stenosis

Clinical

- Most common cause is rheumatic fever
- More common in women
- Latent period of several years followed by progressive stenosis, leading to conditions such as pulmonary hypertenion, left atrial thrombosis, systemic thromboembolism, and infective endocarditis

Macroscopic

- Pronounced fibrosis along valvular free edges and lines of closure, and fusion of posterior leaflet scallops, fused and shortened chordae tendinae
- New subendocardial blood vessel formation on valves themselves may be seen

Microscopic

- Fibrosis, thick-walled blood vessels, calcification, lymphocytes, and sometime myxomatous change

Prosthetic Valves

- Complications include mechanical fatigue, failure of valve, thrombosis and thromboembolism, infection (most commonly Staphylococcus), perivalvular leaks in suture area

Cardiac Transplantation (*also see* Chapter 6)

Acute Humoral Rejection (Hyperacute Rejection)

Clinical

- Abrupt failure of allograft, due to preformed recipient cytotoxic antibodies, ABO incompatibility, or major histocompatibility antigen mismatch
- Occur intraoperatively or immediately perioperatively

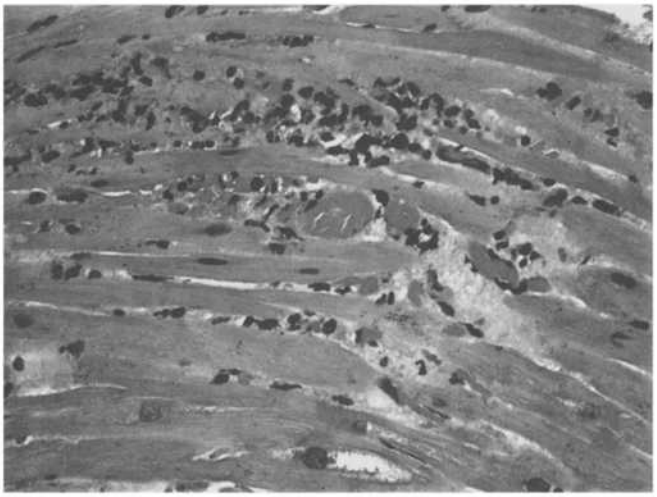


Fig. 10. Acute cardiac allograft rejection.



Fig. 11. Quilty lesion.

Macroscopic

- Dusky, edematous, hemorrhagic appearance

Microscopic

- Diffuse interstitial edema and hemorrhage
- Intravascular fibrin thrombi
- Myocyte necrosis

Immunohistochemistry/Immunofluorescence

- Myocardial deposition of cytotoxic antibody(ies)

Acute Cellular Rejection

Clinical

- Failure of allograft resulting cardiac dysfunction

Macroscopic

- May be grossly normal in mild cases
- Edema and endocardial hemorrhages

Microscopic

- Perivascular and interstitial myocardial lymphocyte infiltrate **(Figure 10)**
- Myocyte degeneration/necrosis
- Five general levels (0–4) of severity which direct treatment (International Working Group for Cardiac Transplantation):
  - Grade 0, no rejection
  - Mild:
    - Grade 1A, focal (usually perivascular) lymphocyte infiltrate, without myocyte damage
    - Grade 1B, diffuse interstitial lymphocyte infiltrate, without myocyte damage
  - Moderate:
    - Grade 2, focal lymphocyte infiltrate, with associated myocyte damage
    - Grade 3A, multifocal lymphocyte infiltrates, with associated myocyte damage
    - Grade 3B, diffuse lymphocyte infiltrates, with myocyte damage
  - Severe:
    - Grade 4, severe, diffuse lymphocyte infiltrate, associated with myocyte necrosis, and neutrophils, often with vasculitis and hemorrhage

Differential Diagnosis

- Old endomyocardial biopsy site with lymphocytic infiltrates associated with fibrosis
- Quilty effect **(Figure 11):**
  - Seen only in adults treated with cyclosporine
  - Predominantly lymphocyte infiltrate centered in the surface endocardium
  - Discrete endocardial lymphoid infiltrate with nodal organization
  - Associated with myocardial degeneration and vascular proliferation
- Lymphoproliferative diseases

Humoral ("Vascular") Rejection

Clinical

- Failure of allograft, due to circulating recipient antibodies directed against the donor heart

Macroscopic

- Dilated cardiomegaly, edema

Microscopic

- Interstitial edema, hemorrhage, few inflammatory cells
- Capillaritis

Immunohistochemistry/Immunofluorescence

- IgG, IgM, C3, fibrinogen deposition on endothelium of intramyocardial vessels

Chronic Rejection

Clinical

- Failure of allograft (ischemic)
- Accelerated atherosclerosis is major long term complication of cardiac transplantation

Macroscopic

- Coronary stenosis, which may extend into intramyocardial branches

Microscopic

- Intimal hyperplasia/fibroplasias/atherosclerosis
- Intimal/adventitial chronic inflammatory cell infiltrate
- Myocyte degeneration and necrosis

Quilty Effect

Clinical

- Lesions of unknown etiology and of doubtful significance
- Should therefore be differentiated from allograft rejection

Microscopic

- Endocardial collections of lymphocytes (predominantly T-cells), with sometimes some around subendocardial myocytes
- Apparent myocyte necrosis may be present, distinguishing so-called Quilty B from Quilty A (no necrosis)
- Distinctive microvascular arrangement within aggregate, with lymphocyte streaming at perimeter

Epstein-Barr Virus (EBV)-Associated Post-Transplant Lymphoproliferative Disorder

Clinical

- Occurs in about 10% of transplant cases
- May regress after withdrawal of immunosuppression

Microscopic

- Hyperplastic to lymphomatous collections of B-lymphocytes of endocardium
- Usually of B-cell type
- May involve other sites (e.g., lung, gastrointestinal tract, lymph nodes, etc.)

Post-Transplantation Infection Cytomegalovirus

- Most common infection of cardiac transplantation
- Characteristic viral inclusion bodies
- Immunohistochemical/*in situ* hybridization and PCR techniques (PCR is most sensitive) are helpful

Toxoplasmosis

- Characteristic appearance of organisms
- Immunohistochemical technique for identification available

Cardiac Neoplasms

BENIGN

Myxoma

Clinical

- Sporadic (usually middle-aged women) and familial types
- Comprise approximately 50% of primary tumors of heart
- Heart failure, secondary to valvular or chamber interference
- Constitutional symptoms (fever, malaise and weight loss) due to interleukin-6 production
- Thromboembolism
- May occur in younger patients with recurrence and extracardiac lesions (myxoma syndrome)
- Extracardiac lesions:
  - Myxoma of other organs
  - Breast myxoid fibroadenoma
  - Sertoli cell tumor of testis
  - Endocrine anomalies (adrenal cortical hyperplasia, pituitary adenoma with acromegaly)
  - Skin lesions (blue nevi, lentiginosis, psammomatous melanocytic schwannoma)

Macroscopic

- Most commonly left atrial (approximately 75%) and right atrial mass
- Located in fossa ovalis in atrial septum
- Attached to endocardium without deeper infiltration

Microscopic ***(Figure 12)***

- Myxoma cells (abundant eosinophilic cytoplasm with indistinct cell borders, ovoid nuclei, nucleoli variably present) forming trabeculae, syncytia, and rings in a myxoid and/or fibrous matrix
- Hemosiderin is present in hemosiderophages and sometimes myxoma cells
- Prominent vascularity
- Inflammation, extramedullary hematopoeisis may be present
- May show well-developed mucin producing glands (glandular myxoma), which may be confused with metastatic adenocarcinoma
- Immunohistochemically, positive staining has been reported for Factor VIII, vimentin, actin, desmin, smooth muscle myosin, alpha-1-antitrypsin, and alpha-1-antichymotrypsin
- Glandular areas may be positive for CEA, EMA, and keratin

Differential Diagnosis

- Myxoid sarcoma, myxoid hemangioma:
  - Both lack myxoma cells and fine capillary vasculature

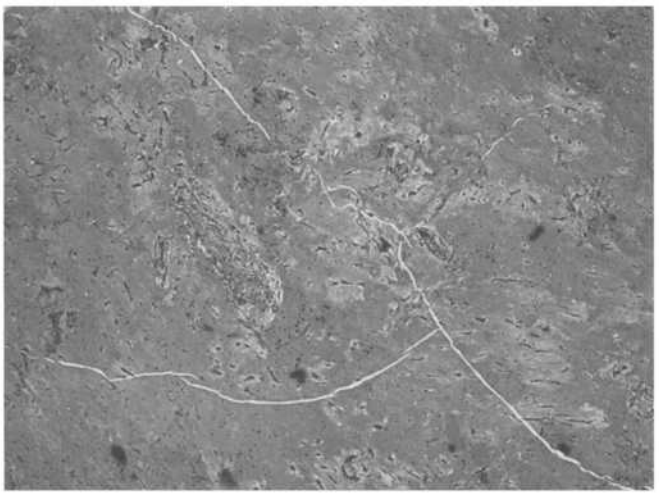


Fig. 12. Atrial myxoma.

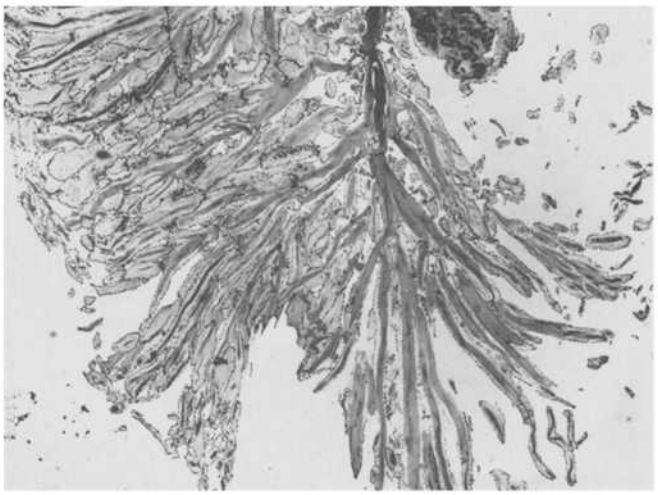


Fig. 13. Papillary fibroeloastoma.

- Mural (organized) thrombus:
  - May be indistinguishable with myxoma
- Papillary fibroelastoma:
  - No predilection for left atrium
  - Usually located on a valve cusp
  - Avascular papillary frond and laminated elastic fibers
  - Myxoid areas often located toward the peripheral of the lesion
- Fibroma:
  - Prominent elastic fibers with frequent calcifications

Papillary Fibroelastoma

Clinical

- Asymtomatic, incidental finding at surgery or autopsy
- May represent organized thrombi (similar to Lambl excrescence)
- May give rise to thromboemboli, rarely obstruction of a coronary ostium, with sudden death

Macroscopic

- Small, papillary structure usually occurs on surface of valves
- May also occur on other endocardial locations

*Microscopic (**Figure 13**)*

- Papillary formation with a paucicellular hyalinized core covered by hyperplastic endocardial cells

Differential Diagnosis

- Lambl's excrescences:
  - Occur along the line of closure and free cuspal edge of valves
  - Smaller and less gelatinous

Fibroma

Clinical

- Occur in children, often <1 year old and may present with congestive heart failure
- No sex predilection
- Probably represent hamartomaous lesions
- May be part of nevoid-basal cell carcinoma syndrome (Gorlin's syndrome)

Macroscopic

- Usually single, well-circumscribed, "fibroid"-like tumors of myocardium
- Located in the ventricular septum
- No hemorrhage or necrosis

Microscopic

- Fibrocytes, collagen, elastic tissue, sometimes calcification and bone-formation
- No necrosis, cellular pleomorphism, or prominent inflammatory infiltrate

Differential Diagnosis

- Old infarcts:
  - Usually contracted areas of fibrous tissue, and not expansile masses
- Inflammatory pseudotumors:
  - Prominent inflammation with plasma cells
- Papillary fibroelastoma:
  - Avascular papillary fronds with endothelial lining
- Fibrosarcoma:
  - Frequent mitotic figures
  - Usually occur in adults, but other age groups as well (cellular fibromas occur exclusively in early childhood)

- Organized mural thrombi and cicatrized myxomas
- Oriented endocardially, unlike intramural location of fibroma

♦ Solitary fibrous tumor of the pericardium:
- Pericardial location

Rhabdomyoma

Clinical

♦ Seen mostly during first decade of life; many are congenital
♦ No sex predilection
♦ Associated with tuberous sclerosis and congenital heart disease
♦ Probably of myocyte origin

Macroscopic

♦ Single or multiple, firm, white, well-circumscribed nodules
♦ The most common locations are the left ventricle and ventricular septum

*Microscopic (**Figure 14**)*

♦ "Spider cells," with radial cytoplasmic extensions:
- Immunohistochemical positivity for myoglobin, actin, desmin, vimentin, and sometimes HMB-45

Lipomatous Hypertrophy of the Interatrial Septum

Clinical

♦ May represent acquired processes related to metabolic disturbance
♦ Often associated with obesity, advanced age and cardiomegaly
♦ May cause arrhythmia with sudden death

Microscopic

♦ Infiltrative, numerous vacuolated adipocytes with interspersed hypertrophic myocytes

Differential Diagnosis

♦ Liposarcoma:
- Lipoblast and mitotic figures

♦ Lipoma:
- Epicardial location

Cystic Tumor of the Atrioventricular Node

Clinical

♦ Usually occur in young adults with female predilection
♦ May cause complete heart block due to its location
♦ Believed to be a developmental abnormality
♦ May be associated with other congenital anomalies

Macroscopic

♦ Cyst-like lesion in the inferior interatrial septum in the region of AV node

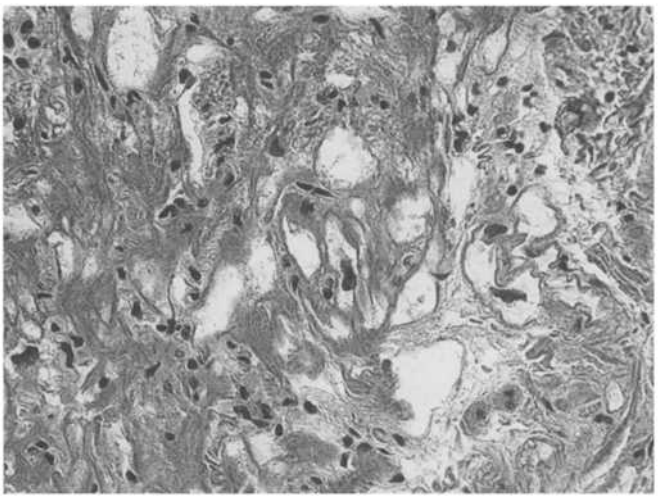


Fig. 14. Cardiac rhabdomyoma.

Microscopic

♦ Ductules, cysts, and solid nests of epithelioid cells
♦ Positive for cytokeratin, epithelial membrane antingen (EMA), carcinoembryonic antigen (CEA), and B72.3
♦ Negative for Factor VIII
♦ Electron microscopy shows desmosomes and microvilli (lesion once thought of as a type of mesothelioma)

Differential Diagnosis

♦ Bronchogenic and mesothelial cyst:
- Usually occur on the epicardial surface
- Larger lesion

♦ Teratoma:
- Presence of neural and other ectodermal components

Paraganglioma (Extra-Adrenal Pheochromocytoma)

Clinical

♦ Young adults
♦ Patients may have hypertension and elevated urine catecholamine levels

Macroscopic

♦ Most commonly a tumor of left atrium

Microscopic

♦ See Chapter 14

Others

♦ Granular cell tumor, hemangioma, lymphangioma, lipoma, angiolipoma, schwannoma, ganglioneuroma, teratoma, ectopic thyroid, and ectopic thyroid tissue

MALIGNANT

♦ In general, primary cardiac sarcomas are very rare
♦ Some may defy classification with present-day diagnostic techniques
♦ Metastatic tumors to heart are much more common

Angiosarcoma

Clinical

- Probably most common primary malignant cardiac neoplasm
- Congestive heart failure, arrythmias, chamber obstruction

Macroscopic

- Large, hemorrhagic, invasive tumor, most frequently of right atrium and pericardium

Microscopic

- Malignant mesenchymal neoplasm, showing endothelial differentiation
- Most are poorly differentiated
- Immunohistochemistry for Factor VIII, CD34, CD31 is positive
- Electron microscopy: Weibel-Pallade bodies

Differential Diagnosis

- Papillary endothelial hyperplasia of hemangioma:
  - Lack mitotic figures or cytologic atypia

Lymphoma

Clinical

- Primary tumors are rare
- Secondary involvement by advance lymphoma or leukemia is much more common

Microscopic

- Usually diffuse large cell type

Neoplasms Metastatic to Heart

Clinical

- Far more common than primary cardiac tumors
- Most result from a primary tumor which is in thoracic cavity (e.g., extension from a contiguous carcinoma of lung)

Microscopic

- Depending on tumor type and includes malignant melanoma, carcinomas of kidney, lung, breast, choriocarcinomas, rhabdomyosarcoma, and others

Others

- Leiomyosarcoma
- Rhabdomyosarcoma
- Malignant fibrous histiocytoma
- Osteosarcoma
- Fibrosarcoma
- Liposarcoma
- Synovial sarcoma
- Malignant peripheral nerve tumor
- Rhabdoid tumor

PATHOLOGY OF BLOOD VESSELS

Arteriosclerosis

- Means literally "hardening of arteries"
- Encompasses several entities, such as atherosclerosis, arteriolosclerosis (see under hypertensive vascular disease, below), and Mönckeberg's medial calcific sclerosis

ATHEROSCLEROSIS

Clinical

- Accounts for more deaths in the West than any other disease
- Predominantly ischemic consequences of narrowed vessels, e.g. myocardial infarction, stroke, gangrene of extremities, etc.
- Aortic aneurysms are another important consequence

Gross

- Affects predominantly elastic, and large and small muscular arteries
- Lesions (atheroma) consists of a raised intimal plaque, with a lipid core of mostly cholesterol and cholesterol esters, and a fibrous cap
- The fatty streak, seen usually in children, thought to be precursor lesion
- In smaller vessels, atherosclerosis results in stenosis
- In larger vessels, lesion results in focal destruction and weakening of wall, with potential to aneurysm formation, thrombosis, and thromboembolism
- Abdominal aorta is affected more severely than thoracic

Microscopic

- Fibrous cap, containing smooth muscle cells and collagen, lipid core with cholesterol clefts and lipid-laden macrophages
- Dystrophic calcification, plaque rupture (**Figure 15**), intra-plaque hemorrhage, and luminal thrombosis

HYPERTENSIVE VASCULAR DISEASE

Hyaline Arteriosclerosis

Clinical

- Most severe in hypertensive subjects, but also seen in normotensive elderly persons
- Vascular narrowing leads to ischemic end-organ damage
- Most notably in kidneys (nephrosclerosis)

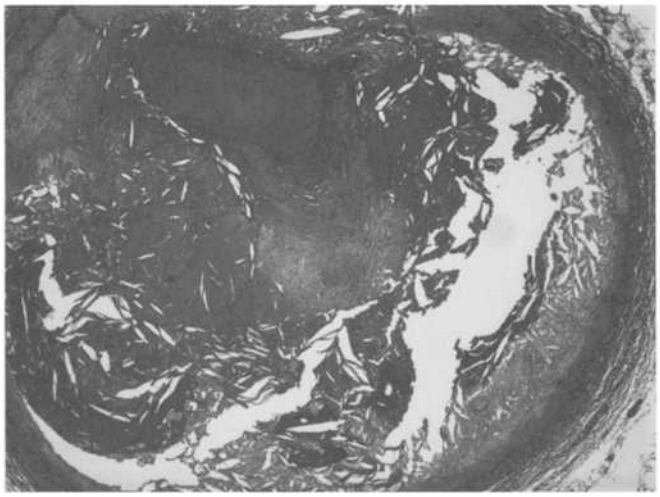


Fig. 15. Ruptured atherosclerotic plaque in a coronary artery.



Fig. 16. Fibromuscular dysplasia.

Microscopic

- Hyaline (pink, glassy) thickening of arteriole walls, concomitant with lumen narrowing

Hyperplastic Arteriolosclerosis

Clinical

- Seen in more severe and acute hypertension, such as "malignant hypertension," when diastolic pressures can exceed 110 mm/Hg

Microscopic

- "Onion-skinning" of arteriole walls by smooth muscle cells forming concentric layers which thicken and narrow vessel
- Basement membrane reduplicated
- Often accompanied by fibrinoid necrosis of vascular wall

Mönckeberg's Medial Calcific Sclerosis

Clinical

- Minor clinical significance, as this lesion rarely, if at all, produces vascular narrowing
- Occurs typically in individuals older than 50
- May be seen radiographically
- May co-exist in same vessel with atherosclerosis
- The cause is unknown

Macroscopic

- Usually affects femoral, tibial, radial, ulnar arteries, and vascular supply to genitalia
- Also seen frequently in arteries of thyroid gland

Microscopic

- Annular calcifications in media of medium to small muscular arteries
- Occasionally with bone and bone marrow formation lesion locally

Fibromuscular Dysplasia

Clinical

- Seen most often in young women (35 years old)
- May be found in virtually any artery of body
- Pathological end-effect is same as any other form of arterial stenosis
- Ischemia, related to degree of blockage
- Complications include aneurysm, emboli, sudden death
- Uncommon cause of renal artery stenosis
- More common in right renal artery with distal two-thirds of artery involved
- Etiology unknown
- Has a characteristic gross and radiographic appearance
- Manifest as a solitary narrowing, or as a grouped series

Gross/Microscopic ***(Figure 16)***

- Arterial wall thickening and consequent lumen narrowing
- Due to non-atheromatous and non-inflammatory fibrous or fibrous and smooth muscle hyperplasia, which can be present in intima, media (the most common location), or adventitia

Myxoid Medial Degeneration (Cystic Medial Necrosis) of Aorta

Clinical

- Cause unknown
- Develops with age
- Important complication of Marfan syndrome
- No necrosis or cyst formation
- Disintegration of elastic fibers (seen best with elastic stain) with "cystic" spaces containing mucopolysaccharide (appears myxoid on H&E section)

- Leads to weakening of aortic wall with potential for aneurysm formation and dissection
- Similar process can be seen in pulmonary artery and represents usually a normal, age related change of little, if any clinical consequence

Aneurysms

- Abnormal dilation of part of vascular wall
- Caused by an acquired or congenital weakness of media
- May assume certain shapes such as saccular, fusiform
- May predispose to dissection

Atherosclerotic Aneurysm of the Abdominal Aorta

Clinical

- Most occur in patients older than 50
- Most frequently seen aneuryms (along with those of common iliac arteries)
- May present as palpable abdominal mass and/or radiographic finding
- Most patients are men, and half are hypertensive
- Larger (>6 cm) are prone to rupture, with fatal internal hemorrhage
- Encroachment on renal, mesenteric, celiac, and/or iliac arteries may lead to ischemia of those respective distributions
- Atherosclerotic aneurysm of thoracic aorta is much less common

Macroscopic

- Most occur between renal artery ostia and iliac aortic bifurcation
- Usually fusiform
- May possess mural thrombus/thrombi

Microscopic

- Atherosclerosis with destruction of media, wall thinning
- Chronic inflammation

Berry Aneurysm of Cerebral Arteries

Clinical

- Associated with autosomal dominant (adult) polycystic kidney disease
- Clinically undetected aneurysms are found in as many as 25% of persons older than 55 years
- May present with focal neurologic deficits, headache, to fatal subarachnoid hemorrhage from a rupture

Macroscopic

- More than 90% are seen at various branch points in circle of Willis
- Multiple aneurysms are seen in approximately 20%
- Most commonly seen at junctions of anterior communicating with anterior cerebral arteries, trifurcation of middle cerebral arteries, and arterial branches of internal carotid artery (internal carotid complex)

Microscopic

- A discontinuity (thought to be congenital) of internal elastic membrane at branch point
- May seen eventual destruction of this membrane with wall thinning and a thin adventitial coat
- Mural thrombus may been seen

Infectious (Mycotic) Aneurysms

Clinical

- A complication of septicemia, and/or endocarditis with embolization of infectious material
- Occur in aorta, cerebral, mesenteric, splenic arteries, and elsewhere
- May also occur next to a nidus of tuberculosis or bacteral abscess
- Abscesses tend to rupture and hemorrhage

Microscopic

- Infectious destruction of vessel wall, with pattern of inflammation depending on type of organism, which can be bacterial, mycobacterial, fungal

Syphilitic Aneurysms

Clinical

- Rare in United States

Macroscopic

- "Tree-barking" of thoracic aorta, with aneurysm formation

Microscopic

- Vasitis vasorum (endarteritis/periarteritis of vasa vasorum) with plasma cells, lymphocytes, and macrophages
- Necrosis and scarring of media, and elastic fiber disintegration
- Not prone to dissection, unlike atherosclerotic aneurysms

Dissection

- Entrance of blood into vessel wall with extension along a certain length of that vessel
- Mistakenly called a "dissecting" aneurysm, when it really is a sort of hematoma

Clinical

- Typically sudden severe chest and/or back pain (in case of aortic dissection)
- May also see hypotension, shock, loss of arterial pulse, cardiac tamponade, and ischemic effects of encroachment upon vessel lumens
- Occurs three times more frequently in men
- Most common in sixth and seventh decades of life
- History of hypertension in common

Macroscopic

- Most often affects aorta, and/or its major branches
- Classified as Debakey's I (ascending aorta), II (ascending and descending aorta), and III (descending only)

- Also Stanford Type A (ascending only or ascending plus descending), and Type B (descending only)
- Aorta shows an intimal tear, typically a few centimeters above aortic ring
- Dissecting hematoma in media may extend into and compromise coronaries, carotids, renal, mesenteric, and/or iliac arteries
- Dissection may penetrate back into original aortic lumen, creating a "double-barrel" aorta
- Dissection into ascending aorta with adventitial tear may give rise to hemopericardium, hemomediastinum, hemothorax, and retroperitoneal hemorrhage
- Other risk factors for ascending thoracic aorta dissection:
  - Hypertension
  - Myxoid medial degeneration
  - Bicuspid aortic valve
- Other risk factors for abdominal aortic aneurysm:
  - Atherosclerosis
  - Hypertension

Vasculitis (also see Chapter 17)

- Classification of vasculitis based on size of involved vessel(s) is practical
- Specific cause can be identified in only a minority of cases
- Can be divided into infectious and non-infectious groups, with latter much more extensive
- There is a correlation between the type of antineutro-phil cytoplasmic autoantibodies (ANCA) and the specific vasculitis syndrome
- C-ANCA (anti-proteinase 3) often seen in:
  - Active Wegener's disease
  - Microscopic polyarteritis
  - Churg-Strauss syndrome (allergic granulomatosis and angiitis)
- P-ANCA (anti-myeloperoxidase) often seen in:
  - Polyarteritis nododa
  - Primary glomerular disease (idiopathic crescentic glomerulonephritis
  - Kawaski's disease

Infectious Vasculitis

- Causes are bacterial (including syphilitic, with characteristic involvement of proximal aorta with vasitis vasorum and gross "tree-barking", with aortic root dilation and clinical insufficiency), rickettsial (Rocky Mountain spotted fever), mycotic, tuberculous (typically small vessels), and viral (herpes, CMV)

Non-Infectious Vasculitis: Medium to Large Sized Vessels

- Large arteries (aorta and its main branches)

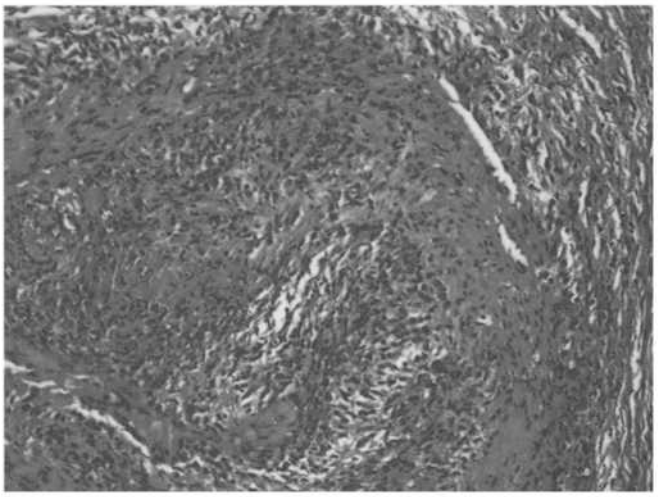


Fig. 17. Giant cell arteritis.

Giant Cell Arteritis/Aortitis (see also Temporal Arteritis, below)

Clinical/Macroscopic

- Most commonly seen in adults
- May be seen associated with rheumatoid arthritis, ankylosing spondylitis, scleroderma, and temporal arteritis
- Aortic insufficiency, aneurysms, dissection

Microscopic

- Chronic inflammation (multinucleated giant cells in giant cell aortitis, see Temporal Arteritis, below), with focal medial destruction (**Figure 17**)

Kawasaki's Disease (Mucocutaneous Lymph Node Syndrome)

Clinical

- Occurs usually in infants (also named infantile polyarteritis nodosa)
- Fever, exanthema, conjunctivitis, reddened tongue, lips, oropharynx, cervical lymphadenopathy
- Sudden death from coronary involvement
- Due to necrotizing vasculitis leading to coronary artery aneurysm with rupture
- Leading cause of acquired heart disease in child
- Treated with i.v. gamma-globulin and aspirin

Macroscopic/Microscopic

- Necrotizing polyarteritis (cardiac and elsewhere), arterial aneurysms
- Recent and/or healed myocardial infarction

Takayasu's Disease

Clinical

- Occurs mostly in young Asian women
- Decreased/absent pulses in upper extremities
- Neurologic/ocular symptoms, renovascular hypertension

Macroscopic

- Involvement of aorta, aortic arch branches, pulmonary arteries and occasionally coronary arteries

Microscopic

- Chronic granulomatous vasculitis (may or may not have giant cells)
- Fibrosis of arterial wall in later stages

Non-Infectious Vasculitis: Small to Medium Sized Vessels

Churg-Strauss Syndrome

Clinical

- Probably a type of polyarteritis nodosa (see below)
- Triad of asthma, blood eosinophilia, eosinophilic vasculitis (pulmonary, systemic, and/or isolated organ involvement)

Microscopic

- Vasculitis with eosinophilic infiltrate
- Necrotizing granuloma
- Both arteries and veins involved

Polyarteritis Nodosa (PAN) (Figure 18)

Clinical

- Ischemic, multiorgan system involvement
- History of hepatitis B infection
- Fever, hypersensitivity, eosinophilia (see also Churg-Strauss, above)
- Treated with steroids and cyclophosphamide

Macroscopic

- Visible/palpable nodular arterial thickenings, typically at branch points
- Involve predominantly renal and visceral muscular arteries and arterioles
- Pulmonary vessels spared

Microscopic

- Segmental necrotizing vasculitis of small to medium sized arteries
- Co-existent healing/healed lesions and segments of normal vessel (skip lesions)
- Medial destruction with interruption of elastic laninae

Differential Diagnosis

- Churg-Strauss syndrome:
  - Asthma, peripheral eosinophilia and pulmonary involvement
  - Both artery and vein involved
  - Microscopically, necrotizing granuloma and eosinophils

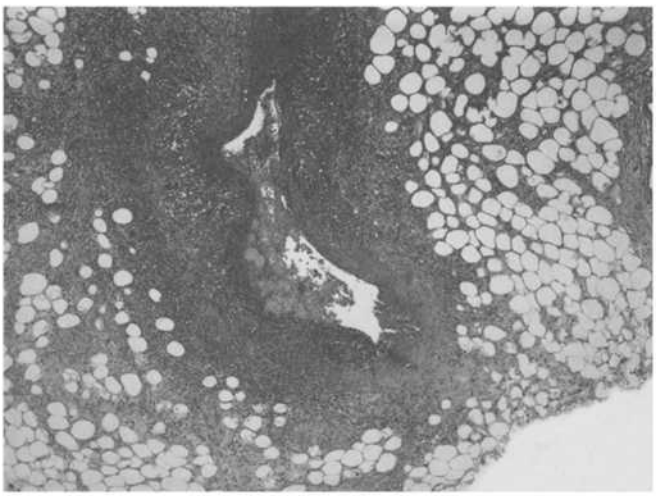


Fig. 18. Acute necrotizing vasculitis in polyarteritis nododa (PAN).

Microscopic Polyarteritis

Clinical

- Depending on severity of organ involvement
- Hemoptysis, hematuria/proteinuria (necrotizing glomerulonephritis), bowel pain/enterorrhagia, muscle pain and weakness, and/or palpable skin purpura may be seen
- Not hypertensive (in contrast to PAN)
- Immune reaction against an antigenic challenge (drugs, microorganisms, etc) can be postulated in many cases

Microscopic

- Vasculitis with fibrinoid necrosis of media and/or leukocytoclastic vasculitis (infiltration of polymorphonuclear neutrophils into vascular wall with neutrophil disintegration) of systemic arterioles, capillaries, and venules
- Lesions of the same age
- Smaller vessels (skin, lung, and kidney) involved than polyarteritis nodosa (PAN)
- Muscular and large arteries spared
- Usually without demonstrable immune complex deposition
- Skin-limited form called cutaneous leukocytoclastic vasculitis may be seen

Differential Diagnosis

- Polyarteritis nodosa:
  - Lesions of various age with skip lesions

Temporal Arteritis (Giant Cell Arteritis)

Clinical

- Predominance in women, usually greater than 50 years of age
- Elevated sedimentation rate

- May be associated with polymyalgia rheumatica and giant cell aortitis (indicating systemic condition and not limited to temporal, cerebral, and retinal arteries)
- Blindness and central nervous system (CNS) manifestations
- Treated with steroids

Microscopic

- Segmental inflammatory destruction of vessel wall
- Destruction of elastica and presence of multinucleated giant cells
- Biopsy should include generous length (some say two centimeters) of superficial temporal artery, as lesion may be missed due to its segmental nature

Differential Diagnosis

- Takayasu's disease

Thromboangiitis Obliterans (Buerger's Disease)

Clinical

- Predominantly young men less than 40 years old
- Associated strongly with using tobacco

Macroscopic

- Segmental stenosis of small to medium sized arteries and veins of extremities, sometimes mesenteric vessels, rarely elsewhere
- Extremital ischemia

Microscopic

- Early stage shows arterial/venous thrombosis with inflammation
- Affecting entire wall of vessel, sometimes with multinucleated giant cells in thrombus itself
- Later stages may be difficult to distinguish from organizing thrombus of other etiology, or atherosclerosis

Wegener's Granulomatosis

Clinical

- Peaks in 5th decade, with pneumonitis, upper-airway inflammation and ulceration, and renal dysfunction (80%)
- C-ANCA detected in over 90% of patients who exhibit active disease
- Most patients die if untreated
- Responds well to immunosuppressive and cytotoxic medication

Microscopic

- Necrotizing vasculitis of small to medium-sized arteries and veins, with granulomatous features
- Pulmonary involvement leads to cavity formation and characteristic geographic necrosis
- Renal involvement may manifest as necrotizing and or crescentic glomerulonephritis
- Vascular and/or glomerular immune complexes may be seen in some patients

Differential Diagnosis

- Mycosis, tuberculosis, lymphomatoid granulomatosis

Other

- Vasculitis may be associated with connective tissue disease (e.g. SLE and rheumatoid arthritis), malignancy (lymphomas and others), cryoglobulinemia, and Henoch-Schonlein purpura

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22

Lung

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CONTENTS

I. Non-neoplastic Diseases of the Lung.....22-4
Congenital Anomalies and Pediatric Lesions....22-4
Pulmonary Sequestration 22-4
Intralobar.....22-4
Extralobar 22-4
Bronchogenic Cysts 22-4
Congenital Pulmonary Airway Malformation 22-4
Pulmonary Lymphangiomatosis 22-5
Bronchopulmonary Dysplasia 22-5
Infantile Lobar Emphysema 22-5
Pediatric Interstitial Lung Disease 22-6
Airways and Obstructive Diseases 22-6
Emphysema.....22-6
Large Airway Disease.....22-7
Bronchiectasis 22-7
Chronic Bronchitis 22-7
Asthma 22-7
Bronchocentric Granulomatosis....22-8
Small Airway Disease.....22-8
Respiratory Bronchioloitis (Smokers') 22-8
Respiratory Bronchiolitis-Associated Interstitial Lung Disease 22-8
Follicular Bronchiolitis 22-9
Constrictive (Obliterative) Bronchiolitis.....22-9
Diffuse Panbronchiolitis 22-9
Cellular Bronchiolitis 22-9
Interstitial Diseases 22-9
Acute Lung Injury 22-9
Diffuse Alveolar Damage (DAD)/Acute Interstitial Pneumonia (AIP) 22-9
Cryptogenic Organizing Pneumonia (COP)/ Bronchiolitis Obliterans Organizing Pneumonia (BOOP).....22-10
Idiopathic Interstitial Pneumonias 22-10
Desquamative Interstitial Pneumonia (DIP) 22-10
Usual Interstitial Pneumonia (UIP).....22-11
Non-Specific Interstitial Pneumonia/Fibrosis 22-11
Other Interstitial Diseases.....22-12
Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis).....22-12
Eosinophilic Pneumonia 22-12
Eosinophilic Granuloma (Pulmonary Histiocytosis-X/ Langerhans' Cell Granulomatosis) 22-13
Sarcoidosis 22-13
Pulmonary Alveolar Proteinosis 22-14
Lymphangio(leio) myomatosis.....22-14

Goodpasture's Disease (Anti-Basement Membrane Antibody Disease [ABMA]) 22-15
Idiopathic Pulmonary Hemosiderosis 22-15
Pneumoconioses 22-15
Silicosis 22-15
Asbestos-Related Reactions 22-16
Coal Worker's Pneumoconiosis (CWP) 22-16
Hard Metal Pneumoconiosis 22-16
Berylliosis 22-17
Vascular Conditions 22-17
Vasculitides 22-17
Wegener's Granulomatosis 22-17
Churg-Strauss Syndrome (Allergic Angiitis Granulomatosis) 22-18
Necrotizing Sacroid Granulomatosis (NSG) 22-18
Necrotizing Capillaritis 22-18
Pulmonary Hypertension 22-19
Plexogenic Arteriopathy 22-19
Pulmonary Veno-Occulsive Disease with Secondary Pulmonary Arterial Hypertension 22-19
Thrombotic Arteriopathy: Pulmonary Infarction 22-20
Pulmonary Capillary Hemangiomatosis 22-20
Infections 22-20
Viral 22-20
Bacteria 22-22
Mycoplasma pneumoniae 22-24
Fungal 22-24
Protozoan 22-26
Lung Transplantation 22-27
Histologic Grading of Pulmonary Allograft Rejection 22-27

II. Neoplastic Diseases of the Lung 22-28

Benign Tumors 22-28
Benign Epithelial Tumor 22-28
Squamous Papillomas and Papillomatosis 22-28
Papillary Adenoma of Type II Cells 22-28
Alveolar Adenoma 22-28
Mucus Gland Adenoma 22-28
Mucinous Cystadenoma 22-29
Benign Mesenchymal Tumors 22-29
Hamartoma 22-29
Lipoma 22-29
Mesenchymal Cystic Hamartoma 22-30
Pre-Invasive Lesions 22-30
Malignant Tumors 22-31
Tumors of Salivary Gland Type 22-31
Mucoepidermoid Carcinoma 22-31
Adenoid Cystic Carcinoma 22-31
Epithelial Tumors 22-31
Squamous Cell Carcinoma 22-32
Adenocarcinoma 22-32
Small Cell Carcinoma 22-34
Large Cell Undifferentiated Carcinoma 22-34
Adenosquamous Carcinoma 22-35
Carcinomas with Pleomorphic, Sarcomatoid, and Sarcomatous Elements 22-35
Carcinoid Tumorlet 22-35
Typical and Atypical Carcinoid 22-36
Large Cell Neuroendocrine Carcinoma 22-36
Unusual Tumors with Neuroendocrine Differentiation 22-37
Mesenchymal Tumors 22-37
Fibrous and Fibro-Histiocytic Tumors 22-37
Inflammatory Pseudotumor 22-37
Malignant Fibrous Histiocytoma 22-37
Smooth Muscle Tumors—Leiomyosarcoma 22-38
Skeletal Muscle Tumor—Rhabdomyosarcomas 22-38
Vascular Tumors and Related Conditions 22-38
Vascular Malformations 22-38
Epithelioid Hemangioendothelioma (Intravascular Bronchioloalveolar Tumors) 22-38
Kaposi's Sarcoma 22-39
Angiosarcoma 22-39
Other Vascular Tumors 22-39
Neurogenic Tumors 22-40
Pleuropulmonary Blastoma 22-41
Lymphoproliferative Lesions of the Lung 22-41
Nodular Lymphoid Hyperplasia (Pseudolymphoma) 22-41

Lymphocytic Interstitial Pneumonitis (Diffuse Lymphoid Hyperplasia) 22-41
Giant Lymph Node Hyperplasia (Castleman's Disease) 22-41
Lymphomas.....22-41
Low Grade Lymphoma of the Mucosa Associated Lymphoid Tissue (MALT) 22-41
Angiocentric Immuno-proliferative Lesions/Angiocentric Lymphomas/Lymphomatoid Granulo-matosis/ Polymorphic Reticulosis 22-42
Post-Transplant Lymphoproliferative Disorder 22-43
Other Lymphoproliferative Lesions 22-43
Intravascular Lymphomatosis (Angiotropic Lymphoma).....22-43
Primary Pulmonary Hodgkin's Disease 22-43
Plasmacytoma 22-43
Mast Cell Tumor 22-43
Tumors of Uncertain Histogenesis 22-43
Sclerosing Hemangioma....22-43
Benign Clear Cell (Sugar) Tumor 22-43
Minute Pulmonary Meningothelial-Like Lesion (Minute Pulmonary Chemodectoma) 22-44
Granular Cell Tumor (Granular Cell Myoblastoma).....22-44
Masses and Tumor-Like Lesions 22-44
Pulmonary Amyloidosis 22-45
Pulmonary Hyalinizing Granuloma 22-45
Inflammatory Myofibroblastic Tumor 22-45
Tracheobronchopathia Osteoplastica 22-46
Benign Metastasizing Leiomyoma.....22-46
Tumors of the Pleura 22-46
Malignant Mesothelioma 22-46
Localized Fibrous Tumor of the Pleura 22-47

III. TNM Classification of Lung Cancer (2002 Revision) 22-47

IV. Suggested Reading.....22-48

NON-NEOPLASTIC DISEASES OF THE LUNG

Congenital Anomalies and Pediatric Lesions

Pulmonary Sequestration

Intralobar

Clinical

- 90% lower lobes; 60% on left; equal incidence in both sexes
- 50% older than 20 years; usually presents with recurrent infections

Macroscopic ***(Figure 1)***

- Firm, cystic area within lobe
- Arterial supply from elastic artery from thoracic aorta or below the diaphragm
- No communication with normal tracheobronchial tree
- Invested by normal visceral pleura

Microscopic

- Young patients: pathology may be normal
- Older patients: pathology shows chronic obstructive pneumonia; honeycomb changes are common

Extralobar

Clinical

- 60% are found in children <1 year; 90% on left side; M : F = 4 : 1
- Frequently found with repair of diaphragmatic defect
- 60% have other congenital anomalies such as diaphragmatic hernia or pectus excavatum (funnel chest)

Macroscopic

- Spongy, pyramidal mass outside of the normal pleura; invested by own pleura
- Systemic anomalous arterial supply; venous drainage through systemic or portal systems

Microscopic

- May appear normal; may resemble congenital adenomatoid malformation

Bronchogenic Cysts

Clinical

- Supernumerary lung buds from foregut; commonly found in subcarinal or middle mediastinum location; usually incidental findings on chest X-ray

Macroscopic

- Usually unilocular cysts with smooth margins; no communication with tracheobronchial tree

Microscopic ***(Figure 2)***

- Respiratory epithelium with smooth muscle, cartilage, and submucosal glands
- Squamous metaplasia, purulent exudate, chronic inflammation and fibrosis if infected

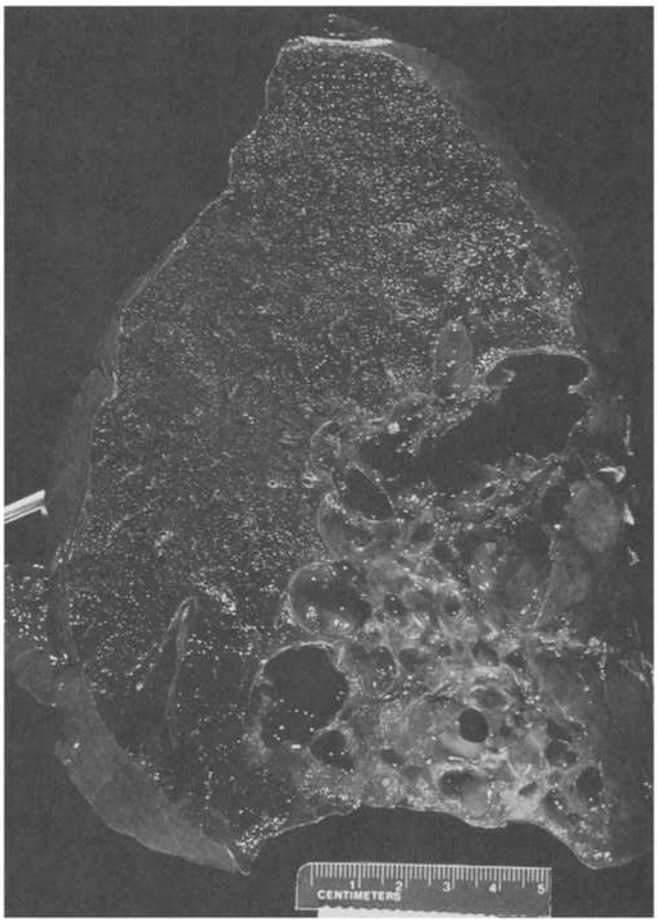


Fig. 1. Intralobar sequestration.

Differential Diagnosis

- Lung abscess:
  - Frequent bronchial communication
- Enteric cysts:
  - Lined by gastric epithelium
- Esophageal cysts:
  - Squamous epithelium
  - Wall contains double layer of smooth muscle and no cartilage

Congenital Pulmonary Airway Malformation

Clinical

- Stillborn with anasarca and newborn with acute respiratory distress
- Most communicate with tracheobronchial tree

Macroscopic

- Five types of lesions:
  - Type 1: one or more large cysts; cured with surgical removal

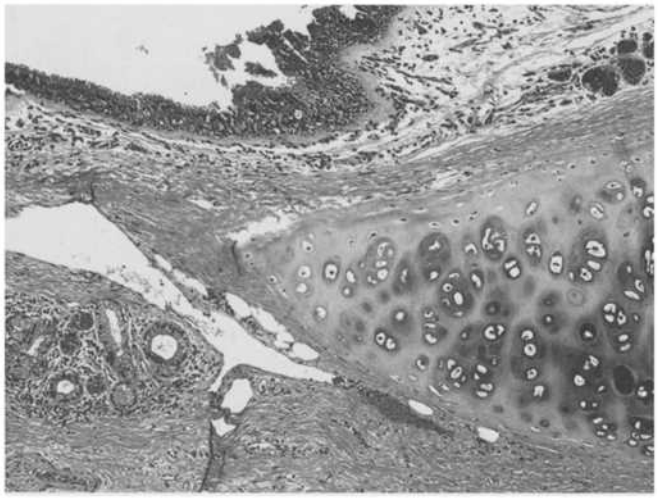


Fig. 2. Bronchogenic cyst.

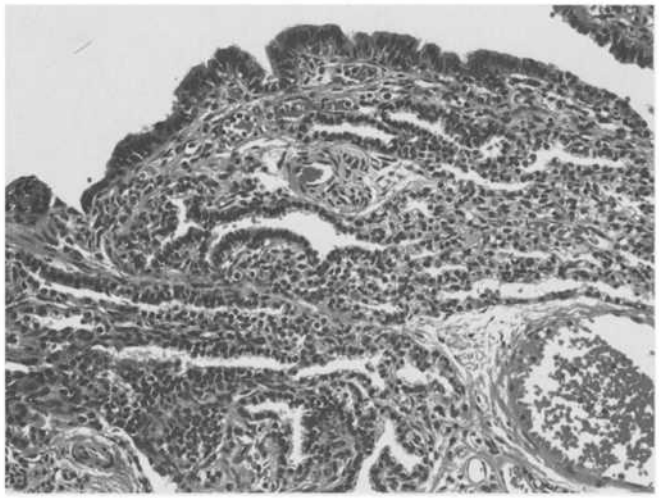


Fig. 3. Type I Congenital cystic adenomatoid malformation.

- Type 2: multiple, evenly spaced cysts; poor prognosis
- Type 3: spongy tissue; no cysts; poor prognosis; mediastinal shift
- Type 4: Thin-walled cysts in peripheral parenchyma

*Microscopic **(Figure 3)***

- Type 1: Pseudostratified, primitive epithelium; cartilagenous islands
- Type 2: Ciliated cuboidal or columnar epithelium
- Type 3: Ciliated cuboidal epithelium
- Type 4: Flattened, alveolar lining cells

Differential Diagnosis

- Extralobar sequestration:
  - Located outside of pleura
  - Have a separate arterial blood supply

Pulmonary Lymphangiomatosis

Clinical

- Occurs in young children; presents with wheezing and dyspnea; slowly progressive

Macroscopic

- Firm, lobulated lung

Microscopic

- Proliferation of dilated, endothelial-lined spaces; may have smooth muscle in walls in lymphatic distribution

Differential Diagnosis

- Lymphangioleiomyomatosis:
  - Occurs only in women of reproductive years
  - Smooth muscle is HMB 45+
- Lymphangiectasis:
  - Dilated channels but not increased number

Bronchopulmonary Dysplasia

Clinical

- Early BPD has features of respiratory distress syndrome (RDS) with hypoxemia and the need for assisted ventilation for at least 28 days
- Established BPD causes chronic respiratory disease, with significant wheezing, retractions and may have an associated pulmonary hypertension

Macroscopic

- Early BPD in non-surfactant-treated infants resembles RDS with firm, congested and heavy lungs
- Late BPD has pleural cobblestoning caused by underlying parenchymal areas that alternate between over-distension and fibrosis **(Figure 4A)**

Microscopic

- Early BPD has hyaline membranes with necrotizing bronchiolitis, atelectasis, interstitial edema
- Late BPD has lobules which alternate between interstitial fibrosis and distension. Lobules with distension have constrictive bronchiolitis as a sequelae of the necrotizing bronchiolitis from the early BPD **(Figure 4B)**

Differential Diagnosis

- Early BPD is similar to DAD
- Late BPD is has features of emphysema, interstitial fibrosis and constrictive bronchiolitis

Infantile Lobar Emphysema

Clinical

- Lobar overinflation within the first six months of life; presents with respiratory distress

Macroscopic

- Lung is overinflated

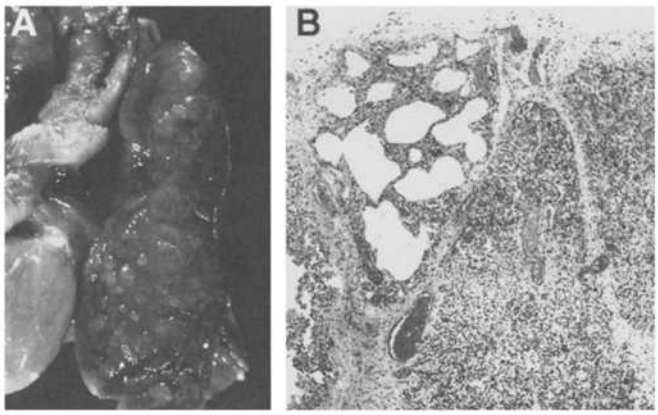


Fig. 4. Bronchopulmonary dysplasia **(A,B)**.

Microscopic

- Absolute increase in the number of alveoli

Differential Diagnosis

- Congenital cystic adenomatoid malformation, solid type
- Congenital lobar inflation:
  - Normal number of alveoli

Pediatric Interstitial Lung Disease

Clinical

- Interstitial lung disease presenting in the pediatric population, (<18 years of age)

Macroscopic

- Varies depending upon interstitial disease involvment; consolidation, fibrosis and hemorrhage are part of the spectrum

Microscopic

- All of the adult forms in interstitial lung disease (DIP, NSIP, UIP, PAP, HP); includes chronic pneumonitis of infancy

Differential Diagnosis

- Varies with the entity

Airways and Obstructive Diseases

Emphysema

Clinical

- Pink puffer
- Four major types found in four different clinical settings:
  - Centrilobular (proximal acinar):
    - Smokers; upper lobes most affected
  - Panacinar:
    - Alpha-1-protease inhibitor deficiency (ZZ); lower lobes most affected
    - Can be seen in talc IV drug abuse and in Ritalin use
  - Distal acinar (Paraseptal):
    - May contribute to spontaneous pneumothoraces and bullae formation in tall, asthenic male adolescent

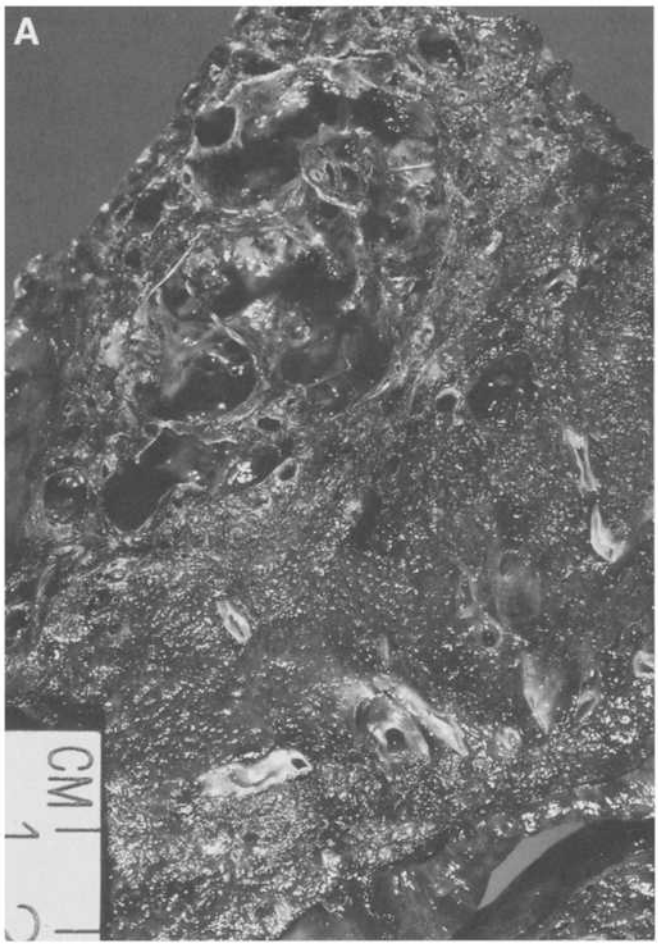


Fig. 5. Emphysema: **(A,B)** centrilobular; **(C)** panacinar.

  - Scar (better known as pericicatricial airspace enlargement):
    - Most common type; around area of fibrosis

Macroscopic

- May manifest as bullae-alveolar spaces >1 cm or blebs-representing airspaces made by dissection of loose connective tissue

*Microscopic **(Figure 5A,B,C)***

- Alveolar wall destruction distal to terminal bronchioles
- No fibrosis
- Four major types:
  - Centrilobular (Proximal acinar): Proximal part of acini
  - Pan acinar: Acini are uniformly involved
  - Distal acinar: Peripheral acinar involved
  - Scar emphysema: Emphysema adjacent to fibrosis

Differential Diagnosis

- Congenital lobar overinflation:
  - No destruction of alveoli

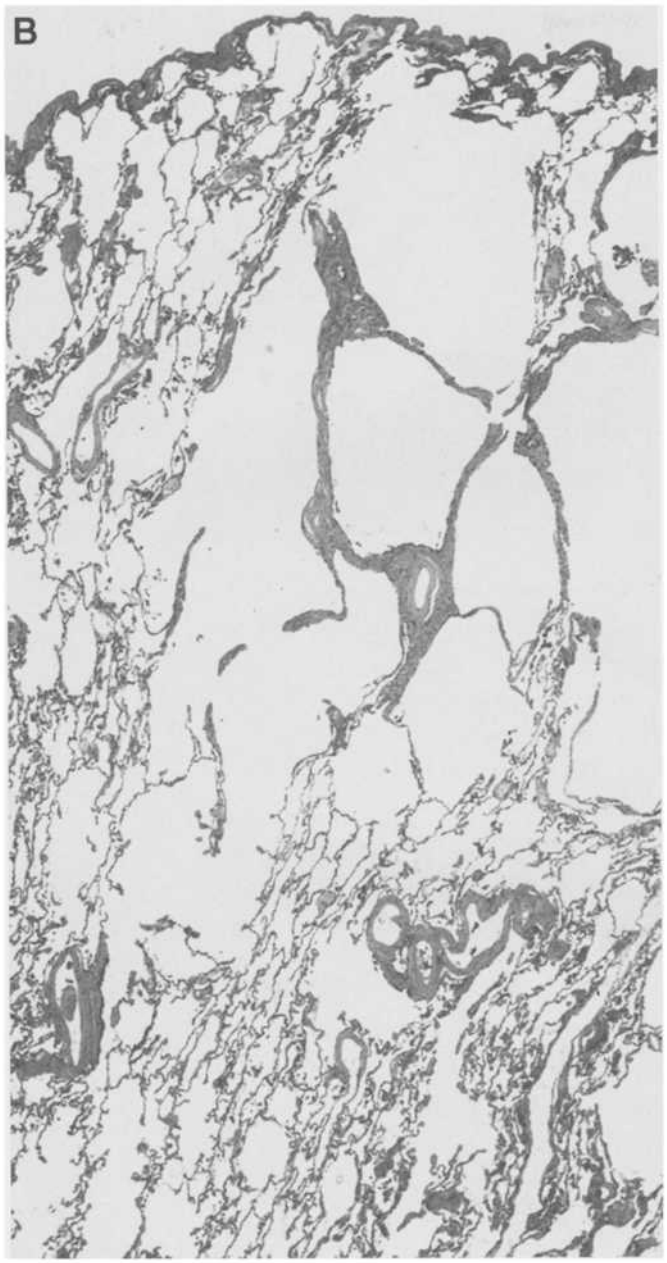


Fig. 5. (*Continued*)

- Honeycomb lung:
  - Fibrosis with metaplastic columnar epithelium

Large Airway Disease

Bronchiectasis

Clinical

- Causes include post-inflammatory and post-obstructive; seen in setting of cystic fibrosis, ciliary disorders, immunologic deficiencies, and idiopathic
- Recurrent acute pneumonias with productive cough; hemoptysis; recurrent fevers:
  - Cystic fibrosis

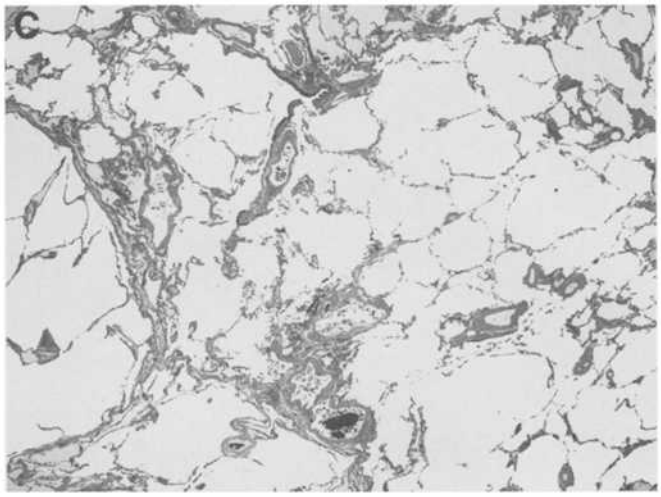


Fig. 5. (*Continued*)

Macroscopic ***(Figure 6A)***

- Diffuse or localized enlarged, fibrotic cartilaginous airways; dilated airways extend to pleural surface; commonly filled with mucopurulent material

Microscopic ***(Figure 6B)***

- Ectatic, dilated airways; chronically inflamed wall; follicular bronchitis may be present
- Acute and organizing pneumonia is common

Differential Diagnosis

- Mucinous tumors of the airways:
  - Malignant epithelium

Chronic Bronchitis

Clinical

- "Blue bloater"

Macroscopic

- Excessive mucous secretion within airways

Microscopic

- Goblet cell hyperplasia, thickened basement membrane, submucosal gland hyperplasia, smooth muscle hypertrophy
- Reid index: thickness of mucous gland layer/thickness of bronchial wall (normal <0.4)

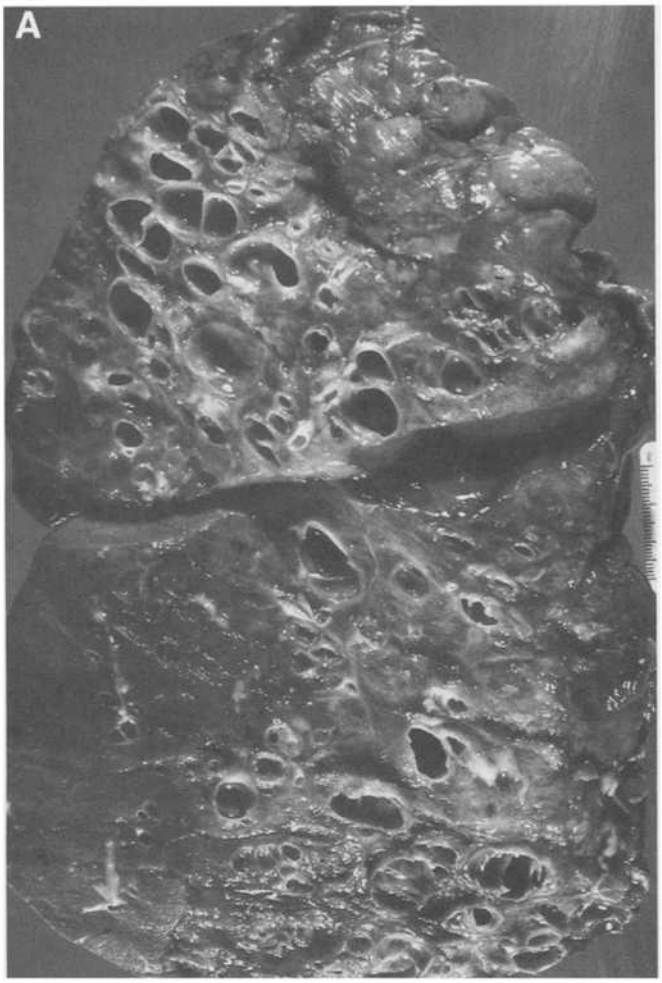
Asthma

Clinical

- Nonproductive cough and wheezing; atopic, nonatopic, exercise, and occupational types
- Affects 5% of all children; 65% of asthmatics have symptoms before age 5
- M : F = 2 : 1

Macroscopic

- Mucous plugging of airways; overdistention with abundant air trapping
- May see saccular bronchiectasis, especially in upper lobe



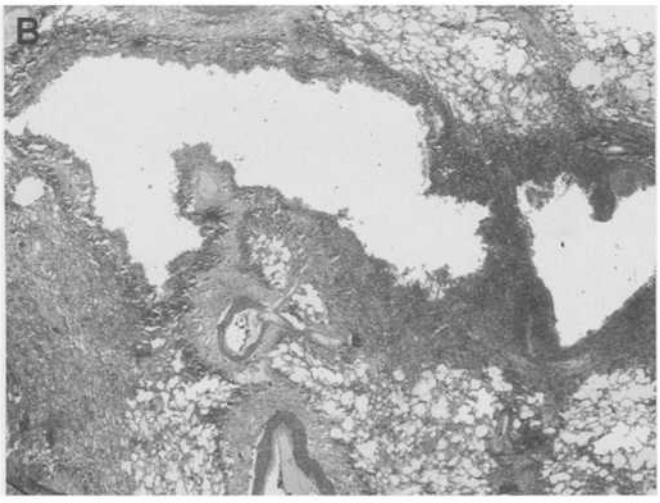


Fig. 6. Bronchiectasis **(A,B)**.

Microscopic

- Thickened basement membranes; mucous plugs; goblet cell hyperplasia
- Submucosal gland hypertrophy; may show eosinophilic infiltrate

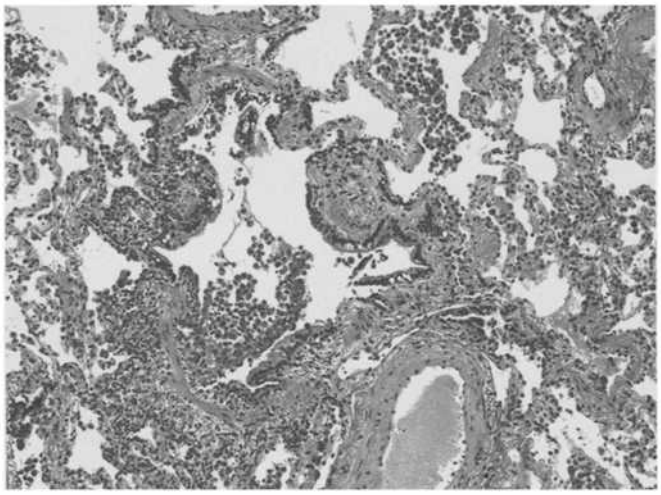


Fig. 7. Respiratory bronchiolitis.

- Smooth muscle hypertrophy
- Curshmann's spirals, Charcot-Leyden crystals, and Creola bodies

Differential Diagnosis

- Chronic bronchitis:
  - Histology very similar to asthma, except found only in smokers

Bronchocentric Granulomatosis

Clinical Features

- 50% of patients have asthma; also may have allergic bronchopulmonary aspergillosis
- High serum IgE; Type I and III reaction

Microscopic

- Bronchocentric granulomatous inflammation

Differential Diagnosis

- Wegener's granulomatosis:
  - Angiocentric vasculitis
  - c-ANCA+

Small Airway Disease

Respiratory Bronchiolitis (Smokers')

Clinical

- Incidental findings in smokers

Microscopic ***(Figure 7)***

- Pigmented macrophages within terminal bronchioles and surrounding alveoli
- Mild chronic inflammation, fibrosis

Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RB-ILD)

Clinical Features

- Smokers' disease
- Dyspnea, cough, mild restrictive defects

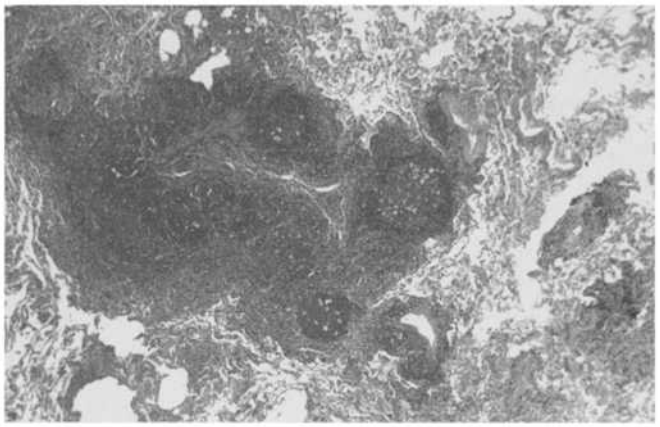


Fig. 8. Follicular bronchiolitis.

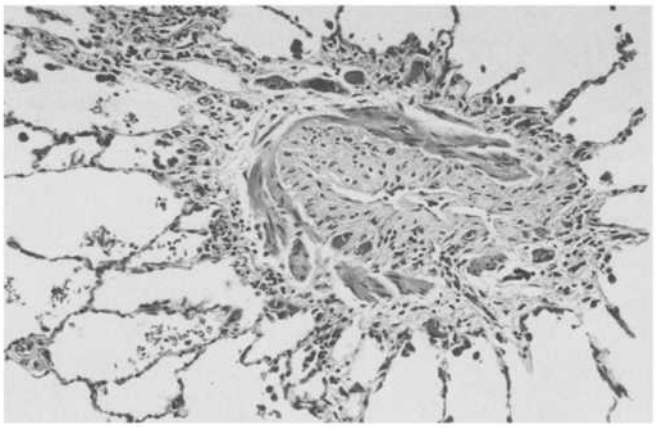


Fig. 9. Constrictive (oblierative) bronchiolitis.

- Chest X-ray usually normal; may present as interstitial infiltrates

Microscopic

- Finely granular pigmented macrophages accumulate within lumina of distal bronchioles and surrounding alveoli; mild chronic bronchiolar inflammation and fibrosis

Differential Diagnosis

- Desquamative interstitial pneumonia:
  - Diffuse accumulation of (smokers') pigmented macrophages
  - Mild interstitial fibrosis, more peripheral Langerhans'
- Eosinophilic granuloma:
  - Characteristic nodules with cells (S-100 protein +, CD1a+)
  - Peribronchiolar-based Langerhan's cells

Follicular Bronchiolitis

Clinical

- Rare small airway disease; associated with collagen vascular diseases, including Sjîgren's disease and rheumatoid arthritis, and with immunodeficiencies

*Microscopic (**Figure 8**)*

- Marked chronic inflammatory infiltrate surrounding small bronchioles; germinal centers are frequent; acute inflammatory cells within lumen can be seen

Constrictive (Obliterative) Bronchiolitis

Clinical

- Complication of lung or bone marrow transplantation; drug toxicity; connective tissue disease and idiopathic disease

*Microscopic (**Figure 9**)*

- Bronchiolar and peribronchiolar fibrosis with narrowing and eventual obliteration of the lumen; may be preceded by cellular bronchiolitis

Diffuse Panbronchiolitis

Clinical

- Seen almost exclusively in Japan; associated with HLA BW54:
  - Etiology unknown; erythromycin offers some benefit

Microscopic

- Dense peribronchiolar infiltrate with characteristic foamy macrophages within the walls of the small bronchioles

Cellular Bronchiolitis

Clinical

- Seen in association with many other lung disorders, rarely by itself

Microscopic

- Smooth muscle hypertrophy; chronic inflammatory infiltrate
- May be part of a more significant lesion not seen on biopsy

Interstitial Diseases

Acute Lung Injury

Diffuse Alveolar Damage (DAD)/Acute Interstitial Pneumonia (AIP)

Clinical

- Pathologic correlate of adult respiratory distress syndrome; acute onset of dyspnea, diffuse pulmonary infiltrates, and rapid respiratory failure
- Causes include pulmonary edema, septic shock, oxygen toxicity, drugs (including chemotherapeutics), radiation, and trauma
- Idiopathic variant is known as acute interstitial pneumonia (AIP)—Hamman-Rich syndrome

Macroscopic

- "Respirator lung"-dense, red/grey diffuse consolidation

*Microscopic (**Figure 10A,B**)*

- Temporally uniform injury
- Two phases: acute and organizing:
  - Acute: interstitial edema, Type I pneumocyte sloughing and hyaline membranes
  - Organizing: proliferating Type II pneumocytes and interstitial fibroblasts with focal airspace organization:
    - Bronchiolar epithelial necrosis, re-epithelialization, and organization within airways

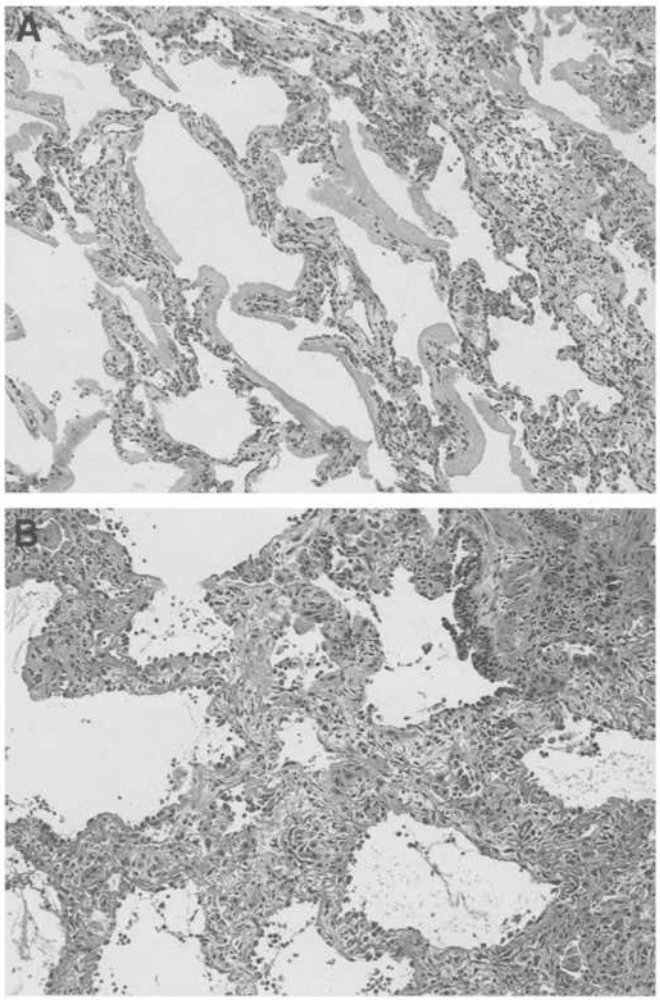


Fig. 10. Acute diffuse alveolar damage **(A,B)**.

- Acute and organizing thrombi within vessels are common

Differential Diagnosis

- ♦ Bronchiolitis obliterans organizing pneumonia:
  - More subacute clinical course
  - Process is patchy around bronchioles
  - Hyaline membranes are not seen
  - Organization is intraluminal

Cryptogenic Organizing Pneumonia (COP)/Bronchiolitis Obliterans Organizing Pneumonia (BOOP)

Clinical

- ♦ Causes include collagen vascular disease, toxic inhalants, post-infectious, bronchial obstruction, and idiopathic
- ♦ Subacute onset of cough, dyspnea, and fever; multiple patchy airspace opacities, usually bilateral, on chest X-ray
- ♦ Treated with steroids; excellent prognosis

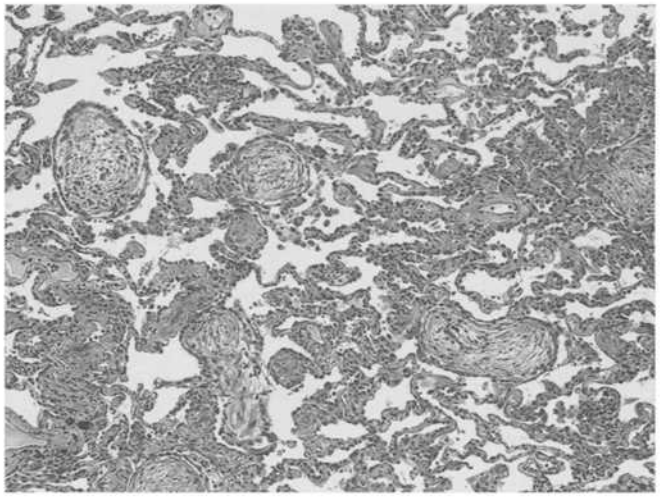


Fig. 11. Brochiolitis obliterans organizing pneumonia (BOOP).

*Microscopic **(Figure 11)***

- ♦ Temporally uniform injury
- ♦ Patchy, immature fibroblastic proliferation within bronchiolar lumina and peribronchiolar airspaces; usually sharply demarcated with adjacent normal parenchyma
- ♦ Foamy macrophages are commonly found in airspaces surrounding fibrosis
- ♦ Interstitial chronic inflammation and Type II pneumocyte hyperplasia in area of fibrosis

Differential Diagnosis

- ♦ Diffuse alveolar damage/acute interstitial pneumonia:
  - More acute clinical course
  - More diffuse process, involving both bronchioles and alveoli
  - Organizing fibrosis is interstitial
- ♦ Usual interstitial pneumonia:
  - Temporally heterogenous injury
  - Interstitial fibrosis is predominantly subpleural and paraseptal with scattered fibroblastic foci
  - Collagen deposition honeycomb foci can be found

Idiopathic Interstitial Pneumonias

Desquamative Interstitial Pneumonitis (DIP)

Clinical

- ♦ Usually middle-aged adults, 90% are smokers; insidious onset of dyspnea
- ♦ Chest X-ray: bilateral, lower lobe, ground-glass opacities
- ♦ Favorable response to corticosteroids
- ♦ Mean survival = 12 years

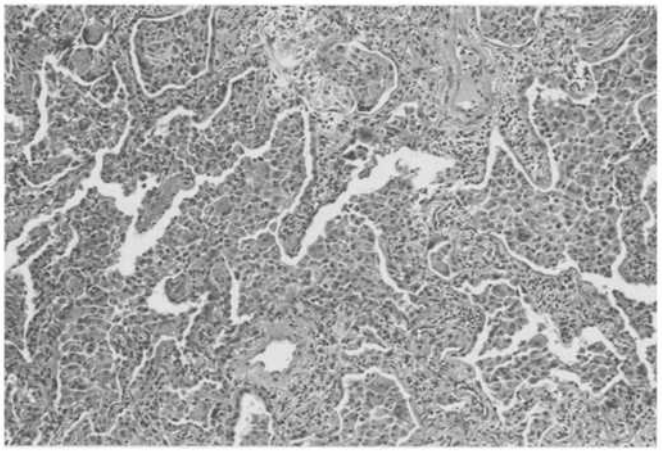


Fig. 12. Desquamative interstitial pneumonitis.

Microscopic ***(Figure 12)***

- Striking pigmented (smokers') macrophages within alveolar spaces; Type 2 pneumocyte hyperplasia with subtle interstitial fibrosis
- Diffuse process; temporally uniform

Differential Diagnosis

- DIP-like reaction of usual interstitial pneumonitis (UIP):
  - Temporally heterogeneous pattern of injury
- Eosinophilic granuloma:
  - Patchy distribution; predominantly bronchiolar
  - Tightly packed macrophages (Langerhans' cells)
  - Can be found in patients <40 years of age
- Respiratory bronchiolitis-associated interstitial lung disease:
  - No interstitial fibrosis
  - Less macrophage accumulation and more airway centered

Usual Interstitial Pneumonia (UIP)

Clinical

- Insidious onset of dyspnea with chronic, progressive downhill course
- Most patients are 40–70 years of age; collagen vascular diseases are commonly present
- 60% of patients die; mean survival = 3 years

Macroscopic ***(Figure 13A)***

- Honeycomb changes are most advanced at bases and periphery

Microscopic ***(Figure 13B,C)***

- Temporally heterogenous pattern of injury; "variegated" low power appearance; fibrosis worse in subpleural and paraseptal regions
- Infiltrate is chronic with plasma cells; germinal centers commonly seen in rheumatoid arthritis
- Most fibrosis is dense collagen; intervening fibromyxoid fibroblastic foci are seen; large, ectatic airspaces with mucin pooling usually found in more advanced areas; areas of normal lung present centrally in lobule
- Smooth muscle hypertrophy and DIP-like reaction around bronchioles is common
- Vascular changes of intimal fibroplasia and medial hypertrophy are common

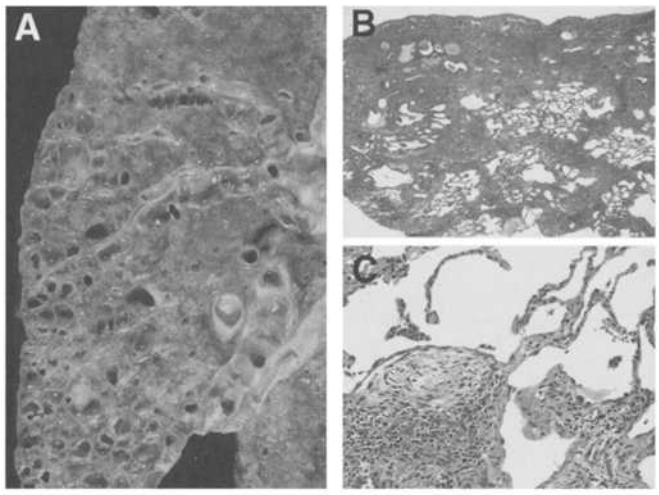


Fig. 13. Usual interstitial pneumonia with honeycomb changes **(A,B)** and fibroblastic foci **(C)**.

Differential Diagnosis

- DIP:
  - Macrophage accumulation is diffuse
  - Process is temporally uniform
- BOOP:
  - Injury is temporally uniform
  - Clinical course is subacute
  - Areas of recent organizations are more pronounced
  - Areas of dense collagen deposition are absent
- Nonspecific interstitial pneumonia:
  - Injury is temporally uniform

Non-Specific Interstitial Pneumonia/Fibrosis

Clinical

- Dyspnea and cough over several months; bilateral interstitial infiltrates on chest X-ray
- Middle-aged adults; underlying connective tissue disease is common; some probably represent hypersensitivity reactions; idiopathic
- Usually steroid responsive with good prognosis

Microscopic ***(Figure 14)***

- Two types:
  - Cellular:
    - Interstitial chronic inflammation with lymphocytes and plasma cells
    - Preserved lung architecture

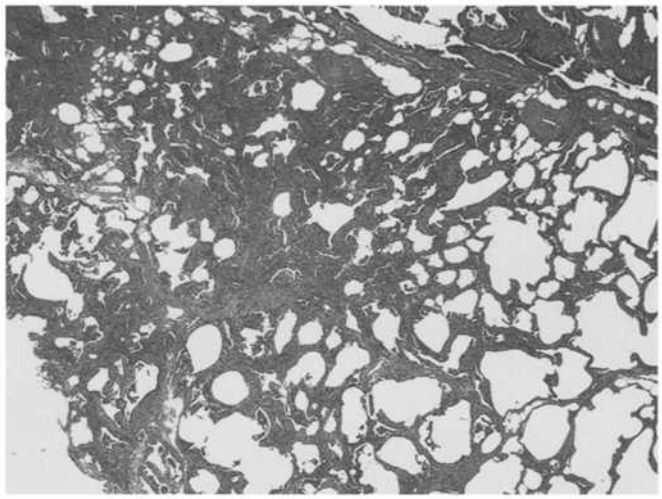


Fig. 14. Non-specific interstitial pneumonia.

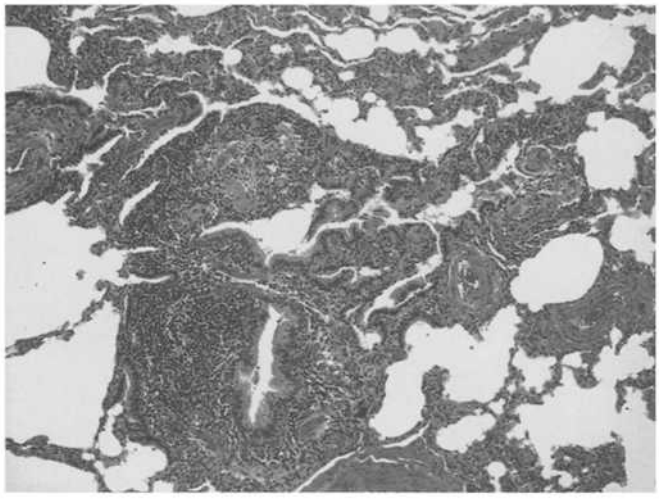


Fig. 15. Extrinsic allergic alveolitis/hypersensitivity pneumonitis.

- Fibrosing:
  - Patchy or diffuse temporally uniform interstitial fibrosis

Differential Diagnosis

- Usual interstitial pneumonia:
  - Injury is temporally heterogenous with fibroblastic foci
  - Collagen deposition and honeycomb changes are seen

Other Interstitial Diseases

Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)

Clinical

- Insidious onset of dyspnea with dry cough, fatigue, and malaise
- Exposure source not identified in 2/3 of cases diagnosed by pathology; diffuse interstitial infiltrates on chest X-ray
- Corticosteroids help after exposure has been eliminated

*Microscopic (**Figure 15**)*

- Triad of features: interstitial pneumonitis; bronchiolitis with areas of organiziation (BOOP) and ill-formed, nonecrotizing granulomas or giant cells in parenchyma

Differential Diagnosis

- Usual interstitial pneumonia:
  - Injury is temporally heterogenous with fibroblastic foci
  - Granulomas usually not seen
- Sarcoidosis:
  - Rarely has interstitial pneumonia
  - Granulomas are well-formed in lymphatic distribution
- Lymphoid interstitial pneumonia:
  - Pathology is more diffusely distributed
  - Does not have areas of BOOP
  - Granulomas not seen

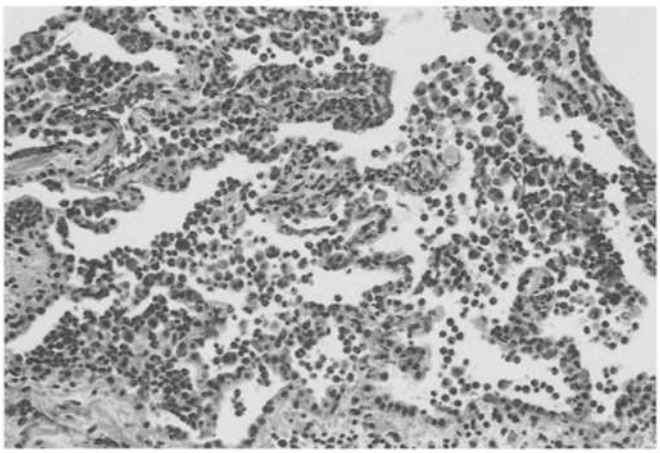


Fig. 16. Eosinophilic pneumonia.

Eosinophilic Pneumonia

Clinical

- Four clinical categories:
  - *Simple:* Loeffler's syndrome; mild; self-limiting
  - *Tropical:* found in tropics due to filarial infestation
  - *Acute:* acute, febrile illness with respiratory failure; unknown etiology
  - *Chronic:* subacute illness; blood eosinophilia; F > M; patchy, peripheral infiltrate (photographic negative of pulmonary edema); etiologic agents: drugs, fungal hypersensitivity, parasites, and idiopathic inhalants

*Microscopic (**Figure 16**)*

- Filling of alveolar spaces with eosinophils and variable number of macrophages

- Eosinophilic abscesses and necrosis of cellular infiltrate; BOOP is common
- Features of DAD have been seen in acute form; mild, nonnecrotizing vasculitis of small arterioles and venules common

Differential Diagnosis

- Churg-Strauss disease:
  - Necrotizing granulomatous vasculitis is present
- Eosinophilic granuloma:
  - Infiltrate is interstitial and usually peribronchiolar
  - Seen only in smokers
- DIP:
  - Eosinophilic abscesses and necrosis of infiltrate rarely seen
  - Vasculitis not seen

Eosinophilic Granuloma (Pulmonary Histiocytosis-X/Langerhans' Cell Granulomatosis)

Clinical

- Occurs almost exclusively in smokers; M : F = 4 : 1; symptoms may be minimal; 4th decade
- Chest X-ray: multiple, bilateral nodules 0.5–1.0 cm in upper lung lobes with cystic lesions

*Microscopic **(Figure 17A,B)***

- Discrete, nodular/stellate lesions; bronchiolocentric
- Langerhans cell: convoluted (kidney-bean) nuclei

Immunohistochemistry

- S100+, CDla+, HLR-DR+

Electron Microscopy

- Birbeck granule ("tennis racket" morphology)

Differential Diagnosis

- Respiratory bronchiolitis-associated interstitial lung disease:
  - Does not destroy bronchiole
  - Minimal fibrosis
  - No Langerhans cells

Sarcoidosis

Clinical

- Most common in young, black female (20–35 years)
- Deficient T cell response (cutaneous T cell anergy and decreased helper T cells)
- Associations: functional hypoparathyroidism; hyper-calciuria – hypercalcemia; erythema nodosum; uveitis
- Kveim test: granulomatous reaction following injection of human spleen extract
- Serum ACE (angiotensin converting enzyme)

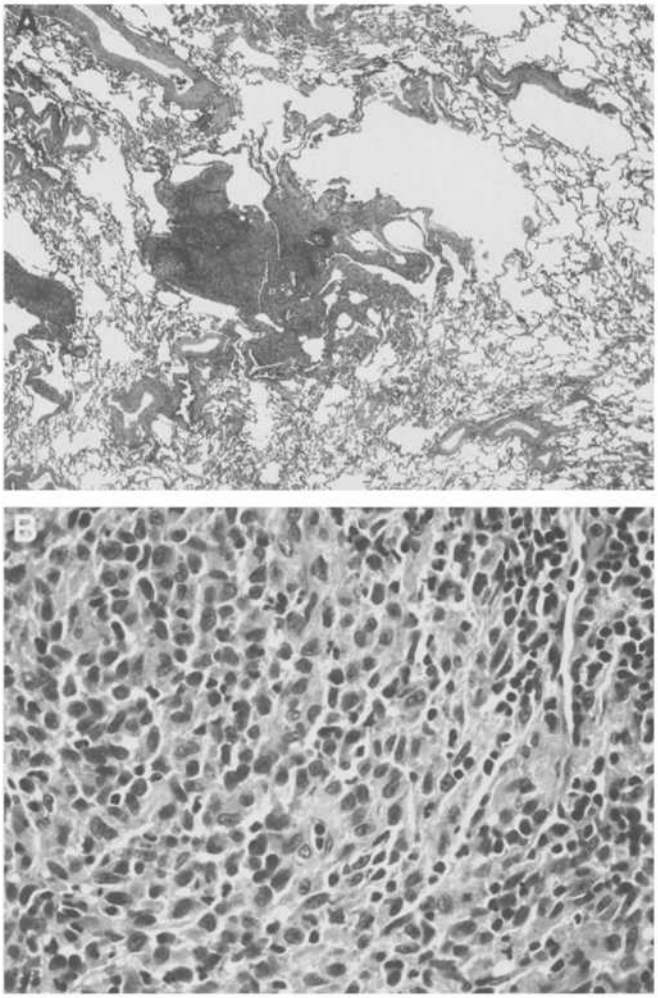


Fig. 17. Pulmonary histiocytosis-X (eosinophilic granuloma) **(A,B)**.

- Radiologic stage:
  - Stage 0: normal chest X-ray
  - Stage 1: hilar/mediastinal adenopathy
  - Stage 2: hilar/mediastinal adenopathy + interstitial pulmonary infiltrate
  - Stage 3: interstitial pulmonary infiltrate only
  - Stage 4: endstage fibrosis with honeycombing

*Microscopic **(Figure 18)***

- Interstitial noncaseating granulomata distributed in lymphatic pathways; vascular and pleural involvement common

Differential Diagnosis

- Chronic berylliosis:
  - Elevated beryllium levels on tissue quantitation
  - Clinical history of beryllium exposure



Fig. 18. Sarcoidosis.

- Extrinsic allergic alveolitis:
  - Ill-formed granulomata; interstitial distribution
  - Accompanying interstitial pneumonia

Pulmonary Alveolar Proteinosis

Clinical Features

- Defect in alveolar macrophage (GM-CSF knockout mice)
- Etiologies: dust, drugs, immunodeficiency, leukemia, kaolin, idiopathic
- Bronchoalveolar lavage: treatment of choice
- Idiopathic or associated with infection

Microscopic ***(Figure 19)***

- Accumulation of granular eosinophilic material in alveoli; PAS+ material

Electron Microscopy

- Lamellar body

Differential Diagnosis

- Pulmonary edema:
  - Interstitial/septal edema
- Mycobacterial, nocardial, or *Pneumocystis carinii* pneumonia:
  - + special stains or microbiologic cultures

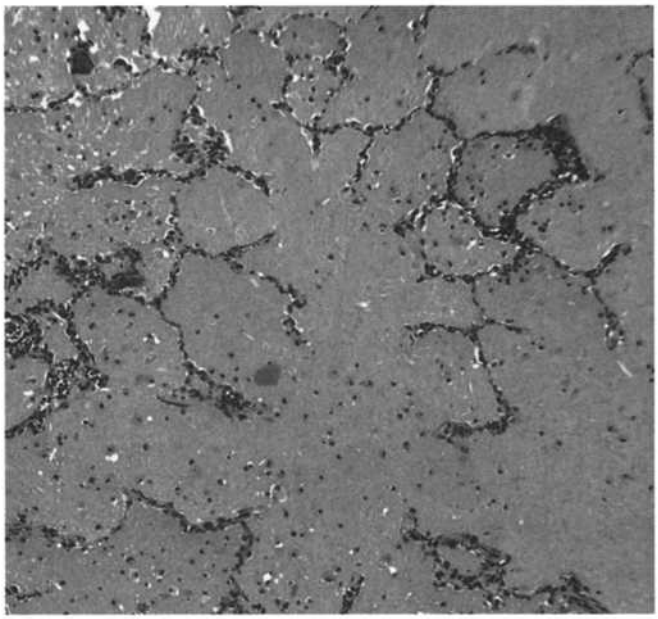


Fig. 19. Pulmonary alveolar proteinosis.

Lymphangio(leio)myomatosis

Clinical

- Occurs exclusively in women of reproductive years
- Progressive dyspnea, chylous pleural effusions, recurrent pneumothoraces
- Chest X-ray: enlarged lungs; can show cystic or "honeycomb" changes
- Found in patients with tuberous sclerosis

Macroscopic ***(Figure 20A)***

- Randomly distributed cystic airspaces with thin walls

Microscopic ***(Figure 20B)***

- Haphazard proliferation of smooth muscle in lymphatics, blood vessels, bronchioles, and alveolar septa
- Hemosiderin-laden macrophages accumulate in the alveoli, especially in the subpleura

Immunohistochemistry

- HMB-45+

Differential Diagnosis

- Benign metastasizing leiomyoma:
  - Discrete nodules, some contain entrapped pulmonary epithelium
- UIP with end-stage changes:
  - Small lungs, lower lobe predominant
  - Chronic inflammatory changes and fibrosis
  - Older age group; men and women

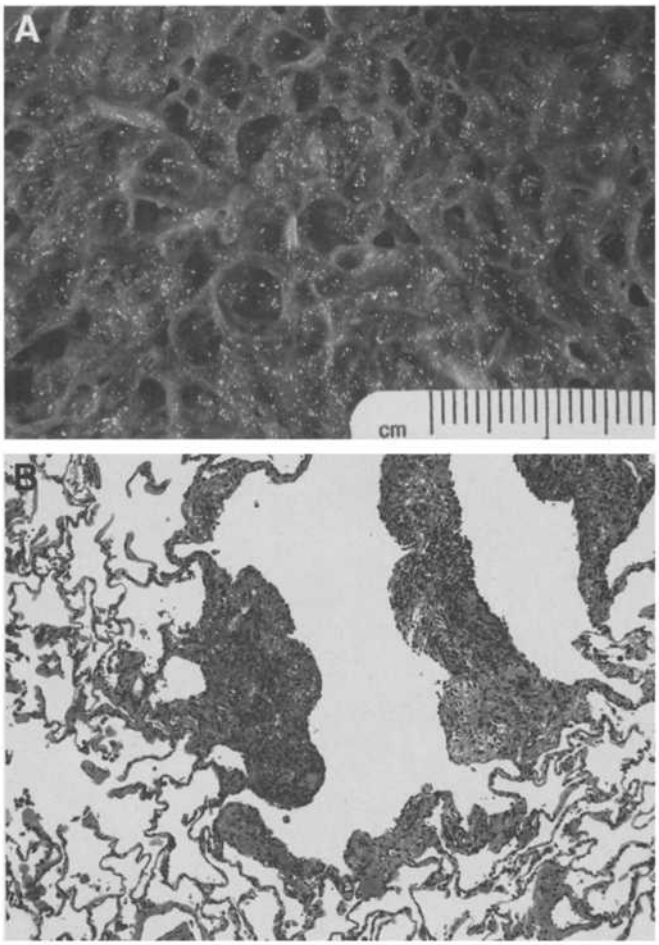


Fig. 20. Lymphangioleiomyomatosis **(A,B)**.

Goodpasture's Disease (Anti-Basement Membrane Antibody Disease [ABMA])

Clinical

- M : F = 9 : 1; young adults; smokers; DRw15, DQw6
- Cytotoxic, antibody-mediated, immune reaction; antibodies to basement membrane in serum cross react to both kidney and lung
- Hemoptysis, anemia, azotemia, and diffuse lung infiltrates

Microscopic

- Capillaritis can be seen, but no large vessel vasculitis
- Extensive intraalveolar hemorrhage; nonspecific Type II pneumocyte hyperplasia

Immunofluorescence

- Linear staining of glomerular and pulmonary basement membranes for IgG

Differential Diagnosis

- Idiopathic pulmonary hemosiderosis:
  - Child and adolescent
  - Immunofluorescent linear pattern is absent
  - No acute hemorrhage

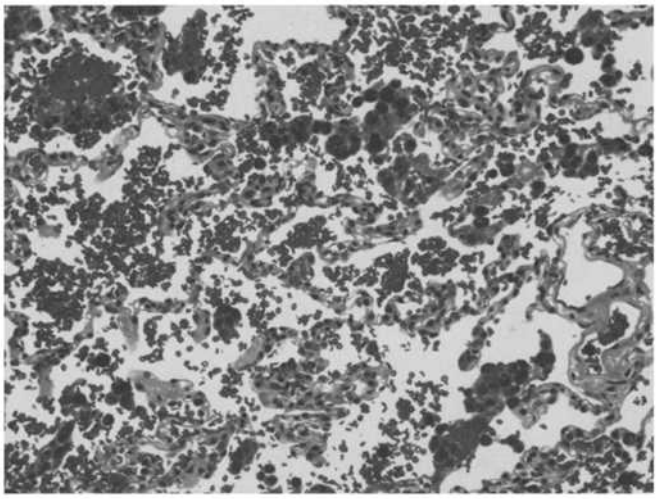


Fig. 21. Idiopathic pulmonary hemosiderosis.

Idiopathic Pulmonary Hemosiderosis

Clinical

- Exclusively in children <16 years; M : F = 1 : 1
- Hemoptysis, chest infiltrates; iron deficiency anemia

Microscopic ***(Figure 21)***

- Intraalveolar hemosiderosis without capillaritis; alveolar wall thickening and Type II pneumocyte hyperplasia

Differential Diagnosis

- Goodpasture's Disease:
  - Linear immunofluorescence pattern (IgG)
  - Kidney involvement

Pneumoconioses

- A non-neoplastic reaction of the lungs to inhaled mineral or organic dust

Silicosis

Clinical

- Reaction in lung to inhaled crystalline silica: stonecutting, quarry work, or sandblasting
- 0.5–2 micron fibers: most fibrogenic
- Predisposed toward tuberculosis (TB)

Macroscopic

- Firm, discrete, rounded lesions with variable amounts of black pigment
- Nodules in lymphatic distribution: around broncho-vascular bundles, in subpleural and interseptal areas

Microscopic ***(Figure 22)***

- Discrete foci of concentric layers of hyalinized collagen; dust-filled histiocytes are abundant; birefringent particles usually present

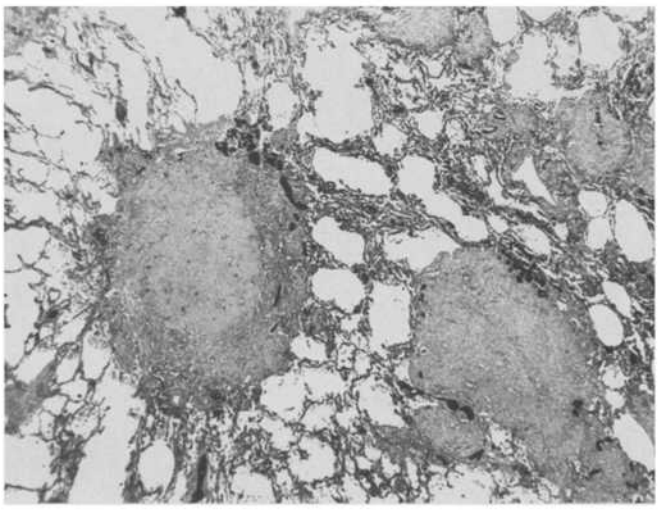


Fig. 22. Silicotic nodule.

- When necrosis is present, consider complicating infection by myobacterial tuberculosis

Differential Diagnosis

- Inactive mycobacterial or fungal infections:
  - Giant cells and palisading histiocytes usually seen
- Hyalinizing pulmonary granuloma:
  - Collagen bundles are disorganized
  - Birefringent material is unusual

Asbestos-Related Reactions

Clinical

- Reactions of the lung to asbestos with accompanying cations (i.e., iron, calcium, magnesium, sodium); serpentine and amphibole are the most common types
- Fibrosis occurs 15–20 years after exposure and can progress after exposure stops

Macroscopic

- Firm, fibrotic lungs with areas of honeycomb change

Microscopic ***(Figure 23)***

- Marked interstitial fibrosis with minimal inflammatory infiltrate; UIP-like reactions common
- The presence of asbestos bodies, fibrosis, and exposure history are needed for definitive diagnosis
- Hyalinizing pleural plaques, pleural fibrosis, and rounded atelectasis can also be seen

Differential Diagnosis

- Usual interstitial pneumonia:
  - Temporally heterogenous
  - Lack of asbestos bodies

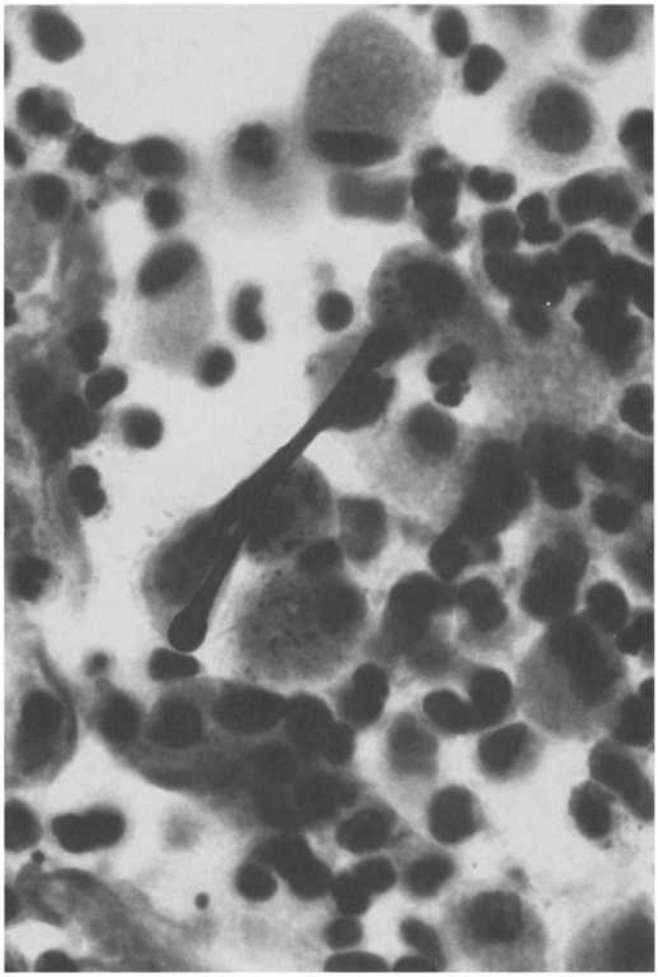


Fig. 23. Asbestos-related reactions—ferrugninous body.

Coal Worker's Pneumoconiosis (CWP)

Clinical

- Simple: single nodule, <2 cm
- Complicated: >2 cm, including progressive massive fibrosis
- Caplan's syndrome: rheumatoid nodule with CWP (progressive massive fibrosis)

Macroscopic ***(Figure 24A)***

- Dense fibrosis and anthracosis, predominantly upper and middle lobes.

Microscopic ***(Figure 24B)***

- Hyalinized nodule with anthracotic pigment in lung and lymph nodes
- Macules adjacent to bronchioles; may have centrilobular emphysema

Hard Metal Pneumoconiosis

Clinical

- Exposure to tungsten carbide and cobalt, usually in grinding, drilling, cutting, or sharpening
- Dyspnea with restrictive pulmonary function tests

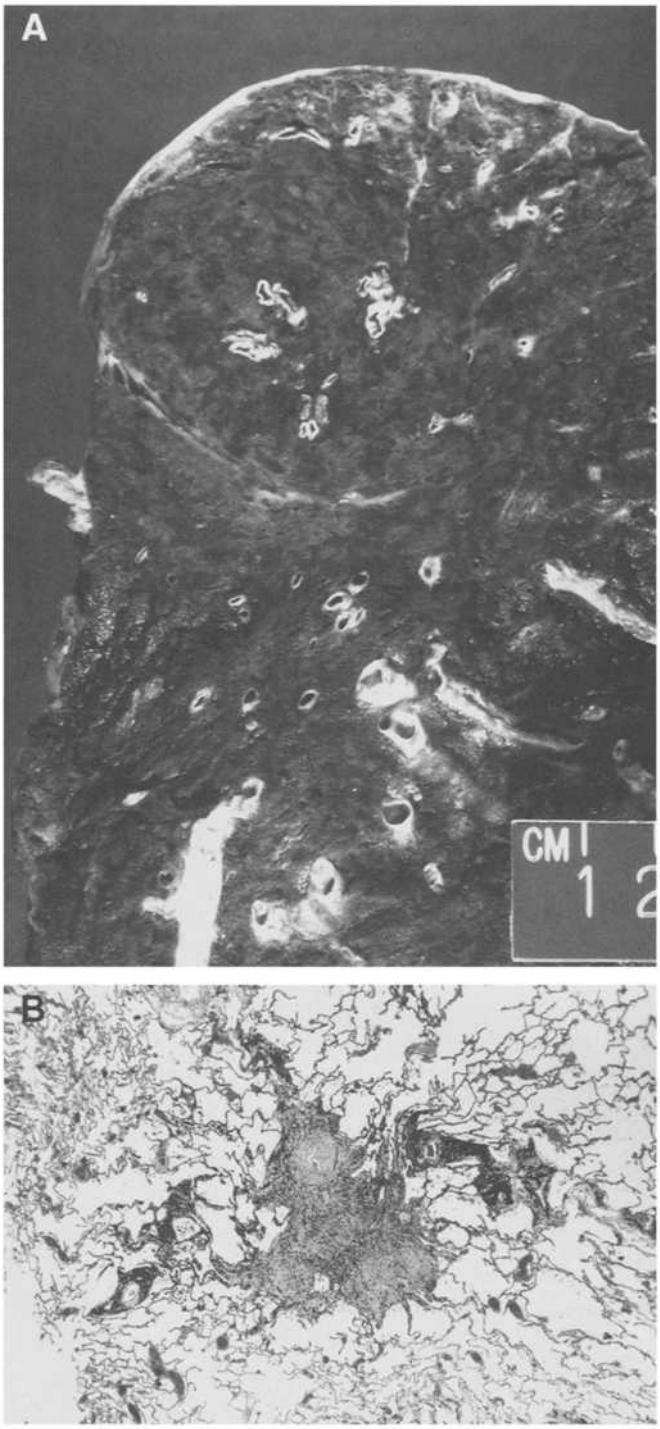


Fig. 24. Progressive massive fibrosis/Coal worker's pneumonconiosis (**A,B**).

Microscopic ***(Figure 25)***

- Giant cell interstitial pneumonitis with interstitial fibrosis, peribronchiolar giant cells, and DIP-like reaction
- Giant cells are multinucleated and commonly engulf other inflammatory cells

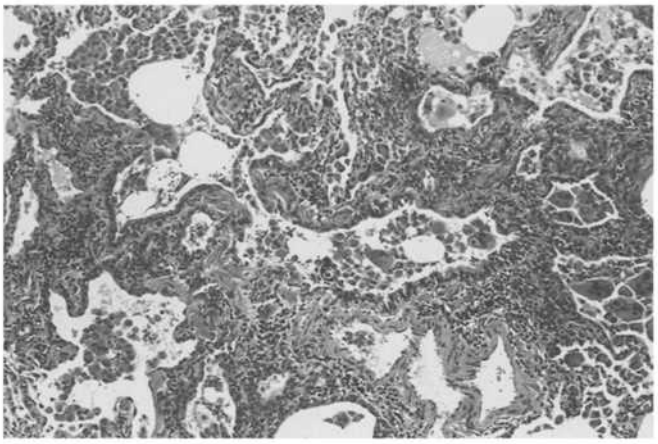


Fig. 25. Hard metal pneuomoconiosis/giant cell pneumonitis.

Differential Diagnosis

- Viral bronchiolitis/pneumonitis:
  - No history of tungsten carbide/cobalt exposure
- Hypersensitivity pneumonitis:
  - Increased interstitial and peribronchiolar inflammatory infiltrate
  - Non-necrotizing granulomas

Berylliosis

Clinical

- Acute: Massive exposures produce ARDS like picture
- Chronic: Progressive dyspnea and cough with imaging studies similar to sarcoidosis; may progress to interstitial fibrosis

Macroscopic

- Nodules (up to 2 cm) with associated emphysema

Microscopic

- Non-necrotizing granulomas in a lymphatic distribution

Differential Diagnosis

- Sarcoidosis: No history of beryllium exposure

Vascular Conditions

VASCULITIDES (ALSO SEE CHAPTER 16)

Wegener's Granulomatosis

Clinical

- Triad: upper airway, lower airway (lung), and kidney; saddle nose; rarely lung only (so called "limited")
- 40% c-ANCA+ (anti-proteinase 3) in remission; 90% c-ANCA+ in active disease
- Chest X-ray: multiple well-demarcated peripheral nodules, lower lobes, rarely as a solitary pulmonary lobule

Microscopic ***(Figure 26A,B)***

- Triad: parenchymal (basophilic) necrosis, vasculitis, granulomatous inflammation

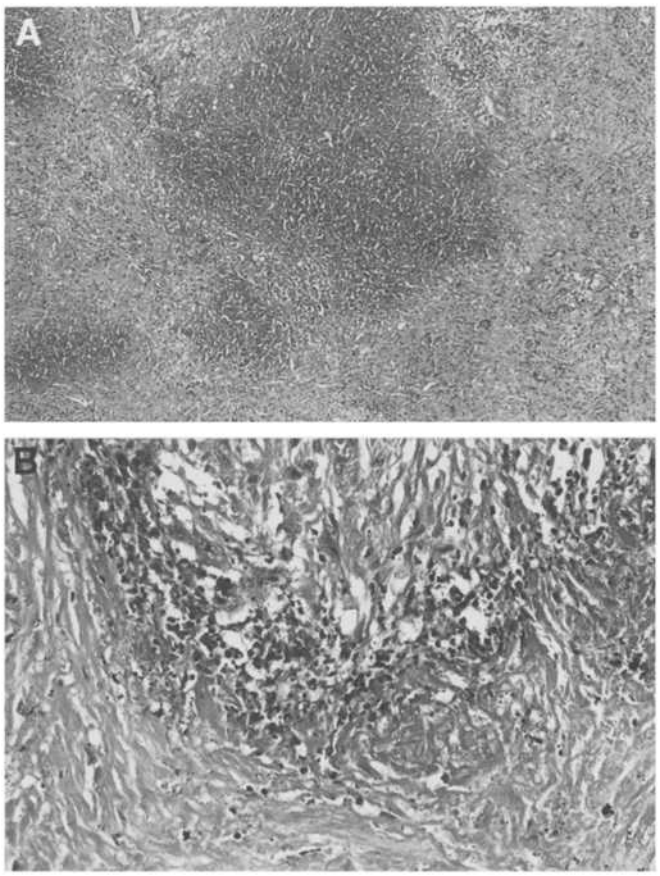


Fig. 26. Wegener's granulomatosis: **(A)** eographic necrosis; **(B)** collagenous necrosis.

- Variants: eosinophil rich, bronchiolocentric, solitary, capillaritis, and diffuse pulmonary hemorrhage
- Parenchymal necrosis may be in form of microabscesses or geographic necrosis
- Vasculitis may affect arteries, veins, or capillaries

Differential Diagnosis ***(Table 1)***

- Lymphomatoid granulomatosis:
  - Atypical cytology
- Granulomatous infections:
  - Well-formed, non-necrotizing granulomas
  - Eosinophilic necrosis

Churg-Strauss Syndrome (Allergic Angiitis Granulomatosis)

Clinical

- Asthma, eosinophilia, systemic vasculitis, mono- or polyneuropathy
- Nonfixed lung infiltrate, paranasal sinus abnormalities; p-ANCA+

Microscopic

- Eosinophilic infiltrates, granulomatous inflammation, and necrotizing vasculitis

Differential Diagnosis ***(Table 1)***

- Chronic eosinophilic pneumonia:
  - Nongranulomatous
- Allergic bronchopulmonary aspergillosis:
  - Bronchocentric
- Drug-induced vasculitis
- Polyarteritis nodosa:
  - Rarely involves the lung
- Wegener's granulomatosis:
  - Geographic necrosis

Necrotizing Sarcoid Granulomatosis (NSG)

Clinical

- F : M = 4 : 1; variable age presentation; cough, chest pain, weight loss, fever
- No systemic vasculitis
- Chest X-ray: bilateral lung nodules – hilar adenopathy

Microscopic

- Lymphoplasmacytic or granulomatous vasculitis; parenchymal necrosis without necrotizing vasculitis; numerous caseating sarcoid-like granulomas

Differential Diagnosis ***(Table 1)***

- Wegener's granulomatosis:
  - No sarcoidal granulomas
- Infection:
  - Vasculitis not prominent component
  - + organismal stains
- Churg-Strauss syndrome (allergic angiitis granulomatosis):
  - No hilar adenopathy
  - History of asthma
  - Peripheral eosinophilia

Necrotizing Capillaritis

Clinical

- Associated conditions: collagen vascular disease, especially systemic lupus eryhthematosis; Wegener's; Henoch-Schonlein purpura, cryoglobulinemia, Behcet's disease, drug reactions (sulfonamides), and Good-pasture's disease

Microscopic ***(Figure 27)***

- Focal necrosis of alveolar septa with neutrophilic infiltration, capillary fibrin thrombi, and interstitial hemorrhage/hemosiderosis
- Often associated with foci of DAD

Differential Diagnosis

- Acute hemorrhagic bronchopneumonia:
  - Neutrophils predominate in alveolar space

Table 1. Differential Diagnosis of Granulomatous Lesions

	*NSG**	*Wegener's*	*Infection*	*Churg-Strauss Syndrome*
Sarcoidal granuloma	++	–	++	+
Vasculitis	++	++	±	++
Necrosis	++	++	++	++
Hilar Adenopathy	±	–	++	–
Cavitation	+	++	+	++
Asthma/peripheral eosinophilia	–	–	–	+

** NSG: Necrotizing Sarcoid Granulomatosis.*

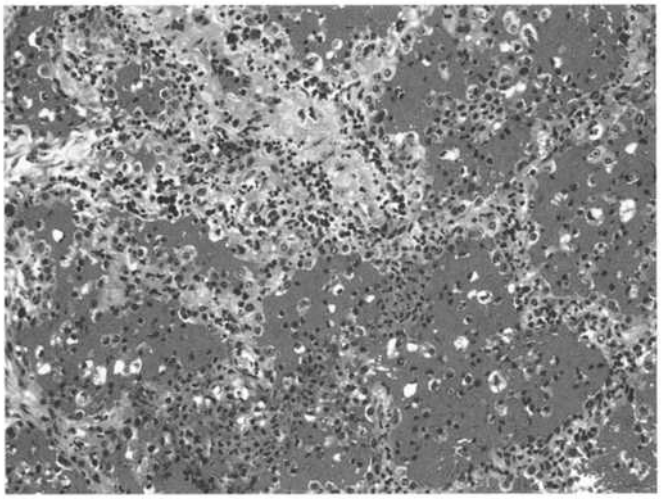


Fig. 27. Necrotizing capillaritis.

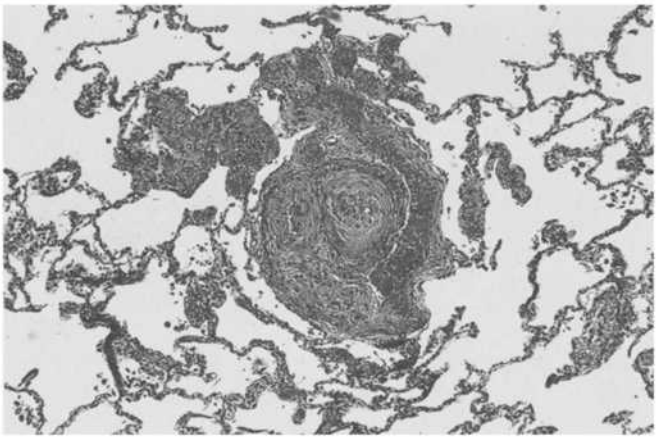


Fig. 28. Pulmonary hypertension plexogenic arteriopathy.

Pulmonary Hypertension

Plexogenic Arteriopathy

Clinical

- Congenital cardiac shunts
- Primary pulmonary hypertension (young female predominant)
- Aminorex fumarate
- Rare cases associated with cirrhosis of the liver
- Rare cases associated with portal vein thrombosis
- Rare cases associated with + HIV infection

Microscopic ***(Figure 28)***

- Grade 1: muscularization of pulmonary arteries
- Grade 2: cellular intimal proliferation
- Grade 3: intimal concentric laminar fibrosis
- Grade 4: plexiform lesions
- Grade 5: plexiform and angiomatoid lesions
- Grade 6: necrotizing arteritis (may actually precede Grades 4 and 5 developmentally)

Pulmonary Veno-Occlusive Disease with Secondary Pulmonary Arterial Hypertension

Clinical

- Rare form of pulmonary hypertension; 1/3 of all cases occur in children
- Causes include drug toxicity, especially chemotherapeutics, possibly viral etiology

Microscopic ***(Figure 29)***

- Congestive changes with hemosiderin-laden macrophages
- Pulmonary hypertensive changes
- Intimal fibrosis and thrombosis of veins; recanalization is common

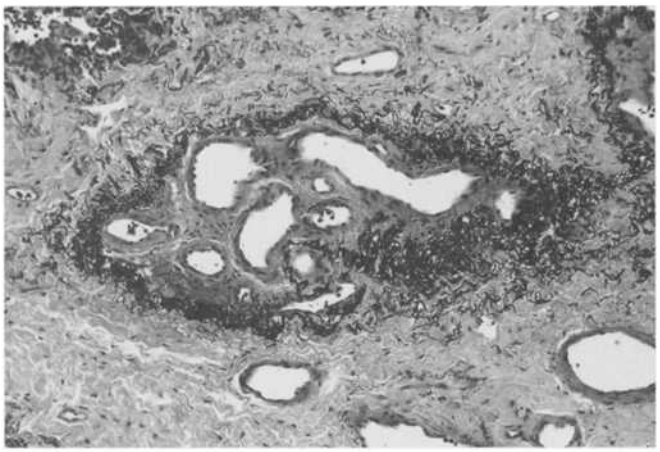


Fig. 29. Pulmonary veno-occlusive disease (PVOD).

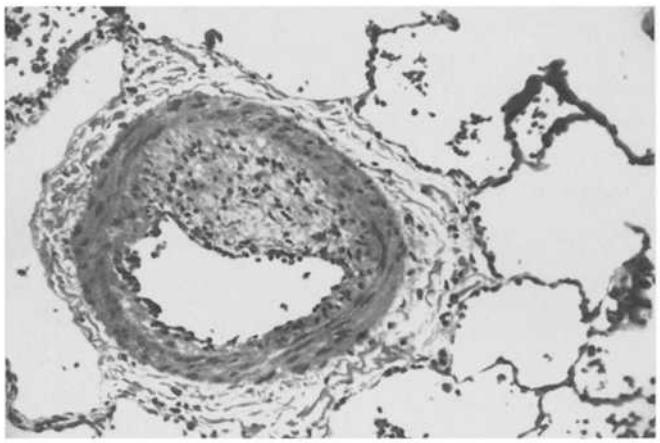


Fig. 30. Thrombotic arteriopathy.

Thrombotic Arteriopathy: Pulmonary Infarction

Microscopic ***(Figure 30)***

- Eccentric intimal fibrosis; collander lesions common; widespread small vessel thrombi
- Plexigenic lesions are rarely found (probably represents plexogenic arteriopathy with superimposed thrombi)

Clinical

- Sudden shortness of breath with pleuritic pain

Macroscopic ***(Figure 31)***

- Hemorrhagic wedge-shaped peripheral lesion

Microscopic

- Ischemic necrosis and surrounding areas of organization and hemosiderin pigment

Differential Diagnosis

- Necrotizing pneumonia



Fig. 31. Pulmonary infarction.

Pulmonary Capillary Hemangiomatosis

Clinical

- Rare cause of pulmonary hypertension; most patients between 20–40 years of age

Microscopic

- Proliferation of capillaries in interstitium; patchy hemosiderin

Infections (also see Chapter 5)

VIRAL

Cytomegalovirus

Clinical

- Found almost exclusively in immunocompromised patients

Microscopic ***(Figure 32)***

- Diffuse interstitial pneumonitis and nodular (miliary) pneumonia; diffuse alveolar damage
- Cytopathic changes include cytomegaly (2–3 times normal cell); ampholic/basophilic nuclear inclusions; basophilic cytoplasmic inclusions
- Inclusions found in pneumocytes; histiocytes and endothelial cells; PAS+; Grocott+

Differential Diagnosis

- Herpes viral pneumonia:
  - Necrotizing pneumonia
  - Cowdry Type A nuclear inclusions
- Adenoviral pneumonia:
  - No cytoplasmic inclusions
  - Smudge cells (nuclear inclusions)

Herpes Simplex Virus

Clinical

- Bloodborne or airborne dissemination; immunocom-promised patient, inhalation injuries and chronic obstructive pulmonary disease patient
- Laryngotracheobronchitis, bronchopneumonia

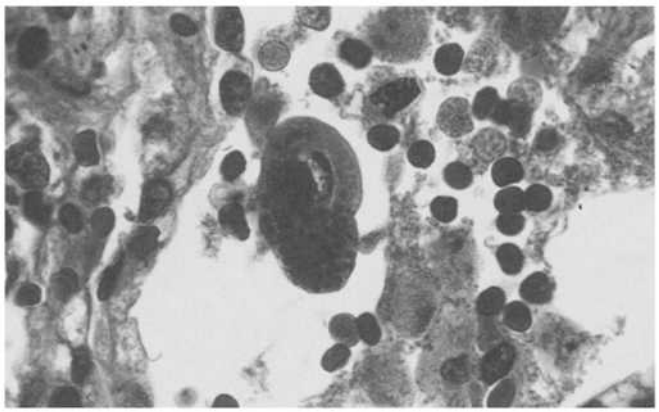


Fig. 32. Cytomegalovirus (CMV) inclusion in alveolar macrophage.

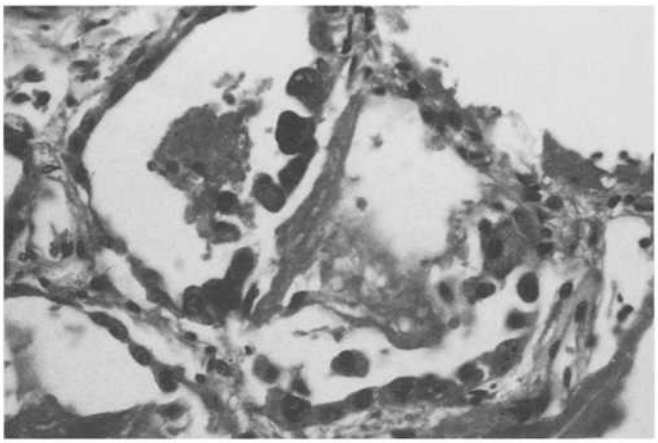


Fig. 33. Adenovirus infection.

Microscopic

- Miliary foci of necrosis
- Cytopathic changes: may be difficult to find in lung; mild nucleomegaly (1.25–1.5 times normal cell); dispersion of nuclear chromatin; condensation of nuclear chromatin on nuclear membrane
- Cowdry type A inclusions: intranuclear viral particles that coalesce
- Multinucleation may be absent in lung
- Epithelial cells mainly affected

Differential Diagnosis

- Cytomegalovirus pneumonia:
  - Affects both epithelial and mesenchymal cells
  - Cytoplasmic inclusions

Measles Virus

Clinical

- Immunocompromised patient

Microscopic

- Diffuse alveolar damage and acute necrotizing bronchopneumonia; multinucleated cells (5–20 nuclei/cell); intranuclear and intracytoplasmic inclusions present (Feulgen–)
- Warthin-Finkeldey cell with lymphoid hyperplasia: CD4+ T cells

Differential Diagnosis

- Giant cell interstitial pneumonitis/hard metal pneumoconiosis
  - Acute lung injury usually not present
  - Giant cells with 2–5 nuclei

Adenovirus

Clinical

- Generally found in children; can cause fulminent pneumonia in immunosuppressed

Microscopic ***(Figure 33)***

- Destruction of bronchioles with sloughing
- Cytopathic changes: smudge-Feulgen+ round eosinophilic intranuclear inclusions

Electron Microscopy

- Lattice-like hexagonal viral particle

Respiratory Syncytial Virus

Clinical

- Usually seen in babies and young children; diagnosis usually made by serologies

Microscopic

- Cellular, lymphocytic bronchiolitis with intraluminal polymorphonuclear leucocytes
- Metaplastic bronchial epithelium; can show multinucleation
- Cytopathic effect: small, inconspicuous eosinophilic cytoplasmic inclusions in bronchiolar cells

Epstein-Barr Virus

Clinical

- Biopsy rarely performed for diagnosis; 10% of patients with mononucleosis show clinical symptoms of respiratory infection

Microscopic

- Perivascular (especially perivenular) chronic inflammation with plasmacytoid and/or immunoblastic features, cellular bronchiolitis, and interstitial infiltrates

Hantavirus Pulmonary Syndrome

Clinical

- Young, healthy adults; rapidly fatal; progressive pulmonary edema and hemorrhage
- Host: deer mice

Microscopic ***(Figure 34)***

- Pulmonary edema and pleural effusions; early DAD

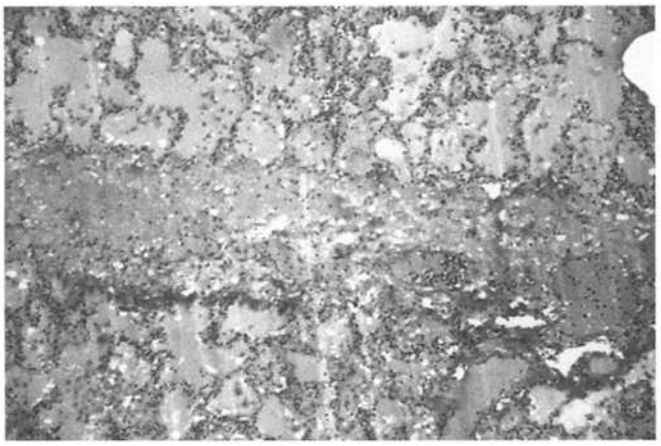


Fig. 34. Hantavirus pulmonary syndrome.

Clinical

- Diagnosis usually made by culture or serologies; biopsy rarely done for diagnosis

Bacteria

Legionnaires' Disease

Clinical

- First recognized in large outbreak in American Legion convention in Philadelphia
- Acute pneumonic process with high fever, cough, chill and chest pain; gastrointestinal symptoms are prominent; renal failure is common
- Renal and bone marrow transplant patients at high risk

Microscopic ***(Figure 35A,B)***

- Acute bronchopneumonia with characteristic intraalveolar exudate of neutrophils, macrophages, and karyorrhectic debris

Special Studies

- Small, pleomorphic Gram–bacillus; cultured in modified Mueller-Hinton agar
- Dieterle's silver stain best for visualizing organism; fluorescent studies of smears and scrapes are most sensitive for diagnosis

Nocardiosis

Clinical

- Localized abscess or miliary bilateral infection (common) in immunocompromised host

Microscopic

- Mixture of acute and chronic inflammation with microabscess formation
- Silver stain is best for diagnosis: fine, filamentous organisms—may be very difficult to find
- Weakly acid-fast (Fite's stain) and Gram+

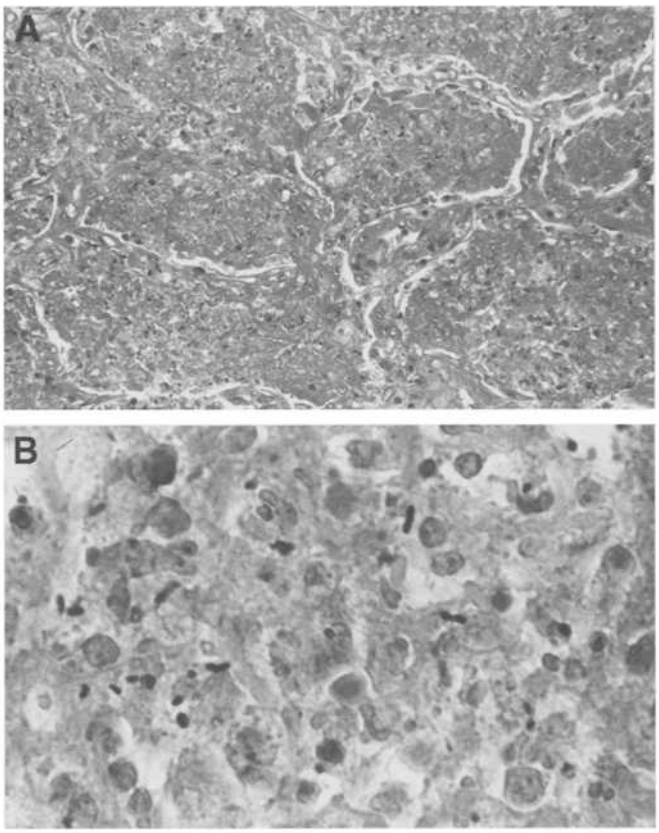


Fig. 35. Legionnaires' disease **(A)**. The organisms are highlighted by Dieterle stain **(B)**.

Actinomycosis

Clinical

- Aspiration of oral or tonsillar organisms; patients with poor dentition or repeated tonsillitis
- May present like carcinoma

Microscopic ***(Figure 36)***

- Abscess in lung or mediastinum; sulphur granules found with palisading eosinophilic proteinaceous halo—Splendore-Hoeppli reaction

Malakoplakia

Clinical

- Nodular lesions in immunocompromised patients, particularly HIV-infected individuals; *Rhodococcus equi* is common etiologic agent

Microscopic

- Chronic infiltrate with plasma cells and lymphocytes with sheets of histiocytes containing abundant Michaelis-Gutmann bodies

Mycobacterial Tuberculosis (TB)

Clinical

- High risk factors include elderly, immigrants, lower socioeconomic groups, aboriginal races, HIV infection,

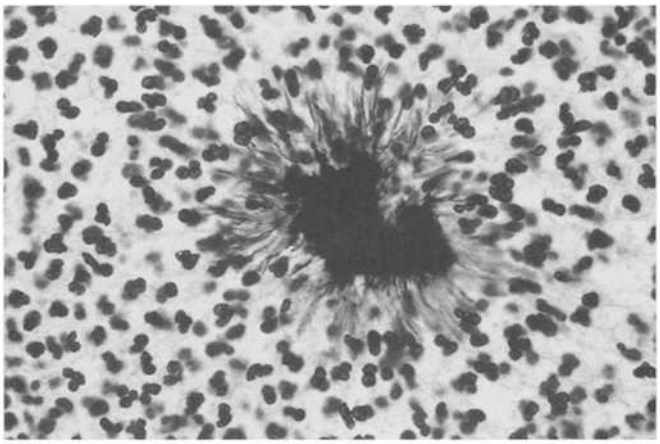


Fig. 36. Actinomyces Gram stain.

silicosis, immunosuppressive therapies, diabetes mellitus, hemodialysis, gastrectomy, nutritional deficiency, IV drug abuse, and organ transplantation

- Clinical classification:
  - Primary TB: exogenous first infection; usually self-limiting
  - Progressive TB: inadequate acquired immunity (infants or elderly); progression of original infection; <10% of patients
  - Postprimary TB (reactivation;secondary): endogenous reactivation

Macroscopic ***(Figure 37A)***

- Primary TB:
  - Ghon focus: single subpleural nodule, above or below interlobar fissure and enlarged hilar caseous lymph nodes
- Progressive TB:
  - Cavitation and progression of initial or reactivation nodule; consolidation or miliary spread can occur
- Postprimary TB:
  - Apical lesion (due to higher oxygen tension); miliary spread can occur

Microscopic ***(Figure 37B)***

- Primary/postprimary TB:
  - Necrotizing granulomatous inflammation, airway-based; nonnecrotizing granulomas commonly present away from main mass
- Progressive TB:
  - Necrotizing granulomatous inflammation with cavitation and spread throughout lung; pleura commonly involved

Non-Tuberculous Mycobacteria

- Most common are *Mycobacterium avium* complex (*M. intracellulare* and *M. avium*) and *M. kansasii*



Fig. 37. Mycobacterial tuberculosis. **(A)** apical cavitary lesion; **(B)** Mycobacterial necronizing granuloma.

Clinical

- Opportunistic infections in HIV-infected patients
- Other risk factors include COPD, bronchiectasis, and pneumoconioses
- Also found in patients without underlying lung disease (non-smoking women): more benign course

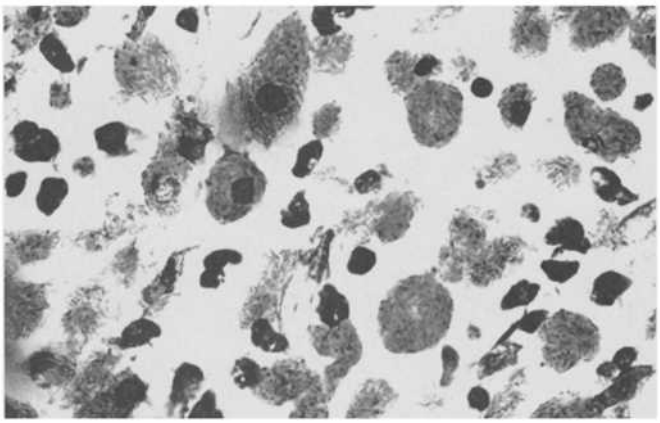


Fig. 38. Mycobacterium avium complex (MAI) in an AIDS patient.

Macroscopic

- Can cause upper lobe cavitary lesion
- Non-cavitating form may be associated with local bronchiectasis

Microscopic

- Necrotizing granulomatous inflammation most common, with nonnecrotizing granulomas present
- Organizing pneumonia and nonnecrotizing granulomas can be seen

Special Studies

- Ziehl-Neelsen stain for acid fast organisms **(Figure 38)**
- Auramine-rhodamine more sensitive

Differential Diagnosis

- Wegener's granulomatosis **(Table 1)**:
  - No sarcoidal-like granulomas
  - Basophilic necrosis
- Necrotizing fungal infections:
  - Results of special stains and microbiologic cultures+

Mycoplasma Pneumoniae

Clinical

- Community-acquired pneumonia; dry cough with subacute course

Microscopic

- Cellular bronchiolitis with acute and chronic inflammation; plasma cells may be abundant
- Metaplastic bronchiolar epithelium without cilia; organism destroys cilia

Special Studies

- Complement fixation tests used for diagnosis; four-fold titer increase is diagnostic of infection
- Stains on Giemsa stain; DNA probe is best way to find organisms in tissue

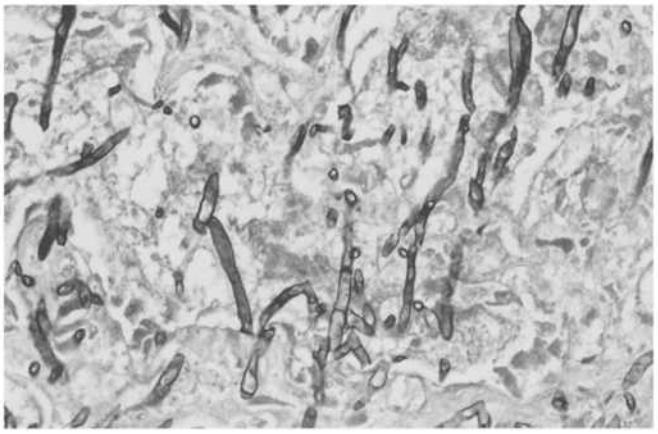


Fig. 39. Aspergillus fungal hyphae, silver stain.

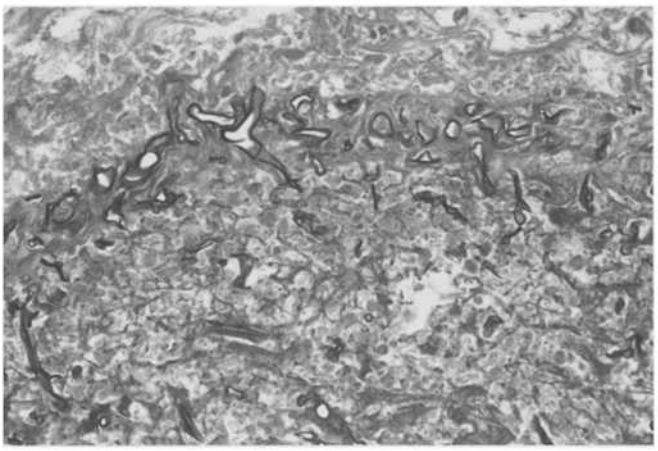


Fig. 40. Mucormycosis.

FUNGAL

Aspergillosis (Figure 39)

- *Asperillus:* thick-walled hyphae, septated and 45° branching; oxalic acid/calcium oxalate crystals seen with *A. niger*
- Four different pathologic patterns:
  - Allergic bronchopulmonary aspergillosis (ABPA):
    - Seen exclusively in asthmatics
    - Mucoid impaction, bronchocentric granulomatosis, and eosinophilic pneumonia
  - Aspergilloma:
    - Fungus ball growing in preexisting cavity, e.g. bulla
  - Chronic necrotizing aspergillosis:
    - Usually single, upper lobe lesion subacute clinical course
    - Chronic, granulomatous inflammation; eosinophils are prominent; hyphae should be readily apparent; no vascular invasion
  - Fulminant invasive aspergillosis:
    - Immunocompromised host; vascular invasion and infarction

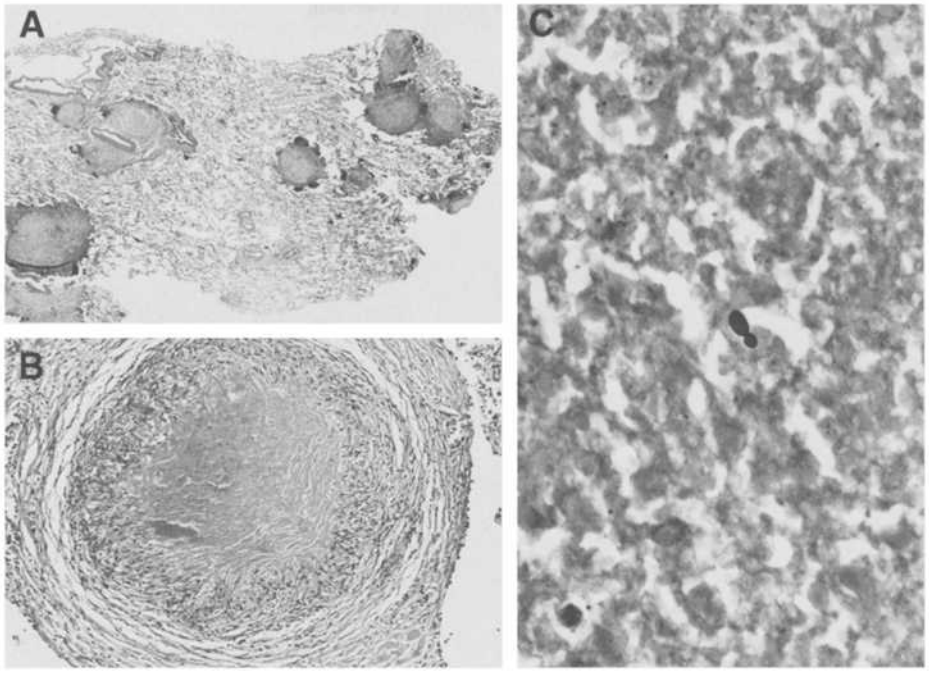


Fig. 41. Histoplasmosis. Necrotizing granuloma over airways **(A,B)**. Histoplasma capsulatum **(C)**.

Differential Diagnosis

- Mucormycosis:
  - Nonseptate, larger, right angle branching
  - Culture needed to distinguish, especially if Asp. is treated
- Alternaria:
  - Golden brown club-shaped macroconidia with longitudinal and transverse septation; bullous swelling near septation in hyphae

Mucormycosis (Phycomycosis)

Clinical

- Immunocompromised host: uncontrolled diabetes, burn injury, and renal failure

*Microscopic **(Figure 40)***

- Nonseptate hyphae 10–25 microns wide; irregular right angle branching; pleomorphic, collapsing walls; necrotizing bronchopneumonia with infarction

Differential Diagnosis

- Aspergillosis:
  - Septate, right angle branching

Candidiasis

Clinical

- Immunocompromised hosts, burns, trauma, catheters, and gastrointestinal surgery

Microscopic

- Yeast forms 2–6 microns; mycelial pseudohyphae forms are common
- Acute bronchopneumonia and emboli to other organs, especially kidney

Histoplasmosis

Clinical

- Can be seen in normal host; commonly found in Mississippi and Ohio River Valley; bird and bat feces

*Microscopic **(Figure 41A,B,C)***

- Necrotizing granulomas, similar to *M. tuberculosis;* yeast forms (2–5 microns), usually degenerating forms are seen; budding is unusual but seen

Coccidioidomycosis

Clinical

- Can be seen in normal host; southwest United States, dry arid climate (San Joaquin Valley Fever); inhaled arthrospores develop into spherules
- C. immitus usual organism; complement fixation tests positive in 90% of patients

*Microscopic **(Figure 42)***

- Necrotizing granulomas, resembling M. tuberculosis

Special Studies

- Spherules (20–200 microns) with endospores: PAS+, GMS+

Sporotrichosis

Clinical

- Male, alcoholic; infects preexisting lung disease (emphysema); *Sporothrix schenckii* usual organism; found in straw, moss, timber, and plants

Microscopic

- Single, necrotizing lesion; significant hilar adenopathy

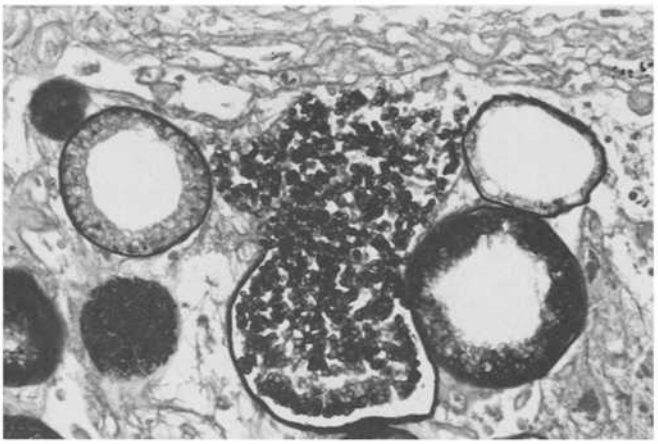


Fig. 42. Coccidioides immitis.

Blastomycosis

Clinical

- Can be seen in normal host; *Blastomyces dermatitidis,* soil-growing fungus; North America around Mississippi and Ohio rivers and Southeast (Georgia)

Microscopic ***(Figure 43A,B)***

- Necrotizing granulomas with central microabscess and multinucleated giant cells; yeast forms: broad-based, budding
- Bronchial lesions are common; bronchial stenosis is common

Cryptococcosis

Clinical

- Can be seen in normal host, most symptomatic cases are in immunocompromised hosts; predilection for CNS
- C. neoformans most common organism; source: pigeons

Microscopic ***(Figure 44)***

- Granulomatous lesions with acute inflammation; pleomorphic yeast forms (2–10 microns); single bud

Special Studies

- Silver+; mucicarmine+ capsule

Pneumocystis jiroveci (carinii) Pneumonia

Clinical

- Immunocompromised host, especially AIDS; insidious onset; bilateral infiltrates

Microscopic ***(Figure 45)***

- Frothy, eosinophilic intraalveolar exudate with faint blue dots
- Mild chronic interstitial pneumonitis
- Unusual reactions include granulomatous inflammation, diffuse alveolar damage, alveolar proteinosis, calcifications, and tissue invasion

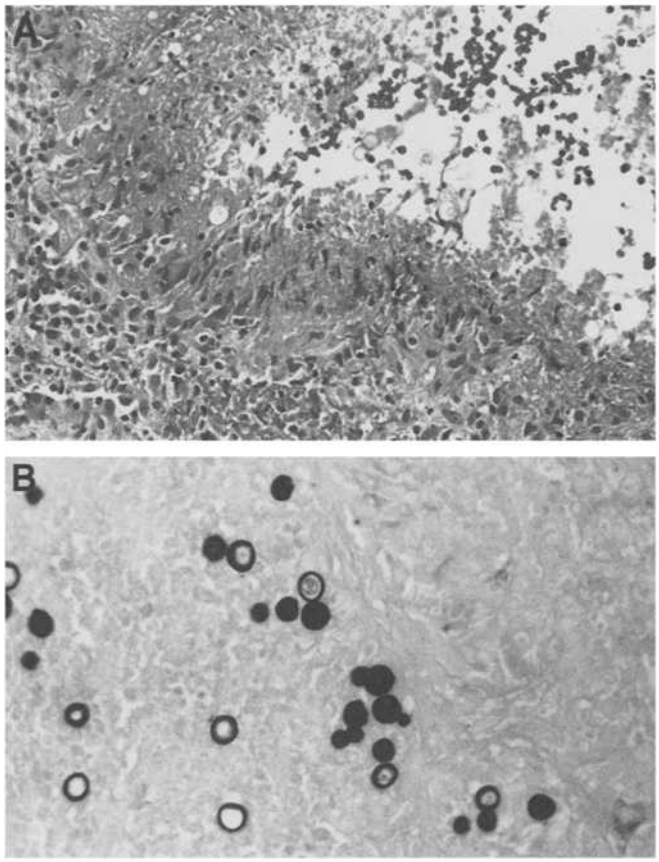


Fig. 43. Blastomycosis. Necrotizing granuloma **(A)**. Blastomyces dermatitides **(B)**.

Special Studies

- Cyst (5–8 microns) best seen on methenamine silver stain
- Trophozoite (1–2 microns) best seen on Giemsa stain

Differential Diagnosis

- Pulmonary alveolar proteinosis:
  - Methenamine silver stain –
  - Minimal interstitial reaction
  - PAS+

PROTOZOAN

Dirofilarial (Dog Heart Worm) Granulomas

Clinical

- Dirofilaria immitis, dog heart worm; adult worm resides in right ventricle/pulmonary artery of dogs; microfilariae in dog blood transmitted to human via mosquito bites
- Asymptomatic coin lesion on chest X-ray

Microscopic

- Pathologic triad: spherical infarct, eosinophilic pneumonia, and endarteritis
- Dirofilarial parasite is present within branch of pulmonary artery within center of infarct
- 100–200 mm thick cuticle with longitudinal ridges

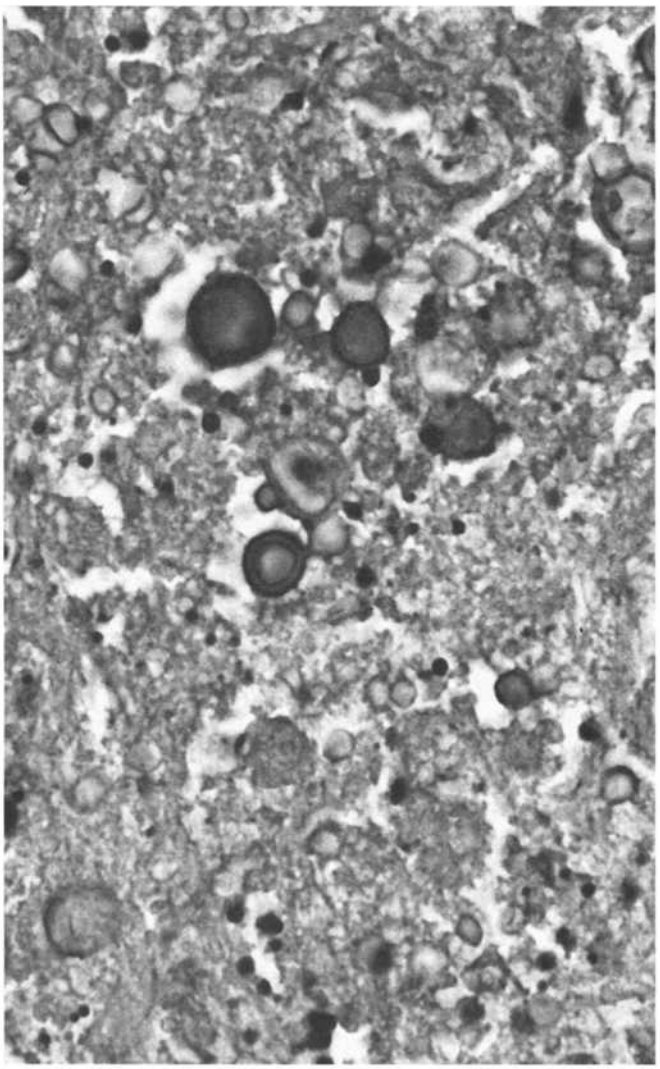


Fig. 44. Cryptococcus neoformans.

Toxoplasma gondii Pneumonia

Clinical

- Immunocompromised host, especially AIDS and neonate; cats are carriers
- Infection of humans is via cat feces or raw meat

Microscopic

- Necrotizing nodules with central coagulative necrosis
- Tachyzoites are present within necrosis
- DAD can be seen

Special Studies

- Giemsa stains tachyzoites
- Immunohistochemical studies helpful for the identification of cysts

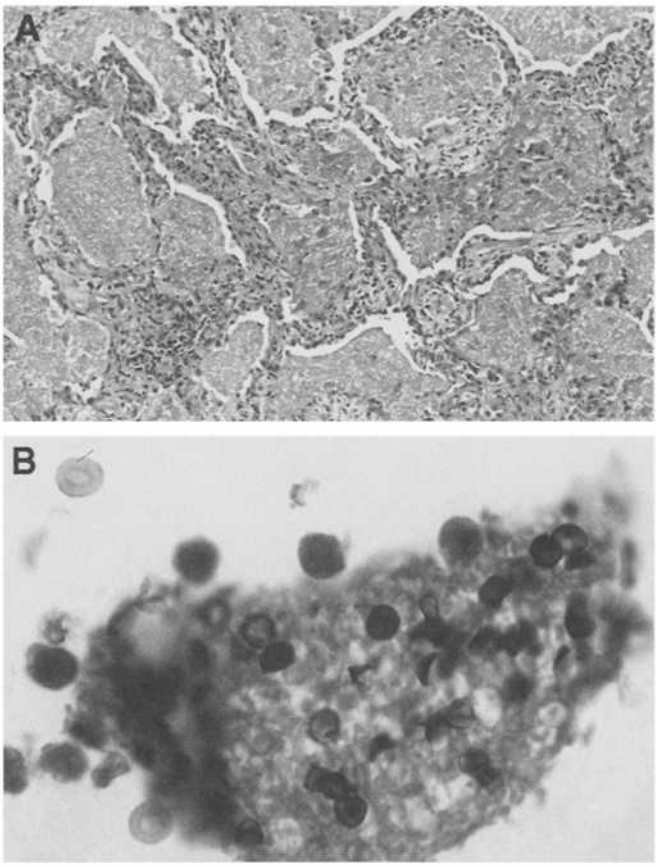


Fig. 45. Pneumocystis carinii pneumonia (PCP). Pneumocystis carinii organisms highlighted by silver stain **(B)**.

Paragonimiasis (Lung Fluke)

Clinical

- Endemic in South America, Africa, India, and Southeast Asia; in immigrants in North America
- "Endemic hemoptysis"; pleural and blood eosinophilia; benign clinical course

Microscopic

- Adult flukes in human lung: red/brown and fleshy; 0.8–1.4 cm in length
- Chronic abscess formation; upper lobes > lower lobes

Special Studies

- Ziehl-Neelsen stains eggshells

Lung Transplantation (also see Chapter 6)

Histologic Grading of Pulmonary Allograft Rejection

Acute Vascular Rejection (Figure 46)

- Perivascular and interstitial mononuclear cell infiltrates:
  - Grade A0: normal pulmonary parenchyma
  - Grade A1: infrequent perivascular mononuclear infiltrates not obvious at low magnification

- Grade A2: frequent perivascular mononuclear infiltrates surrounding venules and arterioles readily recognizable at low magnification
- Grade A3: readily recognizable cuffing of venules and arterioles by dense perivascular mononuclear cell infiltrates, usually associated with endo-thelialitis; interstitial mononuclear cell infiltrates
- Grade A4: diffuse perivascular, interstitial, and air space infiltrates of mononuclear cells and prominent alveolar pneumocyte damage usually associated with inflammatory cell debris

Airway Inflammation-Lymophocytic Bronchitis/ Bronchiolitis

- Grade B0: no airway inflammation
- Grade B1: minimal airway inflammation
- Grade B2: mild airway inflammation
- Grade B3: moderate airway inflammation
- Grade B4: severe airway inflammation

CHRONIC AIRWAY REJECTION

- Active/inactive bronchiolitis obliterans (constrictive bronchiolitis)

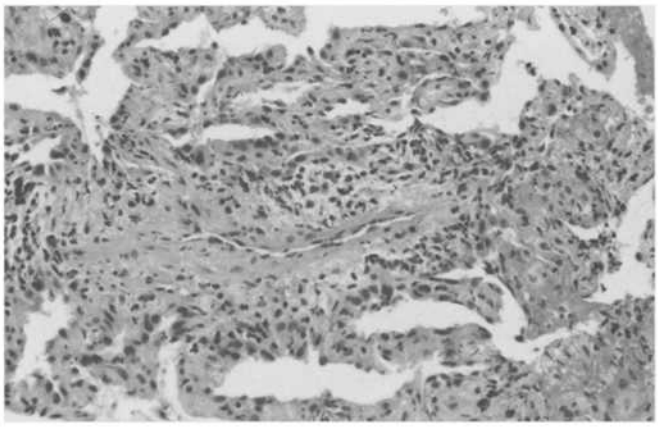


Fig. 46. Minimal acute vascular rejection of pulmonary allograft.

CHRONIC VASCULAR REJECTION-ACCELERATED GRAFT SCLEROSIS

- Fibrointimal thickening of arteries and veins of uncertain clinical significance

NEOPLASTIC DISEASES OF THE LUNG

Benign Tumors

BENIGN EPITHELIAL TUMORS

Squamous Papillomas and Papillomatosis

Clinical

- Upper airway–solitary; adult smoker
- Lower airway–multiple; papillomatosis: children and young adults

*Macroscopic (**Figure 47A**)*

- Multiple lobulated escrescences in bronchioles; distal bronchiectasis common

*Microscopic (**Figure 47B**)*

- Fibrovascular core with cytologically bland nonkeratinizing squamous epithelium; koilocytotic changes are common; mucus-secreting, transitional, or intermediate cells are sometimes interspersed

Differential Diagnosis

- Well-differentiated squamous cell carcinoma/verrucous carcinoma:
  - Lack of maturation
  - Marked cytologic atypia
  - Invasion into adjacent tissue
  - Increased dyskeratosis and hyperkeratosis

Papillary Adenoma of Type II Cells

Clinical

- Asymptomatic, coin lesion

Microscopic

- Circumscribed lesion of branching, papillary fronds lined by cytologically bland columnar cells; no mitoses, necrosis; intranuclear cytoplasmic inclusions common

Differential Diagnosis

- Metastatic papillary carcinoma:
  - Rule out primary ovarian, thyroid, kidney, colon, and breast
- Sclerosing hemangioma:
  - More diversity of pathology, with solid areas and blood-filled spaces
- Papillary adenocarcinoma:
  - Cytologic atypia, necrosis, and mitoses
  - Irregular

Alveolar Adenoma

Clinical

- Solitary nodule in women

Microscopic

- Multicystic, well-circumscribed with ectatic spaces filled with eosinophilic material; flat lining cells;

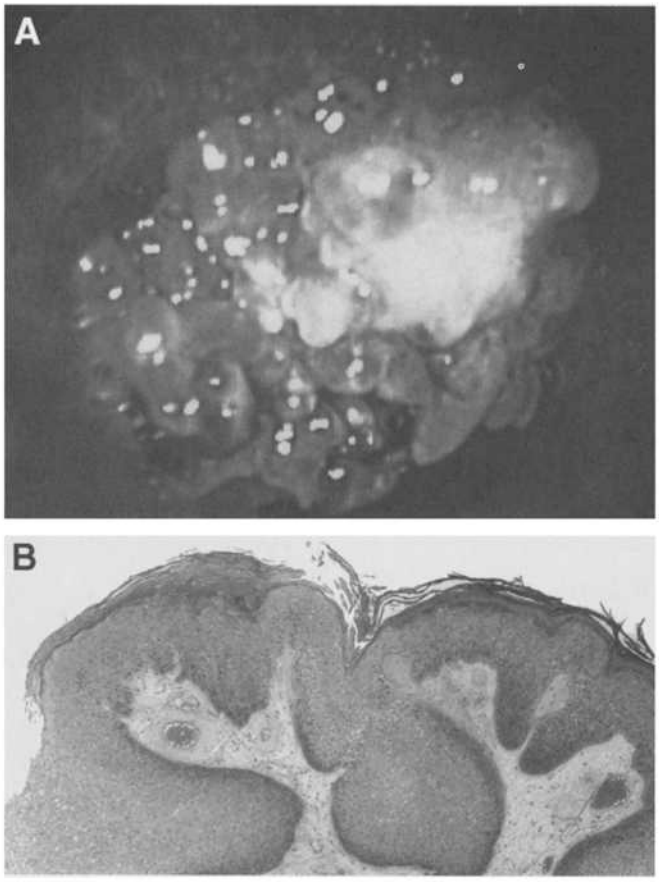


Fig. 47. Squamous papillomatosis **(A,B)**.

interstitium contains collagenous matrix with myofibroblasts

Differential Diagnosis

- Lymphangioma:
  - Endothelial-lined spaces; cytokeratin–

Mucus Gland Adenoma

Clinical

- Occurs in both children and adults; more common in women
- Large airway obstruction/irritation

Macroscopic

- Polypoid, endobronchial lesions in lobar or segmental bronchi

Microscopic

- Cystic, mucous-filled glands with cytologically bland, mucus-secreting epithelium; oncocytic metaplasia can be seen

Differential Diagnosis

- Low-grade mucoepidermoid carcinoma:
  - Intermediate cells present
- Adenocarcinomas:
  - Cytologic atypia, necrosis, mitoses, lack of large cystic spaces

Mucinous Cystadenoma

Clinical

- Nodule in adult smokers

Macroscopic

- Mucus-filled cysts

Microscopic

- Cystic spaces lined by benign, mucus-secreting epithelium; no invasion into adjacent tissue; borderline lesions show increased cytologic atypia

Differential Diagnosis

- Well-differentiated adenocarcinoma and mucinous bronchioloalveolar carcinomas:
  - No fibrous cyst wall
- Mucinous cystadenocarcinoma:
  - Invasive growth into surrounding lung

Benign Mesenchymal Tumors

Hamartoma

Clinical

- Two locations: central endobronchial and parenchymal
- Only central type causes symptoms

*Macroscopic (**Figure 48A**)*

- Well-circumscribed white, bulging nodules of cartilaginous consistency
- Calcium or bone may be present

*Microscopic (**Figure 48B**)*

- Usually composed predominantly of cartilage; fat, smooth muscle and fibromyxoid tissue can be seen
- Surrounded by clefts of benign ciliated or nonciliated epithelium, probably entrapped metaplastic epithelium

Cytogenetics

- 6p21 rearrangement activates high-mobility group gene (HMGI-Y)

Differential Diagnosis

- Bronchial chondromas as seen in young women with Carney's triad: pulmonary chondromas, gastric epithelioid tumors, and extra-adrenal paragangliomas:
  - Are usually connected to airway cartilage
- Benign metastasizing leiomyoma:
  - Fat, cartilage, and other fibromyxoid elements are not seen
- Intrapulmonary solitary fibrous tumor

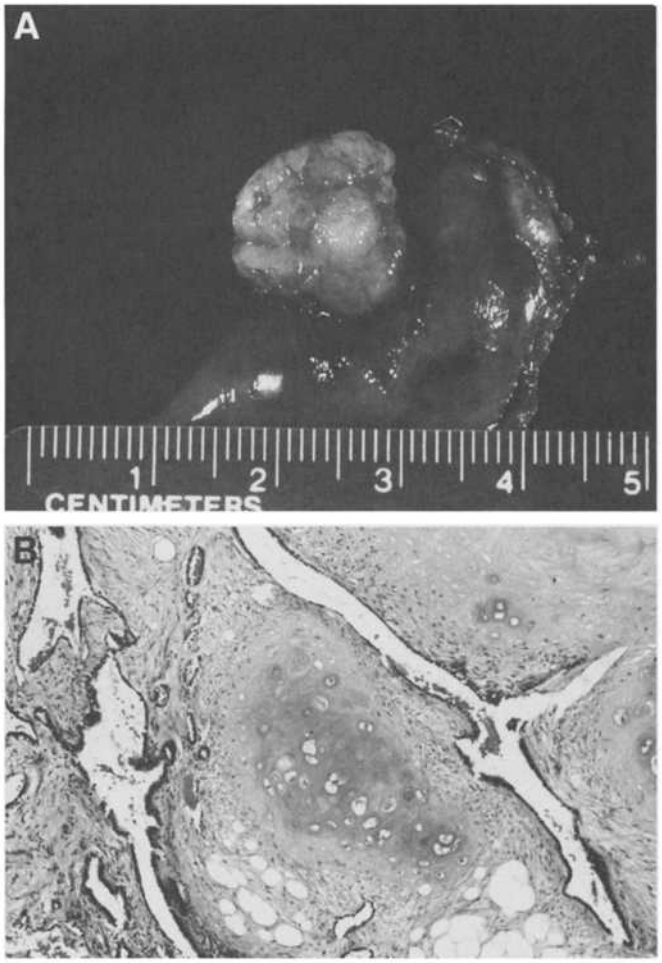


Fig. 48. Hamartoma (**A,B**).

Lipoma

Clinical

- Usually arise in central bronchi; lead to obstruction, wheezing, and bronchiectasis
- Large variant completely enveloping bronchus can be sequelae of chronic bronchiectasis

Macroscopic

- More frequent in left main bronchus than on right side
- Smooth-walled polyps projecting into lumen

Microscopic

- Mature adipose tissue; can have giant cells

Differential Diagnosis

- Hamartoma:
  - Other mesenchymal elements present

Mesenchymal Cystic Hamartoma

Clinical

- Lung cysts causing hemoptysis, pneumothoraces, and pleuritic chest pain
- Can be seen in children

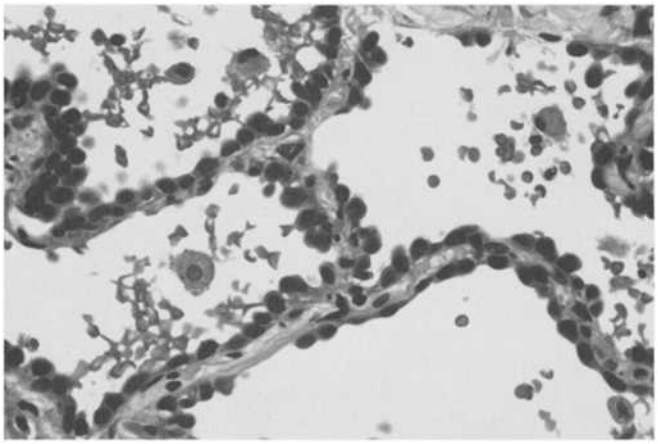


Fig. 49. Atypical adenomatous hyperplasia.

Macroscopic

- Small cysts with connections to bronchioles

Microscopic

- Normal respiratory or cuboidal epithelium; underlying primitive mesenchymal cells
- Hypertrophic arteries within mesenchyme

Differential Diagnosis

- Sequestration of the lung
- Congenital cystic adenomatoid malformation
- Cystic bronchiectasis:
  - None of the above contain primitive mesenchymal cells beneath epithelium
- Metastasis:
  - Primary sarcoma (many of the reported cases have been metastases from uterine neoplasms)

Pre-Invasive Lesions

Squamous Dysplasia/Carcinoma In Situ

Microscopic

- Dysplasia: cytologic atypia, nuclear enlargement in lower, middle, and upper third of mucosa (grades: mild, moderate, and severe); superficial surface maturation
- CIS: entire mucosal involvement by dysplasia; no invasion below basement membrane

Atypical Adenomatous Hyperplasia

Microscopic ***(Figure 49)***

- May be precursor to adenocarcinoma
- Difficult to separate from nonmucinous variant of bronchioloalveolar carcinoma
- Focal lesions, often ≤5 mm; atypical cuboidal/low columnar epithelium; mitoses rare

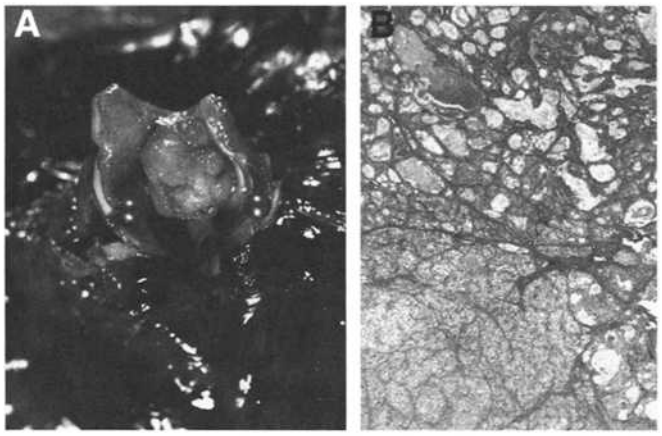


Fig. 50. Mucoepidermoid carcinoma (**A,B**).

Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

Microscopic

- Increased number of neuroendocrine cells
- Precursor to the development of multiple tumorlets and carcinoids; typical and atypical carcinoids can arise in this setting
- Usually secondary to airway fibrosis and/or inflammation; rarely, seen as diffuse idiopathic variant

Malignant Tumors

TUMORS OF SALIVARY GLAND TYPE

Mucoepidermoid Carcinoma

Clinical

- Half are in patients <30 years; symptoms of large airway obstruction/irritation

*Macroscopic (**Figure 50A**)*

- Tan/pink endobronchial nodule, most common in main or lobar bronchi
- Mucoid surface with underlying cystic areas; can ulcerate on surface

*Microscopic (**Figure 50B**)*

- Mucin-secreting, squamous and intermediate cells:
  - Low grade: mitoses, nuclear pleomorphism, and necrosis are absent
  - High grade: mitoses (>4/10 HPF), nuclear pleomorphism, and necrosis are present

Differential Diagnosis

- Bronchial mucous gland adenoma:
  - No intermediate or squamous cells
- Adenosquamous cell carcinomas:
  - Peripheral lesions with adjacent in situ changes
  - Common to have keratinization
  - Intermediate cells are absent

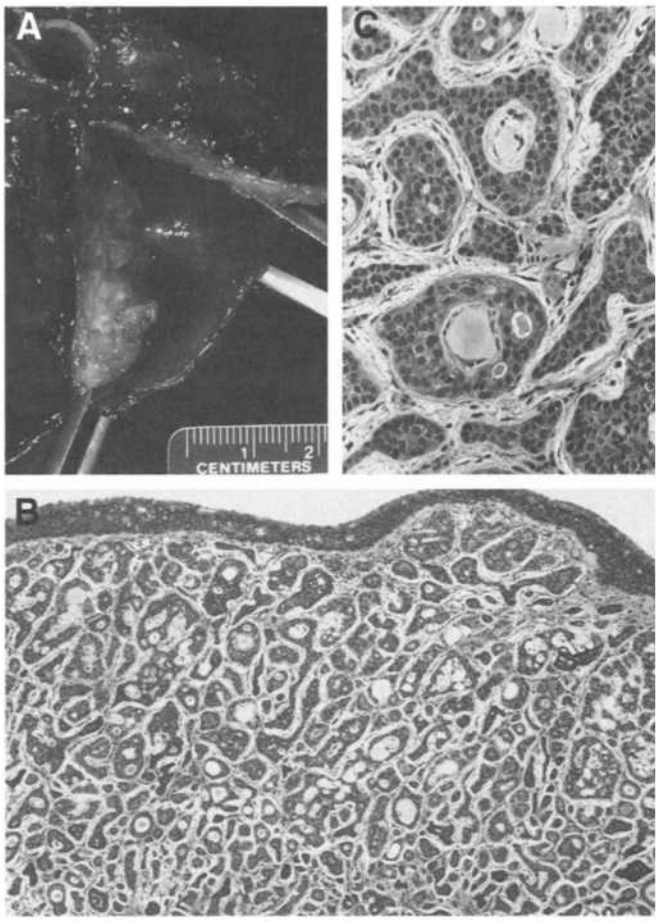


Fig. 51. Adenoid cystic carcinoma (**A–C**).

Adenoid Cystic Carcinoma

Clinical

- Most common salivary gland type tumor of the lower respiratory tract
- Lower trachea, mainstem bronchi, or lobar bronchi
- Large airway obstruction/irritation
- Recurrence is common

Macroscopic

- Tan/grey tumors intrude bronchial wall with sessile or annular lesions; can spread submucosally along bronchial wall and diffusely involve adjacent airways

*Microscopic (**Figure 51A,B,C**)*

- Small cells with hyperchromatic nuclei in cribriform, cylindromatous, trabecular, or glandular architecture; commonly infiltrates through airway cartilage; spaces contain alcian blue + basal lamina-type material; perineural invasion common

Differential Diagnosis

- Pleomorphic adenoma:
  - No cribriform or cylindromatous areas

- Mucoepidermoid carcinoma:
  - Smooth, well-circumscribed mass
  - Squamous and intermediate cells
- Adenocarcinomas of the lung:
  - Cytologic atypia, mitoses, and necrosis

Epithelial Tumors

- See TNM Classification of Lung Cancer for pathologic staging of non-small cell carcinomas

Squamous Cell Carcinoma

Clinical

- 2/3 are central; more commonly found in men; second most common bronchogenic carcinoma; strong association with smoking
- Hypercalcemia due to parathormone-related protein secretion by tumor

*Macroscopic (**Figure 52A**)*

- Vary from small to large, obstructive lesions; commonly cavitate
- Usually found in segmental or subsegmental bronchi

*Microscopic (**Figure 52B**)*

- Characterized by the presence of cytokeratin differentiation with keratinization and intercellular bridges by light microscopy
- Graded according to degree of squamous differentiation
- Spindle cells, osteoclastic-type and tumor giant cells, and clear cell changes can be seen
- Histologic variants include papillary, clear cell, small cell, and basaloid

Differential Diagnosis

- Squamous metaplasia:
  - Minimal cytologic atypia; maturation; lack of stromal invasion
- Adenosquamous carcinoma and mucoepidermoid carcinoma:
  - Glandular component
- Small cell carcinoma:
  - Lack nucleoli, increased nuclear molding, and crush artifact
  - Less cytoplasm; increased N/C ratio
  - No squamous differentiation

Adenocarcinoma

Clinical

- Most common form of bronchogenic carcinoma; most common lung cancer in women
- Hypertrophic pulmonary osteoarthropathy

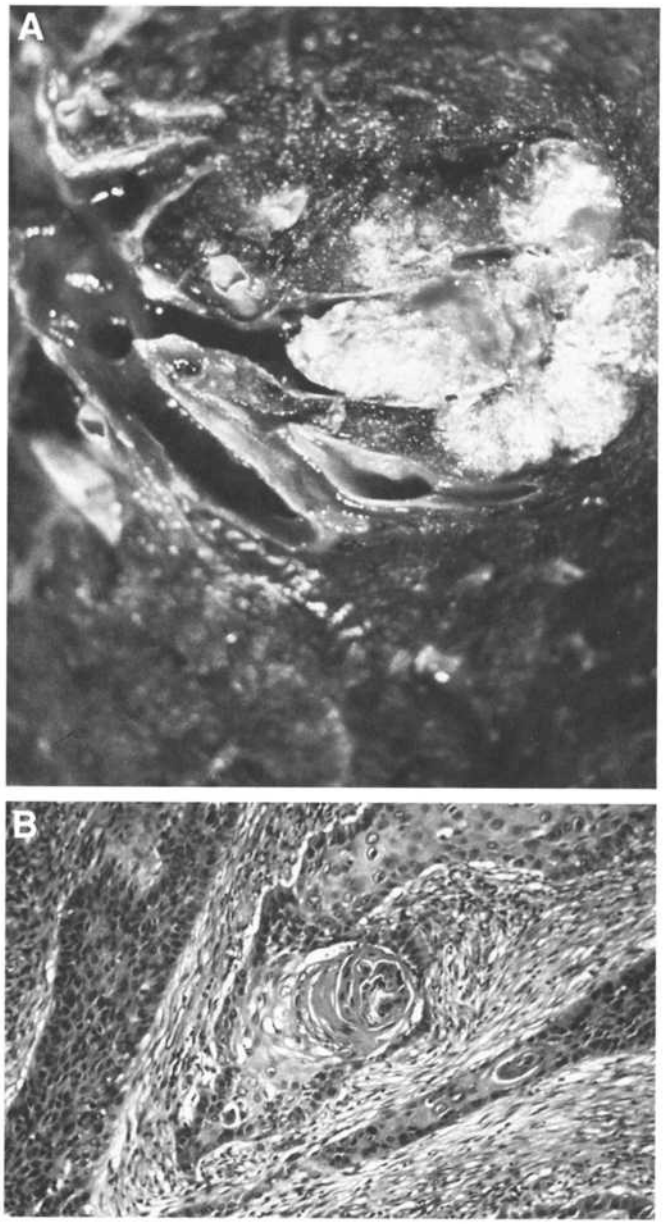


Fig. 52. Squamous cell carcinoma **(A,B)**.

- Smoking history is more variable than in other bronchogenic carcinomas

*Macroscopic (**Figure 53A**)*

- More commonly peripheral
- Desmoplasia can be prominent (but true "scar carcinomas" also occur)

*Microscopic (**Figure 53B**)*

- Glandular differentiation present
- Heterogeneous histology with different growth patterns:
  - Papillary
  - Acinar

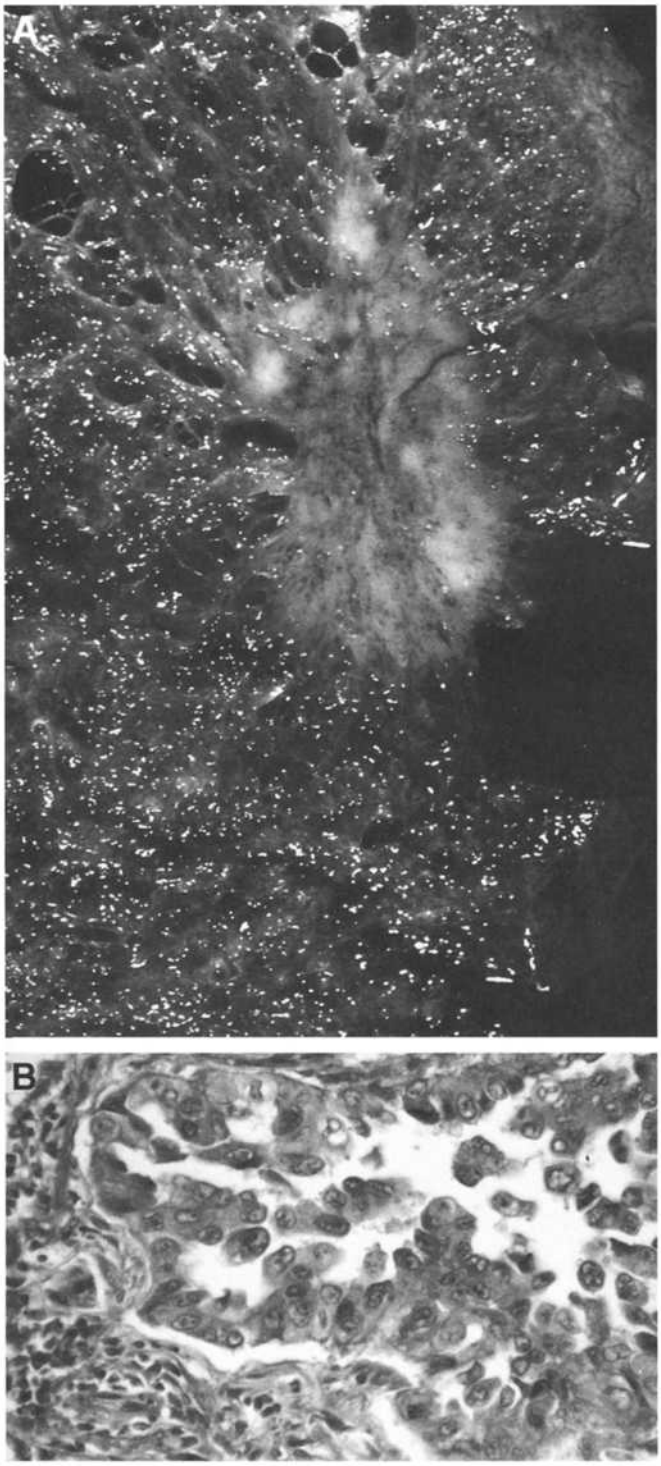


Fig. 53. Adenocarcinoma: **(B)** acinar type.

- Bronchioloalveolar
- Solid

♦ Bronchioloalveolar carcinoma is considered a subtype of adenocarcinoma **(Figure 54)**:

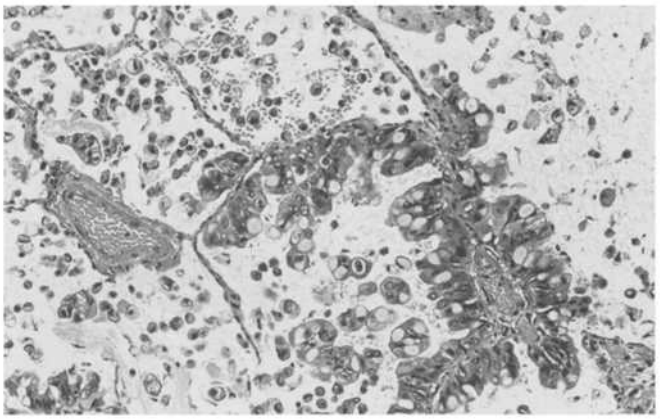


Fig. 54. Bronchioloalveolar adenocarcinoma.

- No invasion of stroma, pleura, or vessel
- May present as single or multiple nodules
- Aerogenous spread with microsatellite lesions is common

♦ Variants include:
- Well differentiated fetal adenocarcinoma
- Mucinous (colloid) adenocarcinoma
- Signet ring cell carcinoma
- Clear cell adenocarcinoma

Immunohistochemistry

♦ Neuron specific enolase: 50% +; Leu 7: 33% +
♦ Chromogranin/Synaptophysin: 10–20% +
♦ Cytokeratin 7 + and Cytokeratin 20 ±
♦ Thyroid transcription factor –1 (TTF –1)+

Electron Microscopy

♦ Microvilli with glycocalx and rootlets

Molecular

♦ K-ras mutations

Differential Diagnosis

♦ Organizing diffuse alveolar damage with treatment-related cytologic atypia:
- History of treatment (chemotherapy/radiation therapy)
- Diffuse pattern on imaging studies
- Heterogeneity of cell types

♦ Metastatic adenocarcinoma from kidney, gastrointestinal tract, and breast:
- Clinical history
- Mucin and cytokeratin 7 negative in renal cell carcinoma
- Cytokeratin 7 negative in colorectal adenocarcinomas

♦ Reactive Type II pneumocyte hyperplasia and other reactive bronchiolar inflammatory lesions:

- No cytologic atypia
- Cilia present
- Lesions limited to bronchioles

♦ Atypical adenomatous hyperplasia:
- Cytologic atypia is less marked
- Typically <1 cm

♦ Bronchioloalveolar cell adenoma/alveolar adenomatous hyperplasia:
- ≤5 mm

♦ Adenocarcinoma, mixed type:
- Invasion into stroma, pleura, or vessels

Bronchioloalveolar Carcinoma

Clinical

♦ No invasion into underlying stroma

♦ Aerogenous spread with microsatellite lesions is common

Small Cell Carcinoma

Clinical

♦ 20–25% of all lung cancer; strong association with smoking

♦ Inappropriate anti-diruetic hormone, Cushing's, and Eaton-Lambert syndrome

♦ Central tumors with early metastases; chemotherapy responsive

Macroscopic

♦ 70% of cases present as perihilar mass

♦ Extensive lymph node metastases are common

♦ Typically peribronchial; endobronchial lesions are uncommon

*Microscopic (**Figure 55**)*

♦ Round to fusiform nuclei; nuclear molding; faint or absent nucleoli; scant cytoplasm

♦ Extensive necrosis

♦ Three histologic categories:
- Small cell
- Mixed small cell/large cell
- Combined small cell/adeno- or squamous cell carcinoma

Immunohistochemistry

♦ Can show chromogranin+, synaptophysin+, and Leu 7+; however, 25% of cases—for neuroendocrine markers

Cytogenetics

♦ 3p deletions

Differential Diagnosis

♦ Non-small cell carcinoma, including large cell neuroendocrine carcinoma:

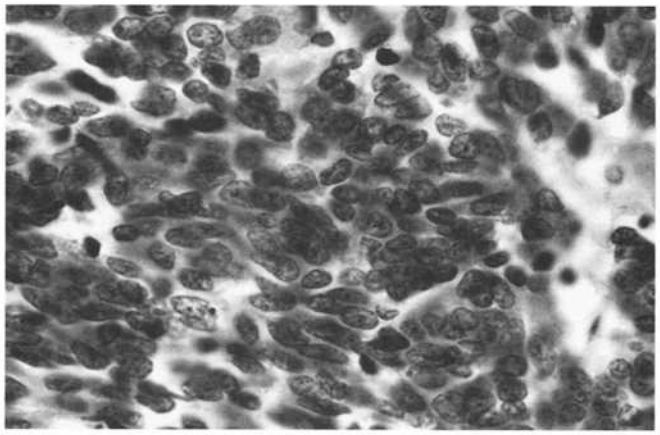


Fig. 55. Small cell carcinoma.

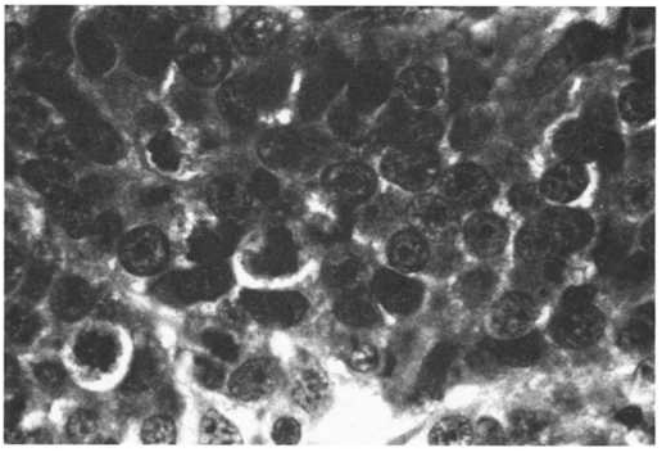


Fig. 56. Large cell undifferentiated carcinoma.

- Larger nuclei
- Prominent nucleoli
- Lower nuclear/cytoplasmic ratio
- Lack of nuclear molding

Large Cell Undifferentiated Carcinoma

Clinical

♦ 10–20% of lung carcinomas; strongly associated with smoking

Macroscopic

♦ Central or peripheral; typically large, with pleural invasion

♦ Rarely occult

*Microscopic (**Figure 56**)*

♦ Sheets and nests growth pattern with extensive necrosis; large nuclei with prominent nucleoli; lack definitive evidence of squamous or glandular differentiation by light microscope

♦ Can have giant cell, clear cell, or spindle cell changes

♦ Variants include large cell neuroendocrine carcinoma (see neuroendocrine tumors), basaloid, lymphoepithelioma-like, and clear cell

Electron Microscopy

♦ 80% show glandular differentiation; 10% show squamous differentiation

Differential Diagnosis

♦ Melanoma:
  – –for cytokeratin by immunohistochemical studies
♦ Large cell lymphoma (including anaplastic type):
  – Nuclei tend to be smaller, with more irregular nuclear membranes
  – Negative for cytokeratin and + for CD45 (leucocyte common antigen) by immunohistochemical studies

Adenosquamous Carcinoma

Clinical

♦ 0.4–4.0% of lung carcinomas
♦ Strong association with smoking

Microscopic

♦ Contains well-defined squamous cell carcinoma and adenocarcinoma
♦ Each component must comprise at least 10% of the tumor

Differential Diagnosis

♦ Adenocarcinoma with metaplastic squamous changes:
  – Squamous metaplasia has benign features
♦ Squamous cell carcinoma with entrapped bronchial epithelium:
  – Entrapped glandular epithelium is benign
♦ High-grade mucoepidermoid carcinoma:
  – Contains areas of low-grade mucoepidermoid carcinoma
  – Glandular component is usually goblet cell

Carcinomas with Pleomorphic, Sarcomatoid, and Sarcomatous Elements

Clinical

♦ Smokers

Macroscopic

♦ Usually large (>10 cm) and peripheral

Microscopic

♦ Poorly differentiated carcinomas associated with sarcoma or sarcoma-like elements
♦ Term for tumors with a continuum of epithelial and mesenchymal differentiation
♦ Includes:
  – Pleomorphic carcinoma (adeno-squamous cell carcinoma with spindle cells and/or giant cells)
  – Sarcomatoid carcinoma (monophasic and biphasic)

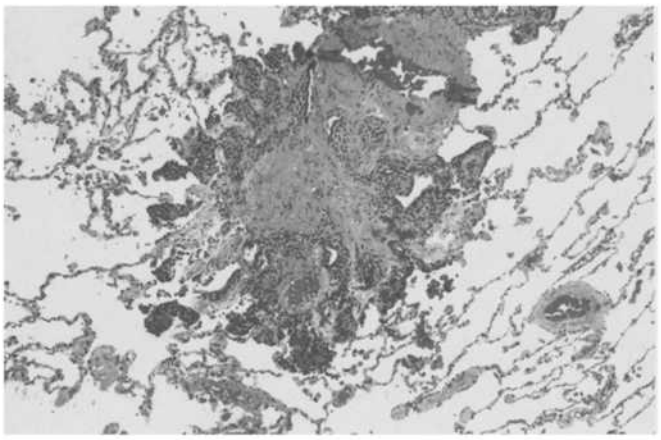


Fig. 57. Carcinoid tumorlet.

  – Spindle cell carcinoma (only spindle cells present—rare)
  – Giant cell carcinoma (large cell carcinoma with only giant cells—very rare)
  – Carcinosarcoma (carcinoma with sarcoma containing heterologous elements; epithelial element is commonly squamous cell carcinoma; osteosarcoma, chondrosarcoma and rhabdomyosarcoma are commonly part of sarcomatous element)
  – Pulmonary blastoma

Immunohistochemistry

♦ Cytokeratin of spindle cell elements can be –

Differential Diagnosis

♦ Metastatic sarcoma:
  – No epithelial differentiation by light or electron microscopy

Neuroendocrine Tumors

Carcinoid Tumorlet

Clinical

♦ Incidental microscopic findings
♦ Most common in adults; rarely in children

Microscopic ***(Figure 57)***

♦ Neuroendocrine cells embedded in fibrotic stroma
♦ ≤0.5 cm
♦ Usually adjacent to bronchiole

Differential Diagnosis

♦ Carcinoid tumor:
  – >0.5 cm
♦ Neuroendocrine cell hyperplasia:
  – Increased neuroendocrine cells within bronchiolar epithelium

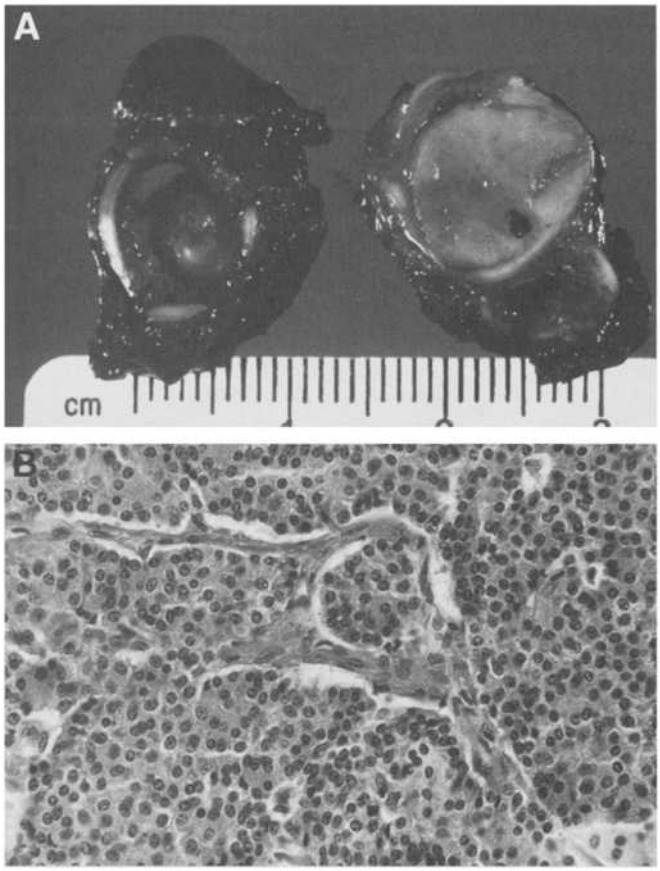


Fig. 58. Typical carcinoid **(A,B)**.

- Bronchiolar metaplasia:
  - No evidence of neuroendocrine differentiation

Typical and Atypical Carcinoid

Clinical

- May present with postobstructive changes
- Most common in adults; can occur in children
- Paraneoplastic syndromes can occur
- Can occur in patients with Multiple Endocrine Neoplasia (MEN-I) (*see* Chapter 2)

*Macroscopic **(Figure 58A)***

- Central and peripheral; central lesions have large, endobronchial component with postobstructive changes distally
- Peripheral lesions are usually subpleural
- Tan/yellow mass; danger of bleeding on biopsy

*Microscopic **(Figure 58B)***

- Neuroendocrine cells with organoid, trabecular, insular, palisading ribbon, rosette-like architecture
- Round to oval nuclei with finely granular chromatin and inconspicuous nucleoli

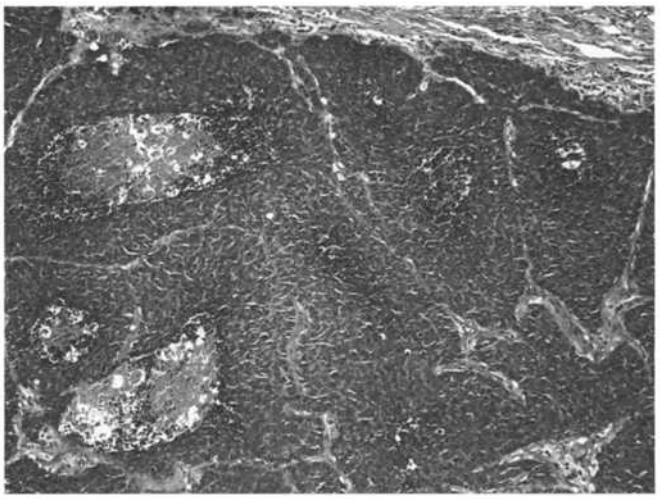


Fig. 59. Large cell neuroendocrine carcinoma.

- Stromal changes include bone, cartilage, dense fibrosis, and amyloid
- Atypical carcinoids have 2–10 mitoses/10 HPF and foci of necrosis
- Spindle cell variant is more common in peripheral lesions

Differential Diagnosis

- Spindle cell lesions (metastatic sarcoma and spindle cell carcinoma):
  - No neuroendocrine differentiation
- Metastatic carcinoma of the breast and prostate:
  - History of primary
  - Multiple lesions

Large Cell Neuroendocrine Carcinoma

Clinical

- Strong association with smoking; average age = 64 years

Macroscopic

- Can extensively replace lung; central or peripheral; can be multinodular

*Microscopic **(Figure 59)***

- Organoid, palisading, trabecular patterns
- Large, polygonal nuclei and low nuclear/cytoplasmic ratio; frequent nucleoli
- High mitotic rate (>10 mitoses/10 HPF); necrosis can be prominent

Immunohistochemistry

- Chromogranin: 80% +; Leu 7: 40% +; Synaptophysin: 40% +; Bombesin: 40% +; CEA 100% +; Cytokeratin: 100% +
- Neuroendocrine differentiation should be confirmed by immunohistochemistry or electron microscopy

Differential Diagnosis

- Small cell carcinoma:
  - Smaller nuclei
  - No nucleoli
  - High nuclear/cytoplasmic ratio
- Atypical carcinoid:
  - 2–10 mitoses/10 HPF
  - Single cell necrosis or focal central necrosis
- Large cell undifferentiated carcinoma:
  - No evidence of neuroendocrine differentiation by light microscopy or immunohistochemical or ultrastructural analysis

Unusual Tumors with Neuroendocrine Differentiation

- Paraganglioma
- Primitive neuroectodermal tumor
- Neuroendocrine carcinoma with rhabdoid phenotype
- Amphicrine neoplasms
- Neuroendrocrine carcinoma with anemone features
- Pulmonary blastoma with neuroendocrine differentiation

Mesenchymal Tumors

Fibrous and Fibro-Histiocytic Tumors

Inflammatory Pseudotumor

Clinical

- 60% occur under the age of 40; represents the majority of benign tumors in children
- Usually an asymptomatic mass

Macroscopic

- Solitary, round, well-circumscribed but unencapsulated mass; can penetrate pleura or extend into adjacent mediastinal structures
- Calcification and foci of necrosis can be seen; xanthoma cells can cause yellow color

*Microscopic (**Figure 60A,B**)*

- Circumscribed, with pushing border of organizing pneumonia
- Mixture of plasma cells, lymphocytes, and macrophages with fibroblasts and connective tissue
- Fibrohistiocytic subtype:
  - Myofibroblasts and fibroblasts predominate and can show pinwheel or storiform architecture
  - Touton giant cells and xanthoma cells can be seen
- Plasma cell granuloma subtype:
  - Abundant plasma cells and lymphocytes
  - Fibroblasts and collagen
  - Mild nuclear atypia can be seen
  - Lymphoid follicles can occur

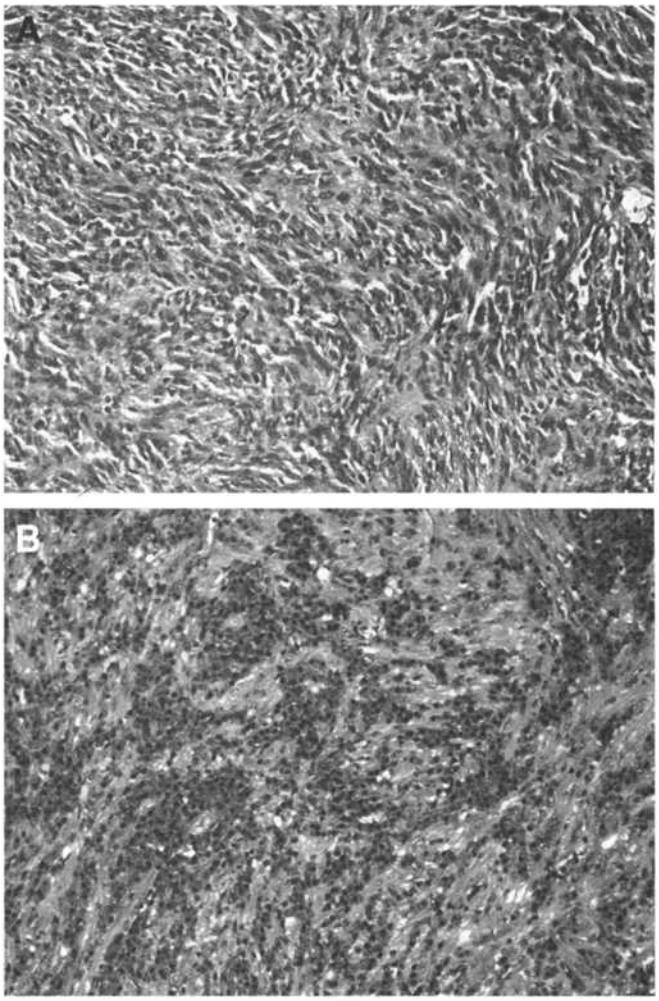


Fig. 60. Inflammatory pseudotumor: **(A)** fibrohistocytic subtype; **(B)** plasma cell granuloma subtype.

Differential Diagnosis

- Malignant fibrous histiocytoma:
  - Increased cytologic atypia, cellularity, and necrosis
  - Mitotic rate >3/50 HPF
- Pleomorphic (spindle cell) carcinoma:
  - Foci of epithelial differentiation
  - Reactivity for cytokeratin
- Pulmonary hyalinizing granuloma:
  - Usually multiple
  - Distinctive, hyalinizing lamellar collagen
- Inflammatory fibrosarcoma:
  - Increased spindle cell atypia
  - Increased cellularity
- Sclerosing hemangioma:
  - Interstitial collections of round, polygonal, or uniform cells
  - + epithelial membrane antigen

Malignant Fibrous Histiocytoma

Clinical

- Older presentation: 60–70 year old; primary is rare, always consider metastatic lesion
- Preoperative diagnosis is difficult due to –cytologic specimens

Macroscopic

- Usually solitary mass (2–10 cm); peripheral location; rarely intrabronchial
- Microscopic
- Spindle cells, pleomorphic giant cells, and histiocyte-like cells are present
- Storiform, fascicular, or pleomorphic architecture
- Inflammatory cells can be a significant component

Differential Diagnosis

- Pleomorphic carcinoma with spindle cells:
  - Evidence of epithelial (squamous or glandular) differentiation
  - Ultrastructural evidence of desmosomes, junctional complexes, microvilli within glands, or cytoplasmic tonofibrils
  - + for carcinoembryonic antigen
- Inflammatory pseudotumor-fibrohistiocytic type:
  - Lack cytologic atypia
  - <3 mitoses/50 HPF
  - No significant necrosis

Smooth Muscle Tumors—Leiomyosarcoma

Clinical

- Rare; consider possibility of metastatic lesion, especially from uterus
- Symptomatic presentation: cough, hemoptysis

Macroscopic

- Large, circumscribed masses; most are parenchymal
- Propensity for hilar region

Differential Diagnosis

- Leiomyoma:
  - <5 mitoses/50 HPF
  - No cytologic atypia
  - No significant necrosis
- Benign metastasizing leiomyoma:
  - Multiple nodules
  - Well-differentiated smooth muscle without mitoses/necrosis/cytologic atypia
- Lymphangioleiomyomatosis:
  - Seen exclusively in women
  - Multifocal, benign smooth muscle and cyst-like spaces

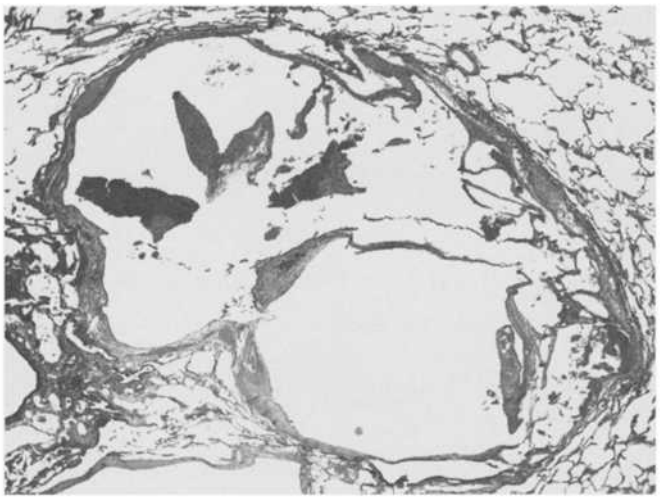


Fig. 61. Arteriovenous malformation.

Skeletal Muscle Tumors—Rhabdomyosarcomas

Clinical

- Seen in both adults and children

Macroscopic

- Large, solid masses; may involve more than one lobe

Microscopic

- Cross striations are present; cells may be small, pleomorphic, or straplike
- Immunoreactive for desmin

Differential Diagnosis

- Metastatic rhabdomyosarcoma
- Carcinosarcoma:
  - Malignant epithelial component
- Pleuropulmonary blastoma:
  - 90% are found in children <10 years of age
  - May have focal malignant primitive epithelial component

Vascular Tumors and Related Conditions

Vascular Malformations (Figure 61)

- Usually diagnosed radiographically; similar to those at other sites
- Multiple: Osler-Weber-Rendu

Epithelioid Hemangioendothelioma (Intravascular Bronchioloalveolar Tumors)

Clinical

- Multiple nodules in young women (M : F = 1 : 4)
- Has been seen in children; >1/2 of patients are <40 years
- Concomitant multifocal disease can be see in bone, soft tissue, and liver

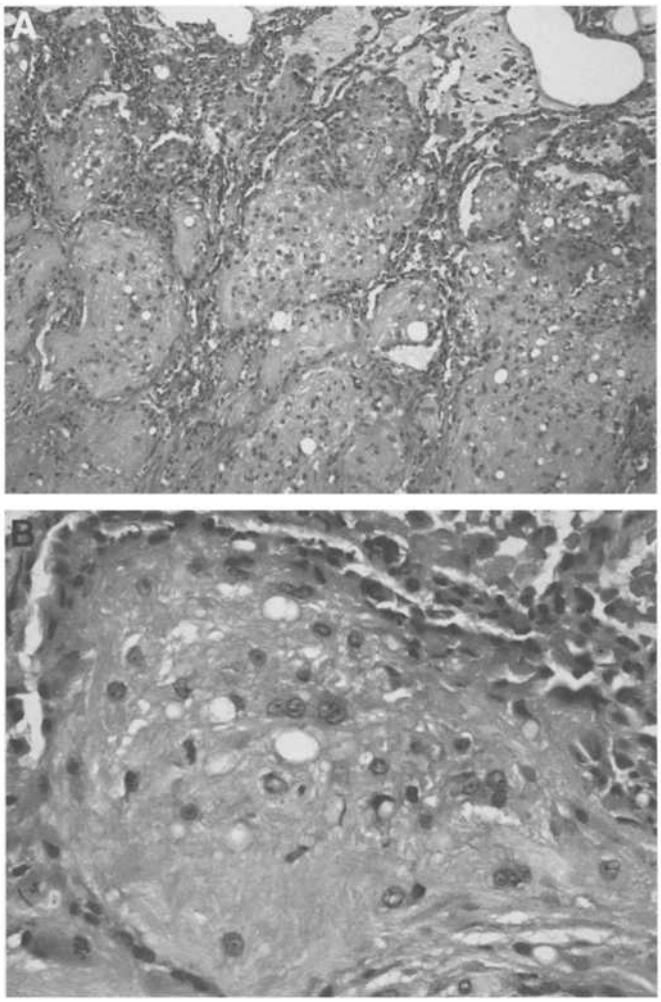


Fig. 62. Epithelioid hemagioendothelioma (intravascular bronchioloalveolar tumor) **(A,B)**.

Macroscopic

- Discrete, firm white nodules (1–2 mm); may resemble cartilage

*Microscopic **(Figure 62A,B)***

- Circumscribed, pale eosinophilic nodules; stroma may resemble cartilage or amyloid
- Cells are cytologically bland with round nuclei and nucleoli; intracytoplasmic vacuoles are present; endothelial differentiation is present

Immunohistochemistry

- Factor VIII+, CD34+, and CD31+

Electron Microscopy

- Weibel-Palade bodies

Differential Diagnosis

- Adenocarcinoma:
  - Mucin+ cytoplasmic vacuoles
  - Cytokeratin+
- Metastatic chondrosarcoma:
  - No endothelial differentiation
  - S-100 protein +
- Amyloid nodules:
  - Acellular
  - Congo red positivity
- Hamartoma:
  - Usually solitary
  - Entrapped epithelium is cytokeratin+
- Angiosarcoma:
  - Marked cytologic atypia
  - Predominantly intra-vascular

Kaposi's Sarcoma

Clinical

- Rare initial site of involvement; 25% of disseminated disease affects the lung
- Hemoptysis

Macroscopic

- Hemorrhagic bronchial plaques or nodules present in a lymphatic distribution

Microscopic

- Spindle cells with intercellular spaces containing red blood cells
- Hemosiderin and plasma cells

Immunohistochemistry

- Spindle cells are CD 34+ and CD 31+

Differential Diagnosis

- Angiosarcoma:
  - Increased cytologic atypia
  - Patients lack risk factors for AIDS
- Benign granulation tissue:
  - Lack red blood cells within slit-like spaces
- Bacillary angiomatosis:
  - Bacteria identified by special stains

Angiosarcoma

Clinical

- Hemoptysis

Macroscopic

- Multiple, hemorrhagic nodules

Microscopic

- Atypical endothelial cells forming vascular spaces
- Intra-arterial or peri-arterial involvement is common
- Epithelioid variant



Fig. 63. Pulmonary artery sarcoma.

Differential Diagnosis

- Kaposi's sarcoma:
  - Lack cytologic atypia
- Metastatic sarcoma:
  - Primary lesion (e.g., heart or pulmonary artery)
- Primary/metastatic carcinoma:
  - Cytokeratin differentiation

Other Vascular Tumors

- Pulmonary artery and vein sarcomas **(Figure 63)**
  - Polypoid mass involving pulmonary vessels
  - 80% involve pulmonary trunk
- Hemangiopericytomas:
  - 10% of all primary hemangiopericytomas occur in lung
  - Poor prognosis associated with >5 cm and increased mitotic rate

Neurogenic Tumors

- All neurogenic tumors are rare as primary lung tumors
- Though the following can be found as primary lesions in the lung, the possibility of metastatic disease should be excluded first:
  - Malignant nerve sheath tumor
  - Malignant psammomatous melanotic schwannoma
  - Neuroblastoma and ganglioneuroblastoma
  - Meningioma
  - Neurilemmoma
  - Neuroma and ganglioneuroma
- All are rare lesions in the lung; consider metastatic disease before primary lung lesions:
  - Chondroma
  - Bronchial variant seen in Carney's triad

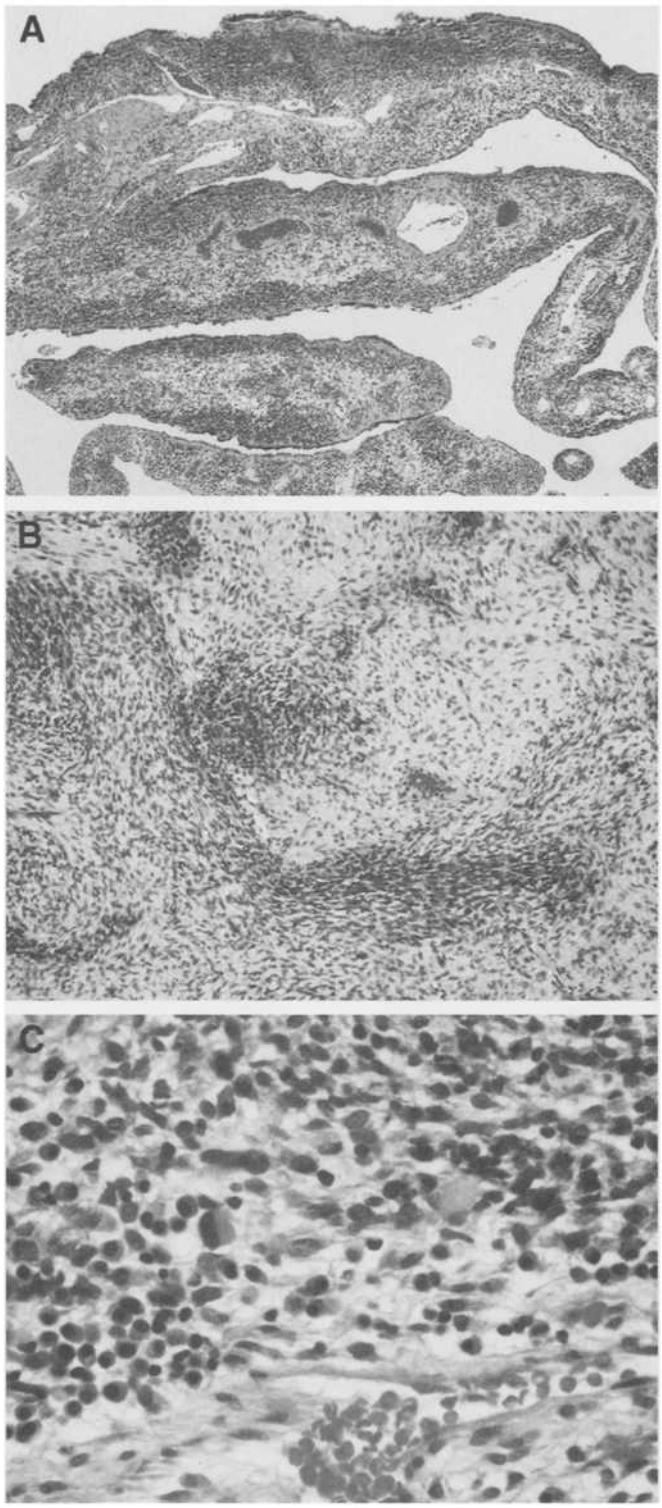


Fig. 64. Pleuropulmonary blastoma. **(A)** Characteristic multicystic lesion with compact small-cell proliferation beneath respiratory epithelium. **(B)** Solid area with blastematous and sarcomatous foci. **(C)** Foci of rhabdomyosarcoma are common.

- Chondroblastoma
- Chondrosarcoma

Cystic and Pleuropulmonary Blastoma of Childhood

Clinical

- In children 1–9 years of age; usually symptomatic
- Family history of similar intrathoracic tumors or other solid tumors of childhood in 25–30% of cases

Macroscopic

- Large, multiloculated cystic mass; can be mediastinal or pleural

Microscopic ***(Figure 64)***

- Cyst lined by benign ciliated columnar epithelium with underlying primitive small cells that can include rhabdomyoblasts
- May contain anaplastic sarcomatous elements such as embryonal rhabdomyosarcoma, fibrosarcoma, chondrosarcoma, and anaplastic undifferentiated sarcoma

Differential Diagnosis

- Pulmonary blastoma:
  - Adult
  - Smoking history
  - Malignant epithelium
  - Chromogranin+
- Congenital cystic adenomatoid malformation:
  - No malignant mesenchyme

Lymphoproliferative Lesions of the Lung

Benign/Hyperplastic Lesions

Nodular Lymphoid Hyperplasia (Pseudolymphoma)

Clinical

- Adults: 30–80 years; most are asymptomatic
- Can be associated with autoimmune diseases such as Sjögren's syndrome and lupus erythematosus
- May have polyclonal hypergammaglobulinemia

Macroscopic

- Most are solitary masses; can present as multinodular lesions or infiltrate
- Rarely >5 cm

Microscopic

- Localized lesion
- Heterogeneous inflammatory infiltrate; germinal centers are commonly seen
- Necrosis is rare; organizing pneumonia is common

Differential Diagnosis

- Low-grade B cell lymphomas of mucosa-associated lymphoid tissue (MALT):
  - Should be monoclonal by immunohistochemistry
  - Heavy chain rearrangements on molecular studies
  - Lymphoepithelial lesions
  - Granulomatous inflammation and amyloid can be seen
  - Airway and vascular invasion
- Lymphocytic interstitial pneumonia—Diffuse bilateral interstitial lymphoplasmacytic infiltrate

Lymphocytic Interstitial Pneumonitis (Diffuse Lymphoid Hyperplasia)

Clinical

- Symptoms of interstitial disease: cough and dyspnea
- Can be seen in children and adults
- Associated with many conditions, including congenital or acquired immunodeficiency syndromes, autoimmune diseases (e.g. Sjögren's), and drug-induced lung disease

Macroscopic

- Firm, consolidated lung

Microscopic

- Dense, diffuse lymphoplasmocytic infiltrates in alveolar walls
- Germinal centers with diffuse lymphoid hyperplasia; granulomas and giant cells can be seen

Differential Diagnosis

- Diffuse low-grade lymphoma:
  - Monomorphous population
  - Lymphatic distribution
  - Airway, vascular, and pleural invasion
- Extrinsic allergic alveolitis (hypersensitivity pneumonitis):
  - Areas of organization
  - Prominent bronchiolitis

Giant Lymph Node Hyperplasia (Castleman's Disease)

- Rare as primary pulmonary lesions
- Germinal center with characteristic hyaline vascular change

Lymphomas (also see Chapter 9)

Low-Grade Lymphoma of the Mucosa Associated Lymphoid Tissue (MALT)

Clinical

- Adults: 60 years; 1/2 are symptomatic
- 20% have monoclonal protein in serum
- Chest X-ray shows localized infiltrate or solitary lesion in 50%

Macroscopic

- Fleshy, nonnecrotizing mass; infiltrative growth pattern

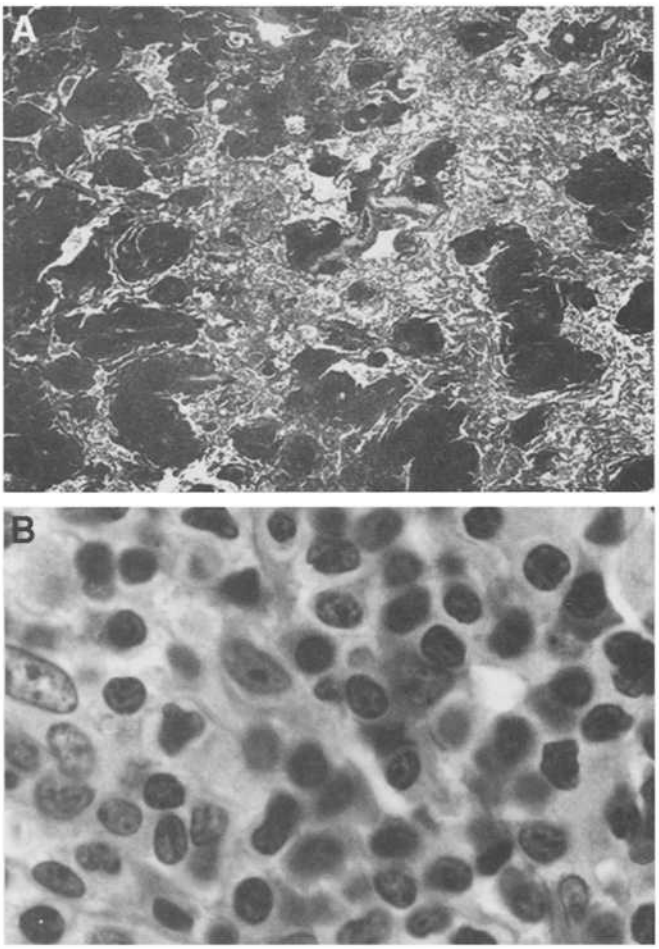


Fig. 65. Marginal zone lymphoma of the BALT type.

Microscopic ***(Figure 65A,B)***

- Dense, lymphoid infiltrate in lymphatic distribution; population may be monotonous
- Germinal centers are commonly seen; lymphoepithelial lesions can be seen
- Large mass lesions may be present
- Airway, vascular, and pleural invasion is common

Immunohistochemistry

- Light chain restriction can usually, but not always, be seen by immunohistochemistry

Molecular Studies

- Clonal B-cell rearrangements are usually seen by molecular studies

Differential Diagnosis

- Pseudolymphoma:
  - Heterogeneous and polyclonal population
  - Solitary nodule
- Lymphocytic interstitial pneumonitis:
  - Heterogeneous and polyclonal population
  - No bronchial, vascular, or pleural invasion
- Secondary pulmonary involvement by chronic lymphocytic leukemia:
  - Peripheral white blood cell count consistent with CLL

Angiocentric Immunoproliferative Lesions/Angiocentric Lymphomas/Lymphomatoid Granulomatosis/Polymorphic Reticulosis

Clinical

- Average age + 40–50 years; most present with multiple lung nodules
- Skin and CNS involvement is frequent
- Poor prognosis
- EBV infection implicated in high-grade progression
- Immunodeficiency is a risk factor

Macroscopic

- Nodular consolidation; nodules may have central necrosis

Microscopic

- Nodules or diffuse infiltrates of lymphoid cells
- Central necrosis and cavitation can be seen in larger nodules; prominent vascular invasion (angiocentric pattern)
- Cell population may be heterogeneous; graded according to degree of cytologic atypia and number of EBV(+) B cells:
  - Grade 1: benign lymphocytic vasculitis with <5 EBV(+) cells
  - Grade 2: lymphomatoid granulomatosis, necrosis with 5–20 EBV(+) cells
  - Grade 3: angiocentric lymphoma with numerous EBV(+) cells

Immunohistochemistry

- Most cells are positive for T-cell markers (CD4,CD8); some are T-cell rich B-cell lymphomas

Molecular Studies

- Either immunoglobulin rearrangements (B-cell) or T-cell receptor rearrangements (T-cell)
- EBV DNA often detected by polymerase chain reaction

Differential Diagnosis

- Necrotizing granulomatous infections:
  - Well-formed granulomas
- Wegener's granulomatosis:
  - Giant cells and neutrophilic microabscesses
- Low-grade lymphomas of MALT:
  - Little necrosis
  - Predominantly lymphatic distribution, not angiocentric
- Hodgkin's disease:
  - Classic Reed-Sternberg cells
  - Classic background of lymphocytes and eosinophils

- Large Cell Lymphoma:
  - Distinction from high-grade angiocentric immunoproliferative lesion (AIL)/lymphomatoid granulomatosis (LYG) may be arbitrary

Post-Transplant Lymphoproliferative Disorder

Clinical

- Found in patients who have undergone organ transplantation
- Associated with EBV infection

Macroscopic

- Single or multiple nodules or infiltrates

Microscopic

- Varied appearance: small cell to large cell; can be polymorphous
- Necrosis and vascular invasion can be seen

Differential Diagnosis

- AIL/LYG:
  - Not restricted to immunosuppressed patients

Other Lymphoproliferative Lesions

Intravascular Lymphomatosis (Angiotropic Lymphoma)

- Aggressive, high-grade lymphoma with tumor cells proliferating within small vessels
- Skin and CNS involvement are most common, but pulmonary involvement is seen

Primary Pulmonary Hodgkin's Disease

- Usually involves lung by direct extension from mediastinum
- Primary lung involvement is rare
- Multiple nodules are common
- Histologic features of Hodgkin's Disease elsewhere

Plasmacytoma

- Extremely rare as primary lung lesion
- Plasma cell granuloma, pseudolymphoma, and pulmonary involvement by multiple myeloma should be ruled out

Mast Cell Tumor

- Very rare as primary lung lesion; should be distinguished from mast cell rich inflammatory pseudotumors

Tumors of Uncertain Histogenesis

Sclerosing Hemangioma

Clinical

- Female predominance (80% found in women); asymptomatic

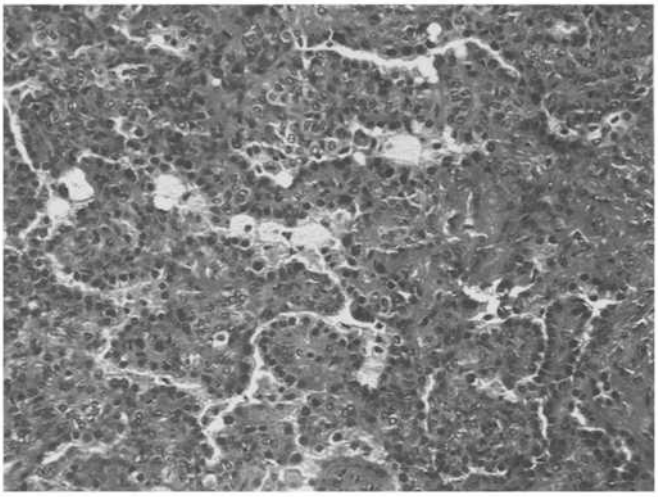


Fig. 66. Sclerosing hemangioma.

Macroscopic

- Grey/red circumscribed mass; 1/2 are in lower lobes

Microscopic ***(Figure 66)***

- Solid, papillary sclerotic and hemorrhagic patterns; round, uniform epithelioid cells
- Mast cells may be numerous
- Papillae lined by cuboidal cells with eosinophilic cytoplasm and cytoplasmic inclusion

Immunohistochemistry

- Epithelial cells in solid areas are EMA+; cytokeratin often–
- CEA and surfactant apoprotein often +
- Cells lining papillae rare cytokeratin(+)

Differential Diagnosis

- Inflammatory pseudotumor:
  - Lack distinct epithelioid cells
  - Bronchioloalveolar carcinoma
  - No distinct cell population within stalk
  - Cytologic atypia

Benign Clear Cell (Sugar) Tumor

Clinical

- Incidental mass on chest X-ray; asymptomatic

Macroscopic

- Small, red/tan masses; shell out from surrounding lung

Microscopic

- Circumscribed mass with round cells with abundant eosinophilic cytoplasm
- Extracellular amorphous eosinophilic material
- May contain fine granular pigment; abundant PAS + material-glycogen
- Thin-walled blood vessels without a muscular coat

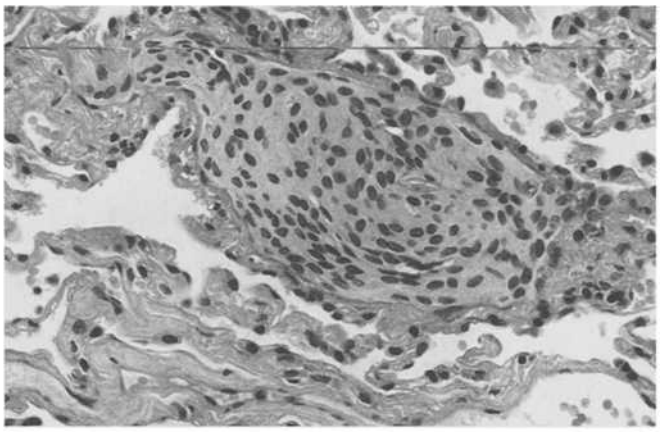


Fig. 67. Pulmonary meningothelial-like lesion (chemodectoma).

Immunohistochemistry

- HMB-45+
- Cytokeratin–

Differential Diagnosis

- Primary lung cancer with clear cell change:
  - HMB-45–
  - Glycogen not prominent
  - Cytologic atypia
- Renal cell carcinoma:
  - CEA–
  - Multiple, thick-walled vessels

Minute Pulmonary Meningothelial-Like Lesion (Minute Pulmonary Chemodectoma)

Clinical

- Incidental microscopic findings; female predominance

*Microscopic (**Figure 67**)*

- Spindle or oval-shaped cell; perivenule location
- Zellballen pattern

Histochemistry

- Do not stain with argyrophil or argentaffin stains

Differential Diagnosis

- Carcinoid tumorlets:
  - Associated with bronchioles
  - Stain for neuroendocrine markers
- Angiomatoid lesions of pulmonary hypertension:
  - Associated with arteries/arterioles
  - CD34(+) and CD31(+)

Granular Cell Tumor (Granular Cell Myoblastoma)

Clinical

- Schwann cell lineage
- Usually solitary mass of trachea or bronchus; can be multicentric

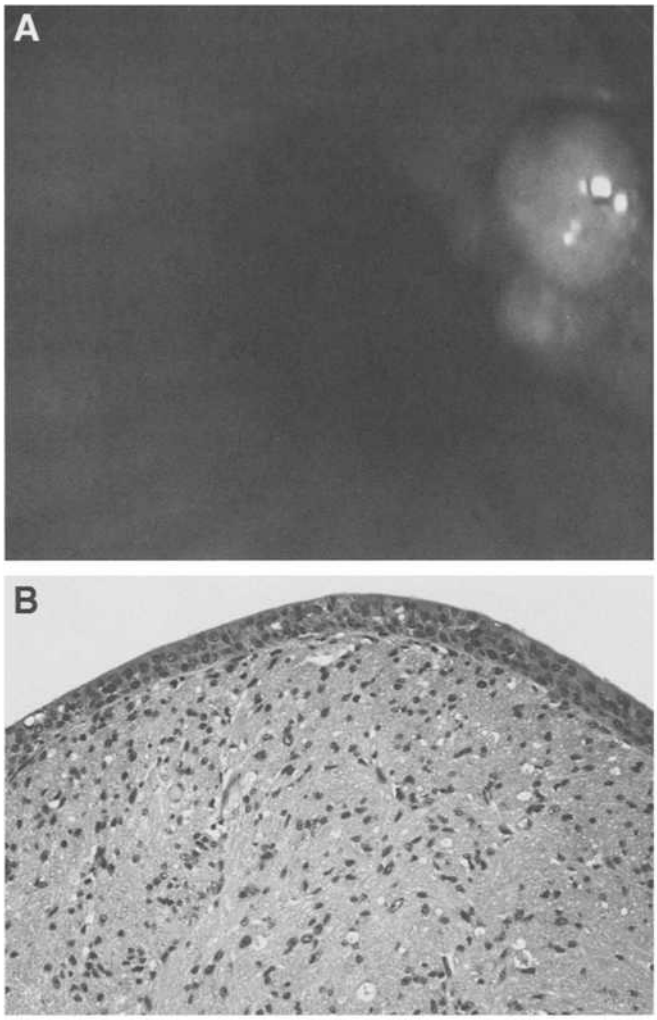


Fig. 68. Granular cell tumor (**A,B**).

- Also found in skin, breast, esophagus, and rectum; respiratory tract may be metastatic lesion
- Primary lung lesions may metastasize

*Macroscopic (**Figure 68A**)*

- Sessile or polypoid lesions with smooth surfaces; grow in walls of airways

*Microscopic (**Figure 68B**)*

- Large, granular foamy cells; some areas may have fusiform cells
- No mitoses

Immunohistochemistry

- S-100+

Electron Microscopy

- Osmophilic inclusions

Differential Diagnosis

- Oncocytic carcinoid
  - + neuroendocrine immunohistochemistry

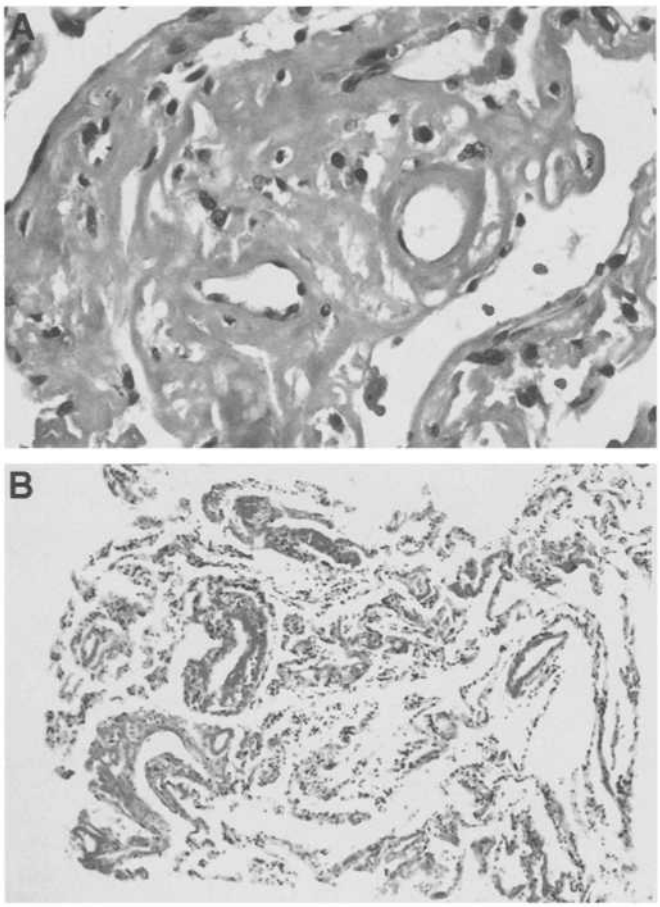


Fig. 69. Amyloidosis. **(B)** Congo red stain.

Masses and Tumor-Like Lesions

Pulmonary Amyloidosis

Clinical

- Patients have monoclonal proteins in serum or urine
- Associated diseases include multiple myeloma, lymphoid interstitial pneumonitis, low-grade lymphomas, and Sjögren's syndrome

Macroscopic

- Five types: nodular, diffuse, alveolar-septal, senile, tracheobronchial
- Waxy, hard irregular nodules

Microscopic ***(Figure 69)***

- Amorphous, eosinophilic material in vessels, airway, or as nodules
- Congo red shows apple green birefringence

Differential Diagnosis

- Kappa light chain disease:
  - Congo red stain not birefringent
- Pulmonary hyalinizing granuloma:
  - Congo red stain birefringent+

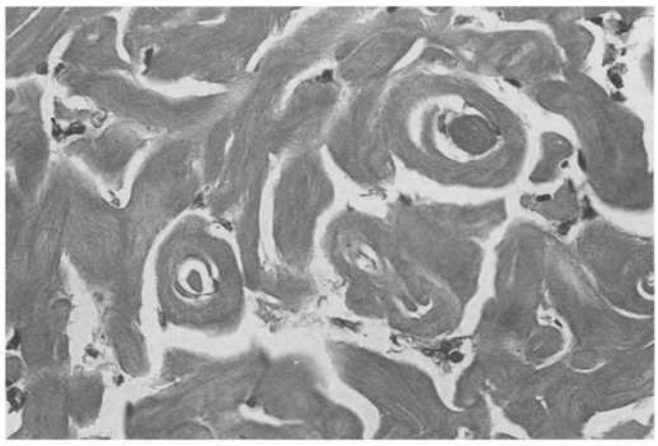


Fig. 70. Pulmonary hyalizing granuloma.

Pulmonary Hyalinizing Granuloma

Clinical

- Asymptomatic; adults
- 60% have serologic evidence of autoimmunity

Macroscopic

- Bilateral nodules; white/gray-"cotton balls"

Microscopic ***(Figure 70)***

- Lamellar collagen in storiform or whorled array—"donuts"; mild lymphoplasmacytic infiltrate

Differential Diagnosis

- Sclerosed plasma cell granuloma:
  - Usually solitary
  - More intense inflammatory infiltrate
- Nodular amyloidosis:
  - Congo red stains for apple green birefringence
- Hyalinized infectious granulomas:
  - Collagen arranged in parallel around center

Inflammatory Myofibroblastic Tumor

Clinical

- Usually solitary
- Most common in children

Microscopic

- Organizing myofibroblastic proliferation
- Inflammatory cell infiltrates are variable
- May have xanthogranulomatous appearance

Differential Diagnosis

- Malignant fibrous histocytoma:
  - Cytologic atypia and numerous mitotic figures
- Sarcomatoid carcinoma:
  - Cytologic atypia and numerous mitotic figures
  - Cytokeratin+

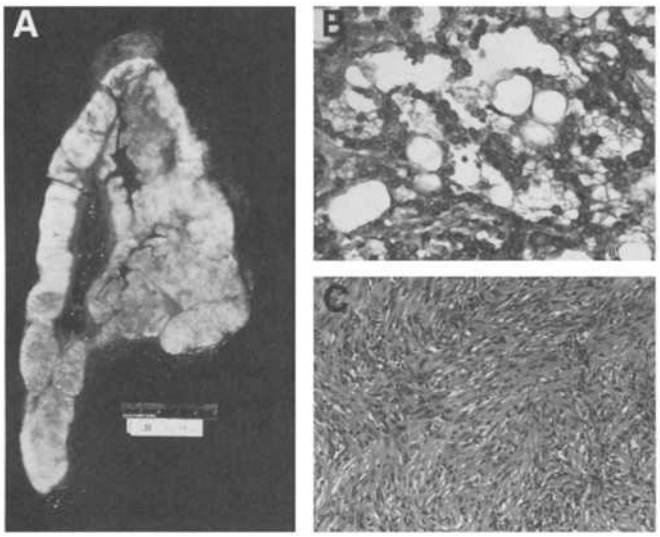


Fig. 71. Malignant mesothelioma. **(A)** Gross appearance; **(B)** epithelioid type; **(C)** sarcomatoid type.

Tracheobronchopathia Osteoplastica

Clinical

- Middle-aged or elderly men with hoarseness, stridor, and hemoptysis; possible relationship to tracheal amyloidosis

Macroscopic

- Hard, yellow-white papilla-like formations on cartilaginous portion of trachea or bronchi

Microscopic

- Nodules of bone and cartilage in submucosa

Benign Metastasizing Leiomyoma

Clinical

- Multiple nodules; invariably in women

Macroscopic

- Grey/white lobulated mass; shells out from lung parenchyma

Microscopic

- Well-differentiated smooth muscle; may have Type 2 epithelial inclusions
- ≤5 mitoses/50HPF

Differential Diagnosis

- Hamartoma:
  - Bronchial epithelium
- Metastatic leiomyosarcoma:
  - >5 mitoses/50 HPF
  - Primary sarcoma
  - Usually multiple lesions

Table 2. Diagnosis of Mesothelioma versus Adenocarcinoma*

	Mesothelioma	*Adeno-carcinoma*
Histochemical Studies		
Periodic and Schiff with Diastase digestion	–	+:40–50%
Mucicarmine	–	+:50%
Alcian Blue or Colloidal Iron	+	+
Alcian Blue or Colloidal Iron with Hyaluronidase digestion	–	+
Immunohistochemical Studies		
Carcinoembryonic antigen	–	+
Leu M1 (CD-15)	–	+
CAM 5.2	+	+
AE1/3	+	+
Ber EP4	–	+
B72.3	–	+
Calretinin	+	–
Thyroid Transcription Factor (TTF –1)	–	+
Ultrastructural Study	Lung, branching villi, length/ diameter <10:1 Perinuclear intermediate filaments	Small microvilli Well-developed rootlets

** Although there are exceptions to each study, + and – signs signify the usual results of the study*

Tumors of the Pleura (also see Chapter 26)

Malignant Mesothelioma

Clinical

- Asbestos is single most important cause of malignant mesothelioma; M > F
- Crocidolite and amosite asbestos are more carcinogenic than asbestos chrysotile

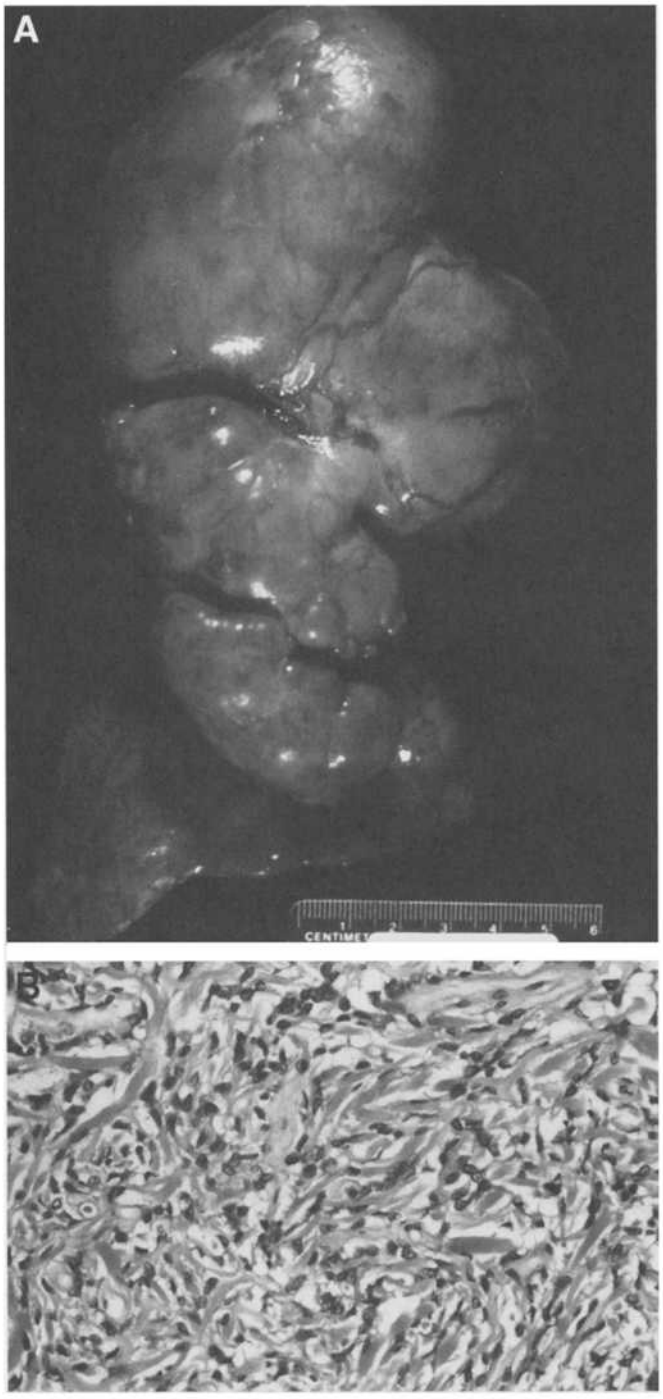


Fig. 72. Solitary fibrous tumor of the pleura **(A,B)**

Macroscopic ***(Figure 71A)***

- Tumor obliterates pleural space and encases lung

Microscopic ***(Figure 71B,C)***

- Four main pathologic types:
  - Epithelial:
    - Most common
    - Subtypes: tubulopapillary and epithelioid are most common
  - Sarcomatoid
  - Mixed epithelial and sarcomatoid
  - Desmoplastic

Histochemistry and Immunohistochemistry

- See **Table 2**

Molecular

- Wilms' Tumor 1 (WT1) overexpression

Differential Diagnosis

- Epithelial type: Metastatic adenocarcinoma
- Sarcomatoid type: Sarcoma:
  - Sarcomas are cytokeratin–
- Desmoplastic: hyalinized pleural plaque:
  - Increased cellularity and cytologic atypia in desmoplastic mesothelioma

Localized Fibrous Tumor of the Pleura

Clinical

- Most are incidental masses
- Hypoglycemia due to insulin-like growth factor

Macroscopic ***(Figure 72A)***

- Usually pedunculated; can be intrapulmonary
- Whorled and fibrous-appearing

Microscopic ***(Figure 72B)***

- Spindle cells with short fascicles or haphazard pattern
- Pericytoma-like vasculature
- Varying amount of collagen; cytologic atypia and necrosis are absent
- Malignant features: >4 mitoses/10HPF; >10 cm; necrosis

Immunohistochemistry

- CD34+

TNM CLASSIFICATION OF LUNG CANCER (2002 REVISION)

T: Primary tumor

- TX: Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
- TO: No evidence of primary tumor

- Tis: Carcinoma in-situ
- T1: Tumor <3 cm in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the labor bronchus* (i.e., not in the main bronchus)
- T2: Tumor with any of the following features of size or extent:
  - >3 cm in greatest dimension
  - Involves main bronchus, 2 cm or more distal to the carina
  - Invades the visceral pleura
  - Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
- T3: Tumor of any size that directly invades any of the following: chest wall (including superior suleus tumors), diaphragm, mediastinal pleura, parietal pericardium or tumor in the main bronchus <2 cm distal to the carina, but without involvement of the carina: or associated atelectasis or obstructive pneumonitis of the entire lung
- T4: Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, esophagus, vertebral body, carina: or tumor with a malignant pleural or pericardial effusion, or with satellite tumor nodule(s) within the ipsilateral primary tumor lobe of the lung
- N: Regional lymph node:
  - NX: Regional lymph nodes cannot be assessed
  - NO: No regional lymph node metastasis
  - N1: Metastasis to ipsilateral peribronchial and/or ipsilateral hilar lymph nodes, and intrapulmonary nodes involved by direct extension of primary tumor
  - N2: Metastasis to ipsilateral mediastinal and/or subcarinal lymph node(s)
  - N3: Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)
- M: Distant metastasis:
  - MX: Presence of distant metastasis cannot be assessed
  - MO: No distant metastasis
  - M1: Distant metastasis present

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23

Breast

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CONTENTS

I. Non-Neoplastic Diseases of the Breast 23-3
Fibrocystic Change 23-3
Microcalcifications 23-3
Mucocele-Like Tumor 23-3
Juvenile Hypertrophy 23-3
Gynecomastia 23-4
Metaplastic Changes 23-4
Apocrine Metaplasia 23-4
Clear Cell Metaplasia 23-5
Squamous Metaplasia 23-5
Mucinous Metaplasia 23-5
Lactational Change (Lactational Metaplasia) 23-5
Sclerosing Adenosis 23-5
Microglandular Adenosis (MGA) 23-6
Complex Sclerosing Lesion/ Radial Scar 23-6
Duct Ectasia (Periductal Mastitis) 23-7
Collagenous Spherulosis 23-7
Mastitis 23-7
Acute Mastitis/ Periareolar Abscess 23-7
Granulomatous Mastitis 23-7
Silicone Reaction 23-7
Lymphocytic Mastitis (Diabetic Mastopathy, Fibrous Mastopathy) 23-8
Amyloidosis 23-8
Fat Necrosis 23-8

II. Neoplasms 23-8
Benign Epithelial Neoplasms 23-8
Adenomas and Variants 23-8
Benign Mesenchymal Tumors 23-9
Fibromatosis 23-9
Myofibroblastoma 23-10
Granular Cell Tumor 23-10
Neurilemmoma (Schwannoma) 23-10
Lipoma 23-10

III. Intraductal Epithelial Proliferations 23-11
Summary of Cytologic Characteristics 23-11
Features of Ductal Proliferations 23-11
Features of Lobular Proliferations 23-11
Ductal Intraepithelial Neoplasia (DIN) 23-11
(Usual) Intraductal Hyperplasia (IDH) 23-11
DIN1, Flat Type: Flat Epithelial Atypia 23-11
DIN1(≤2 mm): Atypical Ductal Hyperplasia (AIDH) 23-11
DIN 1(>2mm): Ductal Carcinoma *In Situ*, Low Grade 23-11
DIN 2: Ductal Carcinoma *In Situ*, Intermediate Grade 23-11
DIN 3: Ductal Carcinoma *In Situ*, High Grade 23-12
Microinvasive Breast Carcinoma 23-14
Variants of DCIS 23-14
Intraductal Papillary Carcinoma 23-14
Apocrine Intraductal Carcinoma 23-14
Intraductal Clear Cell Carcinoma 23-14
Intraductal Signet Ring Carcinoma 23-14
Intraductal Carcinoma with Secretory Features 23-14
Intraductal Spindle Cell Carcinoma 23-14
Lobular Intraepithelial Neoplasia (LIN) 23-15

IV. Infiltrating Carcinoma 23-16
Infiltrating Ductal Carcinoma 23-16
Reporting of Infiltrating Breast Carcinoma 23-16
Grading of Invasive Carcinomas 23-16
Axillary Lymph Node Status 23-16
Infiltrating Ductal Carcinoma NOS 23-17
Variants of Infiltrating Ductal Carcinoma 23-18
Tubular Carcinoma 23-18
Mucinous (Colloid) Carcinoma 23-19
Medullary Carcinoma 23-19
Apocrine Carcinoma 23-20
Histiocytoid Carcinoma 23-20
Lipid-Rich Carcinoma 23-20
Secretory Carcinoma 23-21
Clear Cell Carcinoma 23-21
Carcinoma with Osteoclast-Like Giant Cells 23-21
Inflammatory Carcinoma 23-22
Adenoid Cystic Carcinoma 23-22
Carcinoma of the Male Breast 23-23
Metaplastic Carcinoma 23-23
Squamous Cell Carcinoma 23-23
Adenosquamous Carcinoma (Mucoepidermoid Carcinoma).....23-24
Adenocarcinoma with Spindle Cell Metaplasia 23-24
Carcinoma with Chondroid Metaplasia 23-24
Infiltrating Lobular Carcinoma 23-24
Papillary Lesions 23-25
Intraductal Papilloma 23-25
Intraductal Papillomatosis 23-25
Atypical Papilloma 23-26
Papillary Carcinoma 23-26
Invasion in Papillary Carcinoma.....23-26
Biphasic Tumors.....23-26
Fibroadenoma 23-26
Phyllodes Tumor.....23-28
Periductal Stromal Sarcoma 23-28
Nipple Lesions 23-29
Paget's Disease 23-29
Nipple Duct Adenoma (Erosive Adenomatosis).....23-29
Syringomatous Adenoma 23-29
Skin Adnexal Tumors 23-30
Myoepithelial Lesions 23-30
Myoepitheliosis.....23-30
Adenomyoepithelioma 23-30
Malignant Myoepithelioma (Myoepithelial Carcinoma) 23-31
Vascular and Vascular-Like Lesions.....23-31
Pseudoangiomatous Hyperplasia 23-31
Vasculitis.....23-32
Microscopic Hemangioma 23-32
Palpable Hemangioma 23-32
Atypical Vascular Lesion 23-32
Angiomatosis 23-32
Hemangiopericytoma 23-32
Angiosarcoma.....23-33
Lymphoid Lesions 23-33
Lymphoma 23-33
Plasmacytoma.....23-34
Granulocytic Sarcoma 23-34
Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease) 23-34

V. TNM Classification of Carcinoma of the Breast (2002 Revision).....23-34

VI. Suggested Reading.....23-35

NON-NEOPLASTIC DISEASES OF THE BREAST

Fibrocystic Change

Clinical

- Occurs in women 20–50 years of age
- May show clinical stages: swelling/tenderness, multiple nodules, larger cysts
- Involutes after menopause unless patient is on hormone replacement therapy
- Alteration of estrogen/progesterone ratio may be cause
- Viewed as aberration of normal involution and development
- No significant increase of cancer risk

Macroscopic

- Variably dense fibrous tissue with cysts 1 mm to 2 cm (blue-domed cysts) in size

Microscopic

- Fibrosis, cyst formation, frequently with apocrine metaplasia, atrophy of acini, variable chronic inflammatory infiltrate, and microcalcifications **(Figure 1)**
- May have some epithelial hyperplasia on the spectrum of ductal intraepithelial neoplasia (DIN, low risk—see discussion later)

Differential Diagnosis

- Lymphocytic mastitis
  - Dense lymphocytic infiltrate around lobules and vessels and atypical stromal cells

Microcalcifications

- May be associated with benign or malignant tissue
- Different patterns seen radiologically can be classified as most likely benign/indeterminate/malignant, but no pattern pathognomonic
- Within malignant breast disease:
  - Microcalcifications present in 94% of comedocarcinoma and 53% of cribriform (low-grade) type
  - Accordingly, mammographic estimation of the extent of DIN is better for higher grade lesions
  - Linear pattern is associated with high-grade DIN; granular pattern with lower grades
- Calcium phosphate:
  - Most common form (90%)
  - Easily visible on H&E
  - Present in benign and malignant lesions
- Calcium oxalate:
  - May be difficult to see on H&E
  - Requires polarized light
  - Usually associated with benign lesions

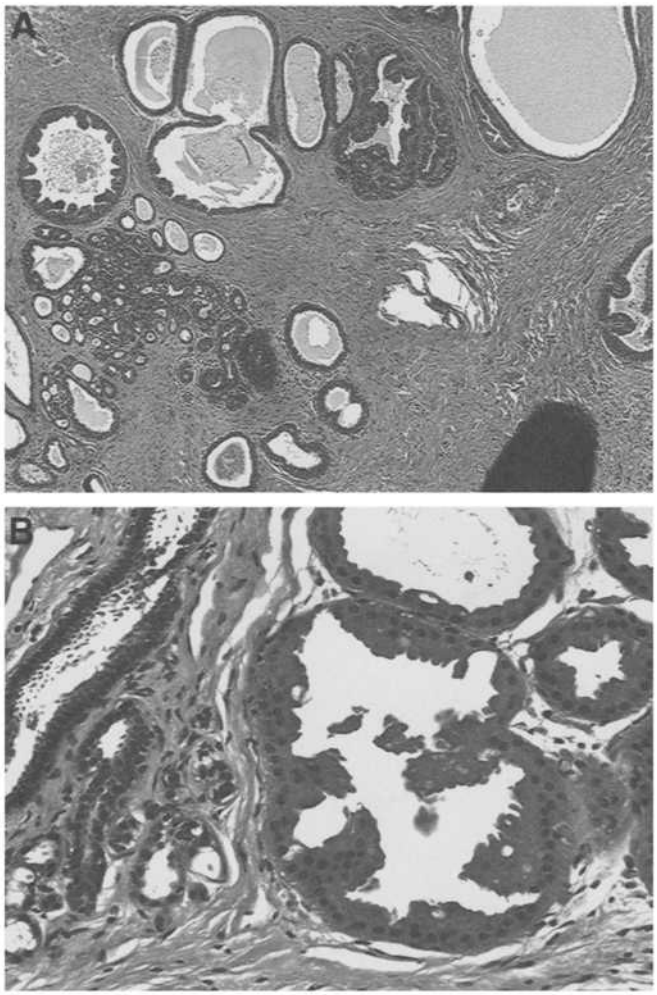


Fig. 1. Fibrocystic changes. **(A)** Cystically dilated ducts and **(B)** Apocrine metaplasia are characteristic.

- Liesegang rings:
  - Laminated inclusions containing calcium, iron, silicone, and sulfur

Mucocele-Like Tumor

Clinical

- Uncommon lesion with no distinctive clinical pattern; microscopic diagnosis

Microscopic

- Single or multiloculated cyst with extravasated mucin
- Epithelium may be in detached strips; occasionally papillary fragments
- Epithelium is cytologically benign and has myoepithelial cells with it
- Cysts have fibrous wall with mild chronic inflammation

Differential Diagnosis

- Mucinous carcinoma:
  - Larger, cytologic atypia; more frequently papillary; cell clusters in lakes of mucin
- Intraductal papillary carcinoma with mucin production
- Infiltrating ductal carcinoma with mucin production

Juvenile Hypertrophy

Clinical

- Excessive and persistent enlargement of one or both breasts in young girls
- Age 11–14 years
- Usually coincides with menarche, but may precede it

Macroscopic

- Appears identical to surrounding breast tissue

Microscopic

- Proliferation of epithelium and stroma
- Proliferation of ductules similar to gynecomastia (see later)
- Proliferation of lobules
- Densely collagenous stroma is common
- Stroma may show pseudoangiomatous hyperplasia

Differential Diagnosis

- Fibroadenoma:
  - Better circumscribed grossly (shells out) and has an intracanalicular or pericanalicular pattern microscopically
- Normal breast tissue:
  - Clinical history may be necessary to distinguish juvenile hypertrophy from normal breast tissue

Gynecomastia

- Gynecomastia is unique to the male breast; other breast lesions/neoplasms may be found in males less commonly than females
- Lesions generally felt to be relatively more common in males include myofibroblastoma (*see* mesenchymal lesions)

Clinical

- Unilateral or bilateral (equal or unequal) breast enlargement
- Most frequent in adolescents and elderly males
- Etiology is either endogenous hormonal imbalance (puberty, senescence, hypogonadism, liver failure) or exogenous (drugs, chemotherapy)

Prognostic Significance

- Usually physiologic if in teens/elderly
- Otherwise requires evaluation of medical status/drug history
- Not a pre-malignant condition

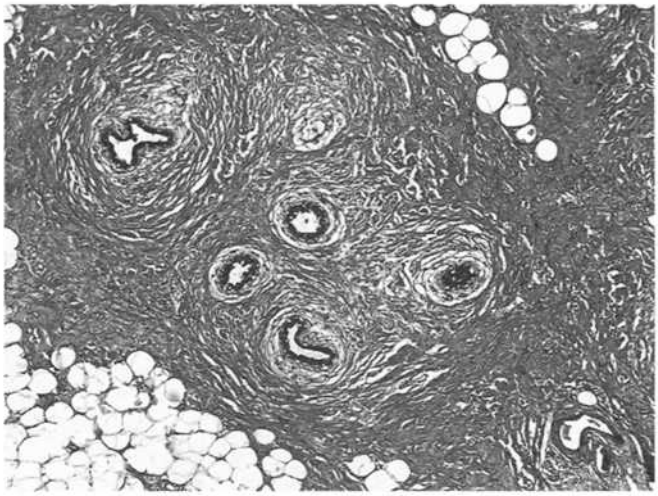


Fig. 2. Gynecomastia: ductules with a cuff of myxedematous stroma proliferate in a dense collagenous stroma.

Macroscopic

- Rubbery gray/white tissue, variable, well-defined

Microscopic

- Florid type:
  - Increased ducts with florid epithelial proliferation, cellular periductal stroma (often myxedematous), and adipose tissue
- Fibrous type:
  - Dilated ducts, mild/moderate epithelial proliferation, hypocellular fibrous stroma, and no adipose tissue **(Figure 2)**
- Hyperplasia is "gynecomastoid:" angulated epithelial tufts with smallest cells at apex
- Myoepithelial layer preserved
- Apocrine and squamous metaplasia may occur
- Lobules are identified in 6% of cases
- Atypical intraductal hyperplasia is occasionally found

Differential Diagnosis

- Not a difficult diagnosis when you suspect it is a male patient

Metaplastic Changes

- Replacement of one cell type (mostly epithelium) with another mature cell type

Apocrine Metaplasia

- Cells with granular eosinophilic cytoplasm, round nuclei, and usually prominent nucleoli **(Figure 1B)**
- Sometimes shows decapitation secretion or coarse hyaline globules
- Frequently occurs in fibrocystic change
- Papillary morphology common in cysts; papillae with fibrovascular cores

Differential Diagnosis

- Apocrine hyperplasia:
  - Diagnosed when there is more than the normal one or two cell thickness
- Atypical apocrine metaplasia or hyperplasia:
  - Nuclei show a three-fold variation in size
- Apocrine intraductal carcinoma:
  - Atypia with luminal necrosis

Clear Cell Metaplasia

- Cytoplasm clear or vacuolated, rather than granular and eosinophilic
- May show PAS+ globules in cytoplasm
- No association with clear cell carcinoma

Squamous Metaplasia

- Associated with:
  - Infarcted papilloma: may follow fine needle aspiration
  - Phyllodes tumor
  - Syringomatous adenoma
  - Ducts associated with periareolar abscess
  - May focally line a biopsy cavity

Mucinous Metaplasia

- Relatively uncommon
- Typically affects normal isolated lobule
- May occur focally in papillomas
- No known pre-neoplastic potential

Lactational Change (Lactational Metaplasia)

Clinical

- Usually reproductive-age females with recent history of pregnancy
- Rarely in postmenopausal females, possibly drug-related (digitalis, neuroleptics); males on stilbestrol
- May present as a mass during pregnancy or at postpartum examination

Macroscopic

- Sharply circumscribed, if involving a pre-existing tubular adenoma (= lactating adenoma), usually <5 cm
- Soft texture

Microscopic

- Lobules expanded
- Secretory pattern:
  - Eosinophilic material in lumen; cells with vacuolated cytoplasm
- Regressive pattern:
  - Less secretion; dilated acini with hobnail hyperchromatic nuclei

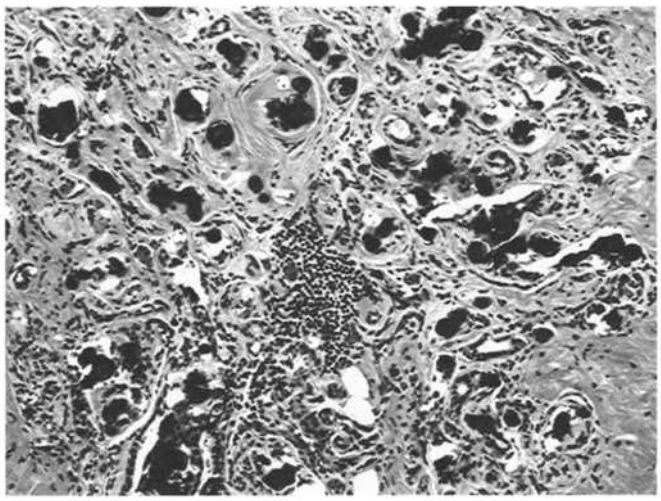


Fig. 3. Sclerosing adenosis retains a lobulated configuration; microcalcification may be abundant.

Differential Diagnosis

- May be mistaken for malignancy on FNA: look for history and foamy background to smear

Sclerosing Adenosis

Clinical

- Relatively common, often bilateral, lesion
- Occasionally forms a palpable mass <2 cm (nodular sclerosing adenosis) in size
- Usually a microscopic finding
- May be associated with increased risk of carcinoma, according to some investigators

Macroscopic

- Cannot be distinguished grossly from fibrocystic change

Microscopic

- Low-power retention of lobulocentric configuration is key to diagnosis **(Figure 3)**
- Fibrosis may distort or obliterate lumens and make myoepithelial cells prominent

Immunohistochemistry

- Smooth muscle actin (SMA) will stain myoepithelial cells, which are preserved in sclerosing adenosis

Differential Diagnosis

- Atypical apocrine adenosis:
  - Shows involvement of lobules by atypical cells with apocrine features
- Invasive carcinoma:
  - No myoepithelial cell layer and no lobulocentric pattern

Table 1. Distinguishing Features of Tubular Carcinoma, Sclerosing Adenosis, and Microglandular Adenosis

	Tubular carcinoma	*Sclerosing adenosis*	*Microglandular adenosis*
Shape of lesion	Stellate, irregular	Lobular, round	Irregular
Shape of glands	Angulated	Round to oval	Round
Luminal contents	Sometimes	Rarely	Frequent, "colloid"
Cell layers	1 (epithelial)	2 (epithelial and myoepithelial)	1 (epithelial)
Cell luminal surface	Snouting	Occasional snouting	Smooth
Cytoplasm	Eosinophilic	Inconspicuous	Clear
Stroma	Desmoplastic	Around lobules	Dense collagenous
Basement membrane	Usually none	Present	Prominent

Microglandular Adenosis (MGA)

Clinical

- Palpable mass in women 28–52 years of age
- Usually 3–4 cm in size

Macroscopic

- No distinguishing features; variably dense, rubbery, fibrous tissue

Microscopic

- Proliferation of duct-like structures in a fibrocollagenous stroma
- PAS+ eosinophilic material in lumen
- Single cell layer; cells with clear cytoplasm
- Stroma varies from hyalinized eosinophilic to loose and paucicellular

Immunohistochemistry

- No myoepithelial cell layer on staining with S-100 or SMA
- Epithelium of MGA is positive for both S-100 and cytokeratin

Ultrastructure

- Preservation of basement membrane, which is often multilayered

*Differential Diagnosis (see **Table 1**)*

- Invasive tubular carcinoma:
  - MGA may also extend into fat
- MGA vs. tubular carcinoma:
  - Characteristic stroma: fibrocollagenous vs. fibroelastotic
  - Round glands vs. angulated
  - Luminal secretions vs. none
  - Clear cytoplasm in lining cells vs. eosinophilic
  - Truncated luminal cell border vs. apocrine snouting
  - Basement membrane vs. none
- Atypical MGA:
  - Some cases of MGA show cytologic atypia and mitotic figures: biologic potential unclear
  - Carcinomas may arise in MGA: most retain S-100 positivity
- Secretory adenosis has a myoepithelial cell layer on immunostaining for actin

Complex Sclerosing Lesion/Radial Scar

Clinical

- Middle age to elderly women
- Frequently multiple and bilateral incidental microscopic findings

Radiology

- May form a stellate mass on mammogram, described as suspicious or malignant

Macroscopic

- May form a palpable mass indistinguishable from invasive carcinoma grossly

Microscopic

- Central fibroelastotic or fibrocollagenous scar
- Stellate arrangement of ducts; zonal pattern may be obscured if only part of lesion is sampled or in core biopsy
- Maximum epithelial proliferation is at periphery
- 30% have some atypical hyperplasia or carcinoma

Differential Diagnosis

- Tubular carcinoma:
  - Distinction may be impossible on needle biopsy
- RS/CSL shows preservation of myoepithelial layer on immunostaining

Duct Ectasia (Periductal Mastitis)

Clinical

- Majority of cases are subclinical
- Patients may have pain and tenderness around nipple or chronic nipple discharge or distortion

Macroscopic

- Periareolar (large) ducts affected
- Dilated ducts with yellow material in lumen, mimicking comedocarcinoma

Microscopic

- Acute stages rarely seen; acute inflammation around and in duct
- Fibrosis leads to duct distortion
- Periductal lymphoplasmacytic infiltrate, pigmented histiocytes
- Foam cells in epithelium and lumen
- Duct may be obliterated by process; "ectasia" a misnomer at this stage

Collagenous Spherulosis

- Incidental microscopic finding; importance is in differential diagnosis

Microscopic

- Spheres of eosinophilic material (20–100 mmm) surrounded by myoepithelial cells, in duct lumens or TDLU (terminal duct-lobular unit)
- Material may be fibrillar, asteroid, or dense and amorphous
- Eosinophilic "cuticle" at periphery characteristic
- Spheres may contain flocculent basophilic material: "mucinous spherulosis"
- The epithelial cell population around collagenous spherulosis may be benign, atypical, or malignant; judge separately from collagenous spherulosis

Immunohistochemistry

- Spheres+ for collagen IV
- Surrounding myoepithelial cells+ for S-100 or SMA

Differential Diagnosis

- Ductal carcinoma *in situ*, cribriform type:
  - May also show basophilic material in spaces; no myoepithelial cells around cribriform spaces
- Adenoid cystic carcinoma:
  - More cellular atypia, usually forms a mass
- Lobular neoplasia with signet ring cells:
  - Look for other cells with intracytoplasmic lumina

Mastitis

Acute Mastitis/Periareolar Abscess

Clinical

- Reproductive years
- Crack in skin of nipple, frequently in nursing women, allows bacterial entry
- Congenital abnormality/inversion of nipple increases risk
- Rarely a surgical specimen

Microscopic

- Squamous metaplasia of large ducts
- Thick-walled abscess cavity
- Staph aureus and anaerobes are usual organisms

Granulomatous Mastitis

- Idiopathic accounts for most cases in the West
- Other causes include:
  - Tuberculosis: necrotizing granulomas; isolation of M tuberculosis required for diagnosis
  - Fungi and protozoa
  - Reaction to duct rupture
  - Reaction to carcinoma
  - Sarcoid: usually in context of established disease elsewhere, rule out other causes
  - Wegener's granulomatosis

Idiopathic Granulomatous Mastitis

Clinical

- Usually reproductive age, but wide range
- Tender, palpable nodule; may be bilateral
- Etiology unknown; epithelial damage may be primary event

Microscopic

- Granulomatous inflammation centered on lobules
- Mixed inflammatory cell infiltrate
- Diagnosis based on excluding other causes of granulomatous inflammation

Silicone Reaction

Clinical

- Leakage of silicone from implants/implant rupture usual cause
- Injection of silicone for augmentation no longer performed
- Reaction may be to additives and/or silicone

Microscopic

- Empty spaces or spaces with refractile foreign material
- Histiocytic or foreign-body giant-cell reaction with fibrosis
- Similar changes frequent in regional nodes

Differential Diagnosis

- Fat necrosis
- Metastatic mucinous carcinoma (lymph nodes or bone marrow)

Lymphocytic Mastitis (Diabetic Mastopathy, Fibrous Mastopathy)

Clinical

- Painless mass
- Wide age range of 24–72 years; occasional cases in males
- Associated with diabetes mellitus or autoimmune diseases

Macroscopic

- Dense rubbery fibrous tissue

Microscopic

- Extensive stromal fibrosis with atrophy of acini
- Dense lymphocytic infiltrate surrounds residual lobules; may have germinal centers
- Lymphocytic perivasculitis or vasculitis a constant feature
- Prominent epithelioid stromal cells, some binucleate

Immunohistochemistry

- Stromal cells negative for keratin; may be KP-1+
- Lymphocytes are B cells

Differential Diagnosis

- Infiltrating carcinoma:
  - Hypocellularity and atypia of stromal cells may suggest lobular carcinoma
- Fibrocystic change:
  - Inflammation in FCC more periductal than perilobular

Amyloidosis

Clinical

- May occur as an amyloid tumor (elderly women) or microscopic finding
- Patients have systemic disease (e.g., rheumatoid arthritis or amyloidosis)

Macroscopic

- Nodule with granular or waxy cut surface

Microscopic

- Amorphous eosinophilic material with giant cell reaction
- Vascular and adipose tissue deposition in non-nodular forms
- Pink on Congo Red stain, apple green birefringence on polarizing

Differential Diagnosis

- May be mistaken for carcinoma clinically and grossly
- Microscopically, elastosis may resemble amyloid
- Areas of collagen in lymphocytic mastitis may resemble amyloid

Fat Necrosis

Clinical

- Usually an incidental microscopic finding, occasionally a palpable mass
- History of trauma or radiotherapy in a minority
- May be accompanied by pain/tenderness/bruising/skin retraction

Macroscopic

- Well-defined, firm area <2 cm in size
- Early lesions show hemorrhage
- Late lesions show scar with cyst formation

Microscopic

- Anucleate fat cells surrounded by foamy histiocytes
- Fibrosis and calcification in later lesions

NEOPLASMS

Benign Epithelial Neoplasms

ADENOMAS

- Benign, well-circumscribed proliferation of tubular structures, lined by epithelium and myoepithelium
- Ductal Adenoma—*See* Sclerosing Papilloma
- Syringomatous Adenoma—*See* Nipple Lesions
- Nipple Duct Adenoma—*See* Nipple Lesions

Tubular Adenoma

Clinical

- 90% of patients <40 years; rare in males
- Mobile mass, may be tender; frequently discovered in pregnancy

Macroscopic

- Solid, firm, tan-yellow nodule >1 cm in size

Microscopic

- Encapsulated or well-defined
- Closely packed tubules
- Hypocellular stroma with scanty lymphocytes
- Epithelium may show mitotic figures, apocrine metaplasia, and lactational or secretory changes; atypia is rare

Differential Diagnosis

- Fibroadenoma has a neoplastic stromal component: Lesions with features of both may occur (combined tubular and fibroadenomas)
- Nodular adenosis: less well-defined/not encapsulated

Lactating Adenoma

Clinical

- Females in reproductive age group; discovered when pregnant or nursing

Macroscopic

- Well-circumscribed, yellow, soft

Microscopic

- May vary according to time of removal
- Sharply circumscribed, lobular arrangement maintained:
  - Pregnancy: secretory material in lumen, vacuolated cytoplasm
  - Postpartum: marked distention, hobnail cells, vacuolated cytoplasm
- Infarction may be seen
- Attenuated myoepithelial cell becomes inconspicuous

Differential Diagnosis

- Lactational change: more diffuse process, similar cytologically
- Carcinoma: pitfall on FNA, look for bubbly background

Pleomorphic Adenoma (Benign Mixed Tumor)

Clinical

- Rare
- Usually elderly female, but also reported in teenagers and males

Macroscopic

- Well-circumscribed, lobulated, myxoid or chondroid appearance

Microscopic

- Identical to those of the salivary glands morphologically
- Epithelial/myoepithelial proliferation in a myxochondroid background with focal ossification

Immunohistochemistry

- Cytokeratin: + in epithelial cells
- SMA/S-100: + in myoepithelial cells
- Glial fibrillary acidic protein: Myoepithelial cells are less commonly + than in salivary gland lesions

Hamartoma

Clinical

- Wide age range, usually 30s or 40s
- Detected on screening; well-delineated density on mammograms

Macroscopic

- Oval, usually approximately 3 cm in size; rubbery consistency

Microscopic

- Well-circumscribed, may be encapsulated
- Variable quantities of fibroadipose or glandular tissue, showing alterations seen in normal breast (fibrocystic change, adenosis)

Differential Diagnosis

- Normal breast:
  - May not be possible to distinguish unless sectioned to show capsule

Benign Mesenchymal Tumors

Fibromatosis

Clinical

- Less common in breast than other sites
- Females, median age = 25; occasionally bilateral
- Mass and skin retraction mimics carcinoma
- Stellate pattern on mammography also suggests carcinoma

Prognostic Significance

- May recur unless fully excised; inking and extensive sampling of specimen important

Macroscopic

- Ill-defined, soft, gray-white lesion, 1–10 cm in size

Microscopic

- Irregular margin with fingers extending into breast tissue and surrounding ducts
- Variably cellular, with intervening collagen; spindle cells are in sheets and occasionally show a storiform pattern of growth
- No or mild atypia
- Mitoses <3/10 HPF with no atypical forms
- No calcification or necrosis; chronic inflammatory cells frequent

Immunohistochemistry

- Spindle cells are + for vimentin and a minority for actin; – for keratin and S-100 protein

Differential Diagnosis

- Low-grade fibrosarcoma:
  - Difficult on occasion; fibrosarcoma has more mitoses and at least some nuclear atypia
- Spindle cell carcinoma:
  - More pleomorphism and mitotic figures with keratin+ spindle cells
- Nodular fasciitis:
  - Rare diagnosis in breast, but may occur on adjacent chest wall; contains occasional multi-nucleated cells; inflammatory infiltrate is at periphery of lesion

Myofibroblastoma

Clinical

- Painless firm mass
- Occurs in males and females
- Excision is curative

Macroscopic

- Nodular, well-circumscribed, rubbery lesions

Microscopic

- Spindle cell proliferation arranged in fascicles and interspersed by bands of dense collagen
- Occasional cases show fat or cartilage
- Some breast ducts may be entrapped in the lesion

Immunohistochemistry

- Vimentin consistently+
- Variable positivity for actin, desmin, S-100, and CD 34
- Negative for cytokeratin

Ultrastructure

- Bundles of 6 nm diameter myofilaments and no tonofilaments
- Rare pinocytotic vesicles
- Elongated nuclei; cytoplasm with prominent rough endoplasmic reticulum and Golgi apparatus

Differential Diagnosis

- Fibromatosis:
  - Has a more infiltrative pattern
- Nodular fasciitis:
  - Stellate pattern, plumper mesenchymal cells
- Neurofibroma:
  - More angulated nuclei
- Neurilemmoma:
  - Antoni A and B areas
- Spindle cell lipoma:
  - Intermixed fat

Granular Cell Tumor

Clinical

- Uncommon in the breast; wide age range; females > males
- May be detected as stellate lesions on mammogram
- May be near the nipple, distorting it
- Cured by excision; <1% malignant

Macroscopic

- Frequently sharply circumscribed firm lesions
- May mimic carcinoma with a stellate shape and firm consistency

Microscopic

- Has a focally infiltrative margin in areas, despite gross appearance
- Sheets, nests, or cords of cells with granular eosinophilic cytoplasm
- Small central nuclei, occasionally mild pleomorphism
- Mitoses rare
- A highly infiltrative variant is often mistaken for carcinoma

Immunohistochemistry

- Diffuse positivity for S-100 protein
- for cytokeratin and EMA

Differential Diagnosis

- Invasive ductal carcinoma:
  - Principally mimics this on gross appearance and FNA
- Normal nipple:
  - Small granular cell tumor may be difficult to see in this region
- Leiomyoma:
  - May arise from smooth muscle in the periareolar region

Neurilemmoma (Schwannoma)

Clinical

- Rare in breast; males and females; wide age range

Microscopic

- Hypercellular (Antoni A) and hypocellular (Antoni B) areas, with Verocay bodies
- Identical to these tumors elsewhere
- Degenerative stromal and nuclear changes may occur

Lipoma

Clinical

- Solitary soft mass; occurs in women in their 40s and 50s

Macroscopic

- Soft, yellow, well-demarcated

Microscopic

- Mature adipose tissue; thin fibrous capsule necessary to make the diagnosis
- Variants:
  - Prominent spindle cells component: spindle cell lipoma
  - Prominent vessels with fibrin thrombi: angiolipoma

Differential Diagnosis

- Normal breast adipose tissue

INTRADUCTAL EPITHELIAL PROLIFERATIONS

- General term = mammary intraepithelial neoplasia
- Divided into DIN and lobular neoplasia (LIN)
- The designation of "mammary intraepithelial neoplasia" may be appropriate when an *in situ* proliferation has both ductal and lobular characteristics or does not quite match one or the other

Summary of Cytologic Characteristics

- See microscopic description of individual categories and **Table 2**

Features of Ductal Proliferations

- Distinct cell borders
- Secondary lumen formation (rosettes)
- Larger nuclei than lobular neoplasia
- Variants: stratified spindle cell, spindle cell, apocrine

Features of Lobular Proliferations

- Indistinct cell borders
- Solid or loosely cohesive pattern of growth
- Intracytoplasmic lumens
- Small, uniform nuclei
- Variants: pleomorphic lobular

Ductal Intraepithelial Neoplasia (see Table 3)

Clinical

- Discovered incidentally on biopsy specimen or following biopsy for mammographically detected microcalcifications
- DIN 1 and higher is a marker for ipsilateral breast tumor recurrence (IBTR); half of these are invasive (*see* Table 3)
- Risk increases with increasing grade
- Risk for an individual patient depends on family history
- Adequacy of surgical margin is increasingly recognized as being of importance in determining the efficacy of breast-conserving therapy for DIN 1 and higher grades

Low risk DIN, (Usual) Intraductal Hyperplasia (IDH)

Microscopic

- Proliferation of cells characterized by difference in cell populations (epithelial and myoepithelial cells participate, heterogenous population), nuclear overlapping, indistinct cell borders, and irregular slit-like secondary lumina **(Figure 4)**

Immunohistochemistry

- Cells react with high molecular weight (HMW) cytokeratins

DIN 1, Flat Type: Flat Epithelial Atypia

Microscopic

- Replacement of native epithelial cells by 1-5 layers of mildly atypical cells
- Monomorphous variant: so-called "clinging carcinoma;" frequently a single layer of abnormal cells around a duct space

Immunohistochemistry

- Cells do not react with HMW cytokeratin
- Cells react with E-cadherin

DIN 1(≤2 mm) : Atypical Intraductal Hyperplasia (AIDH)

- Quantification is required when there is complete duct Involvement

Microscopic

- Proliferation with some cytologic (monotonous population, rounded nuclei, distinct cell borders) and architectural (rounded secondary lumina) atypia
- Quantitatively limited: maximum complete involvement of one or more ducts not exceeding 2 mm in aggregate cross sectional diameter **(Figure 5)**
- Uncommon: AIDH is usually focal

DIN 1(>2 mm): Ductal Carcinoma In Situ, Low Grade

- Patterns of low-grade DCIS include cribriform and micropapillary patterns without necrosis **(Figure 6)**
- small monomorphic cells with round nuclei, regular chromatin pattern and inconspicuous nucleoli

DIN 2: Ductal Carcinoma In Situ, Intermediate Grade

Microscopic

- Low-grade patterns promoted one grade by the presence of necrosis, or low-grade patterns with moderate cytologic atypia

Table 2. Intraductal Hyperplasia (IDH) versus Atypical Intraductal Hyperplasia (AIDH): Distinguishing Features

	IDH	*AIDH*
Cellular proliferation	Two cell types (mixed pattern)	Epithelial only (monotonous pattern)
Secondary lumina	Slit-like, irregular	Rigid "Roman bridges"
Cell borders	Indistinct	Distinct
Nuclei	Variable in shape	Round contour
Nucleoli	Usually absent	Frequently present
Necrosis	May be present	If present = ductal carcinoma *in situ*
High molecular weight cytokeratin	Present	Absent
Smooth muscle actin	+ throughout proliferation	+ at periphery of duct

Table 3. Spectrum of Preinvasive Mammary Ductal Proliferations (Ductal Intraepithelial Neoplasia, DIN)

DIN	*Current designation*	*Atypia/Anaplastic Pleomorphism*	*Necrosis*	*Abs risk of invasion*	*Molecular findings*	*Re-excision if + or close margin*
Low risk DIN	IDH	–/–	– or +*	1.9%	Clonal*/MSI	No
DIN 1, flat type	Flat epithelial atypia	+[f]/–	–**	5.1%–12%	Clonal/LOH	No
DIN 1 (<2 mm)	AIDH	+[f]/–	–**	10%–32%	Clonal/LOH	Yes, if multifocal
DIN 1 (>2 mm)	DCIS, grade 1 (crib/micropapillary)	+[f]/–	–**	?	Clonal/LOH	Yes
DIN 2	DCIS, grade 2 (crib/micropapillary +/– necrosis)	+/minimal or –	+ or –	20%–75%	Clonal/LOH	Yes
DIN 3	DCIS, grade 3 (anaplastic DCIS +/– necrosis)	+++/ +++	Usually present	20%–75%	Clonal/LOH	Yes

IDH = (usual) intraductal hyperplasia, AIDH = atypical intraductal hyperplasia, DCIS = ductal carcinoma in situ, MSI = microsatellite instability
[f]The atypia in all DIN 1 lesions is subtle and in the form of increased nuclear cytoplasmic ratio and without anaplastic pleomorphism
**A few cases of IDH have been shown to be clonal, the presence of necrosis does not exclude the diagnosis of IDH*
***The presence of necrosis in DIN 1 will move it up a grade even when the pleomorphism is minimal*

- Necrosis is nuclear debris of 5 or more cells; apoptosis of individual cells or granular amorphous luminal debris should not be used to diagnose it

Immunohistochemistry

- Cells negative for HMW cytokeratin
- Cells positive for E. cadherin

DIN 3: ductal carcinoma in situ, high grade

Macroscopic

- May be recognized grossly as multiple punctate yellow areas approximately 1 mm in size
- May be up to 8–9 cm in size, with fibrosis around ducts mimicking an invasive carcinoma

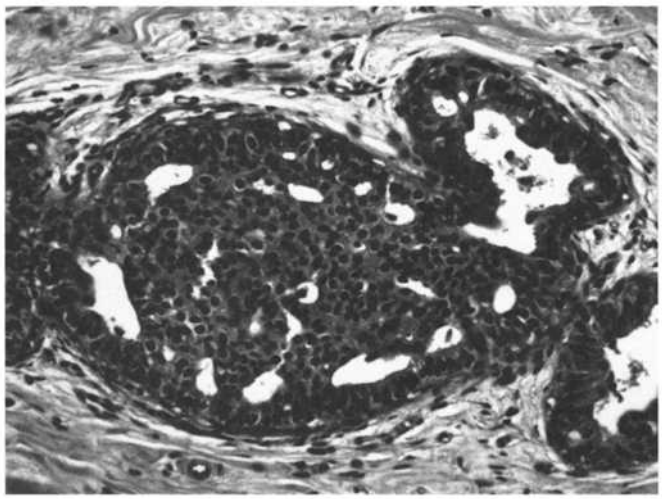


Fig. 4. Low risk DIN (Intraductal hyperplasia). Prominence of peripheral irregularly sized and shaped fenestrations is characteristic. This proliferation is associated with a slightly increased risk for subsequent development of invasive carcinoma.

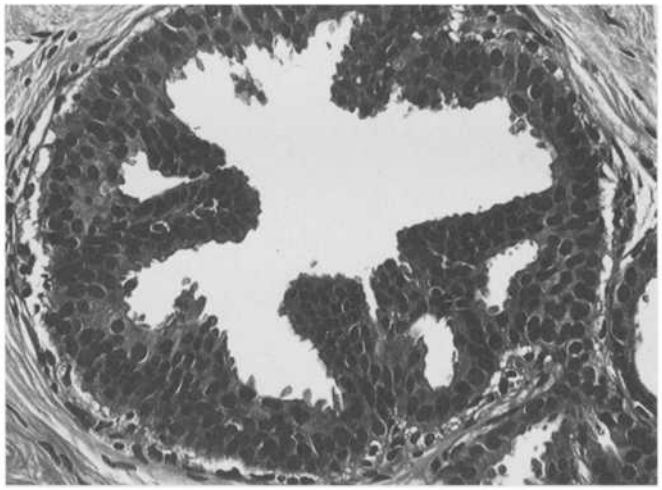


Fig. 5. DIN 1, <2 mm (atypical intraductal hyperplasia). Micropapillae composed of uniform cells partially involve the duct cross section. This limited neoplastic proliferation has a moderately increased risk for subsequent development of invasive carcinoma.

Microscopic

- Any case with severe cytologic atypia is grade 3
- Cases with moderate atypia and necrosis are also grade 3
- Comedocarcinoma should be reserved for grade 3 nuclei with necrosis **(Figure 7)**
- Extensive periductal fibrosis and inflammation common

Immunohistochemistry

- Cells negative for HMW cytokeratin
- Cells positive for E. cadherin

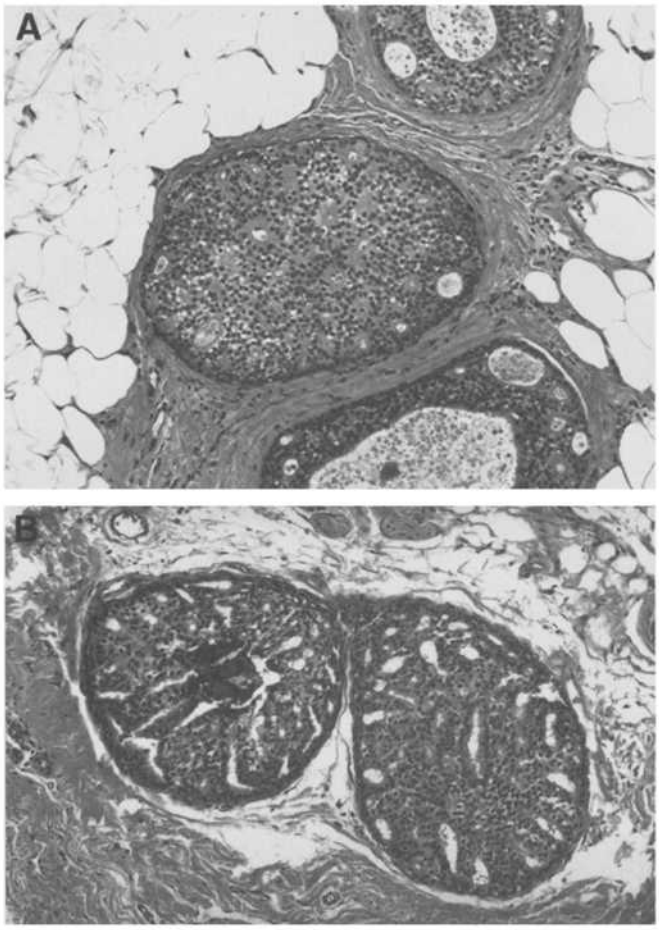


Fig. 6. DIN 1, DCIS, grade 1. **(A)** A sieve-like/cribriform proliferation of uniform cells. **(B)** Microcalcifications are the basis for mammographic detection of these lesions.

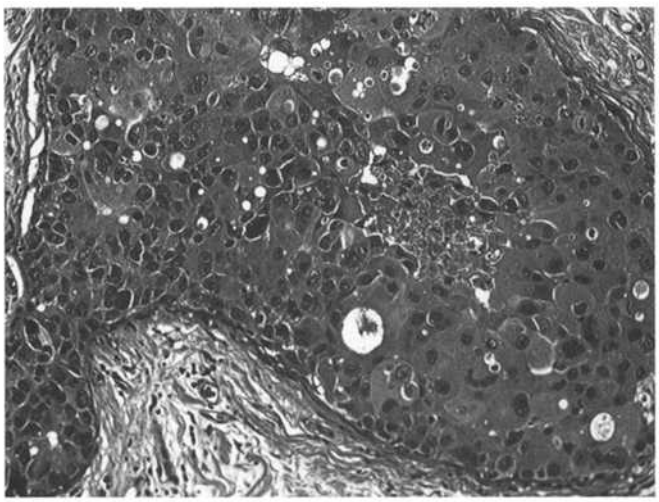


Fig. 7. DIN 3 (Ductal carcinoma *in situ*, grade 3), comedo type. Intraluminal necrosis and cytologic atypia are present. DIN 3 is preinvasive lesion with the highest risk for progression to an invasive carcinoma.

- C-erb-B2 and p53 status correlates with grade
- ER/PR not generally performed on *in situ* lesions

Microinvasive Breast Carcinoma

- A cluster of tumor cells breaking through the basement membrane infiltrating the periductal stroma, with or without visible continuity with that duct, the diameter of the area not exceeding 2 mm
- If multiple, up to 3 foci, each up to 1 mm in diameter

Clinical

- If clearly defined, cases with microinvasion can be managed as DCIS
- Up to 3% of cases diagnosed as DCIS reportedly have lymph node metastases. These arise from areas of invasive carcinoma not detected in the biopsied or sampled areas

Macroscopic

- Cannot be distinguished from intraductal carcinoma

Microscopic

- Tongue-like projection from a duct or small group of cells beside a duct with DCIS
- Stroma frequently fibroblastic and myxoid

Variants of DCIS

Intraductal Papillary Carcinoma

- *See* separate section (Papillary Lesions)

Apocrine Intraductal Carcinoma

Clinical

- No definitive clinical significance; importance is in differential diagnosis
- High proportion have androgen receptors and are devoid of estrogen and progesterone receptors

Microscopic

- Apocrine cytology: granular eosinophilic cytoplasm, prominent nucleoli
- Apical snouting and cytoplasmic vacuolization variable
- Architectural patterns include solid or cribriform, rarely papillary types
- Two variants described:
  - Necrotic variant shows luminal necrosis and severe atypia
  - Non-necrotic variant has more variable atypia, usually solid or cribriform

Differential Diagnosis

- Apocrine metaplasia/hyperplasia:
  - No nuclear atypia; papillary fronds have fibrovascular cores
- Atypical apocrine metaplasia:
  - Atypia = 3-fold variation in nuclear size
- Atypical apocrine hyperplasia:
  - Atypia and more than 2 cell layers
  - Epithelial bridges lacking fibrovascular cores, even with bland cytology; imply a diagnosis of atypical apocrine hyperplasia

Intraductal Clear Cell Carcinoma

Microscopic

- Cells with optically clear cytoplasm and distinct cell borders
- May be mixed with other patterns
- May have associated invasive clear cell carcinoma

Intraductal Signet Ring Carcinoma

Microscopic

- Rare variant, composed of cells with a signet ring morphology

Differential Diagnosis

- Intraductal papillary carcinoma:
  - May have a signet ring component
- Mammary intraepithelial neoplasia:
  - Proliferation may have mixed ductal and lobular features
- Collagenous spherulosis:
  - Flattened myoepithelial cell nuclei at periphery of aggregates of collagen may mimic signet ring cells

Intraductal Carcinoma with Secretory Features

Microscopic

- Rare variant
- Dilated ducts with eosinophilic luminal secretion
- Epithelial tufting (papillary), cribriform growth most usual
- Mitotic figures present
- Moderate nuclear atypia
- Cytoplasmic vacuolization

Differential Diagnosis

- Lactational change:
  - More generalized change (but not invariably); cribriform growth not a feature

Intraductal Spindle Cell Carcinoma

Microscopic

- Rare variant; importance lies in differential diagnosis
- Monotonous proliferation of elongated cells, forming solid pattern
- Often admixed with a relatively solid variant of cribriform DCIS

Differential Diagnosis

- Intraductal hyperplasia:
  - Has a spindle cell population, but does not display the monotony of spindle cell IDCA
- Solid papillary carcinoma:
  - May have spindle cell component

Lobular Intraepithelial Neoplasia (LIN)

Clinical

- A pathologic diagnosis
- Occurs in 0.3–3.8% of all breast biopsies
- Natural history difficult to determine
- Marks patients as being at increased risk of invasive carcinoma, both lobular and ductal, in both breasts
- Risk is higher in the ipsilateral breast
- Patients with grade 3 lesions are at higher risk
- Ductal involvement is not a risk factor for recurrence
- Role of family history in increasing risk not determined

Macroscopic

- Not detectable macroscopically

Microscopic

- Generally, a population of small uniform cells lacking nucleoli **(Figure 8)**
- Intracytoplasmic lumina present
- Cell borders indistinct; cells frequently loosely cohesive
- Extension into terminal ducts found in approximately 2/3 of cases **(Figure 9)**
- Necrosis or calcification rare
- "Clover-leaf pattern" due to unfolding of TDLU

Immunohistochemistry

- Cells are negative for E. cadherin
- Cells are positive for HMW cytokeratin

Grading (Adapted from the 2003 WHO Classification of Breast Tumors)

- LIN grade 1:
  - Partial or complete replacement of normal acinar epithelium; lobules are not distended
- LIN grade 2:
  - Distention of some acini, but preservation of interlobular stroma
- LIN grade 3:
  - Massive distention and confluence of acini
  - Necrosis is rarely observed with or without microcalcifications
  - Signet ring cell form also graded as 3

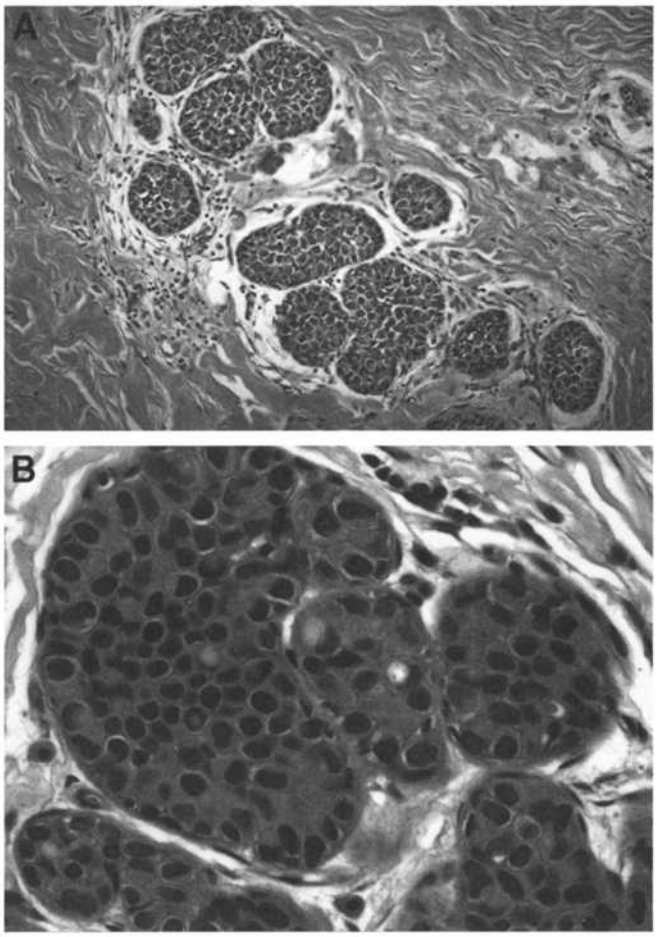


Fig. 8. Lobular intraepithelial neoplasia. **(A)** Solid occlusive proliferation of uniform, loosely cohesive small cells. **(B)** Nuclear pleomorphism/atypia occurs in a small proportion of LIN lesions.

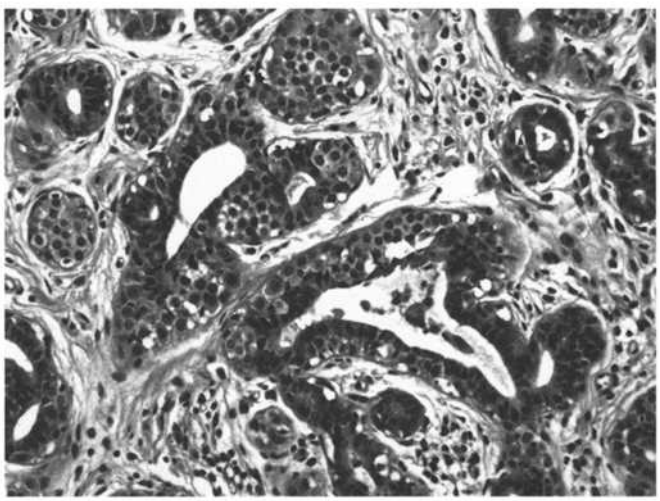


Fig. 9. Pagetoid extension of neoplastic lobular cells to adjacent ducts.

Differential Diagnosis

- Atypical intraductal hyperplasia:
  - *See* cytologic features listed above
  - Some cases may be impossible to distinguish from AIDH
  - Use the designation "mammary intraepithelial neoplasia"
- Collagenous/mucinous spherulosis:
  - Increased difficulty when LIN involves a pre-existing benign lesion that alters architectural pattern (e.g., sclerosing adenosis, complex sclerosing lesions)

INFILTRATING CARCINOMA

Infiltrating Ductal Carcinoma

- Most cases are "not otherwise specified" (NOS); to be regarded as a subtype, a pattern should comprise >90% of the tumor

Reporting of Infiltrating Breast Carcinoma

- Essential features include:
  - Laterality
  - Type of biopsy specimen
  - Size of tumor (maximum dimension in cm)
  - Grade of tumor
  - Margin status
  - *In situ* component
  - Presence or absence of lymphovascular invasion
  - ER/PR status

Grading of Invasive Carcinomas

- Modified Scarff-Bloom-Richardson system is the one most commonly used
- Tumor is graded by scoring each of the following features:
  - Tubule formation:
    - >75% = 1
    - 10–75% = 2
    - <10% = 3
  - Nuclear pleomorphism:
    - This is both a qualitative and a quantitative assessment
    - Uniform small regular nuclei = 1
    - Moderate variation in size and shape, occasional nucleoli = 2
    - Marked variation in size and shape, prominent nucleoli = 3
  - Mitotic activity:
    - Unequivocal mitotic figures are counted at the periphery of the tumor
    - At least 10 high power fields are counted
    - The range of figures that gives each score correlates with field diameter (and field area); for example, for Olympus BX 40, HPF (x400) = 0.55 mm diameter, scores are
      - 0–7/10 HPF = 1
      - 8–15/10 HPF = 2
      - >15/10 HPF = 3
- The scores are added to give the grade:
  - 3–5 = well-differentiated, Grade 1
  - 6–7 = moderately differentiated, Grade 2
  - 8–9 = poorly differentiated, Grade 3

Axillary Lymph Node Status

Clinical

- Clinical assessment of nodal status is incorrect in 50% of cases
- Nodes should be submitted entirely, unless grossly involved (sampled)
- Highest node should be designated by the surgeon (i.e., level 2 or level 3)

Macroscopic

- Metastatic tumor gives firm yellow-white appearance
- Sinus histiocytosis (especially with previous biopsy) may give soft enlarged pale node

Microscopic

- Metastatic tumor fills and expands sinuses first, may replace node
- May resemble primary tumor pattern or show variation in pattern
- Extracapsular extension should be documented in report

Differential Diagnosis

- Negative lymph node:
  - Deeper levels will increase yield in 9–33% of cases
  - Immunostain for keratin may be necessary to detect small metastases, especially lobular carcinoma
- Sinus histiocytosis:
  - Bland reniform nuclei, sinuses expanded
- Metastatic melanoma:
  - Breast cancer may also be S-100+; only melanoma is HMB-45+ also
- Benign inclusions:
  - Epithelial or melanocytic, located in capsule of node

Table 4. Infiltrating Ductal Carcinoma versus Infiltrating Lobular Carcinoma*

	Ductal carcinoma	*Lobular carcinoma*
Relative frequency	80–85%	< 10%
Pattern of infiltration	Nests/sheets of cells	Single file, "targetoid"
Intervening stroma	Often scanty	Extensive
Tubule formation	Present	Absent
Cell size	Moderate to large	Usually small
Signet ring cells	Rare	Frequent
Associated lesions**	Ductal carcinoma *in situ*	Lobular neoplasia

** Borderline forms occur (i.e., ductal carcinoma with lobular features); rarely, the two types coexist. A combined pattern—tubulolobular*

*** An in situ component is not necessary for diagnosis*

Infiltrating Ductal Carcinoma NOS (Table 4)

Clinical

- Increasing proportion detected mammographically
- Many detected on clinical examination; average size has decreased from 2 cm to 1.2 cm
- If there is "extensive ductal carcinoma *in situ*" (i.e., DCIS comprising >25% of the tumor and extending beyond the invasive component), conservative therapy is less likely to be successful
- Mutations in BRCA1 (located on chromosome 17q21) and BRCA2 (located on chromosome 13q12-13) genes are responsible for approximately 80% of familial early-onset cases
- Individuals who carry BRCA1 mutation have high risk (up to 85%) of developing breast cancer by age 70
- Patients with Her-2/neu oncogene amplification may have worse prognosis

Macroscopic

- Firm, gray, stellate or discrete nodule **(Figure 10)**
- Adjacent fat shows deep yellow-orange tinge
- Cutting gives a texture described as "unripe pear"
- May have punctate yellow foci representing *in situ* component with comedo necrosis

Microscopic

- Proliferation of epithelial cells with varying degrees of glandular differentiation and nuclear atypia **(Figures 11,12)**
- Intraductal carcinoma present in 80% of cases, confirms a primary breast neoplasm
- Variable lymphoplasmacytic reaction

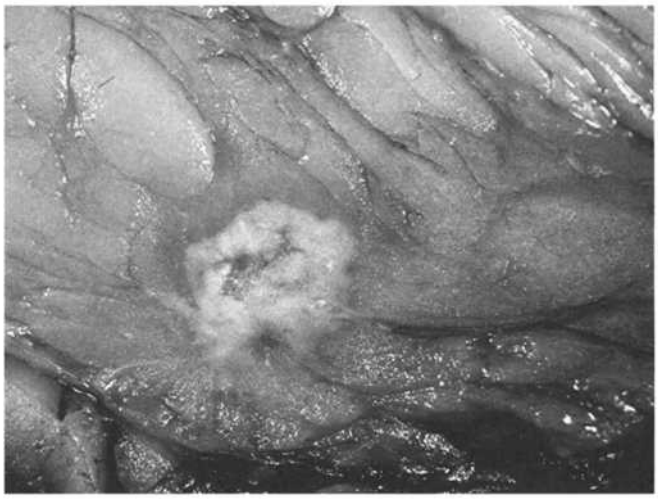


Fig. 10. Infiltrating duct carcinoma—a sharply delineated mass was clinically palpable in a 69 y/o.

Immunohistochemistry

- ER/PR can be performed on formalin-fixed paraffin embedded material, called + if ≤ 10% of tumor cell nuclei are + **(Figure 13)**
- SMA may be useful in confirming invasive carcinoma
- Neuroendocrine markers (chromogranin A and synaptophysin) confirm neuroendocrine differentiation in some tumors: no definitive prognostic significance
- Gross Cystic Disease Fluid Protein-15 is +

Differential Diagnosis

- Intraductal carcinoma:
  - Most important differential; establishing this is more important than keeping frozen tissue for markers

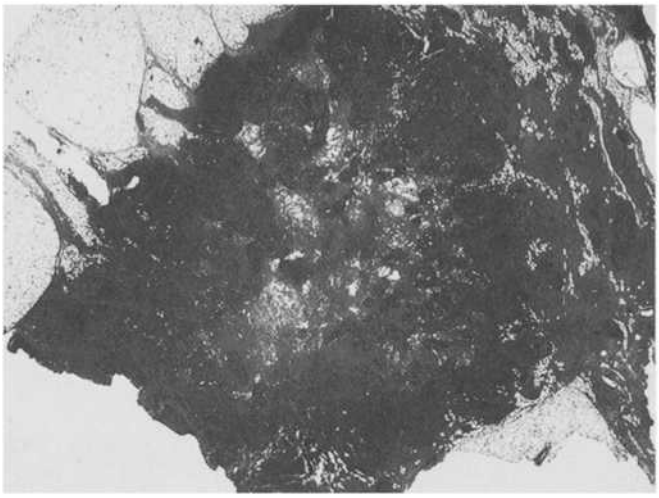


Fig. 11. An infiltrating duct carcinoma at low magnification appears well defined.

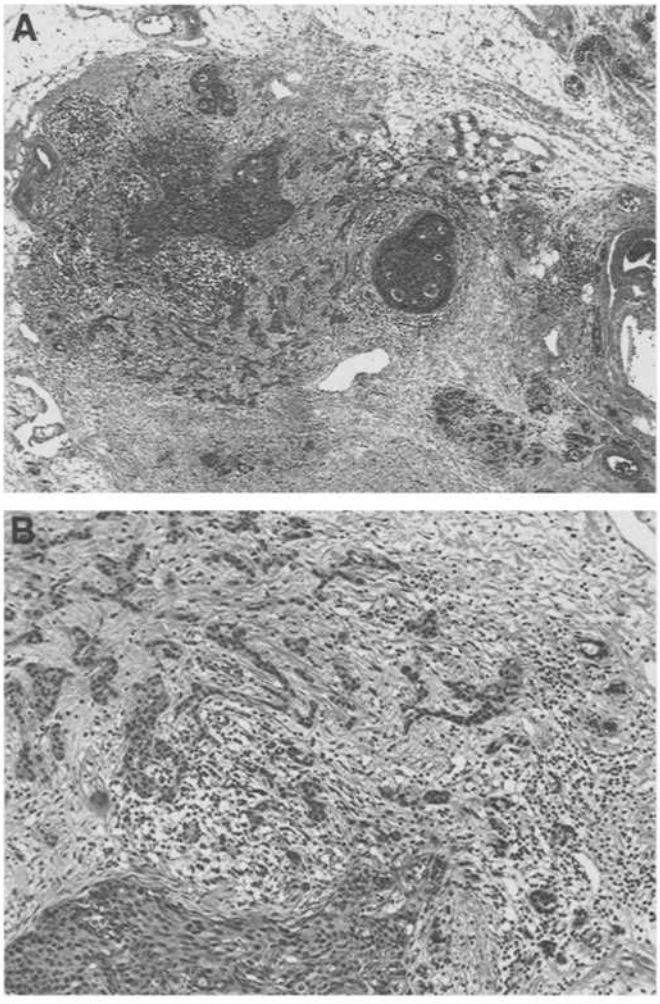


Fig. 12. Early infiltrating duct carcinoma **(A)**; at higher magnification shows infiltration of stroma in irregular angulated clusters **(B)**.

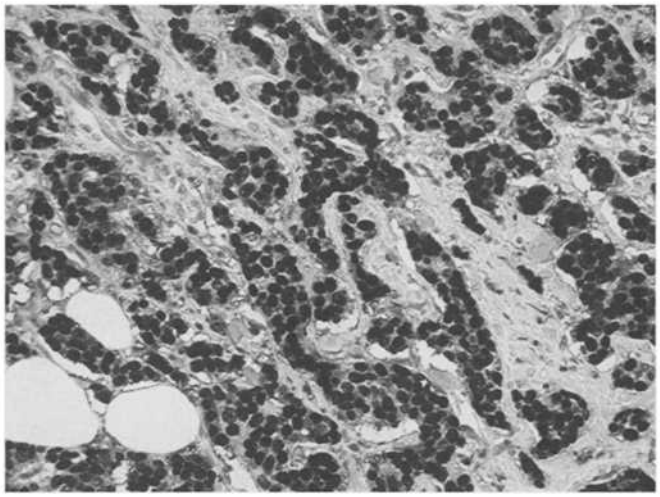


Fig. 13. Nearly all well differentiated invasive carcinomas show immunoreaction for estrogen receptor. Estrogen receptor- immunostain shows nuclear positivity in 100% of tumor cells in this case.

- Specific subtypes of breast carcinoma (*see* below)
- Metastatic carcinoma:
  - *In situ* component is not present

Variants of Infiltrating Ductal Carcinoma

Tubular Carcinoma

Clinical

- Over-represented in carcinomas detected by screening/carcinomas <1 cm (8%)
- Appears as a stellate lesion on mammogram
- Median age is slightly younger than other breast carcinomas

Prognostic Significance

- Lower incidence of axillary nodal metastases (8–20%, 1.4% if tumor is <1 cm)
- Excellent survival (>90% 10 years) for pure variety
- Misdiagnosis as radial scar is a pitfall

Macroscopic

- No distinguishing features from other ductal carcinomas; usually small, firm, gray/white lesion

Microscopic

- Requirement of a pure pattern for this diagnosis ascertains a distinctive category with excellent prognosis
- Many authors also accept up to 25% of other (usually cribriform) component
- Haphazard arrangement of tubules with open lumens, frequently comma-shaped **(Figure 14)**
- Single cell lining

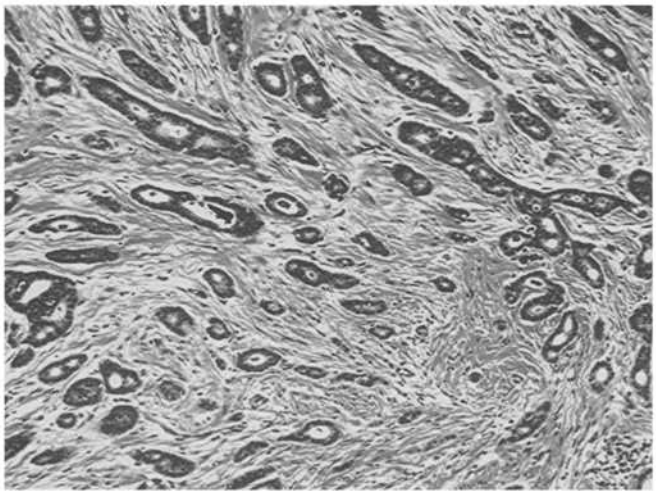


Fig. 14. Tubular carcinoma shows a haphazard distribution of tubules in a prominent reactive stroma.

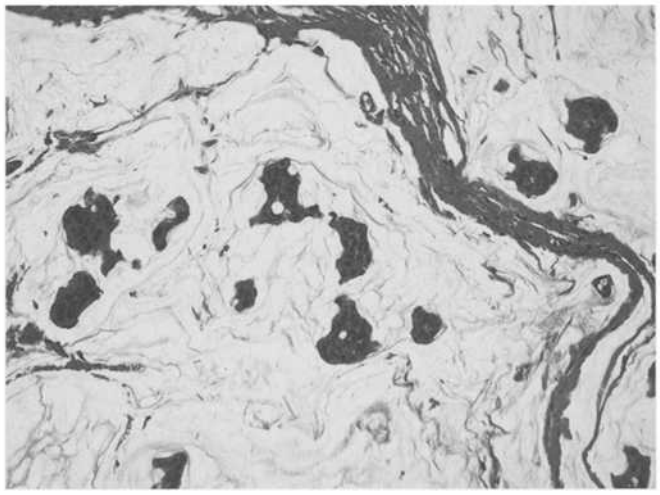


Fig. 15. Mucinous carcinoma—clusters of carcinomas cells float in lakes of mucin. an uncommon variant of invasive mammary carcinoma is associated with an excellent prognosis and a low frequency of node metastases.

- Nuclei show little pleomorphism; mitoses rare
- Apical snouting common
- Classic lesions show a reactive fibroblastic stroma, but it may be densely collagenous, or show smooth muscle metaplasia
- Basement membrane patchy/absent (PAS stain)

*Differential Diagnosis (see **Table 1**)*

- Radial scar:
  - Similar mammographic appearance; immunostain for actin shows myoepithelial layer present in radial scar
  - Secondary features that help make the distinction include elastotic core in RS
- Mixed tubular carcinoma (75–99% tubular):
  - Term is used where tubular pattern is not pure (solid areas, higher grade nuclei)
- Sclerosing adenosis:
  - Retains a lobulated outline, lumens compressed/obliterated, two cell layer present
- Microglandular adenosis:
  - More rounded glands with central secretory material and stroma densely collagenous

Mucinous (Colloid) Carcinoma

Clinical

- Rare carcinoma (1–6% of infiltrating ductal carcinomas)
- Mean age = 60 years, slightly older than other forms

Prognostic Significance

- Low rate of axillary node metastases (3–15%) in pure form
- Better survival (>80% at 10 years) than ductal carcinoma NOS
- Increased size, hypercellularity, and nodal metastases predict more aggressive course

Macroscopic

- Well-circumscribed, gray, gelatinous nodule; may be multiple

Microscopic

- May occur in pure or mixed (with infiltrating ductal carcinoma NOS) forms
- Pure form can be divided into hypocellular and hypercellular variants
- Small clusters of tumor cells, in solid, papillary, or glandular patterns, floating in abundant extracellular mucin **(Figure 15)**

Immunohistochemistry

- Chromogranin and S-100 protein frequently +
- ER + in ~50–75% of cases, PR + in 14%

Differential Diagnosis

- Infiltrating ductal carcinoma NOS
- Mucocele-like lesions:
  - A ruptured cyst with benign epithelial and myoepithelial elements in mucus
  - Usually <5 mm in size
  - Immunostain for actin may help in the demonstration of myoepithelial cells

Medullary Carcinoma

Clinical

- Uncommon (5–7% of ductal carcinomas); *see* below
- Occurs at average age (50 years)

Prognostic Significance

- Better prognosis: 80–90% 10-year survival
- In contrast, "atypical medullary carcinoma" does not differ in prognostic terms from ductal carcinoma NOS

Macroscopic

- Well-circumscribed, soft, fleshy tumor, yellow/hemorrhagic appearance; may show necrosis and cyst formation

Microscopic

- When strict criteria are used in diagnosis, this is a rare tumor
- Essential features:
  - Circumscribed, non-infiltrative periphery
  - Lymphoplasmacytic infiltrate of at least moderate degree at periphery
  - Syncytial growth pattern makes up >75% of tumor mass; no discrete cell borders
  - Fine (not dense) collagen bands intersect tumor
  - Grade 2-3 nuclei; usually vesicular with prominent nucleoli
  - Absence of intraductal component
- Also seen are:
  - Lymphoplasmacytic infiltrate extending into fibrous septa
  - Necrosis/cyst formation
  - Prominent mitoses
  - Squamous metaplasia
  - Granulomatous reaction

Immunohistochemistry

- ER+ in <1/3 of cases

Differential Diagnosis

- "Atypical medullary carcinoma":
  - An infiltrating ductal carcinoma with some, but not all, of the above features; far more common than true medullary carcinoma
  - This term no longer utilized

Apocrine Carcinoma

- Carcinoma composed predominantly of cells with abundant granular, eosinophilic cytoplasm; distinct cell borders; and central nuclei with prominent nucleoli

Clinical

- Frequency depends on application of definition, probably < 0.5% of carcinomas
- Males and females, generally older ages

Prognostic Significance

- No conclusive evidence of better or worse behavior than ductal carcinoma NOS

Macroscopic

- Firm, partly cystic, occasionally tan color

Microscopic

- Apocrine cytology as above
- Nuclear pleomorphism may be marked and overlap with that seen in benign apocrine lesions
- Cytoplasm may contain coarse eosinophilic granules and lipofuscin
- Luminal/cystic areas show decapitation secretion
- Intraductal component is usually apocrine IDCA

Immunohistochemistry

- Gross cystic disease fluid protein (GCDFP-15) staining is variable (~75%)
- Androgen receptor+; high-grade lesions loose AR expression
- B72.3, CEA, cytokeratins also+
- S-100 protein–

Differential Diagnosis

- Apocrine metaplasia, with or without atypia, in sclerosing adenosis:
  - Definite infiltrative pattern should be seen for a diagnosis of invasive carcinoma
- Sclerosing adenosis:
  - Lobular configuration retained
- Histiocytoid (pleomorphic lobular) carcinoma:
  - Has eosinophilic cytoplasm, intracytoplasmic lumina, and mucin
- Lipid-rich carcinoma:
  - More vacuolated and foamy cytoplasm
- Squamous cell carcinoma:
  - Cytologically may be similar, but contains glycogen on PAS staining
- Granular cell tumor:
  - Small nuclei, S-100+

Histiocytoid Carcinoma

- *see* Lobular Carcinoma, Pleomorphic Variant

Lipid-Rich Carcinoma

- Invasive carcinoma, in which at least 80% of cells contain neutral lipid and show cytoplasmic vacuolization; extremely rare subtype

Clinical

- Little distinctive features; chalky elastotic foci less likely

Prognostic Significance

- May be a more aggressive variant; too few cases reported to reach a definitive conclusion

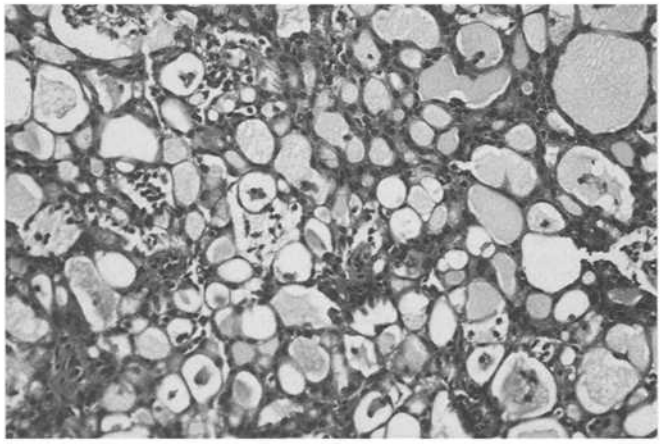


Fig. 16. Secretory carcinoma has abundant intra and extracellular secretory material.

Microscopic

- Fixed material shows cells with foamy cytoplasm and nuclei with prominent nucleoli
- Frozen tissue stained with oil-red O (ORO) demonstrates fat. Diagnosis must be considered at time of frozen section to enable confirmation by optimal ORO stain

Immunohistochemistry

- ER/PR–

Differential Diagnosis

- Ductal carcinoma NOS:
  - May have sebaceous foci and lipid on ORO staining
- Pleomorphic lobular carcinoma

Secretory Carcinoma

Clinical

- Younger age (median = 25 years) than other breast carcinomas
- Has been reported in males pre- and post-puberty

Prognostic Significance

- Age dependent: patients <20 years do well, recurrences may be years later and the course indolent; axillary node metastases rare in children, but occur in adults
- Course resembles ductal carcinoma NOS in older patients

Macroscopic

- Firm, usually well-circumscribed, gray-white lesions; can mimic fibroadenoma

Microscopic

- Abundant intra- and extracellular eosinophilic secretory material **(Figure 16)**
- Bland nuclei; scanty mitotic figures
- Intraductal component may be present and have a secretory pattern
- Papillary pattern may be present
- Pushing margin
- Histochemistry: PAS and DPAS+, alcian blue+, focal mucicarmine positivity

Clear Cell Carcinoma

Clinical

- Uncommon variant; middle aged to elderly females

Prognostic Significance

- More aggressive than ductal carcinoma NOS; higher incidence of nodal metastases; more aggressive course

Macroscopic

- Mass 2–8 cm, no specific gross features

Microscopic

- 90% of cells should have clear or finely granular eosinophilic cytoplasm for diagnosis
- Clear pattern is due to glycogen (PAS+, removed by diastase)
- Grows in solid nests, occasionally papillary formations
- Intraductal clear cell component may be present
- Nuclei are usually grade 2; tumor is usually grade 3 on SBR grading

Differential Diagnosis

- Ductal carcinoma NOS with clear cell areas comprising < 90% of tumor
- Adenomyoepithelioma:
  - Shows positivity for actin and/or S-100
- Clear cell hidradenoma (eccrine acrospiroma):
  - Look for two cell types and evidence of duct differentiation
- Lipid-rich carcinoma:
  - ORO and PAS stains+
- Metastatic clear cell tumors, especially renal cell carcinoma; look for intraductal component

Immunohistochemistry

- Few cases studied are ER/PR–

Carcinoma with Osteoclast-Like Giant Cells

Clinical

- No specific features: uncommon variant
- Frequently well-circumscribed on mammography

Prognostic Significance

- Recurrences and metastases in 1/3 of cases: no significant prognostic difference from ductal carcinoma NOS

Macroscopic

- Soft, hemorrhagic, red-brown tumor in contrast to most breast carcinomas

Microscopic

- Numerous osteoclast-like giant cells present adjacent to tumor cells
- Characteristic hemorrhagic fibroblastic stroma with chronic inflammatory cell infiltrate
- Giant cells may be present in metastatic deposits

Immunohistochemistry

- Giant cells are acid phosphatase, KP-1 and α-1-anti-trypsin+ and keratin–, confirming histiocytic origin

Differential Diagnosis

- Metaplastic carcinoma:
  - May have giant cells in addition to chondroid and osseous differentiation
- Poorly differentiated carcinoma with tumor giant cells:
  - Keratin+
- Granulomatous inflammation with giant cells:
  - Keratin–

Inflammatory Carcinoma

Clinical

- Characterized by the clinical appearance of red, tender/painful, warm lesion with skin dimpling/peau d'orange, and diffuse induration of the breast **(Figure 17)**
- The clinical diagnosis is more frequent (5–10%) than the pathologic counterpart (0.5–1%) (see below)

Prognostic Significance

- Axillary nodal metastases are present in most cases
- Tumors with either clinical or pathological features of inflammatory carcinoma are aggressive; fatal within 2 years before chemotherapy
- Currently, 25–50% 5-year survival; worse than ductal carcinoma NOS

Macroscopic

- Large tumor or diffuse mammary involvement
- Skin thickening apparent
- Changes may spread to chest wall

Microscopic

- Invasive ductal carcinoma with plugging of dermal lymphatics by tumor emboli is the usual pathologic finding
- This may be prominent or focal
- May show a mononuclear infiltrate
- Increase in dermal collagen and lymphatic dilatation also seen
- There is not an absolute correlation between the clinical and pathological picture; there may be clinically inflammatory carcinoma without lymphatic plugging and vice versa

Immunohistochemistry

- ER – in > ½ of tumors, PR – in ⅔

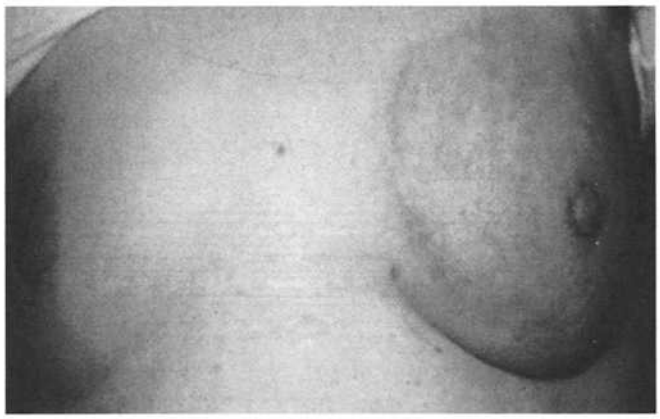


Fig. 17. Inflammatory carcinoma- the breast appears red, inflamed and with a peau d'orange appearance of skin. This aggressive form of breast carcinoma with an inflamed appearance to the skin and nipple retraction is due to invasion of dermal lymphatics by carcinoma.

Differential Diagnosis

- Clinical picture resembles acute inflammation/erysipelas; skin does not contain neutrophils

Adenoid Cystic Carcinoma

Clinical

- Rare tumor in this location
- Presents as painless mass, occasionally of some years duration; median age = 50–63 years; females > males

Prognostic Significance

- Much less aggressive than its salivary gland counterpart; reason unclear
- Lymph node or pulmonary metastasis rare but long-term follow-up required
- Most cases treated by mastectomy; has usually been curative

Macroscopic

- Variable size, mean = 2 cm
- Well-circumscribed, firm, gray/yellow mass; occasionally cysts present

Microscopic

- Histologically identical to salivary gland ACCs
- Two cell types:
  - Basaloid cells and cells with eosinophilic or clear cytoplasm
- Lumens contain three types of material in very variable proportions:
  - Hyaline bodies: dense eosinophilic, PAS+ replicated basal lamina
  - Mucoid secretory material
  - Eosinophilic "cuticle" with or without luminal material

- Sebaceous differentiation seen in a minority of tumors
- Perineural invasion occasionally seen
- Histologic grading of limited use: low grade show dominant cribriform pattern; high grade show predominant solid basaloid pattern

Immunohistochemistry

- Basaloid cells are vimentin + and variably + for actin and S-100
- Eosinophilic cells are keratin and EMA+

Differential Diagnosis

- Collagenous spherulosis:
  - Usually an incidental microscopic finding; spherules are surrounded by myoepithelial cells with no atypia
- Cribriform carcinoma:
  - Does not have two cell types

Carcinoma of the Male Breast

Clinical

- ~1% of incidence of breast cancer in women
- Occurs in an older age group than in women (mean = 60+ years vs. 50+ years)
- May present as an asymptomatic mass, nipple discharge, or Paget's disease
- Most are located centrally in the breast
- Risk factors include Klinefelter's syndrome (47 XXY); 3–6% develop breast carcinoma

Prognostic Significance

- Formerly thought to have a much worse prognosis; more recent studies suggest it is similar to stage-matched female patients
- High incidence of metastases (55%)
- Central location means increased internal mammary lymph node metastases
- Tumors should be graded as in carcinomas from female patients

Macroscopic

- Most tumors < 3 cm

Microscopic

- All tumor types except *in situ* and invasive lobular carcinoma are found
- Most are infiltrating ductal carcinoma
- Papillary carcinomas comprise a greater percentage than in women

Immunohistochemistry

- A higher proportion are ER + (80–90%) than in women and >50% of these are hormone-responsive
- PR are + 25–75% of cases
- Prostate-specific antigen (PSA) has been demonstrated in primary breast carcinomas

Differential Diagnosis

- Metastatic adenocarcinoma:
  - Especially from prostate, in a male treated with estrogen for prostate cancer
  - Less common with antiandrogen treatment (now preferred)
  - Clinical history and PSA and PSAP needed for diagnosis

Metaplastic Carcinomas

- Malignant tumors with an epithelial or mesenchymal population different from or in addition to adenocarcinoma
- Histogenesis is uncertain and designation is on the basis of morphology and immunohistochemistry and/or ultrastructure
- Traditionally, the more common metaplastic carcinomas (i.e., apocrine carcinomas) are not designated as such

Squamous Cell Carcinoma

Clinical

- Very rare tumor in pure form; significantly < 1% of primary breast carcinomas

Prognostic Significance

- Variable reports claiming better or worse than ductal carcinoma NOS; prognosis may be more related to grade than squamous features

Macroscopic

- Characteristic feature is multiple cysts

Microscopic

- Variable appearance: Keratinizing, acantholytic, and spindled are described
- Intercellular bridges and keratohyaline granules seen in benign or well-differentiated squamous elements
- Mixtures of these types are common
- Central cyst and prominent reactive stroma are frequent

Immunohistochemistry

- Keratin:+ in squamous cells
- Vimentin ± actin, desmin in mesenchymal cells

Ultrastructure

- Squamous cells show desmosomes and tonofilaments

Differential Diagnosis

- Primary squamous cell carcinoma of the skin
- Metastatic squamous cell carcinoma
- Carcinosarcoma (see separate section)
- Syringomatous adenoma: usually near nipple, infiltrative, but cytologically bland

Adenosquamous Carcinoma (Mucoepidermoid Carcinoma)

Clinical

- No significant difference from ductal carcinoma NOS
- Incidence unknown; squamous component may not be reported if small

Prognostic Significance

- Low-grade tumors mainly recur
- High-grade tumors are aggressive and metastasize

Macroscopic

- Poorly defined mass median = 2.5 cm with variable foci of white keratinous debris

Microscopic

- Variable mixture of adenocarcinoma (often peripheral) and squamous carcinoma (often more central)
- Mucin stains demonstrate adenocarcinomatous component
- Histologic grading of tumor should be performed

Adenocarcinoma with Spindle Cell Metaplasia

Prognostic Significance

- Too few cases reported to provide clear information

Microscopic

- Adenocarcinoma cells merge with malignant spindle cells

Immunohistochemistry

- Necessary for diagnosis, demonstration of cytokeratin in the spindle cell component

Carcinoma with Chondroid Metaplasia

Clinical

- Rare tumors, cases show wide age range and may reach a large size (20 cm)

Prognostic Significance

- Difficult to ascertain, as studies have not always separated them from carcinosarcomas (vi)
- Many cases within this group are categorized with carcinomas displaying osseous differentiation; again, prognostic significance is uncertain

Microscopic

- Variable extent and distribution of cartilage
- Associated carcinoma is usually an infiltrating ductal carcinoma

Infiltrating Lobular Carcinoma

Clinical

- Less common pattern: 0.7–14% of invasive carcinomas
- Same median age (5th and 6th decades) as invasive ductal carcinoma

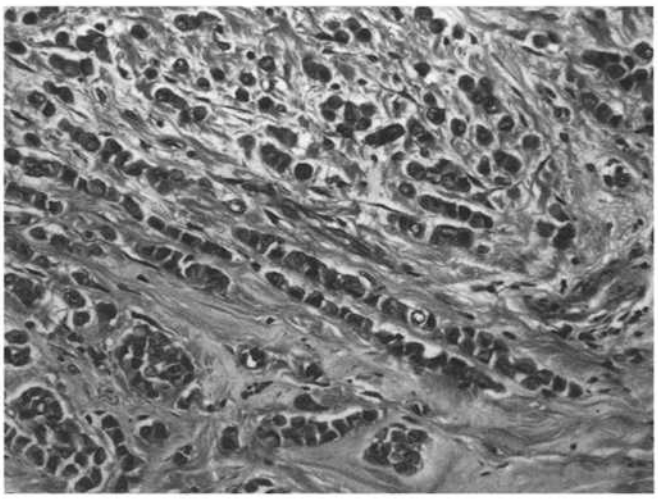


Fig. 18. Infiltrating lobular carcinoma—pleomorphic type-infiltrating tumor cells arranged in a single layer, small cells arranged in single files.

- Detection may be difficult:
  - Lack of calcification hampers mammographic detection
  - Tumor may be poorly defined on palpation
  - Tumor may be multifocal

Prognostic Significance

- Studies vary as to survival; may be better or the same as infiltrating ductal
- Pattern of metastases differ: Lobular has predilection for viscera, bone marrow, and meninges; ductal for lung/pleura
- Metastases in nodes and other sites may be difficult/impossible to detect on H&E; keratin immunostain useful
- Histologic variants may have slightly poorer prognosis than classic form

Macroscopic

- Small foci are not visible
- Larger tumors appear as indurated, ill-defined masses
- Less commonly a multinodular texture "grains of sand"

Microscopic

- Classic form and variant forms:
  - Classic:
    - Small cells with ovoid nuclei and little cytoplasm, arranged in single file, frequently in a targetoid pattern around ducts **(Figure 18)**
    - Intracytoplasmic lumens present in a minority of cells; mucin stains useful
    - Signet ring forms occasionally seen

- Stroma is desmoplastic, but with an overall eosinophilic appearance
- Lobular neoplasia present in 90% of all cases

– Solid:
- Closely packed small cells forming large nests with thin fibrous trabeculae

– Alveolar:
- Smaller, closely packed islands of uniform small cells

♦ Mixed patterns common (30% of cases); a pattern should comprise >70% of the tumor to justify designation as a subtype

♦ Variants show a lower incidence of coexistent lobular neoplasia in some series:
– Histiocytoid variant (pleomorphic lobular carcinoma):
- Bland, histiocytoid-appearing cells
- Comprises ~5% of infiltrating lobular carcinoma
- Larger cells, more pleomorphic nuclei than other variants
- Similar growth pattern, intracytoplasmic lumens, association with LN, and/or admixture with classic pattern confirm its interpretation as a lobular carcinoma variant

♦ Grading:
– Should be performed as for infiltrating ductal carcinoma
– Lobular carcinoma will score 3 for tubules; usually has little pleomorphism or mitoses, so it qualifies as a well- or moderately differentiated carcinoma

Immunohistochemistry

♦ 70–90% are ER+; ≥ 70% are PR+

♦ 60%+ for S-100 protein

♦ As with other carcinomas, keratin and EMA+ and LCA

Differential Diagnosis

♦ Inflammation:
– Lobular carcinoma cells can resemble lymphocytes, especially on frozen section

♦ Lymphoma:
– Especially solid variant, lymphoma cells do not have intracytoplasmic lumens (but rare signet ring forms have been described); immunostains for LCA and keratin useful

♦ Infiltrating ductal carcinoma:
– So-called tubulolobular variant is a well-differentiated ductal carcinoma with lobular features

♦ Infiltrating apocrine carcinoma:
– Differential with pleomorphic lobular carcinoma, which does not have nucleoli

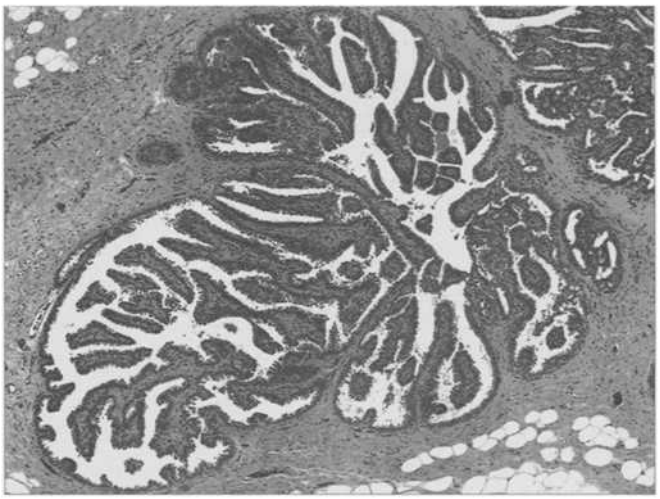


Fig. 19. Papilloma is characterized by papillary processes with fibrovascular cores.

Papillary Lesions

♦ Lesions characterized by an arborizing growth pattern and fibrovascular cores **(Figure 19)**

♦ May be either central, in large peri-areolar ducts/lactiferous sinuses (frequently solitary), or peripheral (usually smaller and multiple)

♦ Differential diagnosis is of lesions on the spectrum and is discussed below

Intraductal Papilloma

Clinical

♦ Most frequent in females >50; may occur in males

♦ Serous or serosanguinous discharge from the nipple in a majority (87%) of cases

Macroscopic

♦ Papillary lesion frequently visible in dilated duct

♦ If duct is dilated such that it appears like a cyst, the term intracystic papilloma is appropriate

Microscopic

♦ Epithelial and myoepithelial cell layer supported by fibrovascular core

♦ Secondary changes are common:
– Torsion/hemorrhagic infarction of papilloma
– Squamous metaplasia secondary to infarction
– Sclerosis/hemosiderin deposition in duct wall and papillary stalk; occasionally, extensive sclerosis dictates the diagnosis of "sclerosing papilloma"

♦ "Ductal adenoma": well-circumscribed, fibrotic nodule, frequently within a duct lumen, but extensive fibrosis may obscure this:
– Prominent myoepithelial proliferation, epithelial component resembles sclerosing adenosis

- Apocrine metaplasia, sometimes with atypia, may occur
- Most likely a variant of sclerosing papilloma

Intraductal Papillomatosis

Clinical

- Occurs in women ~10 years younger than solitary papilloma
- Associated with a discharge from the nipple in a minority (33%) of cases

Prognostic Significance

- Not completely established: currently believed not to have a significantly increased risk for cancer unless there is associated atypia

Macroscopic

- Not visible grossly

Microscopic

- Papillary fronds with a myoepithelial cell layer; in multiple TDLUs
- Ducts smaller and walls less sclerotic
- Multiple foci of mural attachment and smaller size mean degenerative changes less prominent

Atypical Papilloma

- Atypical papilloma contains papillary lesions with:
  - Up to 1/3 of papillary fronds lacking myoepithelial cells, or
  - Up to 1/3 of area composed of an atypical intraductal proliferation, or
  - Fronds covered by a stratified spindle cell proliferation
- Carcinoma arising in a papilloma:
  - Similar changes involving 33–90% of lesion
  - Recent study suggests a similar course for lesions in categories 1 and 2. These can be combined under the designation of atypical papilloma
- Papillary carcinoma:
  - >90% of lesion involved

Papillary Carcinoma

Clinical

- Accounts for ~2% of carcinomas
- Similar demographics to papilloma; nipple discharge less common (1/4 patients)
- May present with nipple distortion or a mass if invasive

Prognostic Significance

- Criteria for atypical papilloma and carcinoma arising in a papilloma are arbitrary; complete excision is advisable; behavior of these entities may not differ significantly
- Presence of atypia in adjacent ducts increases risk of subsequent invasive carcinoma
- Invasive papillary carcinoma is only rarely associated with nodal metastases. These are in lower axillary nodes and systemic metastases/death is rare

Microscopic

- Myoepithelial layer is central diagnostic point
- Cytology may be bland, but cellular monotony is a key factor in recognition
- Patterns of papillary carcinoma include:
  - Cribriform proliferation between fibrovascular stalks
  - Solid: may be difficult to see few residual stalks; minority of cells have eosinophilic cytoplasmic granules
  - Spindle cell proliferation: often associated with mucin production
  - Transitional cell: rare variant
- Adjacent duct spaces often contain atypical intraductal hyperplasia

Immunohistochemistry

- Myoepithelial layer stains for SMA
- With very fine fibrovascular cores, actin + endothelial cells may cause problems; endothelial cells are Factor VIII+, but they are negative for S-100 protein, which stains myoepithelial cells
- Some solid and spindle cell variants are positive for chromogranin and synaptophysin

Invasion in Papillary Carcinoma

- Occurs in minority of cases
- Unequivocal invasion is tumor cells infiltrating outside duct into fat
- Irregular tubules trapped in sclerotic duct wall or stalk is common; these retain a myoepithelial cell layer
- Invasion of tumor into sclerotic wall is called "early stromal invasion"

Differential Diagnosis

- Application of percentage criteria distinguishes benign/atypical/carcinoma
- Application can be on H&E slides or actin
- If diagnosis of carcinoma is made, should be qualified as either "intraductal" or "invasive"
- Skin adnexal tumors may mimic central papillomas, especially eccrine acrospiroma (clear cell hidradenoma)
- "Ductal adenoma" may be mistaken for invasive carcinoma

Biphasic Tumors (Table 5)

Fibroadenoma

Clinical

- Women in reproductive age range, average 25–35 years
- African American > Caucasian
- Usually presents as a solitary mobile breast mass

Table 5. Biphasic Neoplasms—Diagnostic Features

	Fibroadenoma	*Low-grade phyllodes*	*High-grade phyllodes*
Size	Variable	Variable	Variable
Spaces	Tubular or slit-like	Leaflike, cystic	Leaflike, cystic
Stromal cellularity	Variable	Moderate to high	High
Margins	"Pushing"	"Pushing"	Infiltrative
Stromal overgrowth	Absent	Absent	Present in some
Stromal nuclear atypia	Minimal	Mild to moderate	Moderate to severe
Mitotic figures	Variable	< 3/10HPF	> 3/10 HPF
Benign heterologous elements	Rare	Frequent	Frequent

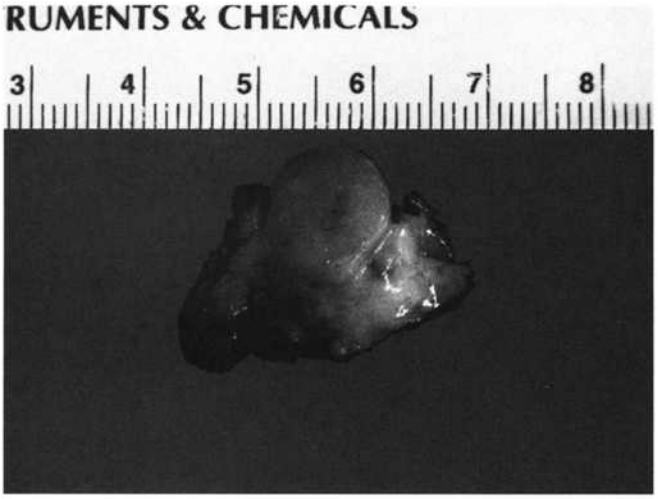


Fig. 20. Fibroadenoma—Grossly, a firm, sharply circumscribed nodule is typical.

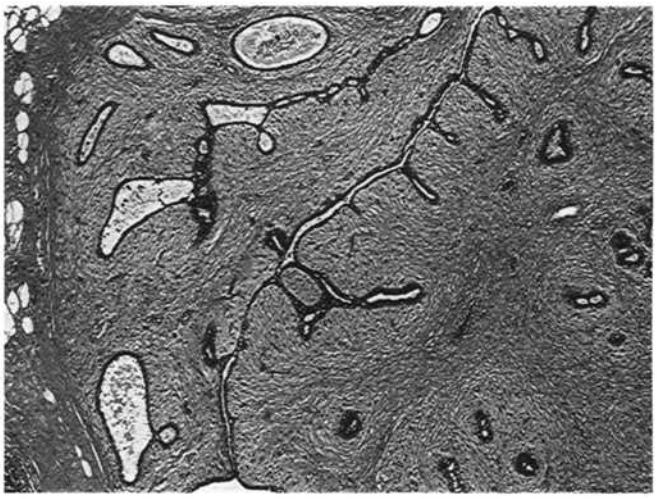


Fig. 21. Fibroadenoma—a combined proliferation of meschymal and epithelial elements.

Prognostic Significance

- Myxoid variant: increased risk of recurrence; may be part of complex of myxomas (cardiac and cutaneous), spotty pigmentation, and endocrine overactivity (Carney's complex)
- Carcinoma arising in a fibroadenoma: rarely results in death from tumor, may be managed conservatively

Macroscopic

- Gray/white, well-circumscribed nodule "shells out" **(Figure 20)**
- Characteristic bulging surface
- Lesions from older women more fibrous and may be calcified

Microscopic

- A proliferation of mesenchymal and epithelial elements **(Figure 21)**
- Fully developed form shows different patterns of stromal proliferation (no clinical significance):
  - Intracanalicular: around compressed cleft-like spaces
  - Pericanalicular: around tubular ducts
- Margin is usually pushing, with some irregularities
- Myxoid change may occur in stroma: association with Carney's complex
- Epithelium shows two cell layers and hyperplasia is frequent
- Apocrine metaplasia seen in some fibroadenomas (11%)
- Benign changes such as sclerosing adenosis are found in fibroadenomas
- Multiple adjacent TDLUs may show these changes without a well-defined mass; this is called fibroadenomatoid change

- Fibroadenomas in elderly women often show stromal hyalinization, epithelial atrophy, and calcification
- Carcinoma arising in fibroadenoma: >50% of these are lobular in type; there is often (50%) invasive carcinoma elsewhere in the breast

Differential Diagnosis

- Phyllodes tumor: leaf-like processes, cystic spaces, stromal hypercellularity
- Juvenile fibroadenoma (occurs in adolescent females): rapid growth, cellular stroma, pericanalicular growth pattern usual

Phyllodes Tumor

- Previously called cystosarcoma phyllodes; however, many do not behave like a sarcoma
- Phyllodes = leaf-like; phylloides = leafy

Clinical

- Accounts for 2.5% of fibroepithelial breast tumors
- Wide age range, but on average 20 years older (45 years) than women with fibroadenoma
- Present as painless breast mass, often longstanding with sudden enlargement
- Median size = 6.4 cm, but size is not a diagnostic criterion

Macroscopic

- Fleshy, white tumor, with bulging leaf-like processes

Microscopic

- Leaf-like processes and cystic spaces lined by epithelium with two-cell layer **(Figure 22)**
- Squamous metaplasia more frequent than in fibroadenoma
- Stromal overgrowth is assessed differently by different authors; should be confined to cases where there is extensive (multiple low-power fields, multiple slides) proliferation of sarcomatous elements
- Hypercellular stroma: Assessment of this is subjective
- Chondroid, osseous, and lipoid metaplasia more frequent than in fibroadenoma
- Rare variant shows stromal cells with intracellular accumulations of actin (identical to infantile digital fibromatosis)

Grading

- No single feature is predictive of biologic behavior
- Low-grade tumors may recur, but do not metastasize:
  - Pushing margin
  - <3 mitoses per 10 HPF
  - Lack of moderate or severe cytologic atypia
- High-grade tumors tend to recur and may metastasize:
  - Infiltrative margin
  - Moderate to severe cytologic atypia
  - 3 or more mitoses/10 HPF

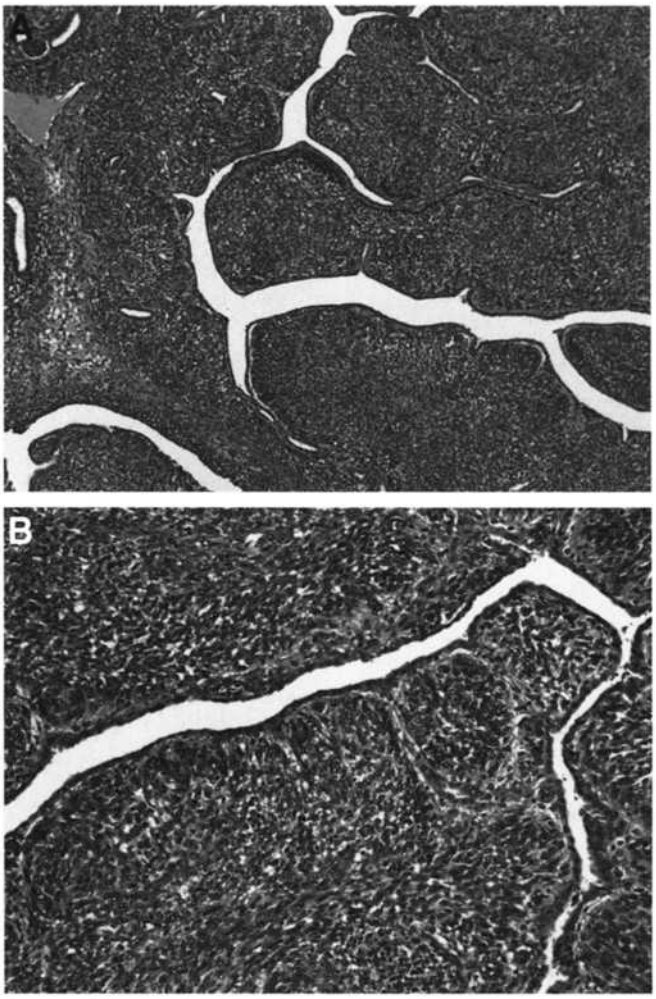


Fig. 22. Phyllodes tumor- leaf-like processes protrude into cystic spaces lined by epithelial and myoepithelial cells **(A,B)**.

  - Presence of specific sarcoma subtypes (liposarcoma, osteosarcoma) classify a tumor as high-grade
- Metastases:
  - Wide range, probably <10% of cases
  - Hematogenous, especially to lungs; axillary node dissection unnecessary

Periductal Stromal Sarcoma

- Term has been used loosely; when defined as below, it is a rare biphasic tumor

Prognostic Significance

- Not well-defined

Microscopic

- Proliferation of stromal spindle cells around tubules with open lumens
- Leaf-like pattern not apparent
- Intervening normal fibro-adipose tissue

Nipple Lesions

- Lesions that are usually, but not exclusively, found in the region of the nipple

Paget's Disease

Clinical

- Presents as unilateral, eczematoid change of nipple, ulceration or distortion of nipple, or more diffuse irregularity of the nipple/periareolar area
- 1–5% of breast carcinomas

Macroscopic

- See clinical ~50% have an underlying mass
- If a mass is felt in a case of Paget's, an invasive carcinoma is extremely likely

Microscopic

- Intraepithelial proliferation of malignant cells, with or without an associated intraductal or infiltrating carcinoma (usually ductal)
- Paget cells are large, with pale cytoplasm and large nuclei **(Figure 23)**
- Present singly or in basally located nests, undermining native epithelium
- Occasional acinar formation
- Paget cells are positive for mucin (PAS, mucicarmine) in 50–60% of cells

Immunohistochemistry

- Paget cells are positive for Cam 5.2 and CK 7
- Variable positivity is seen for EMA and polyclonal CEA
- They are negative for S-100 protein and HMB-45

Differential Diagnosis

- Eczema:
  - Particularly due to clinical appearance
- Toker cells:
  - Normal variant, clear cells in nipple epithelium; these are not cytologically malignant
- Squamous cell carcinoma:
  - Rare in nipple
- Melanoma:
  - Rare in nipple also, immunos as above confirm Paget's

Nipple Duct Adenoma (Erosive Adenomatosis)

Clinical

- Uncommon lesion; females > males; 5th decade
- Nipple discharge, induration, or ulceration may occur
- ~25% of cases are asymptomatic/incidental findings

Prognostic Significance

- Clinically, may be mistaken for Paget's disease; not a pathologic diagnosis

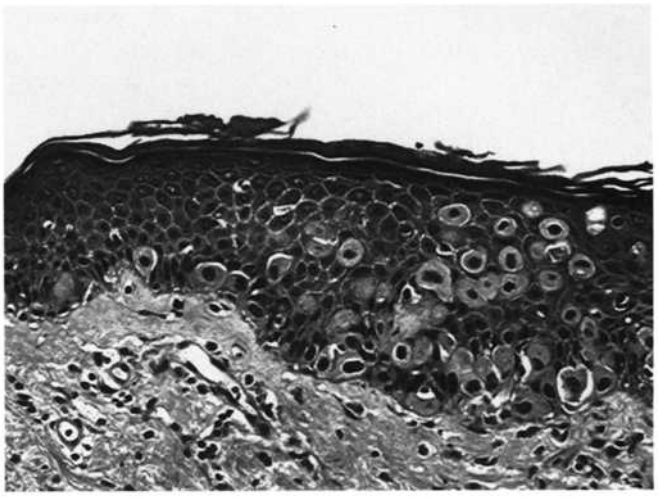


Fig. 23. Paget's disease—large pale cells proliferate in the skin of the nipple.

- May recur if incompletely excised
- May occur in association with carcinoma, but not generally felt to be pre-malignant

Macroscopic

- Well-circumscribed lesion; may cause cystic dilatation of ducts

Microscopic

- Proliferation of tubules replacing the nipple
- Sclerosis of adjacent stroma
- Associated papilloma formation/papillomatosis
- Epithelial hyperplasia and squamous metaplasia frequent
- Atypia may also be present

Immunohistochemistry

- Actin confirms retention of myoepithelial cell layer

Differential Diagnosis

- Infiltrating carcinoma, especially tubular carcinoma; use actin to differentiate
- Papilloma: Adenoma component of NDA may be quite focal
- Sclerosing adenosis
- Syringomatous adenoma:
  - Tubules are closer together in NDA
  - Syringomatous adenoma permeates the nipple stroma; NDA replaces it

Syringomatous Adenoma

Clinical

- Uncommon lesion, unilateral, in region of nipple in 80% of cases
- Presents as a firm mass; nipple discharge or pain less common

- Females > males
- May recur locally if incompletely excised

Macroscopic

- Poorly defined gray nodule; may have small cystic areas
- Tend to be small in size (1–3 cm)

Microscopic

- Irregular, angulated tubules widely separated by fibrous stroma
- Occasional connections to surface epithelium, but erosion/ulceration rare
- Permeates nipple structures
- Tubules have myoepithelial cell layer
- Squamous metaplasia common; squamous cysts may develop
- Stroma usually has few or no mitoses, with chronic inflammatory infiltrate in occasional cases

Differential Diagnosis

- Tubular carcinoma:
  - Single cell layer, apical snouting, squamous metaplasia less common
  - Rarely occurs in the nipple
- Nipple duct adenoma:
  - Displaces/destroys rather than permeates the nipple

Skin Adnexal Tumors

Clinical

- Rarely involve nipple

Macroscopic

- No distinguishing features

Microscopic

- Basal cell carcinoma:
  - Hyperchromatic basaloid cells with stromal retraction and peripheral palisading
- Eccrine acrospiroma (clear cell hidradenoma):
  - Clear cells and eosinophilic cells
  - May show solid or papillary pattern
  - Differential diagnoses includes papillary transitional cell carcinoma

Myoepithelial Lesions

- Classified as myoepitheliosis, adenomyoepithelioma, and malignant myoepithelioma
- Differential diagnosis and ultrastructural features are discussed for the whole group

Prognostic Significance

- Myoepitheliosis:
  - No recurrences or malignant change reported
- Adenomyoepithelioma:
  - Tubular variant appears most likely to recur: histologic features do not predict which cases will recur
  - Metastases may develop from carcinoma arising in this lesion
- Malignant myoepithelioma:
  - Small number of cases, but a risk of nodal metastases exists

Myoepitheliosis

Clinical

- Does not form a palpable mass
- It is the most common of the three groups in this class

Macroscopic

- May be detected as firm areas within breast biopsy specimen

Microscopic

- Multifocal proliferation of spindle cells in TDLU
- Intraductal or periductal pattern
- Epithelial cells may be entrapped and lumens obliterated
- No atypia or mitotic figures seen in spindle cells

*Immunohistochemistry (see **Table 6**)*

- Strong positivity for S-100 protein
- Moderate positivity for actin
- Weak positivity for keratin
- Negative for GFAP

Adenomyoepithelioma

Clinical

- Females; median age = 62 years
- Solitary, centrally located lesions
- May have an associated nipple discharge

Macroscopic

- Usually well-circumscribed, white-gray nodules 1–7 cm in size

Microscopic

- Spindle cell, tubular, and lobulated types:
  - Spindle cell:
    - Solid mass with small foci of epithelium, frequently apocrine in type
  - Tubular:
    - Rounded tubules lined by both epithelial and myoepithelial cells
    - Myoepithelial cells may be hyperplastic and obliterate lumens
    - Up to 3 mitoses per 10 HPF seen
    - Margin shows focal irregularity

Table 6. Myoepithelial Lesions of the Breast

	Myoepitheliosis	*Adenomyoepithelioma*	*Myoepithelial carcinoma*
Frequency	Common	Uncommon	Rare
Gross	Usually not seen	Solitary mass	Mass(es)
Microscopic	Spindle cells	Variable, usually spindle	Spindle cells
SI 00 protein	+++	+++	++
Smooth muscle actin	++	+	++–+++
Cyto keratin	+	+	+

+ = weakly positive; ++ = moderately positive; +++ = strongly positive

- Lobulated:
  - Solid nests with fibrous capsule, some margin irregularity
  - Myoepithelial cells are clear, eosinophilic, or plasmacytoid
  - Stroma is hyalinized, with frequent calcification or infarction
  - Mitoses usually <3/10 HPF, occasionally more

*Immunohistochemistry (see **Table 6**)*

- Strong positivity for S-100 protein (less in clear cells)
- Weak positivity for actin and keratin
- Generally negative for GFAP, unlike the salivary gland counterpart

Malignant Myoepithelioma (Myoepithelial Carcinoma)

Clinical

- Female, middle aged to elderly
- Central breast mass, with or without nipple discharge

Macroscopic

- Stellate or well-circumscribed masses 1–21 cm in size
- Satellite nodules may be visible grossly

Microscopic

- Spindle cell proliferation only
- Cellular pleomorphism present; cells may be plump or oval
- Mitotic figures > 3/10 HPF
- Infiltrative margins

*Immunohistochemistry (see **Table 6**)*

- Positive for actin and/or S-100 protein

Ultrastructure

- Features vary somewhat according to cell type studied
- Constant features are:
  - Multilayered basal lamina
  - Desmosomes and hemidesmosomes
  - Aggregates of myofibrils with dense bodies
  - Pinocytotic vesicles (fewer in clear cells)
  - Occasional tonofilaments (in malignant myoepithelioma)

Differential Diagnosis

- Myoepitheliosis is an incidental microscopic finding and blends with myoepithelial prominence in sclerosing adenosis
- Lobulated adenomyoepithelioma may be mistaken for high-grade ductal carcinoma. Look for hyalinized stroma and clear/plasmacytoid cells
- Malignant myoepithelioma resembles:
  - Spindle cell carcinoma: This shows stronger staining for keratin
  - Fibromatosis: more infiltrative, little or no atypia, <3 mitoses/10 HPF, – for keratin and S-100 protein
  - Stromal (spindle cell) sarcoma: – for epithelial markers
- Ultrastructural demonstration of pinocytotic vesicles strongly favors myoepithelial origin over epithelial origin

Carcinoma Arising in Adenomyoepithelioma

- Either component (epithelial or myoepithelial) may give rise to carcinoma
- Epithelial tumors reported include ductal carcinoma and adenoid cystic carcinoma

Vascular and Vascular-Like Lesions

Pseudoangiomatous Hyperplasia

Clinical

- Most cases are incidental microscopic findings (23% of breast biopsies)
- Symptomatic cases present as a painless mass in women with a mean age of 40 years

Macroscopic

- Firm, rubbery lesion, 2–7 cm in size

Microscopic

- Usually discrete and multifocal, resembling a vascular lesion on low power
- Dense collagenous stroma with slit-like channels lined by stromal, not endothelial, cells

Immunohistochemistry

- Lining cells are vimentin and PR+,– for vascular markers Factor VIII and CD34

Vasculitis

Clinical

- Rare, accompanied by systemic symptoms
- Tender nodules, cord-like lesion if a superficial vein (Mondor's disease)

Microscopic

- Giant cell arteritis and polyarteritis nodosa have been described
- Mondor's disease involves a vein

Prognostic Significance

- Arteritis should prompt systemic assessment
- Mondor's disease may be secondary to trauma and needs symptomatic treatment only

Microscopic Hemangioma

Microscopic

- Incidental microscopic findings < 5mm in size
- Perilobular hemangioma is most common form: aggregate of red blood cell-filled vascular channels in perilobular stroma
- No atypia or endothelial proliferation

Palpable Hemangioma

Clinical

- Definition: >5mm in size
- Female > male

Prognostic Significance

- No convincing evidence that hemangiomas are precursors of angiosarcoma
- Atypical hemangiomas do not recur or require reexcision

Macroscopic

- May be apparent as well-defined blood-filled lesions

Microscopic

- Vascular proliferation in intra- and interlobular stroma
- Cavernous, capillary, and arteriovenous forms described
- Some lesions show focal endothelial hyperplasia or anastomosing channels: "atypical hemangiomas"

Atypical Vascular Lesion

Clinical

- Solitary or multiple skin or breast nodules
- Occurs 2–5 years after radiotherapy to the breast
- Not associated with skin discoloration

Prognostic Significance

- Atypical vascular lesion does not recur and has no metastatic potential

Macroscopic

- Pink or tan-white nodules

Microscopic

- Located in dermis or present as circumscribed lesions in breast
- Dilated vascular spaces with anastomosing pattern
- Endothelium is plump, with occasional projections or tufting
- No endothelial mitoses or stromal blood lakes

Differential Diagnosis

- Angiosarcoma: more atypia, endothelial proliferation

Angiomatosis

Clinical

- A rare, congenital lesion; often manifests in young females, mean age = 33 years
- One case reported in a male

Microscopic

- Extensive in distribution
- Proliferation of irregular vascular channels
- No anastomosing pattern or endothelial atypia
- Does not dissect into lobular stroma

Differential Diagnosis

- Low-grade angiosarcoma (*see* below)

Hemangiopericytoma

Clinical

- Rare lesion; males and females

Prognostic Significance

- Complete local excision appears adequate; no recurrence reported
- Follow-up is recommended when there is hemorrhage, necrosis, or significant mitotic activity

Macroscopic

- Well-circumscribed, pink/tan mass

Microscopic

- Well-circumscribed cellular lesions
- Densely packed spindle cells surround endothelial-lined spaces
- Larger spaces classically show a staghorn shape; smaller may be slit-like
- Hemorrhage, necrosis, and significant mitotic activity are uncommon
- Stroma may have myxoid change

Immunohistochemistry

- + for vimentin, CD 34, and Factor XIIIa
- Tumor cells are – for Factor VIII or Ulex (endothelial cells are + for these) and – for keratin and SMA

Angiosarcoma

Clinical

- Rare neoplasm; females > males; mean age = 35 years
- May present as a well-defined, painless, rapid growing mass
- A minority present with diffuse discoloration of the overlying skin
- May develop post-radiotherapy (typically after 12 years, but reported within 4 years of treatment)

Prognostic Significance

- Well- and moderately differentiated lesions have median cancer-free survival of 12–15 years
- Poorly differentiated lesions have 15 months median survival
- Metastases to lungs, liver, skin: axillary nodes rarely involved

Macroscopic

- Spongy, hemorrhagic tissue in breast; may extend to overlying skin
- Extensive sampling is necessary for grading (vi)

Microscopic

- Variable appearance makes up basis for grading
- Low grade (well differentiated):
  - Anastomosing vascular channels
  - 1–2 cell layer lining
  - No necrosis or pleomorphism; mitoses rare
  - No blood lakes
- Intermediate grade (moderately differentiated):
  - Solid areas comprise <20% of total tumor mass
  - Endothelial tufts present
- High grade (poorly differentiated):
  - Predominance of solid spindle cell areas
  - Mitoses, pleomorphism, necrosis, and hemorrhage present

Immunohistochemistry

- Positivity for vascular markers (FVIII-related antigen, Ulex, CD 31) is maximal in better differentiated tumors, and very variable in poorly differentiated ones

Ultrastructure

- Malignant cells show pinocytotic vesicles, desmosomes, tight junctions, and Weibel-Palade bodies. The latter are seen mainly in some low-grade lesions

Differential Diagnosis

- Pseudoangiomatous hyperplasia:
  - Does not infiltrate lobules and is – for vascular markers
- Hemangioma (microscopic, perilobular):
  - No angiosarcomas have been found with this pattern
- (Post radiation) atypical vascular lesion:
  - Lacks atypia, mitoses, or endothelial proliferation and does not infiltrate subcutis
- Angiolipoma:
  - Well-demarcated/non-infiltrative, vessels contain microthrombi
- Angiomatosis:
  - Lacks atypia, mitotic activity (<1mitosis/10HPF, if any), endothelial cell proliferation, and dissection into lobular stroma

Lymphoid Lesions

- May be primary in the breast or in an intramammary/axillary node

Lymphoma

Clinical

- Primary lymphoma is rare. There is concurrent axillary node disease in 30–50% of all cases
- Secondary involvement of the breast by disseminated disease is more common
- Primary: bimodal incidence reported (38 and 58 years)
- Usually unilateral, but may be bilateral; small number in males
- Presentation can be with mass, pain, or constitutional (B-type) symptoms

Prognostic Significance

- Prognosis depends on stage and type
- Primary mammary lymphoma recurs locally in ~50% of all cases

Macroscopic

- Fleshy, gray-white tissue

Microscopic

- Non-Hodgkin's lymphoma (NHL) is much more common than Hodgkin's lymphoma

- B-cell is far more common than T-cell
- NHL types include diffuse large cell and diffuse, non-cleaved, small cell (Burkitt's like)
- No histologic features can distinguish primary from secondary forms
- Lymphocytic infiltration of epithelium may be seen in benign and malignant breast disease

Immunohistochemistry

- Appropriate panel to type lymphoma should be performed (see chapter 7)
- Immunoglobulin or T-cell receptor gene rearrangement studies as needed

Differential Diagnosis

- Poorly differentiated carcinoma: keratin+, LCA–
- Solid and alveolar variants of infiltrating lobular carcinoma: keratin+, intracytoplasmic lumens best seen in periphery, mucicarmine+
- "Pseudolymphoma": Many of these atypical lymphoid proliferations evolve into lymphoma; they have a mixed cell population
- Lymphocytic mastitis: localized; no atypia; associated with dense collagen and atypical epithelioid stromal cells

Plasmacytoma

Clinical

- Rare lesion in the breast; may be presentation of myeloma

Microscopic

- Similar to extramedullary plasmacytoma at other sites; cellular aggregate of variably atypical plasma cells (*see* lymph nodes, chapter 7)

Granulocytic Sarcoma

Clinical

- Uncommon; occurs either synchronously with, or shortly prior to, onset of acute myeloid leukemia
- Presents as a unilateral breast mass in patients aged 34–56 years

Macroscopic

- May show the characteristic green color

Microscopic

- Immature myeloid cells: mononuclear forms with granular eosinophilic cytoplasm, chloroacetate esterase (Leder) stain+

Sinus Histiocytosis with Massive Lymphadenopathy (Rosai-Dorfman Disease)

Clinical

- Rare in breast, but may involve axillary nodes
- Occurs at any age, but especially younger women

Microscopic

- Selective involvement of sinuses with expansion by S-100+ histiocytes
- Emperipolesis: engulfment of lymphocytes by histiocytes is characteristic
- Prominent polyclonal plasmacytosis

TNM CLASSIFICATION OF CARCINOMA OF THE BREAST*

- T: Primary Tumor:
  - Tis: *In situ* carcinoma
  - T1: ≤ 2 cm in greatest dimension
    - T1 mic: ≤ 0.1 cm
    - T1a: > 0.1 cm, ≤ 0.5 cm
    - T1b: > 0.5 cm, ≤ 1 cm
    - T1c: > 1 cm, ≤ 2 cm
  - T2: > 2 cm, ≤ 5 cm
  - T3: > 5 cm
  - T4: extension to chest wall/skin
    - T4a: chest wall
    - T4b: skin edema/ulceration, satellite skin nodules
    - T4c: both 4a and 4b
    - T4d: inflammatory carcinoma
- N: Regional Lymph Nodes
- Nx regional nodes cannot be assessed
- p N1 mi: micrometastasis ≥ 0.2mm, ≤ 0.2 cm
  - p N1: metastasis in 1-3 ipsilateral axillary nodes
  - p N2: metastasis in 4-9 ipsilateral axillary nodes
  - p N3: >10 axillary nodes, or internal mammary, infra or supraclavicular nodes involved

UICC TNM Classification of malignant tumours: Sobin LH, Wittekind CH. eds. 6th ed 2002 New York: Wiley-Liss

p, pathologist staged; pT categories correspond to T categories

*** This group may be further subdivided according to the number of nodes involved*

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24

Vulva and Vagina

Wenxin Zheng, MD

CONTENTS

VULVA

I. Inflammatory Lesions 24-3
- Vulva Vestibulitis 24-3
- Plasma Cell Vulvitis 24-3
- Lichen Simplex Chronicus (LSC) 24-3
- Behcet's Disease 24-3
- Fox-Fordyce Disease (FFD) 24-3
- Hidradenitis Suppurativa 24-4

II. Infectious Lesions 24-4
- Human Papillomavirus (HPV) Infections 24-4
- Candidiasis 24-4
- Molluscum contagiosum 24-4
- Herpesvirus infection 24-4
- Cytomegalovirus (CMV) 24-5
- Syphilis 24-5
- Lymphogranuloma Venereum (LGV) 24-5

III. Cystic Lesions 24-5
- Batholin's Duct Cyst 24-5
- Skene's Duct Cyst 24-5
- Epidermal Inclusion Cyst 24-6
- Mesonephric (Gartner's Duct) Cyst 24-6

IV. Benign Discolored Lesions 24-6
- Lichen Sclerosus (LS) 24-6
- Squamous Cell Hyperplasia 24-6
- Lichen Planus (LP) 24-6
- Seborrheic Keratosis 24-6
- Lentigo Simplex and Melanosis 24-7
- Melanocytic Nevi 24-7

V. Benign Tumors 24-8
- Hidradenoma Papilliferum (HP) 24-8
- Granular Cell Tumor (GCT) 24-8
- Squamous Vestibular Papillomatosis (SVP) 24-8
- Angiokeratoma 24-8
- Cellular Angiofibroma 24-8
- Angiomyofibroblastoma 24-8
- Fibroepithelial Polyp (Acrochordon) 24-9
- Endometriosis 24-9
- Leiomyoma 24-9
- Other Benign Mesenchymal Tumors 24-9

VI. Malignant Epithelial Tumors 24-9
- Vulva Intraepithelial Neoplasia (VIN) 24-9
- Paget's Disease (PD) 24-10
- Invasive Squamous Cell Carcinoma (ISCC) 24-11
- Verrucous Carcinoma (VC) 24-12
- Basal Cell Carcinoma (BCC) 24-12
- Carcinoma of Bartholin's Glands 24-12
- Keratoacanthoma 24-12
- Adenocarcinoma of Skin Appendage 24-12

VII. Malignant Non-Epithelial Tumors 24-13
- Malignant Melanoma 24-13
- Aggressive Angiomyxoma 24-13
- Sarcoma Botryoides 24-13
- Epithelioid Sarcoma 24-14
- Yolk Sac Tumor 24-14
- Merkel Cell Tumor 24-14
- Other Sarcomas, Hematopoetic Tumors and Secondary Tumors 24-14

THE VAGINA

I. Benign Non-Neoplastic Lesions 24-14
- Mullerian Papilloma 24-14
- Vaginal Adenosis (VA) 24-14
- Prolapse of Fallopian Tube 24-15
- Postoperative Spindle Cell Nodule 24-15
- Emphysematous Vaginitis 24-15
- Ectopic Decidua 24-15

II. Benign Tumors 24-15
- Condylomas 24-15
- Tubular, Tubulovillous, and Villous Adenomas 24-15
- Brenner Tumor 24-15
- Benign Mixed Tumor (Spindle Cell Epithelioma) 24-15

III. Malignant Epithelial Tumors 24-15
- Vaginal Intraepithelial Neoplasia (VAIN) 24-15
- Squamous Cell Carcinoma 24-16
- Atypical Adenosis 24-16
- Clear Cell Carcinoma (CCC) 24-16
- Endometrioid Adenocarcinoma 24-16
- Mesonephric Adenocarcinoma 24-16

IV. Other Malignant Tumors 24-17
- Sarcoma Botryoides 24-17
- Malignant Melanoma 24-17
- Carcinosarcoma 24-17
- Primitive Neuroectodermal Tumor (PNET) 24-17
- Leiomyosarcoma 24-17
- Yolk Sac Tumor 24-17
- Hematopoietic Tumors 24-17
- Secondary Tumors 24-17

V. FIGO Staging of the Vulva and Vagina 24-18

Vulva

INFLAMMATORY LESIONS

Vulva Vestibulitis

Clinical

- Affects up to 15% of gynecologic patients
- Generally occurs in reproductive age women with an average age of 30s
- Severe pain on vaginal entry and variable vulva erythema
- Unknown etiology, but may be related to an increased number of nerve fibers per square unit in the vestibular area

Microscopic

- Squamous mucosa with variable degree of chronic inflammation in the lamina properia. Lymphoid follicles may be seen in some cases
- Squmous metaplasia of the vestibular glands and ducts is common, sometimes can be extensive

Plasma Cell Vulvitis

Clinical

- Also called as a Zoon's vulvitis
- Itching, burning red, and sometimes multiple maculae
- Unknown etiology

Microscopic

- Thin vulva skin
- Flattened rete ridges
- Spongiotic parabasal keratinocytes
- Lichenoid infiltrate with predominant plasma cells
- Prominent dermal blood vessels
- Dermal hemorrhage
- Hemosiderin deposition

Lichen Simplex Chronicus (LSC)

Clinical

- A chronic eczematous inflammatory condition
- Increased thickeness of skin
- Often associated with excoriation and fissures
- Moderate to severe pruritus is characteristic
- Block itch scratch cycle to control

Microscopic ***(Figure 1)***

- Thickened epithelium with acanthosis and hyperkeratosis
- Superficial dermal collagen zone
- Chronic inflammatory infiltrate
- Sometimes surface erosion
- Exocytosis seen secondary to scratching

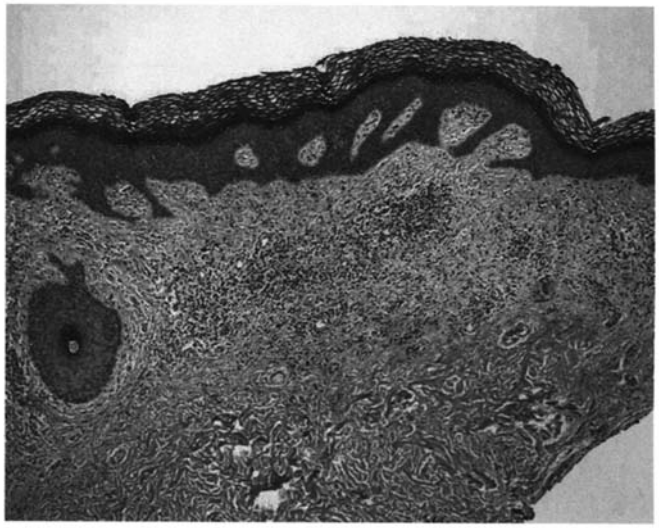


Fig. 1. Lichen simplex chronicus.

- If acanthosis is evident without dermal changes, the diagnosis of squamous cell hyperplasia is pertinent (see *Squamous Cell Hyperplasia*)

Behcet's Disease

Clinical

- Most commonly seen in women in Japan and Mediterranean countries in the age of 30s
- Systemic vasculopathy
- Manifesting oral ulceration
- Genital ulcer
- Skin lesions such as pustules
- Erythema nodosa like lesions
- Eye lesions including uveitis and retinal vasculitis

Microscopic

- Necrotizing vasculitis
- Involving all types of dermal and subcutaneous vessels
- Mural necrosis and thrombosis may be present

Fox-Fordyce Disease

- Usually occurs after puberty
- Involves genital and axilla skin glands
- Multiple small pink reddish papules on mons pubis
- Disorder sweat duct glands
- Caused by obstruction of ducts by keratin plugs in the opening of the hair follicles
- Inflammatory responses due to leakage of the apocrine secretion into dermis

Hidradenitis Suppurativa

- A chronic debilitating disease
- Affects vulva and perineum
- Intercourse extremely uncomfortable
- Initiated by obstruction and inflammation of apocrine glands
- Resultant sinus tract and abscess formation

INFECTIOUS LESIONS

Vulva condyloma accuminata (Human Papillomavirus [HPV] infections)

Clinical

- Caused by HPV-6 and less commonly HPV-11
- Associated with condylomas of perineal
- Perianal skin
- Anal urethral mucosa
- Associated with condylomas on vagina and cervix
- Visible only colpospically
- Can be large sessile or exophytic growth
- Often multiple and sometimes confluent
- Involves labia majora and vestibules
- Lesions may be influenced by hormonal and immune status. Vulva condylomas may enlarge or increase in number during pregnancy but may regress postpartum. However, there is no particular association between oral contraceptive use and vulva condyloma development. The lesions may be associated with or progress to vulva intraepithelial neoplasia (VIN) or invasive squamous cell carcinoma, especially in immunosuppressed women

Microscopic

- The presence of koilocytes in superficial layers
- Koilocytes are HPV-infected keratinocytes that have atypical nuclei and a perinuclear clear zone (halo)
- The atypical nuclei have three features: Enlarged nuclei in size, hyperchromatin or coarse chromatin, and irregular nuclear membrane. Usually, presence of any two of the three features is qualified as an aypical nucleus
- Binucleated or multinucleated koilocytes are seen. Koilocytes may vary in size and shape. Architecturally, condylomas show complex branching papillae composed of acanthotic squamous epithelium and fibrovascular cores. Sometimes, endophytic or downward growth of rete pegs is seen
- MIB-1 or Ki-67 stained nuclei in the upper two thirds of squamous epithelium. They may aid diagnosis when unequivocal diagnostic features not present
- Some authorities group condylomas into low grade VIN (VIN I)
- Pay attention to presence of any high grade VINs (see VIN sections)

Differential Diagnosis

- Verrucous carcinoma (see section of Malignant Tumor of the Vulva) sometimes called giant condylomas
- Usually large and solitary in older women
- Lack fine branching papillae
- No koilocytes as seen in condylomas
- Warty VINs usually have more severe nuclear atypia and more obvious mitosis
- Vestibular papillomatosis typically lack of koilocytes or lack of hyperkeratosis
- Condyloma lata, lesions of Syphilis (see below)

Candidiasis

- Commonly present with intense pruritus
- Common external manifestation of vaginal infection with *Candida*
- Key histologic feature of candidiasis is finding acute inflammatory cells within epidermis
- Identification of fungal hyphae on GMS or PAS stains
- Fungal hyphae may be found in keratin layer

Molluscum contagiosum

- Caused by pox DNA virus infection
- More common in immunosuppressed patients
- Squamous epithelial cells contain characteristic intracytoplasmic inclusions (Molluscum bodies) **(Figure 2)**

Herpesvirus infection

- Commonly caused by herpes simplex virus (HSV) type 2
- Vulva pain is characteristic
- Classic ground-glass nuclei or eosinophilic intranuclear inclusions may be seen in base or edge of vesicles or ulcers
- Anti-HSV can be used to aid diagnosis in certain clinical settings

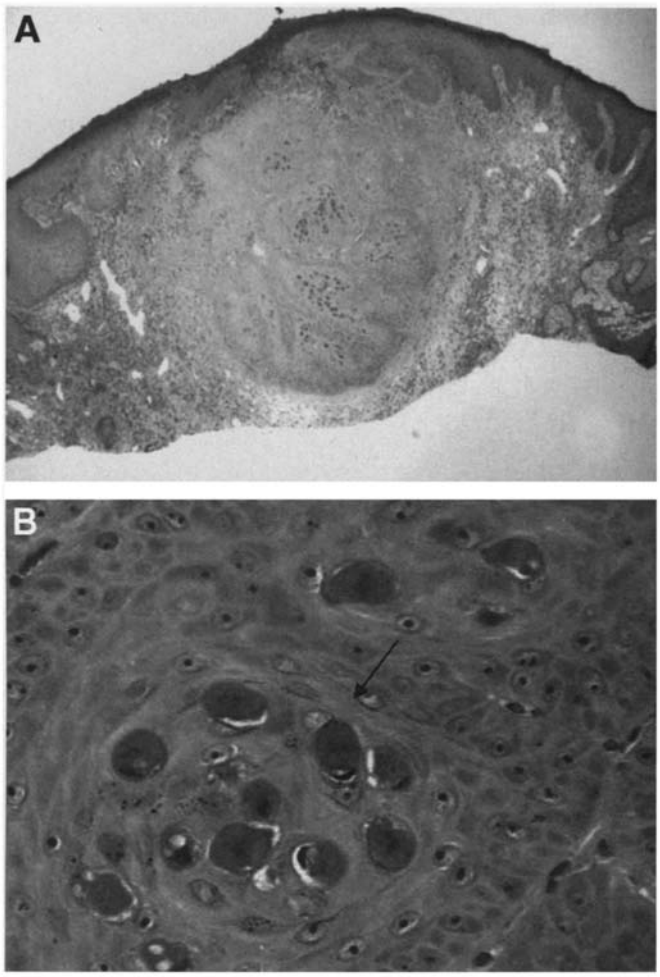


Fig. 2. Molluscum contagiosum. **(A)** Affected epithelium shows acanthotic changes and extends downward into the superficial dermis. **(B)** Molluscum bodies consists of homogeneous intracytoplasmic DNA virus inclusions (arrow).

Cytomegalovirus (CMV)

- Mostly seen in HIV infected women
- CMV-inclusion bodies (intranuclear and cytoplasmic) in epithelium or endothelium are diagnostic

Syphilis

- Caused by sexually transmitted spirochete *Treponema Pallidum*
- Chancre (superficial ulcer) as primary lesion occurs within days or months of sexual contact
- Condyloma lata as a second phase lesion becomes evident by additional several months forming a mucocutaneous rash and papules, which have marked acanthosis, papillomotosis and neutrophil infiltration in the epidermis
- Prominent perivescular plasma cell infiltrate and endothelial cell proliferation are characteristic
- Warthin-Starry stain or dark-field examination or immunofluorescence stain to demonstrate spirochetes in lesions
- Gummas as tertiary lesions rarely seen on vulva

Lymphogranuloma Venereum (LGV)

- Caused by *Chlamydia Trachomatis*
- Most commonly seen in tropical and subtropical regions
- Uncommon in United States
- Typically present ulcers followed by painful inguinal lymphadenitis
- Chronic inflammation extensive, but not specific
- Diagnosis relied on characteristic clinical findings, culture results and complement fixation tests

CYSTIC LESIONS

Batholin's Duct Cyst

Clinical

- Batholin's cyst and/or abscess formation may account for majority of symptomatic vulva cysts observed in gynecologic clinic
- Average size 1–2 cm but can be much larger
- Mostly located in posterior introitus in region of Batholin's duct opening into vestibule
- Obstruction of Batholin's duct system results in cysts formation
- Obstructed infected gland may form abscess
- Lined by squamous, transitional, mucinous, ciliated, or flattened nonspecific epithelium
- Typical clinical location and presence of normal Bartholin's glands adjacent to cyst facilitate distinction from cysts arising in minor vestibule glands **(Figure 3)**

Skene's Duct Cyst

Clinical

- Skene's ducts visible as bilateral single small opening adjacent to urethral meatus
- Skene's duct cysts are cystic dilations of glands within the vulva vestibule



Fig. 3. Bartholin's gland cyst. The cyst is lined by cuboidal mucinous and transitional or indifferent cells. Atrophic changes are seen in adjacent Bartholin's glands.

- Usually solitary, sometimes painful, subcutaneous mass in vulva vestibule in women of reproductive age

Microscopic

- Lined by single layer of columnar mucinous epithelium, ciliated non-mucinous epithelium, or in combination of the two
- Squamous metaplasia or urothelial like epithelium may be seen

Epidermal Inclusion Cyst

- Commonly seen in vulva, usually in the labia majora
- May be a consequence of obstruction of pilosebaceous ducts and glands
- Patient may present complaining of palpable nodularity within vulva
- Lined by stratified squamous epithelium and filled with keratinaceous debris

Mesonephric (Gartner's Duct) Cyst

- Very rare and located in the lateral aspects of vulva or vagina
- Lined by cuboidal to flattened epithelial cells that are devoid of cytoplasmic mucin

BENIGN DISCOLORED LESIONS

Lichen Sclerosus (LS)

Clinical

- A common vulva disease
- Accounts for 30–40% of vulva non-neoplastic epithelial lesions
- Most commonly in peri- and postmenopausal women
- Unclear etiology although various mechanisms proposed, including immunologic, genetic, androgen receptor deficiency, and epidermal growth factor deficiency
- Characterized by irregular ill-defined hypopigmented patches
- Majority of lesions are multiple and sometimes symmetric
- At end stage of the disease affected skin is shiny and wrinkled (sometimes referred as "cigarette paper")
- Although not considered a premalignant lesion, areas of hyperplastic epithelium occurring within fields of LS may be sites of premalignant or malignant changes
- Squamous cell carcinoma in situ or invasive carcinoma is associated with adjacent LS in as many as 60% of cases

*Microscopic (**Figure 4**)*

- Loss of rete ridges
- Homogeneous appearance to superficial dermis
- Associated edema, fibrin, and apparent decrease in collagen and vascularity
- Chronic inflammatory infiltrate present in superficial dermis
- Epithelium may be strikingly thinned, eroded, or ulcerated
- Markedly thickened epithelium with hyperkeratosis and parakeratosis may be seen in adjacent areas

Squamous Cell Hyperplasia

- Proposed in 1987 to replace term *hyperplastic dystrophy*
- Pruritus is an usual symptom
- Unilateral irregular white plaque like lesion noted
- Nonspecific thickening of vulva epithelium characterized by acanthosis with elongation, widening and deepening of rete ridges but without prominent inflammatory component (**Figure 5**)
- Hyperkeratosis and parakeratosis are usually present
- Cases demonstrating cellular atypia should be classified as vulvar intraepithelial neoplasia
- When lichen sclerosus or squamous hyperplasia is associated with vulvar intraepithelial neoplasia (VIN), both diagnoses should be reported

Lichen Planus

- Uncommon inflammatory disease of unknown etiology
- Typically involves vulva vestibule and vagina
- Markedly erythematous and serosanguinous discharge may be present
- Diagnostic features include lichnoid interface chronic inflammatory infiltrate and pointed rete ridges
- Severe cases may present cytoid bodies with keratinocyte liquification necrosis, bullae, and ulceration
- Special stainings for bacteria or fungi are negative

Seborrheic Keratosis

- Raised, well-circumscribed, pigmented warty lesion
- May be multiple or form clusters on vulva
- Microscopically consists of basaloid cells in solid sheets and multiple horn cysts

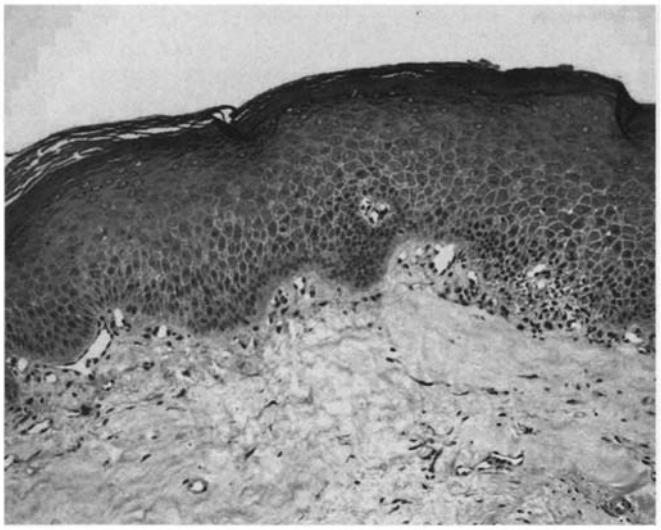


Fig. 4. Lichen sclerosus. This picture shows early changes of lichen sclerosus.

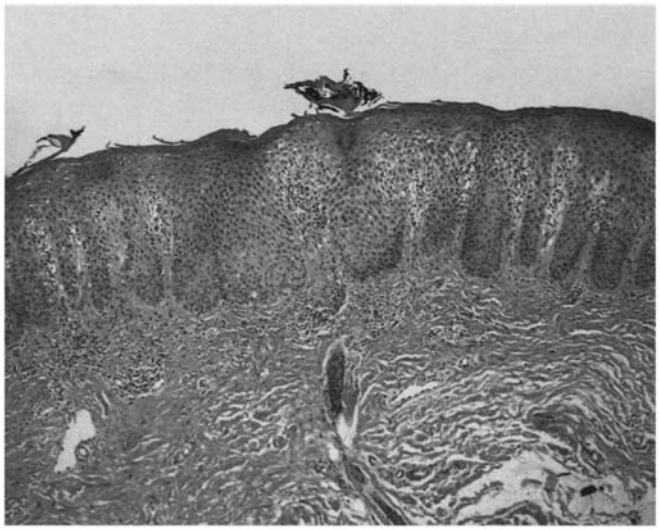


Fig. 5. Squamous cell hyperplasia. Epidermis shows prominent acanthosis with elongated rete pegs. No dysplasia or nuclear atypia is present.

- Common to see hyperkeratosis, acanthosis, and papillomatosis of epithelium and increase of melanin pigment in basal and parabasal layers **(Figure 6)**

Lentigo Simplex (<4 mm) and Melanosis (>4 mm)

- Hyperpigmented macular lesions resulting from localized excess production of melanin by melanocytes
- Typically occur in white reproductive age women
- Basal layer hyperpigmentation and slight basal melanocytic hyperplasia without nesting or atypia **(Figure 7)**
- Microscopic findings of lentigo simplex and melanosis typically lack distinctions other than size
- 4 mm is an arbitrary line dividing the two lesions
- Melanosis sometimes can reach or exceed 10 cm in size

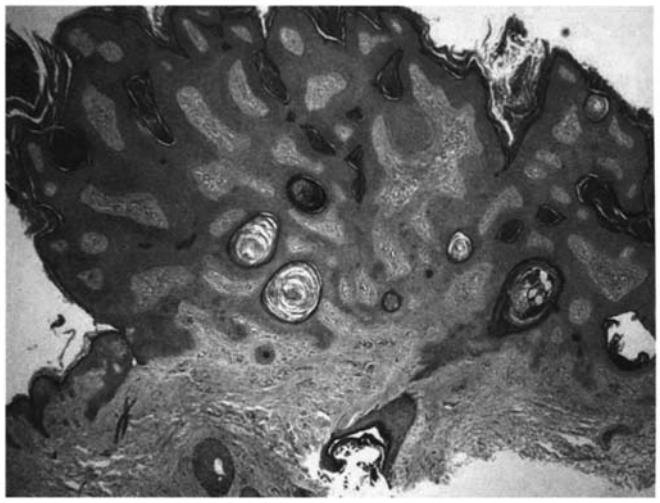


Fig. 6. Seborrheic keratosis.

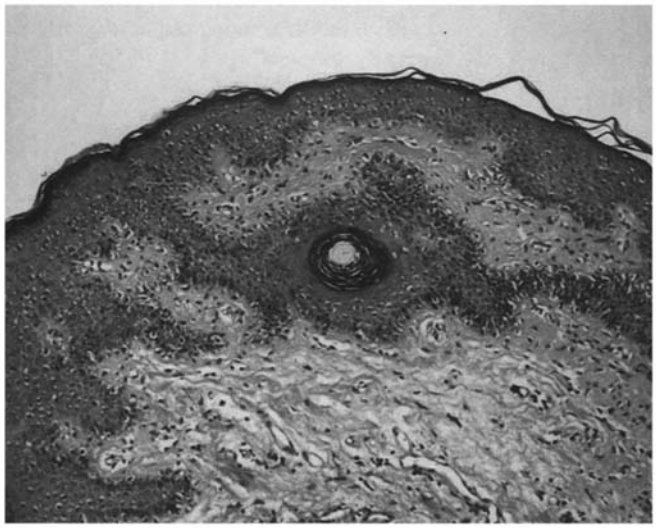


Fig. 7. Lentigo simplex or melanosis (depending on the size).

Melanocytic Nevi

- Vulva nevi only 1/3 as frequent as in other skin areas
- Vast majority of nevi require no therapy
- Concern regarding potential for malignancy results in excision of most vulva nevi
- Small percentage of vulva nevi show distinctive, atypical features that differ from those of usual dysplastic nevus, which have been referred as atypical melanocytic nevi of genital type (AMNGT) by Clark and colleagues. They are usually 4 cm or less in size and are compound nevi. They are typically symmetrical on cross section and have maturation of melanocytes in dermis. They usually do not have significant pagetoid spread and no mitosis in the melanocytes. Differential diagnosis of AMNGT includes dysplastic nevi and superficial spreading melanoma. Please read a comprehensive chapter in Clark et al., if any concerns of differential diagnosis arise

BENIGN TUMORS

Hidradenoma Papilliferum (HP)

Clinical

- Benign glandular epithelial tumor arising in specialized anogenital sweat glands
- More commonly seen in white adult women in interlabial sulci

Microscopic ***(Figure 8)***

- Composed of complex, glandular epithelial cells
- Well defined tumor cells with discreet margins
- Common papillary and cribriform in configuration with myoepithelial cells present
- Mild atypia and stratification with occasional mitotic figures
- Malignant transformation is extremely rare
- Atypical or HP with borderline malignancy potential has never been reported
- Differential diagnosis includes intraductal papillomas arising in ectopic breast tissue

Granular Cell Tumor

Clinical

- Usually benign, believed to arise in peripheral nerve sheath of reproductive or postmenopausal women
- Typically present solitary or rarely with several subcutaneous non-tender nodules in labia majora or in vicinity of the clitoris

Microscopic

- Often showing striking psuedoepitheliomatous hyperplasia of overlying squamous epithelium
- This feature can be confused with well-differentiated squamous cell carcinoma, especially in a superficial biopsy specimen **(Figure 9)**
- Bland tumor cells with poorly defined cell borders with coarse eosinophilic granular cytoplasm
- Commonly intermingled with strands of collagen and occasional chronic inflammatory cells
- Positive S-100 and myelin basic protein

Squamous Vestibular Papillomatosis

- These are multiple, often numerous, small papillary projections occurring within vestibule exterior to hymenal ring
- Presenting symptoms include pruritus burning sensation and dyspareunia
- Some women may be asymptomatic
- No causal relationship between HPV infection and SVP
- Each papilloma about 1 mm in diameter
- Papillary fronds of plain nonkeratinized glycogenated squamous epithelium with an underlying proliferation of capillaries in dermal papillae
- Key features: no koilocytes or nuclear atypia

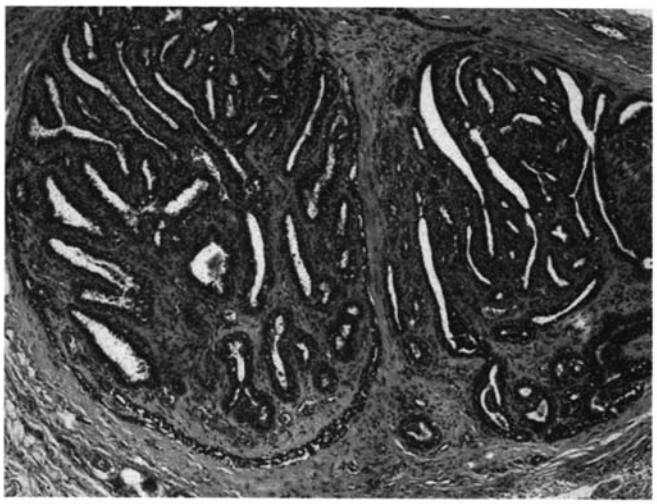


Fig. 8. Hidradenoma papilliferum or papillary hidradenoma.

Angiokeratoma

- Vascular lesions containing ecstatic subepithelial dermal blood vessels that abut basal epithelial layer
- Unknown cause
- Patient with multiple angiokeratomas on the vulva should receive consultation for Fabry's disease, which is an X-linked recessive disease associated with deficiency of galactosidase A
- Usually asymptomatic with 2–5 mm popular lesions on vulva
- Characterized by prominent endothelial-lined blood vessels immediately beneath the basement membrane of overlying epithelium and separated by rete ridges
- Rete ridges form epithelial cords, which separate vascular channels, resulting in a multilocular appearance of lesion

Cellular Angiofibroma

- Six cases reported in reproductive age women
- Usually less than 3 cm in size
- Well circumscribed lesion with uniform bland proliferative fibroblasts
- Numerous thick-walled vessels
- Short bundles of collagen
- Sparse adipose tissue
- Positive for vimentin and CD34
- Negative for smooth muscle actin, desmin, and EMA

Angiomyofibroblastoma

- Mostly in reproductive age women
- Slow growing
- Well-circumscribed painless mass in subcutaneous area
- Less than 5 cm in greatest dimension

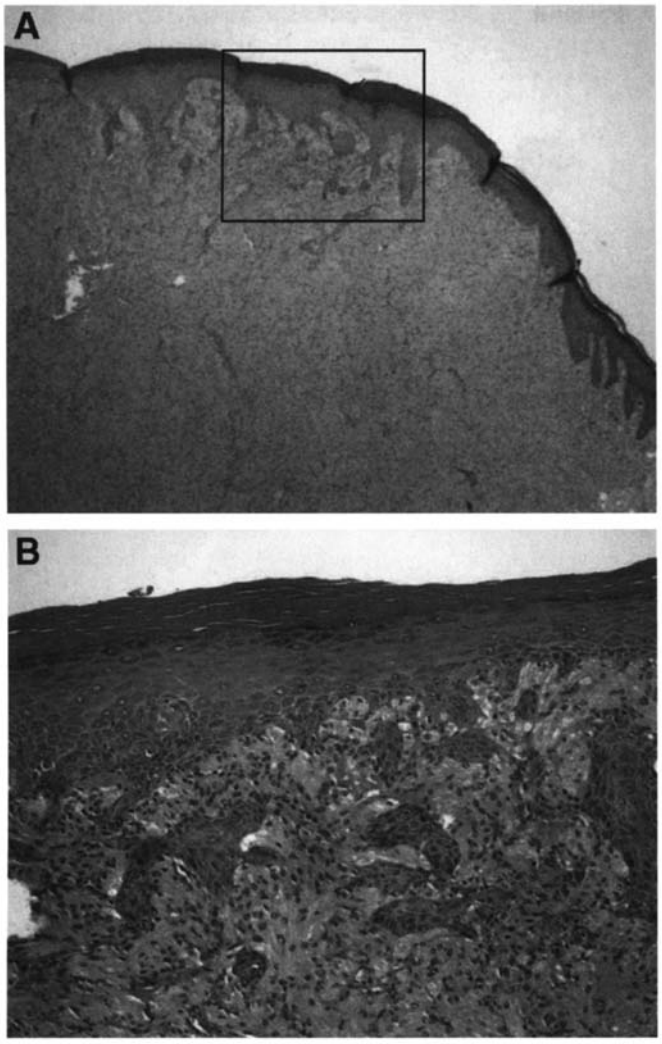


Fig. 9. Granular cell tumor. The tumor is localized in the dermis. Tumor cells are bland looking. The epidermis shows pseudoepitheliomatous hyperplasia. The pattern could be misdiagnosed as invasive squamous cell carcinoma. Squared area from **(A)** is magnified in **(B)** to appreciate the pseudoinvasive pattern.

- Alternating hypercellular and hypocellular areas associated with prominent vasculature
- Either spindle or round myofibroblasts, commonly binucleated or multinucleated
- Tend to concentrate around vessels
- Rare mitotic figures
- Major differential diagnosis includes aggressive angiomyxoma (see below)

Fibroepithelial Polyp (Acrochordon)

- Benign polypoid mass
- Composed of fibrovascular core
- Covered by stratified keratinized squamous epithelium
- Usually soft but can be fleshy
- May be pigmented
- Stromal cells may show nuclear pleomorphism and atypia, particularly when patient is pregnant
- The term "soft tumor" is given when mature adipose tissue is present in dermal and subdermal area

Endometriosis

- Almost always found in the episiotomy sites
- Thought to be secondary to implantation of endometrial tissue, although metaplastic process as a possible pathogenesis has been proposed
- Symptoms are no different from endometriosis elsewhere
- Sometimes a tumor like mass (endometrioma) may be presented
- Some molecular studies indicate that endometriosis may be a clonal process, which raises a concern of neoplastic disease

Leiomyoma

- Relatively rare entity in vulva
- Arise from smooth muscle in blood vessels, erectile tissue, and skin smooth muscle of erector pili
- Microscopically, no difference from usual uterine leiomyoma

Other Benign Mesenchymal Tumors

- Lipoma, rhabdomyomas, desmoid tumor, neurofibromas, schwannomas, glomus tumor, and hemangiomas belong to this category
- Histologic features of these tumors are not different from similar tumor elsewhere

MALIGNANT EPITHELIAL TUMORS

Vulva Intraepithelial Neoplasia (VIN)

Clinical

- Noninvasive squamous dysplastic lesions of the vulva
- HPV infection is main risk factor
- Presenting with maculopapular or plaque like labial lesions
- With pruritic, burning, or asymptomatic lightly pigmented appearance **(Figure 10A)**
- More than 50% of women with VIN have similar HPV lesions in the cervix, vagina, urethra, perineum, and anus
- The lesions are graded as VIN 1 (mild dysplasia), VIN 2 (moderate dysplasia), and VIN 3 (severe dysplasia or carcinoma in situ)

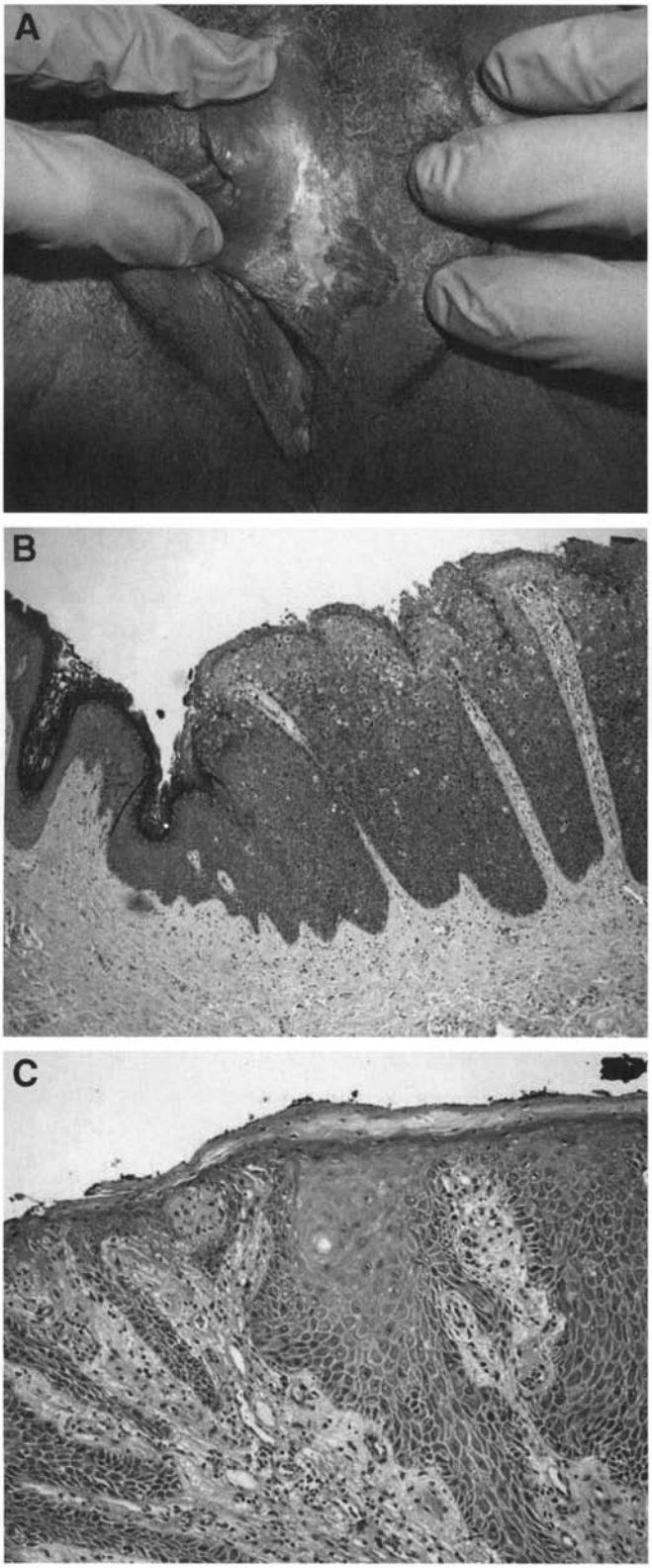


Fig. 10. Gross picture of VIN 3 prior to surgery (**top**), basaloid VIN 3 (**middle**) and well-differentiated VIN 3 contains prominent nucleoli in the center of the picture (**bottom**).

- Subtypes include basaloid (undifferentiated), warty (condylomatous), and simplex (well differentiated VIN)

VIN 3 encompasses Bowen's disease, erythroplasia of Querat, and carcinoma in situ

- Bowenoid papulosis is not histopathologic diagnosis, but clinical presentation

Microscopic

- Basaloid VIN composed of small uniform basaloid cells with scanty cytoplasm, ill-defined cell borders, large hyperchromatic nuclei, clumped chromatin patterns, conspicuous nucleoli, and many mitoses **(Figure 10B)**
- Warty VIN shows acanthotic, sometimes hyperkeratotic and parakeratotic, epithelium with spiky surface. Neoplastic cells are large with abundant eosinophilic cytoplasm, well-defined cell boarders, dyskeratosis, coarse chromatin patterns, and easily visible mitotic figures
- Well-differentiated VIN occurs more frequently in postmenopausal women. Usually HPV-negative and associated with lichen sclerosus and/or with invasive squamous cell carcinoma of vulva **(Figure 10C)**

Differential Diagnosis

- Warty VIN versus condylomas
- Paget's disease and radial growth of malignant melanoma
- Inflammatory or reactive changes

Paget's Disease

Clinical

- Mostly in peri- and postmenopausal women
- Accounts for about 1% of vulva cancers
- Presenting as pruritic, eczematous, erythematous, weeping patches
- Ulceration may occur
- Up to 30% of patients are associated with internal carcinomas including breast, low GI tract (rectum) urogenital system (cervix and bladder)
- Generally considered to arise in intraepidermal stem cell of sweat ducts
- Clinically unsuspected dermal invasion is present up to 30% of cases

*Microscopic **(Figure 11)***

- Characterized by presence of distinctive Paget's cells within vulva epithelium
- Large Paget's cells can be single or clusters throughout the epithelium
- Generally more in the basal and parabasal layers
- Vesicular nucleus with prominent nucleolus and amphophilic cytoplasm is characteristic
- The depth of invasion is measured from the basement membrane

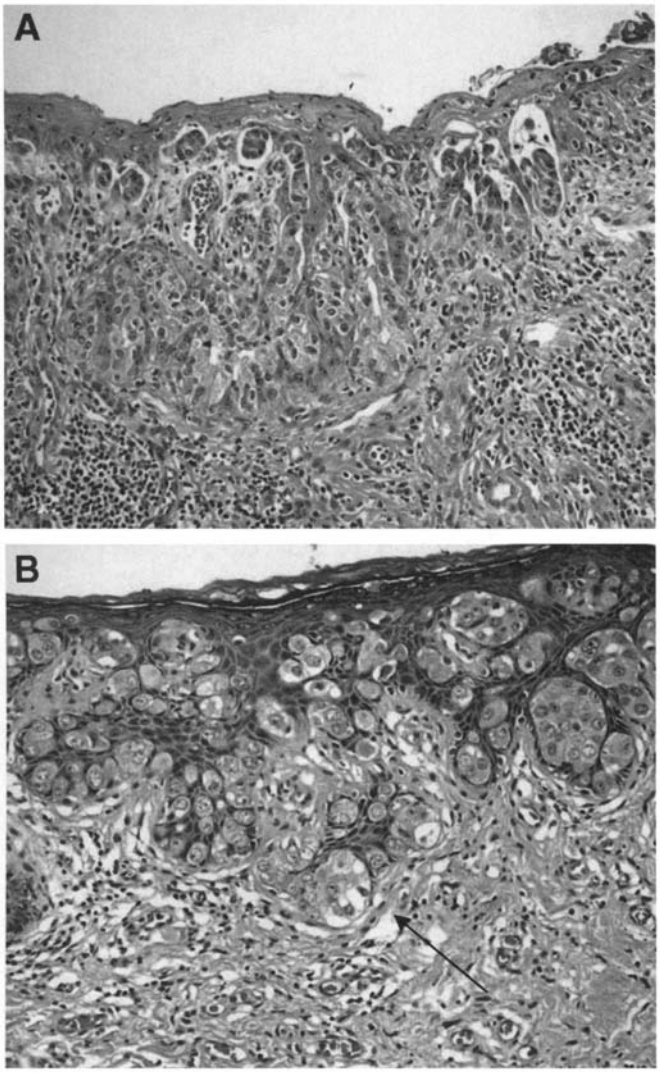


Fig. 11. **(A)** Paget's disease, non-invasive. The number of Paget's cells decreases from basal layer to the superficial layer of the epidermis. **(B)** Paget's disease with microinvasion. Paget's cells migrate through the epidermis and superficially invade into dermis (arrow). The Paget's cells have abundant clear, vacuolated cytoplasm and atypical nuclei.

- Lymphatic vascular space involvement should be reported, if any

Immunohistochemistry and Special Stainings

- CK7, GCDFP, and CEA positive
- Mucin positive

Differential Diagnosis

- Pagetoid VIN
- Superficial spreading malignant melanoma
- Clear cell papulosis
- Merkel cell carcinoma and histeocytosis X

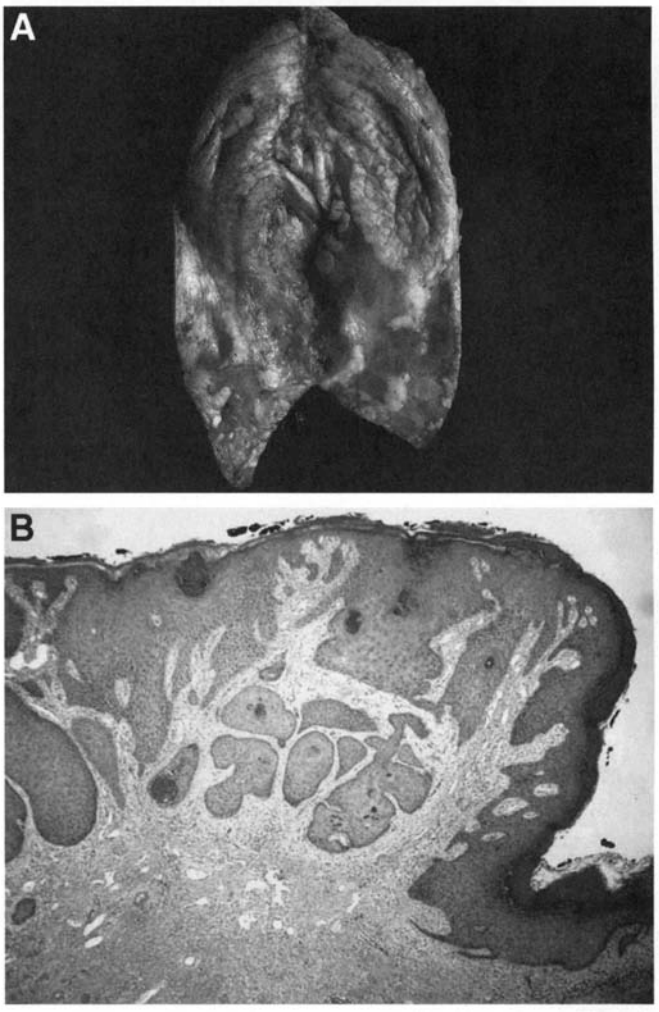


Fig. 12. Gross picture **(A)** of vulvar invasive squamous cell carcinoma. This is an example of advanced stage of squamous cell carcinoma. The cancer extensively involves bilateral labia with ulcerations. Satellite lesions (whitish patches) in the lower part of the specimen are present. The clitoris (arrow) is also involved by the squamous cell carcinoma. **(B)** A microscopic picture of early invasive squamous cell carcinoma.

Invasive Squamous Cell Carcinoma (ISCC)

Clinical

- Most common (90%) vulva cancer
- Mostly in postmenopausal women
- Rare cases may be seen in young immunosuppressed women
- Vulva or groin mass, which may be pruritic or painful
- 10% are multifocal **(Figure 12A)**
- Three types of ISCC: keratinizing, basaloid, and warty
- Similar to VINs, basaloid and warty types associated with HPV infection and in relatively younger women
- Keratinized ISCC is mostly HPV negative and occurs mostly in elderly women

Microscopic

- Keratinizing ISCC resembles ISCC elsewhere. Commonly associated with lichen sclerosus, squamous hyperplasia, and simplex type VIN **(Figure 12B)**
- Basaloid ISCC resembles basaloid VIN. Sheet or nests of neoplastic basaloid cells seen in desmoplastic stroma. Focal cellular maturation and keratinization may occur. Ajacent basaloid VIN may be seen in majority cases
- Warty ISCC are similar to warty VIN except for apparent invasion
- Similarly, noninvasive warty VIN may be present in up to 80% of cases
- Tumor grading is controversial
- Use of nuclear grade is recommended
- Term microinvasion is not recommended to use in pathology report
- Infiltrating pattern ("pushing" versus "spray") and lymphatic space involvement should be mentioned since they may be associated with prognosis

Differential Diagnosis

- Malignant melanoma without melanin expression versus poorly differentiated keratinizing ISCC
- Basal cell carcinoma versus basaloid ISCC, Merkel cell carcinoma, or metastatic small cell carcinoma
- Epithelioid sarcoma versus keratinizing ISCC
- Verrucous carcinoma versus warty ISCC
- Granular cell tumor with psuedoinvasive squamous hyperplasia

Verrucous Carcinoma (VC)

- Account for 1–2% of all vulva cancers
- Indolent in nature with little or no metastatic potential
- Giant condyloma is considered by some authorities to be synonymous with VC
- Highly differentiated ISCC with hyperkeratinized, undulating, and warty surface
- Invading underlying stroma in a form of bulbous pegs with a pushing border
- Cells show minimal nuclear atypia and abundant cytoplasm and rare mitosis

Basal Cell Carcinoma (BCC)

Clinical

- Account for 2–3% of vulva cancers
- Typically in elderly women
- Peak incidence in 70s
- A slowly growing, locally invasive, rarely metastasizing tumor
- Requires local excision for treatment

Microscopic

- BCC is composed of aggregates of uniform basal cells with peripheral palisading arrangement
- May show superficial, solid, and adenoid patterns
- BCC with morphea pattern in vulva is extremely rare

Differential Diagnosis

- Basaloid invasive squsmous cell carcinoma
- Adenoid basal cell carcinoma versus adenoid cystic carcinoma

Carcinoma of Bartholin's Glands

Clinical

- Occurs predominantly in peri- and postmenopausal women
- Accounts for 5% of vulva cancers
- Presents as enlargement or cystic mass in area of Bartholin's gland opening
- Most tumors are associated with HPV infections
- 40% patients present with advanced stage
- 5-year survival rate is about 80%

Microscopic

- Various types of carcinoma have been described, including squamous cell carcinoma (40%). adenocarcinoma (25%). adenoid cystic carcinoma (15%), and adenosquamous cell carcinoma (5%)
- Rare transitional and small cell carcinomas
- Diagnostic criteria are:
  - Identifying transitional areas between normal glands and carcinoma
  - Exclude primary tumors elsewhere, particularly other carcinomas in vulva
  - Histologically, the tumor is compatible with Bartholin's origin

Keratoacanthoma

- A rare squamous cell proliferative lesion
- Originally thought to be benign
- Has a central keratin-filled crater with focal infiltration at superficial dermis
- Currently has accepted as a variant form of well differentiated ISCC

Adenocarcinoma of Skin Appendage

- Eccrine origin with aggressive behavior
- Including mucinous adenocarcinoma, clear cell hidradenocarcinoma, and eccrine porocarcinoma
- Some vulva adenocarcinomas resemble mammary carcinomas
- May arise in apocrine sweat duct glands
- Occasional sebaceous carcinomas reported

MALIGNANT NON-EPITHELIAL TUMORS

Malignant Melanoma (Figure 13)

- Account for 5–10% of vulva cancers
- Peak incidence in postmenapausal women
- Pathologic and histologic features have no difference compared with malignant melanoma elsewhere
- Some melanomas can be mimicked by benign pigmented lesion
- AJCC for melanoma staging incorporates depth of invasion (see Chapter 12 TNM Classification of Melanoma)
- Diagnosis of melanoma should always be considered when a poorly differentiated malignant tumor, which is difficult to classify
- HMB-45 and S-100 positive



Fig. 13. Melanoma on the introitus.

Aggressive Angiomyxoma

Clinical

- Mainly occur in reproductive age women with mean age of 32 years
- Mostly presents with large, often greater than 10 cm in size, slowly growing painless ill-defined mass in pelvic perineal region
- Vague increased pressure related symptoms in urogenital or anorectal areas
- Image studies show mass to be substantially larger than clinically suspected
- Locally infiltrative but non-metastasizing tumor

Microscopic ***(Figure 14)***

- Paucicellular
- Composed of fibroblasts, myofibroblasts and numerous characteristically thick-walled vessels in abundant myxoid matrix
- Multinucleated cells may be present. Sometimes, there is morphologic overlap with angiomyofibroblastoma
- Local invasiveness can be identified such as perineural invasion
- HMGI, Desmin and actin are positive but S-100 is negative. HMGI seems more specific

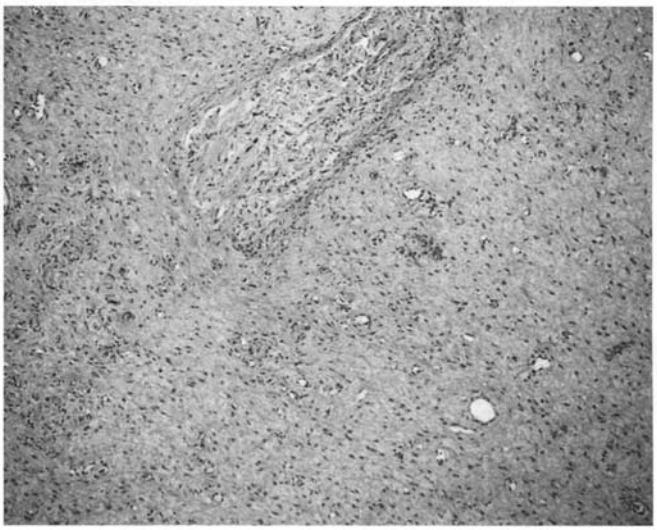


Fig. 14. Perineural invasion of aggressive angiomyxoma.

Sarcoma Botryoides

Clinical

- Typically arises in the labial or perineal areas
- Presents with bleeding and ulceration in young girls less than 10 years old
- Presents as a solid mass on vulva
- Appearance of "bunch of grapes" more characteristic
- When both vulva and vagina are involved, tumor is considered as vaginal origin
- Alveolar histologic pattern shows adverse prognosis

Microscopic

- Typical histologic features described in section of Tumor of the Vagina
- Two types: embryonal and alveolar
- Largely paucicellular tumor with variable pronounced cambium layer
- Spindle shaped cells including rhabdomyoblasts in myxoid zones
- Infiltrative growth with inconspicuous vessels
- Evidence of striated muscle differentiation may be seen
- Mitosis easily found
- Desmin, myogenin, and myo D_1 positive

Epithelioid Sarcoma

Clinical

- Also called proximal-type epithelioid sarcoma or adult type malignant rhabdoid tumor
- Frequent recurrence
- High tendency of metastasis

Microscopic

- Similar histologic and immunologic features to epithelioid sarcoma of extremeties
- Grow in a nodular pattern with abundant amphophilic cytoplasm
- Keratin and vimentin positive in most tumor cells
- CD34 is positive in only 50% of the cases

Yolk Sac Tumor

- Also called endodermal sinus tumor
- Mainly occur in children and young women
- Histologic features are similar to those tumors in ovary

Merkel Cell Tumor

- Also called as neuroendocrine carcinoma of skin
- Derived from neuroendocrine cells in epidermis
- Rare and aggressive tumor ofvulva
- Tumor cells are small with scanty cytoplasm and finely stippled chromatin
- Glandular and sqaumous differentiation may be seen
- Keratin (CK20) and neuroendocrine markers are positive

Other Sarcomas, Hematopoetic Tumors and Secondary Tumors

- The following vulva soft tissue sarcomas have also been reported
- Leiomyosarcoma, liposarcoma, dermatofibrosarcoma protuberans, malignant fibrous histeocytoma, malignant schwannoma, fibrosarcoma, angiosarcoma including Kaposi's sarcoma, alveolar soft part sarcoma, Ewing's sarcoma, and chondrosarcoma
- Vulva can be the initial site of involvement of widespread lymphomas
- A case of large cell lymphoma involving Bartholin's gland has been reported
- Vulva with metastatic tumor accounts for 8% of all vulva malignancy
- Most common primary sites include cervical squamous cell carcinoma, endometrial carcinoma, renal cell carcinoma, urethra or urinary bladder carcinoma and anorectal carcinoma

Vagina

- Many vaginal lesions are similar to the lesions either in the vulva or in the cervix. More specific lesions of the vagina are described as follows

BENIGN NON-NEOPLASTIC LESIONS

Mullerian Papilloma

- Also known as benign mesonephric papilloma of childhood
- Typically occur in girls younger than 10 years
- Mostly present with vaginal bleeding or discharge
- Polypoid papillary tumor measuring 1–3 cm in upper vaginal or cervical mucosa
- Fibrous-cored papillae with bland eosinophilic cells

Vaginal Adenosis (VA)

Clinical

- VA refers to the presence of glandular epithelium in vagina
- Derived from embryonic mullerian epithelium
- About 30% related to exposure of diethylstilbestrol (DES) in utero. Congenital VA may be seen in less than 10% of unexposed women
- Other congenital malformation of cervix and vaginal may be present
- Usually asymptomatic
- Increased discharge, bleeding, or dyspareunia
- VA lesions show red granular appearance with negative iodine stain
- Associated with clear cell carcinoma of the vagina
- Not considered as immediate precursor for the clear cell carcinoma

Microscopic

- Benign glandular epithelium replaces normal squamous epithelium or forms glands in superficial stroma
- Typically endocervical type glandular cells
- Endometrioid epithelium may be seen
- Squamous metaplasia in glandular areas is common

Differential Diagnosis

- Atypical adenosis
- Invasive sqaumous cell carcinoma involving VA

Prolapse of Fallopian Tube

- A rare condition found after vaginal hysterectomy
- Granulation tissue like lesion visible at vaginal apex
- Histologically it may be confused with adenocarcinoma when tubal plicae and tubal linings are not correctly recognized
- Diagnostic features: presence of ciliated, secretory, and Peg cells as in usual fallopian tube

Postoperative Spindle Cell Nodule

- Refers to proliferative psuedosarcomatous spindle cell lesion
- Vaginal involvement is more common than in cervix or endometrium
- Often found in operation site 1–12 weeks after surgery
- Soft polypoid masses less than 4 cm in size
- Spindle cells arranging in intersecting fascicles
- Often with network of small blood vessels
- No cellular atypia
- Mitotic figures can be abundant, up to 25/10 HPF
- Inflammatory component usually present
- Differential diagnosis include leiomyosarcoma

Emphysematous Vaginitis

- Mostly in reproductive and postmenopausal women
- Unclear etiology
- May be caused by gas-producing bacteria
- Cystic spaces beneath squamous epithelium
- Focal foreign body giant cells and chronic inflammatory cells

Ectopic Decidua

- Similar to those of eutopic or ectopic deciduas in other sites
- Pregnancy status or recent delivery extremely helpful
- Differential diagnosis includes squamous or glassy cell carcinoma
- Cytokeratin negative and vimentin positive

BENIGN TUMORS

Condylomas

- Vaginal condylomas have same histologic features as condylomas in vulva (see above)

Tubular, Tubulovillous, and Villous Adenomas

- Rare enteric type vaginal tubulovillous adenomas reported
- Tumors have goblet and Paneth cells
- Similar to those in gastrointestinal tract

Brenner Tumor

- Occasional Brenner tumors reported in literature
- Histologic appearance show no difference from ovarian Brenner tumors

Benign Mixed Tumor (Spindle Cell Epithelioma)

Clinical

- Benign tumors in young to middle aged women
- Well-circumscribed grey soft to rubbery masses measuring 1–6 cm in size
- Tend to localize in hymenal region

Microscopic

- Resembling mixed tumor of salivary glands with predominant mesenchymal-appering component
- Stromal-like component showing spindle cells with no atypia or insignificant mitosis
- Interspersed benign squamous epithelium
- Usually forming nests
- Occasional glands lined by low cuboidal to columnar epithelium
- May have squamous metaplasia
- Hyaline globular aggregates of stromal matrix also frequently seen
- Cytokeratin is strongly positive in both epithelial and mesenchymal-appearing components

MALIGNANT EPITHELIAL TUMORS

Vaginal Intraepithelial Neoplasia (VAIN)

- Occurring only 1% as frequent as its cervical intraepithelial neoplasia (CIN)
- Tends to occur in women who are elder than those women with CIN
- In majority cases, prior or synchronous non-invasive or invasive squamous carcinoma elsewhere in the lower genital tract are present
- HPV as a known risk factor for VAIN as well as corresponding invasive carcinoma

- Colposcopy helps to identify lesions
- Histologic features as well as grading are same as those for CIN
- About 3 to 10% of cases progress to invasive squamous cell carcinoma

Squamous Cell Carcinoma

- A primary vaginal SCC is defined by presence of vaginal SCC without involvement of cervix or vulva
- Demonstrated by clinical or histologic examination
- Most common cancer of vagina
- Occur mostly in postmenopausal women and about 10 years elder than those in cervical counterpart
- In limited form the SCC may present as indurated or ulcerated nodules or exophytic growth
- In advanced disease friable mass with fistula may be seen
- Histologic diagnosis is same as in cervical SCC
- Microinvasion defined as stromal invasion less than 2.5 mm

Atypical Adenosis

- Occurs mostly in tuboendometrioid type of adenosis
- Often associated with adjacent clear cell carcinoma of vagina (see below)
- Atypical adenosis presents more complex glandular proliferation than those mucinous adenosis (**Figure 15**)
- Lined by atypical cells with prominent nucleoli
- Atypical cells with hobnailing features and rare mitosis may be seen
- Atypical adenosis is considered as immediate precursor lesions of clear cell carcinoma

Clear Cell Carcinoma

Clinical

- About 80% associated with DES (a synthetic estrogen) exposure in utero
- Mostly occur in young adult women with mean age of 19 years
- Either asymptomatic or abnormal bleeding
- History of DES exposure should prompt a careful vaginal examination
- Mostly found in the upper third of the vagina on the anterior wall
- Large cancer with possible ulceration form nodular or polypoid masses
- DES-related carcinomas have a better prognosis than DES-unrelated cases

Microscopic

- Adenosis or atypical adenosis usually is seen in adjacent areas
- Similar to classic clear cell carcinoma elsewhere in female reproductive system

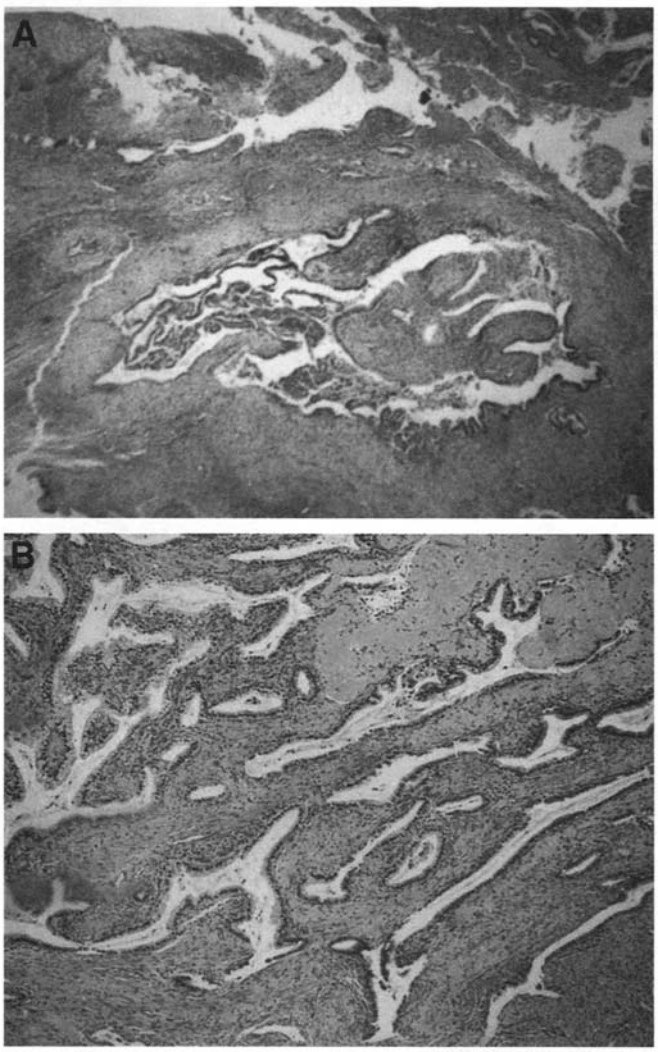


Fig. 15. Atypical adenosis of the vagina.

Differential Diagnosis

- Vaginal adenosis with microglandular hyperplasia
- Atypical vaginal adenosis
- Vaginal adenosis with Arias-Stella reaction

Endometrioid Adenocarcinoma

- Occasional endometrioid adenocarcinoma of the vagina reported
- Mostly associated with endometriosis
- Rarely related to DES exposures

Mesonephric Adenocarcinoma

- Rare cases of mesonephric adenocarcinoma reported
- Derived from paravaginal mesonephric remnants
- Histologically similar to those in cervix

OTHER MALIGNANT TUMORS

Sarcoma Botryoides

- Most common vaginal sarcoma
- Similar clinical and pathologic findings as described in Vulva section

Malignant Melanoma

- Rare but very aggressive malignant tumor in vagina
- Mostly located in lower third of anterior vaginal wall
- Usually 2–3 cm in size
- Histologically similar to those melanomas in other sites
- Clark level assessment is not practical in vagina due to lack of normal cutaneous anatomic landmarks
- Tumor size, depth of invasion, and lymphatic space involvement should be mentioned in pathology report

Carcinosarcoma

- Another rare form of malignancy in vagina
- Very poor prognosis
- Diagnosis of primary vaginal carcinosarcoma requires exclusion of metastasis from elsewhere in female genital tract
- Macroscopic and microscopic features resemble those in endometrial counterpart

Primitive Neuroectodermal Tumor (PNET)

- Three cases have been reported in vagina
- It represents those tumors of uncertain lineage within small round blue cell family
- Histology characteristics are similar to PNET or Ewing's sarcoma elsewhere
- Representative picture is presented from author's personal collection **(Figure 16)**
- Positive CD99
- Diagnosis can be further confirmed by presence of MIC2 gene, EWS/FL-1 chimeric transcripts

Leiomyosarcoma

Clinical

- Most common vaginal sarcoma in adult women
- Second most common vaginal sarcoma in all women
- Usually multilobulated solid tumor masses ranging from 3 to 5 cm in vagina
- As in uterus, leiomyomas are not considered as precursor lesions

Microscopic

- Diagnostic criteria include:
  - Smooth muscle tumors larger than 3 cm in size
  - Nuclear atypia more than moderate
  - Mitosis more than 5/10 HPF
  - Coagulative necrosis helpful
  - Infiltrating margins
- Differential diagnosis includes post operative spindle cell nodules (see above)

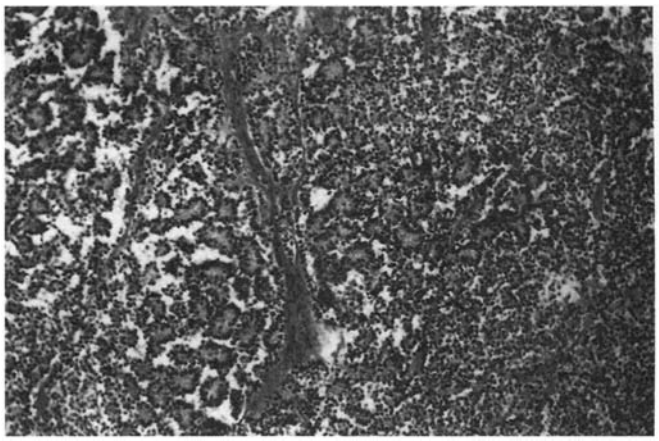


Fig. 16. Vaginal primitive neuroectodermal tumor. A representative picture from a 29 years old oriental woman who presented with a 5 cm vaginal mass. Microscopically, the tumor consists of sheets of primitive small round cells with numerous Homer-Wright rosettes. The tumor cells were characterized by scanty cytoplasm, round to oval hyperchromatic nuclei, finely stippled chromatin and conspicuous single nucleoli. CD99 was positive. Picture was provided by Dr. Xiaoyun Liao at Beijing Medical University.

Yolk Sac Tumor

- Occurs usually in young girls under 3 years old
- Vaginal discharge and bleeding are common
- Serum AFP may be elevated
- Pathologic features resemble its ovarian counterpart
- Differential diagnosis includes clear cell and endometrioid adenocarcinomas

Hematopoietic Tumors

- Rare lymphomas may occur in vagina
- Primary vaginal lymphomas may present as abnormal bleeding
- Usually occur in women younger than those of secondary lymphomas involving vagina
- Mostly non-Hodgkins type and large B-cell lymphomas
- Definitive diagnosis requires histology and immunophenotyping similar to lymphomas elsewhere

Secondary Tumors

- Tumors in vagina are more commonly from metastasis

- Metastatic tumors may either from direct extension or from distant metastasis
- Direct extension most commonly comes from cervix and vulva
- Metastasis may be derived from endometrium, colon, rectum, bladder, ovary, kidney, and breast
- Choriocarcinoma is known to have a high tendency to involve vagina

FIGO STAGING OF THE VULVA AND VAGINA

FIGO Staging of Carcinoma of the Vulva*

- **Stage 0** Carcinoma in situ; intraepithelial carcinoma
- Tis
- **Stage I** Tumor confined to the vulva and/or perineum, ≤2 cm in greatest dimension:
  - T1aN0M0 Depth of invasion not exceeding 1 mm**
  - T1bN0M0 Depth of invasion >1 mm
  - **Stage II***** Tumor confined to the vulva and/or perineum, >2 cm in greatest dimension
  - T2N0M0
- **Stage III** Tumor of any size with:
  - T3 N0 M0 1. Adjacent spread to the lower urethra, and/or
  - T3 N1 M0 vagina, and/or the anus (T3) and/or
  - T1 N1 M0 2. Unilateral regional lymph node metastasis
  - T2 N1 M0 (N1)
- **Stage IVa** Tumor invades any of the following: upper
  - T1 N2 M0 urethra, bladder mucosa, rectal mucosa, pelvic
  - T2 N2 M0 bone (T4) and/or bilateral regional lymph node
  - T3 N2 M0 metastasis (N2)
  - T4 Any N M0
- **Stage IVb** Any distant metastasis including pelvic lymph nodes:
  - Any T Any N M1

**The definition of the T categories correspond to the stage accepted by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO).*

***The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial dermal papillae to the deepest point of invasion.*

****Lymphatic invasion does not increase the stage.*

FIGO Staging of Carcinoma of The Vagina*

- **Stage I** The carcinoma is limited to the vaginal wall
- **Stage II** The carcinoma has involved the subvaginal tissue, but tumor has not extended to the pelvic wall:
  - IIa Paravaginal submucosal extension only
  - IIb Parametrial extension
- **Stage III** The carcinoma has extended to the pelvic wall (fascia, muscle, neurovascular structure, or skeletal portion of the bony pelvis) or any regional lymph node metastasis
- **Stage IV** The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum. A bullous edema does not allow designation of this stage:
  - IVa Spread of tumor to adjacent organs and/or direct extension beyond the true pelvis
  - IVb Spread of tumor to distant organs

**The definition of the T categories correspond to the stage accepted by the Federation Internationale de Gynecologie et d'Obstetrique (FIGO).*

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25

Uterus and Fallopian Tube

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CONTENTS

UTERUS—CERVIX

I. Non neoplastic Lesions 25-4
- Noninfectious Cervicitis 25-4
- Infectious Cervicitis.....25-4
- Atypia of Repair 25-6
- Radiation Induced Atypia 25-6
- Tubal Metaplasia 25-6
- Tuboendometrioid Metaplasia.....25-7
- Transitional Cell Metaplasia 25-7
- Arias-Stella Reaction.....25-7
- Microglandular Endocervical Hyperplasia 25-7
- Nabothian Cyst 25-7
- Tunnel Clusters 25-8
- Mesonephric Remnants and Mesonephric Hyperplasia 25-8
- Endometriosis 25-8
- Lymphoma-Like lesion 25-9
- Postoperative Spindle Cell Nodule 25-9
- Decidual Pseudopolyp and Decidualization 25-9
- Mesodermal Stromal Polyp (Pseudosarcoma Botryoides) 25-9

II. Epithelial Tumors and Precursors....25-9
- Benign Squamous Cell Lesions.....25-9
  - Fibroepithelial Polyps 25-9
  - Squamous Papilloma 25-10
- Benign Glandular Lesions.....25-10
  - Endocervical Polyp 25-10
  - Müllerian Papilloma.....25-10
- Squamous Tumors and Precursors 25-11
- Cervical Intraepithelial Neoplasia.....25-11
- Early Invasive (Microinuasive) Squamous Cell Carcinoma 25-12
- Squamous Cell Carcinoma 25-13
  - Keratinizing 25-13
  - Non-Keratinizing 25-13
  - Basaloid 25-13
  - Verrucous 25-13
  - Warty 25-13
  - Papillary 25-13
  - Lymphoepithelioma-Like 25-14
  - Squamotransitional Cell 25-14
- Glandular Tumors and Precursors Lesions 25-14
  - Adenocarcinoma in situ (AIS) 25-14
  - Atypical Hyperplasia (Glandular Dysplasia) 25-14
  - Early Invasive (Microinvasive) Adenocarcinoma 25-14
  - Adenocarcinoma.....25-15
    - Mucinous Adenocarcinoma 25-15
      - Endocervical 25-15
      - Intestinal 25-15
      - Signet-ring Cell 25-15
      - Minimal Deviation 25-15
      - Villoglandular 25-15
    - Endometrioid Adenocarcinoma 25-16

Clear Cell Adenocarcinoma 25-16
Serous Adenocarcinoma 25-16
Mesonephric Adenocarcinoma 25-16
Other Epithelial Tumors....25-16
Adenosquamous carcinoma....25-16
Glassy Cell Carcinoma Variant 25-16
Neuroendocrine Tumors 25-17
Carcinoid 25-17
Atypical Carcinoid....25-17
Small Cell Carcinoma 25-17
Undifferentiated Carcinoma 25-17

III. Mesenchymal Tumors....25-17
Smooth Muscle Tumors....25-17
Leiomyoma 25-17
Leiomyosarcoma 25-17
Other Benign Mesenchymal Tumors....25-17
Other Malignant Mesenchymal Tumors 25-18

IV. Mixed Epithelial and Mesenchymal Tumors 25-18
Adenomyoma....25-18
Adenofibroma 25-18
Adenosarcoma 25-18
Carcinosarcoma (Malignant Mixed Mesodermal Tumor) 25-18

V. Melanocytic Tumors....25-19
Blue Nevus 25-19
Malignant Melanoma....25-19

VI. Tumors of Germ Cell Type 25-19

VII. Lymphoid and Hematopoietic Tumors 25-19

VIII. Secondary Tumors 25-19

IX. TNM Classification and FIGO Staging System for Cervical Carcinoma 25-20

UTERUS—CORPUS

X. Morphology of the Endometrium 25-20
Endometrial Cycle....25-20
Proliferative Phase 25-20
Secretory Pase 25-21
Menstrual Phase....25-21
Inactive Endometrium 25-21
Atrophic Endometrium 25-21
Pregnancy Related Changes 25-21
Arias Stella Reaction 25-21
Optically Clear Nuclei 25-22
Decidual Reaction 25-22
Effects of Hormone Administration 25-22

XI. Dysfunctional Uterine Bleeding 25-22
Glandular and Stromal Breakdown Associated with Anovulation 25-22
Inadequate Luteal Phase Defect 25-22
Irregular Shedding....25-23

XII. Non-neoplastic Lesions 25-23
Acute and Chronic Endometritis....25-23
Specific Types of Chronic Endometritis 25-23
Changes Related to Intrauterine Devices 25-24
Adenomyosis....25-24
Endometrial Cellular Changes (Metaplasias)....25-24
Miscellaneous Lesions....25-25

XIII. Epithelial Tumors and Related Lesions 25-25
Endometrial Polyps 25-25
Precursor Lesions of Endometrial Carcinoma....25-26
Endometrial Hyperplasia 25-26
Simple Hyperplasia 25-26
Complex Hyperplasia....25-26
Atypical Hyperplasias 25-27
Endometrial Intraepithelial Carcinoma 25-27
Endometrial Carcinoma....25-28
Endometrioid Carcinoma....25-29
Mucinous Adenocarcinoma 25-30
Serous Carcinoma 25-30
Clear Cell Carcinoma 25-31
Mixed Cell Adenocarcinoma 25-31
Squamous Cell Carcinoma 25-31
Transitional Cell Carcinoma 25-31
Small Cell Carcinoma 25-31
Undifferentiated Carcinoma....25-31

XIV. Mesenchymal Tumors and Related Lesions 25-32
Smooth Muscle Tumors....25-32
Leiomyoma 25-32
Histological Variants 25-32
Growth Pattern Variants 25-34

Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP) ..25-34
Leiomyosarcoma 25-34
Endometrial Stromal and Related Tumors 25-35
Endometrial Stromal Nodule 25-35
Endometrial Stromal Sarcoma, Low Grade....25-35
Undifferentiated Endometrial Sarcoma....25-37
Miscellaneous Mesenchymal Tumors 25-37
Mixed Endometrial Stromal and Smooth Muscle Tumor....25-37
Perivascular Epithelioid Cell Tumor (PEComa) 25-37
Adenomatoid Tumor 25-37
Other Rare Mesenchymal Tumors....25-38

XV. Mixed Epithelial and Mesenchymal Tumors 25-38
Adenomyoma....25-38
Atypical Polypoid Adenomyoma 25-38
Adenofibroma 25-38
Adenosarcoma 25-39
Carcinosarcoma (Malignant Mixed Müllerian Tumor) 25-40

XVI. Miscellaneous Tumors 25-40
Sex Cord-like Tumors 25-40
Neuroectodermal Tumors 25-40
Melanotic Paraganglioma 25-40

XVII. Lymphomas and Leukemias 25-41

XVIII. Tumors of Germ Cell Type 25-41

XIX. Metastatic (Secondary) Tumors 25-41
Tumors from other Genital Organs 25-41
Tumors from Extragenital Sites....25-41

XX. TNM Classification and FIGO Staging System for Endometrial Carcinoma 25-41

FALLOPIAN TUBES

XXI. Non-Neoplastic Lesions 25-42
Acute Salpingitis 25-42
Chronic Salpingitis 25-42
Granulomatous Salpingitis 25-42
Salpingitis Isthmica Nodosa 25-43
Ectopic Pregnancy 25-43
Inclusion Cysts and Walthard Nests 25-44
Paratubal Cysts 25-44
Tubal Prolapse 25-44

XXII. Epithelial Tumors 25-44
Benign 25-44
Papilloma and Cystadenoma 25-44
Adenofibroma and Cystadenofibroma 25-45
Metaplastic Papillary Tumor 25-45
Endometrioid Polyp 25-45
Carcinoma In Situ 25-45
Borderline Epithelial Tumors 25-45
Malignant Epithelial Tumors....25-45

XXIII. Mixed Epithelial Mesenchymal Tumors 25-46
Carcinosarcoma (Malignant Mixed Mesodermal Tumor) 25-46

XXIV. Mesenchymal Tumors....25-46
Mesothelial Tumors....25-46
Adenomatoid Tumor 25-46

XXV. Germ Cell Tumors 25-47

XXVI. Trophoblastic Disease 25-47

XXVII. Lymphoid and Hematopoietic Tumors 25-47

XXVIII. Secondary Tumors 25-47

XXIX. Tumors of the Uterine Ligaments....25-48
Epithelial Tumors of Müllerian Type 25-48
Wolffian Adnexal Tumor....25-48
Other Tumors of the Uterine Ligaments 25-48

XXX. TNM Classification and FIGO Staging of Fallopian Tube Carcinoma 25-48

XXXI. Suggested Reading 25-48

Uterus—Cervix

NON-NEOPLASTIC LESIONS

Noninfectious Cervicitis

- Usually results from chemical irritation or mechanical trauma
- Non specific inflammatory response

Acute Cervicitis

- Swollen, erythematous, and friable cervix, purulent endocervical discharge may be present
- Neutrophilic infiltration of the stroma and epithelium
- Stromal edema and vascular congestion

Chronic Cervicitis

- Extremely common in adult females
- Commonly affects the squamocolumnar junction and endocervix
- Cervical mucosa is hyperemic, epithelial erosions may be present
- Inflammatory infiltrate predominantly of lymphocytes, plasma cells, and histiocytes
- Granulation tissue and fibrosis in variable amounts

Follicular Cervicitis

- Seen in noninfectious and infectious cervicitis (commonly with *Clamidia trachomatis*)
- Lymphoid follicles beneath the epithelium

Papillary Endocervicitis

- Secondary to an inflammatory process
- Cervicitis with a papillary growth pattern
- Nuclei with finely stippled and prominent nucleoli
- Should not be mistaken for glandular neoplasia

Infectious Cervicitis

- Central role in the pathogenesis of pelvic inflammatory disease and endometrial infections
- Initial event in the pathogenesis of pelvic inflammatory disease
- Primary focus in postpartum and postabortal endometritis
- Spontaneous abortion, premature delivery, chorioamnionitis, stillbirth, neonatal pneumonia and septicemia have been related to bacterial infection of the cervix
- Infectious agents causing endocervicitis and exocervicitis tend to differ, but some can cause both

Bacterial and Chlamydial Cervicitis

Clinical

- Most common cause of infectious cervicitis
- *Chlamydia trachomatis* and *Neisseria gonorrhea* are the most common cause of mucopurulent cervicitis
- Infection rates are greater in women 15–21 years of age
- ~2/3 of women are asymptomatic
- Associated endometritis in 40%, and salpingitis in 11% of cases
- *C. trachomatis* cervicitis is most accurately diagnosed by culture or molecular diagnostic methods (PCR or LCR)

Macroscopic

- Yellow-green endocervical exudates
- Erythema, friable cervical ectropion

Microscopic

- Dense diffuse inflammatory exudates, acute and chronic inflammatory cell infiltrate in the stroma and epithelium
- Reactive squamous and endocervical atypia
- *C. trachomatis* cervicitis is a major cause of follicular cervicitis in young women
- Intracytoplasmic inclusions in endocervical columnar or metaplastic cells may be seen in *C. trachomatis* infection, but are nonspecific

Actinomycosis

Clinical

- *Actinomyces israelii* is a frequent commensual organism found in the female genital tract
- Seen in 3–27% of asymptomatic women without risk factors
- Most frequently identified in women with intrauterine devices
- Identification of *A. israelii* in asyptomatic patients has little clinical significance and does no warrant therapy
- Rarely can be associated with pelvic abscesses

Macroscopic

- Yellow and granular lesions

Microscopic

- Branching, gram-positive filaments with peripheral palisading clubs (sulfur granules)
- Pseudoactinomycotic radiate granules can be identified in endocervical curettings of asymptomatic women
- Granulomas may be present

Tuberculosis

Clinical

- Typically associated with pulmonary tuberculosis, and almost always secondary to tuberculous salpingitis or endometritis

Macroscopic

- Unremarkable or erythematous
- May simulate invasive carcinoma

Microscopic

- Caseating granulomas, but may also appear as a noncaseating granulomatous lesion
- Heavy lymphocytic infiltrate surrounding the granulomas
- Diagnosis requires identification of acid-fast *Mycobacterium tuberculosis*

Differential Diagnosis

- Foreign body giant cell granulomas
- Lymphogranuloma venereum
- Sarcoidosis
- Schistosomiasis

Other Granulomatous Infections

- Syphilis, lymphogranuloma venereum, granuloma inguinale and chancroid
- Clinically, all may resemble carcinoma

Herpesvirus Infection (HSV)

Clinical

- Caused mainly by HSV-2
- HSV-2 is acquired through sexual contact
- Up to 70% of HSV-2 infections are asymptomatic
- Cervical involvement is detected in 70–90% of primary infections, and in 15–20% with recurrent infection
- May result in spontaneous abortion, fetal morbidity and mortality
- Diagnosed by culture, PCR, Pap smear, serology

Macroscopic

- Multiple painful vesicles evolving into shallow, painful ulceration **(Figure 1)**
- Extensive ulcerations that can be mistaken for carcinoma may occur
- Vulva, vagina, perineum and cervix may be involved

Microscopic

- Papanicolaou smear shows large multinucleated cells with intranuclear grouud glass viral inclusions **(Figure 2)**
- Cervical biopsy during the vesicular phase shows suprabasal intraepidermal vesicles filled with serum, degenerated epidermal cells, and multinucleated giant cells, some with eosinophilic intranuclear inclusions

Human Papilloma Virus Infection

Clinical

- >35 of different types of HPV can infect the anogenital tract
- The resulting infections produce a variety of gross and histological lesions

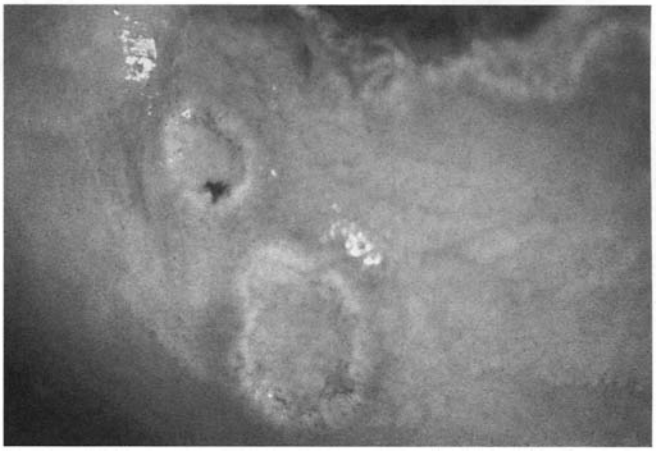


Fig. 1.Herpetic cervicitis. Shallow ulcers are present in the cervix.

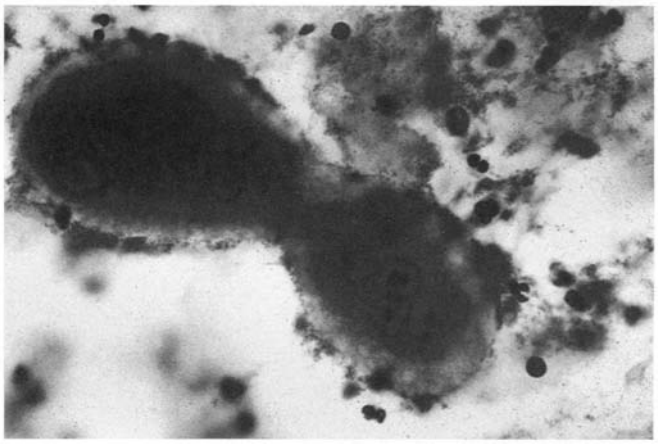


Fig. 2. Large multinucleated cell with characteristic ground glass viral inclusions in herpesvirus infection.

- Linked to a variety of cervical diseases ranging from condyloma acuminatum to invasive carcinoma and its precursors
- Most prevalent anogenital HPVs are divided into three oncogenic risk groups:
  - Low risk: 6,11,42,43 and 44; usually associated with condyloma acuminatum, occasionally with low-grade SIL, only rarely with high-grade SIL, and almost never with invasive carcinoma
  - High risk: 16,18,45,56, and 58; type most frequently associated with invasive squamous cell carcinoma
  - Intermediate risk: 31,33,35,39,51,52,59 and 68; features of high oncogenic risk viruses, but found less frequently in invasive squamous cell carcinoma; however, recent evidence suggests that they should also be considered high risk types
- "Gold standard" for HPV identification is Southern blot hybridization

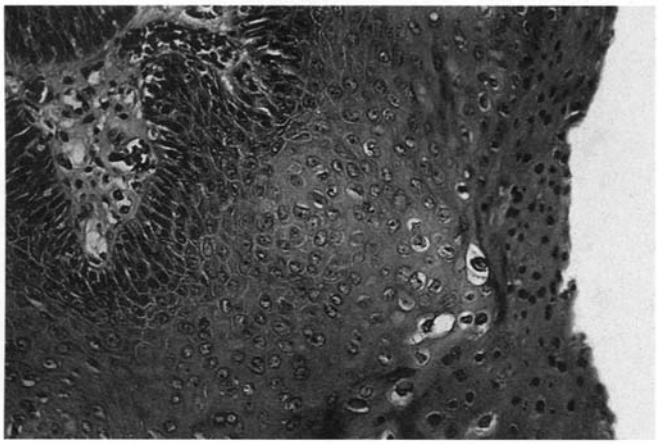


Fig. 3. Cytopathic effects of HPV.

Microscopic

- Cytopathic effects of HPV (**Figure 3**):
  - Perinuclear cytoplasmic vacuolization
  - Nuclear atypia: enlargement, hyperchromasia, irregularity and wrinkling of the nuclear membrane. (*Koilocytosis* = nuclear atypia and perinuclear vacuolization)
  - Anisocytosis
  - Binucleation and multinucleation

Fungal Diseases

- Most caused by *Candida albicans*
- Usually part of a generalized lower genital tract infection involving the vagina and vulva
- Antibiotic therapy, poorly controlled diabetes mellitus, and immunosuppression favor fungal overgrowth
- Viscous vaginal discharge containing white flakes and vulvar pruritus
- Increased number of polymorpholeukocytes in the epithelium
- Fungal hyphae can be identified with PAS

Protozoal Diseases

- Cervical infestation by *Trichomona vaginalis* is frequent
- Most often associated with concurrent trichomonal vaginitis
- Typically, a foamy yellow green vaginal discharge is present
- Intense inflammatory response with prominent reparative atypia may be present
- Diagnosis made by wet mount, culture, Pap smear

Parasitic Diseases

- Schistosomiasis (bilharziasis) caused by *Schistosoma mansoni* very common in Africa (Egypt), South America, Puerto Rico and Asia
- Associated with urinary schistosomiasis and sterility
- Noncaseating granulomas with ova, often calcified, surrounded by multinucleated giant cells
- May be associated with extensive pseudoepitheliomatous hyperplasia of the cervical squamous epithelium

Atypia of Repair

Clinical

- Can be associated with severe, acute long-standing chronic inflammation or epithelial injury

Microscopic

- Epithelial disorganization and nuclear atypia of the squamous and endocervical epithelium
- Squamous epithelium:
  - Well defined cytoplasmic membrane
  - Uniform nuclei, chromatin in prominent aggregates or clumps
  - Infiltration by migrating inflammatory cells
  - Normal mitotic figures confined to the basal and parabasal layers
  - Cells of the upper half of the epithelium are normal, orderly maturation
- Endocervical columnar cells:
  - Nuclear enlargement and hyperchromasia
  - Irregular nuclear size and shape and smudgy chromatin
  - Cytoplasmic eosinophilia and loss of mucinous droplets

Differential Diagnosis

- CIN: loss of normal maturation, increase mitotic activity, abnormal mitotic figures can be present
- Adenocarcinoma in situ: epithelial stratification, increased nuclear atypia and mitotic figures

Radiation Induced Atypia

- Squamous cells have nuclear enlargement with abundant vacuolated cytoplasm, can be multinucleated
- Changes in the endocervical glandular epithelium include cellular enlargement, loss of nuclear polarity, and dense enlarged eosinophilic nucleoli that can be multiple
- Fibrotic, hyalinized stroma
- Blood vessels often have intimal hyaline thickening and can be totally occluded

Tubal metaplasia

Clinical

- Found in up to 31% of patients
- Does not appear to be related to inflammatory changes or low-grade SIL
- Atypical tubal metaplasia is frequently found in association with adenocarcinoma in situ

Microscopic

- The epithelium lining the endocervical glands resemble that of the fallopian tube, containing numerous ciliated cells and tubal-type secretory cells
- Bland cytologic features, absent or rare mitotic figures
- Tipically confined to the superficial third of the cervical wall (extend <7 mm into the cervical stroma)
- Only slight variation in size and shape of the glands
- The surrounding stroma is normal appearing
- Atypical tubal metaplasia, form of tubal metaplasia in which the glands are lined by ciliated and nonciliated cells that are crowded with larger and more hyperchromatic nuclei

Differential Diagnosis

- Endocervical glandular neoplasia
- Adenocarcinoma in situ:
  - Cytologic atypia, significant mitotic activity, cribriforming and papillary projections

Tuboendometrioid Metaplasia

- Occurs commonly after cervical conization
- Endocervical glands are lined by a pseudostratified epithelium composed of columnar cells
- Many of the cells are ciliated or have apical snouts
- Superficial location, minimal variation in size and shape, and lack of desmoplastic stromal response differentiates them form a neoplastic process

Transitional Cell Metaplasia

Clinical

- Almost always in postmenopausal women
- Usually seen in association with atrophy

Microscopic

- Can arise in the transformation zone, exocervix or vagina
- The epithelium is composed of >10 cell layers of cells
- The cells have oval to spindle-shaped nuclei and are oriented vertically in the deeper layers
- The cells in the superficial layer resemble the umbrella cells of the normal urothelium
- Lacks cytologic atypia and mitotic activity

Differential Diagnosis

- High grade CIN:
  - Cytologic atypia and high mitotic activity

Arias-Stella Reaction

Clinical

- Occurs in association with intrauterine and extrauterine pregnancies and gestational trophoblastic disease

Microscopic

- Can develop in endocervical glands or ectopic endometrial glands within the cervix

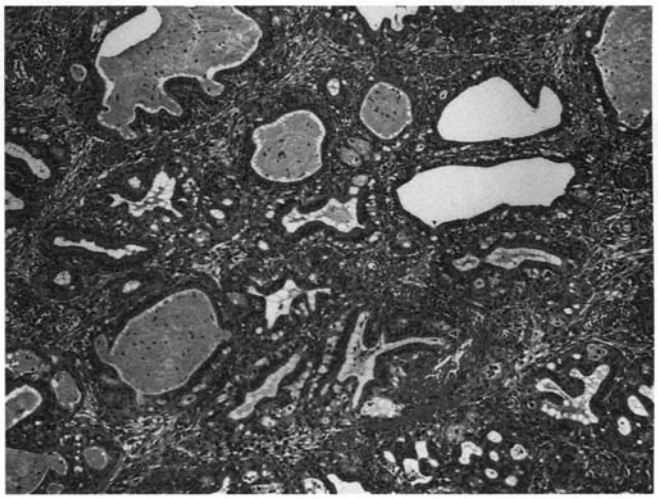


Fig. 4. Microglandular hyperplasia.

- Identically to that occurring in the endometrium
- Usually focal, superficial, and in the proximal portion of the endocervix
- Glands with markedly enlarged cells with hyperchromatic nuclei that can project into the lumen in a hobnail pattern, and vacuolated cytoplasm
- Mitotic activity rare

Differential Diagnosis

- Clear cell carcinoma:
  - Mass lesion, stromal invasion, high mitotic rate, and classic tubular and papillary areas
- Adenocarcinoma in situ:
  - More uniform nuclei, less cytoplasmic vacuolation, increased mitoses

Microglandular Endocervical Hyperplasia

Clinical

- Benign proliferation of endocervical glands
- Most common in women of reproductive age, usually with history of oral contraceptive use or pregnancy
- Frequently represents an incidental finding
- Postcoital bleeding or spotting when presenting as a polyp

Macroscopic

- May be polypoid, 1–2 cm

*Microscopic **(Figure 4)***

- Single or multiple foci
- Crowded glandular or tubular units of varying size lined by flattened to cuboidal cells with eosinophilic cytoplasm and scant mucin
- Predominantly uniform nuclei, with occasional pleomorphism and hyperchromasia
- Low mitotic activity (1 mf/10 hpf)

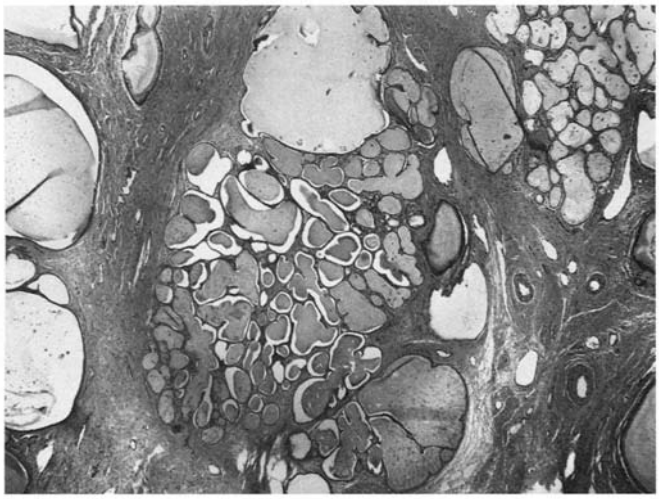


Fig. 5. Endocervical tunnel cluster.

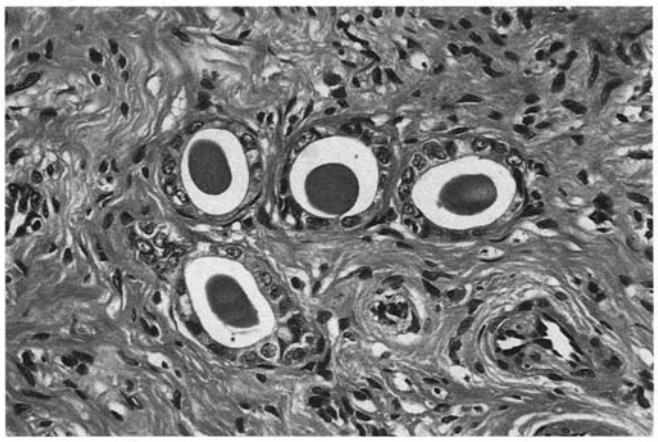


Fig. 6. Mesonephric remnants. Tubules lined by cuboidal epithelium with eosinophilic luminal secretionx.

- Squamous metaplasia and subcolumnar reserve cell hyperplasia usually present
- Stroma is infiltrated with acute and chronic inflammatory cells
- Solid proliferations and signet cells can be present

Differential Diagnosis

- Endocervical adenocarcinoma:
  - Stromal invasion and high mitotic activity
  - Clear cell carcinoma contains intracellular glycogen

Nabothian Cyst

Clinical

- Most common cervical cyst
- Develop within the transformation zone secondary to squamous metaplasia covering and obstructing endocervical glands

Macroscopic

- Yellow-white cysts measuring up to 1.5 cm, frequently multiple

Microscopic

- Lined by flattened single layer mucin producing (endocervical) epithelium
- Squamous metaplasia of the lining epithelium may occur

Tunnel Clusters

Clinical

- Benign collections of endocervical glands
- Common, and become more prevalent with increasing age, also common in pregnant women
- Asymptomatic, incidental finding

*Microscopic **(Figure 5)***

- Usually located close to the surface epithelium of the cervix
- Cluster of closely packed glands noncystic, lined by columnar epithelium; or cystic lined by cuboidal or flattened epithelium
- Well demarcated, do not extend beyond the depth of normal endocervical glands
- Nucelar atypia and mitotic acivity are absent

Differential Diagnosis

- Minimal deviation adenocarcinoma of the cervix: nuclear atypia, increased mitotic activity, and deep stromal invasion

Mesonephric Remnants and Mesonephric Hyperplasia

Clinical

- Vestigial elements of the distal ends of the mesonephric ducts
- Seen in up to 20% of cervices, prevalence is sampling dependant
- Commonly present in the lateral aspects of the cervix
- Incidental finding, almost always asymptomatic
- Differentiation between remnant and hyperplasia may be arbitrary and of no clinical significance

*Microscopic **(Figure 6)***

- Small tubules or cysts, arranged in small clusters, lined by nonciliated low columnar or cuboidal epithelium without glycogen or mucin
- Tubular lumen often filled with pink homogeneous, PAS+ secretions
- May become hyperplastic (mesonephric hyperplasia) resulting in a florid tuboglandular proliferation
- Mitotic activity absent

Differential Diagnosis

- Mesonephric carcinoma:
  - Complex glandular pattern, mitoses
- Cervical adenocarcinoma: CEA+, high Ki-67

Endometriosis

Clinical

- Mechanism unknown, but frequently develops following cervical trauma
- Large lesions may present with abnormal vaginal bleeding

Macroscopic

- Located in the portio or endocervical canal, usually confined to the superficial third
- One or more small, blue or red nodules, several millimeters in diameter
- Occasionally may be larger or cystic

Microscopic

- Composed of ectopic endometrial glands and stroma, resembling proliferative endometrium
- Rarely the glands are secretory and decidua may be seen in pregnancy or with progestin therapy

Lymphoma-Like Lesion

- Extensive marked inflammatory lesions that may cause confusion with a lymphoproliferative lesion
- Composed of a superficial band of large lymphoid cells admixed with mature lymphocytes and plasma cells
- Features that help distinguish them from lymphoma:
  - Macrophages and germinal centers are commonly present
  - Superficial, rarely infiltrate deeper than 3 mm from the surface epithelium
  - Polyclonal staining pattern with immunohistochemistry

Postoperative Spindle Cell Nodule

- Clinically and histologically identical to those found in the vagina and vulva
- May develop after cervical biopsy or other trauma
- Actively proliferating spindle cells with oval nuclei arranged in interlacing bundles
- Mitotic figures are often present
- Neutrophils and erythrocytes are characteristic, giving an appearance of granulation tissue

Decidual Pseudopolyp and Decidualization

Clinical

- The cervical stroma can undergo focal decidual changes during gestation

Macroscopic

- In the exocervix it presents as a raised plaque or pseudopolyp

Microscopic

- The decidual cells are present just underneath the surface epithelium, have oval bland nuclei, abundant eosinophilic cytoplasm and prominent cytoplasmic membranes
- Cervical polyps may also have focal and rarely massive decidual changes

Differential Diagnosis

- Invasive nonkeratinizing squamous cells carcinoma: nuclear atypia, high mitotic activity, cytokeratin+
- Extruded fragments of decidua

Mesodermal Stromal Polyp (Pseudosarcoma Botryoides)

- Benign exophytic proliferations of stroma and epithelium
- Occur more commonly in the vagina
- Seen most frequently in pregnant patients
- Composed of an edematous stroma covered by a benign appearing, stratified squamous epithelium
- Stroma composed of bland appearing plump stromal fibroblasts
- Focal areas of bizarre fibroblasts with hyperchromatic nuclei, occasionally multinucleated, simulating the appearance of sarcoma botryoides, may be present
- Cabbium layer and rhabdomyoblasts are absent

EPITHELIAL TUMORS AND PRECURSORS

Benign Squamous Cell Lesions

Fibroepithelial Polyp

Clinical

- Can occur at any age, but has a predilection for pregnant woman

Macroscopic

- Polypoid lesions, usually solitary

Microscopic

- Single papillary frond composed of a central fibrovascular stalk covered by mature squamous epithelium
- Aypia and koilocytosis are absent

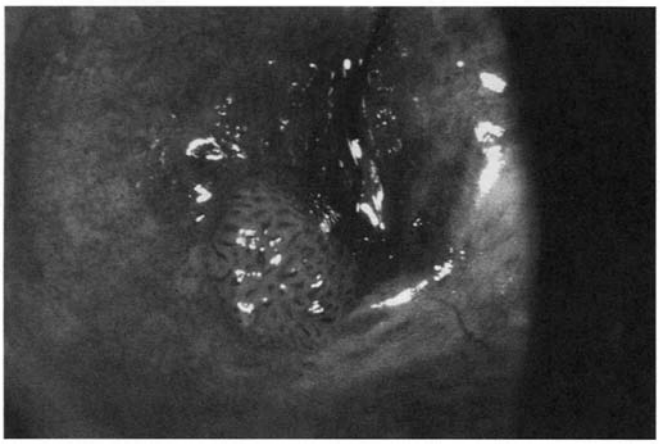


Fig. 7. Condyloma acuminata.

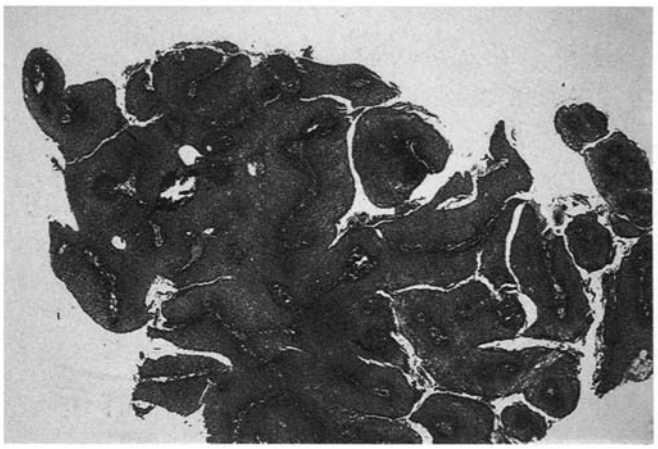


Fig. 8. Exophytic condyloma acuminata.

Differential Diagnosis

- Condyloma acuminatum: koilocytosis

Squamous Papilloma

- Similar to squamous papillomas of the vagina and vulva
- Usually solitary, arising on the ectocervix or squamocolumnar junction
- Single papillary frond, in which mature squamous epithelium without atypia or koilocytosis lines a fibrovascular stalk

Condyloma Acuminatum

Clinical

- One of the most common manifestations of HPV infection in the lower anogenital tract
- Usually caused by HPV types 6 and 11
- Are commonly multifocal
- Usually, spontaneous regression and good response to conservative therapy
- Recurrences are unpredictable, may be persistent
- Immunosuppression may modify the natural history
- Increasing concern for vertical transmission during pregnancy

*Macroscopic (**Figure 7**)*

- Raised white papillary projections

*Microscopic (**Figure 8**)*

- Papillomatosis, acanthosis, hyperkeratosis
- Koilocytosis (squamous cell with sharply demarcated perinuclear vacuolization and enlarged nunucleus, with wrinkled nuclear membrane)
- Binucleated or multinucleated cells are frequently seen

Benign Glandular Lesions

Endocervical Polyps

Clinical

- Most common new growth of the uterine cervix
- Most often found during the fourth to sixth decades and in multigravidas
- May present with profuse leukorrhea or abnormal bleeding from ulceration of the surface epithelium
- Extremely uncommon for in situ or invasive carcinoma to arise in cervical polyps

Macroscopic

- Rounded or elongated with a smooth or lobulated surface
- Most are single, measuring from a few millimeters to 2–3 cm, rarely they may reach gigantic proportions

Microscopic

- Variety of patterns according to the tissue components
- Most common type is the endocervical mucosal polyp, composed of mucinous epithelium that lines crypts with or without cystic changes
- Squamous metaplasia involving the surface or glands is often seen
- They may be mainly fibrous or blood vessels may predominate (vascular polyp)
- Stroma is composed of loose connective tissue with centrally placed thick-wall vessels, usually infiltrated by a chronic inflammatory infiltrate

Müllerian Papilloma

Clinical

- Rare; occurs almost exclusively in children; age range 1–9 years
- Presents with bleeding or discharge

Macroscopic

- Usually <2 cm, polypoid to papillary mass

Microscopic

- Multiple small polypoid projections composed of fibrous stroma lined by simple epithelium
- Occasional cells may have hobnail appearance
- Clear cells and mitoses are absent

Differential Diagnosis

- Clear cell carcinoma

Squamous Tumors and Precursors

- Cervical carcinoma is the third most common cancer in females world-wide
- The incidence has been declining in the last four decades in most developed countries predominantly due to cervical screening programs
- Adenocarcinoma of the cervix, which accounts for 10–15% of all cervical cancers, has shown an increase incidence in the last three decades
- HPV is the major etiologic factor in both squamous and glandular tumors
- Host and environmental factors contribute in enhancing the probability of HPV persistence and progression to cervical neoplasia
- The products of two early genes, E6 and E7, have been shown to play a major role in HPV-mediated cervical carcinogenesis
- Increased risk with increased number of sexual partners, decreased age at time of initial sexual intercourse, promiscuity of male partner, and cigarette smoking
- Stage is the most important prognostic factor; histologic typing and grading have little direct influence on survival within any stage

Cervical Intraepithelial Neoplasia (CIN)

Clinical

- Conventionally divided in three grades: CIN 1, 2, and 3
- Increasing tendency to use a two-tiered classification of low grade (CIN1) and high grade CIN (CIN2 and 3)
- May also be referred to as low and high grade squamous intraepithelial lesion (SIL)
- Because of the difficulty in distinguishing pure HPV infection from unequivocal CIN 1, HPV infection alone is included in the low grade SIL
- Natural history of CIN (difficult to study):
  - CIN 1 (low grade SIL):
    - ~44% regress spontaneously
    - ~46% persist
    - ~15% have the potential for progression to high grade CIN
    - 1–5% of untreated cases eventually progress to invasive cancer

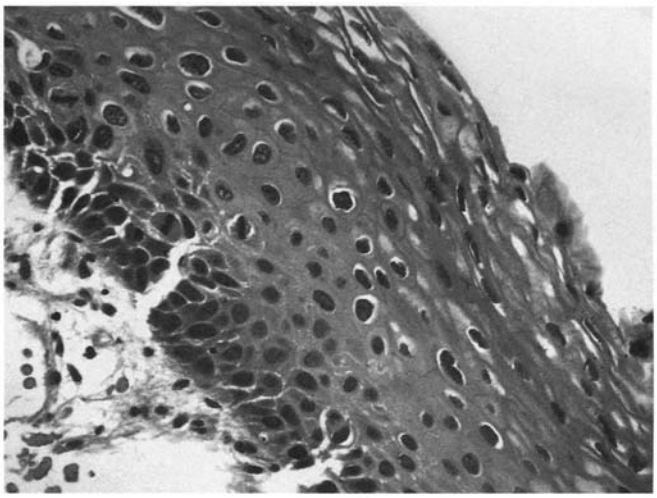


Fig. 9. CIN 1. The upper two-thirds of the epithelium show focal koilocytosis.

  - High grade CIN (CIN 2 and 3, high grade SIL):
    - Fewer high grade lesions regress spontaneously and more progress to invasive cancer
    - Progression rates of CIN 3 (carcinoma in situ) to invasive carcinoma varies from 22–72% in different studies

Macroscopic

- Best evaluated by colposcopic examination after application of 3–5% acetic acid
- Evaluation of the surface contour, color tone and border of the lesions
- The subepithelial vascular network undergoes alterations, resulting in a variety of colposcopic patterens

Microscopic

- Begins in the transformation zone and replaces adjacent squamous and glandular epithelium
- Abnormal cellular proliferation beginning in the basal layer
- Abnormal maturation with loss of polarity and cellular disorganization
- Microscopic grading is based on extent of replacement of epithelium by abnormal proliferating parabasal cells, degree of nuclear atypia, and level at which mitotic figures are found
- CIN 1 **(Figure 9)**:
  - Maturation is present in the upper two thirds of the epithelium
  - Mild atypia, including viral cytopathic effect (koilocytosis) of the superficial cells
  - Nuclear abnormalities are present throughout, but are slight
  - Mitotic figures are present in the basal third, not numerous, abnormal forms are rare

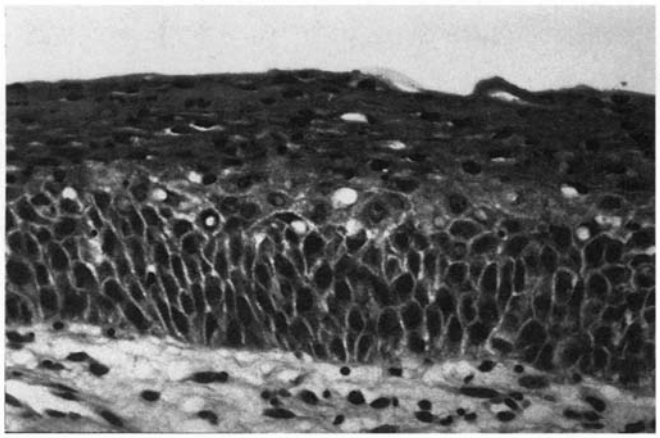


Fig. 10. CIN 2. The upper third of the epithelium shows maturation, mitoses are confined to the basal two thirds and nuclear abnormalities are more striking than in CIN 1.

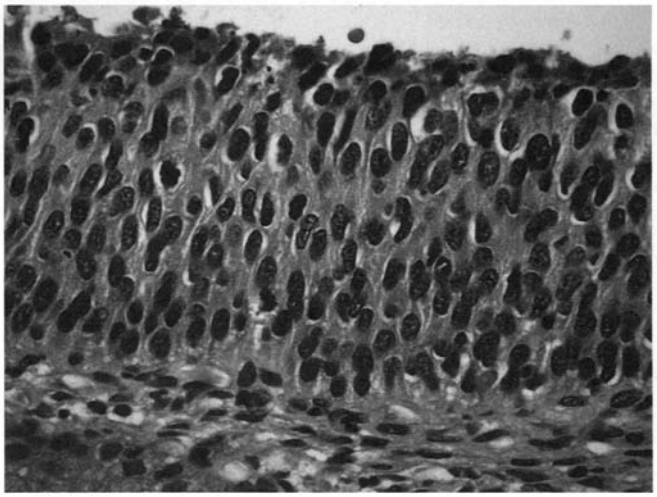


Fig. 11. CIN 3. Nuclear abnormalities throughout the entire thickness of the epithelium, numerous mitotic figures at all levels of the epithelium.

- CIN 2 **(Figure 10)**:
  - Maturation is present in the upper half of the epithelium
  - Nuclear atypia is conspicuous in both the upper and lower epithelial layers
  - Mitotic figures are confined to the basal two thirds of the epithelium
  - Abnormal mitotic figures may be seen
- CIN 3 **(Figure 11)**:
  - Maturation absent or confined to the superficial third of the epithelium
  - Nuclear abnormalities are marked throughout most or all the thickness
  - Numerous mitotic figures, found at all levels
  - Abnormal mitoses are frequent

Differential Diagnosis

- Immature metaplasia: nuclear pleomorphism and abnormal mitotic figures are absent
- Atrophic epithelium: basal and parabasal cells with no differentiation; nuclear pleomorphism, atypia and mitotic figures are absent
- Transitional cell metaplasia: nuclear atypia and mitoses absent
- Microinvasive carcinoma

Early Invasive (Microinvasive) Squamous Cell Carcinoma

Clinical

- Controversial, with lack of agreement over diagnostic criteria
- FIGO stage IA1 (stromal invasion no greater than 3 mm in depth and 7 mm or less in horizontal spread) tumors are frequently referred to as microinvasive carcinoma
- Vascular space involvement does not affect stage, but should be indicated in the report
- The diagnosis is always based on histologic examination of a cone biopsy that includes the entire lesion
- The first sign of invasion is referred to as early stromal invasion (encompassed in the term microinvasive carcinoma):
  - Unmeasurable lesion <1 mm in depth
  - Can be managed in the same way as high grade CIN
  - Focus of early stromal invasion appears to be better differentiated than overlying CIN
- Lymph node metastases are very uncommon (<1%) in patients with stromal invasion of 3 mm or less; in contrast to 5.8% with 3.1–5 mm of invasion

Macroscopic

- Similar to CIN on colposcopic examination
- Variety of patterns including abnormal vessels

Microscopic

- One or more tongues of malignant cells penetrating through the basement membrane of the squamous epithelium
- The intraepithelial lesion is usually CIN 3
- Invasive cells have increased eosinophilic cytoplasm and may show keratinization
- The margin of the invading nest has irregular contours
- Desmoplastic response of the adjacent stroma and often lymphoplasmacytic infiltrate

Differential Diagnosis

- CIN 3 with gland involvement:
  - Borders of the glands involved are round and regular, absent stromal desmoplastic response

- If luminal necrosis and intraepithelial squamous maturation within the epithelium are present, should carefully search for microinvasion

♦ Nests of intraepithelial neoplastic epithelium disrupted and incorporated into the stroma by previous biopsy

Squamous Cell Carcinoma

Clinical

♦ Uncommon before age 30, but can occur at almost any age between 17 and 90 years (mean 51.4 years)

♦ HPV DNA is detected in >90% of cases

♦ Presenting symptoms depend on size and stage, and include postcoital bleeding, intermittent spotting, discharge; patients with stage I disease usually asymptomatic

♦ Diagnosis include cytology and cervical biopsy

Macroscopic

♦ May be exophytic, often as a polypoid excrescence; or mainly endophytic infiltrating into surrounding structures

♦ Early lesions may present as focally indurated, ulcerated or granular area that bleeds readily on touch

Microscopic

♦ Considerable morphologic variation

♦ Infiltrating nests and clusters with irregular contours

♦ May infiltrate as single cells or with large masses of neoplastic squamous cells

♦ Cells in the center of the invading nests frequently become necrotic or undergo extensive keratinization

♦ Individual cells are generally polygonal or oval with eosinophilic cytoplasm

♦ Nuclei vary from uniform to pleomorphic

♦ Common mitotic figures, including abnormal forms

Differential Diagnosis

♦ Squamous metaplasia with extensive endocervical gland involvement: significant nuclear atypia is absent and mitotic activity is low

♦ High-grade SIL with extensive endocervical gland involvement: borders of the endocervical glands involved are rounded and distinct, lack desmoplastic stroma

♦ Marked decidual reaction

Histologic Types of Squamous Cell Carcinoma

Keratinizing

♦ Contain keratin pearls composed of circular whorls of squamous cells with central nests of keratin **(Figure 12)**

♦ Intercellular bridges, keratohyline granules and cytoplasmic keratinization are usually observed

♦ Mitotic figures are not frequent, usually seen in less well differentiated cells

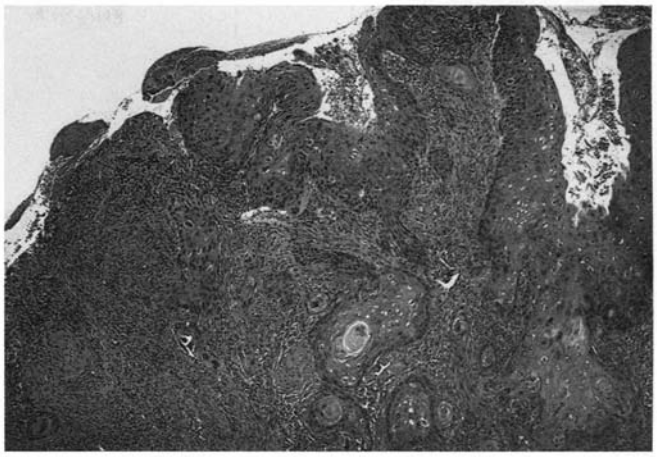


Fig. 12. Squamous cell carcinoma of the cervix, keratinizing type.

Non-Keratinizing

♦ Polygonal squamous cells, individual cell keratinization may be present, but keratin pearls are absent

♦ Mitotic figures are usually numerous

Basaloid

♦ Aggressive tumor

♦ Composed of nests of immature, basal type squamous cells with scanty cytoplasm

♦ Keratin pearls are rarely present

Verrucous

Clinical

♦ Highly differentiated squamous cells carcinoma

♦ Have a tendency to recur locally after excision, but do not metastasize

Macroscopic

♦ Large bulky tumors with warty, fungating appearance

Microscopic

♦ Hyperkeratotic, undulating, warty surface

♦ Invades the underlying stroma in the form of bulbous pegs with a pushing border

♦ Tumor cells have abundant cytoplasm and nuclei with minimal atypia

Differential Diagnosis

♦ Condyloma: fibrovascular cords, koilocytosis

♦ More common types of squamous cell carcinoma: show higher nuclear atypia

Warty

♦ Warty surface and cellular features of HPV infection

Papillary

♦ Thin or broad papillae with connective tissue stroma are covered by epithelium showing the features of CIN

- The underlying invasive carcinoma is usually a typical squamous cell carcinoma

Lymphoepithelioma-Like

- Similar to the nasopharingeal tumor of the same name
- Poorly defined islands of undifferentiated cells in a background intensely infiltrated by lymphocytes
- The tumor cells have uniform nuclei with prominent nucleoli and eosinophilic cytoplasm
- Indistinct cell borders, with a syncytial-like appearance
- EBV may play a role in the etiology of this tumor

Differential Diagnosis

- Glassy cell carcinoma
- Lymphoproliferative disorders

Squamotransitional Cell

- Rare, apparently indistinguishable from transitional cell carcinomas of the urinary bladder
- May occur in a pure form or may contain epithelial elements
- Characterized by papillary architecture with fibrovascular cores lined by a multilayered atypical epithelium resembling CIN 3
- Appear to be more closely related to squamous cell carcinomas than to urothelial tumors

Glandular Tumors and Precursor Lesions

Adenocarcinoma in situ (AIS)

Clinical

- Less common than CIN
- Mean age at diagnosis 28.8 years
- Patients are usually 1–2 decades younger than those with invasive carcinoma
- Similar risk factors as those for squamous lesions
- Occurs in association with CIN in at least 50% of cases
- ~90% contain HPV, most commonly type 16 or 18

Macroscopic

- Difficult to detect colposcopically
- Often superior to squamocolumnar junction
- No distinctive gross lesion

*Microscopic (**Figure 13**)*

- Involves the surface and glands in most cases
- Gland lined by atypical columnar cells with elongated, cigar-shaped, hyperchromatic nuclei; the cytoplasm is reduced with minimal intracytoplasmic mucin
- Cells are crowded and pseudostratified
- Glands may be focally, multifocally or diffusely involved
- Transition between AIS and normal epithelium may be abrupt in some glands

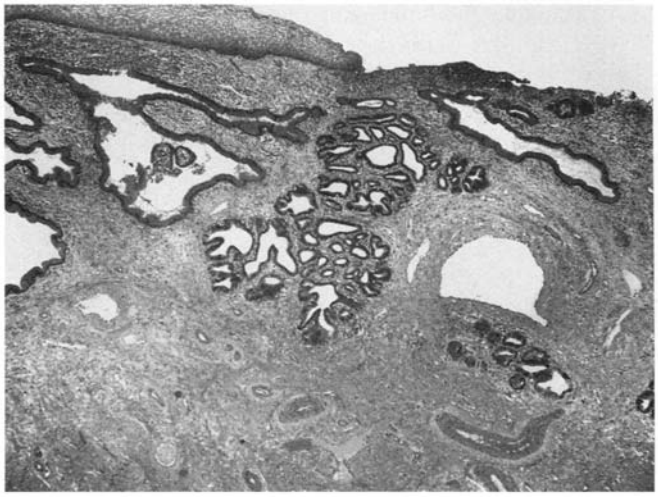


Fig. 13. Adenocarcinoma in situ.

- Mitotic figures, including abnormal forms, and apoptotic bodies, are common
- Cribriform, outpouchings and papillary infoldings may be seen
- The neoplastic glands do not extend the deepest normal crypt
- Other types include intestinal (goblet cell) and endometrioid

Differential Diagnosis

- Reparative/reactive glandular atypia: nuclear clearing and lack hyperchromasia, mitotic activity is absent or minimal
- Reactive glandular atypia secondary to irradiation: vacuolated cytoplasm, mitotic figures are absent
- Adenocarcinoma with early invasion
- Arias-Stella reaction
- Microglandular hyperplasia
- Endometriosis
- Mesonephric remnants
- Tubal metaplasia

Atypical Hyperplasia (Glandular Dysplasia)

- Glandular lesion characterized by nuclear abnormalities, but fall short of the criteria for adenocarcinoma in situ
- Prominent pseudostratification of hyperchromatic, enlarged cells, but uniform size and shape
- Cribriform and papillary formations are absent
- The nuclei are not cytologically malignant and mitoses are less numerous than in AIS

Early Invasive (Microinvasive) Adenocarcinoma

- Controversy as to whether stage IA1 adenocarcinomas exist
- Irregular distribution and architecture of normal endocervical crypts make the distinction between early stromal invasion and adenocarcinoma in situ very difficult

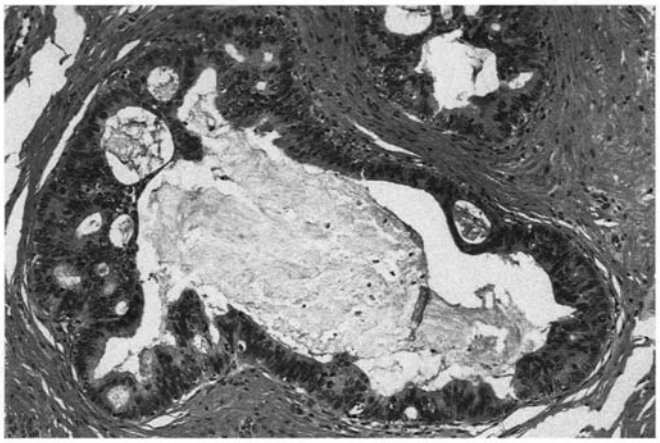


Fig. 14. Adenocarcinoma of endocervical type.

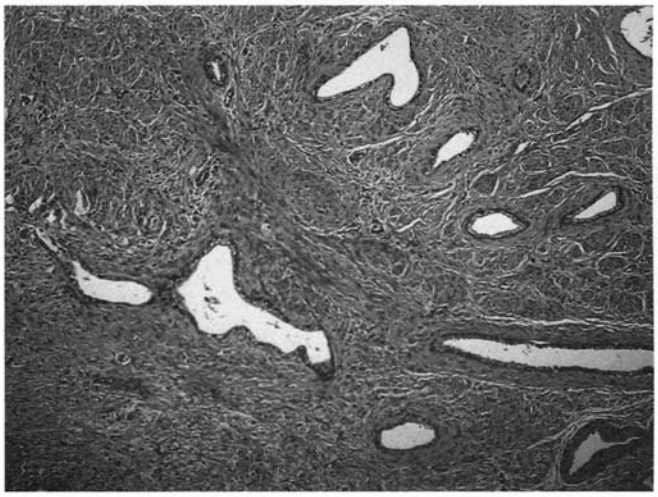


Fig. 15. Minimal deviation adenocarcinoma.

- ♦ Histologic patterns considered indicative of invasion:
  - Small detached tumor cell islands adjacent to AIS that elicit a stromal response
  - Closely packed collections of glands that have lost their smooth outlines
  - Smooth-countered, dilated glands with complex intraglandular cribriform or papillary growth pattern
- ♦ The prognosis is excellent and essentially the same as its squamous counterpart

Adenocarcinoma

Clinical

- ♦ 75% of patients present with abnormal vaginal bleeding
- ♦ May present with vaginal discharge, pelvic pain, or asymptomatic
- ♦ At diagnosis, up to 85% will have stage I or stage II disease

Macroscopic

- ♦ Majority arise in the transformation zone
- ♦ Fungating, polypoid or papillary mass; diffusely enlarged or nodular cervix
- ♦ In 15% no gross lesion is visible

Histologic Subtypes

Mucinous Adenocarcinoma

- ♦ Most common type
- ♦ Histologic variants:
  - Endocervical (**Figure 14**):
    - Accounts for 70% of cervical adenocarcinomas
    - Cells with basal nuclei and abundant pale granular cytoplasm, positive with mucicarmine stain, resembling the columnar cells of the normal endocervical mucosa
  - Intestinal variant:
    - Composed of cells similar to those of adenocarcinomas of the large intestine
    - Pseudostratified cells with only small amounts of intracellular mucin
    - Frequently contain goblet cells and more rarely Paneth cells
  - Signet ring variant:
    - Rare in pure form
    - More commonly a focal finding in poorly differentiated mucinous adenocarcinomas and adenosquamous carcinomas
  - Minimal deviation variant (**Figure 15**):
    - Rare, highly differentiated mucinous adenocarcinoma, originally referred to as adenoma malignum
    - Commonly precede or develop coincidentally with an ovarian carcinoma
    - Associated with ovarian sex cord tumors with annular tubules and Peutz-Jeghers syndrome
    - Cytologically low grade, but architecturally atypical glands that vary in size, shape and location
    - Glands lined by a single layer of tall columnar epithelium with minimal atypia
    - Occasional mitoses
    - Neoplastic glands extend deeper than the normal endocervical glands (>7 mm from the surface epithelium)
  - Villoglandular variant:
    - Generally occur in young women and has an excellent prognosis
    - Surface component composed of papillae lined by one or several layers of columnar cells, some containing mucin
    - If intracellular mucin is absent is considered as the endometrioid variant
    - The epithelium has only mild cytologic atypia; scattered mitoses are present

- Usually superficial invasive, but deep invasion may occur
- Invasive component is composed of elongated branching glands separated by fibrous stroma

Endometrioid Adenocarcinoma

- Up to 30% of cervical adenocarcinomas
- Histologic features of an endometrioid adenocarcinoma of the endometrium, however, squamous elements are less common
- Little or no intracellular mucin is present

Clear Cell Adenocarcinoma

- Rare, histologically similar to their ovarian counterparts
- Associated with in uteru DES exposure

Serous Adenocarcinoma

- Rare, histologically identical to their ovarian counterparts
- Spread from the endometrium, ovaries or peritoneum should be excluded

Mesonephric Adenocarcinoma

- Rare, arise from mesonephric remnants
- Tubular glands lined by mucin-free cuboidal epithelium containing eosinophilic, hyaline secretions in their lumens
- Cytologic atypia and increased mitotic activity

Other Epithelial Tumors

Adenosquamous Carcinoma

Clinical

- Accounts for 5–25% of all cervical cancers
- Occurs in both young and old women, can be associated with pregnancy

Macroscopic

- Ulcerarted and nodular or polypoid

Microscopic

- Admixure of histologically malignant squamous and glandular cells
- Squamous component generally contains either keratin pearls or sheets of cells with individual keratinization
- Histologically recognizable glands must be present for the diagnosis

Differential Diagnosis

- Poorly differentiated endometrial adenocarcinoma with squamous diffrentiation involving the cervix
- Collision tumor of adenocarcinoma with intraepithelial neoplasia or squamous cell carcinoma
- Endometrioid adenocarcinoma of the cervix with squamous differentiation

Glassy Cell Carcinoma Variant

Clinical

- Poorly differentiated variant of adenosquamous carcinoma
- Accounts for <1% of cervical cancers
- Younger mean age (31–41 years) than patients with cervical adenocarcinoma or squamous cell carcinoma
- Reported to have an extremely aggressive clinical course

Macroscopic

- Large and produce a barrel-shaped cervix

Microscopic

- Uniform large polygonal cells with finely granular ground glass-type cytoplasm
- Distinct cell membranes
- Prominent nucleoli
- The cells lack intercellular bridges, dyskeratosis and intracellular collagen
- Abundant mitotic figures
- Stroma is heavily infiltrated by lymphoplasmacytic and eosinophilic inflammatory cells

Differential Diagnosis

- Poorly differentiated nonkeratinizing squamous cell carcinoma

Adenoid Cystic Carcinoma

Clinical

- Rare; most patients >60 years old
- Majority present with post menopausal bleeding, mass on pelvic exam
- Frequently recurs locally or metastasizes to distant organs; unfavorable prognosis

Microscopic

- Histologic appearance similar to its counterpart in the salivary glands, but greater nuclear pleomorphism, high mitotic rate and necrosis
- Characteristic spaces filled with eosinophilic hyaline material or basophilic mucin and surrounded by palisaded epithelial cells
- Collagen type IV and laminin+; S-100 and HHF35+ suggesting myoepithelial differentiaton

Differential Diagnosis

- Small cell carcinoma; adenoid basal cell carcinoma and no-keratinizing squamous cell carcinoma

Adenoid Basal Carcinoma

Clinical

- Rare; usually >50 years old
- Usually asymptomatic, often discovered as an incidental finding
- Low grade, rarely metastasizes

Microscopic

- Small nests of basaloid cells; the cells are small with scanty cytoplasm arranged in nests and cords with focal glandular or squamous differentiation
- Frequently associated CIN or small invasive squamous cell carcinomas

Neuroendocrine Tumors

Carcinoid

- Generally benign
- Characteristic organoid appearance as seen in other sites
- Chromogranin and synaptophysin+

Atypical Carcinoid

- Carcinoid with cytologic atypia, increased mitotic activity (5–10 mf/10 hpf) and foci of necrosis

Small Cell Carcinoma

Clinical

- Accounts for 2–5% of all carcinomas of the cervix
- Tends to occur in younger woman than squamous cell carcinoma
- Aggressive neoplasm with early metastases
- Frequently associated with HPV 18, type 16 has also been found

Macroscopic

- Often large ulcerated lesions
- Frequently deeply infiltrative

Microscopic

- Histologically identical to their counterparts at other sites such as the lung
- Sheets and cords of small anaplastic cells with scant cytoplasm, finely stippled chromatin and inconspicuous nucleoli
- Hyperchromatic nuclei, high nuclear cytoplasmic ratio, high mitotic rate
- Areas of squamous or glandular differentiation if present should represent <5% of the total tumor volume
- Necrosis common

Immunoprofile

- Chromogranin, synaptophysin and NSE+

Differential Diagnosis

- Poorly differentiated squamous cell carcinoma composed of small cells:
  - Lack nuclear molding and crush artifact; 40% are positive for neuroendocrine markers
- Poorly differentiated adenocarcinoma with carcinoid features

Undifferentiated Carcinoma

- Carcinoma lacking specific differentiation

MESENCHYMAL TUMORS

Smooth Muscle Tumors

Leiomyoma

- Most common benign mesenchymal tumor of the cervix
- ~8% of uterine leiomyomas are primary in the cervix
- Usually single, produce unilateral enlargement of the cervical portio
- May protrude through the canal resembling an endocervical polyp
- Are similarly grossly and microscopically to those observed in the myometrium (see smooth muscle tumors of the uterine corpus)
- A variety of histologic patterns may be encountered

Leiomyosarcoma

Clinical

- Primary cervical sarcomas are extremely rare, leiomyosarcoma is the most common; <30 cases reported
- Usually in perimenopausal women, most present with vaginal bleeding

Macroscopic

- Mass replacing and expanding the cervix or as a polypoid growth

Microscopic

- Hypercellular interlacing fascicles of large spindle-shaped or round cells
- Diffuse moderate to marked nuclear atypia
- High mitotic rate, including atypical forms; tumor cell necrosis
- Infiltrative borders and vascular invasion are frequent

Other Benign Mesenchymal Tumors

- Lipoma
- Hemangioma
- Schwannoma
- Paraganglioma

Other Malignant Mesenchymal Tumors

- Endometrioid stromal sarcoma, low grade
- Undifferentiated endocervical sarcoma
- Sarcoma Botryoides (embryonal rhabdomyosarcoma)
- Alveolar soft-part sarcoma
- Malignant peripheral nerve sheath tumor
- Osteosarcoma

MIXED EPITHELIAL AND MESENCHYMAL TUMORS

Adenomyoma

Clinical

- Rare in the cervix
- Benign, may recur following local excision

Macroscopic

- Usually polypoid with a firm surface, small cystic areas may be present
- Rare tumors are intramural

Microscopic

- Composed of a benign glandular and benign mesenchymal component composed exclusively or predominantly of smooth muscle
- The glandular component may be lined by endocervical-type epithelium, or endometrial type glands surrounded by endometrial-type stroma

Adenofibroma

Clinical

- Uncommon in the cervix
- Benign, recurrence may follow incomplete removal

Macroscopic

- Polypoid, usually protrude into the endocervical canal
- Small cystic spaces may be present

Microscopic

- Papillary fronds lined by glandular type epithelium, cuboidal, columnar, ciliated, mucinous or attenuated
- Benign squamous epithelium may be present
- Mesenchymal component composed of nonspecific fibrous tissue, with minimal mitotic activity

Differential Diagnosis

- Adenosarcoma

Adenosarcoma

Clinical

- Much less common than their counterparts in the uterine corpus
- Reported in women between 14 and 67 years of age
- Presents with vaginal bleeding or recurrent cervical polyps
- Prognosis is typically good after surgical therapy, recurrent tumor and death can occur

Macroscopic

- Broad based polyp arising from the cervix

Microscopic

- Biphasic tumor composed of malignant stroma admixed with benign epithelial elements
- Similar to its counterpart in the endometrium, however, the epithelium is more likely to be squamous or mucinous
- The sarcomatous component may consist of mitotically active spindle cells forming periglandular cuffs; or contain foci with a more embryonic appearance with small undifferentiated mitotically active cells
- Heterologous sarcomatous elements may be present
- May or may not invade the underlying cervical stroma

Carcinosarcoma (Malignant Mixed Mesodermal Tumor)

Clinical

- Much less common than their uterine counterparts
- Usually occur in postmenopausal women
- Aggressive neoplasms
- Compared to their uterine counterparts, appear to be more often contained to the uterus and may have a better prognosis

Macroscopic

- Polypoid or pedunculated masses

Microscopic

- Composed of an admixture of malignant epithelial and mesenchymal components
- Similar histologic features to its counterpart in the uterine corpus, however, the carcinomatous component is most commonly a basaloid pattern
- Other epithelial patterns include squamous cells carcinoma, endometrioid adenocarcinoma, and less commonly adenoid basal and adenoid cystic components

MELANOCYTIC TUMORS

Blue Nevus

- Benign, typically incidental finding
- Most occur in the endocervical canal
- Poorly circumscribed collections of heavily pigmented, bland, spindle-shaped cells in the superficial cervical stroma

Malignant Melanoma

Clinical

- Rare, considerably less common than vulvar or vaginal melanoma
- Presents with abnormal vaginal bleeding
- Spread to vagina is often present at the time of presentation
- Poor prognosis

Macroscopic

- Polypopid or fungating pigmented masses
- May also be amelanotic

Microscopic

- Similar histologic features as those in the skin, vulva and vagina
- Spindle-shaped cells are frequently present
- Junctional component is present in 50% of cases

Differential Diagnosis

- Metastatic melanoma involving the cervix

TUMORS OF GERM CELL TYPE

Yolk Sac Tumor

- Second most common site in the lower genital tract after the vagina
- Presents with abnormal vaginal bleeding
- Polypoid friable masses
- Histological features similar to their counterparts at other sites

Mature Cystic Teratoma

- Presents as smooth cervical polyps
- Glial and squamous epithelial elements are common
- It has been suggested that they represent implanted fetal tissues rather than true neoplasms

LYMPHOID AND HEMATOPOIETIC TUMORS

- Lymphomas and leukemias can involve the cervix
- Most often are secondary, as a manifestation of a systemic disease
- Primary lymphomas can occasionally arise in the cervix, usually in premenopausal women; 70% are of diffuse large cell type and 20% are lower grade follicular lymphomas

SECONDARY TUMORS

- Most common source represents direct extension from local pelvic tumor (endometrial, rectal and bladder carcinomas)
- Up to 50% result from direct extension from an endometrial primary
- Lymphatic or vascular metastasis are less frequent, associated with ovarian carcinoma
- Metastases from distant primary tumors are rare; the most common sites are gastrointestinal tract (colon and stomach) and breast

TNM CLASSIFICATION AND FIGO STAGING SYSTEM FOR CERVICAL CARCINOMA

- T: Primary tumor (FIGO Stage):
  - TX: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - Tis: Carcinoma in situ
  - T1(I): Cervical carcinoma confined to uterus (extension to the corpus should be disregarded):
    - T1a(IA): Invasive carcinoma diagnosed only by microscopy; all macroscopically visible lesions, even with superficial invasion, are T1b/stage IB:
      - T1a1(IA1): Stromal invasion no greater than 3.0 mm. in depth and 7.0 mm. or less in horizontal spread
      - T1a2(IA2): Stromal invasion more than 3.0 mm. and not more than 5.0 mm. with a horizontal spread of 7.0 mm. or less *
    - T1b(IB): Clinically visible lesion confined to the cervix or microscopic lesion greater than T1a2/ IA2:
      - T1b1(IB1): Clinically visible lesion 4.0 cm. or less in greatest dimension
      - T1b2(IB2): Clinically visible lesion more than 4.0 cm. in greatest dimension
  - T2(II): Tumor invades beyond the uterus but not to pelvic wall or to lower third of the vagina:
    - T2a(IIA): Without parametrial invasion
    - T2b(IIB): With parametrial invasion
  - T3 (III:)Tumor extends to the pelvic wall, involves lower third of vagina, or causes hydronephrosis or non-functioning kidney:
    - T3a(IIIA):Tumor involves lower third of vagina with no extension to pelvic wall
    - T3b(IIIB):Tumor extends to pelvic wall and/or causes hydronephrosis or nonfunctioning kidney
  - T4(IVA:)Tumor invades mucosa of bladder or rectum and/or extends beyond true pelvis
  - M1(IVB):Distant metastasis
- N: Regional Lymph Nodes:
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis
- M: Distant Metastasis:
  - MX: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

**The depth of invasion should not be more than 5 mm taken from the base of the epithelium, either surface or glandular, from which it originates. The depth of invasion is defined as the measurement of the tumor from the epithelial-stromal junction of the adjacent most superficial epithelial papillae to the deepest point of invasion. Vascular space involvement, venous or lymphatic, does not affect classification.*

Uterus—Corpus

MORPHOLOGY OF THE ENDOMETRIUM

Endometrial Cycle

- The morphologic variations of the endometrium throughout the cycle allow documentation whether ovulation has occurred and diagnosis of specific causes of infertility
- The first day of bleeding is considered day 1 of the cycle

Proliferative Phase

- Preovulatory phase, variable in length
- Daily morphologic alterations are not sufficiently obvious to allow accurate dating, can be divided into early, mid and late phases
- Early proliferative:
  - thin regenerating surface epithelium
  - straight short narrow glands with mitoses
  - compact stroma with some mitotic activity and large nuclei with scant cytoplasm ("naked nuclei")
- Midproliferative:
  - columnar surface epithelium
  - longer curving glands
  - variable stromal edema; numerous mitoses in naked nuclei
- Late proliferative:
  - somewhat undulant surface
  - tortuous glands with active pseudostratified epithelium
  - moderately dense stroma

Interphase

- Scattered subnuclear vacuoles are present (<50% of the glands exhibit uniform subnuclear vacuolization)
- Although the normal endometrium from POD 1 to POD 2 has this appearance, this pattern does not guarantee that ovulation has occurred

Secretory Phase

- Postovulatory phase
- Daily morphologic changes are distinct and allow accurate dating
- Early secretory:
  - POD 2: >50% of the glands exhibit uniform subnuclear vacuolization, exaggerated nuclear pseudostratification; mitotic figures present
  - POD 3: Subnuclear vacuoles and nuclei uniformly aligned; scattered mitotic figures
  - POD 4: Vacuoles in luminal position
  - POD 5: Vacuoles infrequent; secretion in gland lumens
- Midsecretory:
  - POD 6: Secretion prominent
  - POD 7: Beginning stromal edema
  - POD 8: Maximal stromal edema
- Late secretory:
  - POD 9: Spiral arteries first prominent
  - POD 10: Thick periarterial cuffs of predecidua
  - POD 11: Islands of predecidua in superficial compactum
  - POD 12: Beginning coalescence of islands of predecidua
  - POD 13: Confluence of surface islands; stromal granulocytes prominent
  - POD 14: Extravasation of red cells in stroma; prominence of stromal granulocytes

Menstrual Phase

- Normally lasts 4±1 day
- Endometrial mucosa rapidly degenerates, with 50% of menstrual detritus expelled in the first 24 hours of menses
- Tissue shedding is followed by regeneration

Microscopic

- Dilated glands lined by flattened cells, often with frayed borders (secretory exhaustion)
- Fully decidualized stroma
- Karyorrhectic fragments present in the subnuclear area of some glands
- Epithelial nuclei are pyknotic
- Fibrin thrombi in vessels and stroma
- Glands break up into strips, crumbling stroma

Inactive Endometrium

- Endometrium is as thick as early to mid proliferative phase, but lacks morphologic features of active proliferation or secretion
- Glands and stroma resemble proliferative endometrium, but with fewer glands usually oriented parallel rather than perpendicular to the surface

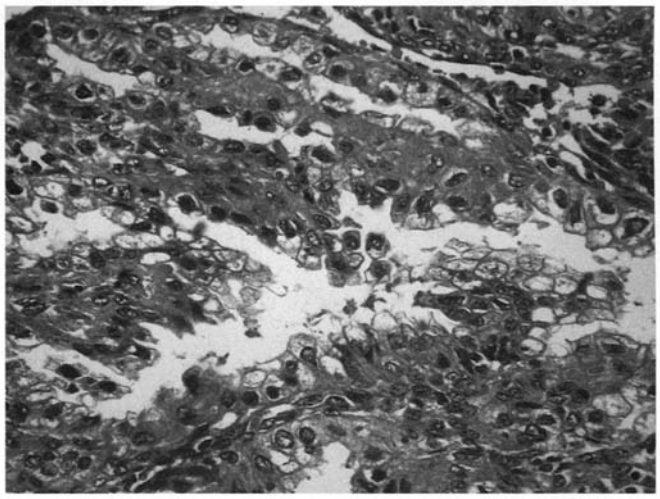


Fig. 16. Gestational endometrium with Arias-Stella reaction. Cells with enlarged hyperchromatic nuclei and clear vacuolated cytoplasm.

- Epithelium at the surface and lining the glands is columnar to cuboidal, with pseudostratified nuclei without mitoses
- Dense stroma, without clear separation between basalis and functionalis

Atrophic Endometrium

- Most common cause of abnormal uterine bleeding in postmenopausal women
- Thinned endometrial mucosa
- Decrease in the number of glands and stromal volume
- Surface and glandular epithelium is low and cuboidal
- Stroma is often collagenized
- Cystically dilated glands are often present

Pregnancy-Related Changes

- Similar findings occasionally occur in patients receiving progestins or rarely with no apparent cause

Arias-Stella Reaction (Figure 16)

- Histologic change within endometrial glands associated with intrauterine or extrauterine pregnancy or trophoblastic disease
- Occasionally can occur in pre- and postmenopausal women on hormonal medication
- Voluminous cells with large hyperchromatic nuclei and irregular nuclear membranes, sometimes with a hobnail appearance, and with clear vacuolated cytoplasm
- Nuclear atypia may be striking
- Nuclear cytoplasmic ratio is normal
- Mitoses are absent or rare
- The focal nature, presence of other pregnancy related changes, and mitotic inactivity help in the differential diagnosis with adenocarcinoma, particularly clear cell carcinoma

Optically Clear Nuclei

- Alteration of nuclei in endometrial glandular epithelium, associated with pregnancy and trophoblastic disease
- Nuclear vacuolization, resembling the ground glass appearance of herpes virus inclusions

Decidual Reaction

- In pregnancy or as result of exogenous progestational therapy; rare examples in women with no apparent cause
- Large epithelioid decidual cells
- Unusual features associated with diagnostic problems include:
  - nuclear pleomorphism and hyperchromasia may mimic sarcoma
  - marked cytoplasmic vacuolation mimic signet-ring carcinoma
  - may be polypoid and necrotic

Effects of Hormone Administration

Tamoxifen

- Synthetic anti-estrogen used in the treatment of breast carcinoma
- Acts as a partial estrogen receptor antagonists in neoplastic breast tissue and as an agonist in the endometrium
- Has been associated with an increased frequency of proliferative endometrial lesions including hyperplasias, polyps and malignant tumors
- Tamoxifen-associated endometrial polyps may show distinctive morphology:
  - Large, sessile with a wide implantation base, frequently show a honeycomb appearance
  - Bizarre stellate shaped glands
  - Frequent epithelial and stromal metaplasia
  - Malignant transformation occurs in up to 3%: endometrioid adenocarcinoma is the most frequent, but other types of malignant neoplasms may develop

Progestins and Estrogen-Progestin Combinations

- Most commonly, atrophic, uncoiled glands embedded in a predecidualized or decidualized stroma
- After prolonged exposure to these agents profound atrophy of the endometrium can occur

DYSFUNCTIONAL UTERINE BLEEDING

- Clinical term bleeding not attributable to an underlying organic pathologic condition

Glandular and Stromal Breakdown Associated with Anovulation

Clinical

- Characteristically occurs at menarche and at menopause, but can occur at any time diring reproductive years
- Patients with polycystic ovarian disease are often anovulatory
- One or more follicles develop in the ovary without development of a corpus luteum
- Stromal and glandular differentiation of the secretory phase do not develop due to lack of progesterone
- When estrogen levels decline, the endometrium can no longer be maintained and bleeding occurs

Microscopic

- The endometrium may appear extensively fragmented
- Background proliferative endometrium
- Stromal cells condense and form compact nests with hyperchromatic nuclei and little or no cytoplasm
- Papillary syncytial metaplasia is frequently associated with stromal breakdown bleeding
- Glands should be carefully examined for abnormal shape, cellular stratification, and nuclear atypia that may reflect concurrent breakdown and hyperplasia

Differential Diagnosis

- Menstrual endometrium:
  - Predecidual reaction is present and the glands are typically dilated and filled with secretions
  - Degenerative cytoplasmic vacuolation may be seen in either
- Hyperplasia:
  - Glands with abnormal shapes, stratified epithelium and atypia

Inadequate Luteal Phase

Clinical

- Thought to result from inadequate progesterone secretion by the corpus luteum
- Usually diagnosed during evaluation for infertility or abnormal bleeding
- Diagnostic findings in at least two consecutive cycles are required for the diagnosis
- Found only in 3–5% of infertile women, and is of controversial significance

Microscopic

- Exact pathologic criteria have not been definitively established

- Endometrium resembles normal secretory endometrium, but is at least 2 days earlier than expected
- Dating may be impossible due to a discordant appearance of the glands and stroma

Irregular Shedding

Clinical

- Diagnosed when endometrial tissue obtained at least 5 days after the onset of bleeding shows a mixture of secretory and proliferative patterns
- Rare cause of abnormal bleeding in women between 24–50 years

Microscopic

- Irregular star-shaped secretory glands admixed with early proliferative glands
- The stroma around proliferative glands is dense and compact, and aroud secretory glands is edematous and may have predecidua cells
- Frequent evidence of glandular and stromal breakdown

NON-NEOPLASTIC LESIONS

Acute and Chronic Endometritis

Clinical

- Usually results from ascending infection through the cervix
- The cervical barrier is altered during menses, abortion, parturition and instrumentation
- Acute endometritis:
  - Clinically significant acute endometritis is usually associated with pregnancy or abortion
  - Most caused by hemolytic *Streptococcus*, *Staphylococcus*, *Neisseria gonorrheae*, and *Clostridium welchii*
- Chronic endometritis:
  - Patients may be asymptomatic or present with menometrorrhagia, mucopurulent cervical discharge, uterine tenderness, elevated erythrocyte sedimentation rate or leukocytosis
  - Associated with abortion, usually due to retained gestational tissue, with salpingitis and with intrauterine device; in 15% of cases a primary cause is not obvious
  - Most commonly caused by *Chlamydia trachomatis* and *Neisseria gonorrheae*
  - Identification of a specific microorganism is based on culture
  - Antibiotic therapy is indicated to prevent other sequelae

Microscopic

- Criteria for the diagnosis of acute endometritis include identification of moderate to large numbers of PMNs in nonbleeding endometrium, microabscesses in the stroma or PMNs filling and disrupting the glands.
- The diagnosis of chronic endometritis is based on the identification of plasma cells
- Lymphocytes, macrophages and PMNs may also be present.
- Features suggestive of chronic endometritis are a spindle cell alteration of the stroma characterized by spindled stromal cells surrounding glands in a pinwheel arrangement, and the inability to date the endometrium

SpecificTypes of Chronic Endometritis

Chlamydia

- Mixed inflammatory infiltrate composed of plasma cells, lymphocytes and PMNs, denser plasma cell infiltrate than gonococcal endometritis
- Lymphoid follicles with transformed lymphocytes

Mycoplasma

- Associated with infertility and fetal wastage

Tuberculosis

- Part of a systemic disease
- Second most frequently affected site in the female genital tract after the fallopian tube
- Typical caseating granulomas, may vary from a focal to diffuse process

Fungal Infections

- Granulomatous endometritis may be seen as part of a disseminated infection in blastomycosis and coccidiomycosis.

Viral Infections

- Herpes simplex virus, cytomegalovirus, and human immunodeficiency virus are known to infect the endometrium

Parasitic Infections

- *Schistosoma*, *Enterobius vermicularis* and *Ehinococcus granulosus*, rare causes in the United States
- Schistosomiasis is endemic in Central America, Africa, Middle East and Far East

Xantogranulomatous or Histiocytic Endometritis

- Postmenopausal women
- Numerous histiocytes with foamy cytoplasm

Malakoplakia

- Rare form of endometritis of probable bacterial origin
- Intracellular and extracellular calcified spherules (Michaelis-Gutman bodies)

Lymphoma-Like Lesion

Clinical

- Usually women of reproductive age
- May present with abnormal bleeding or incidental microscopic finding
- No history of malignant lymphoma

Macroscopic

- Usually no gross mass

Microscopic

- Aggregates of lymphoid cells resembling reactive germinal centers with a mixed inflammatory infiltrate at the periphery of the aggregates
- Usually a background of chronic endometritis
- Myometrial involvement is absent

Differential Diagnosis

- Malignant lymphoma

Changes Related to Intrauterine Devices

- Vary with the type of device and duration of use
- Include chronic endometritis, squamous metaplasia, reparative hobnail cell metaplasia, and progestational changes in progesterone impregnated devices
- Predisposes to colonization or infection with *Actinomyces;* infection characterized by typical sulfur granules
- Actinomyces must be distinguished from the Splendore-Hoeppli phenomenon, a pseudoactinomycotic radiate granule related to a tissue response to IUD

Adenomyosis

Clinical

- Common condition characterized by the finding of endometrial glands and stroma within the myometrium
- Usually in pre or perimenopausal women
- Commonly associated with abnormal bleeding and dysmenorrhea, but may be asymptomatic
- Clinical diagnosis can be confirmed by imaging studies

Macroscopic

- Moderately enlarged uterus
- Focally or diffusely thickened and trabeculated myometrium
- Occasionally, small blood-filled cysts may be present

Microscopic

- Exact criteria for histologic diagnosis are not clear
- Some authors recommend to make the diagnosis when the distance between the lower border of the endometrium and the adenomyosis is greater than one half of a low-power field (about 2.5 mm), others use a distance of one high power field
- Variable response to ovarian hormones
- Usually proliferative or inactive endometrium
- Hyperplastic or carcinomatous changes may involve adenomyosis
- Variants of adenomyosis important to differentiate with malignant tumors:
  - Intravascular endometrial tissue, consisting of stroma only or glands and stroma
  - Adenomyosis with sparse glands, typically in postmenopausal women, adenomyotic foci consist mainly or exclusively of endometrial stroma
  - Adenomyosis with atrophic stroma, typically in postmenopausal women, glands deep within the myometrium are surrounded directly by smooth muscle

Differential Diagnosis

- Normal penetration of endometrium into the myometrium
- Low-grade endometrial estromal sarcoma
- Invasive adenocarcinoma

Endometrial Cellular Changes (Metaplasias)

- Variety of benign cytoplasmic alterations of the endometrial epithelium that are not encountered in normal proliferative endometrium
- Develop most commonly in response to estrogenic and progestational stimulation
- Often coexist with hyperplasia, most likely because both result from a hyperestrogenic state
- May be focal or diffuse, endometrial polyps may also be affected
- Cytoplasmic alterations by themselves have no prognostic significance, the most important aspect is to recognize these benign processes and not confuse them with hyperplasia or carcinoma

Eosinophilic Change (Including Syncytial Change)

- Most common cytoplasmic alteration
- Endometrial glands or the surface epithelium are replaced by nonciliated cells with abundant eopsinophilic cytoplasm, uniform, round central nuclei
- Mitotic figures are rare
- On the endometrial surface the eosinophilic cells may form a syncytium or a papillary process that lacks stromal cores
- Eosinophilic syncytial change is commonly associated with endometrial stromal breakdown

Squamous Differentiation (Squamous Metaplasia)

- May occur in all forms of hyperplasia as well as in carcinoma, most commonly with atypical hyperplasias and low grade carcinoma
- Is rare in normal cycling endometrium or hyperplasia without atypia
- Typically cytologically bland squamous cells with moderate amount of eosinophilic cytoplasm and well-defined cell membrane, mitotic activity is rare
- The squamous cells may be spindle shaped forming intraglandular nests (morules), reflecting immature or incomplete squamous differentiation

Ciliated Cell Change (Tubal Metaplasia)

- Refers to the presence of a significant number of ciliated glandular cells with intercalated (peg) cells resembling the epithelium of the fallopian tube
- Reflects estrogenic stimulation and is frequently associated with simple, complex or atypical hyperplasia

Secretory, Clear Cell and Hobnail Change

- Secretory change is characterized by columnar cells with sub or supranuclear vacuoles with clear glycogenated cytoplasm, resembling glandular cells of early secretory endometrium, is seen more often in association with hyperplasia or carcinoma
- Rarely the cells in secretory change can display hobnail morphology resembling Arias-Stella reaction
- Clear cell change refers to polygonal cells with clear cytoplasm containing glycogen and bland nuclei in glands or on the surface endometrial epithelium
- Distinguished from clear cell carcinoma by the noninvasive nature of the glands and absence of mitotic activity

Mucinous Change

- Endometrial glands or the surface endometrial epithelium is replaced by mucinous epithelium resembling that of the endocervix
- Mucinous change can be accompanied by a papillary proliferation
- Mitotic figures are rare
- Perimenopausal and postmenopausal women with complex mucinous proliferations have a high risk of coexistent carcinoma

Miscellaneous Lesions

- Inflammatory pseudotumor
- Postoperative spindle cell nodule
- Arteriovenous malformations
- Heterologous tissues (bone, cartilage, smooth muscle and glial tissue)
- Giant cell arteritis
- Intravascular menstrual endometrium

EPITHELIAL TUMORS AND RELATED LESIONS

Endometrial Polyps

Clinical

- Common over age 40, rare before menarche
- Most commonly present with intermenstrual bleeding or menometrorrhagia in young women, and as postmenopausal bleeding
- There is no evidence that polyps have a significantly higher propensity for developing carcinoma than adjacent endometrium, but may represent a marker of increased cancer risk

*Macroscopic (**Figure 17**)*

- Sessile or pedunculated
- Vary in size from 1 mm to large masses filling the endometrial cavity
- Large pedunculated polyps may protrude through the cervix
- Surface is usually smooth and glistening, but may have focal erosion or hemorrhage

*Microscopic (**Figure 18**)*

- Composed of irregularly distributed endometrial glands and stroma
- Glands may be inactive, exhibit normal prolifetative or secretory features, and focally dilated
- May be categorized as hyperplastic, atrophic or functional
- The stroma is focally or diffusely fibrotic and contains thick-walled blood vessels
- Uncommonly, the stroma may contain foci of smooth muscle (classified as adenomyoma if prominent), multinucleated stromal giant cells and decidua
- Polyps may contain atypical hyperplasia or carcinoma

Differential Diagnosis

- Endometrial hyperplasia
- Polypoid adenocarcinomas
- Adenosarcoma
- Adenofibroma



Fig. 17. Endometrial polyps.

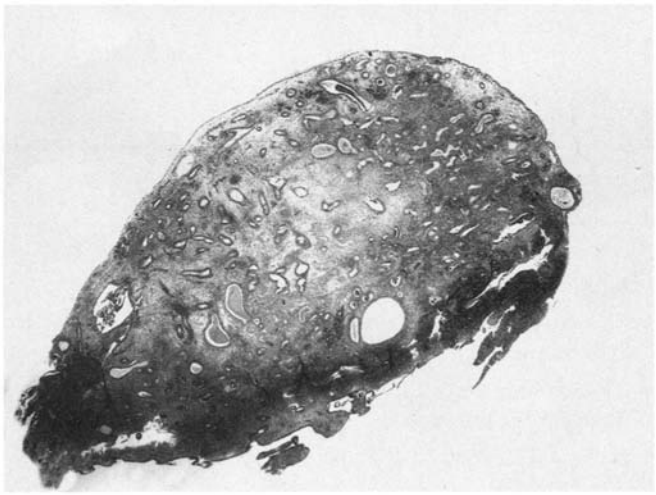


Fig. 18. Endometrial polyp.

Precursor Lesions of Endometrial Carcinoma

Endometrial Hyperplasia

Clinical

- Heterogeneous group of abnormal endometrial proliferations that develop as a result of unopposed estrogenic stimulation
- Proliferation of glands of irregular size and shape with an increase in the gland/stroma ratio compared with proliferative endometrium

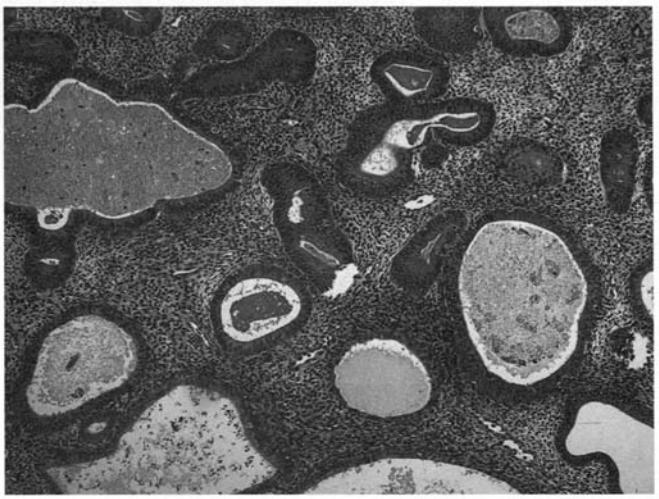


Fig. 19. Simple hyperplasia. Slight crowding of glands with abnormal branching.

- Usually presents with abnormal bleeding
- Endometrial hyperplasias are classified by their degree of architectural complexity as simple or complex, and by their cytologic (nuclear) features as hyperplasia without atypia or atypical hyperplasia
- The hyperplastic process may be focal or involve the entire endometrium
- WHO classification of endometrial hyperplasia:
  - Hyperplasias (typical):
    - Simple hyperplasia
    - Complex hyperplasia
  - Atypical hyperplasias:
    - Simple atypical hyperplasia
    - Complex atypical hyperplasia
- 23% of atypical hyperplasias progress to carcinoma; whereas <2% of hyperplasias without cytologic atypia progress to carcinoma
- Atypical hyperplasia is recognized as the precursor lesion for the endometrioid type of endometrial carcinoma

Microscopic

- Simple Hyperplasia **(Figure 19)**:
  - Cystically dilated glands with glandular outpouchings surrounded by an abundant cellular stroma
  - In some cases the glands are only minimally dilated but focally crowded
  - The glands are lined by pseudostratified columnar cells without cytologic atypia
  - Mitotic activity is variable
- Complex Hyperplasia **(Figure 20)**:
  - Complex glands with little intervening stroma (back-to-back glandular crowding)

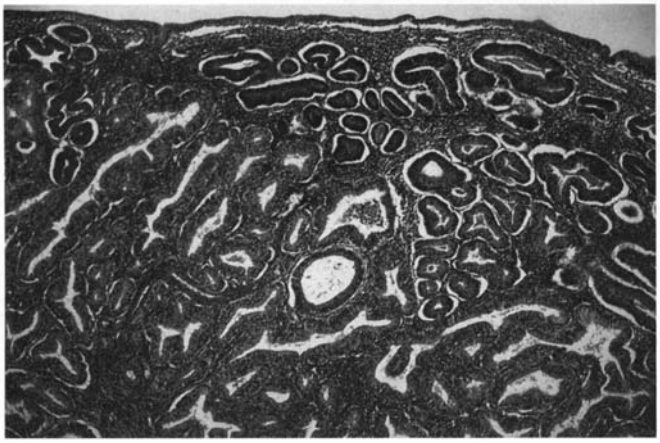


Fig. 20. Complex hyperplasia. There is marked glandular crowding resulting in a "back to back" appearance and the glands show complex glandular outlines.

- Usually glandular outlines are highly complex with epithelial budding into both lumina and stroma, but can be tubular
- Epithelial stratification can range from two to four layers lacking nuclear atypia
- Variable mitotic activity, usually <5 mitotic figures per 10 high-power fields

♦ Atypical Hyperplasias:
- Glands lined by cytologically atypical cells (loss of polarity, increased nuclear: cytoplasmic ratio, prominent nucleoli and cleared or dense chromatin)
- Atypia is usually focal
- Simple atypical hyperplasia is rare, features atypical glandular cytology superimposed on the architecture of simple hyperplasia
- Complex atypical hyperplasia, is characterized by atypical glandular cytology superimposed on the architecture of complex hyperplasia **(Figure 21)**

Differential Diagnosis

♦ Disordered proliferative phase:
- Reproductive age, premenopausal
- Irregularly shaped and enlarged glands focally interspread within normal proliferative glands

♦ Endometrial polyps:
- Often have areas of simple or complex hyperplasia
- Have dense fibrous stroma with thick-walled blood vessels and usually covered on three sides by surface epithelium

♦ Endometrial and stromal breakdown:
- Glandular fragmentation, nuclear dust and clusters of stromal cells are usually absent in hyperplasia

♦ Atypical polypoid adenomyoma

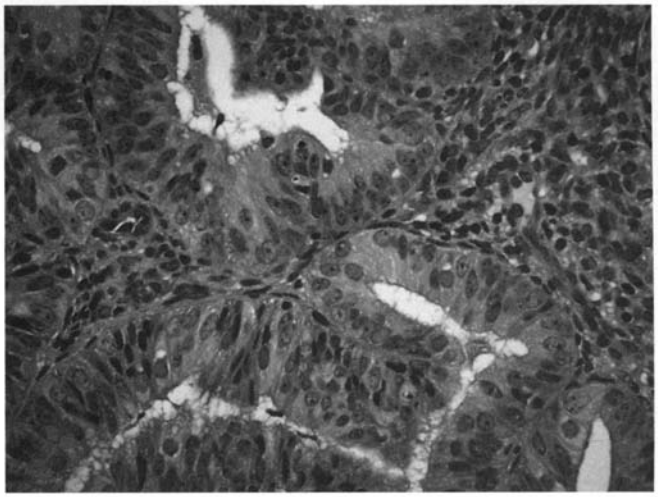


Fig. 21. Atypical complex hyperplasia. Rounded nuclei with loss of polarity.

♦ Well-differentiated carcinoma:
- Evidence of stromal invasion
- Criteria which identifies stromal invasion:
  - Altered fibroblastic stroma (desmoplastic response)
  - Confluent glandular pattern uninterrupted by stroma; at times cribriform
  - Extensive papillary pattern

Endometrial Intraepithelial Carcinoma

Clinical

♦ Recognized as the precursor lesion for serous carcinoma, the prototypic endometrial carcinoma not related to estrogenic stimulation

♦ Typically occurs in the setting of endometrial atrophy

♦ Clinical significance similar to invasive serous carcinoma since it can be associated with disseminated disease in the absence of an invasive carcinoma in the endometrium

♦ Potential future application of the term for precursor lesions of other subtypes of carcinoma

*Microscopic **(Figure 22)***

♦ Noninvasive replacement of endometrial glandular epithelium by markedly atypical cells identical to those of invasive serous carcinomas

♦ Enlarged nuclei with granular or vesicular chromatin, and enlarged eosinophilic nucleoli

♦ Numerous mitotic figures, including atypical forms

♦ Usually background atrophic endometrium

Immunoprofile

♦ Diffuse intense p53+; very high proliferation index with Ki-67

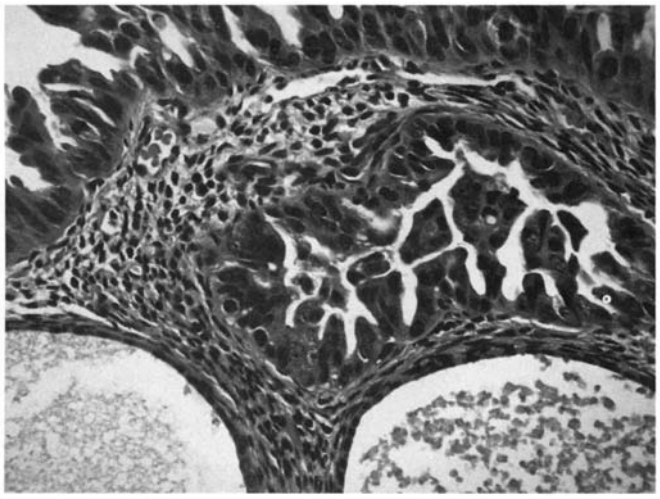


Fig. 22. Endometrial intraepithelial carcinoma. Highly atypical cells replacing the surface endometrium and underlying gland. Non-neoplastic endometrium is atrophic.

Differential Diagnosis

- Serous carcinoma:
  - If glandular confluence or stromal invasion are present, or a proliferation of crowded glands measuring >1 cm is present, the lesion qualifies as serous carcinoma
- Benign metaplastic endometrial lesions:
  - Very low proliferative indices assessed with K1-67 immunostain, and tipically p53–

Endometrial Carcinoma

Classification (WHO)

- Endometrioid carcinoma:
  - Variant with squamous differentiation
  - Villoglandular variant
  - Secretory variant
  - Ciliated variant
- Mucinous adenocarcinoma
- Serous adenocarcinoma
- Clear cell adenocarcinoma
- Mixed cell adenocarcinoma
- Squamous cell carcinoma
- Transitional cell carcinoma
- Small cell carcinoma
- Undifferentiated carcinoma
- Others

Epidemiology/Clinical

- Most common invasive neoplasm of the female genital tract in developed countries
- Most occur in perimenopausal and postmenopausal women
- Majority of cases present clinically with abnormal uterine bleeding
- Risk factors include:
  - Unopposed estrogen stimulation
  - Obesity
  - Nulliparity
  - Hypertension
  - Diabetes mellitus
  - Early menarche and late menopause
- Clinically and epidemiologically endometrial carcinoma can be classified in two types:
  - Type I (estrogen related):
    - Unopposed estrogen present
    - Pre-and perimenopausal
    - Precursor lesion: atypical hyperplasia
    - Tends to be low grade with minimal myometrial invasion
    - Endometrioid subtype
    - Tends to have indolent behavior
    - *PTEN* mutation, microsatellite instability, K-ras mutation
  - Type II (non-estrogen-related):
    - Unopposed estrogen absent
    - Postmenopausal
    - Precusrsor lesion: endometrial intraepithelial carcinoma
    - High grade, often with deep myometrial invasion
    - Serous and clear cell subtypes
    - Aggressive behavior
    - p53 mutation

Grade and Stage

- Architectural and nuclear grading is applied to endometrioid and mucinous carcinomas
- The grading for serous, clear cell and squamous carcinomas uses nuclear grade only
- Architectural grading is based only in the glandular component, squamous/morular areas are excluded:
  - Grade 1: no more than 5% of the tumor has a solid growth pattern
  - Grade 2: 6–50% of the tumor has a solid growth pattern
  - Grade 3: >50% of the tumor has a solid growth pattern
- Nuclear grade:
  - Grade 1: oval, mildly enlarged nuclei with evenly dispersed chromatin
  - Grade 2: features intermediate to grades 1 and 2

- Grade 3: markedly enlarged and pleomorphic nuclei, with coarse chromatin and prominent eosinophilic nucleoli

♦ The grade of tumors that are architecturally grade 1 or 2 should be increased by one in the presence of nuclear grade 3

Macroscopic

♦ Usually arises in the corpus, less frequently in the lower uterine segment

♦ The uterus is usually enlarged, but may be small, particularly in serous type

♦ Gross appearance is similar regardless of the histologic type

♦ Single dominant mass, most frequently in the posterior than anterior wall

♦ Exophytic with a shaggy, frequently ulcerated surface, with an underlying firm tumor with variable extension into the myometrium

Endometrioid Carcinoma

Clinical

♦ Most common type, accounting for 80% of all endometrial carcinomas

♦ Most women are postmenopausal

♦ Usually present with abnormal bleeding

♦ Typifies the type I endometrial carcinoma

Macroscopic

♦ Similar to the various other types

*Microscopic (**Figure 23**)*

♦ Composed of tubular glands or villoglandular structures lined by simple or pseudostratified columnar cells that have their long axis perpendicular to the basement membrane

♦ Spectrum of histological differentiation, from a very well differentiated carcinoma with a predominant glandular differentiation to higher grade carcinomas characterized by solid nests and sheets of cells

♦ Deep myometrial invasion and lymph node metastasis are more frequent in higher grade carcinomas

♦ Associated endometrial hyperplasia is present in 20–40% of cases

♦ Variants of endometrioid carcinoma:

- With squamous differentiation (**Figure 24**):
  - The squamous component must be at least 10% of the tumor
  - Squamous componet may be benign or malignant-appearing
  - No difference in clinical features
- Villoglandular:
  - Thin papillary fronds covered by stratified columnar cells with mild to moderate atypia

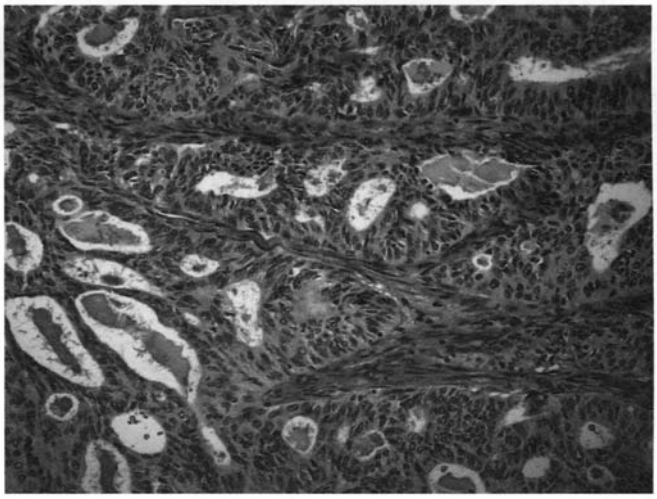


Fig. 23. Well differentiated endometrioid carcinoma.

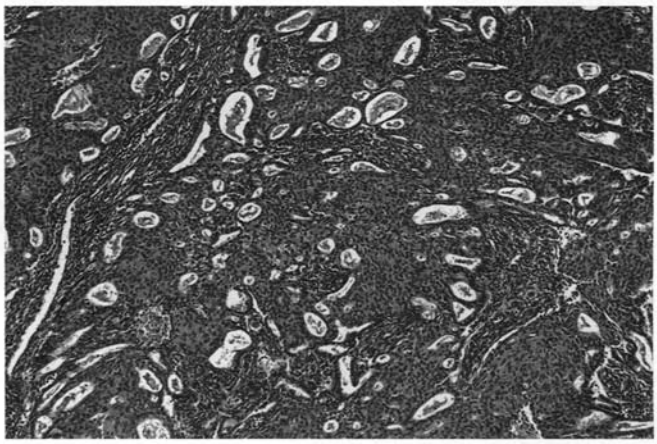


Fig. 24. Well differentiated endometrioid adenocarcinoma with squamous differentiation.

- Ciliated:
  - Rare, almost always well differentiated
  - Cells with eosinophilic cytoplasm and cilia
- Secretory:
  - Rare, usually well differentiated
  - The majority of cells exhibit subnuclear or supranuclear cytoplasmic vacuoles, resembling early secretory endometrium
  - Associated with favorable prognosis

Differential Diagnosis

♦ Atypical hyperplasia:

- Stromal invasion is absent (see differential diagnosis for hyperplasia)

♦ Primary endocervical carcinoma:

- Usually negative for estrogen and progesterone receptor, in contrast with endometrial adenocarcinoma

- Express CEA more commonly and vimentin less commonly than endometrial carcinoma
- Usually contain HPV DNA detected by PCR

- Cytoplasmic alterations (metaplasias)
- Atypical polypoid adenomyoma
- Arias-Stella reaction
- Menstrual endometrium

Mucinous Adenocarcinoma

Clinical

- Uncommon type of endometrial carcinoma
- Most of the tumors are stage I and low grade
- Clinical features do not differ from endometrioid carcinoma

Macroscopic

- No distinctive gross features

*Microscopic (**Figure 25**)*

- > 50% of the cell population of the tumor must contain intracytoplasmic mucin
- Glands and papillary processes lined by uniform columnar cells with minimal stratification
- Papillary fronds surrounded by extracellular lakes of mucin containing neutrophils

Differential Diagnosis

- Primary endocervical carcinoma
- Clear cell carcinoma
- Secretory carcinoma
- Microglandular hyperplasia of the endocervix

Serous Carcinoma

Clinical

- Comprises 5–10% of all endometrial carcinomas
- Patients typically are postmenopausal with an average age that is 10 years older than that of patients with endometrioid carcinoma
- Typifies the type II endometrial carcinoma
- Aggressive behavior with early dissemination to pelvis and abdomen as in ovarian serous carcinoma
- Considered a high grade carcinoma by definition

Macroscopic

- Often the uterus is small and atrophic
- Generally exophytic with papillary appearance
- Frequently develops within a polyp

*Microscopic (**Figure 26**)*

- Papillae with broad fibrovascular cores, with secondary and tertiary papillary processes and sloughing of the cells

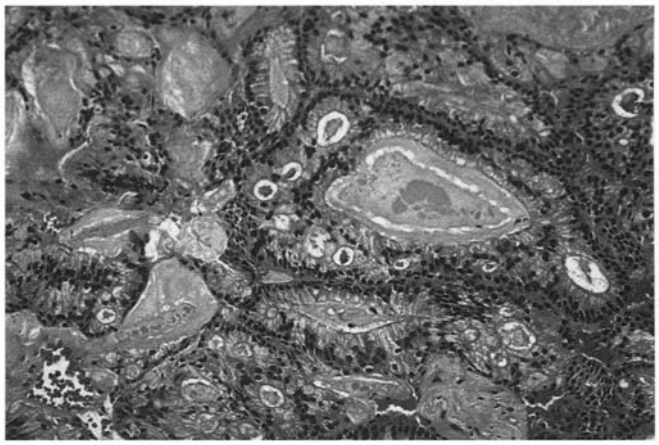


Fig. 25. Mucinous adenocarcinoma of the endometrium. The tumor cells contain intracytoplasmic mucin.

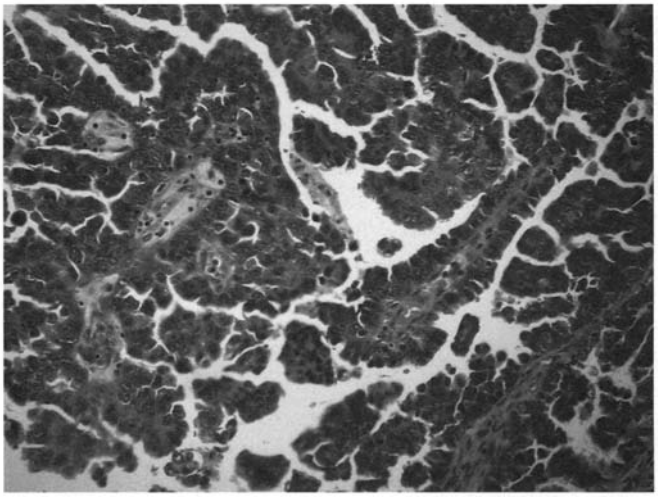


Fig. 26. Serous carcinoma. Papillae lined by cells with marked nuclear atypia.

- A papillary pattern typically predominates, but glandular and solid patterns also occur
- Cells and nuclei are usually round rather than columnar and lack a perpendicular orientation to the basement membrane
- High grade nuclei, often atypically situated with large eosinophilic macronucleoli, multinucleated tumor cells are commonly present
- Frequent mitotic figures, often atypical, and necrotic foci are common
- Psammoma bodies found in about 30% of cases
- Deep myometrial invasion and vascular invasion are frequently found
- The adjacent endometrium is atrophic in almost all cases
- Endometrial intraepithelial carcinoma is present in nearly 90% of cases

Immunoprofile

- Strong and diffuse p53+
- Low frequency of estrogen and progesterone receptors expression
- Very high proliferation index with Ki-67

Differential Diagnosis

- Villoglandular carcinoma:
  - Delicate papillary fronds
  - Lack high-grade nuclear atypia
- Endometrioid carcinoma:
  - Immunohistochemistry for p53, Ki-67 and hormone receptors can be useful:
    - Usually ER/PR+
    - P53-(usually, but high grade tumors may also be positive)
- Clear cell carcinoma
- Papillary syncytial eosinophilic change

Clear Cell Carcinoma

Clinical

- Comprises 1–5% of all endometrial carcinomas
- Considered the other major type II carcinoma of the endometrium, after serous carcinoma

Macroscopic

- No distinctive gross features

*Microscopic (**Figure 27**)*

- May exhibit solid, papillary, tubular and cystic patterns
- Solid pattern composed of masses of clear cells admixed with eosinophilic cells
- Papillary, tubular and cystic patterns composed of predominantly hobnail-shaped cells with interspread clear and eosinophilic cells
- Cells are usually large with clear cytoplasm due to glycogen
- Generally marked nuclear atypia is present
- Mitotic activity is high

Differential Diagnosis

- Secretory carcinoma
- Serous carcinoma
- Yolk sac tumor:
  - Schiller-Duval bodies
  - Elevated serum AFP
  - AFP+ with immunohistochemistry

Mixed Cell Adenocarcinoma

- Tumor composed of an admixture of a type I (endometrioid carcinoma, including its variants, and mucinous carcinoma) and a type II carcinoma (serous or clear cell)
- The minor cell type must compose at least 10% of the total tumor

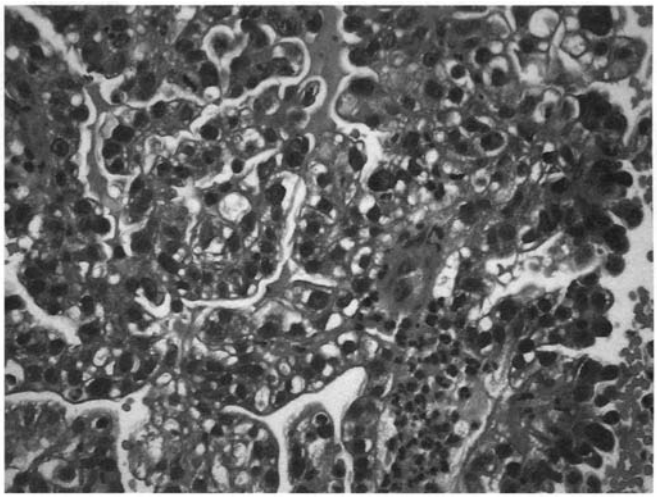


Fig. 27. Clear cell carcinoma. Large cells with clear cytoplasm and marked nuclear atypia.

Squamous Cell Carcinoma

- Extremely rare
- Diagnosed only in the absence of squamous cell carcinoma of the cervix or connection to the cervical squamous epithelium, and in the absence of adenocarcinoma in the endometrium
- Associated with cervical stenosis, pyometria and chronic inflammation
- Histologically, resembles squamous cell carcinomas found in other sites
- Prognosis related to stage at diagnosis

Transitional Cell Carcinoma

- Extremely rare
- 90% or more of the tumor should be composed of cells resembling urothelial transitional cells to qualify for the diagnosis
- Polypoid or papillary tumors
- Invariably admixed with other patterns of endometrial carcinoma
- The transitional cell component is often grade 2 or 3 with papillary configuration

Small Cell Carcinoma

- Uncommon, <1% of all carcinomas
- Histological appearance is similar to that of small cell carcinoma in other organs
- Positive for keratin and mostly positive for neuroendocrine markers
- The prognosis is better in contrast to small cell carcinoma elsewhere in the genital tract

Undifferentiated Carcinoma

- Tumors lacking any evidence of differentiation

Smooth Muscle Tumors

LEIOMYOMA

Clinical

- Most common uterine neoplasm
- Most common in the fourth and fifth decades
- Occurs in 20–40% of women >30 years of age
- Rare in women <18 years of age
- Clinical presentation depends on their size and location, most common symptoms include pain, sensation of pressure and abnormal uterine bleeding
- Pedunculated leiomyomas may protrude through the cervical os **(Figure 28)**

Macroscopic

- Multiple in two thirds of patients
- May be submucosal, intramural or subserosal **(Figure 29)**
- Spherical, firm, well circumscribed and bulge from the surrounding myometrium
- White to tan cut surface with a whorled trabecular pattern
- Degenerative changes include hemorrhage, hyalinization, necrosis, calcification, myxoid and cystic degeneration

Microscopic

- Composed of whorled, anastomosing fascicles of uniform fusiform smooth muscle cells
- Nuclei are uniform, elongated with blunt or tapered ends (cigar-shaped) with small nucleoli
- Mitotic figures usually infrequent
- Usually more cellular than surrounding myometrium
- Degenerative changes are common, including hyaline fibrosis, infarct-type necrosis, edema, hemorrhage and myxoid change
- Margins usually microscopically circumscribed

Immunoprofile

- Muscle-specific actin, SMA, desmin and h-caldesmon+
- Frequent cytokeratin+
- EMA-
- May be focally CD10+

*Differential Diagnosis **(Table 1)***

- Leiomyosarcoma
- Endometrial stromal tumors (see endometrial stromal tumors)

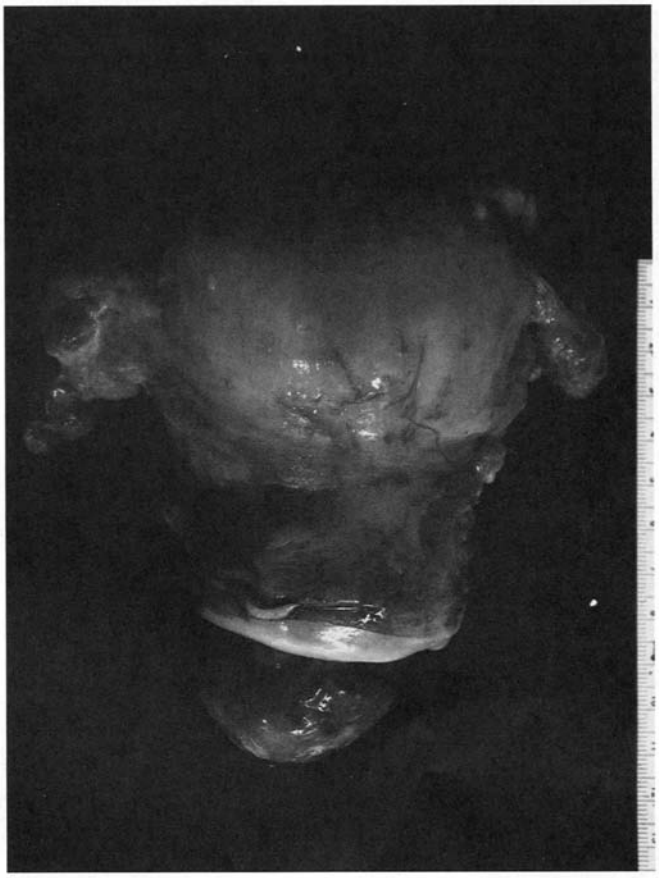


Fig. 28. Prolapsed sumucosal leiomyoma.

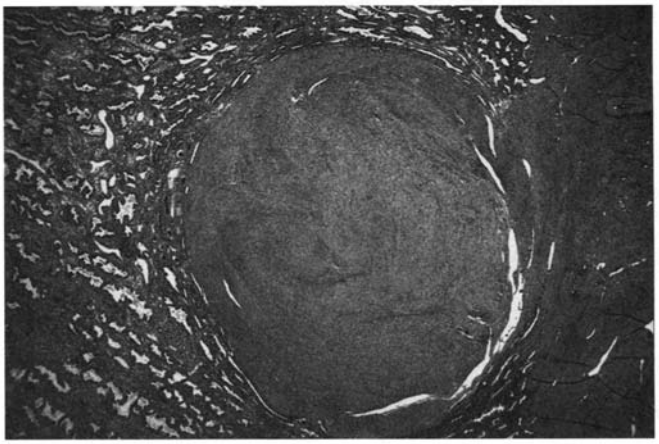


Fig. 29. Submucosal leiomyoma.

Histological Variants

- Mitotically active leiomyoma:
  - Occur most frequently in premenopausal women
  - 5 or more mitotic figures per 10 high power fields, in a leiomyoma with otherwise typical histologic features
  - The clinical evolution is benign
  - The term mitotically active leiomyoma with limited experience is used when the tumor contains >15 mitosis per 10 high power fields

Table 1. Histologic Criteria for the Diagnosis of Uterine Smooth Muscle Tumors with Standard Smooth Muscle Differentiation

Tumor cell necrosis	*Atypia*	*Mitotic index MF/10 HPF*	*Diagnosis*
Present	Diffuse, moderate to severe	Any level	Leiomyosarcoma
	None to mild	Greater than 10	Leiomyosarcoma
		Less than 10	Leiomyosarcoma (R/O, recent infarction of leiomyoma due to torsion or others)
Absent	Diffuse, moderate to severe	Greater than 10	Leiomyosarcoma
		Less than 10	Atypical leiomyoma with low risk of recurrence
	None to mild	Less than 10	Leiomyoma
		Greater than 10	Mitotically active leiomyoma
	Focal, moderate to severe	Less than 15	Leiomyoma with limited experience or if MI>15: STUMP (smooth muscle tumor of uncertain malignant potential)

- This diagnosis should not be used for neoplasms exhibiting moderate to severe atypia, abnormal mitotic figures or coagulative tumor cell necrosis

♦ Cellular leiomyoma:
- Significantly more cellular than surrounding myometrium
- No clinical differences with other leiomyomas

♦ Hemorrhagic leiomyoma (apoplectic):
- Occurs mainly in women who are taking oral contraceptives, are pregnant or postpartum
- Is often also cellular
- Stellate areas of hemorrhage
- Increased mitotic activity adjacent to hemorrhagic areas
- Coagulative tumor necrosis, abnormal mitotic figures and nuclear atypia are absent

♦ Epithelioid leiomyoma:
- Most are solitary, yellow or gray, tend to be softer than the usual leiomyoma, hemorrhagic and necrotic areas may be present
- Composed of round or polygonal cells arranged in clusters or cords often with transition to more typical spindle smooth muscle cell
- Three subtypes:
  - Leiomyoblastoma: round cells with eosinophilic cytoplasm
  - Clear cell leiomyoma: polygonal cells with abundant clear cytoplasm
  - Plexiform leiomyoma: cords or nests of round cells with scant cytoplasm, invariably benign
- The behaviour of epithelioid leiomyomas with two or more of the following features is not well stablished; such tumors should be classified in the uncertain malignant potential category:
  - Size > 6 cm
  - 2–4 mitotic figures per 10 high-power fields
  - Necrosis
- Neoplasms with 5 or more mitotic figures per 10 high power fields should be regarded as epithelioid leiomyosarcoma

♦ Myxoid leiomyoma:
- Abundant myxoid material is present between smooth muscle cells

♦ Atypical leiomyoma **(Figure 30)**:
- Other names include pleomorphic, bizarre or symplastic leiomyoma

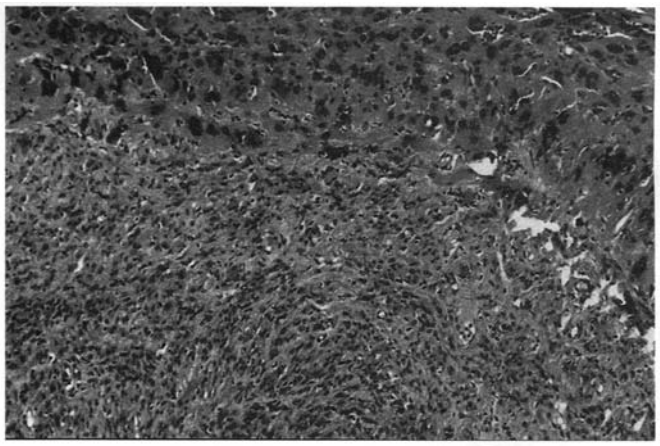


Fig. 30. Atypical leiomyoma. Atypical enlarged cells with hyperchromatic nuclei.

- Benign smooth muscle tumor with atypical cells with enlarged hyperchromatic nuclei with smudged chromatin
- Large cytoplasmic pseudonuclear inclusions often present
- Atypia may be diffuse, focal or multifocal
- Mitotic figures <10 per 10 high power fields, coagulative necrosis and abnormal mitotic figures are absent

♦ Lipoleiomyoma:
- Significant number of adipocytes

Growth Pattern Variants

♦ Diffuse Leiomyomatosis:
- Rare, benign condition
- Numerous small smooth muscle nodules produce symmetric enlargement of the uterus
- Uniform, bland spindle smooth muscle cells less circumscribed than typical leiomyomas

♦ Dissecting Leiomyoma:
- Benign smooth muscle proliferation
- Border marked by the dissection of compressive tongues of smooth muscle into surrounding myometrium and occasionally, into broad ligament and pelvis

♦ Intravenous Leiomyomatosis

Clinical

♦ Very rare smooth muscle tumor
♦ Main symptoms are abnormal bleeding and pelvic discomfort
♦ Hormonally dependent tumor
♦ Overall, favorable prognosis, but may cause significant morbidity and sometimes mortality

Macroscopic

♦ Complex nodular growth within the myometrium with convoluted, worm-like extensions into the uterine veins in the broad ligament or other pelvic veins
♦ May extend into the inferior vena cava and even the heart

Microscopic

♦ Nodular masses of histologically benign smooth muscle cells growing within venous channels **(Figure 31)**
♦ Cellular composition similar to leiomyoma, most contain prominent fibrosis or hyalinization
♦ Any leiomyoma histologic variant may be seen
♦ Mitotic figures are minimal or absent

Smooth Muscle Tumor of Uncertain Malignant Potential (STUMP)

♦ Smooth muscle tumor that cannot be diagnosed reliably as benign or malignant on the basis of generally applied criteria

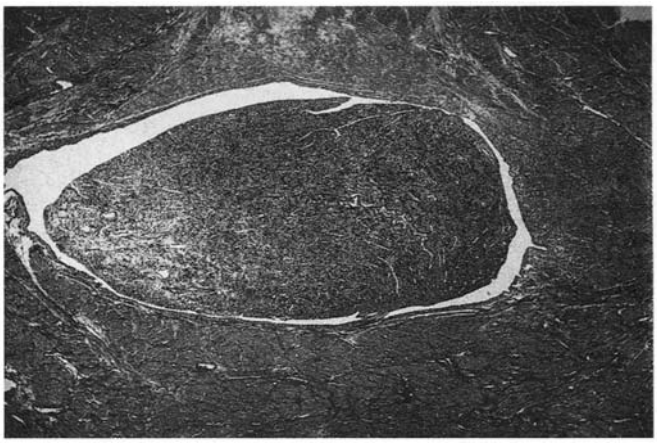


Fig. 31. Intravenous leiomyomatosis. Tumor in myometrial vessels.

♦ This category should be used sparingly and reserved for neoplasms whose appearance is ambiguous

LEIOMYOSARCOMA

Clinical

♦ Most common pure uterine sarcoma, comprises ~1% of all uterine malignancies
♦ Usually in postmenopausal women, average age 52 years (a decade older than women with leiomyoma)
♦ Main symptoms are abnormal bleeding, lower abdominal pain, pelvic or abdominal mass
♦ Highly malignant neoplasm, may spread locally, regionally or by hematogenous dissemination (most often to the lungs)
♦ A diagnosis of leiomyosarcoma should be made with great caution in women <30 years of age and only after exclusion of exposure to Leuprolide, which may induce a pattern of necrosis identical to coagulative tumor cell necrosis

Macroscopic

♦ Usually intramural, large, solitary and poorly circumscribed
♦ Soft, fleshy, yellow-gray with areas of hemorrhage and necrosis
♦ Usually not associated with leiomyomas

*Microscopic **(Figure 32)***

♦ Cellular tumor composed of fascicles of atypical spindle shaped cells with eosinophilic cytoplasm
♦ Hyperchromatic nuclei with rounded ends and prominent nucleoli
♦ Multinucleated giant cells present in 50% of cases
♦ Tumor cell necrosis is typically prominent, but may be absent
♦ Frequently invades the surrounding myometrium
♦ Vascular invasion is identified in 10–22% of cases

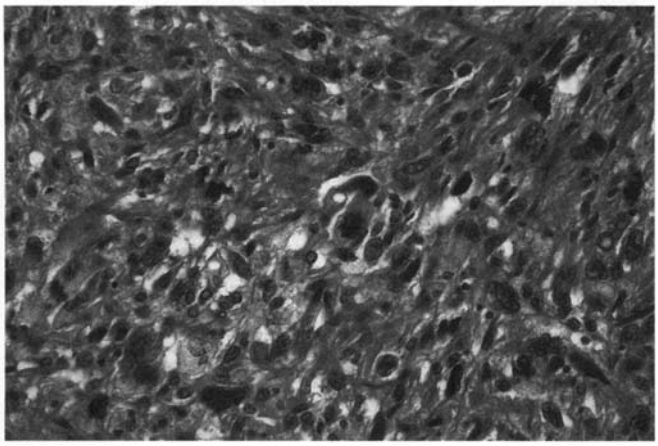


Fig. 32. Uterine leiomyosarcoma. Moderate to severe atypia and numerous mitotic figures.

- Diagnostic criteria:
  - Any coagulative tumor cells necrosis
  - In the absence of coagulative tumor cell necrosis:
    - Diffuse moderate to severe atypia, and
    - Mitotic index ≥ 10 mf/10 hpf

Differential Diagnosis

- Leiomyoma and variants:
  - Coagulative tumor cell necrosis is absent
  - Less cellular, no significant cytologic atypia and minimal mitotic activity
- Intravascular leiomyomatosis
- Undifferentiated endometrial sarcoma (High grade endometrial stromal sarcoma)
- Poorly differentiated endometrial carcinoma

Leiomyosarcoma Variants

- Epithelioid Leiomyosarcoma:
  - Combines the epithelioid phenotype with the features of malignancy of conventional leiomyosarcoma
- Myxoid Leiomyosarcoma:
  - Large gelatinous neoplasm, usually appears circumscribed on gross examination
  - Smooth muscle cells widely separated by myxoid material
  - The characteristic low cellularity largely accounts for the low mitotic index, however, sometimes the mitotic index is high and high degree of atypia
  - Commonly show myometrial and vascular invasion

Endometrial Stromal and Related Tumors (Tables 2 and 3)

- Rare, can be benign (endometrial stromal nodule) or malignant (endometrial stromal sarcoma)
- Endometrial stromal sarcomas have been traditionally divided into low and high grade type, however, since the high grade endometrial stromal sarcoma lacks specific differentiation and bears no resemblance to endometrial stroma, it has been proposed that they be designated undifferentiated endometrial sarcoma

Endometrial Stromal Nodule

Clinical

- Rare, benign neoplasm, represent <25% of endometrial stromal tumors
- ~75% occur in premenopausal women, average age is 47 years
- Usually present with abnormal vaginal bleeding, ~10% are asymptomatic

Macroscopic

- May be polypoid and protrude into the endometrial cavity, or grow entirely within the myometrium
- Circumscribed contour
- Fleshy yellow or tan cut surface and tend to bulge from the surrounding myometrium
- Usually single, but ~5% of patients have two or more nodules
- Cervix is seldom involved

Microscopic

- Composed of cells resembling those of proliferative phase endometrial stroma
- Tumor cells have uniform, small round nuclei and inconspicuous nucleoli
- Expansile non infiltrative margins, invasion of surrounding myometrium indicates that the tumor is a stromal sarcoma **(Figure 33)**
- Mitotic activity is usually low (<3 mf/10 hpf), but may be higher (rarely may exceed 10–15/mf/10 hpf)

*Differential Diagnosis (**Tables 2 and 3**)*

- Cellular leiomyoma:
  - Cellular leiomyomas are strongly actin and desmin+, and CD10-; while stromal nodules usually only weak patchy staining for smooth muscle actin, and typically desmin- , and CD10+
- Endometrial stromal sarcoma, low grade:
  - Infiltrates the myometrium and invades vascular spaces

Endometrial Stromal Sarcoma, Low Grade

Clinical

- Rare tumor, 0.2% of all genital tract malignant neoplasms
- In general, occurs in younger women than other uterine malignancies, mean age ranges from 42–58 years
- Presenting symptoms include abnormal bleeding and abdominal pain

Table 2. Immunohistochemical findings in endometrial stromal and smooth muscle tumors

Antibody	*Endometrial stromal tumor*	*Smooth muscle tumor*
CD10	+	–
Smooth muscle actin	– /focally+	+
h-caldesmon	–	+
Desmin	–	+

- Characterized by indolent growth and late recurrences
- Frequently respond to progestin therapy
- Fusion of two zinc finger genes (JAZF1 and JJAZ1) by translocation t(7;17) is present in most low grade endometrial mstromal tumors

Macroscopic

- Extensive permeation of the myometrium is commonly present, but may present as a solitary well delineated intramural mass
- Cut surface is yellow to tan and softer than that of a leiomyoma
- Worm-like plugs of tumor within the vessels of the broad ligament and adnexae may be present

Microscopic

- The tumor permeates the myometrium as irregular tongues **(Figure 34)**
- Densely cellular tumor, composed of uniform oval to spindle cells of endometrial stromal type
- By definition, significant atypia and pleomorphism are absent
- Usually low mitotic activity, but occasional >10 mf/ 10 hpf may be encountered not altering the diagnosis
- Small vessels and arterioles resembling endometrial spiral arteries are characteristic
- Myxoid and fibrous change may occur focally or diffusely
- Cells with foamy cytoplasm may be prominent in some cases
- Limited smooth muscle differentiation (<30%) is occasionally present
- Epithelial-like differentiation occurs in about 25% of cases (endometrial type glands or a pattern reminiscent of ovarian sex cord tumor)
- Invasion of lymphatic and vascular channels is a characteristic finding

Immunoprofile

- CD10+, almost always ER/PR+, and focally actin+
- Desmin and h-caldesmon– (usually, but not always)
- Areas with sex cord pattern are inhibin+, cytokeratin+ , and may also be desmin+

Differential Diagnosis

- Endometrial Stromal Nodule
- Intravenous leiomyomatosis
- Adenomyosis with sparse glands
- The distinction of low grade endometrial stromal sarcoma, stromal nodule, a non-neoplstic stromal proliferatin or a cellular leiomyoma is often impossible in biopsy or curettage specimens

Undifferentiated Endometrial Sarcoma

Clinical

- Previously designated as high grade endometrial stromal sarcoma
- Aggressive behavior, high mortality rate
- Usually do not respond to progestin therapy

Macroscopic

- One or more fleshy, grey to yellow polypoid endometrial masses
- Necrosis and hemorrhage are often present

Microscopic

- Marked cellular atypia and abundant mitotic activity, often including atypical forms
- Lack the typical growth pattern and vascularity of low grade endometrial stromal sarcoma
- Displace the myometrium in contrast to the infiltrative pattern of low grade endometrial stromal sarcoma
- Are most often ER/PR-

Differential Diagnosis

- Carcinosarcoma
- Leiomyosarcoma

Miscellaneous Mesenchymal Tumors

Mixed Endometrial Stromal and Smooth Muscle Tumor

- Rare neoplasms composed of an admixture of endometrial stromal and smooth muscle elements
- A minimum of 30% of the minor component should be present for the diagnosis
- Recommended to report them in the same way as endometrial stromal neoplasms; malignant if there is myometrial and vascular invasion, benign otherwise

Perivascular Epithelioid Cell Tumor (PEComa)

- Tumor composed predominantly or exclusively of HMB-45+ perivascular epithelioid cells

Table 3. Pathologic Characteristics of Endometrial Stromal and Related Tumors

	Endometrial Stromal Nodule	*Endometrial Stromal Sarcoma, Low Grade*	*Undifferentiated Endometrial Sarcoma*
Histologic Features	Uniform cells resembling proliferative endometrial cells Significant atypia and pleomorphism absent Plexiform vascular pattern	Identical to endometrial stromal nodule	Cellular, marked nuclear atypia and pleomorphism. Tumor cells do not resemble proliferative phase endometrial stroma
Mitotic Activity	Usually low (<3 mf 10/hpf)	Usually low, but occasionally >10 mf 10/hpf	High (>10 mf 10/hpf), common abnormal forms
Borders	Circumscribed with pushing margins	Myometrial infiltration characterized by "tongue-like" tumor masses	Infiltrating margins with extensive myometrial infiltration
Vascular Invasion	Absent	Common, grossly distinctive "worm-like" appearance	Less often grossly visible
Extension Beyond the Uterus	Confined to the uterus	May extend beyond the uterus May metastasize	Frequently extends beyond the uterus Metastases common
Immunoprofile	CD10+ actin focally+ Desmin—(usually) h-caldesman—(usually)	CD10+ actin focally+ desmin—(usually) h-caldesman—(usually) ER/PR (+) Sex-cord like areas: inhibin, CK and EMA+; may also be desmin+	ER/PR—

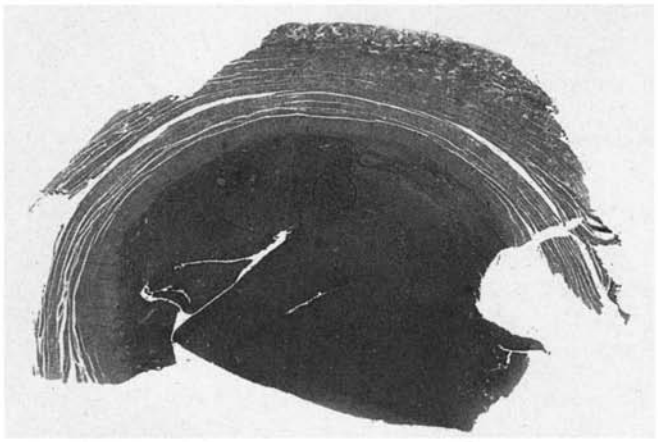


Fig. 33. Endometrial stromal nodule. Non invasive growth pattern with a circumscribed expansile margin.

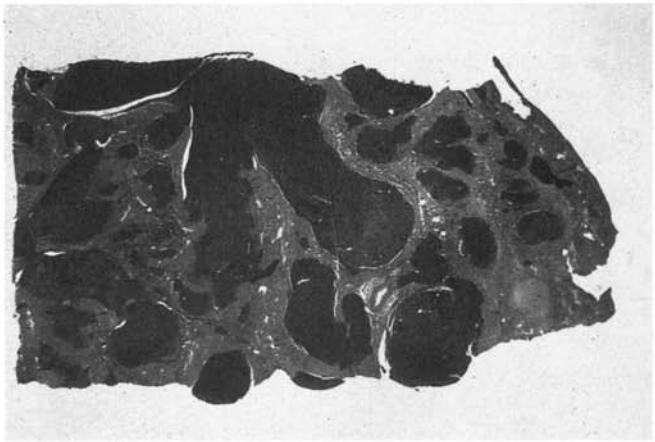


Fig. 34. Endometrial stromal sarcoma, low grade. The broad bands of tumor extensively permeate the myometrium.

- ♦ May have a prominent tongue-like growth pattern
- ♦ Cells have abundant clear to eosinophilic pale cytoplasm
- ♦ Should be considered of uncertain malignant potential until long term data is available

Adenomatoid Tumor

Clinical

- ♦ Benign tumor of the uterine serosa and myometrium, probably derived from serosal mesothelium

- Usually an incidental finding, seen in up to 1% of uteri

Macroscopic

- May be multiple or associated with a similar lesion in the fallopian tube
- Grey or tan, with rubbery consistency
- Well circumscribed intramural masses that may resemble a leiomyoma, often located towards the serosal surface

Microscopic

- Multiple small, slit-like, interconnecting spaces within the myometrium
- Composed of tubules lined by cells that may be cuboidal or flat
- Nuclear atypia or mitotic activity are minimal or absent
- No stromal desmoplastic response

Immunoprofile

- Cytokeratin+, mesothelial markers+, Ber-EP4-

Differential Diagnosis

- Lymphangioma
- Carcinoma

Other Rare Mesenchymal Tumors

Benign

- Lipoma
- Hemangioma
- Lymphangioma
- Rhabdomyoma

Malignant

- Rhabdomyosracoma
- Malignant fibrous histiocytoma
- Angiosarcoma
- Osteosarcoma

MIXED EPITHELIAL AND MESENCHYMAL TUMORS

Adenomyoma

- May occur at any age
- Usually polypoid submucosal lesions, rarely intramural or subserosal
- Circumscribed, nodular aggregate of smooth muscle, benign endometrial glands, and, usually, endometrial stroma
- Designation not recommended for a localized adenomyosis forming a discrete mass

Atypical Polypoid Adenomyoma

Clinical

- Characteristically occurs in premenopausal women
- Usually present with abnormal uterine bleeding
- Benign lesion that can be cured by curettage, but may recur

Macroscopic

- Polypoid mass, resembling a typical polyp
- Often in the lower uterine segment

*Microscopic (**Figure 35**)*

- Irregularly shaped endometrial glands with architectural and cytologic atypia within stroma containing abundant smooth muscle
- Extensive morular squamous metaplasia may be present
- Foci that architecturally resemble well differentiated adenocarcinoma may be present, the designation of atypical polypoid adenomyoma of low malignant potential has been used

Differential Diagnosis

- Endometrial hyperplasia
- Endometrial carcinoma invading myometrium
- Adenosarcoma
- Malignant mixed mesodermal tumor
- Adenomyoma

Adenofibroma

Clinical

- Uncommon neoplasm
- Most often in postmenopausal women, but may occur in younger patients
- Benign tumor, but may recur if incompletely excised or curetted

Macroscopic

- Lobulated polypoid tumor that can arise anywhere in the uterus or in the cervix
- May contain small cysts resulting and a spongy or mucoid appearance

Microscopic

- Mixture of histologically benign epithelium and mesenchyme
- Broad papillary fronds projecting from the surface into cystic spaces

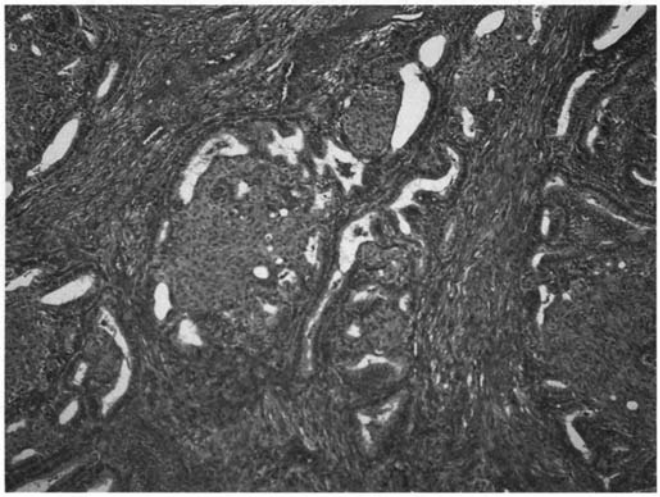


Fig. 35. Atypical polypoid adenomyoma. Atypical endometrial glands with squamous morules separated by a fibromuscular stroma.

- Cysts and cleft like spaces lined by columnar or cuboidal epithelial cells, most often of endometrioid type
- The stromal component is usually fibroblastic, but benign endometrial stromal cells or a mixture of stromal cells and fibroblasts may be present
- Stromal cell atypia is absent and mitotic figures are rare

Differential Diagnosis

- Endometrial polyp
- Atypical polipoid adenomyoma
- Adenosarcoma

Adenosarcoma

Clinical

- Typically occur in postmenopausal women, but 30% occur in premenopausal women
- Usually present with abnormal vaginal bleeding, pelvic pain, enlarged uterus, and tumor protruding through the cervix
- Considered a low grade neoplasm, but recurs in 25–40% of cases
- Predictive factors of a poor outcome are extrauterine spread, deep myometrial invasion and sarcomatous overgrowth

Macroscopic

- Soft or firm polypoid mass that grows into the cavity and can enlarge the uterus
- Cut surface is fleshy, tan or gray and contains small cysts
- Hemorrhage and necrosis are present in 25% of tumors

*Microscopic (**Figure 36**)*

- Biphasic tumor with a characteristic leaf-like pattern on low power examination

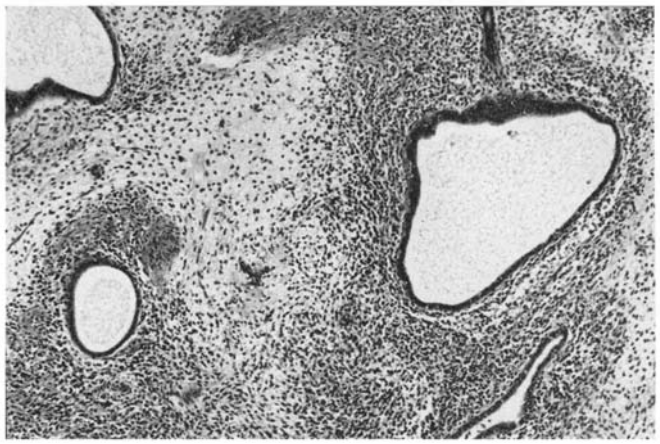


Fig. 36. Adenosarcoma. Cytologically bland tubular glands of endometrioid type, surrounded by a cuff of cellular mesenchyma containing mitoses.

- Glands often dilated and compressed into thin slits are dispersed throughout the mesenchymal component
- By definition, the epithelium is benign, most commonly resembles inactive or proliferative endometrial epithelium, but many other types may also occur
- The mesenchymal component generally is a homologous sarcoma such as stromal sarcoma or fibrosarcoma
- Stromal condensation surrounding the glands and clefts is a characteristic finding
- In most tumors mesenchymal cells show mild to moderate atypia
- Mitotic figures in the mesenchymal component generally 4 mf/10 hpf or more, but even 1 mf/hpf is enough for the diagnosis if the characteristic features are present
- Heterologous mesenchymal elements are present in 20–25% of cases, striated muscle the most common
- Sarcomatous overgrowth, present in 10% of cases, occurs when the sarcomatous component of the tumor represents ≥25% of the total tumor volume; usually associated with increased cellularity, nuclear atypia and mitotic activity and absence of epithelial elements
- Myometrial invasion is present in 15–20%, both glands and stroma
- Distant metastases are usually composed purely of the sarcomatous component

Differential Diagnosis

- Adenofibroma:
  - Less cellularity, mitotic activity and stromal nuclear atypia
  - Periglandular stromal cuffing is absent
- Malignant mixed Müllerian tumor (carcinosarcoma)
- Endometrial polyp

Carcinosarcoma (Malignant Mixed Müllerian Tumor)

Clinical

- By definition, tumors composed of malignant epithelial and mesenchymal components
- Increasing evidence that they are monoclonal and should be considered subsets of endometrial carcinoma
- Represent <5% of malignant neoplasms of the uterine corpus
- Occurs almost exclusively in postmenopausal women
- A history of pelvic radiation exists in some cases
- Most common presentation is vaginal bleeding, others include abdominal mass, pelvic pain and enlarged uterus with tumor protruding through the cervix
- Poor prognosis, clinical behavior is significantly worse than grade 3 endometrioid carcinoma, serous and clear cell carcinoma

Macroscopic

- Large polypoid mass filling the entire endometrial cavity and frequently protruding through the cervical os
- Variably soft to firm, tan and friable with areas of necrosis and hemorrhage
- Many invade the myometrium, but may be confined to a polyp
- ~25% of cases the tumor extends into the endocervix

Microscopic

- Composed of histologically malignant epithelial and mesenchymal components **(Figure 37)**
- The epithelial component is frequently endometrioid carcinoma, but any of the other subtypes of endometrial carcinoma may be present

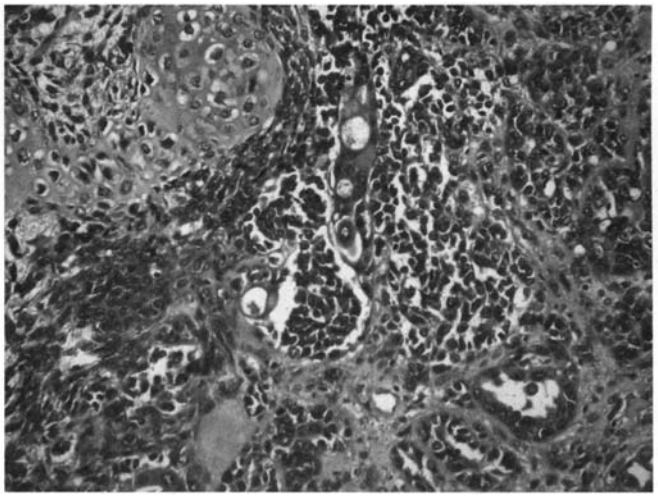


Fig. 37. Carcinosarcoma. Malignant epithelium admixed with heterologous sarcomatous elements (chondrosarcoma).

- The sarcoma component is homologous in ~50% of cases, usually undifferentiated sarcoma, endometrial stromal sarcoma, fibrosarcoma and occasionally leiomyosarcoma
- Heterologous mesenchymal elements most commonly consist of rhabdomyosarcoma and chondrosarcoma
- The histologic appearance of metastases is variable, most commonly pure carcinoma is encountered

Differential Diagnosis

- Poorly differentiated endometrial carcinoma
- Pure sarcoma
- Adenosarcoma

MISCELLANEOUS TUMORS

Sex Cord-Like Tumors

- Tumors of the uterine corpus that closely resemble ovarian sex cord tumors
- Only diagnosed when areas of endometrial stromal or smooth muscle tumors are not present
- Characterized by trabecular ribbons and nodules or isolated cells with luteinized or foamy cytoplasm
- Immunohistochemically, strongly positive for alpha inhibin, calretinin and CD99, also show frequent positivity for cytokeratins and smooth muscle actin
- A prominent tubular, retiform or glomeruloid epithelial component may be present
- Most have behaved in a benign fashion, a few have recurred or metastasized

Neuroectodermal Tumors

- Pure forms or mixed with carcinoma or carcinosarcoma
- Most often, the tumor cells differentiate into neuroblastic, neuroepithelial, glial and neuronal elements
- Highly malignant behavior

Melanotic Paraganglioma

- Morphologically identical to paraganglioma, but produces melanin pigment instead of neuroendocrine granules
- Cases reported were free of recurrences

LYMPHOMAS AND LEUKEMIAS

- Most lymphomas and leukemias involving the uterine corpus are a manifestation of systemic disease
- On rare occasions the corpus is the first known site of a malignant lymphoma
- Majority are of the large B cell type
- Differential diagnosis includes lymphoma-like lesion and leiomyoma massively infiltrated by lymphocytes

TUMORS OF GERM CELL TYPE

- Teratomas and yolk sac tumors can develop in the endometrium, as pure forms or associated with endometrioid tumors

METASTATIC (SECONDARY) TUMORS

Tumors From Other Genital Organs

- Usually result from direct extension of vaginal, cervical or tubal carcinoma or ingrowth of ovarian carcinoma involving the uterine serosa, with the primary tumor being clinically apparent
- Simultaneous cancers involving the endometrium and the ovary may represent:
  - Metastasis from the endometrium to the ovary
  - Metastasis from the ovary to the endometrium
  - Independent primary tumors
- Most likely a metastasis from the endometrium to the ovary with:
  - Small ovaries (<5 cm)
  - Bilateral ovarian involvement
  - Deep myometrial invasion
  - Vascular invasion
  - Fallopian tube involvement
- Independent tumors are usually well differentiated endometrioid tumors, whereas grade 3 endometrioid carcinoma, serous and clear cell carcinomas, and carcinosarcomas are generally primary in one organ and metastatic to the other

Tumors from Extragenital sites

- Metastatic breast cancer is the most frequent, followed by stomach, cutaneous melanoma, lung, colon, pancreas and kidney
- Abnormal uterine bleeding most common presentation
- Usually associated with obvious dissemination, on rare occasions may represent the first sign of an extrauterine primary tumor
- Most infiltrate the endometrium diffusely, the myometrium may also be involved

TNM CLASSIFICATION AND FIGO STAGING SYSTEM FOR ENDOMETRIAL CARCINOMA

- T: Primary Tumor (FIGO Stage):
  - TX: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - Tis: Carcinoma in situ (preinvasive carcinoma)
  - T1 (I): Tumor confined to corpus uteri:
    - T1a (IA): Tumor limited to the endometrium
    - T1b (IB): Tumor invades <1/2 of the myometrium
    - T1c (IC): Tumor invades > 1/2 of the myometrium
  - T2 (II): Tumor invades cervix but does not extend beyond uterus:
    - T2a (IIA): Endocervical glandular involvement only
    - T2b (IIB): Cervical stromal invasion
  - T3 and/or N1(III): Local and/or regional spread as specified in T3a, b, N1,and FIGO IIIA, B, C below:
    - T3a (IIIA): Tumor involves serosa and/or adenexae (direct extension or metastasis) and/or cancer cells in ascitis or peritoneal washings
    - T3b (IIIB): Vaginal involvement (direct extension or metastasis)
    - N1 (IIIC): Metastasis to pelvic and/or para-aortic lymph nodes

- T4 (IVA): Tumor invades bladder mucosa and/or bowel mucosa
- M1 (IVB): Distant metastasis (excluding metastasis to vagina, pelvic serosa, or adnexa)

♦ N: Regional Lymph Nodes:
- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

♦ M: Distant Metastasis:
- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

Fallopian Tubes

NON-NEOPLASTIC LESIONS

Acute Salpingitis

Clinical

♦ Usually secondary to the passage of bacteria from the uterine cavity into the tubal lumen
♦ *Neisseria gonorrhoeae* and *Chlamidia trachomatis* are considered the most common causative organisms, but most are polymicrobial
♦ Presents with abdominal and pelvic pain
♦ In gonococcal salpingitis the onset of acute pain typically occurs a few days after menses
♦ Recurrent infections result in chronic salpingitis

Macroscopic

♦ Distended, edematous, erythematous tube
♦ Fibrinous exudates on serosal surface
♦ Pus may be seen dripping from the fimbriated end
♦ May be adherent to adjacent structures, including ovary
♦ Tubo-ovarian abscess may be present

Microscopic

♦ Initial marked neutrophilic transmural and mucosal infiltrate with intraluminal exudate
♦ Plicae are distended with granulocytes, histiocytes, lymphocytes and plasma cells
♦ Surface fibrin deposition resulting in adherence of mucosal plicae

Chronic Salpingitis

Clinical

♦ Caused by chronic, recurrent infections
♦ Result in loss of tubal function

Macroscopic ***(Figure 38)***

♦ Large dilated tube with shaggy lining and thick walls
♦ Multiple tubo-ovarian adhesions
♦ Tubo-ovarian abscess may be present

Microscopic

♦ Healing and organization lead to permanent bridging between folds, resulting in follicular salpingitis (formation of dilated glad-like spaces between adhered plicae) **(Figure 39)**
♦ The mucosa may become hyperplastic, forming cribriform pseudoglands, with mild to moderate atypia **(Figure 40)**
♦ Fimbriae may occlude and form pyosalpinx; as inflammation subsides result in hydrosalpinx
♦ In hydrosalpinx, the tube contains clear serous fluid, most of the epithelium consists of low cuboidal cells, but occasional plicae may persist; a few lymphocytes may be present

Granulomatous Salpingitis

♦ Caused by a variety of organisms or noninfectious processes
♦ Tuberculous Salpingitis

Clinical

♦ *Mycobacterium tuberculosis* is the predominant etiologic agent of granulomatous salpingitis
♦ Most commonly occurs from secondary spread, usually from a primary pulmonary infection
♦ The tubes are more frequently affected than other parts of the female genital tract
♦ Pelvic pain, sterility and menstrual irregularities are the most common complaints

Macroscopic

♦ May be dilated and nodular
♦ In the adhesive form, dense adhesions between the tube and ovary, and fimbriae and ostium may be obliterated
♦ An identifiable ostium and fimbriae in a grossly diseased tube, is considered a characteristic of tumerculous salpingitis
♦ In the exudative form, distension mimics bacterial pyosalpinx



Fig. 38. Bilateral pyosalpinx. The tubes are markedly dilated and the fimbriae are obliterated.



Fig. 39. Salpingitis follicularis. Agglutination of plicae result in the formation of glandlike spaces.



Fig. 40. Acute and chronic salpingitis. The mucosa is hyperplastic forming cribriform pseudoglands with reactive atypia; should not be confused with carcinoma.

Microscopic

- Mucosal granulomatous reaction with central caseation, focal or massive
- Extension to the muscularis and serosa may occur
- Progressive scarring, with plical distorsion and conglutination
- Calcification may occur in areas of fibrosis

Other Granulomatous Salpingitis

- Actinomycosis
- Parasitic Salpingitis
- Sarcoid
- Chrohn's Disease
- Pseudoxantomatous Salpingitis

Salpingitis Isthmica Nodosa

Clinical

- Consists of one or more outpouchings or diverticula of tubal epithelium in the isthmic region usually accompanied by nodular hyperplasia of the surrounding muscularis
- Often bilateral
- Found in women between the ages of 25 and 60 years
- Unknown etiology; possible causes include postinflammatory distortion or an adenomyosis-like process
- Infertility and ectopic pregnancy are the most serious clinical complications

Macroscopic

- One or more nodular swellings in the isthmus 1–2 cm in diameter
- Firm cut surface, dilated diverticula may be seen

Microscopic

- The diverticula appear on cross section as dispersed glands of tubal epithelium surrounded by broad bands of muscularis **(Figure 41)**
- Endometrial-like stromal cells beneath the epithelium may be present

Ectopic Pregnancy

Clinical

- >95% of ectopic pregnancies occur in the fallopian tube; most are found in the ampulla (75–80%), 10–15% isthmic and 5% at the fimbriae
- Previous history of pelvic inflammatory disease in 35–45% of patients
- May present with tubal rupture and hemorrhagic shock
- If not recognized, rupture typically occurs around the eighth gestational week

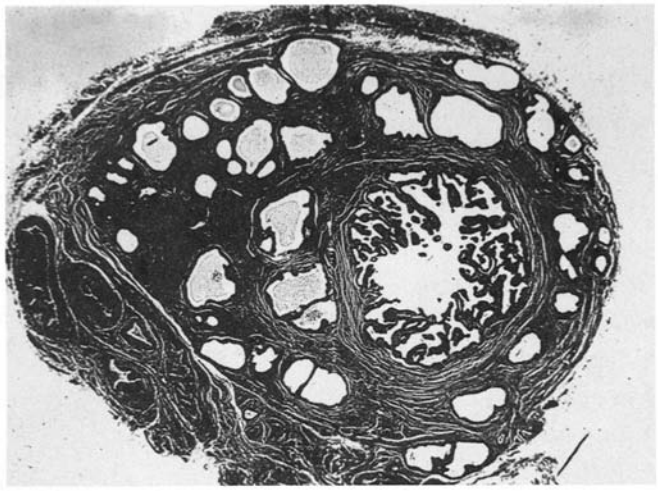


Fig. 41. Salpingitis isthmica nodosa. Variably sized cystic diverticuli within a thickened myosalpinx.

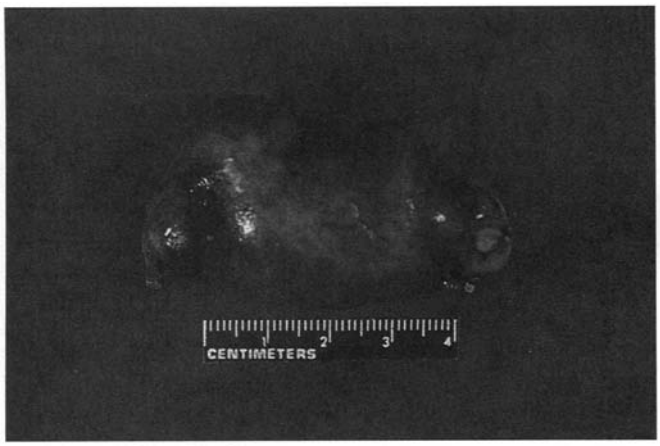


Fig. 42. Unruptured ectopic pregnancy. Irregular dilatation of the tube, with a bluish discoloration.

Macroscopic

- If unruptured, an irregular sausage-like dilatation of the tube, with a bluish discoloration is seen **(Figure 42)**
- Chorionic villi usually identified within the lumen
- ~2/3 of cases an embryo may be identified grossly or microscopically

Microscopic

- Chorionic villi and extravillous intermediate trophoblast can grow intraluminally or penetrate deep into the tubal wall
- Evidence of chronic salpingitis found in ~50% of cases

Inclusion Cysts and Walthard Nests

- Common incidental findings of no clinical significance
- Inclusion cysts originate from invaginations of the tubal serosa and consist of 1–2 mm unilocular cysts located beneath the serosal surface, lined by one or more layers of mesothelial cells (mesothelial inclusion cysts)
- Walthard nests result from a process of metaplasia, inclusion cysts become filled with polygonal epithelial-like cells with ovoid nuclei with nuclear grooves with a coffee-bean appearance

Paratubal Cysts

- Arise from mesonephric (wolffian) or paramesonephric (Müllerian) structures or from mesothelial inclusions:
  - Paramesonephric cyst:
    - Lined by epithelium containing ciliated cells
    - May have papillary infoldings
    - Hydatid of Morgagni is the most common:
      - 2–10 mm ovoid or round cyst attached by a pedicle to the fimbriae
      - Filled with clear serous fluid with a thin translucent wall
  - Mesonephric cysts:
    - May have a more prominent muscular coat
    - Contain only a few or no ciliated cells
  - Mesothelial cysts:
    - >80% of paratubal cysts measuring 3 cm are mesothelial cysts
    - Lined by flat cells and surrounded by thin fibrous wall

Tubal Prolapse

- Tubal prolapse into the vagina may occur rarely as a complication of vaginal or abdominal hysterectomy
- Grossly, an excresence in the vaginal vault, suggestive of granulation tissue or carcinoma is seen

EPITHELIAL TUMORS

Benign

Papilloma and Cystadenoma

- Uncommon lesions
- Papillomas:
  - Intramural or located in the fimbriated end and are loosely attached to the tubal mucosa
  - Consist of delicate branching fibrovascular stalks lined by indifferent or tubal type epithelium
- Cystadenomas are similar but lack papillary features

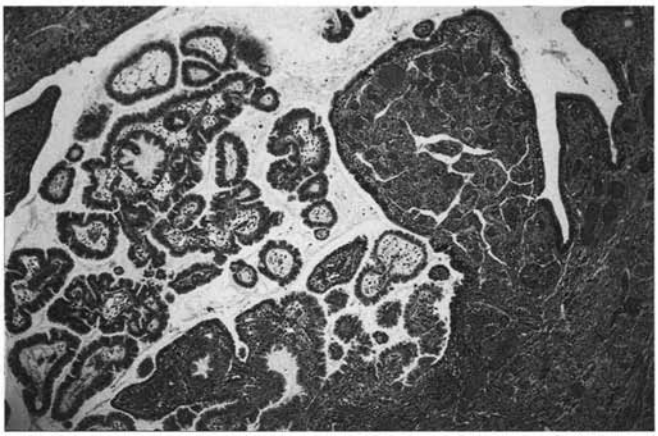


Fig. 43. Metaplastic papillary tumor. Papillae and cellular buds composed of cells with abundant eosinophilic cytoplasm.

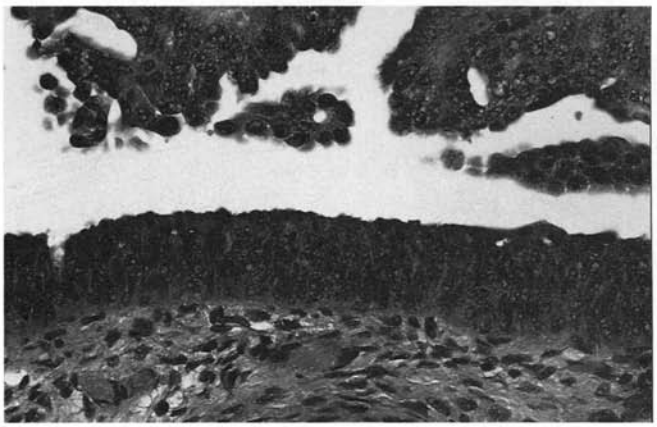


Fig. 44. Carcinoma in situ of the fallopian tube.

Adenofibroma and Cystadenofibroma

- Rare, majority are incidental findings
- Round solitary mass (0.5 – 3 cm.)
- Intraluminal or attached to the fimbriated end or serosal surface
- Connective tissue stroma and papillary structures or tubal structures lined by epithelial cells, usually serous type

Metaplastic Papillary Tumor

Clinical

- Uncommon, usually an incidental finding in segments of fallopian tube removed during post partum for sterilization
- Only rarely occurs in women who are not recently pregnant

Microscopic

- Variable sized papillae covered by cells with abundant eosinophilic cytoplasm, showing cellular budding **(Figure 43)**
- Some cells may contain intracellular mucin, and extracellular mucin may be abundant
- Mitotic figures are rarely observed

Endometrioid Polyp

Clinical

- Also referred to as adenomatous polyp
- May obstruct the lumen and result in infertility or tubal pregnancy

Macroscopic

- Most not recognized grossly, but can measure ~1 cm

Microscopic

- Occur in the interstitial portion of the fallopian tube
- Often attached to the tubal epithelium by a broad base, resembling endometrial polyps
- Are frequently associated with mucosal endometriosis

Carcinoma In Situ

- Not detected on macroscopic examination
- The tubal epithelium is replaced by cytologically malignant glandular epithelial cells with pleomorphic nuclei **(Figure 44)**
- Loss of polarity of the epithelial cells and form papillae without stromal cores
- Numerous mitoses are present
- Florid epithelial proliferation associated with salpingitis should not be mistaken for carcinoma in situ

Borderline Epithelial Tumors

- Rare; include serous, mucinous and endometrioid types
- Borderline serous tumors involve the tube, including the fimbriated portion, and resemble those of the ovary
- Mucinous tumors can be associated with mucinous metaplasia of the fallopian tube or Peutz-Jegers syndrome
- In patients with multiple organ involvement or pseudomyxoma peritonei, a metastatic lesion to the tube should be excluded
- Long term follow up is limited, but the prognosis appears to be favorable

Malignant Epithelial Tumors

Clinical

- Uncommon; 0.2%–0.5% of primary genital malignancies
- Usually postmenopausal, sixth or seventh decade
- Some patients harbor a *BRCA1* germline mutation
- Classic signs and symptoms include vaginal bleeding, clear or serosanguinous vaginal discharge, pelvic pain and pelvic mass
- Diagnosis is rarely made before operation

- Positive cytology associated with a negative endometrial curettage may suggest a tubal location

Macroscopic

- Swollen secondary to intraluminal growth
- Lumen filled and dilated by papillary or solid tumor
- Frequently bilateral

Microscopic

- All carcinoma subtypes documented in the ovaries have been identified in the fallopian tube
- Serous carcinoma is the most common subtype, comprising ~70% of cases; endometrioid and transitional cell types ~10% each
- Serous carcinomas resemble their ovarian counterparts with papillary cellular buds, slit-like, slender spaces, solid sheets and psammoma bodies **(Figure 45)**
- May be associated with contiguous in situ carcinoma
- Synchronous mucinous primaries have been described in the tube and endocervix

Differential Diagnosis

- Tubal extension by primary uterine or ovarian carcinoma:

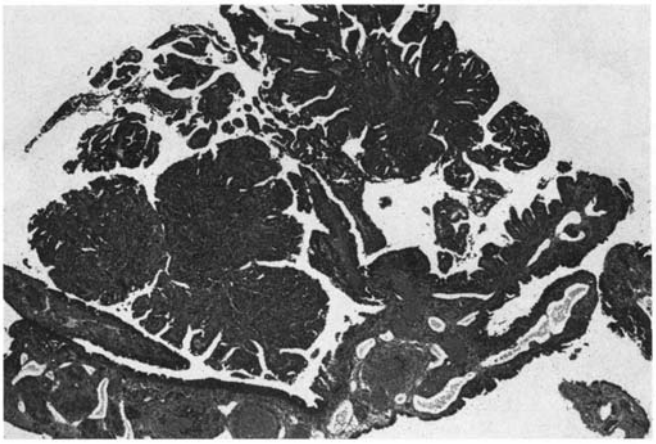


Fig. 45. Primary tubal serous carcinoma.

  - In order to be considered a primary carcinoma of fallopian tube the tumor must be located macroscopically within the tube or its fimbriated end, and the uterus and ovaries must either not contain carcinoma or if they do, it must be different from the fallopian tube lesion

MIXED EPITHELIAL MESENCHYMAL TUMORS

Carcinosarcoma (Malignant Mixed Mesodermal Tumor)

Clinical

- Rarely primary in the fallopian tube
- Almost always postmenopausal
- May present with abdominal pain, abnormal vaginal bleeding or abdominal distention
- Poor prognosis

Macroscopic

- Distended tube
- Usually evidence of extension to adjacent pelvic and abdominal structures

Microscopic

- Admixture of histologically malignant epithelial and mesenchymal elements

MESENCHYMAL TUMORS

Leiomyoma

- Uncommon in the fallopian tube
- May originate from the tubal muscularis, from smooth muscle of the broad ligament or from walls of blood vessels
- Histologically similar to those found in the uterus, and can also undergo similar degenerative changes

Leiomyosarcoma

- Primary sarcomas of the fallopian tube are extremely rare; leiomyosarcoma is the most common type

Mesothelial Tumors

Adenomatoid Tumor

Clinical

- Most frequent type of benign tubal tumor
- Usually found as an incidental finding

- Rarely bilateral
- Presumed mesothelial derivation

Macroscopic

- 1–2 cm nodular swelling beneath the tubal serosa
- Yellow or whitish gray on section

Microscopic

- Multiple, small, slit-like or ovoid spaces lined by single layer of low cuboidal or flattened epithelial-like cells **(Figure 46)**
- May infiltrate into the stroma of the luminal folds

Differential Diagnosis

- Infiltrating adenocarcinoma

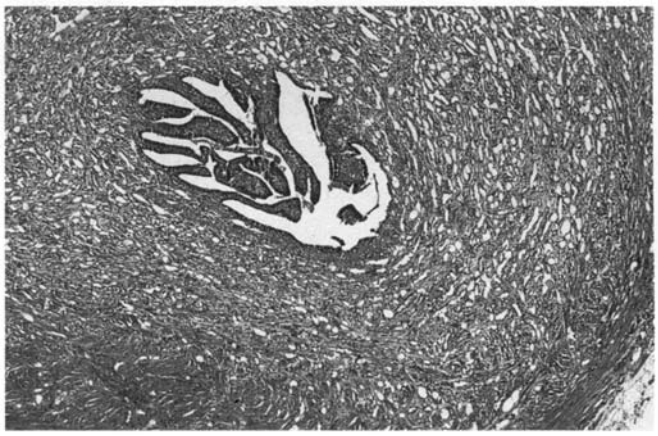


Fig. 46. Adenomatoid tumor. Multiple small, slitlike spaces proliferate in the wall of the tube.

GERM CELL TUMORS

Teratoma

Clinical

- Rare; usually nulliparous and in the fourth decade
- Majority are mature

Macroscopic

- Most frequently intraluminal, attached by a pedicle to the tubal wall; but may be intramural or attached to the serosa
- Size ranges from 1–20 cm
- On cut section most often cystic than solid

Microscopic

- Similar to their ovarian counterparts
- Mixture of well-differentiated mature ectodermal, mesodermal and endodermal tissues

TROPHOBLASTIC DISEASE

- Placental site nodule
- Hydatiform mole
- Placental site trophoblastic tumor
- Choriocarcinoma

LYMPHOID AND HEMATOPOETIC TUMORS

- Tubal involvement by lymphoma is rare
- Almost always associated with simultaneous involvement of the ipsilateral ovary
- Most often by Burkitt or Burkitt-like lymphoma or diffuse large cell lymphoma

SECONDARY TUMORS

- Usually secondary to spread from carcinomas of the ovary or endometrium; in most cases by direct extension
- Much more common than primary tubal carcinoma
- Blood-borne metastasis from breast carcinoma or other extrapelvic tumors may also occur

TUMORS OF THE UTERINE LIGAMENTS

- Benign and malignant tumors that arise in the broad ligament and other uterine ligaments

Epithelial Tumors of Müllerian Type

- Most frequent neoplasms of the broad and other ligaments
- Tumors of every Müllerian cell type and of every degree of malignancy can occur, but are infrequent compared to their occurrence in the ovary

Miscellaneous Tumors

Wolffian Adnexal Tumor

Clinical

- Rare; <50 examples described
- Tumor of presumptive Wolffian origen
- Age range 15–81 years
- Most present with a unilateral mass
- Occur mainly in the broad ligament, but also in the mesosalpinx, serosa of the fallopian tube, ovary and retroperitoneum

Macroscopic

- Solid; range in size from 0.5–18 cm
- Firm to rubbery, yellow-tan to gray-white cut surface with variably sized cysts

Microscopic

- Characterized by a variety of epithelial patterns
- Solid masses of epithelial cells may be present, or tubular areas similar to a well-differentiated Sertoli-Leydig tumor of the ovary

Other Tumors of the Uterine Ligaments

- Leiomyoma
- Papillary cystadenoma associated with von Hippel-Lindau disease

TNM CLASSIFICATION AND FIGO STAGING SYSTEM FOR FALLOPIAN TUBE CARCINOMA

- T: Primary tumor:
  - TX: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - Tis: Carcinoma in situ (limited to tubal mucosa)
  - T1(I): Tumor limited to fallopian tube(s):
    - T1a(IA): Tumor limited to one tube without penetrating the serosal surface; no ascites
    - T1b(IB): Tumor limited to both tubes without penetrating the serosal surface; no ascites
    - T1c(IC): Tumor limited to one or both tube(s) with extension onto or through the tubal serosa, or with malignant cells in ascites or peritoneal washings
  - T2(II): Tumor involves one or both fallopian tube(s) with pelvic extension:
    - T2a(IIA): Extension and/or metastasis to uterus and/or ovaries
    - T2b(IIB): Extension to other pelvic tissues
    - T2c(IIC): Pelvic extension (T2a or T2b/IIA or IIB) with malignant cells in ascites or peritoneal washings
  - T3 and/or N1(III): Tumor involves one or both fallopian tube(s) with peritoneal implants outside pelvis and/or positive regional lymph nodes:
    - T3a(IIIA): Microscopic peritoneal metastasis outside the pelvis
    - T3b(IIIB): Macroscopic peritoneal metastasis outside the pelvis 2 cm or less in greatest dimension
  - T3 and or N1(IIIC): Peritoneal metastasis more than 2 cm in greatest dimension and/or positive regional lymph nodes
  - M1(IV): Distant metastasis (excludes peritoneal metastasis)
- N: Regional Lymph Nodes:
  - NX: Regional lymph nodes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis
- M: Distant Metastasis:
  - MX: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

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26

Ovary and Peritoneum

Kevin J. Wu, MD
and Gary L. Keeney, MD

CONTENTS

I. Ovary 26-3
General 26-3
Inflammatory Lesions 26-3
Benign Ovary 26-3
Gonadal Dysgenesis/Abnormalities of Sexual Development 26-3
Adrenal Cortical Rest 26-4
Ectopic/Supernumerary Ovary 26-4
Ovarian Remnant Syndrome 26-4
Follicle Cysts 26-4
Polycystic Ovarian Disease (POCD)/Multiple Fllicular Cysts/ Stein-Leventhal Syndrome 26-4
Large Solitary Luteinized Follicle Cyst of Pregnancy and Puerperium 26-5
Corpus Luteoma/Corpus Luteum Cyst 26-5
Hyperreactio Luteinalis (Multiple Luteinized Follicle Cysts) 26-5
Pregnancy Luteoma 26-5
Epithelial Inclusion Glands/Cyst in Ovarian Cortex 26-6
Surface Nodular/Papillary Stromal Proliferation 26-6
Cortical Granuloma (Hyaline Scar) 26-6
Stromal Hyperplasia (Hyperthecosis, Diffuse Thecomatosis) 26-6
Stromal/Hilar Leydig Cell Hyperplasia 26-6
Granulosa Cell Proliferation 26-6
Ectopic Decidual Reaction 26-6
Rete Ovarii (Rete Adenoma/Cyst) 26-6
Massive Ovarian Edema 26-7
Ovarian Fibromatosis 26-7
Endometriosis 26-7
Neoplasms of Ovary 26-8
Surface Epithelial Stromal Tumor 26-8
Serous Tumors 26-9
Serous Psammocarcinoma 26-11
Mucinous Tumors 26-11
Endometrioid Tumors 26-12
Malignant Mixed Müllerian Tumors 26-13
Clear Cell (Mesonephroid) Tumors 26-13
Transitional Cell Tumors 26-14
Brenner Tumors 26-14
Atypical Proliferating Brenner Tumor 26-15
Malignant Brenner Tumor 26-15
Transitional Cell Carcinoma (TCC) 26-15
Germ Cell Tumors 26-15
Dysgerminoma 26-15
Yolk Sac Tumors (Endodermal Sinus Tumors) 26-16
Embryonal Carcinoma 26-16
Polyembryoma 26-16
Choriocarcinoma 26-16
Teratoma 26-17
Struma Ovarii 26-17
Carcinoids 26-18
Sex Cord Stromal Tumors 26-18
Granulosa Cell Tumors 26-18

Adult-type Granulosa Cell 26-18
Juvenile Granulosa Cell Tumors 26-19
Fibrothecoma/Thecoma.....26-19
Fibroma 26-19
Sclerosing Stromal Tumor 26-20
Sertoli-Leydig Cell Tumors (Androblastoma, Arrehenblastoma).....26-20
Gynandroblastoma 26-21
Sex Cord Tumor with Annular Tubules 26-21
Ovarian Tumors of Wolffian Origin 26-21
Lipid (Steroid) Cell Tumor 26-21
Stromal Luteoma.....26-21
Other Tumors 26-21
Myxoma 26-21
Gonadoblastoma (Dysgenetic Genadoma) 26-21
Metastatic Tumors.....26-22
Lymphoma/Leukemia 26-22
Small Cell Carcinoma.....26-22
Hepatoid Carcinoma 26-22

II. Peritoneum 26-22

General 26-22
Inflammation 26-22
Peritonitis 26-22
Mesothelial Hyperplasia and Metaplasia 26-23
Mesothelial Metaplasia 26-23
Cysts.....26-23
Pseudocysts.....26-23
Solitary Cysts 26-23
Cystic Lymphangioma..... 26-23
Endometriosis/Endometriotic Cyst.....26-23
Cyst of Müllerian Origin 26-23
Neoplasms of Serous Membrane 26-23
Solitary Fibrous Tumor.....26-23
Adenomatoid Tumor.....26-23
Multilocular Peritoneal Inclusion Cysts (Multicystic Benign Mesothelioma) 26-23
Primary Serous Papillary Carcinoma of Peritoneum 26-24
Malignant Mesothelioma 26-24
Intra-Abdominal Desmoplastic Small Round Cell Tumor 26-24
Miscellaneous Lesions of Peritoneum 26-25
Endosalpingiosis.....26-25
Infarcted Appendix Epiploica.....26-25
Leiomyomatous Peritonealis Disseminata 26-25
Inflammatory Pseudotumor/ Myofibroblastic Tumor 26-25
Walthard Nest 26-25
Urachal Remnant 26-25
Endocervicosis 26-25
Tailgut Cyst (Retrorectal Cystic Hamartoma) 26-26
Necrotic Pseudoxanthomatous Nodule 26-26
Ectopic Decidual Reaction 26-26
Metastatic Tumors 26-26
Pseudomyxoma Peritonei 26-26

III. TNM (FIGO) Classification of Ovarian Carcinoma (2002) 26-26

IV. Suggested Reading.....26-26

OVARY

General

Mesodermal Origin Except Germ Cell Component (Endodermally Derived)

Macroscopic

- Outer cortex, inner medulla, hilus, cystic follicles, corpora lutea, corpora albicantia
- Adult premenopausal ovaries vary from 3–5 cm in greatest dimension
- Average weight during reproductive years is 5–8 g

Microscopic

- Surface epithelium (germinal epithelium):
  - Continuous with peritoneal mesothelium
- Stroma: cortex and medullary regions:
  - Spindle-shaped cells
  - Luteinized cells
  - Adipose cells
  - Neuroendocrine cells
- Germ cells: primordial follicles:
  - Primary
  - Secondary
  - Tertiary
  - Graffian follicles
  - Oocytes
  - Granulosa cells
  - Internal and external theca cell layers
  - Leydig cells
  - Rete ovarii

Inflammatory Lesions

Bacterial Infections

- Often related to pelvic inflammatory diseases with subclinical infections common
- Neisseria, chlamydia, and coliform bacteria most common
- Often secondary to salpingitis
- May lead to tubo-ovarian abscesses, tubo-ovarian cysts, fibrous adhesions, hydrosalpinx, or pyosalpinx

Uncommon Infections

- Actinomycosis: associated with intrauterine devices (IUDs); branching gram + filamentous rods, sulfur granules
- Syphilis
- Schistosomiasis
- Enterobius vermicularis
- Tuberculosis
- Cytomegalovirus: intranuclear/cytoplasmic inclusions
- Mumps oophoritis
- Malacoplakia: Michaelis-Gutmann bodies
- Echinococcus
- Fungi: blastomycosis, coccidiomyocosis, aspergillus
- Mycobacterium leprae (leprosy)

Noninfectious Granulomatous Inflammation

- Foreign body granulomas:
  - Secondary to starch granules
  - Contrast material
  - Keratin (ruptured dermoid cysts)
  - Free bowel contents
- Systemic disease:
  - Sarcoidosis
  - Crohn's disease: due to direct extension of bowel inflammatory process
  - Cortical granulomas: see later

Miscellaneous Inflammatory Lesions

- Xanthogranulomatous oophoritis:
  - Foamy macrophages
  - Plasma cells
  - Lymphocyte infiltrate secondary to chronic ovarian abscess
- Autoimmune oophoritis:
  - Plasma cells and lymphocytes around developing ovarian follicles:
    - Associated with other autoimmune phenomena such as Addison's disease, diabetes, hypothyroidism, pernicious anemia, and others
- Giant cell arteritis

Benign Ovary

Gonadal Dysgenesis / Abnormalities of Sexual Development

- Testicular feminization:
  - XY males with end organ testosterone receptor defects:
    - Cryptorchid testes, vagina, no uterus
    - Increased risk of testicular malignancy
- Kleinfelter's 47, XXY
- Turner's syndrome:
  - 45, XO
  - 45, XX/XO mosaic
- Streak gonads: increased incidence of gonadoblastoma
- Hermaphroditism

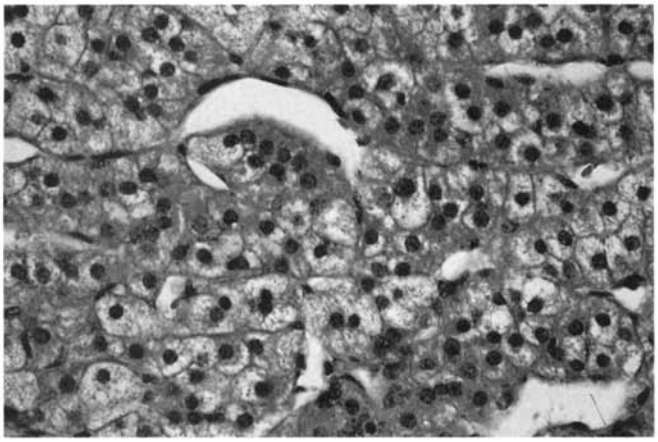


Fig. 1. Adrenal cortical rest.

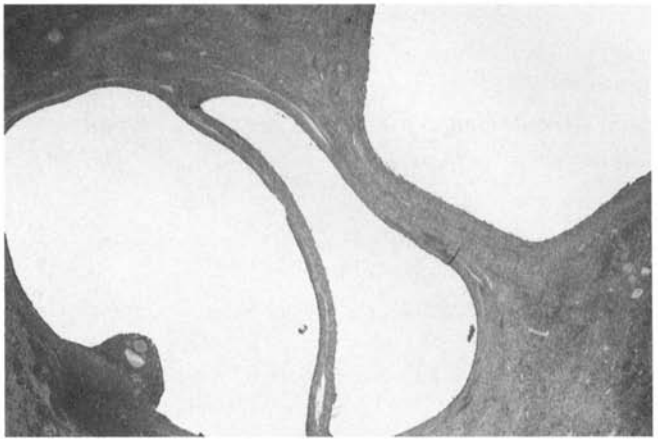


Fig. 2. Cystic follicles.

Adrenal Cortical Rest

- Small round yellow mass in ovary or fallopian tube (more common)
- Nests of adrenal-type cells with foamy cytoplasm (**Figure 1**)

Ectopic/Supernumerary Ovary

- Ovarian tissue located away from normal ovary
- Sites include pelvis, bladder, retroperitoneal, periaortic, and mesentery
- May be multiple or bilateral
- Associated with other genitourinary disorders
- Differentiate from accessory ovary (ovarian tissue immediately adjacent or connected to the native ovary)

Ovarian Remnant Syndrome

- Associated with previous oophorectomy (often bilateral) complicated by pelvic adhesions
- Cyclic pelvic pain
- May have elevated follicle-stimulating hormone (FSH) and Leutenizing hormone (LH) levels despite prior oophorectomy
- Abdominal exploration may reveal cystic mass adherent to pelvic sidewalls and intra-abdominal organs
- Ovarian tissue present histologically

Follicle Cysts

Clinical

- Common after menarche
- Seen in childhood to menopause
- May be seen in cases of precocious puberty
- Benign

Macroscopic

- Corpus follicle:
  - Physiologic secondary ovarian follicle <1 cm
- Cystic follicle (**Figure 2**):
  - Physiologic secondary follicle 1–3 cm in size
- Follicular cyst:
  - Unilocular smooth-walled cyst or cysts 3–10 cm
- Associated with metrorrhagia and endometrial hyperplasia

Microscopic

- Cyst wall lined by inner theca layer and outer granulosa layer

Differential Diagnosis

- Surface epithelial inclusion cyst:
  - Flattened epithelium and/or tubal metaplasia
- Epidermoid cyst:
  - Squamous epithelium
  - Considered monodermal teratoma
- Endometriosis:
  - Endometrial stroma and glands with hemorrhage
- Unilocular cystic granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves, granulosa cells

Polycystic Ovarian Disease (POCD)/Multiple Follicular Cysts/Stein-Leventhal Syndrome

Clinical

- Young women presenting with symptoms/signs of ovarian failure:
  - Oligomenorrhea or amenorrhea
  - Infertility
  - Hirsutism
- Incidence in up to 7% of women
- Dysregulation of ovarian 17-hydroxylase, 11 beta-hydroxylase, and C-17,20 lyase described
- Associated with hypothyroidism in some

- Responds to hormonal therapy:
  - Oophorectomy no longer treatment of choice
- Endometrium may be weakly proliferative or show cystic atrophy, atypical hyperplasia, or well-differentiated carcinoma

Macroscopic

- Normal to slightly enlarged ovaries
- Multiple cysts usually <1 cm
- Often no coropora lueta or follicular cysts

Microscopic

- Fibrous hypocellular ovarian cortex
- Multiple cysts with inner layer(s) of nonluteinized granulosa cells and prominent outer layer of luteinized theca cells
- Hyperthecosis often present
- Primordial follicles can be identified

Differential Diagnosis

- Chronic anovulation
- Hypothalamic-pituitary axis disorders

Large Solitary Luteinized Follicle Cyst of Pregnancy and Puerperium

Clinical

- Palpable adnexal mass
- Seen in pregnancy:
  - Related to human chorionic galadotropin (hCG) stimulation
- No associated clinical endocrine abnormalities

Macroscopic

- Grossly resembles follicular cyst except cyst may be large (>25 cm)

Microscopic

- Single to multiple layers of luteinized cells and/or focal atypia

Differential Diagnosis

- Unilocular cystic granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves, no luteinization

Corpus Luteoma/Corpus Lutuem Cyst

Clinical

- Most common during reproductive years
- Rarely reported to be seen at birth
- Rare rupture with hemoperitoneum

Macroscopic

- Often yellow coloration of cyst wall and/or hemorrhage
- Corpus luteum/cystic corpus luteum 1–2.5 cm (physiologic)
- Corpus luteum cyst >2.5 cm

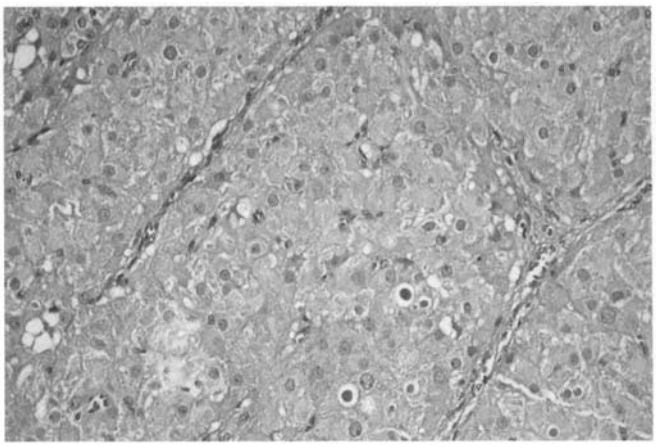


Fig. 3. Corpus luteum of pregnancy.

Microscopic

- Physiologic cyst lined by luteinized granulosa cells and theca layer and/or hemorrhage and central necrosis

Treatment

- None
- Commonly removed for suspicious cystic adnexal mass

Hyperreactio Luteinalis (Multiple Luteinized Follicle Cysts)

- Enlarged ovaries with multiple luteinized follicles and stromal edema
- Due to hCG stimulation
- Common with hydatidiform mole; also described in choriocarcinoma and twin pregnancies
- Usually regresses after pregnancy or treatment of gestational disease

Pregnancy Luteoma

Clinical

- Adnexal mass during pregnancy
- Benign, regresses after pregnancy
- Related to hCG stimulation
- No association with gestational trophoblastic disease

Macroscopic

- Bilateral, multifocal nodule

Microscopic ***(Figure 3)***

- Coalescing masses of luteinized cells
- May represent an exaggerated luteinization of pre-existing stromal hyperthecosis

Differential Diagnosis

- Steroid cell tumor (stromal luteoma and Leydig cell tumor)

Epithelial Inclusion Glands/Cyst in Ovarian Cortex

Clinical

- Occurs at any age but most common in older women
- Occasionally seen in infants and children
- Often incidental finding

Macroscopic

- Multiple small thin-walled cysts in ovarian cortex
- Usually <1 cm:
  - Most are identified only microscopically

Microscopic

- Thin-walled cysts lined by attenuated to slightly columnar epithelium
- Epithelium may show tubal metaplasia or rare psamomma bodies

Differential Diagnosis

- Endometriosis:
  - Endometrial glands and stroma, hemorrhage
- Surface epithelial tumors:
  - Epithelial atypia and stratification

Surface Nodular/Papillary Stromal Proliferation

- Most commonly seen in older women
- Hyalinized ovarian stroma with overlying single layer of benign surface epithelium producing a small nodular surface protuberance (**Figure 4**)
- No clinical significance

Cortical Granuloma (Hyaline Scar)

- Common incidental finding in peri/postmenopausal women
- Pathogenesis unknown
- No known clinical significance

Stromal Hyperplasia (Hyperthecosis, Diffuse Thecomatosis)

Clinical

- May present as virilization with/without steroidogenic effects such as obesity, hypertension, diabetes, and so forth
- More resistant to treatment than POCD; may require oophorectomy

Macroscopic

- Nodularity or enlargement of both ovaries
- Stromal thecomas or luteomas may also be present

Microscopic

- Bilateral nodular to diffuse proliferation of ovarian stromal cells and/or luteinization

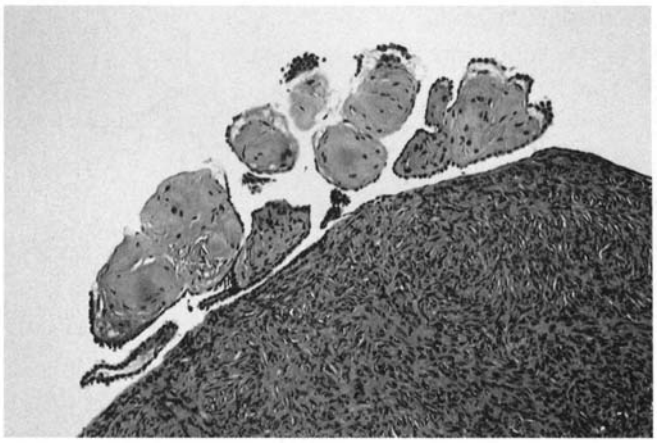


Fig. 4. Surface papillation.

Differential Diagnosis

- Polycystic ovarian disease:
  - Multiple follicle cysts
- Thecoma/fibroma:
  - Unilateral distinct mass

Stromal/Hilar Leydig Cell Hyperplasia

Stromal Leydig Cell Hyperplasia

- Microscopic aggregates of Leydig cells with Reinke crystalloids in ovarian stroma often showing changes of hyperthecosis

Hilar Leydig Cell Hyperplasia

- Nodular aggregates of hilar Leydig cells seen during pregnancy and sometimes in postmenopausal women
- Stromal hyperthecosis or hilar cell tumor may be present

Granulosa Cell Proliferation

- Focal proliferation of granulosa cells found incidentally in ovary
- Associated with pregnancy
- Differential includes adult granulosa cell tumor: forms a mass; majority occur in postmenopausal patient

Ectopic Decidual Reaction

- May occur in ovary during pregnancy
- Corpus luteum usually present in one ovary

Rete Ovarii (Rete Adenoma/Cyst) (Figure 5)

- Benign
- Female analogue of rete testis in male
- Found in hilus of all ovaries
- Cords, tubules, and cysts lined by flat to columnar epithelium with smooth muscle bundles
- May form small nodules (rete adenoma) or cysts

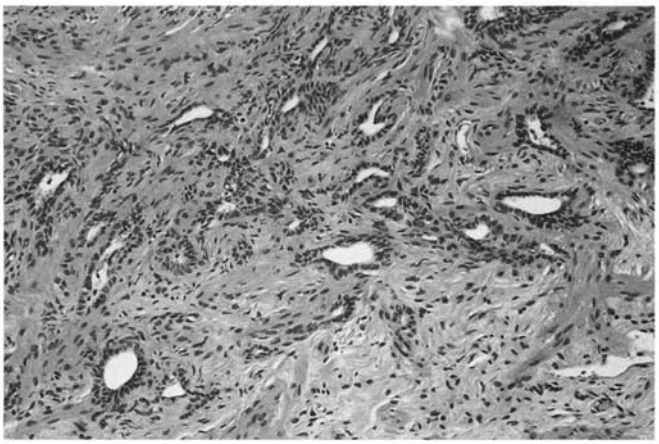


Fig. 5. Rete ovarii.

Massive Ovarian Edema

Clinical

- Young women ~20 years
- Pelvic/abdominal pain, and/or abdominal swelling
- Unilateral palpable adnexal mass
- Ovarian torsion present in 50% of cases
- Conservative treatment; may require oophorectomy

Macroscopic

- Enlarged soft, edematous ovary up to 35 cm
- White surface coloration with tan cut surface and "weeping fluid"

Microscopic

- Stromal edema surrounding ovarian follicles and/or focal necrosis

Differential Diagnosis

- Edematous fibroma: older patients
- Myxoma: rare; hypocellular without follicular derivatives

Ovarian Fibromatosis

Clinical

- Young women ~20–30s
- Abdominal pain, abnormal menses, usually unilateral adnexal mass

Macroscopic

- Enlarged, firm, solid ovary 6–12 cm
- White coloration

Microscopic

- Spindle cell proliferation with variable amounts of collagen surrounding follicles

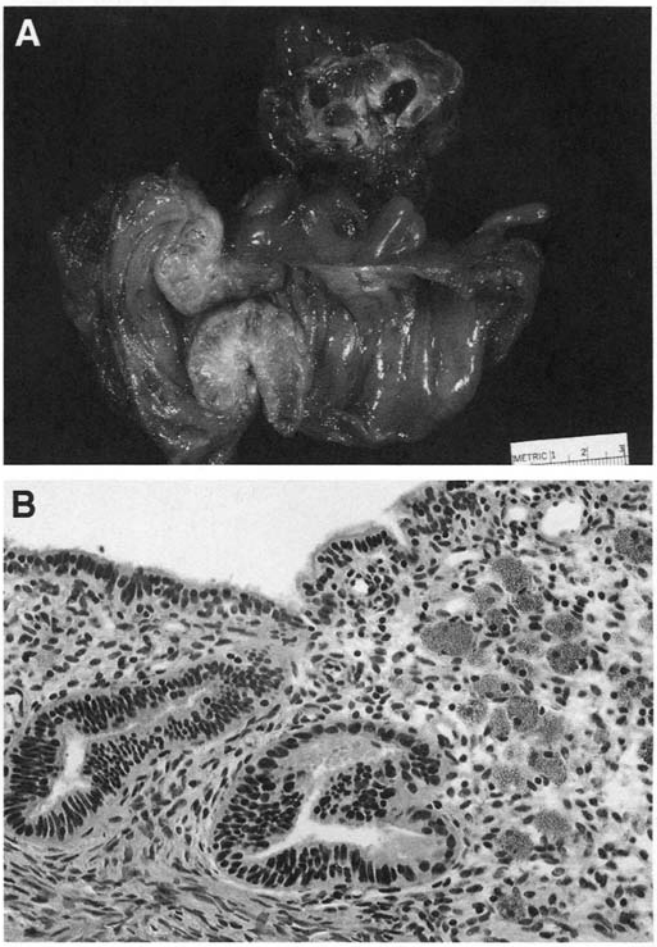


Fig. 6. Endometriosis **(A,B)** – endometriotic cysts are present in an adherent ovary (top) with involvement of the bowel wall seen as thickening of the muscularis.

Differential Diagnosis

- Fibroma: older patients, few ovarian follicles, rim of normal surrounding tissue

Endometriosis (Figure 6)

Clinical

- Women in reproductive years
- Ovary is the most common site of involvement
- Often present with pain and fertility problems
- May give rise to hyperplasia or carcinoma as in uterus
- Hormonal therapy is often initial treatment

Macroscopic

- Bluish-red macules on serosal surfaces or "chocolate cysts" in ovary

Microscopic

- Three components: endometrial type glands, endometrial stroma, and hemorrhage/hemosiderin-laden macrophages

Table 1. Immunohistochemical Profiles In Ovarian Neoplasms

	Keratin	*Vimentin*	*OCT4*	*AFP*	*Inhibin*	*CEA*	*HCG*
Serous Carcinoma	+	+	–	–	–/+	+/–	–
Endometriod Carcinoma	+	+/–	–	–	–	–/+	–
Mucinous Carcinoma	+	–	–	–	–	++	–
Dysgerminoma	–	–	+	–	–	–	+/–
Yolk sac	+	–	–	+	–	–	+
Embryonal	+	–	+	+	–	–	+
Granulosa cell	–/+	+	–	–	+	–	–
Sertoli-Leydig	+	–	–	–	+	–	–
Brenner	+	–	–	–	–	+	–
Clear cell	+	+	+ (focal)	–/+	+/–	+/–	–
Choricarcinoma	+	–	–	–	–/+	–	+
Fibrothecoma	–/+	+	–	–	+	–	–

Note: AFP = alpha fetoprotein; CEA = carcinoembryonic antigen; hCG = human chorionic gonadotropin.

Table 2. Summary of Surface Epithelial Tumors

	Incidence	*Relative size*	*Cell type*	*Squamous diff.*	*Psamomma*	*Bilaterality*
Serous	50% to 70%	Small-mod	Flat-cuboidal	Rare	30%	30% to 50%
Mucinous	15% to 25%	Large	Columnar	Rare	Rare	10% to 20%
Endometrioid	5% to 10%	Small-mod	Columnar	30%	Rare	10% to 30%

Neoplasms of Ovary (Table 1)

Surface Epithelial-Stromal Tumors (Table 2)

General

- 2/3 of all ovarian tumors; 90% of all malignant ovarian tumors
- Thought to originate from surface epithelial invaginations
- Tumor classification based on:
  - Cell type: serous, mucinous, endometrioid, undifferentiated, and so forth:
    - Tumors with multiple cell types comprising <10% should be classified under predominant cell type
  - And/or presence of prominent fibrous stromal component
  - Pattern of growth: exophytic tumors = "surface," cystic, papillary, combination
  - Presence/absence of invasion: benign, borderline (see below), malignant

Borderline Surface Tumors of the Ovary

- Atypical proliferating, of low malignant potential
- Show intermediate features between benign and malignant neoplasms
- Epithelial proliferation greater than that in benign tumors
- Cellular stratification with epithelial budding and tufting:
  - Cellular buds may appear detached from lining
  - May have cribriform patterns
  - Mild-moderate nuclear atypia
  - Mitotic figures rare to prominent
- No widespread destructive stromal invasion:
  - Rare lymphatic metastases
  - May have "implants" (see below in section on borderline tumors)
- Benign and borderline tumors generally diploid; carcinomas aneuploid

- Prognosis generally good even with advanced disease (similar to benign serous tumors); some, however, may kill patient; typically, long clinical course (bowel obstruction, etc.)
- Differential Diagnosis:
  - Low-grade ovarian carcinomas: absence of destructive stromal invasion helps distinguish borderline tumors from low-grade carcinomas

Treatment

- Benign and most borderline ovarian tumors:
  - Benign course
  - Benign tumors treated by unilateral salpingo-oophorectomy alone to preserve fertility in young patients
  - Borderline tumors in the past were treated by salpingo-oophorectomy; many now treated similar to benign tumors (dependent on stage)
  - Adjuvant therapy controversial
- Carcinomas:
  - Many cases advanced with poor outcome
  - Treated by hysterectomy and bilateral salpingo-oophorectomy with surgical staging by biopsy of pelvic, peritoneal, diaphragmatic, omental surfaces and lymph nodes (pelvic and retroperitoneal)
  - Peritoneal washings for cytologic examination also routinely performed
  - Adjuvant therapy with chemotherapeutic agents and radiation given for high-stage or high-grade lesions
  - Serum marker CA125 found to be elevated in malignancies and particularly useful in following patients for recurrence of ovarian neoplasms

Prognosis

- Poor prognosis of ovarian carcinomas overall due to patients presenting with advanced disease due to lack of symptoms early in disease
- 5-year survival rate overall <30%
- Factors adversely influencing survival include:
  - Older age: more likely to have higher grade/stage lesions
  - Clinical stage
  - Tumor grade
  - DNA ploidy of tumor: aneuploid tumors more aggressive than diploid tumors
  - Presence of ascites
  - Overexpression of p53 and HER-2/neu correlated with worse prognosis in some studies and no statistical differences in others

Serous Tumors

General

- Serous tumors account for ~50–70% of ovarian neoplasms
- Approximately 70% of serous tumors are benign, 25% are carcinomas, and 5% to 10% are borderline tumors

Benign Serous Tumors

Clinical

- May occur at any age with peak incidence around 50 years
- Adnexal mass

Macroscopic

- Predominantly unilateral (bilateral in 30% to 50% of cases)
- Unilocular thin-walled cyst, occasionally multilocular, 1–30 cm
- Thin watery to slightly viscous fluid
- Moderate size
- And/or small polypoid excrescenses

Microscopic

- Cysts and papillary fronds lined by stratified, cuboidal, columnar, or tubal epithelium
- ±Psamomma bodies (30%), usually inconspicuous
- ±Fibrous stroma

Variants

- Serous cystadenoma/papillary cystadenoma:
  - Endophytic growth pattern
- Serous surface papilloma:
  - Exophytic growth pattern
- Cystadenofibroma:
  - Cystic tumor with firm, hard nodules with fibrous stroma
- Adenofibroma:
  - Firm, solid tumor with fibrous stroma without prominent cysts
- Adenoacanthofibroma:
  - Squamous differentiation

Borderline Serous Tumors (Figure 7)

- Borderline serous tumors more likely to have slightly finer papillae and viscous fluid grossly
- More prominent epithelial proliferation/stratification and cellular atypia microscopically
- Absence of stromal invasion
- Up to 40% may have cystic/papillary serous lesions arising in omentum, lymph nodes, or pelvic organs (implants), which does not generally change prognosis (see exception below)
- Should be distinguished from endosalpingiosis or mesothelial hyperplasia
- Tumor implants may be noninvasive or invasive (worse prognosis): often difficult to distinguish:
  - Noninvasive implants that are more common are either epithelial (peritoneal surface) or desmoplastic (tumor cells with dense reactive stroma)

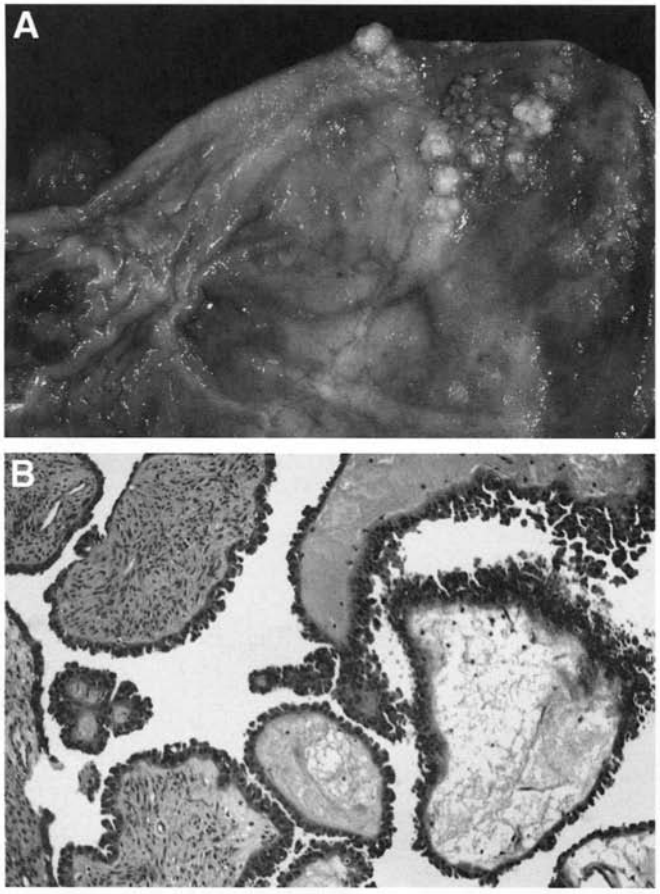


Fig. 7. Serous borderline tumor **(A,B)**.

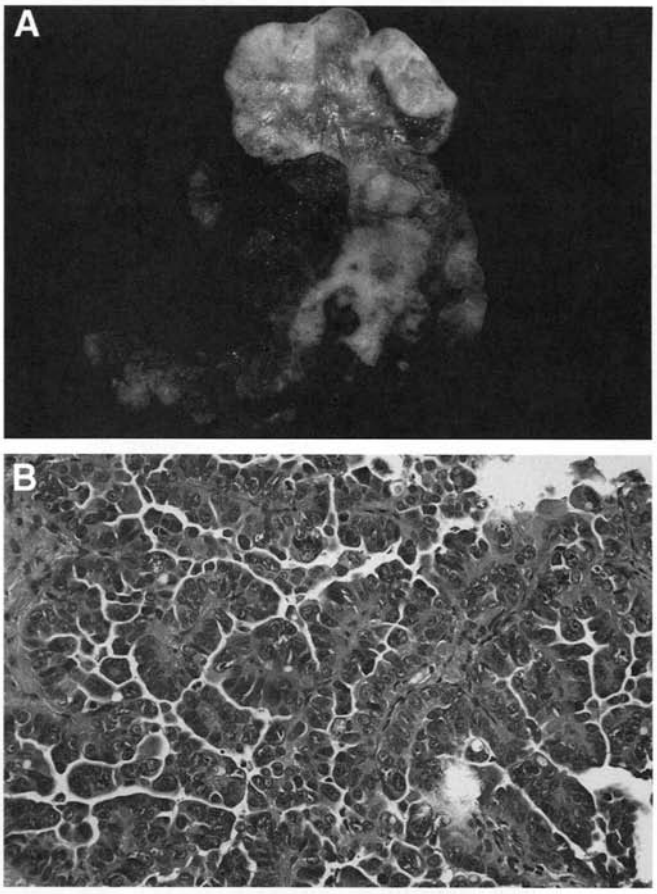


Fig. 8. Serous carcinoma replacing an ovary and involving adnexal tissue **(A,B)**.

- Both noninvasive types show sharp demarcation with tumor and stroma in contrast to invasive implants showing infiltration of adjacent tissue and often higher grade cytology
- Tumor classification based on primary tumor in ovary
- Tumors with invasive implants are more likely to have progression of disease than noninvasive implants

♦ Some borderline serous tumors may have areas of microinvasion of stroma in a background of typical borderline tumor:
- Characterized by papillary clusters, single eosinophilic neoplastic cells in papillae or cribriform clusters, or infrequently, lymphatic invasion
- Microinvasion should not exceed 3 mm (10 mm^2)
- Prognosis is similar to tumors without microinvasion

♦ A micropapillary growth pattern may portend a worse prognosis

Variants

♦ Borderline cystic tumor and papillary cystic tumor
♦ Borderline surface papilloma
♦ Borderline adenofibroma and cystadenofibroma

Differential

♦ Low-grade serous carcinoma: stromal invasion

Malignant Serous Tumors (Figure 8)

Clinical

♦ Occur at slightly older age than benign serous lesions, 50–60 years
♦ Bilateral ovaries in 2/3 of cases
♦ Most patients present with advanced stage disease

Macroscopic

♦ Any size from few millimeters to >20 cm
♦ Cystic, papillary with turbid and hemorrhagic fluid, necrosis
♦ Surface papillae may be present
♦ Psamomma bodies usually present ~70%

Microscopic

♦ Tumors with stromal invasion, nuclear atypia, numerous mitoses, and complex architectural features (slit-like glandular lumina, tight nests, etc.)

Variants

- Adenocarcinoma
- Papillary adenocarcinoma
- Papillary cystadenocarcinoma
- Adenocarcinofibroma and cystadenocarcinofibroma
- Surface papillary adenocarcinoma

Serous Psammocarcinoma

- Rare form of low-grade serous carcinoma typically involving peritoneum
- Appears to behave more like serous borderline tumors rather than serous cancer
- Four criteria necessary for diagnosis:
  - Invasion
  - Nuclear atypia
  - Solid epithelial nests <15 cells thick
  - Psamomma bodies in at least 75% of nests or papillae

Differential Diagnosis

- Mesothelioma:
  - No psamomma bodies or columnar epithelium
  - Presence of cytoplasmic neutral mucins (mucicarmine or PAS-D)
- Serous borderline tumor/carcinoma of peritoneal primary:
  - Extensive involvement of peritoneum with no or minimal involvement of ovaries

Mucinous Tumors

General

- 15% to 25% of ovarian tumors
- 85% of mucinous tumors are benign
- Bilateral in 10% to 20% of cases

Benign Mucinous Tumors

Clinical

- Adnexal mass
- Most frequent around 30–50 years (borderline mucinous tumors 40–70 years)
- Association with Brenner tumors, Peutz-Jehger's syndrome, pseudomyxoma peritonei (intestinal type), and teratoma

Macroscopic

- Tendency toward larger size when compared to serous tumors (up to 50 cm)
- Often multilocular with thin-walled cysts and thick mucinous fluid
- Papillations not a prominent feature

*Microscopic (**Figure 9**)*

- Cyst wall lined by columnar epithelium with basal nuclei similar to endocervix or intestinal-type lining

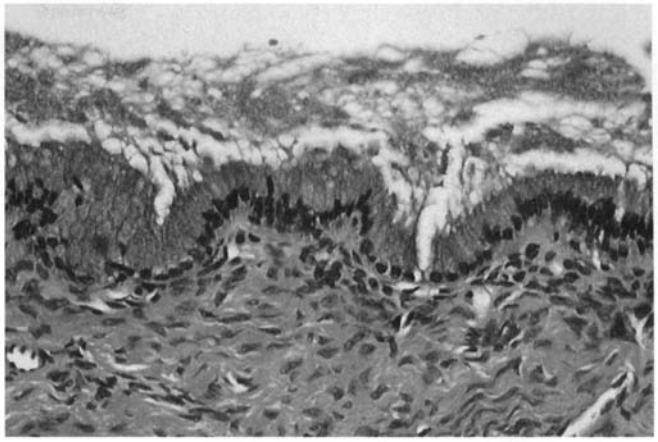


Fig. 9. Mucinous tumor, benign.

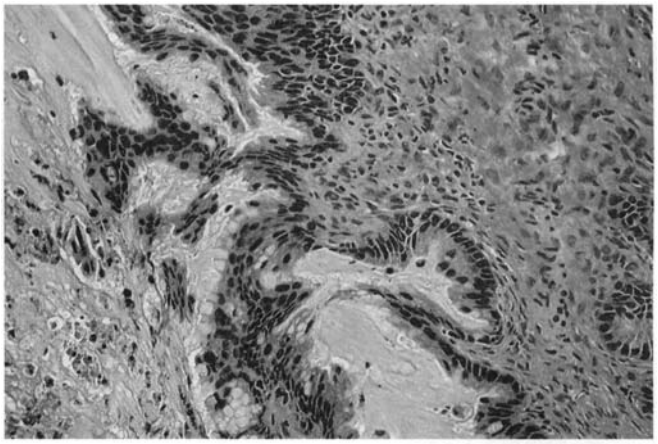


Fig. 10. Mucinous borderline tumor.

(borderline tumors) with occasional goblet cells, Paneth cells, or mixed types

- Stroma shows variable degrees of fibrous component, usually not prominent
- Minor nuclear atypia may be seen in mucinous tumors without other features of borderline tumors/carcinomas
- Some mucinous tumors may contain mural nodules that microscopically resemble high-grade sarcomas/carcinomas or have giant cells

Variants

- Mucinous cystadenoma
- Adenofibroma
- Cystadenofibroma

Borderline Mucinous Tumors

Clinical

- Peak incidence around 30 years

*Microscopic (**Figure 10**)*

- Greater epithelial proliferation than benign mucinous tumors

- Borderline tumors more likely to have solid areas or excrescences
- Lining epithelium more likely to be intestinal type (89%); müllerian (15%)
- Tumors of intestinal type associated with pseudomyxoma peritonei:
  - Müllerian type associated with extraovarian implants
- Some tumors may show foreign body giant cell reaction due to mucin extravasation
- Occasional cases show mural nodules containing numerous sarcoma-like osteoclast-type giant cells; should be differentiated from true sarcomas or poorly differentiated carcinomas that, unlike the former, carry a worse prognosis

Variants

- Borderline cystic tumor
- Borderline adenofibroma
- Borderline cystadenofibroma

Malignant Mucinous Tumors

Clinical

- Women 40–70 years
- 10% to 20% bilateral
- Pseudomyxoma peritonei:
  - Synchronous tumor of appendix usually identified
  - Consider metastasis if appendiceal primary present

Macroscopic

- Necrosis and hemorrhage more commonly associated with carcinoma
- Solid areas and mural nodules more common

Microscopic

- Malignant tumors show nuclear atypia, epithelial stratification, architectural complexity, and ± invasion
- CEA positivity seen in 100% malignant mucinous tumors as compared to 30% of endometrioid and serous types

Variants

- Adenocarcinoma
- Cystadenocarcinoma
- Adenocarcinofibroma
- Cystadenocarcinofibroma

Differential Diagnosis

- Endometrioid carcinoma:
  - Has only minor intracellular mucin and/or focal mucinous-type epithelium
  - Squamous differentiation favors endometrioid carcinoma
- Metastatic mucin-producing tumor:
  - Usually gastrointestinal primary
  - Mixture of borderline and benign components favors ovarian primary

Table 3. Colonic Versus Ovarian Carcinoma

*Tumor type**	*Cytokeratin 7*	*Cytokeratin 20*
Colonic	–	+
Ovarian	+	±

**See Table 30-6 for detailed description in other cancers*

- Cytokeratin may be useful in differentiating metastatic colon cancer from ovarian primary (see **Table 3**)

Endometrioid Tumors

Clinical

- 5% to 10% of ovarian neoplasms; account for 10% to 20% of ovarian carcinomas
- Most (>75%) are malignant with benign and borderline endometrioid tumors rare
- Origin in endometriosis seen in 10% of cases
- May be associated with independent uterine carcinoma or represent spread from uterus (33%)
- Most carcinomas are well-differentiated, low stage, with good prognosis

Macroscopic

- Solid and/or cystic mass
- Often hemorrhagic
- May grossly resemble adenofibromas

*Microscopic (**Figure 11**)*

- Tubular glands resembling endometrial adenocarcinoma/hyperplasia
- Pseudostratified, non-mucinous epithelium (rarely focal mucin)
- ±squamous differentiation (30%):
  - Usually benign
  - Occasionally malignant
- Secretory change may be present; not to be confused with clear cell carcinoma
- Adenofibroma-like stroma

Variants

- Benign:
  - Cystadenoma with squamous differentiation
  - Adenofibroma and cystadenofibroma ± squamous differentiation
- Borderline (rare):
  - Adenofibroma
  - Cystadenfibroma

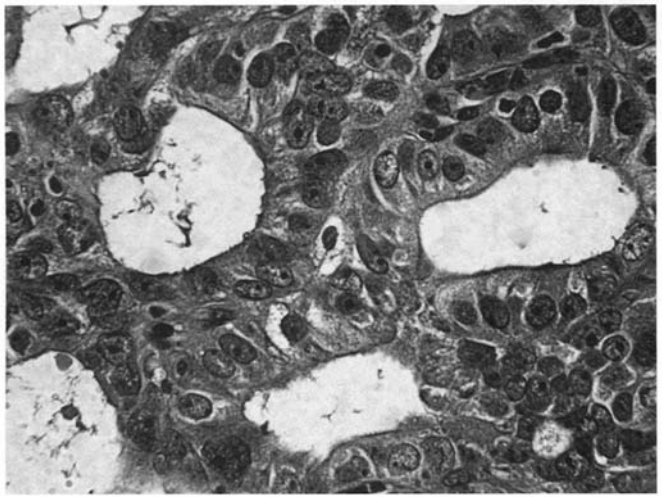


Fig. 11. Endometrioid carcinoma.

- Malignant:
  - Adenocarcinoma
  - Cystadenocarcinoma
  - Adenocarcinofibroma and cystadenocarcinofibroma
  - Endometrial stromal sarcoma
  - Mesodermal mixed tumors (carcinosarcoma)

Malignant Mixed Müllerian Tumors (Figure 12)

- Postmenopausal women
- Similar macro- and microscopic appearance as in uterus:
  - Heterologous type: malignant heterologous component (most commonly chondrosarcoma compared to rhabdomyosarcoma in uterus)
  - Homologous type: malignant epithelium and malignant stroma without specific features (carcinosarcoma)
- Stage most important but poor prognosis overall
- Differential includes malignant teratoma: younger patients, presence of immature neural and other germ cell components
- Mullerian adenosarcoma: malignant stroma and benign glandular component

Differential Diagnosis

- Poorly differentiated serous carcinoma
- Mucinous carcinomas:
  - Squamous differentiation favors diagnosis of endometrioid neoplasm
- Sertoli-Leydig cell tumors:
  - No squamous differentiation or true gland formation, less nuclear atypia and mitotic activity
- Metastatic adenocarcinoma:
  - Bilaterality. multiple tumor nodules, cribriform patterns with central necrosis, diffuse CEA positivity, lack of squamous differentiation and cytokeratin staining pattern (**Tables 26-3** and **25-6**)

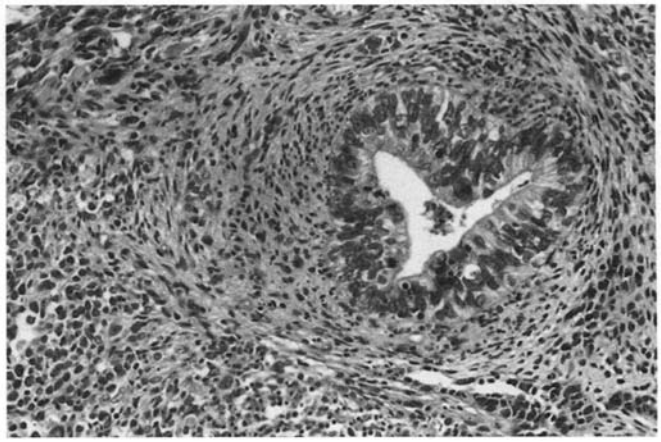


Fig. 12. Malignant mixed mullerian tumor.

- Clear cell carcinoma:
  - Hobnail pattern, prominent clear cell change

Clear Cell (Mesonephroid) Tumor

Clinical

- Uncommon (5% of ovarian tumors)
- Benign, borderline, and malignant categories
- Benign and borderline clear cell tumors are uncommon
- Most commonly occur in ages 50–70
- Usually unilateral, infrequently bilateral (<10%)
- Malignant clear cell carcinoma associated with pelvic endometriosis or endometriotic cyst
- Prognosis based on stage, similar to epithelial tumors

Macroscopic

- Gross resemblance to adenofibromas with white/yellow color and/or hemorrhage, necrosis; may be spongy or cystic
- Average diameter = ~15 cm
- Often unilocular thick-walled cyst with solid nodules in cyst wall
- Occasional tumors multilocular or solid neoplasms
- May arise in endometriotic cyst

Microscopic

- Clear cell adenofibroma:
  - Fibrous stroma with glands lined by flat to slightly hobnail cells and clear cells
- Clear cell carcinoma (**Figure 13**):
  - Fibrous stroma with prominent hobnail cells and clear cells
  - Complex papillae with hyalinized cords
  - Diffuse, tubulocystic, papillary, and trabecular patterns
  - Hyaline bodies may be present (25%)
  - Few to moderate mitoses
  - Often seen in association with endometrioid carcinoma

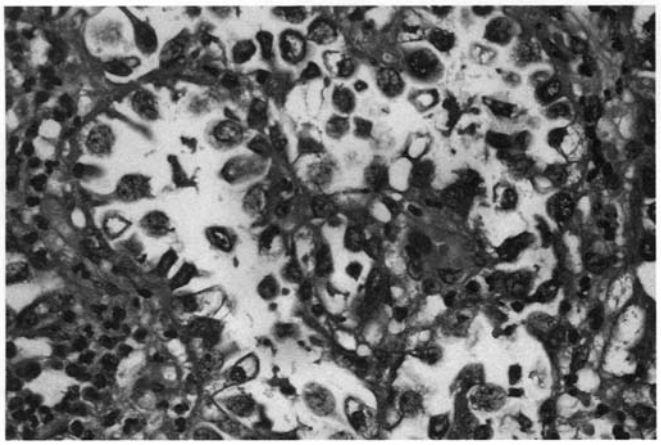


Fig. 13. Clear cell carcinoma.

Immunohistochemistry

- Keratin+, LEU-M1+, alpha-fetoprotein±

Variants

- Clear cell cystadenoma
- Adenofibroma and cystadenofibroma
- Borderline cystic tumor
- Borderline adenofibroma
- Cystadenofibroma adenocarcinoma
- Adenocarcinofibroma
- Cystadenocarcinofibroma

Differential Diagnosis

- Endometrioid adenofibroma/carcinoma: clear cell change not prominent, no hobnail cells
- Germ cell tumors (younger age, <20):
  - Yolk sac tumors: primitive nuclei, no hyaline papillary cores, strong AFP+
  - Dysgerminoma: lymphocytes present, no mucin
- Metastatic renal cell carcinoma:
  - Renal mass, bony metastases

Transitional Cell Tumors

Brenner Tumors (Figure 14)

Clinical

- <2% of all ovarian tumors
- Women 40–80 years old
- Slow-growing neoplasm, often incidental finding
- Associated with mucinous tumors
- Most are benign, with <2% borderline or malignant
- May have signs of estrogen hyperstimulation

Macroscopic

- Typically unilateral (6% bilateral) and small (<2 cm)

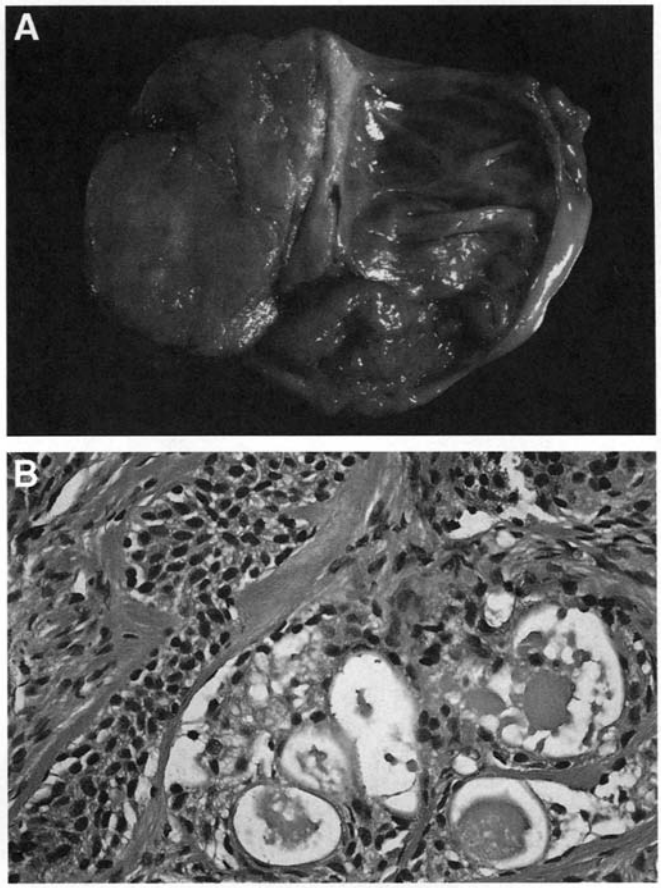


Fig. 14. Brenner tumor **(A,B)**.

- Predominantly solid, firm, white/yellow color resembling fibromas
- Small cysts with yellowish fluid
- ± calcifications
- May arise as solid nodule in mucinous cystadenoma

Microscopic

- Nests of bland round/polygonal cells surrounded by dense fibroblastic stroma
- Transitional cell-like cells with sharply defined borders, clear cytoplasm, and distinct nucleus with longitudinal groove (similar to Walthard nest)
- Abundant mucinous change and prominent cystic change without papillary fronds or nuclear atypia = metaplastic Brenner tumor

Immunohistochemistry

- Keratin+, glycogen + (PAS), EMA+, CEA+

Differential Diagnosis

- Low-grade stromal sarcoma:
  - Concentric pattern of cells around vessels

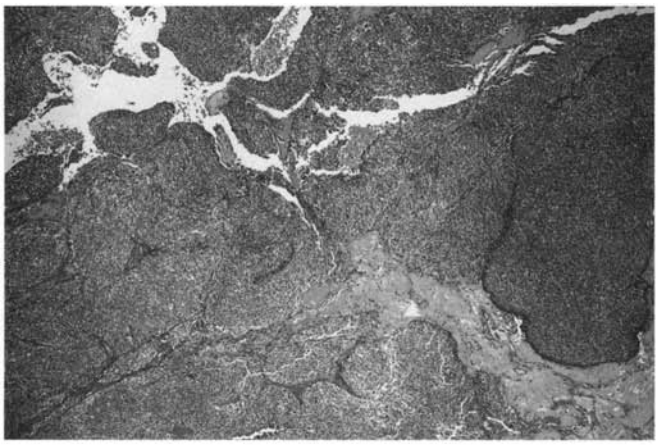


Fig. 15. Transitional cell carcinoma.

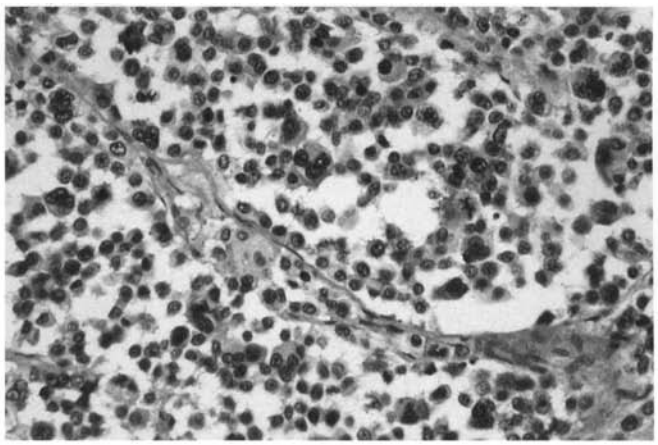


Fig. 16. Dysgerminoma.

- Thecoma/fibroma:
  - Fascicles of spindle cells with central nuclei and moderate pale cytoplasm, no clear cells
- Granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves
- Good prognosis for benign, metaplastic, proliferating, and borderline tumors

Atypical Proliferating Brenner Tumor

- Borderline Brenner tumors are typically a unilocular cyst to multilocular cyst with papillary nodules protruding into the cyst
- Rarely solid
- Histology similar to Grade 1–2 (of 3) papillary transitional cell carcinoma of the bladder
- No invasion

Malignant Brenner Tumor

- Brenner tumors with invasion and identifiable benign Brenner component

Transitional Cell Carcinoma (TCC) (Figure 15)

- Uncommon
- Solid or cystic
- Primary surface epithelial origin with histology similar to TCC at other sites
- Squamous or glandular differentiation common within tumor
- No identifiable benign Brenner component

Differential

- Metastatic transitional cell carcinoma of urinary tract:
  - Clinical history of invasive urinary tract TCC neoplasm
  - Bilateral ovarian involvement
  - May be more responsive to chemotherapy than surface epithelial cancers
  - Immunophenotypic differences of TCC of bladder origin (+cytokeratin 20, +/– cytokeratin 7, +Wilm's tumor protein –(WT1), +uroplakin) versus TCC of ovary (–cytokeratin 20, +cytokeratin 7, –WT1, –uroplakin)

Germ Cell Tumors

Dysgerminoma

Clinical

- Young patients (children and young adults <30)
- ± elevated hCG
- Arise in both normal and abnormal gonads (gonado-blastoma)
- Female counterpart of seminoma in males
- Usually unilateral, 15% bilateral
- Good prognosis, >95% survival rate
- Oophorectomy treatment of choice, +chemotherapy, ± radiotherapy

Macroscopic

- Solid, grayish-white surface with fibrous capsule
- Focal hemorrhage or necrosis can be seen

*Microscopic (**Figure 16**)*

- Similar appearance to seminoma in testis
- Nests of uniform cells with large nuclei and prominent nucleoli and clear cytoplasm
- Fibrous septae intermixed with lymphocytes, separate tumor nests
- Focal hemorrhage, necrosis, and infrequently, calcification
- Other germ cell components occasionally seen
- Nests of hCG+ syncytiotrophoblast giant cells seen (<10%)

Immunohistochemistry

- OCT4+, c-kit+, Placental alkaline phosphatase+, scattered hCG + syncytiotrophoblastic cells, ± glial fibrillary acidic protein (GFAP), occ. keratin+ (focal), alpha feto-protein (AFP) – (presence of AFP indicates yolk sac)

Differential Diagnosis

- Lymphoma:
  - Large cells in dysgerminoma negative for leukocyte common antigen
- Other germ cell components should be ruled out by adequate sampling of tumor

Yolk Sac Tumors (Endodermal Sinus Tumors)

Clinical

- Young patients, most <20 years
- Elevated serum AFP
- Normal hCG
- Highly aggressive tumor with tendency for widespread metastasis; stage most important prognostic factor

Macroscopic

- Smooth external surface, often partially cystic
- Foci of necrosis and hemorrhage
- Average size ~15 cm

Microscopic

- Cuboidal cells with loose reticular pattern and micro-cystic areas
- Schiller-Duval bodies (papillary processes with central vessels)
- PAS + droplets in cytoplasm
- Myxoid background
- Polyvesicular vitelline pattern
- Cystic structures lined by columnar or cuboidal cells separated by spindle stroma
- Hepatoid pattern with nests or sheets of large polyhedral cells and glandular lumina
- Glandular pattern
- Resembles secretory or typical endometioid carcinoma

Immunohistochemistry

- Keratin+, AFP+, alpha-1-antitrypsin±, hCG+ (in scattered syncytiotrophoblast cells if present)

Differential Diagnosis

- Clear cell carcinoma

Embryonal Carcinoma

Clinical

- Young patients <20 years
- Elevated serum AFP

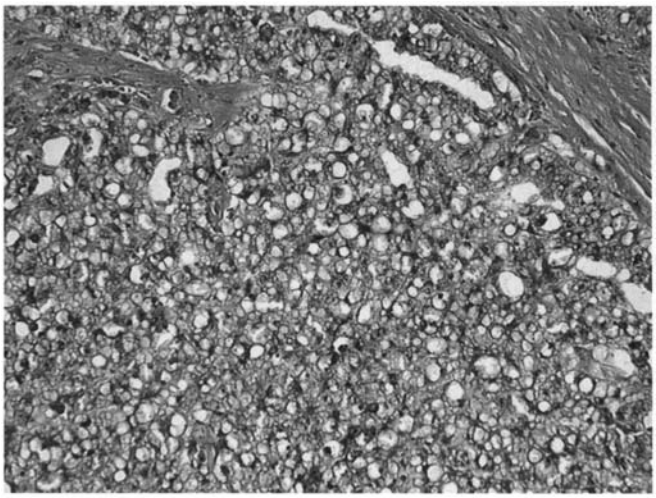


Fig. 17. Embryonal carcinoma.

- Elevated human chorionic gonadotropin (β-hCG)
- Aggressive malignant tumor with early metastases

Macroscopic

- Median size = 17 cm
- Smooth external surface, predominantly solid
- Variegated cut surface with necrosis and hemorrhage

*Microscopic (**Figure 17**)*

- Sheets or nests of large undifferentiated cells with abortive glandular formations
- Large and prominent centrally located nucleus
- Numerous mitoses
- Syncytiotrophoblastic giant cells sometimes present

Immunohistochemistry

- Keratin+, hCG+, AFP+ CD30+, EMA–, OCT4+

Differential Diagnosis

- Dysgerminoma:
  - AFP and keratin–, lymphocytic infiltrate

Polyembryoma

- Rare germ cell tumor, usually unilateral
- Young patients
- Numerous embryoid bodies microscopically (structures composed of embryonic disk, amnionic sac, and yolk sac)
- Highly malignant tumor with aggressive clinical course

Choriocarcinoma

Clinical

- Most ovarian choriocarcinomas represent metastases from the uterus
- May arise as choriocarcinomatous differentiation in germ cell tumor or pure ovarian primary

- Young women
- Elevated hCG
- Aggressive neoplasm; gestational tumors associated with better prognosis than non-gestational type

Macroscopic

- Solid grayish-white mass with hemorrhage and or necrosis

Microscopic

- Syncytiotrophoblastic and cytotrophoblastic cells
- Necrosis and prominent hemorrhage

Immunohistochemistry

- hCG+, keratin+

Differential Diagnosis

- Germ cell tumors with choriocarinomatous differentiation

TERATOMA

Mature Teratoma

- Mature teratoma, solid type:
  - Common tumor comprising up to 30% of ovarian tumors (85% of childhood ovarian tumors)
  - Young women in second decade
  - Usually unilateral
  - Grossly solid with multiple small cysts
  - Microscopically composed of mature, adult tissues
  - Tumor should be sampled adequately to exclude immature elements (immature malignant teratoma)
  - Good prognosis
- Mature teratoma, cystic type (dermoid cyst) (**Figure 18**):
  - Most common childhood ovarian neoplasm
  - Usually unilateral
  - Multiloculated mass with teeth (Rokitansky's pro-tuberance), hair, and caseous-like keratinous material
  - Fetiform teratoma:
    - Cystic teratomas with identifiable body-like structures
  - Microscopically, many mature tissues seen from all three germ cell layers:
    - Skin and neural-type tissue and cartilage most often seen
    - Foci of immature neural-type tissue may be found, which does not generally affect good prognosis; need to distinguish from immature teratoma, which has greater amount of immature elements
  - Squamous cell carcinomas most common malignancy to arise in cystic teratomas
  - Epidermoid cyst:
    - Cystic teratoma with skin epithelium without skin adnexae or other elements

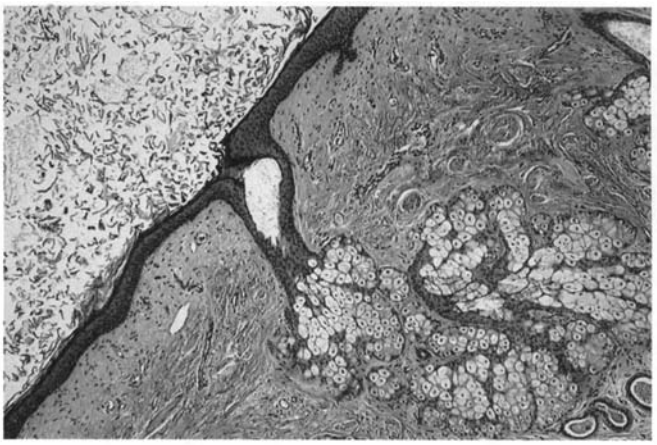


Fig. 18. Mature cystic teratoma.

- Immature teratoma (malignant):
  - Adult and primitive or embryonal-type tissues seen microscopically
  - Grossly solid, solid and cystic, or mostly cystic
  - Immature neural type tissue most often seen but any immature tissue from ectoderm, mesoderm, or endoderm can be encountered
  - The amount of immature tissue should be reported relative to all tissues examined
  - GFAP can be useful to identify glial tissues, both mature and immature
  - Prognosis based on amount and type of immature components; best when a predominance of neural tissues is seen
  - Grading:
    - Grade 1: predominantly mature tissues with loose mesenchymal tissue, immature cartilage, and tooth anlagae
    - Grade 2: fewer mature tissues; focal neuroepithelial tissue with mitotic figures <3/HPF
    - Grade 3: few to no mature tissues and abundant neuroepithelium
  - Cellular stroma occupies = 4 low power fields
  - Malignant neuroectodermal tumors are tumors with an exclusive malignant neural component
  - Teratomas exclusively composed of ependymal structures are designated as ependymomas

Struma Ovarii

Clinical

- Overgrowth of thyroid tissue in association with teratoma
- Associated with Brenner tumor, mucinous cystadenoma, and carcinoid tumors

Macroscopic

- Gross appearance of thyroid tissue with red, meaty consistency
- Occasionally cystic

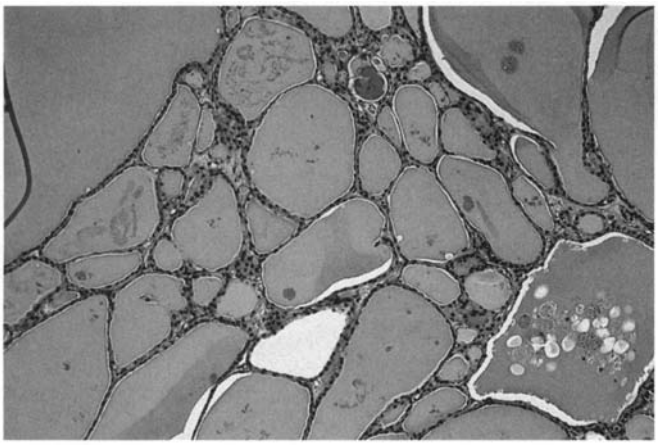


Fig. 19. Struma ovarii.

Microscopic ***(Figure 19)***

- Normal to nodular thyroid tissue that can show features of thyroiditis, hyperplasia, carcinoma
- Cystic changes may be prominent

Treatment/Prognosis

- Surgical removal
- Prognosis same as in other teratomas

Carcinoids

Clinical

- Carcinoid tumors may arise as an element of a teratoma, a metastasis, or a primary ovarian neoplasm
- Carcinoid syndrome (flushing, wheezing, etc.) may occur due to a release of serotonin and other neuropeptides
- Strumal carcinoids are tumors that show features of struma ovarii and carcinoid tumors

Macroscopic

- Solid mass with yellow-tan color
- Average diameter = 10 cm

Microscopic

- Nests of round cells forming trabecular or acinar groups
- Nucleus with "salt and pepper" chromatin
- Similar appearance to carcinoid tumors in gut, lung, and so forth
- May have abundant fibrous stroma

Immunohistochemistry

- Chromogranin+, neuron-specific enolase+, synaptophysin+, serotonin+

Differential Diagnosis

- Granulosa cell tumor:
  - Call-Exner bodies, nuclear grooves
- Brenner tumor:
  - Grooved nuclei, presence of mucinous epithelium
- Metastatic carcinoid tumor:
  - May be difficult to differentiate met vs. primary: presence of teratomatous component favors latter; bilateral tumors favors metastatic; clinical history important
- Sertoli-Leydig cell tumor:
  - Less well-formed trabecular cords; lack of neuroendocrine differentiation

Sex Cord Stromal Tumors

General

- Approximately 5% of all ovarian tumors
- Tumors that show differentiation following sex cords or stroma
- Granulosa and Sertoli-Leydig type cells
- Inhibin (TGF-B family of peptides) positivity found in many sex cord-stromal tumors by immunhistochemical techniques that may be useful in differential diagnosis

Granulosa Cell Tumors

- Two subtypes:
  - Adult and juvenile granulosa cell tumors
- Cytogenetic studies of tumors associated with trisomy 12

Treatment/Prognosis

- Treated by hysterectomy and salpingo-oophorectomy for adult form; conservative treatment for younger patients
- Prognosis dependent on tumor stage

Adult-Type Granulosa Cell

Clinical

- Most commonly in postmenopausal women
- Associated with symptoms of hyperestrinism (metrorrhagia) and endometrial hyperplasia
- Rarely androgenic effects
- Most low stage at presentation (Stage 1); good prognosis
- Recurrences tend to be late (>5 years)

Macroscopic

- Unilateral >90%
- Solid mass with smooth external surface
- Small cysts with thin fluid sometimes present
- Cysts occasionally large
- Grey to yellow color cut surface

Microscopic ***(Figure 20)***

- Variable architectural patterns with microfollicular (Call-Exner bodies), macrofollicular, diffuse, trabecular. Nuclei with folds or grooves "coffee bean nuclei" (inconspicuous in diffuse pattern)

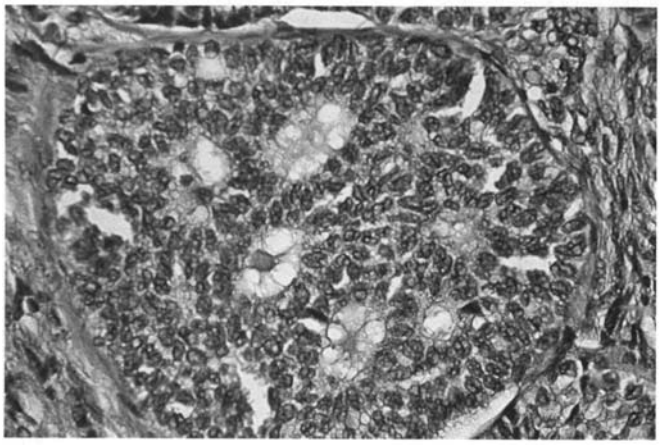


Fig. 20. Granulosa cell tumor.

- Occasional bizarre multinucleated cells that probably represent degenerative changes may be seen
- Variable leuteinization

Immunohistochemical

- Vimentin+, progesterone+, estrogen+, keratin –/+ (dot-like pattern), smooth muscle actin+, S-100+ (50%), inhibin+

Differential Diagnosis

- Carcinoid tumors:
  - "Salt and pepper" chromatin, no nuclear grooves
- Poorly differentiated surface epithelial carcinomas:
  - Strong cytoplasmic keratin positivity, more atypia, high mitotic rate, bilateral involvement, psamomma bodies favor carcinoma
- Endometrial stromal sarcoma
- Small cell carcinoma:
  - High mitotic rate, lack of features seen in typical granulosa cell tumors
- Fibroma/thecoma:
  - Exclusive spindle cell component
- Metastatic carcinoma

Juvenile Granulosa Cell Tumors

Clinical

- Diagnosed in women <20 years, many prepubertal
- Associated with precocious puberty
- Very good prognosis; may be treated conservatively with unilateral salpingo-oophorectomy
- Recurrence tends to be early (<5 years)

Macroscopic

- Similar to adult type

Microscopic

- Diffuse pattern most common with larger cells and abundant eosinophilic luteinized cytoplasm
- Nuclear grooves and Call-Exner bodies less common than in adult form
- Nuclear atypia and numerous mitoses more common
- Inhibin+

Differential Diagnosis

- Small cell carcinoma:
  - Scanty cytoplasm, high mitotic rate

Fibrothecoma/Thecoma

Clinical

- Postmenopausal women
- Usually unilateral
- Associated with excesses of estrogen (e.g., endometrial hyperplasia)
- Luteinized theomas may be associated with sclerosing peritonitis
- Benign

Macroscopic

- Firm, encapsulated mass
- Generally solid, may have few small cysts
- Yellow color
- Calcification ±

Microscopic

- Spindle cells with varying amounts of collagen production
- Hyaline plaques may be present
- Stromal hyperplasia of ovary may be prominent
- Luteinized cells sometimes seen (luteinized thecoma)
- Inhibin+

Fibroma

Clinical

- Any age; account for ~4% ovarian tumors
- Arise from ovarian stromal cells
- Unilateral
- Patients may have endometrial hyperplasia
- Associated with:
  - Gorlin's syndrome (basal nevus cell syndrome)
  - Meig's syndrome (fibroma, ascites, pleural effusion)
- Benign clinical course

Macroscopic

- Firm, solid, white-colored mass; average size = 12 cm
- Some with cystic or myxoid changes

Microscopic ***(Figure 21)***

- Spindle cells with storiform pattern or intersecting bundles
- Hypercellular fibromas referred to as cellular fibromas

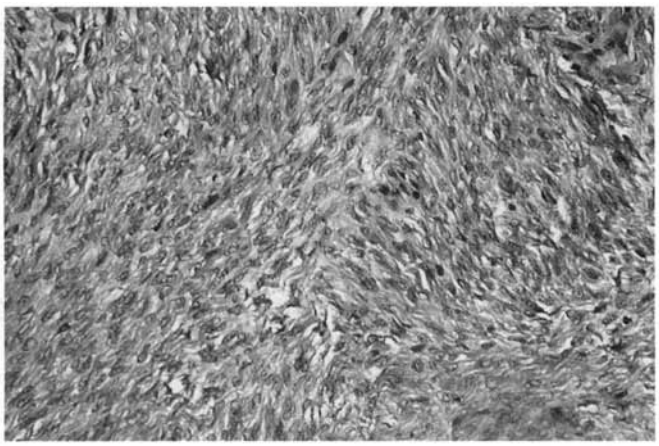


Fig. 21. Fibroma.

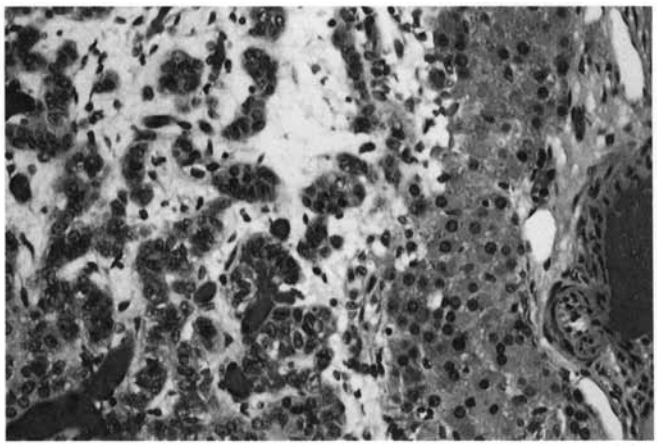


Fig. 22. Sertoli-Leydig cell tumor.

- Mitoses should not exceed >3 per 10 HPF (= fibrosarcoma)
- Inhibin+

Differential Diagnosis

- Thecoma:
  - Yellow in color, fibromas tend to be white in color
- Fibrosarcoma:
  - Hypercellularity with mitoses >3/10 HPF, necrosis
- Fibromatosis:
  - Young patients
- Massive edema:
  - Younger patient
  - Differentiate from edematous fibroma (older patients)

Sclerosing Stromal Tumor

- Younger patients (20–30 years)
- Rarely hormonally active
- Sharply defined gray mass with cellular pseudolobules, alternating hypercellular areas, and numerous dilated thin- walled vessels with hemangiopericytomatous-like vascular pattern separated by collagenous to fibrous stroma with round lipidized cells and spindle cells

Sertoli-Leydig Cell Tumors (Androblastoma, Arrhenblastoma)

Clinical

- Uncommon tumor (<0.5%)
- Young women, rarely postmenopausal
- Predominantly unilateral
- Symptoms of androgen excess (hirsutism, acne, balding, etc.) in 30% to 40% of cases
- Relatively good prognosis, most Stage I

Macroscopic

- Solid and cystic mass, 5–15 cm

*Microscopic (**Figure 22**)*

- Variable histology/clinical behavior; most categorized as follows:
  - Well-differentiated or Meyer's Type I (11%):
    - Tubular formations lined by Sertoli-like cells with clusters of Leydig cells
  - Intermediate type or Meyer's Type II (54%):
    - Sertoli-like cells in sheets or cord formations separated by Leydig cells and spindled cells
  - Poorly differentiated or Meyer's Type III (13%):
    - Spindle cells with sarcomatoid appearance
  - Retiform (15%):
    - Sertoli and Leydig cell elements with irregular clefts resembling rete testis
  - With heterologous elements (22%):
    - Sertoli-Leydig cell elements and other tissue elements such as skeletal muscle, gastrointestinal epithelium, cartilage, liver, and so forth
  - Pure sertoli cell tumor (**Figure 23**):
    - Similar appearance as well-differentiated sertoli cell tumor but without Leydig cells or spindle stroma; abundant cytoplasmic lipid sometimes seen

Immunohistochemical

- Testosterone and estradiol+, keratin+ (sertoli cells), inhibin+
- EMA, PLAP, CEA, and S100–

Differential Diagnosis

- Metastatic carcinoma:
  - Signet ring cells, abundant mucin, and atypia
- Carcinoid tumors: Neuroendocrine markers+
- Granulosa cell tumor:
  - Lack of prominent tubules or Leydig cells, greater number of granulosa cells, nuclear grooves

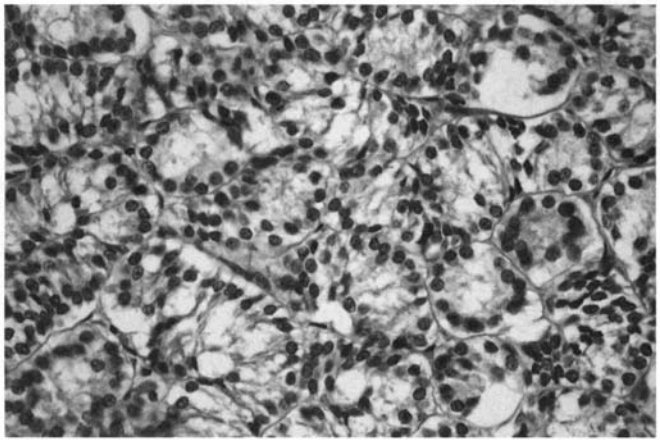


Fig. 23. Sertoli cell tumor.

- Yolk sac tumor:
  - May be confused with retiform variant of Sertoli-Leydig cell tumor (SLCT), AFP+
- Teratoma:
  - May be confused with heterologous SLCT; SLCT lacks neural type tissues

Gynandroblastoma

- Rare
- Sex cord-stromal tumor with Sertoli-Leydig cell and granulosa cell components in similar proportions

Sex Cord Tumor With Annular Tubules

- Associated with Peutz-Jehger's syndrome (30%)
- Simple and complex tubules surrounding hyaline material, which may be partially calcified
- Hyperestrinism may be present clinically
- Two types:
  - Unilateral large tumor often mixed with germ cell tumor elements
  - Small bilateral microscopic and multifocal lesions associated with Peutz-Jehger's syndrome

Differential Diagnosis

- Gonadoblastoma:
  - Sex cord tumor with annular tubules may have sex cord elements, hyaline bodies, and calcification resembling gonadoblastoma, but does not have germ cell elements

Ovarian Tumor of Wolffian Origin

- Epithelial cells with oval to elongated nuclei forming cystic or tubular structures, imparting a "sieve-like" appearance microscopically
- Occurs in broad ligament, ovary, and retroperitoneum
- Probably arises from Wolffian/mesonephric derivatives
- Behaves in benign fashion

Lipid (Steroid) Cell Tumors

- Leydig cell and adrenal cortical types
- Occur at any age, often virilizing clinically
- Unilateral yellowish/yellow-brown nodules separated by fibrous trabeculae
- Large round to polyhedral cells with lipid-rich cytoplasm (+ for fat stains)
- Reinke's crystalloids may be present (Leydig cell tumors)
- Vimentin+, keratin+ (50%)
- Most follow benign course
- Differential includes stromal luteoma, fibrothecomas, and granulosa cell tumors with luteinization

Stromal Luteoma

- Postmenopausal women
- >1/2 are estrogenic, with associated ovarian hyper-thecosis
- Most tumors are circumscribed small lesions up to 3 cm in size
- Aggregates of eosinophilic luteinized cells in nests and cords with little stroma intervening:
  - Pseudovascular spaces may be present secondary to degenerative changes within tumor

Unclassified Sex Cord-Stromal Tumors

- Tumors with features that do not fit into a well-defined category

Other Tumors

Myxoma

- Cystic and solid myxoid mass
- Microscopic appearance similar to myxomas elsewhere
- Benign

Gonadoblastoma (Dysgenetic Genadoma)

Clinical

- Occurs in patients with gonadal dysgenesis (XY gonadal dysgenesis and XO-XY mosaicism):
  - Rarely in normal individuals
- Described in ataxia-telangiectasia

Macroscopic

- Bilateral in 1/3 cases
- Small mass, may be incidental finding

Microscopic

- Mixture of germ cells and sex-cord stromal elements with features of granulosa or sertoli cells
- Calcification and or hyalinization present

Sarcomas

- Primary ovarian sarcomas are rare
- Fibrosarcoma:
  - High mitotic rate (>3/10 hpf), necrosis; aggressive clinical course

- Endometrial stromal sarcomas:
  - Spindle cells arranged around vessels
  - High- and low-grade types as in uterus
- Chondrosarcomas, rhabdomyosarcoma, and leiomyosarcomas also described

Metastatic Tumors

- >50% bilateral
- Gastrointestinal tract, breast, lung, uterus, and skin common sites of origin
- Krukenberg tumor:
  - Metastatic carcinoma, often bilateral, with numerous signet ring cells

Lymphoma/Leukemia

- Primary involvement rare:
  - Usually result of generalized disease
- Lymphomas predominately non-Hodgkin's type

Differential Diagnosis

- Dysgerminoma, poorly differentiated carcinoma, or granulosa cell tumor

Small Cell Carcinoma

Clinical

- Young women with average age = 22 years
- Two types:
  - Hypercalcemic type:
    - Hypercalcemia resolves after surgery
  - Pulmonary type:
    - Resembles small cell carcinoma of lung
- Poor prognosis for both types

Macroscopic

- Usually bilateral
- Large and solid mass with necrosis and hemorrhage

Microscopic

- Small cells with scanty cytoplasm
- Follicle-like structures and larger pleomorphic cells may be seen
- Keratin+, vimentin+, EMA+, chromogranin+, S100–

Differential Diagnosis

- Juvenile granulosa cell tumor
- Lymphoma: LCA+

Hepatoid Carcinoma

- Rare tumor with aggressive clinical course
- Features resemble hepatocellular and gastric hepatoid carcinomas
- Most postmenopausal women
- AFP+
- Differentiate from metastatic hepatic tumors to ovary

PERITONEUM

General

- The peritoneum is the mesodermally derived mesothelial lining that covers the abdominal cavity and intrabdominal organs:
  - Visceral peritoneum
  - Parietal peritoneum
- Immunohistochemical studies of peritoneal tissues are characteristically + for cytokeratin and vimentin and – for CEA, LEU-M1, and B72.3
- Electron microscopic studies show desmosomes, tonofillaments, and long surface microvilli

Inflammation

Peritonitis

- Generalized inflammation of peritoneal tissues due to a variety of causes that may resolve completely or result in adhesions or abscess cavities:
  - Chemical: bile, pancreatic, or gastrointestinal fluids
  - Bacterial:
    - Primary: streptococci, mostly children and adults with severe liver disease
    - Secondary: perforation of a viscus, mycobacteria, fungi
  - Foreign substances: granulomatous inflammation due to talc, starch granules, keratin (endometrioid adenocarcinomas with squamous differentiation)
  - Schlerosing peritonitis (mesenteric panniculitis):
    - Idiopathic fibrous thickening of mesentery, rare; characterized by chronic inflammatory infiltrate, fat necrosis, foamy histiocytes, and myofibroblasts
- Associated with luteinized thecomas of the ovary

Differential Diagnosis

- Desmoplastic mesothelioma:
  - More atypia, necrosis, invasion
- Fibrous/hyaline plaques:
  - Paucicellular plaques most commonly found on splenic capsule

Mesothelial Hyperplasia and Metaplasia

Mesothelial Hyperplasia

- Diffuse or nodular proliferation of mesothelial cells due to irritation/inflammation, viral infection, collagen vascular disease, or chronic peritoneal effusions (e.g., liver disease):
  - Nodular hyperplasia sometimes seen in strangulated hernia sacs
- Nests, papillary, or tubule formations microscopically
- Psamomma bodies may be present

Differential Diagnosis

- Mesothelioma:
  - Features favoring malignancy over hyperplasia are:
    - Necrosis and severe nuclear atypia
    - Grossly apparent nodules
    - Invasion
- Serous borderline tumor of peritoneal primary:
  - Hyperplasia of mesothelium common with nearby ovarian tumors
  - Psamomma bodies, columnar type epithelium favor serous tumor

Mesothelial Metaplasia

- Squamous metaplasia
- Mullerian metaplasia (exclusively in pelvis of females):
  - Endometriosis
  - Endosalpingiosis
  - Ectopic decidual reaction
- Cartilaginous metaplasia

Cysts

Pseudocyst

- Cyst without an epithelial lining
- Probably due to resolved inflammatory process

Solitary Cyst

- Small cyst ranging in size from 1–6 cm
- Attached to abdominal wall or free in pelvis
- Also likely to be related to inflammatory process

Cystic Lymphangioma

- Multiloculated thin-walled cyst filled with milky white fluid
- Cyst wall lined by flattened endothelial cells and may have wisps of smooth muscle bundles
- Originates from lymphatic vessels
- Benign

Endometriosis/Endometriotic Cyst

- See ovary section

Cyst of Müllerian Origin

- Cystic mass in males lined by epithelium resembling fallopian tubal epithelium
- Located in pelvis in the region of the bladder or rectum and also mesentery
- Thought to originate from persistence of Müllerian tissues

Neoplasms of Serous Membrane

Solitary Fibrous Tumor

- Benign
- Thought to arise from submesothelial fibroblasts
- Histologically identical to tumors seen in pleura:
  - Spindle cells separated by bundles of collagen
  - Hemangiopericytomatous vascular pattern
  - Thick-walled vessels
- Tumor cells stain + for CD34, – for cytokeratin
- Differential includes fibrosarcoma, which shows more atypia, CD34–

Adenomatoid Tumor

- "Localized epithelial meosthelioma" characterized by smooth muscle and glandular proliferation as seen in genital tract
- Benign
- Uncommon

Multilocular Peritoneal Inclusion Cysts (Multicystic Benign Mesothelioma)

Clinical

- Predominantly a disease of young women
- Present with chronic pelvic pain and/or mass

Macroscopic

- Multiple thin-walled translucent cysts (<1–20 cm) with thin serous fluid:
  - Usually in pelvis

Microscopic

- Cystic spaces lined by cuboidal to flattened mesothelial cells
- May have focal areas with mesothelial hyperplasia
- Foci of chronic inflammatory cells in cyst wall

Differential Diagnosis

- Cystic lymphangioma:
  - Located in mesentery; cysts with milky fluid; cyst wall may have smooth muscle bundles
- Cystic malignant mesothelioma
- Greater mesothelial proliferation and atypia

Treatment/Prognosis

- Benign but tend to recur

Primary Serous Papillary Carcinoma of Peritoneum

- Histologically similar to ovarian serous papillary carcinoma with tubular and papillary pattern, epithelial tufting, and psamomma bodies
- Some tumors may resemble serous borderline tumors:
  - Differentiate borderline tumors from carcinoma by high-grade cytology and desmoplastic stromal invasion of the latter
  - Generally have good prognosis
  - Prognosis for serous carcinoma similar to Stage III ovarian carcinoma
- Ovaries are minimally (surface granularity) or not involved by tumor
- Differentiation from mesothelioma aided by immunohistochemistry (see Table 22-2)

Malignant Mesothelioma

Clinical

- Male predilection
- Less common than in thoracic cavity
- Present with ascites, abdominal pain, and weight loss
- Associated with asbestos exposure; long latency
- May metastasize to regional lymph nodes and rarely to lung

Macroscopic

- Multiple nodules and plaques studding peritoneal surface
- Combined pleural and peritoneal involvement may be seen occasionally

Microscopic

- Histologic types:
  - Epithelial:
    - Tubulopapillary and epithelioid
    - Most common subtype
  - Sarcomatous
  - Biphasic
  - Undifferentiated

Electron Microscopy

- Elongated, thin, bushy microvilli
- Length/diameter of microvilli >15:1
- Numerous tonofillaments

Immunohistochemistry (also see Table 22-2)

- LEU-M1–, CEA–, B72.3–, and Ber-EP4–
- EMA+, cytokeratin+, vimentin+, calretinint
- Rare mesotheliomas+ for bcl-2
- Positive for human milk fat globulin (HMFG) with membranous staining pattern
- Presence of hyaluronic acid is suggestive of mesothelioma

Variants

- Desmoplastic mesothelioma:
  - Abundant collagen deposition (>50%)
  - Differential includes fibromatosis
- Well-differentiated papillary mesothelioma:
  - Rare
  - Mostly in women
  - Lacks stratified epithelium or significant cytologic atypia
  - Rare to no mitoses
  - Most follow benign clinical course
- Malignant mesothelioma of tunica vaginalis testis:
  - Papillary or tubular pattern involving tunica vaginalis
  - Rare
  - Clinically may act in indolent or agressive course
- Deciduoid peritoneal mesothelioma:
  - Rare aggressive tumor of young women with prominent decidual change

Differential Diagnosis

- Mesothelial hyperplasia:
  - Less atypia
  - No necrosis or invasion
  - No gross nodules
  - Smaller nuclei
- Metastatic adenocarcinoma:
  - See Table 22-2
- Primary peritoneal serous carcinomas:
  - Female patients
  - Histologically indistinguishable from ovarian primary
  - Psamomma bodies and bizarre nuclear features favor peritoneal serous carcinomas

Treatment/Prognosis

- Poor prognosis, especially sarcomatoid variant
- Chemotherapy
- Radiotherapy ineffective

Intra-Abdominal Desmoplastic Small Round Cell Tumor

Clinical

- Young adults
- Males > females
- Abdominal pain, and/or abdominal mass or ascites
- Associated with t(11;22) translocation

Macroscopic

- Large solid mass with multiple small peritoneal implants
- White to gray coloration
- Focal necrosis and hemorrhage

Microscopic

- Nests of uniform small cells with scanty cytoplasm and slightly epithelioid or spindled cells within a fibrous stroma
- Numerous mitotic figures
- Necrosis
- Lymphatic invasion common

Immunohistochemistry

- Positive for cytokeratin, NSE, desmin (dot-like paranuclear), vimentin, EMA
- Chromogranin/synaptophysin±
- Negative for actin

Electron Microscopy

- Paranuclear intermediate cytoplasmic filaments
- Dense core granules

Treatment/Prognosis

- Aggressive course with poor prognosis
- Tumor debulking with chemotherapy and radiation

Miscellaneous Lesions of Peritoneum

Endosalpingiosis

Clinical

- Presence of fallopian tubal epithelium outside the fallopian tube
- Occurs in many locations:
  - Ovary
  - Omentum
  - Pelvic peritoneum
  - Upper female genital tract

Macroscopic

- Often incidental finding on microscopic exam

Microscopic

- Three cell types as in fallopian tubal epithelium:
  - Secretory cells
  - Peg cells
  - Ciliated epithelial cells
- ± occasional psamomma bodies

Differential Diagnosis

- Borderline serous tumor of ovary:
  - Cellular stratification/tufting, more atypia
- Mesonephric remnant:
  - Cuboidal nonciliated epithelium
- Salpingiosis isthmica nodosa (see fallopian tube section)
- Endometriosis:
  - Endometrial glands and stroma with evidence of hemorrhage

Infarcted Appendix Epiploica

- Mesenteric adipose tissue that becomes twisted, leading to infarction
- Infarcted tissue may be attached to the abdominopelvic wall or lay loose in pelvis
- May become calcified

Leiomyomatous Peritonealis Disseminata

- Rare
- Nodular submesothelial proliferation of benign smooth muscle cells
- Uterine leiomyomata commonly present
- May rarely involve regional lymph nodes; differentiate from metastatic leiomyosarcoma

Inflammatory Psuedotumor/Myofibroblastic Tumor

- Young patients, benign course
- Systemic symptoms include weight loss, fever, anemia/thrombocytopenia, and polyclonal hypergamma-globulinemia
- Histological examination shows plasma cells, lymphocytes, and "myofibroblastic" type spindle cells

Walthard Nest

- Benign
- Women of any age
- Tunica vaginalis of men
- Small nests of transitional type epithelium as in ovary/fallopian tube

Urachal Remant

- Developmental defect characterized by sinus tract or cyst formation connecting the bladder (dome) and umbilicus or as blind sinuses originating from either site
- Cyst wall may be transitional or glandular type
- May give rise to adenocarcinomas or squamous or transitional carcinoma

Endocervicosis

- Benign endocervical type glands within peritoneum or smooth muscle of pelvic viscera, usually around uterus and bladder
- Rare
- Benign
- Differential includes metastatic low-grade adenocarcinoma

Tailgut Cyst (Retrorectal Cystic Hamartoma)

- Benign, developmental anomaly
- Precoccygeal multiloculated cyst with squamous, transitional, or glandular epithelium and smooth muscle
- Differential includes teratoma:
  - Other germ cell layer elements present

Necrotic Pseudoxanthomatous Nodule

- Peritoneal nodules with an outer rim of palisaded pseudoxanthoma cells and fibrous tissue surrounding necrotic centers
- Evidence of endometriosis may be sparse or absent
- Condition may be seen after treatment or spontaneously
- Infection should be ruled out

Ectopic Decidual Reaction

- Seen during pregnancy as whitish peritoneal nodules on peritoneal surface
- Nodular aggregates of submesothelial decidualized cells

Metastatic Tumor

- Most common primary site is from ovary
- Other sites include gastrointestinal tract, breast, lung, skin (melanoma) and others

Pseudomyxoma Peritonei

- Mucinous neoplasm involving peritoneum (jelly belly)
- Appendiceal (most common) or ovarian primary (borderline or mucinous carcinoma)
- Pools of mucin with intestinal type epithelium

TNM (FIGO) CLASSIFICATION OF OVARIAN CARCINOMA (2002)

Primary Tumor (T)

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- T1 (I) Tumor limited to ovaries:
  - T1a (IA) Tumor limited to one ovary; capsule intact, no tumor on ovarian surface. No malignant
  - cells in ascites or peritoneal washings
  - T1b (IB) Tumor limited to both ovaries; capsule intact, no tumor on ovarian surface. No malignant
  - cells in ascites or peritoneal washings
  - T1c (IC) Tumor limited to one or both ovaries with any of the following: capsule ruptured, tumor on ovarian surface, malignant cells in ascites or peritoneal washings
- T2 (II) Tumor involves one or both ovaries with pelvic extension:
  - T2a (IIA) Extension and/or implants on uterus and/or one or both tubes. No malignant cells in ascites or peritoneal washings
  - T2b (IIB) Extension to and/or implants on other pelvic tissues. No malignant cells in ascites or peritoneal washings
  - T2c (IIC) Pelvic extension and/or implants (T2a or T2b) with malignant cells in ascites or peritoneal washings
- T3 (III) Tumor involves one or both ovaries with microscopically confirmed peritoneal metastasis outside the pelvis:
  - T3a (IIIA) Microscopic peritoneal metastasis beyond pelvis (no macroscopic tumor)
  - T3b (IIIB) Macroscopic peritoneal metastasis beyond pelvis 2 cm or less
  - T3c (IIIC) Peritoneal metastasis beyond pelvis >2 cm and/or regional lymph node metastasis

Regional Lymph Nodes (N)

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 (IIIC) Regional lymph node metastasis

Distant Metastasis (M)

- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 (IV) Distant metastasis (excludes peritoneal metastasis)

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27

Placenta and Gestational Trophoblastic Disease

Raymond W. Redline, MD

CONTENTS

I. Gestational Trophoblastic Disease (GTD) 27-2
- Precursor Lesions 27-2
  - Partial Hydatidiform Mole 27-2
  - Complete Hydatidiform Mole 27-2
- Malignant Trophoblastic Tumors 27-4
  - Choriocarcinoma 27-4
  - Placental Site Trophoblastic Tumor 27-5
  - Epithelioid Trophoblastic Tumor 27-5

II. Placenta 27-5
- Acute Chorioamnionitis 27-6
- Meconium and Subacute Hypoxia 27-8
- Maternal Arteriopathies and Preeclampsia 27-10
- Hemorrhagic Lesions 27-11
  - Intervillous Thrombus (Fetomaternal Hemorrhage) 27-11
  - Retroplacental Hemorrhage Consistent with Abruptio Placenta 27-13
  - Retroplacental Hemorrhage Consistent with Marginal Separation 27-13
  - Fetal Thromboocclusive Lesions 27-14
    - Changes consistent with Fetal Vascular Obstruction (Fetal Thrombolic Vasculopathy) 27-14
    - Changes consistent with Vascular Stasis (Overlaps with "Hemorrhagic Endovasculitis") 27-15
- Chronic Inflammation and Coagulation 27-15
  - Congenital Infection 27-15
  - Villitis of Unknown Etiology (VUE) 27-16
  - Chronic Histiocytic Intervillositis (Massive Chronic Intervillositis) 27-16
  - Massive Perivillous Fibrinoid (Maternal Floor Infarction) 27-17

III. Multiple Pregnancy 27-18

IV. Suggested Reading 27-19

GESTATIONAL TROPHOBLASTIC DISEASE (GTD)

Precursor Lesions

Partial Hydatidiform Mole

Clinical

- Diandric triploidy only:
  - Three complete haploid sets of chromosomes ($n = 69$)
  - Two sets derived from the father
- Never seen in digynic triploid
- Trophoblast hyperplasia results from unbalanced over-expression of paternal gene products (genomic imprinting)
- Presentation:
  - Late first or early second trimester spontaneous abortion
  - Occasionally presents with increased maternal human chorionic gonadotropin (hCG)
- 1/13 spontaneous abortions are triploid:
  - 2/3 of these are diandric; 1/2 fulfill diagnostic criteria for partial mole
  - Prevalence of Partial Mole = 1/39 spontaneous abortions
- Incidence of persistent GTD requiring chemotherapy = 0.5% to 20%
- Subsequent invasive mole, choriocarcinoma, and placental site trophoblastic tumors are rare

Gross Findings

- Spongy villous tissue with small 1–2 mm fluid-filled vesicles (as in hydropic abortus and complete hydatidiform mole)
- Fetal fragments or malformed fetus may be seen occasionally

Microscopic

- Diagnostic criteria **(Figure 1):**
  - Villous trophoblast hyperplasia (usually predominantly syncytiotrophoblast)
  - Dimorphic population of large and small villi without intermediate forms
  - Hydropic villi >0.5 mm
  - Irregular villous contour often with multicellular trophoblast inclusions within villous stroma
- Other features:
  - Mazelike villous capillary vascular pattern
  - Atypical implantation site trophoblast
  - Molar villi with well-delineated central cisterns
  - Villous stromal karyomegaly (nuclei 2–3 times normal size)

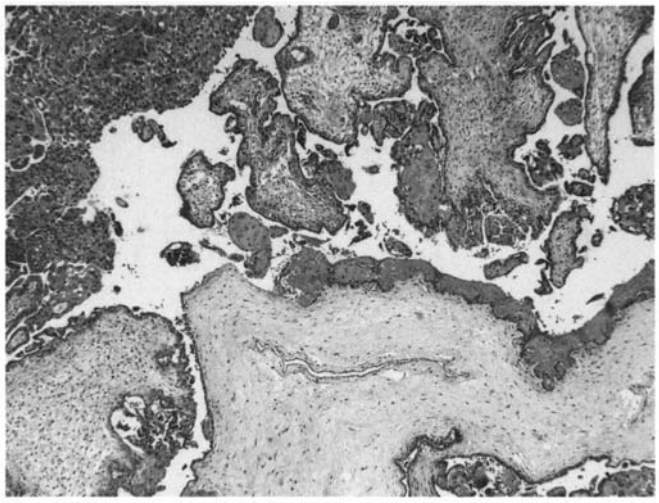


Fig. 1. Partial hydatidiform mole.

Flow Cytometry or Image Analysis

- Occasionally helpful in differentiating partial versus complete mole or partial mole versus hydropic abortus (modal DNA index = 1.5 vs. 1.0 for the other two conditions)

Differential Diagnosis

- Hydropic Abortus:
  - Lacks dimorphic population: large and small villi with intermediate forms
  - Generally lacks villous trophoblast hyperplasia
  - Focal trophoblast hyperplasia can be seen in approximately 3% of nonmolar abortions:
    - May require a limited hCG follow-up, depending on severity
  - Lacks atypical implantation site (intermediate trophoblast with enlarged irregular hyperchromatic nuclei)
- Complete Hydatidiform Mole:
  - Uniformly hydropic villi with central cisterns
  - Lacks second population of small villi
  - Villous trophoblast hyperplasia is generally more diffuse and atypical, and involves cytotrophoblast and syncytiotrophoblast equally

Complete Hydatidiform Mole

Clinical

- Diandric diploid gestation (two sets of chromosomes with both sets derived from the father; Karyotype 46, XX or XY)
- Trophoblast hyperplasia results from an overexpression of paternally derived gene products and/or a lack of maternally derived gene products (genomic imprinting)

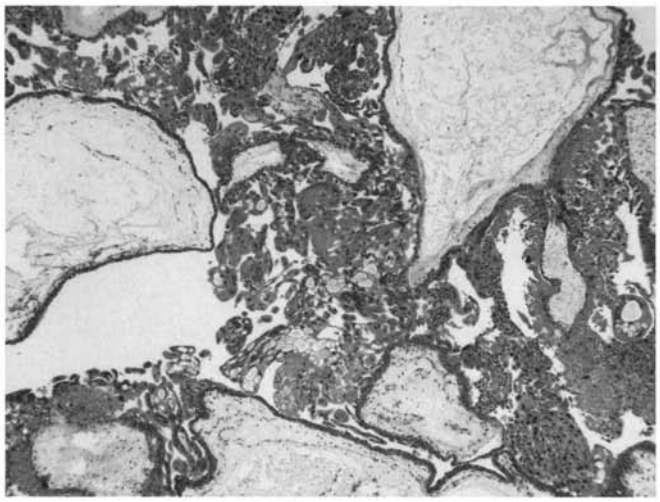


Fig. 2. Complete hydatidiform mole.

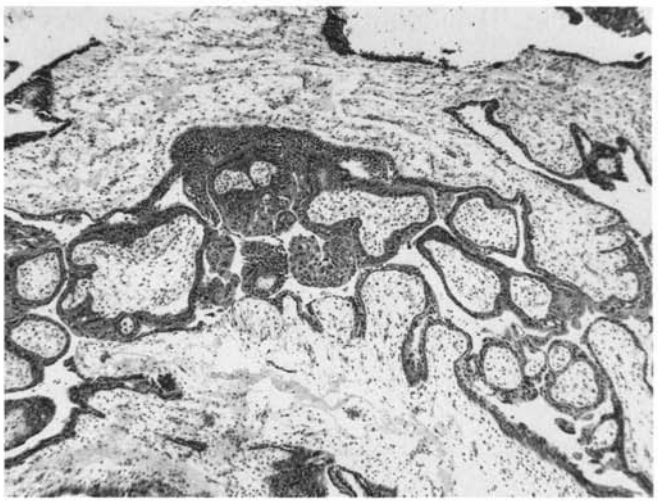


Fig. 3. Early complete hydatidiform mole.

- Early presentation (<8 weeks):
  - Anembryonic missed abortion by ultrasound
- Late presentation (>8 weeks):
  - Large for dates
  - Vaginal bleeding
  - Elevated hCG
  - Occasionally: hyperemesis, preeclampsia, thyrotoxicosis, or bilateral adnexal masses (theca lutein cysts)
- Incidence of persistent GTD requiring chemotherapy = 20% to 30%
- Rate of subsequent choriocarcinoma is approximately 1/40

Gross Findings

- Usually a discohesive collection of swollen grape-like molar villi up to 5–10 mm in diameter. Occasionally at <8 weeks, hydropic/molar changes are inconspicuous

Microscopic

- Classic complete hydatidiform mole (**Figure 2**):
  - Diffuse, circumferential villous trophoblast hyperplasia
  - Involves both cytotrophoblast and syncytiotrophoblast
  - Uniformly hydropic villi, many with well-defined central cisterns
  - Lack of fetal vessels and nucleated red blood cells
  - Frequent atypical implantation site
- Early complete hydatidiform mole (**Figure 3**):
  - Focal cytotrophoblast and syncytiotrophoblast hyperplasia of both villi and the undersurface of the chorion
  - Redundant bulbous terminal villi (± focal hydrops)
  - Hypercellular myxoid villous stroma often with stromal karyorrhexis
  - Labyrinthine network of villous stromal canaliculi
  - Atypical implantation site
  - Fetal vessels or nucleated red blood cells may be seen

Immunocytochemistry

- p57KIP2 immunostaining is negative in the nuclei of stromal and cytotrophoablst cells in complete mole. Positive in partial mole and hydropic abortus. Only expressed from the female genome which is lacking in diandric complete moles

DNA Studies

- PCR-based microsatellite analysis on microdissected maternal and fetal tissue removed from the paraffin blocks can be used to confirm diandric origin (not routinely available)

Differential Diagnosis

- Partial hydatidiform mole:
  - *See* above
  - p57KIP2 positive
- Hydropic abortus:
  - Generally lacks trophoblast hyperplasia and atypical implantation site
  - Degenerative features:
    - Hypocellular villous stroma and intervillous fibrin
  - p57KIP2 positive
- Early spontaneous/elective abortion:
  - Generally lacks trophoblast hyperplasia and atypical implantation site
  - Lacks villous stromal hypercellularity and canaliculi
  - P57KIP2 positive

Malignant Trophoblastic Tumors

Choriocarcinoma

Clinical

- Rapidly growing and invasive, with frequent metastases
- Generally curable with multiagent chemotherapy
- Can follow any pregnancy at any stage
- Frequency of preceding pregnancy types:
  - Hydatidiform mole 45%
  - Term pregnancy 25%
  - Spontaneous abortion 25%
  - Ectopic pregnancy 5%
- Cytogenetics:
  - Diploid or near diploid, with frequent polyploid subpopulations
  - Gains or losses of chromosomes 1, 3, 8, 10, and 12
- Three partially overlapping definitions:
  - Clinical:
    - Radiologically confirmed metastatic GTD following pathologically confirmed molar pregnancy
  - Pathologic:
    - Biphasic avillous trophoblast at any site with cytologic features of malignancy
  - Primary placental:
    - Parenchymal nodules of biphasic malignant trophoblast in a normal placenta
- Clinical Staging:
  - 0 Elevated hCG only
  - 1 Uterine corpus involvement
  - 2 Lung metastases
  - 3 Pelvic and/or vaginal metastasis
  - 4 Distant metastasis
- Adverse prognostic factors:
  - Older age
  - Preceding nonmolar pregnancy
  - Longer interval to preceding pregnancy
  - Tumor size (>5 cm)
  - hCG level (>10^5 mIU/liter)
  - Number of metastases
  - Metastasis to brain, liver, or GI tract
  - Previous chemotherapy
- Clinical management:
  - Serial maternal serum hCG determinations
  - Metastatic workup and chemotherapy instituted if hCG levels plateau or rise

Gross Findings

- Grossly hemorrhagic, ill-defined lesions within the uterovaginal wall or in the parenchyma of other organs

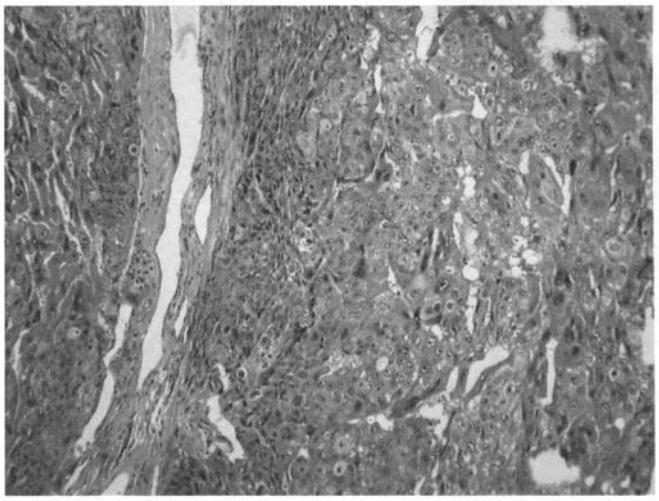


Fig. 4. Choriocarcinoma.

- Often difficult to detect nonhemorrhagic tumor tissue

Microscopic

- Biphasic tumor composed of malignant villous cytotrophoblast and syncytiotrophoblast
- Classic pattern (**Figure 4**):
  - Groups of 10–50 cytotrophoblast:
    - Uniformly enlarged central nuclei, prominent nucleoli, and margination of chromatin
    - Scant, watery, clear cytoplasms
  - Surrounded by a wreath-like arcade of multinucleate syncytiotrophoblast:
    - Enlarged irregular hyperchromatic nuclei and glassy eosinophilic cytoplasm
- Extensive tumor hemorrhage, necrosis, and perpendicular invasion of myometrial fibers (especially useful in the absence of classic pattern described above)

Immunocytochemistry

	CYTOTROPHOBLAST	SYNCYTIOTROPHOBLAST
♦ Cytokeratin	+	+
hCG	–	+
Human placental lactogen (hPL)	–	+
Placental alkaline phosphatase (PLAP)	–	variable
Desmin	–	–
Vimentin	–	–
Carcinoembryonic antigen (CEA)	–	–
Alpha fetoprotein (AFP)	–	–

Differential Diagnosis

- Intervillous X-cell nodules:
  - Aggregates of intermediate trophoblast found in term placentas:
    - Lack nuclear atypia
    - Dense eosinophilic to purplish cytoplasm
    - Fibrinoid matrix
- Placental site trophoblastic tumor (PSTT):
  - Less hemorrhagic by gross exam
  - Tumor cells have dense eosinophilic cytoplasm and larger, more irregular and hyperchromatic nuclei than malignant cytotrophoblast
  - Syncytiotrophoblasts are rare
- Epithelioid trophoblastic tumor :
  - Tumors with features intermediate between choriocarcinoma and PSTT
  - Extremely rare; tumors are often seen in patients with previously treated choriocarcinomas

Placental Site Trophoblastic Tumor

Clinical

- Rare, generally indolent tumors
- 15% to 20% manifest malignant behavior (local invasion and distant metastasis)
- Resistant to chemotherapy
- Low serum hCG, generally <10,000 mIU/ml
- Usually follow term pregnancy (95% of cases), often with a long interval (up to 15 years)
- Precursor lesions:
  - Rarely if ever molar pregnancy
  - Possibly derived from placental site nodules

Gross Findings

- Presents as a uterine mass; generally nodular or polypoid
- Occasionally diffusely infiltrative

*Microscopic (**Figure 5**)*

- Cohesive sheets of mononuclear intermediate trophoblast
- Often associated with zonal necrosis and prominent vascular invasion and remodelling (recapitulates normal implantation site)
- Individual cells generally mononuclear
- Occasionally binucleate, with abundant eosinophilic cytoplasm
- Enlarged, round to oval nuclei with coarse clumped chromatin and prominent nucleoli
- Tumors with a mitotic rate >5/10 high power fields, prominent necrosis, and less dense eosinophilic cytoplasm may have a worse prognosis

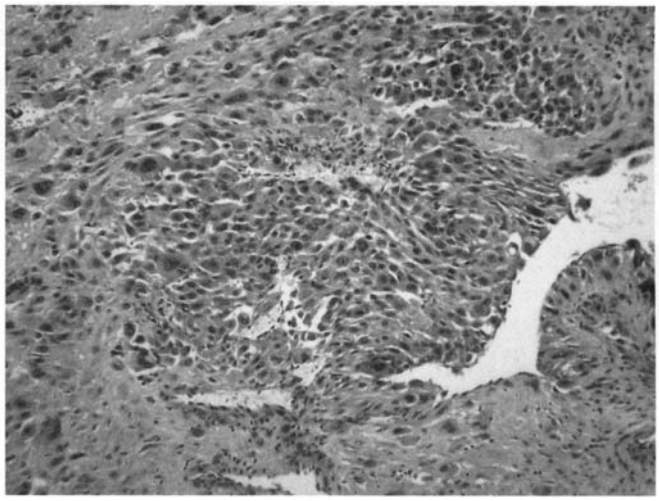


Fig. 5. Placental site trophoblastic tumor (PSTT).

Immunocytochemistry

- Cytokeratin, hPL: diffusely+; hCG: weak or focal positivity only

Differential Diagnosis

- Placental site nodule (involuting or remote implantation site):
  - Well-circumscribed aggregates of intermediate trophoblast embedded in a fibrinoid matrix
  - Low cellularity
  - Bland cytologic features
  - Cytokeratin+; hPL, hCG, PLAP: variable
- Exaggerated implantation site (recent implantation site):
  - Seen with abortions (spontaneous or elective)
  - Intermediate trophoblast infiltrate decidua and myometrium as single or small groups of cells
  - Multinucleate placental site giant cells seen in specimen:
    - Lacks necrosis and destructive myometrial invasion

Epithelioid Trophoblastic Tumor

Clinical

- Rare, generally presents with vaginal bleeding:
  - extrauterine disease common
  - 50% follow a previous hydatidiform mole or choriocarcinoma, often after a long interval
- Can develop from a resistant nodule within choriocarcinoma following multiagent chemotherapy
- Low serum hCG, generally <10,000 mIU/ml

Gross Findings

- Presents as a uterine or cervical mass; generally nodular



Fig. 6. Epithelioid trophoblastic tumor (ETT).

Microscopic ***(Figure 6)***

- Cords and nests of mononuclear intermediate trophoblast with clear or eosinophilic cytoplasm—resembles membrane trophoblast (chorion laevae). Smaller cells with a higher N/C ration than the intermediate trophoblast seen with PSTT
- Tumor cell aggregates are often associated with eosinophilic fibrillar, hylaine like material resembling keratin
- Occasionally grows along the surface of endocervical glands

Immunocytochemistry

- Cytokeratin+ ; hPL hCG variable (also positive for Mel-CAM, CD146)

Differential Diagnosis

- Choriocarcinoma:
  - No multinucleate syncytiotrophoblast
  - Less associated hemorrhage
  - More abundant cytoplasm in mononuclear tumor cells
  - Lower serum hCG titers
- Placental site trophoblastic tumor:
  - Intermediate trophoblast lacks abundant eosinophilic cytoplasm
  - Negative or focal HPL immunopositivity
  - Lacks implantation site arterial remodelling
  - Higher serum hCG titers
- Squamous cell carcinoma:
  - lacks positivity for HPV
  - expresses cytokeratin 18 and Inhibin-α
  - lacks overlying squamous atypia
- Epithelioid leiomyosarcoma:
  - lacks positivity for smooth muscle markers
  - expresses low and high MW keratin filaments
  - lacks typical smooth muscle cells Placenta

PLACENTA

Acute Chorioamnionitis

Clinical

- Leading cause of preterm birth
- >60% of infants <1.5 kg have placentas with chorioamnionitis
- Risk factor for cerebral palsy especially with intense fetal inflammatory response (histologic or as reflected by increased cytokines in fetal circulation)
- Pathogenesis:
  - Ascending infection (common)
  - Hematogenous (rare)
  - Transuterine from UTI, peritonitis (possible)
- Risk factors:
  - Incompetent cervix or preterm labor causing premature cervical dilation
  - Change in cervicovaginal flora—bacterial vaginosis
  - Foreign body: cerclage, IUD
- Organisms:
  - Predominantly normal flora: anaerobes, mycoplasmas
  - Less common: Group B streptococci, *E. coli*
  - With foreign body (cerclage, IUD): candidal species
  - Rare: *Listeria monocytogenes*, *Campylobacter fetus* spp

Gross Findings

- Grayish discoloration of membranes
- Haziness and blurring of chorionic plate vessels
- Frank yellow-green exudate if severe
- Candida:
  - Yellow microabsesses on umbilical cord surface
- *L. monocytogenes* and *C. fetus*:
  - Intervillous abscesses and septic infarcts

Microscopic

- Maternal inflammatory response:
  - Membranes (PMN from decidual venules)/chorionic plate (PMN from intervillous space):
    - Early (**Figure 7**): PMNs in subchorionic fibrin or diffuse band of PMNs in chorion
    - Intermediate (**Figure 8**): diffuse PMN in chorion and amnion
    - Late (**Figure 9**): necrosis and sloughing of amniocytes, PMN karyorrhexis (necrotizing chorioamnionitis)

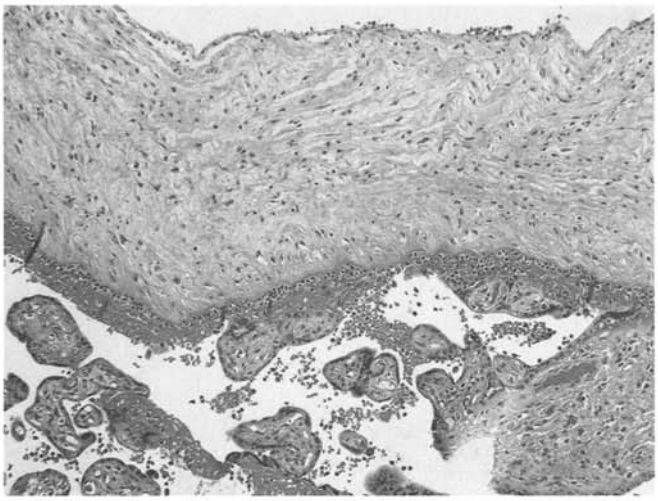


Fig. 7. Early acute subchorionitis.

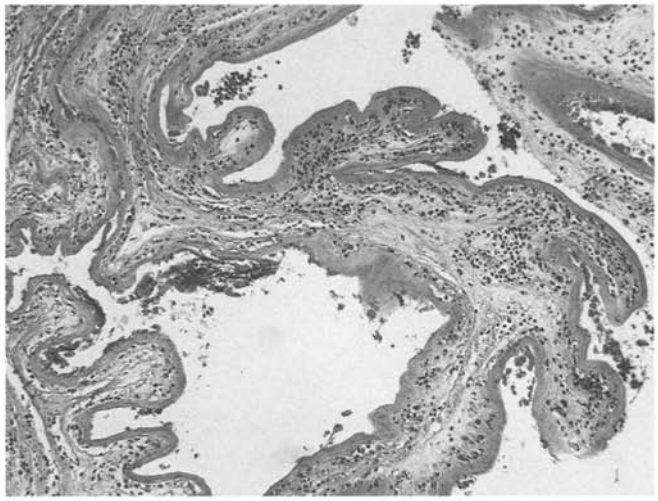


Fig. 9. Necrotizing chorioamnionitis.

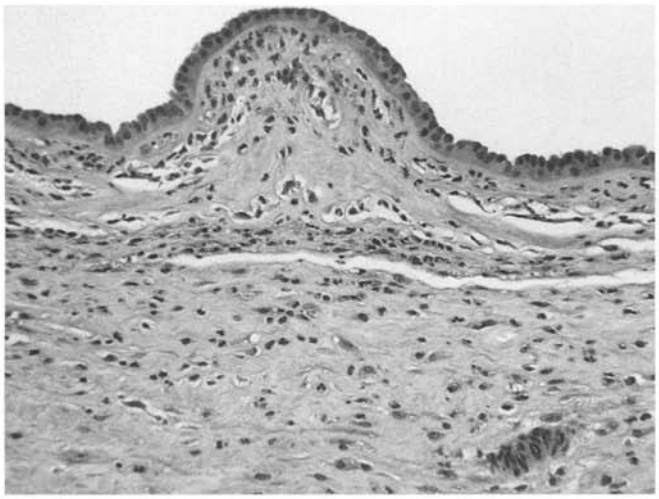


Fig. 8. Acute chorioamnionitis.

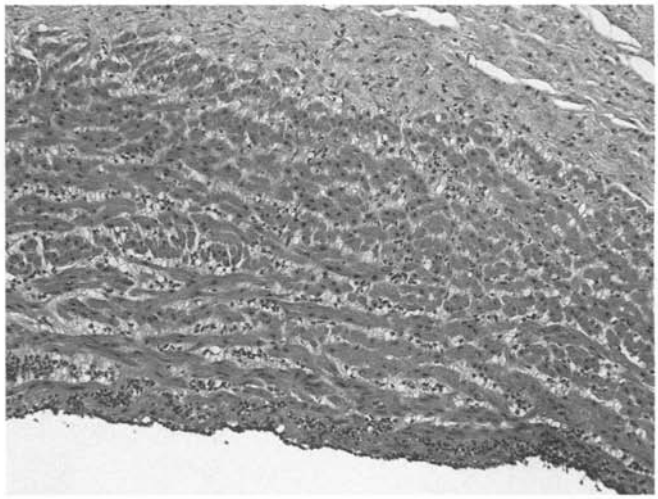


Fig. 10. Acute umbilical phlebitis.

- Fetal inflammatory response:
  - Chorionic plate (PMN from chorionic vessels)/umbilical cord (PMN from umbilical vessels):
    - Early : PMNs in chorionic vessel wall or umbilical vein **(Figure 10)**
    - Intermediate **(Figure 11)**: PMNs in umbilical artery(ies)
    - Late **(Figure 12)**: Degenerating PMNs in arcs around vessels (necrotizing or subnecrotizing funisitis)
    - Severe **(Figure 13)**:Near confluent PMN in fetal vessels wall ± mural thrombosis **(Figure 14)**
- Candidal species:
  - Peripheral funisitis with microabsesses **(Figure 15)**
- *L. monocytogenes/C. fetus*:
  - Acute intervillositis with intervillous abscesses **(Figure 16)**

Special Stains and Cultures

- Candida (GMS and/or PAS of cord and membranes)
- Group B streptococci, *L. monocytogenes* (tissue gram stain)
- Anaerobes, *C. fetus*, other bacteria (Silver stains: Dieterle, Warthin-Starry, or Steiner)
- Bacterial cultures generally not useful

Differential Diagnosis

- Ischemic necrosis of decidua:
  - Degenerating PMNs, often focal
  - Predominantly confined to membranous decidual layer
- Isolated umbilical phlebitis:
  - Occasionally seen with meconium exposure
  - Lacks PMNs in amnion, chorion, and subchorionic fibrin

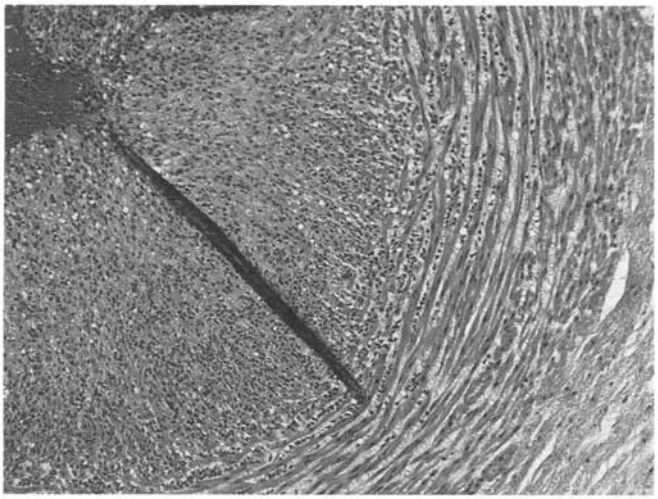


Fig. 11. Acute umbilical arteritis.

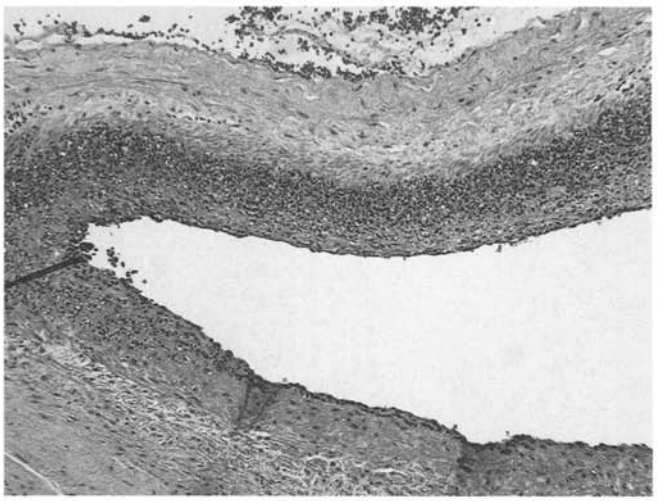


Fig. 13. Severe fetal vasculitis (intense chorionic vascultis).

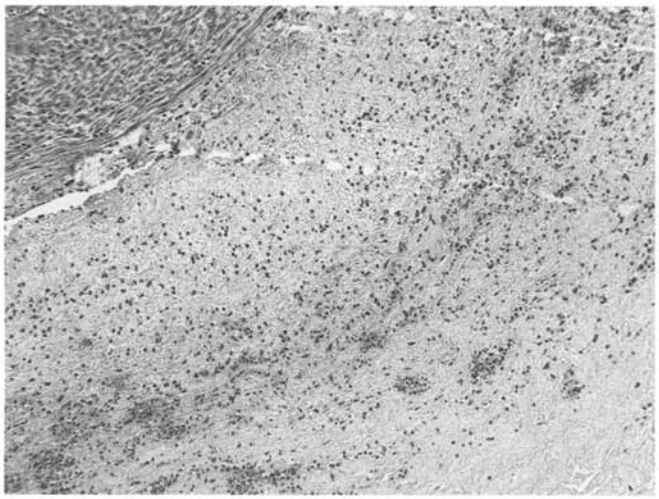


Fig. 12. Necrotizing funisitis (acute concentric perivasculitis).

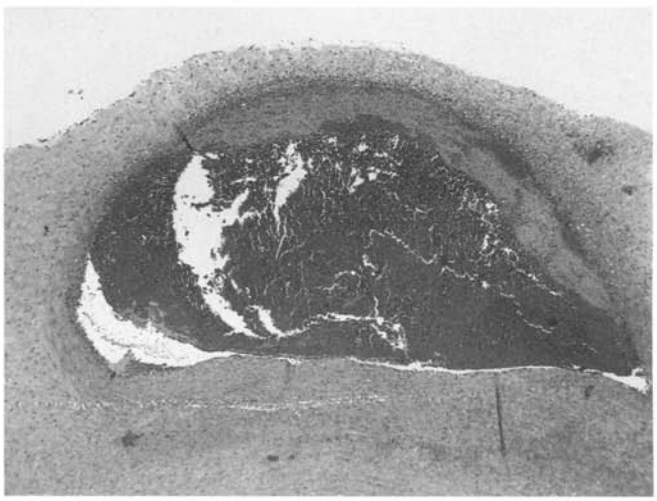


Fig. 14. Fetal vasculitis with nonocclusive chorionic vessel thrombus.

Meconium and Subacute Hypoxia

Clinical

- Pathogenesis:
  - Cord occlusion
  - Umbilical vein collapse
  - Vagally-mediated intestinal vasoconstriction
  - Reflex defecation
- Predisposing factors:
  - Large active babies
  - Long umbilical cord
  - Decreased amniotic fluid (common postdates, >42 weeks)
- Common (10% to 20% of all term deliveries); rarely if ever seen prior to 34 weeks
- Meconium aspiration syndrome:
  - Occurs in 8.6% of meconium-stained infants
  - Definition: Respiratory distress in a term infant requiring oxygen with an abnormal CXR
- Severe meconium aspiration syndrome/birth asphyxia:
  - Occurs in 2.9% of meconium-stained infants
  - Chemical pneumonitis
  - Extrapulmonary air leaks
  - Pulmonary hypertension
  - Hypoxic-ischemic encephalopathy
  - High morbidity and mortality
  - Often coexistent with other placental findings indicative of subacute (in utero) hypoxia

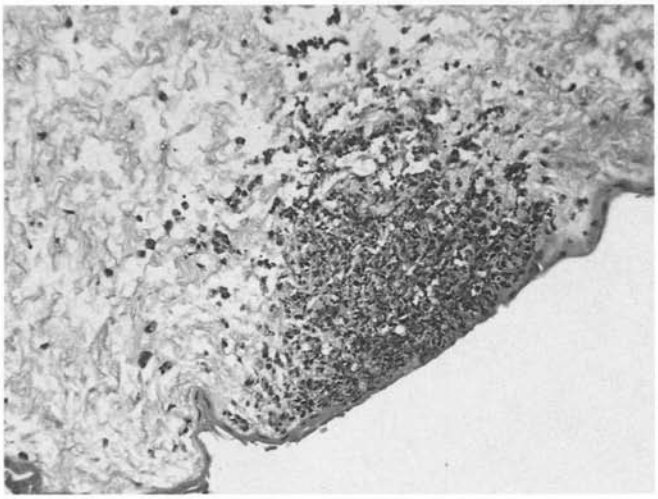


Fig. 15. Peripheral funisitis (*Candida* spp).

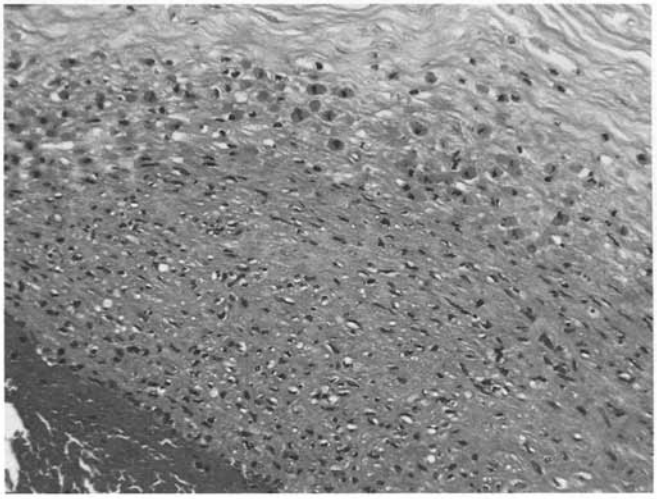


Fig. 17. Meconium associated peripheral vascular necrosis.

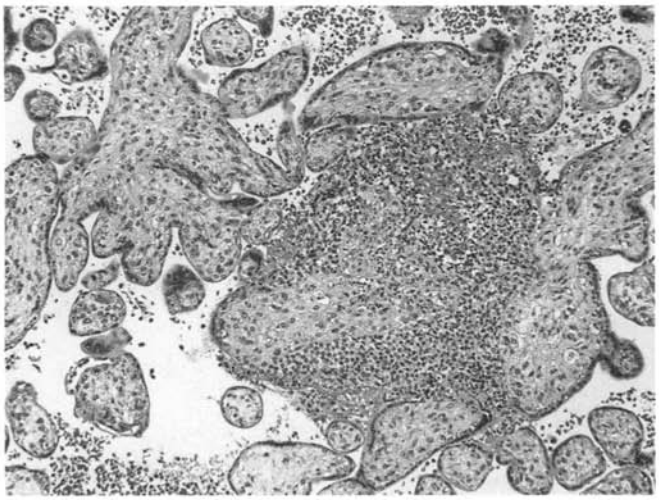


Fig. 16. Acute villitis and intervillositis (*Listeria moncytogenes*).

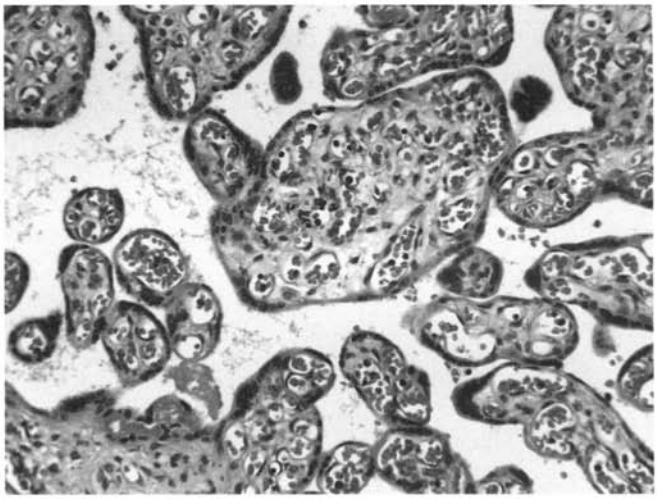


Fig. 18. Increased circulating fetal NRBC.

Gross Findings

- Green staining of membranes and chorionic plate (focal or diffuse)
- Green staining of umbilical cord (with prolonged exposure)
- Slippery edematous membranes with chorion-amnion separation
- Occasionally associated with signs of umbilical cord compression:
  - True knots, hypercoiling, peripheral cord insertion, tethered cord, focal attenuation or edema

Microscopic

- Meconium:
  - Pigment-laden macrophages, often with cytoplasmic vacuoles:
    - Early: amnion only
    - ≥3hrs: membranous decidua
    - Late: chorionic plate, Wharton's jelly
  - Number of macrophages correlates with amount of meconium within the first few hours after discharge
- Peripheral vascular necrosis (very late change) **(Figure 17)**:
  - Extensive apoptosis of vascular smooth muscle cells (cellular dehiscence, nuclear pyknosis, cytoplasmic eosinophilia)
  - Seen at the periphery of umbilical or chorionic vessels (bad prognostic sign)
- Associated changes suggestive of subacute hypoxia:
  - Increased nucleated red blood cells **(Figure 18)**:
    - Indicator of significant in utero hypoxia leading to erythropoietin release

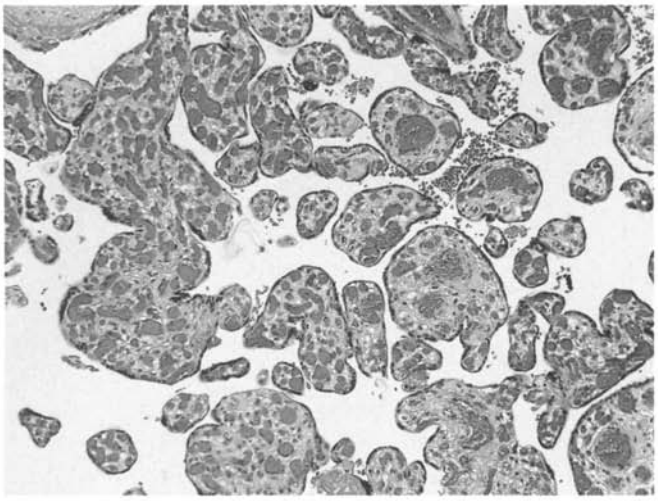


Fig. 19. Villous chorangiosis.

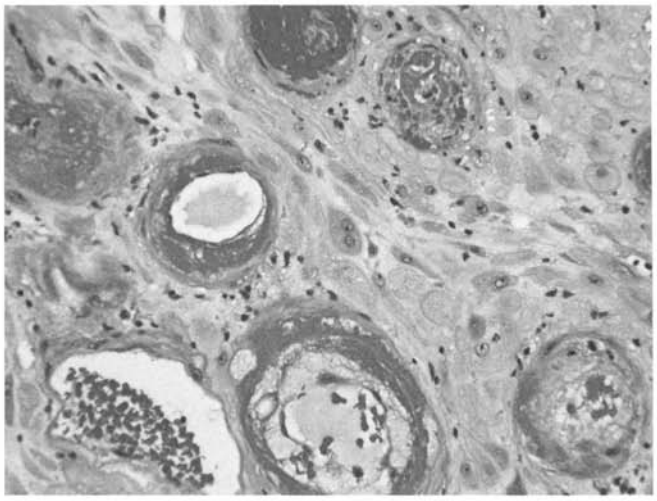


Fig. 20. Acute atherosis of decidual arterioles.

- Villous chorangiosis (**Figure 19**):
  - Numerical increase in the number of capillaries per terminal villus
  - >10 capillaries in >10 villi in several areas of the placenta
  - Seen in women delivering at high altitudes
  - Capillary proliferation in response to decreased oxygen availability or other angiogenic factors

Differential Diagnosis of Green Color

- Severe acute chorioamnionitis
- Chronic marginal separation/abruption with hemoglobin breakdown products
- Immune hemolytic anemia with bilirubin
- Pigment-laden macrophages:
  - Hemosiderin (chronic marginal separation/ abruption)
  - Nonspecific (lipofuschin)

Maternal Arteriopathies and Preeclampsia

Clinical

- Primary (pregnancy-specific):
  - Superficial implantation
  - Failure of trophoblast to remodel spiral arteries predisposing to hypoxia and trophoblast-induced endothelial damage with subsequent fibrinoid necrosis of spiral arteries ("acute atherosis")
  - Increased circulating soluble VEGF-receptor (correlated with specific glomerular changes)
- Secondary (underlying maternal disease):
  - Coagulopathy: antiphospholipid antibodies, others
  - Essential hypertension
  - Insulin-dependent diabetes mellitus
  - Autoimmune disease
  - Chronic renal disease
- Risk factors for primary disease:
  - Primiparity (or multiparity with different father)
  - Positive family history
  - Metabolic syndrome: obesity/glucose intolerance/hypertension/hyperlipidemia
- Presentations:
  - Preeclampsia (hypertension, edema, and proteinuria)
  - Intrauterine growth retardation (IUGR)
  - Placental insufficiency and chronic fetal hypoxia
  - Abruptio placenta
  - Preterm labor

Gross Findings

- Placental weight less than expected for gestational age
- Old and recent infarcts
- Retroplacental hematoma consistent with abruptio placenta
- Thin umbilical cord indicative of fetal volume depletion

Microscopic

- Membrane decidua:
  - Fibrinoid necrosis ("atherosis") of spiral arterioles **(Figure 20)**
  - Mural smooth muscle hypertrophy of spiral arterioles **(Figure 21)**
- Villous parenchyma:
  - Chronic undergrowth: distal villous hypoplasia (decreased terminal villi) **(Figure 22)**
  - "Accelerated maturation":
    - Increased syncytial knots **(Figure 23)**
    - Villous agglutination **(Figure 24)**

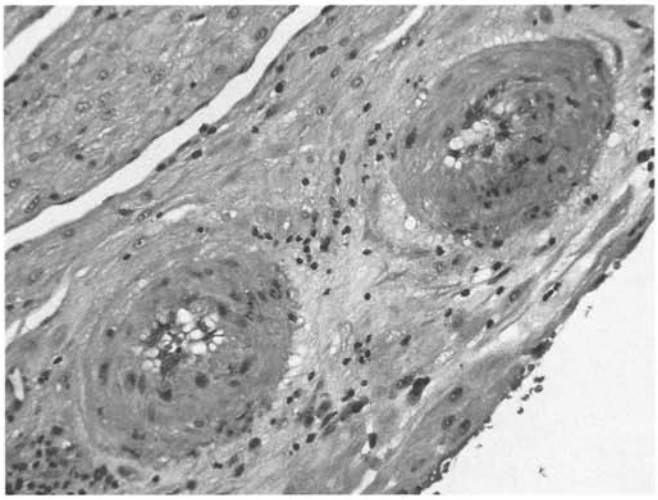


Fig. 21. Mural hypertrophy of decidual arterioles.

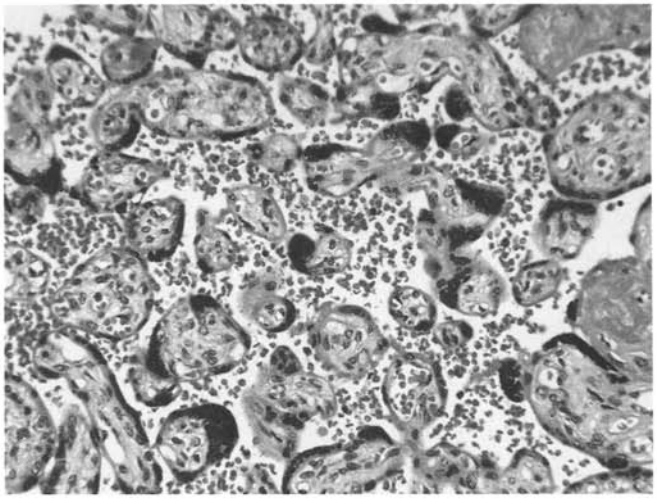


Fig. 23. Increased syncytial knots.

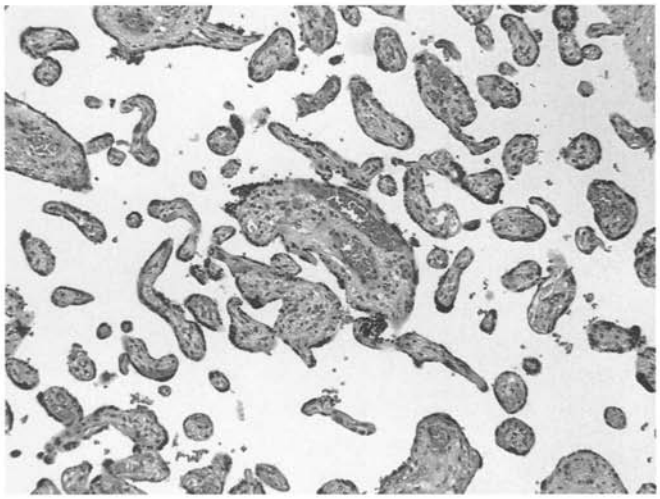


Fig. 22. Distal villous hypoplasia.

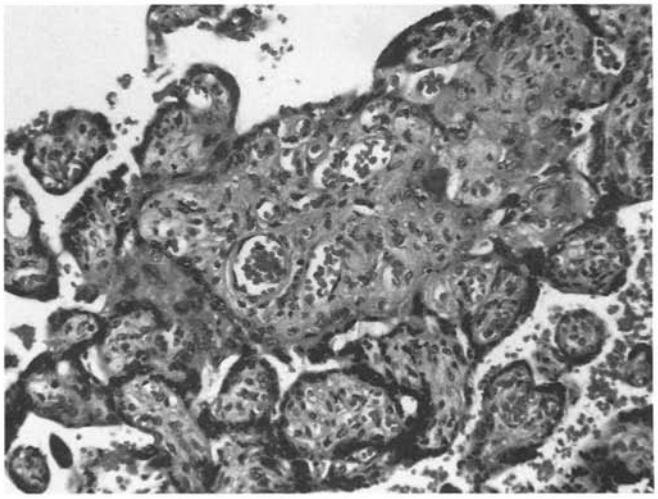


Fig. 24. Villous agglutination.

- Intervillous space:
  - Increased intervillous fibrin (proximal and distal stem villi) **(Figure 25)**
  - Villous infarcts **(Figure 26)**
- ♦ Basal plate:
  - Excessive immature intermediate trophoblast
  - Large amounts of decidua containing only placental site trophoblastic giant cells
  - Unremodelled spiral arteries with persistent smooth muscle walls

Differential Diagnosis (Villous Infarcts)

- ♦ Perivillous fibrin plaques:
  - Lack villous agglutination, karyorrhectic trophoblast, and PMN debris
- ♦ Intervillous thrombi **(Figure 27)**:
  - Spherical, nonbasal, and show only focal pressure-related infarction of adjacent villi

Hemorrhagic Lesions

Intervillous Thrombus (Fetomaternal Hemorrhage)

Clinical

- ♦ Pathogenesis:
  - Traumatic rupture of terminal villous vessels with fetal bleeding into maternal circulation
- ♦ Kleihauer-Betke acid elution technique (or flow cytometry):
  - Quantifies volume of fetomaternal hemorrhage by staining for cells containing fetal hemoglobin in the maternal circulation
- ♦ Intervillous thrombi and small amounts of fetomaternal hemorrhages both common

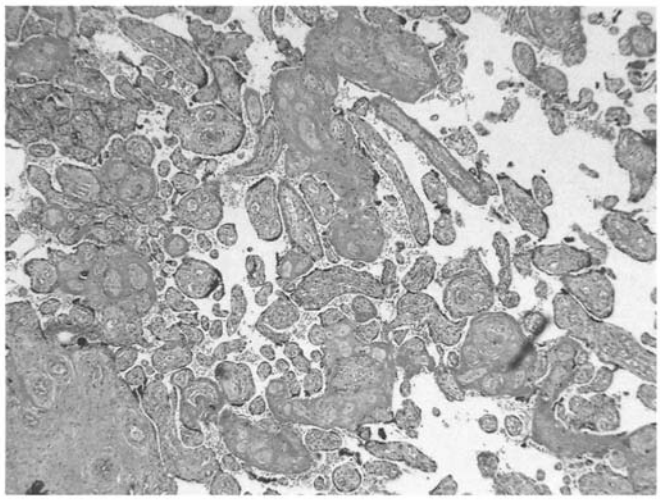


Fig. 25. Increased intervillous fibrin.

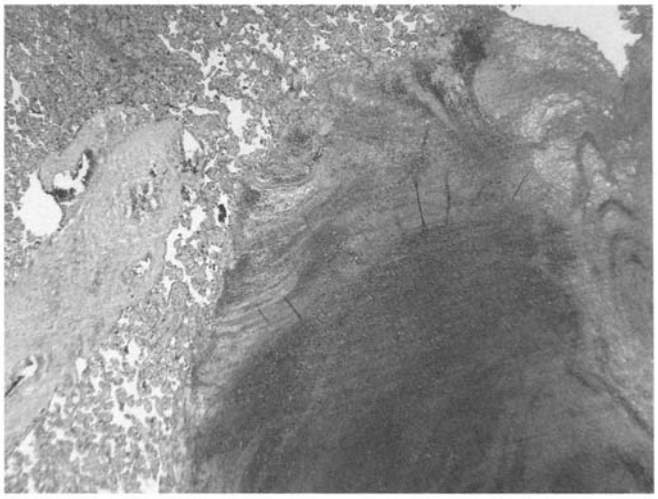


Fig. 27. Intervillous thrombus.

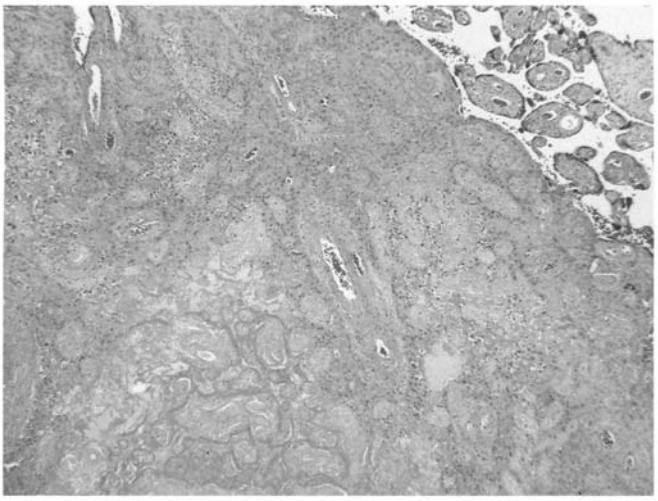


Fig. 26. Villous infarct.

- Volume of hemorrhage correlates with number and size of thrombi
- Massive fetomaternal hemorrhage (associations):
  - Nonimmune hydrops fetalis:
    - Intrauterine fetal death
    - Cerebral palsy
  - Abnormal fetal monitoring (sinusoidal heart rate)

Gross Findings

- Spherical lesions displacing and surrounded by villi:
  - Recent: firm, glassy, dark red
  - Old: firm, light red, laminated

Microscopic **(Figure 27)**

- Recent or organizing hemorrhage in the intervillous space
- Surrounded by and displacing villi without significant adjacent villous infarction
- Significance is enhanced by the findings of increased nucleated red blood cells and changes suggestive of hydrops fetalis (villous edema, cytotrophoblast proliferation, and increased Hofbauer cells)

Differential Diagnosis

- Villous infarct with central hemorrhage:
  - Surrounding rim of infarcted villi
- Retroplacental hemorrhage with intraplacental extension:
  - Irregular with focal extension to basal plate
- Massive subchorial thrombus:
  - Laminated expansile subchorionic hemorrhages elevating the chorionic plate
  - Probably due to ruptured stem villous vessels
  - Associated with very bad prognosis
- Septal cyst:
  - Clear-blood-tinged fluid-filled cyst of villous parenchyma
  - Surrounded by intermediate trophoblast

Retroplacental Hemorrhage Consistent with Abruptio Placenta

Clinical

- Classical presentation:
  - Vaginal bleeding, uterine rigidity, abdominal pain, hypotension, anemia
- Pathogenesis:
  - Premature rupture of one of the major arteries supplying the intervillous space, resulting in forceful separation of the placenta from the uterus

- Risk factors:
  - Preeclampsia/maternal uterine arteriopathy
  - Substance abuse: cocaine and smoking
  - Physical trauma
- Clinicopathologic correlation recommended:
  - Only 1/2 of clinical abruptio placentae are pathologically apparent
  - Only 1/2 of pathologic retroplacental hematomas are associated with clinical abruptio placenta
- Sequela:
  - Acute birth asphyxia
  - Intrauterine fetal death
  - Long term neurologic impairment

Gross Findings

- Retroplacental hematoma
- Usually central or eccentric, indenting or rupturing into the villous parenchyma
- Concave indentation of the basal plate without a retroplacental hematoma
- Irregular basal intervillous thrombus

Microscopic

- Basal plate: intradecidual hemorrhage, rupture through basal plate, maternal arteriopathy (rare)
- Parenchyma: intravillous stromal hemorrhage, irregular basal intervillous thrombus

Differential Diagnosis

- Subacute abruption:
  - Retroplacental hematoma with overlying recent villous infarction)
- Acute peripheral separation:
  - Marginal hematoma without significant indentation or rupture of basal plate

Retroplacental Hemorrhage Consistent with Peripheral Separation

Acute Peripheral Separation (Marginal Abruption)

Clinical

- Classical presentation:
  - Preterm labor with vaginal bleeding
  - Premature rupture of membranes
  - Rapid delivery at any gestation
- Pathogenesis:
  - Rupture of dilated or inflamed marginal veins as a consequence of increased venous pressure
  - Collapse of the gestational sac following rupture of membranes, or acute inflammation
- Risk factors:
  - Premature rupture of membranes
  - Acute chorioamnionitis
  - Prior history of preterm birth
- Clinicopathologic correlation: probably accounts for much of the poor correlation between clinical abruptio placenta and pathologic retroplacental hemorrhages (*see* above)

Gross Findings

- Marginal retroplacental hematoma without significant indentation of villous parenchyma

Microscopic

- Marginal decidual venous dilatation, hemorrhage, and ischemic necrosis

Differential Diagnosis

- Abruptio placenta:
  - Usually central or paracentral, indentation of parenchyma
  - Overlying villous ischemia (stromal hemorrhage or infarction)

Chronic Peripheral Separation (Chronic Abruption)

Clinical

- Classical presentation:
  - Recurrent vaginal bleeding throughout pregnancy, often with preterm labor and watery vaginal discharge (due to clot retraction)
- Pathogenesis:
  - Chronic marginal venous hemorrhage without progression to retroplacental separation; possibly related to abnormal, poorly supported implantation
- Risk factors:
  - Prior history of pregnancy loss
- Sequela:
  - IUGR
  - Preterm labor
  - Long term neurologic impairment (term births)

Gross Findings

- Old, pale brown, marginal blood clot
- Circumvallate membrane insertion (complete or partial)
- Greenish discoloration of chorionic plate

Microscopic

- Hemosiderin-laden macrophages in membranes and chorionic plate **(Figure 28)**
- Ridge of old blood clot pushing membranes away from margin (circumvallation) **(Figure 29)**

Special Stains

- Iron stain to confirm hemosiderin deposition

Differential Diagnosis

- Circummarginate membrane insertion: membranes inserted away from the placental margin, but lacking the ridge of old blood clot and hemosiderin deposits; often accompanied by redundant folding of membranes at the placental margin

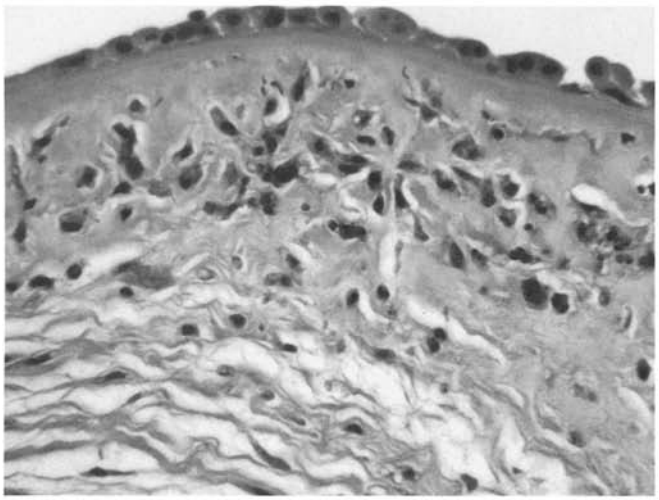


Fig. 28. Chronic peripheral separation (diffuse chorioamnionic hemosiderosis).

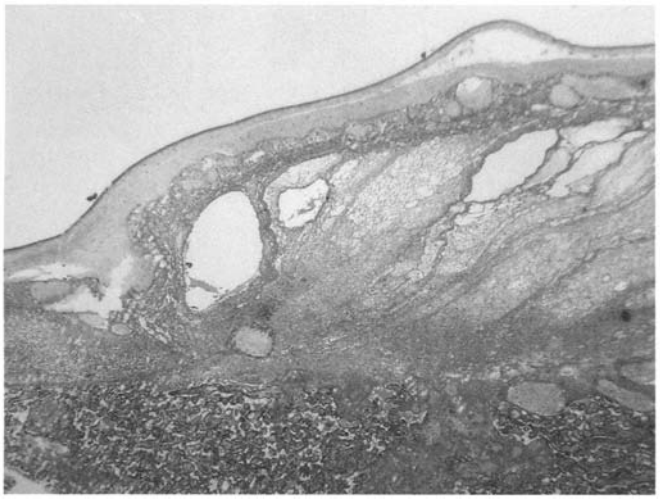


Fig. 29. Chronic peripheral separation (circumvallate membrane insertion).

Fetal Thromboocclusive Lesions

Changes Consistent with Fetal Vascular Obstruction (Fetal Thrombotic Vasculopathy)

Clinical

- Pathogenesis:
  - Thrombosis or other decrease in blood flow affecting umbilical, chorionic plate or stem villous arteries resulting in downstream hyaline villous collagenization and loss of fetal capillaries
- Risk factors:
  - Coagulopathy:
    - Maternal antiphospholipid or antiplatelet antibodies
    - Inherited fetal defect in coagulation cascade
    - Hypoxia or traumatic endothelial damage
  - Chronic umbilical cord obstruction
  - Diabetes mellitus
- Sequela:
  - Intrauterine fetal death
  - Fetal thromoembolic disease (especially CNS)
  - Subacute hypoxia

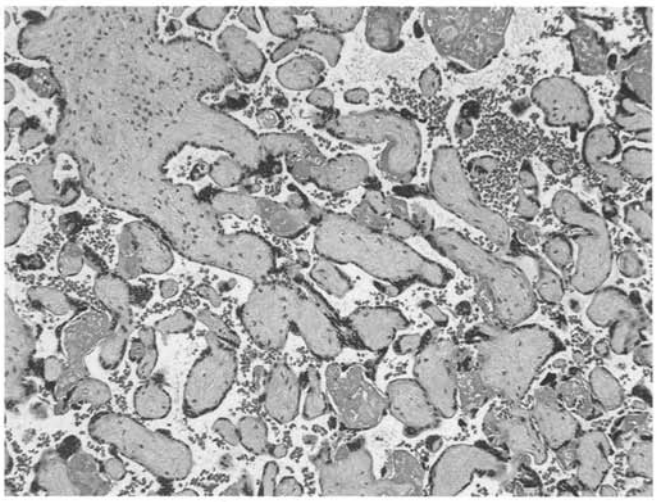


Fig. 30. Hyalinized avascular villi (fetal thrombotic vasculopathy).

Gross Findings

- Occasional: thrombus in chorionic plate vessel
- Segmental or arcuate region of relative villous pallor

*Microscopic **(Figure 30)***

- Vascular thrombi (adherent, laminated, and/or calcified)
- Large or small groups of avascular terminal villi with stromal hyalinization (average of 15 affected villi/slide required to make diagnosis of Fetal Thrombotic Vasculopathy)

Differential Diagnosis

- Changes consistent with vascular stasis ("hemorrhagic endovasculitis") (*see* below)
- Maternal infarct:
  - Collapsed intervillous space
  - Aggregated villi
  - Karyorrhexis, PMN debris, and trophoblast necrosis
- Villitis of unknown etiology with obliterative fetal vasculopathy:
  - Avascular villi with other terminal and stem villous vessels showing a chronic lymphohistiocytic infiltrate

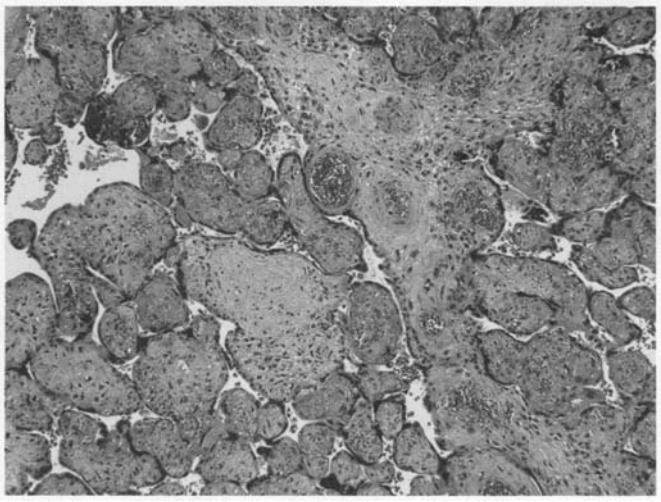


Fig. 31. Villous stromal karyorrhexis (hemorrhagic endovasculitis).

Changes Consistent with Vascular Stasis (overlaps with "Hemorrhagic Endovasculitis")

Clinical

- Pathogenesis:
  - Decreased flow through terminal villi (stasis):
    - Consequence of umbilical or chorionic venous occlusion, mimics changes accompanying stillbirth
    - May progress to hyalinized avascular villi
- Risk factors:
  - Chronic or recurrent umbilical cord obstruction
  - Fetal heart failure or polycythemia
  - Venous thrombosis
- Sequela:
  - Acute or subacute fetal hypoxia
  - Intrauterine fetal death

Gross Findings

- Large, congested, and often meconium-stained placenta and cord

Microscopic

- Terminal villi **(Figure 31):**
  - stromal karyorrhexis
  - Old and recent hemorrhage
  - Increased Hofbauer cells
  - Hypovascularity
- Chorionic plate and stem villous vasculature:
  - Fibromuscular sclerosis
  - Intimal fibrin cushions (fibrinoid material entrapped within chorionic vessel wall)
  - Recent thrombi

Differential Diagnosis

- Changes due to recent stillbirth:
  - The diagnosis of venous thromboocclusive disease (hemorrhagic endovasculitis) in stillborns should be made with caution and depends on seeing nonaffected areas of the placenta
- Changes consequent to improper placental storage:
  - Fresh or incompletely fixed placentas stored for prolonged periods without refrigeration also mimic stillbirth and venous thromboocclusive change
- Fetal thrombotic vasculopathy:
  - Avascular villi with stromal hyalinization
  - Lack hemorrhage or significant villous stromal karyorrhexis

Chronic Inflammation and Coagulation

Congenital Infection

Clinical

- TORCH (pnemonic for organisms and serologic screening test):
  - *Toxoplasma gondii*
  - Others (syphilis, other organisms rarely found in the United States)
  - Rubella virus
  - Cytomegalovirus
  - Herpes viruses (herpes simplex, EBV, varicella zoster)
- Pathogenesis:
  - Hematogenous infection of the fetus and placenta with a diffuse inflammatory response in the placenta and direct teratogenic effects on the fetus
- Typical features:
  - All: hepatosplenomegaly, cytopenias, pneumonitis
  - *T. gondii*: CNS calcifications, retinitis
  - Rubella: congenital heart disease, cataracts, skin rash
  - Cytomegalovirus: CNS calcifications, retinitis, ascites
  - Herpes simplex: IUGR, microcephaly, hepatic necrosis
  - Syphilis: bone, skin, and mucosal membranes; GI lesions
  - Varicella zoster: limb and radicular skin defects
- Recurrence risk: Most TORCH infections are primary and confer protective immunity, preventing recurrence.

Gross Findings

- Small for gestational age placenta: herpes viruses, rubella
- Large for gestational age placenta: syphilis, *T. gondii*

Microscopic

- Common:
  - Diffuse lymphohistiocytic villitis with villous fibrosis and calcification

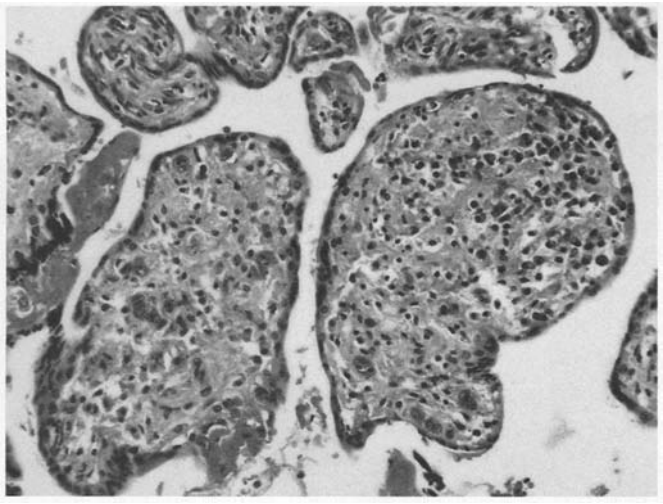


Fig. 32. Placental cytomegalovirus.

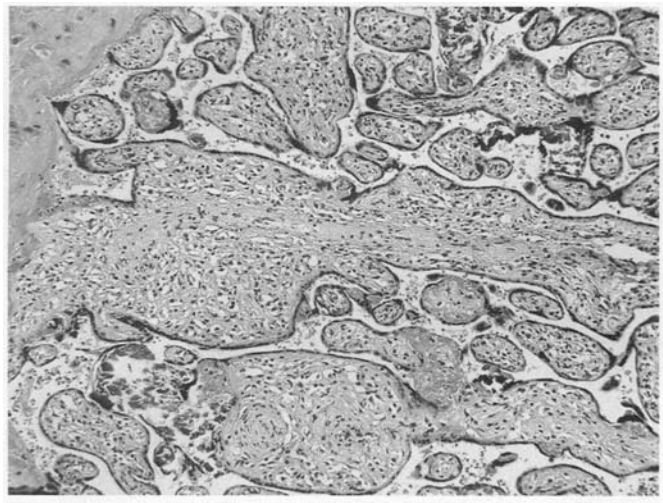


Fig. 33. Placental syphilis.

- Chronic choriodeciduitis
- Increased nucleated red blood cells

♦ Specific:
- *T. gondii*: umbilical cord pseudocysts
- Rubella: viral inclusions, endothelial necrosis
- Cytomegalovirus **(Figure 32)**: viral inclusions, villous plasma cells
- Herpes simplex, Varicella: viral inclusions. prominent necrosis
- Syphilis **(Figure 33)**: necrotizing umbilical periphlebitis, proliferative stem villous periarteritis

Special Studies

♦ Immunocytochemistry: CMV, HSV

♦ Silver stains (Warthin-Starry, Dieterle, Steiner): syphilis

Differential Diagnosis

♦ Villitis of unknown etiology (VUE):
- Nonuniform patchy involvement
- Predominantly lymphocytic
- More intervillositis, less choriodeciduitis, less necrosis
- Later gestational age, no fetal anomalies

♦ Nonspecific increase in Hofbauer cells (especially common with hydrops):
- Lack lymphocytes, fibrosis, necrosis, or chorio-deciduitis

Villitis of Unknown Etiology (VUE)

Clinical

♦ Presentation:
- Nonhypertensive IUGR
- Intrauterine fetal death:
  - Recurrent reproductive failure
  - Cerebral palsy, especially in cases with stem vasculitis and avascular villi

♦ Pathogenesis:
- Infiltration of fetal villous stroma by maternal T-lymphocytes derived from the intervillous space
- Basis for transepithelial migration and recurrence is poorly understood:
  - Relatively common (3% to 5% of term pregnancies)
  - 20% to 30% recurrence risk

♦ IUGR and other fetal morbidities parallel the extent of involvement

♦ Focal VUE relatively benign

*Microscopic **(Figure 34)***

♦ Nonuniform chronic inflammation of terminal and stem villi

♦ Lymphocytic, lymphohistiocytic, granulomatous, and active (with PMNs) variants:

♦ Basal and diffuse subtypes

♦ Obliterative fetal vasculopathy: involvement of stem villi with stem vasculitis, vascular occlusion, and extensive downstream avascular villi associated with adverse fetal outcome

♦ Chronic intervillositis and perivillous fibrin common

♦ Plasma cells common in decidua, never in villi

Chronic Histiocytic Intervillositis (Massive Chronic Intervillositis)

Clinical

♦ Rare lesion associated with spontaneous abortion and recurrent reproductive failure

♦ May be related to autoimmune disease and/or maternal alloimmune responses to oncofetal antigen

*Microscopic **(Figure 35)***

♦ Diffuse infiltration of intervillous space by monocyte-macrophages

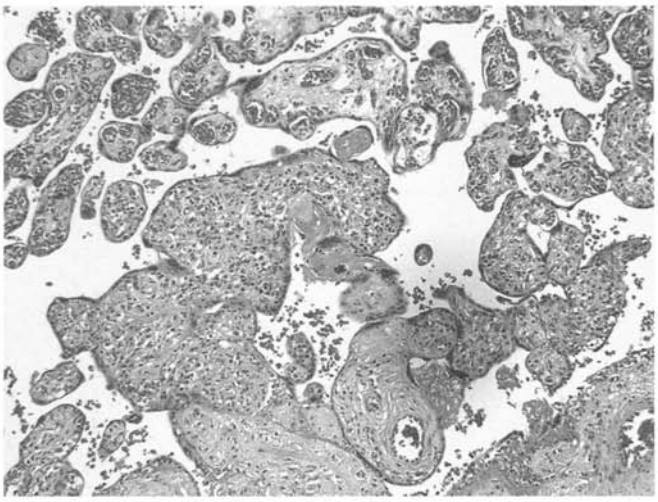


Fig. 34. Villitis of unknown etiology (VUE).

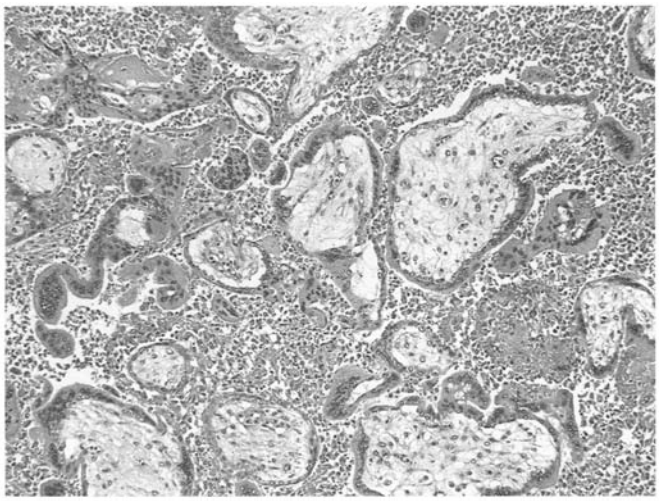


Fig. 35. Chronic histiocytic intervillositis (massive chronic intervillositis).

- Abundant perivillous fibrin and trophoblast necrosis
- Lacks a significant component of VUE

Differential Diagnosis

- Placental malaria:
  - Same histology; malarial pigment and/or organisms present
  - No history of recurrent reproductive failure
- VUE with prominent chronic intervillositis:
  - Villous inflammation
  - Polymorphous intervillous infiltrate (lymphs, monocytes, PMN)
- Acute villitis with intervillous abscesses (often *L. monocytogenes*):
  - Predominance of neutrophils, often with prominent eosinophils and plasma cells; stainable organisms

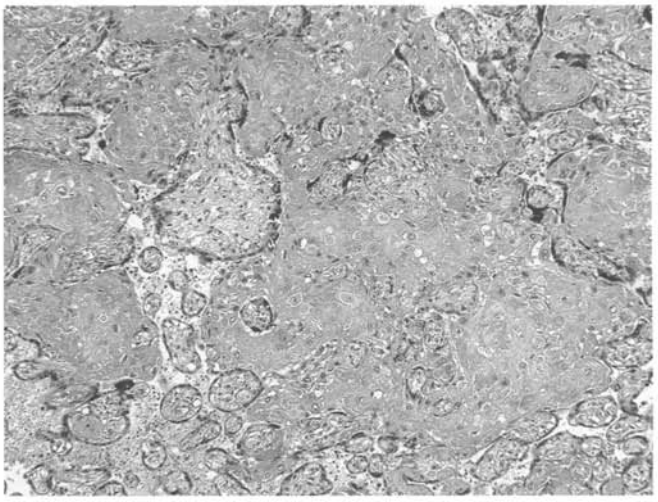


Fig. 36. Diffuse perivillous fibrin(oid) deposition (maternal floor infarction).

Massive Perivillous Fibrinoid Deposition (Maternal Floor Infarction)

Clinical

- Presentation:
  - Recurrent reproductive failure
  - Severe normotensive intrauterine growth retardation
- Pathogenesis (poorly understood):
  - ? Anomalous procoagulant expression on trophoblast
  - ? Inappropriate secretion of fibrinoid by trophoblast
  - ? Intervillous stasis due to relative maternal hypovolemia
- Very high recurrence risk:
  - Requires vigorous early fetal surveillance with early elective delivery or experimental therapy (steroids, aspirin, heparin, IVIG)

Gross Findings

- Placenta generally small for gestational age
- Placenta occasionally large (depending on the volume and distribution of fibrin)
- Classic maternal floor infarction has diffuse "orange rind-like" thickening of the basal plate
- Most cases show diffuse parenchymal thickening

*Microscopic (**Figure 36**)*

- Extensive fibrin (matrix type-fibrinoidoid) surrounds and displaces terminal villi often with focal villous degeneration
- Diffuse infiltration of fibrin(oid) by intermediate trophoblast (X cells)
- Accentuation of fibrin(oid) near and within the basal plate

Differential Diagnosis

- Perivillous fibrin plaque:
  - Localized lesion in term placentas
  - Transmural, no basal predominance
  - All villi within plaque are involved, intervillous space is collapsed, but villi lack degenerative changes
- VUE with chronic intervillositis:
  - Presence of polymorphous inflammatory infiltrate
  - Absence of X cells
- Perivillous fibrin (fibrin-type fibrinoid) associated with placental atrophy:
  - Focal change associated with thinning and attenuation of placental parenchyma
- Increased intervillous fibrin (fibrin-type fibrinoid):
  - Exageration of normal subchorionic fibrin to envelop stem villi and portions of the distal villous tree
  - Seen with other signs of maternal underperfusion (increasaed syncytial knots, villous agglutination, distal villous hypoplasia
  - Terminal and basal villi usually spared
- Old villous infarcts:
  - Intervillous space is collapsed and villi show degenerative changes
  - Localized, well-circumscribed, and extend up from basal plate

MULTIPLE PREGNANCY

General

- Monochorionic twin placentas are almost invariably monozygous (identical twins):
  - Derived from a single fertilized egg:
    - Usually have twin-twin anastomoses
    - Rare fraternal twins with dizygous monochorionic placentas reported in assisted reproductive technology (ART) patients
- Dichorionic twin placentas:
  - Either dizygous (derived from two independent fertilized eggs) or monozygous
  - Rarely, if ever, have vascular anastomoses

Clinical

- Dizygous (fraternal) twinning (depends on ovarian function):
  - Familial
  - Increased with African ancestry
  - Increased with ovulation induction (clomiphene) and other ART patients
- Monozygous twinning (error in embryogenesis):
  - Sporadic, also increased in ART patients
  - Spectrum extends from conjoined twins to monochorionic monoamnionic twins to monochorionic diamnionic to dichorionic diamnionic, depending on the exact timing of the error
- Clinical syndromes:
  - Increased incidence of preterm labor, preeclampsia, and cerebral palsy, all twins
  - Cord entanglement and IUFD, monoamnionic twins only
  - Twin oligohydramnios polyhydramnios syndrome (TOPS):
    - Twin-twin transfusion syndrome:
      - Monochorionic only; usually diamnionic
      - Size discrepancy with circulatory imbalance
      - Due to vascular anastomoses (1 small twin/1 large twin)
      - Often with hydrops of either or both twins
    - Occasionally acute following IUFD of one twin with high rate of cerebral palsy in survivor
    - Non-TTS:
      - Dichorionic twins with asymmetric placental insufficiency resulting in worsening IUGR of the disadvantaged twin (1 small twin/1 normal twin)

Gross Findings

- Separate placentas (dichorionic):
  - No assessment of dividing membranes required; injection studies not indicated
- One placenta with dividing membrane (mono- or dichorionic):
  - Peel dividing membrane (2 vs. 3 layers):
    - Three layers = diamnionic dichorionic:
      - Divide placentas, weigh, and process separately
      - Injection studies not necessary
      - Submit dividing membrane for histology
    - Two layers = diamnionic monochorionic:
      - Look for surface anastomoses (transfusion syndrome cases lack these)
      - Perform air (or other) injection studies for deep vascular anastomoses (potential for transfusion syndrome)
      - Do not separate placentas
      - Take sections from each twin's vascular territory
      - Submit dividing membrane for histology
- One placenta without dividing membrane = monoamnionic:
  - Process as described above for diamnionic monochorionic twins (except for dividing membrane)

Microscopic

- Monochorionic:
  - Dividing membrane has two layers of amnion only
  - Rule out fetal vascular occlusive lesions and asymmetry of villous developmenti secondary to differences in maternal vascular underperfusion
- Dichorionic:
  - Dividing membrane has two layers of amnion separated by a fused layer consisting of two chorions
  - Look for causes of placental insufficiency associated with TOPS syndrome or other placental lesions affecting one infant only

Air Injection Studies

- Select twin with lower birth weight (or smaller umbilical cord)
- Ligate and serially inject air distal to the ligation for each of the two to four arteries branching off cord (arteries travel over veins)
- Look for air appearing in veins (or arteries) of the second twin
- If negative, repeat with arteries from the second twin

Differential Diagnosis

- Monochorionic placenta with twins of different sexes:
  - Consider 46,XY/45,XO with loss of an X chromosome in one twin
- Separate placentas with vascular anastomoses:
  - Consider severe atrophy of the region between the umbilical cords in a monochorionic placenta

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28

Non-Neoplastic Renal Diseases

Donna J. Lager, MD

CONTENTS

I. Glomerular Diseases 28-3
- Morphologic Classification 28-3
- Primary Glomerular Diseases 28-3
  - Minimal Change Disease (MCD).....28-3
  - Focal Segmental Glomerulosclerosis (FSGS) 28-3
  - Membranous Nephropathy (MN).....28-5
  - IgA Nephropathy (IgAN) 28-6
  - Membranoproliferative (Mesangiocapillary) Glomerulonephritis (MPGN).....28-7
  - Post-Infectious Glomerulonephritis (PIGN) 28-7
  - Crescentic Glomerulonephritis.....28-8
  - Fibrillary Glomerulonephritis.....28-9
- Secondary Glomerular Diseases 28-10
  - Diabetes Mellitus (Diabetic Nephropathy) 28-10
  - Paraproteinemia 28-10
  - Systemic Lupus Erythematosus (Lupus Nephritis).....28-13
  - HIV Nephropathy 28-14
- Hereditary Systemic Disorders With Renal Involvement 28-15
  - Fabry's Disease.....28-15
  - Lecithin Cholesterol Acyltransferase (LCAT) Deficiency 28-16
  - Nail-Patella Syndrome 28-16
  - Lipodystrophy.....28-17
  - Hereditary Nephritis 28-18
    - Alport Syndrome.....28-18
    - Thin Glomerular Basement Membrane Syndrome 28-18
- Congenital and Infantile Nephrotic Syndrome.....28-19
  - Congenital Nephrotic Syndrome of the Finnish type 28-19
  - Diffuse Mesangial Sclerosis 28-19

II. Tubulointerstitial Diseases of the Kidney 28-21
- Acute Infectious Pyelonephritis (Ascending or Hematogenous Infection) 28-21
- Chronic Pyelonephritis.....28-21
  - Chronic Obstructive Pyelonephritis 28-21
  - Chronic Non-Obstructive Pyelonephritis (Reflux Nephropathy) 28-21
- Acute Tubulointerstitial Nephritis 28-22
- Acute Tubular Necrosis (ATN) 28-22
  - Ischemic Injury.....28-22
  - Nephrotoxic Injury 28-22
  - Light Chain Cast Nephropathy (Myeloma Kidney).....28-23

III. Vascular Diseases of the Kidney 28-23
- Benign Nephrosclerosis 28-23
- Malignant Nephrosclerosis.....28-24
  - Renovascular Hypertension (Renal Artery Stenosis) 28-24
  - Atherosclerosis 28-24
  - Fibromuscular Dysplasia (FMD) 28-24
- Thromboembolic Diseases 28-25
  - Cortical Infarcts 28-25
  - Renal Cholesterol Microembolism Syndrome 28-26

Thrombotic Microangiopathy.....28-26
Vasculitis 28-26

IV. Developmental and Cystic Diseases of the Kidney 28-27
Renal Dysplasia 28-27
Autosomal Dominant Polycystic Kidney Disease (ADPKD) 28-27
Autosomal Recessive Polycystic Kidney Disease (ARPKD) 28-29
Juvenile Nephrophthisis (Medullary Cystic Disease) 28-29
Acquired Renal Cystic Disease 28-29

V. Suggested Reading 28-30

GLOMERULAR DISEASES

Morphologic Classification (Table 1)

Table 1. Morphologic Classification

Normal glomeruli by light microscopy

Minimal change disease

Thin Glomerular Basement Membrane Disease

Early Alport disease

(Early membranous glomerulonephritis)

Focal/segmental lesions

Focal segmental glomerulosclerosis

Idiopathic vs. secondary

Focal segmental proliferative glomerulonephritis

Focal segmental necrotizing and crescentic glomerulonephritis

Diffuse glomerulonephritis

Membranous glomerulonephritis

Idiopathic vs. secondary

Proliferative glomerulonephritis

Mesangial proliferative glomerulonephritis

IgA nephropathy

Mesangial proliferative lupus nephritis

Endocapillary proliferative glomerulonephritis

Acute post-infectious glomerulonephritis

Mesangiocapillary glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN)

Diffuse proliferative lupus nephritis

Cryoglobulinemic glomerulonephritis

Chronic thrombotic microangiopathy

Crescentic glomerulonephritis

Immune complex mediated crescentic glomerulonephritis

Pauci-immune (Antineutrophil cytoplasmic antibody-associated) crescentic glomerulonephritis

Anti-glomerular basement membrane antibody mediated

Diffuse/nodular mesangial expansion

Diabetic glomerulosclerosis

Light chain deposition disease

Fibrillary glomerulonephritis

Amyloidosis

Primary Glomerular Diseases

Minimal Change Disease (MCD)

Clinical

- The most common cause of the nephrotic syndrome in children **(Table 2)**
- Mild periorbital edema, prior to the rapid onset of the nephrotic syndrome
- Proteinuria is "selective" or composed primarily of albumin
- Microscopic hematuria is rare; hypertension is unusual

Microscopic

- Light microscopy:
  - The glomeruli, tubules, and interstitium appear normal **(Figure 1)**
- Immunofluorescence microscopy:
  - Usually negative, mesangial IgM may occasionally be present
- Electron microscopy **(Figure 2)**:
  - Diffuse effacement of the epithelial cell (podocyte) foot processes (also see chapter 4)

Differential Diagnosis

- An early membranous lesion may look normal by light microscopy

Focal Segmental Glomerulosclerosis (FSGS)

Clinical

- Focal segmental glomerulosclerosis may be primary (idiopathic) or secondary to a number of etiologic agents, including:
  - Unilateral renal agenesis
  - Renal ablation
  - Sickle cell disease
  - Morbid obesity (with or without sleep apnea)
  - Reflux nephropathy
  - HIV nephropathy

Microscopic

- Light microscopy:
  - Focal and segmental glomerular sclerosis with capillary loop collapse, hyaline and lipid deposition, and often adhesion to Bowman's capsule **(Figure 3)**

Table 2. Classification of Primary Glomerulonephritis by Predominant Clinical Manifestations

	Nephrotic syndrome	*Nephritic syndrome*
Minimal change disease	+++++	–
Focal segmental glomerulosclerosis	++++	+
Membranous glomerulonephritis	++++	+
IgA nephropathy	+++	++
Membranoproliferative GN	++	+++
Acute post-infectious GN	+	++++
Crescentic glomerulonephritis	+	++++

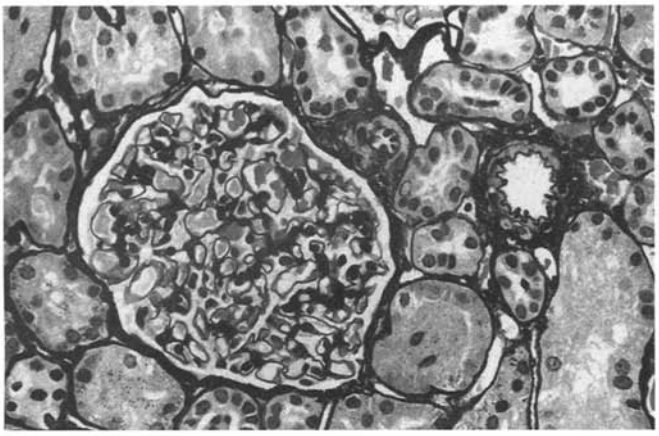


Fig. 1. Minimal change disease with normal glomerulus, tubules and arteriole.

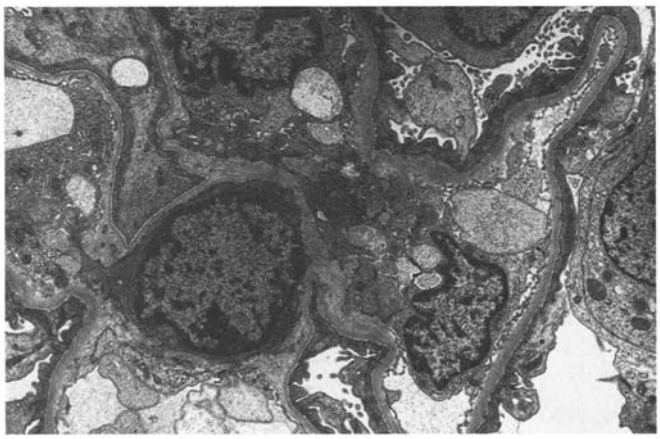


Fig. 2. Electron micrograph of minimal change disease showing global podocyte foot process effacement.

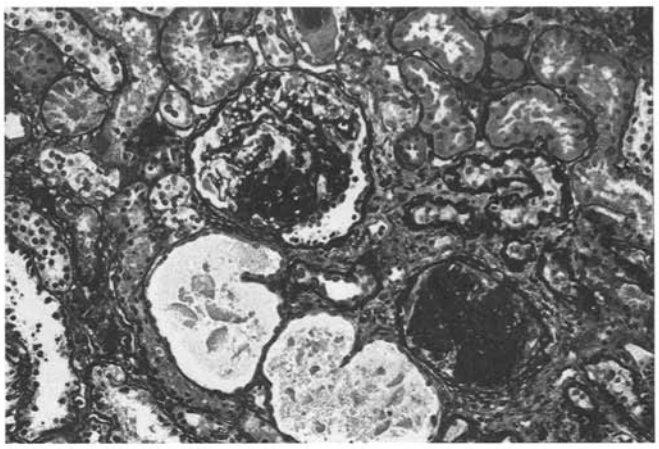


Fig. 3. Segmental (upper glomerulus) and global glomerulosclerosis (lower glomerulus) on silver stain.

  - The remainder of the glomerular tuft appears normal
  - Lesions begin or are more common near the cortico-medullary junction
- Immunofluorescence microscopy:
  - Deposition of IgM and C3 in mesangium or in segmental sclerosis
  - May be negative
- Electron microscopy: (also see chapter 4)
  - Effacement of podocyte foot processes
  - Podocyte denudation may be present focally as an early lesion
  - Segmental sclerosis may also be seen

Differential Diagnosis

- May be secondary (see earlier) and may be end result of segmental necrotizing disease

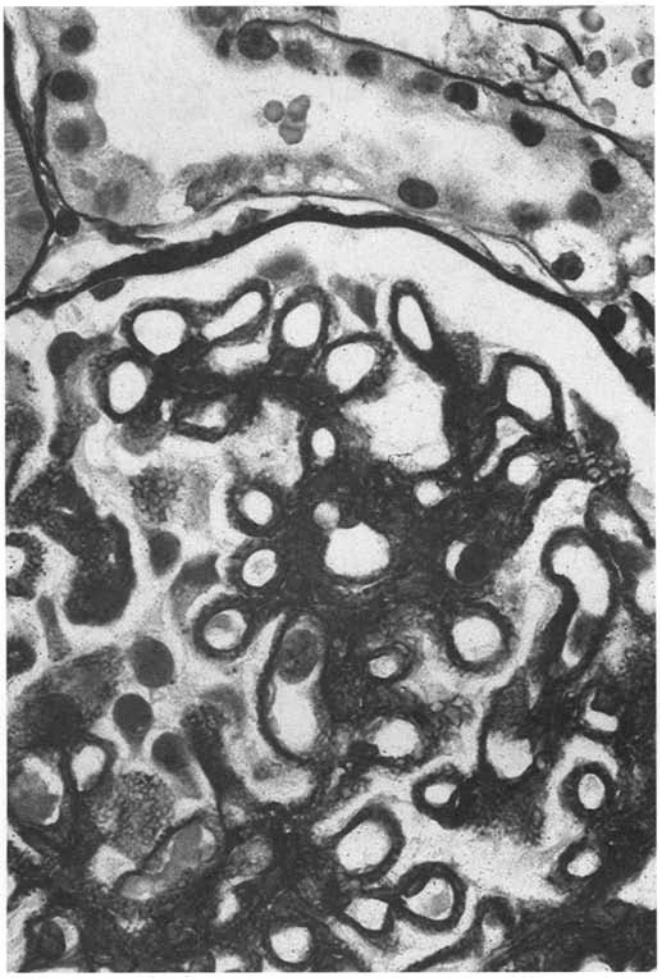


Fig. 4. Membranous nephropathy with subepithelial basement membrane "spikes" on silver stain.

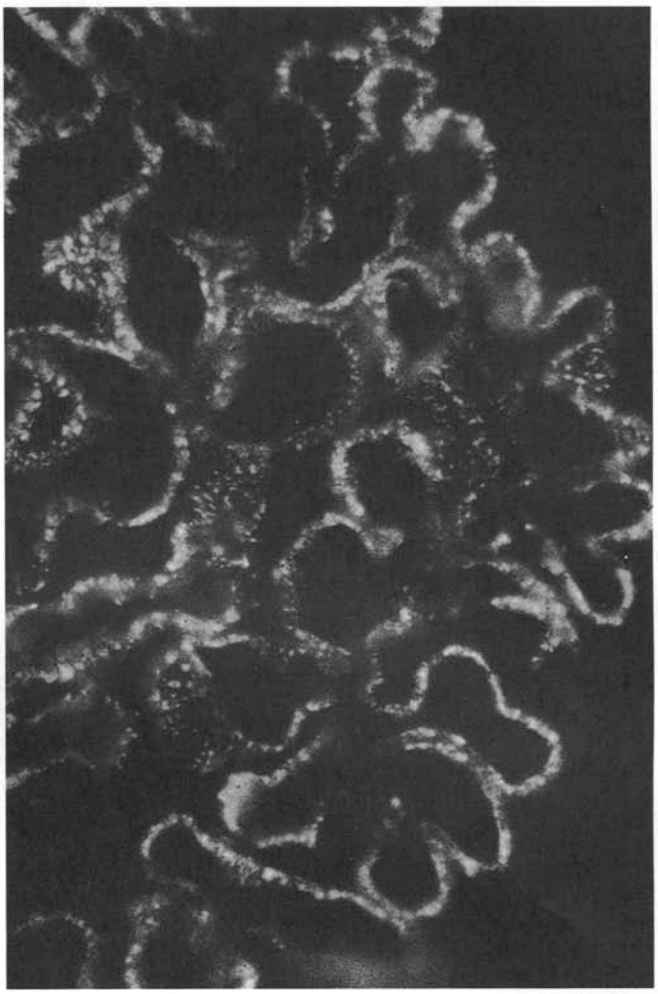


Fig. 5. Granular capillary wall staining with anti-IgG in membranous nephropathy.

Membranous Nephropathy (MN)

Clinical

- A major cause of the nephrotic syndrome in adults
- May occur in association with a number of disorders or exposure to antigenic substances, including:
  - Systemic lupus erythematosus
  - Malignant neoplasms
  - Exposure to gold and mercury
  - Penicillamine, captopril and NSAIDS
  - Hepatitis B
  - In association with metabolic disorders
- Thought to be a chronic antigen-antibody mediated disease in which the antigens are planted within the subepithelial space of the glomerular capillary loops

Microscopic

- Light microscopy (**Figure 4**):
  - The glomeruli may appear normal if the deposits are small (early disease)
  - Capillary walls are thickened, with subepithelial spikes on silver stain
- Immunofluorescence microscopy:
  - Bright granular staining of the capillary loops with anti-IgG and C3 **(Figure 5)**
- Electron microscopy: (also see chapter 4)
  - Subepithelial electron dense deposits with intervening basement membrane spikes **(Figure 6)**
  - Stage of disease correlates with incorporation of deposits into the glomerular basement membrane (GBM)

Differential Diagnosis

- Secondary causes of MGN are common, especially systemic lupus euthematosus
- In SLE, see mesangial deposits and reticulotubular structures
- An early lesion may be confused with minimal change disease (MCD) by light microscopy

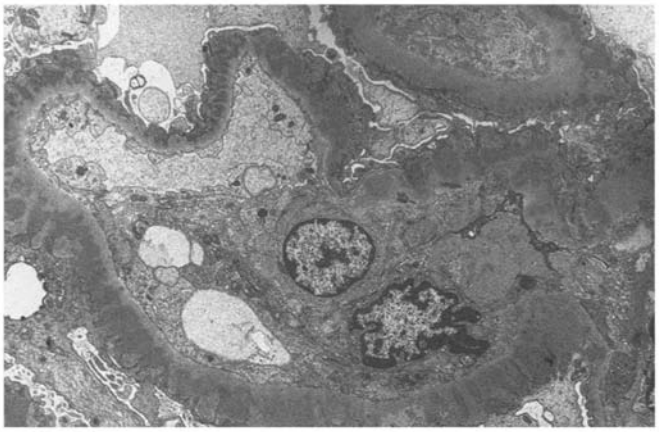


Fig. 6. Electron micrograph of subepithelial electron dense deposits and adjacent GBM spikes in membranous nephropathy.

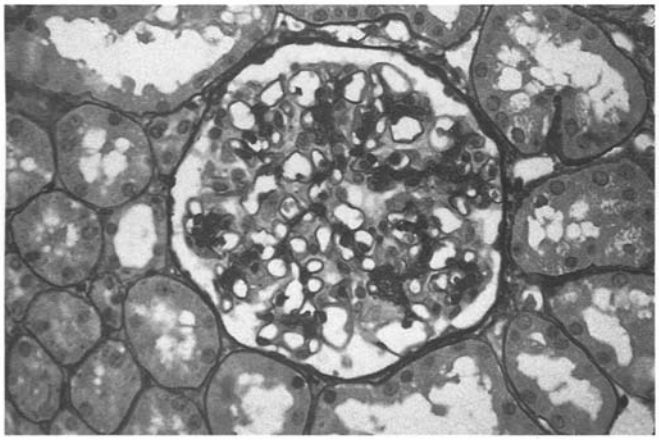


Fig. 7. Glomerulus with mild mesangial proliferation in IgA nephropathy.

IgA Nephropathy (IgAN)

Clinical

- Most common form of primary glomerulonephritis in the world
- Geographically variable
- May be related to a genetic or acquired abnormality of immune regulation leading to increased mucosal IgA synthesis in response to respiratory or gastro-intestinal exposure to environmental agents
- Occurs with increased frequency in patients with:
  - Celiac disease
  - Dermatitis herpetiformis
  - Liver disease
- Patients usually present with one of three syndromes:
  - Macroscopic hematuria concurrent with an upper respiratory infection; so-called synpharyngitic hematuria
  - Asymptomatic microscopic hematuria and variable proteinuria, including the nephrotic syndrome

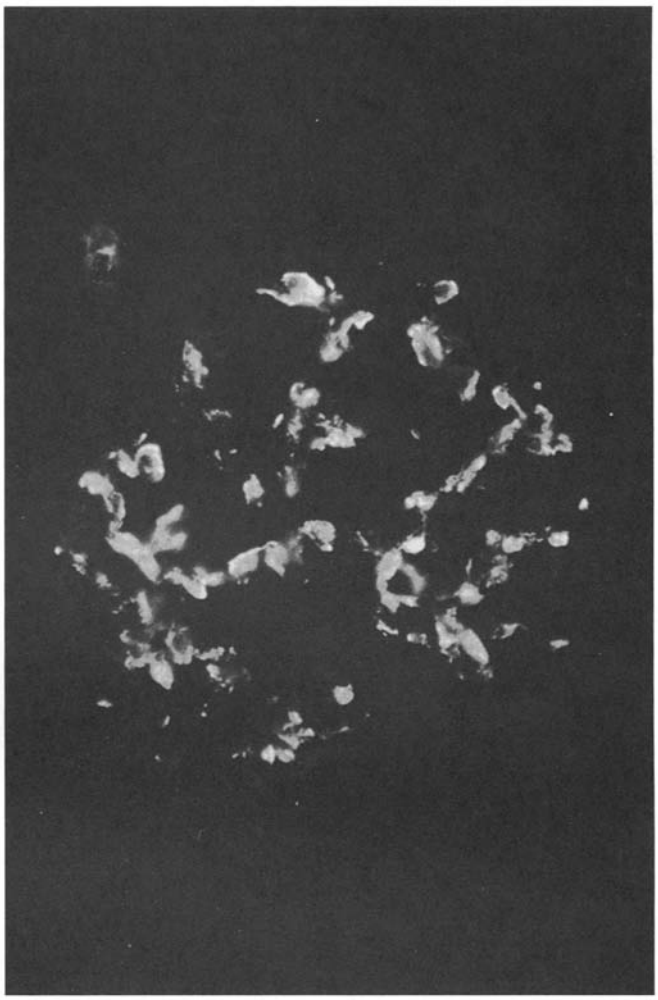


Fig. 8. Granular mesangial staining with anti-IgA in IgA nephropathy.

  - Henoch-Schonlein purpura is the systemic form of the disease process causing IgA nephropathy, and occurs more frequently in children than adults:
    - Patients with Henoch-Schonlein purpura manifest skin, joint, and intestinal involvement

Microscopic

- Light microscopy:
  - The glomeruli show some degree of mesangial hyper-cellularity **(Figure 7)**
  - Segmental proliferation, segmental sclerosis, and necrosis with crescents may be seen
- Immunofluorescence microscopy:
  - Mesangial deposits of IgA; IgG and C3 are variably present **(Figure 8)**
- Electron microscopy:
  - Deposits are present in the mesangium
  - Deposits often "paramesangial", beneath the basement membrane as it covers mesangium **(Figure 9)**

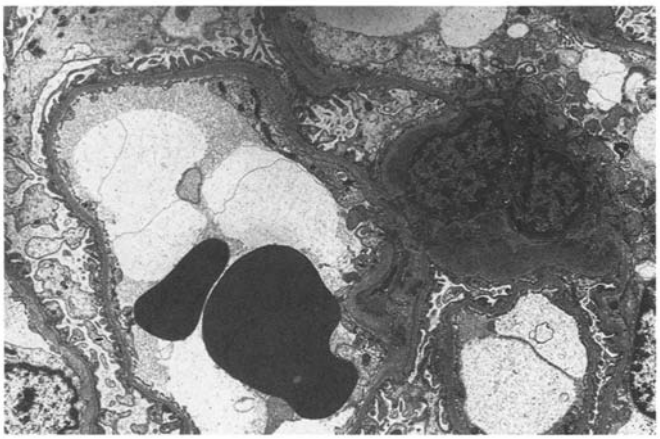


Fig. 9. Paramesangial electron dense deposits in IgA nephropathy.

Differential Diagnosis

- Mesangial deposits may also be seen in SLE (WHO Class II lupus nephritis) and post-infectious glomerulonephritis (later disease)

Membranoproliferative (Mesangiocapillary) Glomerulonephritis (MPGN)

Clinical

- Chronic progressive glomerulonephritis in older children and adults
- Circulating immune complexes have been identified in 50% of patients
- Activation of the complement system with hypo-complementemia is a hallmark of MPGN
- Patients may present with:
  - Nephrotic syndrome
  - Abnormal urinary sediment with non-nephrotic proteinuria
  - Acute nephritis
- May be primary or associated with other systemic disorders (secondary)
- Secondary causes of MPGN include:
  - Hepatitis B and hepatitis C infection
  - Infected ventriculoatrial shunts
  - Schistosomiasis
  - Alpha-1-antitrypsin deficiency
  - Chronic liver disease
- Patients with partial lipodystrophy may develop Type II MPGN

Microscopic

- Three types of MPGN (Types I, II, and III) have been described. All types feature mesangial hypercellularity and matrix expansion, and mesangial interposition

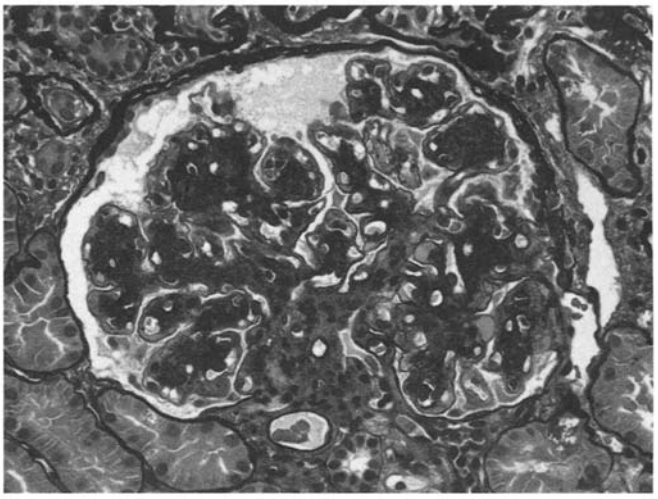


Fig. 10. Mesangial and endocapillary proliferation with GBM duplication in MPGN type I.

beneath the endothelium with formation of double contours:

  - Type I MPGN (**Figure 10**):
    - Subendothelial and mesangial deposits that frequently contain C3 and immunoglobulins
    - Most cases of secondary MPGN are Type I
  - Type II MPGN (dense deposit disease) (**Figure 11**):
    - Electron dense deposits within lamina densa of the GBM contain C3 in a linear pattern in the peripheral capillary loops with ring-like patterns in the mesangium
  - Type III MPGN:
    - Prominent mesangial, subendothelial, and subepithelial immune deposits
    - Type III is the least common form of MPGN

Post-Infectious Glomerulonephritis (PIGN)

Clinical

- May be caused by a number of infectious agents
- Post-streptococcal glomerulonephritis is primarily a disease of children, 6 to 7 years of age:
  - The onset is usually abrupt, with a latent period of 7–21 days between infection and the development of nephritis
  - During epidemics, the clinical attack rate is 10% to 12%, but subclinical disease occurs four times more frequently than overt disease; asymptomatic contacts may have hematuria
- Common initial clinical manifestations of post-streptococcal glomerulonephritis are:
  - Hematuria (microscopic or macroscopic)
  - Edema
  - Hypertension
  - Oliguria

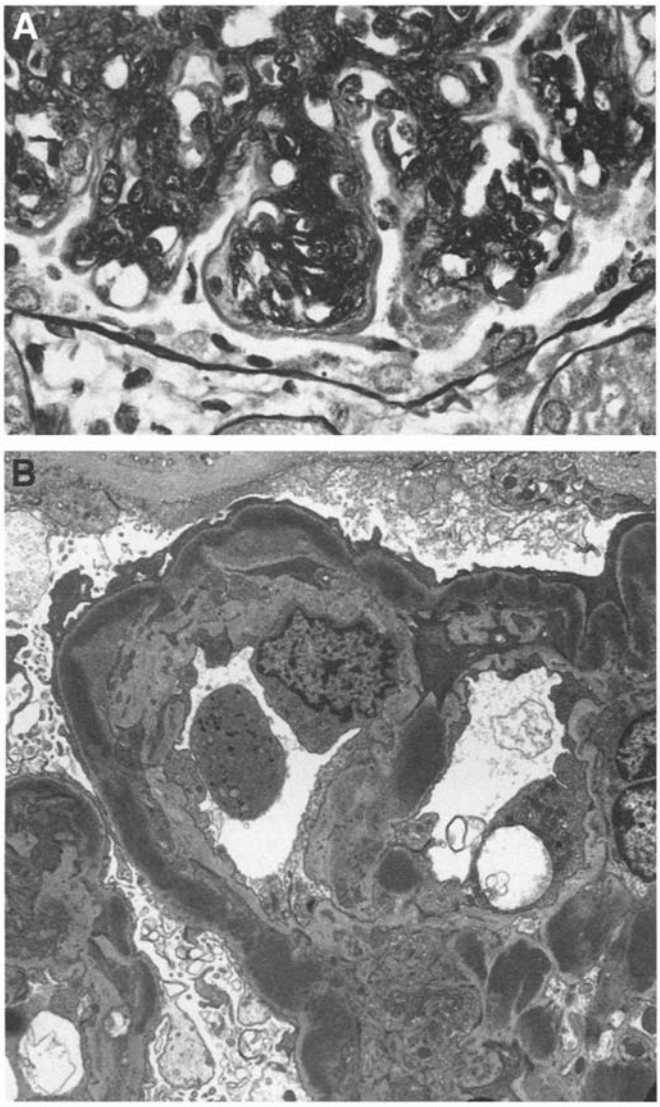


Fig. 11. **(A)** Dense deposit disease (MPGN type II) with thickened, silver negative capillary wall. **(B)** Electron micrograph of interrupted, intra-membranous electron dense deposits in dense deposit disease.

- The acute clinical episode of post-streptococcal glomerulonephritis is usually self-limited, and complement levels, which are usually depressed acutely, return to normal within 6 weeks
- In most patients, hematuria disappears by 6 months, but proteinuria may persist for 2 years in one-third of patients

Microscopic

- Light microscopy:
  - The glomeruli show diffuse mesangial proliferation and endocapillary proliferation with infiltration of neutrophils and mononuclear inflammatory cells **(Figure 12)**
  - Crescents may also be present

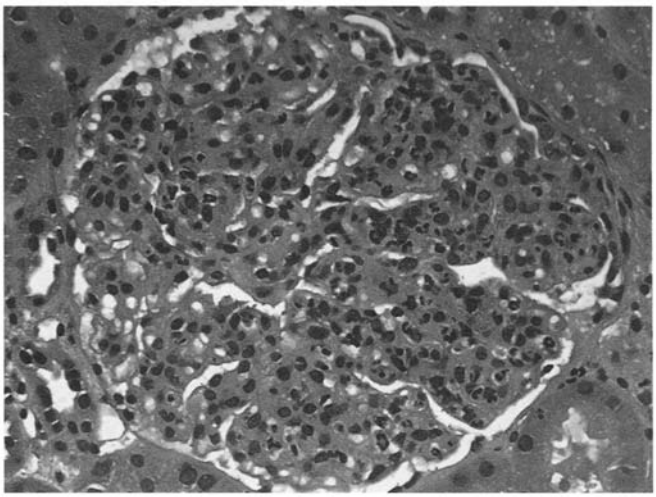


Fig. 12. Diffuse mesangial and endocapillary proliferation in acute post-infectious glomerulonephritis.

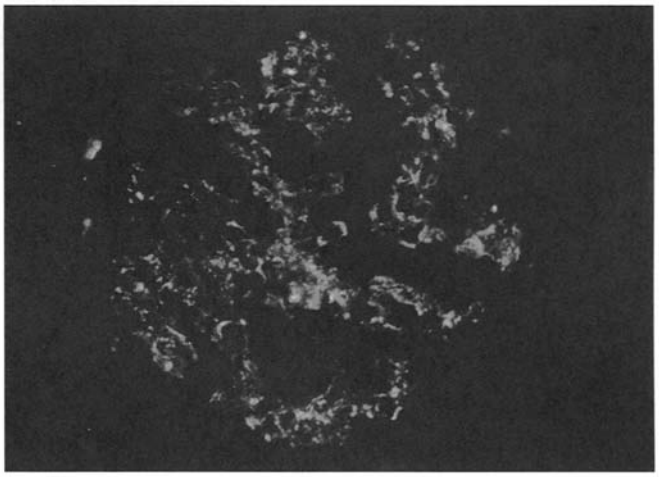


Fig. 13. Granular capillary wall and mesangial staining with anti-IgG in acute post-infectious glomerulonephritis.

- Immunofluorescence microscopy:
  - Granular deposits of C3 and IgG along the capillary loops and in the mesangium **(Figure 13)**
- Electron microscopy:
  - Large subepithelial, "hump-like" deposits as well as mesangial deposits **(Figure 14)**
  - The capillary loop deposits become less frequent after a few weeks, but the mesangial deposits persist for a longer period

Crescentic Glomerulonephritis

Clinical

- May be:
  - Immune complex mediated
  - Pauci-immune (ANCA associated)

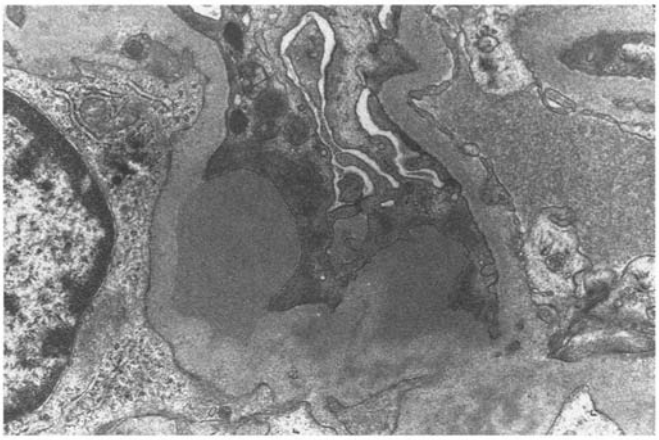


Fig. 14. Large sub-epithelial deposits in acute post-infectious glomerulonephritis.

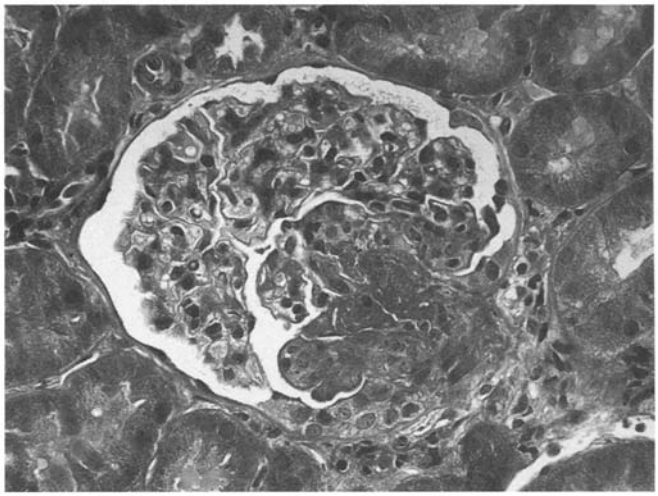


Fig. 15. Segmental glomerular necrotizing lesion (lower right) with overlying crescent.

- Mediated by anti-glomerular basement membrane antibody

♦ Patients with crescentic glomerulonephritis secondary to anti-glomerular basement membrane disease may also have pulmonary hemorrhage (Goodpasture's disease)

♦ The prognosis depends on the number of crescents present in the biopsy; a more diffuse crescentic process predicts a worse prognosis

Microscopic

♦ Light microscopy:
- Disruption of the glomerular capillary loops with extravasation of blood and cells into Bowman's space, forming a cellular crescent **(Figure 15)**

♦ Immunofluorescence microscopy:
- Bright linear staining of GBM for IgG in anti-glomerular basement membrane mediated disease **(Figure 16)**
- Negative in ANCA-associated crescentic GN
- Other immune complexes present in immune complex mediated disease

♦ Electron microscopy:
- Disruption of capillary wall with ± immune deposits

Fibrillary Glomerulonephritis

Clinical

♦ Most patients are 40–50 years of age, with a slight female predominance and a greater frequency in whites

♦ Most patients present with proteinuria, and occasionally the nephrotic syndrome, or with symptoms of nephritis

♦ Renal insufficiency is progressive, with renal failure usually occurring within 2–4 years

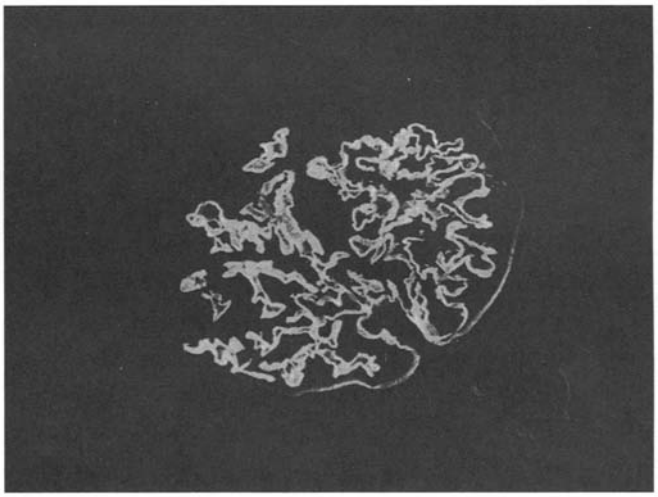


Fig. 16. Bright, linear capillary wall staining with anti-IgG in anti-GBM mediated glomerulonephritis.

Microscopic

♦ Light microscopy:
- The glomeruli show mesangial matrix expansion, variable hypercellularity, and capillary wall thickening **(Figure 17)**

♦ Immunofluorescence microscopy:
- Mesangial and capillary wall staining for IgG and C3 are present

♦ Electron microscopy:
- There is glomerular deposition of fibrils that are thicker than amyloid fibrils and lack congo red birefringence **(Figure 18)**
- The 18–22 nm thick fibrils are randomly oriented and non-branching and are present in the mesangium and at least segmentally along the capillary loop basement membranes

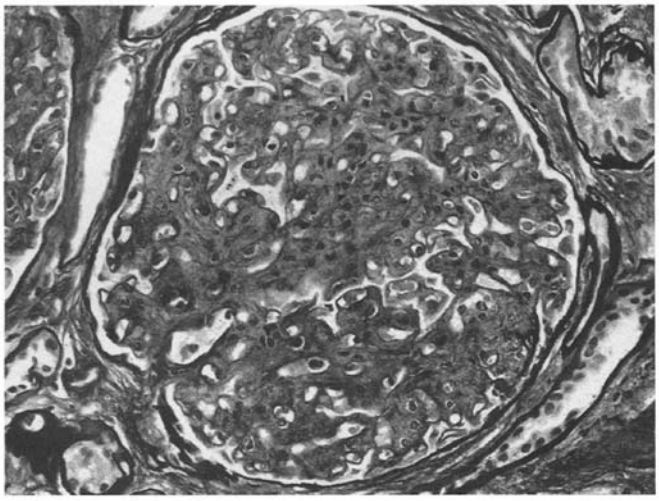


Fig. 17. Fibrillary glomerulonephritis with pale mesangial expansion and thickened capillary walls on silver stain.

Secondary Glomerular Diseases

Diabetes Mellitus (Diabetic Nephropathy)

Clinical

- Major cause of end-stage renal failure in the United States
- Approximately one-third of patients entering dialysis programs have lost renal function as a result of diabetes
- Patients with diabetes mellitus rarely develop clinically detectable glomerular injury before 10 years
- Nodular mesangial sclerosis (Kimmelstiel-Wilson lesion)

Microscopic

- Light microscopy:
  - Thickened tubular and glomerular basement (after 2–3 years)
  - Interstitial fibrosis and expansion of mesangial regions with formation of mesangial nodules begins after 3–5 years; parallels progressive loss of renal function **(Figure 19)**
- Electron microscopy:
  - Diffuse thickening of the capillary loop basement membranes and mesangial matrix expansion **(Figure 20)**

Paraproteinemia

- A group of disorders characterized by tissue damage associated with the overproduction of monoclonal immunoglobulin proteins and their components
- The renal manifestations occur as a result of the interaction of the abnormal protein with normal tissue components

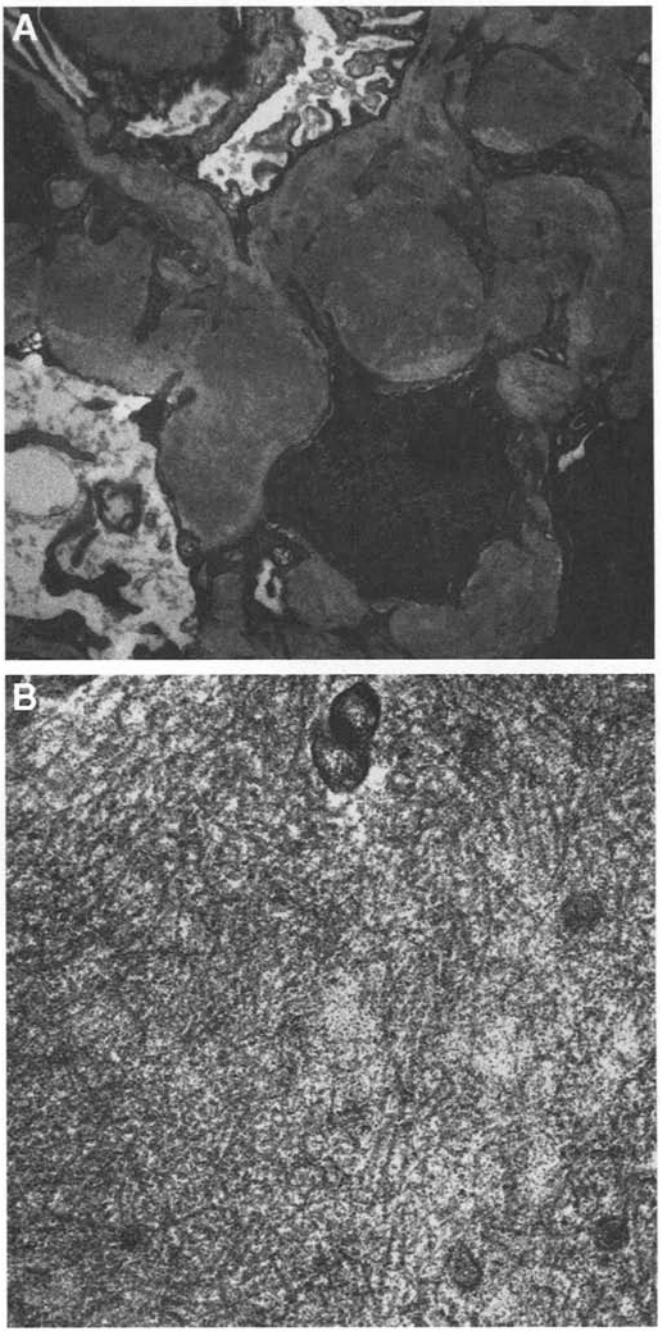


Fig. 18. Electron micrograph of fibrillary glomerulonephritis with mesangial electron dense deposits at low magnification **(A)**. Electron micrograph of fibrillary glomerulonephritis with mesangial fibrils at higher magnification **(B)**.

Amyloidosis

- Extracellular deposition of insoluble fibrillar proteins with a characteristic β-pleated sheet configuration; most proteins have an α-helical structure:
  - Primary or AL amyloid is caused by a plasma cell dyscrasia with overproduction of a monoclonal

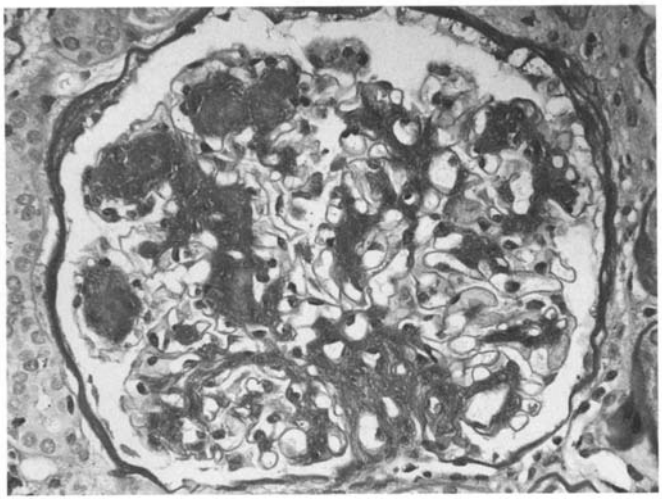


Fig. 19. Diabetic glomerulosclerosis with PAS positive mesangial nodules.

immunoglobulin light chain, which in most patients is λ light chain; overt myeloma is present in 20% of these patients

- Secondary or AA amyloid occurs in chronic infections and chronic inflammatory states, including rheumatoid arthritis, ankylosing spondylitis, tuberculosis, osteomyelitis, and intravenous drug abuse

Microscopic

- Light microscopy:
  - Amyloid deposits occur predominantly in glomeruli and appear as amorphous, eosinophilic nodules within the mesangium, and as thickened capillaries
  - The amyloid deposits do not stain with the silver stain (non-argyrophillic) and show green birefringence under polarized light with the congo red stain **(Figure 21)**
- Electron microscopy:
  - The amyloid deposits are composed of nonbranching, randomly oriented, twisted fibrils that measure 8– 12 μm in diameter **(Figure 22)**
  - They accumulate first in the mesangium and later in the subendothelial space and may penetrate the basement membrane, producing long silver-positive bundles that extend subepithelially, perpendicular to the basement membrane (spicules)

Light Chain Deposition Disease

- A systemic disease caused by overproduction of a monoclonal immunoglobulin light chain (usually κ), which deposits in various sites

Microscopic

- Light microscopy:
  - The glomeruli contain eosinophilic mesangial nodules similar to the nodules seen in diabetic nephropathy and in amyloidosis

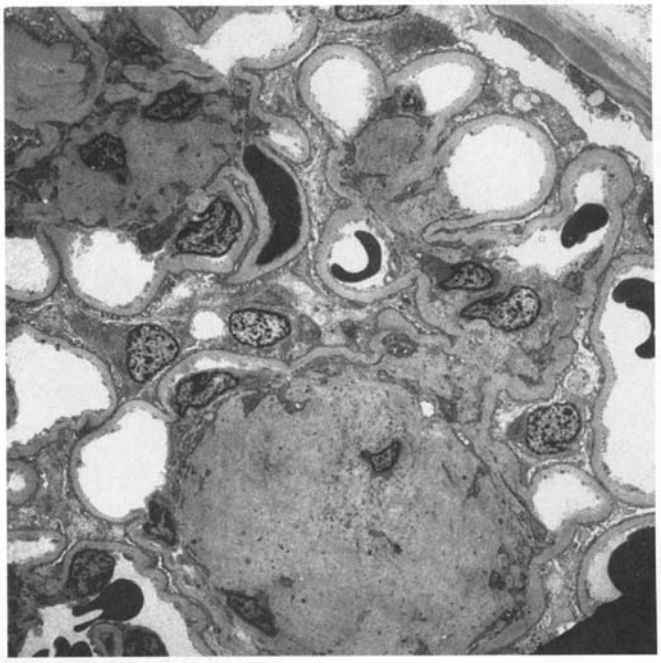


Fig. 20. Electron micrograph of diabetic glomerulosclerosis with nodular mesangial sclerosis and thickened GBM's.

  - Like amyloid, the mesangial nodules in light chain deposition disease are non-argyrophillic **(Figure 23)**
- Immunofluorescence microscopy:
  - There is bright linear staining of tubular basement membranes for κ light chains and less intense staining of the glomeruli; other immunoglobulins may be present rarely **(Figure 24)**
- Electron microscopy:
  - Punctate granular deposits in the lamina rara interna of the glomerular basement membrane with extension into the lamina densa and lamina rara externa less commonly:
    - Mesangial deposits are less prominent
  - The deposits are more consistently present in the tubular basement membranes and have a similar granular appearance

Cryoglobulinemic Glomerulonephritis

- Cryoglobulins are circulating immunoglobulins that precipitate on cooling and resolubilize on warming
- Three types of cryoglobulinemia have been described:
  - In Type I cryoglobulinemia, the immunoglobulin is a single monoclonal immunoglobulin usually without associated antibody activity
  - In Type II cryoglobulinemia, a monoclonal immunoglobulin (usually IgM-κ) is directed against polyclonal immunoglobulin (usually IgG)
  - In Type III cryoglobulinemia, a polyclonal immunoglobulin is directed against a polyclonal immunoglobulin

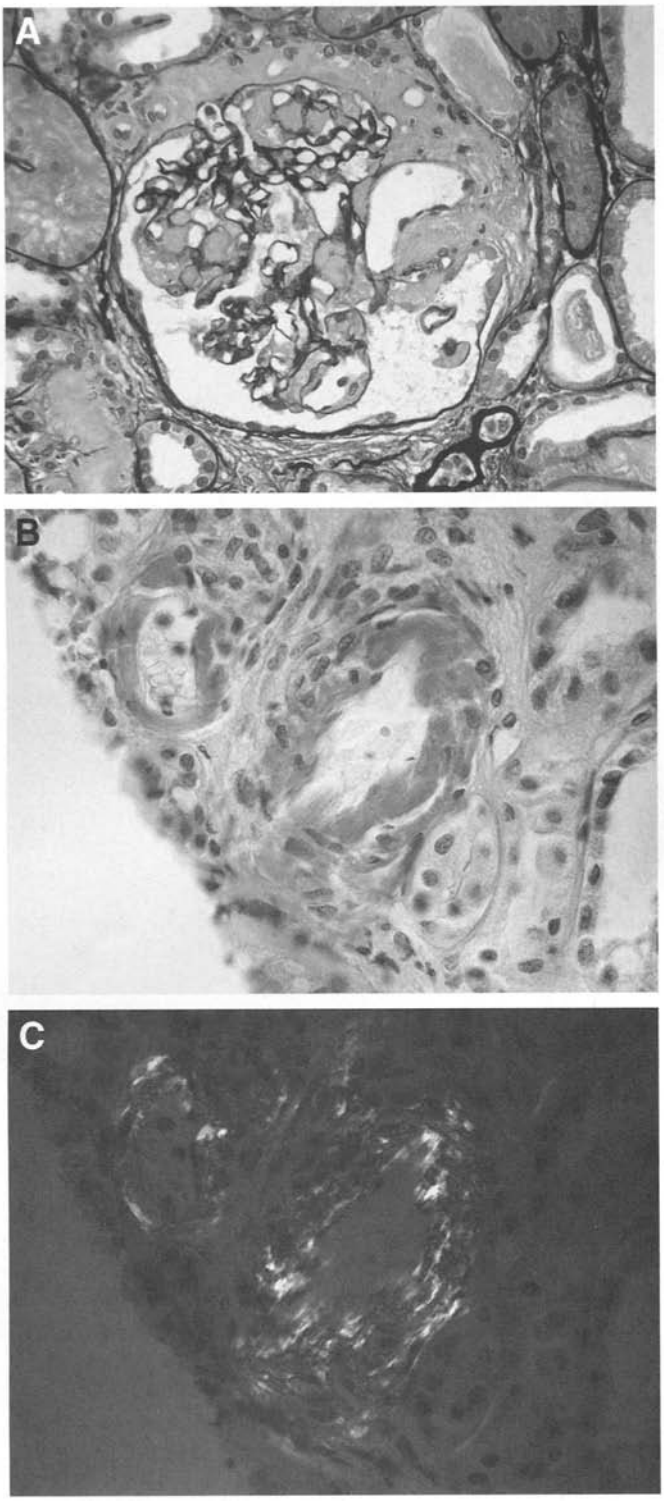


Fig. 21. Pale staining glomerular amyloid deposition on silver stain **(A)**. Arteriolar amyloid showing Congo red positivity **(B)**. Arteriolar amyloid showing positive birefringence of Congo red stain with polarized light **(C)**.

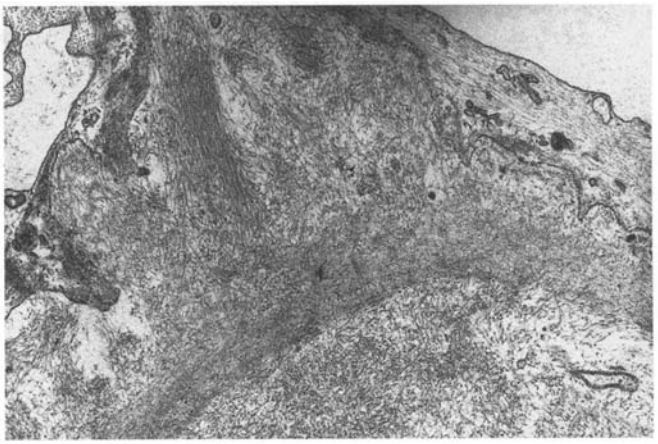


Fig. 22. Electron micrograph of capillary wall amyloid with subepithelial "spicules".

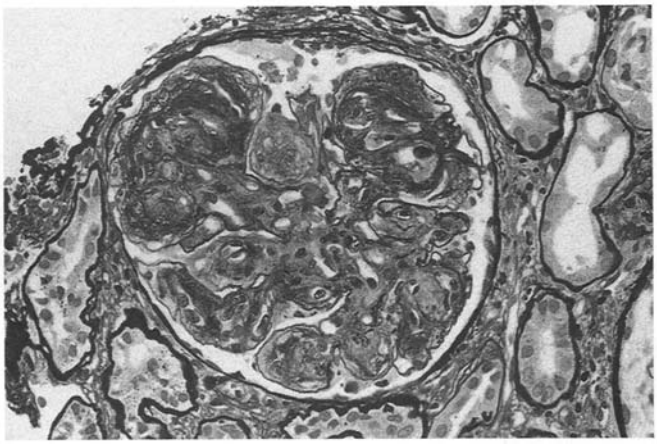


Fig. 23. Light chain deposition disease with pale staining mesangial nodules on silver stain.

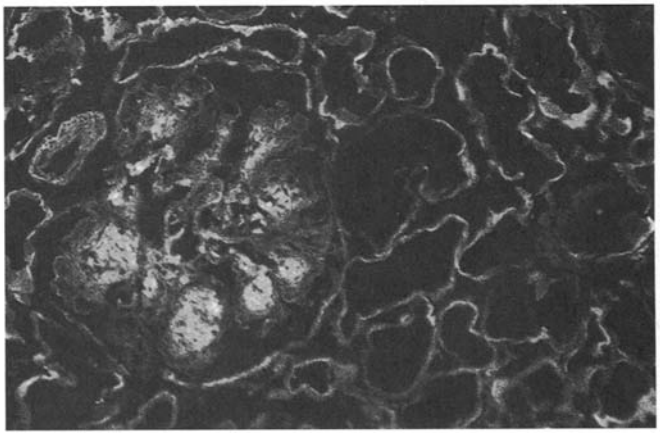


Fig. 24. Bright tubular basement membrane and glomerular staining for kappa light chain in light chain deposition disease.

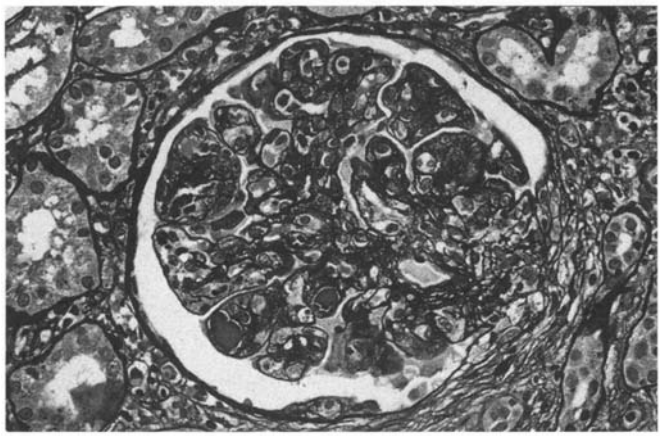


Fig. 25. Cryoglobulinemic glomerulonephritis with mesangial and endocapillary proliferation and intraluminal cryoglobulin.

Clinical

- Type I cyroglobulinemia is most often associated with lymphoproliferative disorders such as multiple myeloma, Waldenstrom's macroglobulinemia, and chronic lymphocytic leukemia
- Mixed cyroglobulinemia (Types II and III) occurs in a variety of settings, including lymphoproliferative disorders, collagen-vascular diseases, and infections including Hepatitis B, C, and Epstein-Barr virus
- Several studies have demonstrated an increased incidence of hepatitis C virus infection in patients with mixed cryoglobulinemia:
  - Antibody to hepatitis C virus has been detected in serum from 91% to 98% of patients with mixed cryoglobulinemia, and hepatitis C virus RNA in 81%

Microscopic

- Light microscopy:
  - The acute glomerular lesion of mixed cryoglobulinemia is a diffuse proliferative glomerulonephritis with prominent subendothelial and intraluminal deposits **(Figure 25)**
  - The mesangial proliferation and mesangial interposition results in a lobular architecture resembling Type I membranoproliferative glomerulonephritis; infiltrating monocytes and occasional neutrophils are also present
  - Renal arteritis may also be present and is found in ~30% of patients
- Immunofluorescence microscopy:
  - The composition of the glomerular deposits corresponds to that of the circulating cryoglobulin; mixed cryoglobulins contain IgG, IgM, C3, C1q, and C4
  - Because of the presence of a monoclonal IgM-κ component, staining for these immunoglobulins is often more intense than for IgG and λ



Fig. 26. Electron micrograph of curved tubular substructure of cryoglobulin.

  - Staining involves the subendothelial aspect of the glomerular capillary wall with focal globular intraluminal deposits and smaller mesangial deposits
- Electron microscopy:
  - The deposits are typically subendothelial. Mesangial deposits are usually smaller and less numerous. Intramembranous and subepithelial deposits may also be seen
  - Often the deposits have a characteristic substructure with curved tubular structures, ~30 μm in diameter, that cluster in curvilinear bundles **(Figure 26)**

Systemic Lupus Erythematosus (Lupus Nephritis)

Clinical

- Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by the overproduction of antibodies to endogenous antigens, usually derived from cell components; the kidneys are almost always affected, giving rise to lupus nephritis
- Lupus nephritis is classified according to a system published in 1982 under the auspices of the WHO
- A revision of the WHO classification has been proposed

Microscopic

- There are six morphologic classes in the WHO scheme **(Figure 27)**:
  - Class I: Normal glomeruli:
    - Minor glomerular abnormalities by light microscopy may be accompanied by deposits identified on immunofluorescence or electron microscopy
    - IA: nil (by all techniques)
    - IB: normal by light microscopy but deposits present

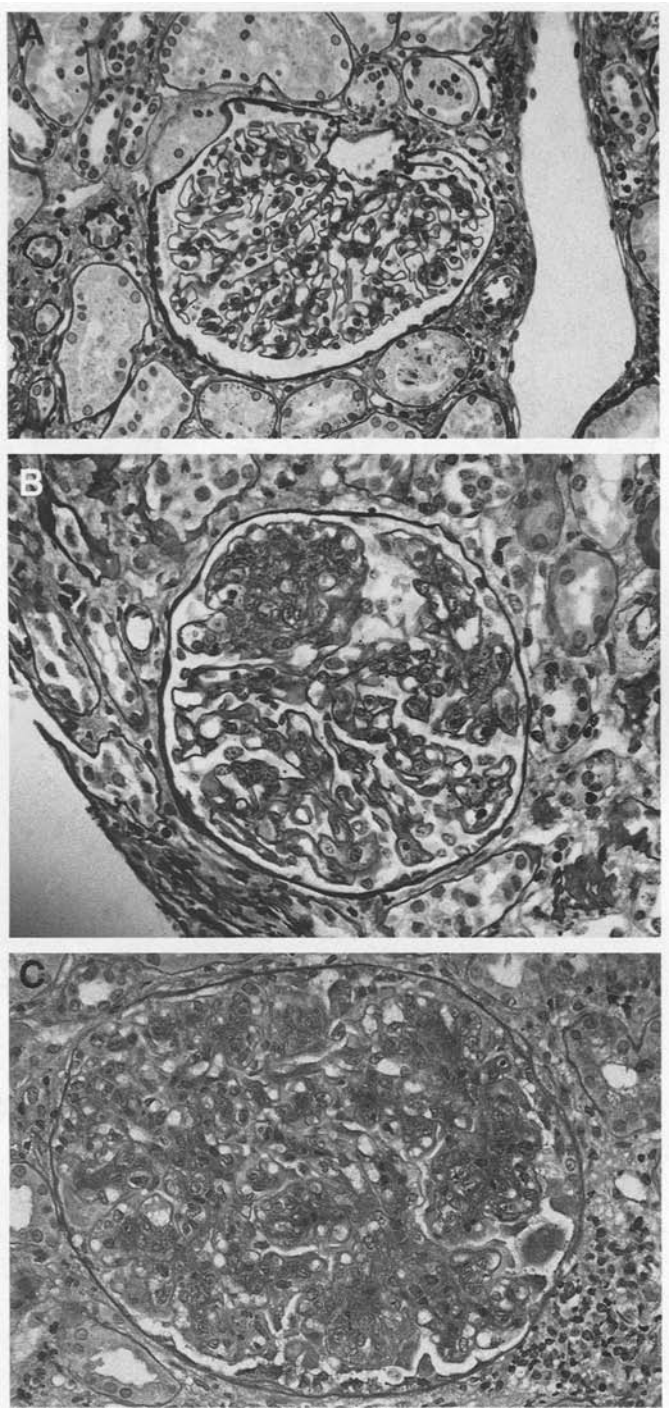


Fig. 27. Mild mesangial proliferation in class II lupus nephritis on silver stain **(A)**. Segmental proliferation (upper left) in class III lupus nephritis on silver stain **(B)**. Diffuse mesangial and endocapillary proliferation in class IV lupus nephritis on PAS stain **(C)**.

- Class II: Mesangial lupus nephritis:
  - IIA: mesangial widening and/or mild hyper-cellularity (+)
  - IIB: moderate hypercellularity (++)
- Class III: Focal and segmental proliferative lupus nephritis:
  - IIIA: active necrotizing lesions
  - IIIB: active and sclerosing lesions
  - IIIC: sclerosing lesions
- Class IV: Diffuse proliferative lupus nephritis:
  - IVA: without segmental necrotizing lesions
  - IVB: with active necrotizing lesions
  - IVC: with active and sclerosing lesions
  - IVD: with sclerosing lesions
- Class V: Diffuse membranous lupus nephritis:
  - VA: pure membranous lupus nephritis
  - VB: associated with lesions of category II (A or B)
  - VC: associated with lesions of category III (A,B, or C)
  - VD: associated with lesions of category IV (A,B,C, or D)
- Class VI: Advanced sclerosing lupus nephritis:
  - This class represents a late stage and resembles any case of advanced glomerulonephritis, usually lacking the specific features of lupus nephritis

HIV Nephropathy

Clinical

- Human immunodeficiency virus (HIV) nephropathy occurs in 5% to 10% of patients with HIV infection and occurs more frequently in blacks
- The clinical presentation of HIV nephropathy is characterized by heavy proteinuria, which is in the nephrotic range in 90% of patients, accompanied by rapid progression to renal failure over 6–12 months
- Therapy with antiviral agents has been attempted with limited success, and immunosuppressive therapy is not generally considered safe because of the immune compromise already present in these patients

Microscopic

- Light microscopy:
  - Swelling and hypertrophy of podocytes with PAS+ inclusion droplets **(Figure 28)**
  - Focal segmental glomerulosclerosis and global collapse of the glomerular tufts
  - Microcystic, dilated tubules containing hyaline occlusive casts
  - Prominent lymphocytic infiltration of the interstitium
- Electron microscopy:
  - Reticulotubular inclusions in endothelial cells and interstitial leukocytes **(Figure 29)**



Fig. 28. Collapsing glomerulopathy with podocyte prominence in HIV nephropathy on silver stain.

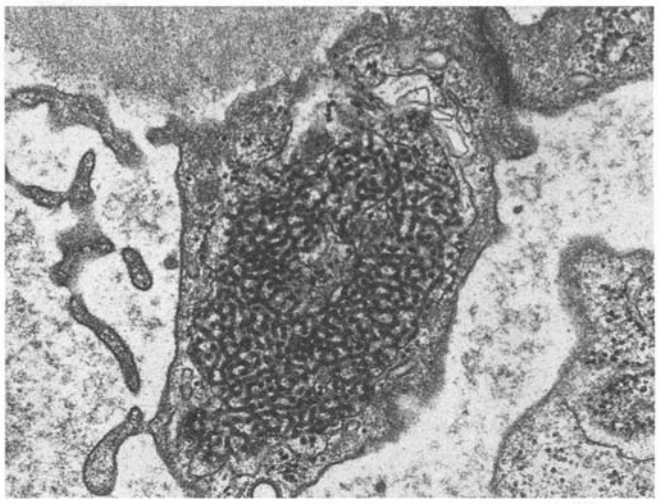


Fig. 29. Electron micrograph of endothelial cell tubuloreticular structure in HIV nephropathy.

Hereditary Systemic Disorders With Renal Involvement

Fabry's Disease

Clinical

- Fabry's disease (Anderson-Fabry's Disease, Alpha-Galactosidase A Deficiency, Angiokeratoma Corporis Diffusum Universale) is an uncommon disorder caused by an inborn error in the catabolism of glyco-sphingolipids, resulting in glycosphingolipidosis
- The central defect is a complete or partial deficiency in α-galactosidase A activity
- It is inherited as an X-linked disorder and is caused by a variety of mutations in the α-galactosidase gene on the long arm of the X chromosome; it has an incidence of 1 : 40,000
- Diagnosis can be made in the setting of typical skin lesions (angiokeratoma corporis diffusum), corneal dystrophy, and birefringent inclusions in urinary sediment:
  - Confirmation of the diagnosis is made by measuring the α-galactosidase A activity in peripheral blood leukocytes
- Renal manifestations include polyuria and polydipsia with a dilute urine:
  - Proteinuria may be mild and insidious in onset
  - Patients eventually progress to renal failure, usually by the time they reach 50 years of age
- Hemizygous males usually develop the disease as children and heterozygous females may develop a more mild form of the disease:
  - Caucasian males with ABO types B or AB usually present with more severe disease

Microscopic

- Light microscopy:
  - The glomeruli show podocyte swelling with cytoplasmic vacuolization **(Figure 30)**

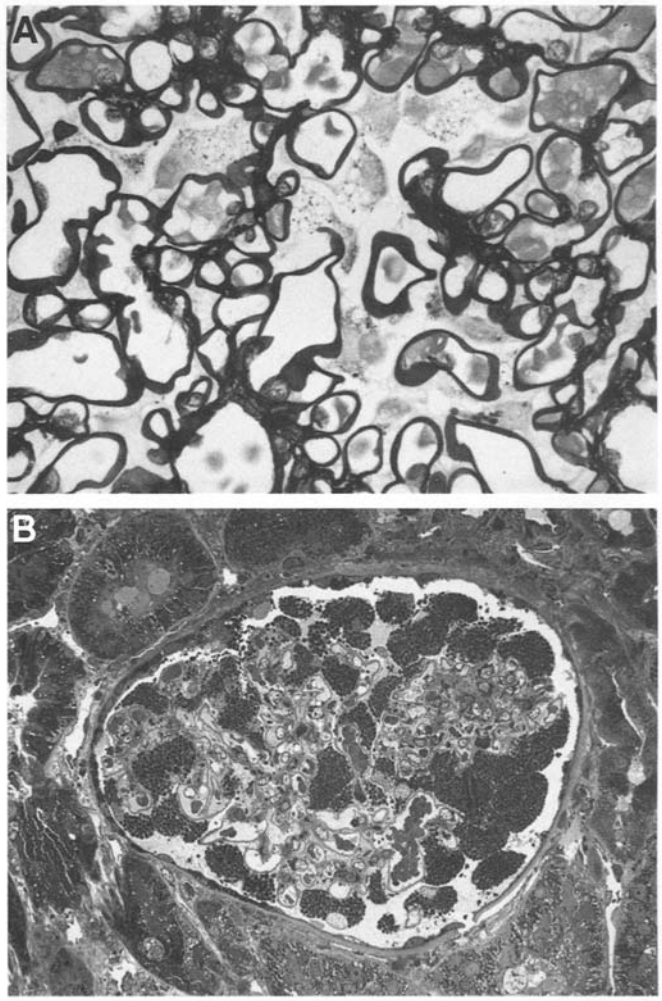


Fig. 30. Fabry disease with vacuolated podocyte cytoplasm on silver stain **(A)**. Fabry disease with podocyte cytoplasmic inclusions on toluidine blue stained section of plastic embedded tissue **(B)**.

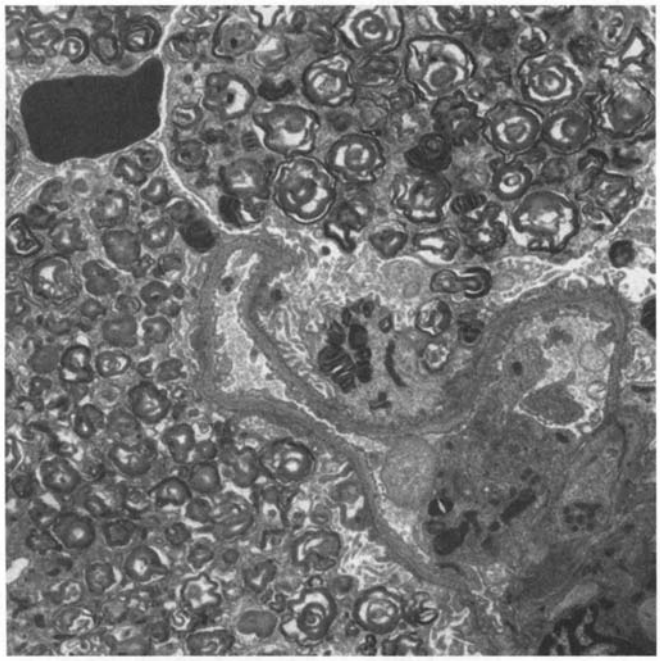


Fig. 31. Electron micrograph of Fabry disease with whorled podocyte cytoplasmic myelin.

- Vacuoles are also present in the cells lining Bowman's capsule, endothelial and mesangial cells, and in cells of the distal convoluted tubule and loop of Henle
- With disease progression, the glomeruli undergo segmental and global glomerulosclerosis accompanied by interstitial fibrosis and tubular atrophy

♦ Electron microscopy:
- Numerous whorled osmiophilic structures (myelin Figure's, zebra bodies) are present within lysosomes in the cell cytoplasm **(Figure 31)**
- Foot processes are generally effaced depending on the degree of proteinuria
- Myelin Figure's may be seen within Bowman's space and in the interstitium and tubular epithelium

Lecithin Cholesterol Acyltransferase (LCAT) Deficiency

Clinical

♦ An autosomal recessive disorder that results from inadequate enzymatic activity of lecithin cholesterol acyltransferase, which is responsible for forming lipoprotein cholesterol esters

♦ Clinical features include corneal opacities, anemia, proteinuria, and premature atherosclerosis

♦ Renal involvement is common and almost all patients with renal involvement progress rapidly to chronic renal failure, usually by the fifth decade of life:
- Atherosclerotic vascular disease is a significant and early cause of morbidity and mortality

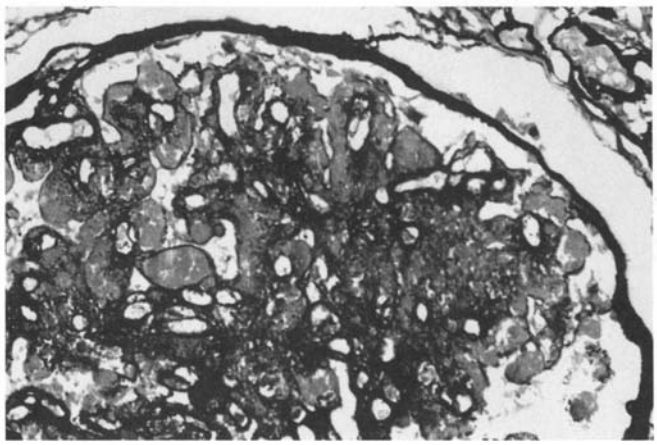


Fig. 32. LCAT deficiency with mesangial expansion and capillary wall sclerosis on silver stain.

♦ There is no known treatment:
- Renal transplantation is of benefit, but does not reverse the lipid abnormalities, and histologic lesions may recur by 6 months post-transplantation

Microscopic

♦ Light microscopy:
- The renal lesion is characterized by mesangial expansion and sclerosis, irregular thickening of the capillary loops with numerous bubbles or holes and foam cells **(Figure 32)**

♦ Electron microscopy:
- Electron-dense, lamellar structures are present within the mesangium and capillary walls and are associated with surrounding lucent spaces **(Figure 33)**
- Podocyte foot process effacement is also present

Nail-Patella Syndrome

Clinical

♦ Nail-Patella syndrome, or osteo-onychodysplasia, is a hereditary disorder characterized by:
- Iliac horns or prominent iliac crests (80%)
- Hypoplastic or absent patellae (60%) and patellar tendons
- Dysplasia of elbows (60-90%)
- Fingernail and less commonly toenail dystrophies (80% to 90%)
- Renal disease (50%)

♦ An autosomal dominant disorder with full penetrance and an incidence of approximately 1 : 50,000:
- The gene is located on chromosome 9 and is closely linked to the ABO blood group and adenylate cyclase loci

♦ Most patients with renal disease present with proteinuria, microscopic hematuria, edema, and hypertension:
- An abnormal urinary sediment, impaired urinary concentrating ability, and abnormalities in urinary acidification have also been described

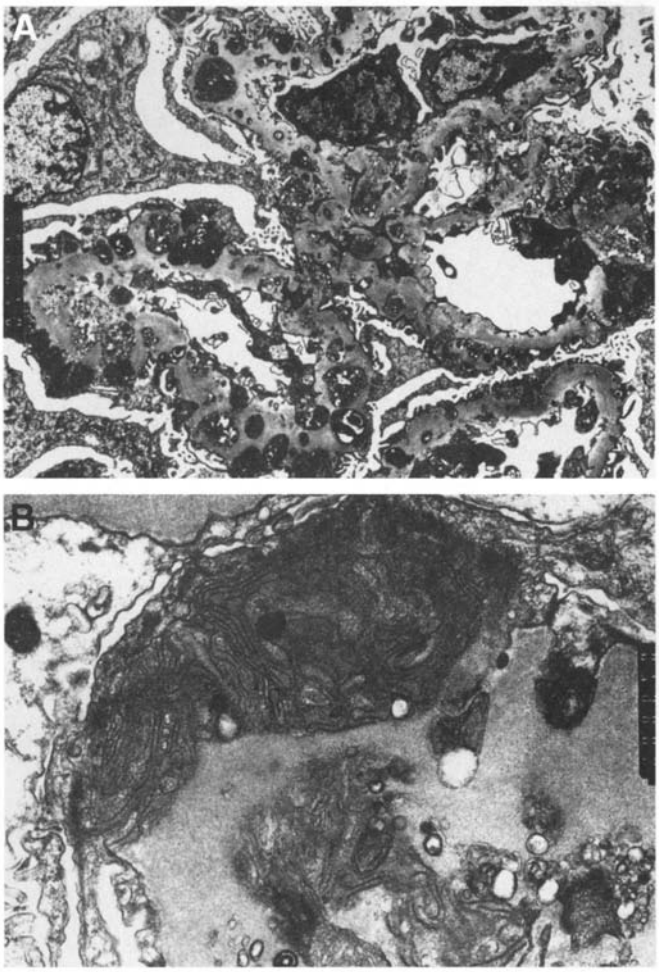


Fig. 33. Electron micrograph of LCAT deficiency with electron dense lamellar structures in GBM **(A)**. Electron micrograph of LCAT deficiency with lamellar structures in GBM (higher magnification) **(B)**.

Microscopic

- Light microscopy:
  - The glomeruli are frequently normal in appearance but capillary loop thickening may be apparent
  - Mesangial sclerosis, segmental sclerosis, tubular atrophy, and interstitial fibrosis may also be present and correlate with the degree of renal functional impairment
- Immunofluorescence microscopy:
  - Generally negative, but occasional nonspecific staining for IgM, C3, or C1q may be present
- Electron microscopy:
  - The pathognomonic renal lesion is the finding of multiple mottled and lucent areas within the glomerular basement membrane and less commonly the mesangium **(Figure 34)**
  - These lucent areas contain clusters of collagen fibrils that are best visualized following phosphotungstic acid staining

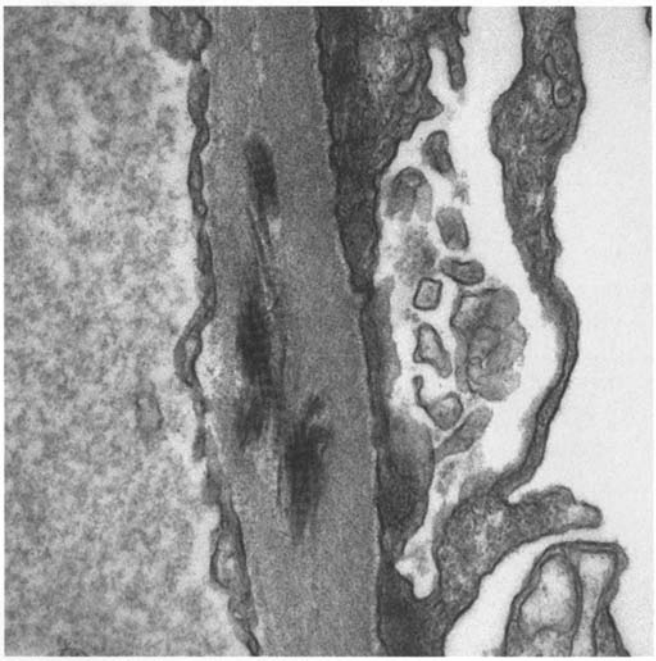


Fig. 34. Electron micrograph of Nail-Patella syndrome with intramembranous collagen fibril cluster.

Lipodystrophy

Clinical

- An uncommon disorder that may be partial or total, and congenital or acquired, and may be associated with:
  - Hyperinsulinism and insulin resistance
  - Hyperlipidemia
  - Hyperproteinemia
  - Euthyroid hypermetabolism
  - Increased basal free fatty acid levels
- Other manifestations include:
  - Tall stature
  - Muscular hypertrophy
  - Hirsutism
  - Macroglossia
  - Abdominal distention
  - Subcutaneous nodules
  - Acanthosis nigricans
  - Hepatomegaly
  - Cirrhosis
  - Clitoral or penile enlargement
  - Adenopathy
  - Neurologic abnormalities
- In the congenital form, which has an autosomal recessive inheritance pattern, lipoatrophy is present at birth and diabetes mellitus develops later in adolescence

- The acquired forms of general lipodystrophy and partial lipodystrophy do not have a heritable basis:
  - Partial lipodystrophy most often presents in young girls between 5–15 years of age
  - In addition to lipoatrophy and renal disease, these patients may have some of the symptoms seen in the generalized lipodystrophy group

Microscopic

- In partial lipodystrophy, the incidence of renal involvement is 15% to 30%, with dense deposit disease or membranoproliferative glomerulonephritis Type II being the predominant lesion, occurring in 80%, and Type I MPGN in the remainder
- Approximately 10% of patients with dense deposit disease have partial lipodystrophy

Hereditary Nephritis

- The term hereditary nephritis encompasses a heterogeneous group of disorders that have in common microscopic hematuria, but differ markedly in clinical course and outcome

Alport Syndrome

Clinical

- A hereditary disorder of basement membrane collagen that is characterized clinically by hematuria, progressive renal failure, and frequently, hearing loss and ocular abnormalities
- In most cases, the disease is inherited as an X-linked trait; absence of a family history is noted in 10% to 15% of patients and these cases may represent new mutations:
  - The gene frequency is estimated at 1 : 5,000–10,000
- The X-linked form of Alport's syndrome has been shown to be caused by mutations in the gene COL4A5 encoding for the α5 chain of Type IV collagen present in the glomerular basement membrane; the gene has been mapped to chromosome Xq22
- Microscopic hematuria is present from birth in affected males and has a 93% penetrance in heterozygous females
- Proteinuria is variable, but occasionally reaches nephrotic range; hemizygous males inevitably progress to end-stage renal failure; heterozygous females are generally less severely affected
- Non-renal features of Alport syndrome include:
  - Bilateral high-frequency hearing loss
  - Ocular defects including lenticonus and retinal flecks
  - Leiomyomatosis, particularly leiomyomas of the esophagus and female genital tract

Microscopic

- Light microscopy:
  - In the early stages of the disease, the glomeruli may appear entirely normal or may show mesangial widening

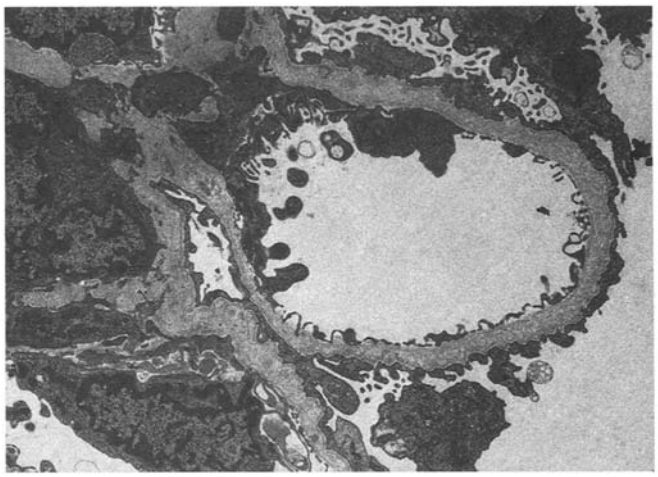


Fig. 35. Electron micrograph of Alport syndrome with variably thickened GBM and GBM lamellations.

  - Progression of the disease is characterized by segmental sclerosis and glomerular obsolescence, tubular atrophy, and interstitial fibrosis
  - Interstitial foam cells are often present but are a non-specific finding
- Immunofluorescence microscopy:
  - Direct immunofluorescence microscopy may be normal or there may be non-specific deposition of IgM and C3
- Electron microscopy:
  - The characteristic ultrastructural changes of the glomerular basement membranes consist of both thickening and thinning, and in early cases, this may be the only abnormality **(Figure 35)**
  - The lamina densa is replaced by irregular lamellae and fragmented strands of lamina densa-like material
  - The extent of lamellation and fragmentation of the lamina densa in the glomeruli is variable, ranging from involvement of short segments to widespread involvement in severely affected cases

Thin Glomerular Basement Membrane Syndrome

Clinical

- Familial thin glomerular basement membrane syndrome, or benign recurrent hematuria, is an autosomal dominant basement membrane glomerulopathy characterized by a glomerular basement membrane that is uniformly thinned to approximately half of the normal thickness
- Some cases consistent with autosomal recessive inheritance have been reported
- The overall incidence is not known; however, it is relatively common (20%) in patients with hematuria
- Patients present with continuous or intermittent microscopic hematuria usually in childhood but rarely as an adult
- Episodic gross hematuria may occur and is usually concurrent with an upper respiratory infection

- A distinction must be made between thin glomerular basement membrane syndrome and Alport syndrome:
  - This is usually accomplished by the lack of renal insufficiency, sensorineural hearing loss, and ocular abnormalities that characterize Alport syndrome

Microscopic

- Light microscopy:
  - The glomeruli appear normal and the tubules contain red blood cells
- Electron microscopy:
  - The glomerular capillary loop basement membranes show focal and segmental or diffuse thinning of the lamina densa (<200 μm in an adult, <180 μm in a child 2–10 yr old) **(Figure 36)**
  - The inner and outer contours of the glomerular basement membrane are smooth, and no disruption or lamellation of the glomerular basement membrane is present

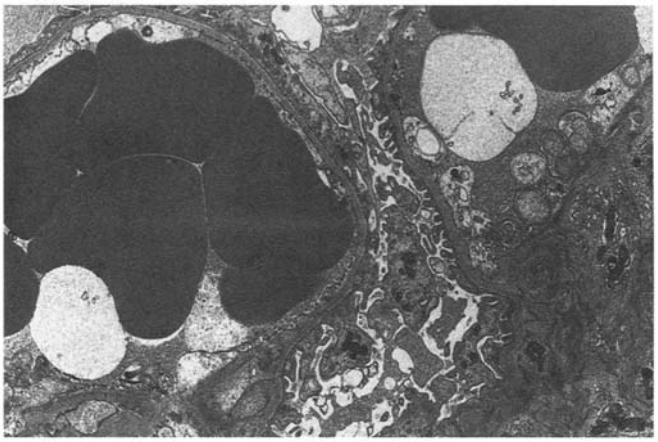


Fig. 36. Electron micrograph of Thin Glomerular basement membrane nephropathy with uniformly thinned GBM.

Congenital and Infantile Nephrotic Syndrome

- The term congenital nephrotic syndrome is used to describe infants who develop nephrotic syndrome at birth or before 3 months of age
- Infantile nephrotic syndrome describes infants with a later onset of nephrotic syndrome (4–12 months of age)
- Causes of congenital and infantile nephrotic syndrome are listed in **Table 3**

Congenital Nephrotic Syndrome of the Finnish Type

Clinical

- Described worldwide, although the highest incidence is in Finland, with a gene frequency of 1 : 200 and an incidence of 1. 2 : 10,000 live births
- Both sporadic and autosomal dominant forms occur and diagnosis is based on family history, perinatal presentation, placental size, and renal pathology
- Common clinical and gestational findings include:
  - Unremarkable pregnancy except for elevated alpha-fetoprotein at week 16–20
  - Premature delivery (usually 35–38 wk)
  - Small for gestational age
  - Breech presentation is more common
  - Low Apgar score including asphyxia
  - Meconium staining (more common)
  - Large placenta, 25% larger than infant by weight
  - Classic appearance (may be due in part to loss of thyroid binding globulin in urine):
    - Low bridged nose
    - Wide cranial sutures
    - Large fontanels
    - Delayed ossification
    - Flexion deformities of the extremities
  - Signs of disease develop in the first 3 months of life
- Renal manifestations include massive proteinuria detectable at birth that is resistant to corticosteroids and immunosuppression
- The pathogenesis is not well understood, but is assumed to be the result of a hereditary error in glomerular basement membrane metabolism that is expressed early in gestation (16–18 weeks)

Microscopic

- Light microscopy:
  - The glomeruli show mesangial proliferation, dilatation of Bowman's space, and microcysts in the cortical tubules **(Figure 37)**
  - Scattered microglomeruli may also be found
- Electron microscopy:
  - Diffuse podocyte foot process effacement, microvillous transformation, and mesangial expansion; no immune deposits are present
  - The capillary loop basement membranes show widening of the lamina rara interna and focal splitting and thinning of the lamina densa

Diffuse Mesangial Sclerosis

Clinical

- Unlike congenital nephrotic syndrome of the Finnish type, diffuse mesangial sclerosis is not associated with premature birth, low birth weight, or placental enlargement
- Most patients present between 3–11 months of age with proteinuria, renal insufficiency, and rapid progression to end-stage renal failure, usually within 6 months of onset
- Approximately 25% of cases are associated with male psuedohermaphroditism, Wilms tumor, and nephropathy—a constellation of features referred to as the Denys-Drash syndrome or Drash syndrome, which appears to be the result of a single gene defect involving WT1, a tumor suppressor gene isolated on chromosome 11p13

Table 3. Causes of Congenital Nephrotic Syndrome

Congenital nephrotic syndrome	*Infantile nephrotic syndrome*
Primary	*Primary*
Finnish-type	Minimal change disease
Diffuse mesangial sclerosis	Focal segmental glomerulosclerosis
Minimal change disease	Mesangial proliferative GN
Focal segmental glomerulosclerosis	Membranous GN
Mesangial proliferative GN	Diffuse mesangial sclerosis
Membranous GN	
Secondary	*Secondary*
Drash Syndrome	Membranous GN
Diffuse mesangial sclerosis	Syphilis
Membranous GN	Fanconi's syndrome
Syphilis	Proliferative GN
Systemic lupus erythematosus	Syphilis
Toxoplasmosis	Cytomegalovirus
Nail-patella syndrome	Alpha-1-antitrypsin deficiency
Hemolytic uremic syndrome	Mercury poisoning
	Drash syndrome
	Diffuse mesangial sclerosis
	Hemolytic uremic syndrome

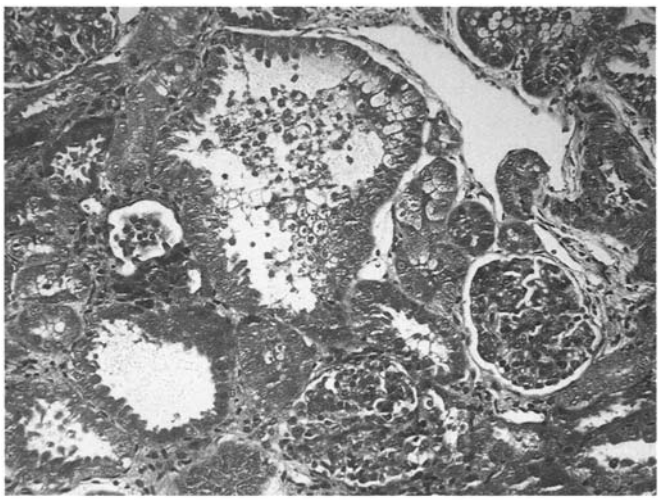


Fig. 37. Focal proximal tubule microcysts in congenital nephrotic syndrome.

- Infants with diffuse mesangial sclerosis, with or without Drash syndrome, demonstrate a rapid decline in renal function within 6 months of diagnosis

Microscopic

- Light microscopy:
  - The early glomerular lesion is characterized by an increase in mesangial matrix without hypercellularity
  - Later, the glomerular tuft becomes an avascular sclerotic mass surrounded by a layer of podocytes, often accompanied by a dilated Bowman's space
  - The tubules show marked ectasia with attenuation of the epithelium and eosinophilic hyaline casts in the lumens
  - A zonal distribution of lesions has been described
- Electron microscopy:
  - The glomeruli show podocyte damage characterized by diffuse effacement of foot processes, microvillous transformation, and pseudocyst formation
  - The glomerular basement membranes show thickening, collapse, subendothelial and subepithelial widening, and foci of lamina densa splitting and lamellation

TUBULOINTERSTITIAL DISEASES OF THE KIDNEY

Acute Infectious Pyelonephritis (Ascending or Hematogenous Infection)

- Acute infectious pyelonephritis is rarely seen grossly except at autopsy

Macroscopic

- The kidney may be enlarged with a bulging cut surface
- Microabscesses may be present in the cortex and studding the subcapsular surface of the kidney **(Figure 38)**
- The cut section of the kidney demonstrates pusfilled collecting ducts that extend into the underlying medulla
- The pelvicaliceal system is dilated and the renal papillae are diffusely blunted, with an inflamed lining mucosa

Microscopic

- There is a dense interstitial and intratubular infiltrate of acute inflammatory cells with tubular destruction **(Figure 39)**

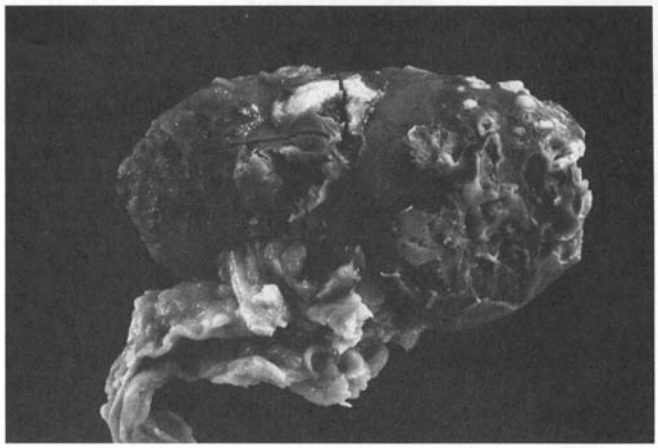


Fig. 38. Acute pyelonephritis with numerous cortical abscesses.

Chronic Pyelonephritis

Chronic Obstructive Pyelonephritis

- May be caused by obstruction of the ureter by calculi (stones), tumor within the ureter, or extrinsic compression

Macroscopic

- The kidney shows pelvicaliceal dilatation and parenchymal thinning, with blunting of papillae
- Coarse cortical and medullary scars are situated over dilated calices
- Staghorn calculi may complicate and contribute to obstruction **(Figure 40)**

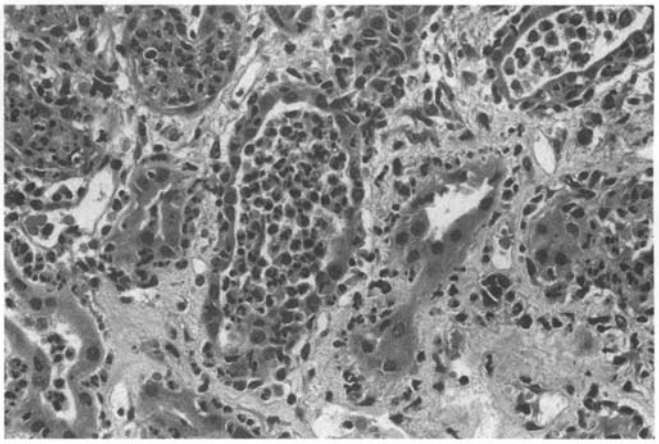


Fig. 39. Acute pyelonephritis with tubular dilatation and intraluminal neutrophils.

Chronic Non-Obstructive Pyelonephritis (Reflux Nephropathy)

- Results from reflux of urine from the bladder into the ureter and renal pelvis

Macroscopic

- Morphologically, it is characterized by coarse, sharply demarcated segmental scarring overlying dilated calices **(Figure 41)**
- The kidney may be reduced in size and process may involve one kidney
- Scarring is more prominent and extensive at the poles of the kidney

Microscopic

- Characterized by tubular atrophy, interstitial fibrosis, chronic inflammation, and periglomerular fibrosis
- Focal segmental glomerulosclerosis has been associated with reflux nephropathy

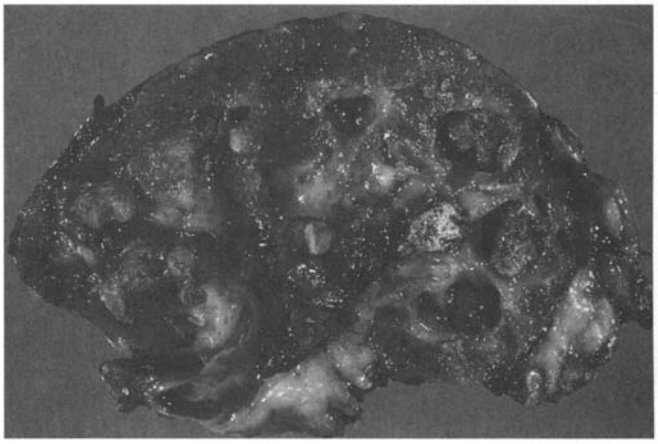


Fig. 40. Chronic pyelonephritis with calyceal blunting and calculi.

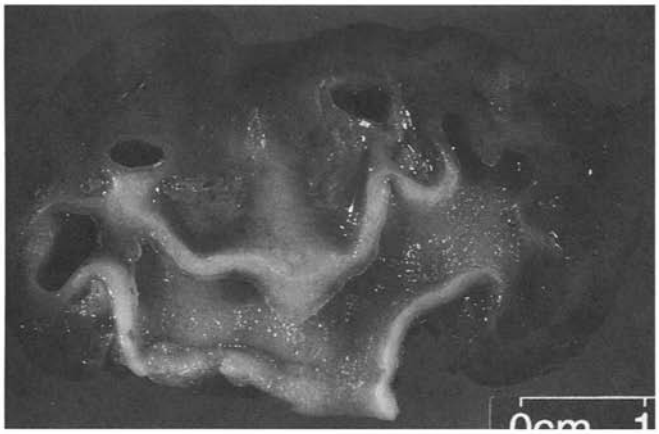


Fig. 41. Reflux nephropathy with calyceal dilatation and cortical thinning at renal poles.

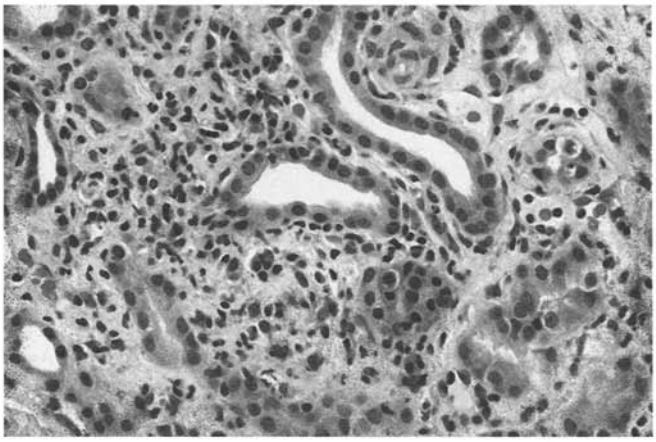


Fig. 42. Acute tubulointerstitial nephritis with interstitial edema and mixed inflammatory cell infiltrate.

Acute Tubulointerstitial Nephritis

- An acute inflammatory disease involving the renal tubules and interstitium; glomeruli and vessels are generally spared
- Acute pyelonephritis is a form of acute tubulointerstitial nephritis; however, a number of other etiologic agents have been identified
- The most common causes of non-infectious acute interstitial nephritis include:
  - Immune mediated:
    - Drug exposure
    - Diuretics
  - Antibiotics:
    - Phenytoin
    - Phenobarbital
    - Probenicid
    - Allopurinol
    - Cimetidine
    - Nonsteroidal anti-inflammatory agents
  - Miscellaneous:
    - Sarcoidosis
    - Lymphoma
  - Leukemia

Microscopic

- The interstitium contains an infiltrate of mixed inflammatory cells composed predominantly of lymphocytes with admixed plasma cells and usually eosinophils **(Figure 42)**
- Interstitial edema and tubulitis are also present
- Granulomatous forms of intersititial nephritis also occur

Acute Tubular Necrosis (ATN)

Ischemic Injury

- May complicate a number of primary disorders, many of which are associated with circulatory shock and hypovolemia
- Conditions that may be complicated include:
  - Extensive trauma and burns
  - Pancreatitis
  - Incompatible blood transfusions
  - Dehydration following diarrhea, vomiting, and excessive sweating
  - Rhabdomyolysis
  - Shock
  - Septicemia
  - Hemolysis
- The straight segment of the proximal tubule is most vulnerable to ischemia

*Microscopic **(Figure 43)***

- Single cell necrosis with desquamation
- Loss of the proximal tubule brush border
- Tubular dilatation
- Pigmented (brown) casts in distal tubules
- Crystals in distal tubules and collecting ducts
- Mild interstitial edema and inflammation
- Accumulation of leukocytes in the vasa recta

Nephrotoxic Injury

- May be defined as acute renal failure caused by a dose-dependent toxic renal injury
- Causes include:
  - Antimicrobials:
    - Aminoglycosides
    - Tetracyclines
    - Amphotericin
    - Polymyxin
    - Cephalosporins

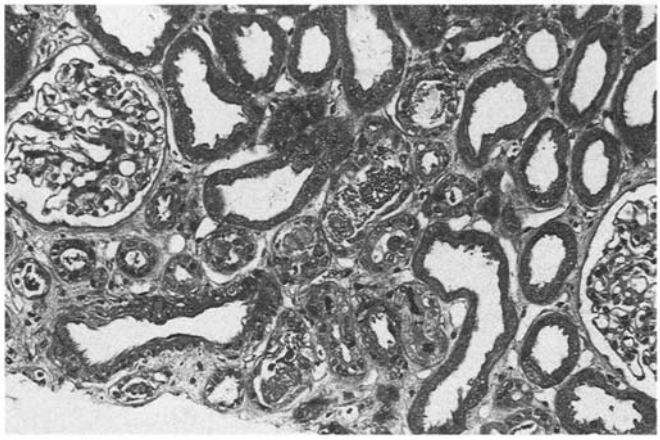


Fig. 43. Acute tubular necrosis with tubular epithelial cell attenuation and intraluminal debris.

- Heavy metals:
  - Mercury
  - Lead
  - Arsenic
  - Gold salts
  - Barium
- Miscellaneous:
  - Cisplatin
  - Doxorubicin
  - Streptozocin
  - Methoxyflurane
  - Halothane
  - Heat stroke
  - Ethylene glycol
  - Carbon tetrachloride
  - Radiographic contrast agents
  - Myoglobinemia

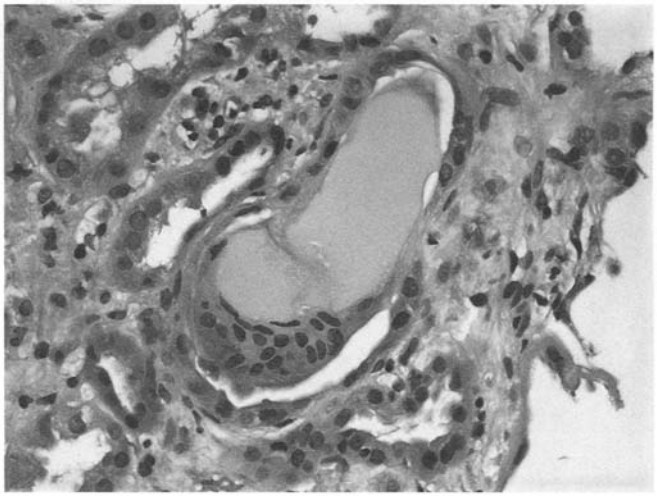


Fig. 44. Light chain cast with associated giant cell reaction.

  - Transfusion reactions
  - Snake and spider bites

Light Chain Cast Nephropathy (Myeloma Kidney)

- Results from the overproduction of immunoglobulins or fragments of immunoglobulins (light chains) by a clone of malignant B cells (plasma cells)
- Filtration of excessive light chains can cause direct toxic damage to renal tubular cells, and tubular obstruction from cast formation

Microscopic

- The term "myeloma kidney" or "cast nephropathy" refers to renal damage that occurs as a result of large numbers of light chain casts forming primarily in the distal tubules
- These casts incite a giant cell inflammatory reaction within the tubules that may cause tubular degeneration and extend into the interstitium **(Figure 44)**
- Volume depletion predisposes to the formation of light chain casts

VASCULAR DISEASES OF THE KIDNEY

Benign Nephrosclerosis

- Estimates suggest that 15% to 25% of adults in the United States are hypertensive
- Less than 95% of individuals with persistently elevated blood pressure are classified as having essential hypertension

Macroscopic

- The kidneys are usually normal to slightly smaller than normal, and in long-standing cases, may be markedly reduced in size
- The subcapsular surface is finely granular and the capsule is often adherent **(Figure 45)**
- The cut surface reveals thinning of the cortex and v-shaped subcapsular scars

Microscopic

- The areas of scarring show varying degrees of glomerular ischemic wrinkling and hyalinization, tubular atrophy, and interstitial fibrosis
- Arterioles show hyaline deposits; larger arteries show elastic fragmentation and reduplication with subendothelial fibrosis, intimal thickening, and focal lipid deposits **(Figure 46)**

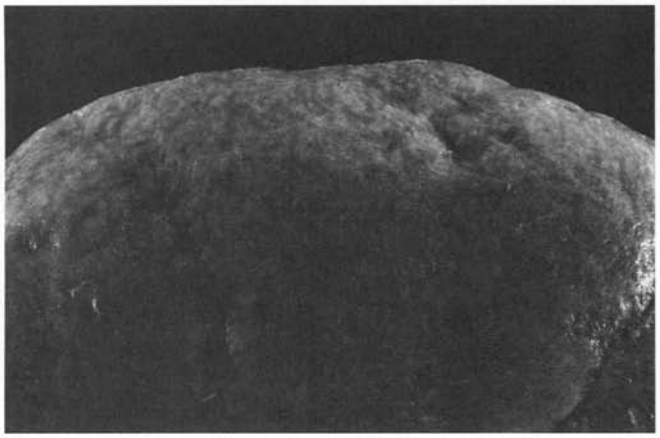


Fig. 45. Essential hypertension with finely granular cortical surface.

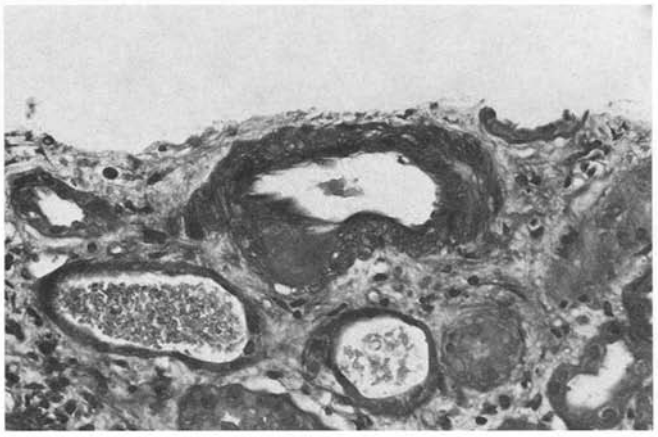


Fig. 46. Essential hypertension with segmental arteriolar hyaline deposition.

Malignant Nephrosclerosis

- Malignant hypertension (papilledema in the presence of diastolic blood pressure >125 mm Hg) develops in 1% to 7% of hypertensive individuals
- Approximately 50% of patients with malignant hypertension have a history of essential hypertension and only 1% to 2% develop the disease de novo

Microscopic

- The glomeruli show wrinkling and duplication of the capillary loop basement membranes and fibrinoid necrosis of the vascular pole
- The blood vessels show proliferative endarteritis in small arteries and arterioles, arteriolar necrosis, and mucoid intimal thickening of medium-sized and small arteries **(Figure 47)**

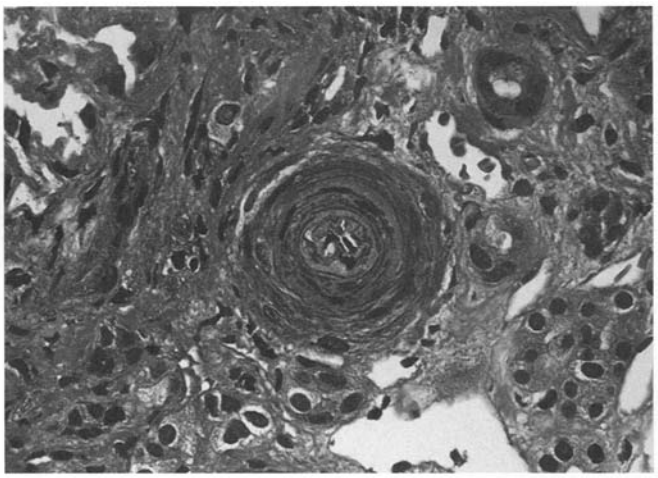


Fig. 47. Malignant/accelerated hypertension with prominent concentric intimal fibrosis and luminal narrowing.

Renovascular Hypertension (Renal Artery Stenosis)

- Defined as stenotic lesions of the main or segmental renal arteries inducing chronically elevated blood pressure that normalizes after correction of the stenosis
- Approximately two-thirds of renovascular hypertension in adults is due to atherosclerosis, which affects more men than women
- Fibromuscular dysplasia accounts for approx 25% of cases and is the most common cause of renovascular hypertension in young people and is found predominantly in young women

Atherosclerosis

- Atherosclerotic stenosis of the renal artery is usually located in the proximal renal artery, and in 50% of patients, is present at the ostium, where the renal artery arises from the aorta

Microscopic

- The involved segments of the renal artery are narrowed by an eccentric plaque that is characterized by subendothelial intimal thickening overlying cell debris, lipid, cholesterol clefts, and foam cells
- Medial and adventitial fibrosis may also be present. The atherosclerotic plaque may be complicated by hemorrhage and dissection **(Figure 48)**
- Calcification, and in some cases, osseous metaplasia, may occur

Fibromuscular Dysplasia (FMD)

- Patients with fibromuscular dysplasia are younger (mean age = 35) and are predominantly women
- There are intimal, medial, and adventitial forms of fibromuscular dysplasia **(Figure 49)**:
  - Intimal fibroplasia (2% to 4%)
  - Medial fibroplasia (25%):
    - Affects distal portion of artery
    - Aneurysmal dilatations

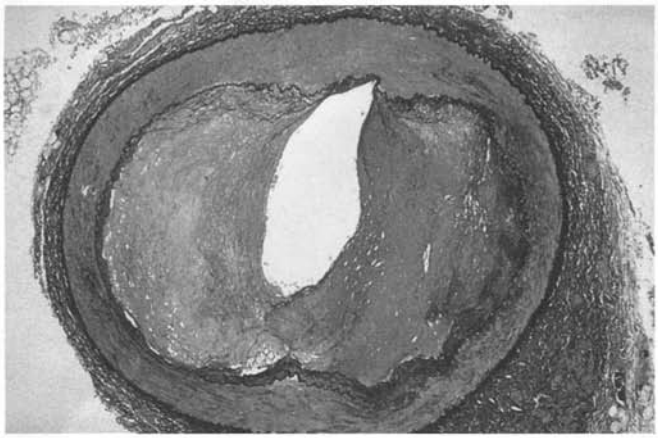


Fig. 48. Atherosclerosis with large arterial plaque.

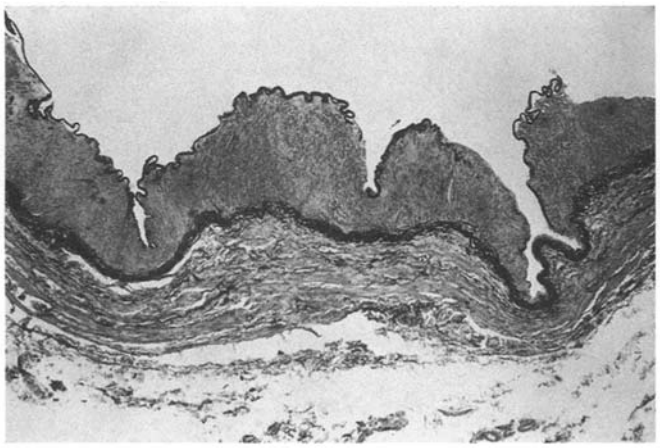


Fig. 49. Medial fibroplasia form of fibromuscular dysplasia with interrupted intimal fibrosis.

  - Often bilateral
  - Fibromuscular ridges alternate with a thinned media
- Perimedial fibroplasia (4% to 5%):
  - Circumferential fibrosis of the outer third of the media
  - Affects women in second and third decades (not men)
- Medial hyperplasia (1% to 2%):
  - Increased medial smooth muscle cells with little fibrosis
  - Medial dissection:
    - Associated with the above forms of fibromuscular dysplasia
- Adventitial fibroplasia (<1%):
  - Adventitial proliferation of fibrous connective tissue
  - May be related to retroperitoneal fibroplasia



Fig. 50. Pale, wedge-shaped cortical infarct.

Thromboembolic Diseases

- Vascular occlusion producing infarction of the renal parenchyma is a relatively rare occurrence
- Thrombosis of major vessels as a consequence of trauma is more common in younger individuals; occlusion as a complication of atherosclerotic vascular disease is more often seen in older persons
- Emboli to the renal artery or one of its major branches is the most common cause of renal artery obstruction, and occurs predominantly in the setting of cardiac disease and arrhythmias
- Cholesterol atheroemboli from peripheral vessels, thrombotic microangiopathy, and sickle cell disease are all causes of small vessel occlusion

Cortical Infarcts

- Sudden complete occlusion of the main renal artery results in infarction of much of the renal parenchyma; occlusion of smaller renal artery branches results in necrosis of wedge-shaped segments of the renal parenchyma

Macroscopic

- The infarcted kidney appears enlarged and pale
- Regions of segmental infarction are pale, with a hyperemic border **(Figure 50)**

Microscopic

- The infarct shows coagulation necrosis with adjacent parenchyma showing changes of acute tubular necrosis
- Hemorrhage and acute inflammation are often present at the edge of the infarct, and there may be a rind of more preserved parenchyma overlying the infarct, that is supplied by penetrating capsular vessels
- Within days to weeks, the infarct becomes fibrotic, with eventual shrinkage of the affected parenchyma:
  - This area contains dense, globally sclerotic glomeruli with intervening dense fibrous tissue and tubule loss. The adjacent parenchyma may show tubular atrophy and varying degrees of glomerular sclerosis

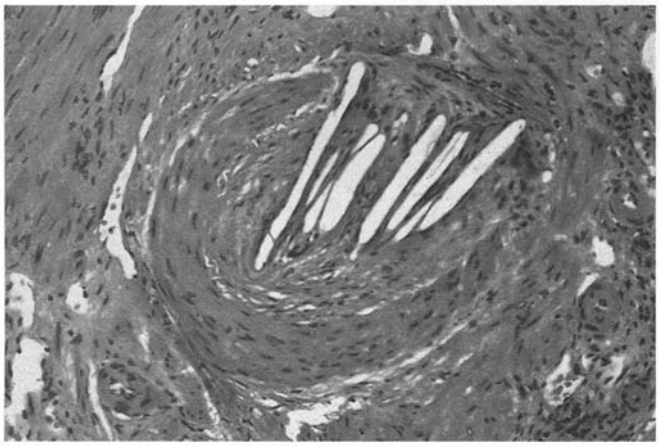


Fig. 51. Cholesterol clefts in arterial atheroembolus.

Renal Cholesterol Microembolism Syndrome

Clinical

- Can occur spontaneously or as a complication of aortic surgery or major vessel angiography in patients with diffuse atherosclerosis
- Renal cholesterol embolism may be diagnosed clinically when renal failure develops following identifiable predisposing factors and when there is evidence of systemic involvement in the form of focal digital ischemia, retinal embolism, and lower extremity livedo reticularis

Microscopic

- The characteristic renal lesion in disseminated cholesterol microembolism syndrome is the finding of atheromatous material in the form of cholesterol clefts within arcuate and interlobular arteries **(Figure 51)**

Thrombotic Microangiopathy

Clinical

- Encompasses a group of disorders characterized by microangiopathic hemolytic anemia, thrombocytopenia, and microvascular thrombi:
  - Hemolytic uremic syndrome (HUS)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Disseminated intravascular coagulation (DIC, shows fibrinolysis)
  - Malignant hypertension
  - Scleroderma
  - Pregnancy associated
  - Therapy associated
  - Chronic transplant glomerulopathy

*Morphologic Features **(Figure 52)***

- Thickening of capillary walls with the formation of "double contours"

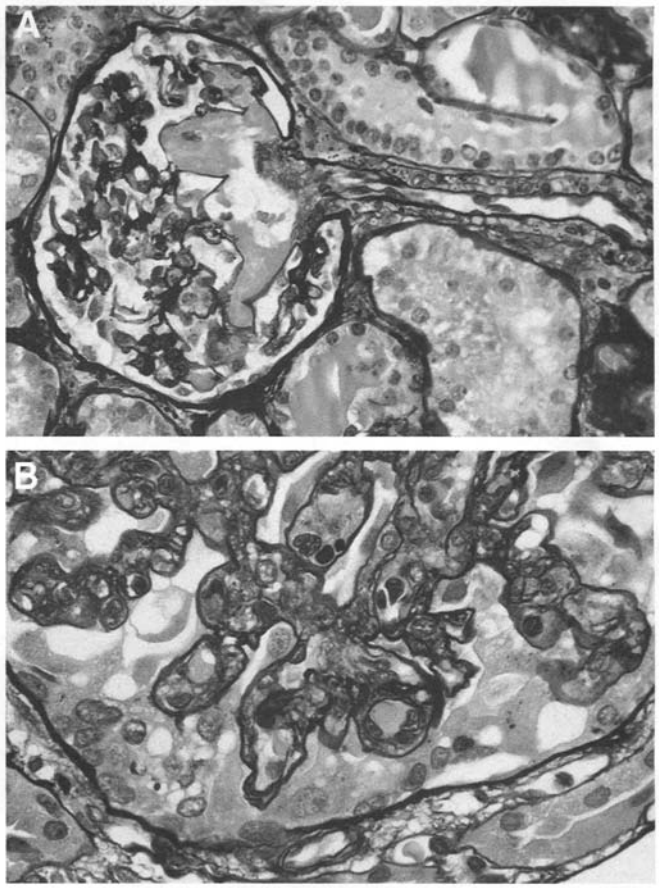


Fig. 52. Acute thrombotic microangiopathy with luminal fibrin and mesangiolytic change **(A)**. Chronic thrombotic microangiopathy with subendothelial lucency and GBM duplication **(B)**.

- Capillary thrombosis
- Fragmented red blood cells
- Mesangiolysis with microaneurysm formation
- Mucoid intimal thickening of arteries with glomerular ischemia

Vasculitis

- Renal involvement in systemic vasculitis is characterized by necrotizing and crescentic glomerulonephritis **(Figure 53)**
- Crescentic glomerulonephritis may be immune complex mediated, mediated by anti-glomerular basement membrane antibody, or characterized by little or no immune deposits (pauci-immune type):
  - Pauci-immune crescentic glomerulonephritis comprises nearly 50% of cases of crescentic glomerulonephritis, and is frequently associated with both polyarteritis and Wegener's granulomatosis, but may also be diagnosed as an isolated renal disease (idiopathic crescentic GN)

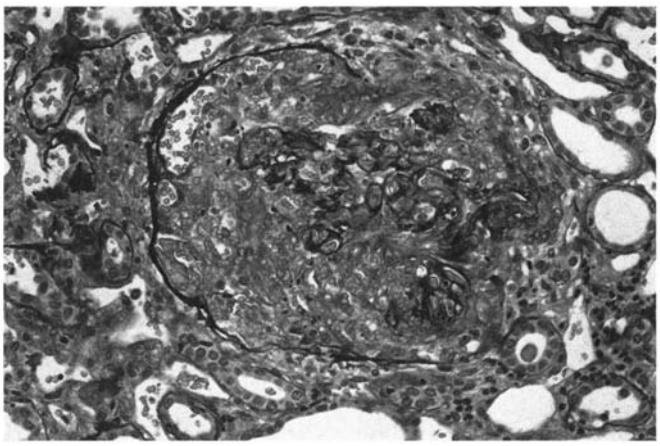


Fig. 53. Necrotizing and crescentic glomerulonephritis in systemic vasculitis.

- Most pauci-immune crescentic glomerulonephritis is associated with a detectable anti-neutrophil cytoplasmic antibody (ANCA) in the serum:
  - ANCA-associated vasculitis includes:
    - Wegener' granulomatosis >90% of cases
    - Microscopic polyarteritis >90%
    - Polyarteritis nodosa 30% to 50%
    - Idiopathic crescentic glomerulonepheritis >90%
    - Kawasaki disease 50%
    - Churg-Strauss syndrome 50% to 60%
  - Wegener's granulomatosis is a necrotizing, granulomatous vasculitis that classically involves the upper and lower respiratory tract and the kidney; other sites such as the eyes, ears, heart, nervous system, skin, and joints are less commonly affected:
    - Clinical signs of renal disease are present in the majority of patients with Wegeners granulomatosis; patients usually present with the acute nephritic syndrome with renal functional impairments ranging from mild to overt renal failure
    - Morphologically, the typical renal lesion in Wegener's granulomatosis is a focal and segmental necrotizing and crescentic glomerulonephritis that lacks immune deposits
  - Involvement of vessels in the kidney in polyarteritis nodosa is frequent, but the caliber of vessel involved varies; this vascular involvement may lead to focal infarction. Significant renal functional impairment more commonly results from necrotizing and crescentic glomerulonephritis. The necrotizing glomerulonephritis of poly-arteritis is morphologically indistinguishable from that of Wegener's granulomatosis

DEVELOPMENTAL AND CYSTIC DISEASES OF THE KIDNEY

Renal Dysplasia

Clinical

- A developmental abnormality that results from aberrant metanephric differentiation
- Although the pathogenesis is unknown, possibilities include in utero urinary tract obstruction and a defect in inducer, the ampullary bud, responder tissue, or metanephric blastema
- Renal dysplasia occurs sporadically and may be associated with obstruction, multi-malformation syndromes (Meckel's syndrome), chromosomal anomalies (trisomy 9 or 13), or hereditary malformation syndromes (chondrodysplasia syndromes)
- Unilateral multicystic renal dysplasia is the most common cause of a renal mass in childhood; bilateral lesions may present in utero or shortly after birth with oligohydramnios and Potter's syndrome
- Adults are usually asymptomatic but may have flank pain or a nonfunctioning small kidney
- The clinical outlook depends on the extent of dysplasia if bilateral, and the function of the contralateral kidney if unilateral
- The recurrence rate in siblings is approx. 2% but may be much greater in syndromic dysplasias

Macroscopic

- Dysplastic kidneys may be unilateral or bilateral, large or small, reniform or irregular, and solid or cystic **(Figure 54)**

Microscopic

- The overall architecture is disorganized. There may be primitive ducts, aberrant glomeruli, cysts lined by flattened epithelium, and immature cartilage, tubules, or mesenchymal tissue, as well as relatively normal tubules and glomeruli **(Figure 55)**

Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Clinical

- The most common cystic renal disease, with an estimated frequency between 1 : 500 and 1 : 1000 and a nearly complete penetrance
- Occurs slightly more frequently in Caucasians than in African Americans

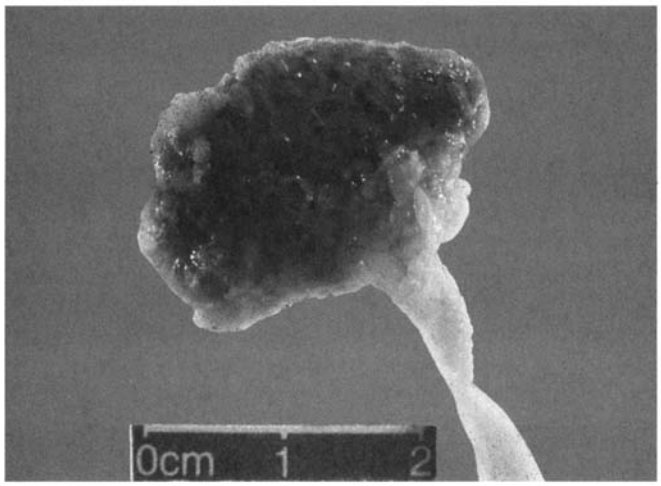


Fig. 54. Multicystic renal dysplasia.

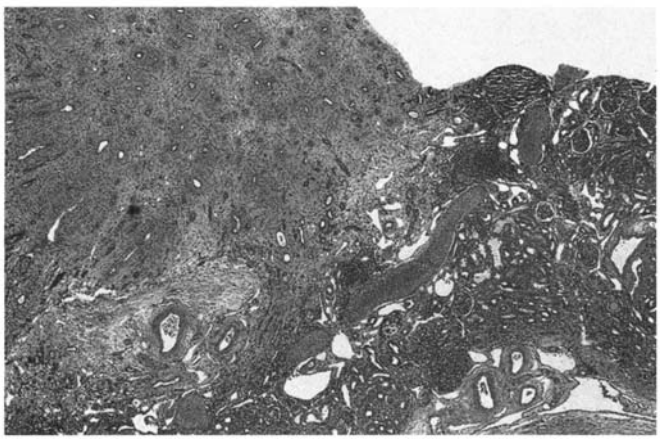


Fig. 55. Renal dysplasia with architectural disarray and focal cartilage.

- There is some genetic heterogeneity but >90% of cases in Caucasians are associated with a defect in chromosome 16p
- The disease course is variable, ranging from cases that are fatal in newborns to cases with minimal functional disturbance at old age; 25% of patients lack a family history
- In children, the process may be nonuniform and the patient may appear to have a unilateral lesion early in the course, even radiographically
- Most patients present in the third to fourth decade with dull abdominal pain and bilaterally palpable kidneys, as well as variable renal insufficiency, gross or microscopic hematuria, hypertension, infection, and mild proteinuria:
  - Other associated manifestations include cardiac abnormalities, congenital intracranial aneurysms (10% to 36%), and cysts of the liver, lungs, pancreas, and spleen
- Renal failure occurs in 50% of patients an average of 10 years after clinical detection
- Patients with ADPKD account for 10% of patients in the United States on dialysis and 6% of renal transplants

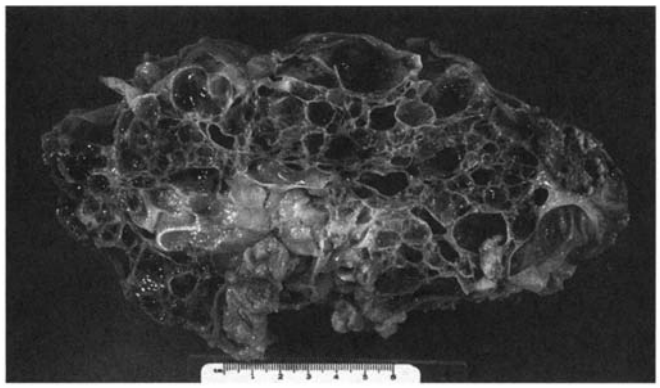


Fig. 56. Autosomal dominant polycystic kidney disease with irregular renal enlargement and numerous parenchymal cysts.

Macroscopic

- The kidneys are large, ranging from 250–4000 g, and usually maintain a somewhat reniform shape
- Variable numbers of spherical, unilocular cysts are present within the cortex and medulla **(Figure 56)**
- The calices, pelvis, and papilla are often greatly distorted

Microscopic

- 1% to 2% of the nephrons show cystic dilation of primarily the collecting tubules, proximal convoluted tubules, and Bowman's space interspersed with normal or compressed renal parenchyma
- Frequently, there is focal hyperplasia of the epithelial lining and polyp formation
- Renal cell carcinoma may also occur

Autosomal Recessive Polycystic Kidney Disease (ARPKD)

Clinical

- Occurs in 1/6,000 to 1/14,000 live births and has a 2 : 1 female predominance
- The etiology and pathogenesis are unknown, but the kidneys appear to have a normal distribution and number of nephrons and collecting ducts
- The clinical presentation is variable depending on the extent and duration of disease:
  - Many affected newborns have severe disease with a grossly enlarged abdomen, kidneys, and signs of oligohydramnios (pulmonary hypoplasia, flattened nose, low set ears, micrognathia, hip dislocation). In the first days of life, these neonates develop fatal respiratory distress, congestive heart failure, and hypertension
  - Older children and adults show a variable course with approx. 30% having an insidious onset of renal failure, which is often associated with anemia, renal osteodystrophy, growth retardation, hypertension, and congestive heart failure

- Also associated with congenital hepatic fibrosis, and there is an inverse relationship between the extent of renal cystic change and the extent of hepatic fibrosis
- Older patients have a smaller number of large cysts with marked, progressive hepatic fibrosis; although liver function is usually well maintained, severe portal hypertension, hepatosplenomegaly, and esophageal varices may develop by 5–10 years of age

Macroscopic

- The renal capsule is smooth with numerous 1–2 mm cysts visible
- On sectioning, the cysts are 1–8 mm, cylindrical, and extend radially throughout the cortex, obscuring the corticomedullary junction **(Figure 57)**
- In older patients, the surface becomes irregular

Microscopic

- In the younger patient, the kidney is almost entirely composed of dilated terminal branches of the collecting ducts; these appear cylindrical in the cortex and round to oval within the medulla:
  - The cysts are lined by cuboidal epithelium, which may have foci of hyperplasia or polyp formation
  - The glomeruli and proximal nephron may be compressed but are otherwise unremarkable
- In older patients, the cysts are fewer in number but are larger and are associated with tubular atrophy, interstitial fibrosis, and glomerular sclerosis:
  - The hepatic lesion is diffuse but is limited to the portal triads, where there is variable fibrosis and increased numbers of irregularly shaped bile ducts

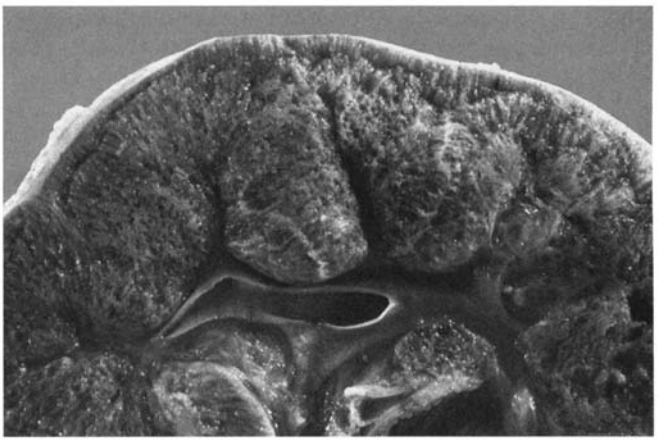


Fig. 57. Autosomal recessive polycystic kidney disease with uniform renal enlargement and small, cylindrical, radially oriented cysts.

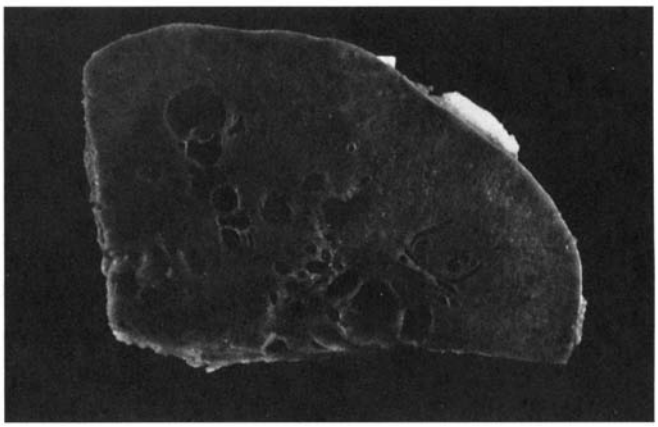


Fig. 58. Medullary cystic disease with cysts near corticomedullary junction.

Juvenile Nephrophthisis (Medullary Cystic Disease)

Clinical

- Juvenile nephronophthisis, or medullary cystic disease, is a complex of progressive renal diseases affecting children, characterized by nephrosclerosis, renal failure, and medullary cysts
- May present as a single morphology and clinical picture, differing only in the pattern of inheritance (sporadic, autosomal recessive, or autosomal dominant)
- Clinical presentation usually occurs between 5–35 years of age with anemia, polyuria, enuresis, and polydipsia secondary to the decreased concentrating ability of the tubules
- Occasionally, patients will present with associated abnormalities of the retina, skeletal, or central nervous system
- Proteinuria, hematuria, infection, stone formation, and pain are not usually present

Macroscopic

- The kidneys in medullary cystic disease are symmetrically small and firm with a finely granular surface, a thin cortex and medulla, and indistinct corticomedullary junction, which is the site of a variable number of cysts **(Figure 58)**

Microscopic

- There is severe, widespread tubular atrophy and interstitial fibrosis with diffuse thickening of the basement membranes and scattered sclerotic glomeruli
- The cysts are lined by cuboidal to flattened epithelium with surrounding fibrosis and inflammation

Acquired Renal Cystic Disease

Clinical

- Affects patients on hemodialysis and peritoneal dialysis as well as azotemic nondialyzed patients
- Cysts develop in 35% to 47% of patients on maintenance hemodialysis and development appears to be dependent on the duration of dialysis

- Acquired cysts occur in as many as 92% of patients who have been dialyzed more than 8 years
- Cyst formation is three to four times more common in males
- Most patients have no symptoms referable to the cysts but may present with renal bleeding or pain
- The cysts form primarily from the proximal convoluted tubules, and are associated with multiple small diverticula elsewhere in the tubule

Macroscopic

- Overall, the kidneys are variably sized, but in a single patient, are usually of equal size
- The kidneys contain a variable number of clear, fluid-filled cysts with some having a few large subcapsular cysts and others having numerous small cysts throughout the parenchyma **(Figure 59)**
- The cysts can be uni- or multilocular and mainly involve the cortex, but can also affect the corticomedullary junction and medulla; often there is evidence of acute or past hemorrhage

Microscopic

- The kidneys show end-stage renal disease with sclerotic glomeruli, tubular atrophy, and interstitial fibrosis



Fig. 59. Acquired renal cystic disease with cortical cysts and cortical atrophy.

- Calcifications, hemosiderin, and arterial intimal and medial hyperplasia may also be present
- The cysts are lined by flattened to cuboidal epithelium and may contain deposits of calcium oxalate
- There is an increased incidence of renal cell carcinoma, particularly papillary renal cell carcinoma, in patients with end-stage renal failure and acquired cystic disease

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29

Tumors of the Kidney

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CONTENTS

I. Renal Neoplasms in Children 29-2
Nephrogenic Rests and Nephroblastomatosis 29-2
Nephroblastoma (Wilms' Tumor) 29-2
Cystic Partially Differentiated Nephroblastoma 29-5
Congenital Mesoblastic Nephroma 29-5
Clear Cell Sarcoma of the Kidney 29-7
Rhabdoid Tumor of the Kidney 29-8

II. Renal Neoplasms in Adults 29-9
Papillary Adenoma 29-9
Oncocytoma 29-9
Renal Cell Carcinoma 29-11
Clear Cell Renal Cell Carcinoma 29-11
Multilocular Cystic Renal Cell Carcinoma 29-13
Papillary Renal Cell Carcinoma 29-13
Chromophobe Renal Cell Carcinoma 29-15
Collecting Duct Carcinoma 29-17
Renal Medullary Carcinoma 29-18
Mucinous Tubular and Spindle Cell Carcinoma 29-18
Tubulocystic Carcinoma 29-19
Renal Cell Carcinoma Unclassified 29-19
Metanephric Neoplasms 29-20
Mesenchymal Neoplasms 29-22
Renomedullary Interstitial Cell Tumor (Medullary Fibroma) 29-22
Angiomyolipoma (AML) 29-22
Juxtaglomerular Cell Tumor 29-23
Mixed Epithelial/Renal Parenchymal Neoplasms 29-23
Cystic Nephroma 29-23
Mixed Epithelial and Stromal Tumor 29-24

III. TNM Classification of Renal Cell Carcinoma (2002 Revision) (AJCC) 29-25

IV. Suggested Reading 29-26

RENAL NEOPLASMS IN CHILDREN

Nephrogenic Rests and Nephroblastomatosis

Nephrogenic rests

- Abnormally persistent foci of embryonal cells
- Identifiable in 1% of post-mortem kidneys in infants
- Considered capable of developing into nephroblastoma
- Identifiable in 25 to 40% of kidneys harboring nephroblastoma
- If diffuse and multifocal, the term "nephroblastomatosis" is applicable
- If identified in a kidney harboring nephroblastoma, risk of tumor formation in opposite kidney is increased; if not found, risk in other kidney is minimal
- Sub-classified into *perilobar (PLNR)* and *intralobar (ILNR)* types

Perilobar nephrogenic rests (PLNR)

- 10X more common than ILNR in routine autopsies
- Most often multifocal
- Sharply circumscribed; no reactive changes at interface with adjacent normal renal parenchyma
- Located at periphery of renal lobule **(Figure 1)**
- Blastema and tubules comprise most of lesion; stroma is scant and indistinct

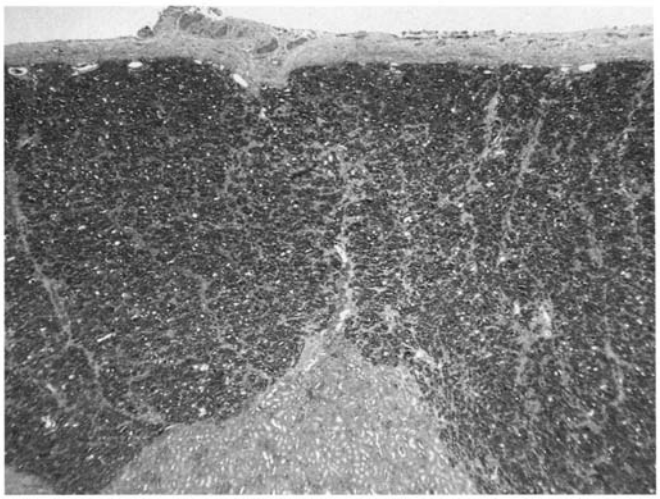


Fig. 1. Hyperplastic perilobar nephrogenic rest immediately beneath renal capsule. Note absence of fibrosis at junction between the rest and the adjacent kidney. Patient status post-chemotherapy for Wilms' tumor, accounting for the scattered microcalcifications.

Intralobar nephrogenic rests (ILNR)

- Most often unifocal
- Indistinct border; irregularly intermingled with adjacent normal kidney
- Located in central portions of renal lobule **(Figure 2)**
- Blastema, tubules, and stroma all readily evident; stroma may predominate
  - Development of malignancy (nephroblastoma)
- Risk of development of nephroblastoma in ILNR is higher than in PLNR; however, since PLNR is usually multifocal, overall risk of malignancy is the same for both conditions
- Development of nephroblastoma is characterized by spherical expansion and development of a fibrous pseudocapsule between neoplasm and normal kidney

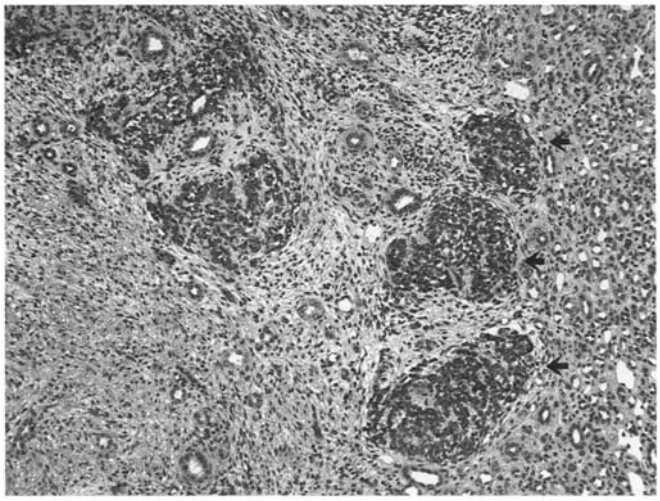


Fig. 2. Intralobar nephrogenic rest. Arrows indicate non-reactive interface between rest and normal kidney. Elements of the rest intermingle with normal kidney elements.

Nephroblastoma (Wilms' Tumor)

Clinical

- M : F = 1 : 1; peak age 2–4 years; highest incidence in African Americans
- Usually occurs between 6 months and 3 years of age; rare after age 3
- Comprises 85% of pediatric renal neoplasms and 5% of childhood cancers
- 5% multicentric, 5% bilateral, and 5% anaplastic
- Lung metastases are common
- Associated with cryptorchidism, hypospadias, hemihypertrophy, aniridia, renal ectopia, and horseshoe kidney
- Risk (*see* Chapter 2 for syndromes):
  - Beckwith-Wiedemann (hemihypertrophy): WT2 gene, 5% develop Wilms' tumor
  - Wilms-aniridia-genital anomaly-retardation syndrome (WAGR): WT1 gene

- Denys-Drash syndrome (glomerulonephritis, pseudohermaphroditism, and nephroblastoma) WT1 gene
- Trisomy 18
- Multicystic dysplastic kidney

Cytogenetics

- WT1:
  - Located on chromosome 11p13, putative tumor suppressor gene
  - 30–40% of Wilms' tumors show loss of heterozygosity (LOH) at 11p13
  - Encodes 45–49 kd protein, homologous to early growth response 1(EGR1)
  - Involved in transcription regulation with sequence-specific DNA binding
- WT2:
  - Located on chromosome 11p15.5
  - Putative tumor suppressor gene
  - Genomic printing and loss of maternal allele
  - IGF2 and H19 are putative candidate genes for WT2
- WT3:
  - Located on chromosome 16q
  - LOH is associated with cancer progression
- LOH on chromosome 1p
- Trisomy 18

Macroscopic

- Large (usually >5 cm) circumscribed tumor with variegated and nodular appearance; in some, extensive cyst formation punctuates solid areas
- 10% multicentric

Microscopic

- Triphasic: **(Figures 3 and 4)**
  - Blastema:
    - Three growth patterns: nodular (organoid), serpentine, and diffuse (no prognostic significance)
    - Small densely packed cells with little cytoplasm
    - Oval to elongate nuclei, overlapping nuclei, and numerous mitotic figures
  - Epithelial component:
    - Abortive tubules and glomeruli
    - May show mucinous, squamous, neural, or neuroendocrine differentiation
  - Stroma:
    - Skeletal muscle (most common), spindle cells, or cartilage
    - Note: Cartilage in the kidney may also be seen in mesoblastic nephroma and renal cystic dysplasia
- Often multicentric (multi centricity also seen in lymphoma and angiomyolipoma)



Fig. 3. Wilms' tumor, low power.

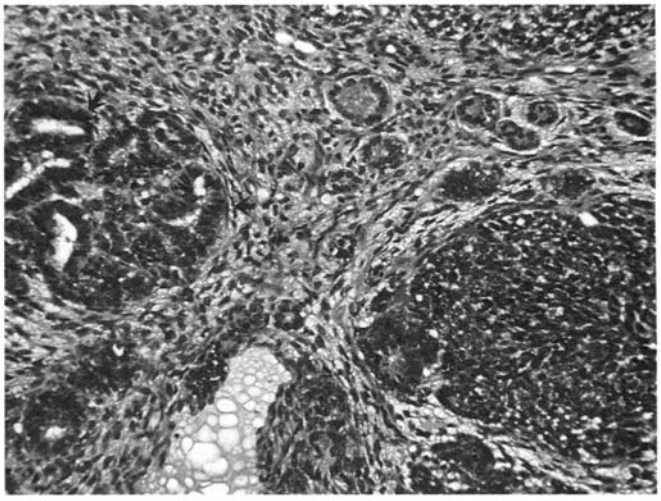


Fig. 4. Wilms' tumor, triphasic, composed of primitive tubules (blue arrows), blastema (red arrows), and stroma (green arrows).

- Pushing border except diffuse blastemal pattern
- Anaplasia:
  - One of the criteria for placing Wilms' tumor into unfavorable histology category; the other is the development of a high-grade malignancy within nephroblastoma
  - Indicates increased resistance to therapy rather than increased aggressiveness
  - Definition of anaplasia **(Figure 5)**:
    - Multipolar polyploid mitotic figures; each component of the abnormal metaphase must be as large or larger than a normal metaphase
    - Markedly enlarged and hyperchromatic nuclei (at least three times larger than adjacent non-neoplastic nuclei in both axes)

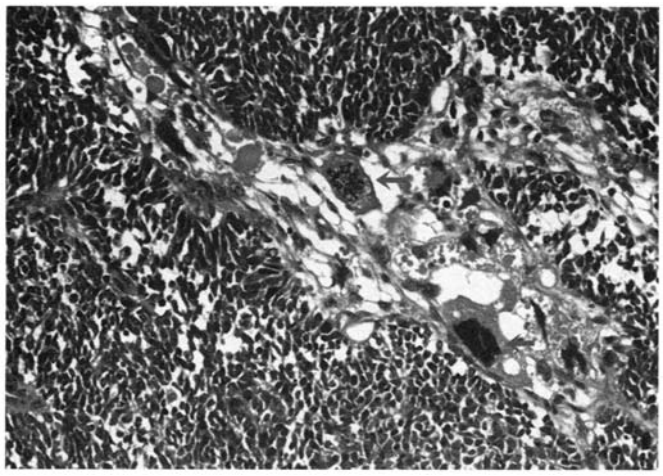


Fig. 5. Anaplasia in Wilms' tumor: markedly enlarged hyperchromatic nuclei, and a markedly abnormal mitotic figure (red arrows).

- Focal anaplasia:
  - One or only a few sharply localized regions of anaplasia within a primary tumor, the majority of which shows no significant nuclear atypia
  - Anaplastic region must be circumscribed and its perimeter must be entirely present for evaluation
  - Anaplasia is confined to renal parenchyma (diagnosis is excluded if anaplasia is seen in tumor in vascular spaces)
- Diffuse anaplasia:
  - Anaplasia that does not meet the criteria for focal anaplasia
  - Diffuse distribution throughout the primary tumor, and presence in advanced-stage tumors consistently portends poor prognosis

Immunohistochemistry (Blastema)

- Vimentin+
- Neuron-specific enolase (NSE)+ (focal)
- Cytokeratin+ (focal)
- Desmin+ (focal)
- WT1+

Differential Diagnosis of Wilms' Tumor

Clear cell sarcoma of the kidney

Macroscopic

- Large, centrally located, single, circumscribed but unencapsulated

Microscopic

- Nests or cords of epithelioid or spindled cells, non-overlapping, separated by arborizing vascular septae of variable thickness
- Subtly infiltrative border and entrapped normal tubules at periphery

Immunohistochemistry

- Vimentin+; BCL2+
  - CD34, S100 protein, desmin, MIC2 (CD99), cytokeratin, and epithelial membrane antigen (EMA) uniformly negative

Rhabdoid tumor of the kidney

Macroscopic

- Large, hemorrhagic, uncircumscribed, extensively necrotic

Microscopic

- Vesicular chromatin
- Distinct cherry-red nucleoli
- Hyaline eosinophilic cytoplasmic inclusions

Immunohistochemistry

- Vimentin strongly+
- EMA focally but intensely+

Renal neuroblastoma

Macroscopic

- Tumors are hemorrhagic and poorly circumscribed

Microscopic

- Absence of distinct peritumoral fibrous capsule
- Organoid arrangement of tumor cells
- "Salt and pepper" nuclear chromatin
- Homer Wright rosettes

Immunohistochemistry

- Positivity for neuron-specific enolase, synaptophysin, S100 protein, and chromogranin supportive of neuronal differentiation

Renal Synovial sarcoma

Macroscopic

- Large (Mean diameter 11 cm) and variably cystic

Microscopic

- Primitive spindle cells with overlapping ovoid nuclei and scant cytoplasm
- Admixed with variably-sized cystic spaces that represent trapped dilated native renal tubules and ducts

Special Studies

- WT1–
- t(X;18) translocation

Renal peripheral neuroectodermal tumor (PNET)

Clinical

- Most patients are adolescent or young adults (range 1 mo to 72 years)

Macroscopic

- Poor circumscription

Microscopic

- Primitive round cells with varying degrees of rosette formation
- Nuclear chromatin course, nuclei do not overlap

Immunohistochemistry

- CD99+; FLI1+; WT1–

Cytogenetics

- Characteristic translocations, especially t(11;22) (q24;q12)

Staging Nephroblastoma (5th Protocol, National Wilms' Tumor Study Group)

- Stage I Limited to kidney and completely resected:
  - Renal capsule is intact
  - Renal sinus soft tissue may be minimally infiltrated
- Stage II Tumor infiltrates beyond kidney, but is completely resected:
  - Tumor extends beyond renal capsule
  - Tumor infiltrates vessels within the renal sinus
  - Tumor with prior open or large bore needle biopsies
  - Tumor with local spillage confined to flank
- Stage III Residual nonhematogenous tumor confined to abdomen:
  - Tumor in abdominal lymph nodes
  - Diffuse peritoneal contamination: direct tumor growth, tumor implants, spillage into peritoneum before or during surgery
  - Gross or microscopic involvement of specimen margins
  - Residual tumor in abdomen
  - Tumor removed non-contiguously (piece-meal resection)
- Stage IV Hematogenous metastases
- Stage V Bilateral renal involvement at diagnosis (Tumor in each kidney should be separately substaged)

Cystic Partially Differentiated Nephroblastoma

Clinical

- Generally no symptoms; most detected as palpable masses
- Twice as common in males
- Seen in children <4 years old; great majority are <2 years old
- Clinical course is benign

Macroscopic

- Most are 5–10 cm, may be up to 18 cm in diameter
- Fibrous pseudocapsule sharply separates tumor from adjacent kidney

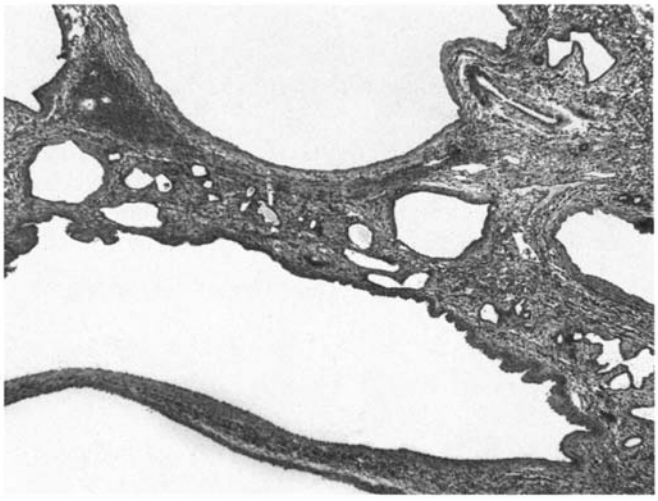


Fig. 6. Cystic partially differentiated nephroblastoma resected from an 18 month old male. Tumor consists entirely of cysts without expansile nodules of Wilms' tumor.

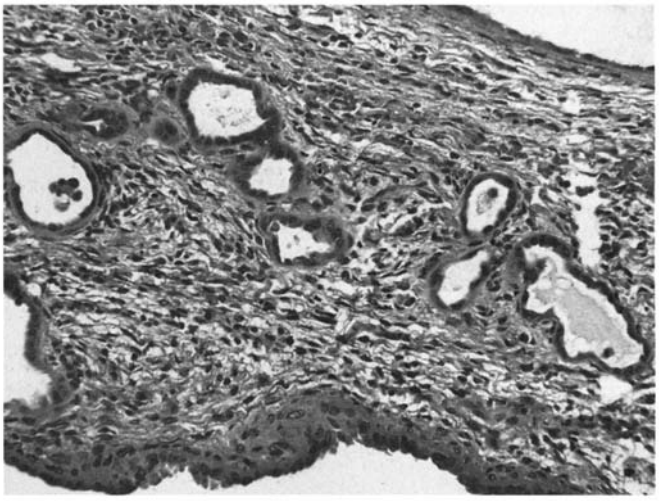


Fig. 7. Cystic partially differentiated nephroblastoma. The septa between the cystic spaces contain stromal tissue and immature tubules. No blastema is present.

- Tumor is entirely composed of variably-sized cysts, some of which may have papillary excrescences projecting into cystic spaces

Microscopic

- Composed of cysts separated by septa of variable thickness
- Cysts are lined by flat, cuboidal, or hobnail epithelium
- Septa contain blastema, nephroblastomatous epithelial elements, and differentiated and/or undifferentiated mesenchymal elements such as skeletal muscle, cartilage, fat, or myxoid mesenchyme **(Figures 6,7)**

Differential Diagnosis

- Solid expansile nodules, evident grossly, or altering the rounded contour of the cysts, warrant a diagnosis of cystic nephroblastoma
- If no nephroblastomatous elements are seen in the fibrous septa, some apply the diagnostic term "cystic nephroma;" however, these lesions are viewed as being different from the morphologically similar lesions that occur in adults

Congenital Mesoblastic Nephroma (CMN)

Clinical

- Accounts for 2% of pediatric renal tumors
- Most common congenital renal neoplasm
- 90% of patients are <1 year old; median age at diagnosis 2 months
- Presents as palpable mass; some are found on prenatal imaging
- Recurrence rate 5%; recurrences attributed to incomplete resection
- Only rare instances of metastasis and tumor-related death

Cytogenetics

- Two morphologic patterns—"classic CMN" and "cellular CMN"
- Cytogenetic profile of cellular CMN (translocation t(12;15)) confirms that it is infantile fibrosarcoma arising within the kidney
- Classic CMN is viewed as infantile fibromatosis involving kidney (no translocation identified)

Macroscopic

- Mean diameter 6 cm (range 1–14 cm)
- Solitary, unilateral
- Classic CMN: indistinctly circumscribed; firm whorled cut surface
- Cellular CMN: soft, appears circumscribed, often with cysts, hemorrhage and necrosis

Microscopic

- Classic CMN:
  - Intersecting bundles of spindle cells resembling fibroblasts, not densely packed
  - Scant collagen background; abundant thin-walled vascular spaces
  - Tongues of tumor insinuate themselves between normal adjacent renal parenchymal structures without distorting them **(Figures 8 and 9)**
  - Mitotic activity inconspicuous
- Cellular CMN:
  - Densely cellular, composed of plump spindle cells, arranged in poorly formed fascicles or in diffuse sheets
  - Prominent irregular vascular spaces ("staghorn vessels") in some
  - Abundant mitotic figures; necrosis frequently evident

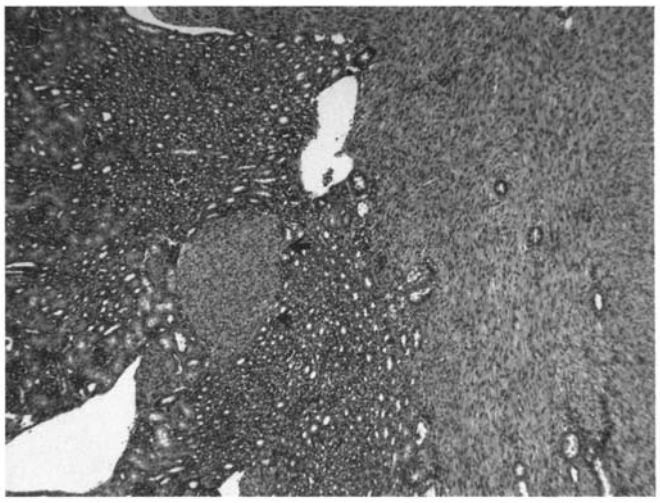


Fig. 8. Congenital mesoblastic nephroma, classic type. Tumor consists of intersecting fascicles of bland uniform spindle cells, encircling and interdigitating between native renal structures.

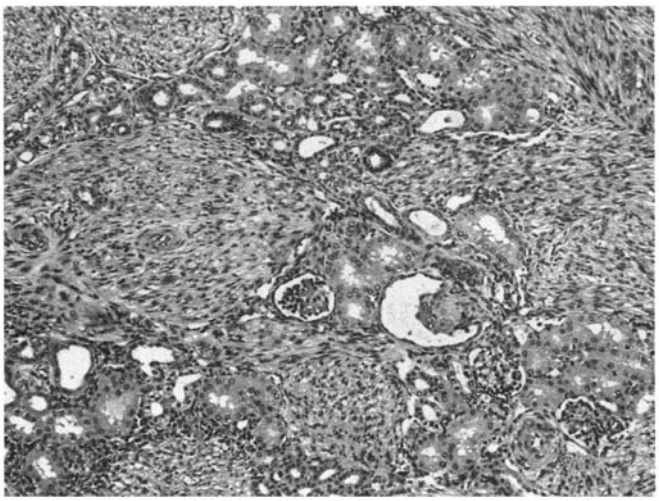


Fig. 9. Congenital mesoblastic nephroma, classic type. Tumor irregularly infiltrates renal parenchyma at the interface between tumor and normal kidney without compressing or distorting native structures.

  - Despite gross circumscription, pseudocapsule is absent, and tumor subtly infiltrates adjacent normal renal tissue **(Figures 10,11)**
  - Interface with adjacent kidney is not "interdigitating" as seen in classic type
- Mixed CMN:
  - Features of both classic and cellular CMN in same tumor (10–20% of cases)

Immunohistochemistry

- Vimentin+
- Actin+ (often)

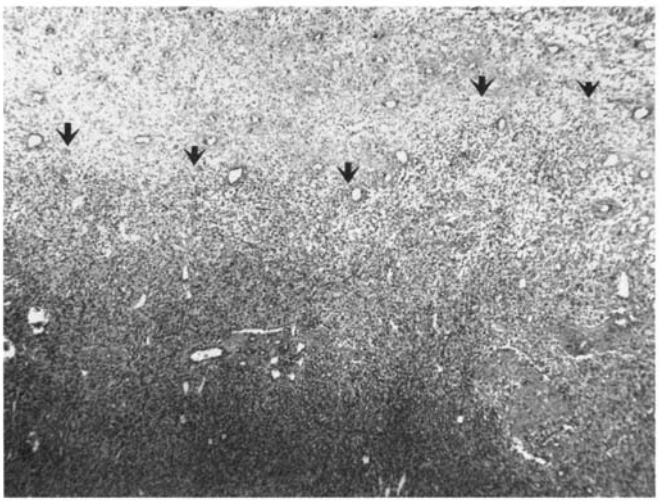


Fig. 10. Congenital mesoblastic nephroma, cellular type. Tumor is more densely cellular than its classic counterpart, and grows diffusely rather than forming intersecting fascicles. Blue arrows highlight the sharply demarcated border of the tumor.

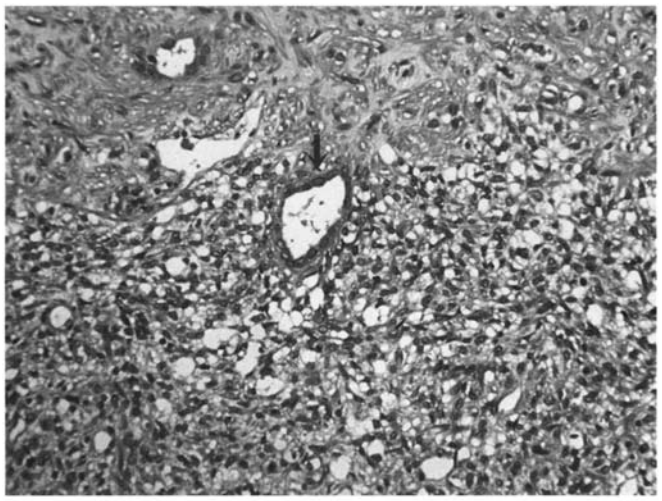


Fig. 11. Congenital mesoblastic nephroma, cellular type. Although the interface between tumor and normal kidney is sharply demarcated, there is no capsule, and the tumor subtly encircles a native tubule (blue arrow).

- ♦ Desmin+ (rarely)
- ♦ CD34, cytokeratins, S100 protein: all negative

Differential Diagnosis: CMN versus Clear cell sarcoma of kidney (CCSK):

- ♦ Challenging!
- ♦ Both occur in infancy
- ♦ Both are entirely mesenchymal:
  - Both show entrapped normal renal elements, & embryonal metaplastic changes
  - Features favoring CCSK over CMN:
    - Age >1 year
    - Metastases (especially to bone)
    - Fine nuclear chromatin, infrequent mitotic figures, extensive sclerosis
    - Absence of staghorn vessels
    - Entrapment of isolated nephrons (rather than groups of nephrons)
    - Negative immunostaining for desmin and actin

Clear Cell Sarcoma of Kidney (CCSK)

Clinical

- ♦ Accounts for about 3% of malignant pediatric renal neoplasms
- ♦ Twice as common in males
- ♦ Peak incidence in second year of life (range 2 months to 54 years)
- ♦ No associations with malformations, cytogenetic abnormalities, syndromes
- ♦ Marked propensity for metastasis to bone (consequently, previously named "bone metastasizing renal tumor of childhood")

Macroscopic

- ♦ Typically large (mean diameter 11 cm, mean weight 500–600 gm)
- ♦ Unilateral, unicentric, soft to firm, homogeneous, light brown or gray
- ♦ Usually confined within renal capsule; cysts common, sometimes prominent
- ♦ Sharply circumscribed interface with normal kidney; no gross capsule
- ♦ 5% involve renal vein

Microscopic (Classic pattern)

- ♦ Epithelioid or spindled cells arranges in nests or cords
- ♦ Nests or cords are separated by regularly spaced branching small blood vessels arranged as fibrovascular septa of variable thickness
- ♦ Cells are separated by myxoid extracellular matrix material that mimics clear cytoplasm **(Figure 12)**
- ♦ Cell nuclei are round/oval, with dispersed chromatin, inconspicuous or absent nucleoli **(Figure 13)**
- ♦ Mitotic activity relatively limited
- ♦ At the interface between tumor and normal kidney, there is subtle tumor infiltration with entrapment of individual tubules and nephrons
- ♦ Many pattern variations—myxoid, sclerosing, cellular, epithelioid, spindle cell, palisading

Differential Diagnosis: CCSK versus Nephroblastoma

- ♦ Features favoring nephroblastoma:
  - Bilaterality, multicentricity
  - Heterologous cell types (e.g., skeletal muscle) (Finding excludes CCSK)

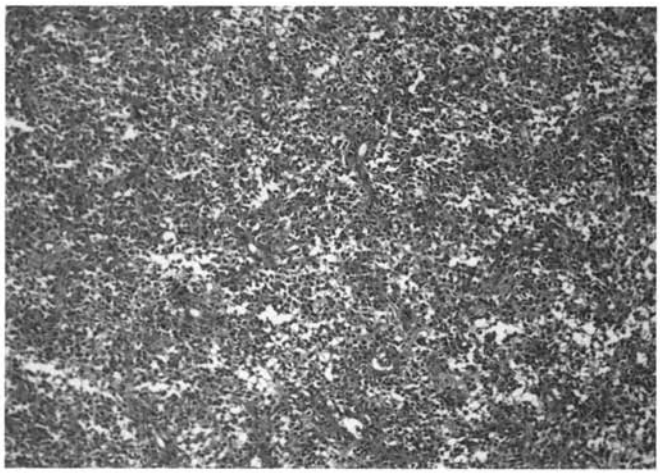


Fig. 12. Clear cell sarcoma of kidney. Regularly spaced fibrovascular channels intersect cords of tumor cells.

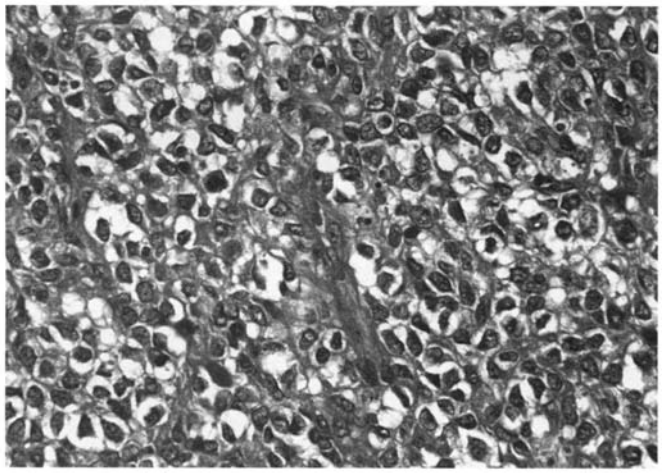


Fig. 13. Clear cell sarcoma of kidney. Tumor cells in upper right corner have minimal cytoplasm, and finely dispersed nuclear chromatin. Extracellular mucopolysaccharide matrix imparts a "clear cell" appearance to the majority of the cells in this image.

- Nodularity
- Botryoid growth within renal pelvis (Finding excludes CCSK)
- Tumor in renal vein
- Nephrogenic rests
- Positive immunostaining for WT1, CD56, epithelial, muscle, or neural markers

♦ Features favoring CCSK:
- Homogeneous pale H & E staining
- Entrapment of individual nephrons at tumor periphery
- Extensive collagen deposition

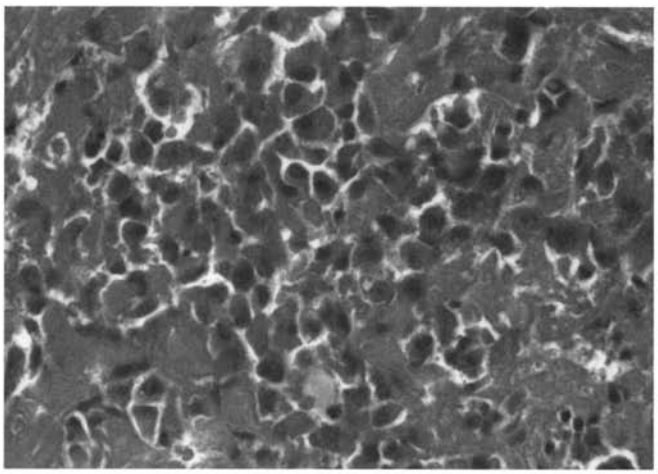


Fig. 14. Rhabdoid tumor of kidney. Tumor cells demonstrate vesicular nuclei with prominent cherry-red nucleoli and hyaline eosinophilic cytoplasmic inclusions that result in nuclear eccentricity.

- Negative immunostaining for virtually all markers except vimentin and BCL2

Rhabdoid Tumor of the Kidney

Clinical

♦ Accounts for about 2% of all pediatric renal tumors

♦ Highly invasive; at least 80% have metastases at time of diagnosis

♦ Very lethal; chemotherapy-resistant; 80% of patients die within one year

♦ Almost all patients are <3 years old; median age 11 months; M : F = 1.5 : 1

♦ Identical tumors involve other sites, especially CNS

♦ Rhabdoid tumors in all sites are characterized cytogenetically by mutation or deletion of the INI1 tumor suppressor gene on long arm of chromosome 22q11

♦ Despite name, the neoplasm is not of myogenic origin

Macroscopic

♦ Unilateral, large, unencapsulated, often with hemorrhage and necrosis, sometimes with satellite nodules representing intrarenal metastases

♦ Tumor-kidney interface is indistinct

Microscopic

♦ Composed of diffuse sheets of monotonous discohesive large cells with:
- vesicular nuclei
- prominent cherry-red nucleoli

- hyaline eosinophilic cytoplasmic inclusions (intermediate filaments) **(Figure 14)**

♦ Usually extensive vascular invasion

♦ Tumor cells often infiltrate between and around native glomeruli or tubules

Immunohistochemistry

♦ Vimentin strongly positive

♦ Intensely positive staining for EMA or cytokeratins in a few cells in a background of adjacent negatively-staining tumor cells (polyphenotypic differentiation)

RENAL NEOPLASMS IN ADULTS

Papillary adenoma

Clinical

♦ Most common renal tubular epithelial neoplasm

♦ Asymptomatic; generally an incidental finding at surgery or autopsy

♦ Incidence: 10% in patients <40 years old; 40% in patients >70 years old

♦ Frequent occurrence (33%) in acquired cystic kidney disease/hemodialysis

♦ Cytogenetics: loss of Y chromosome and combined trisomy of chromosome 7 and 17

Macroscopic

♦ Well circumscribed round or wedge-shaped yellow or grey nodule, 0.1–0.5 cm

♦ Location: Cortex, usually just beneath renal capsule

♦ Usually solitary, sometimes multiple and bilateral

Microscopic

♦ Tubular, papillary, or tubulopapillary structures **(Figure 15)**

♦ "Seamless" interface with adjacent kidney (no capsule)

♦ Tumor cells are small with scant cytoplasm; nuclei are round or oval, sometimes grooved, with punctate chromatin and inconspicuous nucleoli **(Figure 16)**

♦ Mitotic figures rare

♦ Some contain psammoma bodies and macrophages

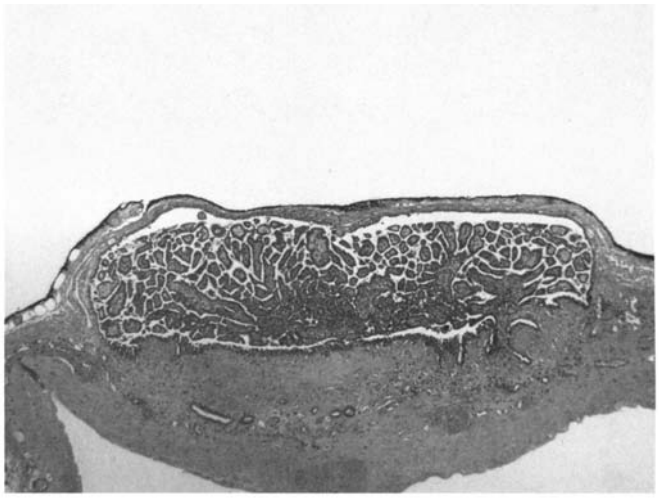


Fig. 15. Papillary adenoma. This 3 mm papillary lesion was noted in the wall of a surgically resected renal cyst.



Fig. 16. Papillary adenoma (higher power view of lesion in Fig. 15). Papillary cores lined by small dark regular cuboidal cells with uniform nuclei lacking nucleoli.

Oncocytoma

Clinical

♦ Accounts for about 5% of resected renal epithelial neoplasms

♦ Twice as common in males; median age 62 years

♦ Usually asymptomatic; some have hematuria, flank pain, or palpable mass

♦ Imaging studies may demonstrate central scarring

♦ Benign (no recorded deaths from metastatic disease)

♦ Cell of origin: Intercalated cell of collecting duct

Cytogenetics

♦ Mixed populations of normal and abnormal karyotypes

♦ Losses of chromosomes 1 and Y, deletions from chromosome 14, rearrangements involving chromosome 11

Macroscopic

♦ Well circumscibed; tan, pale yellow, or mahogany brown **(Figure 17)**

♦ Typically solitary; multiple in about 5% of cases; median size 6 cm

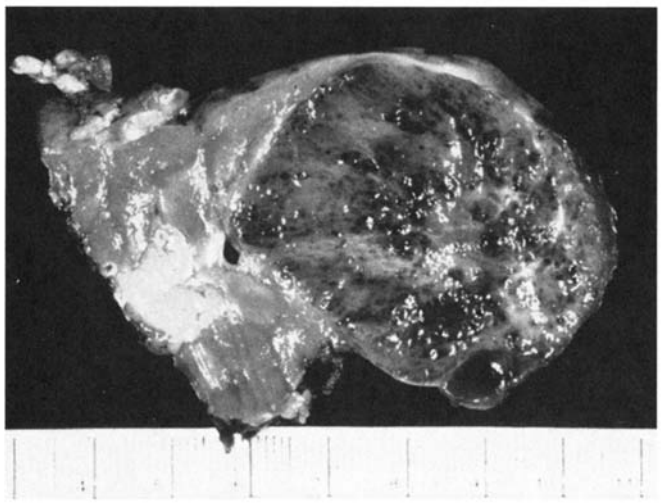


Fig. 17. Oncocytoma, gross specimen. Well circumscribed tan-brown lesion with focal hemorrhage and extensive central scarring.

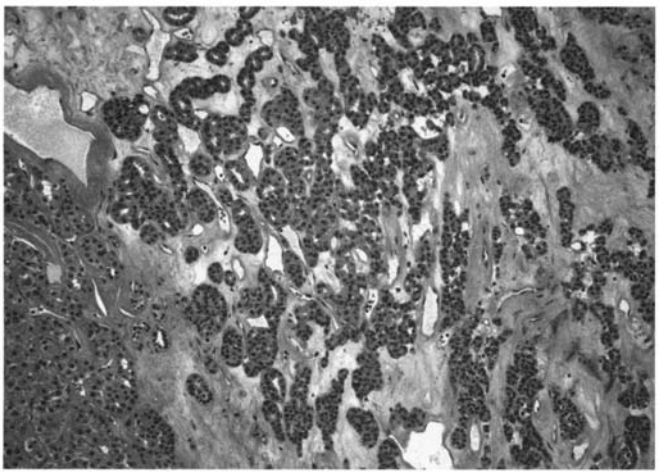


Fig. 18. Oncocytoma, composed of solid nests of oncocytic cells in a hyalinized fibrous stroma.

- Central stellate scar in 33%; focal hemorrhage in up to 20%

Microscopic

- Cells are arranged in solid nests, tubules, or microcysts in a loose fibrous stroma **(Figure 18)**
- Tumor is composed entirely of cells with abundant granular eosinophilic cytoplasm **(Figure 19)**
- Nuclei are typically round to oval, ≤10 μm, evenly dispersed chromatin, small central nucleoli
- Some nuclei show hyperchromasia and pleomorphism (degenerative) **(Figure 20)**
- Mitotic figures absent or very rare; atypical mitotic figures are not seen

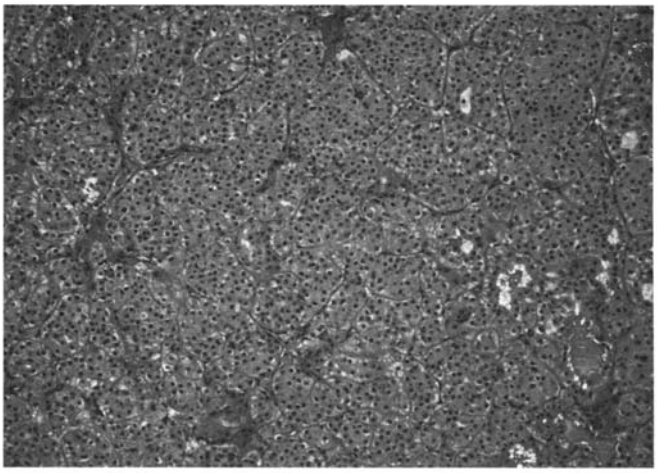


Fig. 19. Oncocytoma with more densely packed but discrete nests of oncocytic cells with small round uniform nuclei.

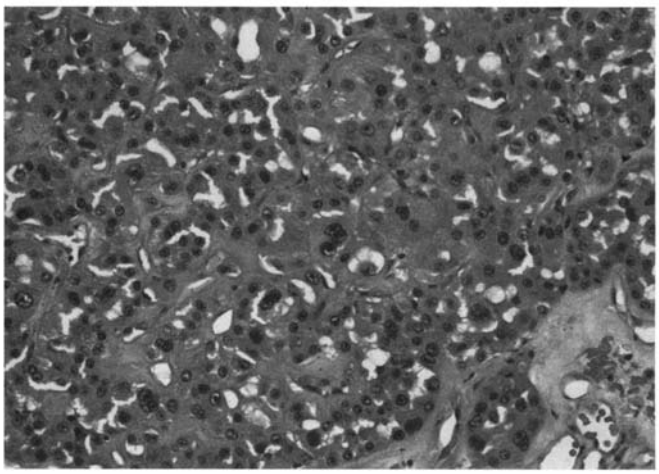


Fig. 20. Oncocytoma. All cells have abundant granular eosinophilic cytoplasm; some have round regular nuclei, and other have pleomorphic hyperchromatic nuclei. Nuclear irregularity without mitotic activity or other exclusion criteria is considered to be a degenerative change in this setting, and of no significance.

- Rarely, microscopic extension into perirenal fat or blood vessels is noted

Special Studies

- Hale's colloidal iron faintly positive, mainly near lumenal surface
- Immunopositive for most cytokeratins, EMA, parvalbumin **(Table 1)**
- Immunostains for vimentin and RCC marker usually negative

Ultrastructure

- Tumor cells show abundant mitochondria; other organelles sparse

Table 1. Immunohistochemical Findings in Renal Epithelial Neoplasms

	CD10	*RCC marker*	*Vimentin*	*EMA*	*CK7*	*34βE12*	*Lectins*
Clear cell renal cell carcinoma	+(81–100%)	+(85%)	+/–	+/–(20–90%)	–	–	–/+f
Papillary renal cell carcinoma	+(63–93%)	+(93%)	+/–	+/–(30–45%)	+	–	–
Chromophobe renal cell carcinoma	–	–	–	+(100%)	+	–	–
Oncocytoma	–/+f	–	–	+(75–100%)	–	–	–
Collecting duct carcinoma	–	–	+	+/–	–/+f	+(majority)	+
Urothelial carcinoma	–/+f	–	–	NA	–/+f	+	–/+f

*EMA = epithelial membrane antigen; CK7 = cytokeratin 7; 34*βE12 = high molecular weight cytokeratin; lectins = peanut lectin or Ulex europaeus agglutinin-1
–/+f = usually negative, occasionally focally positive
+/– = positive or negative; varies with individual tumor
NA = insufficient data available

Exclusion criteria

- Foci of clear cells
- Papillary architecture
- Sheet-like growth pattern
- "Plant-like" cells
- More than rare mitotic figures, or atypical mitotic figures
- Gross extension into perirenal fat or large vessels
- Ultrastructural findings compatible with chromophobe carcinoma

Renal Cell Carcinoma (RCC)

Clear Cell Renal Cell Carcinoma

Clinical

- M : F = 2 : 1; peak in the sixth and seventh decade
- Comprises about 70% of RCC (23,000 newly diagnosed cases annually)
- Cytogenetics:
  - Deletion of 3p13
  - Somatic mutation or inactivation of the von Hippel-Lindau gene (tumor suppressor gene RAF-1 at 3p25)
- Arises from renal tubular epithelium, differentiated toward proximal tubular epithelium
- May present with hematogenous metastases in unusual sites
- Most common malignancy to receive metastasis from other sites
- Classic triad: hematuria (40% of patients), flank pain (40%), and palpable mass (35%)
- Hepatic dysfunction unrelated to metastases, with nonspecific biopsy findings, occurs in about 20% of patients; reversible after nephrectomy; prognosis is poor
- Paraneoplastic endocrine syndromes:
  - Polycythemia (due to erythropoietin production)
  - Hypercalcemia (often seen in advanced stage)
  - Hypertension (due to renin production)
  - Cushing's syndrome
  - Sex hormonal imbalance (feminization, gynecomastia, or masculinization)
- Risk factors for development of renal cell carcinoma:
  - Tobacco use
  - Hypertension
  - Obesity (especially in women)
  - Acquired renal cystic disease (long-term dialysis)
  - Chronic renal failure
  - Tuberous sclerosis
  - von Hippel-Lindau syndrome
  - Familial renal cancers

Macroscopic

- Usually solitary; 4% multicentric in same kidney; 0.5–3.0% bilateral
- Rounded, nodular, often protrudes from cortical surface
- Well demarcated from adjacent kidney; often a pseudocapsule; "pushing" margin
- Typically golden yellow; cut surface often has a variegated appearance with varying amounts of hemorrhage, necrosis, cystic change and calcification

Microscopic

- Typically composed of cells with abundant cytoplasm that appears optically clear due to loss of intracellular glycogen and lipids during histologic processing, and with distinct cell membranes

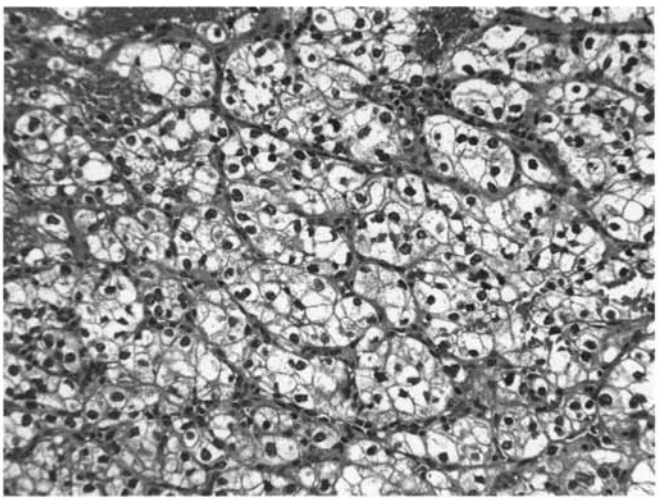


Fig. 21. Clear cell renal cell carcinoma. A prominent network of delicate blood vessels separates solid nests of cells with abundant clear cytoplasm.

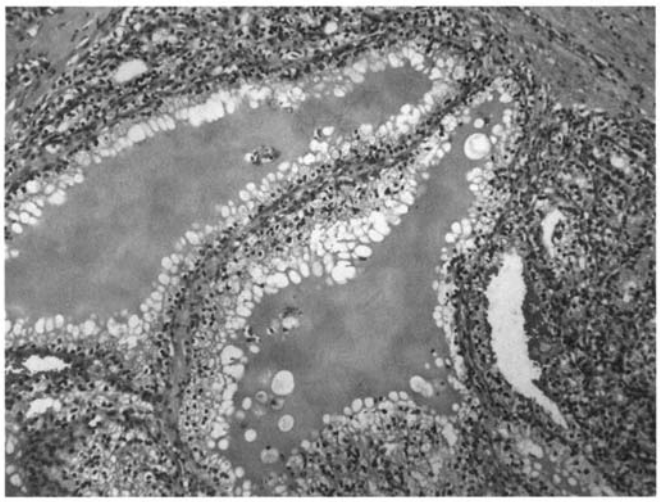


Fig. 22. Clear cell renal cell carcinoma forming small tubules and microcysts containing amorphous eosinophilic proteinaceous fluid.

- Tumor architecture is diverse—solid, alveolar, and acinar patterns
- Tumor cells are set in a regular network of small delicate blood vessels **(Figure 21)**
- Microcysts and macrocysts may be present, containing eosinophilic fluid **(Figure 22)**
- Many cytologic variations may be seen:
  - cells with granular eosinophilic cytoplasm
  - cells with rhabdoid morphology
  - interlacing or whorled bundles of spindle cells, sometimes with marked nuclear pleomorphism (sarcomatoid change)

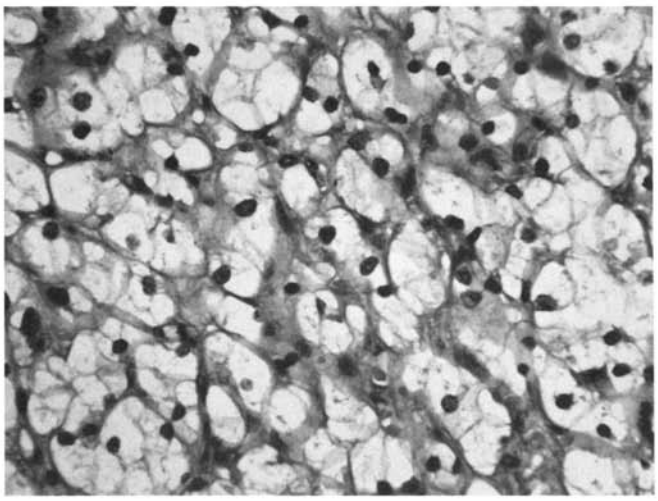


Fig. 23. Clear cell renal cell carcinoma, grade 1.

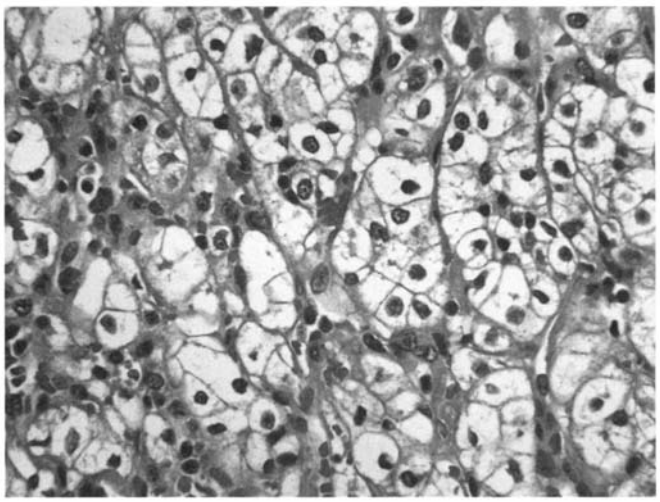


Fig. 24. Clear cell renal cell carcinoma, grade 2.

- Nuclear grade is second only to tumor stage in defining prognosis; grade is assigned according to the following nuclear findings:
  - Grade 1: Small round uniform nuclei, up to 10 μm, nucleoli not visible **(Figure 23)**
  - Grade 2: Nuclei slightly irregular, up to 15 μm, nucleoli inconspicuous **(Figure 24)**
  - Grade 3: Nuclei very irregular, up to 20 μm, large prominent nucleoli **(Figure 25)**
  - Grade 4: Nuclei bizarre, spindled or multilobated, over 20 μm, macronucleoli **(Figure 26)**

Immunohistochemistry (Table 1)

- Tendency to be immunoreactive to antibodies against:
  - Brush border antigens (frequent)
  - Low molecular weight cytokeratins (CK8, 18, 19) (frequent)

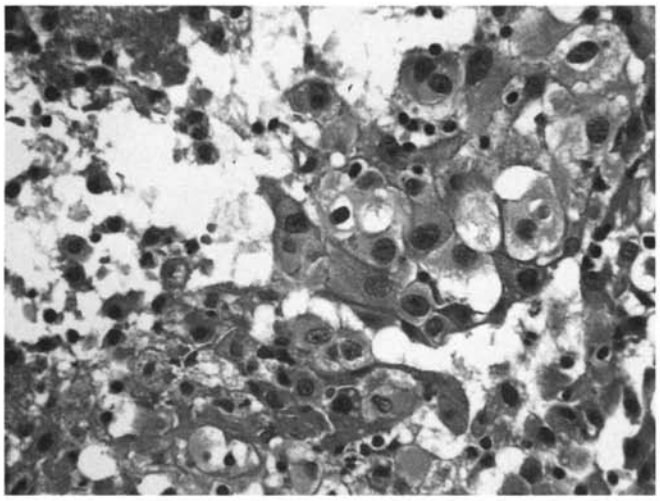


Fig. 25. Clear cell renal cell carcinoma, grade 3.

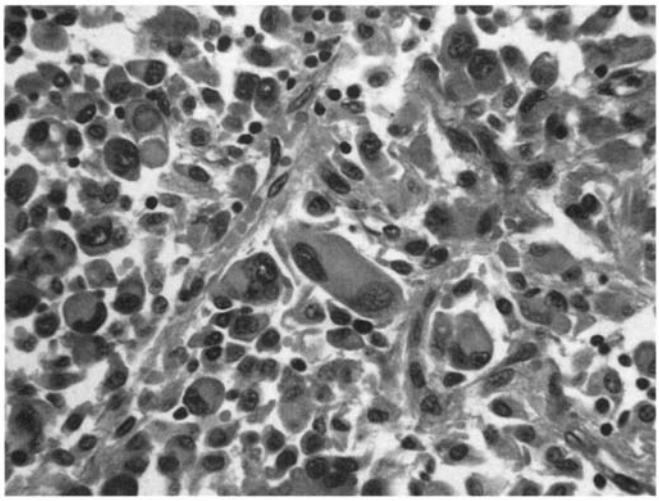


Fig. 26. Clear cell renal cell carcinoma, grade 4.

- AE1, Cam 5.2, vimentin (frequent)
- High molecular weight cytokeratins (14, 34βE12) (rarely)
- RCC marker, CD10, and EMA (majority)
- MUC1 and MUC3 (consistently)

♦ Clear cell RCC is not immunoreactive for parvalbumin

Multilocular Cystic Renal Cell Carcinoma

Clinical

♦ Adults, mean age 51 years (range 20–76), M : F = 3 : 1

♦ Account for about 5% of cases of RCC with clear cell morphology

♦ Favorable prognosis after nephrectomy

♦ No recorded instances of recurrence or metastasis

Macroscopic

♦ Well circumscribed, with fibrous capsule

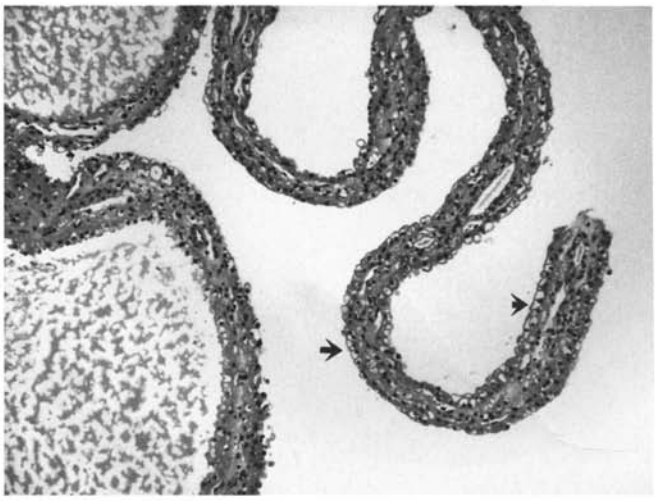


Fig. 27. Multilocular cystic renal cell carcinoma. Delicate septa between the cystic spaces are lined by clear cells (blue arrows) and flat cuboidal cells.

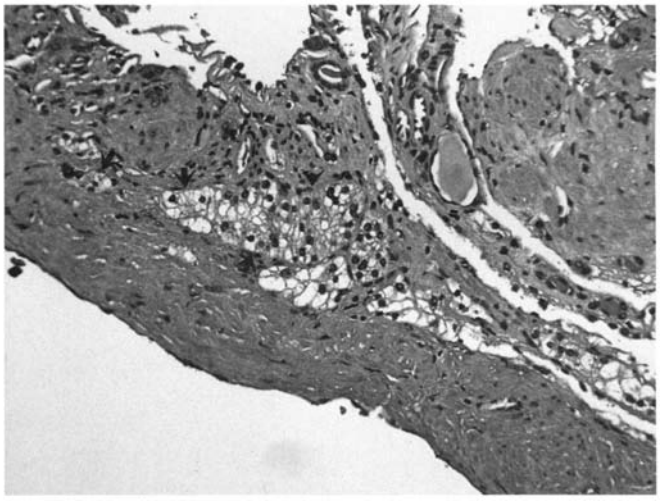


Fig. 28. Multilocular cystic renal cell carcinoma. Aggregates of clear cells are present in the septa; the aggregates are noted only by microscopic examination; they are not "expansile".

♦ Composed entirely of cysts containing serous or hemorrhagic fluid

♦ Cysts are separated by irregular septa of variable thickness

♦ No grossly evident solid nodules of tumor

Microscopic

♦ Cysts are lined by simple cuboidal cells and clear cells **(Figure 27)**

♦ Septa consist of fibrous tissue, variable in thickness

♦ Septa contain aggregates of clear cells, with grade 1 nuclear characteristics **(Figure 28)**

♦ Small papillae may extend into the cysts

- Clear cell aggregates in septa do not form expansile nodules

Immunohistochemistry

- Clear cell population shows immunoreactivity to antibodies against epithelial membrane antigen and cytokeratins; no immunoreactivity to antibodies against macrophage markers (CD68)

Differential Diagnosis

- Extensively cystic clear cell RCC:
  - Contains grossly evident solid nodules of tumor, or microscopically evident expansile nodules of carcinoma
- Cystic nephroma:
  - Cysts may be lined partially by clear cells, but no clear cell aggregates are seen within the septa
- Tubulocystic carcinoma:
  - Cysts are not lined by clear cells; no clear cell aggregates are seen within the septa

Papillary Renal Cell Carcinoma

Clinical

- M : F = 2 : 1; mean age = 50–55
- Accounts for 10–15% of RCC (second most common renal cell carcinoma)
- By definition, papillary tumors greater than 0.5 cm are considered carcinoma
- Hereditary papillary RCC (rare) is related to germline mutation of *c-met* gene
- Associated with end-stage renal disease

Cytogenetics

- Trisomy or tetrasomy 7, trisomy 17, loss of chromosome Y most commonly
- Trisomy of chromosomes 12, 16, and 20 also common

Macroscopic

- Well-circumscribed cortical tumor, often with thick fibrous pseudocapsule
- Hemorrhage, necrosis, and cystic degeneration common
- More often multiple than other types of RCC
- May contain golden-yellow areas reflecting macrophage content

Microscopic

- Tumor is composed of papillary structures and tubules in varying proportions
- Papillary cores are lined by a single cell layer that may show pseudostratification
- Fibrovascular cores may be sclerotic, edematous, or expanded by foamy or hemosiderin-laden macrophages, psammoma bodies, or cholesterol clefts

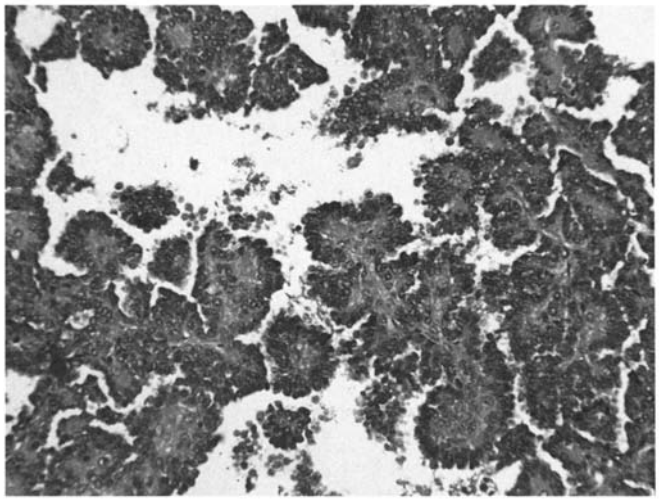


Fig. 29. Papillary renal cell carcinoma, type 1. A tumor larger than 5 mm, composed of papillary structures lined by small dark uniform cells with minimal cytoplasm and grade 1 nuclear characteristics.

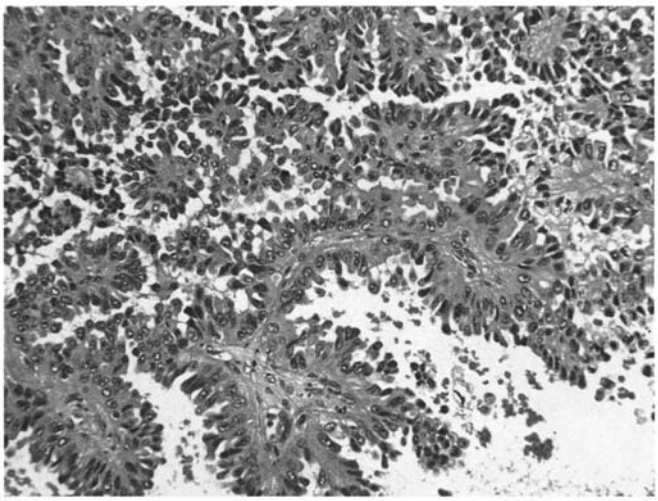


Fig. 30. Papillary renal cell carcinoma, type 2. A tumor larger than 5 mm, composed of papillary structures lined by pseudostratified cells with abundant pink cytoplasm and high grade (grade 3) nuclear characteristics.

- Two morphologic variants:
  - Type 1: Single layer of small dark cells with scant cytoplasm; low nuclear grade **(Figure 29)**
  - Type 2: Lining cells are large, pseudostratified, with more abundant pink cytoplasm, and of higher nuclear grade **(Figure 30)**
- Tubules may be compacted to form "parallel arrays" **(Figure 31)**
- Papillary stalks often contain abundant foamy macrophages **(Figure 32)**
- Sarcomatoid change may be observed in up to 5% of cases **(Figures 33 and 34)**

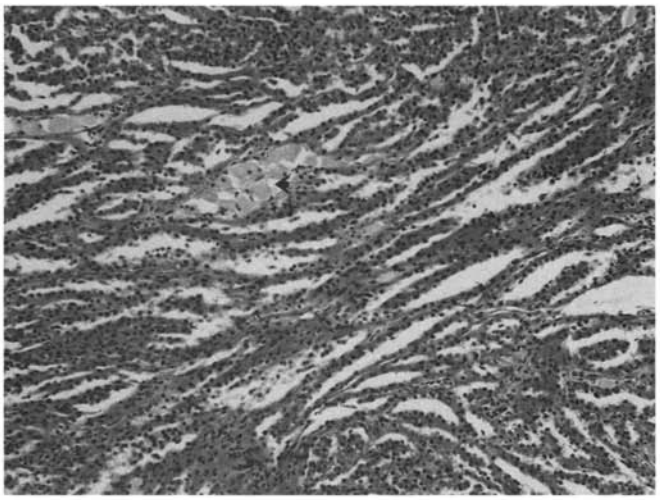


Fig. 31. Papillary renal cell carcinoma. The papillary structures are compressed, and form "parallel arrays". Arrow indicates stromal macrophages.

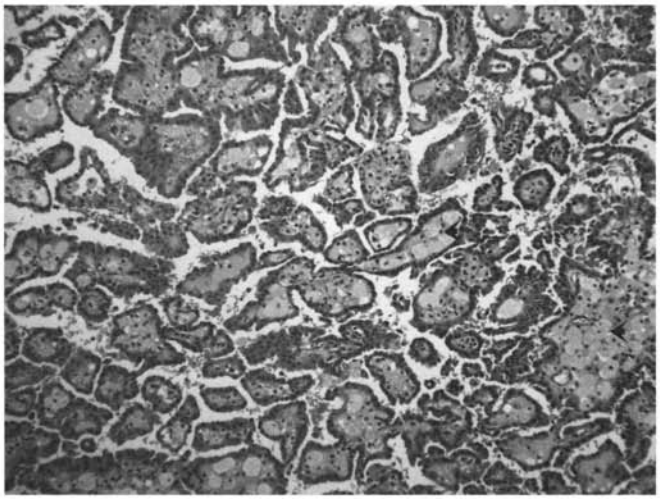


Fig. 32. Papillary renal cell carcinoma. In this example, numerous foamy macrophages are present in the fibrovascular cores, a feature that is characteristic of this type of RCC.

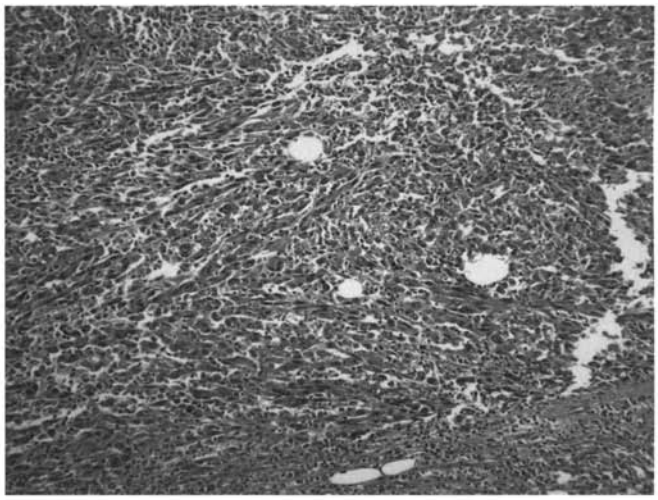


Fig. 33. Sarcomatoid change (spindle cell morphology) comprising part of a papillary RCC. This type of change may occur in clear cell, papillary, chromophobe, or collecting duct RCC.

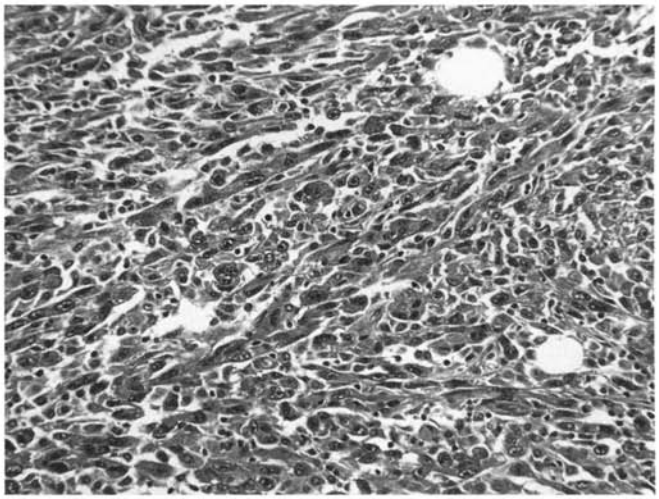


Fig. 34. Sarcomatoid carcinoma, characterized by pleomorphic and spindle cell morphology reminiscent of sarcoma, but present in a background of papillary RCC.

Immunohistochemistry

- Frequently immunoreactive to antibodies against pancytokeratins, CK7, RCC marker
- Usually not immunoreactive to antibodies against high molecular weight cytokeratins

Differential Diagnosis

- Papillary adenoma:
  - Diagnosis is based on 0.5 cm size cut-point
- Papillary urothelial carcinoma:
  - Fibrovascular cores are lined by multiple layers of epithelium
- Collecting duct carcinoma:
  - May have areas of papillary architecture
  - Constellation of other characteristic findings (lack of fibrous pseudocapsule, aggressive invasion of adjacent renal parenchyma, peri-tumoral inflammation, stromal desmoplasia) are features generally not observed in papillary RCC

Chromophobe Renal Cell Carcinoma

Clinical

- Accounts for about 5% of resected renal epithelial tumors
- Believed to originate from intercalated cells of collecting duct epithelium

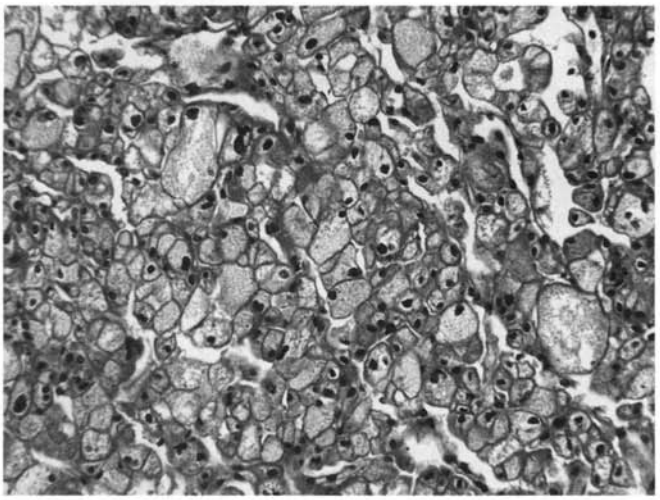


Fig. 35. Chromophobe renal cell carcinoma, "classic cell type": Large polygonal cells with thick distinct "plant-like" cell membranes and abundant pale or translucent flocculent pink cytoplasm.

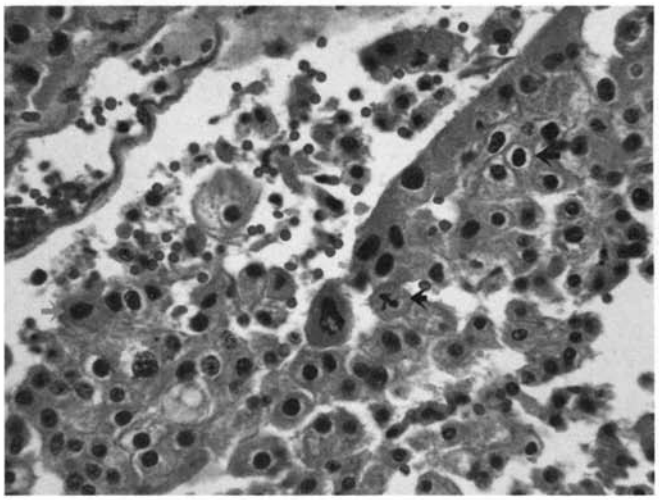


Fig. 36. Chromophobe renal cell carcinoma, "eosinophilic cell type": Cytoplasm is less abundant and is darkly eosinophilic. Blue arrow indicates a round regular nucleus with characteristic perinuclear halo; black arrow indicates a mitotic figure; green arrow indicates an irregular "raisinoid" nucleus.

- M = F; mean age = 55 years
- Cytogenetics: typically, extensive loss of chromosomes (-1, -2, -6, -10, -13, -17, -21) with hypodiploid DNA index
- Commonly of low stage when detected, hence overall survival characteristics relatively favorable

Macroscopic

- Typically solid, well circumscribed, light tan or brown
- Necrosis, hemorrhage, scarring are minimal or absent

Microscopic

- Growth pattern generally solid, sometimes with limited tubule formation
- Sheets of cells are intersected by fibrovascular septa which may be thin and delicate but are often broad and hyalinized
- Composed of varying proportions of two cell types:
- "Classic cell type" **(Figure 35)**:
  - Large polygonal cells, thick distinct "plant-like" cell membranes
  - Abundant pale or translucent flocculent pink cytoplasm
  - Tend to aggregate adjacent to fibrovascular septa
- "Eosinophilic cell type" **(Figure 36)**:
  - Smaller cells, arranged in small nests or intermingled with "classic" cells
  - Cytoplasm less abundant, granular, and more darkly eosinophilic
  - Distinctive perinuclear halos often present due to accumulation of cytoplasmic organelles around nuclei
- In either cell type, nuclei may be round and uniform, or irregular and "raisinoid"
- Sarcomatoid change may be observed in some cases; presence of this finding markedly worsens the prognosis

Special Studies

- Hale's colloidal iron stain for acid mucopolysaccharides strongly & diffusely+
- Pancytokeratin+
- EMA+
- CK7+
- Parvalbumin+
- Vimentin, CD10, and high molecular weight cytokeratins–

Ultrastructure

- Numerous cytoplasmic microvesicles (150–300 nm) of unknown origin

Differential Diagnosis

- Oncocytoma:
  - Organoid growth pattern
  - Lacks the following features that may be seen in eosinophilic chromophobe RCC:
    - Mitotic activity
    - Necrosis
    - Sheet-like growth pattern
    - "Raisinoid" nuclei and perinuclear halos
  - Lack of diffuse cytoplasmic staining with Hale's colloidal iron
- Clear cell renal cell carcinoma
  - Optically clear cytoplasm is not typical of chromophobe RCC

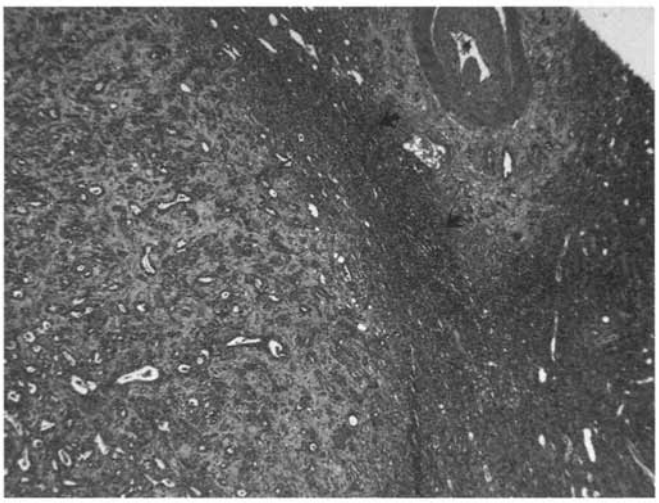


Fig. 37. Collecting duct carcinoma. This low power view illustrates the tubular architecture of the tumor, stromal desmoplasia in the tumor and the "pushing" border, with pronounced inflammation (blue arrows) at the interface between tumor and normal kidney.

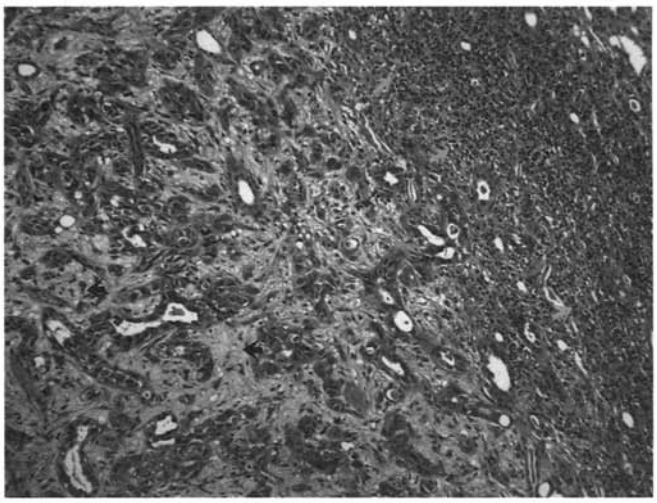


Fig. 38. Collecting duct carcinoma. Tumor is composed of irregular tubules in a desmoplastic stroma (blue arrows), with considerable peri-tumoral chronic inflammatory cell infiltrate (green arrows).

- Many clear cell RCC show positive immunostaining for vimentin; chromophobe RCC is virtually always negative for this marker
- Hale's colloidal iron staining in clear cell RCC is usually absent or "clumped" as compared to the diffuse strong finely granular cytoplasmic staining seen in chromophobe RCC

Collecting Duct Carcinoma

Clinical

- Accounts for less than 1% of RCC cases
- M : F = 2 : 1; mean age about 55 (range 13–83 years)
- Nearly one third have metastases at the time of diagnosis

Cytogenetics

- Reports of LOH on multiple chromosome arms (1q, 3p, 6p, 8p, 13q, 21q)

Macroscopic

- Grey-white, 2.5–12 cm, average 5 cm
- Centered in the renal medulla, irregular border, infiltrates peripherally

Microscopic

- Composed of tubular or tubulopapillary structures
- Lined by cytologically malignant cells, some of which may show a hobnail appearance
- Irregular angulated glands infiltrate renal parenchyma
- Infiltration is accompanied by prominent stromal desmoplasia, and frequently by a pronounced chronic inflammatory response at the interface between advancing tumor and normal adjacent renal parenchyma **(Figures 37 and 38)**
- Intraluminal and intracytoplasmic mucin may be seen
- Dysplasia may be noted in epithelium of adjacent collecting ducts **(Figure 39)**
- Sarcomatoid change is common (up to 30%)



Fig. 39. Collecting duct carcinoma, with high grade nuclear dysplasia in some native renal tubules (blue arrows); normal tubules are indicated by green arrows.

Immunohistochemistry

- Positive immunostaining for:
  - Low molecular weight keratin and pancytokeratins (usually)

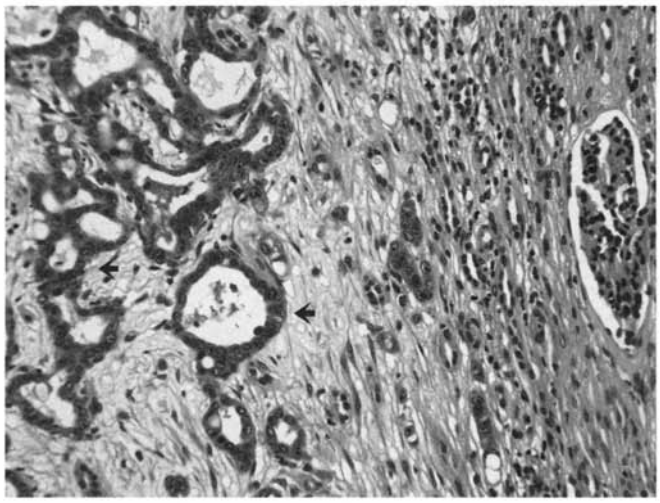


Fig. 40. Renal medullary carcinoma. This type of RCC commonly demonstrates several different morphologic patterns. The malignant tubules in this example are similar to those seen in collecting duct carcinoma.

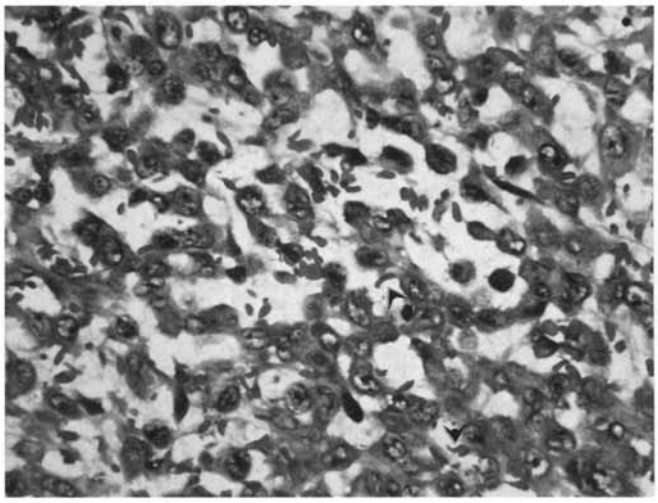


Fig. 41. Renal medullary carcinoma. Arrows indicate sickled red cells in a background of poorly differentiated renal carcinoma. Patient was a 22 year old African American male with sickle cell trait; he died of widespread metastases three months after the diagnosis of renal medullary carcinoma was made.

- High molecular weight keratins (34βE12, CK19) (commonly)
- Ulex europaeus agglutinin-1 (UEA-1) (commonly)

♦ CD10 negative

Renal Medullary Carcinoma

Clinical

♦ Young persons with sickle cell trait; M : F = 2 : 1
♦ Age range 11–39 years, mean 22 years
♦ Weight loss, hematuria, flank or abdominal mass common
♦ Presenting symptoms may be related to metastases
♦ Believed to originate in collecting duct epithelium; may be a very aggressive variant of collecting duct carcinoma
♦ Prognosis poor: most patients die within 1 year of diagnosis (mean survival = 15 weeks)

Macroscopic

♦ Grey-white, centered in renal medulla, infiltrates peripherally

Microscopic

♦ Variety of architectural patterns may be present:
- Reticular or yolk-sac appearance
- Adenoid cystic appearance
- Solid sheets, nests, or tubules **(Figure 40)**

♦ Tumor cells may show rhabdoid morphology
♦ Intracytoplasmic mucin and sickled erythrocytes in the majority **(Figure 41)**
♦ May be striking tumor infiltration by neutrophils

Immunohistochemistry

♦ Usually positive: pancytokeratins, EMA, and CEA

Mucinous Tubular and Spindle Cell Carcinoma

Clinical

♦ Rare tumor, originally described as part of the spectrum of low grade collecting duct carcinoma, more recently believed to originate from cells of loop of Henle
♦ Generally asymptomatic and found incidentally
♦ M : F = 1 : 4; mean age 53 years (range 17–82 years)

Cytogenetic

♦ Consistent losses involving chromosomes 1, 4, 6, 8, 9, 13, 14, 15, and 22
♦ Tumor is indolent; only one reported case with metastases

Macroscopic

♦ Well circumscribed, grey or light tan, glistening cut surface

Microscopic

♦ Tightly packed elongated tubules, arranged in parallel with some branching **(Figure 42)**
♦ Abundant pale eosinophilic or basophilic extracellular mucin **(Figures 42,43)**
♦ Collapsed tubules may impart a spindled appearance
♦ Tumor cells are cytologically low grade, round or oval

Immunohistochemistry

♦ Most express cytokeratins 18 and 19, EMA, and UEA-1; expression of Cam 5.2 and 34βE12 also reported
♦ CD10 negative

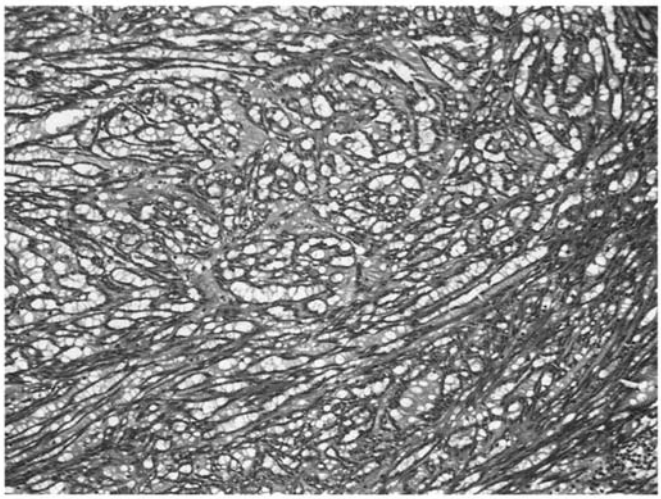


Fig. 42. Mucinous tubular and spindle cell carcinoma. Elongated tubules in a bubbly myxoid stroma consisting of abundant extracellular mucin.

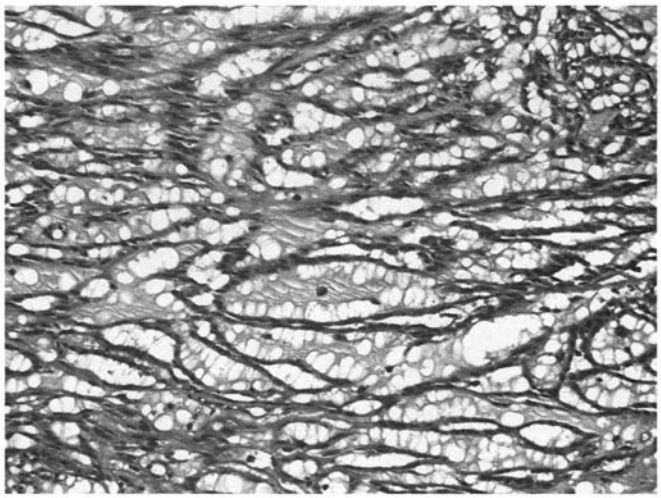


Fig. 43. Mucinous tubular and spindle cell carcinoma. Higher power view of the tumor shown in Fig. 42, illustrating the extremely bland nuclear characteristics of the tumor, possibly accounting for its very indolent behavior.

Tubulocystic Carcinoma (Figures 44,45)

Clinical

- Rare tumor, originally described as part of the spectrum of low grade collecting duct carcinoma; assessment of cell of origin presently under investigation
- Two thirds of patients are asymptomatic, tumor found incidentally
- M : F = 6 : 1; mean age 55 years (range 34–81 years)
- Tumor is relatively indolent; survival rate exceeds 90%
- Generally low stage at presentation

Cytogenetics: Insufficient data available



Fig. 44. Tubulocystic carcinoma, low power view, illustrating the "spider-web" appearance of the cysts and septa of which the tumor is composed.

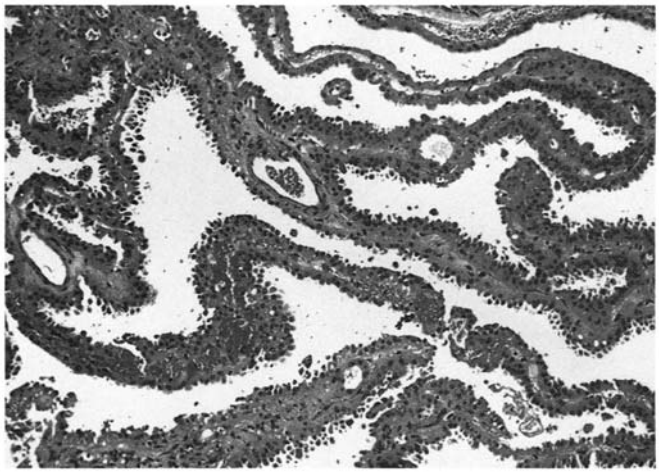


Fig. 45. Tubulocystic carcinoma. The tumor bears some resemblance to multilocular cystic renal cell carcinoma, but the septa are not lined by clear cells, nor are there clear cell aggregates within the septa.

Macroscopic

- Well circumscribed, mean size 4 cm (range 1.6–17 cm)
- Spongy "bubble wrap-like" cut surface; grossly cystic

Microscopic

- Cystically dilated tubules of variable size, separated by thin "spidery" septa **(Figure 44)**
- Single layer of flat, cuboidal or hobnail cells **(Figure 45)**
- Nuclear cytology generally low grade **(Figure 46)**

Immunohistochemistry

- Immunoreactive for parvalbumin, CK18, CK19, P504S, CK7, CD10, 34βE12

Renal Cell Carcinoma, Unclassified

- Category comprises 6–7% of all renal cell neoplasms

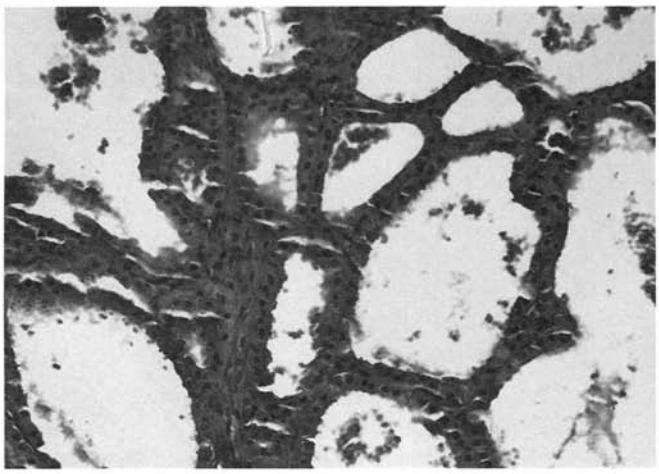


Fig. 46. Tubulocystic carcinoma, illustrating the very low grade nuclear characteristics of the cells that typically line the septa.

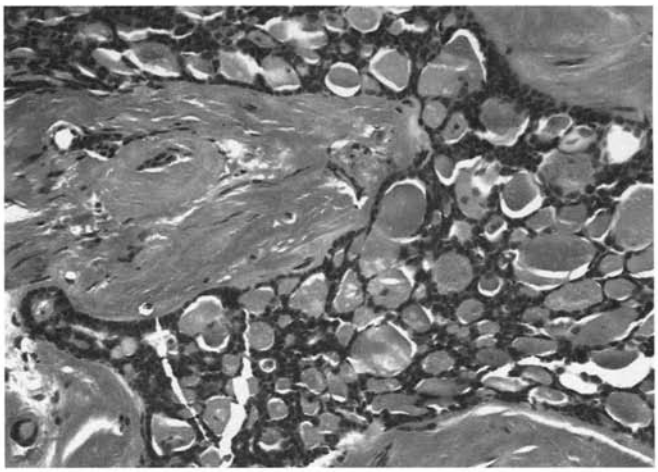


Fig. 48. Renal cell carcinoma, unclassified. The architecture of this tumor is unlike that of any of the recognized types of RCC.

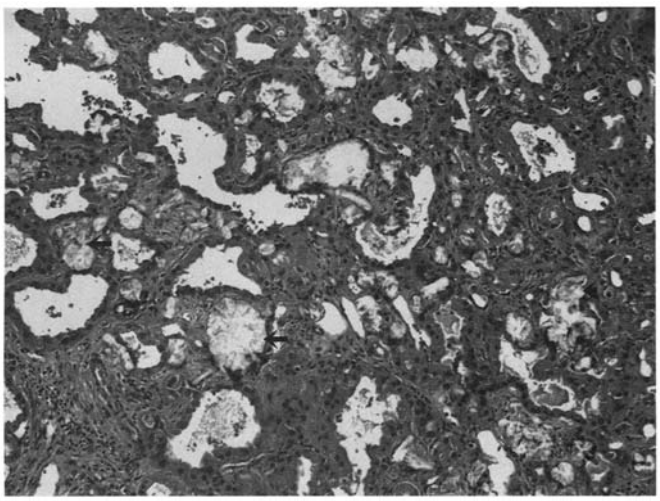


Fig. 47. Renal cell carcinoma, unclassified. The architecture of this tumor is unlike that of any of the recognized types of RCC. Arrows indicate the presence of abundant oxalate crystals within the tubules that comprise this very unusual renal neoplasm.

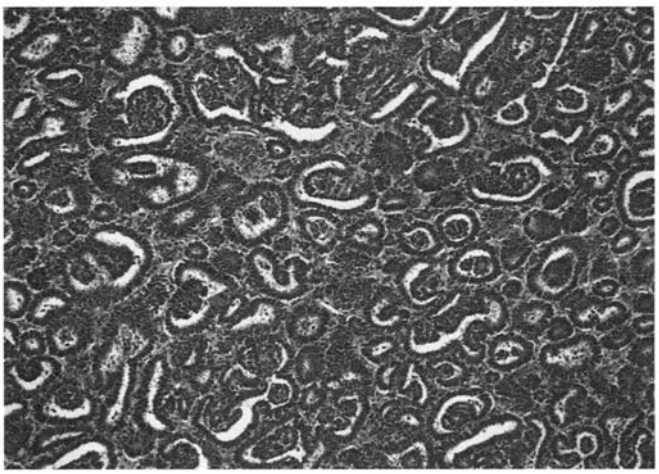


Fig. 49. Metanephric adenoma, consisting of a very cellular neoplasm composed of closely packed acinar structures in an extremely paucicellular stroma. Arrows indicate "glomeruloid bodies", often seen in this neoplasm.

- Criteria for assignment of a renal epithelial neoplasm to this category:
  - Tumor is cytologically and/or architecturally inconsistent with any of the aforementioned types of renal cell carcinoma **(Figures 47,48)**
  - Tumor shows only sarcomatoid morphology, although immunohistochemically it is consistent with carcinoma

Metanephric Neoplasms

Metanephric Adenoma

Clinical

- Twice as common in females
- Mean age at diagnosis 41 years (range 5–83 years)
- About 50% of patients have flank pain, mass, or hematuria, or are noted to have polycythemia; tumor is found incidentally in the rest

Macroscopic

- Sharply circumscribed, solid or lobulated, unencapsulated, gray, tan, or yellow
- Most are 3 to 6 cm in diameter (range up to 15 cm)
- Hemorrhage - common; calcification – 20%; cyst formation–10%

Microscopic

- Highly cellular; composed of densely packed small round uniform acini in a virtually acellular stroma; papillary structures and glomeruloid bodies in some **(Figure 49)**

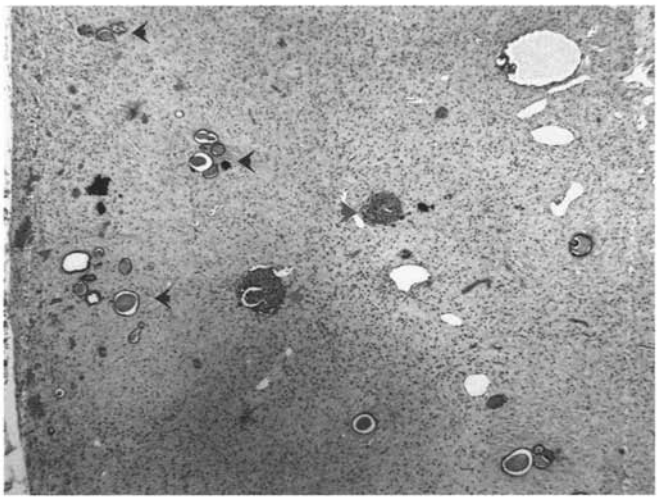


Fig. 50. Metanephric stromal tumor entrapping renal tubules (blue arrows) and glomeruli (red arrows).

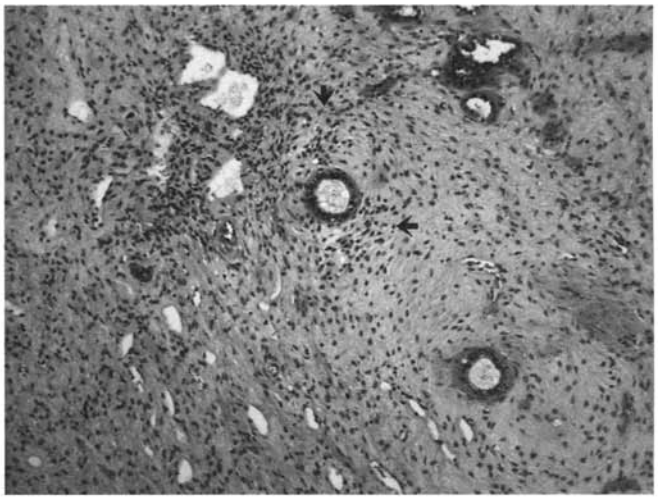


Fig. 52. Metanephric stromal tumor demonstrating "onion-skin" change around an entrapped native renal tubule.

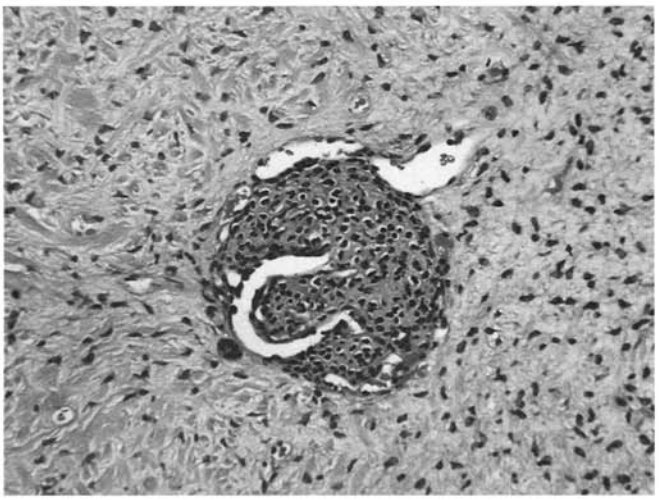


Fig. 51. Metanephric stromal tumor demonstrating juxtaglomerular cell hyperplasia.

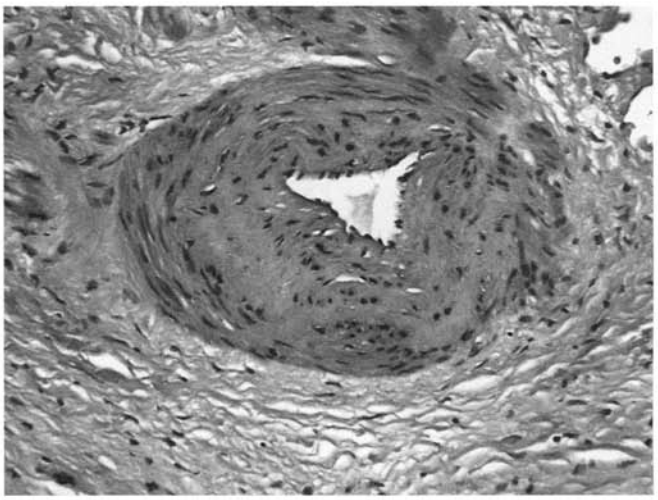


Fig. 53. Metanephric stromal tumor demonstrating angiodysplasia.

- Sharp interface with normal kidney, without a fibrous pseudocapsule
- Long angular or branching ductal strucures may be present
- Psammoma bodies are common, sometimes abundant
- Cells have scant pale or pink cytoplasm
- Cell nuclei are small, monotonous, round, smooth and dark-staining, with absent or inconspicuous nucleoli

Differential Diagnosis

- Chief entities in differential are papillary renal cell carcinoma and nephroblastoma
- EMA and CK7 are negative in metanephric adenoma, and typically positive in papillary RCC; WT1 is positive in metanephric adenoma and negative in papillary RCC
- Nephroblastoma is usually triphasic, with blastema
- Presence of a fibrous pseudocapsule excludes metanephric adenoma
- Metanephric adenoma should have no nucleoli and should have virtually no mitotic figures; presence of these features should exclude the diagnosis

The Metanephric Tumor Family

- A spectrum of tumors, all originating from metanephric blastema
- *Metanephric adenoma* is entirely composed of epithelial nephroblastic cells
- *Metanephric stromal tumor* is entirely composed of stromal elements **(Figures 50–53)**

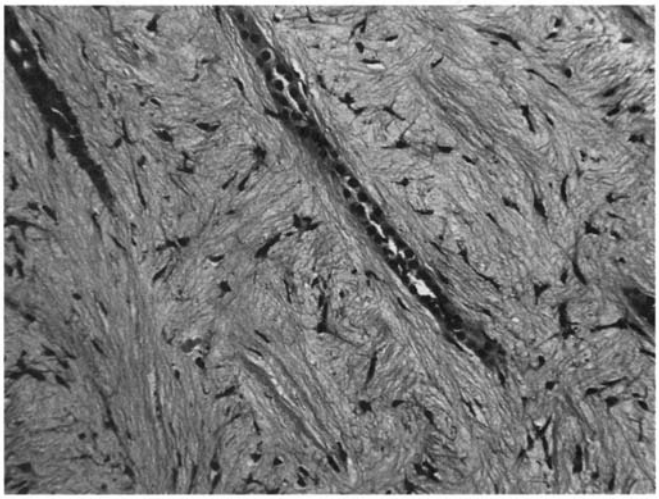


Fig. 54. Renomedullary interstitial cell tumor. Stellate and spindle cells in a loose myxoid stroma.

- *Metanephric adenofibroma* includes both epithelial and stromal elements
- *Metanephric adenosarcoma*—one case reported

Mesenchymal Neoplasms

Renomedullary Interstitial Cell Tumor (Medullary Fibroma)

Clinical

- Asymptomatic; found incidentally at autopsy or surgery
- Present (and very often multiple) in 50% of autopsy kidneys
- Rarely noted in persons ≤18 years old
- Cell of origin: prostaglandin-producing interstitial cell in renal medulla that regulates intrarenal blood pressure
- Tumors are not believed to cause systemic hypertension

Macroscopic

- White or grey nodule, 0.1–0.5 cm, in renal medullary pyramid (very rarely larger)

Microscopic

- Circumscribed but unencapsulated paucicellular tumor
- Small stellate, spindly or polygonal cells in a loose background of faintly basophilic stroma; amyloid present in some **(Figure 54)**

Angiomyolipoma (AML)

Clinical

- Associated with several hereditary disorders:
  - Tuberous sclerosis
  - von Recklinghausen disease
  - von Hippel-Lindau syndrome
  - Autosomal dominant (adult) polycystic kidney disease
- Occurs in 80% of patients with tuberous sclerosis (TS); presence of multiple AML in a kidney is presumptive evidence of TS
- Fewer than 50% of patients with AML have the TS complex
- Accounts for about 1% of surgically excised renal tumors
- Mean age for "sporadic" AML: 45–55 years; for TS patients: 25–35 years
- In sporadic cases: 4X times as common in females; in TS cases, M = F
- Cell of origin: Neoplastic (clonal) proliferation of perivascular epithelioid cell
- Cytogenetics: Frequently loss of heterozygosity (LOH) in portions of the TSC2 gene locus on chromosome 16p13 (sporadic and TS cases), and less often LOH in TSC1 gene on chromosome 9q34
- Growth sites: Renal cortex or medulla; some arise in perirenal soft tissues
- Symptoms:
  - in TS patients, often none; detected by radiologic screening
  - in sporadic cases there may be flank pain, hematuria, palpable mass, or spontaneous retroperitoneal hemorrhage
- May co-exist with other renal neoplasms (RCC, oncocytoma)
- Sometimes associated with lymphangioleiomyomatosis of lung
- In most cases, accurate radiologic diagnosis is possible (due to fat content)
- Although benign, classic AML can be life-threatening if:
  - Massive hemorrhage occurs
  - Renal failure supervenes due to progressive loss of renal tissue
  - Progression to high-grade malignancy supervenes

Macroscopic

- Intrarenal tumor, well demarcated, unencapsulated, lobular
- Yellow to tan-pink; hemorrhage is common and sometimes massive
- Mean size 9.4 cm (range 3 to 20 cm)

Microscopic

- Variable admixtures of mature adipose tissue, smooth muscle and abnormally formed blood vessels with variably thickened walls **(Figures 55,56)**
- Smooth muscle proliferations often appear to spin off perpendicularly from outer layers of blood vessel walls – "hair on end" appearance
- Smooth muscle cells may be spindled or epithelioid, and may show mild degrees of nuclear atypia
- Involvement of intrarenal veins, renal vein, vena cava, and regional lymph nodes by classic AML are indicative of multifocal growth (not invasion or metastasis)

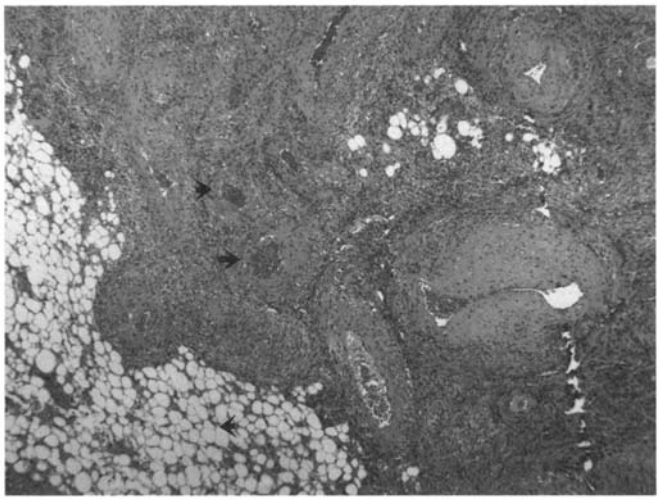


Fig. 55. Angiomyolipoma, composed of fat (black arrow), blood vessels (blue arrows) and smooth muscle (green arrow).

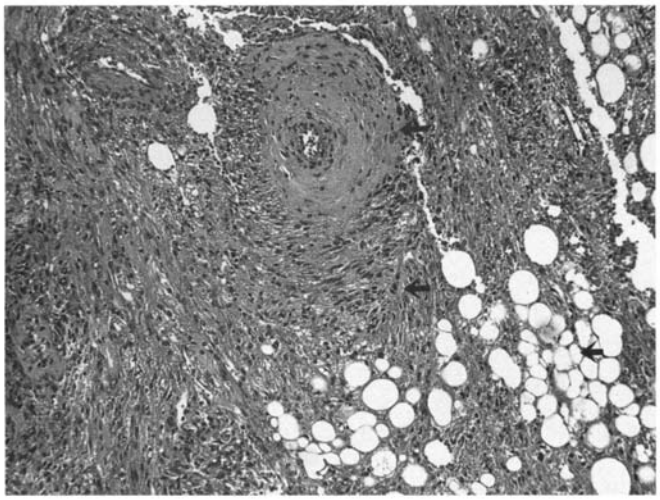


Fig. 56. Angiomyolipoma, demonstrating fat (black arrow), a thick-walled blood vessel (red arrow), and smooth muscle cells that appear to be proliferating away from the wall of the blood vessel.

Immunohistochemistry

- Coexpression of:
  - Melanocytic markers (HMB-45, HMB50, CD63, MART-1/Melan A, microphthalmia transcription factor)
  - Smooth muscle markers (muscle-specific actin, smooth muscle actin, desmin)
- Epithelial markers are always negative

Variant

- Epithelioid Angiomyolipoma:
  - Malignant mesenchymal neoplasm closely related to classic triphasic AML
  - Believed to originate from perivascular epithe-lioid cell
  - Half of recorded cases have a history of tuberous sclerosis
  - Allelic loss of TS2-containing region (chromosomal arm 16p)
  - Large hemorrhagic and locally infiltrative tumors, one third of which metastasize

Microscopic

- Sheets of cytologically malignant epithelioid cells; easy to misdiagnose as high grade carcinoma

Immunohistochemical

- Similar findings as in classic AML

Juxtaglomerular Cell Tumor

Clinical

- Benign renin-secreting tumor derived from modified smooth muscle cells of juxtaglomerular apparatus
- Patients have refractory hypertension and high plasma renin activity; secondary hyperaldosteronism and hypokalemia in some
- Mean age 27 years (range 6 to 69 years); twice as common in females

Macroscopic

- Unilateral, solitary, and cortical in location
- Typically <4 cm in diameter; rarely larger
- Solid, well circumscribed, grey-white or yellow-tan, hemorrhage common
- Typically a fibrous pseudocapsule is present

Microscopic

- Sheets of uniform round, polygonal or spindled cells with moderate amounts of granular eosinophilic cytoplasm **(Figures 57,58)**
- Nuclei are uniform, round to oval; scattered mitotic figures
- Thin and thick-walled blood vessels are common and often prominent

Immunohistochemistry

- Tumor cells show immunoreactivity for renin, actin, vimentin, and CD34

Ultrastructure

- Tumor cells contain rhomboid renin-specific crystals

Mixed Epithelial/Renal Parenchymal Neoplasms

Cystic Nephroma

Clinical

- Typically occur in women >30 years old (F : M ratio 8 : 1)
- Usually asymptomatic; found incidentally

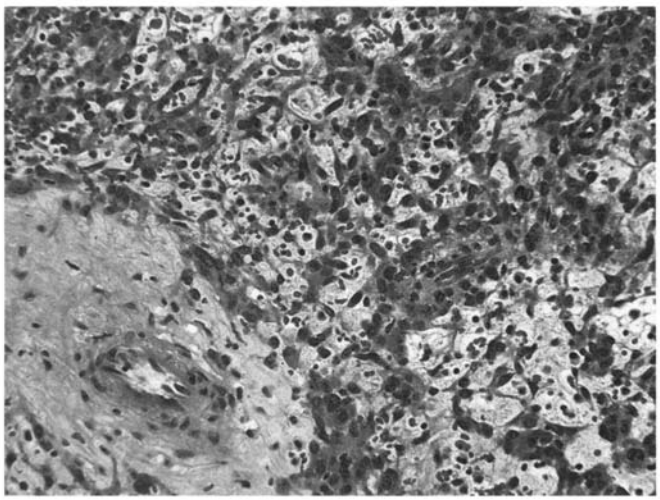


Fig. 57. Juxtaglomerular cell tumor, composed of sheets of cells with smooth round, oval or spindled nuclei and moderately abundant eosinophilic cytoplasm. A thick-walled blood vessel is also present (lower left).

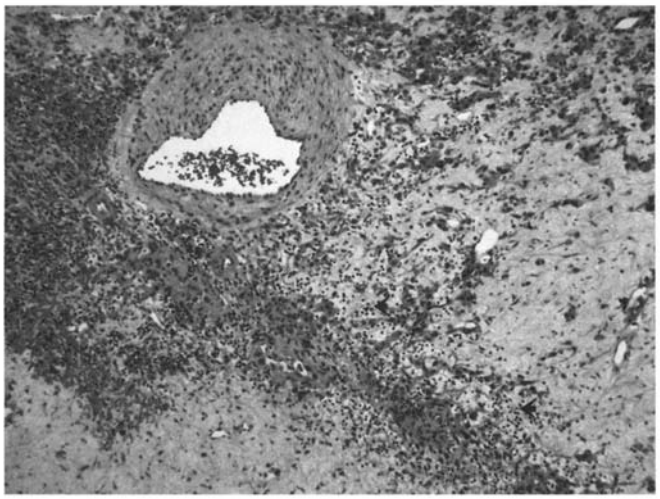


Fig. 58. Juxtaglomerular cell tumor. Stroma is hyalinized and focally myxoid. In some tumors (as in this case) a striking infiltrate of chronic inflammatory cells may be present (blue arrows). Note large thick-walled blood vessel.

Macroscopic

- Most often located in upper pole
- Solitary, unilateral, encapsulated, well demarcated from adjacent kidney
- Tumor is composed of numerous cysts of variable size
- Adjacent renal parenchyma is compressed but normal

Microscopic

- Multilocular cysts of variable size, lined by a single layer of flat, low cuboidal, or hobnail epithelium **(Figures 59,60)**

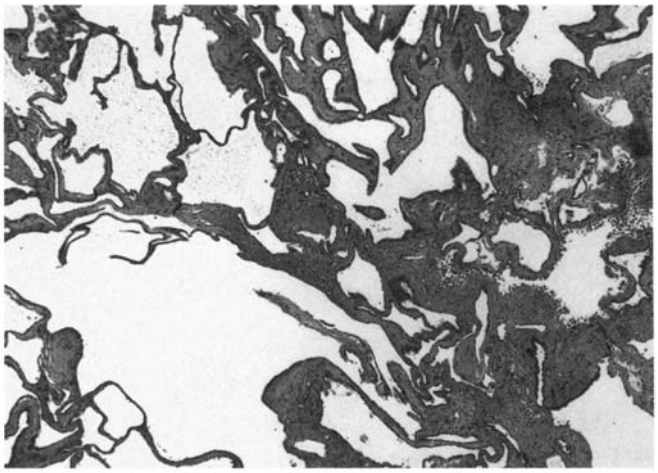


Fig. 59. Cystic nephroma, composed of multilocular cysts separated by fibrous septa of variable thickness.

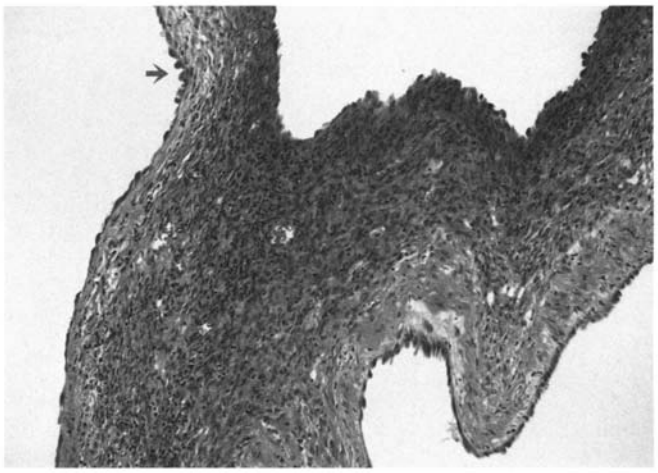


Fig. 60. Cystic nephroma. Cells lining the fibrous septa may be flat, cuboidal, or "hobnail" (red arrow) in appearance.

- Cytoplasm of lining cells may be eosinophilic or clear
- Stromal septa between cysts is dense fibroconnective tissue that may be cellular or paucicellular **(Figure 60)**
- Fibrous septa do not contain:
  - Elements of nephrons
  - Elements of nephroblastoma
  - Nests of clear cells

Mixed Epithelial and Stromal Tumor

Clinical

- Patients are predominantly female (F : M ratio 8 : 1); all are adults

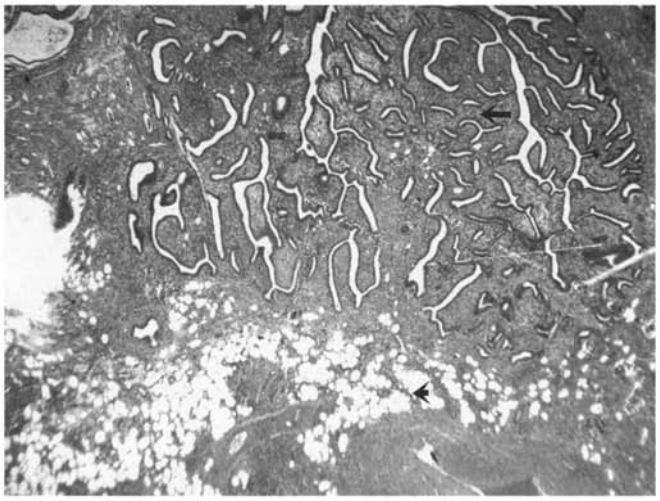


Fig. 61. Mixed epithelial and stromal tumor of kidney. Complex epithelial-lined papillae (blue arrow); mature fat in the stroma (black arrow).

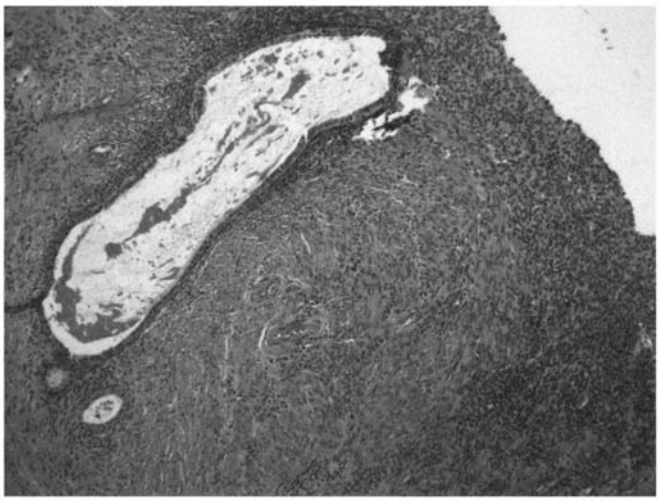


Fig. 62. Mixed epithelial and stromal tumor of kidney. Stroma is variable, and may resemble smooth muscle or fibrous tissue. Epithelium lining the cystic space is columnar.

- Mean age 46 years
- Flank pain, hematuria, symptoms of urinary infection; 25% incidental

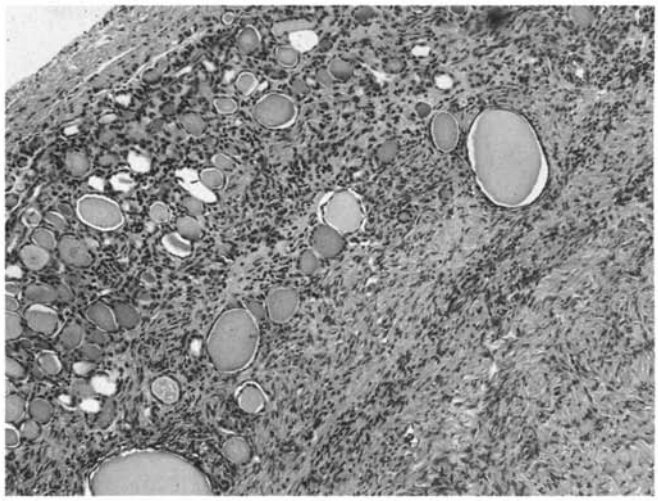


Fig. 63. Mixed epithelial and stromal tumor of kidney. Stroma resembles that of normal ovary. Epithelium lining the small tubules is flat and inconspicuous.

Macroscopic

- Centrally located; some protrude into renal pelvis
- Usually circumscribed and encapsulated
- Composed of solid and cystic areas

Microscopic

- Complex tumors composed of a stromal component punctuated by epithelial-lined microcysts and macrocysts, as well as complex branching tubules **(Figure 61)**
- Stromal component consists of spindle cells with plump nuclei and abundant cytoplasm; stromal cellularity is markedly variable **(Figure 62)**
- Stroma is sometimes myxoid, and may contain collagen, smooth muscle, or fat
- Epithelial cells may be low cuboidal, columnar, or hobnail **(Figures 62,63)**

Immunohistochemistry

- Stromal spindle cells show smooth muscle differentiation (actin and desmin positive) and often are immunoreactive to antibodies against estrogen and progesterone receptors
- Epithelial cells are immunoreactive to antibodies against cytokeratins and vimentin

TNM STAGING OF RENAL CELL CARCINOMA (2002 REVISION) (AJCC)

Primary Tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- T1a: Confined to kidney, ≤4.0 cm
- T1b: Confined to kidney, >4.0 cm and ≤7.0 cm
- T2: Confined to kidney, >7.0 cm
- T3a: Tumor invades perirenal and/or renal sinus fat or adrenal gland, but not beyond Gerota's fascia

- T3b: Tumor grossly extends into the renal vein(s) or vena cava below the diaphragm
- T3c: Tumor grossly extends into the renal vein(s) or vena cava above the diaphragm
- T4: Tumor invades beyond Gerota's fascia

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastases
- N1: Metastasis in a single regional lymph node
- N2: Metastases in more than one regional lymph node

Distant Metastases (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

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30

Urinary Bladder

Liang Cheng, MD, Antonio Lopez-Beltran, MD,
and David G. Bostwick, MD

CONTENTS

I. Congenital Anomalies 30-3
Urachal Abnormalities 30-3
Exstrophy 30-3

II. Cystitis 30-3
Acute Cystitis 30-3
Variants 30-4
Ulcerative Cystitis 30-4
Suppurative Membranous Cystitis 30-4
Emphysematous Cystitis 30-4
Viral Cystitis 30-4
Fungal Cystitis 30-4
Actinomycosis 30-4
Chronic Cystits 30-4
Variants 30-4
Proliferative Papillary Cystitis (Papillary-polypoid Cystitis) 30-4
Follicular Cystitis 30-5
Encrusted Cystitis 30-5
Granulomatous Cystitis 30-5
Tuberculous Cystitis 30-5
BCG-Induced Cystitis 30-6
Post-Surgical Granuloma 30-6
Malakoplakia 30-6
Schistosomiasis 30-6
Treatment-Induced Cystitis 30-7
Radiation Cystitis 30-7
BCG-Induced Cystitis 30-8
Cytoxan-Induced Hemorrhagic Cystitis 30-8
Special Variants of Cystitis 30-8
Interstitial Cystitis 30-8
Eosinophilic Cystitis 30-10

III. Benign Lesions and Mimics of Cancer 30-10
Hyperplasia 30-10
Urothelial Hyperplasia 30-10
Papillary Urothelial Hyperplasia 30-10
Metaplasia 30-10
Squamous Metaplasia 30-10
Nephrogenic Metaplasia 30-11
Intestinal Metaplasia (Glandular Metaplasia) 30-12
von Brunn's Nests 30-12
Cystitis Cystica 30-12
Florid Cystitis Glandularis 30-12
Endocervicosis 30-13
Müllerianosis 30-13
Proliferative Papillary Cystitis (Papillary-Polypoid Cystitis) 30-13
Diverticulosis 30-13
Post-Operative Spindle Cell Nodule 30-14
Inflammatory Myofibroblastic Tumor 30-14
Urethral Polyp 30-15
Inflammatory Polyp 30-15
Urethral Caruncle 30-15
Fibroepithelial Polyp 30-16
Ectopic Prostatic Tissue 30-16
Nephrogenic Metaplasia 30-16
Proliferative Papillary Urethritis 30-16
Pyogenic Granuloma 30-17
Urothelial Papilloma 30-17

Inverted Papilloma 30-17
Condyloma Acuminata 30-17
Squamous Cell Papilloma.....30-17

IV. Neoplasms of the Bladder 30-17
Benign Urothelial Neoplasms 30-17
Urothelial Papilloma.....30-17
Inverted Papilloma 30-17
Squamous Cell Papilloma.....30-18
Flat Urothelial Lesions with Atypia.....30-18
Reactive Changes 30-18
Urothelial Atypia of Unknown Significance 30-18
Urothelial Dysplasia 30-19
Urothelial Carcinoma *In Situ* (CIS) 30-20
Non-Invasive Papillary Urothelial Tumors....30-20
Infiltrating Urothelial Carcinoma.....30-23
Histologic Variants of Urothelial Carcinoma 30-27
Urothelial Carcinoma with Mixed Differentiation....30-27
Micropapillary Variant 30-28
Nested Variant.....30-28
Microcystic Variant (Microglandular Variant) 30-30
Inverted Papilloma-Like Carcinoma (Inverted Variant) 30-30
Lymphoepithelioma-Like Carcinoma 30-31
Lymphoma-like and Plasmacytoid Variant 30-31
Urothelial Carcinoma, Clear Cell (Glycogen-Rich) Variant 30-32
Urothelial Carcinoma, Lipoid Cell Variant.....30-32
Undifferentiated Carcinoma 30-32
Urothelial Carcinoma with Giant Cells (Giant Cell Carcinoma).....30-32
Urothelial Carcinoma with Syncytiotrophoblasts (UC with Trophoblastic Differentiation).....30-33
Urothelial Carcinoma with Osteoclast-Type Giant Cells....30-33
Urothelial Carcinoma with Pseudosarcomatous Stroma....30-33
Urothelial Carcinoma with Stromal Osseous or Cartilaginous Metaplasia 30-33
Squamous Cell Carcinoma.....30-33
Variants: Verrucous Carcinoma 30-34
Adenocarcinoma.....30-34
Clear Cell Carcinoma (Mesonephric Carcinoma).....30-36
Sarcomatoid Carcinoma (Metaplastic Carcinoma; Carcinosarcoma with Homologous Elements).....30-37
Small Cell Carcinoma 30-37
Villous Adenoma 30-37

V. Soft Tissue Tumors 30-38
Benign 30-38
Leiomyoma.....30-38
Hemangioma.....30-38
Malignant 30-39
Leiomyosarcoma 30-39
Rhabdomyosarcoma 30-39
Carcinosarcoma (Sarcomatoid Carcinoma with Heterologous Elements) 30-39

VI. Miscellaneous 30-41
Lymphoma 30-41
Paraganglioma (Pheochromocytoma) 30-41
Carcinoid 30-41
Clear Cell Myomelanocytic Tumor 30-42

VII. TNM Classification of Bladder Cancer (2002 Revision) 30-42

VIII. Suggested Reading.....30-42

CONGENITAL ANOMALIES

Urachal Abnormalities

- The urachus is the vestigial remnant of the connection from the apex of the bladder to the allantois (located at the umbilicus)
- Derived from the ventral cloaca and allantois
- Normally, the urachus closes by the fourth month of fetal life
- A spectrum of anatomic abnormalities may result in abnormal persistence or malformation, and presents in children
- A number of malformations have been described:
  - Patent urachus:
    - Communicating duct between the bladder and the umbilicus that allows the flow of urine
    - Predisposes to infection
    - Spontaneous closure may occur, but usually requires surgical intervention
  - Urachal cyst:
    - Presents as a suprapubic palpable mass
    - Usually located in the lower part of the urachus
    - Lined by columnar or urothelial cells
  - Blind sinuses and vesicourachal diverticuli:
    - An external opening of the urachal duct
    - History of chronically infected urachal cyst
    - Vesicourachal diverticuli are associated with the prune-belly syndrome
  - Hamartomatous polyp:
    - Presents as polypoid mass in the bladder near the urachus
    - Composed of nests and glands of urothelial cells
- A variety of tumors may arise from urachal remnants:
  - Villous adenoma
  - Adenocarcinoma
  - Urothelial carcinoma
  - Squamous cell carcinoma

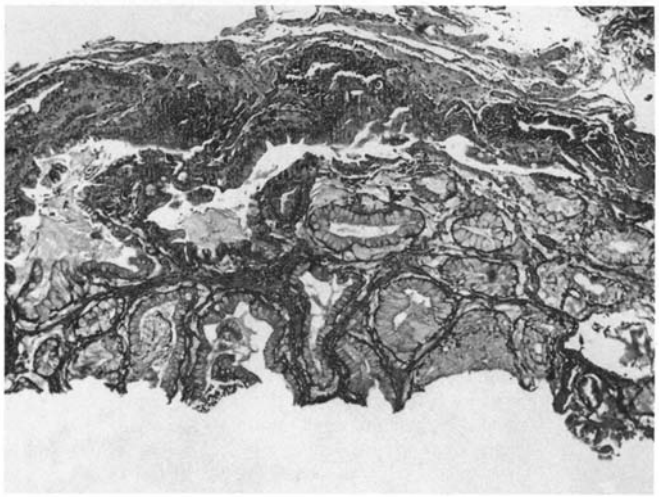


Fig. 1. Exstrophy.

Exstrophy

Clinical

- Congenital malformation in which the anterior bladder wall and abdominal wall are absent
- Thought to arise from failure of the midline to close properly in development
- Associated with other urogenital abnormalities (e.g., epispadia, bilateral inguinal hernia, bifid clitoris, vaginal stenosis)
- The exposure of the bladder mucosa to the external environment, with subsequent risk of infection and carcinoma (usually adenocarcinoma)

Macroscopic

- Anterior abdominal wall defect with simultaneous absence of anterior bladder wall, resulting in exposure of the bladder mucosa to the environment
- Usually accompanied by some degree of bladder eversion

Microscopic

- Squamous metaplasia, cystitis glandularis, and intestinal metaplasia (**Figure 1**)

CYSTITIS

- Refers to a variety of benign inflammatory lesions
- Often descriptive and non-specific
- May be associated with proliferative and metaplastic conditions

Acute Cystitis

- Predominantly neutrophilic infiltration of the lamina propria and urothelium
- Edema of lamina propria
- Frequent urothelial denudation

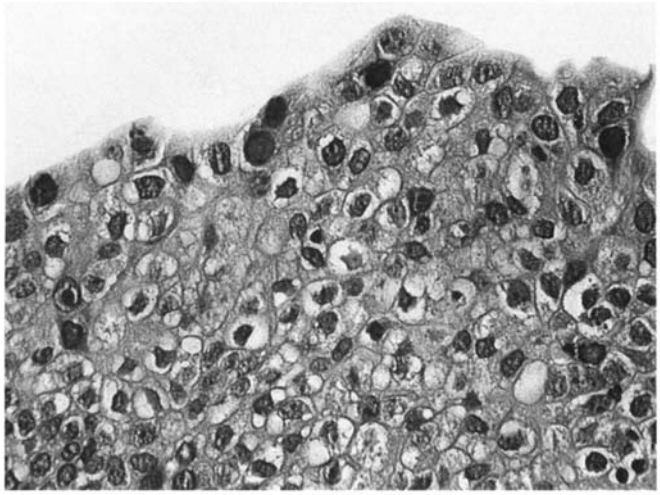


Fig. 2. Polyoma virus infection.

Variants

- Ulcerative cystitis:
  - The urothelium is denuded and ulcerated
- Suppurative membranous cystitis:
  - The surface urothelium is covered by exudate and necrotic debris
- Emphysematous cystitis:
  - Inflammatory condition caused by infection by gas-forming bacteria such as *Clostridium perfringens*
  - Usually limited to patients with predispositions to unusual infections, including diabetes, neurogenic bladder, and chronic urinary tract infection
  - Gas-filled blebs with giant cell reaction in the lamina propria
- Viral cystitis:
  - Adenovirus, herpes simplex type 2 virus, and polyoma **(Figure 2)** viruses have been implicated
  - Patients with bladder involvement are usually immunosuppressed renal or bone marrow allograft recipients with hemorrhagic cystitis
  - The identification of inclusions in histologic tissue sections is rare
  - Herpes zoster and cytomegalovirus have also been rarely implicated in bladder infections
  - No specific gross features
- Fungal cystitis:
  - Rare
  - Candida albicans, Torulopsis glabrata, aspergillosis, and Coccidioides immitis have been implicated
  - Nocturia, pain, discomfort and frequency
  - Grossly, bladder mucosa slightly elevated, irregular with white plaques
  - Ulceration and submucosal mixed inflammation

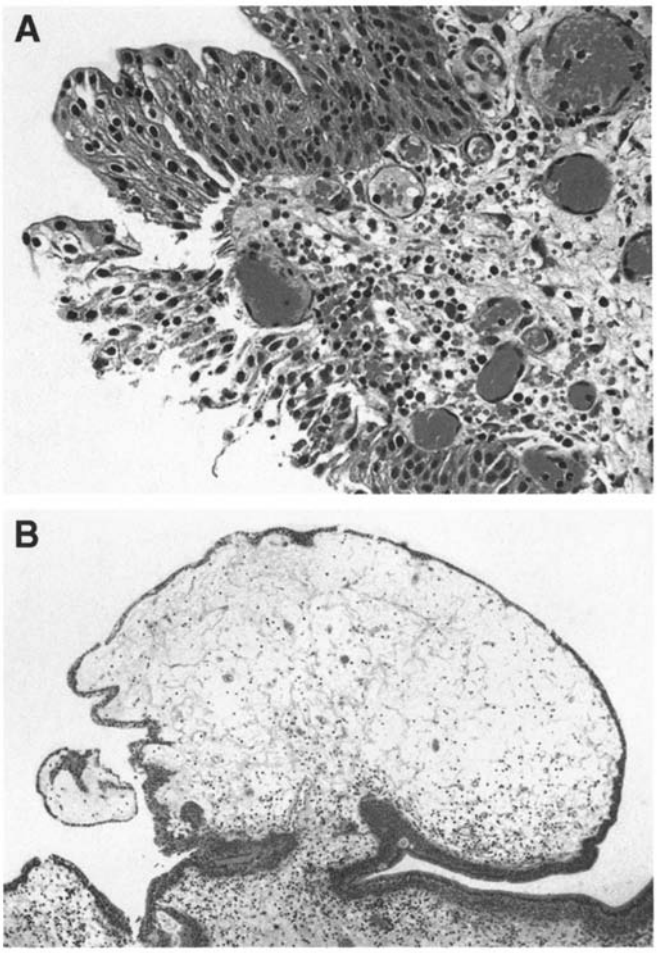


Fig. 3. Proliferative papillary cystitis. **(A)** papillary cystitis; **(B)** polypoid cystitis.

  - Typical fungal spores and hyphae are present within fibrinopurulent debris
- Actinomycosis:
  - Rare; a localized mass simulating a tumor may be present
  - The submucosa and muscularis propria contain abundant granulation tissue and numerous abscesses.
  - "Sulfur granules" consisting of masses of filamentous mycelia with peripheral array of swollen eosinophilic "clubs"

Chronic Cystitis

- Chronic inflammatory infiltrate of lamina propria
- Edema and fibrosis of the lamina propria

Variants

- Proliferative papillary cystitis (papillary-polypoid cystitis) **(Figure 3)**:
  - History of indwelling catheter or vesical fistula
  - Located in the dome or posterior wall

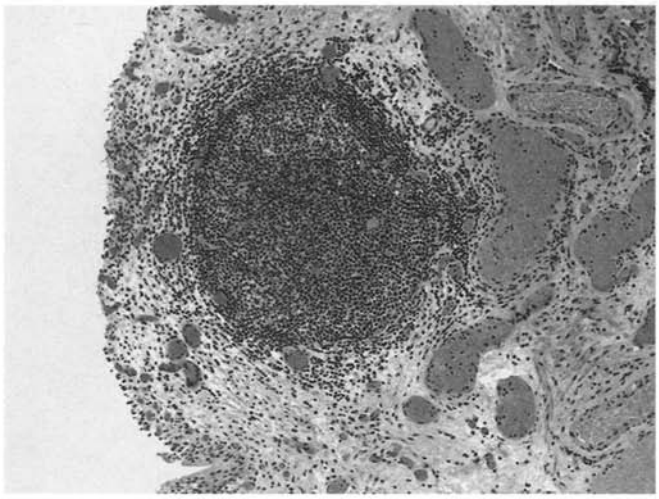


Fig. 4. Follicular cystitis.

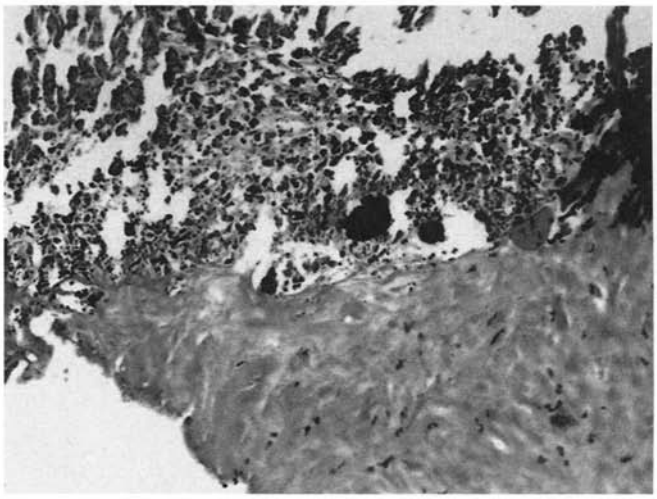


Fig. 5. Encrusted cystitis.

- Broad papillary projection of inflamed lamina propria with overlying hyperplastic urothelium
- The designation papillary cystitis is used when thin, finger-like papillae are present
- Polypoid cystitis refers to lesions with edematous and broad-based papillae
- Superficial umbrella cell preserved
- Prominent stromal edema, congestion, and inflammatory infiltrate

♦ Follicular cystitis (**Figure 4**):
- Incidental finding
- May be associated with history of infection, biopsy, or intravesical Bacillus Calmette-Guerin (BCG) therapy
- Bladder mucosa may appear normal or have a finely nodular appearance endoscopically
- Subepithelial lymphoid follicles with germinal centers microscopically

♦ Encrusted cystitis (**Figure 5**):
- Associated with infection of urea-splitting bacteria in alkalinized urine
- The ulcers are coated with calcium and phosphate salt
- Mononuclear cell infiltrate and foreign body giant cell reaction
- May extend into muscularis propria

Granulomatous Cystitis

♦ Etiology:
- Infection:
  - Bacterial:
    - Tuberculosis, syphilis
  - Fungal:
    - Coccidiodomycosis, histoplasmosis
  - Parasitic:
    - Schistosoma hematobium
- Iatrogenic:
  - Post surgery or radiation
  - Post intravesical (BCG) therapy
- Malakoplakia
- Systemic granulomatous disease:
  - Crohn's disease
  - Sarcoidosis
  - Rheumatoid disease
- Chronic granulomatous disease of childhood
- Xanthoma (with elevated serum cholesterol)
- Vasculitis:
  - Wegener's granulomatosis
  - Polyarteritis nodosa
  - Churg-Strauss Syndrome
- Idiopathic

Tuberculous Cystitis

Clinical

♦ Secondary to generalized spread from pulmomary infection by Mycobacterium tuberculosis

♦ Associated with renal tuberculosis

♦ Common cause of bladder disease worldwide

♦ Complications include scarring, obstruction, and fistula formation

Macroscopic

♦ Solitary or confluent ulcerated mucosal lesions, usually in the region of the ureteral orifices (trigone)

Microscopic

♦ Caseating granulomatous inflammation and fibrosis involving the lamina propria

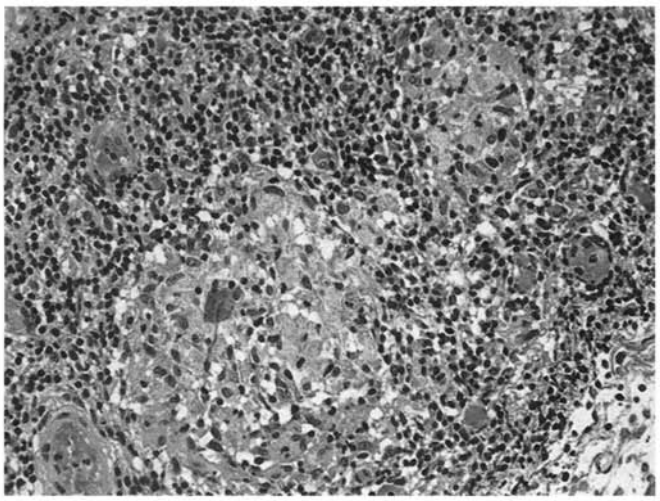


Fig. 6. BCG-induced cystitis.

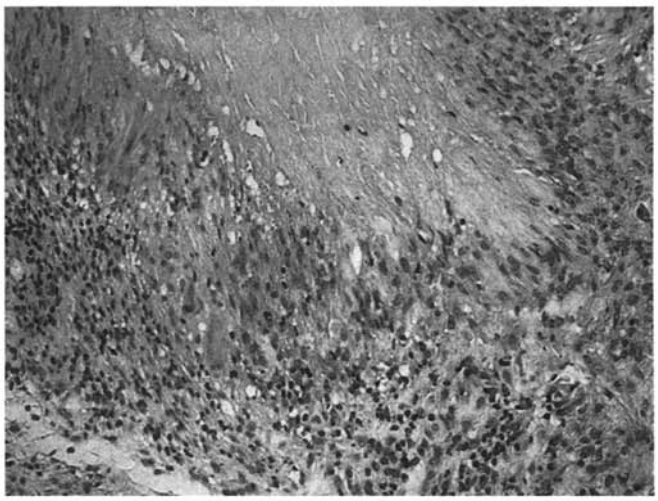


Fig. 7. Post-surgical granuloma.

- Ulceration of the overlying mucosa
- Special stains (auramine-rhodamine or other AFB stain) demonstrate acid-fast bacilli

BCG-Induced Cystitis

Clinical

- Clinical history is critical in determining the etiology
- Used to treat patients with superficial bladder carcinoma
- Symptoms include dysuria, frequency, fever, and other systemic reactions (e.g., pneumonitis, hepatitis, rash, and arthralgia)

Macroscopic

- Erosion and ulceration

Microscopic

- Sarcoid-like non-necrotizing granuloma with giant cells **(Figure 6)**
- Edema, congestion, and chronic inflammatory infiltrate in the lamina propria

Post-Surgical Granuloma

Clinical

- History of prior surgery or instrumentation
- Etiology related to immunologic reaction to altered antigen induced by the procedure

Macroscopic

- Hemorrhage, necrosis, and mucosal irregularity

Microscopic

- Areas of granulomatous inflammation, usually focal
- A central zone of fibrinoid necrosis surrounded by a peripheral rim of palisading epithelioid histiocytes **(Figure 7)**
- Chronic inflammatory infiltrate composed of histiocytes, giant cells, lymphocytes, plasma cells, and eosinophils

Malakoplakia

Clinical

- Female predilection, with peak incidence in the fifth decade
- Atypical infection by bacteria (usually Gram-negative bacteria, such as *E. coli*) in patients with lysosomal defects (defects in histiocyte function with impaired lysosome movement and inability of phagosomes to destroy bacteria)
- Symptoms include recurrent fever, hematuria, pyuria, urgency, pain, and weight loss
- Others organs may be involved
- "Malakoplakia" means soft plaque in Greek

Macroscopic

- Multiple small yellow mucosal nodules or plaques, usually in the area of the trigone

*Microscopic **(Figure 8)***

- Mixed inflammatory infiltrate in the lamina propria
- Large numbers of epithelioid histiocytes (von Hansemann histiocytes) with abundant granular eosinophilic cytoplasm and intracytoplasmic inclusions (Michaelis-Gutmann bodies, 3–10 μm)
- Concentrically laminated basophilic round to oval calcospherites (Michaelis-Gutmann bodies) may be seen in the stroma freely or as intracytoplasmic inclusions
- PAS+, iron+, and calcium (von Kossa stain)+

Electron Microscopy

- Concentrically laminated structure with a central electron-dense core and radially oriented spicules (hydroxyapatite crystals) **(Figure 8C)**

Schistosomiasis

- Endemic in southwestern Asia and in some parts of Africa, especially Egypt

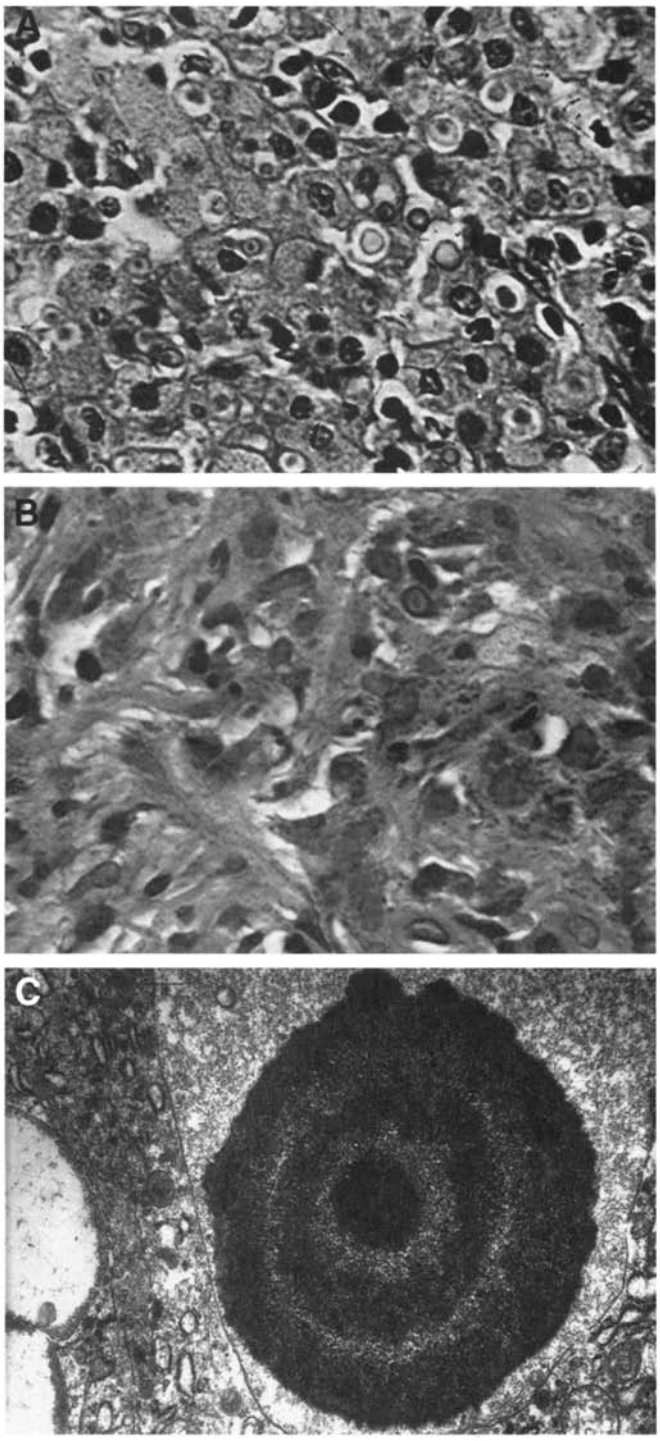


Fig. 8. Malakoplakia. **(A)** H&E staining; **(B)** PAS staining; **(C)** electron microsopy.

- Graulomatous inflammation and fibrosis of lamina propria or muscular wall
- Identification of schistosomal eggs (100 μm) in the bladder wall is diagnostic **(Figure 9)**

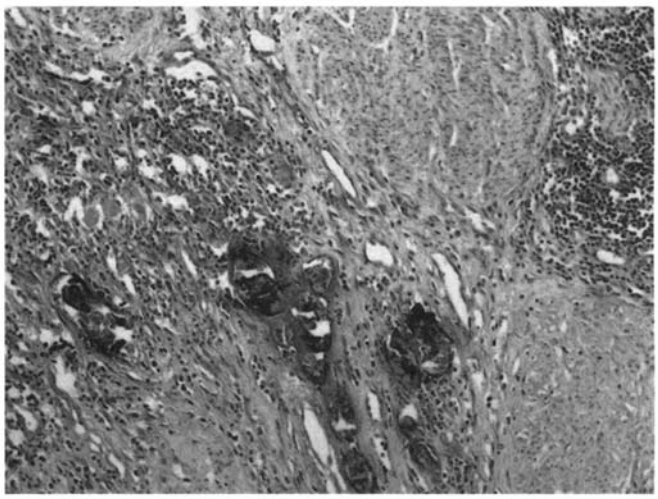


Fig. 9. Shistosomiasis.

Treatment-Induced Cystitis

Radiation Cystitis

Clinical

- Inflammatory condition (with acute and chronic phases) associated with pelvic radiation treatment
- Highly dose dependent (50% risk if receiving 70 Gy but only 5% risk with 60 Gy)
- Acute phase occurs in <6 months (usually manifests within 6 weeks of treatment); subacute phase occurs from 6 months to 2 years after treatment; chronic phase usually takes 2–5 years to appear

Macroscopic

- Acute phase:
  - Hyperemia/congestion, petechiae
  - Marked edema with thick mucosal folds ("bullous cystitis")
  - Mucosal erosion and ulceration
- Subacute phase:
  - Mucosal erythema, ulceration, edema, and fistulae formation
- Chronic phase:
  - Thin, atrophic mucosa with ulceration

*Microscopic **(Figure 10)***

- Acute phase:
  - Epithelial denudation and ulceration
  - Marked cellular atypia with large hyperchromatic, bizarre nuclei
  - Lamina propria edema and congestion
- Subacute phase:
  - Edema and chronic inflammation
  - Mucosal ulceration, variable atrophy and/or hyperplasia

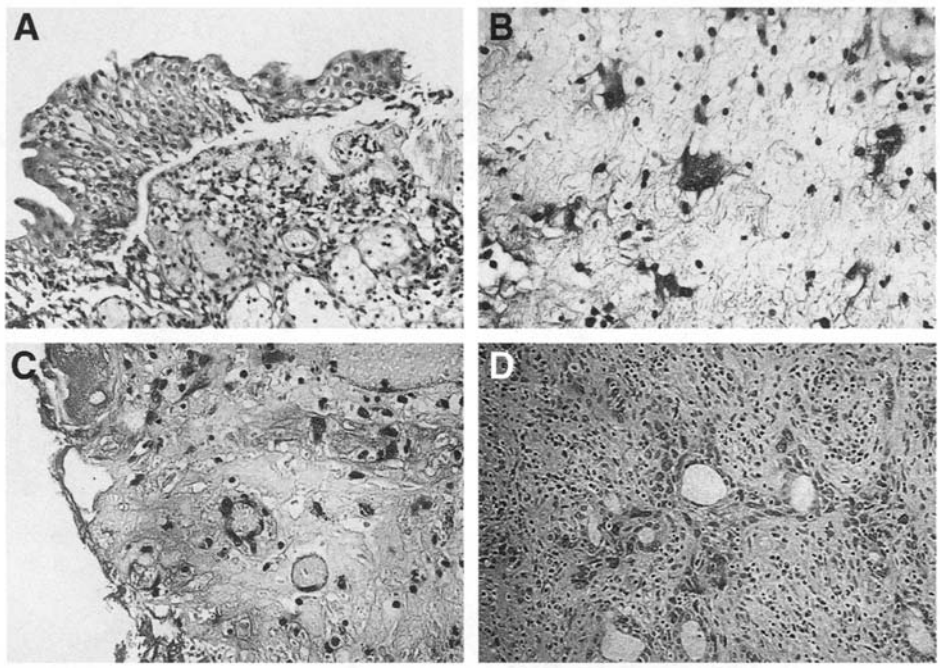


Fig. 10. Radiation cystitis **(A-D)**.

- Chronic phase:
  - Some degree of residual epithelial atypia and areas of ulceration
  - Urothelial metaplasia
  - Fibrosis and collagen deposition in the lamina propria and muscularis propria with scattered atypical fibroblasts
  - Endothelial proliferation, arteriolar hyalinization, subendothelial and medial fibrosis (endarteritis obliterans)

Differential Diagnosis

- Carcinoma *in situ*
  - High nucleus: cytoplasmic ratio and nuclear membrane irregularity
  - Collagenization and atypical fibroblasts are not seen

BCG-Induced Cystitis

- *See* page 30-6

Cytoxan-Induced Hemorrhagic Cystitis

Clinical

- Occurs in up to 8% of patients treated with cyclophosphamide (cytoxan)
- Secondary to toxic metabolite acrolein (an aldehyde and oxidizing agent) that is excreted in the urine
- May result in severe, intractable hematuria, which may require cystectomy
- Diffuse, severe hyperemia with edema and ulceration endoscopically

Macroscopic

- Mucosal erosion, ulceration, edema, and erythema

*Microscopic **(Figure 11)***

- Urothelial denudation, ulceration, and regeneration with reparative changes
- Marked edema and extensive hemorrhage within the lamina propria
- Activation of polyoma virus or adenovirus infection may be seen in immunocompromised patients

Special Variants of Cystitis

Interstitial Cystitis (Figure 12)

Clinical

- Uncommon inflammatory process seen in middle-aged women (30–50 years)
- Patients present with dysuria, urgency, frequency, hematuria, or generalized pelvic pain
- Diagnosis is made clinically based on symptoms and cystoscopic examination and after negative testing for bacterial, fungal, or viral pathogens
- Associated with allergic and immunologic disorder (rheumatoid arthritis, systemic lupus erythematosus, or autoimmune thyroiditis)
- Antinuclear antigen test is positive in >50% of cases

Macroscopic

- Scattered petechial hemorrhages
- Wedge-shaped ulcerations (Hunner's ulcers)

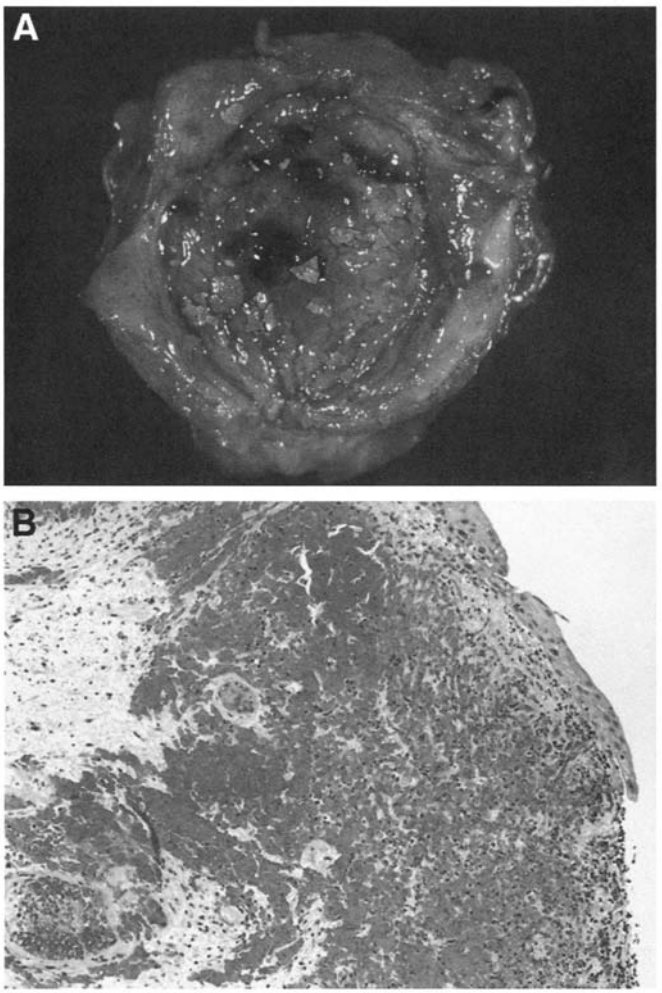


Fig. 11. Hemorrhagic cystitis **(A,B)**.

Microscopic

- Mucosa may be denuded or ulcerated, with granulation tissue
- Lamina propria shows edema and congestion, with a mononuclear inflammatory infiltrate
- Mononuclear and mast cell infiltrate in the lamina propria and muscularis propria
- Perineural mononuclear infiltrate
- Fibrosis of the lamina propria and muscularis propria
- Discontinuous uroplakin immunostaining in superficial (umbrella) cells of patients with interstitial cystitis and continuous immunostaining in urothelium of patients without disease

Differential Diagnosis

- Other forms of cystitis, including:
  - Tuberculous cystitis
    - Caseating granulomas containing acid-fast bacteria

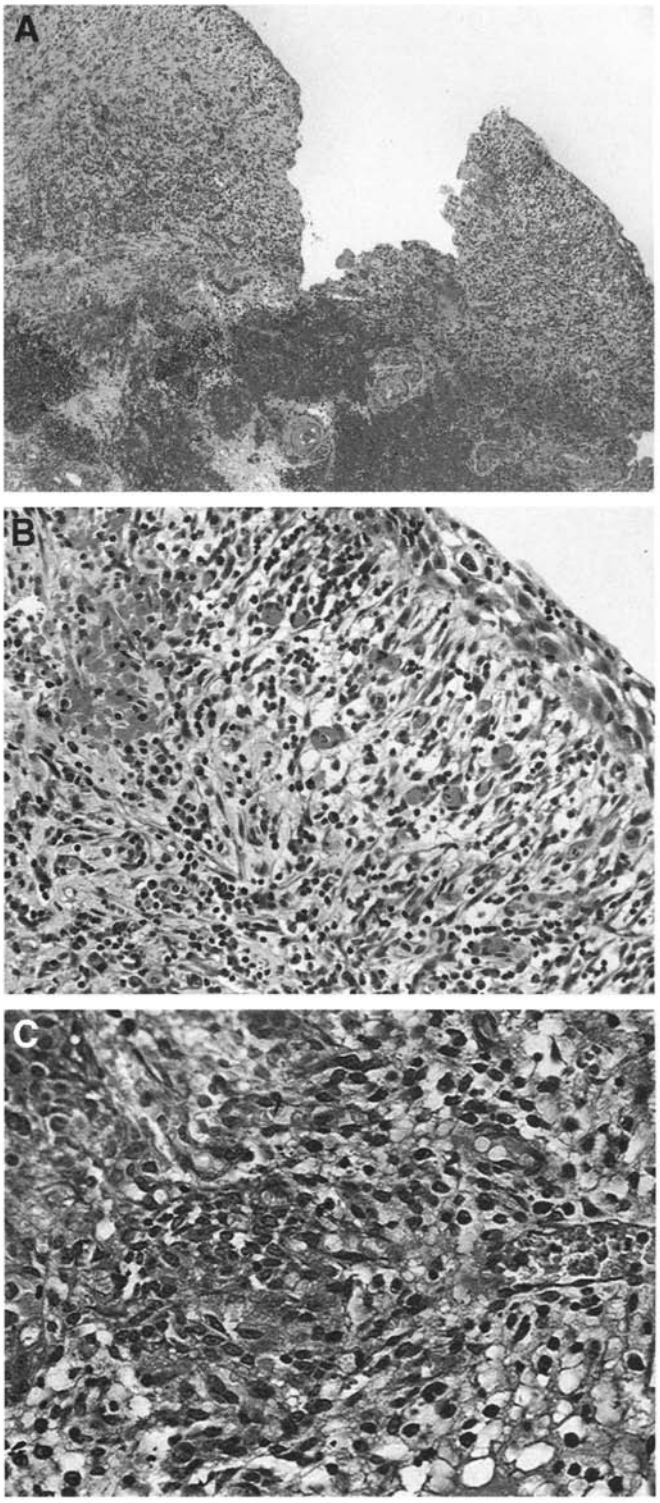


Fig. 12. Interstitial cystitis. **(A)** Hunner's ulcer; **(B)** non-ulcer form; **(C)** toluidine blue staining highlights mast cells.

  - Eosinophilic cystitis
    - Mononuclear and eosinophilic infiltrate in the lamina propria and muscularis propria

Eosinophilic Cystitis

Clinical

- Inflammatory process found in women and children; seen with allergic disorders and other diseases associated with peripheral eosinophilia
- Uncommonly seen in elderly men with bladder injury or history of transurethral resection
- Symptoms include severe frequency, urgency, dysuria, and hematuria, with periods of remission and exacerbation
- Spontaneous resolution is common

Macroscopic

- Diffuse mucosal edema and erythema or as velvety yellow plaque
- Tumor-like polypoid growths that appear erythematous and may demonstrate ulceration or necrosis

Microscopic

- Mononuclear and eosinophilic infiltrate in the lamina propria and muscularis **(Figure 13)**
- Early disease is characterized by marked edema, congestion, and a mixed mononuclear and eosinophilic infiltrate
- In severe cases, muscle necrosis may be seen
- As the disease progresses, the inflammatory infiltrate tends to subside and varying degrees of fibrosis may be seen in the lamina propria and muscularis

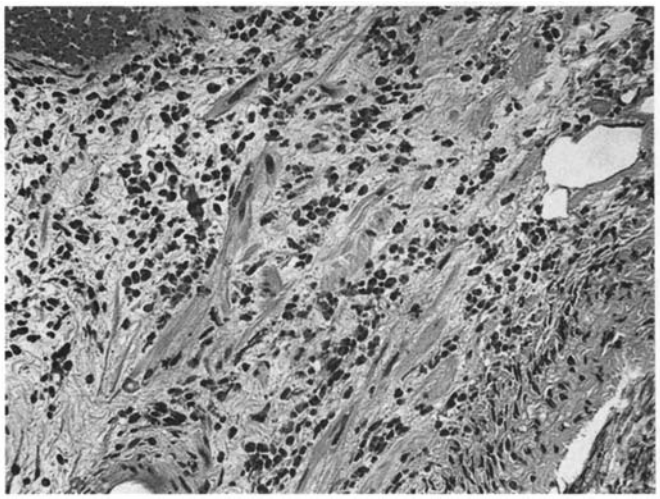


Fig. 13. Eosinophilic cystitis.

Differential Diagnosis

- Other forms of cystitis, including:
  - Tuberculous cystitis:
    - Caseating granulomas containing acid-fast bacteria
  - Follicular cystitis:
    - Subepithelial lymphoid follicles with germinal centers
  - Interstitial cystitis:
    - Mononuclear and mast cell infiltrate in the lamina propria and muscularis propria

BENIGN LESIONS AND MIMICS OF CANCER

Hyperplasia

Urothelial Hyperplasia

- Thickened benign urothelium (>7 cell layers) without cytologic atypia **(Figure 14)**
- Often associated with inflammatory condition or urothelial neoplasm

Papillary Urothelial Hyperplasia

- Undulating pseudopapillary proliferation of urothelium without cytologic atypia **(Figure 15)**
- No requirement of cell thickness for diagnosis
- Lacks well-developed fibrovascular cores
- Considered as a precursor to grade 1 papillary urothelial carcinoma by some investigators

Metaplasia

Squamous Metaplasia

Clinical

- More commonly seen in men (4x higher incidence than in women)
- Non-keratinizing squamous metaplasia of the trigone in women is a normal finding secondary to estrogen stimulation
- Benign metaplasia of the bladder epithelium, usually in the setting of chronic inflammation, but may be seen in normal bladder
- Associated conditions include:
  - Exstrophy
  - Neurogenic bladder, indwelling catheter
  - Surgery or biopsy
  - Recurrent infection (e.g., schistosomiasis)
  - Calculi
- Non-keratinizing squamous metaplasia is not associated with increased risk of carcinoma
- May interfere with bladder contraction and dilation if extensive and produce renal colic with renal pelvic involvement

Macroscopic

- May appear as multiple small nodular/papular mucosal lesions, or as dull white plaques

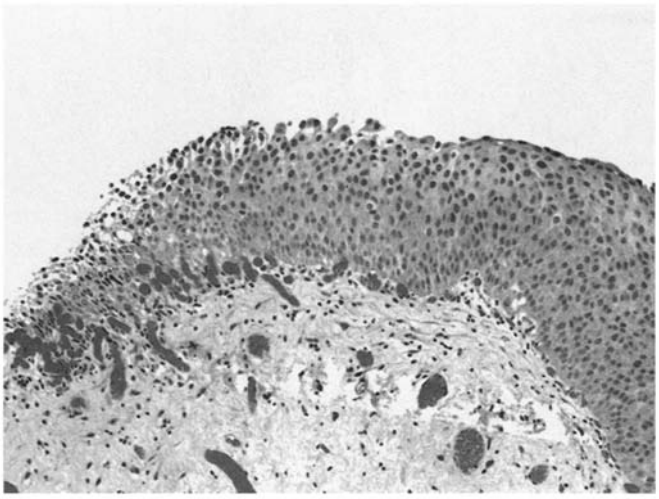


Fig. 14. Urothelial hyperplasia.

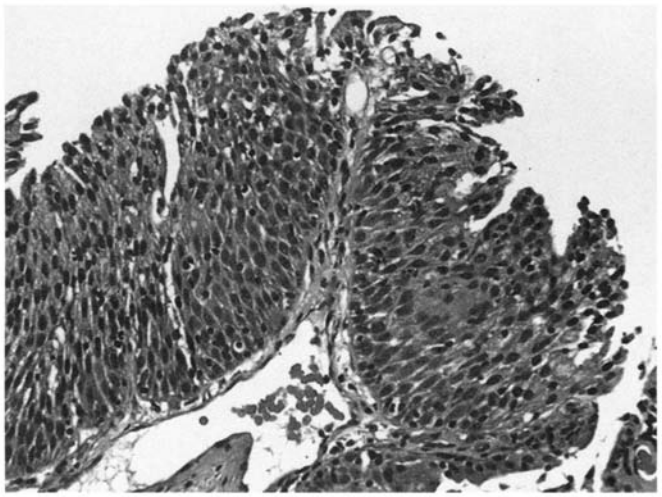


Fig. 15. Papillary urothelial hyperplasia.

- Trigone is the region most commonly affected
- Renal pelvic involvement may produce filling defect on excretory urogram

Microscopic

- Mature keratinizing **(Figure 16)** or nonkeratinizing squamous epithelium

Nephrogenic Metaplasia

Clinical

- Usually occurs in middle-aged men (M : F = 2 : 1, mean age = 41 years)
- Occurs in the setting of long-standing chronic irritation
- 20% of cases occur in children and adolescents
- 8% of patients have undergone kidney transplantation; in these patients, cells of nephrogenic adenoma derive from tubular cells of the renal transplant, and are not metaplastic proliferations of the recipient's bladder urothelium

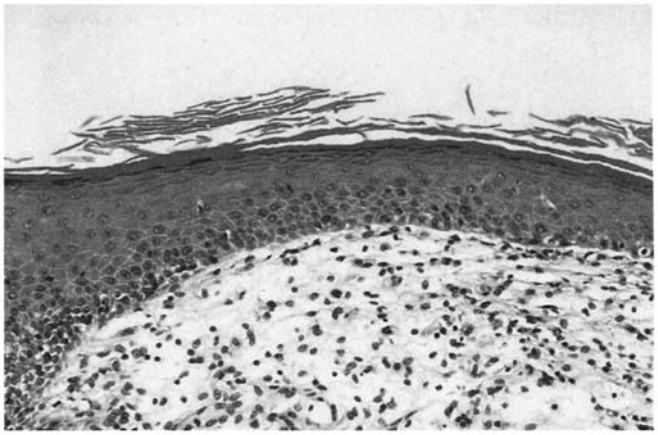


Fig. 16. Keratinizing squamous metaplasia.

Macroscopic

- Papillary or polypoid small solitary yellow nodules (usually <1 cm)
- Erythematous irregular mucosa
- Predilection for trigone

Microscopic

- Well-circumscribed proliferation of orderly small compact tubules, cysts, and delicate filiform papillae lined by columnar or cuboidal hobnail cells **(Figure 17)**
- Cells have clear to eosinophilic cytoplasm and uniform nuclei
- Inconspicuous mitotic figures
- Intracytoplasmic vacuoles (glycogen+) may be seen, imparting a signet ring-cell appearance
- Tubules have thickened PAS+ basement membrane and may contain eosinophilic PAS+ secretions
- Chronic inflammatory infiltrate in the lamina propria
- Cytologic atypia may be seen (Cheng et al: Cancer 88:853, 2000) **(Figure 17B)**
- Often associated with squamous metaplasia, cystitis cystica, and cystitis glandularis

Immunohistochemistry

- Cytokeratin+, EMA+, CEA–, alpha-methylacyl-CoA racemase (P504S)+

Differential Diagnosis

- Clear cell adenocarcinoma:
  - Usually occurs in elderly women
  - Not confined to the lamina propria
  - Infiltrative rather than well-circumscribed growth
  - Cytologic atypia and frequent mitotic figures
  - Cytokeratin+, EMA+, CEA±
- Urothelial carcinoma with tubulo-glandular pattern:
  - Tubules lined by multiple layers of urothelial cells rather than single cell layer

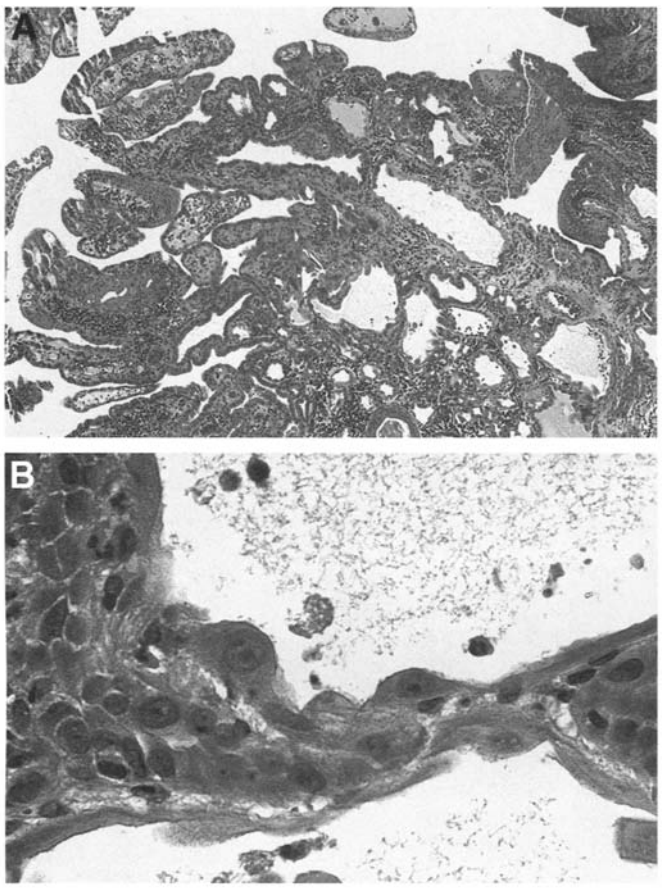


Fig. 17. Nephrogenic metaplasia. Papillae and tubules are common patterns **(A)**. Prominent nucleoli may be seen **(B)**.

- Cytologic atypia, infiltrative growth, and mitotic figures
- Lacks prominent basement membrane and architectural heterogeneity

Intestinal Metaplasia (Glandular Metaplasia)

Clinical

- Occurs in the setting of long-standing chronic irritation
- Little or no malignant potential

Microscopic

- Glands lined by mucin-producing colonic-type columnar goblet cells **(Figure 18)**
- Paneth cell differentiation may be seen
- Inflammatory background

von Brunn's Nests

- Occur in ~85% of autopsy patients
- Represent a normal variant of bladder mucosa
- Solid nests of urothelium project into the lamina propria
- May contain luminal eosinophilic secretions

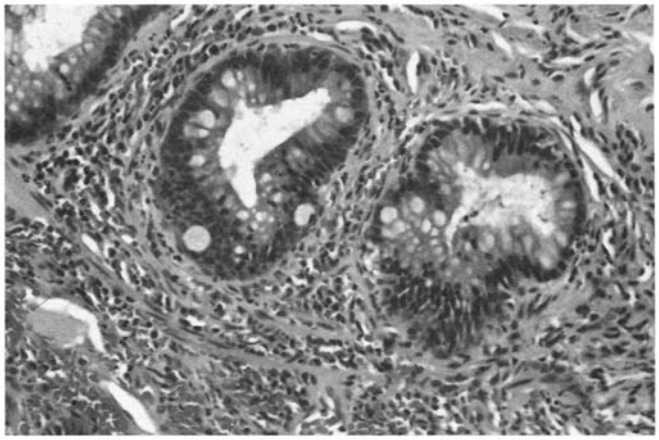


Fig. 18. Intestinal metaplasia.

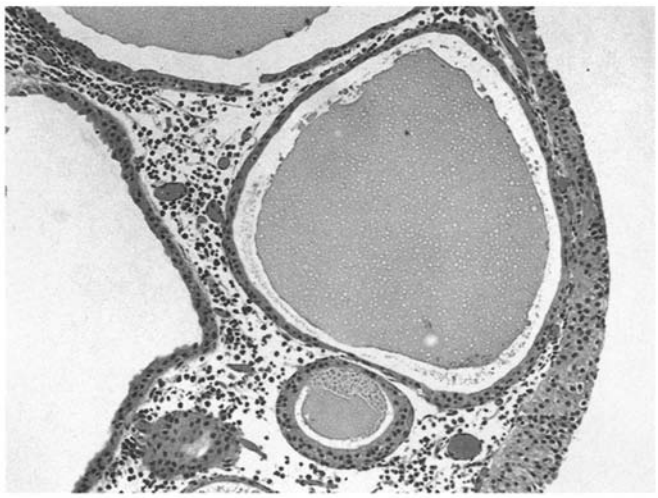


Fig. 19. Cystitis cystica.

Cystitis Cystica

- May appear as small (1–5 μm) yellow cysts in the lamina propria
- Unilocular cysts lined by single or multiple layers of cuboidal urothelial cells **(Figure 19)**
- Acute and chronic inflammation may be present

Florid Cystitis Glandularis

Clinical

- Usually an incidental finding
- Patients may present with irritative obstructive symptoms or hematuria
- No malignant potential

Macroscopic

- Nodular or polypoid lesion, with predilection for the trigone and bladder neck

Microscopic

- Involvement of von Brunn's nest by glandular metaplasia
- Exuberant proliferation of glands lined by columnar cells with or without goblet cells (intestinal metaplasia)
- Lesions are confined to the lamina propria
- Lacks significant cytologic atypia
- Focal extravasation of mucin into the stroma may be seen
- Overlying mucosa may be atrophic, normal, or hyperplastic
- Edema and inflammation in the lamina propria

Differential Diagnosis

- Endocervicosis:
  - Muscularis propria is usually involved
  - Pronounced stromal inflammatory response
- Mullerianosis:
  - Involves the muscularis propria and lamina propria
  - The presence of tubal type epithelium with ciliated cells
  - Lacks identifiable urothelial cells
- Adenocarcinoma (colloid adenocarcinoma):
  - Cytologic atypia and mucin lakes
  - Infiltrative growth and invasion into muscularis propria

Endocervicosis

- Occurs in women of reproductive age
- Predilection for posterior wall or posterior dome
- Proliferation of endocervical-type glands, which are often cystically dilated and display reactive changes **(Figure 20)**
- Lacks significant cytologic atypia
- Usually involves muscularis propria
- Extravasated mucin is associated with stromal edema, fibrosis, and prominent inflammatory response
- May be associated with endometriotic stroma

Müllerianosis (Figure 21)

- Occurs in women of reproductive age (37–46 years)
- Located in the posterior wall of the bladder
- Characterized by the presence of at least two of three components: endosalpingiosis, endocervicosis, and endometriosis (triad of endometrial glands, stroma, and hemosiderin-laden histiocytes) **(Figure 21B)**
- CD10+ cells in stroma help to recognize endometriosis
- Involves the lamina propria and muscularis propria
- Proliferation of tubules and cysts lined by endocervical-type epithelium or tubal epithelium (ciliated cells, peg cells, and intercalated cells)

Proliferative Papillary Cystitis (Papillary-Polypoid Cystitis)

- See previous discussion (page 30-4)

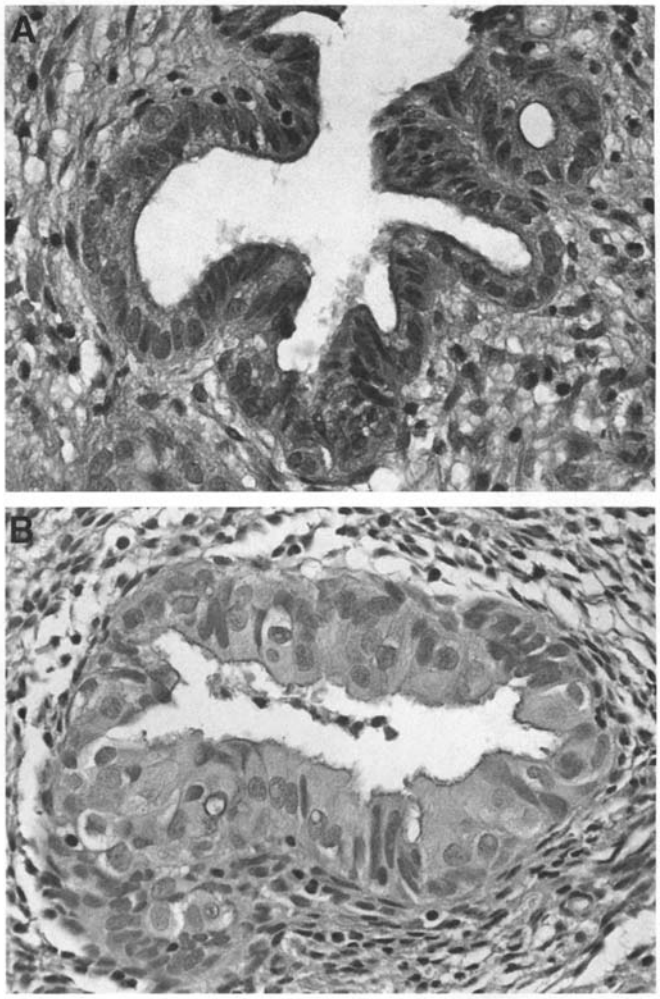


Fig. 20. Endocervicosis **(A,B)**.

Diverticulosis

Clinical

- Acquired outpocketing of the mucosa through the muscularis propria, usually due to the increased pressure associated with bladder outlet obstruction (most commonly prostatic hyperplasia)
- Usually occurs in elderly patients, M>F
- The diverticuli may give rise to calculi or tumor

Macroscopic

- Pockets of bladder mucosa projecting into (and sometimes through) the muscularis propria
- Usually located in the posterior wall, the dome, and the region of the urachus
- May contain calculi

Microscopic

- Lining is usually urothelial
- Varying degree of inflammation and squamous metaplasia may be seen

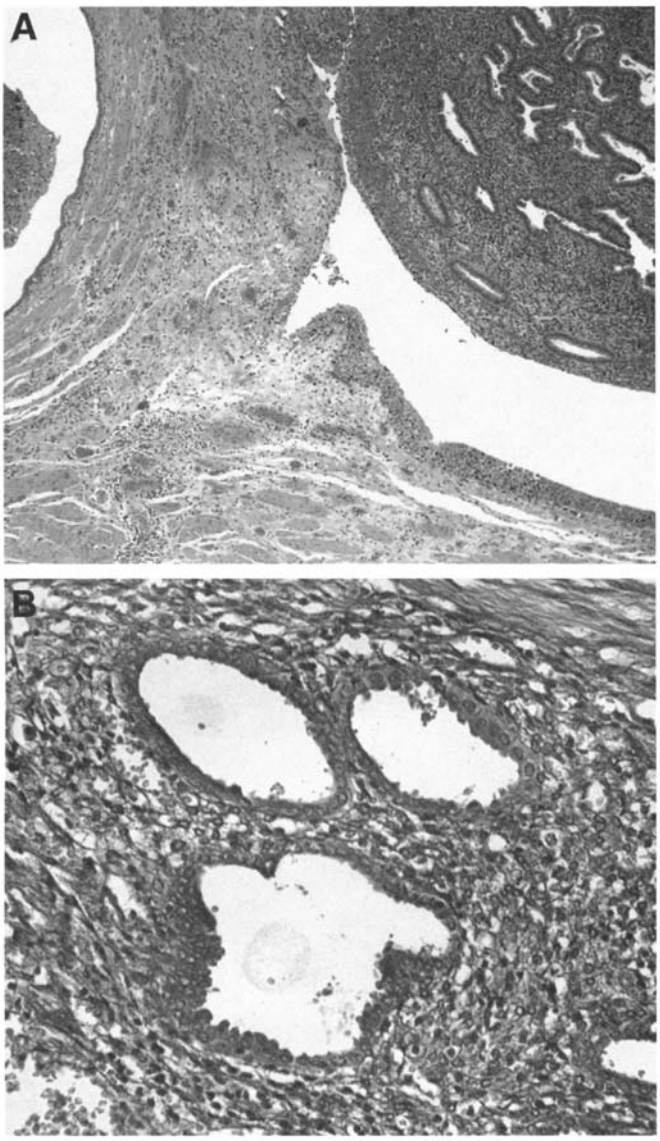


Fig. 21. Müllerianosis **(A)** two components of müllerianosis (endocervicosis and endometriosis) are seen; **(B)** endometriosis.

- Associated tumor is usually urothelial carcinoma, but adenocarcinoma or squamous cell carcinoma may be seen

Post-Operative Spindle Cell Nodule

Clinical

- Post-operative reactive proliferation mimicking cancer
- A rare sequelae of bladder or prostate surgery, especially transurethral resection
- Usually presents weeks to months after surgery, either during follow-up, or due to hematuria or obstruction

Macroscopic

- Polypoid or nodular growth, typically in the same area as the previous surgery
- Small lesion

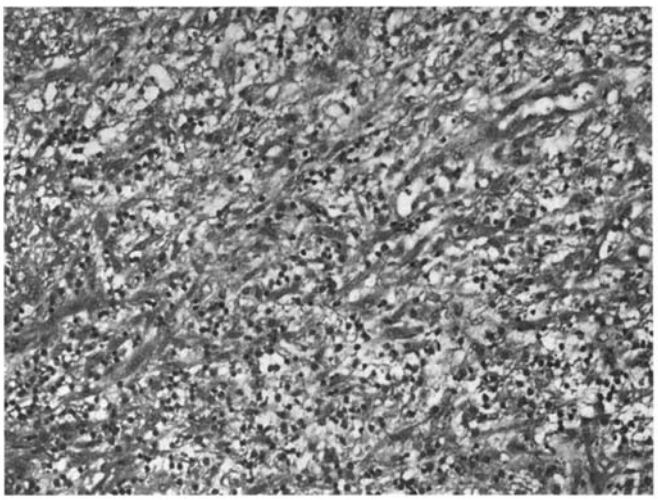


Fig. 22. Post-operative spindle cell nodule.

Microscopic

- Highly cellular spindle cell neoplasm mimicking sarcoma
- Cells are loosely arranged in a myxoid vascular stroma
- The tumor edge may have a pseudoinfiltrative appearance
- Mitotic figures are numerous, but not atypical
- Lacks significant cytologic atypia
- A significant amount of mononuclear inflammatory infiltrate is usually present **(Figure 22)**

Immunohistochemistry

- Cytokeratin–, smooth muscle actin±, vimentin–

Differential Diagnosis

- Sarcoma (leiomyosarcoma, fibrosarcoma):
  - Sarcoma will show compact, dense cellularity as well as cytologic atypia, atypical mitotic figures, and tumor necrosis
  - Clinical history (documentation of surgery or other intervention in the last 6–8 weeks) is helpful in determining the diagnosis
- Sarcomatoid carcinoma:
  - Cytokeratin+, biphasic tumor with identifiable epithelial elements, cytologic abnormalities

Inflammatory Myofibroblastic Tumor

Clinical

- Reactive myofibroblastic proliferative process in children and adults.
- Clonality analysis suggests a neoplastic nature of some of these cases
- Some consider it as low grade neoplasm
- May recur; complete excision is recommended
- Usually occurs in young adults (mean age = 28 years), M : F = 1 : 2

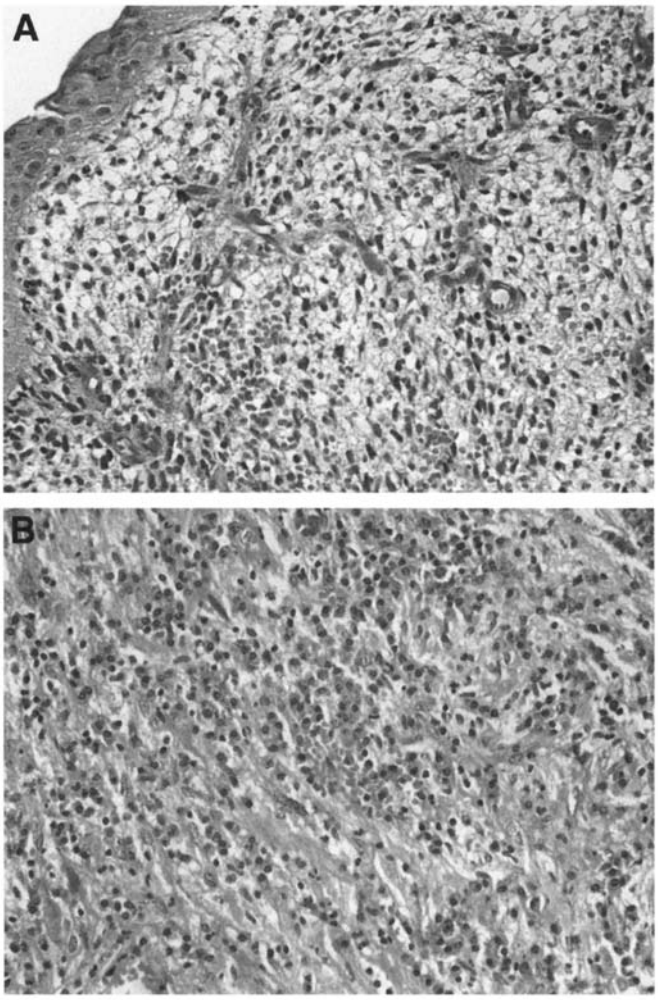


Fig. 23. Inflammatory myofibroblastic tumor. **(A)** myxoid pattern; **(B)** plasma cell predominance.

Macroscopic

- Nodular or polypoid exophytic mass, usually 2–5 cm in size

Microscopic ***(Figure 23)***

- Loosely arranged spindle cells in an edematous myxoid vascular stroma
- Spindle cells may demonstrate some mild atypia and scattered mitotic figures but not atypical ones
- Edges may be infiltrative
- Extravasation of red blood cells and focal hemorrhage
- Often associated with mononuclear inflammatory infiltrate; eosinophils may be prominent

Immunohistochemistry

- Cytokeratin±, vimentin+, muscle specific actin±, smooth muscle actin±
- Anaplastic lymphoma kinase (ALK-1) + in 89% of cases. ALK1 gene translocation 50% by FISH

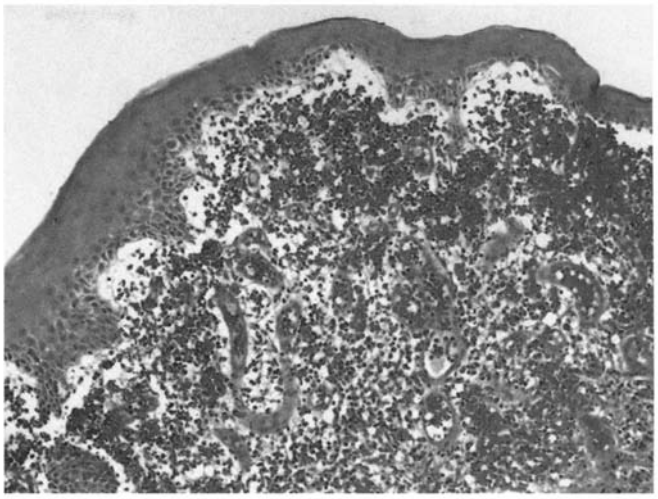


Fig. 24. Urethral caruncle.

Differential Diagnosis

- Sarcoma (myxoid fibrosarcoma or myxoid leiomyosarcoma):
  - Marked cytologic abnormalities with frequent mitotic figures, including atypical forms
  - More diffuse infiltrative growth
  - Areas of tumor necrosis
  - ALK-1 negative by immunohistochemistry
- Sarcomatoid carcinoma:
  - Cytokeratin+, biphasic tumor with identifiable epithelial elements, cytologic abnormalities
  - More common in elderly men
  - ALK-1 negative by immunohistochemistry

Urethral Polyp

Inflammatory Polyp

- Composed of inflamed and vascular stroma lined by normal or hyperplastic urothelium

Urethral Caruncle

Clinical

- Usually occurs in postmenopausal women (mean age = 56 years)
- Typically presents as red painful mass at the external urethral meatus
- Etiology uncertain
- Asymptomatic or presents with hematuria, dysuria, and pain

Macroscopic

- Nodular or pedunculated erythematous lesion in the posterior or lateral distal urethral wall

Microscopic

- Exuberant proliferation of fibroblasts and endothelial cells in an inflammatory background, similar to granulation tissue **(Figure 24)**

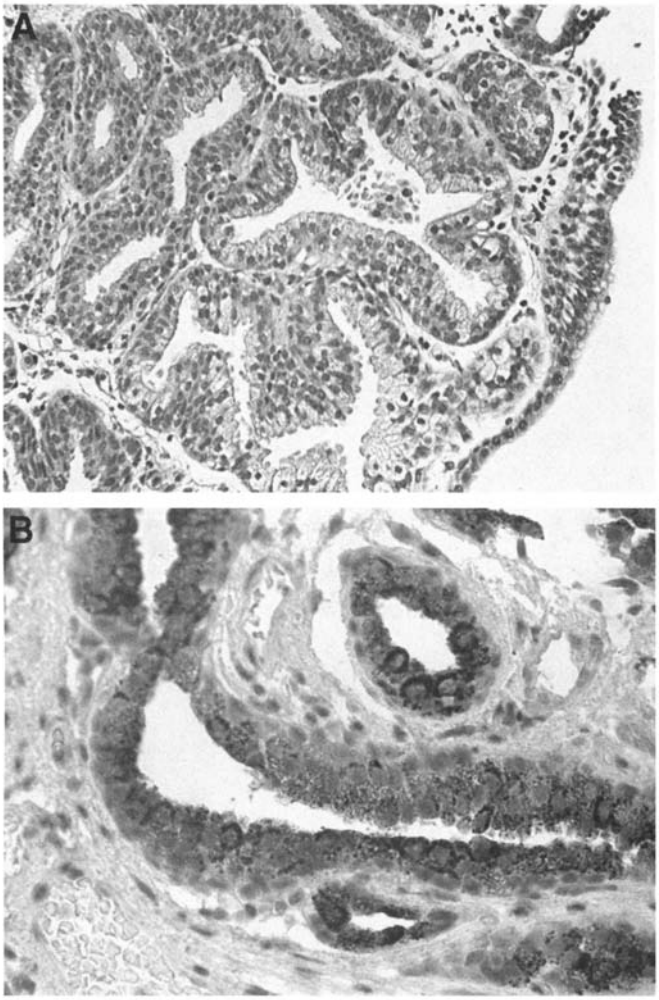


Fig. 25. Ectopic prostatic tissue. **(A)** H&E; **(B)** PSA immunostaining.

- Lacks significant cytologic atypia
- Mitotic figures inconspicuous
- Atypical stromal cells may be seen (cytokeratin–)
- Urothelium may show hyperplasia, metaplasia, or be denuded

Differential Diagnosis

- Carcinosarcoma:
  - Cytokeratin+, biphasic tumor, cytologic abnormalities, invasion

Fibroepithelial Polyp

Clinical

- Occurs in young adult men
- Presents with hematuria and intermittent flank pain

Macroscopic

- Polyp in the region of verumontanum or posterior urethra
- Also occurs in proximal ureter (left > right)

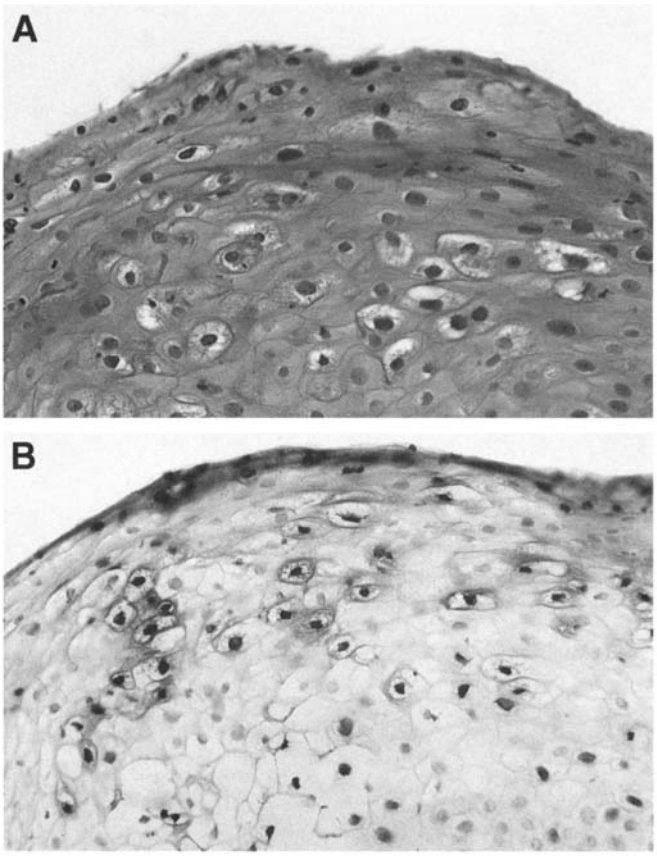


Fig. 26. Condyloma acuminata. Koilocytic change can be subtle **(A)** and human papillomavirus *in situ* hybridization is positive **(B)**.

Microscopic

- Polypoid projection of edematous vascular stroma with overlying atrophic or hyperplasic urothelium
- Chronic inflammatory infiltrate

Ectopic Prostatic Tissue

Clinical

- Occurs in adolescents or young adults
- Presents with hematuria or irritative symptoms

Macroscopic

- Located in posterior portion of prostatic urethra

Microscopic

- Benign prostatic glands with overlying intact urothelium, PSA+ **(Figure 25)**

Nephrogenic Metaplasia

- Described elsewhere (page 30-11)

Proliferative Papillary Urethritis

- See proliferative papillary cystitis (page 30-4)

Pyogenic Granuloma

- Similar to those seen at other organ sites

Urothelial Papilloma

- Described elsewhere (page 30-17)

Inverted Papilloma

- Described elsewhere (page 30-17)

Condyloma Acuminata

- Male-to-female ratio = 1 : 2
- Occurs in all ages
- Usually coexists with condyloma of the urethra, vulva, vagina, anus, or perineum
- At cystoscopy, isolated or multiple exophytic lesions mainly in bladder neck or trigone
- HPV DNA type 6 has been found in some cases **(Figure 26)**

Squamous Papilloma

- Benign; very rare in the bladder
- Described elsewhere (page 30-18)

NEOPLASMS OF THE BLADDER

Benign Urothelial Neoplasms

Urothelial Papilloma

Clinical

- Rare benign urothelial neoplasm
- Accounts for 1% to 2% of papillary urothelial neoplasms
- Usually occurs in young adults (<50 years old)
- May present with painless hematuria
- Post-treatment recurrence is uncommon

Diagnostic Criteria

- Patient age <50 years
- Small solitary lesion (<2 cm)
- The urothelium lining the papillae is normal in thickness (<7 cell layers)
- Minimal or no cytologic atypia

Macroscopic

- Exophytic solitary papillary small lesion (<2 cm)

*Microscopic **(Figure 27)***

- Cytologically and architecturally normal urothelium covering delicate fibrovascular stalks
- <7 layers in thickness
- Normal polarity retained
- Lacks mitotic figures
- Lacks cytologic atypia
- Cytokeratin 20 expression is identical to that in normal urothelium (superficial "umbrella" cells only)

Differential Diagnosis

- Grade 1 (of 3) urothelial carcinoma (Papillary urothelial neoplasm of low malignant potential):
  - Thickened urothelium (>7 cell layers) with some degree of cytologic atypia

Inverted Papilloma

Clinical

- Rare benign urothelial neoplasm
- Comprises less than 1% of urothelial tumors
- Occurs in elderly patients (60–70 years), with male predominance (M : F = 6 : 1)
- Presents with hematuria and irritative symptoms
- No recurrence after complete excision

Macroscopic

- Solitary, small (1–3 cm), smooth, dome-shaped, pedunculated, or polypoid lesions
- Usually located in the region of the trigone, as well as bladder neck, ureteral orifice, and posterior urethra

Microscopic

- Anastomosing cords, columns, and trabeculae of invaginated urothelium separated by thin fibrovascular septae **(Figure 28)**
- Peripheral palisading of basaloid cells and preservation of superficial cells
- Prominent thickened basement membrane
- Lacks exophytic growth, fibrovascular cores, or infiltrative borders
- Areas of glandular or squamous differentiation and microcyst formation may be seen in the central areas of solid nests
- Occasional neuroendocrine differentiation
- Minimal cytologic atypia and inconspicuous mitotic figures
- The overlying mucosa is intact and covered by a normal, hyperplastic, or attenuated urothelium
- May be associated with urothelial carcinoma in the same patient
- Very low tumor cell proliferation (ki67-MIB1) and p53 nuclear accumulation

Differential Diagnosis

- Florid proliferation of von Brunn nests
- Low-grade urothelial carcinoma:
  - Cytologic atypia, mitotic figures, and infiltrative growth
- Inverted variant of urothelial carcinoma:
  - Thicker and more irregular column with loss of polarity
  - Lacks peripheral palisading of basaloid cells

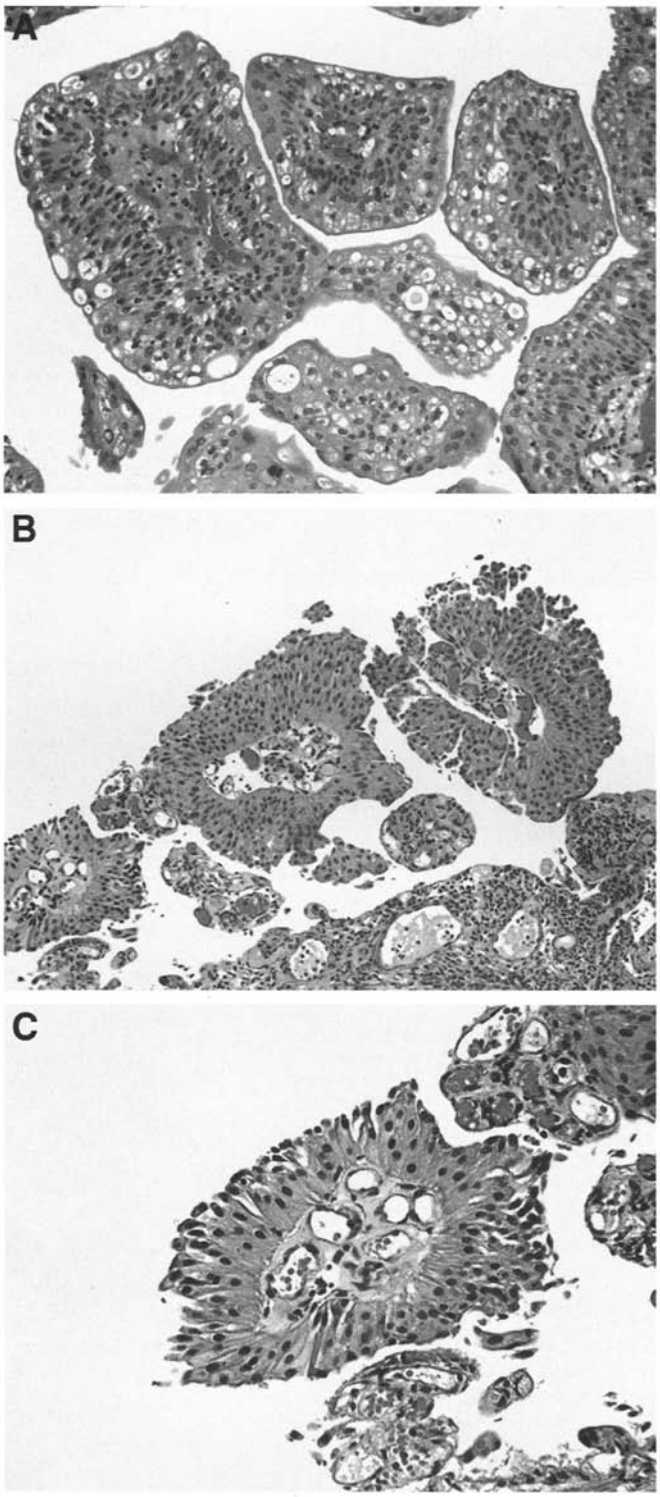


Fig. 27. Urothelial papilloma (**A–C**).

- Cytologic atypia and invariable mitotic figures
- Extensive keratinization rare in inverted papilloma

Squamous Cell Papilloma

- Rare benign neoplasm
- Presumably the squamous counterpart of urothelial papilloma

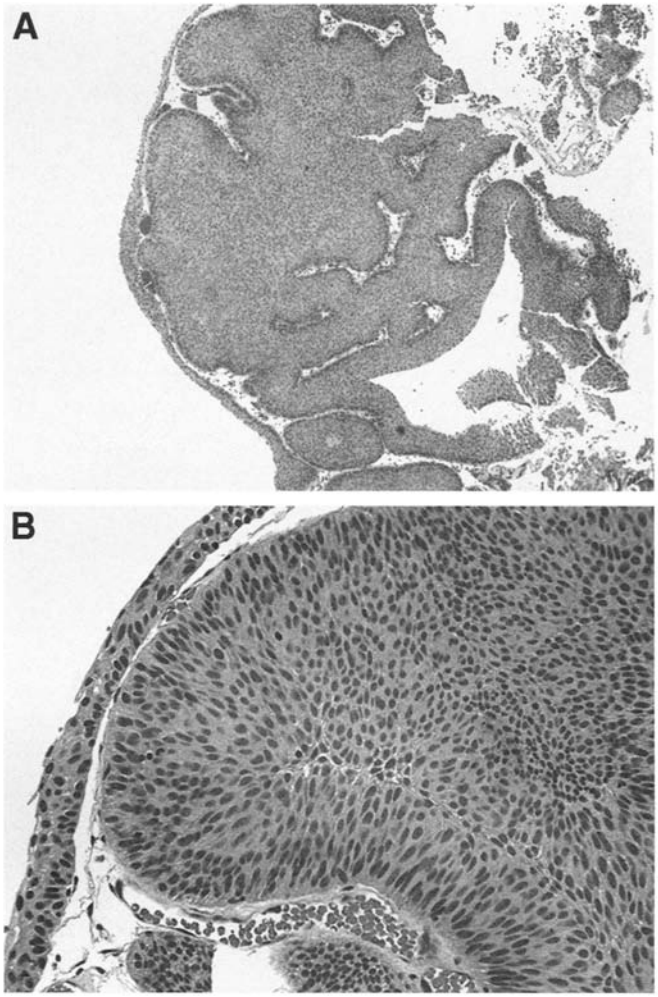


Fig. 28. Inverted papilloma (**A,B**).

- Not associated with human papillomavirus infection
- Composed of papillary cores with overlying benign squamous epithelium

Flat Urothelial Lesions with Atypia (Table 1)

Reactive Changes (Figure 29)

- Often cccurs in the setting of chronic irritation such as instrumentation, urolithiasis, or intravesical therapy
- Acutely or chonically inflamed urothelium with inflammatory infiltrate
- Uniformly enlarged cells with single prominent nucleoli and evenly distributed vesicular chromatin
- Mitotic figures are often seen

Urothelial Atypia of Unknown Significance

- A diagnostic category encompassing a spectrum of histologic abnormalities that may not be attributed to reactive or inflammatory atypia alone, but fall below the threshold for the diagnosis of dysplasia

Table 1. Comparison of reactive atypia, hyperplasia, dysplasia, and urothelial carcinoma *in situ*

Characteristics	*Reactive Atypia*	*Hyperplasia*	*Dysplasia*	*Carcinoma in situ**
Cell layers	Variable	> 7	Variable	Variable
Polarization	Slightly abnormal	Normal	Disordered	Disordered
Cytoplasm	Often vacuolated	Homogeneous	Variable, homogeneous to granular	Variable
N/C ratio	Normal or slightly Increased	Normal or slightly increased	Slightly increased	Increased
Nuclei				
Size	Enlarged	Normal	Enlarged	Enlarged with variation in size
Position	Normal	Normal	Mild	Eccentric anysonucleosis
Borders	Regular/smooth	Regular/Smooth	Notches/creases	Pleomorphic
Chromatin	Fine/dusty	Fine	Slight hyperchromasia	Coarse
Nuceoli	Large, single	Small/absent	Small	Large, often multiple
Mitotic figures	Variable	Absent	Rare, basal	Prominent
Umbrella cells	Present	Present	Present	May be present
Denudation	Variable	No	No	Variable
CK20 expression	Surface	Surface	Variable	Variable

**Full thickness involvement is not required for the diagnosis of urothelial carcinoma in situ.*

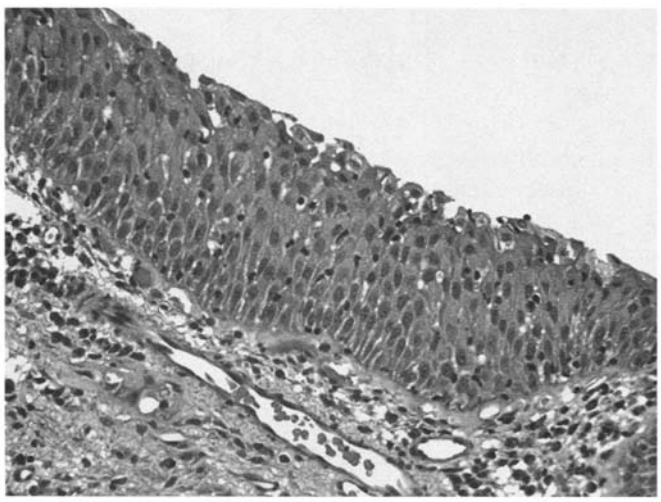


Fig. 29. Reactive changes.

- No adverse clinical outcome
- The authors do not advocate use of this diagnostic category in surgical pathology reports (Lopez-Beltral A, Cheng L, et al. *Virchows Arch.* 2002;440:3–11)

Urothelial Dysplasia

Clinical

- Mean age = 60 years, with male predominance (M : F = 3 : 1)
- Primary dysplasia is rare, and is a strong risk factor for the development of urothelial carcinoma *in situ* and invasive cancer
- Usually associated with concurrent or prior history of urothelial carcinoma; a risk factor for recurrence and progression (14–19%)
- Presents with irritative obstructive symptoms and/or hematuria

Macroscopic

- Non-specific findings, erythematous or normal

*Microscopic (**Figure 30**)*

- The term dysplasia is used to encompass previously designated mild and moderate dysplasia and does not include severe dysplasia (see carcinoma *in situ* [CIS])
- Abnormal architectural and cytologic changes fall short of the diagnostic criteria for an unequivocal diagnosis of CIS/severe dysplasia

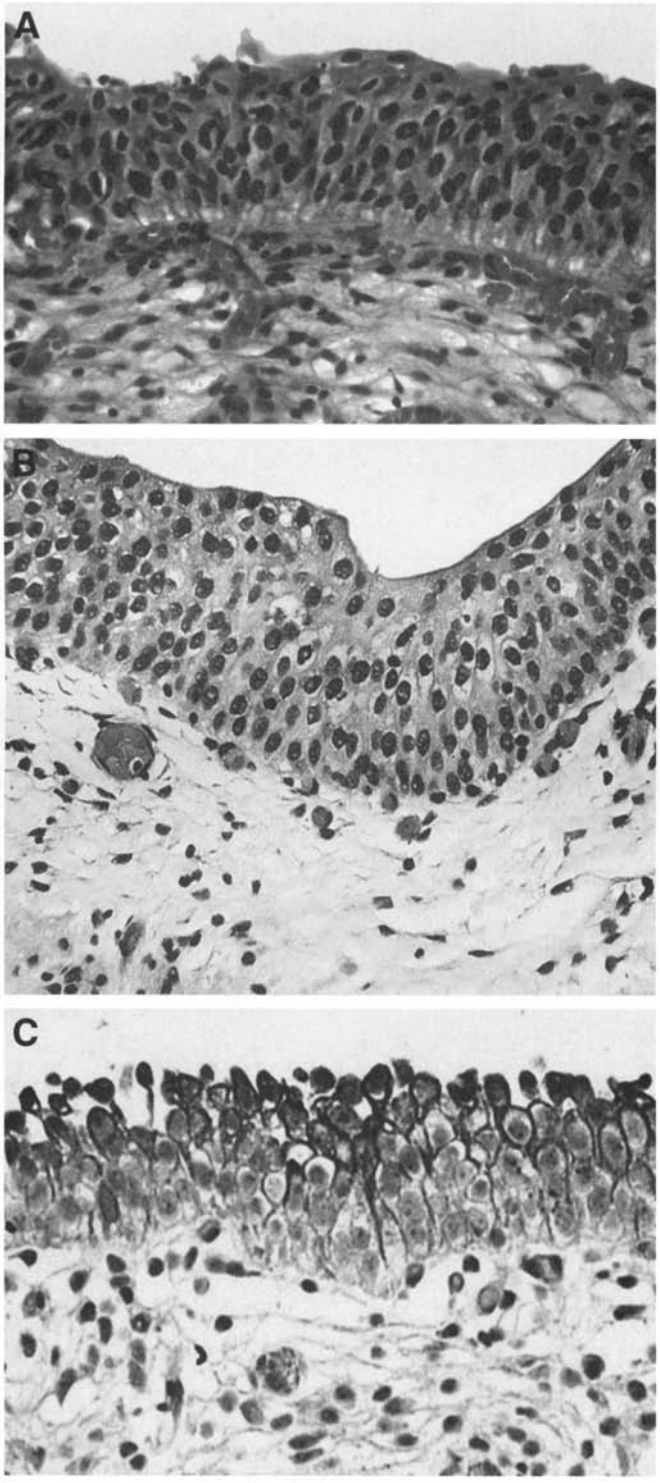


Fig. 30. Urothelial dysplasia (**A,B**). Aberrant expression of CK20 was noted (**C**).

- Altered polarity with preservation of superficial cells and cytoplasmic clearing
- Cells vary in size and shape
- Cells with irregular granular chromatin, irregular nuclear membranes, nuclear crowding, and hyperchromasia
- The long axes of nuclei are parallel to the basement membrane
- Lacks cytoplasmic vacuoles, prominent nucleoli, or atypical mitotic figures
- Aberrant expression of cytokeratin 20 in the upper layers of the urothelium (**Figure 30C**)

Urothelial Carcinoma In Situ (CIS)

Clinical

- Occurs in elderly men (60–70 years old), with male predilection (M : F = 10 : 1)
- Usually associated with concurrent or prior history of urothelial carcinoma
- Presents with irritative obstructive symptoms and/or hematuria
- May masquerade clinically as interstitial cystitis

Macroscopic

- Nonspecific velvety erythematous lesion with granular or cobblestone appearance
- Often occurs in the regions of trigone and base of the bladder
- Multifocal

*Microscopic (**Figure 31**)*

- Full thickness involvement is not a prerequisite for diagnosis
- The cytologic spectrum includes previously designated severe dysplasia (urothelial CIS and severe dysplasia are indistinguishable histologically)
- Always high grade (grading unnecessary)
- Disorderly proliferation of malignant urothelial cells
- Loss of polarity and cellular cohesion
- High N/C ratio, nuclear pleomorphism, hyperchromasia, irregular nuclear contours, coarsely granular chromatin, prominent nucleoli, and mitotic figures
- Small cell variant has hyperchromatic nuclei and inconspicuous nucleoli
- Urothelium is often denuded. The term denuding cystitis is mostly related to urothelial CIS
- In cases of denuding CIS a few neoplastic cells may remain attached to the surface; this is known as the "clinging" pattern of CIS (**Figure 32**)
- Pagetoid spread (**Figure 33**) and von Brunn's nest involvement (**Figure 34**) may be seen
- Micropapillary variant shows pseudopapillary (without fibrovascular core) projections onto the lumenal surface

Non-Invasive Papillary Urothelial Tumors

Clinical

- Most common bladder tumor (90%)
- Occurs in older adults (median age = 65 years); rare before age 50

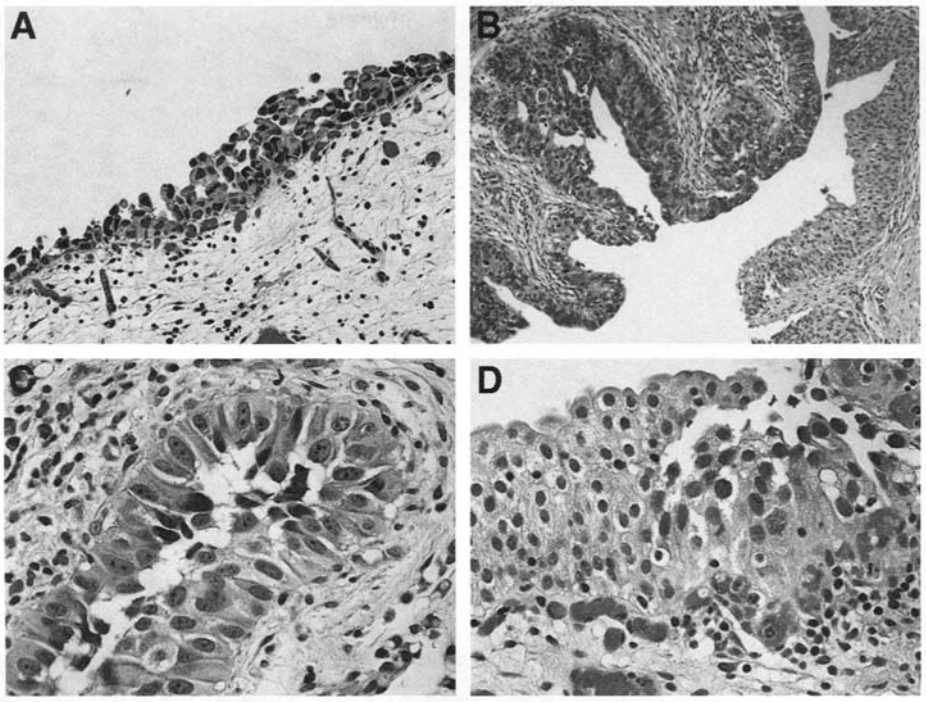


Fig. 31. Urothelial carcinoma *in situ* **(A–D)**.

- More common in men (M : F = 3 : 1)
- Presents with hematuria and irritative obstructive symptoms
- Risk factors include:
  - Smoking (four-fold higher risk)
  - Occupational exposure to certain organic compounds, especially benzadine and aromatic amines (up to 50-fold higher risk)
  - Cyclophosphamide treatment (estimated 10% absolute risk for treated patients)
  - Radiation (up to four-fold higher risk)
- Some tumors are readily amenable to transurethral resection, although there is a significant risk of recurrence
- The following are considered unfavorable prognostic factors **(Table 2)**:
  - Deletion of surface blood group antigen (ABO, H, Lewis)
  - Alteration of Thomser-Friedenreich (T) antigen
  - Marker chromosome (ring or A-1 chromosome)
  - Downregulation of $p21^{Waf1}$ and $p27^{Kip1}$
  - Upregulation of Cyclins D1 and D3
  - High tumor cell proliferation by Ki-67/MIB1
  - Aneuploidy
- Cytogenetic abnormalities:
  - Chromosome 9 and 17p deletion
  - p53 mutation
  - Trisomy 7
  - Structural anomalies of chromosomes 1 and 11

Macroscopic

- Single or multiple exophytic papillary masses **(Figure 35)**

Microscopic

- Exophytic growth pattern with thickened urothelium (>7 cell layers)
- Papillae with delicate fibrovascular cores
- Cells may appear nearly normal or show varying degrees of nuclear atypia (nuclear hyperchromasia, crowding, enlargement, pleomorphism, irregular contour, coarse granular chromatin, and prominent nucleoli) (see Grading)
- Foci of squamous or glandular differentiation (10% of cases, more common in high-grade carcinoma)
- Small to medium-sized tubules may be seen in otherwise typical urothelial carcinoma (tubulo-glandular pattern)
- Plasmacytoid changes of urothelial cells have been reported

*Grading **(Table 3; Figure 36)***

- Grading remains controversial
- 1973 WHO grading system still widely used in both pathology and urology community
- 2004 WHO/ISUP (former 1998 ISUP/WHO) classification is considered a work in progress
- Bladder cancer grading is subjective with substantial inter and intra-observer variability
- Substantial interobserver variability still exists using the new 1998 ISUP/WHO or 2004 WHO classification (J Urol, 168: 968, 2002; J Urol, 169: 1291, 2003; Virchows Arch 443: 734, 2003)

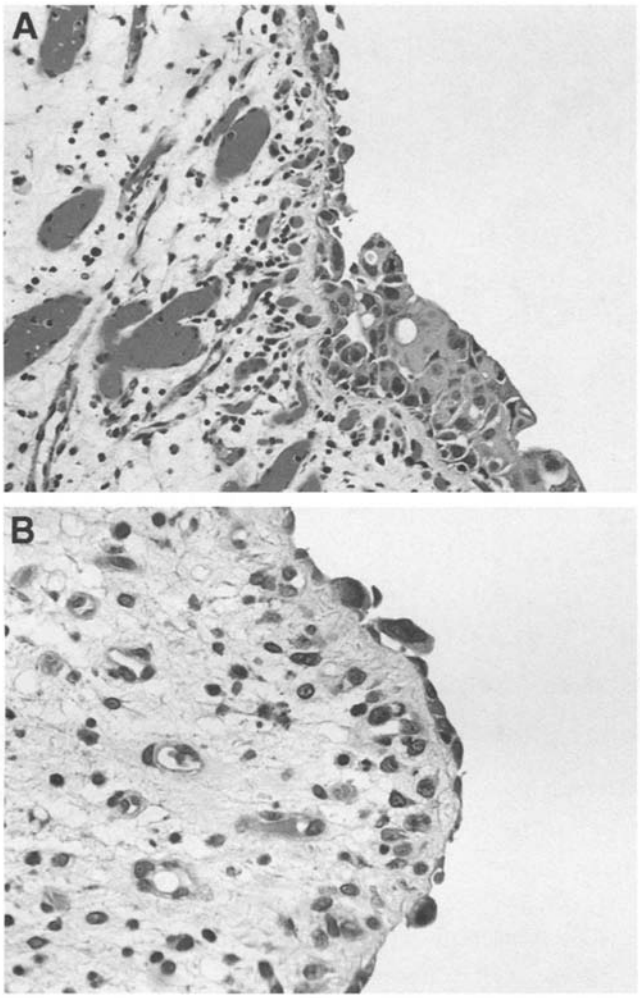


Fig. 32. Urothelial carcinoma *in situ*, clinging pattern **(A,B)**.

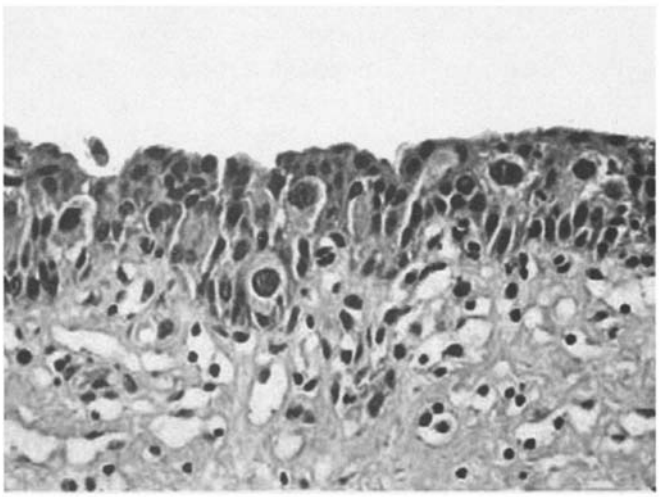


Fig. 33. Pagetoid spread of CIS.

- Agreement among pathologists on the diagnosis of papillary urothelial neoplasm of low malignant potential (PUNLMP) was 0% in one study (J Urol 169:1291, 2003)

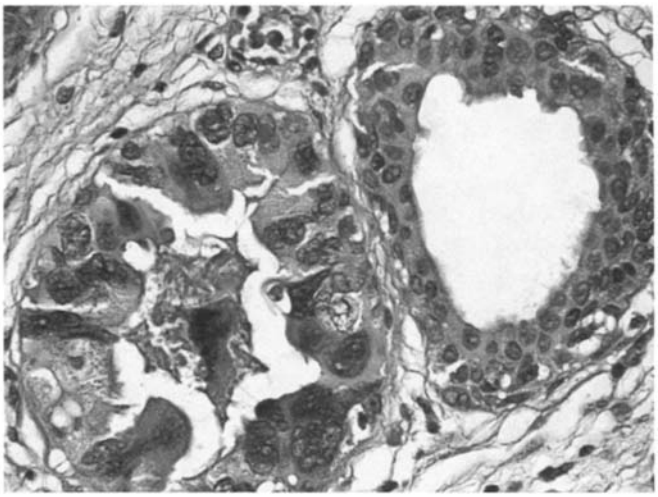


Fig. 34. Involvement of von Brunn's nest by CIS. This should not be interpreted as adenocarcinoma *in situ*.

Table 2. Current prognostic factors in bladder cancer specimens

- Histological grade
- Tumor extent (stage)
- Cancer size > 3 cm in diameter
- Depth of invasion (>1.5 mm) for T1 tumor
- Number of tumors
- Coexistent dysplasia or CIS
- Tumor growth pattern
- Vascular/lymphatic invasion
- Lymph node involvement
- Recurrence at 3 month follow-up cystoscopy
- Molecular markers (DNA ploidy, Ki67/MIB1, p53, RB, cadherins, p63, cyclin D1 and D3, etc)

- In another study, PUNLMP and low-grade urothelial carcinoma had a progression rate of 8% and 13%, respectively (Urology 15: 315, 2002)
- We prefer to use 1973 WHO classification at this time until validation of new classification is available
- Grading should be based on the worst area (highest grade) of the tumor:
  - Grade 1:
    - Most cases are designated as papillary urothelial neoplasm of low malignant potential in the 2004 WHO (former 1998 ISUP/WHO) classification
    - Thickened urothelium with normal architectural arrangement of cells

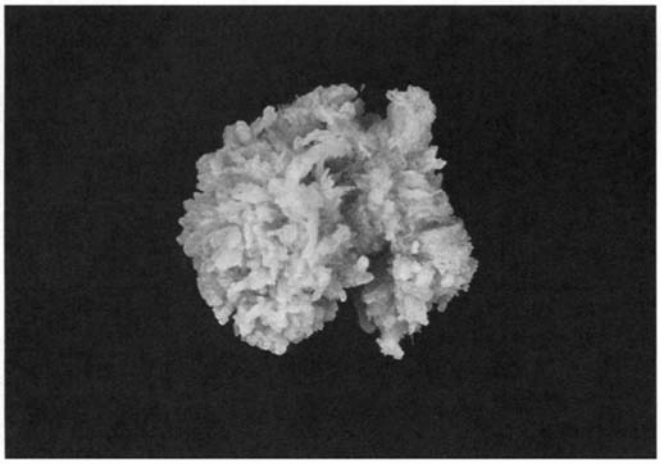


Fig. 35. Gross appearance of papillary urothelial carcinoma.

- Well-formed papillae with fibrovascular cores
- Superficial cells intact with preservation of cell polarity
- Slight nuclear enlargement, crowding, hyperchromasia, minimal nuclear pleomorphism
- Lacks mitotic figures, cytoplasmic vacuoles, or prominent nucleoli
- Diploid tumor, with absence of marker chromosome
- Low risk for invasion and metastasis
- Increased risk for developing recurrent or new papillary urothelial carcinoma

– Grade 2:
- Most are designated as low grade papillary urothelial carcinoma in the 2004 WHO classification
- Some degree of architectural irregularity and discohesion
- Disorderly maturation with variable loss of superficial cells
- Increased nuclear atypia and mitotic figures
- Loss of cytoplasmic homogeneity and clearing
- High risk of tumor recurrence
- Low risk of stage progression and metastasis

– Grade 3:
- Designated as high grade urothelial carcinoma in the 2004 WHO (former 1998 classification)
- Loss of normal architectural arrangement of cells
- Marked nuclear abnormalities with increased numbers of atypical mitotic figures
- Aneuploid tumor with marker chromosome (ring or A1)
- Loss of surface blood group antigen
- High tumor recurrence rate
- High risk of stage progression and metastasis

Differential Diagnosis ***(Table 3)***

♦ Urothelial papilloma:
- The urothelium lining the papillae are normal in thickness (<7 cell layers)
- Minimal or no cytologic atypia
- Small solitary lesion (<2 cm)
- Patient age <50 years
- Blunt rather than finger-like papillae
- Multiple layers of umbrella cells are often present

♦ Inverted papilloma:
- Well-circumscribed, confined within the lamina propria
- Orderly endophytic growth of anastomosing cords and trabeculae of benign-looking urothelial cells with an intact urothelium on the luminal surface
- Lacks central fibrovascular cores
- Peripheral palisading of basaloid cells
- The arborizing invaginations of urothelium are in continuity with the overlying mucosa
- Lacks cytologic atypia; occasional squamous differentiation

♦ Nephrogenic metaplasia:
- Well-circumscribed proliferation of small tubules with intervening stroma, single cell layer
- Confined to superficial lamina propria in an inflammatory stroma
- Lacks significant cytologic atypia

♦ Proliferative papillary cystitis (polypoid-papillary cystitis):
- Broad papillae with prominent inflammation and edema of the lamina propria
- Lacks cytologic atypia
- History of indwelling catheter or vesical fistula

Infiltrating Urothelial Carcinoma

Clinical

♦ Usually high-grade malignant urothelial neoplasm, stage T1-T4

♦ Risk factors and cytogenetic abnormalities similar to those of papillary carcinoma

Macroscopic ***(Figure 37)***

♦ Appears as a nodular or ulcerative mucosal lesion with infiltration of the tumor down toward the muscularis

Grading

♦ See papillary urothelial carcinoma. Most invasive carcinomas are high grade

Reporting of Biopsy Specimens ***(Tables 4,5)***

♦ Biopsy site

♦ Total weight of resected tissue fragments

♦ A minimum of 6 g or 3 cassettes should be submitted for TURB

Table 3. Grading of Urothelial Tumors

Characteristics	*Papilloma*	*Grade 1*	*Grade 2*	*Grade 3*
Cell layers	<7	>7	Variable	Variable
Umbrella cells	Present	Present	Usually present	May be absent
Polarization	Normal	Normal/slightly abnormal	Disordered	Disordered
Cytoplasm	Clear/homogenous	Clear/homogenous	Loss of homogeneity	Loss of Homogeneity
N/C ratio	Normal	Normal or slightly increased	Slightly increased	Increased
Nuclei Size	Normal	Normal or slightly increased	Enlarged with variation in size	Enlarged with variation in size
Borders	Regular/smooth	Regular/Smooth	Slight variation	Pleomorphic
Chromatin	Fine	Fine	Fine to granular	Coarse with hyperchromasia
Nuceoli	Absent	Small/absent	Small	Large
Necrosis	Absent	Absent	Absent	May be present
Mitotic figures	Absent	Rare/inconspicuous, at basal level	Present	Prominent

- Transurethral resection of the bladder (TURB): proportion of tissue embedded
- Cold-cup: record the number of pieces, dimensions (mm), and presence of papillary growth
- Histopathologic type of carcinoma
- Grade
- Papillary vs. nonpapillary
- Presence or absence of muscularis propria (detrusor muscle)
- Invasion, including depth of invasion (lamina propria vs. muscularis propria) and extent (focal vs. extensive):
  - Muscularis mucosa is variable, and is optional for reporting
  - Inner and outer half of muscularis propria invasion cannot be reliably discerned in biopsy specimens; substaging is not recommended
  - The term "superficial (or deep) invasion" should be discouraged (imprecise)
  - Ocular measurement of depth of invasion for T1 tumor provides additional prognositic information (J Clin Oncol 17: 3182, 1999)
- Vascular invasion
- Presence or absence of urothelial dysplasia and carcinoma *in situ*
- Associated conditions (e.g., nephrogenic metaplasia)
- Ancillary studies (e.g., DNA ploidy, p53 status, chromosome markers)

Reporting of Cystectomy Specimens ***(Tables 4,5)***

- Histopathologic type of carcinoma
- Grade: see grading of papillary urothelial carcinoma
- Papillary vs. nonpapillary
- Location of cancer
- Tumor size
- Multifocality
- Invasion, including depth of invasion:
  - Lamina propria invasion
  - Muscularis propria invasion, inner half vs. outer half
- Surgical margins:
  - Urethral margin
  - Ureteral margins
  - Perivesical soft tissue margins
- Perivesical soft tissue involvement
- Vascular invasion
- Presence or absence of urothelial dysplasia and carcinoma *in situ*
- Lymph node status:
  - Anatomic sites
  - Number of nodes sampled
  - Number of positive nodes
  - Largest dimension of positive nodes
- Involvement of adjacent organs:
  - Prostate:
    - Non-invasive urothelial carcinoma of the prostatic urethra
    - Invasive urothelial carcinoma
  - Vagina and uterus

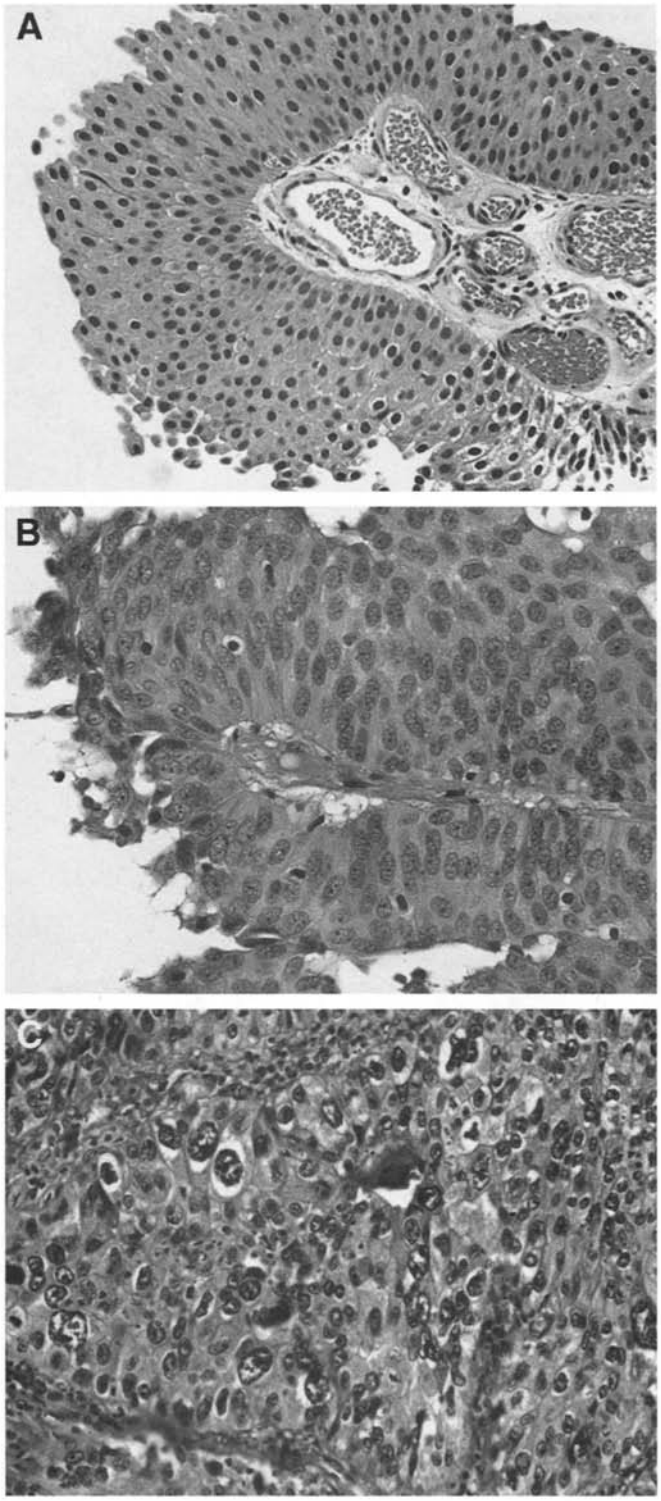


Fig. 36. Grading of urothelial carcinoma, **(A)** grade 1; **(B)** grade 2; **(C)** grade 3.

- Associated conditions (e.g., cystitis glandularis)
- Ancillary studies (e.g., DNA ploidy, p53 status, chromosome markers)
- Pathologic stage

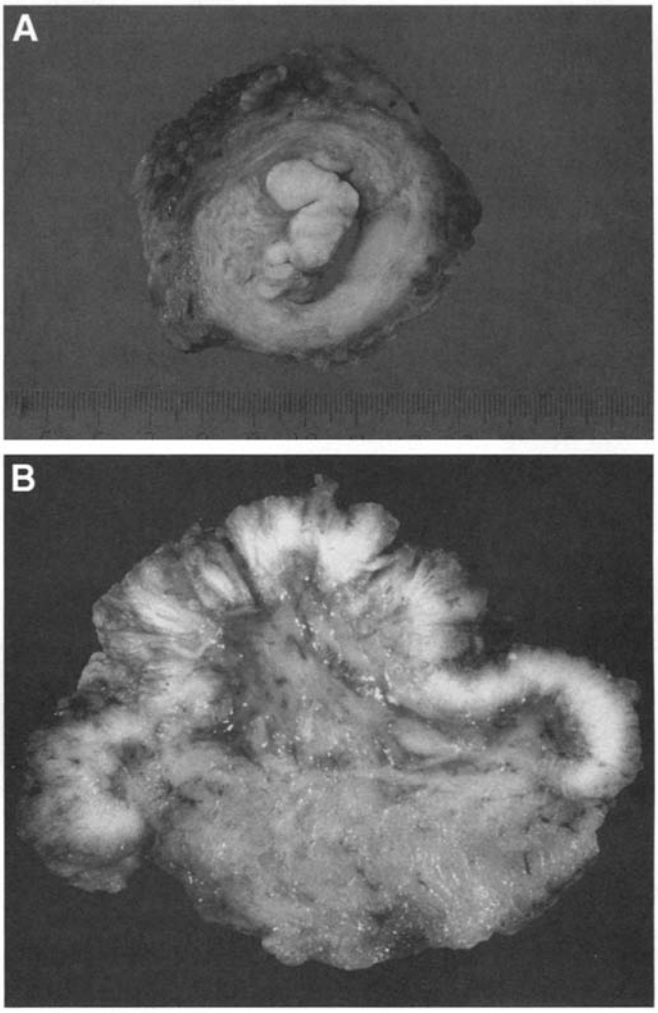


Fig. 37. Gross appearance of urothelial carcinoma. Cystectomy **(A)** and partial cystectomy **(B)** specimens.

Microscopic ***(Figure 38)***

- Islands and trabeculae of tumor cells infiltrating into the lamina propria and muscularis propria
- Large round cells with hyperchromatic, pleomorphic irregular nuclei
- Cells with abundant eosinophilic or clear cytoplasm
- Mitotic figures are numerous
- Areas of squamous or glandular differentiation may be seen in some cases because of divergent differentiation
- Virtually the whole spectrum of bladder cancer variants may be seen accompanying otherwise typical urothelial carcinoma
- Depth of invasion
- The most important element in pathologic evaluation of urothelial cancer is the presence and extent of invasion
- In T1 carcinoma, nests, clusters or single cells are within the papillary core or lamina propria **(Figure 39)**

Table 4. Practice parameters for handling and reporting bladder specimens with cancer (Checklist)

General information

- Pertinent clinical information: name, medical record number, data, referring physician, relevant clinical history past and present.

Gross description

- Fresh or fixed specimen
- Nature of the specimens: biopsy, chips (TURB), partial cystectomy, radical cystectomy, cystoprostatectomy, "En bloc" resection.
- Total weight of resected tissue fragments (TURB); three dimensional measurements of recognizable anatomic structures and tumors or other recognizable lesions
- Site of involvement, gross fat extension

Diagnostic and prognostic information

- Histologic tumor type: urothelial, squamous, adenocarcinoma, other
- Tumor grade: use current grading schemes (WHO 2004, WHO 1973, or both)
- Extent of tumor in bladder (degree of invasion)
  - No invasion
  - *Invasion of the suburothelial connective tissue (provide ocular measurement for T1 tumor), muscularis propria, perivesical tissue
  - Presence or absence of lymphatic/vascular invasion
  - Tumor arising in a diverticulum (state whether muscularis propria is present)
- Intraepithelial abnormalities (dysplasia, CIS)
  - Report focality or multifocality
  - Report presence of pagetoid spread of CIS
- Ureter and urethra: Report any dysplastic/neoplastic change of the mucosa, and report any invasion into adjacent suburothelial connective tissue or muscularis propria
- Extent of tumor in organs attached to the bladder
- Prostate: direct extension to the prostate, involvement of prostatic urethra, involvement of prostatic ducts with or without stromal involvement
- Seminal vesicles: report spread of carcinoma in these organs either through epithelium or by direct extension of an infiltrative tumor
- Vagina/uterus: report direct extension or metastasis to either organ
- Surgical margins:
  - Report status of ureteral/urethral margins
  - Report perivesical margin involvement
- Lymph nodes: report presence or absence of metastasis. If metastases are present state number and size of the largest one (<2.0 cm, 2.1 to 5 cm, >5 cm)

Features considered optional in the final report

- Invasion of the muscularis mucosa, if present
- Genetic abnormalities
- Cytometric examination
- Morphometric examination
- p53, Ki-67
- Growth factors and receptors
- Other immunohistochemical markers

**Immunohistochemistry may be useful in selected cases using either cytokeratin for suburothelial connective tissue invasion or vascular endothelial markers for vascular invasion.*

Table 5. Histologic type of tumors of the urinary bladder (WHO, 2004)

- Urothelial Tumors
  - Urothelial hyperplasia
  - Urothelial dysplasia
  - Urothelial papilloma
  - Inverted papilloma
  - Papillary urothelial neoplasia of low malignant potential
  - Non-invasive papillary urothelial carcinoma, low grade
  - Non-invasive papillary urothelial carcinoma, high grade
  - Urothelial carcinoma *in situ*
  - Invasive carcinoma
    - Variants
      - With squamous differentiation
      - With glandular differentiation
      - With trophoblastic differentiation
      - Nested
      - Microcystic
      - Micropapillary
      - Lymphoepithelioma-like
      - Lymphoma-like and plasmocytoid
      - Sarcomatoid
      - Giant cell
      - Clear cell (glycogen-rich)
      - Lipoid-cell
      - Undifferentiated
- Squamous Neoplasms
  - Squmaous cell carcinoma
  - Verrucous squamous cell carcinoma
  - Squamous cell papilloma
- Glandular Neoplasms
  - Adenocarcinoma
  - Urachal adenocarcinoma
  - Clear cell adenocarcinoma
  - Villous adenoma
- Neuroendocrine Tumors
  - Small cell carcinoma
  - Paraganglioma
  - Carcinoid
- Soft Tissue Tumors
  - Rhabdomyosarcoma
  - Leiomyosarcoma
  - Angiosarcoma
  - Osteosarcoma
  - Malignant fibrous histiocytoma
  - Leiomyoma
  - Granular cell tumor
  - Neurofibroma
  - Hemangioma
  - Malignant Melanoma
  - Lymphoma
- Metastatic tumors and secondary extension

- In microinvasive carcinoma, the invasive tumor cells may acquire abundant eosinophilic cytoplasm, a feature known as paradoxical differentiation **(Figure 40)**
- Recognizing the level of invasion may be problematic because of tangential sectioning, thermal artifact or marked inflammatory infiltrate that obscures the neoplastic cells
- Reporting of the level of muscularis mucosae invasion is not recommended
- Ocular measurement of the depth of invasion for pT1 tumor provides important prognostic information
- 5-year progression-free survival for patients with depth of invasion ≥1.5 mm was 67%, compared with 93% for those with depth of invasion <1.5 mm (J Clin Oncol 10: 3128, 1999)
- Immunohistochemistry with cytokeratin antibodies can help in difficult cases with marked inflammation or thermal artifact
- Thermal artifact can hamper the interpretation of muscularis propria invasion
- The presence of tumor cells and fat in transurethral resection specimens does not necessary mean extravesical extension since fat may be present in the lamina propria

Immunohistochemistry

- See **Tables 6,7**

Histologic Variants of Urothelial Carcinoma

Urothelial Carcinoma with Mixed Differentiation:

- Squamous differentiation **(Figure 41A)**:
  - Defined by the presence of intercellular bridges or keratinization
  - Occurs in 21% of urothelial carcinomas of the bladder
  - Frequency increases with grade and stage
  - These cases may have a less favorable response to therapy than pure urothelial carcinoma

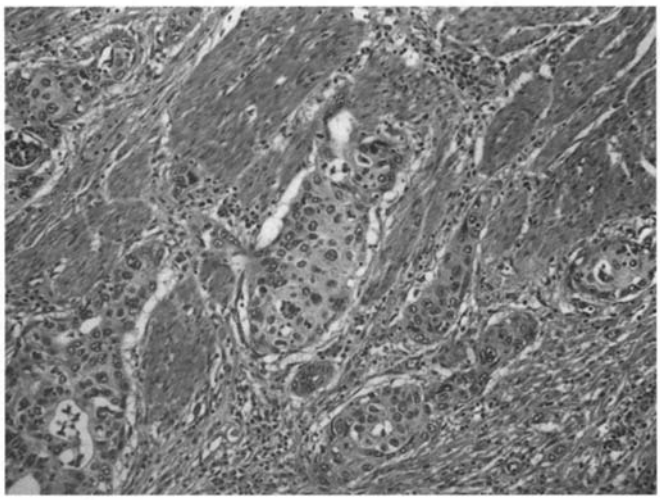


Fig. 38. Urothelial carcinoma with muscularis propria invasion.

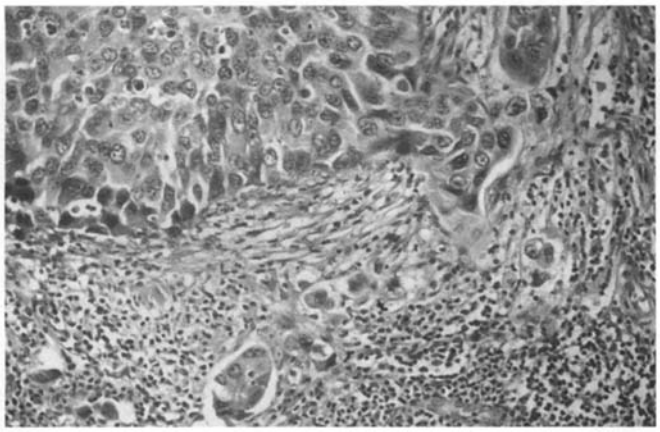


Fig. 39. Infiltrating urothelial carcinoma, pT1.

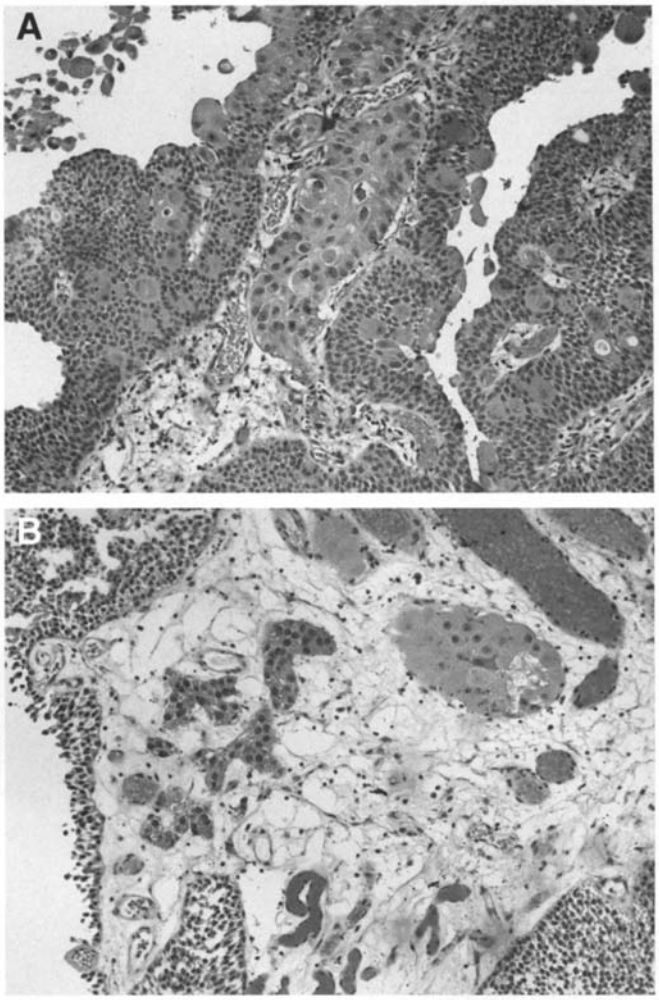


Fig. 40. Paradoxical differentiation in pT1 cancer. The invading nests have a greater amount of eosinophilic cytoplasm **(A,B)**.

- The diagnosis of squamous cell carcinoma is reserved for pure lesions without any associated urothelial component, including urothelial carcinoma *in situ*
- Squamous differentiation may show basaloid or clear cell features

♦ Glandular differentiation **(Figure 41B)**:

- Less common than squamous differentiation
- May be present in about 6% of urothelial carcinomas of the bladder
- Defined as the presence of true glandular spaces within the tumor
- These may be tubular or enteric glands with mucin secretion
- A colloid-mucinous pattern characterized by nests of cells "floating" in extracellular mucin occasionally with signet ring cells may be present
- The diagnosis of adenocarcinoma is reserved for pure tumors
- The clinical significance of glandular differentiation and mucin positivity in urothelial carcinoma remains uncertain

Micropapillary Variant (Figure 42)

♦ M : F = 5 : 1; mean age = 67 years

♦ Associated with high-stage cancer and poor prognosis

♦ Require >50% of the tumor show a micropapillary pattern for diagnosis

♦ Micropapillary growth with delicate filiform processes or small papillary cell clusters, resembling serous papillary carcinoma of female genital tract

♦ Retraction artifact with "halos"

♦ High nuclear grade

♦ Recent studies suggest that it might be a morphologic variant of adenocarcinoma

Nested Variant (Figure 43)

♦ Highly aggressive

Table 6. Common Patterns of Cytokeration 7 and 20 Immunostaining in Various Cancers

	CK7	*CK 20*
Urothelial carcinoma*	+	+
Prostatic adenocarcinoma	–	–
Clear cell renal cell carcinoma	–	–
Ovarian serous and endometrioid adenocarcinoma	+	–
Ovarian mucinous tumors*	+	+
Uterine endometrial adenocarcinoma	+	–
Breast ductal and lobular adenocarcinoma	+	–
Breast colloid adenocarcinoma	+	–
Colorectal and appendiceal adenocarcinoma**	–	+
Gastric adenocarcinoma	±	+
Pancreatic adenocarcinoma*	+	+
Hepatocellular adenocarcinoma	–	–
Small cell carcinoma	–	–
Lung adenocarcinoma	+	–
Lung squamous cell and neuroendocrine carcinoma	–	–
Mesothelioma	+	–

** Common cytokeratin 7+/cytokeratin 20+ tumors; **Cytokeratin 7-/cytokeratin 20+ pattern is uncommon in other tumors.*

Table 7. Immunohistochemical Profiles of Spindle Cell Lesions of the Bladder

	CK	*SMA/MSA/desmin*	*EMA*	*Vimentin*	*ALK-1*
Post-operative spindle cell nodule	–/+	+/–	–	+	Not tested
Inflammatory myofibroblastic tumor	–/+	+/–	–	+	+
Malakoplakia and caruncle	–	–	–	+	–
Sarcomatoid carcinoma	+	–	+	+	–
Leiomyosarcoma	–	+	–	+	–
Lymphoepithelioma-like carcinoma	+	–	+	+	–

Note: CK = cytokeratin; SMA = smooth muscle actin; MSA = muscle-specific actin; EMA = epithelial membrane antigen; ALK1=Anaplastic lymphoma kinase 1.

- Irregularly distributed and compact nests of atypical cells in the lamina propria, mimicking von Brunn's nests
- Infiltrative growth
- Some nests have small tubular lumens
- Deep portions of the tumor often show typical urothelial carcinoma
- Often lacks intervening stroma (in contrast to von Brunn's nests)

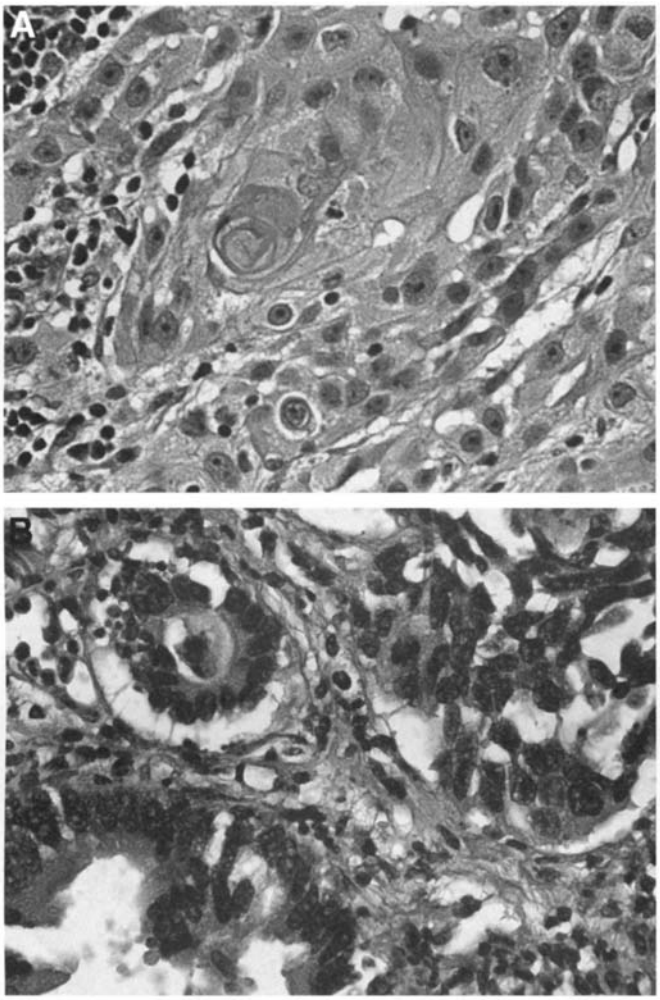


Fig. 41. Urothelial carcinoma with mixed differentiation. **(A)** Squamous differentiation; **(B)** Glandular differentiation.

- Cells have nuclear pleomorphism and prominent nucleoli
- Inconspicuous mitotic figures
- Low $p27^{kip1}$ expression and high proliferation rate

Microcystic Variant (Microglandular Variant) (Figure 44)

- Microcystic change in typical urothelial carcinoma with eosinophilic secretions, necrotic debris, or mucin
- Multiple small cystic spaces lined by atypical urothelial cells

Inverted Papilloma-Like Carcinoma (Inverted Variant) (Figure 45)

- Potential for misinterpretation as inverted papilloma (benign tumor)
- By definition, this variant has significant nuclear pleomorphism, mitotic figures, and architectural abnormalities consistent with low- or high-grade urothelial carcinoma
- In most cases, the overlying epithelium has similar abnormalities of typical urothelial carcinoma

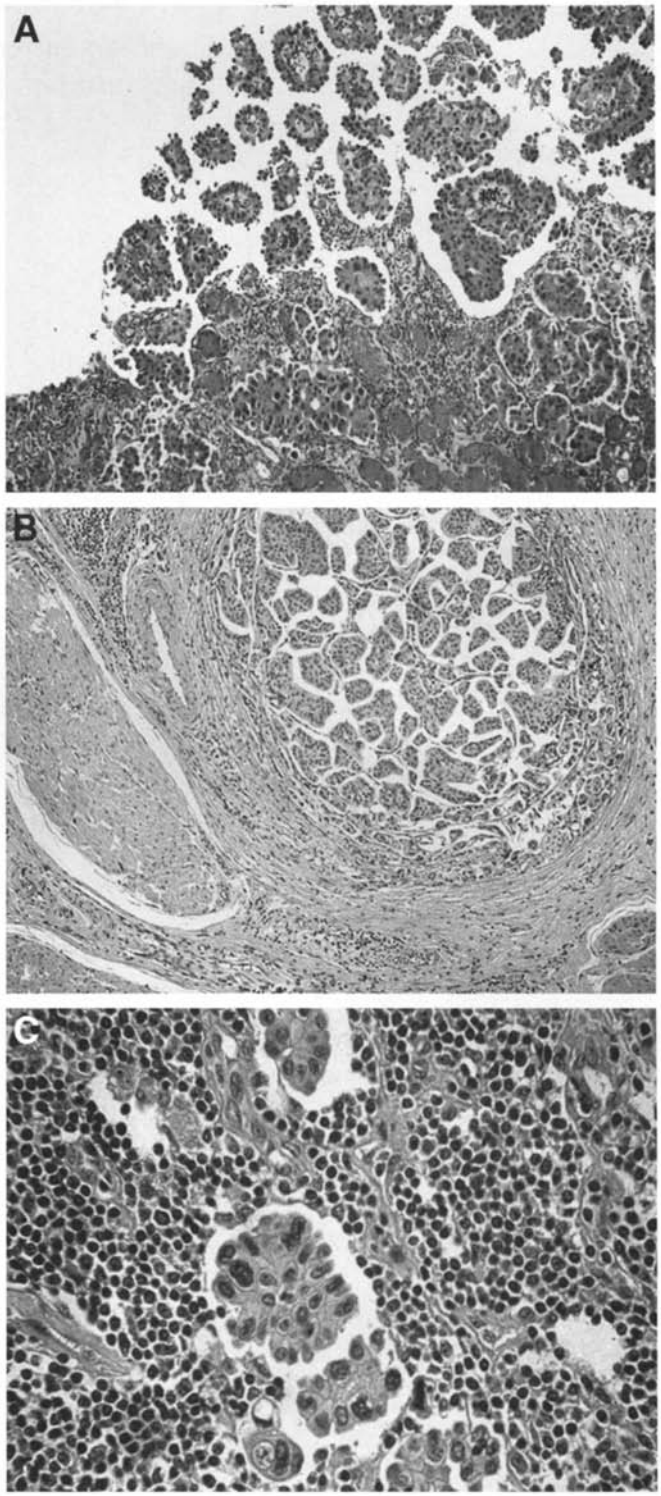


Fig. 42. Urothelial carcinoma, micropapillary variant. Surface **(A)**, bladder wall **(B)**, and lymph note metastasis **(C)**.

- An exophytic papillary or invasive component is often associated with the inverted type
- In large papillary tumors with prominent endophytic growth; these carcinomas "invade" the lamina propria with a pushing border

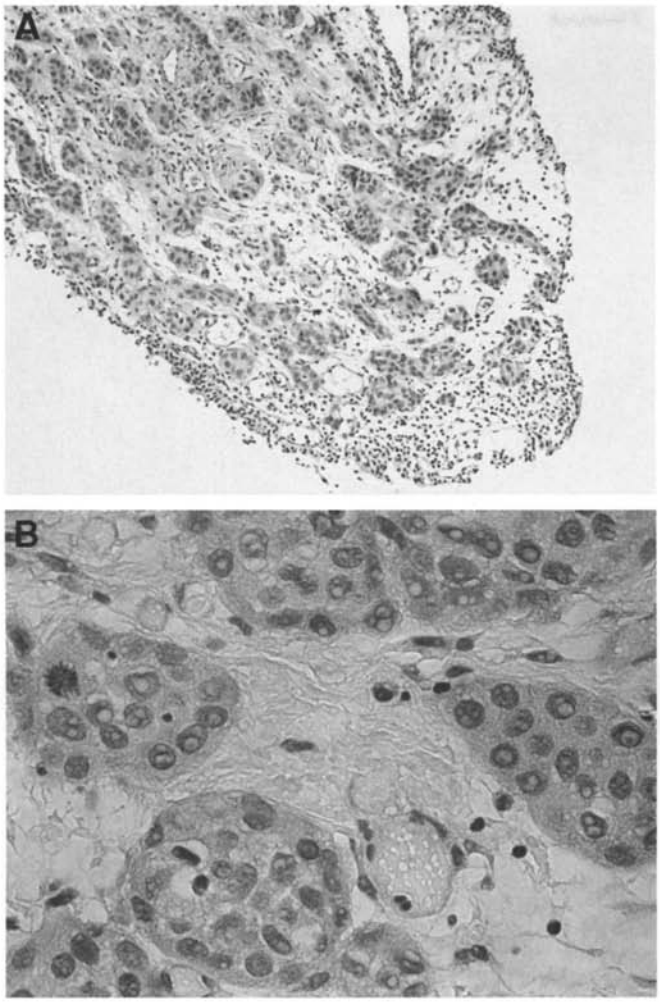


Fig. 43. Urothelial carcinoma, nested variant. Low (**A**) and high (**B**) power views.

- Endophytic growth with anastomosing cords and trebeculae of urothelial cells
- Thick and irregular column with loss of polarity
- Lacks peripheral palisading of basaloid cells in contrast to inverted papilloma
- Cytologic atypia and invariable mitotic figures
- Foci of keratinization may be present
- Unless this pattern is accompanied by true destructive stromal invasion the likelihood of metastasis is minimal, because the basement membrane is not truly breached
- Immunohistochemistry: low-to-high proliferation rate (Ki67-MIB1) and variable p53 reactivity

Lymphoepithelioma-Like Carcinoma (Figure 46)

Clinical

- Occurs in elderly patients (mean age = 69 years), M : F = 3 : 1
- Presents with hematuria
- Rarely associated with Epstein-Barr viral infection
- Pure tumors respond well to chemotherapy. Mixed tumors behave as the associated urothelial component

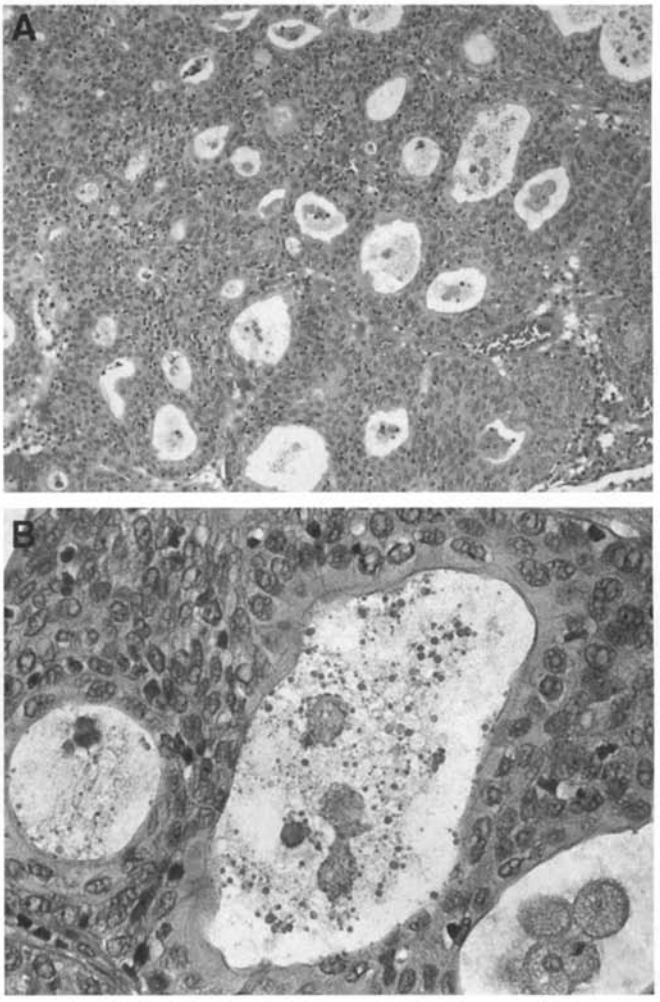


Fig. 44. Urothelial carcinoma, microcystic variant. Low (**A**) and high (**B**) power views.

Macroscopic

- Infiltrating or fungating mass in the dome, posterior wall, or trigone

Microscopic

- Syncytial sheets and nests of large round to polygonal cells with abundant basophilic to clear cytoplasm and indistinct cell borders (cytokeratin+)
- Enlarged nuclei with nuclear pleomorphism, irregular nuclear membranes, coarse granular chromatin, and large prominent nucleoli
- Heavy inflammatory infiltrate composed predominantly of lymphocytes, histiocytes, and plasma cells. Neutrophils and eosinophils may be prominent

Immunohistochemistry

- Cytokeratin+

Lymphoma-Like and Plasmacytoid Variant (Figure 47)

- Tumor cells are medium-sized, with eosinophilic cytoplasm and eccentric nuclei producing a plasmacytoid appearance

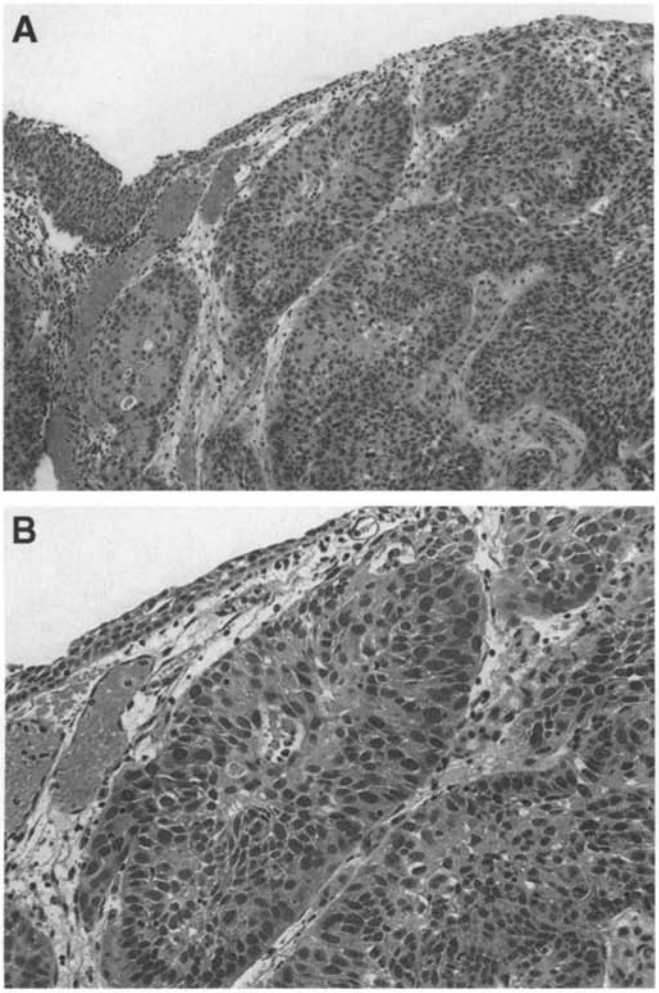


Fig. 45. Urothelial carcinoma, inverted variant **(A,B)**.

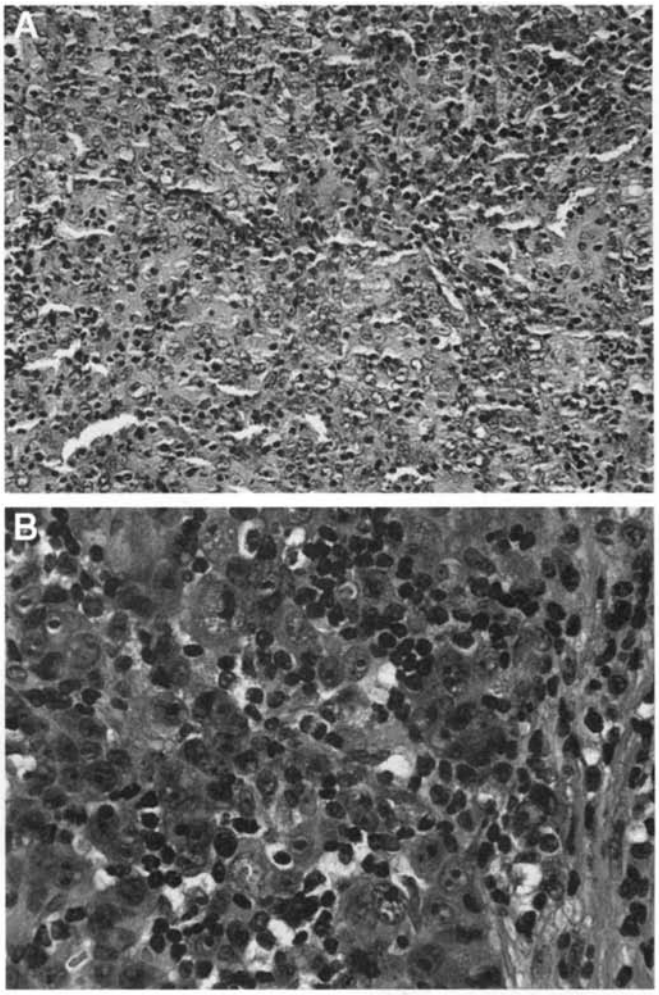


Fig. 46. Urothelial carcinoma, lymphoepithelioma-like variant **(A,B)**.

- Differential diagnostic considerations include lymphoma (plasmacytoid type) and multiple myeloma
- Tumor cells are cytokeratin+

Urothelial Carcinoma, Clear Cell (Glycogen-Rich) Variant (Figure 48)

- Two-thirds of cases of urothelial carcinoma have foci of clear cell change resulting from abundant glycogen
- The clear cell "variant" of urothelial carcinoma appears to represent the extreme end of the morphologic spectrum, consisting predominantly or exclusively of cells with abundant clear cytoplasm
- Recognition of this pattern avoids confusion with clear cell adenocarcinoma of the bladder and metastatic clear cell carcinoma of the kidney and prostate
- Clear cell change is relatively more common in poorly differentiated urothelial carcinoma
- Cytokeratin 7+

Urothelial Carcinoma, Lipoid Cell Variant (Figure 49)

- Rare urothelial carcinoma which exhibits transition to a cell type resembling signet-ring lipoblasts
- Male, 63-to-94 (mean 74) years with gross hematuria
- The lipoid cell pattern varied from 10%-to-30% of the specimen
- Epithelial phenotype of the lipoid cell component with cytokeratins+

Undifferentiated Carcinoma

- This category contains tumors that cannot be otherwise classified
- Extremely rare

Urothelial Carcinoma with Giant Cells (Giant Gell Carcinoma) (Figure 50)

- High grade urothelial carcinoma may appear undifferentiated resembling giant cell carcinoma of the lung
- Rare and with poor prognosis, similar to giant cell carcinoma in the lung
- The differential diagnosis includes giant cells associated with trophoblastic differentiation, osteoclast-type giant cells in invasive urothelial carcinoma, sarcomatoid carcinoma with giant cells, and metastatic giant cell carcinoma to the bladder
- Giant cells are cytokeratin+

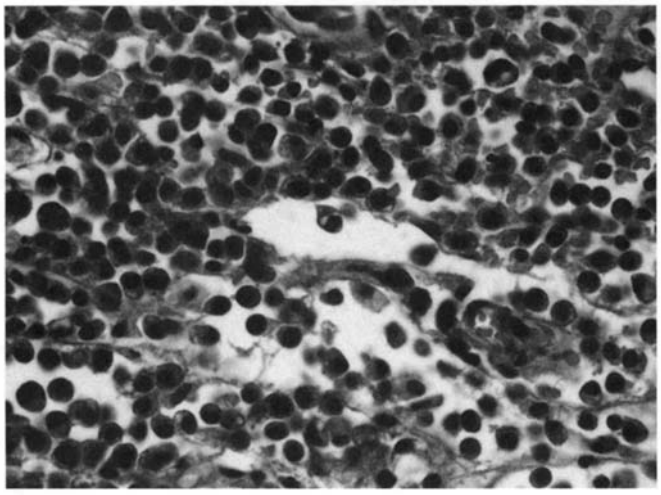


Fig. 47. Urothelial carcinoma, plasmacytoid variant.

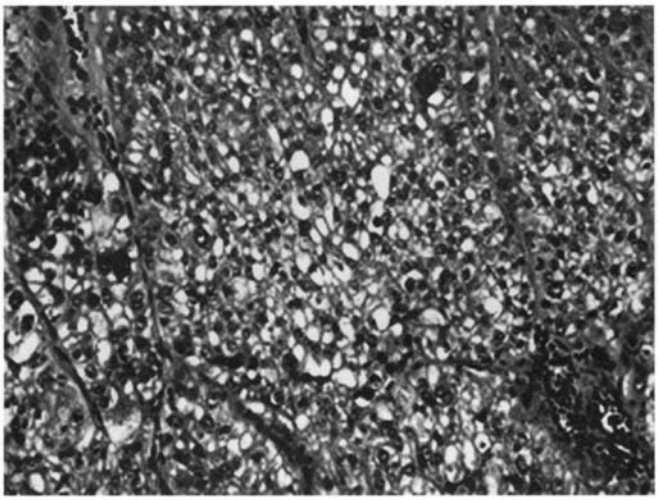


Fig. 48. Urothelial carcinoma, clear cell (glycogen-rich) variant.

Urothelial Carcinoma with Syncytiotrophoblasts (UC with Trophoblastic Differentiaion) (Figure 51)

- The presence of syncytiotrophoblasts may be associated with a poor prognosis and most cases are of high grade and stage
- The prognostic significance of human chorionic gonadotropin (hCG) immunoreactivity is uncertain

Urothelial Carcinoma with Osteoclast-Type Giant Cells

- Cytokeratin– (giant cell carcinoma: cytokeratin +), CD68+

Urothelial Carcinoma with Pseudosarcomatous Stroma (Figure 52)

- Atypical spindle stromal cells with abundant eosinophilic cytoplasm and bizarre hyperchromatic degenerative nuclei
- Inconspicuous nucleoli
- Stromal cells cytokeratin–, EMA–, CEA–, vimentin+, actin+

Urothelial Carcinoma with Stromal Osseous or Cartilaginous Metaplasia

- Lacks cytologic atypia: in the metaplastic stroma

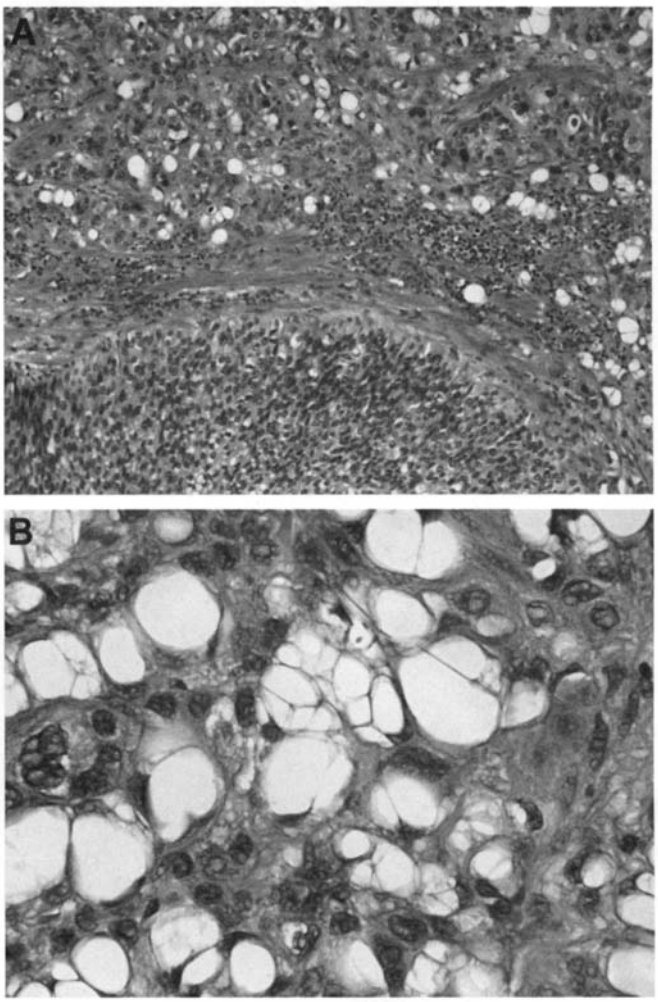


Fig. 49. Urothelial carcinoma, lipoid cell variant as compared with conventional urothelial carcinoma **(A)**. High power view of lipoid cells **(B)**.

Squamous Cell Carcinoma

Clinical

- Represents <5% of bladder carcinomas in Western countries
- M = F, often presents with advanced cancer stage
- Grading is of little prognostic significance
- Associated with infection by *Schistosoma haematobium,* and, consequently, represents >70% of bladder carcinomas in endemic countries
- Schistosomiasis-associated squamous cell carcinoma may have better prognosis than nonschistosomal counterpart
- Other risk factors include:
  - Recurrent bladder infection
  - Diverticuli
  - Calculi (vesical lithiasis)
  - Indwelling catheter in patient with nonfunctioning bladder
  - History of urethral stricture
  - Renal transplantation

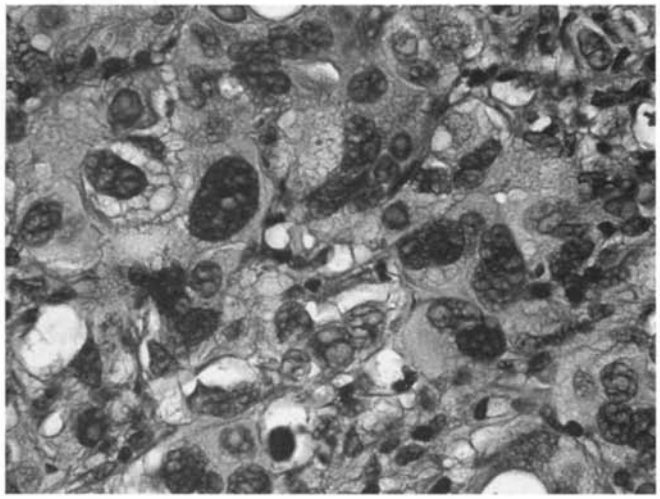


Fig. 50. Urothelial carcinoma, giant cell variant.

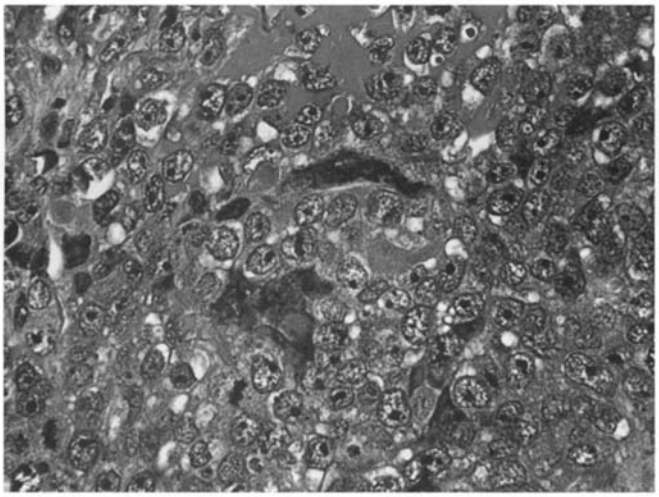


Fig. 51. Urothelial carcinoma with trophoblastic differentiation.

Macroscopic

- Exophytic or infiltrative ulcerative nodular, white-tan mass, solitary
- Frequently shows multiple small areas of necrosis

Microscopic ***(Figure 53)***

- Infiltrating tongues of large polygonal squamous cells with distinct cell borders, intercellular bridges, and abundant eosinophilic cytoplasm
- Dyskeratotic cells with nuclear pleomorphism, hyperchromasia, and coarsely granular chromatin
- Frequent mitotic figures and areas of necrosis
- Well-differentiated neoplasms may demonstrate keratin pearls
- Often associated with keratinizing squamous metaplasia
- Schistosoma eggs may be seen in epidemic areas **(Figure 53C)**

Variants: Verrucous Carcinoma

- Rare, low-grade tumor

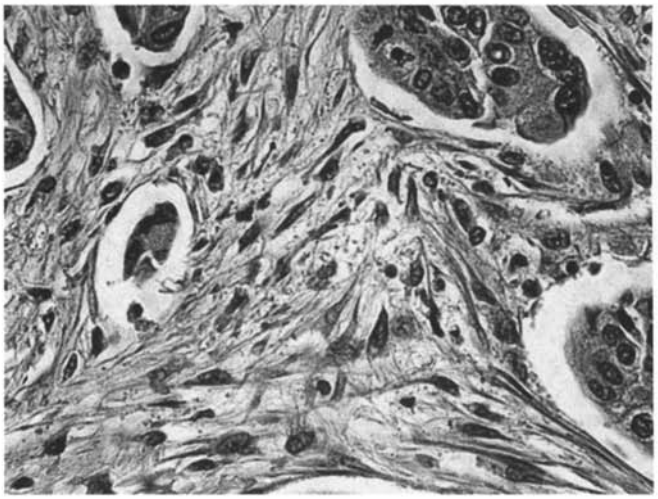


Fig. 52. Urothelial carcinoma with pseudosarcomatous stroma.

- May undergo transformation to aggressive anaplastic carcinoma after radiation therapy
- Composed of well differentiated squamous epithelium with complex papillary and exophytic growth and invasive bulbous broad rete ridges **(Figure 54)**

Differential Diagnosis

- Urothelial carcinoma:
  - Non-papillary urothelial carcinoma may show areas of squamous differentiation
  - Careful sampling of the tumor will usually show areas of typical urothelial cell differentiation
  - In populations with low incidence of squamous cell carcinoma of the bladder (i.e., Western countries), sample tumor carefully for evidence of urothelial features
  - The findings of squamous metaplasia or squamous dysplasia of the bladder epithelium support the diagnosis of squamous cell carcinoma

Adenocarcinoma

Clinical

- Uncommon malignant glandular neoplasm, which accounts for approximately 1% to 2% of bladder cancer
- M : F = 2 : 1, elderly patients (mean age = 58 years)
- May arise from urachal elements or from metaplastic urothelium
- No prognostic difference between urachal and non-urachal adenocarcinoma
- Associations with exstrophy, patent urachus, schistosomiasis, bladder augmentation, and neurogenic bladder has been documented
- Presenting symptoms similar to other bladder carcinomas (hematuria and irritative symptoms) but also demonstrates mucosuria in up to 25% of cases
- Advanced cancer stage at presentation

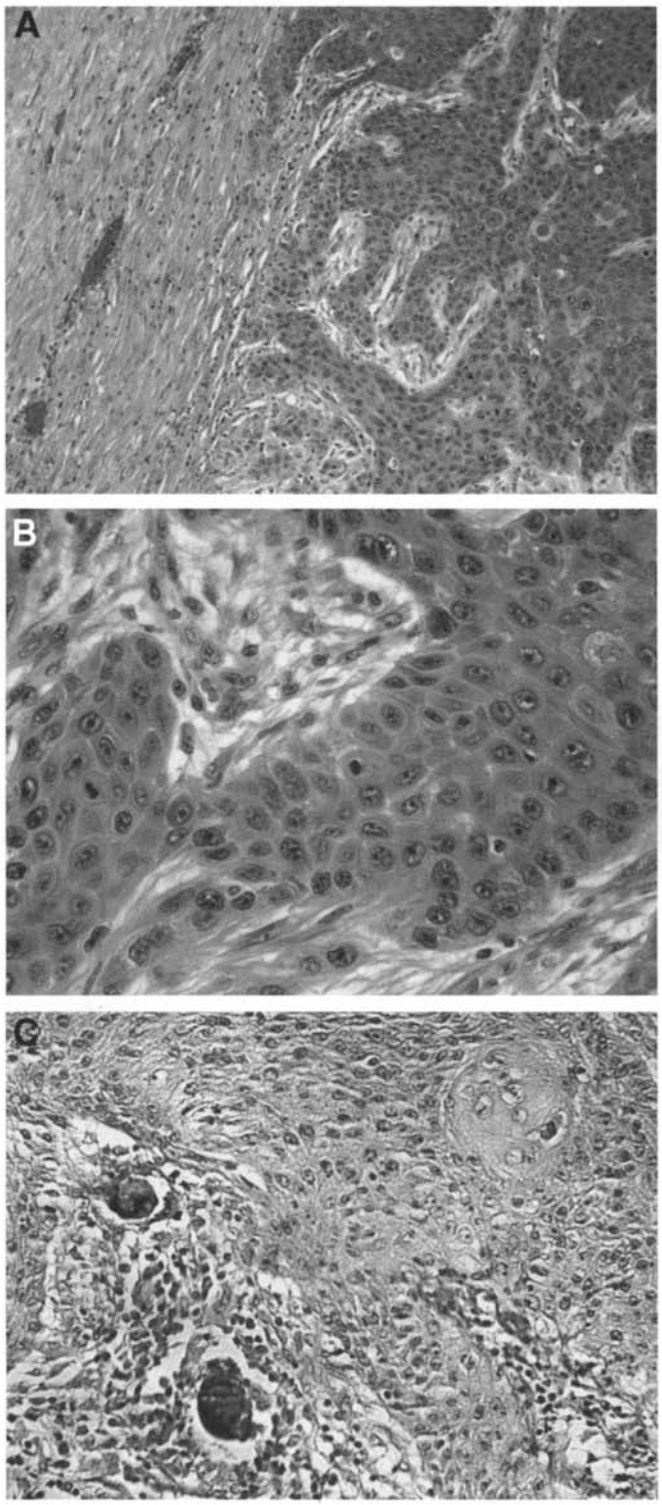


Fig. 53. Squamous cell carcinoma (**A–C**). Calcified *Schistosoma haematobium* eggs are seen (**C**).

- Non-urachal adenocarcinoma (**Figure 55**):
  - May be found anywhere in the bladder with a predilection for trigone and lateral wall

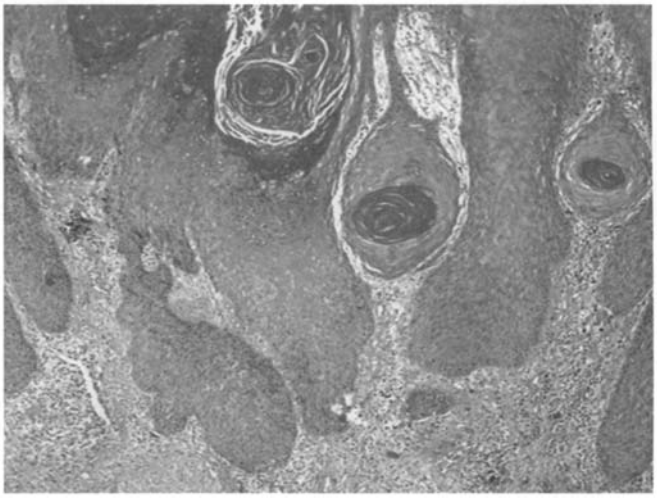


Fig. 54. Verrucous squamous cell carcinoma.

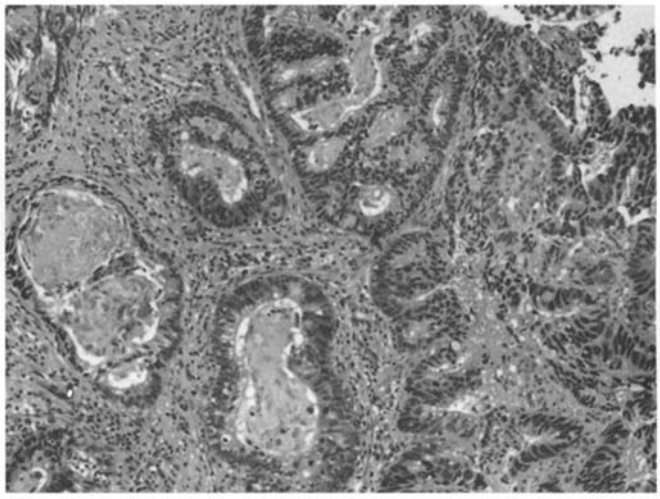


Fig. 55. Non-urachal adenocarcinoma.

- Grossly, exophytic papillary growth or infiltrative fungating mass
- Urachal adenocarcinoma (**Figure 56**):
  - Exclusion of adenocarcinoma elsewhere
  - Located in the dome and anterior wall
  - Predominantly involving the muscularis propria rather than lamina propria
  - Intact overlying normal mucosa or ulcerated urothelium with sharp demarcation from the underlying tumor
  - Absence of intestinal metaplasia, cystitis cystica, or cystitis glandularis in dome
  - Usually occurs in younger patients (M >F, mean age = 50 years)
  - Urachal remnant connected with cancer
  - May extend toward the umbilicus in the space of Retzius
  - Treatment: partial cystectomy with en bloc resection of entire length of urachal-median umbilical ligament, including umbilicus

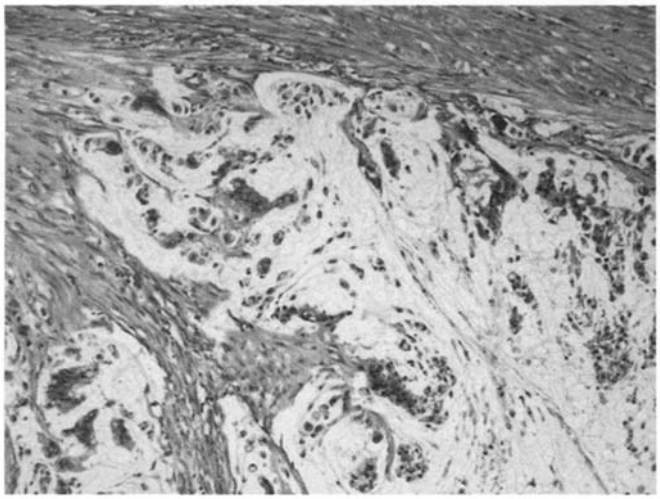


Fig. 56. Urachal mucinous adenocarcinoma.

Macroscopic

- Bulging intramural infiltrative or polypoid masses

Variants

- Mucinous (colloid) adenocarcinoma:
  - Island of tumor cells suspended in mucinous lake
  - More commonly seen in tumors of urachal origin
- Signet ring cell carcinoma:
  - Worst prognosis; >50% of patients dead of cancer within 1 year of diagnosis
  - Composed of signet ring cells with intracytoplasmic mucin
  - Infiltrative growth with prominent desmoplasia
- Papillary adenocarcinoma:
  - Composed of tall columnar cells lining papillae with variable mucin production

Differential Diagnosis

- Villous adenoma:
  - Histologically identical to villous adenoma of the colon
  - Nuclear crowding, overlapping, and atypia, but no invasion
- Nephrogenic metaplasia:
  - Well-circumscribed proliferation of compact tubules
  - Confined to superficial lamina propria in an inflammatory stroma
  - Lacks significant cytologic atypia
- Cystitis glandularis:
  - Often co-exists with von Brunn's nests and cystitis cystica
  - Well-circumscribed and confined to the lamina propria
  - Lacks cytologic atypia
  - Difficult differential diagnosis in cases of florid cystitis glandularis

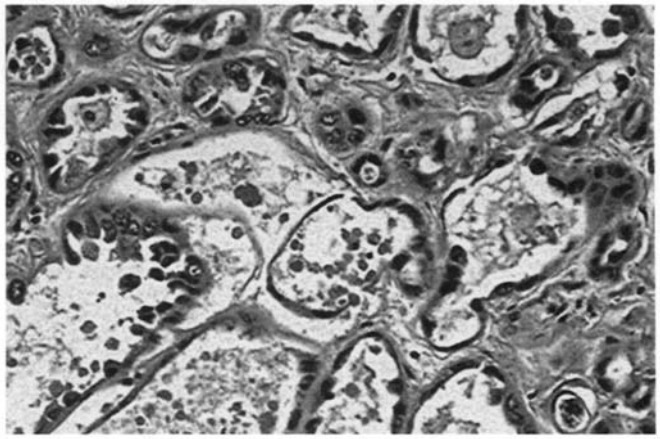


Fig. 57. Clear cell carcinoma.

- Mullerianosis:
  - Occurs in women of reproductive age (37–46 years)
  - Small lesion, located in the posterior wall of the bladder
  - Proliferation of tubules and cysts lined by endocervical-type epithelium and tubal epithelium (ciliated cells, peg cells, and intercalated cells).
  - Some cases associated with endometriosis
  - Lacks cytologic atypia and prominent mucin extravasation

Clear Cell Carcinoma (Mesonephric Carcinoma)

Clinical

- Often occurs in older patients (>35 years, mean = 58 years), with female predilection
- More commonly seen in the urethra, especially in diverticulae
- Unknown histogenesis, possibly Müllerian origin
- Aggressive course

Macroscopic

- Papillary or sessile infiltrative mass in trigone and neck

Microscopic

- Infiltrative growth of cysts, trabeculae, fine papillae, and tubules lined by clear cells with hobnail appearance **(Figure 57)**
- Tubules contain eosinophilic secretions
- Cells have moderate amount of clear to eosinophilic cytoplasm (glycogen+)
- Mitotic figures are frequent

Immunohistochemistry

- Cytokeratin+, EMA+, CEA±

Differential Diagnosis

- Nephrogenic adenoma:
  - Occurs in younger patients with male predominance
  - Associated with predisposing factors such as long-standing irritative events

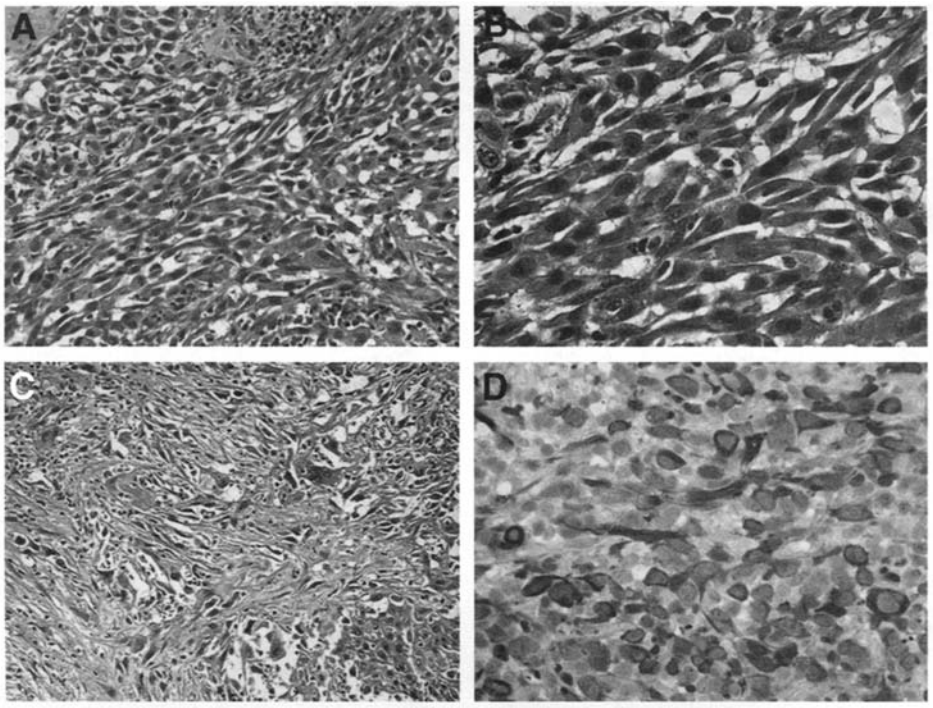


Fig. 58. Sarcomatoid carcinoma **(A–C)**. Cytokeratin staining was positive **(D)**.

- Small, well-circumscribed, and confined to the lamina propria
- Lacks mitotic figures or necrosis
- Cytokeratin+, EMA+, CEA–

Sarcomatoid Carcinoma (Metaplastic Carcinoma; Carcinosarcoma with Homologous Elements)

Clinical

- Occurs in elderly patients (mean age = 67 years), M : F = 4 : 1
- Highly aggressive, mean survival = 10 months
- No prognostic difference in comparison to carcinosarcoma with heterologous elements
- Pathologic stage is the main predictor of survival
- Presents with hematuria and irritative symptoms
- Some patients had history of radiation therapy for unrelated causes

Macroscopic

- Polypoid or nodular mass

*Microscopic (**Figure 58**)*

- Diffuse infiltration of malignant spindle cells
- Urothelial carcinoma is most commonly recognized epithelial component, followed by squamous cell carcinoma
- Necrosis and hemorrhage

*Immunohistochemistry (**Table 7**)*

- Cytokeratin+

Small Cell Carcinoma

Clinical

- Occurs in elderly men, highly aggressive
- Accounts for 0.5% of bladder cancer
- Often (50%) associated with invasive urothelial carcinoma or CIS
- Pure form occurs in ~50% of cases
- May present with paraneoplastic syndrome (ectopic ACTH production-Cushings syndrome, hypercalcemia, and hypophosphatemia)

Macroscopic

- Fungating, infiltrative or ulcerative mass

*Microscopic (**Figure 59**)*

- Sheets and cords of small cells with high N/C ratio, nuclear hyperchromasia, and inconspicuous nucleoli
- Tumor necrosis and crush artifact

Immunohistochemistry

- Neuroendocrine markers are positive, with dot-like cytokeratin positivity
- TTF-1 frequently +
- Uroplakin and CK20 are often negative

Villous Adenoma

Clinical

- Benign glandular epithelial neoplasm
- Often associated with urachal adenocarcinoma, but may be seen elsewhere in the bladder

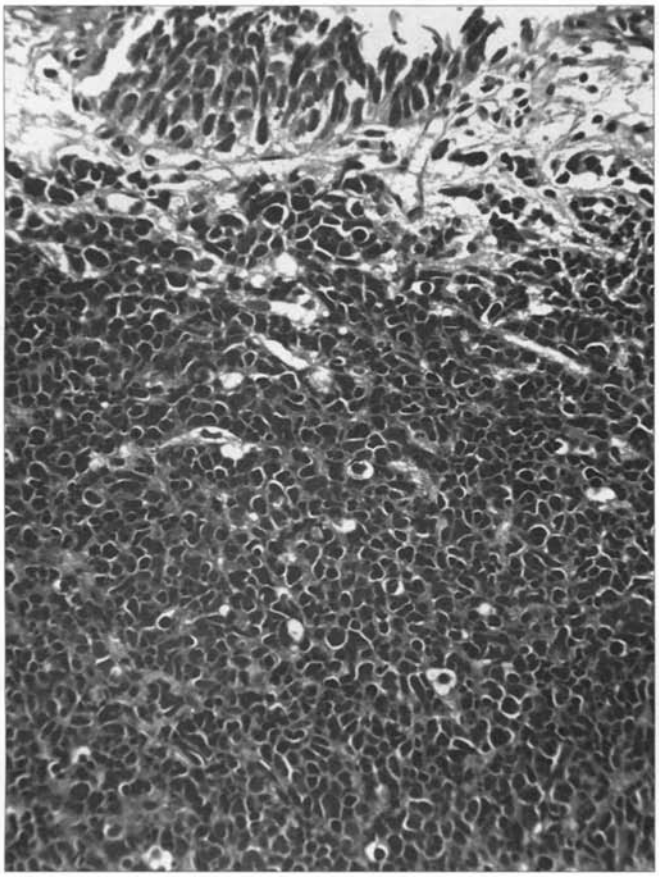


Fig. 59. Small cell carcinoma.

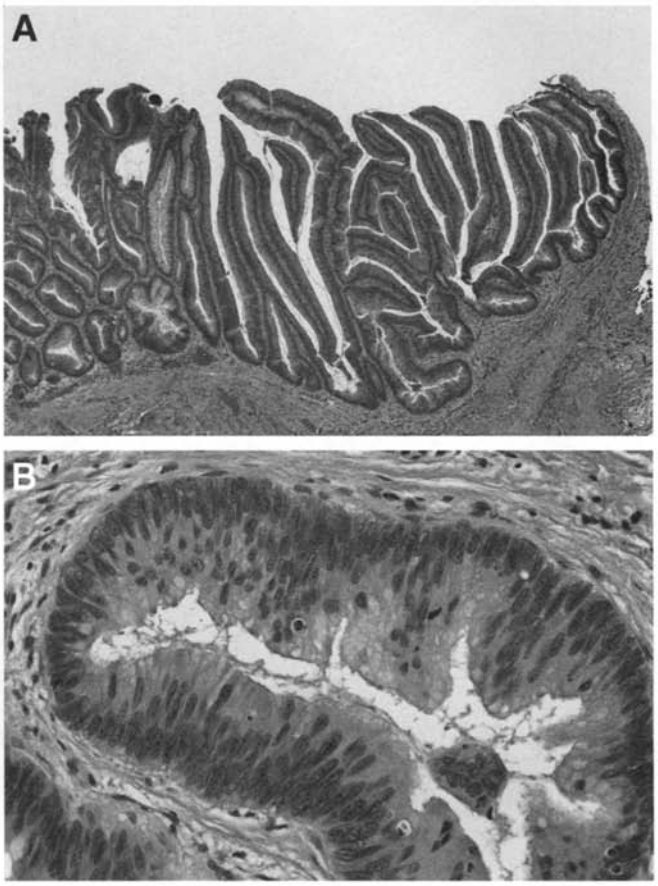


Fig. 60. Villous adenoma **(A,B)**.

Macroscopic

- Exophytic papillary or polypoid tumor

*Microscopic **(Figure 60)***

- Histologically identical to villous adenoma of the colon
- Columnar mucinous cells and goblet cells lining delicate fibrovascular stalks
- Nuclear stratification, crowding, and nuclear hyperchromasia

Differential Diagnosis

- Adenocarcinoma:
  - Significant nuclear atypia, numerous mitotic figures, and invasion

SOFT TISSUE TUMORS

BENIGN

Leiomyoma (Figure 61)

- Occurs in adults, M : F = 1 : 2
- Presents with irritative obstructive symptoms
- Grossly, polypoid or pedunculated submucosal mass
- Well-circumscribed, lacks significant cytologic atypia
- Inconspicuous mitotic figures

Hemangioma

- Often occurs in young adults (<30 years) with slight male predominance
- Presents with gross hematuria and obstructive symptoms
- Small, well-circumscribed lesion composed of dilated vascular channels
- Three types have been recognized: capillary (**Figure 62**), cavernous, and arteriovenous type (Cheng et al. Cancer 86:498, 1999)

Neurofibroma (Figure 63)

- Usually occurs in young patients with neurofibromatosis type I
- The mean age at diagnosis is 17 years, M : F = 2.3 : 1
- Clinical symptoms include hematuria, irritative voiding syndrome, and pelvic mass

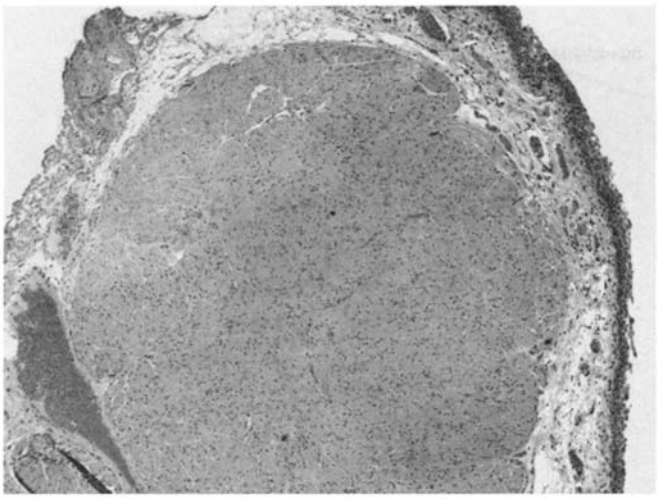


Fig. 61. Submucosal leiomyoma.

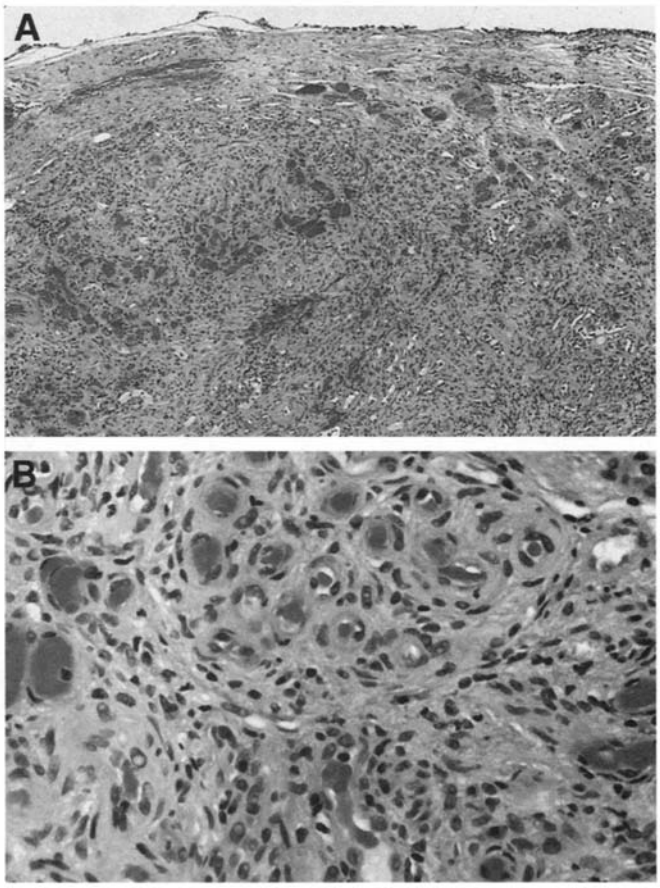


Fig. 62. Hemangioma, capillary type **(A,B)**.

- Histologically, the tumors are usually of the plexifrom and diffuse type
- Proliferation of spindle cells with ovoid or elongate nuclei in an Alcian blue positive, variably collagenized matrix
- S-100 protein+

Malignant

Leiomyosarcoma

Clinical

- Most common sarcoma of the bladder
- M>F; elderly patients (60–70 years old)

Macroscopic

- Large bulging polypoid mass in the dome and lateral wall
- Hemorrhage and necrosis

Microscopic (Figure 64)

- Interlacing fascicles of spindle cells with blunt-ended nuclei
- Deeply infiltrative growth pattern with destructive muscle invasion
- Cytologic atypia, mitotic figures, hemorrhage, and necrosis
- Inflammatory myxoid background with fine vasculature may be seen
- Smooth muscle differentiation rather than myofibroblastic differentiation

Immunohistochemistry

- See **Table 7**

Differential Diagnosis

- Inflammatory myofibroblastic tumor:
  - Small lesion with circumscribed margin
  - Lacks significant cytologic atypia
  - Lacks necrosis
  - More pronounced inflammatory response

Rhabdomyosarcoma

Clinical

- Occurs predominantly in infants and children, with male predominance
- 20% of childhood embryonal rhabdomysarcomas occur in the genitourinary system, and 25% of these occur in the bladder

Macroscopic

- Multiple broad-based bulging polypoid grape-like masses
- Predilection for trigone and prostatic urethra

Microscopic (Figure 65)

- Sheets and cords of primitive small cells with high N/C ratio, nuclear hyperchromasia
- Variable rhabdomyoblasts with or without cross-striations
- The cambium layer of rhabdomyoblasts beneath the surface in the botryoid variant

Immunohistochemistry

- Desmin+, muscle specific actin+, myoglobin+, myogenin+, MyoD1+, LCA–

Carcinosarcoma (Sarcomatoid Carcinoma with Heterologous Elements)

Clinical

- Occurs in elderly patients (mean age = 66 years), M : F = 2 : 1
- Highly aggressive, mean survival = 17 months

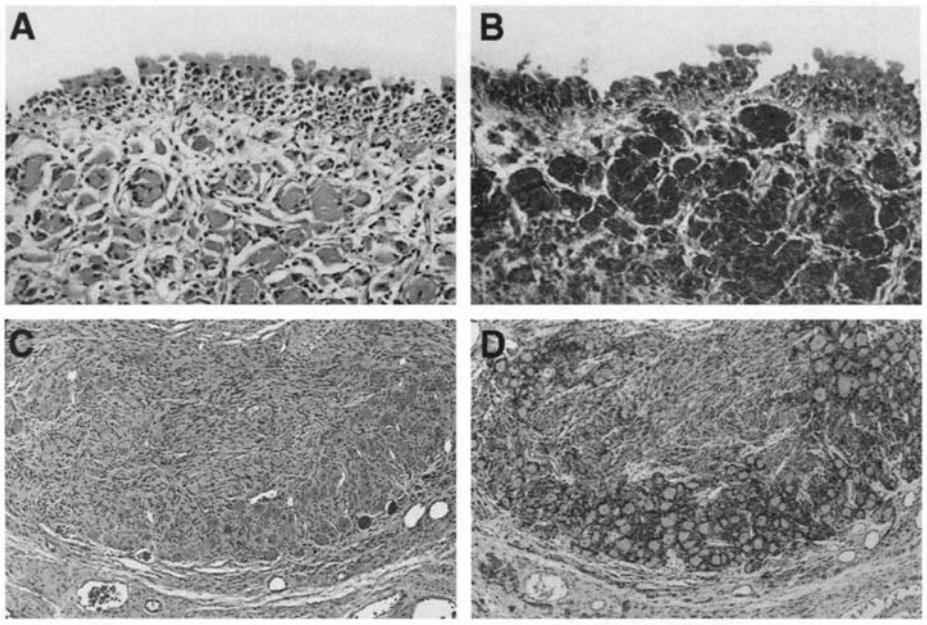


Fig. 63. Neurofibroma. Superficial, bandlike subepithelial, pseudo-Meissnerian corpuscles are prominent **(A)**. These peudo-Meissnerian corpuscles are immunoreactive for S-100 protein **(B)**. Ganglion cells show involvement with neurofibroma **(C)**. S-100 protein immunostaining is diffusely positive **(D)**.

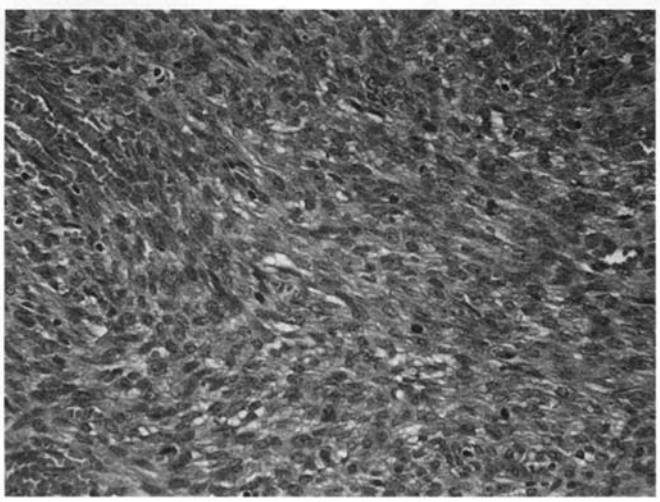


Fig. 64. Leiomyosarcoma.

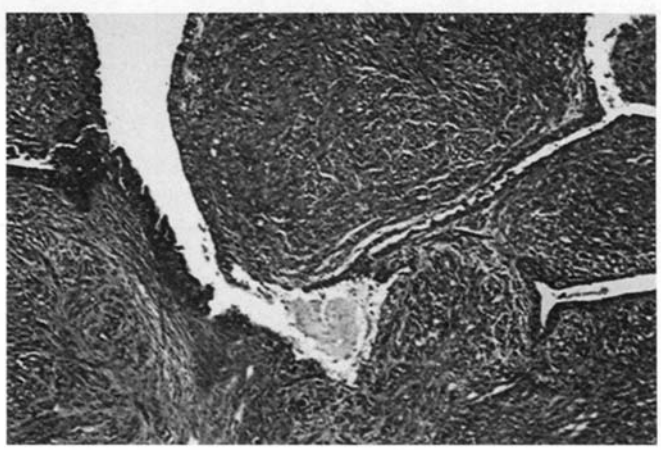


Fig. 65. Rhabdomyosarcoma.

- ♦ Pathologic stage is the main predictor of survival
- ♦ Presents with hematuria and irritative symptoms

Macroscopic

- ♦ Polypoid or nodular mass

Microscopic

- ♦ Biphasic tumors composed of carcinoma and distinct heterologous nonepithelial sarcomatous components
- ♦ Infiltrative sheets of anaplastic spindle cells and identifiable epithelial components merge imperceptibly
- ♦ Urothelial carcinoma is the most commonly recognized epithelial component, followed by squamous cell carcinoma or adenocarcinoma
- ♦ Heterologous elements (bone, cartilage, or skeletal muscle)
- ♦ The most common sarcomatous elements are chondrosarcoma, osteosarcoma, leiomyosarcoma, and malignant fibrous histiocytoma (undifferentiated sarcoma)
- ♦ Necrosis and hemorrhage

Immunohistochemistry

- ♦ Cytokeratin+ (in the epithelial component)

MISCELLANEOUS

Lymphoma

♦ *See* also Chapter 7

Clinical

♦ Female predominance in primary lymphoma (M : F = 1 : 5, mean age = 56 years); slight male predominance in secondary lymphoma (mean age = 50 years)

♦ Presents with hematuria and irritative symptoms

♦ Median survival of primary lymphoma is 9 years and secondary lymphoma is 6 months

♦ Criteria for the diagnosis of primary bladder lymphoma:

- Presenting symptoms related to bladder involvement
- No involvement of adjacent tissue
- Absence of involvement of liver, spleen, lymph node, peripheral blood, and bone marrow within 6 months of the diagnosis
- The dome and the trigone are the most common sites involved

Microscopic

♦ Low-grade lymphoma of the muscosa-associated lymphoid tissue (MALT) type is the most frequent type of primary bladder lymphoma

♦ Diffuse large cell lymphoma is the most common type of secondary lymphoma

♦ The histology of the MALT-type lymphoma is similar to those from other sites, and is characterized by centrocyte-like cells with irregular nuclear contours, clumped chromatin, and abundant pale to clear cytoplasm

Paraganglioma (Pheochromocytoma) (Figure 66)

♦ Slight female predominance (M : F = 1 : 1.4); usually occurs in young patients (<50 years)

♦ >80% of cases are functional

♦ May present with hematuria and hypertension during voiding, cystoscopic examination, and biopsy

♦ Small (<3 cm), dome-shaped nodules covered by normal mucosa, usually located in the trigone or dome

♦ Histologically similar to paraganglioma of other body sites, with intact urothelium

♦ Chromogranin is characteristically positive

♦ S100 protein highlights flattened sustentacular cells

♦ Some urothelial carcinomas may mimic morphologically paraganglioma in transurethral resection specimens

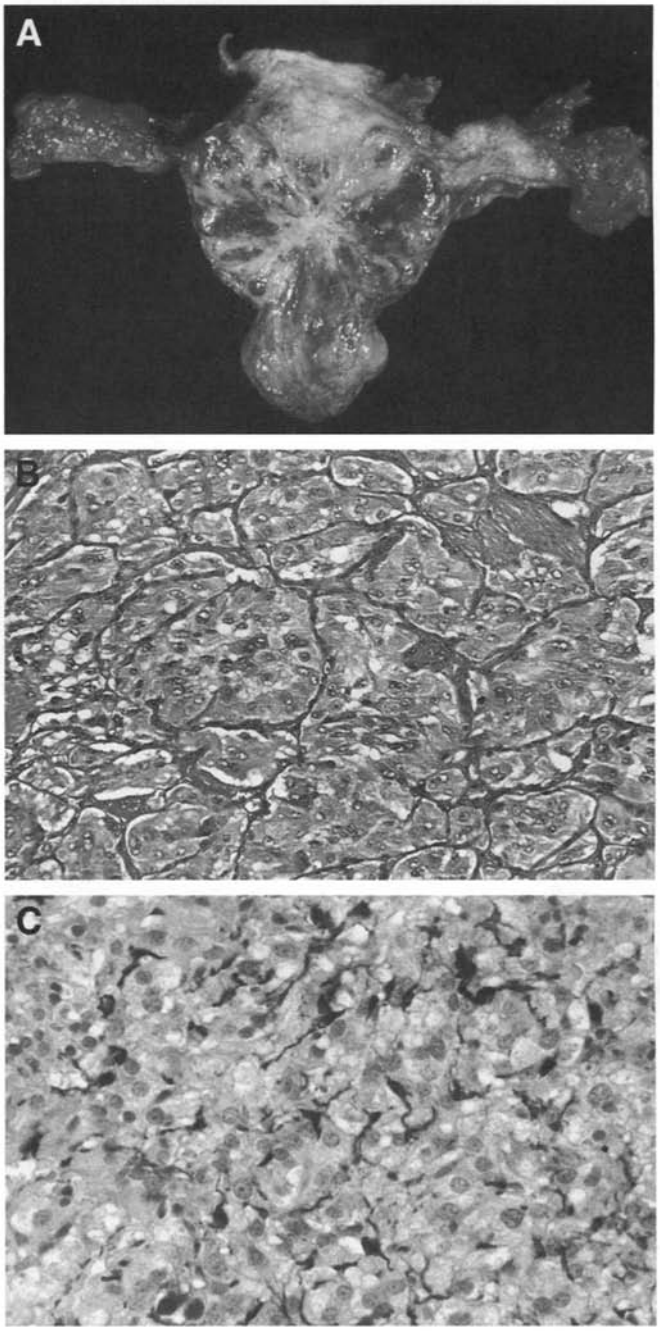


Fig. 66. Paraganglioma. **(A)** Gross appearance; **(B)** Typical zellballen growth pattern is seen; **(C)** Sustentacular cells are highlighted by S-100 protein immunostainings.

Carcinoid

♦ Usually occurs in elderly patients (mean age, 56 years; range, 29–75 years)

♦ Slight male predominance (M : F = 1.8 : 1)

♦ Hematuria is the most common presentation

♦ Submucosal location with a predilection for the trigone

♦ The tumor cells have abundant eosinophilic cytoplasm and finely stippled chromatin

♦ Arranged in an insular, acinar, trabecular or pseudoglandular pattern in a vascular stroma

♦ Neuroendocrine markers are positive

Clear Cell Myomelanocytic Tumor

- Member of the family of perivascular epithelioid cell tumors
- One case reported arising from the muscularis propria of the urinary bladder in a 33-year-old woman; this patient has been free of the disease since the excision of the tumor 6 years ago
- Clear to eosinophilic, epithelioid, and spindled cells arranged in fascicles or packets
- Delicate vascular stroma among the nests
- Immunohistochemically HMB-45+, smooth muscle actin+, S-100 protein–, Melan-A–, desmin–, and pan-cytokeratin–.

TNM CLASSIFICATION OF BLADDER CANCER (2002 REVISION)

Primary Tumor (T): Urinary Bladder

- TX: Primary tumor can not be assessed
- T0: No evidence of primary tumor
- Ta: Papillary non-invasive carcinoma
- Tis: Carcinoma *in situ*: "flat tumor"
- T1: Tumor invades sub-epithelial connective tissue
- T2: Tumor invades muscle
  - T2a: Tumor invades superficial muscle (inner half)
  - T2b: Tumor invades deep muscle (outer half)
- T3: Tumor invades perivesical tissue
  - T3a: Microscopically
  - T3b: Macroscopically (extra-vesical mass)
- T4: Tumor invades any of the following: prostate, uterus, vagina, pelvic wall, and abdominal wall
  - T4a: Tumor invades prostate or uterus or vagina
  - T4b: Tumor invades pelvic wall or abdominal wall

The suffix "m" should be added to the appropriate T category to indicate multiple tumors. The suffix "is" may be added to any T to indicate the presence of associated carcinoma *in situ*

Regional Lymph Nodes (N)

- NX: Regional Lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Metastases in a single lymph node, 2cm or less in greatest dimension
- N2: Metastases in a single lymph node, more than 2 cm but not more than 5 cm in greatest dimension, or multiple lymph nodes, none more than 5 cm in greatest dimension
- N3: Metastasis in a lymph node more than 5 cm in greatest dimension

Distant Metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

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31

Prostate

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CONTENTS

I. Inflammatory Lesions 31-3
Acute Bacterial Prostatitis 31-3
Chronic Bacterial and Non-Bacterial Prostatitis 31-3
Granulomatous Prostatitis 31-3

II. Benign Lesions and Mimics of Adenocarcinoma 31-4
Benign Prostatic Hyperplasia 31-4
Stromal Hyperplasia With Atypia 31-4
Cribriform Hyperplasia 31-4
Basal Cell Proliferation 31-4
Basal Cell Hyperplasia 31-5
Atypical Basal Cell Hyperplasia (ABCH) 31-5
Basal Cell Adenoma 31-5
Sclerosing Adenosis 31-6
Metaplasia 31-7
Squamous Metaplasia 31-7
Mucinous Metaplasia 31-7
Urothelial Metaplasia 31-7
Nephrogenic Metaplasia 31-8
Atrophy 31-8
Post-Atrophic Hyperplasia 31-8
Hyperplasia of Mesonephric Remnants (Florid Mesonephric Hyperplasia) 31-8
Verumontanum Mucosal Gland Hyperplasia 31-8
Seminal Vesicles and Ejaculatory Ducts 31-9
Senile Seminal Vesicle Amyloidosis 31-9
Cowper's Glands 31-9
Paraganglia 31-10
Prostatic Urethral Polyp 31-10
Proliferative Papillary Urethritis 31-10
Ectopic Prostatic Tissue (Benign Polyp With Prostatic-Type Epithelium) 31-10
Nephrogenic Metaplasia 31-10
Benign Urothelial Papilloma 31-10
Inverted Papilloma 31-10

III. Putative Precursor of Adenocarcinoma 31-10
High-Grade Prostatic Intraepithelial Neoplasia (HGPIN) 31-10
Atypical Adenomatous Hyperplasia (AAH) 31-12

IV. Atypical Small Acinar Proliferation (ASAP), Suspicious for Malignancy 31-13

V. Malignant Tumors 31-14
Prostatic Adenocarcinoma 31-14
Prostatic Adenocarcinoma Variants 31-20
Ductal (Endometrioid) Adenocarcinoma 31-20
Mucinous Adenocarcinoma 31-20
Small Cell Carcinoma (High-Grade Neuroendocrine Carcinoma) 31-21
Signet Ring Cell Carcinoma 31-21
Squamous Cell and Adenosquamous Carcinoma 31-21
Sarcomatoid Carcinoma (Carcinosarcoma) 31-22
Lymphoepithelioma-Like Carcinoma 31-22

Comedocarcinoma 31-22
Cribriform Carcinoma 31-22
Adenocarcinoma with Glomeruloid Features 31-22
Adenocarcinoma with Atrophic Features 31-22
Adenocarcinoma with Microvacuolated Cytoplasm (Foamy Gland Carcinoma).....31-23
Pseudohyperplastic Pattern of Carcinoma 31-23
Adenoid Cystic/Basal Cell Carcinoma 31-23
Urothelial Carcinoma 31-24
Rhabdomyosarcoma 31-24
Leiomyosarcoma 31-24
Phyllodes Tumor 31-25
Lymphoma 31-25

VI. Treatment Effects 31-26
Androgen Deprivation Therapy 31-26
Radiation Therapy 31-27

VII. TNM Classification of Prostate Cancer (2002 Revision) 31-27

VIII. Suggested Reading 31-27

INFLAMMATORY LESIONS

Table 1. Etiology of Granulomatous Prostatitis

Infections		**Malakoplakia**	
Bacterial	Tuberculosis (AFB staining), syphilis	**Systemic granulomatous disease**	
Fungal	Coccidioidomycosis, cryptococcosis, histoplasmosis	Allergic	
		Sarcoidosis	
Parasitic	Schistosomiasis	Systemic vascular diseases	
Viral	Herpes zoster	Wegner's granulomatosis	
Iatrogenic		Polyarteritis nodosa	
Post-surgery or radiation		Churg-Strauss syndrome	
Post-BCG treatment		**Idiopathic**	

Acute Bacterial Prostatitis

Clinical

- Sudden onset of fever, chills, pain, and irritative and obstructive symptoms
- Swollen, tender, and indurated on digital rectal examination
- *E. coli* infection accounts for 80% of cases
- Diagnosis confirmed by culture of midstream urine and/or prostatic secretions
- Biopsy contraindicated

Microscopic

- Microabscess formation and heavy infiltrate of acute and chronic inflammatory cells
- Acinar destruction and epithelial cell degeneration
- Stromal hemorrhage and edema

Chronic Bacterial and Non-Bacterial Prostatitis

Clinical

- Chronic nonbacterial prostatitis is more common than bacterial prostatitis (*E. coli*)
- Chlamydia trachomatis and ureaplasma urealyticum are common etiologic agents
- Often follows an indolent clinical course with relapses and remissions

Microscopic

- Epithelial degeneration and metaplasia
- Chronic inflammation

Differential Diagnosis

- High-grade prostatic intraepithelial neoplasia (HGPIN):
  - Partial acinar involvement, nuclear stratification, and prominent nucleoli
  - Caution is urged in diagnosing PIN in the setting of inflammation

Granulomatous Prostatitis

Clinical

- Prior history of urinary tract infection is common **(Table 1)**
- Suspicious for carcinoma on digital rectal examination
- Probably caused by blockage of prostatic ducts and stasis of secretion

Microscopic

- Specific etiology often cannot be determined from histologic examination
- Glandular disruption, epithelial degeneration, and metaplasia
- Granulomatous inflammation with or without necrosis
- Polymorphous chronic inflammation composed of multinucleated giant cells, histiocytes, lymphocytes, plasma cells, and neutrophils
- Intracellular and extracellular Michaelis-Gutman bodies in malakoplakia highlighted by PAS and von Kossa stains
- Stellate and geographic granulomas with palisading histiocytes and vasculitis are often seen in Wegener's granulomatosis
- Necrotizing vasculitis with fibrin deposition and tissue eosinophilia is often seen in Churg-Strauss vasculitis

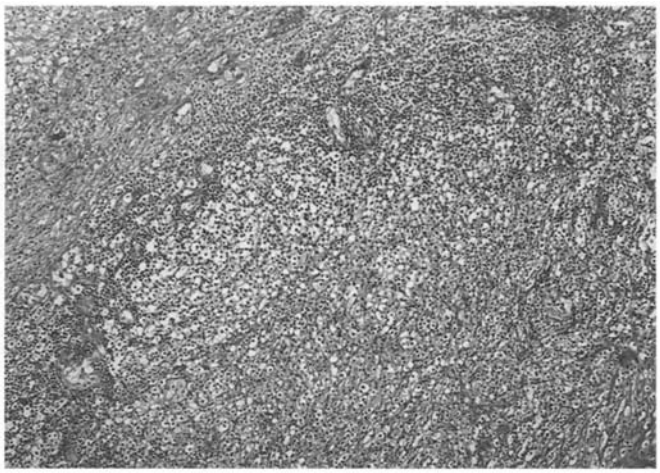


Fig. 1. Xanthogranulomatous prostatitis. Lymphocytes rim a massive monomorphous collection of macrophages with abundant clear cytoplasm. This case was initially misdiagnosed as high-grade carcinoma.

- Central zone of fibrinoid necrosis surrounded by peripheral palisading epithelioid histiocytes is often seen in postsurgical granuloma

Variants

- Xanthoma:
  - Incidental findings in elderly men
  - Clusters and sheets of lipid-laden histiocytes in a nodular configuration
  - CD68+ , cytokeratin–
- Xanthogranulomatous prostatitis:
  - Non-specific granulomatous prostatitis
  - Composed predominantly of sheets of epithelioid histiocytes **(Figure 1)**
  - Polymorphous inflammatory infiltrate
  - Associated with atrophy and acinar disruption

Immunohistochemistry

- PSA–, PAP–, Cytokeratin–

BENIGN LESIONS AND MIMICS OF ADENOCARCINOMA

Benign Prostatic Hyperplasia (BPH)

Clinical

- Occurs in 50% or more of men >50 years
- Often presents with lower urinary tract symptoms
- Develops in transition zone, resulting from stromal and epithelial proliferation
- Etiology and pathogenesis not completely understood
- Hormonal regulation is mainly via dihydrotestosterone (DHT), derived from testosterone by the activity of 5-alpha-reductase
- Growth factors also play an important role in the development of BPH
- Epidermal growth factor (stimulatory) and transforming growth factor-β (inhibitory) alter prostatic growth

Macroscopic

- Yellow-gray rubbery to firm and bulging nodules in the transition zone and periurethral region
- For transurethral resection specimens, submit a minimum of six cassettes for the first 30 g of tissue and one cassette for every 10 g thereafter

Microscopic

- Epithelial and stromal hyperplasia in the transition zone and periurethral region **(Figure 2)**
- Stromal nodules consist of fibromuscular spindle cell proliferations with thin- or thick-walled vessels and scattered lymphocytic infiltrate (mainly T-helper cells)
- Often associated with prostatic infarct with squamous and urothelial metaplasia
- At least part of a nodule should be present for the diagnosis to be made on biopsies (uncommon)

Stromal Hyperplasia With Atypia

- Often occurs in the transition zone
- Variant of nodular hyperplasia
- Increased stromal cellularity with bizarre giant cells and nuclear degenerative changes **(Figure 3)**
- Nuclear pleomorphism, nuclear hyperchromasia, and pyknosis
- Lacks the circumscription of leiomyoma
- No mitotic figures

Cribriform Hyperplasia

- Often occurs in the transition zone
- Variant of nodular hyperplasia
- Cribriform pattern of acinar proliferation with intact basal cell layer **(Figure 4)**
- Uniform cells with clear or granular cytoplasm and inconspicuous nucleoli

Basal Cell Proliferation

- Basal cells probably contain the regenerative or stem cells of the prostate
- Occurs in 6% of biopsies and 9% of transurethral resection specimens

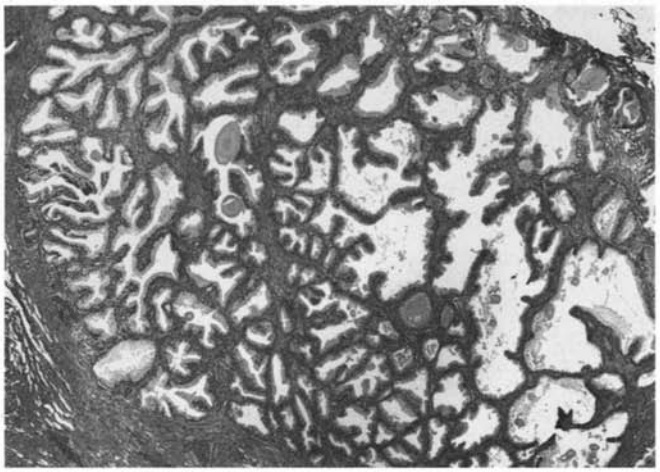


Fig. 2. BPH. This epithelium-predominent round nodule is typical.

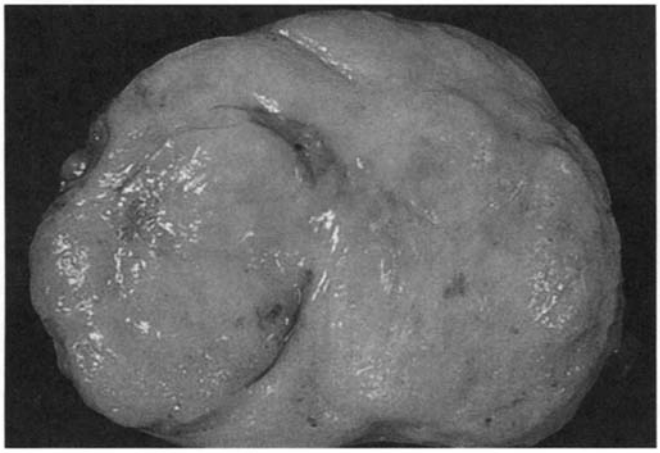


Fig. 3. BPH, stromal variant. Bulging from the cut surface of this adenectomy specimen is a fleshy firm stromal nodule.

Basal Cell Hyperplasia (BCH)

- Often occurs in the transition zone
- Variant of BPH
- Proliferation of basal cells with multiple layers (≥2) **(Figure 5)**
- Often eccentrically located with partial involvement of acini, retaining the overlying columnar or cuboidal secretory cells
- Basal cells have enlarged nuclei, fine powdery chromatin, and occasional nuclear grooves
- Nuclear "bubble" artifact or intranuclear vacuole often seen in formalin-fixed tissue but not in frozen section
- Often associated with chronic inflammation

Atypical Basal Cell Hyperplasia (ABCH)

- Same as basal cell hyperplasia but with prominent nucleoli **(Figure 6)**
- Require >10% of cells displaying prominent nucleoli for diagnosis

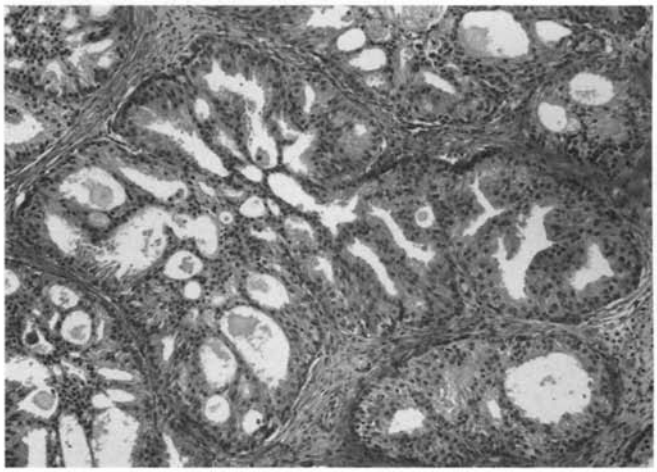


Fig. 4. Cribriform hyperplasia. Note the variable size and collapsible nature of the luminal fenestrations. Unlike high-grade PIN and ductal adenocarcinoma, there is no cytologic abnormalities. In this preparation, the basal cell layers at the periphery of the acini are especially prominent.

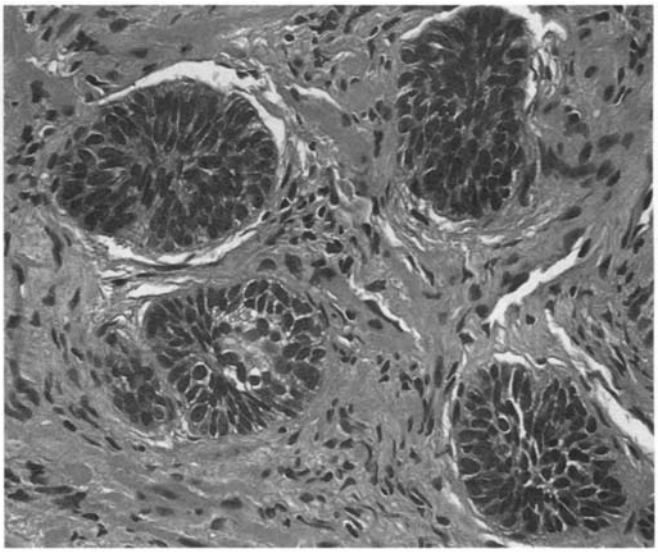


Fig. 5. Basal cell hyperplasia. These tight nests of basaloid cells are characteristic of BCH.

Basal Cell Adenoma

- Variant of BPH
- Nodule formation with basal cell hyperplasia
- Well-circumscribed solid nests and aggregates of hyperplastic basal cells in a condensed fibrous stroma
- Plump nuclei, high nucleocytoplasmic ratio, and inconspicuous nucleoli
- High molecular weight cytokeratin 34βE12+
- PSA± (patchy), PAP± (patchy)
- S100 and chromogranin ±

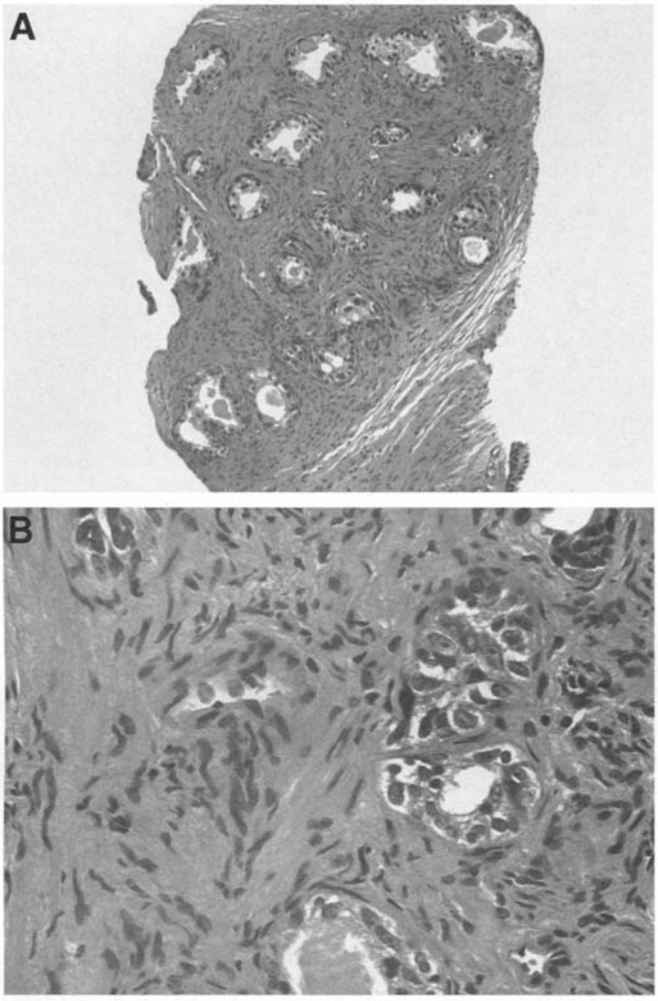


Fig. 6. Atypical basal cell hyperplasia. **(A)** The acini are set in a moderately fibrotic stroma. **(B)** The acini contain basal cells with prominent nucleoli.

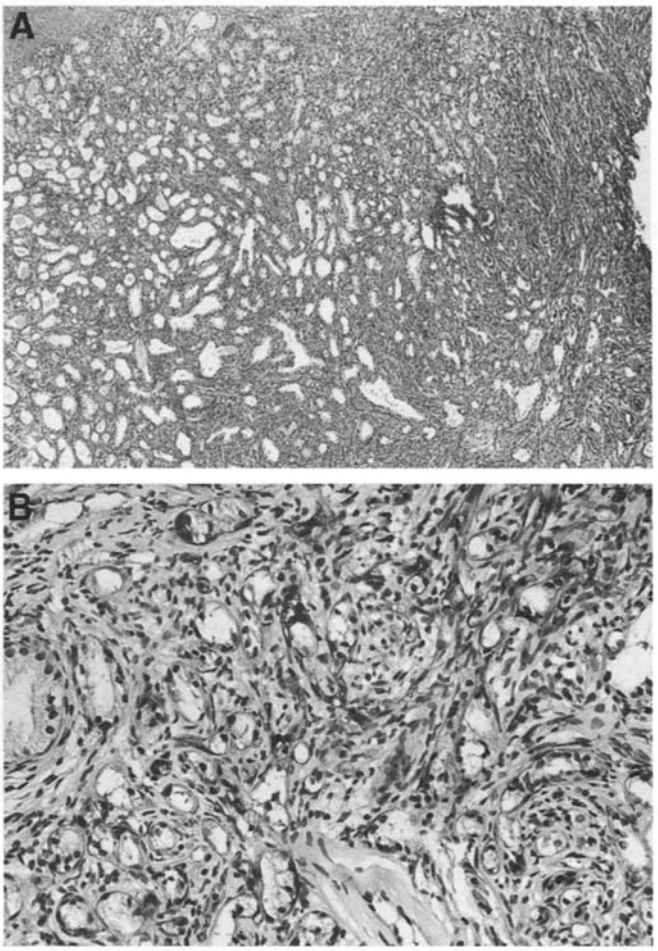


Fig. 7. Sclerosing adenosis. **(A)** Packed circumscribed cluster of small acini of variable size set in a densely cellular stroma. **(B)** Intense S-100 protein immunoreactivity in the basal cells of virtually every acinus.

Sclerosing Adenosis

Clinical

- Incidental findings in 2% of transurethral resection specimens
- An unusual variant of BPH
- Occurs in transition zone, usually solitary and microscopic
- The only prostatic lesion with myoepithelial differentiation of basal cells

Microscopic

- Well-circumscribed proliferation of small acini in a densely myofibroblastic stroma **(Figure 7)**
- Thickened basement membrane with prominent myoepithelial cells
- Acini appear to merge with adjacent pale staining cellular stroma with abundant loose ground substance
- Compressed and distorted glands imparting a pseudo-infiltrative pattern
- Occasional nuclear and nucleolar enlargement
- Moderate amount of clear to eosinophilic cytoplasm

Electron Microscopy

- Myoepithelial differentiation with aggregates of thin filaments

*Immunohistochemistry **(Table 2)***

- High molecular weight cytokeratin 34βE12 and p63+
- Muscle-specific actin (MSA)+
- S-100 protein+ **(Figure 7B)**

Differential Diagnosis

- Atypical adenomatous hyperplasia:
  - Lacks densely hyalinized stroma and fragmented basal cell layer
  - MSA–, S-100 protein–

Table 2. Immunohistochemical Profiles of Benign Lesions in the Prostate

	PSA/PAP	HMW CK	Cytokeratin* Protein	S-100	SMA	Zonal predilection
Xanthoma/xanthogranulomatous prostatitis	–	–	–	–	–	Peripheral
Nephrogenic metaplasia	–	+	+	–	–	Periurethral
Post-atrophic hyperplasia	+	+	+	–	–	Peripheral
Atypical basal cell hyperplasia	±	+	+	±	–	Transition
Cribriform hyperplasia	+	+	+	–	–	Transition
Sclerosing adenosis	+	+	+	+	+	Transition
Stromal hyperplasia with atypia	–	–	–	–	+	Transition
Hyperplasia of mesonephric remnants	–	+	+	–	–	Unknown
Verumontanum mucosal gland hyperplasia	+	+	+	–	–	Verumontanum
Seminal vesicles/ejaculatory ducts	–	+	+	–	–	Seminal vesicles
Cowper's gland	–	+	+	–	–	Urogenital diaphragm
Paraganglion	–	–	±	±	–	Base>apex

** Broad spectrum cytokeration*
Note: PSA/PAP = prostate-specific antigen/prostate acid phosphatase, HMW CK = high molecular weight cytokeratin (34βE12), SMA = smooth muscle actin

- Prostatic adenocarcinoma:
  - Cytologic atypia with nucleomegaly and prominent nucleoli
  - Lacks hyalinized stroma
  - Absence of MSA, HMW cytokeratin, and S-100 protein staining

Metaplasia

Squamous Metaplasia

- Often seen at edges of prostatic infarct and after hormonal therapy or cryotherapy **(Figure 8)**
- Common in the region of prostatic urethra in patients with an indwelling catheter
- Syncytial aggregates of polygonal cells with abundant eosinophilic cytoplasm and hyperchromatic nuclei

Mucinous Metaplasia

- Cluster of columnar cells with mucin production **(Figure 9)**
- Focal or complete involvement of acini and lack of involvement of the entire lobular unit of acini
- Negative immunostaining for PSA and PAP
- High molecular weight cytokeratin 34βE12+
- Mucicarmine+, PAS with diastase+, alcian blue+

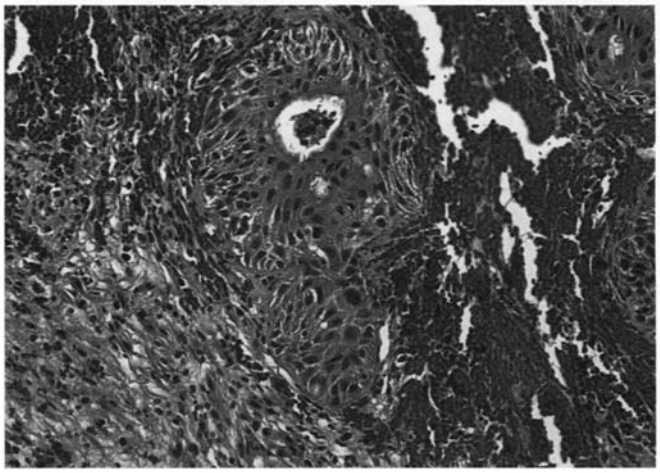


Fig. 8. Squamous metaplasia of benign epithelium following cryosurgery.

Urothelial Metaplasia

- Presence of urothelium beyond the normal urothelial-columnar junction
- Stratified epithelium with streaming effect of nuclei
- Ovoid cells with pale cytoplasm, uniform nuclei, nuclear grooves, perinuclear halos, fine granular chromatin, and inconspicuous nucleoli

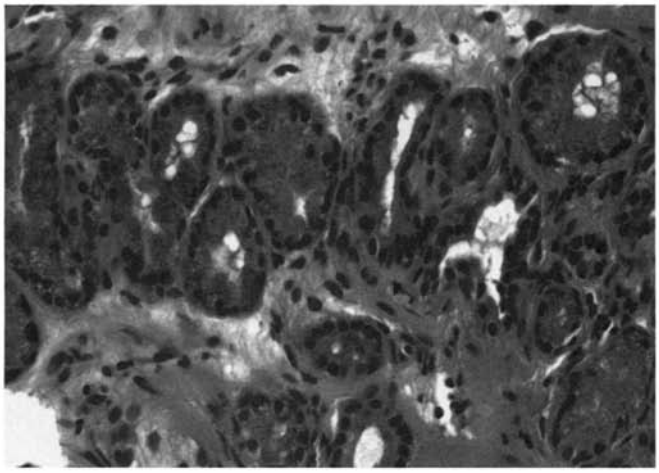


Fig. 9. Mucinous metaplasia.

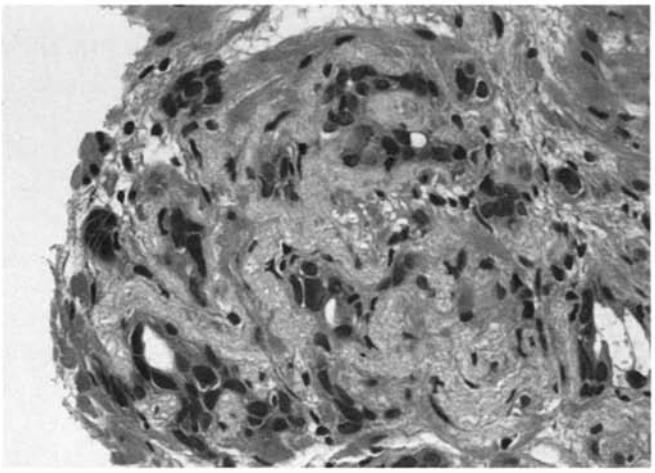


Fig. 10. Post-atrophic hyperplasia. Irregular circumscribed aggregate of markedly atrophic distorted acini set in a fibrous stroma.

- The long axis of the cells is perpendicular to the basement membrane

Nephrogenic Metaplasia

- Suburethral location; composed of exophytic mass of small tubules or papillae with solid and cystic appearance
- Uniform nuclei with fine granular chromatin and inconspicuous nucleoli
- Edematous and often inflamed stroma without desmoplasia
- Often associated with proliferative papillary urethritis
- Negative immunoreactivity for PSA, PAP, and CEA
- High molecular weight cytokeratin 34βE12+

Atrophy

- Often located in the peripheral zone
- Lobular configuration of atrophic glands with open ectatic lumina in a sclerotic stroma
- Variable acinar architectural distortion and irregularity
- Cystic dilation of acini and ducts lined by flattened attenuated epithelial cells with scant cytoplasm, hyperchromatic nuclei, and inconspicuous nucleoli
- Basal cell layer may be fragmented

Post-Atrophic Hyperplasia

- Occurs in all zones with predilection for the peripheral zone
- Occurs in 18% of radical prostatectomy specimens
- Lobular cluster of atrophic acini surrounding central dilated larger acini in a hyalinized stroma **(Figure 10)**
- Variable acinar architectural distortion and irregularity
- Acini lined by a single layer of secretory cells with proliferative changes
- Moderate cytoplasm with luminal apocrine blebs
- Enlarged nuclei with evenly distributed fine granular chromatin and occasional enlarged nucleoli
- Fragmented basal cell layer
- Often associated with adjacent inflammation

Hyperplasia of Mesonephric Remnants (Florid Mesonephric Hyperplasia)

- Occurs in all zones, mainly in the transition zone
- Rare lobular proliferation of small acini lined by single layer of cuboidal cells
- Two growth patterns:
  - Closely packed small round to oval tubules lined by cuboidal hobnail cells with eosinophilic cytoplasm
  - Proliferation of small acini with empty lumens or solid nests
- May have haphazard arrangement at periphery, imparting pseudoinfiltrative growth pattern
- Ectatic tubules with lumenal colloid-like eosinophilic inclusions and micropapillary infoldings
- Uniform cells with occasional nuclear and nucleolar enlargement
- PSA–, PAP–, high molecular weight cytokeratin 34βE12 and p63+

Verumontanum Mucosal Gland Hyperplasia

- Located in the posterior wall of the mid prostatic urethra
- Used as a landmark during transurethral resection of the prostate (resection is proximal)
- Recognized in 14% of radical prostatectomy specimens
- Rare in biopsies and not seen in transurethral resection specimens
- Often intimately associated with urothelium
- Multifocal lobular proliferation of closely packed small (>25) acini usually with intact basal cell layer
- Uniform cells with basophilic cytoplasm and lack of cytologic atypia

- Numerous corpora amylacea and distinctive orange-red non-laminated concretions that are often fragmented
- Luminal secretory cells may contain lipofuscin pigment
- Intact basal cell layer
- PSA+, PAP+, high molecular weight cytokeratin 34βE12+

Seminal Vesicles and Ejaculatory Ducts

Microscopic

- Well-circumscribed
- Complex papillary folds with irregular convoluted lumens **(Figure 11)**
- Lined by non-ciliated pseudostratified columnar epithelium
- Ejaculatory ducts have large lumens with more prominent mucosal folding and prominent circumferential layer of muscular wall
- Stromal (eosinophilic) hyaline bodies:
  - Often seen within the muscular wall, resulting from smooth muscle degeneration
  - Highlighted by Masson's trichrome and PAS stain
- Bizarre smudged cells with granular refractile golden yellow lipofuscin pigment
- Enlarged nuclei with nuclear hyperchromasia, coarse granular chromatin, prominent nucleoli, and occasional nuclear halos
- Multinucleated giant cells with pyknotic nuclei and a lack of mitotic figures
- DNA aneuploid in 6.7% of seminal vesicles

Immunohistochemistry

- PSA–, PAP–, HMW cytokeratin 34βE12 and p63+

Differential Diagnosis

- Pigmented prostatic epithelium:
  - Scant, finely granular, yellow-brown pigment
  - PSA+, PAP+
- Post-atrophic hyperplasia:
  - Lobular arrangement of acini surrounding central dilated acini; proliferative change
  - Lacks lipofuscin or cytologic atypia
- High-Grade PIN:
  - Lacks lipofuscin; displays significant nuclear pleomorphism
- Adenocarcinoma:
  - Lacks lipofuscin; displays nuclear degeneration; bizarre nuclei uncommon
  - PSA+, PAP+, 34βE12–

Senile Seminal Vesicle Amyloidosis

Clinical

- Occurs in up to 8% of men 46–60 years, 23% between age 61–75 years, and 40% >75 years

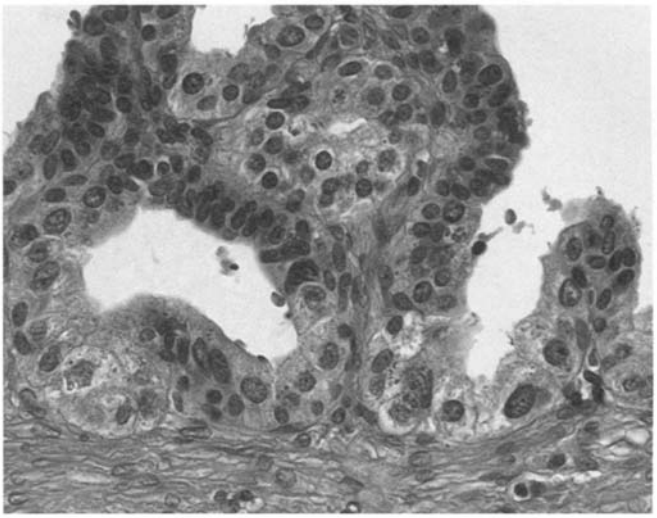


Fig. 11. Seminal vesicle. The epithelium contains scattered refractile golden brown pigment, as well as moderate anisonucleosis.

- Derived from secretory protein of the epithelium
- Benign; not associated with systemic amyloidosis

Microscopic

- Linear or nodular subepithelial deposition of amorphous eosinophilic amyloid
- Basement membrane thickening

Immunohistochemistry

- Congo red+, crystal violet+, toluidine blue+, PAS+

Cowper's Glands

Microscopic

- Located within the urogenital diaphragm; seen in apex biopsies
- Not present in transurethral resection specimens
- Equivalent to Bartholin's glands of female genital tract
- Small paired bulbomembranous urethral glands surrounded by skeletal muscle
- Well-circumscribed small acinar proliferation **(Figure 12)**
- Uniform cells with abundant apical mucinous cytoplasm
- Lack nuclear and nucleolar enlargement

Immunohistochemistry

- PSA–, high molecular weight cytokeratin+, mucicarmine+, PAS with diastase+

Differential Diagnosis

- Mucinous metaplasia:
  - Focal involvement of a small number of acini
  - Lacks skeletal muscle
- Mucinous adenocarcinoma:
  - Nests and clusters of epithelial cells floating in extravasated mucin pool

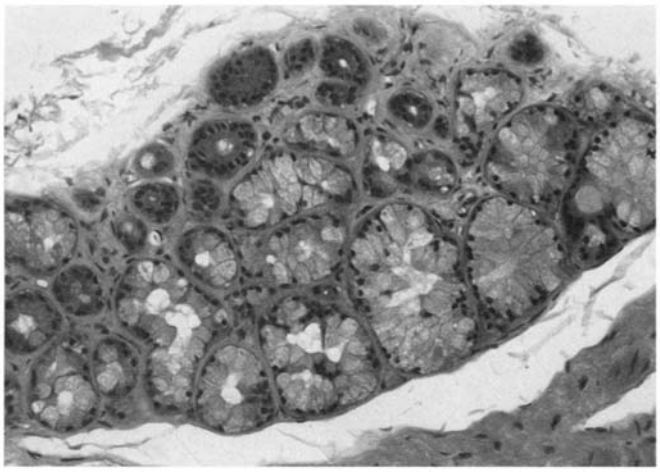


Fig. 12. Cowpers' gland.

- Well-differentiated adenocarcinoma:
  - Prominent nucleoli

Paraganglia

- Located closer to the base than the apex of the prostate
- Usually associated with neurovascular structures
- Solid nests and organoid arrangement of closely packed polygonal cells with abundant clear cytoplasm **(Figure 13)**
- Centrally located uniform nuclei with or without prominent nucleoli
- PSA–, PAP–, cytokeratin–, neuroendocrine markers+

Prostatic Urethral Polyp

Proliferative Papillary Urethritis

- Papillary proliferation of urothelium with metaplastic changes and reactive atypia
- Inflammation and stromal edema

Ectopic Prostatic Tissue (Benign Polyp With Prostatic-Type Epithelium)

- Adolescents or young adults present with hematuria
- Delicate papillae with fibrovascular core and prostatic epithelial lining

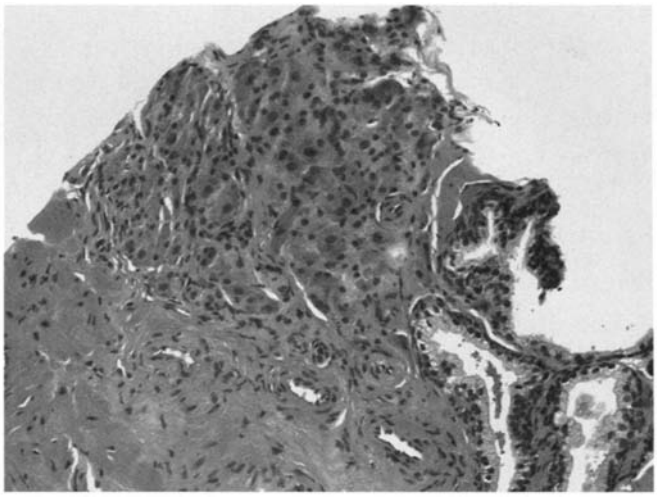


Fig. 13. Intraprostate ganglionic tissue. In contrast with the benign acini (lower right), the ganglion cells are small, closely packed, and contain a light dusting of brown pigment. This focus was initially misdiagnosed as adenocarcinoma.

Nephrogenic Metaplasia (Described Elsewhere)

Benign Urothelial Papilloma

- Patient <50 years with solitary lesion <2 cm in greatest dimension
- <7 cells in thickness with intact superficial (umbrella) cell layer
- No significant cytologic atypia (no more than Grade 1 urothelial carcinoma)

Inverted Papilloma

- Patients present with hematuria and urinary obstructive symptoms
- Smooth contoured invaginated cords and columns of urothelial cells with intact overlying urothelium
- Peripheral palisading basaloid cells and thickened basement membrane
- Squamous metaplasia and microcystic change
- Scant stroma
- Lacks fibrovascular cores

PUTATIVE PRECURSOR OF ADENOCARCINOMA

High-Grade Prostatic Intraepithelial Neoplasia (HGPIN)

Definition

- Precancerous end of the morphologic continuum of cellular proliferations within preexisiting prostatic ducts, ductules, and acini

Clinical

- Divided into low-grade (formerly PIN 1) and high-grade (formerly PIN 2 and 3)
- Some pathologists prefer not to report low-grade PIN, recognizing the difficulty in separating this lesion from benign epithelium and reactive atypia

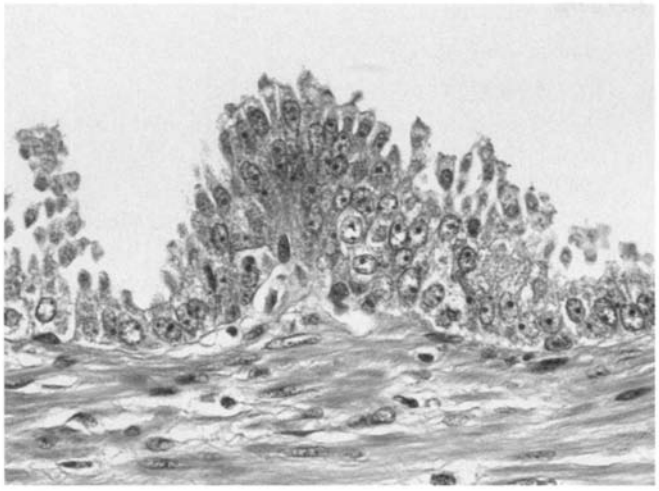


Fig. 14. Tufting pattern of high grade PIN. Small mounds of cells protrude into the lumen. This focus has a prominent basal cell layer at the periphery.

- Morphometrically, PIN is genotypically and phenotypically linked to cancer
- Precedes the onset of carcinoma by 5–10 years
- Multifocal (63% of cases) and co-exists with cancer in 86% of prostatectomy specimens
- Occurs in the nontransition zone (63% of cases) and all zones (36%)
- Present in up to 4.2% of transurethral resection specimens (2.8% without cancer, 10.2% with cancer)
- The volume of HGPIN increases with the pathologic stage, Gleason grade, and positive surgical margins in patients with prostate cancer
- More prevalent and extensive and occurs approximately a decade earlier in African American men than Caucasian men
- Prevalence and extent of HGPIN are decreased after androgen deprivation therapy
- No influence on serum PSA concentration
- Occurs in up to 16% of contemporary needle biopsies
- The diagnosis of HGPIN confers a 35% to 50% predictive value for cancer on repeat biopsy
- Follow-up is suggested at 3- or 6-month intervals, and thereafter at 12-month intervals for life after diagnosis

Patterns of Growth

- Tufting (97% of specimens with HGPIN, most common) **(Figure 14)**
- Micropapillary (66%) **(Figure 15)**
- Flat (21%) **(Figure 16)**
- Cribriform (19%) **(Figure 17)**

Pattern of Spread

- Replacement of normal luminal secretory cells with preservation of the basal cell layer

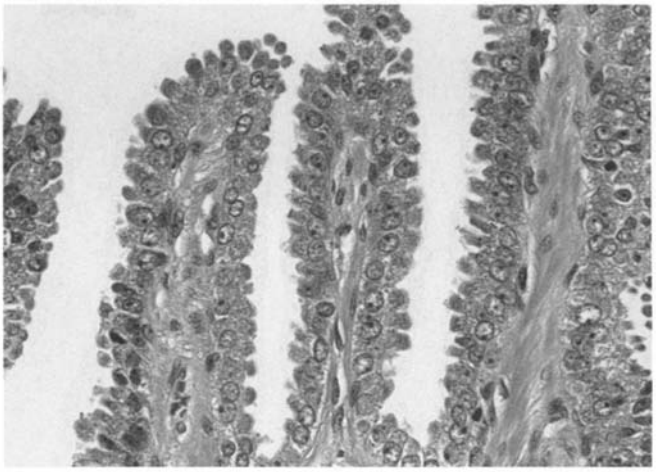


Fig. 15. Micropapillary pattern of high grade PIN. Elongate finger-like projections of epithelium protrude into the lumens.

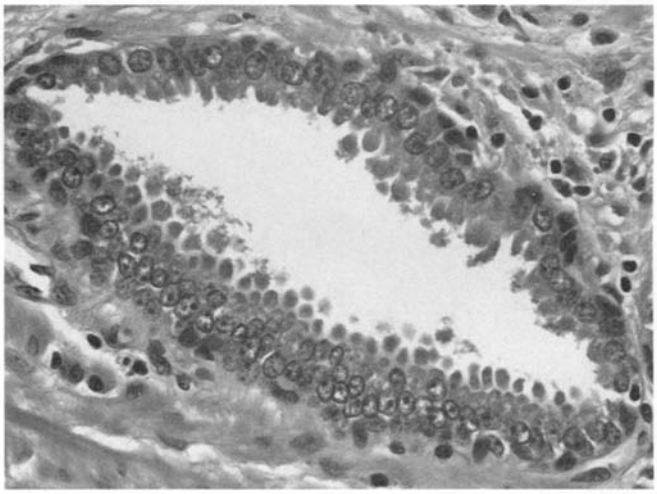


Fig. 16. Flat pattern of high grade PIN.

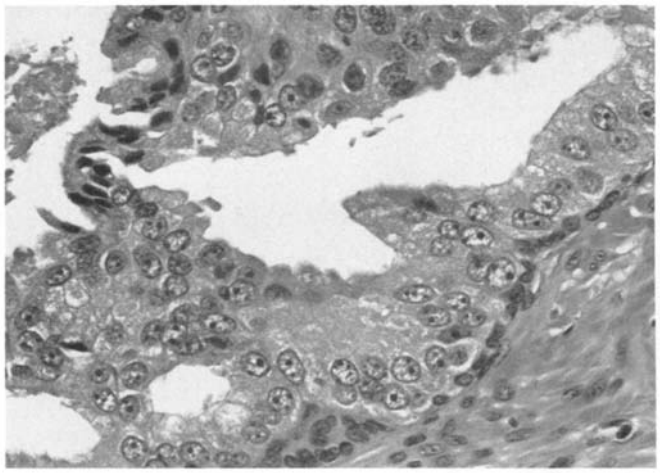


Fig. 17. Cribriform pattern of high grade PIN.

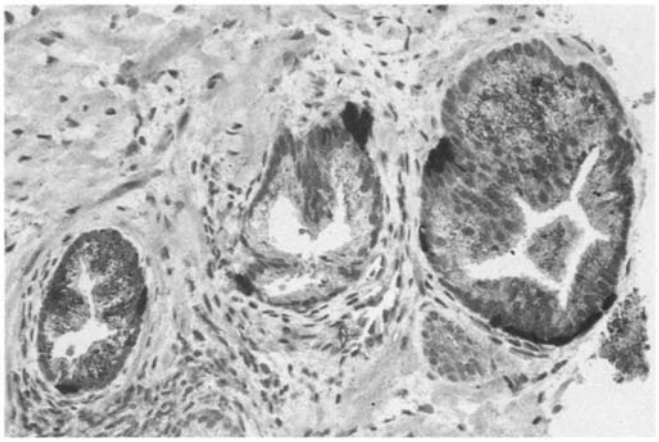


Fig. 18. High-grade PIN, triple immunostain: Brown reaction product indicates a patchy and fragmented pattern of immunoreactivity for high molecular weight cytokeratin 34βE12 in basal cell cytoplasm and p63 in basal cell nuclei; red reaction product indicates immunoreactivity for racemase in luminal secretory cells.

- Direct invasion with disruption of the basal cell layer
- Pagetoid spread (rare)

Microscopic

- Nuclear and nucleolar enlargement are the cytologic hallmark of HGPIN
- Cellular crowding, irregular spacing, nuclear stratification, and overlapping
- Partial acinar involvement may be seen
- Cells usually display cytoplasmic blebs along the luminal surface
- Disruption of the basal cell layer is highlighted by high molecular weight cytokeratin and p63 **(Figure 18)**
- Racemase (P504S) staining positive **(Figure 18)**

Differential Diagnosis

- Inflammatory reactive atypia:
  - Metaplastic (eosinophilic) changes and inflammatory background
- Urothelial metaplasia:
  - Lacks prominent nucleoli
- Seminal vesicles and ejaculatory ducts:
  - Bizarre cells with lipofuscin pigment
  - Nuclear hyperchromasia, nuclear pleomorphism, and degenerative changes
  - PSA and PAP–
- Cribriform hyperplasia:
  - Occurs in transition zone; sieve-like pattern
  - Uniform cells with clear cytoplasm
  - Lacks nuclear and nucleolar enlargement
- Post-atrophic hyperplasia:
  - Lacks prominent nucleoli
- Atypical basal cell hyperplasia:
  - Small solid nests or eccentric expansion of the basal cell layers between normal columnar secretory cells and basement membrane
  - The long axis of basal cells is usually parallel to the basement membrane
  - Enlarged nuclei with delicate stippled chromatin, occasional nuclear grooves, and nuclear "bubble" artifact
  - Often associated with inflammatory background
  - Cytokerain 34βE12+
- Low-grade PIN:
  - The epithelium lining ducts and acini are heaped up, crowded, and irregularly spaced
  - Lacks prominent nucleoli and less nuclear hyperchromasia
  - Intact basal cell layer without disruption
- Ductal (endometrioid) prostatic adenocarcinoma:
  - Lacks basal cell layer
- Large gland variant of Gleason pattern 3 carcinoma and cribriform variant:
  - More extensive involvement, infiltrative growth pattern
  - Often associated with small acinar carcinoma
  - Lacks circumferential basal cell layer

Atypical Adenomatous Hyperplasia (AAH)

Clinical

- Usually occurs in the transition zone and is found in ~23% of prostatectomy specimens
- Multicentric in ~46% of cases
- The biologic significance is uncertain and was proposed as a putative precursor lesion
- The extent and zonal distribution of AAH and carcinoma share a weak but significant association
- Shares less frequent, but similar allelic imbalance with prostatic adenocarcinoma
- May be associated with a subset of low-grade carcinoma arising in the transition zone
- The identification of AAH should not influence or dictate therapeutic decisions

Microscopic

- Requires most or all of the focus to be present for diagnosis of AAH on biopsy
- Well-circumscribed nodular proliferation of small acini at the periphery of BPH; sometimes involves the entire nodule **(Figure 19)**
- Parent gland with larger branching lumina in the central location

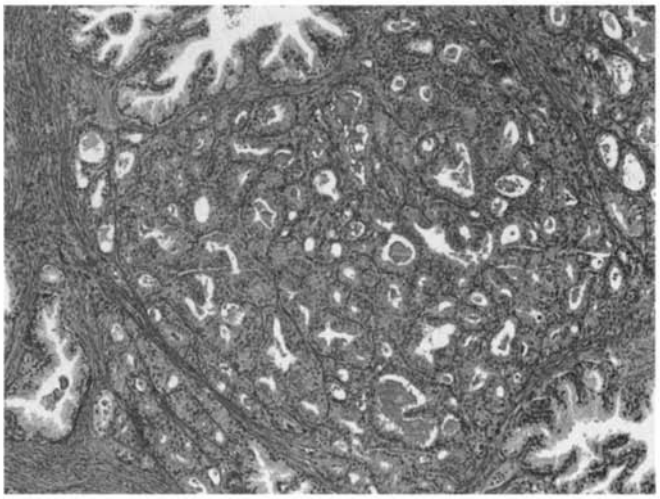


Fig. 19. Atypical adenomatous hyperplasia. This circumscribed cluster of small to intermediate acini was initially misdiagnosed as Gleason pattern 1 + 1 carcinoma; however, a fragmented basal cell layer was identified by immunohistochemistry (*see* **Figure 20**).

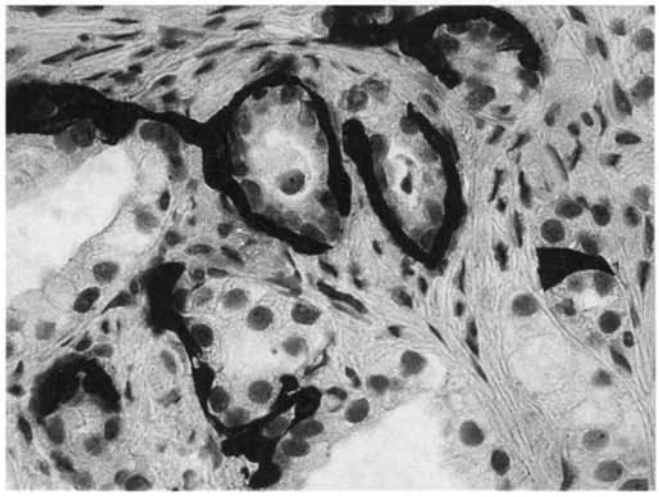


Fig. 20. Atypical adenomatous hyperplasia, immunostain for high molecular weight cytokeratin 34βE12. Note fragmented basal cell layer, typical of AAH.

- Lacks diffuse nucleolar enlargement
- Infrequent intraluminal mucin secretions and crystalloids
- Basal cell layer fragmented **(Figure 20)**
- Racemase (P504S) immunostaining may be positive

Differential Diagnosis

- Verumontanum mucosal gland hyperplasia:
  - Located in the posterior wall of the distal prostatic urethra
  - Back-to-back arrangement of small acini with prominent corpora amylacea
  - Fragmented nonlamellated orange-red concretions
  - Cytoplasmic lipofuscin
  - Intact basal cell layer and intimately associated with urothelial-lined ducts
- Post-atrophic hyperplasia:
  - Lobular cluster of atrophic acini with proliferative change
  - Not intimately associated with nodular hyperplasia
  - Associated with adjacent atrophy with inflammation, stromal fibrosis, or smooth muscle atrophy
- Sclerosing adenosis:
  - Biphasic pattern with hyalinized periacinar stroma
  - S-100 protein+, actin+
- Low-grade small acinar prostatic adenocarcinoma:
  - Nucleolar enlargement
  - Lacks basal cell layer

ATYPICAL SMALL ACINAR PROLIFERATION (ASAP), SUSPICIOUS FOR MALIGNANCY

Clinical

- A diagnostic category encompassing a spectrum of histologic abnormalities that fall below the threshold for the diagnosis of cancer
- The incidence of ASAP is ~2.5% in contemporary prostate biopsies
- Predicts ~45% likelihood for cancer on repeat biopsy
- Many ASAP foci may represent marginally sampled cancer
- 99% of cancers were diagnosed on second and third biopsy, usually within 6 months after the ASAP diagnosis (73%)
- 41% of cancers were detected exclusively in other sites of initial ASAP lesion
- The entire prostate should be rebiopsied due to random sampling variation

Microscopic

- Lacks the full complement of requisite architectural and cytologic features of cancer
- Usually very small in size—invariably less than 2 dozen acini **(Figure 21)**
- The focus often disappears on deeper levels
- Lacks unequivocal cytologic features of malignancy
- Enlarged nucleoli are often difficult to find
- Clustered growth of acini

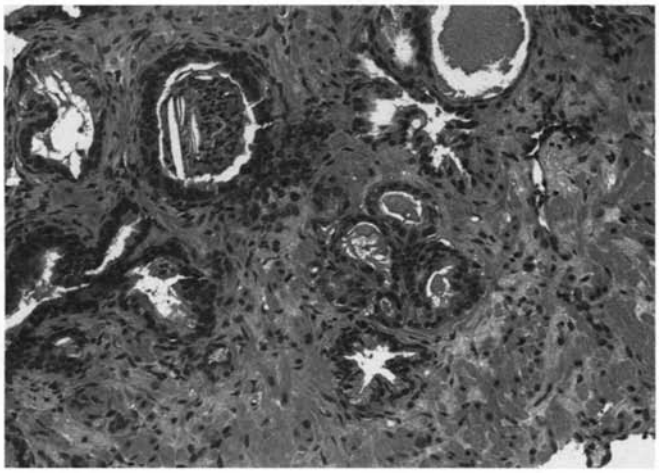


Fig. 21. Atypical small acinar proliferation suspicious for but not diagnostic of malignancy. The aggregate of about half a dozen small acini with variable size, shape, and spacing stands in marked contrast with the adjacent benign acini. Note cholesterol clefts and intraluminal neutrophils, raising the concern for reactive changes rather than neoplasia. Compare with **Figure 22.**

- May represent partial sampling of AAH, sclerosing adenosis, or low-grade cancer
- Confounding acinar atrophy and prominent inflammation in the immediate vicinity of suspicious acini, and poor histologic preparations
- Features that may be present include:
  - Infiltrative growth
  - Variation in acinar size
  - Nucleomegaly
  - Nucleolar enlargement
  - Microvacuolated cytoplasm
  - Intraluminal proteinaceous secretions
  - Luminal mucin
  - Crystalloids

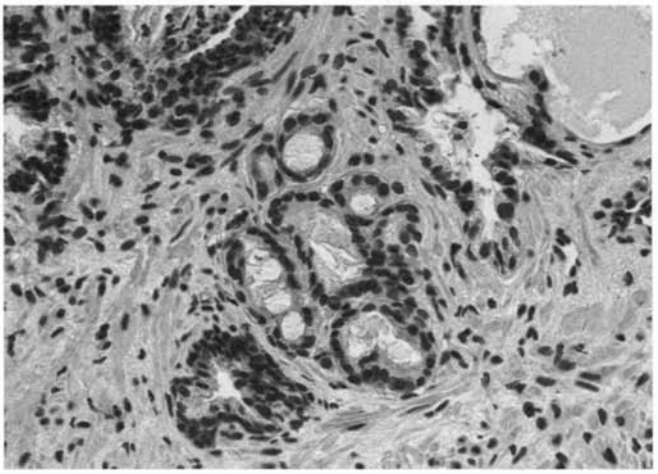


Fig. 22. Same focus as **Figure 21**, immunostained for high molecular weight cytokeratin 34βE12. The absence of staining in the acini of concern compounds the suspicion of malignancy. Note weak to moderate staining of basal cells in the adjacent benign acini.

Immunohistochemistry

- High molecular weight cytokeratin (34βE12) and p63 negative or equivocal **(Figure 22)**
- Racemase negative, weak, or equivocal

Differential Diagnosis (see Prostatic Adenocarcinoma)

- Prostatic adenocarcinoma:
  - Usually requires a minimum of three malignant acini for the diagnosis, unless:
    - Prominent cytologic anaplasia was present
    - No confounding inflammation
    - Persistence of cancer on serial sections
    - The possibility of seminal vesicle/ejaculatory ducts and other mimics has been excluded
- HGPIN
- Atrophy and post-atrophic hyperplasia
- Sclerosing adenosis
- Basal cell hyperplasia
- Atypical adenomatous hyperplasia

MALIGNANT TUMORS

Prostatic Adenocarcinoma

Clinical

- Most common non-skin cancer in American men
- Accounted for 232,090 newly diagnosed cancers and 30,350 cancer deaths in 2005
- One in six men will develop clinically evident prostate cancer during his life
- Prevalence increases from 10% at age 50 years to ~80% at age 80 years
- Proposed risk factors include age, family history, race, dietary fat, heavy metal exposure (cadmium, zinc), vasectomy, obesity, alcohol, and HGPIN or ASAP on biopsy
- The American Cancer Society recommended in 1997 that men age 50 with a minimum life expectancy of 10 years undergo digital rectal examination and PSA screening annually

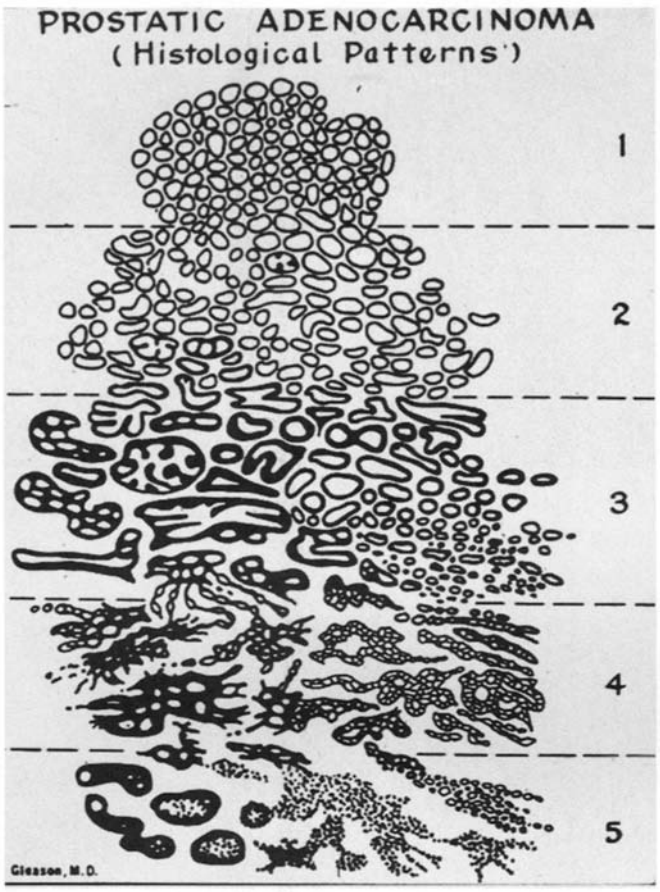


Fig. 23. Original Gleason grading diagram for prostate cancer.

- An abnormal serum PSA concentration is most commonly defined as a value >4.0 ng/ml
- Up to 25% of men with cancer have normal serum PSA (<4 ng/ml)
- Serum PSA half-life is 2–3 days
- 70% to 80% of prostate cancers arise in the peripheral zone (often referred to as the posterior lobe in the older literature), 15% to 25% in the transition zone, and 10% in the central zone
- Prostatic carcinoma in the transition zone is usually well-differentiated

Macroscopic

- Yellow-white mass with a firm consistency in the peripheral zone
- Many are grossly inapparent

Gleason Grading

- Based on the degree of architectural differentiation **(Figures 23–29)**
- The predominant grade is recorded as the primary grade, and the nondominant grade is assigned secondary grade
- When only one pattern exists (frequently encountered on biopsies), then double the grade

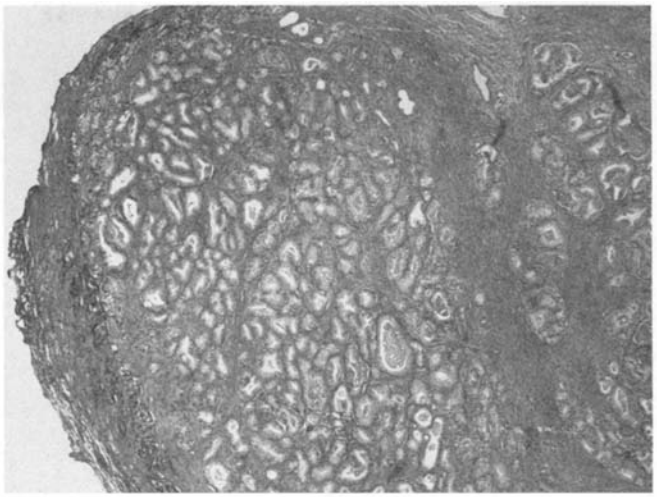


Fig. 24. Gleason 1 + 1 = 2 adenocarcinoma on transurethral resection. At this magnification, BPH cannot be excluded. However, the acini throughout displayed emlarged nuclei and prominent nucleoli; further, the acini were negative for high molecular weight cytokeratin 34βE12.

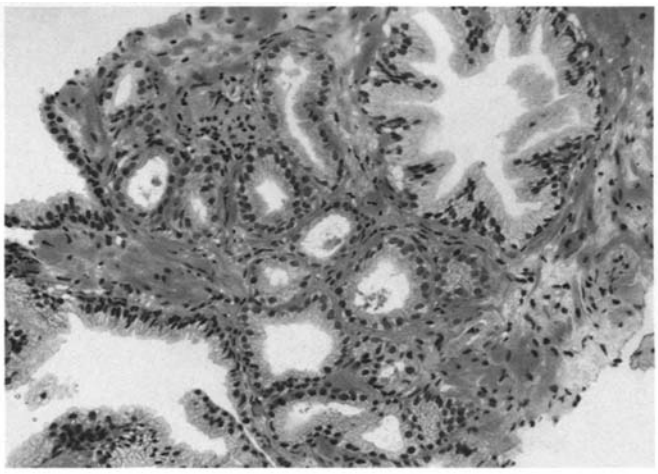


Fig. 25. Gleason pattern 2 + 2 = 4 adenocarcinoma. There is only mild to moderate variation in acinar size and shape, and the acinar contours are chiefly round and smoothly sculpted.

- Gleason score = primary grade + secondary grade
- Needle biopsy underestimates tumor grade in 33% to 45% cases, and overestimates grade in 4% to 32% cases

Reporting

- Biopsy specimens:
  - Biopsy site
  - Histopathologic type of carcinoma
  - Gleason grade
  - Extent of cancer:
    - % of specimen involved
    - Number of cancer foci

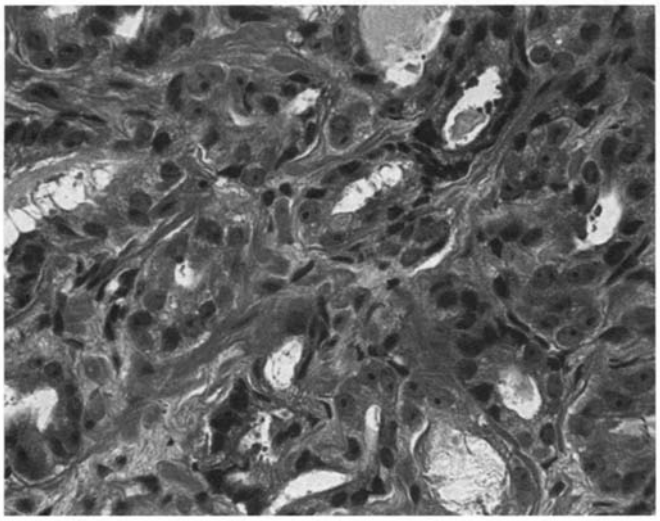


Fig. 26. Gleason pattern 3 + 3 = 6 adenocarcinoma. There is greater variation in size, shape, and spacing of acini than in pattern 1 and 2. Note prominent nucleolomegaly.

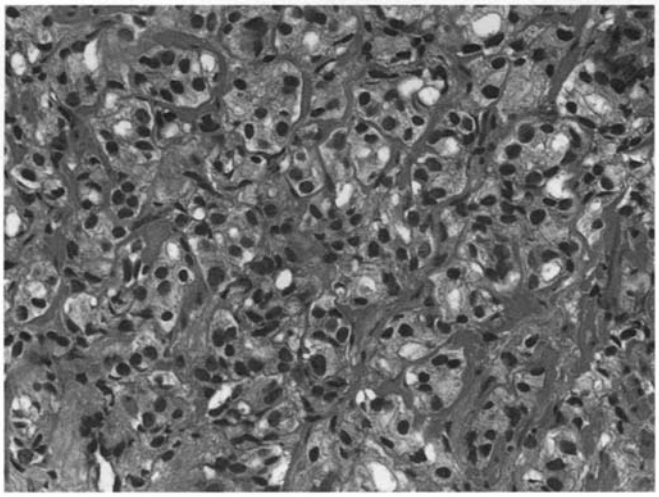


Fig. 27. Gleason pattern 4 + 4 = 8 adenocarcinoma. The malignant acini display fusion and are lined by cells with enlarged nuclei and prominent nucleioli.

- Perineural invasion (not an independent predictive factor)
- Extraprostatic extension (rare)
- Associated conditions (e.g., post-atrophic hyperplasia)
- Ancillary studies (e.g., DNA ploidy by digital imaging analysis)

♦ Transurethral resection specimens
- Weight:
  - 12 g, embed totally; >12 g, a minimum of six cassettes for the first 12 g, and thereafter one cassette for every 10 g; if cancer involves <5% of tissue submitted, all remaining tissue should be examined)

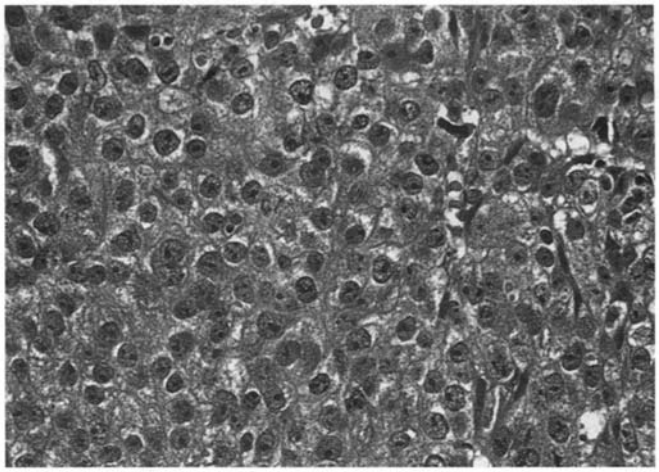


Fig. 28. Gleason 5 + 5 = 10 adenocarcinoma. There are sheets of cells with nuclear and nucleolar enlargement.

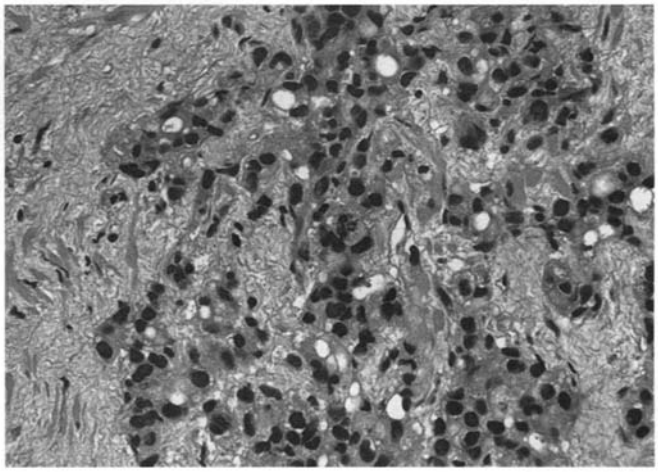


Fig. 29. Gleason 5 + 5 = 10 adenocarcinoma. There are distorted solid nests and cords of cells with only rare abortive lumens. Note abnormal mitotic figure centrally.

- Histopathologic type of carcinoma

♦ Gleason grade
♦ Extent of cancer (% of specimens)
♦ HGPIN
♦ Radical prostatectomy specimens:
- Weight and size of the prostate
- Histopathologic type of carcinoma
- Gleason grade
- Location of cancer:
  - Bilateral vs. unilateral (left or right)
  - Anterior vs. posterior
  - Peripheral zone vs. transition zone
- Estimated cancer volume (% of specimens)

- Extraprostatic extension (EPE):
  - Location and extent
  - Definition of EPE:
    - Cancer in adipose tissue
    - Cancer in perineural spaces of the neuromuscular bundles outside the prostate
    - Cancer in anterior muscle beyond the rounded interface between the fibromuscular stroma and skeletal muscle
- Seminal vesicle invasion:
  - Cancer in the adventitia but not in the muscular wall of the seminal vesicle does not qualify for seminal vesicle invasion
- Surgical margin status:
  - Positive margins are defined as cancer cells at the inked surface
  - Sites and extent of margin involved may be used
- Vascular invasion
- HGPIN
- Associated conditions (e.g., nodular hyperplasia)
- Lymph node status:
  - Anatomic sites
  - Number of positive nodes
  - Size of nodal metastasis
  - Extranodal extension (we exclude this because of recent data)
- Ancillary studies (e.g., DNA ploidy by digital imaging analysis or flow cytometry)
- Pathologic stage

Microscopic

- The diagnosis of cancer is made in the presence of ≥3 malignant acini in most cases
- Angulated and distorted acini with an irregular haphazard arrangement and infiltrative growth pattern
- Acini vary in size, shape, and spacing, and lack basal cell layer
- Enlarged nuclei with large eccentrically located prominent nucleoli (>1 μm)
- The presence of multiple nucleoli in a single cell is strong evidence of malignancy
- Vacuolated or microvacuolated cytoplasm
- Collagenous micronodules are a specific finding of prostatic adenocarcinoma, correlated with mucin production by the tumor (0.6% of biopsies and 12.7% of prostatectomies)
- Perineural invasion is of diagnostic value, but has no apparent clinical significance
- Complete circumferential perineural growth, intraneural and/or ganglion invasion are diagnostic for cancer
- Intraluminal crystalloids and amorphous wispy basophilic acid mucin secretions are helpful, but not specific findings of cancer
- Neuroendocrine cells with large eosinophilic granules are seen focally in 10% of cases, but have no diagnostic or prognostic significance
- Co-exists with HGPIN in 86% of cases

*Immunohistochemistry **(Table 3)***

- PSA (located in endoplasmic reticulum, vesicle vacuoles, lumina cells)+
- PAP (lysosome)+
- Basal cell-specific cytoplasmic high molecular weight cytokeratin (34βE12)– **(Figure 30)**
- Basal cell-specific nuclear P63– **(Figure 30)**
- Racemase (P504S) positive in a granular distribution along the luminal surfaces of the neoplastic secretory cells **(Figure 30)**

*Differential Diagnosis **(Table 4)***

- Inflammatory reactive atypia:
  - Associated with inflammation and metaplasia
  - Lacks nucleolar enlargement
  - High molecular weight cytokeratin (34βE12)+
- Xanthoma and xanthogranulomatous prostatitis:
  - Sheets of foamy histiocytes
  - PSA/PAP–, cytokeratin–, macrophage markers (CD68)+
- Post-atrophic hyperplasia (PAH):
  - Lobular clusters of atrophic acini with epithelial proliferative changes
  - Central large dilated atrophic acini or ducts
  - Moderate cytoplasm with occasional apical cytoplasmic blebs
  - Lacks diffuse nucleolar enlargement
  - Background of inflammation, atrophy, and stromal fibrosis
  - Intact or fragmented basal cell layer
- Atypical basal cell hyperplasia:
  - Proliferation of basal cells between normal columnar secretory cells and basement membrane
  - Eccentric expansion of multiple basal cell layers
  - The long axis of basal cells is often oriented parallel to the luminal surface
  - Clear cytoplasm
  - Enlarged nuclei with fine powdery chromatin, occasional nuclear grooves, and nuclear "bubble" artifact
  - Often associated with inflammation
  - High molecular weight cytokeratin (34βE12) and p63+

Table 3. Immunohistochemical Profiles of Preinvasive and Malignant Lesions in the Prostate

	PSA/PAP	*HMW CK*	*Cytokeratin**	*SMA*	*Desmin*
HGPIN	+	± (fragmented)	+	–	–
Atypical adenomatous hyperplasia	+	± (fragmented)	+	–	–
Prostatic adenocarcinoma	+	–	+	–	–
Ductal adenocarcinoma	+	–	+	–	–
Mucinous adenocarcinoma	+	–	+	–	–
Small cell carcinoma	±	–	±	–	–
Signet ring cell carcinoma	+	–	+	–	–
Squamous cell carcinoma	±	–	+	–	–
Sarcomatoid carcinoma	±	–	+	±	±
Adenoid cystic/basal cell carcinoma	±	+	+	–	–
Urothelial carcinoma	–	+	+	–	–
Phyllodes tumor	+	+	+	±	+
Leiomyosarcoma	–	–	±	+	+
Lymphoma	–	–	–	–	–

** Broad spectrum cytokeration*
Note: PSA/PAP = prostate-specific antigen/prostate acid phosphatase, HMW CK = high molecular weight cytokeratin (34βE12), SMA = smooth-muscle actin

- Atypical adenomatous hyperplasia (AAH):
  - Lobular architecture maintained with fragmented basal cell layer
  - Closely packed small acini
  - Lacks cytologic features of malignancy
  - Intimately associated with nodular hyperplasia with similar cytologic findings
- Seminal vesicles and ejaculatory ducts:
  - Circumscribed pushing border rather than haphazard arrangement
  - Bizarre cells with golden-yellow lipofuscin pigment
  - Nuclear hyperchromasia, nuclear pleomorphism, and degenerative changes
  - Negative immunoreactivity for PSA or PAP
- Paraganglion:
  - Closely associated with nerves or blood vessels
  - Lobular cluster of polygonal cells with abundant clear cytoplasm
  - Centrally located nuclei with prominent nucleoli
  - PSA–, PAP–, broad spectrum cytokeratin–, neuroendocrine markers +
- Clear cell changes:
  - Atypical adenomatous hyperplasia (AAH)
  - Cribriform hyperplasia
  - Basal cell hyperplasia
  - Cowper's glands
  - Mucinous metaplasia
  - Paraganglion
  - Xanthoma and xanthogranulomatous prostatitis (PSA– and broad spectrum cytokeratin–)
  - Metabolic storage disease
  - Sclerosing adenosis
- Basal cell layer disruption:
  - HGPIN
  - Inflammatory atypia
  - Atypical adenomatous hyperplasia
  - Atrophy and post-atrophic hyperplasia (PAH)
- Sclerosing adenosis:
  - Compressed and distorted acini in cellular fibrous stroma
  - Lobular pattern is retained, and lacks cytologic atypia
  - HMW cytokeratin (34βE12) and p63+, S100+, MSA+

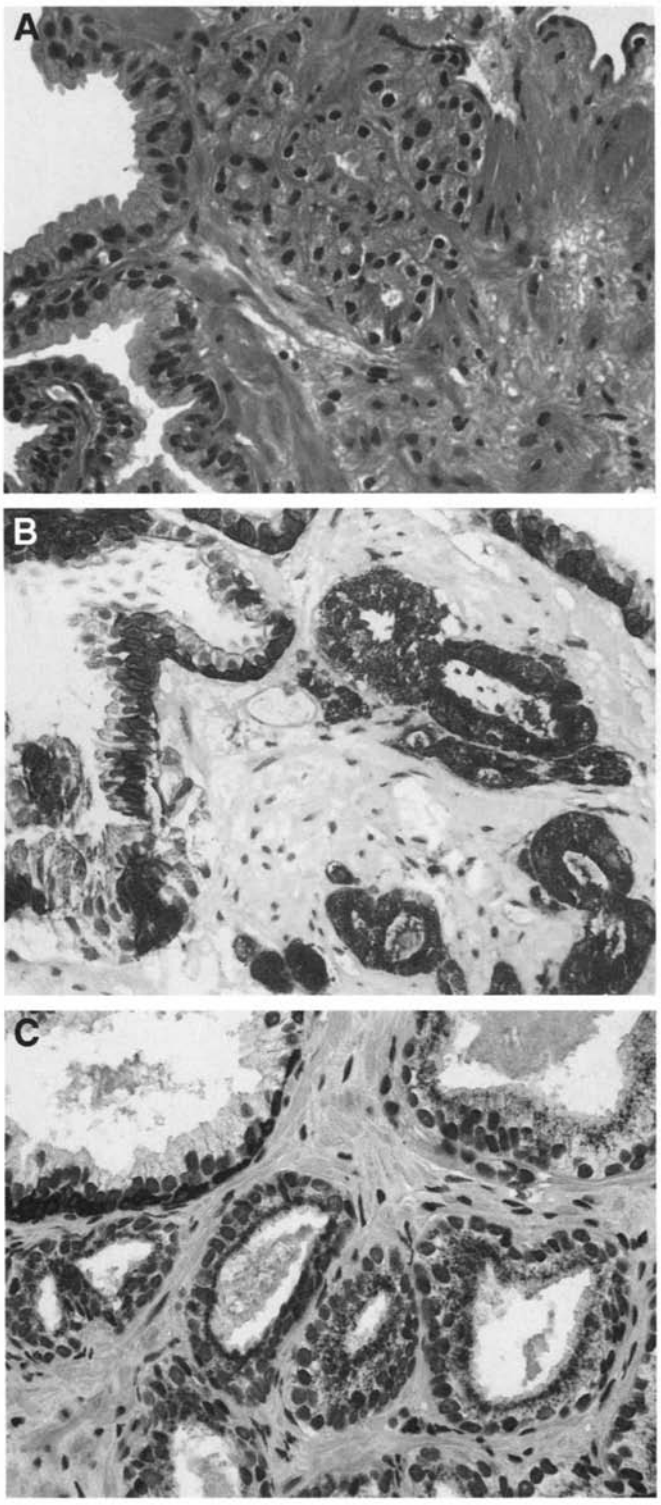


Fig. 30. **(A)** Gleason 3 + 3 = 6 adenocarcinoma, consisting of less than a dozen acini with hyperchromatic nuclei. **(B)** Triple immunostain reveals brown reaction product in benign acini but not the cancer acini (high molecular weight cytokeratin 34βE12 in basal cell cytoplasm and p63 in basal cell nuclei), and red reaction product for racemase in luminal secretory cells.

Table 4. Variants and Histologic Subtypes of Prostate Cancer That May Cause Diagnostic Confusion

Ductal adenocarcinoma (Adenocarcinoma with endometrioid features)
Mucinous carcinoma
Small cell undifferentiated carcinoma (High-grade neuroendocrine carcinoma)
Signet ring-cell carcinoma
Adenocarcinoma with neuroendocrine differentiation
Squamous cell and Adenosquamous cell carcinoma
Sarcomatoid carcinoma (carcinosarcoma)
Lymphoepithelioma-like carcinoma
Comedocarcinoma
Cribriform carcinoma
Adenocarcinoma with glomeruloid features
Adenocarcinoma with atrophic features
Adenocarcinoma with microvacuolated cytoplasm (foamy gland carcinoma)
Pseudohyperplastic adenocarcinoma
Adenoid cystic/basal cell carcinoma
Urothelial carcinoma

- Hyperplasia of mesonephric remnants:
  - Lobular arrangement of small tubular acini
  - Often contains intraluminal eosinophilic colloid-like material
- Nephrogenic metaplasia:
  - Polypoid proliferation of small tubules and papillae lined by hobnail cells
  - Thickened basement membrane and intraluminal eosinophilic secretions
  - Edematous stroma and cystic dilation of some tubule
  - Associated with adjacent urothelium-lined ducts
  - Positive racemase staining in nephrogenic metaplasia may cause diagnostic confusion
- Urothelial carcinoma:
  - Often co-existing urothelial dysplasia and carcinoma *in situ*

Fig. 30. (*Continued*) **(C)** Another case of Gleason 3 + 3 = 6 adenocarcinoma (large acinar pattern) with immunophenotype diagnostic of malignancy (note benign acinus in top left of image for comparison).

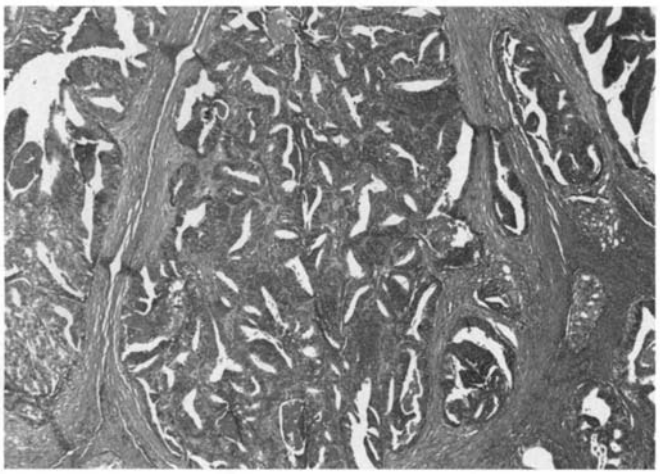


Fig. 31. Ductal adenocarcinoma. This papillary proliferation filled the large periurethral prostatic ducts and protruded into the urethra.

- May have history of bladder carcinoma
- Nuclear pleomorphism, eosinophilic cytoplasm
- Often associated with heavy inflammation
- PSA/PAP–, HMW cytokeratin (34βE12) and p63+

Prostatic Adenocarcinoma Variants

Ductal (Endometrioid) Adenocarcinoma

Clinical

- Accounts for 0.8% of prostatic adenocarcinomas
- Similar clinical presentation and prognosis as conventional acinar carcinoma
- Occurs almost exclusively in elderly men with urinary obstructive symptoms
- Most cases have concurrent invasive acinar carcinoma
- Serum PSA concentration is often normal, probably due to secretion of PSA directly into the prostatic urethra by tumor cells

Macroscopic

- Polypoid tumor located in the urethra at or near the verumontanum

Microscopic

- Considered Gleason pattern 3 (no necrosis) or 5 (with necrosis) cancer
- Cribriform and papillary proliferation of medium to large-sized acini **(Figure 31)**
- Acini lined by stratified tall columnar cells with cytologic atypia
- May have prominent central necrosis and frequent mitotic figures

Immunohistochemistry

- PSA+, PAP+, racemase+, CEA+ (focal)

Differential Diagnosis

- Cribriform hyperplasia:
  - Lacks cytologic atypia
- HGPIN (Cribriform pattern):
  - Less extensive; lacks infiltrative growth
  - Basal cell layer is focally present
- Urothelial carcinoma:
  - Dysplasia and carcinoma *in situ* of adjacent urothelium
  - PSA–
- Large gland variant of Gleason pattern 3 adenocarcinoma
- Ectopic prostatic tissue (prostatic urethral polyp):
  - Lacks cytologic atypia
- Proliferative papillary urethritis:
  - Lacks cytologic atypia
  - PSA–

Mucinous Adenocarcinoma

Clinical

- Accounts for 0.04% of prostate carcinoma (pure mucinous pattern)
- Similar clinical presentation as typical acinar carcinoma
- Aggressive, may not respond well to radiotherapy or androgen deprivation
- Elevated serum PSA concentration and bone metastasis

Macroscopic

- Often located in peripheral zone

Microscopic

- Usually considered Gleason pattern 4 adenocarcinoma
- Requires 25% of tumor to contain extracellular mucin, (excluding non-dilated glands with mucin) for diagnosis
- The presence of epithelial nests or glands in mucin pools is diagnostic **(Figure 32)**
- May present with acinar or cribriform carcinoma with luminal distention
- Collagenous micronodules are often seen

Immunohistochemistry

- PSA+, PAP+, racemase+

Differential Diagnosis

- Metastatic or contiguous spread of mucinous adenocarcinoma (e.g., colon cancer):
  - PSA–, PAP–
- Cowper's glands:
  - Circumscribed lobules of closely packed small uniform acini
  - Embedded in skeletal muscle
  - Uniform cells with mucinous cytoplasm and basally located small nuclei

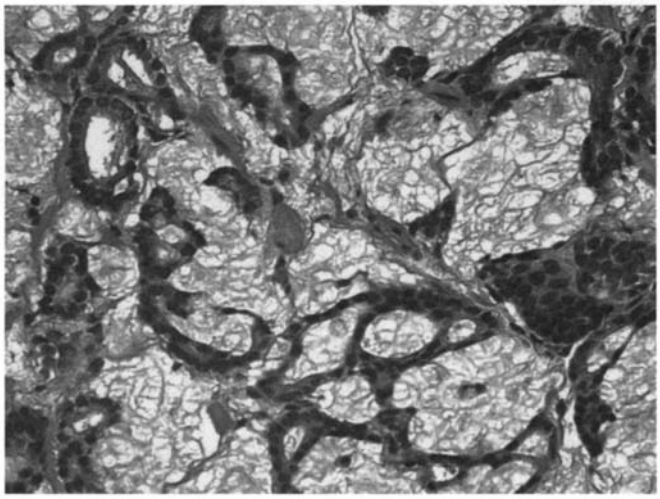


Fig. 32. Mucinous (colloid) carcinoma, with pools of mucin punctuated by floating islands and trabeculae of cancer cells.

- PSA–, high molecular weight cytokeratin and p63+

Small Cell Carcinoma (High-Grade Neuroendocrine Carcinoma)

Clinical

- Highly aggressive; most patients dead within 2 years
- May present with paraneoplastic syndromes
- May develop after radiation therapy and hormonal therapy for acinar adenocarcinoma
- Serum PSA varies according to cancer volume and stage

Microscopic

- Considered Gleason pattern 5 adenocarcinoma
- Infiltrating cords and sheets of small cells with high N/C ratio and crush artifact
- Nuclear hyperchromasia, nuclear molding, and inconspicuous nucleoli
- Mixed with typical adenocarcinoma in about half of cases

Immunohistochemistry

- Neuroendocrine markers (chromogranin A, synaptophysin, serotonin)+, PSA ±, PAP ±

Adenocarcinoma with Neuroendocrine Differentiation

- All adenocarcinomas have scattered cells with neuroendocrine features
- No prognostic significance for number of neuroendocrine cells other than pure small cell carcinoma
- Rare cancers have neuroendocrine cells with large eosinophilic granules (formerly referred to as paneth cell-like change)

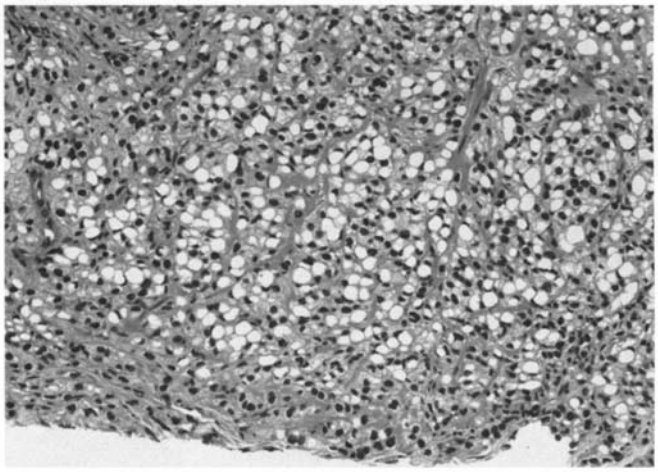


Fig. 33. Signet ring-cell carcinoma.

Signet Ring Cell Carcinoma

Clinical

- Similar clinical presentation as typical acinar carcinoma
- High stage presentation with unfavorable prognosis

Microscopic

- Considered Gleason pattern 5 adenocarcinoma
- Requires 25% tumor with signet ring cells for diagnosis **(Figure 33)**

Immunohistochemistry

- PSA+, PAP+, CEA±, mucin±, oil-red O±

Differential Diagnosis

- Paraganglion:
  - Organoid nests of polygonal cells with centrally located nuclei
- Vacuolated smooth muscle cells or lymphocytes:
  - PSA–, PAP–

Squamous Cell and Adenosquamous Carcinoma

Clinical

- Extremely rare in the prostate
- Account for <0.5% of cases of prostatic carcinoma
- Similar clinical presentation as typical acinar carcinoma
- Patients often have a prior history of hormonal or radiation therapy
- May be associated with schistosomiasis
- Aggressive; patients often present with osteolytic bone metastasis and are refractory to hormonal therapy
- Serum PSA may be normal even in the presence of metastasis

Macroscopic

- Often located in the periurethral region

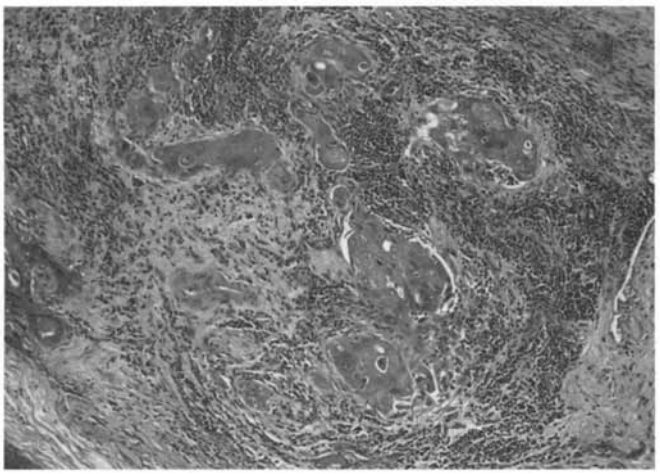


Fig. 34. Squamous cell carcinoma in the prostate arising ten years after radiation and hormonal therapy for high-grade adenocarcinoma.

Microscopic

- Usually high grade
- Nests and cords of malignant cells with squamous differentiation **(Figure 34)**
- Requires the absence of acinar carcinoma and bladder involvement for diagnosis of pure squamous cell carcinoma

Immunohistochemistry

- PSA ±, PAP ±, high molecular weight cytokeratin ±

Differential Diagnosis

- Squamous metaplasia:
  - Lacks significant nuclear pleomorphism
- Metastatic squamous cell carcinoma:
  - PSA–, PAP–

Sarcomatoid Carcinoma (Carcinosarcoma)

Clinical

- Often occurs in elderly patients with urinary obstructive symptoms
- Patients often have prior history of hormonal or radiation therapy
- Highly aggressive, with median survival of 12 months
- No differences in outcome for those with or without heterologous elements

Microscopic

- Considered Gleason pattern 5 adenocarcinoma
- Spindle cell proliferation with epithelial differentiation
- Nuclear pleomorphism and numerous mitotic figures
- Heterologous components variable, including osteosarcoma, leiomyosarcom, etc.



Fig. 35. Glomeruloid pattern of adenocarcinoma.

Immunohistochemistry

- PSA ±, PAP ±, broad-spectrum cytokeratin+

Differential Diagnosis

- Postoperative spindle cell nodule:
  - Clinical history of prior surgery
  - Lacks significant nuclear pleomorphism
- Sarcoma:
  - Lacks evidence of epithelial differentiation

Lymphoepithelioma-Like carcinoma

- Histologic features: Islands of closely packed glands set in a dense lymphocytic stroma
- Very rare; unknown prognostic significance

Comedocarcinoma

- Necrotic debris within lumens indicates Gleason pattern 5 cancer
- Used as a descriptive term—not a specific entity

Cribriform Carcinoma

- Collapsible fenestrations indicates Gleason pattern 3 cancer; near-solid rigid openings indicate Gleason pattern 4 cancer
- Main differential diagnostic consideration: extensive high-grade PIN
- Used as a descriptive term—not a specific entity

Adenocarcinoma with Glomeruloid Features

- Unique Gleason grade 3 pattern consisting of a tightly cohesive tuft of cancer cells within a larger malignant acinus reminiscent of a glomerulus **(Figure 35)**

Adenocarcinoma with Atrophic Features

- Occurs in up to 2% of contemporary needle biopsies
- Not considered as a specific clinicopathologic entity
- Similar prognosis as conventional prostatic adenocarcinoma

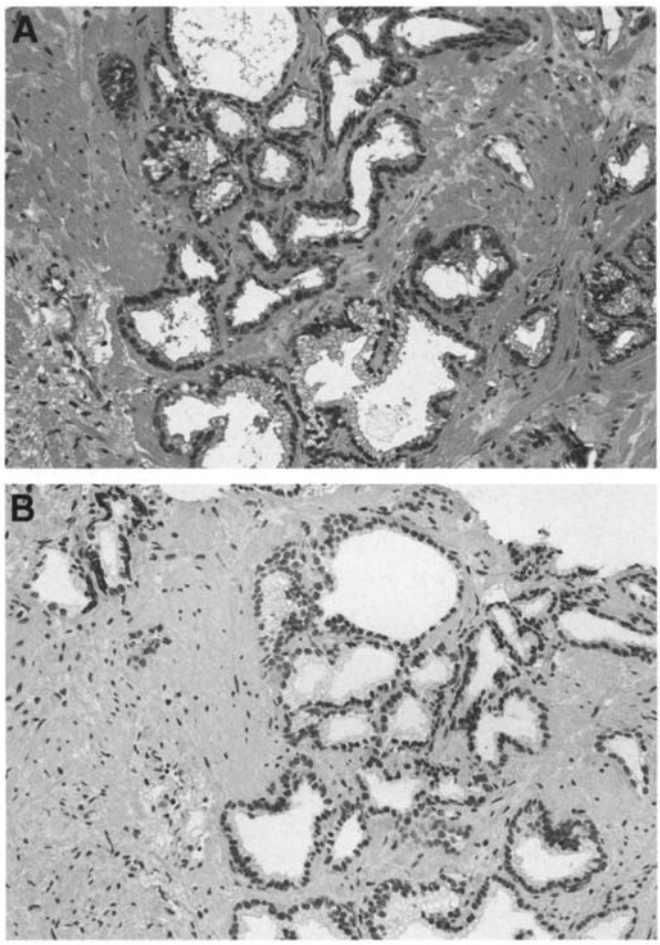


Fig. 36. Atrophic pattern of adenocarcinoma. **(A)** Large acini lined by flattened epithelium reminiscent of atrophy. **(B)** Same focus as A immunostained for high molecular weight cytokeratin 34βE12. The absence of staining in the acini of concern confirms the diagnosis of malignancy. Note benign acini with immunostain acting as positive internal control for the staining reaction.

- Cancer consisting of acini with dilated lumens that may be mistaken for atrophy at low power (cancer mimicking atrophy) **(Figure 36)**

Adenocarcinoma with Microvacuolated Cytoplasm (Foamy Gland Carcinoma)

- Abundant microvacuolated cytoplasm, often with small shrunken nuclei and nucleoli **(Figure 37)**
- May be more aggressive—unconfirmed
- Difficult to diagnose owing to similarity to mucinous metaplasia
- Usually mixed with typical acinar adenocarcinoma

Pseudohyperplastic Pattern of Carcinoma

- Resembles nodular hyperplasia **(Figure 38)**
- Rare
- No clinical significance

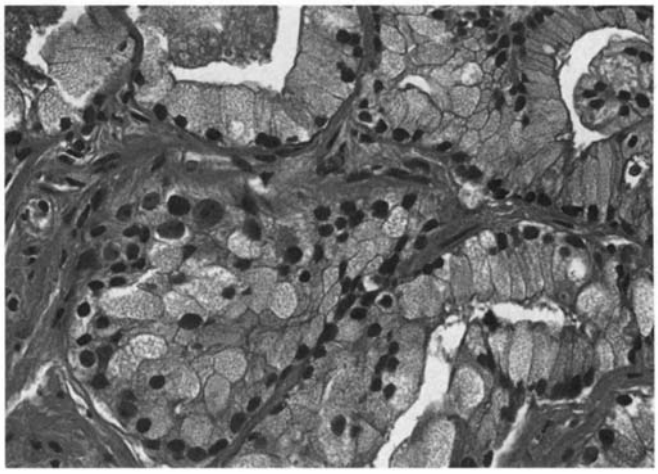


Fig. 37. Microvacuolated (foamy gland) adenocarcinoma. The nuclei are often basally located and hyperchromatic, creating diagnostic difficulty.

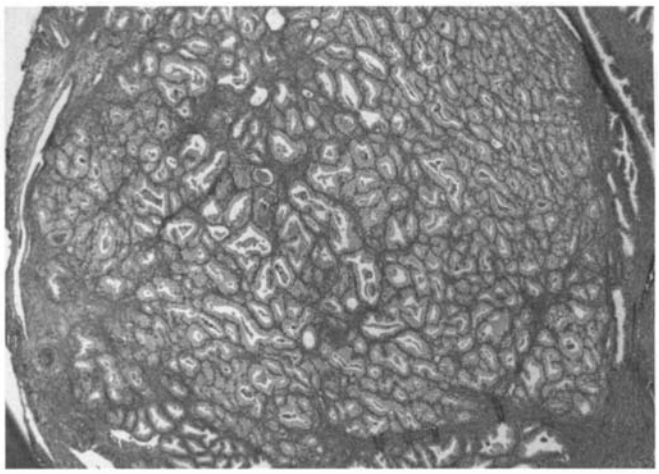


Fig. 38. Pseudohyperplastic adenocarcinoma. At low magnification, this focus could easily be misinterpreted as BPH. However, cytologic features and immunphenotype were diagnostic of malignancy. This focus is considered Gleason 1 + 1 = 2 adenocarcinoma.

Adenoid Cystic/Basal Cell Carcinoma

Clinical

- Similar clinical presentation as typical acinar carcinoma
- Considered cancer of low malignant potential
- Serum PSA concentration not elevated.

Microscopic

- Irregular and infiltrating nests of basal cells in a myxoid stroma
- Predilection for perineural invasion
- Often coexistence of adenoid cystic pattern with rounded fenestrations and basaloid pattern with cell nests and peripheral palisading

- Elongated cells with crowding, stippled chromatin, and inconspicuous nucleoli
- May be associated with squamous differentiation with keratin production
- Two cell populations: peripheral basaloid cells and inner columnar ductal cells

Immunohistochemistry

- PSA ±, PAP ±, high molecular weight cytokeratin and p63+

Differential Diagnosis

- Basal cell hyperplasia/adenoma:
  - Solitary, well-circumscribed nodules associated with benign prostatic hyperplasia (BPH)
  - Uniformly distributed solid nests of hyperplastic basal cells
  - Condensed stroma at the peripheral of nodules

Urothelial Carcinoma

Clinical

- Accounts for <1% of prostate cancers
- Patients present with hematuria and urinary obstructive symptoms
- Poor prognosis, with osteolytic bone metastasis; most die within 2 years of diagnosis
- Refractory to hormonal therapy
- Serum PSA concentration is normal

Microscopic

- Marked cytologic atypia with nuclear pleomorphism and high mitotic figures
- Often associated with prominent stromal response
- Dysplasia and carcinoma in situ common in adjacent urothelium
- Usually coexistent bladder cancer

Immunohistochemistry

- CEA+, PSA–, PAP–, high molecular weight cytokeratin (34βE12)+, cytokeratin 20±

Differential Diagnosis

- Prostatic adenocarcinoma:
  - Acinar differentiation with less nuclear pleomorphism
  - PSA+, PAP+, high molecular weight cytokeratin–
- Inverted papilloma:
  - Complex arborizing invagination with peripheral palisading
  - Lack fibrovascular core
- HGPIN
- Rhabdomyosarcoma:
  - Very rare, occurs mainly in children
  - Embryonal rhabdomyosarcoma is most frequent type

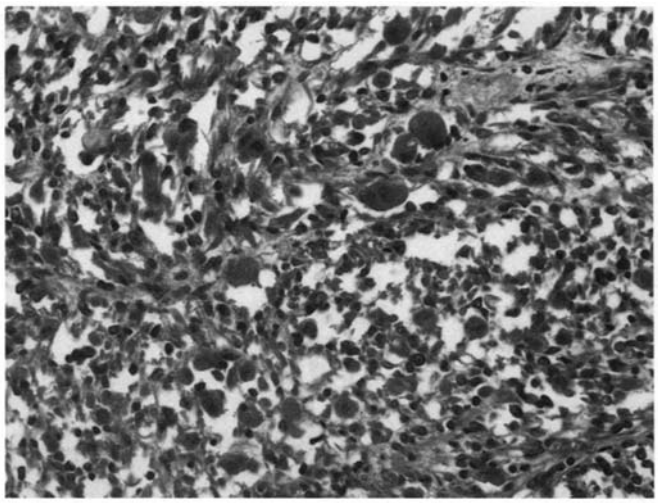


Fig. 39. Rhabdomyosarcoma with an abundance of malignant rhabdomyoblasts.

  - Sheets of immature spindle cells and occasional rhabdomyoblasts in myxoid stroma **(Figure 39)**
  - Myoglobin+, MSA+, desmin+, PSA–, PAP–

Leiomyosarcoma

Clinical

- Most common prostatic sarcoma in adults; accounts for 26% of all prostatic sarcomas
- Aggressive; usually recurs and results in death

Microscopic

- Similar to leiomyosarcoma of other sites
- Interlacing fascicles of spindle cells with eosinophilic cytoplasm and fusiform nuclei
- Necrosis, cytologic atypia, and increased number of mitotic figures

Immunohistochemistry

- Smooth muscle actin+, desmin+

Differential Diagnosis

- Symplastic leiomyoma:
  - Multinuclear giant cells and bizarre cells with nuclear degeneration
  - Mitotic figures inconspicuous
- Stromal hyperplasia with atypia:
  - Bizarre hyperchromatic nuclei with inconspicuous nucleoli, rarely vacuolated
  - No mitotic figures or necrosis
- Postoperative spindle cell nodule:
  - Small size of lesion
  - Fascicles of relatively uniform spindle cells in a myxoid stroma



Fig. 40. Phyllodes tumor. Leaf-like projections with a benign proliferation of epithelium and stroma.

- Cells with abundant cytoplasm
- Enlarged nuclei with fine granular chromatin and prominent nucleoli
- Mitotic figures may be frequent
- Lacks atypical mitotic figures and nuclear pleomorphism
- Prominent vasculature and associated with inflammation

♦ Blue nevi:
- Pigmented dendritic bipolar cells in fibrous stroma

Phyllodes Tumor

Clinical

♦ Patients usually present with urinary obstructive symptoms
♦ Potentially aggressive and often recurrent
♦ May dedifferentiate after recurrence (stromal overgrowth)
♦ Histogenesis is uncertain

Macroscopic

♦ Cystic and spongy tumor with prostatic enlargement, similar to BPH

Microscopic

♦ Biphasic growth of stromal and epithelial components
♦ Interlacing fascicles of spindle cells with leaf-like projections into duct-like spaces **(Figure 40)**
♦ Increased stromal cellularity and overgrowth with compressed, elongated channels
♦ Uniform nuclei with inconspicuous nucleoli
♦ Grading is not reliable in predicting recurrence.
♦ May undergo sarcomatous transformation after recurrence (stromal overgrowth)

Immunohistochemistry

♦ Stroma: actin+, vimentin+, desmin–, S-100 protein–
♦ Luminal epithelial cells: PSA+, PAP+, keratin+

Differential Diagnosis

♦ Stromal hyperplasia with atypia:
- Increased stromal cellularity and nuclear atypia
- Bizarre cells with nuclear degenerative change
- Associated with BPH

♦ Nodular hyperplasia with fibroadenoma-like areas:
- Cystically dilated acini associated with hyperplastic epithelium

♦ Multilocular prostatic cystadenoma:
- Epithelial cell-lined cyst in a fibrous stroma
- Lacks stromal cellularity

♦ Leiomyosarcoma:
- Lacks biphasic growth pattern of Phyllodes tumor

♦ Seminal vesicle cyst (lateral location) and Mullerian duct cyst (midline location):
- Unilocular cyst
- No stromal cellularity
- PSA–, PAP–

Lymphoma

Clinical

♦ Occurs in elderly patients presenting with urinary obstructive symptoms
♦ Secondary involvement more common than primary involvement (55% vs. 35%)
♦ Poor prognosis (median survival = 23–28 months) regardless of age, histologic type, treatment, clinical stage at presentation, or type of involvement (primary vs. secondary)
♦ Criteria for the diagnosis of primary lymphoma:
- Absence of hematopoeitic involvement (spleen, lymph nodes, peripheral blood, or liver) within 1 month prior to diagnosis
- Limited to the prostate and adjacent soft tissue

Macroscopic

♦ Diffusely enlarged with firm to rubbery consistency

Microscopic

♦ Diffuse large cell and small lymphocytic lymphoma are two most common types
♦ Diffuse irregular infiltrates of monotonous lymphocytes
♦ Preservation of acini

Differential Diagnosis

♦ Granulomatous prostatitis:
♦ Acinar destruction with polymorphous inflammatory infiltrate

TREATMENT EFFECTS

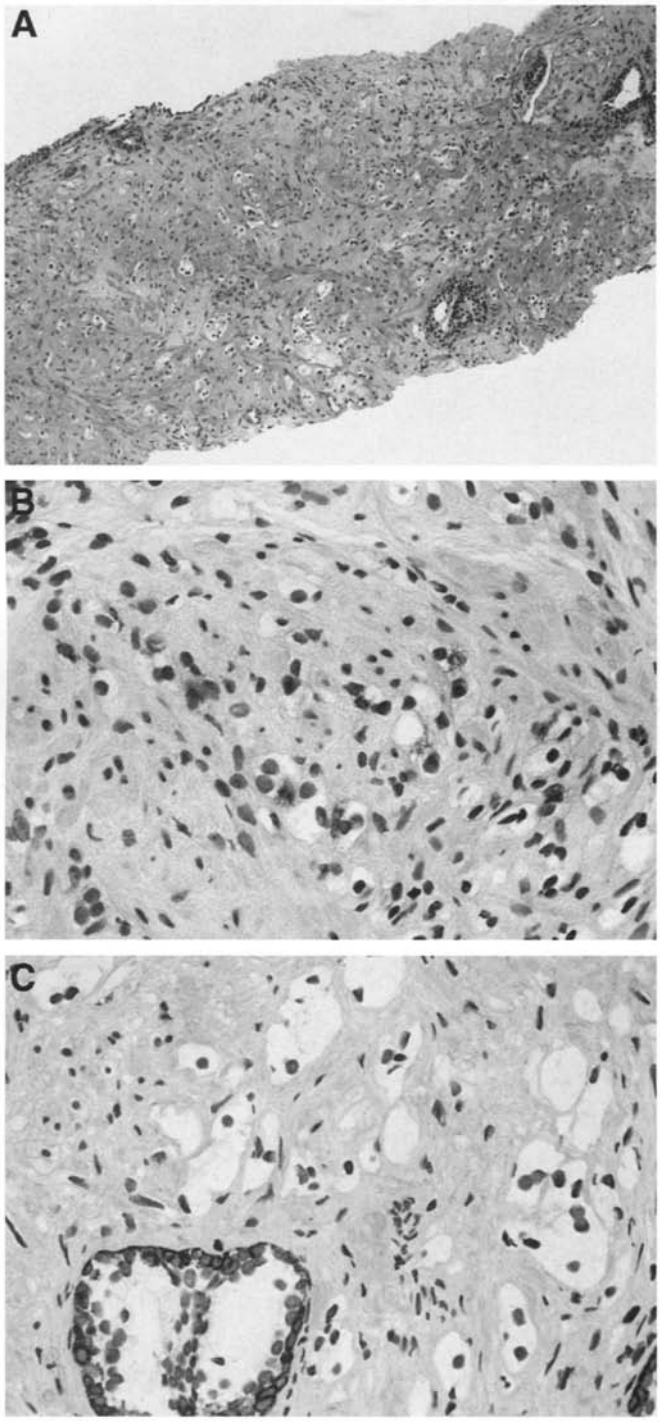


Fig. 41. Androgen deprivation therapy-treated adenocarcinoma. **(A)** Needle biopsy contains numerous minute nests of malignant cells with small nuclei and abundant clear cytoplasm. These nests stand in contrast with the large adjacent atrophic acini. **(B)** Brown staining indicated PSA immunoreactivity in the cytoplasm of most of the malignant cells, confirming prostatic epithelial origin. **(C)** Immunostain for high molecular weight cytokeratin 34βE12 reveals an absence of staining in the malignant acini. Benign acini are positive.

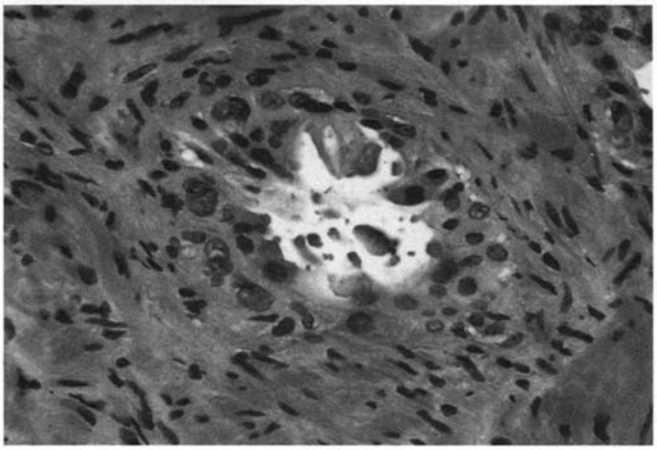


Fig. 42. Radiation change of the benign prostatic epithelium initially misdiagnosed as adenocarcinoma. There are marked nuclear abnormalities, including variation in size and shape and hyperchromasia.

Androgen Deprivation Therapy

Benign

- Acinar atrophy and distortion
- Decreased ratio of acini to stroma, with stromal fibrosis and hyalinization
- Atypical basal cell hyperplasia, squamous metaplasia, and urothelial metaplasia
- Acinar rupture with preservation of basal cell layer
- Cytoplasmic vacuolization and nuclear shrinkage

Cancer

- Linear arrays and ragged infiltrate of malignant acini with cytoplasmic vacuolization, nuclear pyknosis, and hyperchromasia **(Figure 40)**
- Nucleoli may be inconspicuous
- Malignant glands are often dilated, with atrophic features and a hemangiopericytoma-like pattern
- Lacks basal cell layer
- Reduced incidence and extent of HGPIN

Immunohistochemistry

- PSA+, PAP+, high molecular weight cytokeratin and p63–, racemase+ (cancer) **(Figure 41)**

Differential Diagnosis

- Clear cell change:
  - AAH
  - Cribriform hyperplasia

- Basal cell hyperplasia
- Cowper's glands
- Mucinous metaplasia
- Paraganglion
- Xanthoma and xanthogranulomatous prostatitis
- Metabolic storage disease
- Sclerosing adenosis

Radiation Therapy

Benign

- Lobular and acinar atrophy, decreased acini to stroma ratio, stromal edema, and fibrosis **(Figure 42)**
- Atypical basal cell hyperplasia, squamous and transitional cell metaplasia
- Acinar rupture with extravasation, dystrophic calcification
- Vascular myointimal proliferation
- Cytoplasmic clearing with nuclear pyknosis

Cancer

- Linear arrays and ragged infiltrate of malignant acini with cytoplasmic vacuolization, nuclear pyknosis, and hyperchromasia
- Nucleoli may be inconspicuous
- Lacks basal cell layer
- Reduced incidence and extent of HGPIN
- Grading of salvage prostatectomy specimens is predictive of survival

Immunohistochemistry

- PSA+, PAP+, high molecular weight cytokeratin and p63–, racemase+ (cancer)

TNM CLASSIFICATION OF PROSTATE CANCER (2002 REVISION)

- T: Primary tumor:
  - Tx: primary cancer cannot be evaluated
  - T1: incidental finding, non-palpable, nor visible by imaging:
    - T1a: ≤5% of tissue resected
    - T1b: >5% of tissue resected
    - T1c: detected by needle biopsy due to screening for PSA (incidental tumor identified in both lobes by needle biopsies, but not palpable or reliably visible by imaging)
  - T2: palpable or visible cancer clinically confined within the prostate:
    - T2a: involves one-half or less of lobe
    - T2b: involves more than one-half of one lobe, but no more than one lobe
    - T2c: involves both lobes
  - T3: extends outside the prostate:
    - T3a: extraprostatic extension (unilateral or bilateral)
    - T3b: seminal vesicle invasion
- T4: fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, or levator muscles
- N: Regional lymph nodes:
  - N0: no regional lymph node metastasis
  - N1: regional lymph node(s) metastasis
- M: Distant metastasis:
  - M0: No distant metastasis
  - M1: Distant metastasis:
    - M1a: non-regional nodes
    - M1b: bone
    - M1c: other sites

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32

Testis and Testicular Adnexa

Kenneth A. Iczkowski, MD

CONTENTS

I. Non-Neoplastic Diseases of Testicle....32-3
- Congenital Abnormalities....32-3
  - Cryptorchidism....32-3
  - Anorchidism....32-3
  - Polyorchidism....32-3
  - Adrenal Cortical Rests....32-4
  - Splenic-Gonadal Fusion....32-4
- Acquired Abnormalities....32-4
  - Testicular Torsion and Infarct....32-4
  - Varicocele....32-4
- Infectious Disease and Inflammatory Conditions of Testis & Epididymis....32-5
  - Viral Orchidoepididymitis....32-5
  - Bacterial Orchidoepididymitis....32-5
- Granulomatous Orchidoepididymitis....32-6
  - Mycobacterial Orchidoepididymitis....32-6
  - Fungal Orchidoepididymitis....32-6
  - Syphilitic Orchidoepididymitis....32-6
  - Leprosy....32-6
  - Sarcoidosis....32-7
  - Malakoplakia....32-7
  - Idiopathic Granulomatous Orchitis....32-7
- Infertility....32-7
  - Normal or Nearly Normal....32-7
  - Hypospermatogenesis....32-8
  - Aspermatogenesis....32-8
  - Early Maturation Arrest....32-9
  - Late Maturation Arrest....32-9
  - Tubular Hyalinization....32-10
    - Klinefelter's Syndrome....32-10
    - Other Causes....32-10

II. Neoplasms of Testis....32-11
- Germ Cell Tumors....32-11
  - Cell of Origin....32-11
  - Risk of Germ Cell Tumors....32-11
  - Ancillary Stains....32-11
  - Staging....32-11
  - Treatment....32-11
  - Intratubular Germ Cell Neoplasia, Unclassified (IGCNU)....32-12
  - Seminoma (Classic Type)....32-12
  - Spermatocytic Seminoma....32-13
  - Embryonal Carcinoma....32-14
  - Yolk Sac Tumor (Endodermal Sinus Tumor)....32-14
  - Teratoma....32-15
  - Dermoid Cyst....32-16
  - Epidermoid Cyst....32-16
  - Choriocarcinoma....32-16
  - Mixed Germ Cell Tumor....32-16
- Sex Cord-Stromal Tumors....32-17
  - Leydig Cell Tumor....32-17
  - Sertoli Cell Tumor, Typical Type....32-18
  - Sclerosing Sertoli Cell Tumor....32-18
  - Large-Cell Calcifying Sertoli Cell Tumor....32-18
  - Granulosa Cell Tumor, Adult Type....32-19
  - Granulosa Cell Tumor, Juvenile Type....32-19
- Mixed Germ Cell and Sex Cord-Stromal Tumor:....32-19
  - Gonadoblastoma....32-19
  - Testicular Tumor of Adrenogenital Syndrome (TTAGS)....32-20

Hematopoietic Neoplasms 32-20
Lymphoma and Plasmacytoma.....32-20
Leukemia 32-20
Vascular Lesions: Capillary Microangioma 32-21

III. Lesions of Epididymis and Tunics.....32-21
Sperm Granuloma 32-21
Adenomatoid Tumor 32-21
Papillary Cystadenoma.....32-21
Hydrocele and Benign Papillary Mesothelioma 32-22
Malignant Mesothelioma 32-22
Tumors Homologous to Ovarian Tumors.....32-22

IV. Lesions of Spermatic Cord.....32-23
Nodular Fibrous Periorchitis 32-23
Vasitis Nodosa 32-23
Proliferative Funiculitis 32-23
Sarcomas 32-23
Rhabdomyosarcoma 32-23
Liposarcoma 32-24
Leiomyosarcoma.....32-24

V. TNM Classification of Testicular Tumors.....32-24

VI. Suggested Reading.....32-25

NON-NEOPLASTIC LESIONS OF TESTIS

Congenital Abnormalities

Cryptorchidism

Clinical

- Condition in which one or both testes fail to descend into the scrotum. They may be found in the inguinal canal, the upper scrotum, or within the abdomen
- Bilateral in 18% of patients; family history of cryptorchid testis in 14%
- Cause unknown:
  - May be related to hormonal abnormalities, mechanical impairment to descent, or unidentified intrinsic abnormality in the testis
- Complications include infertility and the development of germ cell tumors:
  - Infertility is most frequent complication; 9% of infertile males have cryptorchid testes:
    - Only 16% to 25% of patients with bilateral cryptorchid testes are fertile
    - Improves to 25% to 81% if only one testicle undescended
    - Orchidopexy (surgical procedure that places the testicle in the scrotum) must be performed before 4 years to maintain fertility in the undescended testicle
- Germ cell tumors are 4 to 10 times more likely in cryptorchid testis:
  - Orchidopexy does not decrease the risk of a germ cell tumor, but allows for regular testicular exam
- Other complications include torsion and infarction

Macroscopic

- May be of normal size or small
- Dependent on age at removal of testicle or orchiopexy

Microscopic

- Histologic appearance of cryptorchid testis varies with age, testicular position, and prior hormonal therapy. Human chorionic gonadotropin or gonadotropin releasing hormone [GnRH] is sometimes used as a hormonal means to bring the testicle into the scrotum
- Prepubertal testis often shows a Sertoli cell nodule called Pick's adenoma (**Figure 1**), or germ cells are present but in decreased numbers
- Following puberty, changes become more pronounced:
  - Tunica propria thickening
  - Reduced tubular diameter
  - Tubular sclerosis
  - Interstitial fibrosis
  - More prominent Leydig cell clusters

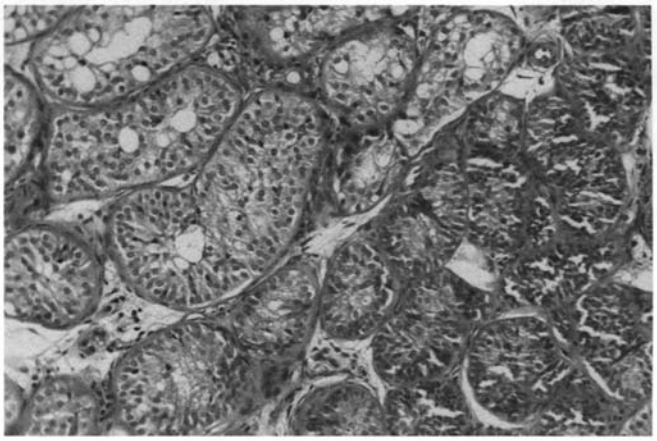


Fig. 1. Cryptorchid testis in 13 year-old boy. Tubules have no germ cells and show aspermatogenesis. Right side of field has a Sertoli cell nodule.

Anorchidism

Clinical

- Absence of both testicles
- Rare condition
- Unilateral in 1 in 5,000 males; bilateral in 1 in 20,000 males
- Gonad may disappear due to multiple causes, including intrinsic gonadal disorder, infection, trauma, torsion, or atrophy resulting from the overproduction of androgens
- Clinical distinction from cryptorchidism is critical

Macroscopic

- No testis is usually identified by a urologist on exploration
- If vas deferens is identified, then an ipsilateral testicle had to exist during gestation
- Epididymis or vas may be all that remains

Polyorchidism

Clinical

- Presence of more than two testicles
- Extremely unusual
- Fewer than 80 reported cases
- Patients present with a scrotal mass that may be confused with a testicular tumor

Macroscopic

- Extra testis may have its own epididymis and a vas deferens that joins other vas distally, or testis may share a common epididymis with another testicle

Microscopic

- Histology of testicle may be normal, or there may be hypospermatogenesis
- Spermatogenic function of supernumary testis varies

Adrenal Cortical Rests

Clinical

- Usually an incidental finding of adrenal cortical tissue in the testis, or adjacent spermatic cord or epididymis
- Identified in 4% to 15% of individuals
- Not clinically significant

Macroscopic

- Encapsulated nodules of adrenal cortical tissue usually in spermatic cord, epididymis, rete testis, or tunica albuginea, and rarely within testis
- Usually <1 cm in size; most only a few millimeters

Microscopic

- Adrenocortical tissue that usually exhibits normal zonation of adrenal tissue seen in cortex
- Adrenal medullary tissue not present

Splenic-Gonadal Fusion

Clinical

- Patients present with a scrotal or inguinal mass consisting of fused spleen and testis
- Strong male predilection
- Two forms:
  - Continuous:
    - Has cord connecting the splenic tissue to the testicle
  - Discontinuous:
    - No cord
- Approximately one-third of patients with continuous form have severe congenital defects in extremities

Macroscopic

- Splenic tissue attached to testicle; typically a discrete mass:
  - May be as large as 12 cm
- Small aggregates of splenic tissue may be found along the length of the cord or the entire cord may be composed of splenic tissue
- Grossly, tissue looks identical to spleen

Microscopic

- Splenic tissue looks like normal spleen histologically

Acquired Abnormalities

Testicular Torsion and Infarct

Clinical

- Describes twisting of the spermatic cord, usually within tunica vaginalis; twisting causes venous obstruction:
  - Testicle becomes hemorrhagic
  - Eventually, arterial flow is interrupted and infarction occurs
- Predisposing conditions include:
  - Absence of scrotal ligaments
  - Shortened attachment of peritoneal ligaments
  - Incomplete descent
  - Testicular atrophy
- Usually in children and young adults:
  - Present with marked testicular pain
  - May develop after physical activity
- Prompt intervention is necessary to prevent infarction:
  - Detorsion should be performed within 6–8 hours of torsion to prevent loss of testicle
  - Infarction is almost certain if torsion is not corrected within 24 hours
- Detorsion may be attempted manually, but it may require surgical intervention (orchidopexy)
- Diagnosis is usually evident by history and exam, but Doppler studies or nuclear-based perfusion scans may be useful to show decreased blood flow in torsion (vs. increased blood flow in epididymitis/inflammatory conditions)

Macroscopic

- Gross examination reveals a swollen blood-filled testicle

Microscopic

- Up to 6 hours after torsion, testis shows venous congestion and interstitial hemorrhage
- At 9 hours, PMNs marginate from capillaries and severe interstitial hemorrhage present
- After 1 to 2 days, hemorrhagic infarction develops
- Trauma can cause infarction in adults (**Figure 2**)

Varicocele

Clinical

- Results from abnormal dilatation and tortuosity to veins of pampiniform plexus of spermatic cord:
  - Thought to be result of insufficient venous valves
- Primarily involves the left side (90% of cases), or may be bilateral (10%)
- Varicocele associated with infertility:
  - A number of hypotheses have been posited regarding the cause of infertility:
    - Endocrinologic insufficiency
    - Venous stasis, resulting in a buildup of toxic metabolites and decreased oxygenation
    - Increased temperature due to blood flow
- Ligation of left spermatic vein may correct varicocele and fertility:
  - Fertility returns in up to 55% of patients undergoing ligation

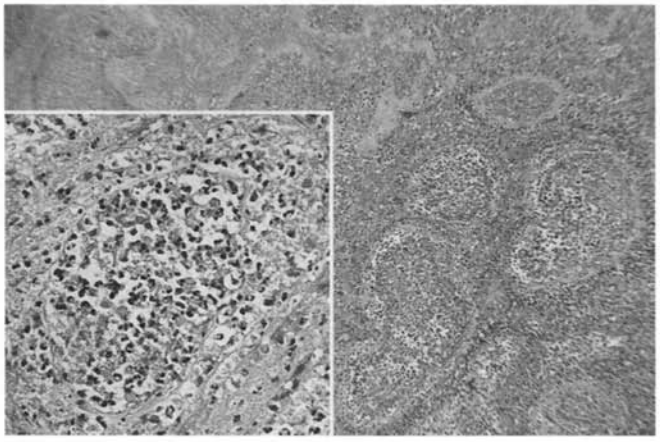


Fig. 2. Infarct of testis. 75 year-old man crushed his testis when it was caught between toilet seat and commode as he sat down. Orchiectomy 4 weeks subsequently shows only shadow outlines of tubules. Inset (left) has necrotic cell debris filling tubular lumen.

Macroscopic

- Tortuous and dilated veins of pampiniform plexus
- Rarely seen by pathologist

Microscopic

- Dilatation of spermatic vein, surrounded by fibrosis (**Figure 3**):
  - Testicular biopsy shows hypospermatogenesis (*see* below) with germ cell sloughing and Leydig cell hyperplasia
- Histologic changes may revert to normal after spermatic vein ligation

Infections and Inflammatory Conditions of Testis and Epididymis

Viral Orchidoepididymitis

Clinical

- Most common virus involved in viral orchidoepididymitis is mumps; also Coxsackie B (second most common), influenza, EBV, echovirus, adenovirus, varicella, vaccinia, rubella, dengue, and others
- May occasionally cause viral orchitis
- AIDS may involve the testicle and is characterized by a lymphocytic infiltrate
- Usually occurs as a complication of up to 35% of adult mumps
- Infrequent in children
- Bilateral in 25% of cases
- Bilateral involvement usually leads to infertility
- Men with unilateral involvement usually maintain fertility
- Testicular involvement typically becomes evident 4–6 days after parotid involvement

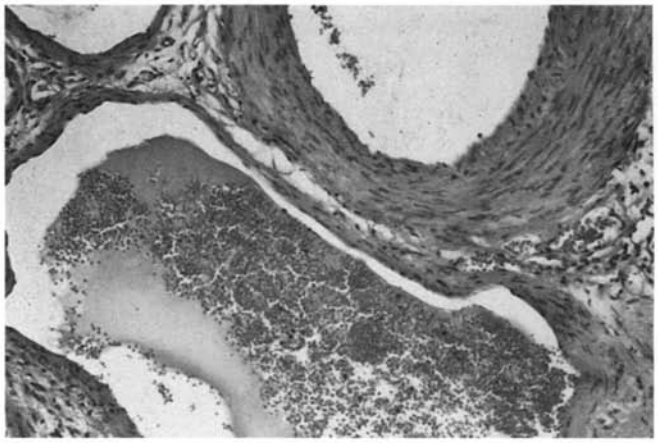


Fig. 3. Varicocele shows dilated venous channels.

Macroscopic

- Early, testis may appear normal
- If involvement is severe, atrophic changes develop

Microscopic

- Changes are multifocal and characterized by acute inflammation of seminiferous tubules and interstitium
- Loss of germ cells; ultimately, tubular sclerosis and interstitial fibrosis develop

Bacterial Orchidoepididymitis

Clinical

- In younger men, acute and chronic bacterial orchitis is most often attributable to *Chlamydia trachomatis,* and *Neisseria gonorrhea*, representing common causes of male infertility (*see* below)
- In older men, *Escherichia coli* from associated urinary tract infection becomes the most common etiologic agent
- Other responsible agents causing seeding from other sites via lymphatics or blood: Klebsiella sp., Streptococci, Staphylococci, Pneumococci, *Salmonella enteritidis*, and *Actinomyces israeli*
- Brucellosis involves the testicle and epididymis in 20% of all cases. Brucellosis is characterized by a testicular mass with constitutional symptoms (undulating fever, malaise, headache, and sweats)
- Complications include an abscess with involvement of the scrotum and scrotal sinus formation

Macroscopic

- Swollen testicle
- Abscess formation may be present

Microscopic

- Polymorphonuclear leukocyte inflammatory infiltrate involving interstitium and seminiferous tubules
- In advanced cases, abscesses develop
- Brucellosis causes an infiltrate of lymphocytes and histiocytes with occasional granulomas present

Granulomatous Orchidoepididymitis

Mycobacterial Orchidoepididymitis

Clinical

- Testicular involvement by *Mycobacterium tuberculosis* is always secondary to infection elsewhere in the body
- In adults, tuberculous orchitis typically occurs as an ascending infection from other sites in the genitourinary tract
- Renal tuberculosis results in bladder and prostatic involvement, with subsequent spread to the epididymis and testicle
- Most patients are adults
- In children, involvement usually occurs by hematogenous spread from the lung
- Patients may have constitutional symptoms but usually present with only testicular swelling and pain

Macroscopic

- Testicle may be enlarged with multiple soft nodular white caseating granulomas that typically are a few millimeters in size or may coalesce (**Figure 4**)
- Fistulae may extend to the scrotum

Microscopic

- Necrotizing and non-necrotizing granulomatous inflammation present
- Granulomas consist of histiocytes, giant cells, and lymphocytes in a fibrotic stroma that surrounds necrotic material
- Inflammatory process is destructive of testicular parenchyma

Fungal Orchidoepididymitis

Clinical

- Rare
- Fungal organisms that can cause orchitis include *Blastomyces hominis, Coccidioidomyces immitis, Histoplasma capsulatum, Cryptococcus neoformans*, and *Trichophyton mentagraphytes*
- Fungal infections involving the genitourinary tract may occur in immunocompromised patients

Macroscopic

- Necrotic granulomas and abscesses are present

Microscopic

- Histologic features are identical to those of fungal infections occurring elsewhere in the body
- Necrotizing and non-necrotizing granulomas and neutrophilic microabscesses are present
- Organisms may be identified using special stains, such as methenamine silver or periodic acid-Schiff stains

Syphilitic Orchidoepididymitis

Clinical

- Congenital and acquired forms occur

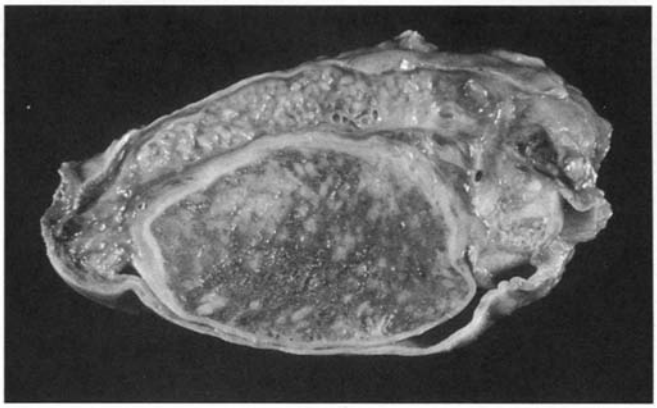


Fig. 4. Tuberculous orchitis and epididymitis. Both organs are expanded by numerous yellow nodules.

- In congenital syphilis, testicular enlargement is present at birth. In the acquired form, the testes are involved in tertiary syphilis

Macroscopic

- In infants, the testes are enlarged; over time, the testes become fibrotic and small
- In adults, the testes are soft, yellow, and necrotic. Gummas may be present

Microscopic

- The testes involved by congenital syphilis exhibit interstitial inflammation with abundant plasma cells
- Arteries show obliterative endarteritis; inflammation destructive; over time, the testes become fibrotic
- Acquired (or tertiary) syphilis has two histologic patterns: interstitial orchitis and gummatous orchitis:
  - Interstitial orchitis is identical to that seen in congenital syphilis, and ultimately leads to small fibrotic testes
  - Gummatous orchitis is characterized by coagulative necrosis with a peripheral zone of fibrous tissue containing lymphocytes, plasma cells, and occasional giant cells
  - Both gummas and interstitial orchitis may occur in the same testicle. Spirochetes may be seen with special silver stains (Warthin-Starry, Dieterle)

Leprosy

Clinical

- Very rare in the United States, but seen in other parts of the world
- May be a cause of infertility
- The testes are frequently involved because lower temperature within the scrotum facilitates the growth of bacillus

Macroscopic

- Gross appearance of testes is dependent on the stage of infection
- Early, testes may look normal
- In latter stages, testes are small and fibrotic

Microscopic

- Three phases of testicular leprosy:
  - Early: a vascular phase characterized by lepra cells containing numerous organisms within blood vessel walls and testicular interstitium
  - Followed by: an interstitial phase with obliterative endarteritis, interstitial fibrosis, and lepra cells
  - Finally: an obliterative phase characterized by a loss of testicular parenchyma and replacement by fibrous tissue

Sarcoidosis

Clinical

- Systemic granulomatous disease of unknown cause
- Genitourinary system is involved in 0.2% of all cases
- Only a few cases involving the testes have been reported
- Testicular sarcoid tends to be unilateral

Macroscopic

- Small nodules may be present

Microscopic

- Non-necrotizing granulomas are present, identical to sarcoid granulomas elsewhere in the body
- Histologically, must exclude a granulomatous reaction due to seminoma, mycobacterial infection, or idiopathic granulomatous orchitis

Malakoplakia

Clinical

- Unusual form of a bacterial infection that most commonly affects middle-aged females
- Patients have a defect in the capacity of their mononuclear cells to kill phagocytized bacteria. Inflammation is histiocytic and forms masses
- Infection is due to coliform bacteria such as *E. coli* (most common), *Proteus vulgaris*, *Klebsiella pneumonia*, and others
- Initially described in bladder and subsequently described in many other organs:
  - The testes are involved in 12% of cases of genitourinary malakoplakia

Macroscopic

- The testes are enlarged, with yellow, soft parenchyma

Microscopic

- Accumulation of histiocytes with abundant, foamy, slightly granular cytoplasm
- Some of the histiocytes contain Michaelis-Gutmann bodies that are intracytoplasmic calcific concretions with target-like appearance
- Causes tubular destruction

Idiopathic Granulomatous Orchitis

Clinical

- Clinically and pathologically defined idiopathic granulomatous inflammatory disorder of older males
- Hypotheses for etiology include infection or autoimmune orchitis
- Presents as a unilateral tender testicular mass mimicking a tumor
- Rare cases have been bilateral; 66% of patients that have symptoms have a urinary tract infection

Macroscopic

- Testis is enlarged and nodular, with white to yellow homogenous parenchyma with areas of necrosis
- Grossly, resembles lymphoma, a leukemic infiltrate, or malakoplakia

Microscopic

- Inflammation may primarily involve tubules (tubular orchitis) or interstitium (interstitial orchitis):
  - In tubular orchitis, inflammatory cells (plasma cells and lymphocytes) ring seminiferous tubules, and there is a loss of germ cells: giant cells may be present within tubules; inflammation is associated with vascular thrombosis and vasculitis
  - In interstitial orchitis, inflammation is interstitial
  - In both forms, a loss of tubules and fibrosis occur as a result of inflammation

Infertility

In men who are azoospermic (no sperm) or oligospermic (decreased sperm), open testicular biopsy has been the standard method to assess spermatogenesis. However, fine-needle aspiration cytology, a less invasive method, has been shown to correlate with biopsy in 94% of cases, its only limitation being that tubular basement membrane status is not assessed (Meng et al., 2001). By either approach, the pathologist can recognize six diagnostic patterns:

- Normal or nearly normal
- Hypospermatogenesis
- Aspermatogenesis
- Early maturation arrest
- Late maturation arrest
- Tubular hyalinization (evaluable in biopsy only)

Normal or Nearly Normal

- Often due to Excurrent Duct Obstruction (blockage of ducts leading away from testis)

Clinical

- Occurs in approximately 10% of biopsied infertile patients
- Patients have azoospermia, normal-sized testicles, and normal spermatogenesis on a testicular biopsy

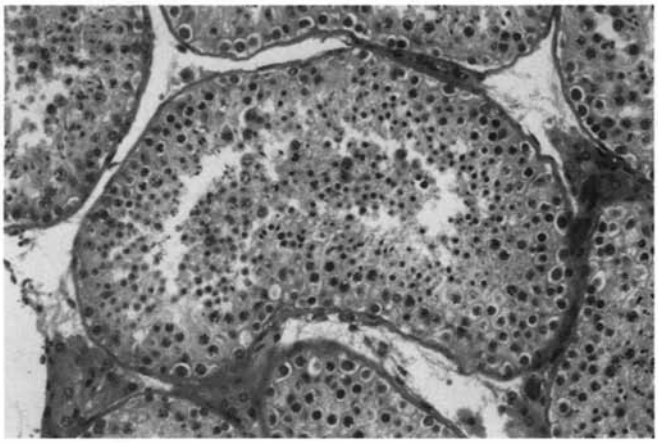


Fig. 5. Normal testis. Tubular profile shows primary spermatocytes peripherally, maturing to spermatids and spermatozoa centrally in the lumen. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

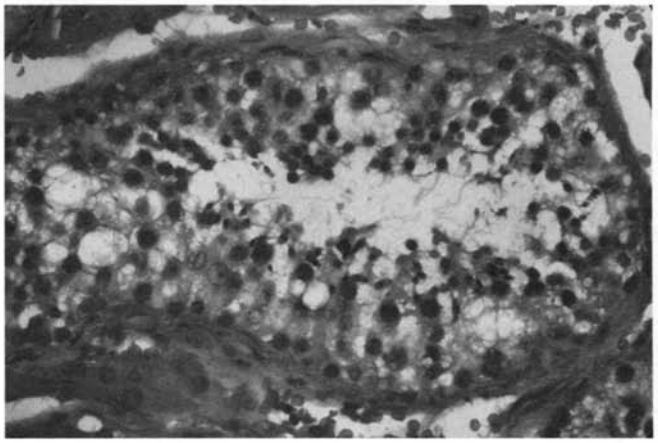


Fig. 6. Hypospermatogenesis. Primary spermatocytes, spermatids, and spermatozoa can be found but in reduced numbers. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

- Can have impaired sperm motility
- Obstruction can be the result of congenital atresia of vas deferens or epididymis, cystic fibrosis, or acquired by infection or surgical ligation (vasectomy)
- Young's syndrome: a lesion at the junction of head and body of epididymis in which the ductus epididymidis is blocked by thick fluid. Patients also have sinusitis and bronchiectasis as children

Macroscopic

- No alterations in testes

Microscopic

- Spermatogenesis is normal for many years following obstruction. Epididymis has ability to store, and phagocytize sperm and sperm products at a rate that matches sperm production
- Testicular biopsy shows active spermatogenesis (**Figure 5**). After vasovasostomy (reversal of vasectomy) there may be some germinal cell disorganization and sloughing, variable amounts of tunica propria thickening, occasional interstitial fibrosis, and sperm granulomata

Hypospermatogenesis

Clinical

- Second most common cause of testicular infertility
- Patients are potent and have normal secondary sexual characteristics but are oligospermic
- Germ cells and developing forms are present in normal proportions, but overall numbers are markedly decreased
- Usually idiopathic, but can be related to:
  - Androgen receptor responsiveness defect (Reifenstein's syndrome)
  - After-effect of cryptorchidism in formerly cryptorchid patients after ordidopexy
  - Exposure to toxins, excess heat, varicocele, or hormonal dysfunction including hypothyroidism

Macroscopic

- No alterations are evident

*Microscopic (**Figure 6**)*

- Proportional hypoplasia of spermatogonia, primary spermatocytes, spermatids, and spermatozoa (sperm with tail), with an overall thinning of the germinal epithelium
- May have diffuse Leydig cell hyperplasia

Aspermatogenesis

- This is most often the result of the Sertoli Cell-Only Syndrome (Absence/Aplasia of Germ Cells). The condition is idiopathic

Clinical

- Patients are potent, with normal secondary sexual characteristics, but azoospermic
- Follicle-stimulating hormone levels are always high as a result of absent spermatogenesis
- Idiopathic but alkylating agents and radiation can cause similar changes, and these may be reversible

Macroscopic

- No alterations are usually present, although occasionally, the testes are smaller than normal

*Microscopic (**Figure 7**)*

- Seminiferous tubules show a moderate decrease in diameter and are devoid of germ cells
- Only Sertoli cells remain
- In a few cases, some tubules show spermatogenesis, so diagnosis is germinal cell aplasia with focal spermatogenesis

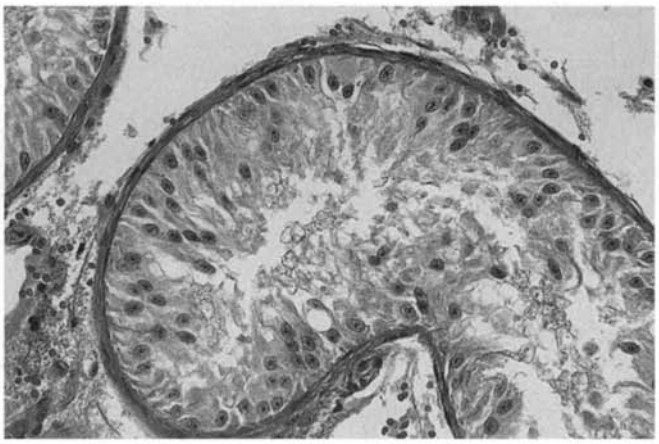


Fig. 7. Sertoli cell only syndrome. The tubule is lined entirely by uniform, columnar Sertoli cells. Germ cells are absent.

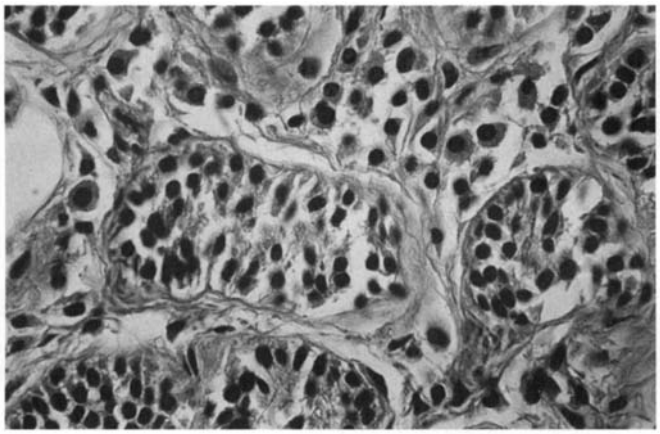


Fig. 8. Testicular feminization syndrome. Seminiferous tubules contain only dysgenetic Sertoli cells, surrounded by Leydig cells. In one-third of patients, spermatogonia are present. Courtesy of Dr. G. M. Farrow, Mayo Clinic-Rochester.

- This pattern also prevails in the following entities:
- Testicular feminization syndrome. A phenotypic female with normal male testosterone levels. Testes will be present in the abdomen, inguinal duct, or labia majora and are removed after puberty to prevent tumors. The size of the testes varies. In most cases, tubules have Sertoli cells only (**Figure 8**)
- Cryptorchid testes may present with this pattern, although early maturation arrest is more common
- Hypogonadotropic hypogonadism: this pattern with greatly increased numbers of Sertoli cells
- Hypergonadortropic hypogonadism, chrmotherapy, radiotherapy, or estrogens can cause a Sertoli cell only picture
- Mixed atrophy: a variant in which some testicular lobules have aspermatogenesis with Sertoli cells only while others have normal tubules with spermatogenesis

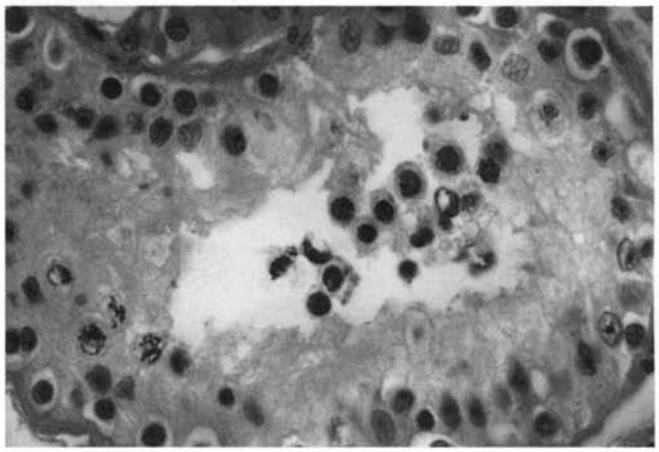


Fig. 9. Early maturation arrest. Only spermatogonia and primary spermatocytes are seen, some with mitotic figures (lower left). The lumen is devoid of spermatids or spermatozoa. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

Early Maturation Arrest

Clinical

- Most common cause of testicular infertility; also called premeiotic or "complete" maturation arrest
- Patients are potent, with normal secondary sexual characteristics, but they are oligospermic or azoospermic
- Usually idiopathic
- Cryptorchidism, alcoholism, exposure to toxins and postpubertal gonadotropin deficiency can result in a similar pattern
- In adulthood, cryptorchid testes most often show this pattern, but may also show aspermatogenesis

Macroscopic

- No alterations are evident

*Microscopic (**Figure 9**)*

- Spermatogonia and primary spermatocytes present, but no spermatids or spermatozoa (sperm with tail)
- Biopsy shows <17 spermatogonia per tubular profile

Late Maturation Arrest

Clinical

- In some patients with oligospermia or azoospermia, this pattern is seen; also called postmeiotic or "incomplete" maturation arrest

Macroscopic

- No alterations are evident

*Microscopic (**Figure 10**)*

- There are primary spermatocytes and spermatids but absent or markedly decreased spermatozoa (sperm with tail)

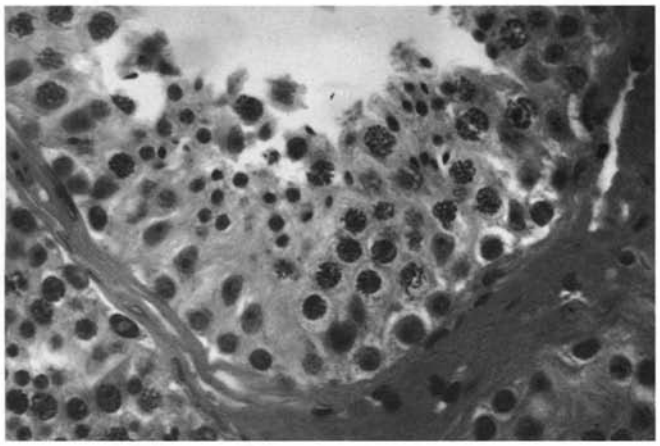


Fig. 10. Late maturation arrest. Small, oval spermatids are present, but not spermatozoa (sperm with tails). Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

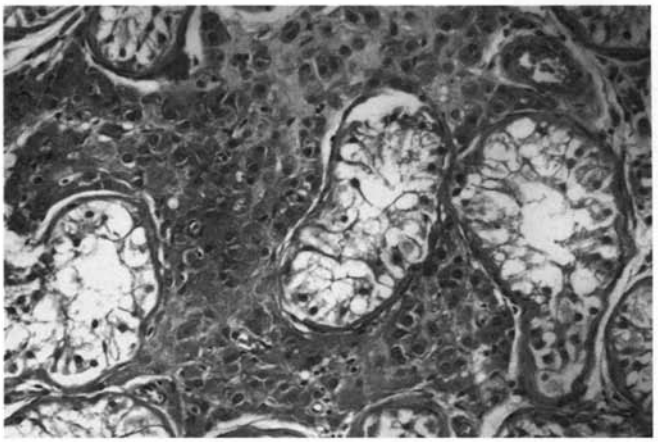


Fig. 11. Tubular hyalinization, a pattern seen in Klinefelter's syndrome and postpubertal cryptorchid testes. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

Tubular Hyalinization (Evaluable In Biopsy Only)

- Klinefelter's Syndrome and other karyotypic abnormalities cause dysgenetic hyalinization

Clinical

- Result of an abnormal number of X chromosomes and primary gonadal insufficiency
- Affects approximately 1 in 1,000 newborns
- Most common phenotype is 47XXY
- Males have a eunuchoid phenotype with tall stature, incomplete virilization (poorly developed secondary sex characteristics), gynecomastia, and mental retardation; phenotypic and testicular changes become evident at puberty
- Increased incidence of breast cancer and extragonadal germ cell tumors of mediastinum

Macroscopic

- The testes are usually small and firm (<2.5 cm in greatest dimension)

*Microscopic (**Figure 11**)*

- The testes show progressive failure of spermatogenesis with a loss of germ cells and Sertoli cells
- Tunica of tubules thickens and eventually all that remains are hyalinized empty tubules lacking elastic fibers
- Leydig cell clusters become more prominent (Debatable over whether this represents Leydig cell hyperplasia or prominence of Leydig cells as a result of testicular volume loss.)

Other causes

- Hormonal deficit:
  - Hypopituitarism of pre- or postpubertal onset
  - Estrogen excess:
    - Endogenous, from cirrhosis or estrogen-producing tumor of adrenal
    - Exogenous, as prostate cancer therapy
- Ischemia:
  - Due to torsion
  - Due to severe atherosclerosis
- Post-obstructive: mosaic of normal and hyalinized tubules:
  - Usually secondary to varicocele of pampiniform plexus or disorders involving dilatation of rete testis
  - Following infection (mumps or Coxsackie B orchitis)
  - Due to physical and chemical agents
  - Occupational exposure (including lead, carbon disulfide)
  - Radiation
  - Chemotherapy
- Autoimmune: Addison's disease
- Androgen excess:
  - Endogenous:
    - Adrenogenital syndrome
    - Androgen-producing tumor
  - Exogenous
- Glucocorticoid excess:
  - Endogenous:
    - Cushing's syndrome
  - Exogenous:
    - Steroid therapy
- Hypothyroidism
- Diabetes mellitus

NEOPLASMS OF TESTIS (SEE TABLE 1)

Table 1. Overview of Testicular Neoplasia

Germ Cell Tumors	**Sex Cord-Stromal Tumors**
Intratubular germ cell neoplasia	Leydig cell tumor
Seminoma:	Sertoli cell tumor:
Classic type	Typical type
Spermatocytic type	Sclerosing type
Non-seminomatous germ cell tumors:	Large-cell calcifying type
Embryonal carcinoma	Granulosa cell tumor:
Yolk sac tumor (endodermal sinus tumor)	Juvenile
Teratoma	Adult
Immature	Unclassified type
Mature	Mixed type
Teratoma with overtly malignant component	**Mixed Sex Cord-Stromal Tumor and Germ Cell Tumor**
Monodermal types	Gonadoblastoma
Carcinoid	**Hematopoietic Tumors**
Primitive neuroectodermal tumor	Lymphoma
Choriocarcinoma	Plasmacytoma
Mixed germ cell tumor	Leukemia
	Metastases

Germ Cell Tumors

Cell of Origin

- Precursor of invasive germ cell tumors is intratubular germ cell neoplasia, unclassified type (IGCNU)
- Hypothesized that seminomas arise from IGCNU, and non-seminomatous germ cell tumors arise from seminoma or from IGCNU
- IGCNU does not give rise to spermatocytic seminoma
- Seminoma cells and IGCNU are identical morphologically, and share many other features, including karyotypic abnormalities, DNA content, ultrastructural changes, and immunohistochemical profiles, including + staining with antibodies to placental alkaline phosphatase

Risk of Germ Cell Tumors

- Certain conditions increase the risk of germ cell tumors in men:
  - Cryptorchidism, history of a prior testicular tumor, first degree relative with a germ cell tumor, gonadal dysgenesis, and androgen insensitivity syndrome

Ancillary Stains

- *See* **Table 2**

Staging

- Numerous staging systems for testicular germ cell tumors (*see* end of chapter)
- Extratesticular extension is present in 16% of cases and occurs at the hilum in 91% of these. The hilum should be sampled in all orchiectomies with tumor

Treatment

Seminoma

- Stage I tumors and nonbulky Stage II tumors are treated by radical orchiectomy and radiation to ipsilateral paraaortic and pelvic lymph nodes
- Some patients with a Stage I tumor are treated by radical orchiectomy alone
- Cure rate is 95% for Stage I tumors and approaches 90% for Stage II tumors
- In patients with bulky Stage II seminoma and advanced stages, orchiectomy, radiation, and chemotherapy are performed, with survival rates of 80%

Table 2. Immunohistochemical Profiles of Testicular Germ Cell Tumors

Tumor	OCT4	CD117 (c-kit)	Cytokeratin	Vimentin	PLAP	AFP	hCG	CD30	PAS	EMA
Seminoma	+	+**	–/+*	+	+	–	±	±	+	–
Spertomatocytic seminoma	–	–/+**	–	–	–	–	–	–	–	–
Embryonal carcinoma	+	–	+	–	+	±	±	+	–	–
Yolk sac tumor	–	–	+	+	+	+	–	–	+	–
Teratoma	–	–	+	+	±	±	±	–	–	±
Choriocarcinoma	–	–	+	–	±	±	+	–	–	+

PLAP = Placental alkaline phosphatase; AFP = alpha-fetoprotein; hCG= human chorionic gonadotropin; PAS = periodic acid-Schiff without diastase; EMA = epithelial membrane antigen
**Wide spectrum cytokeratin is focally positive in 36% of cases (Cheville et al., 2000).*
***Only membranous staining is true positivity for c-kit. c-kit is reactive in 40% of spermatocytic seminomas (Kraggerud et al., 1999).*

Non-Seminomatous Germ Cell Tumors

- Stage I:
  - Option A: Radical orchiectomy and retroperitoneal lymph node dissection:
    - Cure rate = 90% to 95%
    - Relapse rate = 5% to 10%
  - Option B: Radical orchiectomy and surveillance:
    - Cure rate = 60% to 70%
    - Relapse rate = 30% to 40%
- Stage II:
  - Non-bulky:
    - Orchiectomy, lymph node dissection, and chemotherapy
    - Cure rate = 90%
  - Bulky:
    - Orchiectomy, chemotherapy, and resection of residual masses
    - Cure rate = 70% to 80%
- In Stage I tumors, a large percentage of embryonal carcinoma (>40%), lymphovascular invasion, and presence of choriocarcinoma are features that put the patient at an increased risk of relapse

Intratubular Germ Cell Neoplasia, Unclassified (IGCNU)

Clinical

- Intratubular germ cell neoplasia is a putative precursor (in situ) lesion for invasive germ cell tumors
- IGCNU is identified in almost all testis with invasive germ cell tumors, except testis with spermatocytic seminoma
- Most patients (>70%) with IGCNU develop an invasive germ cell tumor within 7 years
- Involvement is patchy, and 40% of cases are bilateral
- Two 3 mm testicular biopsies will identify the majority of patients with IGCNU
- IGCNU is identified in 1% of all testicular biopsies performed for infertility
- Treatment is orchiectomy in unilateral cases and bilateral orchiectomy or radiation in bilateral cases

Macroscopic

- No alterations

*Microscopic (**Figure 12**)*

- Seminiferous tubules contain seminoma cells that are large with oval nuclei, prominent nucleoli, and clear cytoplasm
- Cells are confined to basal aspect of tubules
- Spermatogenesis is absent in involved tubules

Immunohistochemistry

- IGCNU is uniformly + with stains for placental alkaline phosphatase (PLAP) in a cytoplasmic membranous staining pattern
- Only rarely are spermatocytes PLAP+ and spermatogonia are PLAP–

Cytogenetics

- DNA content triploid or hypotetraploid
- Contains isochromosome 12p

Seminoma (Classic Type)

Clinical

- Most common germ cell tumor, accounting for 50% of all germ cell tumors
- Mean age at diagnosis is 40 years
- Very rare in children

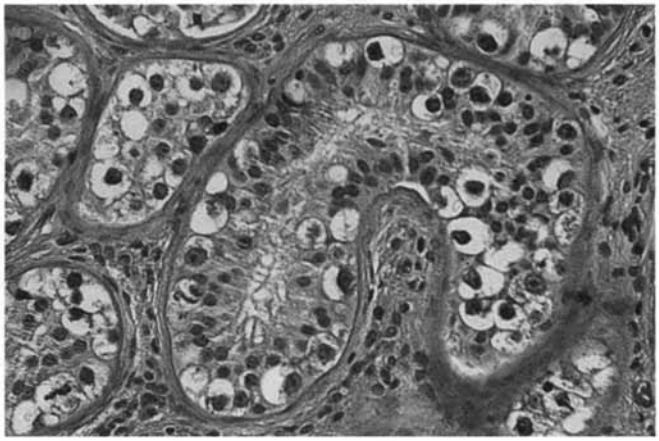


Fig. 12. Intratubular germ cell neoplasia, unclassified (IGCNU). Germ cells show abundant clear cytoplasm, atypical, pleomorphic nuclei, and prominent nucleoli. There is no spermatogenesis.

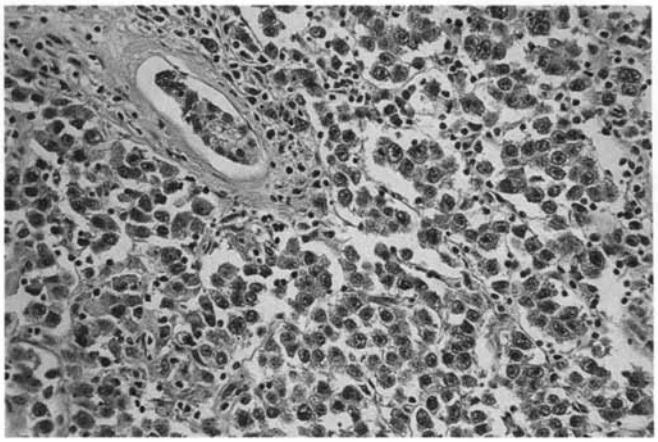


Fig. 13. Seminoma. Nests of tumor cells with clear cytoplasm and mild nuclear pleomorphism are separated by delicate fibrous trabeculae (not very prominent in this field) which contain a lymphocytic infiltrate. Vascular invasion (upper left) is an important finding.

- Patients present with a painless testicular mass, but up to 15% may have a normal exam
- 30% have metastases at presentation, but only 3% have symptoms related to metastases
- Serum alpha-fetoprotein is normal
- Beta human chorionic gonadotrophin is elevated in 10% to 20% of patients with Stage I seminoma

Macroscopic

- Characterized by a circumscribed lobular gray-white fleshy tumor that can have areas of necrosis and hemorrhage

*Microscopic (**Figure 13**)*

- Cells have round to oval nuclei with one to several nucleoli and clear to slightly eosinophilic cytoplasm
- Cell borders are well-defined
- Arranged in solid nests separated by fibrous septa
- Lymphoid infiltrate is present within septa
- Interstitial growth with preservation of tubules can occur at the periphery of the tumor
- Cord-like and tubular growth patterns can predominate in rare cases
- Granulomatous infiltrate present in 50% of all cases
- Anaplastic seminomas were defined as seminomas with increased mitotic activity. These behave no differently than other seminomas, and the use of the term "anaplastic" has been discontinued
- Syncytiotrophoblastic cells are present in up to 20% of all cases
- Differential diagnosis includes sex-cord stromal tumors (which have cells with clear cytoplasm), solid pattern of embryonal carcinoma, and metastatic adenocarcinoma (particularly renal cell)

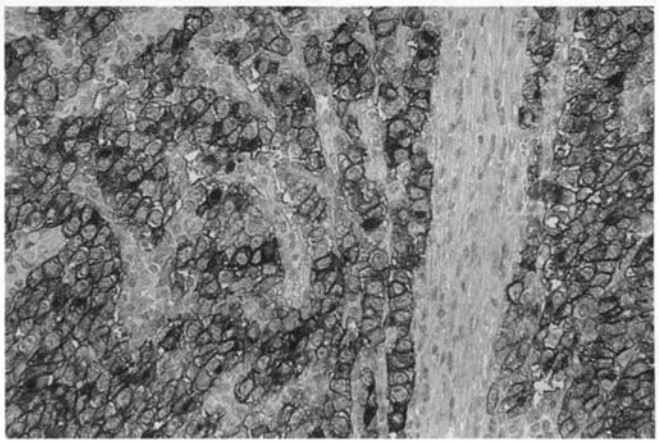


Fig. 14. Seminoma with strong cytoplasmic reactivity for placental alkaline phosphatase (PLAP).

*Immunohistochemistry (see **Table 2**)*

- Cells are OCT4+, PLAP+, and c-kit+, identical to IGCNU (**Figure 14**)
- Contains cytokeratins, although only 36% of cases are positive. Punctate perinuclear reactivity (**Figure 15**) is almost always confined to <10% of tumor cells (Cheville et al., 2000)
- EMA–

Spermatocytic Seminoma

Clinical

- Unique tumor with distinct morphological and clinical features
- Occurs only in testis and represents up to 2% of germ cell tumors

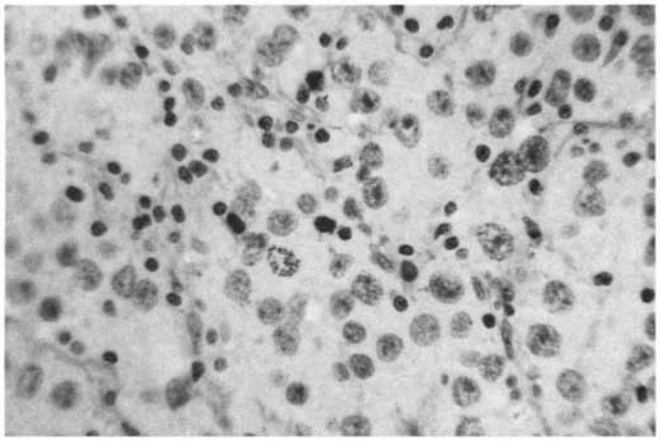


Fig. 15. In seminoma, tumor cells may show punctate cytoplasmic reactivity for cytokeratin AE1/3 (shown here) or other cytokeratin cocktails.

- Patients are in their 50s and present with a testicular mass
- Very rarely metastasize
- Usually cured by orchiectomy
- Unusual cases: may be associated with sarcoma:
  - Either rhabdomyosarcoma or undifferentiated sarcoma
  - Aggressive lethal neoplasms

Macroscopic

- Tumors are multinodular and have a yellow edematous appearance
- Hemorrhage and cystic change can be present

*Microscopic (**Figure 16**)*

- Characterized by a polymorphous cell population composed of small cells to multinucleate giant cells
- Cells are arranged in sheets and microcysts are present
- Nests and pseudoglandular structures are also identified
- Mitotic figures may be numerous
- Lymphoid and granulomatous infiltrate are absent

Immunohistochemistry

- Cells are PLAP–, vimentin–, muscle marker–, cytokeratin–, alpha-fetoprotein–, human chorionic gonadotropin–, EMA–, and CEA–

Electron Microscopy

- EM features are similar to those of leptotene stage spermatocytes

Embryonal Carcinoma

Clinical

- Second most common germ cell tumor, comprising approximately 20% of all cases
- Present in the majority of mixed germ cell tumors

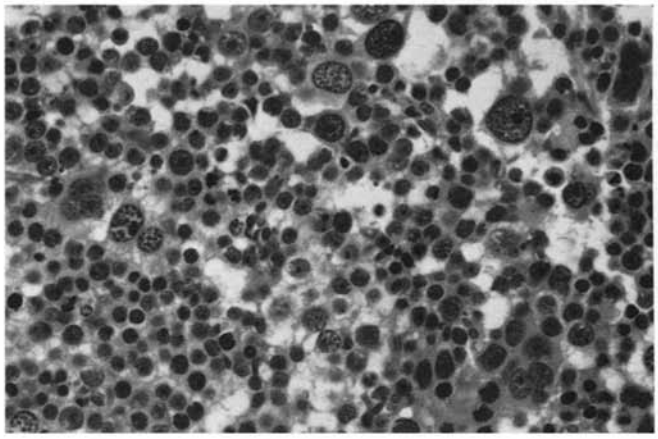


Fig. 16. Spermatocytic seminoma. Note the polymorphous cell population. Most cells are small, but some intermediate cells are seen with stippled chromatin. This has been called "spireme chromatin" because of the similarity to meiotic, non-neoplastic spermatocytes. Edematous or microcystic stroma is usually interspersed between cells. Courtesy of Dr. Jae Ro, M.D. Anderson Cancer Center.

- Most men present in their 20s to 30s with a testicular mass
- Very rare in children and older men
- More than two-thirds of patients have metastases, but only 10% of patients have symptoms related to metastases
- Serum AFP is normal, and beta hCG is elevated in 60% of cases

Macroscopic

- Fleshy gray-white tumor with prominent necrosis and hemorrhage

*Microscopic (**Figure 17**)*

- Cells of embryonal carcinoma are large, with vesicular nuclei, prominent nucleoli, and indistinct cell borders
- Tumor cells are arranged in sheets, cords, and glandular structures
- Necrosis and hemorrhage may be prominent
- May be intimately admixed with a yolk sac tumor

*Immunohistochemistry (see **Table 2**)*

- Tumor cells are CD30+, a finding unique to embryonal carcinoma, and useful in ruling out the solid pattern of embryonal carcinoma, which can simulate seminoma. Also, OCT4+, PLAP+, cytokeratin+, c-kit–, and EMA–

Yolk Sac Tumor (Endodermal Sinus Tumor)

Clinical

- Most common germ cell tumor (and most common testicular tumor) in children, where it occurs in its pure form

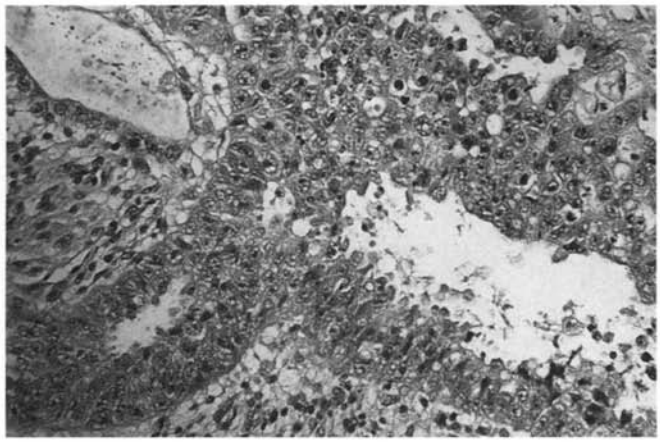


Fig. 17. Embryonal carcinoma. A gland-like structure is formed by cells with markedly pleomorphic nuclei. Nuclei are more crowded and vesicular than in seminoma, and the cytoplasm is granular. Nucleoli are also more prominent than in seminoma.

- In children, majority of cases are diagnosed before 24 months
- In adults, it is unusual in pure form, but is found in approximately 50% of mixed germ cell tumors
- Both children and adults have elevated serum AFP
- In children, orchiectomy alone results in a cure rate of 90%
- Most adults and children present with a testicular mass

Macroscopic

- White to tan masses, with myxoid and cystic change

Microscopic

- Many histologic patterns:
  - Endodermal sinus pattern
  - Reticular
  - Solid
  - Papillary
  - Microcystic (most common, **Figure 18**)
  - Macrocystic
  - Alveolar
  - Myxomatous
  - Sarcomatoid
  - Polyvesicular-vitelline
  - Hepatoid
  - Parietal
- Deposition of basement membrane material, and Schiller-Duval bodies (central vessel rimmed by loose connective tissue that in turn is lined by malignant epithelium, all within a cystic space), are characteristic

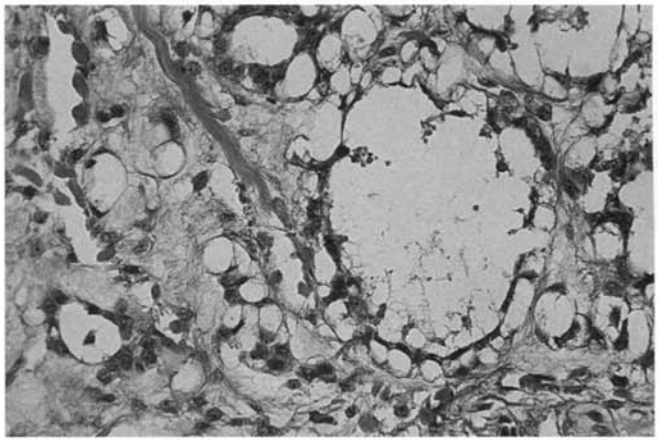


Fig. 18. Yolk sac tumor, microcystic pattern. Cells have elongated cytoplasmic processes. The basement membrane globules (center right) in a cystic space are characteristic.

*Immunohistochemistry (see **Table 2**)*

- AFP+ (focal or patchy), cytokeratin+, PLAP variable, EMA–, CD 30–

Teratoma

Clinical

- Adults and children present with a testicular mass
- In children, second most common germ cell tumor
- Occurs in its pure form with a mean age of diagnosis at 20 months
- In children, metastases do not occur
- In adults, occurs as a component of a mixed germ cell tumor and is identified in >50% of mixed tumors
- In adults, teratoma is treated like a nonseminomatous germ cell tumor
- In adults, metastases occur, even in pure teratomas

Macroscopic

- In mixed germ cell tumors, teratomatous component is solid and can contain multiple small cysts

Microscopic

- Composed of somatic-type tissues that can include enteric-type glands, respiratory epithelium, cartilage, muscle, squamous epithelium (**Figure 19**), and others. May have atypia. Associated with IGCNU
- Immature teratomas contain immature neuroepithelium, blastema, or cellular stroma. Significance of immature elements not clear (unlike immature teratoma of ovary)
- Can give rise to carcinoma, such as adenocarcinoma and squamous cell carcinoma, or sarcoma, such as rhabdomyosarcoma, Wilms-like tumor, or primitive neuroectodermal tumor (PNET)

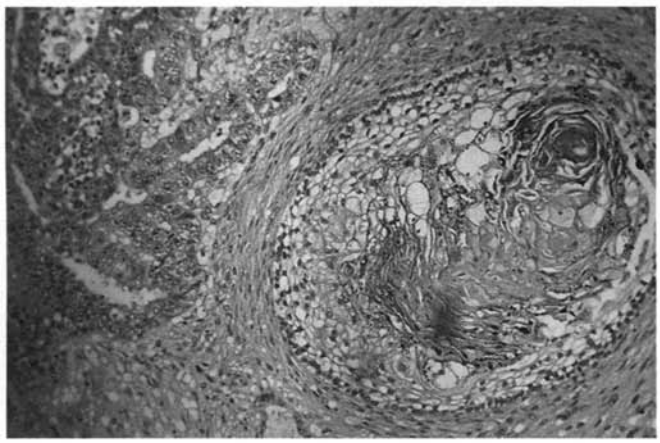


Fig. 19. Teratoma in mixed germ cell tumor. Embryonal carcinoma at left. Nest of keratinizing squamous cells at right is an element of mature teratoma.

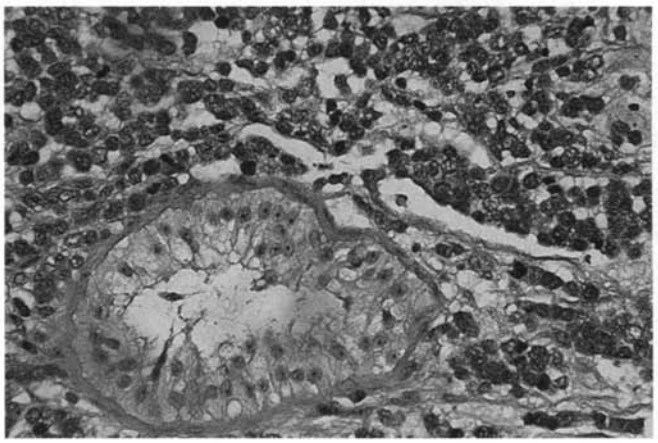


Fig. 20. Immature teratoma. Predominant primitive neuro-endocrine tumor (PNET) component surrounds a remaining tubule in lower field.

- Clinical significance of development of sarcoma or carcinoma not known
- Two monodermal forms: carcinoid tumor and PNET:
  - Carcinoid tumors can be associated with other teratomatous elements (15% of cases):
    - Have a good prognosis, with 10% to 14% developing metastases
    - Carcinoid syndrome occurs rarely
    - Overgrowth of immature elements in a teratoma may result in predominance of PNET (**Figure 20**)
    - Highly malignant
  - EMA may be reactive or not

Dermoid cyst

Clinical

- Because of benign outcome after orchiectomy, this belongs in a separate category from mature teratoma (Ulbright et al., 2001)

Microscopic

- Composed of mature skin with adnexal structures and smooth muscle bundles in the wall (like arrector pili); may have ciliated epithelium, intestinal mucosa, or bone
- Unlike in mature teratoma, they lack atypia or mitotic activity, and no association with IGCNU has been described

Epidermoid cyst

Clinical

- Benign outcome after orchiectomy, although they may have loss of heterozygosity of same chromosomes as in malignant germ cell tumors (Younger et al., 2003)

Microscopic

- Squamous lining, keratin-filled
- Unlike dermoid cyst, they lack adnexal structures or heterologous elements

Choriocarcinoma

Clinical

- Pure choriocarcinoma is very unusual (<1% of germ cell tumors) and is a component of 15% of mixed germ cell tumors
- Many patients present with symptoms related to metastases to the brain or lungs
- Serum β-hCG elevated
- Children do not develop choriocarcinoma
- Patients have a poorer prognosis, but the tumor is sensitive to chemotherapy

Macroscopic

- Hemorrhagic and necrotic

Microscopic

- Contains multinucleated syncytiotrophoblastic cells and mononuclear cytotrophoblast or intermediate trophoblast:
  - Both elements need to be present for diagnosis of choriocarcinoma

Immunohistochemistry (see Table 2)

- EMA reactivity particularly helpful in differential diagnosis; hCG+, can be PLAP+, cytokeratin+, CEA+, human placental lactogen+

Mixed Germ Cell Tumor

- Composed of two or more germ cell tumor types

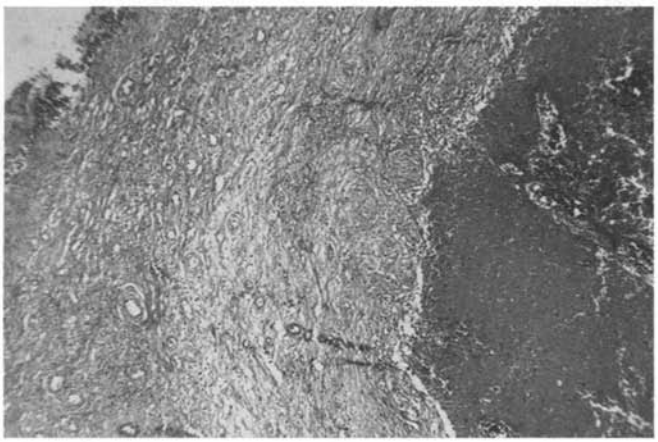


Fig. 21. Regressed germ cell tumor in 36 year-old. Testis is replaced by fibrovascular tissue (left) and coagulative necrosis (right).

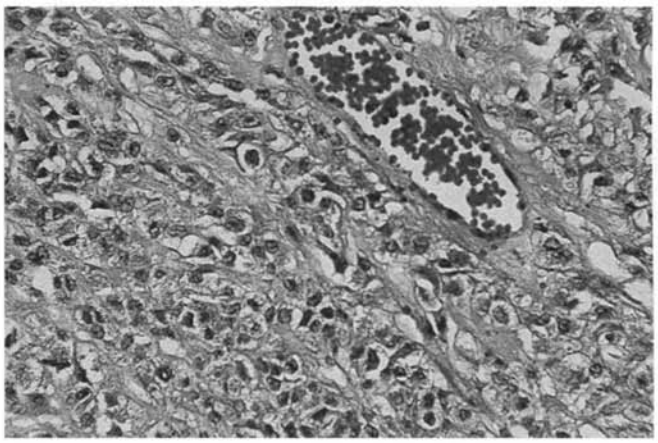


Fig. 22. Leydig cell tumor. Cells have clear cytoplasm and small, moderately pleomorphic nuclei. There is prominent microvasculature. Unlike in seminoma, cells are not nested, and there are no lymphocytic infiltrates or granulomas.

- Comprises 33% of all germ cell tumors, often seminoma and non-seminomatous components

Regressed Tumor

- Germ cell tumors can regress
- Microscopic: Replacement of the testis by viable and necrotic fibrovascular tissue precludes typing of pre-existing tumor (**Figure 21**)

Sex Cord-Stromal Tumors

Leydig Cell Tumor

Clinical

- Normal Leydig cells produce testosterone and are located in the interstitium of the testis
- Leydig cell tumors comprise 3% to 5% of testicular neoplasms
- Leydig cell tumors occur in both adults (majority: 80%) and children
- Children present with endocrinologic symptoms (virilization, gynecomastia) and adults present with a testicular mass and some (10% to 30%) have gynecomastia
- In children, are benign
- In adults, 10–17% are malignant
- Unilateral with rare exceptions
- Benign tumors are treated by orchiectomy; malignant tumors by orchiectomy and retroperitoneal lymph node dissection

Macroscopic

- Leydig cells impart a yellow to yellow-tan color; tumor is solid and lobulated
- Malignant tumors tend to be larger (>5 cm) than benign tumors. Necrosis can be seen in malignant tumors

Microscopic

- Leydig cells vary in size but usually have round nuclei, single prominent nucleoli, and abundant eosinophilic cytoplasm or abundant clear cytoplasm (**Figure 22**)
- Reinke's crystals are present in 40% to 70% of cases, and lipochrome can be abundant in some cases
- Electron microscopy shows mitochondria with tubular cristae
- Rarely, adipose differentiation or spindle cell growth (**Figure 22**) are noted
- Malignant features include large size (>5 cm), increased mitotic activity (>5/10 hpf), necrosis, angiolymphatic invasion, and invasion of surrounding structures, such as tunica, epididymis, and spermatic cord. Malignant behavior is difficult to predict from histologic features
- Differential diagnosis includes testicular tumor of adrenogenital syndrome (see below) which is bilateral, dark brown grossly, and less often immunoreactive with inhibin-α. Lack of inhibin-α reactivity also rules out a germ cell tumor. Leydig cell hyperplasia is multifocal rather than forming a single mass and does not efface seminiferous tubules

Immunohistochemistry

- Inhibin-α+ (Iczkowski et al., 1998), and tumor shows variable reactivity with cytokeratins, S-100 protein, chromogranin, synaptophysin, and estrogen and progesterone receptors

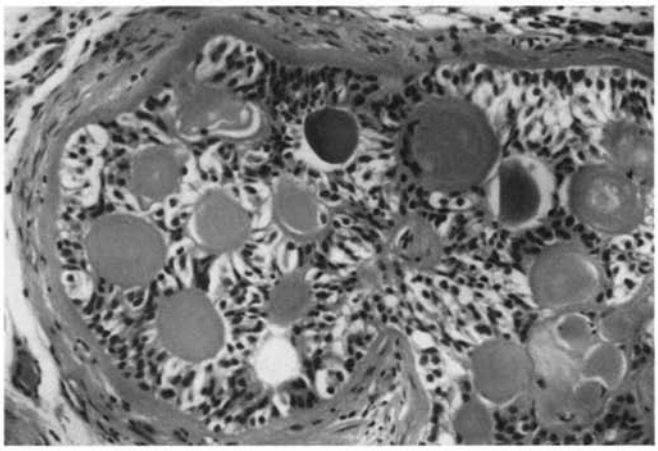


Fig. 23. Tubular adenoma or Sertoli cell adenoma. This irregular nodule from a cryptorchid testis is composed of tubules with immature Sertoli cells with small, dense nuclei. Many tubules have central laminated deposits. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

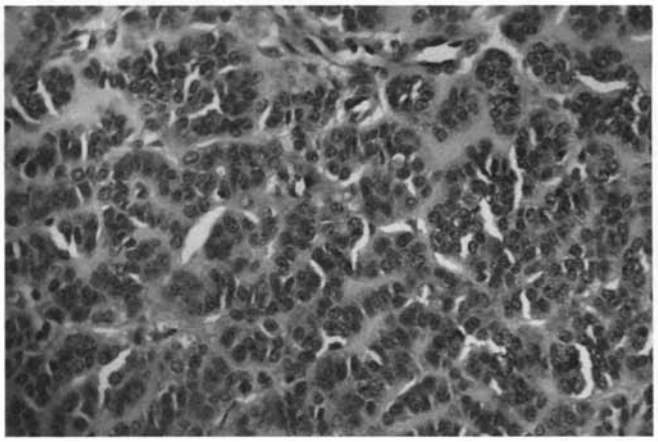


Fig. 24. Sertoli cell tumor. Tumor cells form closely packed cords. Tumor cell nuclei are small and uniform.

Sertoli Cell Tumor, Typical Type

Clinical

- Sertoli cells are located within seminiferous tubules, and they help support spermatogenesis
- Account for <1% of testicular tumors
- Occur both in children (15% of cases) and in middle-aged adults, and can be malignant (10% of cases) in both. Malignant cases often are misinterpreted as seminoma (Henley et al., 2002)
- Patients present with a testicular mass, and estrogen production by the tumor can result in gynecomastia and impotence
- Treatment is orchiectomy
- Proliferation of Sertoli cells may also be seen in androgen insensitivity syndrome in XY male patients with male, female, or ambiguous phenotype ("tubular adenoma" or Sertoli cell adenoma, **Figure 23**) and in the cryptorchid testis (Sertoli cell nodule or Pick's adenoma, **Figure 1**). Estrogens secreted by the Sertoli cells may promote the female phenotype

Macroscopic

- Tumors are well-circumscribed, solid pale yellow, or white to gray masses
- Large size and necrosis are worrisome features for malignancy

Microscopic

- Typically composed of solid tubules containing Sertoli cells
- Cells may be arranged in cords (**Figure 24**), solid nests, and sheets
- Tubules can contain lumina
- Malignant behavior can be difficult to predict
- Features worrisome for malignancy are identical to those seen in Leydig cell tumors

Immunohistochemistry

- Inhibin-α+ (Iczkowski et al., 1998) but less consistently than in Leydig cell tumor (47% of cases in combined series), and can be + with synaptophysin, chromogranin, S-100 protein, and cytokeratin AE1/3 and CAM5.2 in 64–100% of cases

Electron Microscopy

- Charcot-Bottcher filaments (perinuclear aggregates of intermediate filaments) are pathognomonic of Sertoli cells or Sertoli cell differentiation

Sclerosing Sertoli Cell Tumor

Clinical

- Rare variant of Sertoli cell tumor
- Patients present with a testicular mass and without endocrinologic symptoms
- No malignant cases have been reported

Macroscopic

- Similar to a typical Sertoli cell tumor

Microscopic

- Cords, nests, and tubules of Sertoli cells are present within a fibrotic stroma (**Figure 25**)

Large-Cell Calcifying Sertoli Cell Tumor

Clinical

- Rare variant of a Sertoli cell tumor, 60 cases reported
- Patients are young, with age at diagnosis ranging from 16 to 37 years

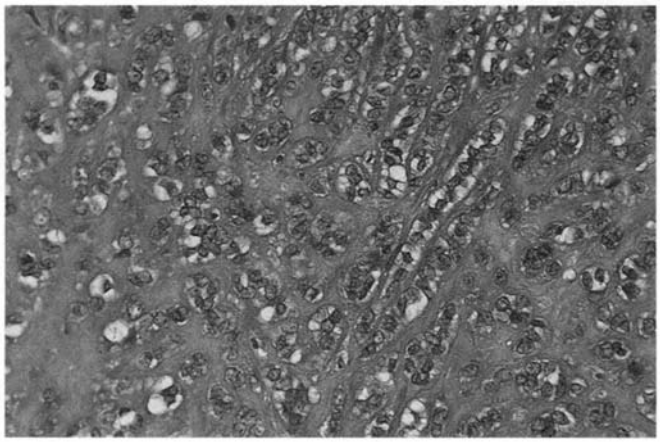


Fig. 25. Sclerosing Sertoli cell tumor. Tumor cells still have a cordlike arrangement, but the stroma is dense and acellular, unlike typical type of Sertoli cell tumor.

- Occurs as part of Carney complex and in patients with Peutz-Jeghers syndrome:
  - In this setting, tends to be multifocal
- Malignant tumors (17% of cases) occur, and usually are sporadic type (only one malignant tumor has been reported associated with Carney's syndrome)

Macroscopic

- Benign tumors are small (usually <2 cm) yellow, tan, or white nodules confined to the testicle
- Malignant tumors are larger and may have areas of necrosis

Microscopic

- Neoplastic cells are arranged in sheets, small nests, and cords, and are present in a myxoid to fibrous stroma
- Dystrophic calcifications, including psammomatous calcifications, are present
- Malignant tumors are large and exhibit extratesticular spread, increased mitotic activity, necrosis, and angiolymphatic invasion

Immunohistochemistry

- S-100+, EMA–, and cytokeratin variable (usually negative to weak staining)

Electron Microscopy

- Charcot-Bottcher filaments are absent or rarely present

Granulosa Cell Tumor, Adult Type

Clinical

- Much less common than in the adult female ovary
- Average age = 42 years
- Often (20%) associated with gynecomastia
- Four patients had metastasis and two died

Macroscopic

- Lobulated, firm and uniformly yellow-gray mass

Microscopic

- Microfollicular with a few larger cysts
- Call-Exner bodies may be seen
- Cells have scant cytoplasm and angular nuclei
- May have nuclear grooves

Granulosa Cell Tumor, Juvenile Type

Clinical

- Rare sex cord-stromal tumor that occurs in males in first few months of life
- May occur in setting of gonadal dysgenesis
- Infants present with a testicular mass
- No malignant cases have been reported
- May be of Sertoli cell origin (debated)

Macroscopic

- Tumors are small and solid and contain multiple small cysts

Microscopic

- Sheets of spindle cells with abundant cytoplasm intermixed with follicle-like cystic spaces
- Hyalinized collagenous stroma is also a feature in cellular areas

Mixed Germ Cell and Sex Cord-Stromal Tumor

Gonadoblastoma

Clinical

- Composed of a mixture of seminoma cells and Sertoli cells
- Occur in dysgenetic gonads in patients with intersex syndrome (80% phenotypically female; 20% phenotypically male)
- May have ambiguous genitalia
- Patient karyotype 46XY or 45X/46XY most commonly
- Invasive germ cell tumors, usually seminoma, arise in gonadoblastoma
- Treatment is the removal of gonads

Macroscopic

- Solid yellow to tan tumors in dysgenetic gonads; in males, testes are cryptorchid, and contain female components (involution of müllerian structures does not occur)

*Microscopic (**Figure 26**)*

- Tumor composed of mainly seminoma-like cells, with admixed sex cord-stromal (Sertoli-like) cells
- Tumor cells form nests with central germ cells and peripheral stromal cells
- Globules of eosinophilic basement membrane material with peripheral palisading stromal cells may be present in nests

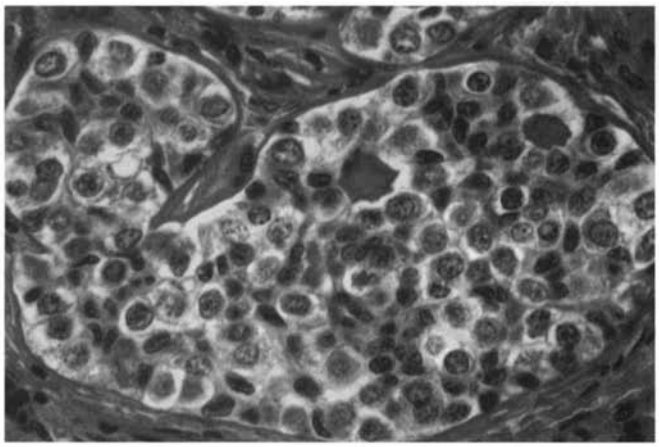


Fig. 26. Gonadoblastoma. The predominant cell type is seminoma-like cells with clear cytoplasm. A few small, dark Sertoli-like or sex cord cells are also present. There are deposits of hyaline basement membrane material.



Fig. 27. Diffuse large cell lymphoma expands testis. Lymphoma is the most common testicular neoplasm in elderly men. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

- Hyaline globules bear resemblance to those in "tubular adenoma," also called Sertoli cell adenoma (above, **Figure 23**), but tubules in the latter have no germ cells

Testicular "Tumor" of Adrenogenital Syndrome (TTAGS)

Clinical

- Occurs in many patients who have adrenogenital syndrome, a salt-losing disorder (21-hydroxylase deficiency) that is untreated or not sufficiently treated
- The "tumor" masses become evident in childhood or adulthood
- Usually synchronous bilateral testicular involvement
- Iincreased ACTH, androstenedione, and 17-hydroxyprogesterone in serum. Tumor responds to administration of corticosteroids to reduce the high ACTH level

Macroscopic

- Originates in testicular hilum and may extend into parenchyma. Dark brown tissue with septa, size up to 10 cm

Microscopic

- Proliferation of large cells with abundant eosinophilic cytoplasm, resembling Leydig cells. Lipochrome pigment may be prominent
- Stroma may be hyalinized
- Cells may originate from adrenocortical rests
- Differential diagnostic consideration is Leydig cell tumor. The bilaterality and dark brown color favor TTAGS. Leydig cell tumor may have crystals of Reinke, which are not present in TTAGS. TTAGS has coarse fibrous tissue septa surrounding lesional cell lobules, whereas septa are delicate in Leydig cell tumor. Finally, inhibin-α reactivity is present in Leydig cell tumor but absent in TTAGS (Iczkowski et al, 1998)

Hematopoietic Neoplasms

Lymphoma and Plasmacytoma (see Chapter 9)

Clinical

- Lymphoma most often result of secondary spread; occasionally, primary lymphoma may occur
- Plasmacytoma also occurs in testes, and is also usually due to secondary spread in a patient with multiple myeloma
- Most men are in their 60s
- Involvement is bilateral in 20% of all cases
- Survival is stage-dependent

Macroscopic

- White to tan fleshy tumor (**Figure 27**)

Microscopic

- In adults, most lymphomas are diffuse large cell types with a B-cell phenotype
- May have immunoblastic features
- In children, small non-cleaved lymphoma is most common
- Has an interstitial growth pattern with sparing of seminiferous tubules
- Plasmacytomas are composed of mature plasma cells that vary in their amount of atypia

Leukemia (see Chapter 11)

Clinical

- Testes are a sanctuary site for leukemia, especially for acute lymphoblastic leukemia

- Testicular biopsies may be + for leukemia when patient is in remission

Macroscopic

- Testes may be normal to enlarged, with a mass

Microscopic

- Leukemia has an interstitial growth, like a lymphoma
- Morphologic features are dependent on the type of leukemia

Vascular lesions: Capillary microangioma

Clinical

- These may be associated with a history of trauma and present as mass lesions (Iczkowski et al., 1998)

Microscopic

- Tiny vascular spaces (**Figure 28**), positive for CD34, factor VIII, and other endothelial markers

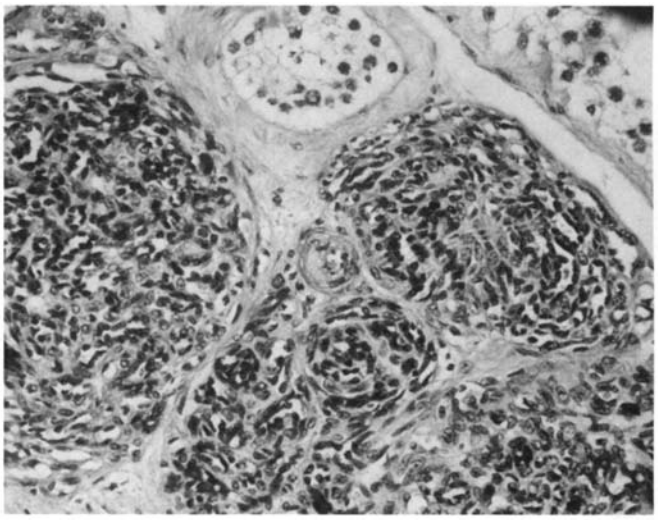


Fig. 28. Capillary microangioma. This lesion is circumscribed and has tiny capillaries. Factor VIII and Ulex were reactive.

LESIONS OF EPIDIDYMIS AND TUNICS

Sperm Granuloma

Clinical

- Commonly occurs in patients after vasectomy
- Presents with pain and swelling of upper pole of epididymis, or is asymptomatic

Macroscopic

- Solitary yellow nodule, measuring up to a few cm

Microscopic

- Exuberant foreign body giant cell reaction to extravasated sperm. Necrosis in early stages (**Figure 29**). Fibrotic tissue surrounds granuloma in late stages

Adenomatoid Tumor

Clinical

- Nodule typically involves epididymis; may also be identified in tunica albuginea and spermatic cord
- Benign lesion cured by complete excision
- Probable mesothelial origin; rare cases described in adrenal and other organs

Macroscopic

- Circumscribed nodule involving epididymis, spermatic cord, or tunica (**Figure 30**)
- May extend into rete testis and testis

Microscopic

- Nests and tubules of epithelioid cells present within a fibrous or fibromuscular stroma (**Figure 31**)
- Epithelioid cells have bland nuclear features
- Cells may be flattened and have an endothelial appearance, mimicking hemangioma and angiosarcoma
- May contain signet-ring-like cells, similar to signet ring adenocarcinoma

Immunohistochemistry

- Epithelioid cells strongly reactive with cytokeratins AE1/3, 7, CAM5.2, calretinin, and vimentin. Lack of reactivity for vascular markers rules out hemangioma and angiosarcoma. Low MIB-1 proliferation index and lack of cytokeratin 20 reactivity rule out gastrointestinal and other primary origins

Papillary Cystadenoma

Clinical

- Associated with von Hippel-Lindau syndrome (Cerebellar hemangioblastoma, retinal angioma, spinal cord hemangioma, cysts of skin, lung, pancreas, kidney)
- Benign lesion cured by excision

Macroscopic

- Epididymis has a cyst; papillary excrescences arise within a cyst wall

Microscopic

- Papillae lined by columnar ciliated cells, like efferent ductules. Cytoplasm is clear to vacuolated, with PAS-positive secretions

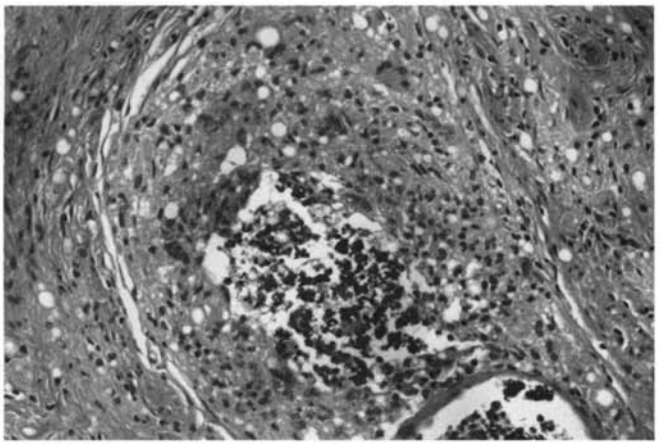


Fig. 29. Sperm granuloma of epididymis. Numerous extravasated sperm are being engulfed by macrophages (spermiophages) and foreign body giant cells are present. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

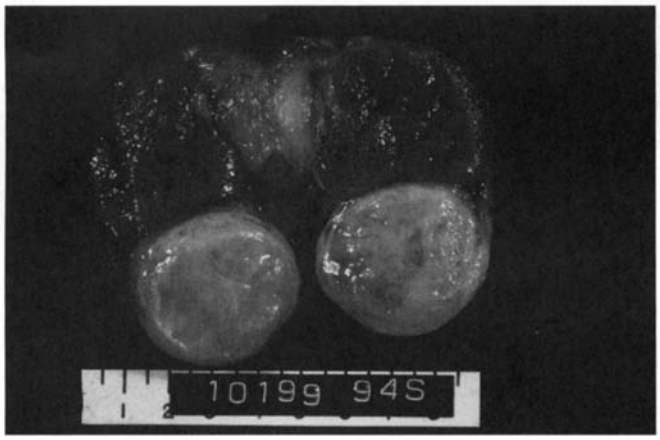


Fig. 30. Adenomatoid tumor. This example is larger than most, almost the size of the bisected testis. Note its circumscription and gray-white color. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

Hydrocele and Benign Papillary Mesothelioma

Clinical

- Hydrocele is most common cause of scrotal swelling. Can become infected (vaginalitis) or hemorrhagic (hematocele)
- Benign papillary mesothelioma occurs in young men who present with hydocele
- Both benign lesions cured by hydrocelectomy

Macroscopic

- Hydrocele forms thin membranous sac. Papillary mesothelioma has papillary excrescences present within tunica vaginalis which forms hydrocele sac

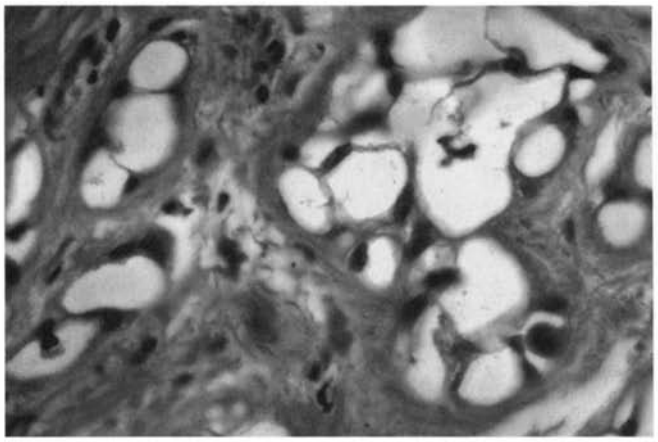


Fig. 31. Adenomatoid tumor. Irregular tumor nests with small nuclei and the vacuolated and filamentous cytoplasm give a "spiderwebby" appearance. Courtesy of Dr. W. M. Murphy, University of Florida, Gainesville.

Microscopic

- Hydrocele lined by flat mesothelium. Papillary mesothelioma has papillae lined by bland cells with large nuclei and nucleoli. Cytoplasm is clear to eosinophilic. Reactivity with calretinin excludes serous borderline tumor (*see* below)

Malignant Mesothelioma

Clinical

- Rare malignant lesion of testicular mesothelium of tunica vaginalis; rarely involves epididymis or spermatic cord
- May be seen in men with asbestos exposure, suggesting a relationship with asbestos exposure similar to pleural and peritoneal mesothelioma
- Patients present with mass, hydrocoele, or hernia sac
- Treatment is radical orchiectomy with high resection of spermatic cord
- 50% survival long-term

Macroscopic

- Solid and cystic masses line hydrocoele sac; necrosis may be present in larger masses

Microscopic

- Identical to mesotheliomas at other locations with spindle cell, epithelial (75% of cases), and biphasic types (also see **Chapter 17 and 20**)

Immunohistochemistry (also see Table 22-2)

- Cytokeratin+, CEA–

Tumors Homologous to Ovarian Tumors

Clinical

- Tumors that appear of Mullerian origin or homologous with ovarian epithelial neoplasms occur in paratesticular region

- Group includes mucinous and serous cystadenoma, serous borderline tumor, cystadenocarcinoma, endometrioid carcinoma, and Brenner tumor
- May present as incidental finding at inguinal herniorrhaphy
- Serous borderline tumor of the paratestis (McClure et al., 2001) presents as a testicular mass. No recurrence reported after resection

Macroscopic

- Serous borderline tumor ranged from 1 to 6 cm. Usually they arose from the tunica albuginea, although one arose from the tunica vaginalis. No association with epididymis or rete testis

Microscopic

- Paratesticular serous borderline tumor was identical to that of the ovary
- Cystic, with numerous broad, intracystic papillae lined by stratified columnar cells with only minimal atypia
- Estrogen and progesterone reactivity, consistent with Mullerian origin; also stained for cytokeratin 7 but not cytokeratin 20 or calretinin
- Differential diagnosis includes adenomatoid tumor (positive for calretinin, negative for hormone receptors) and malignant mesothelioma (higher MIB-1 activity)

LESIONS OF SPERMATIC CORD

Nodular Fibrous Periorchitis

Clinical

- Benign fibrous lesion of spermatic cord; also may involve tunica, epididymis
- Also known as inflammatory pseudotumor or fibrous pseudotumor
- Patients present with a testicular mass mimicking a neoplasm; wide range of patient ages
- Patients may also have a hydrocoele

Macroscopic

- Nodular or diffuse thickening of tunica, spermatic cord, or epididymis

Microscopic

- Appearance (**Figure 32**) similar to inflammatory pseudotumors in other sites
- Active inflammation in a loose stroma to densely collagenized fibrous tissue

Vasitis Nodosa (Figure 33)

Clinical

- Usually observed after vasectomy

Macroscopic

- Nodularity of blind end of transected vas deferens

Microscopic

- Sperm-containing ductules, which communicate with the central lumen of the vas deferens, extend into the muscularis and periadventitial fibroadipose tissue. Associated with chronic inflammation, possibly sperm granuloma (*see* above)
- Intramuscular location resembles invasive adenocarcinoma, but the presence of sperm, chronic inflammation, and lack of atypia are key

Proliferative Funiculitis

Clinical

- Benign spermatic cord lesion presenting as a swelling in the inguinal area. Etiology may relate to ischemia or torsion
- May present as incidental finding at inguinal herniorrhaphy
- Testicular mass mimicking a neoplasm; wide range of patient ages

Macroscopic

- Nodular or diffuse thickening of spermatic cord

Microscopic

- Similar to pseudotumor or fasciitis-like lesions. Pseudosarcomatous myofibroblastic proliferation; exhibits fibroblastic/myofibroblastic differentiation
- Chronic inflammation in a loose stroma
- Actin positivity
- Differential diagnosis includes aggressive fibromatosis (desmoid tumor), which is locally invasive, and sarcomas, which metastasize. Desmoid has cellular center and collagenized periphery

Sarcoma

Rhabdomyosarcoma

Clinical

- May arise in tunica, spermatic cord, or epididymis
- Patients present with large scrotal mass
- Occurs at any age, but is most common sarcoma of paratesticular region in children
- Most tumors occur before the age of 10
- Effective therapy (radical orchiectomy, radiation and chemotherapy) has resulted in survivals in excess of 80% of cases

Macroscopic

- Large gray-white masses in scrotum; site of origin is often impossible to locate

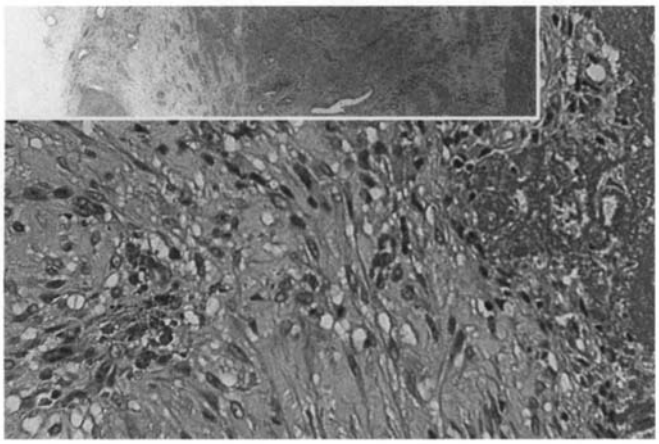


Fig. 32. Nodular fibrous periorchitis. *Inset:* The mass arises in the dartos smooth muscle bundles; no testis or epididymis is present. *Main image:* Fibroblasts have a loose, "tissue culture" appearance. Some hemosiderin deposits are at the left and hemorrage is at the right.

Microscopic

- Embryonal rhabdomyosarcoma is the most common type seen in the paratesticular region
- Spindled types may occur, as well as alveolar, pleomorphic, and botryoid types

Liposarcoma

- Most common paratesticular sarcoma in adults
- Most often well-differentiated (sclerosing), but may show dedifferentiation
- In high-grade sarcomas, areas of well-differentiated liposarcoma should be sought with thorough sampling

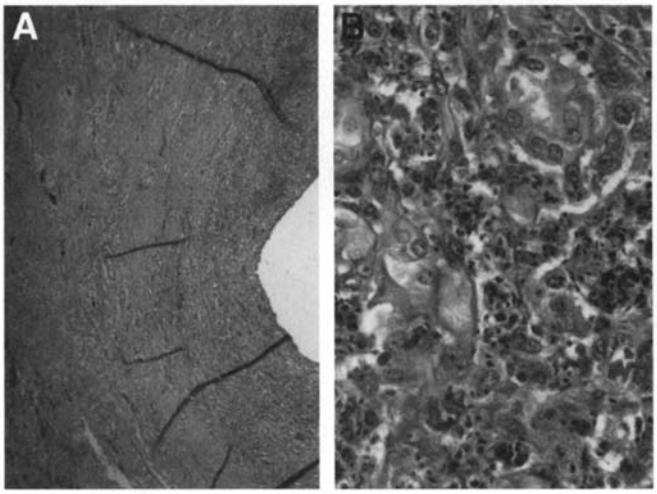


Fig. 33. Vasitis Nodosa. **(A)** Ductular epithelial infoldings of the vas deferens infiltrate into the smooth muscle wall. **(B)** Despite this infiltrative appearance, the presence of lymphohistocytic inflammation and extravasated sperm in the ductules bespeak a benign diagnosis.

- Treated by radical orchiectomy
- 23% develop recurrence after surgery; 10% develop metastases

Leiomyosarcoma

- Occurs in adults, and most often involves testicular tunica or spermatic cord (Fisher et al., 2001)
- Treated by radical orchiectomy
- Majority are low-grade lesions but high-grade lesions behave aggressively. Long-term survival is obtained in 67%

TNM CLASSIFICATION OF TESTICULAR TUMORS (2002 REVISION)

Testis

Primary Tumor (T)

- Tx: Unknown status of testis
- T0: No apparent primary (includes scars)
- Tis: Intratubular neoplasia; no invasion
- T1: Tumor confined to testicle
- T2: Tumor extending through the tunica albuginea with involvement of tunica vaginalis or the presence of angiolymphatic invasion
- T3: Spermatic cord involvement
- T4: Scrotal involvement

Regional Lymph Nodes (N)

- Nx: Nodal status unknown
- N1: Single lymph node involved, <2 cm
- N2: Single node, 2–5 cm or multiple nodes <5 cm
- N3: Any nodes >5 cm

Distant Metastasis (M)

- Mx: Status of metastases unkown
- M0: No distant metastases
- M1: Distant metastases

Serum Markers (S)

- SX: marker studies not performed
- S1: LDH 1.5 times "normal" (upper limit of normal for assay) and hCG <5000 mU/mL, and AFP <1000 μg/mL
- S2: LDH 1.5–10 times "normal" or hCG 5000–50,000 mU/mL, or AFP 1000–10,000 μg/mL
- S3: LDH 10 times "normal" or hCG >50,000 mU/mL, or AFP >10,000 μg/mL

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33

Penis

Gustavo Ayala, MD, PhD and Antonio L. Cubilla, MD

CONTENTS

I. Congenital Anomalies 33-2
- Hypospadias 33-2
- Epispadias 33-2
- Aphalia 33-2
- Micropenis (Hypoplasia) 33-2
- Diphallus 33-2
- Concealed Penis 33-2
- Webbed Penis 33-2
- Median Raphe Cyst 33-2
- Lateral Curvature of the Penis 33-2

II. Inflammatory Conditions and Other Benign Conditions 33-2
- Bacterial Infections 33-2
  - Gonorrhea 33-2
  - Mycobacteria 33-3
  - Granuloma Inguinale 33-3
  - Chancroid (Soft Chancre) 33-3
- Syphilis 33-3
- Fungal Infections 33-4
- Viral Infections 33-4
  - Herpes Simplex 33-4
  - Molluscum Contagiosum 33-4
- Lymphogranuloma Venereum 33-4
- Parasitic Infections 33-4
- Other Inflammatory Conditions 33-4
  - Balanoposthitis and Balanitis 33-4
  - Phimosis and Paraphimosis 33-5
  - Lichen Sclerosis 33-5
  - Plasma Cell Balanitis 33-5
  - Gangrenous Balanitis 33-5
  - Tancho's Nodules and Paraffinoma 33-5
  - Mondor's Phlebitis 33-5
  - Peyronie's Disease 33-5
  - Priapism 33-5
  - Lentiginous Melanosis 33-5
  - Papillomatosis of Glans Corona 33-5
  - Other Benign Conditions 33-6

III. Putative Precursor Lesions of the Penis 33-6
- Condyloma Acuminata 33-6
- Squamous Hyperplasia 33-6
- Penile Intraepithelial Neoplasia (PeIN) 33-6
  - Hypertrophic-Hyperplastic Dysplasia 33-6
  - High-grade PeIN, Basaloid Subtype 33-6
  - High-grade PeIN, Warty Subtype 33-6
  - PeIN, Not Otherwise Specified 33-6
- Bowenoid Papulosis 33-7

IV. Penis Cancer 33-7
- Clinical 33-7
- Gross Findings 33-8
  - Superficially Spreading Growth 33-8
  - Vertical Growth 33-8
  - Verruciform Growth 33-8
  - Multicentric Growth 33-9
  - Squamous Cell Carcinoma of the Usual Type 33-9
- Microscopic 33-10
  - Squamous Cell Carcinoma, Basaloid Subtype 33-10
  - Warty/Condylomatous Carcinoma 33-10
  - Verrucous Carcinoma 33-10
  - Giant Condyloma of Buschke-Lowenstein 33-12
  - Papillary Carcinoma 33-12
  - Sarcomatoid (Spindle Cell) Subtype 33-12
  - Rare Variants 33-12

V. TNM Classification of Penis Cancer 2002 33-13

VI. Suggested Reading 33-13

CONGENITAL ANOMALIES

Hypospadias

- Most common congenital anomaly
- Occurs in 1 in 300 male births
- Urethra opens on the ventral surface of the penis (usually on glans) or the perineum **(Figure 1)**
- May be associated with chordee (chordee is bending of the penis, and it is congenital in hypospadias, and is a result of maldeveloped fascia distally)
- Associated with other GU congenital abnormalities and blocked ejaculation, like epispadias

Epispadias

- Urethra opens on the dorsal aspect of the penis
- Occurs in 1 in 117,000 male births
- Associated with other abnormalities, including cryptorchidism, renal agenesis, ectopic kidney, and bladder exstrophy
- Urethral opening may be constricted, and the location may impair normal ejaculation and subsequent insemination, resulting in infertility

Aphalia

- Absence of penis (penile agenesis)
- Normal scrotum is present, but no penile shaft
- Genital tubercle does not develop
- Occurs in 1 in 10,000,000 male births
- Associated with cryptorchidism, imperforate anus, renal agenesis and other renal malformations, and musculoskeletal and cardiopulmonary defects

Micropenis (Hypoplasia)

- Small penis <2 or more standard deviations below mean
- Causes include idiopathic, hypogonadotropic hypogonadism, and hypergonadotropic hypogonadism

Diphallus

- Double penis

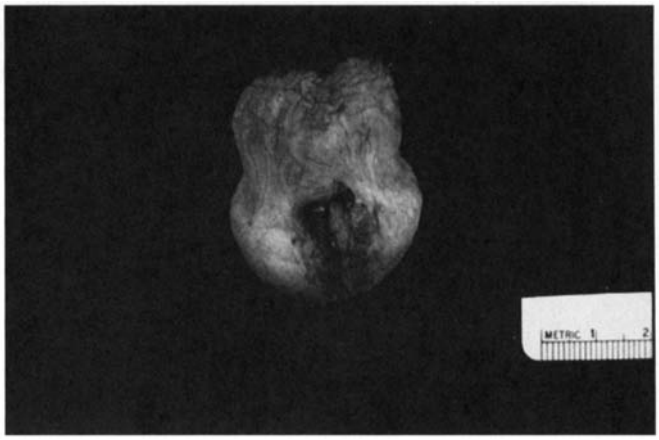


Fig. 1. Ventral view of penis with hypospadia.

- Associated with other congenital anomalies, including hypospadias, renal agenesis, imperforate anus, heart defects, and others

Concealed Penis

- The penis is normally developed, but hidden under fat in the suprapubic area, scrotum, perineum, or thigh

Webbed Penis

- Most common congenital anomaly. The scrotal skin extends to the ventrum of the penis and hides it

Median Raphe Cyst

- Results from anomalies in the development of the urethral groove
- Asymptomatic
- Benign cyst forms a midline ventral translucent subcutaneous mass

Lateral Curvature of the Penis

- Results from overgrowth or hypoplasia of one corporeal body

INFLAMMATORY CONDITIONS AND OTHER BENIGN CONDITIONS

Bacterial Infections

- Bacterial infections of the genitourinary tract are most frequent in females and uncircumcised male newborns
- Localized infections of the penis can spread and produce cellulitis by group A streptococcus
- Predisposing factors include local or perineal trauma, burns, anorectal disease, and debilitating conditions such as diabetes, leukemia, and alcoholic cirrhosis
- Streptococci and staphylococci are the most common causative agents in children

Gonorrhea

Clinical

- Caused by pyogenic Gram-negative, diplococci *Neisseria gonorrhoea*
- Sexually transmitted
- Causes urethritis with suppurative discharge and dysuria

- If untreated, may spread to posterior urethra, prostate, and epididymis
- Urethral stricture is a complication
- Untreated males may be silent carriers of gonococci
- Treated with antibiotics

Microscopic

- Neutrophilic infiltrate is present within urethra, may ulcerate
- Gonococci seen within neutrophils on smears of urethral swabs
- Abscess formation may occur in prolonged cases

Myobacteria

- Tuberculosis may present as a primary lesion, direct spread from nearby site such as lymph nodes, or as hematogenous spread in systemic infection
- Histology similar to tuberculous granulomas at other sites

Granuloma Inguinale

Clinical

- Caused by Gram-negative facultative intracellular bacillus, *Calymmatobacterium granulomatis*
- Organism is difficult to culture
- Unusual in United States; most frequent in Asia (India and New Guinea) and the Caribbean
- Infections involve penis, perineum, and vulva (males more frequently affected than females)
- Painless papules develop at the site of infections and then ulcerate
- Cured with antibiotics

Microscopic

- Epidermal ulceration associated with epidermal hyperplasia is present
- Massive plasma cell infiltrate within granulation tissue at the ulcer base
- Few or no lymphocytes
- Donovan bodies are characteristic 50 micron diameter dark bipolar inclusions within cytoplasmic vacuoles of macrophages
- Donovan bodies seen best with Giemsa or silver stains

Chancroid (Soft Chancre)

Clinical

- Caused by sexually transmitted gram-negative anaerobic *Hemophilus ducreyi*
- Disease hallmark: soft painful ulcer
- Lymphadenopathy frequently develops
- Uncommon in United States, but increasing in frequency; more common in Asia, parts of Africa, and the Caribbean

Microscopic

- Soft chancre consists of three zones:
  - Uppermostzone: Ulcer base with necrosis, fibrin, neutrophils, and debris
  - Middle zone: abundant granulation tissue with palisading vascular proliferation:
    - Thrombosed vessels may be present
  - Deepest zone: intense plasma cell and lymphocytic inflammation
- Organisms can be identified in tissues (best on smears) with Giemsa, Gram, or methylene blue stains
- Lymph nodes may enlarge with bubo formation

Syphilis

Clinical

- Caused by spirochete *Treponema pallidum*
- Three stages: primary, secondary, and tertiary:
  - Primary syphilis:
    - Characterized by a reddened papule on glans penis, prepuce, or shaft that ulcerates to form characteristic chancre:
      - In 10% of cases, chancre may not be on the genitals
    - Chancre is a well-circumscribed clean-based ulcer with an *indurated* base
    - Lymphadenopathy is present
    - Ulcer heals in 6–8 weeks
  - Secondary syphilis:
    - Characterized by maculopapular rash (condyloma lata); involves skin and mucosal surfaces, and is associated with generalized lymphadenopathy
    - May also be manifest by an elevated broad-based plaque on genital region (condyloma lata)
  - Tertiary syphilis:
    - Very rare
    - Characterized by gummas that are nodules formed of granulomas that may be necrotic
    - Most commonly involves cardiovascular system (80% of cases) and CNS (10% of cases)
    - Cured with antibiotics in primary stage

Microscopic

- Histologic features of chancre include ulceration of epidermis, with underlying dermis containing an infiltrate of plasma cells and lymphocytes that obscures the dermoepidermal junction
- Inflammation may be perivascular and endothelial proliferation may be pronounced; typically, there is obliterative endarteritis surrounded by a predominantly plasmacytic infiltrate
- Lymph nodes exhibit follicular hyperplasia and a paracortical plasmacytosis
- Capsule is thickened
- These findings are not specific for syphilis

- Spirochetes may be seen in chancre, and lymph nodes with dark field microscopy or special stains (Warthin-Starry)
- Skin changes in secondary syphilis are non-specific
- Dark-field microscopy may show spirochetes
- Gummas in tertiary syphilis are granulomatous with or without necrosis

Fungal Infections

- Superficial infections are caused by dermatophytes and infect the penis through local spread from more commonly affected areas such as the groin
- Causes nonspecific inflammation associated with hyperkeratosis amd parakeratosis
- Candida albicans carried asymptomatically by 15% to 20% of men
- Deep mycotic infections of the penis are rare and represent hematogenous spread from other sites

Viral Infections

Herpes Simplex

Clinical

- Sexually transmitted disease caused by the DNA virus herpes simplex Type II
- Initial episode of infection is most pronounced, with systemic symptoms (headache, fever, and malaise) and genital lesions
- Multiple millimeter-sized vesicles develop and become pustules that eventually rupture to form painful ulcers
- Recurrent episodes are less severe and consist of genital lesions
- Antivirals, such as acyclovir, will decrease the severity and duration of lesions but will not eliminate the virus or recurrent infections

Microscopic

- Intraepidermal vesicles caused by acantholysis
- Neutrophilic infiltrate and ulceration present
- Viral inclusions are typically seen within epidermal cells and are characterized by intranuclear acidophilic and ground-glass inclusions
- Cell fusion results in multinucleated giant cells; nuclei of giant cells contain inclusions
- Tzank preparation (examination of vesicle fluid or smear of ulcer and staining with Wright-Giemsa, toluidine blue, or Papanicolaou stains) reveals cells with diagnostic inclusions

Molluscum Contagiosum

Clinical

- Sexually transmitted disease caused by a DNA pox virus
- The lesion is a 3- to 6-mm dome-shaped pearly papule with central umbilication

Microscopic

- Histologically, it shows lobular acanthosis of the epidermis, which causes an inverted pattern of epidermal hyperplasia
- Intracytoplasmatic eosinophilic inclusions called Henderson-Paterson bodies identified in the stratum spinosum and granulosum

Lymphogranuloma Venereum

Clinical

- Sexually transmitted infection caused by L-1, L-2, and L-3 serotypes of chlamydia trachomatis
- Culture is diagnostic
- Three stages:
  - Primary genital stage characterized by a small painless epidermal vesicle or papule that ulcerates and heals spontaneously
  - Followed by painful lymph node involvement: lymph nodes become matted together and fluctuant (bubo formation)
  - Rare third stage with ulcers, fistulas, and strictures

Microscopic

- Histologic features of genital cutaneous lesion are non-specific
- Lymph nodes show stellate microabscesses identical to cat-scratch disease
- Abscesses may enlarge and rupture to the skin surface
- Chlamydial inclusions may be identified by immunofluorescence techniques
- Third stage is characterized by resolution of suppurative granulomas with sinus tracts and fibrosis

Parasitic Infections

Scabies

- Caused by the burrowing mite, Sarcoptes scabiei
- Most common parasitic infection

Other Inflammatory Conditions

Balanoposthitis and Balanitis

- Inflammation of glans penis and prepuce (balanoposthitis) and glans penis (balanitis)
- Occurs in uncircumcised men who fail to keep foreskin clean
- Debris accumulates (smegma) and becomes infected by a variety of organisms, including staphylococci, streptococci, coliforms, or gonococci
- Collection of infected smegma results in inflammation
- May lead to scarring and phimosis (inability to retract foreskin over glans penis)

Phimosis and Paraphimosis

- Phimosis is the inability to retract the foreskin over the glans penis; paraphimosis is a persistently retracted foreskin
- Most commonly the result of balanitis or balanoposthitis, but may be congenital due to abnormally long foreskin
- Phimosis prevents the ability to clean the foreskin
- Treatment of both conditions is circumcision
- Penile cancer more frequent in patients with phimotic foreskins than in long foreskins without phimosis
- It is important to sample liberally foreskin specimens from adults to rule out dysplasia, CIS, or carcinoma
- Nonspecific lymphoplasmacytic inflammnation in the lamina propria of glans and foreskin

Lichen Sclerosus (Balanitis Xerotica Obliterans)

Clinical

- Idiopathic atrophic condition of genital and perianal skin
- May be autoimmune in origin
- Similar changes may be seen in foreskins removed for phimosis
- Occurs in older males
- Asymptomatic
- Treatment is circumcision, topical steroids, and laser therapy
- Cases have been associated with subtypes of squamous cell carcinoma, including usual squamous cell carcinoma, verrucous carcinoma, and papillary carcinoma

Gross Findings

- Well-circumscribed white patch that usually involves glans penis; may also involve prepuce, shaft of penis, and urethral meatus

Microscopic

- Atrophic epidermis (thin epidermis with loss of rete and dermal adnexal structures) with hyperkeratosis and fibrosis (hyalinization) of dermis
- Sparse lymphocytic infiltrate in the deep submucosa
- Sparing of preputial dartos and corpus spongiosum of the glans

Plasma Cell Balanitis (Zoon's Balanitis; Balanitis Circumscripta Plasmacellularis)

- Inflammatory condition of unknown etiology
- Occurs in uncircumscribed men
- Solitary or multiple well-defined brown or red plaques; may clinically simulate CIS
- Edema and dense plasma cell infiltrate with scattered histiocytes

Gangrenous Balanitis (Corbus' Disease)

- Rapidly progressive necrotizing inflammation, similar to scrotal Fournier's gangrene
- Anaerobic infection involving the glans penis
- May also result from penile prosthesis reaction

Tancho's Nodule and Paraffinoma

- Foreign body reaction owing to injection or insertion into the penis of paraffin, silicone, or wax

Mondor's Phlebitis

- Very firm subcutaneous cord-like swellings located along the dorsal shaft or around the coronal sulcus
- Massive thrombosis of the superficial venous plexus of the penis
- Results from trauma or associated Herpes simplex infection

Peyronie's Disease

Clinical

- Form of fibromatosis involving penis
- Bending of penis during erection
- Causes painful erection
- Palpable plaques and firm nodules over the mid-dorsal surface of the penis
- Associated with urethritis, trauma during intercourse, and urethral instrumentation

Gross Findings

- Single or multiple plaques are present on the dorsal surface of the penis creating abnormal curvature

Microscopic

- Fibrosis of tunica albuginea forming dense fibrous plaques of dermis and Buck's fascia
- May calcify and ossify

Priapism

- Persistent erection that becomes painful from ischemia
- Multiple causes, including drugs (oral, intravenous, and intracavernous), sickle cell anemia, leukemic and other malignant infiltrates (rare cause), trauma, neurologic disorders, and others
- May be idiopathic

Lentiginous Melanosis

- Frequent benign lesions of the glans and foreskin
- Flat pigmented macules with irregular borders
- Melanotic hyperplasia with hyperpigmentation of the basal layers and elongation of rete pegs

Papillomatosis of Glans Corona

- Asymptomatic and benign; present in 20–30% of normal men
- May be related to excessive sexual activity

- Consists of pearly gray-white fibroepithelial papillomas forming 2–3 rows in the dorsal aspect of the glans corona

Other Benign Conditions

- Os penis: Heterotopic bone, usually in elderly men in association with Peyronie's disease
- Verruciform xanthoma: warty lesion with acanthosis, hyperkeratosis, and parakeratosis
- Miscellaneous: keratotic horn, pyogenic granuloma, inflammatory psuedotumor, ectopic sebaceous glands, Wegener's granulomatosis

PUTATIVE PRECURSOR LESIONS OF THE PENIS

Condyloma Acuminata

Clinical

- Caused by sexually transmitted human papilloma virus (HPV)
- Affects young sexually active males
- HPV types 6, 11, 16, 18, 31, and 33 cause condylomata
- Types 16, 18, 31, and 33 are most frequently associated with dysplastic changes
- Treated with podophyllin and laser therapy

Gross Findings

- Condyloma consists of warty papillary growths

Microscopic

- Condylomata papillary with acanthotic parakeratotic (retention of nuclei in superficial epidermis) and hyper-keratotic squamous epithelium
- Koilocytotic change (irregular "boxcar" nuclei, multinucleation, perinuclear halos) is usually minimal (unlike cervix)

Squamous Hyperplasia

- Benign acanthotic thickening of squamous epithelium involving the glans, sulcus, and foreskin
- Frequently associated with squamous cell carcinoma, particularly the verrucous and low-grade papillary subtypes
- White or pigmented flat, papillary, mixed flat-papillary or pseudoepitheliomatous lesion with normal maturation
- No evidence of parakeratosis, atypia, or koilocytotic change

Penile Intraepithelial Neoplasia (PeIN; Squamous Intraepithelial Lesion [SIL])

Clinical

- Approximately 10% of patients with PeIN develop invasive squamous cell carcinoma
- High risk HPVs (16 and 18) present in 80–100% of cases of PeIN
- Mean age at presentation: 33 years

Microscopic **(Figure 2)**

- Low-grade PeIN has dysplastic changes present in the lower half of the epithelium **(Figure 2A)**; in high-grade PeIN, the dysplastic changes involve the entire thickness of the epithelium
- Subtypes are identifiable, and these have clear association with histologic subtypes of penile carcinoma **(Figure 2)**
- Hypertophic-hyperplastic dysplasia (Pseudo-epitheliomatous, hyperkeratotic, micaceous balanitis):
  - Poorly recognized lesion associated with verrucous carcinoma
  - Characterized by thickened squamous epithelium without significant atypia and with spiky base (pseudo-epitheliomatous) surrounded by inflammation
  - Frequently present adjacent to invasive verrucous carcinoma
  - Because of lack of atypia, this lesion is commonly unrecognized and is one of the causes of recurrence of verrucous carcinoma
- High-grade PeIN, warty subtype:
  - Characteristic architectural and cytologic changes
  - Cells have prominent koilocytic changes throughout the epithelium as well as marked atypia and atypical mitotic figures
  - Growth pattern is spiky and condylomatous
  - Associated with warty/condylomatous carcinoma **(Figure 2B)**
- High-grade PeIN, basaloid subtype:
  - Composed of small basophilic immature cells that crowd and thicken the epithelium and create a dark acanthotic epithelial layer
  - Usually has a flat base and surface
  - Associated with invasive basaloid carcinomas in more than half of the cases **(Figure 2C)**
  - Mixture of basaloid and warty in situ and invasive lesions are relatively common, for they both appear to have a common oncogenic pathway (HPV)
- PeIN, Not Otherwise Specified:
  - Similar to CIS in other parts of the body such as the cervix and skin **(Figure 2D)**

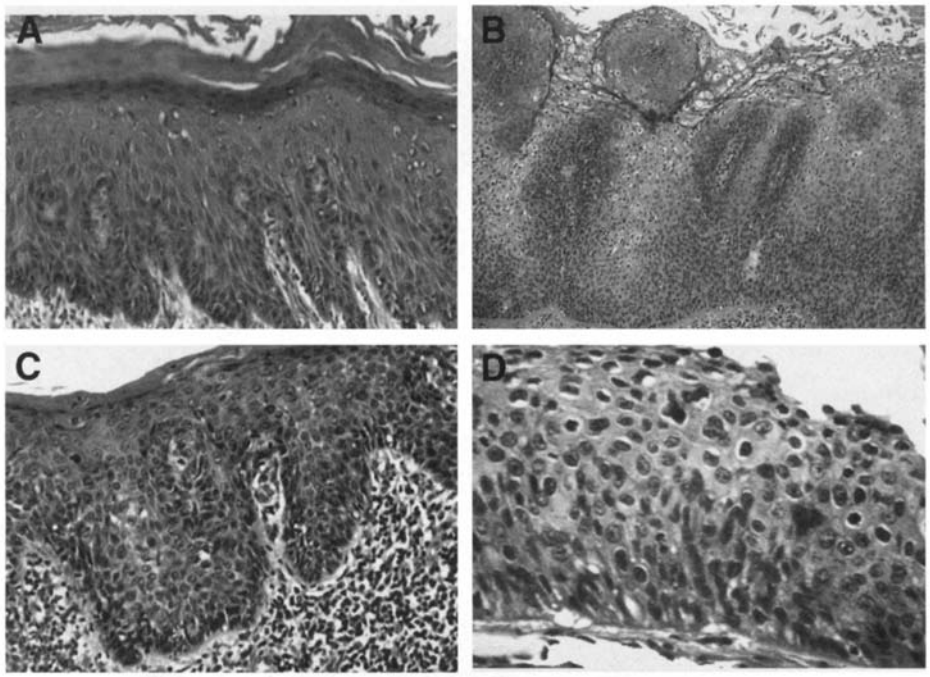


Fig. 2. Subtypes of Penile Intraepithelial Neoplasia (PeIN). **(A)** Low-grade PeIN; **(B)** High-grade PeIN, warty subtype; **(C)** High-grade PeIN, basaloid subtype; **(D)** High-grade PeIN, usual type.

Bowenoid Papulosis

Clinical

- Affects younger men than high-grade PeIN
- Tends to be multifocal and involves penile shaft
- HPV Type 16 is identified in 80% of all cases
- Red-brown verrucoid papules that spontaneously regress
- Not associated with the development of squamous cell carcinoma

Microscopic

- Resembles PeIN, but exhibits some maturation—thus, is best classified as low-grade PeIN

PENIS CANCER

Squamous Cell Carcinoma

Clinical

- Affects 1 in 100,000 U.S. men; 1% of all male cancer in the United States
- Usually affects men in the seventh decade of life, although warty and basaloid carcinoma occur a decade earlier
- Lack of circumcision is strongest risk factor; associated with up to 12% of cancers in men in some locations
- Uncircumcised men with phimosis (poor hygiene) affected
- Early circumcision is protective (relative risk decreased 3.2); also protects against HPV infection
- HPV types 16 and 18 are identified in 50% of cancers; HPV 6 and 11 most common in condylomas
- HPV more frequently associated with basaloid and warty subtypes; only 11% HPV detection in typical squamous cell carcinoma
- Higher HPV detection in PeIN (80–100%) compared with cancer (20–60%)—unknown cause of difference
- Basaloid carcinoma may arise in HPV 8-positive epidermodysplasia verruciformis
- Primary and metastastic penis cancer often contain integrated HPV subtype (HPV 16) with identical cleavage patterns
- Chronic damage to penile mucosa also linked to penis cancer
- Cancer in 5.8% of patients with balanitis xerotica obliterans (mean lag, 17 years); progression from BXO to dysplasia and cancer is frequent, particularly in the foreskin
- Tobacco use linked to penis cancer (relative risk of 2.8; dose-dependent); 80% of patients with penis cancer are heavy smokers
- Radiation to the penis may cause secondary cancers that are particularly aggressive; this includes transformation of verrucous carcinoma to anaplastic carcinoma (radiation is contraindicated with verrucous carcinoma)
- Psoralens and ultraviolet radiation (PUVA) have a strong dose-dependent correlation with penis cancer (relative risk of 286)

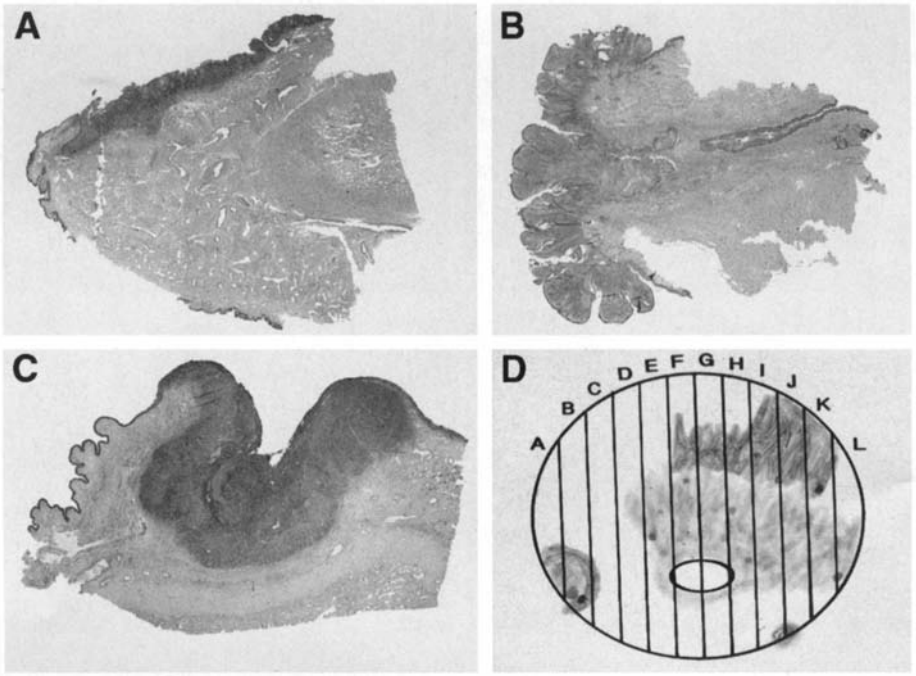


Fig. 3. Growth patterns of penis cancer: **(A)** Superficially spreading, **(B)** Verruciform, **(C)** Vertical growth, and **(D)** Multicentric.

- Other risk factors include Hailey-Hailey disease, burns, asbestos, sinus tracts, hypospadia, mineral oil injection, sexual activity, lichen planus, and plasma cell balanitis
- Penis cancer not related to syphilis, Herpes simplex, or Epstein-Barr virus
- Approximately 40% of patients have nodal metastases at presentation; hematogenous or distant metastases are rare at presentation:
  - A combination of histologic grade and depth of penetration are the best predictors of metastasis
  - Low-grade cancer that invades superficial layers or as deeply as 6 mm are not associated with regional meta-stasis. High grade cancer with invasion of the deep corpora spongiosa, dartos, or corpora cavernosa (8–10 mm) predicts metastasis in up to 80% of the cases
  - Other adverse prognostic variables are lymphatic invasion,vertical growth pattern, histologic subtype (basaloid, sarcomatoid) and mitotic count (>20 mitosis)
  - Carcinoma of the foreskin has a better prognosis than that of the glans, but this seems to be due to the predominance of verruciform cancer in the former

Gross Findings

- Glans penis and inner surface of prepuce are most frequently involved (70% of cases)
- Growth pattern may determine best therapeutic approach **(Figure 3)**:
  - Large tumors of the penis may be treated conservatively if verruciform or superficially spreading, while small vertical growth tumors often require radical surgery and lymphadenectomy
  - Thorough evaluation of normal appearing mucosa must be performed before attempting conservative therapy to asses multicentricity. Many recurrences arise fromincipient neoplasms overlooked at the time of therapy for the overt carcinoma
- Superficially Spreading Growth **(Figure 4)**:
  - Extensive superficial lesion that exhibits a preferential centripetal growth pattern
  - Composed of a mixture of PeIN and invasive carcinoma
  - Focal deep infiltration can occur
  - Usually large tumors that involve more than one anatomic compartment
  - PeIN may extend further than the grossly visible tumor. It is, therefore, important to evaluate the surgical margins before attempting conservative surgery
- Vertical Growth **(Figure 5)**:
  - Aggressive cancer associated with high risk of regional metastasis and death
  - Relatively circumscribed cancer with deep extension
  - Tends to invade deeply before becoming large
  - Most common are high-grade histologic variants such as basaloid, sarcomatoid, and anaplastic carcinoma
- Verruciform Growth **(Figure 6)**:
  - Large slow growing cancer with exophytic appearance
  - Usually superficial, but may be deeply invasive if left to develop for long periods of time
  - Among these are the classic verrucous carcinoma, the warty/condylomatous, the papillary and the buschke-lowenstein giant condyloma

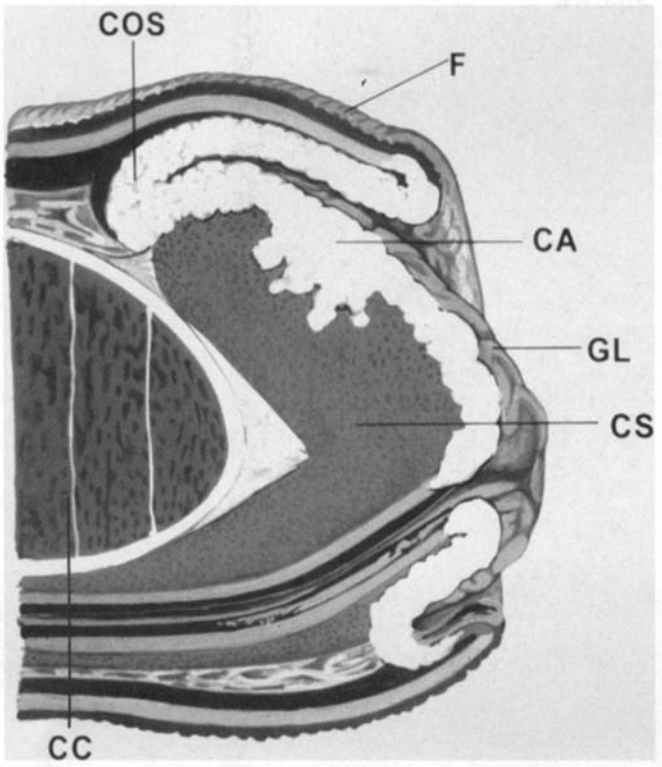


Fig. 4. Superficially spreading cancer involving all three compartments of the penis. CC: corpora cavernosa; CS: corpora spogiosa; GL: glands; F: foreskin; COS: coronal sulcus; CA: cancer.

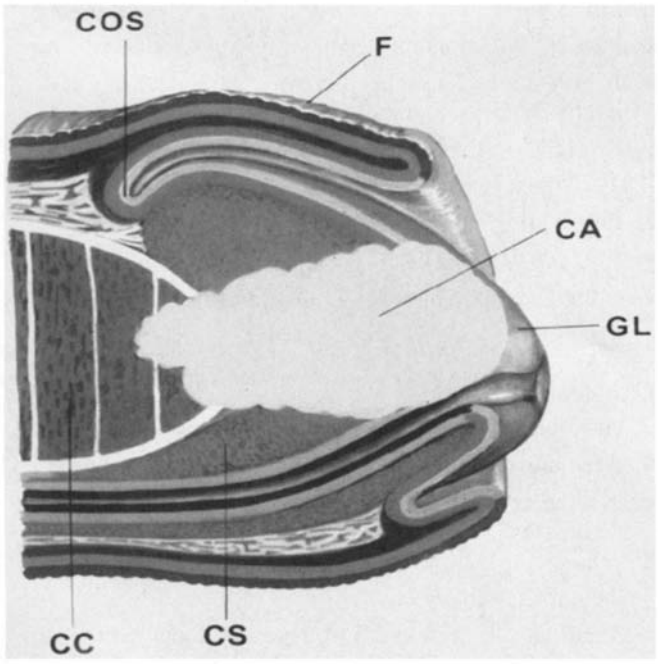


Fig. 5. Vertical growth pattern of cancer with deep infiltration into the corpora cavernosa. CC: corpora cavernosa; CS: corpora spogiosa; GL: glands; F: foreskin; COS: coronal sulcus; CA: cancer.)

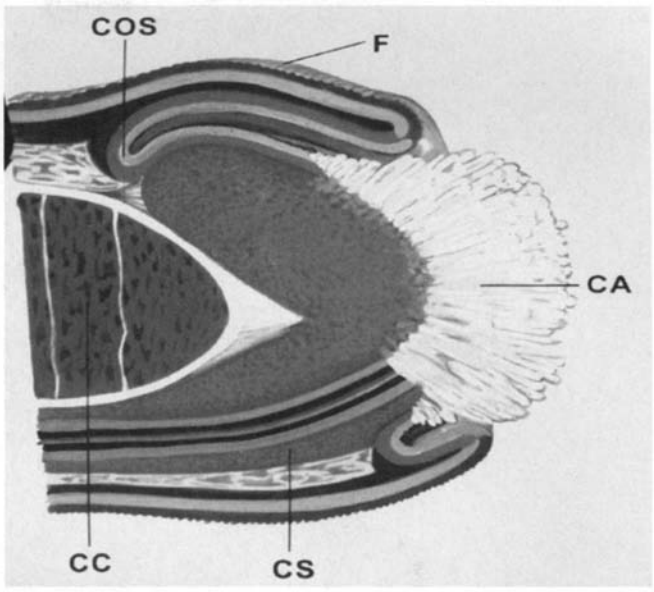


Fig. 6. Verruciform growth of penis cancer with superficial invasion. CC: corpora cavernosa; CS: corpora spogiosa; F: foreskin; COS: coronal sulcus; CA: cancer.

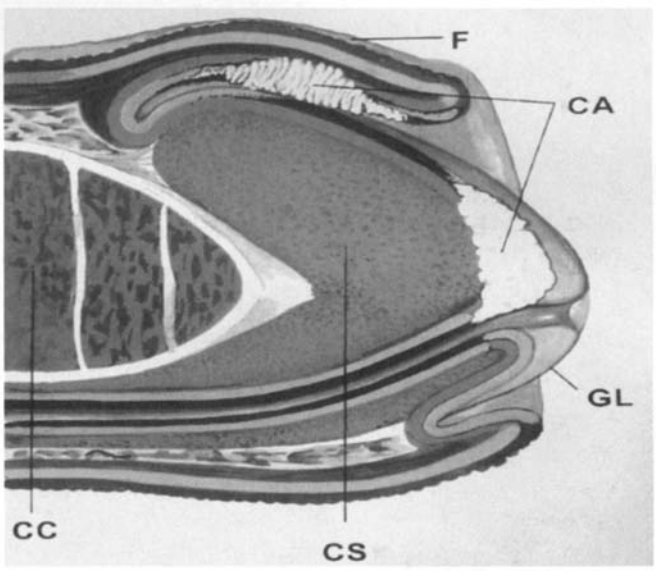


Fig. 7. Multicentric cancer involving the glans and foreskin.

- Multicentric Growth **(Figure 7)**
  - It is important to be aware of this growth pattern in order to provide accurate assessment of previously undetected lesions
  - The presence of two or more foci entirely separated by normal epithelium is characteristic

Squamous Cell Carcinoma of the Usual Type

Clinical

- Most common histologic subtype of penis carcinoma
- Accounts for approximately 60% of cases of penis carcinoma
- Median age at diagnosis is 58 years

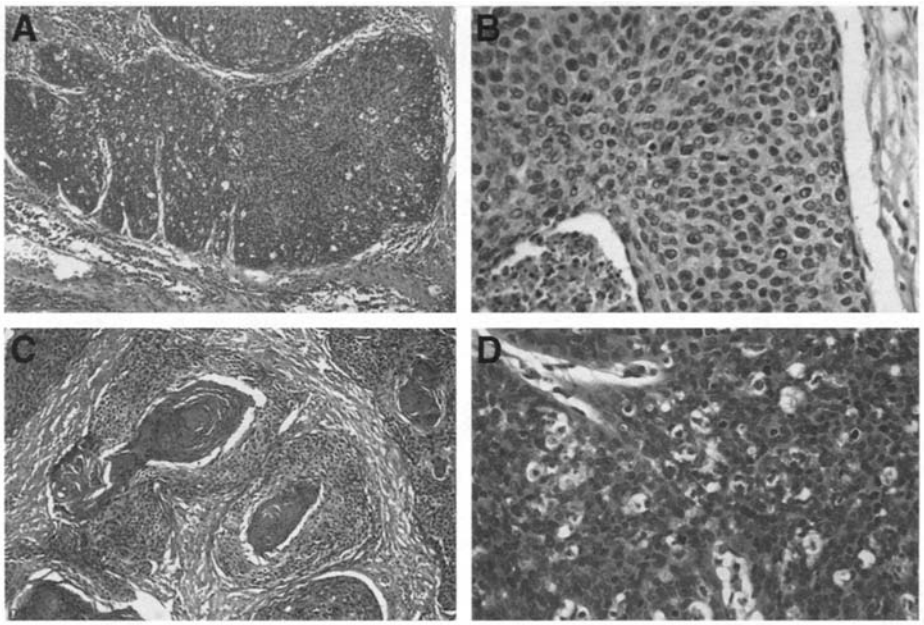


Fig. 8. Basaloid carcinoma with islands of tumor growth showing central necrosis and retraction artifact (**A–C**). Note partial keratinization (**B**) and extensive apoptosis (**D**).

Macroscopic

- All growth patterns possible

Microscopic

- Similar to squamous cell carcinoma in other parts of the body
- Most are moderately differentiated keratinizing carcinoma
- Low and high grade PeIN present in 2/3 of cases

Squamous Cell Carcinoma, Basaloid Sybtype (Figure 8)

Clinical

- Aggressive deeply infiltrating cancer
- Strongly associated with HPV
- Accounts for approximately 10% of cases of penis carcinoma
- Median age at diagnosis is 52 years

Macroscopic

- Deeply infiltrating

Microscopic

- Composed of small uniform, pyknotic cells growing in nests
- Comedonecrosis, peripheral cleft artifact, brisk mitotic activity, and starry sky appearance owing to apoptotic bodies are characteristic
- Frequently associated with basaloid PeIN

Warty/Condylomatous Carcinoma (Figure 9,10)

Clinical

- Intermediate prognosis despite high-grade histologic appearance
- Metastases seen with deeply infiltrating cancer
- Strongly associated with HPV
- Mixed basaloid/warty carcinoma is frequent

Macroscopic

- Exophytic growth

Microscopic

- Papillary growth pattern similar to condyloma
- Arborizing papillae have fibrovascular cores, microabscesses, and koilocytic cellular changes throughout the cancer
- Significant nuclear atypia
- Infiltrating, ragged margin

Differential Diagnosis

- Other exophytic tumors (**Table 1, Figure 9**)

Verrucous Carcinoma

Clinical

- Histologically and clinically low-grade exophytic cancer
- Accounts for about 8% of cases of penis carcinoma
- Median age is 69 years; mean duration of cancer is 56 months
- Cured by resection, an does not metastasize; recurs if incompletely resected
- Recurrence is seen in 1/3 of the cases, mostly owing to undertreatment for the unrecognized precursor lesion
- Verrucous carcinoma is not associated with HPV

Macroscopic

- Exophytic

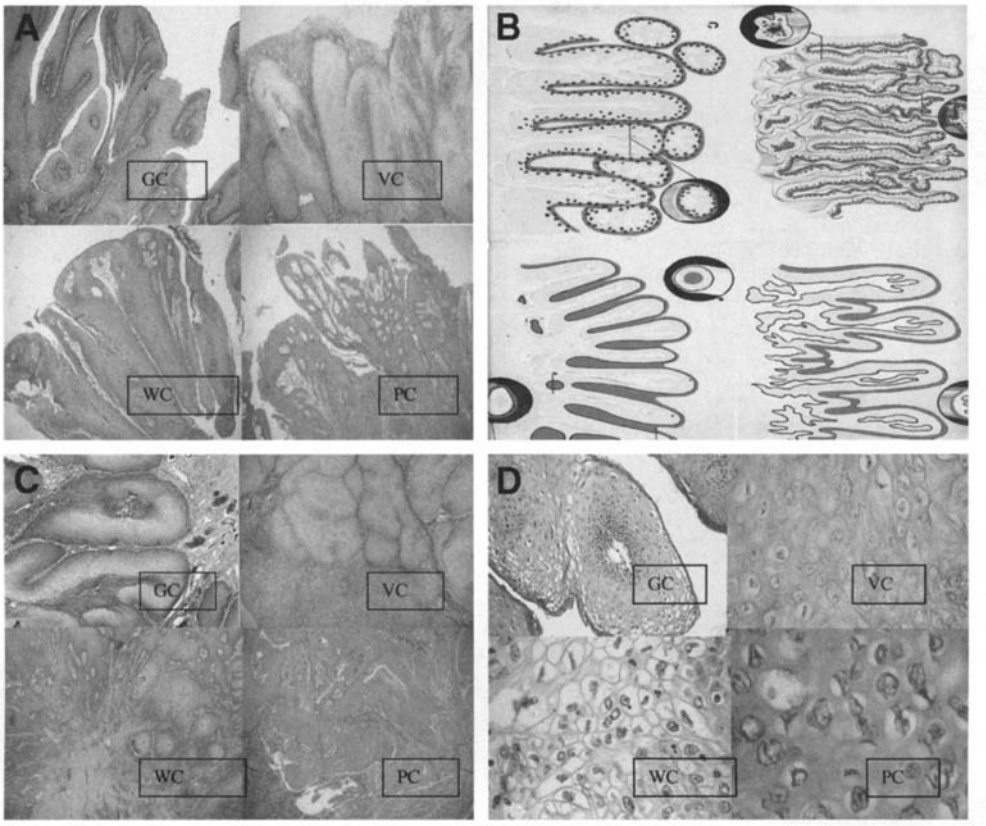


Fig. 9. Types of exophytic growth penis cancer. **(A)** External growth; **(B)** Invasive edge; **(C)** Distinct types of papillae; and **(D)** Cytologic characteristics. GC, Giant condyloma of Buschke-Lowenstein; VC, verrucous carcinoma; WC, Warty/condylomatous carcinoma; PC, papillary carcinoma.

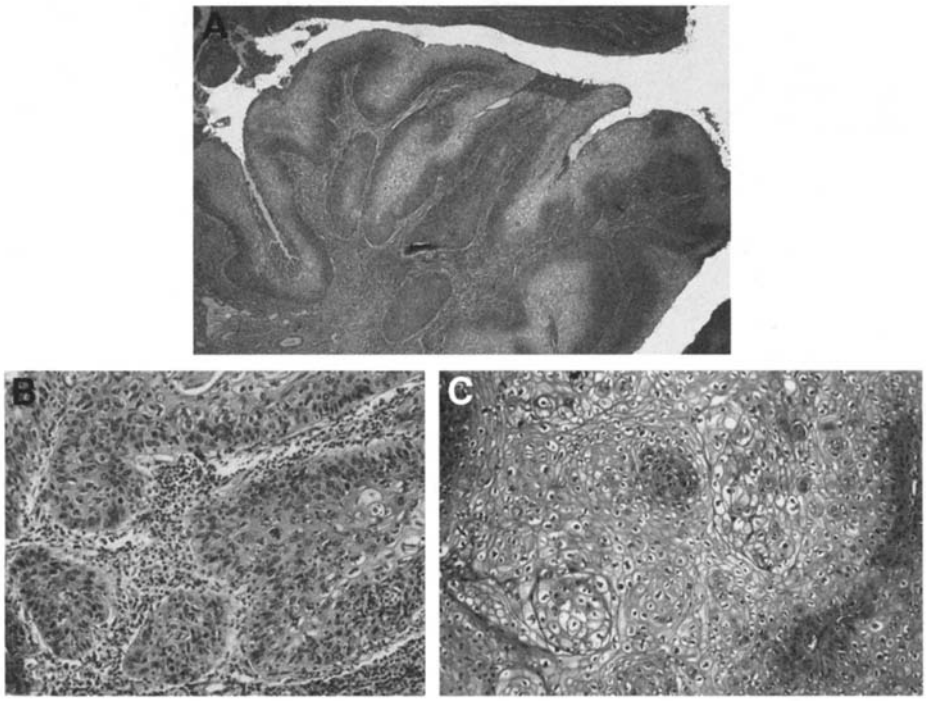


Fig. 10. Warty carcinoma with exophytic growth superficially **(A)** and infiltrating invasive growing edge **(B)**. Note the koilocytic changes **(C)**.

Table 1. Comparison of Warty Carcinoma and Other Exophytic Tumors

	Warty Carcinoma	*Giant Condyloma*	*Verrucous Carcinoma*	*Papillary Carcinoma, NOS*
Papilae	Long, undulating. Condylomatous complex	Arbolzing, nonundulating	Straight	Variable, complex
Fibrovascular cores	Prominent	Prominent	Rare	Present
Koilocytic atypia	Prominent and diffuse	Present at surface	Absent	Absent
Base	Rounded or irregular	Regular, broad, and pushing	Regular, broad, and pushing	Irregular and jagged
Grade	I/II	I	I	I/II
HPV	HPV 16	HPV 6 and 11	Absent	Absent
Metastasis	Yes	No	No	Yes

Microscopic ***(Figure 11)***

- Strict diagnostic criteria include the presence of an exophytic tumor consisting of polygonal squamous cells with glassy cytoplasm, centrally located vesicular nuclei, intercellular edema, well-formed cellular bridges, and absence or paucity of koilocytes, true fibrovascular cores, or keratohyaline granules
- The base of the tumor is broadly infiltrating or pushing

Differential Diagnosis

- Other exophytic tumors **(Table 1, Figure 9)**

Giant Condyloma of Buschke-Lowenstein (Figure 9)

Clinical

- Large slow growing superficial lesion
- Development of typical squamous cell carcinoma within these lesions has been described
- Many consider this to be within the spectrum of warty/condylomatous carcinoma

Macroscopic

- Superficially invasive (if invasive) exophytic lesion that usually occupies larger areas of the perineum

Microscopic

- Large condylomatous tumor with superficial koilocytic changes **(Figure 9)**

Papillary Carcinoma (Figure 9)

Clinical

- Behavior indeterminate

Macroscopic

- Exophytic tumor

Microscopic

- Condylomatous growth with serrated appearance and an irregular infiltrating margin

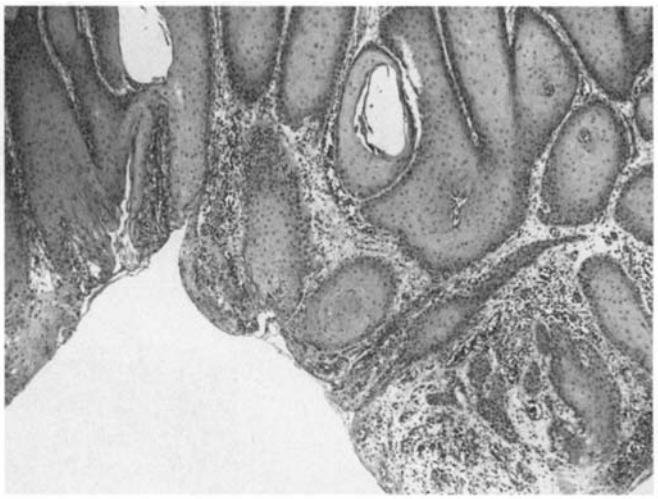


Fig. 11. Well differentiated verrucous carcinoma with broad pushing borders and abundant glassy cytoplasm.

Differential Diagnosis

- Very similar to veruccous carcinoma; diagnosis is made by exclusion of other more classic verruciform tumors

Squamous cell carcinoma, sarcomatoid (spindle cell) subtype

- Very rare, poorly differentiated tumor

Rare Variants

- Pseudohyperplastic carcinoma
- True adenosquamous carcinoma is a distal superficial tumor that must be distinguished from adenocarcinoma arising from Littre's glands and pseudoglandular squamous cell carcinoma
- Small cell carcinoma (high-grade neuroendocrine carcinoma) and basal cell carcinoma arise in the shaft

TNM CLASSIFICATION OF PENILE CANCERS (2002 REVISION)

Primary tumor

- TX Primary tumor cannot be assessed
- T0 No evidence of primary tumor
- Tis Caricinoma in situ
- Ta Non-invasive verrucous carcinoma
- T1 Tumor invades subepithelial connective tissue
- T2 Tumor invades corpus spongiosum or cavernosum
- T3 Tumor invades urethra of prostate
- T4 Tumor invades other adjacent structures

Regional Lymph nodes

- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Metastasis in a single superficial inguinal lymph node
- N2 Metastasis in multiple or bilateral superficial inguinal lymph nodes
- N3 Metastasis in deep inguinal or pelvic node(s); unilateral or bilateral

Distant metastasis

- MX Cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

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34

Esophagus and Stomach

Elias A. Castilla, MD and John R. Goldblum, MD

CONTENTS

I. Esophagus 34-2
- Non-Neoplastic Anomalies 34-2
  - Webs and Rings 34-2
  - Atresia 34-2
  - Achalasia 34-2
  - Glycogen Acanthosis 34-2
  - Cysts 34-3
  - Diverticulae 34-3
  - Heterotopic Gastric Mucosa 34-3
- Esophagitis 34-3
  - Caustic (Corrosive) 34-3
  - Pill-Induced 34-4
  - Radiation 34-4
  - Eosinophilic 34-4
  - Infectious 34-4
- Gastroesophageal Reflux Disease 34-5
- Varices 34-6
- Metaplasia 34-6
  - Barrett's Esophagus 34-6
  - Sebaceous Gland Metaplasia 34-7
- Neoplastic—Epithelial 34-7
  - Squamous Papilloma 34-7
  - Squamous Cell Carcinoma 34-8
  - Adenocarcinoma 34-10
  - Adenosquamous Carcinoma 34-11
  - Small Cell Carcinoma 34-11
- Neoplastic—Mesenchymal 34-11
  - Granular Cell Tumor 34-11
  - Fibrovascular Polyp 34-12
- Neoplastic—Miscellaneous Tumors 34-12
  - Lymphoma 34-12
  - Melanoma 34-13
  - Metastastic 34-13
- Staging Esophageal Malignancies 34-13

II. Stomach 34-13
- Non-Neoplastic—Anomalies 34-13
  - Hypertrophic Pyloric Stenosis 34-13
  - Diverticula 34-14
  - Heterotopic Pancreas 34-14
  - Pancreatic Acinar Metaplasia 34-14
- Non-Neoplastic—Hyperplasia and Polyps 34-14
  - Hyperplastic Polyp 34-14
  - Fundic Gland Polyp 34-15
  - Polyposis Syndromes 34-15
  - Reactive Gastropathy 34-15
  - Inflammatory Fibroid Polyp 34-15
  - Menetrier's Disease 34-15
  - Zollinger-Ellison Syndrome 34-16
  - Gastric Antral Vascular Ectasia 34-17
- Gastritis 34-17
  - *Helicobacter pylori*-Associated 34-17
  - Autoimmune 34-18
  - Acute Hemorrhagic 34-19
  - Lymphocytic 34-19
  - Granulomatous 34-19
- Gastric Ulcer 34-20
- Neoplastic—Epithelial 34-20
  - Adenoma 34-20
  - Adenocarcinoma 34-20
- Neoplastic—Mesenchymal 34-23
  - Gastrointestinal Stromal Tumor(GIST) 34-23
  - Leiomyoma 34-24
  - Lymphoid Neoplasms 34-24
- Neoplastic—Miscellaneous Tumors 34-25
  - Carcinoid 34-25
  - Glomus Tumor 34-26
- Staging Gastric Malignancies 34-26

III. Recommended Reading 34-27

ESOPHAGUS

Non-Neoplastic Anomalies

Webs and Rings

Clinical

- Rings (lower esophagus) vs. webs (upper and middle)
- Primary symptom is dysphagia
- May be associated with Plummer-Vinson syndrome (triad of glossitis, esophageal webs, and iron-deficiency anemia)
- Lower esophageal ring (Schatzki's ring) is the commonest

Atresia

Clinical

- *See* **Table 1**
- Newborns present in the first few days of life with regurgitation, choking, aspiration, and cyanosis
- Isolated complete atresia is rare (1:30,000 live births), but atresia associated with tracheo-esophageal fistula is more common (1:3000–4,000 live births)
- Usually associated with other abnormalities (cardiac, genitourinary, skeletal)

Table 1. Types of Tracheoesophageal Fistula/Esophageal Atresia

Type	*Macroscopic Description*
I	Esophageal atresia; No tracheoesophageal fistula
II	Esophageal atresia with upper-pouch fistula (upper pouch connected to the trachea)
III*	Esophageal atresia with lower-pouch fistula (lower pouch connect to the trachea or main-stem bronchus)
IV	Esophageal atresia with upper and lower pouch fistula
V	Tracheoesophageal fistula; no atresia

**Most common*

Achalasia

Clinical

- Motility disorder whose cause is still unknown
- Due to failure of the lower esophageal sphincter to relax
- Distal "beaklike" deformity and proximal dilatation on barium studies
- Adults (occasionally children)
- Risk of squamous cell carcinoma if untreated

Macroscopic

- Esophagus dilated proximally
- Distal fibrosis, stenosis, and ulceration

Microscopic ***(Figure 1)***

- Loss of myenteric ganglion cells
- Secondary changes such as hypertrophy of all muscle layers, squamous hyperplasia, and fibrosis
- Lymphocytic inflammatory infiltrate with germinal centers in mucosa and around myenteric plexus

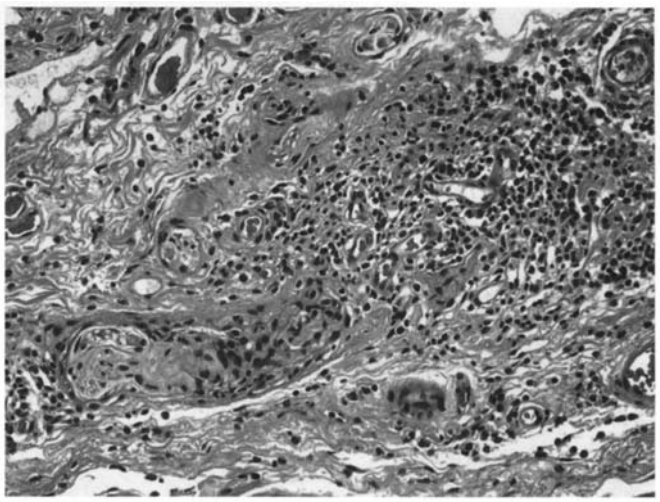


Fig. 1. Achalasia.

Glycogen Acanthosis

Clinical

- Common (found in 15–30% of individuals)
- Asymptomatic
- Distal esophagus
- Endoscopic differential includes candidiasis and exudate
- Occasionally seen in association with the PTEN hamartoma tumor syndrome (mutations on 10q23.3) that includes Cowden's syndrome (facial trichilemmomas, acral keratosis, gastrointestinal hamartomatous polyposis)

Macroscopic

- Uniform, round-oval white plaques
- Size <3 mm
- Longitudinal orientation
- Single or multiple (cobblestone appearance)

Microscopic

- Epithelial hyperplasia
- Glycogenization of superficial cells

Table 2. Types of Cysts

Type	*Location*	*Etiology*
Zenker's	Upper third	Weakness in the muscle wall
Traction	Lower third	Caused by attachment of inflamed lymph nodes
Epiphrenic	Immediately superior to the diaphragm	Unknown

Table 3. Types of Diverticulae

Type	*Macroscopic Description*
Bronchogenic	Ciliated columnar (respiratory epithelium lining; wall with smooth muscle, mucous glands, cartilage)
Esophageal	Stratified squamous lining; wall with muscularis mucosa, submucosal glands
Duplication	Squamous, gastric (fundic), ciliated columnar or small intestinal epithelial wall with muscularis mucosa, submucosa, and muscularis propria

Cysts

Clinical

- *See* **Table 2**
- Majority is asymptomatic but may present with dysphagia and cough
- Appear in childhood or adulthood

Macroscopic

- Dilatation generally in the wall of the esophagus

Diverticulae

- *See* **Table 3**

Heterotopic Gastric Mucosa ("Inlet patch")

Clinical

- Seen in 1–10% of patients undergoing upper endoscopy
- Segment of gastric or intestinal-type mucosa totally surrounded by squamous mucosa
- Usually cervical esophagus
- No higher risk of cancer

Macroscopic

- Orange-reddish patch with sharply demarcated borders

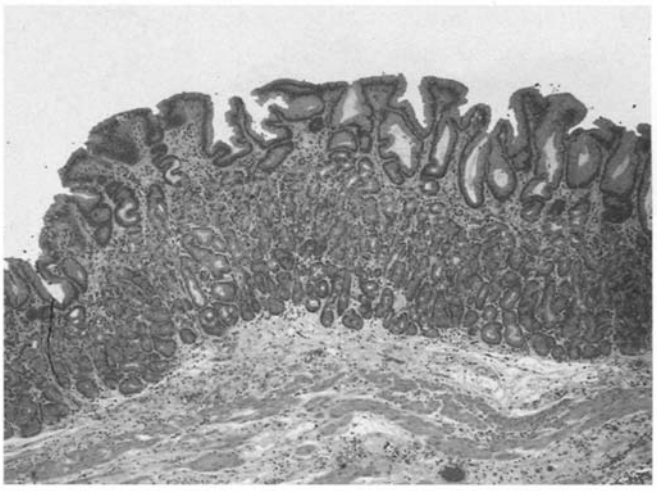


Fig. 2. Inlet Patch.

*Microscopic (**Figure 2**)*

- Fundic glands or foveolar-type epithelium
- Goblet cells may be present

Differential Diagnosis

- Adenocarcinoma:
  - Infiltrative
  - Cytologically malignant
- Barrett's esophagus:
  - Starts at the gastroesophageal junction

Esophagitis

Caustic (Corrosive)

Clinical

- Accidental in children and intentional in adults (suicidal)
- Signs and symptoms include nausea, vomiting, dysphagia, refusal to drink, abdominal pain, increased salivation, and oropharyngeal burns
- Alkali (drain openers) and acids (cleaners, battery fluids)
- Occurs most commonly at narrow sites (level of aortic arch)
- Radiography reveals mediastinitis, pneumonitis, pleural effusion, and perforation
- Chronic complication is stricture formation

Macroscopic

- Ranges from erythema to ulceration and extensive tissue necrosis
- May perforate

Microscopic

- Mucosal congestion, ulceration or necrosis are early events
- Mural scarring (chronic)

Differential Diagnosis

- Infectious esophagitis:
  - Gomori methenamine silver (GMS) for fungal organisms
  - Viral cytopathic effect

Pill-Induced

Clinical

- Due to prolonged contact of medication with esophageal mucosa
- Multiple medications implicated (doxiciline, ferrous sulfate, NSAIDs, alendronate, chemotherapeutic drugs and many others)
- Associated with drinking inadequate fluid and lying down after ingesting medications

Macroscopic

- Mid-esophagus
- Erythema/ulceration surrounded by normal mucosa

Microscopic

- Active inflammation with eosinophilic infiltration
- Occasional ulceration
- May be indistinguishable from reflux esophagitis
- Rarely polarizable or iron stainable material is found

Radiation

Clinical

- Second most tolerant gastrointestinal (GI) organ to radiation (rectum is first)
- Primary symptom is retrosternal burning
- Significant sequelae are fistula and stricture

Macroscopic

- Erythema
- Ulceration
- Necrosis
- Telangiectasia

Microscopic

- Inhibition of mitosis
- Basal cell degeneration
- Increased apoptosis in basal layers is most subtle change
- Bizarre epithelial and stromal cells with low N/C ratio
- Vascular sclerosis, hyalinization and fibrosis

Eosinophilic

Clinical

- Clinicopathologic entity
- It requires exclusion of pathologic gastroesophageal reflux
- Refractory to standard antireflux medical therapy

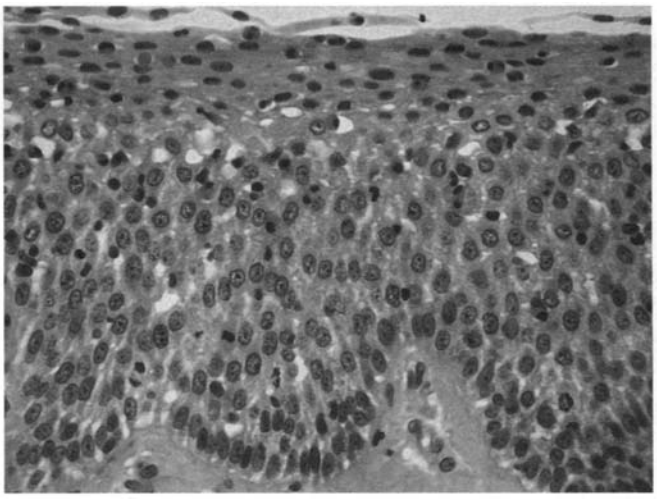


Fig. 3. Esophageal Eosinophilia.

- Children > adults
- Male > Female

Macroscopic

- Esophageal rings and linear furrows have been associated with eosinophilic esophagitis
- May produce strictures

Microscopic ***(Figure 3)***

- Marked eosinophilic infiltrate (usually >20 eos/hpf)

Differential Diagnosis

- Esophageal eosinophilia may be seen in idiopathic eosinophilic esophagitis, eosinophilic gastroenteritis, severe GERD, allergic, parasitic and drug-induced esophagitis (clinical correlation is required)

Infectious

Candida Species

Clinical

- Mainly *C. albicans*; also *C. glabrata, C. tropicalis* and *C. parapsilosis*
- Prevalence unknown (many asymptomatic)
- High risk: Diabetes mellitus, transplantation, leukemia, lymphoma, and AIDS, but can be seen in any patient on broad-spectrum antibiotics, H_2 receptor antagonists, proton pump inhibitors, or corticosteroids
- Symptoms include dysphagia and odynophagia
- Complications are rare (hemorrhage and stricture)
- Most accurately diagnosed if using endoscopic brushing and biopsy together

Macroscopic

- Multiple yellow-white plaques
- Plaques are focal and discrete or confluent
- Erythematous, edematous base

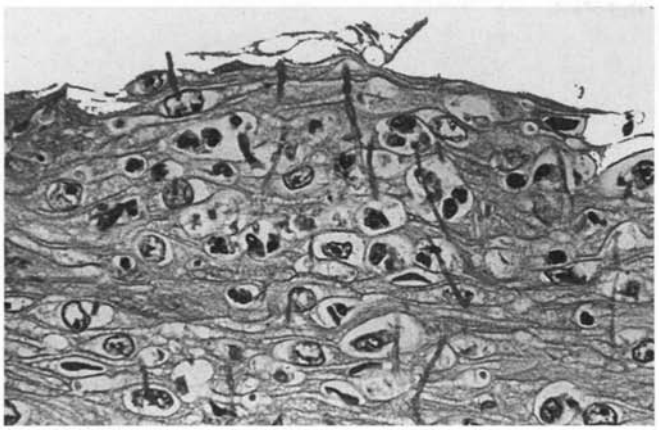


Fig. 4. Candida esophagitis.

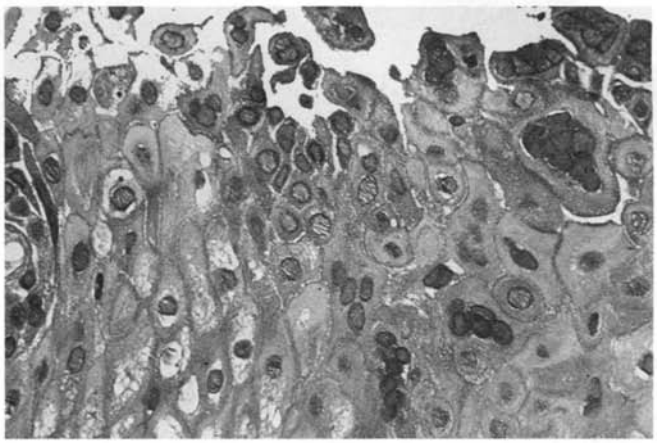


Fig. 5. Herpes esophagitis.

Microscopic ***(Figure 4)***

- Fibrinopurulent exudate with multiple fungal forms (budding yeasts, pseudohyphae or true hyphae) that are PAS and GMS positive
- Adjacent bacterial colonies are common

Differential Diagnosis

- Aspergillosis:
  - True septated hyphae branching at 45-degree angles
  - Refractory to Candida therapy
  - Culture

Herpes Simplex Virus (HSV)

Clinical

- 100% of adults show serologic evidence of a previous infection
- Shedding of viable virus seen in 2% of adults
- Frequently preceded by 3–7 days of upper respiratory infection with fever, sore throat, and myalgia
- Symptoms include odynophagia, nausea, vomiting, hematemesis, and fever
- Transmitted through direct contact
- Esophagus is the organ most commonly involved in immunodeficient patients
- Risk factors for infection include malignancy, radiotherapy, and immunosuppression; however may occur among immunocompetent patients
- Diagnosis is based on identifying HSV by histology, cytology, and culture

Macroscopic

- Vesicles and Ulcerations
- Sharply demarcated

Microscopic ***(Figure 5)***

- Epithelial ulceration
- Ground glass nuclei at edge of ulcer (squamous cells)
- Nuclear molding
- Cowdry type A intranuclear inclusions
- Multinucleated cells
- HSV immunostain available

Cytomegalovirus

Clinical

- Most frequently seen in post-transplant (60–70%) and AIDS patients; rare among immunocompetent
- Asymptomatic or mild mononucleosis-like syndrome
- Symptoms include nausea, vomiting, GI bleeding, and fever
- Diagnosis is based on a positive culture (blood, throat, stool, urine)

Macroscopic

- Ulcerations, erosions
- Mucosal hemorrhage

Microscopic ***(Figure 6)***

- CMV inclusion bodies ("Owl's eye") present at the base of the ulcer (fibroblasts and endothelial cells)
- Not found in squamous cells
- Associated granulation tissue

Immunohistochemistry and InSitu Hybridization

- CMV+

Gastroesophageal Reflux Disease (GERD)

Clinical

- Regurgitation, heartburn, pain, and dysphagia are symptoms
- Pathogenesis poorly understood since GER is a normal physiologic process (probable imbalance between reflux and epithelial resistance)
- Associated with hiatal hernia, acid hypersecretion (e.g. Zollinger-Ellison syndrome), nasogastric intubation, pregnancy, diabetes and scleroderma
- Clinical correlation imperative

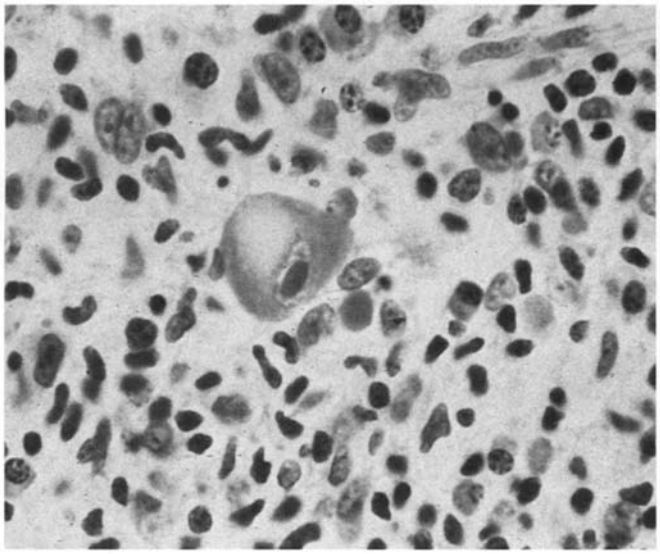


Fig. 6. Cytomegalovirus esophagitis.

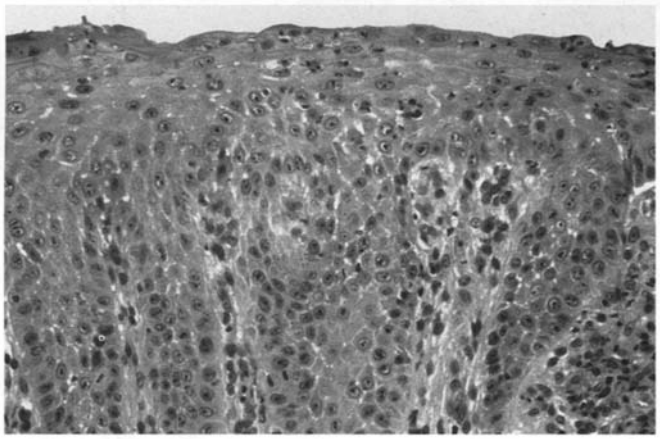


Fig. 7. Gastroesophageal reflux.

- Distal 2.5 cm of "normal" tubular esophagus may have similar histologic changes

Macroscopic

- Hyperemia
- Superficial ulceration
- Strictures

*Microscopic **(Figure 7)***

- Epithelial hyperplasia with neutrophils, eosinophils and lymphocytes
- Basal cell proliferation (>15% of the total epithelial thickness)
- Heightened papillae (>67% of the epithelial thickness)
- Dilatation and congestion of capillaries in the lamina propria
- Erosion, ulceration



Fig. 8. Varices.

- Atypical mesenchymal cells and multinucleated cells may be present
- Features may be similar to those seen in pill-induced, corrosive, radiation, and even eosinophilic esophagitis

Varices (Figure 8)

Clinical

- Occurs with portal vein pressure >12 mm Hg
- Etiology, *see* **Table 4**

Macroscopic

- Congested blood vessels in the mucosa
- Short, bright red, curved streaks on the surface of the varices

Metaplasia

Barrett's Esophagus

Clinical

- Adults > Children; Males > Females; Caucasians > African-Americans or Asians
- Etiology unknown, but perhaps genetic predisposition with ulcerative changes from reflux
- Diagnosis suspected with barium swallow, manometry, and pH monitoring
- Diagnosis requires both endoscopic and histopathologic confirmation
- A risk factor for stricture formation, dysplasia, and adenocarcinoma (30–125-fold)
- Associated with hiatal hernia, GERD and poor esophageal motility
- Affects 10–15% of patients with GERD

*Macroscopic **(Figure 9)***

- Flat, salmon-pink mucosa involving a portion of the lower tubular esophagus

Table 4. Etiology of Varices

Cirrhotic	*Non-cirrhotic*
Alcohol	AV fistula
Hepatitis	Splenomegaly
	Splenic/portal vein thrombosis
	Idiopathic portal hypertension
	Toxins
	Schistosomiasis
	Malignancy
	Sarcoidosis
	Nodular regenerative hyperplasia
	Focal nodular hyperplasia
	Hepatic vein thrombosis
	Veno-occlusive disease
	Right-sided heart disease

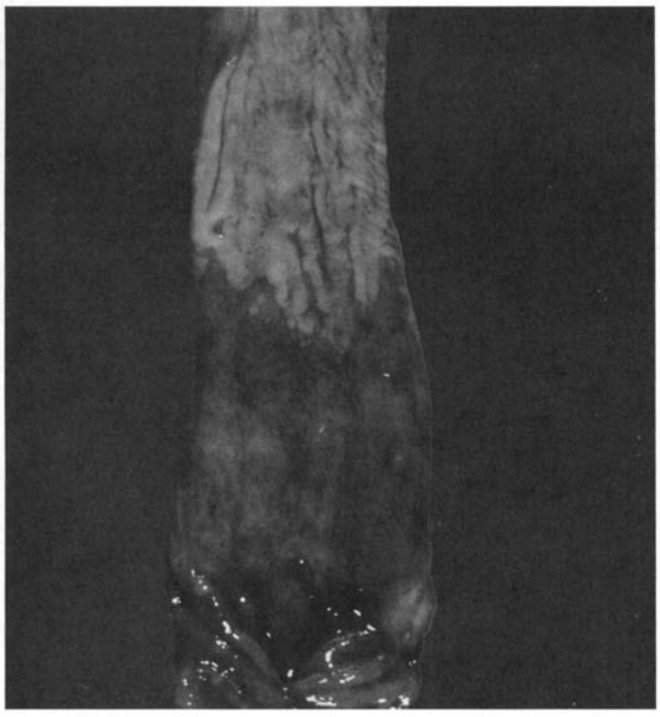


Fig. 9. Barrett's Esophagus.

Microscopic ***(Figure 10)***

- Specialized columnar epithelium (intestinal metaplasia) with underlying submucosal glands
- Goblet cells (blue on alcian blue stain at pH 2.5) are the hallmark

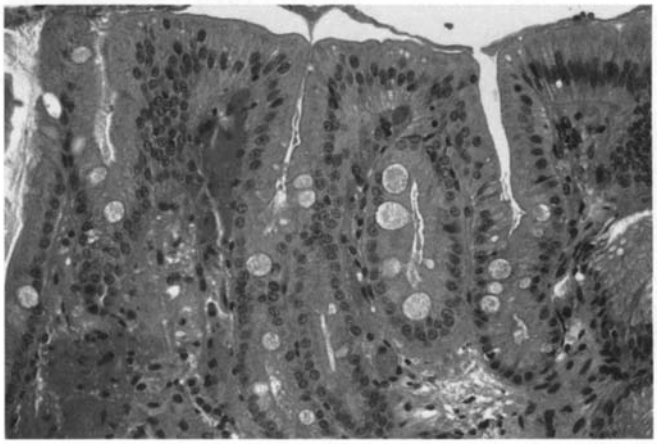


Fig. 10. Barrett's esophagus without dysplasia.

- A Barrett's cytokeratin 7/20 pattern is characteristically present
- Grading dysplasia requires expertise (**Table 5** and **Figure 11**)

Differential Diagnosis

- Intestinal metaplasia of the cardias:
  - Endoscopic findings could be helpful
  - Cytokeratin 7/20 pattern is different (in Barrett's CK7 is present in superficial and deep glands; CK20 in superficial glands)
- Pancreatic acinar metaplasia:
  - Benign acinar cells
  - No goblet cells
- Inlet Patch:
  - Gastric-type mucosa
  - Upper esophagus

Sebaceous Gland Metaplasia

Clinical

- Rare (prevalence approximately 2%)
- Occurs at all levels of the esophagus
- Multifocal involvement
- Accepted as a metaplastic process, but possibly heterotopic tissue

Microscopic ***(Figure 12)***

- Sebaceous glands in the lamina propria or epithelium
- Lymphocytic infiltrate

Neoplastic—Epithelial

Squamous Papilloma

Clinical

- Most are asymptomatic
- Uncommon
- Male predominance
- Malignant degeneration is exceedingly rare

Table 5. Dysplasia in Barrett's Esophagus

Negative	*Indefinite for Dysplasia*	*Low-grade Dysplasia*	*High-grade Dysplasia*
Regular glands	Mild cyto-architectural changes with surface involvement	Preserved regular glands	Distortion of crypt architecture (marked crowding, villiform, cribiform or back-to-back glandular patterns)
Mild nuclear crowding and hyperchromasia restricted to the basal portion	Marked changes with erosion-ulceration or evaluation of surface involvement is not possible	Nuclear enlargement, crowding and hyperchromasia affecting also the surface epithelium	Marked nuclear enlargement, crowding, hypercromasia and pleomorphism
Maturation onto the surface	Falls short to low-grade dysplasia	Preservation of nuclear polarity (long nuclear axis perpendicular to the basement membrane)	Loss of nuclear polarity
			Dilated glands containing necrotic debris

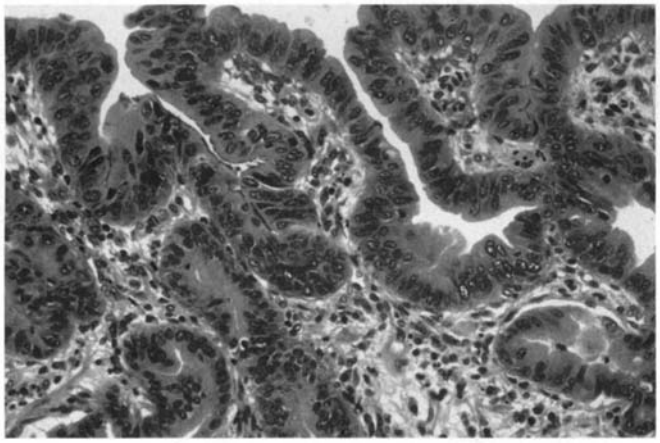


Fig. 11. Barrett's esophagus with high-grade dysplasia.

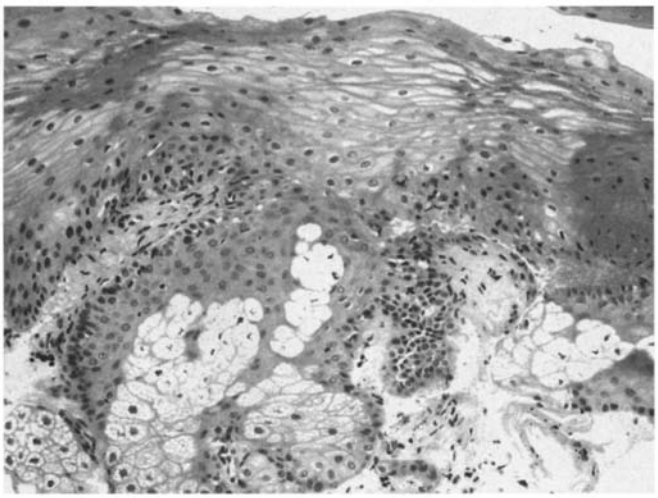


Fig. 12. Sebaceous gland metaplasia.

- Human papilloma virus (HPV) implicated in the pathogenesis

Macroscopic

- At the gastroesophageal junction
- Cauliflower-like polypoid appearance
- Less commonly sessile (verrucoid) or smooth nodular (endophytic)

Microscopic ***(Figure 13)***

- Exophytic growth with fibrovascular cores
- Koilocytosis, binucleation and enlarged nuclei are inconsistently present

Squamous Cell Carcinoma

Clinical

- Most common neoplasm of the esophagus (worldwide)
- In US incidence roughly equals adenocarcinoma
- M : F = 3–4:1
- Average age = 50–60 years
- Increased incidence among African-Americans
- Risks include smoking, alcohol, food rich in nitrates and nitrosamines, hot beverages, achalasia and Plummer-Vinson syndrome
- Primary symptoms are dysphagia (with advanced disease) and weight loss
- HPV as etiologic agent is controversial
- Diagnosed by endoscopic biopsy and cytologic brushing (99% diagnostic yield when combined)
- In 60% there are lymph node metastases at diagnosis
- Poor prognosis, with a median survival of 1 year after diagnosis
- Abnormalities of p53, cyclin D1, and/or epidermal growth factor receptor (EGFR) contribute to the pathogenesis



Fig. 13. Squamous papilloma.

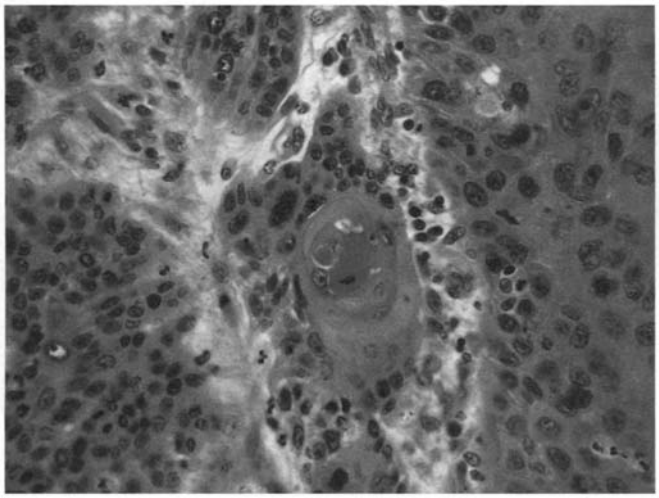


Fig. 14. Invasive squamous cell carcinoma.

Macroscopic

- Most common sites are middle and lower thirds of the esophagus
- Multicentric in up to 20% of patients
- Gray-white
- Circumferential mass
- May be fungating, ulcerative, or infiltrative
- Sharply demarcated margins

*Microscopic (**Figure 14**)*

- Invasive (pushing and budding)
- Variable desmoplasia, mitotic rate, pleomorphism and keratinization
- Gland formation is not uncommon
- Submucosal spread up to 5 cm beyond grossly visible margins
- Vascular invasion in 75% of cases

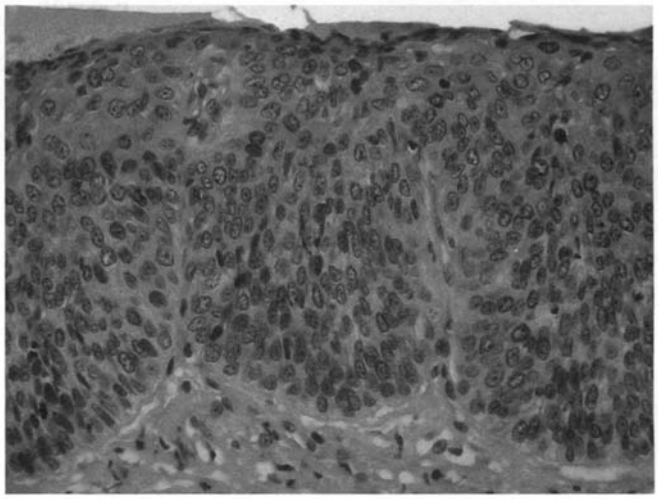


Fig. 15. Squamous dysplasia.

Precursor/Related Lesions

- Squamous Dysplasia (**Figure 15**):
  - Found at the periphery of 60–90% of invasive cancers
  - Low grade if lesion is confined to basal half of the epithelium; high grade if more than a half with greater cytologic atypia
  - Dysplastic features include: nuclear overlapping, pleomorphism, increased N/C ratio, architectural disarray and lack of maturation
  - Carcinoma in situ (CIS) if full-thickness

Variants

- Spindle cell carcinoma (**Figure 16**):
  - a.k.a. Carcinosarcoma or polypoid carcinoma
  - Polypoid mass with a short, thick stalk
  - Smooth or knobby surface
  - Superficial erosions
  - Biphasic histology with both sarcomatous and carcinomatous elements
  - Edematous, undifferentiated stroma
  - 10% have stromal differentiation toward bone, cartilage, and skeletal muscle
  - Keratin and vimentin+
- Basaloid Squamous Carcinoma (**Figure 17**):
  - Large, basaloid cells with open chromatin
  - High-grade cytology
  - High mitotic rate
  - Cells form cords, tubules, and solid nests
  - Central necrosis
  - Peripheral palisading
  - Squamous differentiation frequently present

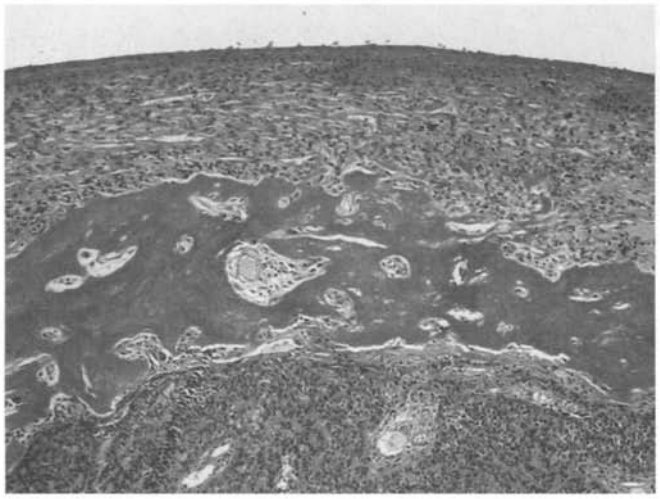


Fig. 16. Spindle cell carcinoma with osseous differentiation.

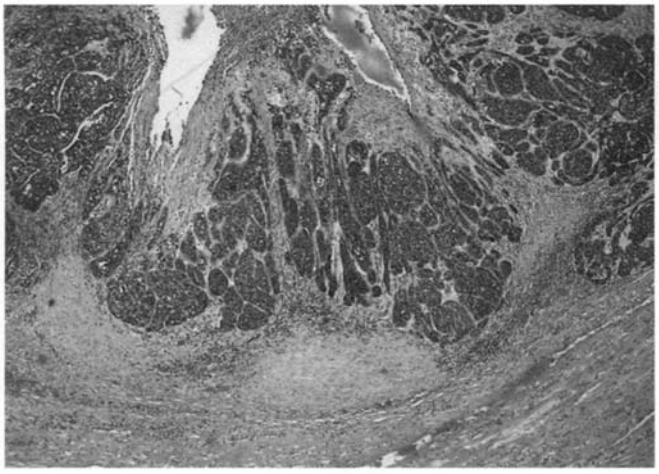


Fig. 17. Basaloid squamous carcinoma.

- Verrucous Carcinoma:
  - Exophytic papillary pattern
  - Spires of well-differentiated squamous epithelium
  - Minimal cytologic atypia
  - Invasive border is blunt and pushing
  - Slow grower with low metastatic potential

Adenocarcinoma

Clinical

- M : F = 3–7 : 1
- Average age = 55–60 years
- More common in the Caucasian population (80% of patients)
- Represents approximately half of all esophageal carcinomas in US; Second most common esophageal neoplasm worldwide
- Increased incidence over the past decade

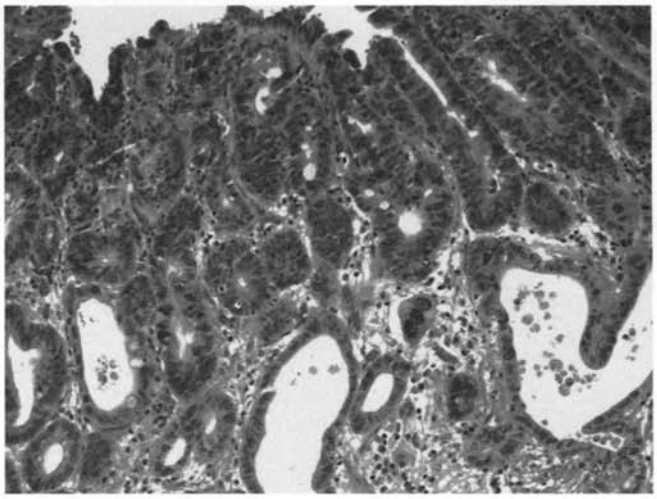


Fig. 18. Intramucosal adenocarcinoma arising in a backaground of Barrett's esophagus.

- Asymptomatic or symptoms of reflux
- 95% arise in Barrett's metaplasia; rarely in esophageal glands and heterotopic gastric mucosa
- 30–125 fold risk in Barrett's population
- Poor prognosis (<20% 5-year survival)

Macroscopic

- Most common (80%) in the lower third of the esophagus
- Varies from slight mucosal irregularities or plaques to large masses
- Typically flat and ulcerated (70%)
- May be polypoid and fungating (30%)
- Previous chemotherapy or radiation therapy may grossly wipe-out the tumor

*Microscopic **(Figures 18,19)***

- Barrett's metaplasia usually present
- Most are well to moderately differentiated
- Infiltration with desmoplastic stromal response
- Nuclear hyperchromasia and pleomorphism
- Increased mitotic rate
- May have mucinous, signet-ring cell and squamous differentiation

Differential Diagnosis

- High-grade dysplasia:
  - By definition no disruption of the basement membrane
  - Often difficult to differentiate from intramucosal adenocarcinoma
  - Lack of invasion (no small, distorted glands in the lamina propria; no closely packed glands, fenestrations, single cells or small clusters) favor high grade dysplasia

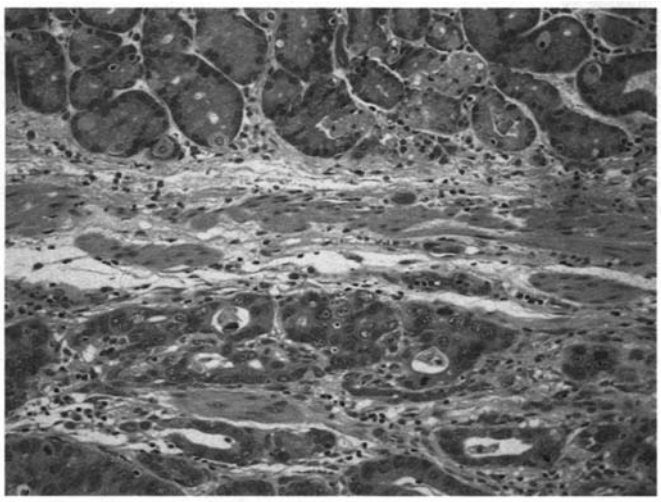


Fig. 19. Invasive adenocarcinoma.

Adenosquamous Carcinoma

Clinical

- Aggressive; prognosis comparable to squamous carcinoma
- Represents either squamous differentiation in adenocarcinoma or glandular metaplasia in squamous carcinoma

Differential Diagnosis

- Mucoepidermoid carcinoma:
  - Islands of squamous carcinoma with mucus-secreting cells rather than distinct elements

Small Cell Carcinoma

Clinical

- M : F = 2 : 1
- Average age = 50–60 years
- Esophagus is the most common extrapulmonary site for small cell carcinoma
- Presentation is usually at an advanced stage
- Risk factors include smoking and achalasia
- Symptoms include severe weight loss, dysphagia, and chest pain
- Poor prognosis with average survival <6 months

Macroscopic

- Most common in the distal half of the esophagus
- Polypoid, fungating mass or stenotic lesion with ulceration

Microscopic

- Similar to pulmonary small cell carcinoma
- Solid sheets, nests, or ribbons of small blue cells
- Diffuse infiltration with a streaming pattern
- Nuclear molding
- Cells are round-oval, hyperchromatic
- Scant cytoplasm
- Frequent mitotic figures

Electron Microscopy

- Dense neurosecretory core granules

Immunohistochemistry

- Keratin+
- Neuron-specific enolase (NSE) and chromogranin+

Neoplastic—Mesenchymal

Leiomyoma

Clinical

- M : F = 2 : 1
- Average age = 45–50 years
- Most common mesenchymal tumor in the esophagus
- Most arise from the inner circular layer of the muscularis propria
- If large, patient becomes symptomatic (dysphagia, chest pain)
- Difficult to see endoscopically
- Radiography reveals a well-defined intramural mass

Macroscopic

- 90% in the lower and middle thirds
- Most are a few millimeters in size
- Most are sessile; few are polypoid
- Generally single; may be multiple
- Well-circumscribed
- Pale pink-white
- Lobulated, with a whorled cut surface
- Firm

Microscopic ***(Figure 20)***

- Fascicles and whorls of mature smooth muscle cells
- Cells typically hypertrophic
- No/low mitotic rate
- Hyalinization is common
- Rarely nuclear atypia without mitotic activity ("symplastic")
- No necrosis

Immunohistochemistry

- Smooth muscle actin+
- CD117 and CD34–

Granular Cell Tumor

Clinical

- Second most common stromal tumor in the esophagus
- M > F
- African-Americans > Caucasians

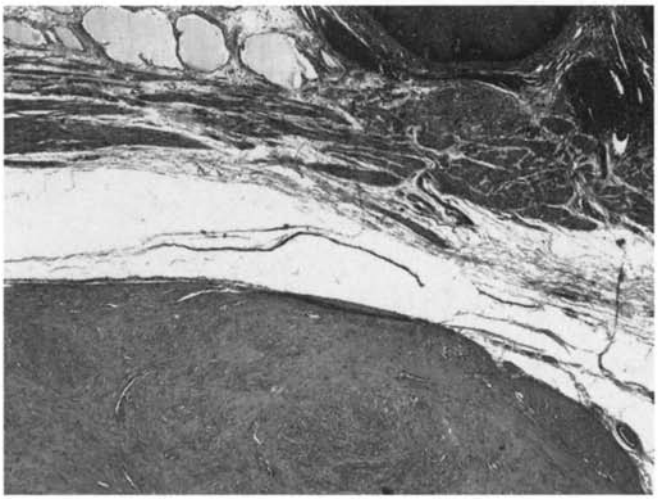


Fig. 20. Leiomyoma.

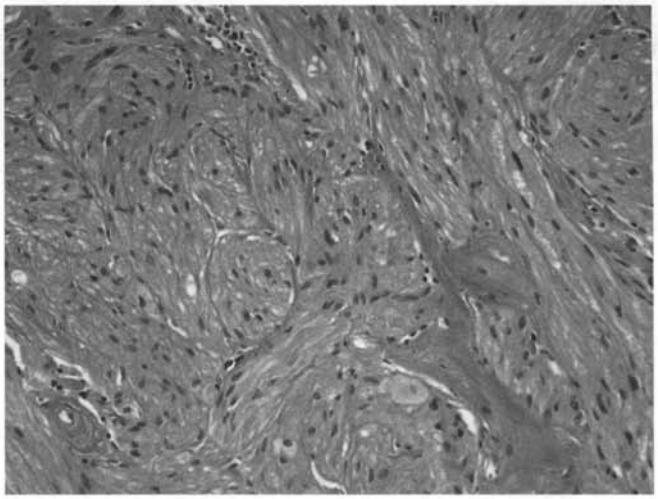


Fig. 21. Granular cell tumor.

- Average age = 40–50 years
- Usually an incidental finding
- Endoscopic features (sessile, yellow-white, firm, intact epithelium) can be strongly suggestive
- Prognosis generally excellent

Macroscopic

- Small size
- Most common site is the distal esophagus

*Microscopic **(Figure 21)***

- Superficial lesion
- Plump, spindled, or epithelioid cells
- Small nuclei
- Abundant eosinophilic granular cytoplasm
- Cells arranged in nests or clusters separated by collagenous septae
- Pseudoepitheliomatous hyperplasia of the overlying epithelium is common

Immunohistochemistry

- S-100+

Fibrovascular Polyp

Clinical

- M : F = 3 : 1
- Rapid growth
- Symptoms range from dysphagia to acute respiratory distress
- Risk of fragmentation with subsequent asphyxiation
- Radiographic findings include a long, smooth, mobile, intraluminal mass
- Local excision is curative

Macroscopic

- Average size: 15 cm
- 80% are located in the proximal third of the esophagus
- Pedunculated
- Long, slender shape
- Soft
- Tan-pink
- Rare mucosal ulcerations

Microscopic

- Fibrous connective tissue covered by hyperplastic squamous mucosa
- Stromal edema with myxoid change
- Numerous, dilated blood vessels
- Collagen deposition
- Inflammatory infiltrate (lymphocytes, plasma cells, mast cells)
- Adipose tissue usually conspicuous (can be the predominant component)

Neoplastic—Miscellaneous Tumors

Lymphoma

Clinical

- Most involve the esophagus secondarily (very rarely primary)
- Symptoms mimic those seen in carcinoma

Macroscopic

- Polypoid
- Proximal dilatation
- Ulcers, strictures, linear rugae

Microscopic

- Most are large cell B-cell type

Immunohistochemistry

- LCA+

Melanoma

Clinical

- Extremely rare (<0.5% of all primary esophageal tumors)
- Average age: 55–60 years
- Symptoms include dysphagia, pain, and weight loss
- Average 5-year survival is 2%

Macroscopic

- Variable size
- Polypoid
- Ulcerated, sometimes pigmented mucosa

Microscopic

- Expansile growth
- Large, atypical melanocytes with clear cytoplasm
- Nucleus typically hyperchromatic and bizarre
- Melanin granules
- Junctional melanocytic component if primary
- Epithelioid or spindled invasive component
- Prominent eosinophilic nuclei

Electron Microscopy

- Melanosomes present

Immunohistochemistry

- S-100 protein, Melan-A/MART-1 and HMB45+

Differential Diagnosis

- Carcinoma:
  - Epithelioid appearance
  - Signet ring cells may be present
  - Keratin+
  - S-100 protein, LCA, Melan-A/MART-1 and HMB45–
- Lymphoma:
  - LCA+
  - Keratin, S-100 protein, Melan-A/MART-1 and HMB45–
- Sarcoma:
  - Spindled (desmoplastic) appearance
  - Keratin, LCA, and HMB45–

Table 6. TNM Classification of Esophageal Tumors (2002 Revision)

T1	Tumor limited to mucosa/submucosa
T2	Tumor involving the muscularis propria
T3	Involvement of adventitia, no extraesophageal structures
T4	Extension into extraesophageal structures (fat, heart, trachea, aorta, etc.)
N0	No nodal involvement
N1	Regional nodes involved Cervical esophagus: cervical, supraclavicular lymph nodes
	Thoracic esophagus: mediastinal, paragastric lymph nodes
M0	No distant metastases
M1	Distant metastases, including distant lymph nodes

Table 7. Group Staging Criteria

Stage I	T1	N0	M0
Stage IIA	T2-3	N0	M0
Stage IIB	T1-2	N1	M0
Stage III	T3	N1	M0
	T4	any N	M0
Stage IV	any T	any N	M1

Metastatic

Clinical

- Most common are lung, breast, and melanoma
- Clinical information is crucial in order to rule out a primary lesion

Staging Esophageal Malignancies

- *See* **Tables 6** and **7**

STOMACH

Non-Neoplastic—Anomalies

Hypertrophic Pyloric Stenosis

Clinical

- One of the most common congenital anomalies (6–8 per 1000 live births)
- First born
- M > F; Caucasians > Blacks
- Average age of onset is 3–12 weeks (rare in adults)
- Projectile vomit; sometimes palpable "tumor"
- X-rays: dilated stomach and distal gas absent

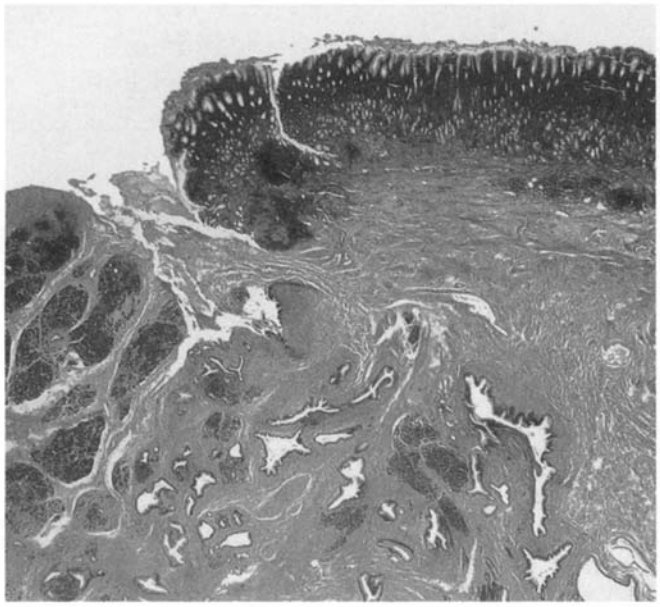


Fig. 22. Heterotopic pancreas.

- Ultrasound measures thickness and length ot pyloric muscle (diagnostic)
- Etiology unknown

Macroscopic

- Thickened pyloric muscle

Diverticula

Clinical

- Most common in the cardia
- Due to anatomic weakness

Heterotopic Pancreas

Clinical

- Discovered incidentally or presents as a mass
- Located in the antrum (60% of cases) or pylorus (25%)
- Most (85%) are in the submucosa

Macroscopic

- Raised lesion with central dimple (pancreatic duct)
- Cut surface resembles normal pancreas
- Occasional cysts seen

Microscopic ***(Figure 22)***

- Typical pancreatic acini and ducts
- 33% with islets

Pancreatic Acinar Metaplasia

Clinical

- 1% of gastric biopsies
- Antral and cardiac locations predominate
- Unknown etiology

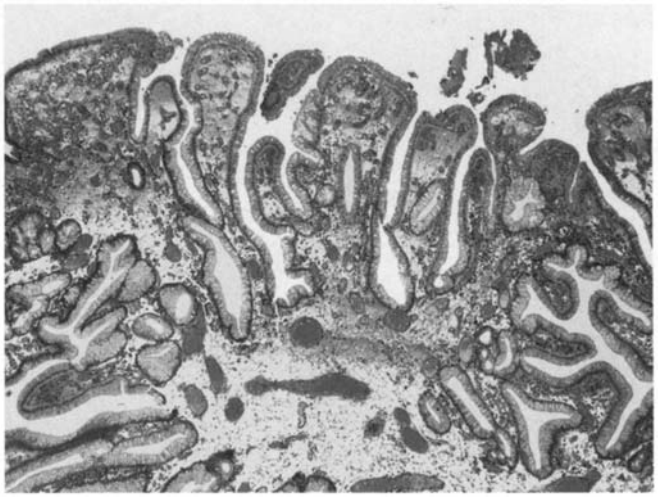


Fig. 23. Hyperplastic polyp.

Macroscopic

- No distinctive macroscopic findings

Microscopic

- Pancreatic acinar cells present in the gastric mucosa
- Lobular arrangement
- No islet cells or ducts

Non-Neoplastic—Hyperplasias, Polyps and Reactive Lesions

Hyperplastic Polyp

Clinical

- Usually a reactive process
- Associated with several types of gastritis, bile reflux, alcohol and NSAIDs
- Accounts for 75% of gastric polyps
- May shrink after treatment for *H. pylori*
- 1–20% harbor dysplasia but very rare progression to adenocarcinoma
- Biopsies of non-polypoid gastric mucosa may be helpful to recognize possible associated gastritis

Macroscopic

- Small
- Single or multiple (random distribution)
- Smooth to slightly lobulated

Microscopic ***(Figure 23)***

- Elongated, tortuous, dilated foveolar epithelium
- Deep fundic glands
- Edematous stroma with rare atypical reactive cells
- Patchy fibrosis
- Inflammatory infiltrate



Fig. 24. Fundic gland polyp.

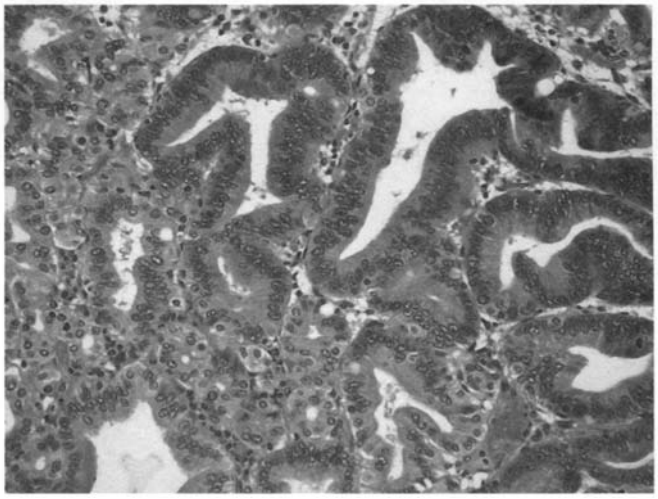


Fig. 25. Foveolar dysplasia in fundic gland polyp.

- Erosion is common
- Granulation tissue if ulcerated

Fundic Gland Polyp

Clinical

- Common
- Females > Males
- Sporadic or in FAP patients
- If FAP related, they have been associated with somatic mutations of the APC gene and high-risk of dysplasia (up to 42%)
- If sporadic, they are present in association with mutations in the β-catenin gene and have a low risk of dysplasia
- Associated with use of proton pump inhibitors in some studies

Macroscopic

- Small (2–3 mm)
- Polypoid

Microscopic ***(Figure 24)***

- Cysts lined by oxyntic epithelium
- Rarely lined by foveolar cells
- If dysplasia is present ("foveolar dysplasia"), strongly suggests FAP **(Figure 25)**

Polyposis Syndromes

- *See* **Table 8**

Reactive Gastropathy

Clinical

- Related to duodenogastric reflux (usually post-gastrectomy) and use of NSAIDs or alcohol
- a.k.a. chemical or bile-reflux gastritis
- Less commonly secondary to burns, trauma or severe illness

Macroscopic

- Normal mucosa to erosions, ulcers or polypoid appearance
- Mucosal petechiae

Microscopic ***(Figure 26)***

- Foveolar hyperplasia
- Reactive epithelial changes (mucin depletion and cytologic atypia)

Inflammatory Fibroid Polyp

Clinical

- Unknown cause
- Antral location
- Radiography reveals a sessile or pedunculated mass.
- Asymptomatic or obstructive symptoms

Macroscopic

- Elevated or sessile
- Submucosal

Microscopic ***(Figure 27)***

- Proliferation of vascular and fibroblastic elements
- Inflammatory infiltrate, especially eosinophils
- Loose stromal background
- Mucosal involvement is common

Immunohistochemistry

- CD117–

Menetrier's Disease

Clinical

- Associated with hypo- or achlorhydria and hypoproteinemia
- Typically adults (patients with chronic and severe disease)
- Rare in children (self-limited disease)
- Fundus and body (spares antrum)

Table 8. Hereditary Polyposis Syndromes and Gastric Manifestations

Syndrome	*Gene (s) Altered*	*Microscopic*	*Associated Gastric Tumor*
Familial Adenomatous Polyposis*	APC gene (5q21-q22)	Adenomas Fundic gland polyps (±dysplasia)	Adenocarcinoma (rare)
Peutz-Jeghers	STK11 gene (19p13.3)	Hamartomatous polyps (± dysplasia)	Adenoma + Adenocarcinoma
Juvenile Polyposis	MADH4 (18q21.1) or BMPR1A (10q22.3)	Hyperplastic-like polyps (rare foveolar dysplasia)	Adenocarcinoma (rare)
PTEN Hamartoma Tumor Syndrome**	PTEN (10q23.3)	Hamartomatous polyps	Not documented
Hereditary Non-Polyposis Colorectal Cancer (HNPCC)***	Multiple DNA mismatch repair genes including MLH1, MSH2, MSH6 and PMS2 (3p21.3, 2p22-p21, 2p16, 7p22)	Non-specific changes	Adenocarcinoma, intestinal type
Cronkhite-Canada****	–	Widespread hyperplastic polyp-like change	Adenocarcinoma

**Includes classical FAP, attenuated FAP, Gardner syndrome and some cases of Turcot syndrome*
***Includes Cowden and Bannayan-Riley-Ruvalcaba Syndromes*
****Includes some cases of Turcot's syndrome*
*****Non-hereditary*

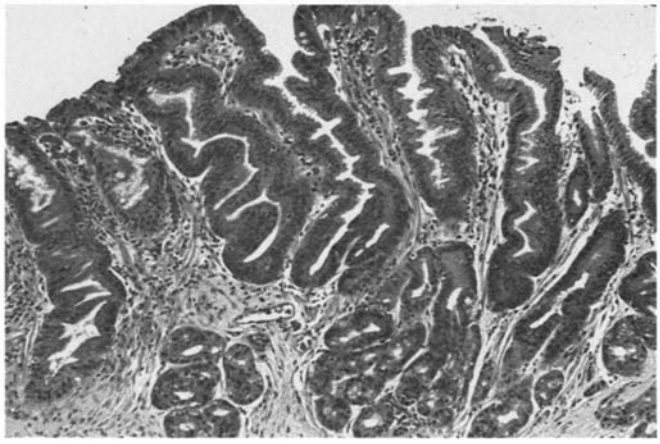


Fig. 26. Reactive gastropathy.



Fig. 27. Inflammatory fibroid polyp.

Macroscopic

- Hypertrophic rugae
- Abrupt transition from normal to diseased mucosa

*Microscopic (**Figure 28**)*

- Tortuous, dilated, hyperplastic foveolae
- Reduced oxyntic component
- Inflamed, edematous stroma

Zollinger-Ellison Syndrome

Clinical

- Part of multiple endocrine neoplasia (MEN) complex
- Radiographically similar to hyperplastic gastropathy

Macroscopic

- Similar to hyperplastic gastropathy

Microscopic

- Parietal cell hyperplasia

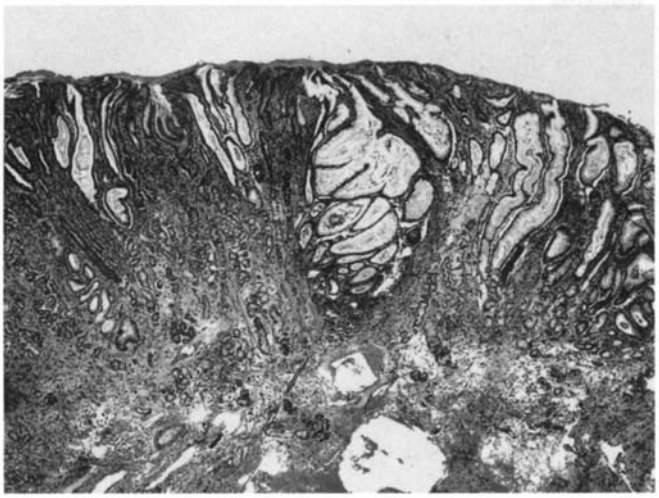


Fig. 28. Menetrier's disease.

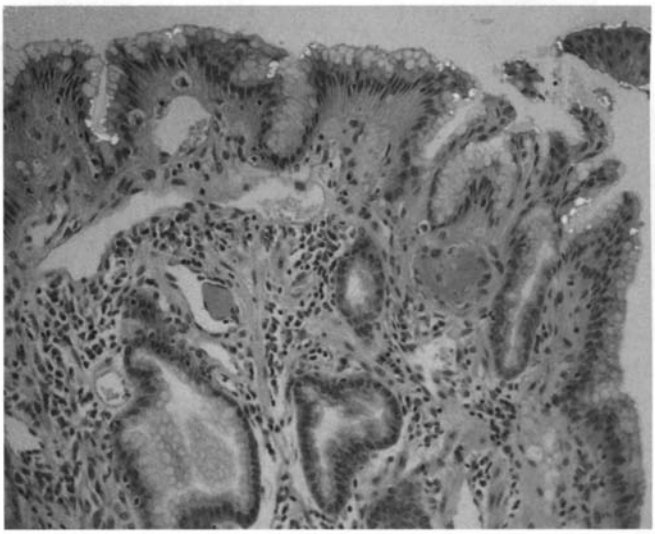


Fig. 29. Gastric antral vascular ectasia.

Gastric Antral Vascular Ectasia (GAVE)

Clinical

- So-called "Watermelon stomach"
- Unknown cause
- Females > Males
- Elderly
- Occult bleeding, hematemesis, melena
- Associated with autoimmune disorders, cirrhosis, and renal insufficiency

Macroscopic

- Antral
- Red longitudinal and nearly parallel linear streaks on endoscopy

*Microscopic (**Figure 29**)*

- Dilated mucosal blood vessels
- Fibrin thrombi within capillaries

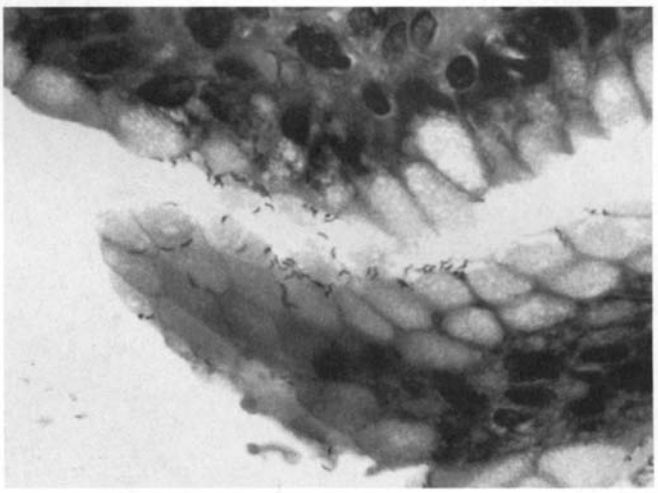


Fig. 30. Helicobacter pylori.

Gastritis

Helicobacter pylori-Associated

- Lack of consensus in classification of "chronic" gastritis
- Sydney system is not widely accepted
- H. pylori affects up to 100% population in several underdeveloped tropical countries and up to 50% of US population **(Figure 30)**
- Two main forms of gastritis associated with H. pylori are recognized: Multifocal atrophic gastritis (MAG) and diffuse antral gastritis (DAG)

Macroscopic

- No distinctive macroscopic findings
- Congestion, erosions, ulcerations and atrophy

DAG (a.k.a. Diffuse Antral-Predominant Gastritis)

Clinical

- H. pylori associated: 90–100%
- No increased risk of gastric adenocarcinoma
- Increased risk of gastric MALT lymphoma and duodenal and pyloric ulcers
- US caucasians
- Antral involvement

*Microscopic (**Figure 31**)*

- Lymphoid follicles
- Active inflammation (neutrophils) common
- Lamina propria expansion by mononuclear cells
- Rare intestinal metaplasia

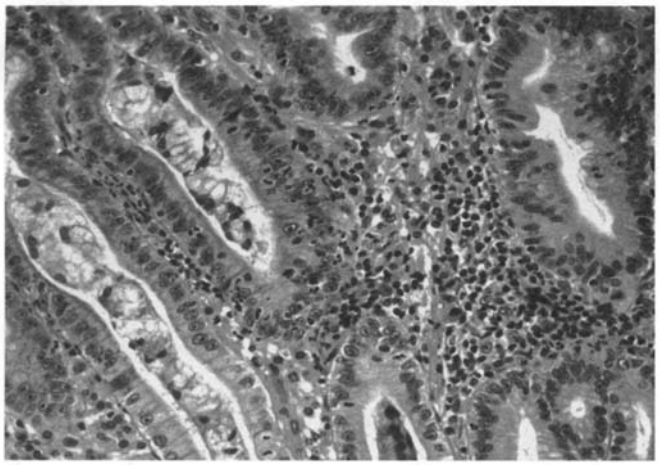


Fig. 31. Diffuse antral gastritis.

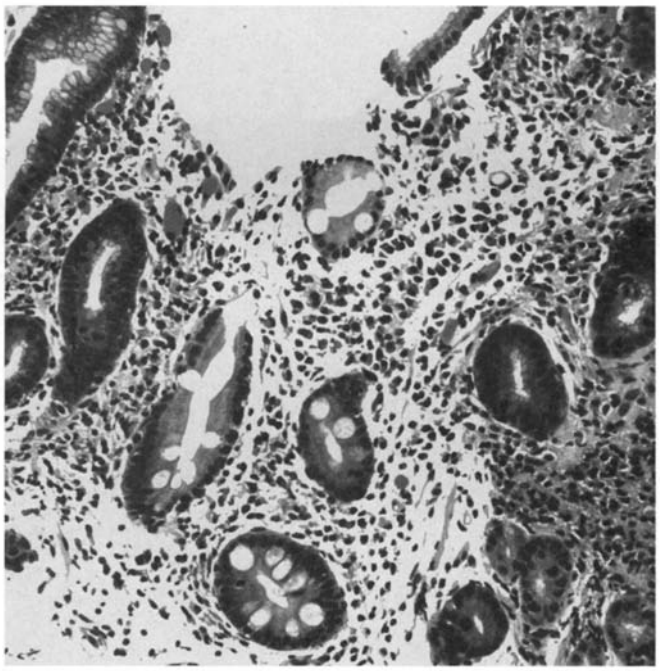


Fig. 32. Multifocal atrophic gastritis.

MAG (a.k.a. Multifocal Intestinalized Pangastritis)

Clinical

- *H. pylori* associated: 75–100%
- Although H. pylori associated, genetic and environmental factors may play a role
- Increased risk of gastric MALT lymphoma, gastric ulcers and gastric adenocarcinoma
- African-American, Asians, Hispanic, Scandinavian and immigrants to the US
- Antrum/body involvement

*Microscopic (**Figure 32**)*

- Lymphoid follicles
- Active inflammation (neutrophils) common

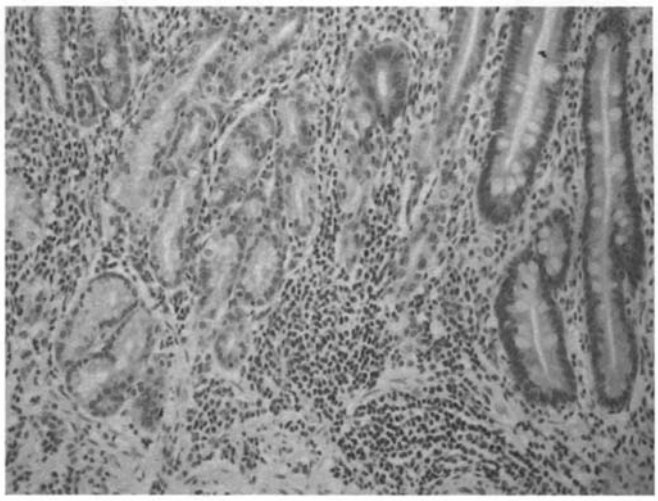


Fig. 33. Autoimmune gastritis.

- Lamina propria expansion by mononuclear cells
- "Pyloric" metaplasia of the fundus is common
- Intestinal metaplasia is characteristic

Histochemistry

- Giemsa, Diff-Quik,Warthin-Starry, Steiner or Genta stains for H. pylori (4 μm, gram negative curved/spiral shaped rod)
- H. heilmannii (spiral shaped) measures 5–9 μm and usually produces less epithelial damage than H. pylori

Immunohistochemistry

- Immunohistochemical stains for H. pylori are slightly more sensitive than histochemical methods

AUTOIMMUNE

Clinical

- Frequently seen as diffuse corporal atrophic gastritis
- No association with H. pylori
- Antibodies anti-parietal cells and anti-intrinsic factor are common
- Genetic factors involved
- Increased risk for gastric adenocarcinoma
- Northern Europeans
- Pernicious anemia may be present
- Hypo or achlorhydria
- Hypergastrinemia

Macroscopic

- Body and fundus
- Atrophy

*Microscopic (**Figure 33**)*

- Common "pyloric metaplasia"
- Intestinal metaplasia is characteristic
- Loss of parietal cells

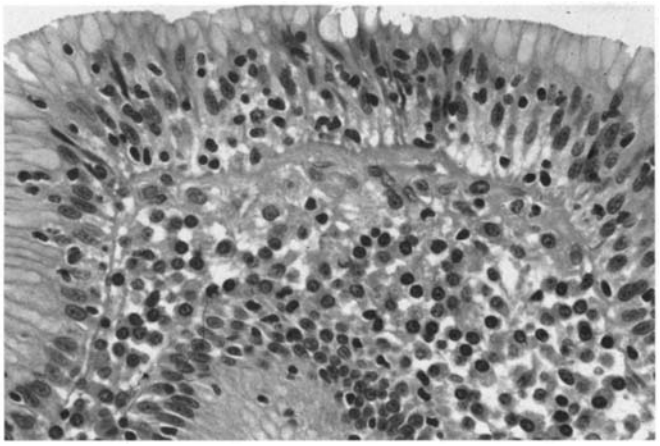


Fig. 34. Lymphocytic gastritis.

- Enterochromaffin-like (ECL) cell hyperplasia is common
- Carcinoid tumors (if present) are not aggressive
- Progression of histopathologic features: Deep lamina propia expansion by lymphoplasmacytic infiltrate + parietal cell pseudohypertrophy > loss of oxyntic glands > marked intestinal and pyloric metaplasia

Acute Hemorrhagic

Clinical

- Asymtomatic to epigastric pain with hematemesis
- NSAIDs, alcohol or stress-related
- Includes Curling's ulcer (secondary to severe burns)

Macroscopic

- Hyperemic and edematous mucosa
- Ulceration
- Hemorrhage

Microscopic

- Rarely biopsied
- Mucosal edema with lamina propria hemorrhage
- Erosions

Lymphocytic

Clinical

- Asymptomatic or weight loss
- Sometimes hypoalbuminemia is present
- Associated with celiac disease and H. pylori infection
- Uncommon

Macroscopic

- Normal endoscopic fundus to "varioliform" (multiple bulging erosions)
- Enlarged mucosal folds may be present

*Microscopic (**Figure 34**)*

- Increased chronic inflammation in lamina propria

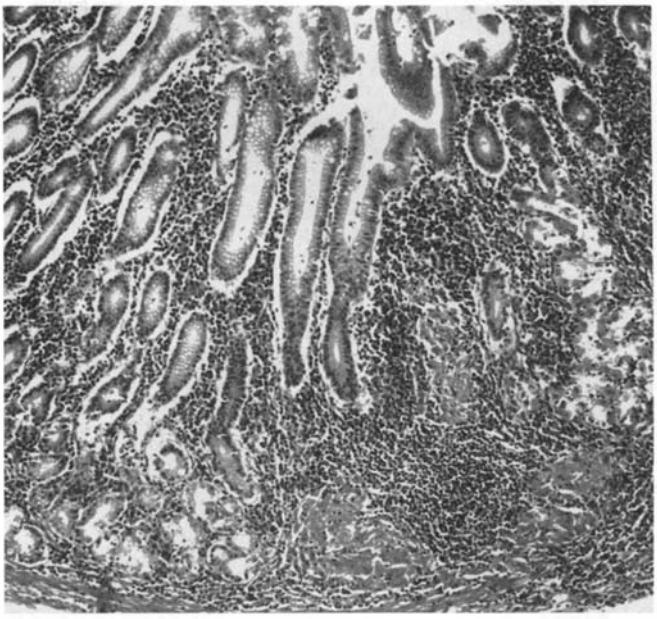


Fig. 35. Granulomatous gastritis.

- Mature lymphocytes infiltrating foveolar and surface epithelium (>25 lymphs per 100 epithelial cells)
- Rare lymphoepithelial lesions cointaining three or more lymphocytes

Immunohistochemistry

- Useful if MALT lymphoma is in the differential diagnosis
- Demostrates a suppressor T cell phenotype (CD3+, CD8+)

Differential Diagnosis

- MALT lymphoma:
  - Monomorphic lymphoid population
  - Epithelial destruction
  - Frequent lymphoepithelial lesions
  - B lymphocytes by immunohistochemistry

Granulomatous

Clinical

- Uncommon
- Most frequently seen in the setting of either H. pylori infection or Crohn's disease
- Other causes include sarcoidosis, post-gastrectomy foreign body reaction, histoplasmosis, tuberculosis, Wegener's and associated with carcinoma or lymphoma
- Idiopathic granulomatous gastritis is diagnosis of exclusion (extremely rare)

*Microscopic (**Figure 35**)*

- Granulomas involving any layer

Histochemistry

- Stains for acid-fast bacilli and fungi are helpful in the differential diagnosis

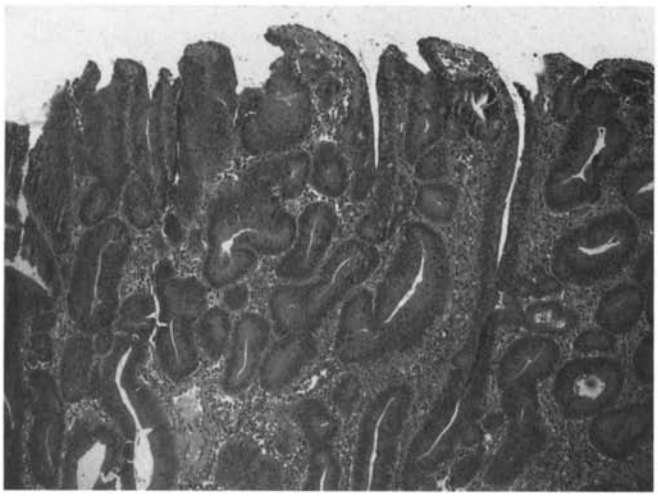


Fig. 36. Gastric adenoma, Intestinal type.

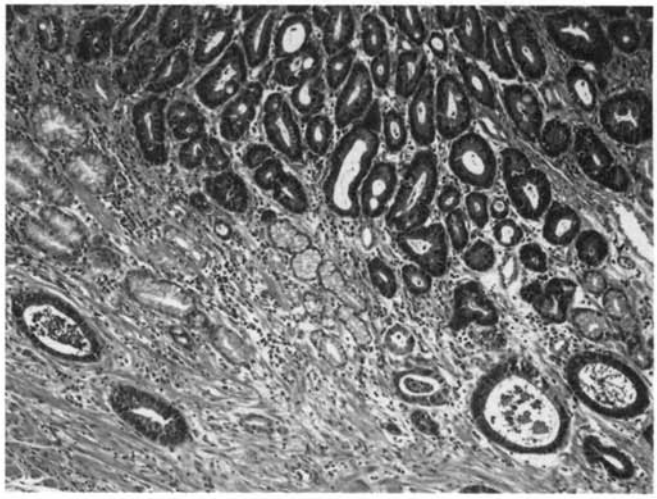


Fig. 37. Adenocarcinoma, Intestinal type.

Gastric Ulcer

Cinical

- M > F
- Average age: 50 years
- Cardinal symptom is nocturnal epigastric pain
- Associated with NSAIDs or H. pylori
- 95% along the lesser curvature
- 95% accuracy with endoscopic and 70% accuracy with radiographic diagnosis

Macroscopic

- 5% multiple
- Sharp delineation
- Oval, round, or linear
- Overhanging proximal and sloping distal borders
- Fibrous replacement of muscle wall
- Subserosal fibrosis
- Reactive lymph node hyperplasia

Microscopic

- Four layers (purulent exudate, fibrinoid necrosis, granulation tissue, fibrosis)
- Thickened blood vessels
- Hypertrophied nerve bundles
- Intestinal metaplasia, with evidence of epithelial regeneration
- *Helicobacter pylori* may be seen

Differential Diagnosis

- Ulcerated carcinoma:
  - Invasion with desmoplastic response
  - Cytokeratin immunostain highlights malignant cells

Neoplastic—Epithelial

Adenoma

Clinical

- Precursor lesion of gastric adenocarcinoma
- Dysplastic change with polypoid growth
- 10% of all gastric polyps
- Majority associated with intestinal metaplasia or FAP
- Adenocarcinoma arises in up to 50% of adenomas

Microscopic ***(Figure 36)***

- Intestinal (most common) or gastric (foveolar) types
- Nuclear pleomorphism
- Architectural distortion
- Increased mitotic rate
- May have low or high grade dysplasia

Adenocarcinoma

Clinical

- >50 years of age
- Arises from the basal cells of the foveolae in a background of chronic atrophic gastritis with intestinal metaplasia
- Strong association with hypochlorhydria
- Factors implicated in the pathogenesis include H. pylori infection, diatary factors and bile reflux
- Incidence: eastern Asia, south America and eastern Europe > US
- Location variable (distal stomach most frequent)
- Carcinoma of the gastric cardias has an increasing frequency in US
- Types (Laurén classification):
  - Intestinal (53% of cases) arises from metaplastic epithelium **(Figure 37)**

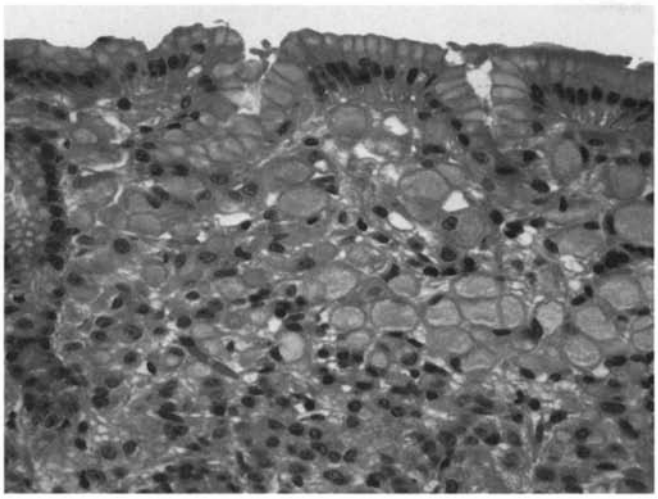


Fig. 38. Adenocarcinoma, Diffuse type.

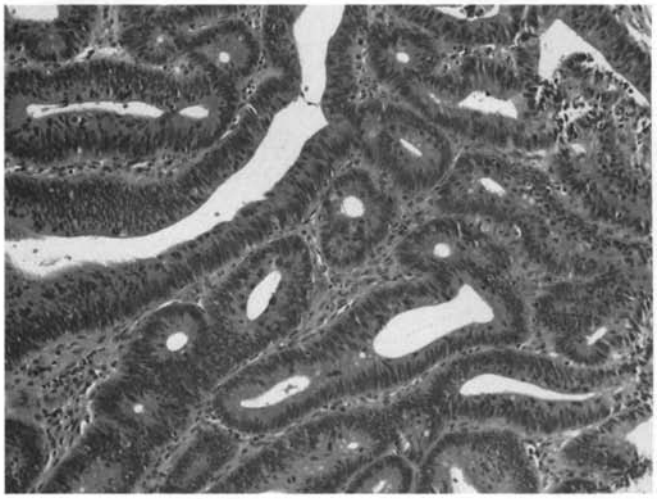


Fig. 39. Intraepithelial neoplasia (dysplasia).

- Diffuse (33%) (linitis plastica, signet ring carcinoma) arises in prepyloric region and results in a thick, rigid organ with pyloric obstruction **(Figure 38)**
- Mixed (14%)

♦ Types (WHO classification):
- Tubular
- Papillary
- Mucinous: >50% mucin pools
- Signet-ring cell: >50% composed by signet-ring cells

♦ Symptoms include anemia, weight loss, abdominal pain and dyspepsia

♦ Diagnosis is based on radiography, endoscopy and biopsy

♦ Local extension to duodenum, esophagus, omentum, colon, pancreas, and spleen

♦ Metastases to lymph nodes, liver, peritoneum, lung, adrenal gland, ovary (Krukenberg tumor), uterus, cervix

♦ Poor prognosis (overall survival rate is 4–13%)

♦ Usually detected in advanced stages (unless mass screening is performed)

Macroscopic

♦ Multiple in 5% of cases

♦ Varies from fungating and exophytic to flat, ulcerated and deeply invasive

♦ Fleshy, fibrous, or gelatinous (depending on amount of mucin present, extent of desmoplastic response) in intestinal type

♦ Submucosal fibrosis, mucosal ulceration, muscular hypertrophy, and subserosal thickening in diffuse type

Microscopic

♦ Glandular to solid growth of columnar, mucus-secreting cells (intestinal type)

♦ Growth of individual signet ring cells, marked desmoplasia, and inflammation (diffuse type)

♦ May have prominent tubular or papillary growth

♦ May have abundant mucin, resulting in mucous lakes with fragments of glands

♦ May be accompanied by granulomas, stromal eosinophilia or chronic inflammatory infiltrate

Histochemistry

♦ Mucicarmine and alcian blue/PAS+

Immunohistochemistry

♦ CEA and cytokeratin+

Precursor/Related Lesions

♦ Dysplasia **(Figure 39)**:
- Must be distinguished from simple or atypical regenerative hyperplasia
- Types: Intestinal (most common) or foveolar
- Increased nuclear to cytoplasmic ratio
- Nuclear pseudostratification
- Reduced or absent mucous secretion
- Nuclear pleomorphism and hyperchromasia
- Frequent mitotic figures
- Cellular crowding
- Glandular complexity
- Divided into low and high grade intraepithelial neoplasia (dysplasia)
- Indefinite for dysplasia if differentiation from reactive/regenerative is not possible
- High grade dysplasia per definition do not show invasion (intact basement membrane)

♦ Intramucosal carcinoma **(Figure 40)**:
- Basement membrane not intact
- Isolated cells or very complex glandular architecture

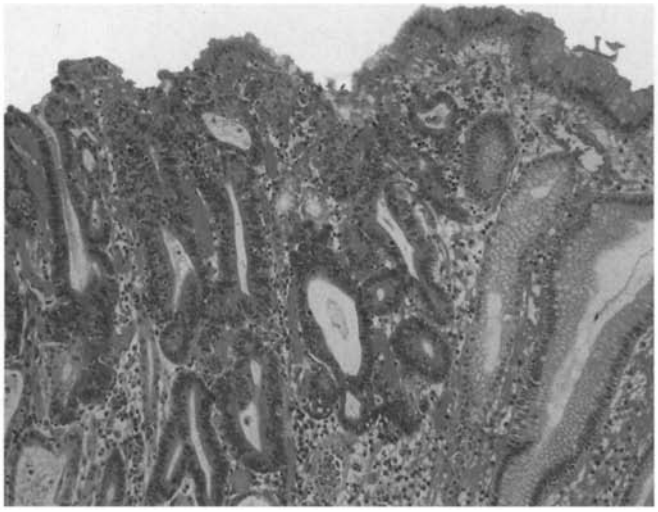


Fig. 40. Intramucosal adenocarcinoma.

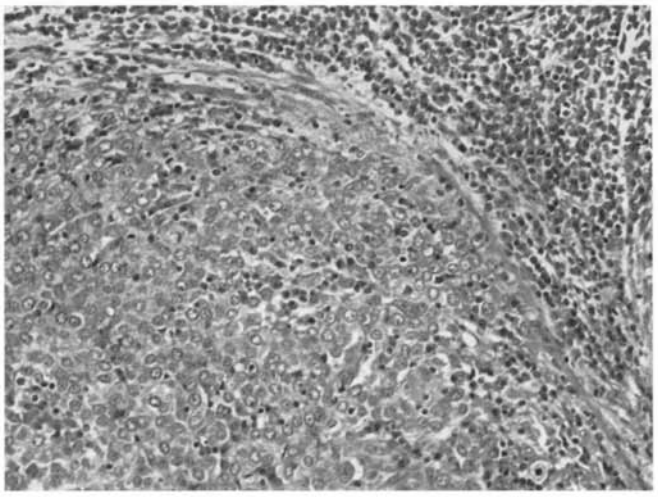


Fig. 41. Medullary carcinoma.

- Risk of metastasis is present
- Some use the term "early gastric cancer" if it is confined to the mucosa and submucosa (no extension into the muscularis propria)

♦ Hereditary diffuse gastric carcinoma:
- Germline E-cadherin mutations
- Autosomal dominant
- Young adults
- Poorly differentiated tumors

Differential Diagnosis

♦ Reactive changes and granulation tissue in an ulcer or erosion:
- Maturation toward the surface
- Regular arrangement of glands
- Decreased mucin
- Low columnar cells
- Uniform vesicular nuclei
- Endothelial cells of granulation tissue may look very atypical (cytokeratin–)

♦ Lymphoma:
- No mucin production
- LCA+
- Keratin–, CEA–

♦ Metastatic carcinoma (breast, lung, melanoma):
- Multicentric
- Lack of metaplastic or dysplastic mucosal change
- Serosal location
- Marked desmoplastic response
- TTF-1, GCDFP-15, Estrogen receptor, melanoma markers, cytokeratin 7/20 pattern and clinical history may be useful

♦ Carcinoid:
- Neuroendocrine markers (chromogranin, synaptophysin) by immunohistochemistry
- Dense core granules present by electron microscopy (EM)

♦ Granular cell tumors:
- Submucosal location
- Small benign-appearing nuclei
- No mitotic figures
- Granular eosinophilic cytoplasm
- S-100+

Variants

♦ Medullary carcinoma **(Figure 41)**:
- Undifferentiated carcinoma with lymphoid stroma (a.k.a. lymphoepithelioma-like carcinoma)
- Pushing borders
- Sheets and syncitia of tumor cells with prominent lymphocytic infiltrate
- Clear to eosinophilic cytoplasm
- Vesicular nuclei
- Most are EBV+

♦ Hepatoid adenocarcinoma **(Figure 42)**:
- Large polygonal cells resembling hepatocytes
- Bile production
- PAS-D resistant hyaline globules
- Abundant cytoplasmic glycogen
- Alpha-fetoprotein, alpha-1-antitrypsin, and albumin+

♦ Adenosquamous carcinoma and squamous cell carcinoma:
- Extensive squamous differentiation
- Variable amount of glandular component in adenosquamous

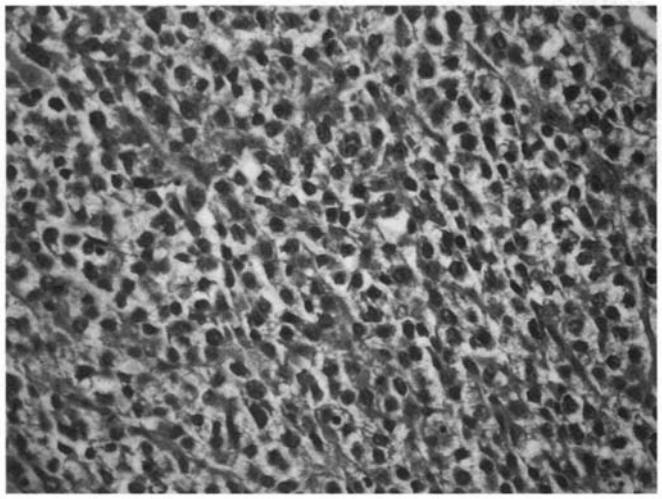


Fig. 42. Hepatoid adenocarcinoma.

Neoplastic—Mesenchymal

Gastrointestinal Stromal Tumor (GIST)

Clinical

- Adults in 6th to 8th decade
- Stomach is the commonest site for GIST (60–70%)
- Derive from interstitial cells of Cajal (pacemaker cells)
- No sex predilection (only in Carney's triad: female predominance)
- Associated with Neurofibromatosis type I (von Recklinhausen's disease) and as part of Carney's triad (malignant epithelioid gastric GIST, pulmonary chondroma and extra-adrenal paraganglioma)
- Symptoms include abdominal pain and GI bleeding
- Many small tumors are asymptomatic (incidentally found during surgery)
- Clinical behavior is variable
- Metastases to the liver, peritoneum, and lungs
- Treatment includes targeted therapy with tyrosine kinase inhibitors (e.g. Imatinib mesylate [Gleevec])
- Associated with c-kit gene activating mutations in exon 11 (less commonly exons 9 and 13)

Macroscopic

- Well circumscribed nodule
- Serosal, submucosal or in muscularis propria
- Granular cut surface
- Ulceration is frequent
- Hemorrhage, necrosis and cystic change may be present
- Microscopic appearance do not predicts behavior

Microscopic

- Majority of gastric GIST are composed of either spindle or epithelioid cells (with benign and malignant counterparts)

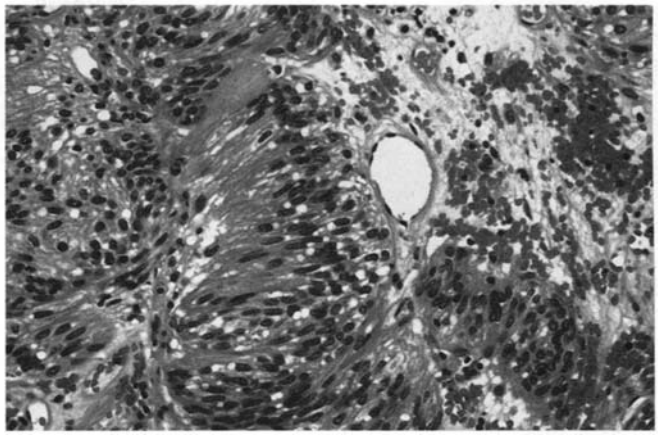


Fig. 43. Spindle cell GIST, histologically benign.

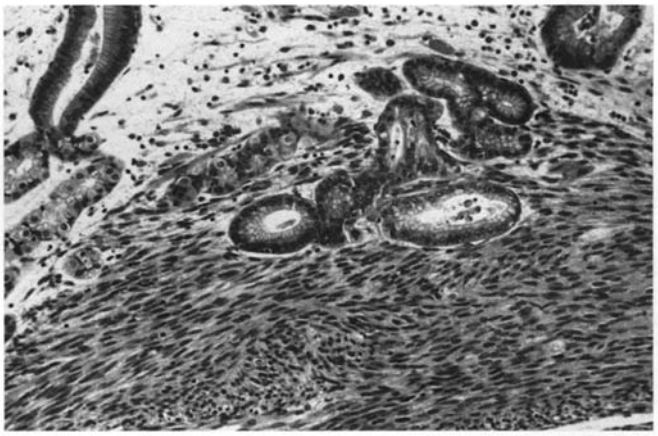


Fig. 44. Malignant spindle cell GIST displaying mucosal invasion.

- Spindle cell gastric GIST (**Figure 43**):
  - Pale to eosinophilic fibrillar cytoplasm
  - Nuclear palisading
  - Perinuclear vacuoles (fixation artifact)
  - May display hyalinized or calcified stroma
  - Malignant tumors (spindle cell sarcomas) have been associated with high cellularity, absence of vacuoles, marked nuclear atypia, >5 mitosis per 50 hpf and mucosal invasion (**Figure 44**)
- Epithelioid gastric GIST (**Figure 45**):
  - Benign epithelioid GIST is the most common type of GIST in the stomach
  - Epithelioid cells with eosinophilic cytoplasm
  - Hyalinization and calcification may be present
  - Scattered multinucleated cells
  - Malignant epithelioid tumors show display high cellularity, mucosal invasion, marked nuclear atypia and >5 mitosis per 50 hpf

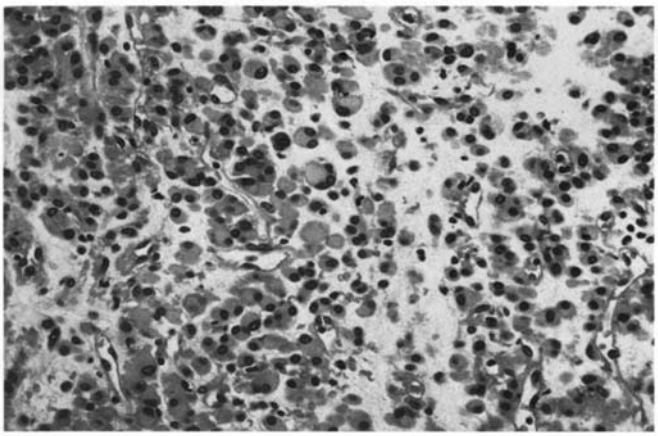


Fig. 45. Benign epithelioid GIST.

Table 9. Proposed NIH GIST Workshop Classification

Risk of Aggressive Behavior	*Size (cm)*	*Mitoses (per 50 hpf)*
Very low	<2	<5
Low	2–5	<5
Intermediate	<5	6–10
	5–10	>5
High	>5	>5
	>10	Any mitotic count
	Any size	>10

- Borderline or "Indeterminate" malignant potential in doubtful cases
- Prediction of clinical behavior should be based in a multiparametric analytic approach; however a NIH sponsored consensus workshop proposed size and mitotic count to define risk for aggressive behavior in GIST **(Table 9)**

Immunohistochemistry

- CD117 (KIT) virtually marks all GIST
- CD34 present in around 70%
- Actin, desmin and S-100 may be positive (usually focal)
- CD117 staining documentation is important for treatment purposes

Leiomyoma

Clinical

- Rare

Macroscopic

- Well-circumscribed, non-encapsulated, and firm
- Whorled, bulging cut surface

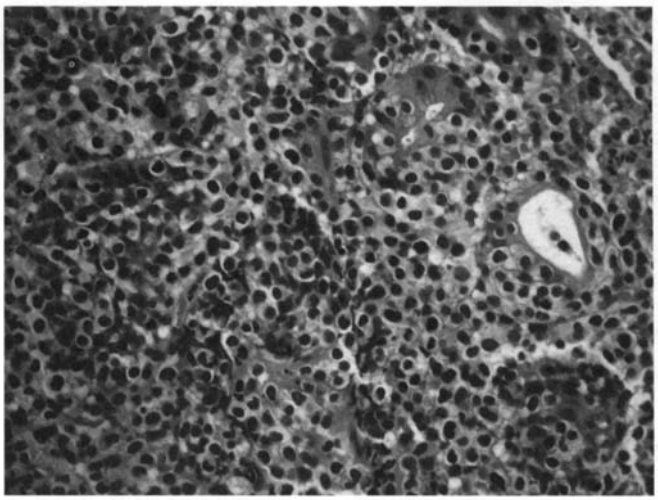


Fig. 46. Low-grade B-cell lymphoma of MALT type.

Microscopic

- Mature, hypertrophic smooth muscle cells
- Whorled, fascicular arrangement

Immunohistochemistry

- Smooth muscle actin and desmin+
- CD117–

Lymphoid Neoplasms (see Chapter 7)

Gastric Marginal Zone B-cell Lymphoma

Clinical

- a.k.a. Low grade B-cell Lymphoma of Mucosa Associated Lymphoid Tissue (MALT) type
- Average age >50 years
- Insidious onset
- Dyspepsia and epigastric pain
- Strong association with H. pylori infection
- Regression after H. pylori eradication is common
- t(11;18)(q21;q21) involving the API2 and MALT1 genes is present in 30–40% and associated with failure to eradicate H. pylori
- 5-year survival rate: 90%

Macroscopic

- Fish-flesh appearance
- Mucosal nodularity
- Erosion and ulceration
- Enlarged rugal folds
- Multifocal
- Background of gastritis

*Microscopic **(Figure 46)***

- Monomorphic population of small, centrocyte-like cells (intermediate size with rim of pale cytoplasm and slightly irregular nucleus)

- Lymphoepithelial lesions
- Large follicles with reactive germinal centers
- Dutcher bodies
- Destruction of gastric glands
- Plasmacytic differentiation is common

Immunohistochemistry

- B-cell phenotype
- Light chain restiction
- CD20+, CD5–, CD10–
- Bcl-2 frequently+
- Cytokeratin useful to highlight lymphoepithelial lesions

Differential Diagnosis

- Florid gastritis:
  - Polymorphic population of small lymphocytes without centrocyte-like morphology
  - Plasma cells predominate over lymphocytes
  - Infrequent lymphoepithelial lesions and loss of gastric glands
  - Policlonality of B-cells and predominance of T-cells
- Follicular lymphoma:
  - Follicular architecture
  - Lymphocytes with irregular nuclear envelopes
  - B cells expressing CD20 and CD10; CD5–

Diffuse Large B-cell Lymphoma

Clinical

- Average age >60 years
- Most common primary lymphoma of the stomach
- Usually symptomatic
- Sometimes palpable mass present
- 5-year survival rate: 65%
- Most important prognostic factor is stage

Macroscopic

- Lobulated or polypoid
- Ulceration, superficial or deep

*Microscopic (**Figure 47**)*

- Monomorphic population of large lymphoid cells
- Vesicular nucleus ± prominent nucleoli
- Increased mitotic rate
- Often deeply invasive

Immunohistochemistry

- B-cell phenotype (CD20+)

Differential Diagnosis

- Undifferentiated carcinoma:
  - More cohesive cells
  - Mucin, cytokeratin and CEA+
  - Lymphoid markers–

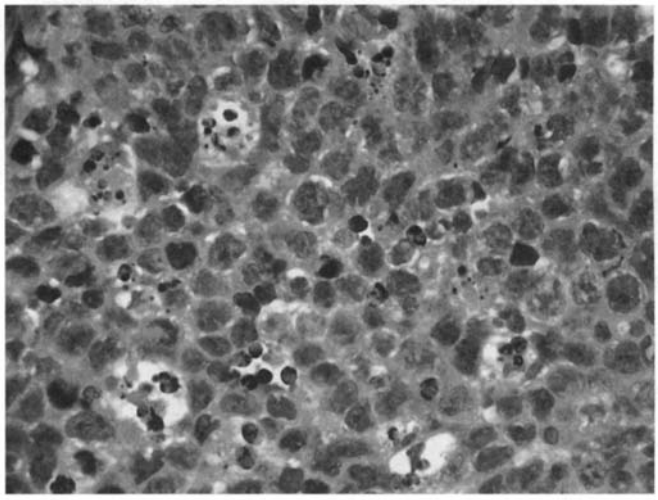


Fig. 47. Diffuse large B-cell lymphoma.

Neoplastic—Miscellaneous Tumors

Carcinoid

Clinical

- Enterochromaffin-like (ECL) carcinoid most common; G (gastrin) cell less frequent
- Three types:
  - Type I: Associated with autoimmune chronic atrophic gastritis (achlorhydria frequent)
  - Type II: Associated with MEN-1 and Zollinger-Ellison syndrome
  - Type III: Sporadic
- Hypergastrinemia in types I and II; ECL cell hyperplasia present
- Type I is the commonest
- Type I: usually benign; Type II: could be aggressive but usually indolent; Type III: Aggressive with 50% metastasis

Macroscopic

- Small submucosal nodules
- Fundic location in ECL-cell carcinoids
- Antral location in G cell carcinoids

*Microscopic (**Figure 48**)*

- Microglandular, trabecular, insular growth
- Regular, normochromatic nuclei
- Few mitotic figures
- Proliferation of blood vessels
- No necrosis

Histochemistry

- Focally mucin+

Immunohistochemistry

- NSE, synaptophysin, chromogranin, and keratin+

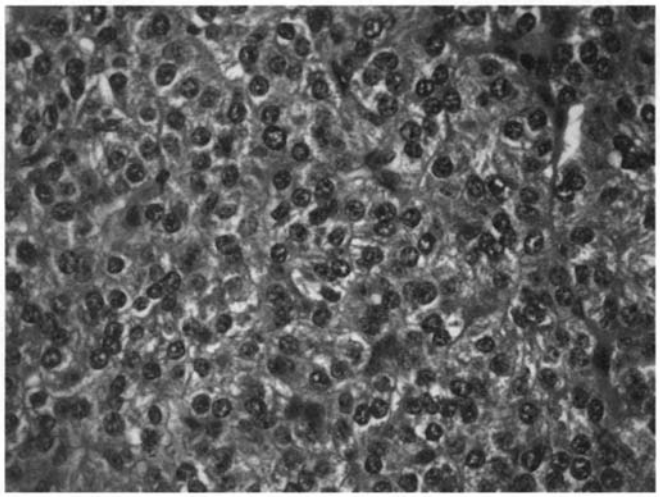


Fig. 48. Carcinoid.

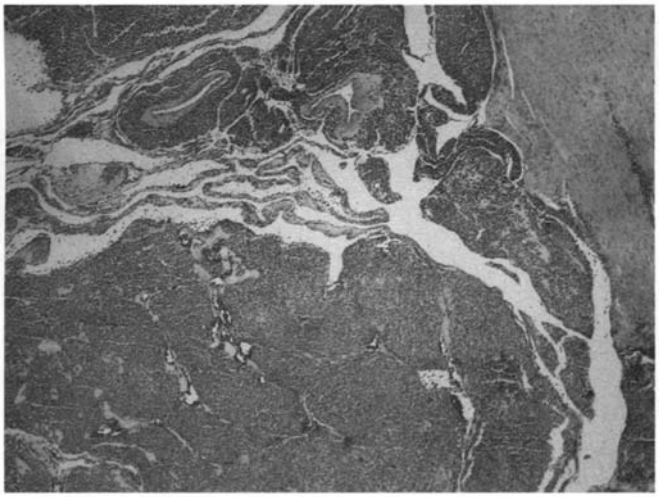


Fig. 49. Glomus tumor.

Electron Microscopy

- Dense core secretory granules present

Glomus Tumor

Clinical

- Rare
- GI bleeding, epigastric pain or incidental
- Good prognosis; metastasis are exceedingly rare

Macroscopic

- Well circumscribed
- Intramural
- Rubbery to spongy
- Frequent hemorrhage

*Microscopic **(Figure 49)***

- Uniform cells
- Well defined cell membranes
- Round, centrally located nuclei with inconspicuous nucleoli
- Oncocytic or clear cell change
- Nodules separated by smooth muscle bundles
- Common atypia and intravascular invasion

Immunohistochemistry

- Smooth muscle actin+; CD117–
- Possible focal CD34

Electron Microscopy

- Abundant myofilaments

Differential Diagnosis

- Epithelioid GIST:
  - CD117+

Staging Gastric Malignancies

- *See* **Tables 10** and **11**

Table 10. TNM Classification of Gastric Tumors (2002 Revision)

Tis	Intraepithelial; no lamina propria invasion
T1	Limited to mucosa or submucosa
T2a	Muscularis propria invasion
T2b	Tumor invades subserosa (not through serosa)
T3	Through serosa without invasion of adjacent tissue
T4	Involvement of adjacent structures
N0	No nodal involvement
N1	Metastasis in 1–6 perigastric lymph nodes
N2	Metastasis in 7–15 perigastric lymph nodes
N3	Metastasis in >15 lymph nodes
M0	No distant metastasis
M1	Distant metastasis

Table 11. Group Staging Criteria

Stage 0	Tis	N0	M0
Stage Ia	T1	N0	M0
Stage Ib	T1	N1	M0
	T2	N0	M0
Stage II	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIIa	T2	N2	M0
	T3	N1	M0
	T4	N0	M0
Stage IIIb	T3	N2	M0
Stage IV	T4	N1-3	M0
	T1-3	N3	M0
	Any T	Any N	M1

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35

Small Intestine, Appendix, Colorectum, and Anus

Shuan C. Li, MD

CONTENTS

I. Inflammatory and Malabsorptive Disorder 35-3
Specific Inflammatory Disease 35-3
Infectious Enteritis Specific 35-3
Acute Infectious Enterocolitis 35-3
Specific Bacterial Infection 35-3
Vibrios 35-3
Shigellosis 35-3
Salmonellosis 35-3
Camypylobacter Enterocolitis 35-3
Yersiniosis 35-3
Pseudomembranous Colitis 35-4
Enterohemorrhagic E. coli 35-4
Whipple's Disease 35-4
Celiac Disease 35-5
Tropical Sprue Syndrome 35-6
Ulcerative Jejunoileitis 35-6
Idiopathic Inflammatory Bowel Disease 35-6
Ulcerative Colitis 35-6
Crohn's Disease 35-7
Microscopic Colitis 35-9
Lymphocytic Colitis 35-9
Collagenous Colitis 35-9
Diversion Colitis 35-9
Solitary Rectal Ulcer Syndrome (SRUS) 35-10
Radiation Proctitis/Colitis 35-10
Diverticular Disease 35-11

II. Vascular Lesions 35-11
Acute Intestinal Ischemia 35-11
Chronic Ischemic Injury 35-12
Angiodysplasia 35-13
Vasculitis 35-113
Scleroderma 35-113

III. Appendix 35-14
Inflammatory Lesions 35-14
Acute Appendicitis 35-14
Tumors 35-15

IV. Intestinal Polyps 35-16
Developmental Polyps 35-16
Hamartomatous Polyp, Peutz-Jeghers Type 35-16
Hamartomatous Polyp, Juvenile Type 35-16
Inflammatory Pseudopolyp 35-17
Hyperplastic Polyp (HPP) 35-17
Inflammatory Fibrous Polyp 35-18
Neoplastic Polyps—Adenomas 35-18
Ganglioneuroma 35-21

V. Malignant Tumors 35-21
Adenocarcinoma 35-21
Carcinoid Tumors 35-22
Gastrointestinal Stromal Tumor (GIST) 25-23
Gastrointestinal Lymphoma 35-24
Specific Types 35-24
B Cell Lymphoma of MALT 35-24
Mantel Cell Lymphoma (Lymphomatous Polyposis) 35-25
Burkitt's and Burkitt-Like Lymphomas 35-25
Sprue-Associated T Cell Lymphoma 35-25

VI. Anus 35-26
Benign Lesions 35-26
Hemorrhoids 25-26
Fissure 35-26
Fistula 35-26
Tumors of Anal Region 35-26
Condyloma Acuminatum 35-26
Anal Intraepithelial Neoplasia (AIN) 25-26
Giant Condyloma Acuminatum 35-26
Squamous Cell Carcinoma 35-26
Adenocarcinoma of Anal Duct/Gland.....35-28
Small Cell Carcinoma.....25-28
Melanoma 35-28

VII. TNM Classification of Colorectal Adenocarcinoma (2002 Revision) 35-28

VIII. Suggested Reading.....35-29

INFLAMMATORY AND MALABSORPTIVE DISORDER

Specific Inflammatory Disease

Infectious Non-specific Enteritis

Clinical

- Viral > bacterial > parasitic
- Acute onset of diarrhea, usually resolves within days
- May develop a chronic malabsorption to one or various test substances
- Transient intolerance to cow's milk or gluten; disaccharidase deficiency may occur in children

Macroscopic

- Normal to mildly erythematous mucosa

Microscopic

- Intraepithelial lymphocytic infiltrate
- Mild villous blunting
- Focal active inflammation may occur

Acute Infectious Enterocolitis (Figure 1)

Clinical

- Acute onset of abdominal pain, diarrhea, and bloody diarrhea
- Symptoms are short-lived or self-limited
- Stool cultures are negative in half of the cases
- Common pathogens: *Campylobacter, Salmonella, Shigella, Yersinia,* and *E. coli*

Macroscopic

- Patchy, extremely variable mucosal erythema, inflammation, and erosion

Microscopic

- Extremely variable
- Mild mucosal edema, congestion, and nonspecific chronic inflammation
- Neutrophils within superficial lamina propria (LP) and crypts
- No chronic mucosal architectural damage
- No basal lymphoplasmacytosis

SPECIFIC BACTERIAL INFECTION

Vibrios

- Unremarkable histology
- Increased mononuclear cell in LP of small intestine
- Widened intercellular spaces and junctional complexes on electron microscopy

Shigellosis

- Almost always involves rectosigmoid with variable proximal extension
- May involve cecum and the terminal ileum

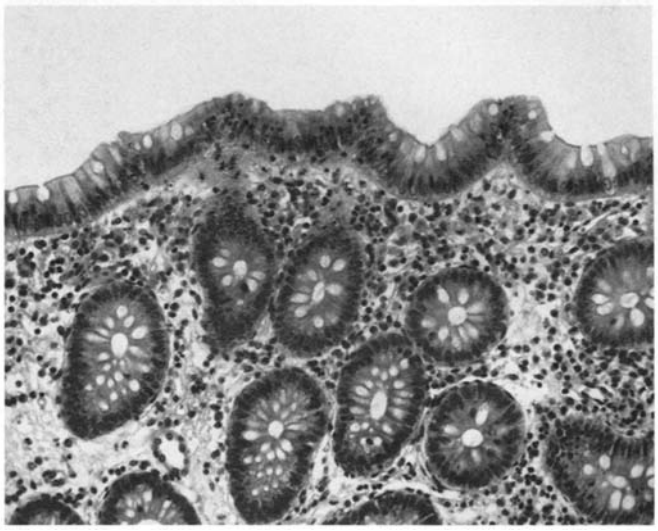


Fig. 1. Infectious colitis.

- Indistinguishable from other enteric infections
- Purulent LP in severe disease, with cryptitis, crypt abscess, and pseudomembrane
- May resolve to an atrophic mucosa, mimicking inactive ulcerative colitis

Salmonellosis

- The most common foodborne pathogens causing outbreaks
- Many serotypes
- Erythematous, friable mucosa, preferentially in proximal colon
- Rectum also frequently involved
- Indistinguishable from other enteric infections

Campylobacter Enterocolitis

- Numerous species
- Fecal-oral transmission in contaminated water, or sexually transmitted
- Rectal involvement with variable proximal extension, mimicking ulcerative colitis endoscopically
- May have focal and segmental diseases mimicking Crohn's disease
- Frequent aphthoid ulcer or inflammation
- Indistinguishable from other enteric infections

Yersiniosis

- Two species:
  - *Y. pseudotuberculosis* and *Y. enterocolitica*
- Cause acute terminal ileitis
- Markedly thickened terminal ileum with enlarged mesenteric lymph nodes

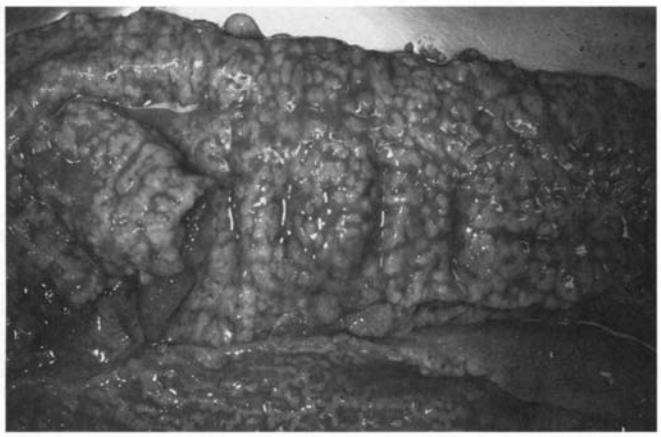


Fig. 2. Pseudomembranous colitis (Gross).

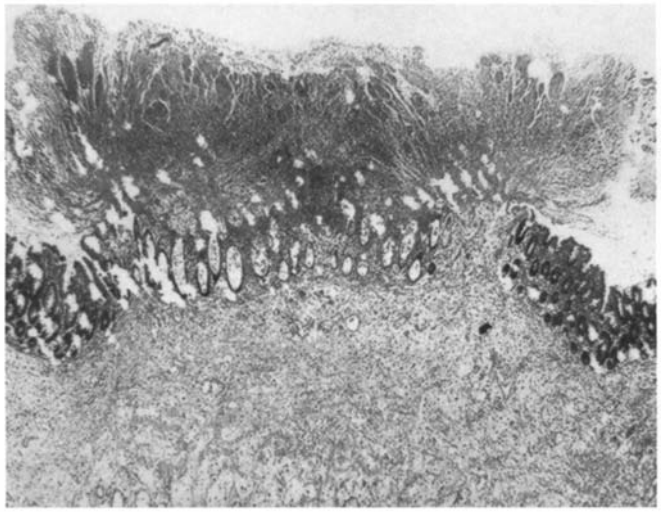


Fig. 3. Pseudomembranous colitis (Micro).

- Necrotizing granulomas with central necrosis, neutrophilic infiltrate, and peripheral palisading histiocytes in the background of dense lymphocytic infiltration

Pseudomembranous Colitis (Figures 2,3)

- Most common in hospitals and nursing homes
- *C. difficile* in 15–20%, occasionally others (verotoxin-producing *E. coli*); unknown cause in most of the remaining cases
- Cramping, abdominal pain, profuse diarrhea, and fever a few days or up to 8 weeks after use of antibiotics
- Affects entire colon, but most severe in the distal colorectum
- Pinpoint or plaque-like smooth, shiny lesions in milder cases
- Diffuse pseudomembrane in severe cases
- Mushroom or volcano-like exudate of neutrophils, mucin, and necrotic epithelium from superficial crypt lumen with relatively intact basal crypt
- Diffuse lamina propria neutrophilic infiltration and edema

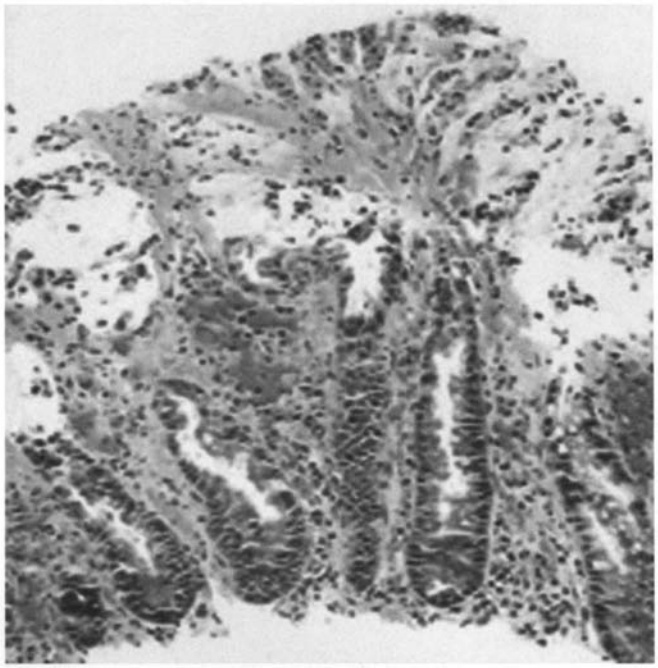


Fig. 4. *E. coli* O157:H7 colitis.

Enterohemorrhagic E. coli (O157:H7) (Figure 4)

- 3% of all acute diarrhea, but 15–36% of all acute bloody diarrhea
- Food (hamburger) outbreaks
- Diffuse friable mucosa with patchy hemorrhagic erosion
- Similar to other infectious colitis plus features of acute ischemia

Whipple's Disease (Figures 5,6)

Clinical

- Rare, a systemic infectious disease often diagnosed through duodenal biopsies
- Caused by *Tropheryma whippelii*
- M > F
- Fever, weight loss, arthritis, diarrhea, and central nervous system (CNS) symptoms

Macroscopic

- Primarily involves the jejunum
- Edematous and thickened intestinal wall with enlarged mesenteric lymph nodes
- Club-shaped villi show white-yellow appearance

Microscopic

- Marked villous blunting
- Foamy macrophages in LP
- Rod-like intracellular organisms strongly + on periodic acid-Schiff (PAS) with diastase stain

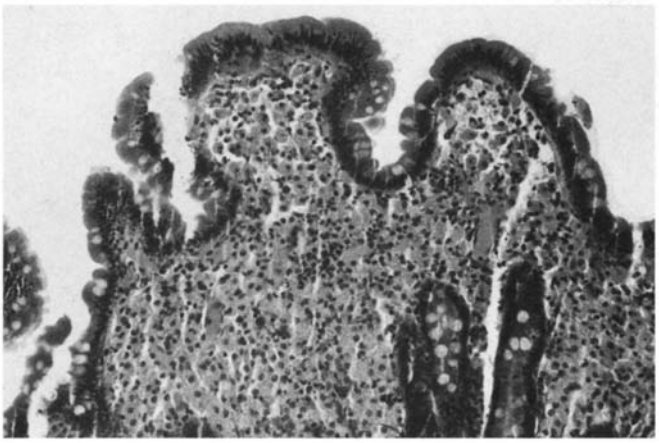


Fig. 5. Whipple's disease (H&E).

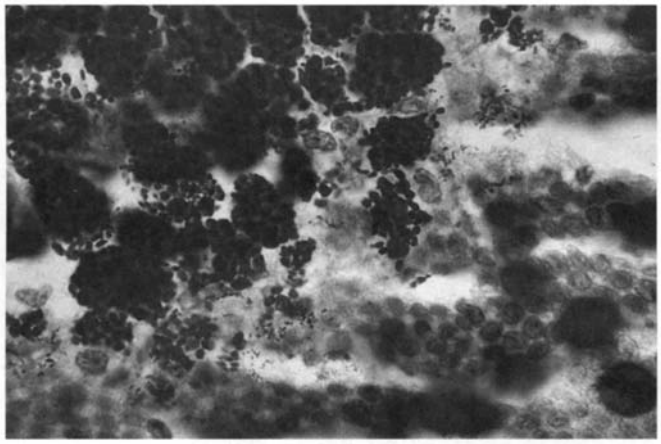


Fig. 6. Whipple's disease (PAS with diastase).

- Polymerase chain reaction (PCR) specifically identifies the bacterial genome

Celiac Disease (Figure 7)

Clinical

- Incidence of 0.5% of general population, but may be severely underestimated
- Strong family clustering: 10% prevalence among first degree relatives, 30% in human leukocyte antigens (HLA) identical siblings, and 70% in identical twins
- Intestinal epithelial injury caused by dietary wheat gluten (and particularly, its alcohol-soluble fraction, gliadin)
- Variable presentation from minor nutritional deficiencies to more severe steatorrhea, malnutrition, and weight loss
- Bimodal peaks: first 3 years of life and 3rd to 5th decades
- Symptoms appear during the first 3 years of life and persist throughout childhood if left untreated
- Often diminish during adolescence, only to reappear in early adult life

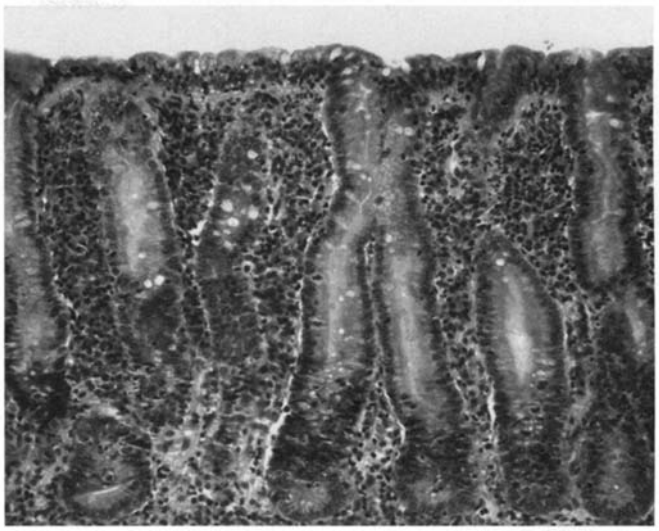


Fig. 7. Celiac disease.

- Circulating antigliadin, antiendomysial, and tissue transglutaminase antibodies + in >90% of the untreated patients
- Increased incidence of malignancy (small intestinal T cell lymphoma and adenocarcinoma)

Macroscopic

- Most severe in the proximal jejunum and duodenum
- Ileum is usually spared or minimally affected
- Loss of valvulae resulting in a smooth, tubular appearance of the small intestine
- Scalloped, ridged appearance of mucosa on a close-up view

Microscopic

- Numerous intraepithelial T lymphocytes
- Villous blunting from mild to totally flat mucosa
- Cuboidal or flattened surface epithelium with loss of goblet cells
- Increased crypt epithelial mitosis
- Dense lymphoplasmacytic infiltrate in LP
- In subclinical sprue, partial villous blunting and mild, patchy changes, as mentioned above
- Mucosal architecture restores quickly following a gluten-free diet along with a dramatic improvement of clinical symptoms

Differential Diagnosis

- Latent Celiac Sprue:
  - Asymptomatic or with skin manifestations (dermatitis herpetiformis)
  - Become symptomatic following an intestinal viral infection or high-gluten diet
  - Mild villous blunting of the duodenal mucosa with increased intraepithelial lymphocytes

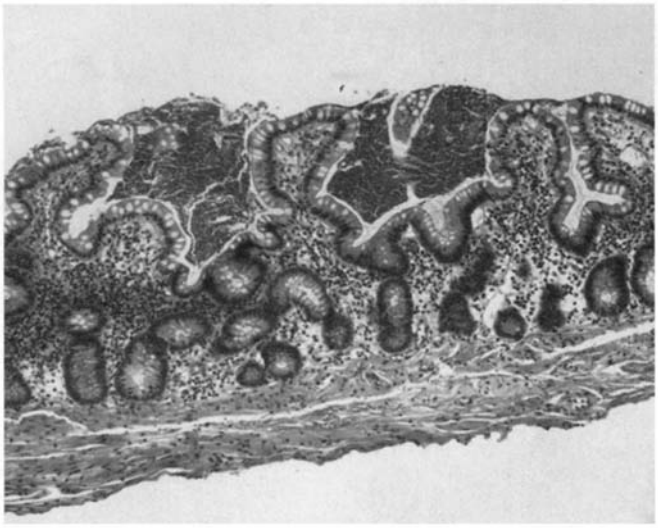


Fig. 8. Tropical sprue.

- Refractory Celiac Sprue:
  - Uncommon, may be *de novo* or initially responsive to a gluten-free diet
  - Relapse while on gluten-free diet; only responsive to corticosteroids
  - Persistent flat mucosal lesion
  - Poor prognosis with relentless and progressive malabsorption
- Collagenous Sprue:
  - Rare complication with ominous prognosis
  - Typical mucosal changes of celiac sprue with a striking broad band of subepithelial collagen layer

Tropical Sprue Syndrome (Figure 8)

- A malabsorptive syndrome associated with small bowel abnormalities
- Occurs in tropical regions in the world
- Unclear pathogenesis, environmental factors? (especially intestinal microbial flora and enterotoxin production)
- Flat mucosal lesion throughout the small intestine
- Responsive to antibiotics, not to a gluten-free diet

Ulcerative Jejunoileitis

- A rare condition in the 6th or 7th decades of life with a poor prognosis
- Unknown pathogenesis; may have a history of celiac sprue
- May be associated with intestinal T cell lymphoma, which typically forms the base of the ulceration
- Multiple mucosal ulcers in the jejunoileum
- Flattened intervening mucosa seen with celiac sprue
- Normal villous height in non-celiac associated lesions
- Non-responsive to a gluten-free diet

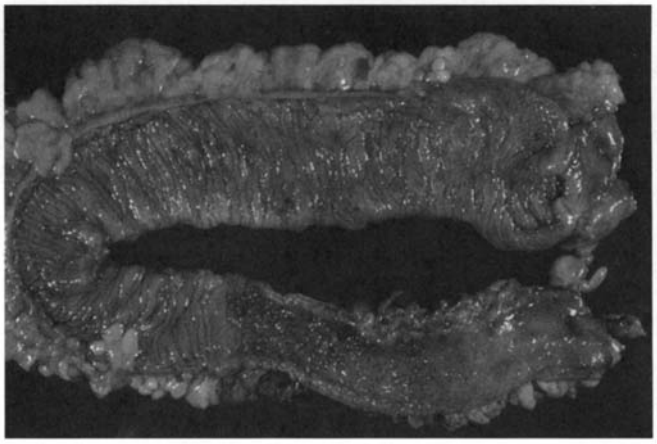


Fig. 9. Ulcerative colitis (Gross).



Fig. 10. Ulcerative colitis (Micro).

Idiopathic Inflammatory Bowel Disease

Ulcerative Colitis (Figures 9,10)

Clinical

- Incidence of 3.8–13/100,000; F slightly > M; Jews > Caucasians > African Americans
- Most common in 20–50 years of life, with second peak at age 70
- Causes unknown
- 10–20% affected 1st degree relatives

Macroscopic

- Involves the rectum with variable proximal spread in a continuous fashion
- No intervening areas of uninvolved mucosa
- The terminal ileum can be involved in 10–20% of the ulcerative pan-colitis cases

- Active phase:
  - Mucosa appears hyperemic and granular, with inconspicuous or multiple punctate ulcers
  - When severe, the ulcers have "tram-line" like appearance
  - Non-ulcerated mucosa often appears polypoid
- Fulminant phase:
  - Toxic megacolon may occur, where the bowel is markedly dilated and thin-walled with diffuse congested and grossly ulcerated mucosa
  - Perforation may also occur
- Quiescent phase:
  - Featureless atrophic mucosa
  - Shortened colon with decreased caliber and thickening of the muscularis propria

Microscopic

- Inflammation exclusively confined to the mucosa in the non-ulcerated area
- Active phase:
  - Diffuse cryptitis, crypt abscess
  - Dense basal lymphoplasmacytosis
  - Marked crypt distortion
  - Paneth cell metaplasia
- Fulminant phase:
  - Indistinguishable from other causes of fulminant colitis, such as ischemic colitis, severe infectious colitis, or Crohn's disease
- Quiescent phase:
  - Lack of cryptitis and crypt abscess
  - Mucosal architectural abnormalities with crypt distortion;
  - Basal lymphoplasmacytosis
  - Paneth cell metaplasia
  - Mucosal atrophy
- Multinucleated giant cells can be seen due to histiocytic response to the ruptured crypts; true noncaseating epithelioid granulomas are not seen

Differential Diagnosis

- Crohn's Disease:
  - Involvement of terminal ileum
  - Skip lesions
  - Focally intense cryptitis
  - Aphthoid lesions
  - Epithelioid granulomas
- Infectious (Bacterial) Colitis:
  - Superficial neutrophilic infiltrate
  - Preservation of mucosal architecture
  - No basal lymphoplasmacytosis
- Collagenous Colitis:
  - Intraepithelial lymphocytosis
  - Subepithelial collagen table thickening
  - Cuboidal or flat surface epithelium
  - Lack of mucosal architectural distortion
  - Lymphocytic Colitis
  - Intraepithelial lymphocytosis
  - Cuboidal or flat surface epithelium
  - Lack of mucosal architectural distortion
- Ischemic Colitis:
  - Mucosal collapse
  - LP neutrophilic infiltrate
  - Microcrypts
  - Intramucosal hyalinization (fibrosis)
- Drug-Induced Colitis and Proctitis:
  - Lack of active inflammation
  - No mucosal architectural distortion
  - May have increased epithelial apoptosis
  - May also mimic ischemic injury
  - Seen with non-steroidal antiinflammatory drugs (NSAID), penicillamine, sulfasalazine, and methyldopa
  - Drug history required for the evaluation

Associated Conditions

- Ulcerative Colitis-Associated Epithelial Dysplasia:
  - Incident increases over the duration of the disease
  - Risk is highest with ulcerative pan-colitis
  - Occur anywhere in the colon as patchy flat or slightly raised mucosal lesions
  - May be focal and often inconspicuous
  - Systemic, multiple mucosal biopsies increase the chance of detection
  - Histologically similar to those of colonic adenomas
  - Three grades: indefinite; low-; and high-grade dysplasia based on both architectural and cytological abnormalities
  - Low-grade dysplasia may regress, or progress to higher grade
  - High-grade dysplasia may coexist with or progress to adenocarcinoma
- Adenocarcinoma:
  - Annual increment of 0.8–1% in risk after 15–20 years of disease
  - Preceded by epithelial dysplasia

Crohn's Disease (Figure 11)

Clinical

- Incidence of 3–8/100,000, and is increasing
- M : F = 1 : 1, 1/3 present before age of 20, 1/5 present after age of 50



Fig. 11. Crohn's colitis.

- Etiology unknown, but strong genetic predisposition; 17–35 times of risk in siblings of patients
- Chronic or nocturnal diarrhea
- Intermittent right lower-quadrant intra-abdominal pain
- Anorexia, weight loss, and fever
- Recurrent oral aphthous ulcerations, perianal fissures, fistulae, or abscesses
- Extra-intestinal manifestations affecting the skin, eyes, and joints
- Complications include small bowel obstruction, malabsorption, salpingitis, fistulae, and perianal abscess formation

Macroscopic

- Inflammation anywhere from mouth to anus
- Most with lesions of small and large intestines:
  - Small intestine only (30–40%)
  - Both small and large intestines (40–50%)
  - Colorectum alone (15–25%)
  - Terminal ileum (90%)
- Colonoscopy:
  - Mucosal cobblestoning, aphthoid or longitudinal ulcers, and strictures
  - Normal intervening mucosa (skip lesions)
- Resected specimen:
  - Markedly thickened bowel wall with luminal narrowing
  - Mucosal cobblestoning, pseudopolyps
  - Fat rapping of the serosal surface
  - Fissures, fistulae, and mesenteric abscesses may also be seen

Microscopic

- Transmural inflammation with multiple lymphoid aggregates
- Noncaseating epithelioid granulomas (in 25–50%)
- Aphthoid and fissuring ulcers
- Focally intense cryptitis, crypt abscess
- Skipped, normal intervening mucosa
- Focal, mild crypt distortion and basal lymphoplasmacytic infiltrates
- Paneth cell metaplasia ±
- Neural hyperplasia, submucosal fibrosis, and hypertrophy of the muscularis mucosae

Differential Diagnosis

- Gastrointestinal Tuberculosis (TB):
  - Very rare
  - Granuloma with central caseous necrosis
  - Travel to or residential history in areas where abdominal TB is common
- Yersinia enterocolitica:
  - Necrotizing granulomas within the lymphoid follicle of the bowel wall and mesenteric lymph nodes
  - Positive *Yersinia* serology with rising antibody titer
- Ulcerative Colitis
  - See above
- Ischemic Enterocolitis:
  - No epithelioid granulomas
  - Lack transmural lymphoid aggregates, neural hyperplasia, or fissuring ulcer
  - May be difficult to distinguish a low-grade ischemic colitis in elderly patients from Crohn's; subsequent clinical course may provide better differentiation
- Infectious Colitis:
  - Most common cause of aphthous ulcers of the small and large intestine
  - Diffuse superficial neutrophilic infiltrates
  - Lack significant chronic inflammation
  - Absence of crypt distortion or basal lymphoplasmacytosis
  - No epithelioid granulomas
- Diverticular-Disease-Associated Segmental Colitis:
  - Commonly seen in sigmoid colon
  - Diverticula per colonoscopy
  - Histologic changes may be very similar to those of Crohn's
  - Foreign body type granulomas
- Solitary Rectal Ulcer Syndrome/Mucosal Prolapse Change:
  - Usually seen in the rectum and distal sigmoid
  - Polypoid, nodular, or mass-like lesion
  - Intramucosal smooth muscle proliferation on histology
  - Normal adjacent flat mucosa and proximal colon

Associated Conditions

- Crohn's Colitis-Associated Epithelial Dysplasia:
  - Similar to ulcerative colitis-associated epithelial dysplasia at slightly lower incidence
- Malignancy in Crohn's Disease:
  - 0.5% of prevalence in both small and large intestines
  - Most tumors occur in the colon

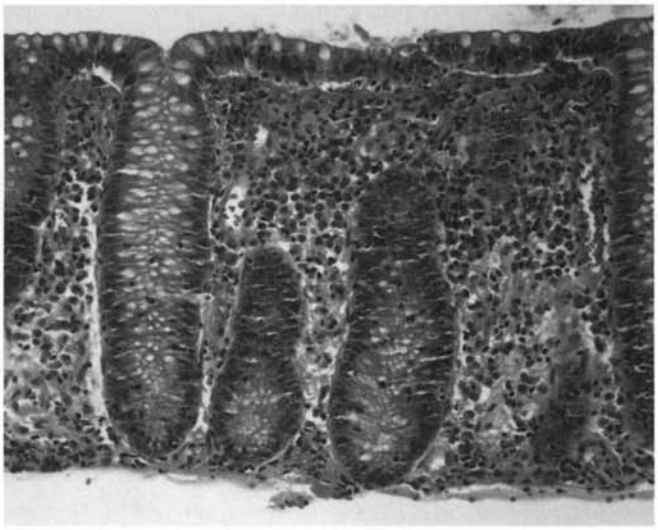


Fig. 12. Lymphocytic colitis.

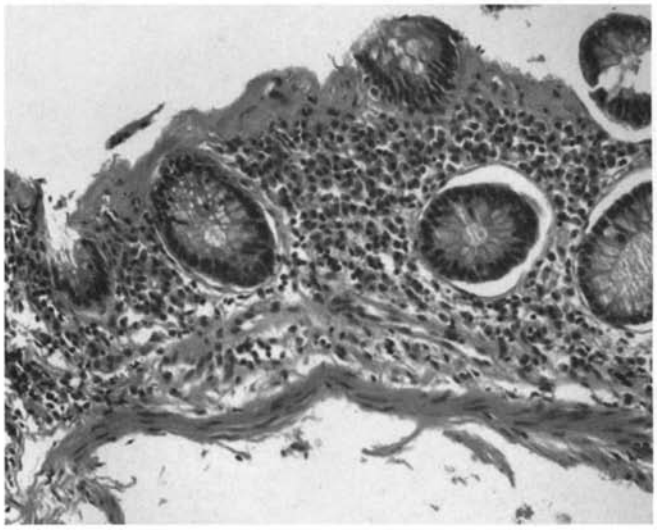


Fig. 13. Collagenous colitis (H & E).

- Adenocarcinoma is the most common type
- Metachronous or synchronous tumors may occur
- May be preceded by detectable epithelial dysplasia

Microscopic Colitis

Lymphocytic Colitis (Figure 12)

Clinical

- Affects all ages, M = F
- Unknown etiology
- Prolonged watery diarrhea
- Associated with autoimmune diseases in some patients (celiac sprue, arthritis, and thyroiditis)

Macroscopic

- Normal colonoscopic and radiographic examinations

Microscopic

- A marked increase of lymphocytes in the surface and crypt epithelium
- Absence of a thickened subepithelial collagen layer
- Cuboidal and flattened surface epithelium
- Chronic inflammation in the LP
- No crypt distortion
- Acute cryptitis may be seen

Collagenous Colitis (Figures 13,14)

Clinical

- Affects middle-aged and older women, F : M = 10 : 1
- Unknown causes
- Protracted watery diarrhea without systemic symptoms

Macroscopic

- Normal colonoscopic and radiographic examinations

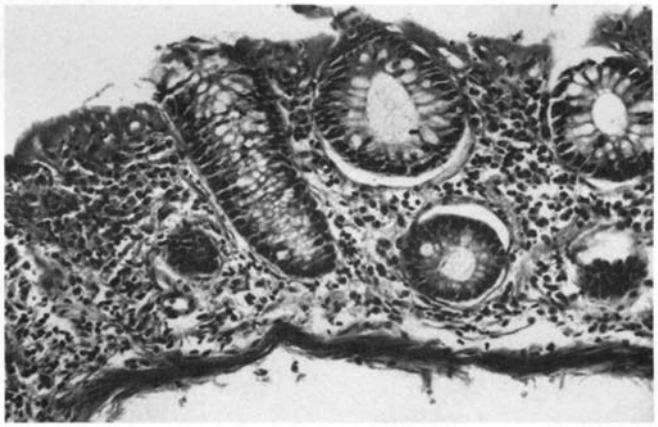


Fig. 14. Collagenous colitis (Trichrome).

Microscopic

- Proximal colon is more affected
- Thickened subepithelial collagen layer (usually >10 μm, Normal: 2–3 μm); best viewed by Masson trichrome stain
- Increased intraepithelial lymphocytes
- Chronic inflammation of the LP
- Surface epithelial damage
- May have active inflammation

Diversion Colitis (Figure 15)

Clinical

- In 90–100% of patients with a history of colostomy or ileostomy for various reasons, including inflammatory bowel disease (IBD)
- Related to the depletion of fecal short-chain-free fatty acids and/or luminal bacterial stasis
- Persistent symptom unless re-anastomosis takes place



Fig. 15. Diversion colitis.

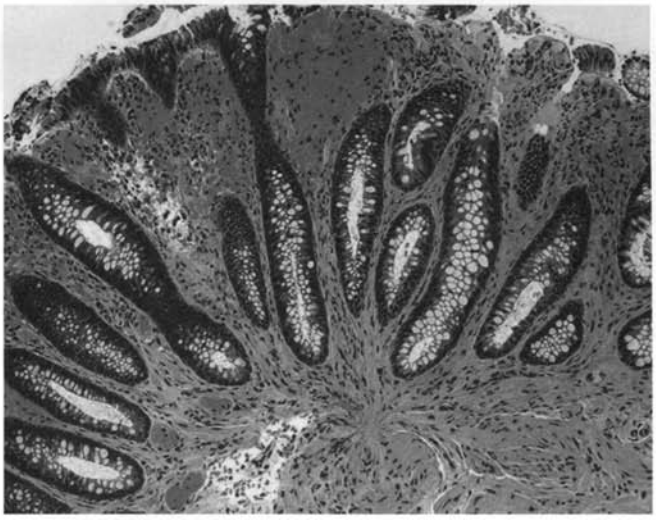


Fig. 16. Solitary rectal ulcer.

Macroscopic

- Mucosa erythema, friability, edema, and granularity, mimicking ulcerative colitis
- More severe in rectum than in the proximal colon

Microscopic

- Mild to moderate chronic inflammation with mild architectural change
- Cryptitis, crypt abscess, and erosion may be seen
- Prominent mucosal lymphoid hyperplasia
- Mucosal atrophy may be seen

Solitary Rectal Ulcer Syndrome (SRUS) (Figure 16)

Clinical

- Affects all age groups, but more common in the young
- Constipation, excessive straining, rectal pain, and mucus discharge

Macroscopic

- Affect anterior and anterolateral rectal wall
- Indurated, polypoid lesion, solitary or multiple
- Surface ulceration

Microscopic

- Thickened muscularis mucosae with intramucosal smooth muscle proliferation between the crypts
- Variable acute and chronic inflammation of the LP
- Surface erosion and inflammatory exudate
- Submucosa entrapment of crypts filled with mucin *(colitis cystica profunda)*

Differential Diagnosis

- Crohn's Disease:
  - See above
  - Clinical history
  - Abnormal proximal colonic biopsies
- Malignancy-Induced SRUS/Mucosal Prolapse:
  - SRUS-like changes in the mucosa overlying a malignant infiltrate located in the submucosa or muscularis propria due to primary tumor or metastasis
  - Tumor cells may be seen in the biopsy
  - Immunohistochemistry may be required to identify these rare tumor cells
  - Perirectal mass or rectal wall thickening on computed tomography
- Radiation Proctitis/Colitis:
  - See below

Radiation Proctitis/Colitis

Clinical

- History of radiation to pelvic or intraabdominal malignancies
- Most common in rectosigmoid
- Symptoms appear during or shortly after therapy; may even appear months or years later
- Acute phase:
  - Diarrhea, tenesmus, mucoid rectal discharge, and rectal bleeding
- Chronic phase/complications:
  - 10% of the cases
  - Tenesmus, mucoid rectal discharge, which may be bloody
  - Persistent decrease in stool caliber and constipation

Macroscopic

- Focal, limited to the immediate field of irradiation
- Variably dusky and edematous mucosa with a blurred vascular pattern
- Friability and ulceration with a high dose of radiation
- Multiple mucosal telangiectasis and luminal narrowing with fibrosis

Microscopic

- Acute changes:
  - Last for 1–2 months
  - Edematous LP with fibrinoid vascular necrosis
  - Reactive endothelial and epithelial cells
  - Excess of apoptosis in the basal crypts
  - Mucosal neutrophilic infiltration
- Late changes:
  - Mucosal atrophy with reduction of crypt epithelium
  - Crypt distortion, Paneth cell metaplasia, fibrosis, and smooth muscle proliferation
  - Dilated, telangiectatic blood vessels approaching the luminal surface

Diverticular Disease

Clinical

- Uncommon before age 40; approaching 50% by the 9th decade of life
- Most common in sigmoid in US; right-sided lesion more common in Asia
- Multifactorial pathogenesis including increased intraluminal pressure, colonic wall aging and motor dysfunction, and lack of dietary fiber
- Majority are asymptomatic
- Presents with bloating, excessive flatulence, and intermittent abdominal pain
- Fever is associated with inflamed diverticula (diverticulitis)

Macroscopic

- Two rows on either side of the colon between mesenteric and antimesenteric teniae
- <1 cm, lie within the pericolic fat, and especially the appendices epiploicae
- Markedly thickened colon wall
- Prominent mucosal ridges and intervening saccular dilatations
- Pericolic abscess formation is common

Microscopic

- Diverticula are lined by mucosa and submucosa and covered by pericolic connective tissue and serosa
- Hypertrophied MP at the neck of diverticulum
- In diverticulitis:
  - Neutrophilic infiltration of the crypts, LP, and surrounding pericolic fat
  - Prominent chronic inflammation and fibrosis
  - Foreign body giant cells

VASCULAR LESIONS

Acute Intestinal Ischemia

Clinical

- Occlusive Causes:
  - Arterial thrombosis and embolism:
    - Most common cause of acute small intestinal ischemia
    - Frequently superimposed on severe superior mesenteric artery (SMA) atherosclerosis
    - Sources of emboli include ischemic heart disease, spontaneous or procedure-related cholesterol emboli, and iatrogenic embolization by "Gelfoam"
  - Atherosclerosis:
    - Most common mesenteric vascular disease, but rarely the cause of acute ischemia by itself
    - Usual cause of chronic ischemia
  - Arteritis:
    - Usually as part of a systemic disorder
    - Examples include polyarteritis nodosa (PAN), rheumatoid arteritis, systemic lupus erythematosus (SLE), and Takayasu's disease
  - Small vessel disease:
    - Henoch-Schönlein purpura, leukocytoclastic vasculitis, and disseminated intravascular coagulation (DIC)
  - Mesenteric venous thrombosis:
    - Rare, less than 10% of the causes
    - Associated with portal hypertension, hypercoagulable state, abdominal surgery or trauma, and intra-abdominal sepsis
  - Mechanical obstruction:
    - Volvulus, strangulation, and intussusception

Table 1. Acute Ischemic Injury of the GI Tract

Stage of injury	*Gross*	*Histology*	*Prognosis*
Mucosal necrosis	Mucosal congestion and erythema	Disintegration of surface and crypt epithelium	Usually reversible
	Small shallow ulcers	Interstitial hemorrhage, edema, and neutrophilic infiltrate	
		Mucosal outline usually preserved	
Mural necrosis	Marked mucosal congestion, hemorrhage, and ulcers	Mucosal and submucosal necrosis and hemorrhage	Progress to transmural necrosis
	Serosal congestion	Eosinophilic necrosis of the inner smooth muscle layer	May heal with interruption of muscularis and
		Neutrophilic infiltrate	submucosal scar, which may lead to stricture
Transmural necrosis	Gangrenous, flaccid, dilated, and serosal fibrinous exudate	Smooth muscle necrosis with marked edema and neutrophilic infiltrate	Perforation
	May have perforation	Marked congestion involving subserosa	Surgery is always indicated; if massive, may not survive

  - Others:
    - Dissecting aneurysm involving SMA
    - Arteriopathies with intimal hypertrophy in systemic hypertension
    - Radiation injury or fibro-elastosis adjacent to carcinoid tumors
- ♦ Nonocclusive Causes:
  - Account for 25–50% of all cases
  - A consequence of vasoconstriction in response to decreased cardiac output, hypotension, hypovolemia, dehydration, or drugs (digitalis, cocaine), frequently with underlying arterial atherosclerosis

Macroscopic and Microscopic (Acute Intestinal Ischemia)

- ♦ *See* **Table 1**

Chronic Ischemic Injury

Clinical

- ♦ A consequence of acute mural infarct or chronic mesenteric insufficiency
- ♦ SMA atherosclerotic narrowing is the most common cause.
- ♦ Other causes include aortic aneurysm and congenital anomalies of SMA
- ♦ Usually manifests as abdominal pain
- ♦ Poor correlation with angiographic studies

Macroscopic

- ♦ Segmental chronic ulcers with excessive fibrosis and stricture

Microscopic

- ♦ Ulcer bed with inflamed granulation tissue, excessive fibrosis, hemosiderin-laden macrophages, and fibrous replacement of the muscle layers
- ♦ Regenerative epithelial hyperplasia at the margins
- ♦ Chronic inflammation at the periphery of the ulcer
- ♦ Mucosa away from the ulcers is usually normal

Differential Diagnosis

- ♦ Crohn's Disease:
  - Mucosal inflammation away from the ulcer
  - Dense, aggregated inflammation extends to the serosa
  - Presence of granulomas
- ♦ Drug-Induced Ulcers:
  - Morphologically very similar
  - History of medication
  - Lack of hypotensive and vascular diseases

Special Forms

Ischemic Colitis (Figure 17)

- ♦ More common in 6th and 7th decades
- ♦ Torsion or hernia strangulation are uncommon causes due to the location of the large intestine being primarily retroperitoneal



Fig. 17. Ischemic colitis.

- More prone to primary vascular causes of ischemia
- Inferior mesenteric artery (IMA) is less prone to embolization than the SMA
- Splenic flexure (watershed area) is the most common site of ischemia
- Acute fulminant disease with progression to transmural necrosis is rare
- Complete resolution of symptoms within 4 weeks in 50% of patients; 5–12% recurrence rate
- Chronic ischemia may lead to progressive stenosis and obstruction

Ischemic Enteritis

- SMA embolism is the most common cause (40–50%), followed by nonocclusive mesenteric ischemia and SMA thrombosis (5–10%), torsion or hernia strangulation
- Most common in elderly with underlying cardiovascular disease
- Frequently presents with an acute onset of abdominal pain

Angiodysplasia

Clinical

- Vast majority occurs in the right colon, occasionally in the small intestine
- Presents with chronic intestinal bleed, anemia, and weight loss
- Three types:
  - Type I: most common, >55 years of age, usually in the right colon
  - Type II: mean age of 29, usually in the stomach and proximal small bowel
  - Type III: with family history and punctate telangiectatic lesions in GI tract, oral mucosa, and skin

Macroscopic

- One or more sharply delineated red flat or slightly raised mucosa with scalloped edges and a prominent draining vein

Microscopic

- Dilated, tortuous submucosal veins with distended branches piercing through the MM, connecting with dilated capillaries between the crypts in the LP
- Ectatic small vessels may fill the entire mucosa
- surface mucosa erosion and acute and chronic inflammation

Vasculitis

Clinical

- Part of systemic vasculitis with GI tract involvement; or an isolated vasculitis affecting only the GI tract (serum autoantibodies frequently negative)
- The frequency of GI tract involvement by a systemic vasculitis:
  - 25% in polyarteritis nodosa
  - 25% in rheumatoid arthritis
  - 2% in SLE
  - Very high frequency in Henoch-Schönlein purpura
- Organ involvement varies among the types of vasculitis:
  - Polyarteritis often affects the small intestine
  - Phlebitis usually affects the colon

Macroscopic

- Solitary or multiple ulcers, mucosal or transmural necrosis
- Short or long segment of involvement
- Stricture may follow recovery of transmural ischemic necrosis
- Unremarkable mesenteric vessels grossly
- Histological examination is required to diagnose vasculitis

Microscopic

- All vasculitides, regardless of systemic or localized forms, demonstrate similar histological changes
- Specific types of vasculitis can only be distinguished by microscopic examinations **(Table 2)**

Scleroderma

Clinical

- A progressive systemic sclerosis involving multiple organs that include skin, cardiovascular system, and GI tract
- Affect medium and small arteries causing tissue damage
- Visceral involvement may precede or occur in the absence of skin changes

Table 2. Types of Vasculitis Affecting the GI Tract

Type of Vasculitis	*Type of Vessel Affected*	*Fibrinoid Necrosis*	*Thrombi*	*Histological Pattern*
Polyarteritis nodosa	Medium arteries, arterioles, large arteries	Very common, often segmental	Uncommon	Mixed acute and chronic necrotizing inflammation May be focal and segmental
Phlebitis	Medium veins, venules, large veins	Uncommon	Uncommon	Lymphocytic infiltrate of veins with sparing of artery
Churg-Strauss angiitis	Medium veins and arteries, arterioles and venules, large veins and arteries (less common)	Common	Uncommon	Extravascular granuloma with eosinophilic microabscess
Small-vessel vasculitis	Arterioles, venules	Common	Uncommon	Lymphocytic cuffing Numerous nuclear dust

- Esophagus is most frequently affected in the GI tract

Macroscopic

- Rigid, fibrotic, and often dilated intestinal tract
- Mucosal inflammation is often seen due to bacterial stasis
- Large diverticula have also been reported

Microscopic

- Atrophy of MP with disappearance and fibrous replacement of inner circular muscle coat
- Concentric intimal thickening, medial fibrosis, and fibrin deposition in medium- and small-sized arteries
- nonspecific mucosal chronic or active inflammation

APPENDIX

Inflammatory Lesions

Acute Appendicitis

Clinical

- Definitive causes unknown, but most likely secondary to luminal obstruction by fecalith, or less commonly, a gallstone, tumor, or worms, which results in ischemic injury
- Usually presents with acute onset of right lower quadrant pain with chills and fever

Macroscopic

- Enlarged and congested appendix with often purulent serosal surface
- Reddened mucosa on cut surface
- Often with luminal pus
- Gangrenous necrosis of the muscular wall in advanced cases
- With or without perforation

Microscopic

- Neutrophilic infiltrate of the mucosa and the muscularis propria; the latter is generally required the diagnosis
- Luminal inflammatory exudate
- Acute inflammation may be focal

Differential Diagnosis

- Yersinia Enterocolitis:
  - Prominent lymphoid aggregate with central zone necrotizing granuloma
- Parasitic Infection:
  - Luminal parasites of enterobius vermicularis, amebiasis, and schistosomiasis
- Crohn's Disease:
  - Lymphoplasmacytic transmural inflammation with lymphoid aggregates
  - Mural thickening
  - Occasional granulomas
- Ischemia:
  - May be involved in ischemic injury of the right colon

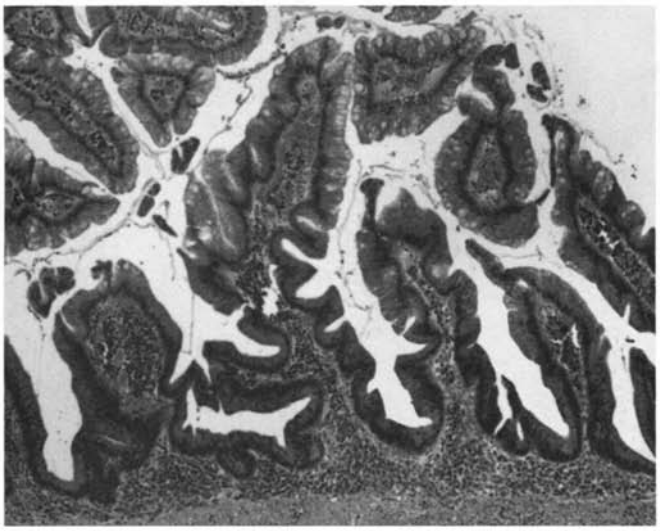


Fig. 18. Appendiceal villous adenoma.

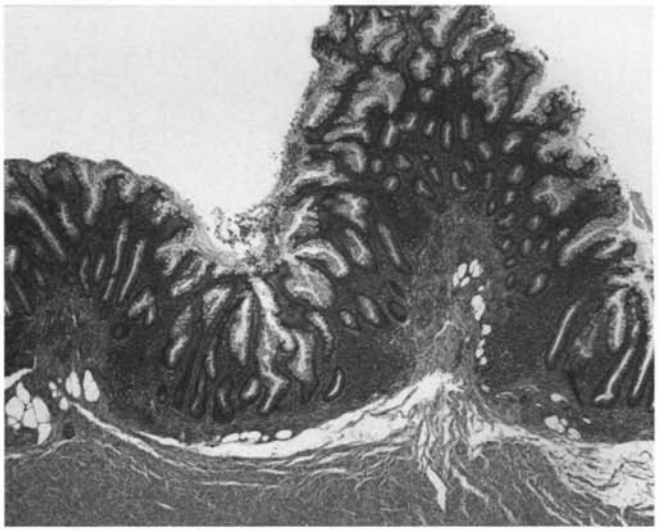


Fig. 19. Appendiceal hyperplastic polyp.

Tumors

Clinical

- Uncommon, with overall incidence of 1–2% of the resected appendiceal specimens
- Often an incidental finding after appendectomy for acute appendicitis
- Adenocarcinoma accounts for 0.3% of all GI tract tumors
- Rarely diagnosed pre- or intra-operatively
- May preceded by metastatic ovarian tumors (Krukenberg tumors)
- The terminology of mucocele and pseudomyxoma peritonei does not truly reflect the underlying pathology

Macroscopic

- Normal, inflamed, or enlarged appendix filled with mucus (mucocele)
- Mucus may be seen on appendiceal or peritoneal surface due to rupture
- May have identifiable tumor

Microscopic

- Adenoma (**Figure 18**):
  - Identical to the colonic counterpart
  - More often tubulovillous adenoma
- Hyperplastic polyps (**Figure 19**):
  - Identical to the colonic counterpart
- Mixed adenoma and hyperplastic polyp:
  - Identical to the colonic counterpart
- Adenocarcinoma:
  - Identical to the colonic counterpart
  - Often mucinous type
  - May be + for both CK7 and CK20
  - Malignant pseudomyxoma peritonei frequently occur

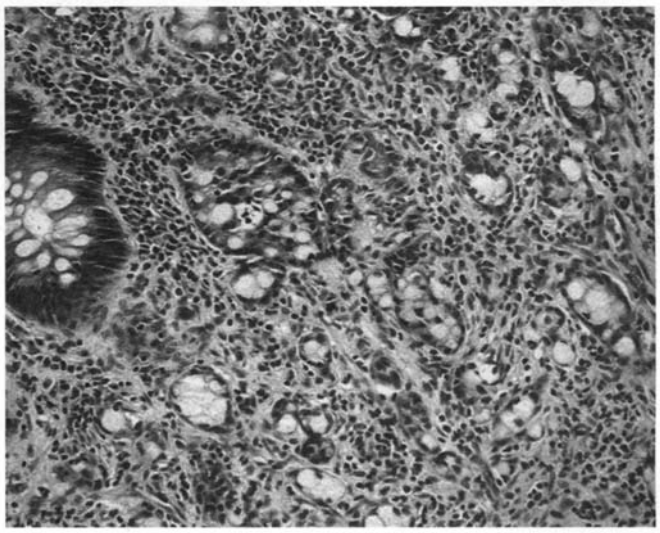


Fig. 20. Appendiceal goblet carcinoid.

- Soft tissue tumors:
  - Leiomyoma and neuroma (fibrous obliteration)
- Lymphoma:
  - Very rare
- Carcinoid tumors (**Figure 20**):
  - Occur near the appendiceal tip
  - Gross nodule or expansion of the appendiceal wall by neuroendocrine cells
  - Neuroendocrine cells in insular or tubular pattern into or through the appendiceal wall
  - Three variants:
  - Insular carcinoid: 5 year survival of 95%
  - Tubular carcinoid: 5 year survival of 95%
  - Goblet cell carcinoid: 5 year survival of 80%
  - Also see intestinal neoplasms (page 35-22)

INTESTINAL POLYPS

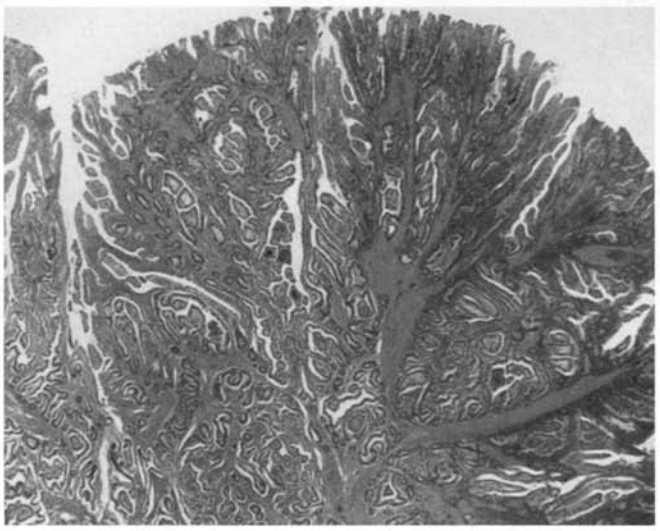


Fig. 21. Peutz-Jeghers polyp.

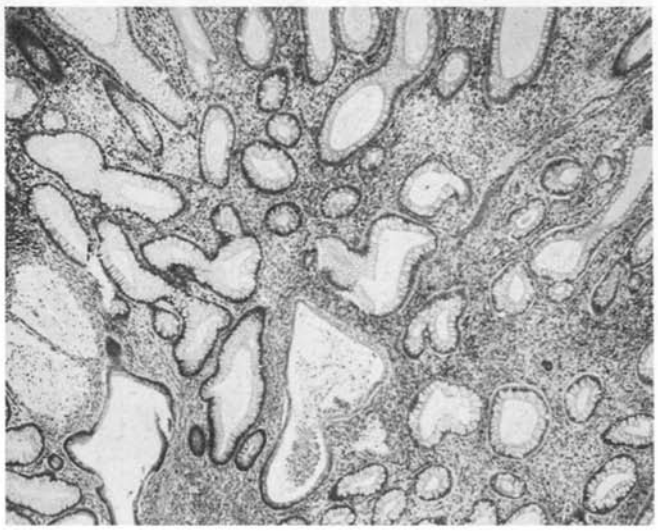


Fig. 22. Juvenile polyp.

Developmental Polyps

Hamartomatous Polyp, Peutz-Jeghers Type (Figure 21)

Clinical

- An autosomal dominant trait with variable penetrance
- Most common manifestation of Peutz-Jeghers syndrome
- Polyp itself has no or very low malignant potential, but epithelial dysplasia can occur
- Increased GI tract malignancy, 2–3% in western countries and up to 17% in Japanese series
- Increased extraintestinal benign and malignant tumors, especially ovarian sex cord tumors and adenoma malignum of the endocervix

Macroscopic

- GI tract polyps, usually <100
- Most common in small bowel, but can occur in the stomach and colon
- Large, lobulated mass, sessile or pedunculated; may cause obstruction and intussusception

Microscopic

- Mucosal components in fairly normal proportion, typical of their site of origin, arranged on a complex branching of MM
- May have surface erosion and active chronic inflammation
- Epithelial dysplasia may occur

Differential Diagnosis

- Juvenile Polyp (see below)

Hamartomatous Polyp, Juvenile Type (Figure 22)

Clinical

- Appear in 1st and 2nd decade of life with the peak incidence at 4–5 years of age
- As isolated cases or as juvenile polyposis (JP) syndrome
- JP is defined as:
  - More than 5 juvenile polyps of the colorectum and/or
  - Juvenile polyps throughout the GI tract and /or
  - Any number of juvenile polyps with a family history of JP
- An autosomal dominant trait with high penetrance in one-third of JP patients; new mutations may occur in non-familial cases
- Presents with small amount of bright red blood during defecation, or less frequently, severe bleed, anemia, intussusception, failure to thrive, and rectal prolapse
- Most lesions, if undetected, regress before adolescence
- High incidence of allergic symptoms such as asthma and hay fever
- Polyp itself has no increased malignant potential
- JP patients have shown an increased incidence of GI cancer (>10%)

Macroscopic

- Commonly occur in colorectum
- A few solitary (in nonpolyposis cases) or multiple (usually 50–200 in JP) pedunculated polyps
- 0.1–5 cm in size
- Smooth rounded surface, may be diffusely ulcerated, and numerous mucus-filled cysts on cut surface



Fig. 23. Inflammatory polyp.

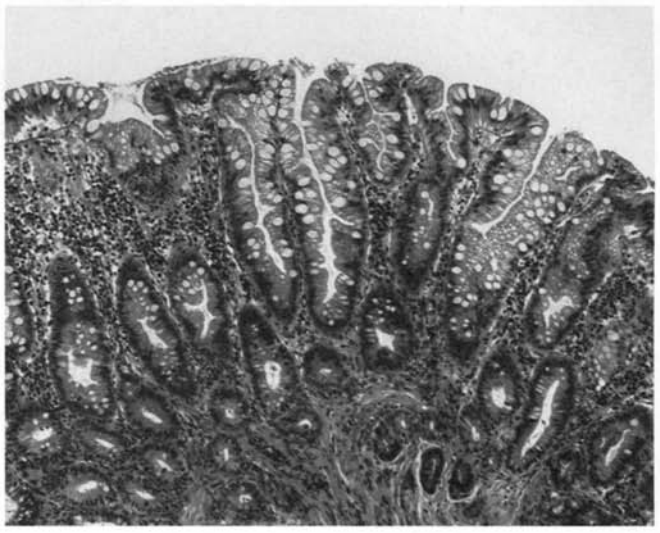


Fig. 24. Hyperplastic polyp.

Microscopic

- Expanded edematous LP permeated with inflammatory cells frequently including eosinophils
- Rare thin strips of smooth muscle of vascular origin in the LP, may become collagenous in older lesions
- Distorted or dilated crypts filled with mucin and inflammatory exudate, and lined by normal colonic-type goblet and absorptive cells with regenerative and hyperplastic features
- May contain adenomatous (dysplastic) foci or true adenomas of all grades of dysplasia

Differential Diagnosis

- Peutz-Jeghers Polyp (see above)
- Inflammatory Polyp (see below)

Inflammatory Pseudopolyp (Figure 23)

Clinical

- As a result of colonic inflammatory condition
- Commonly seen in ulcerative colitis and Crohn's disease
- Rare in infectious colitis
- Polyp itself has no intrinsic malignant potential

Macroscopic

- Multiple
- Polypoid mucosal projections with varying length of stalk
- Abnormal surrounding mucosa that may be diffusely ulcerated

Microscopic

- Polypoid mucosal lesions composed of distorted, dilated, and branched crypts surrounded by inflammatory granulation tissue that usually contains bundles of smooth muscle
- Cryptitis or crypt abscess is commonly seen:
  - Some crypts may show regenerative changes
  - Some may be composed entirely of granulation tissue
  - Some may be composed of relatively normal looking residual mucosa among an ulcer bed
- Adjacent or distant colonic mucosa shows underlying disease if associated with IBD

Differential Diagnosis

- Juvenile Polyp (see above)

Hyperplastic Polyp (HPP) (Figure 24)

Clinical

- The most common colonic polyps (10 times that of colonic adenomas)
- Caused by delayed surface epithelial loss and normal basal crypt production
- Asymptomatic; increasing incidence with age
- No clear association with IBD or neoplasms
- Generally not considered as a neoplastic polyp
- Possible link to cancer through serrated pathway in giant HPP or hyperplastic polyposis

Macroscopic

- Occur only in the colorectum and appendix
- Frequently multiple rounded to oval mucosal elevations or plaques
- 1–3 mm, but may rarely reach 1 cm

Microscopic

- Localized mucosal expansion (both crypts and LP)
- Mature columnar and goblet cells piling up along the crypt creating a serrated surface

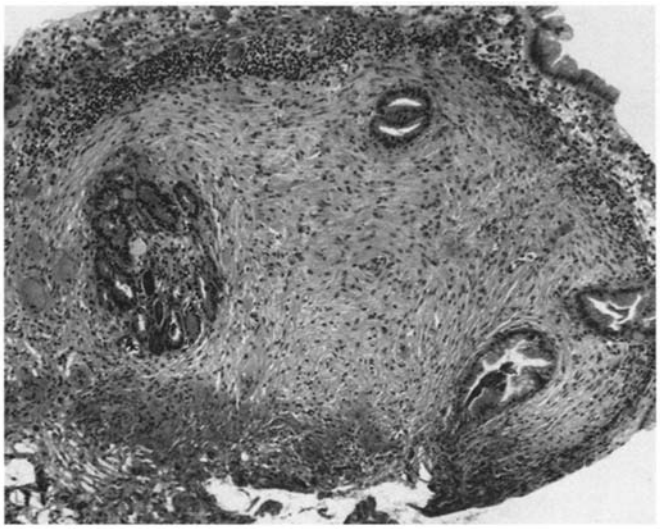


Fig. 25. Inflammatory fibrous polyp.

- Thickened subepithelial basement membrane
- Occasional crypt epithelial neutrophilic infiltration
- May occasionally superimpose on an adenoma (mixed adenoma and hyperplastic polyp)

Differential Diagnosis

- Sessile serrated adenoma/polyp
- See below

Inflammatory Fibrous Polyp (Figure 25)

- Mostly seen in ileum (following stomach), rare in the colon
- Episodic pain, intussusception, and bleed
- Pedunculated polyp with surface erosion
- Hypocellular fibrous and myxoid stroma with CD34(+) stromal cells
- Numerous small vessels with hyalinized wall
- Increased inflammatory cells, especially eosinophils

Neoplastic Polyps—Adenomas

Clinical

- Second most common GI tract polyps
- A precancerous lesion
- Affecting 30% or more individuals after 40 years of age
- Peak incidence in the 6th and 7th decade of life
- Mostly sporadic and are not associated with familiar adenomatous polyposis (FAP) syndrome
- Asymptomatic, discovered by colonoscopy examination
- Tumor of rectosigmoid location may be traumatized and bleed
- Multiple factors in adenoma to cancer progression:
  - Tumor size, number, and duration
  - Family history of colorectal cancer
  - Additional molecular alterations
- Overall 21–41% recurrent rate after polypectomy
- Incomplete removal is common in villous and sessile adenomas

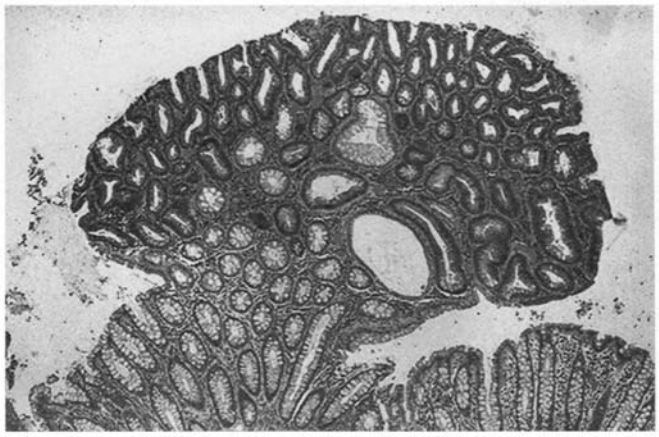


Fig. 26. Tubular adenoma.

Macroscopic

- Pedunculated, sessile, or carpet-like mucosal lesions with multi-lobulated, friable outer surface and homogeneous cut surface
- Tubular adenomas predominate and usually measure >1 cm
- Villous adenomas or tubulovillous adenomas are usually larger and sessile, and they are more likely to be located in the cecum and rectosigmoid

Microscopic

- Four types based on architecture:
  - Tubular adenoma: tube-like crypts **(Figure 26)**
  - Villous adenoma: finger-like crypts **(Figure 27)**
- Tubulovillous adenoma: both tubule and finger-like features
- Serrated adenoma: **(Figure 28)**
- Rare, <1%
- Nuclear features of adenoma but architectural features of hyperplastic polyp
- Tall columnar cells with enlarged, elongated, and hyperchromatic nuclei arranged in a pseudostratified pattern, usually along the basement membrane
- Intraepithelial mucus content may be decreased, increased, or of no change
- Dystrophic goblet cells, endocrine cells, Paneth cells, or even squamous cells
- Non-specific chronic inflammation and immature fibro-blasts in the LP
- Sharp transition between adenomas and adjacent normal crypts
- Pedunculated stalk usually contains submucosa

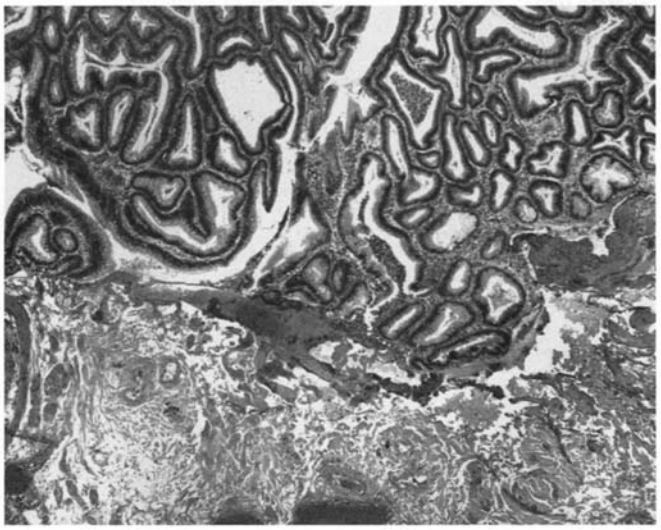


Fig. 27. Villous Adenoma.

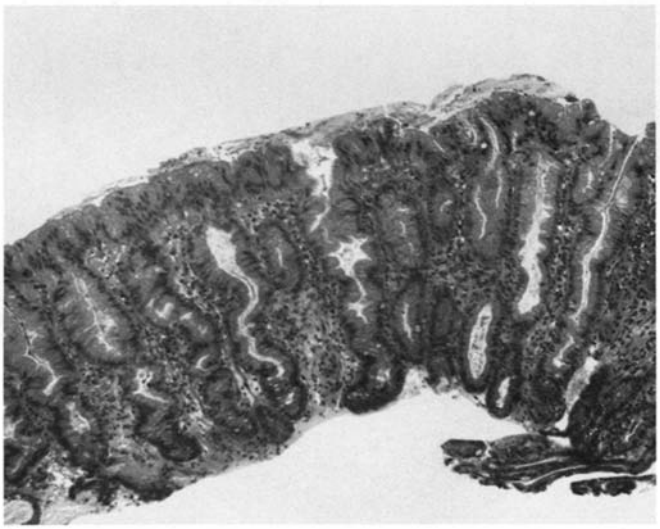


Fig. 28. Serrated adenoma.

Special Considerations

- Serrated Adenoma (SA):
  - See above
- Mixed Hyperplastic and Adenomatous Polyp:
  - Polyp with both adenomatous and hyperplastic components of variable proportion
- Sessile serrated adenoma/polyp (SSA/P) **(Figure 29)**:
  - Tendency to be right sided
  - Endoscopically poorly circumscribed, mimicking enlarged folds
  - Basal crypt dilatation with horizontal orientation
  - Prominent surface serration with inverted crypts
  - Nuclear dysplasia with mitosis in mid/upper crypts
  - Focal loss of hMHL-1 positivity

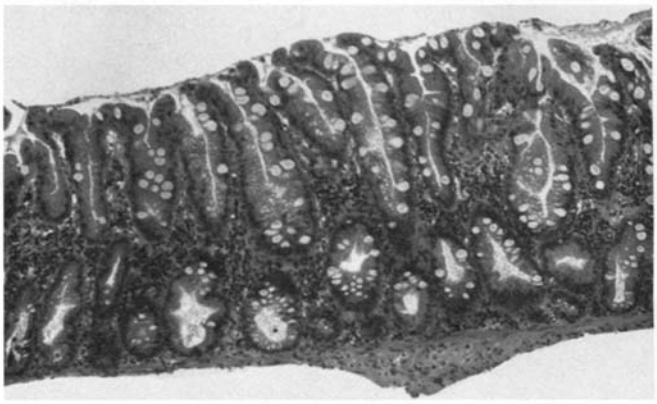


Fig. 29. Sessile serrated adenoma.

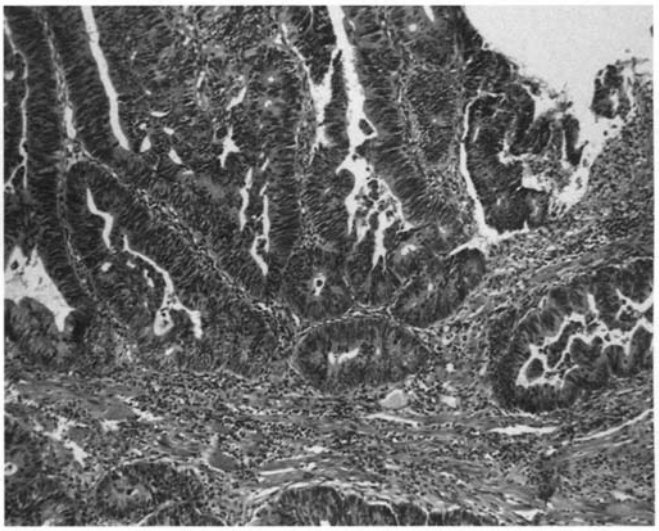


Fig. 30. Adenoma with high grade dysplasia.

- Dysplasia associated lesion or mass (DALM) in IBD:
  - Two morphologic subtypes
  - Adenoma-like: may be indistinguishable from sporadic adenoma
  - Non-adenoma like: large, sessile irregular masses/nodules/strictures
  - Flat dysplasia at the base of polyp stalk or surrounding mucosa
  - Histological evidence of IBD in adjacent mucosa
  - Younger age favors IBD-dysplasia
- Adenoma with High-Grade Dysplasia **(Figure 30)**:
  - Confined entirely within the LP
  - Complex and cribriform glands lined by enlarged, rounded nuclei containing vesicular nuclear chromatin and prominent nucleolus
  - Loss of nuclei polarity
  - Focal or multifocal in a large adenoma

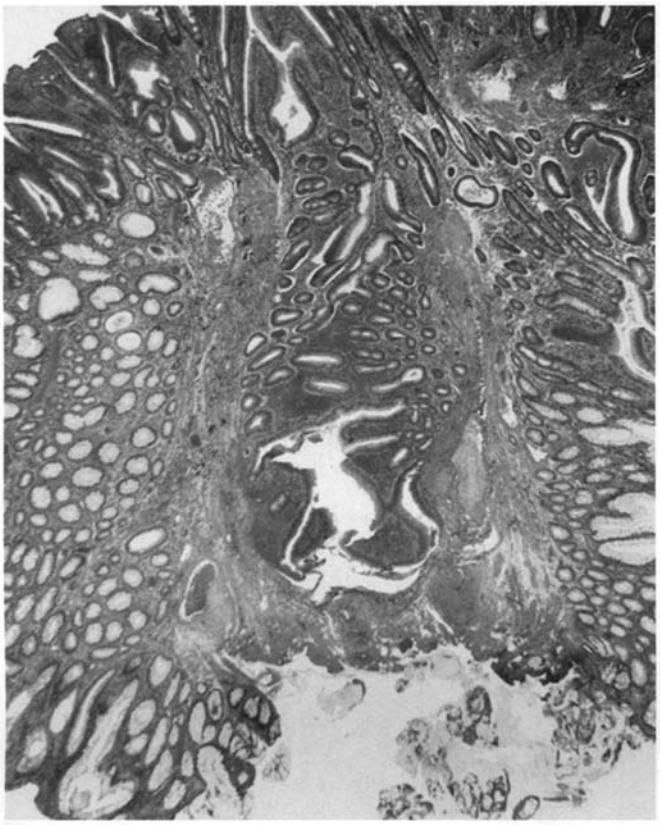


Fig. 31. Adenoma with pseudo invasion.



Fig. 32. Familial adenomatous polyposis (Gross).



Fig. 33. Ganglioneuroma.

- May overlay invasive adenocarcinoma if a mass lesion is present
- No metastatic potential
- Not to be confused with polypoid adenocarcinoma (see below)

♦ Adenoma with Pseudo invasion **(Figure 31)**:
- Misplaced adenomatous glands in the submucosa, therefore mimicking submucosal invasion by carcinoma
- Caused by ulceration and healing fibrosis due to trauma to the polyp; therefore, more common in the rectosigmoid
- Lack of cancer-like cytology and desmoplasia of the surrounding stroma
- Frequent submucosal hemosiderin pigment

♦ Polypoid Adenocarcinoma:
- Carcinoma entirely fills the polyp
- Often with intramucosal or submucosal invasion
- Has metastatic potential, and therefore cannot be cured by polypectomy

♦ Familiar Adenomatous Polyposis (FAP) **(Figure 32)**:
- One of the two best understood inherited predispositions to colorectal cancer
- Caused by germ-line mutations of the APC *(adenomatous polyposis coli)* gene, located on 5q21
- Overall incidence of 1 in every 10,000 births
- Two-thirds inherit the disease as an autosomal dominant trait, and one-third have no family history (represent new mutation)
- Average of onset of polyposis is 25 years of age
- Colonoscopy and molecular test detect patients at a much younger age
- Hundreds to thousands polyps (usu. <1 cm) evenly distributed throughout colorectum with occasional rectal sparing
- Adenocarcinoma inevitably develops in all patients if left unattended, usually during the 3rd decade of life
- Colonic carcinomas rarely exceeds 3 in numbers
- Early carcinomas are usually found in polyps >1 cm
- Histologically similar to those of sporadic tubular adenomas

- Microadenomas the flat mucosa are more characteristic of FAP
- Extracolonic manifestations:
  - Periampullary, jejunal, ileal, and rarely gastric adenomas with an overall incidence of upper GI tract carcinoma of 4.5%
  - Desmoid tumor (Gardener's syndrome)
  - Medulloblastoma (Turcot's syndrome)

Ganglioneuroma (Figure 33)

- Affect colon
- Mixture of S-100 (+) neurogenic fibers and ganglion cells
- Ganglioneuromatous polyposis is associated with multiple skin lipomas
- Diffuse intestinal ganglioneuromatosis is associated with MEN2b, von Recklinghausen's disease

MALIGNANT TUMORS

Adenocarcinoma

Clinical

- The most common malignant tumors of the large intestine; account for 98% of all large intestinal cancers
- Approximately 160,000 new cases and 60,000 deaths each year; account for 15% of all cancer-related death
- Peak incidence in 60–70 years of age; 20% occur under the age of 50
- If seen in younger patients, predispositions such as ulcerative colitis, FAP, or hereditary non-polyposis colorectal carcinoma (HNPCC) should be suspected
- 90–93% are sporadic; HNPCC- and FAP-associated carcinomas account for 5% and 1% respectively
- Rare in the small intestine, accounts for <1% of all GI tract malignancies
- Within the small bowel, the tumor favors the duodenum, including ampulla vater
- Most of the cancers are located in the rectosigmoid region. The incidence of right-sided tumor is rising
- Prognosis correlates best with tumor staging (see TMN classification of colorectal Adenocarcinoma)

Macroscopic

- Polypoid type:
  - Exophytic intraluminal mass
  - More common in the cecum and the right colon
  - Likely to arise in an adenoma
- Fungating type:
  - Polypoid type with prominent ulceration
- Ulcerative type:
  - Invades deeply into the colonic wall with ulcerative surface
- Infiltrative type:
  - Invades intestinal wall diffusely and often circumferentially, without forming a nodular mass

Microscopic

- Most are well to moderately differentiated gland-forming adenocarcinoma
- Well-differentiated type:
  - >75% of the tumor contains glands
- Moderately differentiated type:
  - >25% of the tumor contains solid sheets of tumor cells
- Poorly differentiated type:
  - >75% of the tumor is solid sheets

SPECIFIC VARIANTS

Mucinous Type

- >50% of the tumor appears mucinous

Colloid Type

- Large extracellular mucinous pools with floating tumor cells
- Tumor cells may not be abundant and often show signet ring features

Signet Ring Cell Type

- Solid sheets of tumor cells with prominent intracellular mucin
- Rare, and are often seen in IBD-associated cancers

Mixed Carcinoid-Adenocarcinoma Type

- Typically affects the appendix, but arises in the colon as well
- Mucinous tumor cells arranged in nests or trabeculae with admixed endocrine or Paneth cells
- Highly aggressive
- Often presents with intraabdominal metastasis such as bilateral ovaries

Small-Cell Carcinoma

- Rare, highly aggressive, favors right colon and rectum
- Mean age of 63
- Grossly indistinguishable from ordinary types
- Histologically similar to those of oat cell carcinoma of the lung

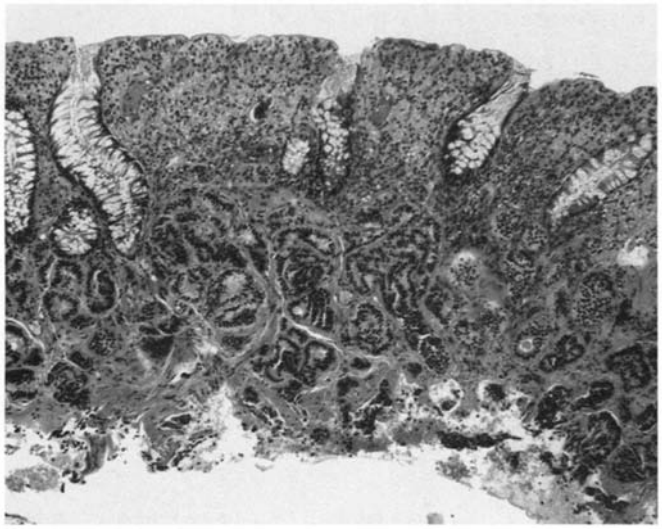


Fig. 34. Carcinoid tumor.

Adenosquamous Type

- Rare (0.05% of colorectal cancers)
- Poor prognosis
- Often occur in the rectosigmoid as fungating masses
- Histologically both adeno- and squamous carcinoma of varying proportion
- Differs from adenocarcinoma, containing occasional metaplastic squamous cells, seen in approximately 5% of the cases

Carcinoid Tumors (Figure 34)

Clinical

- Malignant, slow growing, locally infiltrative with the potential for metastasis
- 2% of all malignant GI tract tumors
- 50% in the small intestine, 34% in the appendix, and the remaining in the colorectum and stomach
- Carcinoid syndrome rare, mostly ileal location, with liver metastasis
- Neuroendocrine cell carcinoma applies for tumor with distant metastasis
- Metastatic potential is related to the site and the size of the tumor **(Table 3)**

Macroscopic

- Duodenal carcinoids:
  - Usually small polypoid lesions up to a few millimeters in size
  - Covered by intact mucosa
- Small intestinal carcinoids (other than duodenum):
  - Usually <2 cm
  - Indurated, yellowish nodules lie predominantly in the submucosa
  - Attenuated, rarely ulcerated overlying mucosa
  - Multiple tumors in up to 40% of the cases
  - When invading the MP and serosa, it often produces dense fibrosis, which causes kinking of the bowel wall and peritoneal adhesions
- Appendiceal carcinoids:
  - Usually small, <1 cm
  - Round nodule located in the tip, forming solid, bulbous swelling and causing luminal obliteration
  - Often discovered incidentally
  - Rarely, patients present with acute appendicitis or mucocele
- Colorectal carcinoids:
  - Vast majority occur in the rectum
  - Solitary, occasionally multiple, small, rubbery, polypoid nodules
  - Attenuated, sometimes friable overlying mucosa
  - Cecal and proximal colonic tumors tend to be large and bulky

Table 3. Metastatic Potential of Carcinoid Tumor of the GI Tract

Site and Size	*Metastasis*
Stomach	
<1.8 cm	15%
>5 cm	80%
Appendix	
<2 cm	Almost never
>2 cm	31%
Small bowel and colorectum	
<1 cm	22%
>1 cm	58%

Microscopic

- Duodenal carcinoids:
  - Trabecular or ribbon patterns with occasional rosette formation
  - May contain gastrin, somatostatin, substance P, serotonin, or glucagon, or may be multi-hormonal
- Carcinoids of the small intestine (excluding duodenum):
  - Monotonous appearing tumor cells
  - Centrally located nuclei, stippled nuclear chromatin, and small nucleoli
  - Indistinct cytoplasmic borders
  - Insular and/or trabecular anastomosing ribbon-like cords in a vascularized stroma
  - Many produce serotonin and other hormones

- Appendiceal carcinoids:
  - Similar to that of small intestinal carcinoids
  - Contain serotonin
  - Often show intimate association with nerve fibers
  - Often show diffuse muscularis invasion
  - Lymphatic permeation is also common
  - Malignancy is exceedingly rare, even with muscular and lymphatic invasion
  - Malignancy best correlates with tumor size
- Tubular carcinoids:
  - Almost entirely composed of tubular structures and trabeculae containing primarily endocrine cells with a few goblet cells
  - Diffusely infiltrative among the smooth muscles of the muscularis
  - Lack cytological atypia
  - Mitotically inactive (0–2 mitosis/10 hpf)
  - Share the same biological behavior with typical appendiceal carcinoids
- Goblet cell carcinoids:
  - Tubular structures containing variable number of goblet lining cells + on mucin stains
  - Diffusely infiltrative among the smooth muscles of the muscularis
  - Usually without cytological atypia
  - Mitosis in average 1/10 high power fields (HPF)
- Colorectal carcinoids:
  - Most tumors show trabecular with mixed alveolar patterns
  - Many are multi-hormonal by immunohistochemistry, but rarely are they functional
  - Therefore, carcinoid syndrome is rare

Immunohistochemistry

- + for chromogranin, synaptophysin, neuron-specific enolase (NSE), and cytokeratin
- Goblet carcinoids may also express carcinoembryonic antigen (CEA)

Differential Diagnosis

- Mixed carcinoid-adenocarcinoma:
  - Usually affects the appendix, and occasionally the colon and stomach
  - Mucous tumor cells arranged in nests, glands, trabeculae, or single signet ring cells with admixed endocrine or Paneth cells
  - Prominent cytological atypia with high mitotic count (average 10/10 HPF)
  - Scattered chromogranin reactivity
  - Highly aggressive
  - Often presents with intraabdominal metastasis such as bilateral ovaries

Gastrointestinsal Stromal Tumor (GIST)

Clinical

- Patients usually present during 4th and 7th decades of life
- Affect male and female equally
- 2/3 occur in the stomach, 25% in the small intestine, and small numbers in the rectosigmoid; very rarely seen in the proximal colon
- Typical presentation includes obstruction, intra-abdominal mass, bleeding, and weight loss

Macroscopic

- Usually single intramural mass
- Expands the wall, or in large tumors, outside the wall, with a narrow attachment to the muscularis propria
- Cut sections show circumscribed, expansile masses with flat, granular surface
- May contain hemorrhage, cystic changes or necrosis

Microscopic

- Spindle cell with elongated nuclei, often arranged in bundles with palisading reassembling those of either leiomyoma or schwannoma
- Some may also contain epithelioid cells that are usually rounded with abundant cytoplasm, admixed with spindle cells
- Stroma may be hyalinized, fibrotic, myxoid, or necrotic
- Evaluation for malignancy is difficult, often requires extensive sampling

Immunohistochemistry

- C-kit: ++++; CD34: +++ to ++++; S-100:±; smooth muscle actin (SMA):±, Cytokeratin±

Benign or Malignant

- Malignant potential of GIST is largely determined by the tumor location, the size, the presence or absence of tumor necrosis and invasion, and finally, mitotic activity
- **Table 4** may be helpful in making such distinction

Differential Diagnosis

- Leiomyoma:
  - Usually located in the esophagus
  - If occurs in the small and large intestine, often as a small submucosal polypoid mass
  - + for SMA, but – for C-kit, CD34, or S-100
- Schwannoma:
  - Almost always occurs in the stomach
  - Can be cystic, and usually associated with lymphoplasmacytic infiltrate
  - + for S-100, but – for SMA, C-kit, or CD34

Table 4. Gastrointestinal Stromal Tumor

Characteristics of tumor	*Likely benign*	*Likely malignant*
Location	Esophagus, 2/3 of stomach	Small and large intestines
Size	<3 cm (<5 cm in stomach)	>3 cm (>5 cm in stomach)
Invasion of mucosa or adjacent organ	No	Yes
Parenchymal necrosis (excluding surface erosion)	No	Yes
Mitotic figures	<5/50 HPF	>10/50 HPF

- Gastrointestinal autonomic nerve tumors (GANT):
  - Rare, have only been described in the stomach and small intestine
  - Ovoid tumor cells with cytoplasmic clearing, resembling epithelioid GIST
  - Usually + for synaptophysin and NSE, – for S-100, CD34, or C-kit
  - Criteria for malignancy are similar to those of GIST
- Mesenteric fibromatosis:
  - The bulk of the tumor is usually in the serosa or the mesentery
  - Often invades the muscularis
  - Spindle tumor cells, but less cellular than GIST
  - Lack nuclear pleomorphism
  - Stroma tends to be myxoid

Gastrointestinal Lymphoma

General Features

- Almost exclusively of non-Hodgkin's type
- Constitute 4–18% of all non-Hodgkin's lymphoma (NHL) and 1–2% of all GI tract malignancies
- May be secondarily involved by systemic non- Hodgkin's lymphoma
- Up to 40% arise as primary GI tract lymphoma, which is defined, as the main bulk of tumor is limited in the GI tract with or without the involvement of contiguous lymph nodes
- Usually arise as sporadic neoplasms (B cell MALTomas)
- Also occur in certain patient populations:
  - Sprue-associated lymphoma (T cell in origin)
  - Mediterranean lymphoma (alpha heavy chain disease)
  - HIV or organ transplantation associated lymphoma (B large cell lymphoma)
- Usually affects adults, with equal sex distribution
- May arise anywhere in the GI tract:
  - Stomach: 50–60%
  - Small intestine: 25–30%
  - Proximal colon: 10–15%
  - Distal colorectum: Up to 10%
- Any lymphoma may occur as a primary tumor of the GI tract
- Most, however, are distinct entities that do not arise in peripheral lymph nodes, and do not form a part of any current lymphoma classification, as is listed in **Table 5**
- Unlike nodal low-grade B cell lymphoma, low-grade mucosa-associated lymphoid tissue (MALT) lymphoma of the GI tract is usually confined to the site of origin at presentation; the prognosis is more favorable than the equivalent nodal disease

Table 5. Lymphomas of the GI Tract

B cell
Lymphomas of mucosa-associated lymphoid tissue (MALT)
Low-grade B cell lymphoma of MALT
High-grade B cell lymphoma of MALT with/without a low-grade component
Mantle cell lymphoma (lymphomatous polyposis)
Burkitt's or Burkitt's-like lymphoma
Other types (corresponding to peripheral lymph node equivalents)
T cell
Sprue-associated T cell lymphoma

Specific Types (also see Chapter 7)

B Cell Lymphoma of MALT

Clinical

- The majority arise in the small intestine of any part as a single lesion
- Colorectal involvement are distinctly rare
- More common in the elderly
- Presents with melena or obstruction

- Mesenteric lymph node involvement is common
- Extra-abdominal spread is unusual at presentation
- Prognosis is not as favorable for tumors arising in the lower GI tract

Macroscopic

- Most are grossly single lesions, although can be multifocal microscopically
- Poorly-defined, fleshy, thickened bowel wall with extensive mucosal ulceration
- Mesenteric lymph nodes may be enlarged

Microscopic

- Heavy intramucosal lymphoid infiltrate that usually forms the base of a mucosal ulceration
- Lymphoepithelial lesions
- Small to medium size lymphocytes with irregular nuclei and moderate amount of cytoplasm (centrocyte-like [CCL] cells) infiltrates around reactive, nonneoplastic follicles (Peyer's patch marginal zone), spreading diffusely into the surrounding mucosa
- Small number of transformed blasts and plasma cell differentiation are characteristic
- Tumor cells invade nonneoplastic follicles in several different ways:
  - Total replacement
  - Partial replacement
  - Striking and uniform blastic transformation
  - Plasma cell differentiation
- High-grade MALT lymphoma is more common, compared to gastric counterpart
- It is characterized by confluent clusters of transformed cells outside of the colonized follicles
- Small foci of tumor are often present at remote distances from the main tumor mass

Immunohistochemistry

- CD20+, CD5–, CD10–, CD43 usually+
- Monoclonal plasma cells

Mantel Cell Lymphoma (Lymphomatous Polyposis)

Clinical

- Affects patients >50 years of age
- Abdominal pain and melena
- Involves any part of the GI tract, but the most predominant mass is usually seen in the ileocecal region
- Tend to disseminate early to lymph nodes, liver, spleen, and bone marrow

Macroscopic

- Multiple fleshy mucosal polyps ranging from 0.5–2 cm, or even larger
- Mesenteric lymph nodes often involved

Microscopic

- Intramucosal lymphoid aggregates, single or multiple
- Entrapped, reactive follicular centers in the lymphomatous infiltrate
- Follicular centers may be entirely replaced
- Lymphomatous infiltrate selectively replaces the mantle zones

Immunohistochemistry

- CD5+, CD20+, CD10– CD43+, bcl-1+

Burkitt's and Burkitt-Like Lymphomas

Clinical

- Two forms:
  - Endemic Burkitt's lymphoma
  - Sporadic Burkitt's lymphoma
- Patients are usually young; present with abdominal pain and obstructive symptoms
- Epstein-Barr virus (EBV) genomes are found in all cases of endemic form, but in only 1/3 of the sporadic form
- t(8,14) in 80% of the cases

Macroscopic

- Favor ileocecal region
- Localized obstructing masses or huge masses involving long segments of intestine
- Mesenteric lymph node and retroperitoneal involvement are common

Microscopic

- Effacement of mucosa by sheets of monomorphic blasts interspersed with macrophages give a characteristic "starry sky" appearance
- The blasts are small, noncleaved cells with granular nuclear chromatin, 3–4 nucleoli, and a well-defined ring of deeply basophilic cytoplasm
- Lymphoepithelial lesions are rare

Immunohistochemistry

- CD10+

Sprue-Associated T Cell Lymphoma

Clinical

- Median age of 60, rare under the age of 30, with slight male predominance
- Most patients have a history of abdominal pain and weight loss for a few months or a few years
- Some patients have a remote history of malabsorption

- Not infrequently, patients present with an acute emergency with GI tract perforation, obstruction, and hemorrhage

Macroscopic

- Most common in the jejunum
- Frequently multiple, circumferential ulcers without forming large tumor masses
- Mesenteric lymph nodes are usually enlarged, due both to tumor involvement and to reactive changes

Microscopic

- Mucosal ulceration is common, with dense lymphocytic infiltration forming the base of the ulcer
- Adjacent, nonulcerated mucosa shows extensive villous atrophy with prominent intra-epithelial T lymphocytes
- Highly pleomorphic T lymphocytes with bizarre, multi-nucleated forms

Immunohistochemistry

- CD3+, CD20–

ANUS

Benign Lesions

Hemorrhoids (Figure 35)

- Cushions blood vessels, smooth muscle, and connective tissue normally present in the anal submucosa above dentate line on left lateral, right anterior, and right posterior
- Become engorged during defecation to protect anal canal
- Gradual loss of support with aging causing luminal bulging, prone to trauma and bleed
- Internal hemorrhoid is covered by rectal mucosa
- External hemorrhoid is covered by anal mucosa or perianal skin
- Large, dilated vessels with prominent mussel wall show congestion and thrombosis

Fissure

- Mostly seen in the posterior midline of the canal below dentate line
- An elongated, triangular ulcer of anal canal due to traumatic tearing
- Histologically non-specific inflammation, granulation tissue, and fibrosis

Fistula

- Result of chronic phase of acute suppurative inflammation of anal duct
- Four types: Intersphincteric; Transsphincteric; Suprasphincteric; and Extrasphincteric
- Lined by granulation tissue and non-specific acute and chronic inflammation
- Giant cells of foreign body type are common
- Differential Dx includes Crohn's disease and carcinoma

Tumors of Anal Region

Condyloma Acuminatum (Figure 36)

Clinical

- Risk factor:
  - HPV infection (HPV 6, 11, 16, 18)
  - Immunosuppression, HIV, homosexuality
  - Genital cancers, irradiation

Macroscopic

- Small warty lesion, often multiple

Microscopic

- Acanthotic squamous papillary hyperplasia
- Elongation of rete ridges
- Maintain cellular polarity
- 1–3 layers of basal cells
- Surface koilocytic changes

Anal Intraepithelial Neoplasia (AIN) (Figure 37)

- Complication of condyloma following recurrence
- Rare as de novo lesion
- Two grades:
  - Low-grade AIN:
    - Dysplastic cells in lower 1/3
    - Maintain cellular maturation
  - High-grade AIN:
    - Dysplastic cells extend to the surface
    - Loss of polarity and maturation

Giant Condyloma Acuminatum (Figure 38)

- Synonymous to verrucous squamous carcinoma
- >2 cm, often single lesion
- Minimal cytologic dysplasia
- Downward growth with broad pushing and infiltrating islands
- Locally recurrent but do not metastasize

Squamous cell Carcinoma (Figure 39)

Clinical

- Accounts for 90–95% of anal region tumors
- Risk factors: Crohn's disease, fistula, and HPV infection

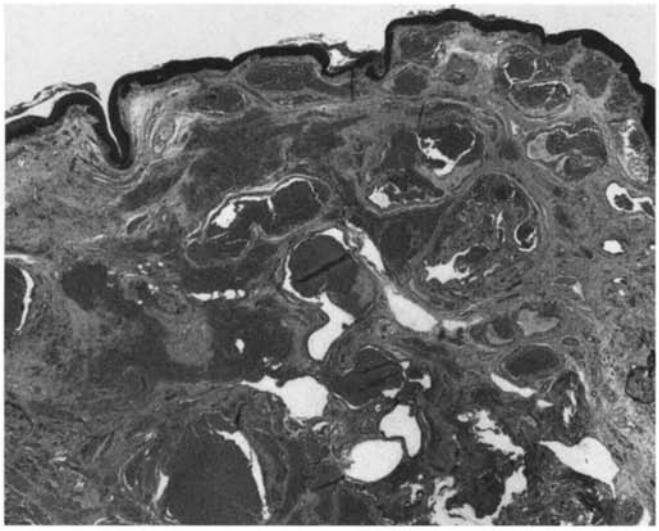


Fig. 35. Hemorrhoid.

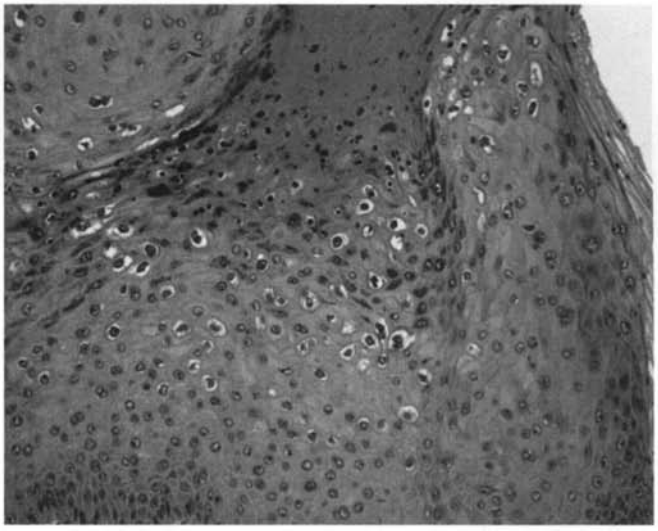


Fig. 37. Low-grade anal intraepithelial neoplasia (AIN).



Fig. 36. Condyloma acuminatum.

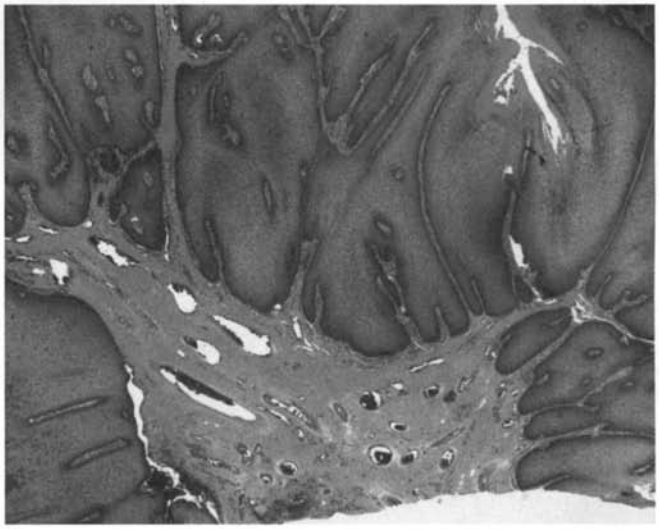


Fig. 38. Giant condyloma.

- F : M=2 : 1 in tumors above dentate line (anal transitional zone, or pectinate)
- F : M=1 : 4 in tumors beneath dentate line (pecten, and perianal skin)

Macroscopic

- Ulcer with raised and everted edge
- Rarely polypoid

Microscopic

- Usual type:
  - 3/4 are moderately to poorly differentiated, typical squamous cell carcinoma
  - Koilocytic (HPV) changes are common
- Basaloid (Cloacogenic) type **(Figure 40)**:
  - Accounts for 1/3 of tumors of anal transitional zone (anal canal)
  - Arise from cloaca
  - Islands of basaloid cells with peripheral palisading and desmoplasia
  - High mitosis with atypical forms
  - May mimic small cell carcinoma (see below)
- Spindle cell type:
  - Rare
  - May be confused with melanoma
  - Cytokeratin positive

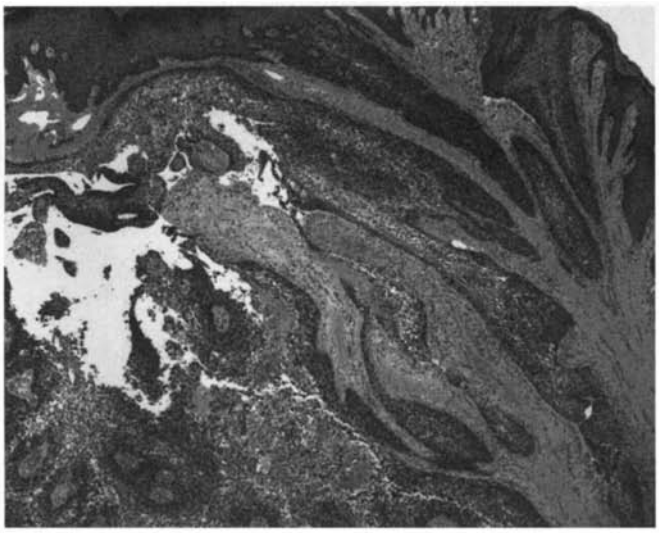


Fig. 39. Squamous cell carcinoma.

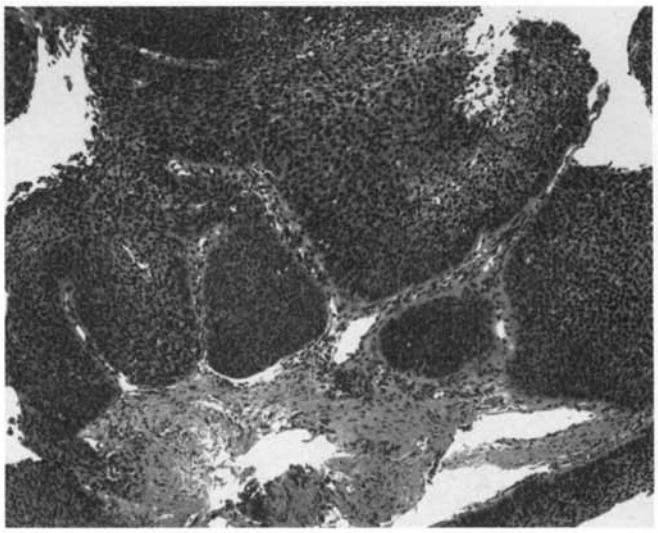


Fig. 40. Cloacogenic carcinoma.

Adenocarcinoma of Anal Duct/Gland

- Rare, direct invasion from rectal carcinoma is more common
- Two types:
  - Intramural type: Haphazard small tumor ducts grow deeply in the muscular wall
  - No surface lesion until late stage
- Low-grade mucinous carcinoma:
  - Present as anal mass with pain and bleed
  - Large, colloid-filled cysts with low grade mucinous lining cells
  - Frequently seen in Crohn's disease, grow around fistular tract

Small Cell Carcinoma

- Arise from the endocrine cells in the anal transitional zone
- Very aggressive, disseminate widely, with poor prognosis
- May mimic basaloid carcinoma
- Synaptophysin and chromogranin positive

Melanoma

- Arise from transitional zone above dentate line
- Present in 3rd to 8th decades of life with pain, bleeding, and a mass
- Sun exposure not a risk factor
- 2/3 of lesions are polypoid, with visible pigment
- Ave. size: 4 cm
- May be an incidental finding of hemorrhoid
- Mostly epithelioid and spindle cell types
- Junctional activity may be hard to find
- Positive for S-100, HMB-45, and Melan-A

TNM CLASSIFICATION OF COLORECTAL ADENOCARCINOMA (2002 REVISION)

T: Primary Tumor

- Tis: carcinoma in situ
- T1: lamina propria or submucosal invasion
- T2: muscularis propria invasion
- T3: subserosa or pericolic tissue invasion (mesentery in small bowel)
- T4: adjacent organ invasion and/or perforates visceral peritoneum

N: Regional lymph nodes

- N0: no nodal metastasis
- N1: 1–3 positive nodes
- N2: ≥4 positive nodes

M: Distant metastasis

- M0: no distant metastasis
- M1: distant metastasis

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36

Pancreas

N. Volkan Adsay, MD and Olca Basturk, MD

CONTENTS

I. Congenital Anomalies 36-2
- Annular Pancreas 36-2
- Heterotopic Pancreas 36-2
- Pancreas Divisum 36-2
- Congenital Cysts 36-2

II. Pancreas In Metabolic and Other Medical Disorders 36-2
- Nesidioblastosis 36-2
- Diabetes Mellitus 36-2
- Cystic Fibrosis 36-2

III. Inflammatory Conditions 36-3
- Acute Pancreatitis 36-3
- Chronic Pancreatitis 36-3
- Pseudocysts 36-4
- Infections 36-5

IV. Neoplasia 36-5
- Ductal Neoplasia 36-5
  - Invasive Ductal Carcinoma 36-5
  - Rare Carcinomas of Presumed Ductal Origin 36-7
    - Osteoclastic Giant-Cell Carcinoma 36-7
    - Colloid Carcinoma 36-8
    - Medullary Carcinoma 36-8
  - Pre-Invasive Ductal Neoplasia 36-9
    - Mucinous Cystic Neoplasms 36-9
    - Intraductal Papillary Mucinous Neoplasms 36-11
    - Intraductal Oncocytic Papillary Neoplasms 36-12
    - Pancreatic Intraepithelial Neoplasia 36-13
  - Serous Cystic Tumors 36-13
- Acinar Cell Carcinoma 36-14
- Endocrine Neoplasia 36-15
- Solid-Pseudopapillary Neoplasm 36-17
- Pancreatoblastoma 36-18
- Mixed Carcinomas 36-18
- Miscellaneous Cystic Lesions 36-18
- Miscellaneous Tumors 36-19
  - Secondary 36-19
  - Mesenchymal 36-19
  - Hematopoietic 36-19

V. Surgical Pathology Report 36-19

VI. TNM Classification of Pancreatic Tumors 36-20

VII. Suggested Reading 36-20

CONGENITAL ANOMALIES

Annular Pancreas

Clinical

- Very rare embryologic abnormality
- Pancreatic parenchyma encircles the duodenum
- Main pancreatic duct follows a different course than usual
- Some associated with Down syndrome or other congenital conditions

Microscopic

- Irregularly shaped islets composed of pancreatic-polypeptide (PP) cells (consistent with ventral bud origin)
- May be associated with pancreatitis

Heterotopic Pancreas

Clinical

- Occurs in a variety of organs; most common in gastrointestinal and biliary tracts
- Most are incidental
- May form macroscopic nodules
- May rarely show pancreatic pathology (pancreatitis, pancreatic neoplasia), or local complications such as ulceration and hemorrhage

Microscopic

- All or some components of the pancreas (acini, ducts or islets)

Differential Diagnosis

- Metaplasia:
  - Microscopic, incidental
  - Usually, acini only

Pancreas Divisum

- Failed fusion of the dorsal and ventral ducts in embryologic life
- "Division" of drainage between the anterosuperior and posteroinferior head
- Usually clinically inconsequential
- Some patients develop pancreatitis, usually dorsally
- Diagnosis is radiologic; pathologic documentation is difficult, if not impossible

Congenital Cysts

- Intestinal duplication may present as a cystic lesion
- Foregut cysts (some with ciliated/respiratory type epithelia)
- "Fibrocystic" type changes may occur in a variety of congenital syndromes

PANCREAS IN METABOLIC AND OTHER MEDICAL DISORDERS

Nesidioblastosis

- Persistent hyperinsulinemic hypoglycemia in infants born to diabetic mothers
- Presumably caused by the withdrawal of the in-utero suppression of islets by excessive maternal glucose, followed by over-compensation of the islets post-natally

Microscopic

- Many islets are large, typically measuring up to several millimeters
- Beta cells are disproportionally higher in number
- Clinicopathologic correlation is necessary; no good criteria for "hyperplastic" versus normal islet

Diabetes Mellitus

- No identifiable changes in most cases
- Subtle alterations in the *islets* of some patients including:
  - Altered number or size (no established criteria)
  - Mild fibrosis
  - Amyloid deposition (of "amyloid islet" type) **(Figure 1)**
  - Mild leukocytic infiltrates

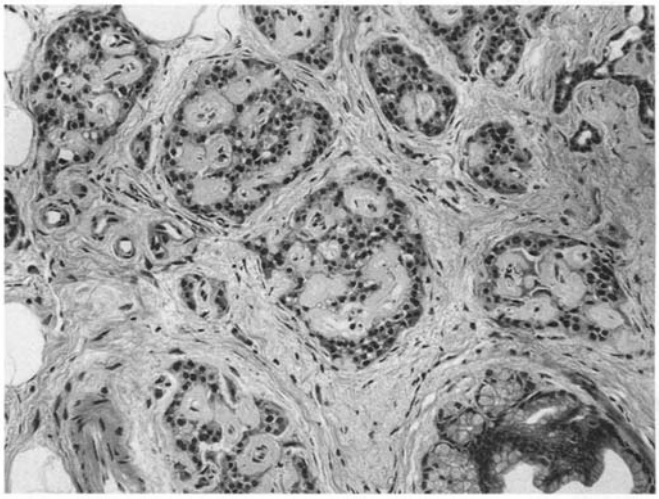


Fig. 1. Amyloid deposition in the islets of Langerhans.

Cystic Fibrosis

- Pancreatic involvement with "fibrocystic" appearance in 80–90%

- Hyper-viscous mucus precipitates in the ducts resulting in ductectasia
- Obstruction-related changes including acinar atrophy and replacement of atrophic lobules by interstitial fibrosis

INFLAMMATORY CONDITIONS

Acute Pancreatitis

Clinical

- Most cases related to gallstone disease or alcohol abuse
- Pain, fever, leucocytosis
- Increased serum enzyme levels (especially amylase)
- Variety of other metabolic complications
- Local anatomic complications such as pseudocysts (*see* below), abscesses, hemorrhage or thrombi

Pathologic

- Findings range from edema to full-blown necrosis or massive hemorrhage
- Fat necrosis **(Figure 2)**:
  - Chalky white-yellow areas grossly
  - Fragmented adipocytes with saponification and/or calcification, and a rim of neutrophils
- Subtle changes in the pancreatic parenchyma:
  - Acini with attenuated cells, lumen formation (tubular complexes) and inspissated secretions
  - Ducts and islets relatively well preserved



Fig. 2. Acute pancreatitis with fat necrosis. There is a rim of neutrophils around the necrotic focus.

Chronic Pancreatitis

Clinical

- Most areas related to alcohol abuse, obstruction (lithiasis or tumors), or other chemical/metabolic factors (hyper calcemia)
- Abdominal pain

Macroscopic

- Fibrosis and effacement of pancreatic lobular architecture
- Calcifications and intraluminal stones in some cases

Microscopic

- Ductal dilatation with eosinophilic mucoprotein plugs (with/without calcifications) **(Figure 3)**
- Remaining small ductules may appear pseudo-infiltrative
- Acinar dilatation and atrophy
- Interstitial fibrosis with variable cellularity
- Remaining islets prominent; may appear pseudo-infiltrative or form micronodules **(Figure 4)**
- Neural hyperplasia, some admixed with islets
- Perineurial cells may become prominent
- Thickening of the walls of medium-sized vessels

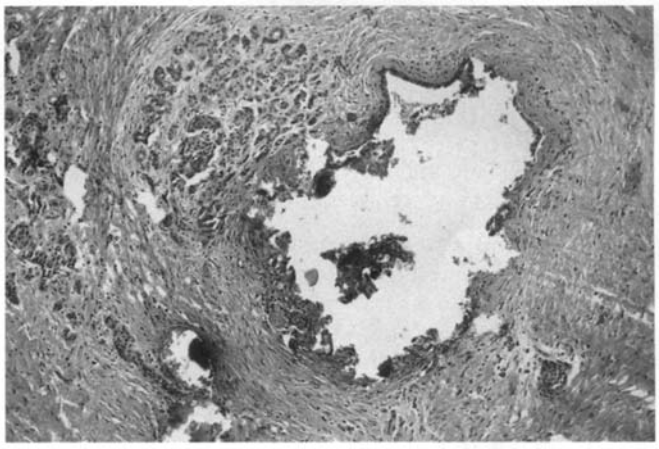


Fig. 3. Chronic pancreatitis (acinar atrophy and interstitial fibrosis) associated with lithiasis represented in this section as calcified intraluminal material.

Differential Diagnosis

- Ductal carcinoma:
  - Irregularities in the number, spacing, distribution and contours of the ducts
  - In some cases: Pale, foamy, microvesicular cytoplasm, and a dense chromophilic, apical condensation
  - Cytologic atypia with nuclear enlargement and contour irregularities

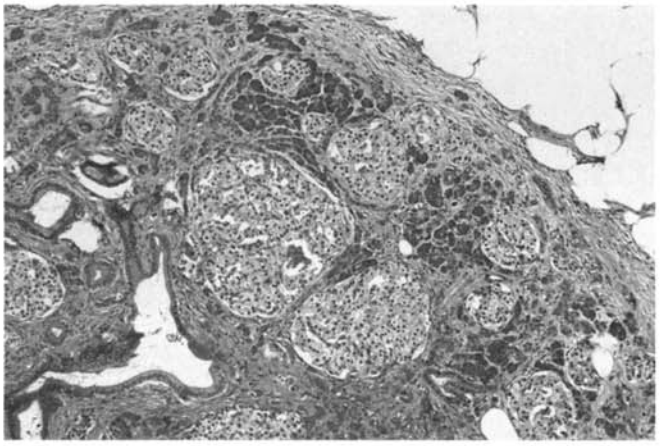


Fig. 4. "Hyperplastic islets". Islets of Langerhans become prominent or appear proliferative in some pathologic conditions of the pancreas, in particular chronic pancreatitis.

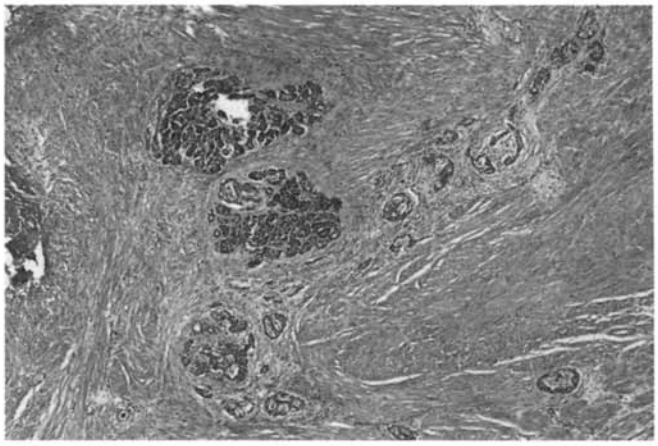


Fig. 5. Paraduodenal pancreatitis. Myoadenomatosis type changes, which are often associated with accessory duct abnormalities, may form a pseudotumor that can be mistaken clinically as cancer.

- Ducts in abnormal locations: Perineurial, intravascular, and in adipose tissue (naked ducts without associated islets or acini)

Autoimmune Pancreatitis

Synonyms

- Duct-centric, lymphoplasmacytic sclerosing pancreatitis

Clinical

- Typically seen in 4–6th decade
- Some (but not all) associated with autoimmune conditions
- Some show "inflammatory fibrosclerosis" (Riedel, orbital pseudotumor, retroperitoneal fibrosis etc.)
- High IgG4 levels
- Often responds well to steroid administration

Macroscopic

- Fibrosis and effacement of pancreatic lobular architecture
- Scarring; adhesions to adjacent organs

Microscopic

- Duct-centric inflammation with predominantly lymphoplasmacytic cells; expansion of periductal fibrous tissue containing numerous inflammatory cells
- Periphlebitis common; frank vasculitis may be seen (not common)
- Interstitial fibroblastic proliferation with storiform architecture ("inflammatory pseudotumor"–like)

Paraduodenal Pancreatitis

Clinical

- Chronic pancreatitis due to "anatomic" or functional variations of the ducts and how they adjoin the duodenum
- Alcohol abuse is a common co-factor
- Accessory duct and minor papilla abnormalities are suspected in some (paraduodenal pancreatitis)
- Some have been referred to as groove pancreatitis

Macroscopic

- Often in the region of the minor papilla
- Scarring of duodenal wall and/or distal common bile duct and/or the "groove" between the duodenum, CBD and pancreas
- Trabeculation of duodenal musculature with occasional cysts
- Paraduodenal wall cyst mimicking intestinal duplication may occur

Microscopic

- Lobules of acini surrounded by myo-fibroblastic cells of variable cellularity ("myoadenomatosis," **Figure 5**)
- Brunner's gland hyperplasia in duodenal wall
- Small cystic spaces lined by cellular stroma
- Extravasated (stromal) mucoprotein plugs surrounded by eosinophils or multinucleated giant cells
- Prominence of nerve bundles mimicking traumatic neuroma

Pseudocysts

Clinical

- Complication of pancreatitis
- Most frequently seen in alcoholic males
- Most common cystic lesion of the pancreatic region (60–70%), but rarely sampled for pathologic examination
- Occurs from post-necrotic resorption of peri-pancreatic fat necrosis
- 1–15 cm unilocular cyst, filled with necrotic material/fluid

- Peri- pancreatic location
- Typically either watched or treated by drainage

Macroscopic

- Fragmented cyst material (subsequent to drainage)
- Complete cystectomy typically not performed

Microscopic

- Depends on the stage of the process
- No epithelial lining by definition
- The wall is dense fibrous tissue with various degrees of granulation type changes
- The lumen contains necrotic adipose tissue, precipitated acinar secretions, mucoprotein plugs

Differential Diagnosis

- Mucinous cystic neoplasm:
  - Mucinous epithelial lining
  - Ovarian-like stroma with more wavy and layered appearance (compared to haphazard cellularity of fibroblastic reaction in pseudocysts)
- Other cystic lesions:
  - Epithelial lining or specific characteristic features

Infections

- Bacterial, fungal or parasitic infections may involve the pancreas but none has any particular affinity for this organ

NEOPLASIA

Ductal Neoplasia

INVASIVE DUCTAL CARCINOMA

Synonyms

- Pancreatobiliary; scirrhous; tubular; ductal adenocarcinoma

Clinical

- >85% of all pancreatic tumors
- More common in developed countries; fourth leading cause of cancer deaths in the US
- M/F = 1.5/1; African American/Caucasian = 2/1; mean age: 63; very uncommon under the age of 40
- Proposed risk factors include smoking and chronic pancreatitis (especially hereditary pancreatitis); a few are familial; some associated with familial atypical mole/melanoma (FAMM) syndrome (p16 related)
- Common symptoms: Abdominal or back pain, weight loss, and jaundice
- >70% occur in the head
- Some patients develop diabetes mellitus
- 80% are deemed "unresectable" due to early spread (to mesenteric vessels/retroperitoneum, liver or peritoneum)
- Median survival: 4 months if untreated, 6 months if unresectable but treated with chemo/radiotherapy, and 12 months if resected; 5-year survival = <5%; very few patients are alive beyond 7 years
- Almost all develop metastasis (mostly to liver or peritoneum)

Macroscopic

- "Scirrhous" pattern: Firm, white-gray or yellow mass with ill-defined boders **(Figure 6)**

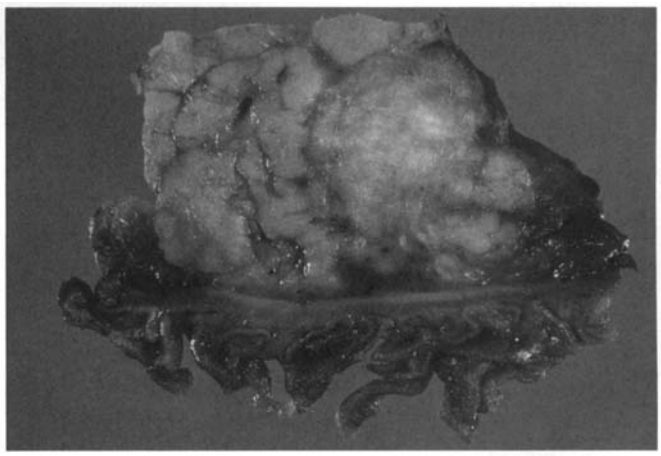


Fig. 6. Ductal adenocarcinoma is grossly a scirrhous carcinoma, characterized by firm, white mass with ill-defined, irregular borders.

- Obstruction of the ducts (in particular, the common bile duct) is typical
- May ulcerate into the duodenum
- Typical size: 3 cm; the tumor is widely disseminated or fatal by the time it reaches 6–7 cm

Microscopic

- Infiltrating tubular units (often widely scattered with open luminae), cords or individual cells **(Figure 7)**
- Abundant desmoplastic stroma of variable cellularity
- Cuboidal to columnar cells with variable amount of mucin and nuclear atypia
- Perineurial invasion in >60% of the cases **(Figure 8)**

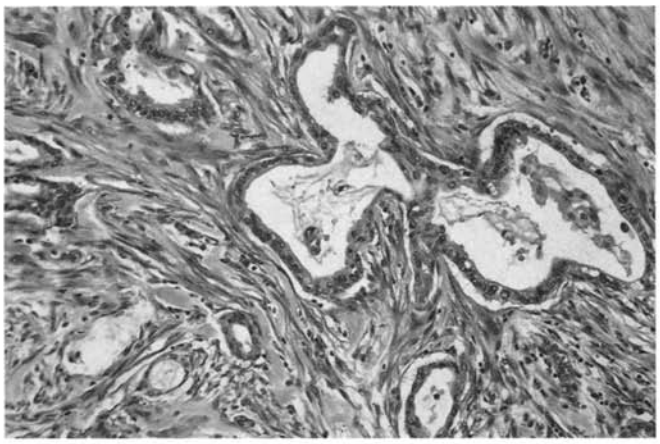


Fig. 7. Invasive ductal carcinomas of the pancreas are characterized by infiltrating small tubular units with open lumina, surrounded by desmoplastic stroma of variable cellularity.

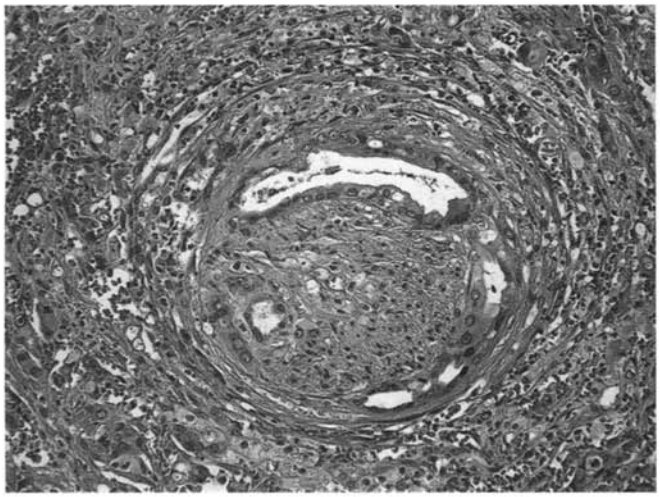


Fig. 8. Perineurial invasion is common in invasive ductal carcinoma.

- Gland formation and bland cytology may be retained even in perineurial or vascular invasion
- Extension into retroperitoneal tissue, especially through the posterior ucinate region is very common

Morphologic Variants

- Foamy gland pattern (**Figure 9**):
  - Abundant pale foamy, microvesicular cytoplasm filled with small, evenly-shaped vesicles
  - Thin, distinct band of chromophilic condensation in the apical cytoplasm forming a brush-border like zone
- Vacuolated-cribriform pattern (**Figure 10**):
  - Multicell-sized vacuoles resembling lipocytes (or signet-ring cells) and forming a cribriform archictecture
  - Vacuoles contain necrotic debris and neutrophils
  - Nuclear atypia prominent



Fig. 9. Invasive ductal adenocarcinoma with foamy-gland pattern can be deceptively benign appearing, as reflected in this focus of lymph node metastasis.

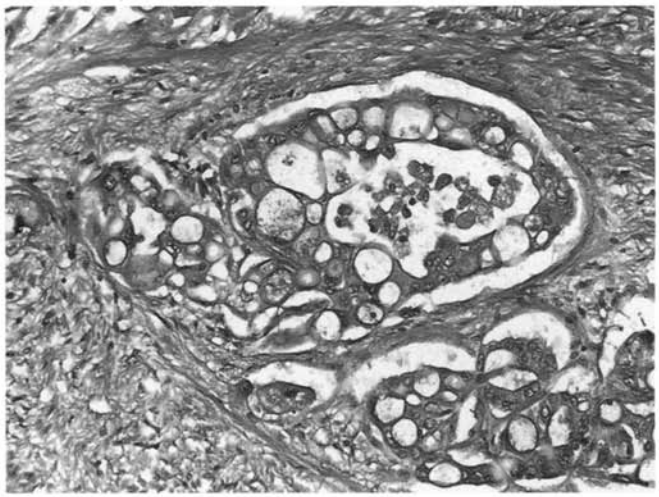


Fig. 10. Cribriform/vacuolated pattern is not uncommon in ductal adenocarcinoma and may help recognize this tumor type in metastatic sites.

- Other rare patterns: Large-duct pattern (mimicking intraductal neoplasia); cord-like formation; clear-cell pattern (mimicking renal cell carcinoma); signet-ring (**Figure 11**); hepatoid; oncocytic; and rhabdoid patterns
- May mimic the primary tumors at metastatic sites:
  - Bronchioloalveolar pattern ("lepidic" growth) in lung
  - Mucinous cystic pattern mimicking primary borderline tumors in ovary

Special Studies

- CK7+, CK20+/–
- Mucin positive, especially acidic sialomucin
- Mucin related glycoproteins and oncoproteins including MUC-1 (**Figure 12**) and others (CA19-9, CEA, B72.3, MUC5AC, DUPAN2)+

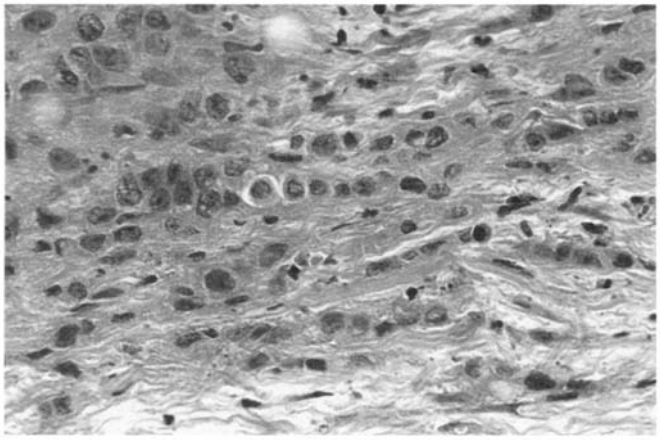


Fig. 11. Invasive ductal carcinoma, cord-like pattern. Often glandular areas are admixed with less differentiated patterns such as this one mimicking mammary lobular carcinoma.

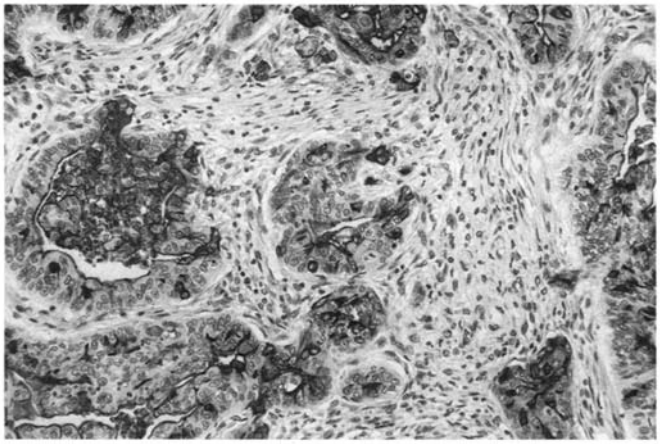


Fig. 12. MUC1 in ductal adenocarcinoma. The labeling is typically apical-membraneous in the glandular areas, and becomes more intracytoplasmic in the less differentiated (non-glandular) component of the tumor.

- ♦ May contain scattered endocrine cells
- ♦ Acinar enzymes typically lacking
- ♦ Alterations in codon12 of K-ras oncogene (>80%), p16 (>80%), p53 (50%), DPC4 (>50%), BRCA-2 (7%), Peutz-Jegher gene (5%)

Differential Diagnosis

- ♦ Non-invasive ducts (benign reactive ducts or intraductal neoplasia):
  - Smooth contours
  - Lobular, organized distribution; spatially related to acini and/or islets
  - Smaller ducts tend to be in clusters; larger ones have elongated lumina
- ♦ Pseudotumoral pancreatitis:
  - Approximately 5% of pancreatectomies performed with the clinical diagnosis of "pancreas cancer" prove to be chronic pancreatitis (*see* pancreatitis section)
- ♦ Ampullary/common bile duct carcinomas:
  - May be morphologically identical
  - Primary site/location is determined by gross examination
  - Pre-invasive neoplasia in the corresponding sites
- ♦ Non-ductal tumors (acinar, endocrine, solid-pseudopapillary neoplasia and pancreatoblastoma-**Table 1**):
  - Stroma-poor (no desmoplasia)
  - Cellular, non-glandular neoplasia with sheet-like or nested growth patterns
  - Relatively uniform cytology
- ♦ *Intestinal-type* adenocarcinoma (gastrointestinal or ampullary origin):
  - Columnar cells; stratification; basophilic appearance; central necrosis
  - Large, tubular units with relatively compressed luminae
  - MUC2+, MUC5AC–, MUC1–/+, CK20+, CK7–
- ♦ Ovarian adenocarcinoma:
  - Cellular; tubular areas composed of long, branching units with slit-like spaces
  - Many psammoma bodies
  - Tufts and micropapillae

Other Related Carcinomas

- ♦ Anaplastic and sarcomatoid (**Figure 13**): Often, ordinary tubular pattern in the background
- ♦ Adenosquamous and squamous:
  - Also have dismal prognosis like ordinary ductal adenocarcinomas
  - Immunohistochemical stains for p63 and K903 confirm the squamous

Rare Carcinomas of Presumed Ductal Origin

Osteoclastic Giant-Cell Carcinoma

Synonym

- ♦ "Sarcomatoid carcinoma with abundant osteoclastic giant cells" is a more accurate name and description of this tumor

Clinical

- ♦ Very rare
- ♦ Size: 5–8 cm
- ♦ Aggressive behavior

Macroscopic

- ♦ May appear well-demarcated
- ♦ Firm, lobulated, white-yellow to tan
- ♦ May be associated with cystic tumor, or have intraductal growth

Table 1. Markers of Differentiation/Lineage in Pancreatic Neoplasia

Lineage	*Light microscopy*	*Histochemical*	*Immunohistochem.*	*Ultrastructural*
Ductal	Gland, papilla, lumen, mucin	Mucin markers +	Mucin/Oncoprotein markers (B72.3, CEA, DUPAN, MUCs, CA19-9)	Mucigen granules, lumina
Acinar	Sheets of cells, prominent nucleoli, chromophilic (basophilic) cytoplasm, sometimes with granules. Some show acinar pattern	PAS and dPAS+ granules	Enzyme markers (trypsin*, lipase, chymotrypsin)	Zymogen granules
Endocrine	Neuroendocrine-type chromatin Nested, trabecular, gyriform, sheet-like patterns, cytologic uniformity with round nuclei,	Silver (Grimelius) positive granules	Neuroendocrine markers (Chromogranin*, Synaptophysin, Leu7 and NSE)	Membrane bound neurosecretory type granules

** The most specific and sensitive markers.*

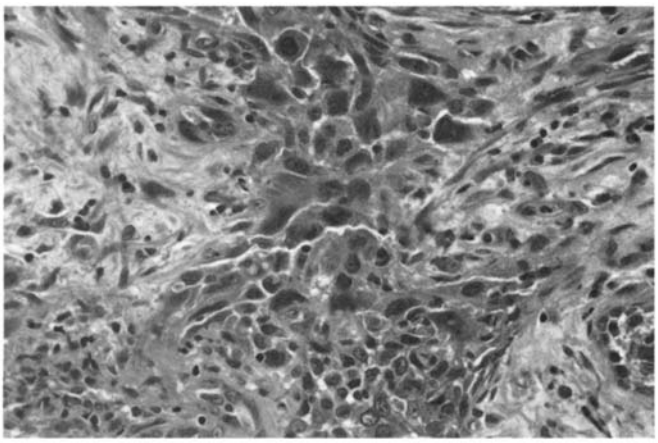


Fig. 13. Anaplastic/sarcomatoid carcinoma. This undifferentiated carcinoma is composed of large, pleomorphic cells with sarcomatoid transformation.

*Microscopic (**Figure 14**)*

- Sarcomatoid background, often with invasive ductal carcinoma
- Abundant benign osteoclastic-type giant cells

Immunohistochemistry

- Giant cells are of macrophagic nature; CD68+
- Sarcomatoid and tubular elements show ductal differentiation (**Table 1**)

Colloid Carcinoma

Definition

- Invasive carcinoma composed almost exclusively of mucin pools that contain scanty, detached carcinoma cells

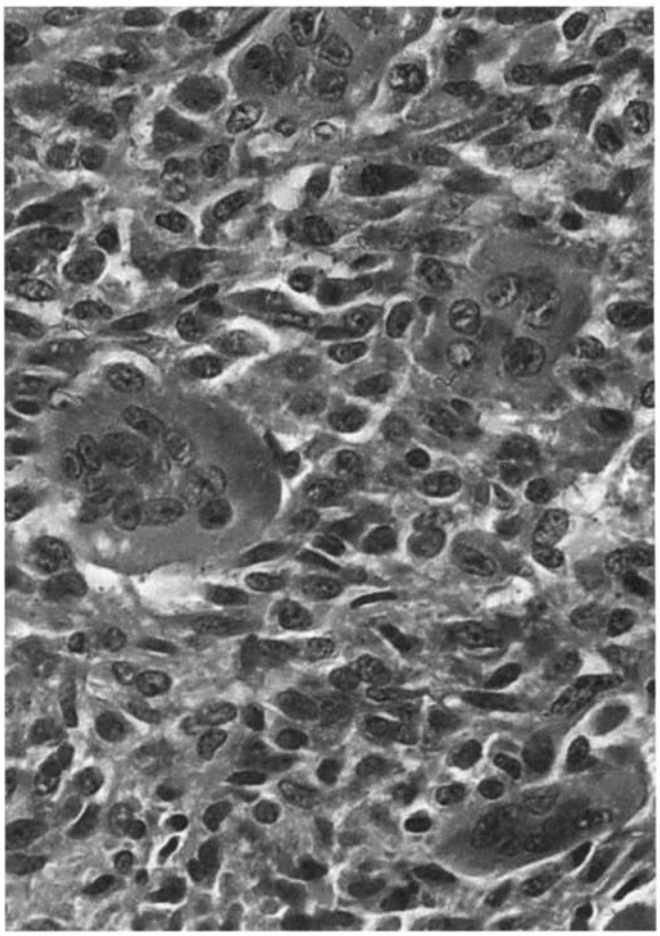


Fig. 14. "Osteoclastic giant cell carcinoma". Sarcomatoid carcinomas with abundant osteoclastic giant cells are also referred to as osteoclastic giant cell carcinoma.

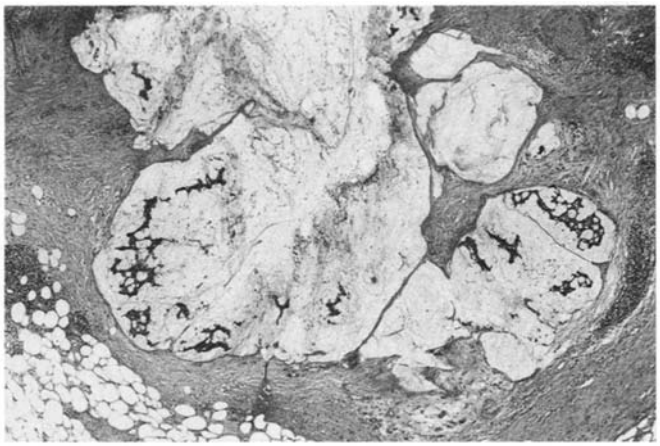


Fig. 15. Colloid carcinoma. Nodules of mucin some of which contain scanty, detached malignant cells.

- Often associated with intraductal papillary mucinous neoplasia

Clinical

- Mean age: mid-60's
- Mean size: 6 cm
- Thromboembolism in some cases
- Pure examples may have a protracted clinical course

Macroscopic

- Relatively well-demarcated
- Gelatinous

Microscopic

- Well-defined pools of mucin that contain scanty, detached carcinoma cells **(Figure 15)**
- Cells floating in mucin may form strips, signet ring cells, glands or stellate clusters

Differential Diagnosis

- Other invasive carcinomas (ductal, signet-ring or others)
  - Invasive carcinoma cells in the stroma (without surrounding mucin), or at least attached to the stroma
  - More cells than mucin
  - Loss of DPC4
- In-situ neoplasia (mucinous cystic tumors, intraductal neoplasia)
  - Epithelium continuous and well-attached to the stroma
  - Mucin not abundant in histologic sections (washed off during processing)

Medullary Carcinoma

- Similar to the medullary carcinomas of the breast and colon
- Associated with microsatellite instability
- Very rare
- A subset with protracted clinical course

Microscopic

- Pushing-border type infiltration
- Syncytial growth pattern
- Lymphoplasmacytic infiltrates

Molecular

- Microsatellite instability

Differential Diagnosis

- Metastatic carcinomas
- Ductal carcinoma
  - Scirrhous (scar-like) pattern
  - Small-unit infiltration (tubules or cords)
  - Desmoplasia

Pre-Invasive Ductal Neoplasia

Mucinous Cystic Neoplasms

Clinical

- Almost exclusively in perimenopausal females (mean age: 48; >95% females)
- Most in the tail
- No communication with the ducts
- Graded as adenoma, borderline, carcinoma in-situ based on the cytoarchitectural atypia
- Invasive carcinoma in some patients usually of tubular type
- Recent studies confirm that grade accurately predicts the outcome, (only) if the tumor is sampled/examined thoroughly

Macroscopic

- Multilocular, thick-walled cyst, typically in the tail **(Figure 16)**
- Do not communicate with the ducts
- Mucinous contents
- May become purulent
- Areas of carcinoma often not evident macroscopically

Microscopic

- Ovarian-type stroma is diagnostic, specific and almost a prerequisite **(Figure 17)**:
  - Identical to ovarian stroma morphologically and immunophenotypically
  - May contain sclerotic foci, hypervascularity and rarely even luteal cells

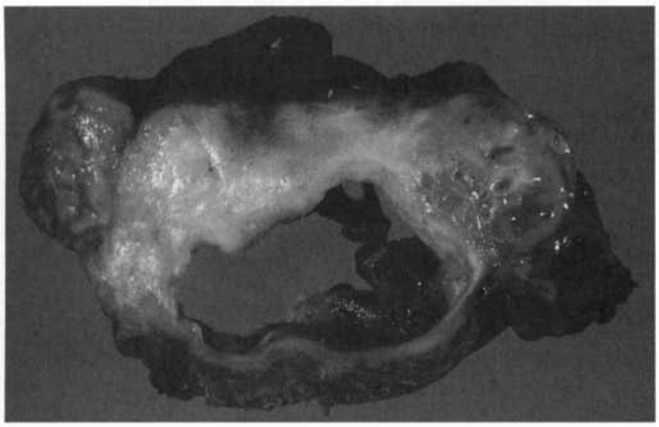


Fig. 16. Mucinous cystic neoplasm typically forms a thick-walled, multilocular cyst in the tail of the pancreas.

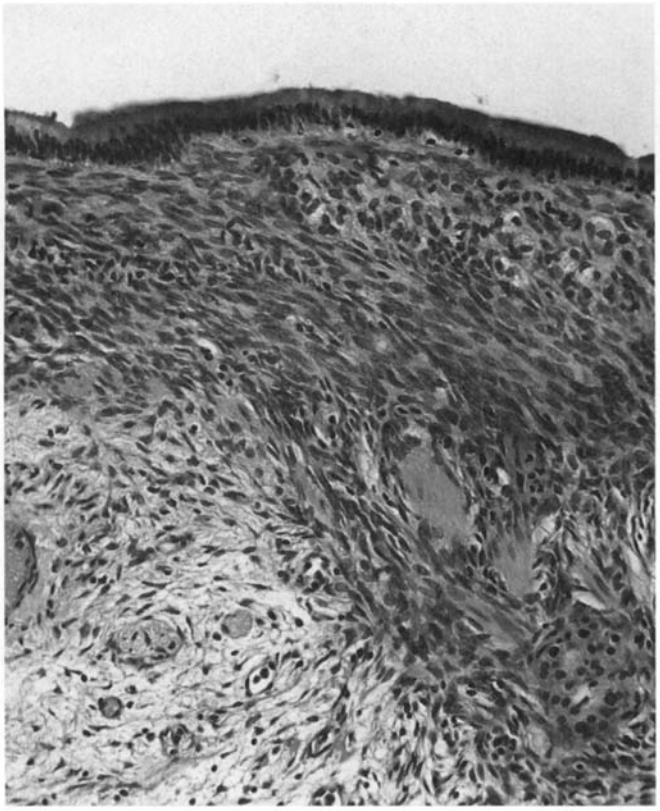


Fig. 17. Ovarian-like stroma is pathognomonic for mucinous cystic neoplasms.

- Mucinous lining with varying degrees of atypia (*see* below)
- Abrupt transition from areas with no atypia to frank CIS is common **(Figure 18)**
- Scattered goblet and endocrine cells
- Papillae may be seen, forming large nodules in some cases

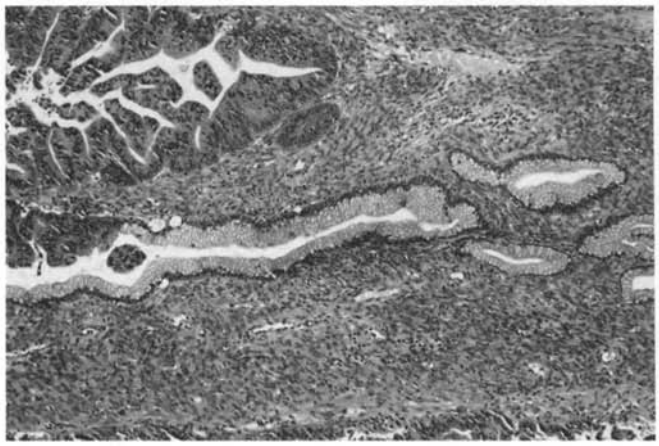


Fig. 18. Mucinous cystadenocarcinoma *in-situ.* The epithelium shows abrupt transition from areas of adenoma to those with frank carcinoma *in-situ.*

Pathologic Classification/Grading

- Pathologic classification and grading are valid only if the tumor is thoroughly examined
- Adenoma: Tall columnar mucinous cells with abundant apical mucin, and well-polarized, uniform small nuclei without atypia **(Figure 17)**
- Borderline category
- Carcinoma *in-situ:* Severe cytologic or architectural atypia (florid papillary nodules) with cuboidal nuclei, prominent nucleoli, mitotic figures, tufts and necrosis **(Figure 18)**
- *Invasive carcinoma* arising in association with MCN: Features of invasive ductal adenocarcinoma (*see* section on ductal adenocarcinoma)
- Some cases are associated with a sarcoma

Immunohistochemistry

- Ductal lineage markers positive (**Table 1**)
- Progesterone receptors+ in ovarian stroma
- Muscle markers (actin, desmin, caldesmon)+ in ovarian stroma

Differential Diagnosis

- Intraductal papillary mucinous neoplasms (**Table 2**):
  - Intraductal (communication with the native ducts demonstrable radiologically or on gross examination)
  - Intestinal type papillae may be seen
  - More common in the head
  - More common in elderly males
- Intraductal oncocytic papillary neoplasms:
  - Complex papillae; intraepithelial lumina; oncocytic cells
- Pseudocyst:
  - No epithelial lining
  - Granulation type tissue (but not ovarian type stroma)
  - Fat necrosis

Table 2. Differential Diagnosis of Pre-invasive Ductal Neoplasia (Intraductal and Cystic Mucinous Neoplasia With/Without Papilla Formation)

Features	*Mucinous cystic neoplasms*	*Intraductal papillary mucinous neoplasms*	*Intraductal oncocytic papillary neoplasms*
Mean age	48	68	67
Gender	Females (>90%)	Males~>females	Males~females
Specific endoscopic finding	None	Mucin extrusion from ampulla	None
Specific radiologic finding	Multilocular cyst in the tail of the pancreas	Cystically dilated pancreatic ducts	Cystically dilated pancreatic ducts
Preferential location	Tail (>90%)	Head (>80%)	None
Ductal communication	No	Yes	Yes (some cases)
Degree of papilla	Variable	Prominent	Prominent
Pattern of papilla	Variable	Intestinal-villous (85%)	Complex- arborizing
		Pancreatobiliary (15%)	
Specific histologic findings	Ovarian stroma (Diagnostic/ pathognomonic; almost a requirement)	Cystically dilated native ducts with villous nodules	Arborizing papilla with intraepithelial lumina and oncocytic cells

Intraductal Papillary Mucinous Neoplasms

Definition

- Intraductal proliferation of mucinous cells of variable papillae formation and cystic change in the ducts:
  - Some look like villous adenoma (**Figure 19**)
  - Some give rise to multilocular cystic transformation of the ducts (with minimal or no papillae)

Clinical

- Recently estimated as 5–10% of pancreatic tumors
- Elderly males (M/F = 2, mean age: 68); some with history of pancreatitis
- 30% have co-existing tumors of other organs
- Endoscopic: Mucin extrusion from ampulla of Vater
- Radiologic: Dilatation of the ductal system
- Graded as adenoma, borderline, carcinoma *in-situ*
- Invasive carcinoma in 30%
- Overall 5-yr survival >70%
- Grade seems to correlate with clinical outcome but unexpected clinical course has been noted in some; invasion is the most important determinant

Macroscopic

- Dilatation of the ducts; sometimes multilocular cysts
- Tan, friable papillary nodules filling the ducts in some cases

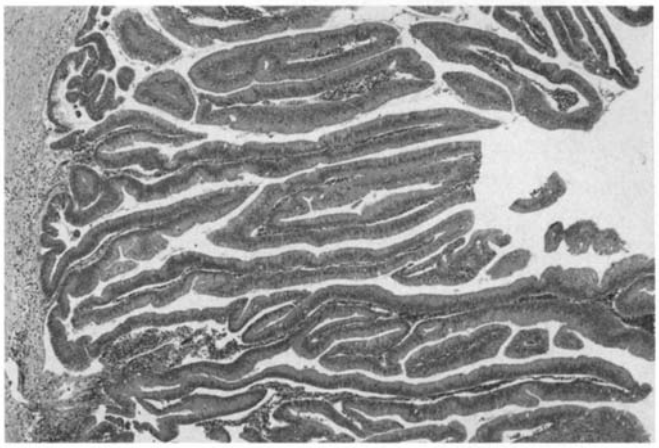


Fig. 19. Intraductal papillary mucinous neoplasm. In many examples of IPMNs, the papillae are morphologically similar to colonic villous adenomas.

Microscopic

- Intraductal proliferation of mucinous cells
- In cystic areas, tall columnar cells with abundant apical mucin
- Papillary areas have more atypia
- Papillae may have intestinal (villous adenoma like-**Figure 19**), pancreatobiliary (similar to biliary papillomatosis), or gastric (foveolar-**Figure 20**) appearance; their significance not yet determined



Fig. 20. Intraductal papillary mucinous neoplasm. In this example, the lining epithelium resembles gastric foveolar epithelium. There is no atypia (i.e., IPM adenoma).

Pathologic Classification/Grading

- Pathologic classification and grading are valid only if the tumor is thoroughly examined
- Adenoma: Tall columnar mucinous cells with abundant apical mucin, and well-polarized, uniform small nuclei without atypia **(Figure 20)**
- Borderline category
- Carcinoma *in-situ:* Severe cytologic or architectural atypia (florid papillary nodules) with cuboidal nuclei, prominent nucleoli, mitotic figures, tufts and necrosis
- Invasive carcinoma (in 30%), more commonly of colloid and sometimes of the ductal (tubular) type

Immunohistochemistry

- MUC2 and CDX2 commonly expressed (especially in those that have villous adenoma pattern)
- Ductal differentiation markers (**Table 1**)

Differential Diagnosis

- Mucinous cystic neoplasms (**Table 2**):
  - No communication with the ducts
  - Perimenopausal females
  - Tail of the pancreas
  - Thick-walled cyst
  - Ovarian-type stroma (most helpful)
- Intraductal oncocytic papillary neoplasms:
  - Complex papillae; intraepithelial lumina; oncocytic cells
- Invasive ductal carcinoma:
  - Contour irregularities
  - Irregular clustering and haphazard distribution
  - Small units with round, open luminae
  - Perineurial invasion
- Pancreatic intraepithelial neoplasia:
  - Microscopic/incidental (not mass-forming)
  - Lack MUC2
  - Simple mucosal folds or at most short papillae

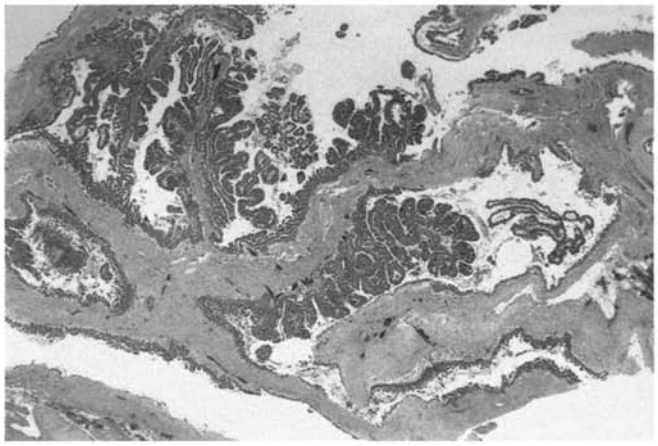


Fig. 21. Intraductal papillary mucinous neoplasms and intraductal oncocytic papillary neoplasms are characterized by cystically dilated ducts, many of which are filled with papillary nodules.

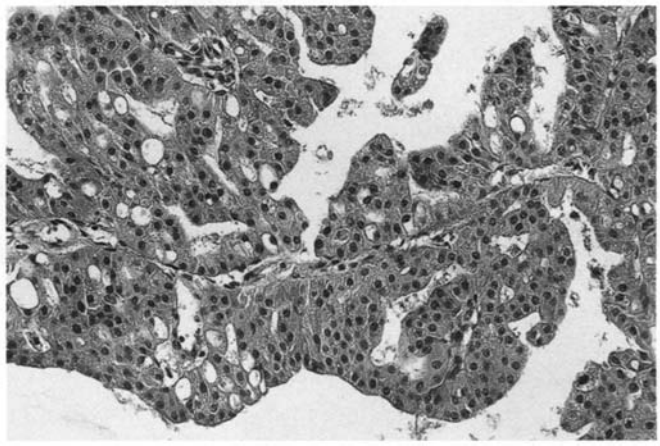


Fig. 22. Intraductal oncocytic papillary neoplasms. These tumors are characterized by complex-branching papillae, oncocytic cells, and intraepithelial lumina formation.

Intraductal Oncocytic Papillary Neoplasms

Clinical and Macroscopic

- Very similar to intraductal papillary mucinous neoplasms; may be a variant

Microscopic

- Complex (arborizing) papillae **(Figure 21)**
- Intraepithelial lumina (multi-cell size punched-out spaces) with mucin **(Figure 22)**
- Oncocytic cells (abundant, granular, acidophilic cytoplasm; round nuclei; prominent, eccentric nucleoli)

Differential Diagnosis

- Same as intraductal papillary mucinous neoplasms

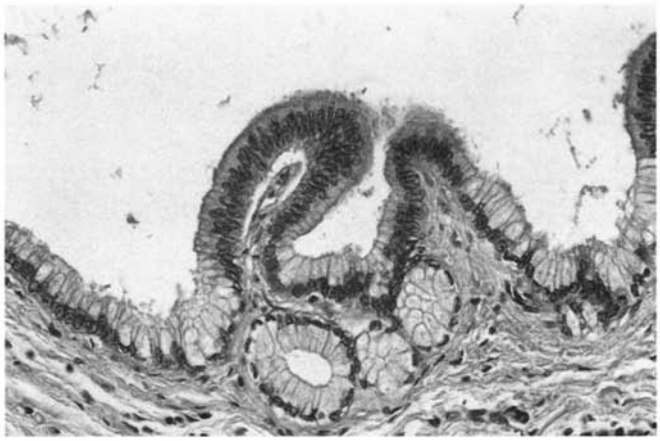


Fig. 23. PanIN-1. In the background of PanIN-1A, the mucosal folds at the center show mild stratification of cells (PanIN-1B).

Pancreatic Intraepithelial Neoplasia

Definition and Classification

- Microscopic/incidental, clinically non-manifest forms of preinvasive neoplasia in the ducts
- Previously also referred to as hyperplasia, atypical hyperplasia, dysplasia, etc.
- Encompasses a spectrum of changes from those previously called mucinous hypertrophy/metaplasia to frank CIS
- Spectrum graded as PanIN-1A (mucinous duct lesion), 1B, 2 and 3 (CIS)
- Presumed precursors of ductal adenocarcinoma
- PanIN-1 is a common, incidental finding even in normal pancreata
- PanIN-3 (CIS) is very common in pancreata with invasive ductal carcinoma, and is exceedingly uncommon otherwise

Pathology

- Not grossly detectable
- Atypical proliferative changes in the native ducts
- Ducts involved are typically <0.5 cm
- PanIN-1A: Simple, columnar, mucin-filled, perfectly polarized cells with small nuclei
- PanIN- 1B: 1A+ mild folding of the epithelium and early (basal) stratification **(Figure 23)**
- PanIN-2: Pseudotratification of nuclei; nuclear enlargement, more prominent folding (papillae); some cytologic atypia **(Figure 24)**
- PanIN-3: Loss of polarity; irregular stratification; tufting; necrosis; mitosis; cytologic atypia (nuclear enlargement, pleomorphism, nuclear irregularities, **Figure 25**)
- Clinical significance and rate of progression to invasive carcinoma undetermined

Special Studies

- Mucin of usually acidic sialomucin type
- Molecular alterations of ductal carcinogenesis increasing from 1A to 3 (*see* ductal adenocarcinoma section)

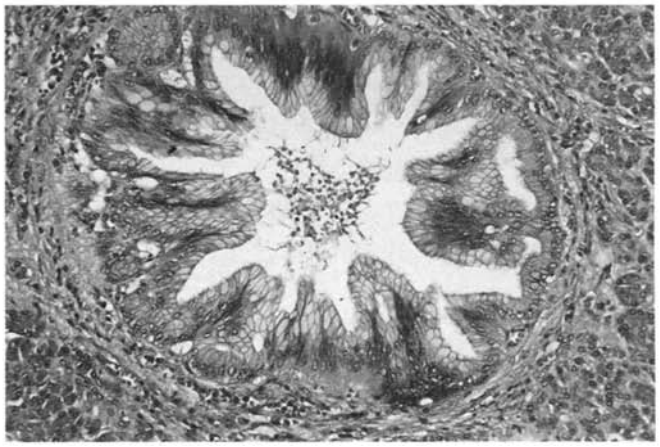


Fig. 24. PanIN-2. This duct shows papillary folds with stratification of mildly irregular cells. Some of the nuclei are dyspolarized.

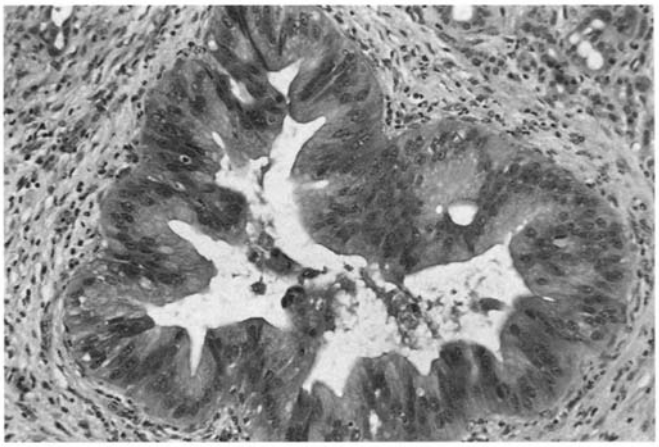


Fig. 25. PanIN-3 (Carcinoma *in-situ*). There is loss of polarity, and tuft formation is evident. There are necrotic cells detached into the lumen of the duct. The nuclei are hyperchromatic and irregular.

Differential Diagnosis

- Intraductal papillary mucinous neoplasms:
  - Mass-forming neoplasia (clinically/grossly detectable papillary or cystic changes)
  - Size typically >1 cm
  - Many clinically symptomatic
  - Tall papillae, some with intestinal phenotype
  - MUC2 and CDX2 expression common
- Invasive ductal carcinoma:
  - Contour irregularities
  - Irregular clustering and haphazard distribution

Serous Cystic Tumors

Synonyms

- Glycogen-rich adenoma, microcystic adenoma

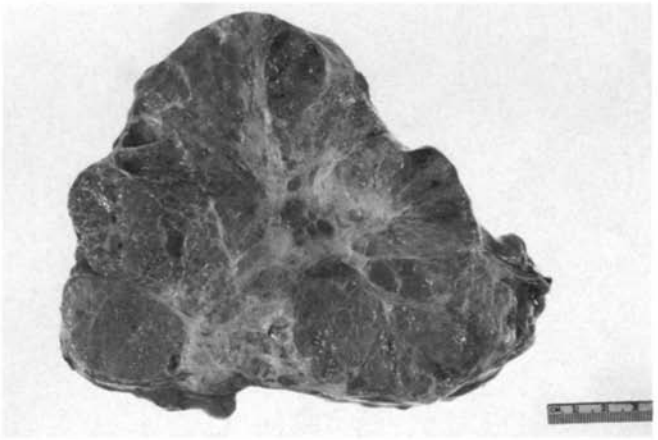


Fig. 26. Serous cystadenoma. Microcystic pattern (innumerable small cysts most of which are smaller than a few millimeters) creating a sponge like appearance is diagnostic. A stellate scar is commonly present. These tumors may become very large.

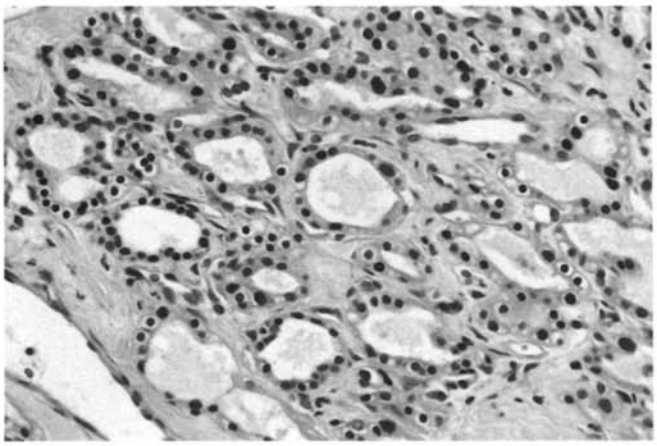


Fig. 27. Microcystic adenoma (serous cystadenoma) is characterized by innumerable, tightly-packed tubular elements that are lined by glycogen-rich cells that show distinct cytoplasmic borders and small, round, uniform nuclei with dense, homogenous chromatin.

Clinical

- Elderly females (mean age: 63; M/F = 1/3)
- Present with non-specific symptoms, or detected incidentally
- Mean size: 9 cm (may become very large, up to 25 cm)
- Cyst fluid analysis does not show oncoproteins seen in mucinous tumors (CEA, CA19-9 and others)
- Almost exclusively benign; very rare (questionable) examples of a malignant counterpart

*Macroscopic (**Figure 26**)*

- Well-demarcated; sponge-like appearance is diagnostic
- Microcystic: Innumerable small cysts, each measuring a few millimeters
- Central stellate scar common

*Microscopic (**Figure 27**)*

- Conglomerate of innumerable tubules and cysts
- Simple cuboidal epithelium
- Clear (glycogen-rich) cells with distinct cytoplasmic borders
- Small, round nuclei with dense, homogenous chromatin

Variants

- Oligocystic variant:
  - Smaller number of larger cysts
  - Slightly more common in men
  - No apparent biologic differences from the microcystic type
- Solid variant:
  - Packed with small gland-like units without cystic transformation
  - Very uncommon

Special Studies

- Epithelial differentiation markers+
- Virtually the only ductal tumor that does not show the "pancreatic ductal" differentiation markers (mucins, mucin related oncoproteins, k-ras mutation)
- Chromosome 10q and von-Hippel Lindau gene alterations in a subset

Differential Diagnosis

- Polycystic disease and von-Hippel Lindau:
  - Individual cysts indistinguishable from serous tumors
  - More widely spread in the pancreas
  - Often multifocal
  - Association with cysts in other organs
- Megacystic tumors (for the rare oligocystic variant):
  - Corresponding patterns in the epithelial lining (*see* corresponding sections in ductal neoplasia and miscellaneous-cysts sections)

Acinar Cell Carcinoma

Clinical

- Uncommon; <1% of pancreatic neoplasia
- Mean age: 60
- Rarely in children
- Acinar-enzyme hypersecretion syndrome (subcutaneous fat necrosis, polyathralgia and polyarthritis) in 10%
- 50% with metastasis (usually to liver) at diagnosis
- 5-year survival <10%

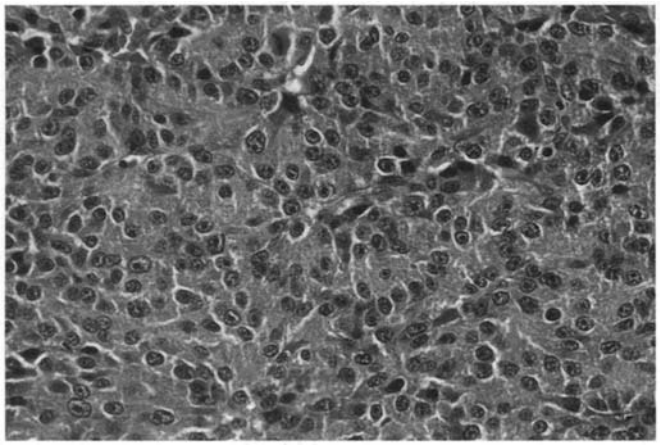


Fig. 28. Acinar cell carcinomas form sheets of round cells with prominent nucleoli. In some cases such as this one, abortive acinar formations resembling rosettes may be seen.

Macroscopic

- Well-delineated, nodular, fleshy (soft yellow-tan) mass with fibrous bands
- Pathcy necrosis is common
- Typically large (>10 cm)

*Microscopic (**Figure 28**)*

- Sheet-like, stroma-poor growth pattern
- Overall basophilia
- Round nuclei with prominent nucleoli
- May contain cytoplasmic granules (sometimes acidophilic)
- Rosette-like acinar formations may be seen
- If trabecular pattern, the cells palisade on the adjacent fibrovascular stroma
- Ultrastructurally, electron-dense large granules typical of zymogenic granules

Special Studies

- Granules demonstrable by PAS, diastase resistant
- Immunoreactivity with enzymatic markers (trypsin most reliable, but also lipases and chymotrypsin); epithelial markers+
- Lack of ductal (mucin and oncoprotein) or endocrine lineage (**Table 1**)

Variants

- Rare cystic and papillo-cystic variants
- Mixed acinar-endocrine carcinomas

*Differential Diagnosis (**Table 3**)*

- Endocrine neoplasia:
  - Nested or trabecular pattern
  - Endocrine chromatin; nucleoli not too prominent
  - Lack of overall basophilia
  - Endocrine markers (chromogranin and synaptophysin) +
- Solid-pseudopapillary tumor:
  - Almost exclusively in young females (mean age: 25 years)
  - Solid and pseudopapillary patterns; may have myxoid stroma
  - Round to ovoid bland-appearing nuclei with small (if at all visible) nucleoli; nuclear grooves
  - Degenerative changes including zones of macrophages and hyaline globules
- Pancreatoblastoma:
  - Ductal and endocrine components (in addition to acinar which is most common)
  - Squamoid corpuscles
- Ductal adenocarcinoma:
  - Scirrhous pattern (firm, ill-defined, scar-like appearance)
  - Often primary tumor is <5 cm at the time of diagnosis
  - Tubular units within desmoplastic stroma

Acinar Cell Cystadenoma

- Also called "cystic acinar transformation"
- Very uncommon
- Usually microscopic; rarely becomes several centimeters

Endocrine Neoplasia

Pancreatic Endocrine Neoplasia (PENs, Islet Cell Tumors)

Clinical

- May be functional (50%) or present as a mass without hormone activity (non-functioning)
- Some are associated with MEN-1 or other syndromes
- MEN-associated examples tend to be multiple and less aggressive
- Most insulinomas follow a benign course, possibly because they are typically functional from the start, and are detected then removed when very small
- PENs have protracted clinical course even in patients with metastatic disease

Pathologic Classification

- Findings more commonly associated with metastatic behavior ("bad" prognostic factors):
  - Size (>3 cm)
  - Non-insulinoma
  - Necrosis
  - Capsular or vascular invasion
  - High mitotic activity
  - High proliferation index (Ki-67 > 2%)
  - Aneuploidy
- WHO classifies PENs as (simplified version):
  - Microadenoma (<0.5 cm and no bad prognostic factors)
  - Macroadenoma (0.5–2 cm and no bad prognostic factors)

Table 3. Differential Diagnosis of Non-Ductal Pancreatic Neoplasia

	Endocrine (PEN)	*Solid Pseudopapillary*	*Acinar cell cancer*	*Pancreatoblastoma*
Clinical	Adults Some syndromic (insulinoma, glucagonoma etc)	Young females (mean age: 25, >90% females)	7th decade	Children, rarely middle ages (bimoda, mean age: 3 and 33)
Histologic	Neuroendocrine type chromatin Nucleoli may be seen Delicate vascularity+	Pseudopapilla Hyaline globles Areas of macrophages Nuclear grooves	Cherry red nucleoli Chromophilic cytoplasm Palisading on the stroma	Squamoid corpuscles Multiphenotypic differentiation (endocrine, acinar, ductal)
Histochem.	Grimelius+	PAS+ globules in the cytoplasm	PAS+ granules in the cytoplasm	—
Immunohisto-chemical	Chromogranin+, Synaptophysin+, Keratin+	CD56, vimentin, Progesteron receptors, β-catenin, Inhibin+	Acinar enzymes (Trypsin best, others also positive). Keratin+	Multiphenotypic differentiation Keratin+

- Borderline category
- Low grade carcinoma (>3 cm or bad prognostic factors)

♦ Some authors avoid the term adenoma and use "neoplasm" instead, since even small PENs may metastasize

Macroscopic

♦ Generally well-delineated with partial to complete encapsulation

♦ Fleshy (tan, soft, homogenous)

*Microscopic (**Figure 29**)*

♦ Nested, gyriform (trabecular), acinar and even gland-like or solid-appearing patterns

♦ Uniform cells with fair amount of acidophilic cytoplasm

♦ Round, centrally located nuclei with distinctive stippled ("salt and pepper") chromatin

♦ Nucleoli may be present but not prominent

♦ Scattered atypical cells ("endocrine atypia") may be seen

♦ Ultrastructurally, membrane-bound neurosecretory granules are typical; some hormones, especially insulin, have a distinctive appearance

Special Studies

♦ Silver stains (Grimelius)+

♦ Neuroendocrine (chromogranin and synaptophysin)+; epithelial markers+

♦ Immunoreactivity with various hormone markers (insulin, glucagon, somatostatin, gastrin, vasoactive intestinal polypeptide and pancreatic polypeptide)

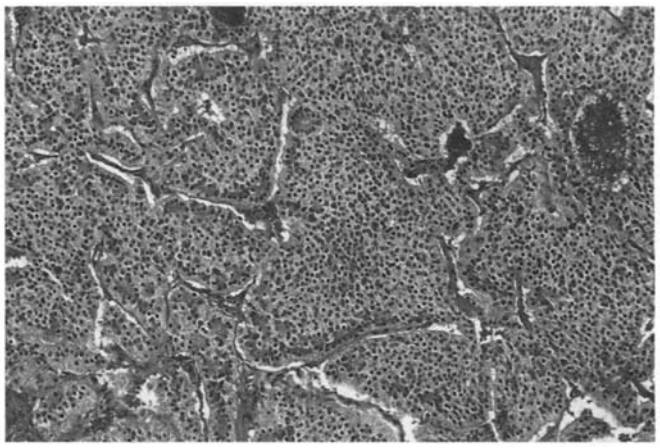


Fig. 29. Pancreatic endocrine neoplasia is characterized by sheets of round, uniform cells forming nests that are separated by delicate fibrovascular stroma.

♦ Hormone immunochemistry in the tumor does not correlate with the "functionality" status

Variants

♦ Cystic: 5% of PENs, results from a degenerative process

♦ Clear cell: May mimic renal cell carcinomas; often associated with von-Hippel Lindau

♦ Pleomorphic: Degenerative endocrine atypia in which many of the nuclei are enlarged, have smudgy, dense chromatin and irregular contours, is more pronounced than usual

- Lipid-rich: Microvesicular, foamy cytoplasm creates a picture indistinguishable from adrenocortical cells
- Signet-ring like or rhabdoid: Homogenous cytoplasmic contents that push the nucleus to the periphery of the cell
- Paraganglioma-like: Nested pattern in which cells form smaller clusters surrounded by stromal cells resembling sustentacular cells

*Differential Diagnosis (**Table 3**)*

- Carcinoid:
  - May be indistinguishable
  - Cytologic uniformity more striking
  - Serotonin activity is typical
  - Cytoplasmic basophilia, granularity at the periphery of the nests, and lipofuscin pigment
- "Hyperplastic islets" (non-neoplastic islets in chronic pancreatitis):
  - Cord-like pseudo-infiltrative pattern or micronodules
  - In the background of other pathologic changes
  - Hormone immunohistoprofile is similar to that of normal islets (the presence of multiple hormones and their spatial distribution)
- Acinar cell carcinoma:
  - Overall basophilia; prominence of nucleoli; nesting not prominent
  - Immunoreactivity with enzymes (trypsin); Chromogranin–
- Solid-pseudopapillary tumor:
  - More ovoid cells with overlapping of nuclei; nesting is vague
  - Pseudopapillary pattern, nuclear grooves, hyaline globules, and zones of macrophages
  - Chromogranin–, keratin may be focal or weak

Poorly Differentiated Endocrine (Small Cell) Carcinoma

- Most small cell carcinomas in the pancreas are metastatic from lung
- Primary high-grade neuroendocrine carcinomas are exceedingly uncommon
- Present with metastasis to liver
- Rapidly fatal
- Pathologically similar to their pulmonary counterparts
- Necrosis and abundant mitotic activity are characteristic

Solid-Pseudopapillary Neoplasm

Clinical

- Uncommon; 1–2% of pancreatic tumors
- Previously known as "papillary-cystic" and "solid and cystic"
- Origin undetermined

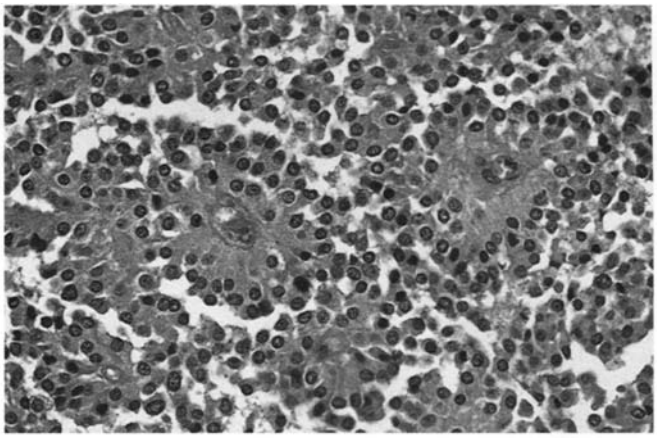


Fig. 30. Solid-pseudopapillary neoplasm. Ependymoma-like pseudopapillary pattern is characteristic. The nuclei are round to ovoid.

- Almost exclusively in young females (mean age: 25; >90% females); other tumors, in particular endocrine neoplasia to be ruled out if in a male
- Indolent (low-grade) neoplasm:
  - Complete removal: 85% cure rate
  - Metastasis, if occurs, is usually to the liver or peritoneum, and often present at the time of diagnosis
  - Even patients with metastases may have a protracted clinical course
  - Almost never fatal
- No reliable criteria to distinguish metastatic cases

Macroscopic

- Round and deceptively well-demarcated (satellites and projections are common under microscopy)
- Commonly cystic and hemorrhagic with scattered fleshy-tan foci of viable tumor
- Typical size: 8–10 cm

*Microscopic (**Figure 30**)*

- Solid areas with sheets of neoplastic cells punctuated by fibrotic and/or myxoid stroma
- Ependymoma-like pseudopapillary pattern
- Round to ovoid, cytologically bland nuclei with small (if at all visible) nucleoli; overlapping of nuclei; nuclear grooves
- Hyaline globules and zones of foamy macrophages in the more degenerated areas
- Satellites and projections to adjacent pancreas; entrapped pancreatic elements within the main lesion
- Calcifications and psammoma bodies may be seen

Variants

- Some have spindle cell areas resembling hemangiopericytomas

Special Studies

- Diffuse and consistent immunoreactivity for vimentin, progesterone receptors, CD56 and NSE

- Inhibin and estrogen receptors less consistent; keratins may be focal or weak; chromogranin– (important for differential with endocrine tumors)
- β-catenin and cyclin-D1 expression (alterations in wnt-signaling pathway)

*Differential Diagnosis (**Table 3**)*

- Pseudocyst- no epithelial lining (may require extensive sampling to prove)
- Pancreatic endocrine neoplasia (islet cell tumors):
  - Nested pattern prominent; neuroendocrine chromatin; more uniform, round cells; less overlapping; chromogranin+
- Acinar cell carcinoma:
  - Overall basophilia; prominent nucleoli; PAS+ acidophilic granules
  - Immunolabeling for acinar enzymes
- Pancreatoblastoma:
  - Squamoid corpuscles
  - Ductal, endocrine and acinar differentiation (**Table 1**)
  - Childhood tumor

Pancreatoblastoma

Clinical

- Extremely rare
- Early childhood tumor (mean age: 4); second peak in 30's
- Two thirds described in Asians
- Elevated alpha-fetoprotein in some cases
- Occasionally Beckwith-Wiedemann and rare cases with FAP syndrome
- 5-year survival 25%

Macroscopic

- Well-demarcated, solitary, solid, multilobulated, encapsulated tumor; yellow-tan cut surface
- Typical size: 7–18 cm

*Microscopic (**Figure 31**)*

- Cellular, stroma-poor neoplasm
- Multiphenotypic differentiation with a mixture of acinar (most consistent), ductal and endocrine elements
- Typically, round non-descript cells with moderate amount of cytoplasm predominate
- Squamoid corpuscles (small, distinct "morule" like formations with meningothelial appearance, including nuclear pseudoinclusions)
- Necrosis may be seen

Special Studies

- Acinar, ductal and endocrine components show corresponding staining patterns (**Table 1**)
- APC/β-catenin pathway and chromosome 11p alterations (**Table 3**)

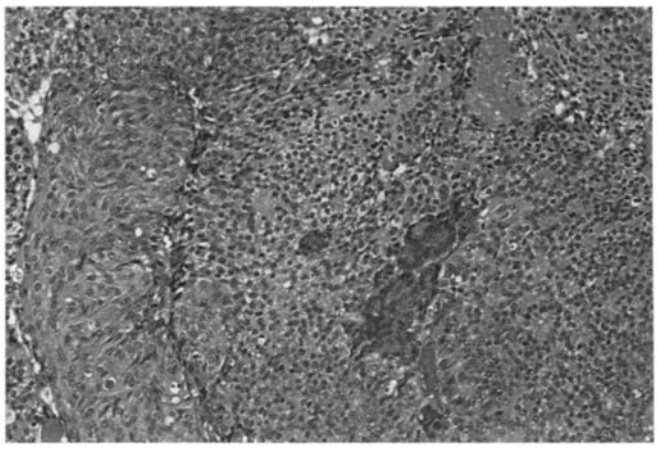


Fig. 31. Pancreatoblastoma. Diffuse sheet of relatively uniform cells, with distinct foci of ductal, acinar and endocrine differentiation. Morule-like formations (squamoid corpuscles) are diagnostic.

Differential Diagnosis

- Acinar cell carcinoma- absence of squamoid corpuscles
- Endocrine neoplasia- adults; absence of squamoid corpuscles and other lineage elements
- Solid-pseudopapillary tumor- pseudopapillary (ependymoma-like) pattern, nuclear grooves, hyaline globules, zones of macrophages; absence of squamoid corpuscles

Mixed Carcinomas (Mixed Endocrine-Acinar and Mixed Ductal-Endocrine)

- Extremely uncommon
- Arbitrarily defined as carcinomas with a second cell type >25%
- Pitfall: Scattered endocrine cells are common in other neoplasia
- Behavior along the more aggressive component ? (*see* the corresponding sections)

Miscellaneous Cystic Lesions

Lymphoepithelial Cyst

Clinical

- Peripancreatic
- Adult men (M/F = 3/1, mean age: 52)
- No association with any syndromes
- No association with malignancy

*Pathology (**Figure 32**)*

- Epidermal-lined cyst with variable keratinization
- Some with transitional or attenuated lining

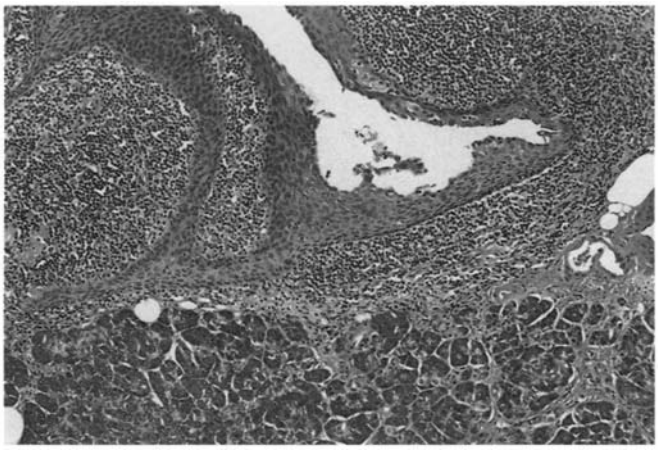


Fig. 32. Lymphoepithelial cyst is characterized by epidermal-lined cyst surrounded by a distinct band of lymphoid tissue.

- Rarely, goblet cells or scanty sebaceous elements
- Distinct band of lymphoid tissue adjacent to epithelium
- Lymphoid tissue may have lymph node architecture (germinal centers, sinusoids, capsule and subcapsular sinus)
- Granulomas, cholesterol clefts and solid epithelial cell nests may be seen

Lymphangiomas

- Young females (M/F = 1/3; mean age: 29)
- Endothelial lined cysts (CD31, CD34, factor VIII+)
- Lymphoid tissue

Epidermoid Cyst in Intrapancreatic Splenic Cyst

- Very rare
- Young patients (mean age: 37)
- Typically in the tail of the pancreas
- Attenuated epidermal lining surrounded by splenic tissue

Miscellaneous Tumors

Secondary Tumors

- Direct spread from ampullary, duodenal and biliary tumors:
  - May be morphologically identical to pancreatobiliary
  - Primary site/location is determined by gross examination
  - Pre-invasive neoplasia in the corresponding sites
- Metastasis to pancreas: Rare
  - Lung and GI tumors are the most common at autopsy
  - Especially, renal cell carcinomas and melanomas may be mistaken clinically as a primary
  - Should be considered in the differential diagnosis if a pattern not described for the primary tumors is encountered

Mesenchymal Tumors

- Most are secondary from neighboring sites (GISTs or retroperitoneal tumors)
- Primary ones are very rare
- Some, especially schwannomas, may be cystic
- Small blue cell tumors of childhood including primitive neuroectodermal tumors and desmoplastic small cell tumors may also occur in the pancreas
- Even PEComas (sugar tumor) have been reported

Hematopoietic Tumors

- Very uncommon
- Virtually every hematopoietic tumor type may present as a primary mass in the pancreas including B-cell, T-cell, Hodgkin and myeloma

SURGICAL PATHOLOGY REPORT

- Contents of the specimen
- Type of operation:
  - Right-sided pancreatectomy: Pancreatoduodenectomy is the preferred term over Whipple (since most current operations are not the original Whipple operation)
  - Left-sided pancreatectomy: Distal pancreatectomy (with or without splenectomy)
- Origin/location of the tumor (mostly based on gross examination and clinical findings):
  - Pancreatic *vs* periampullary (non-specific), ampullary, common bile duct, duodenal or peripancreatic
- Type of the tumor:
  - e.g., pancreatobiliary *vs* adenosquamous, colloid, medullary, intestinal etc.
  - Invasive and pre-invasive (non-invasive) components reported separately
  - Generic diagnoses such as "mucinous carcinoma" should be further specified
- Size of the tumor:
  - Size of invasive and non-invasive components reported separately
  - Correlation of gross and microscopic findings necessary for determination of size in many cases

- Distribution of the tumor:
  - Specify involvement of organs (ampulla, CBD, duodenum, etc.)
- Pre-invasive neoplasia:
  - Even if associated with invasive carcinoma, the features of intraductal neoplasia, mucinous cystic neoplasia, etc. should be duly noted
- Vascular and perineurial invasion:
  - Some authors use perineurial invasion as an additional "soft" criteria for inclusion into radiotherapy protocols
- Lymph nodes:
  - An average of 12 lymph nodes are identifiable in a typical pancreatoduodenectomy specimen; most are embedded on the surfaces of the pancreatic head and pancreatoduodenal groove
- Margins:
  - In a right-sided (pancreatoduodenectomy) specimen:
    - Retroperitoneal (uncinate), pancreatic duct (neck), common bile duct, and gastrointestinal mucosal margins
    - Posterior and anterior free surfaces are reported separately as "surfaces" by some and as "margins" by others
    - Retroperitoneal margin is the most important. If sampled like the prostatic apex (removed as a 3–4 mm slice, serially sectioned and submitted entirely as perpendicular margin), this margin proves positive in 50–85% of the cases with ductal carcinoma. This area also contains lymph nodes
  - In a left-sided (distal) pancreatectomy:
    - Pancreatic ductal margin, anterior surface, posterior surface and perisplenic soft tissue surface
- Uninvolved segments of organs
- Uninvolved pancreas (for PanINs, other precursor lesions, pancreatitis etc), as well as uninvolved CBD, gastro-intestinal, gallbladder, spleen
- Surgical hardware, especially stents

TNM CLASSIFICATION OF PANCREATIC TUMORS

Primary Tumor (T)

- TX: Primary tumor cannot be assessed
- T0: No evidence of primary tumor
- Tis: Carcinoma *in situ**
- T1: Tumor limited to the pancreas, 2 cm or less in greatest dimension
- T2: Tumor limited to the pancreas, more than 2 cm in greatest dimension
- T3: Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery
- T4: Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)

*This also includes the "PanInIII" classification

Regional Lymph Nodes (N)

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis

Distant Metastasis (M)

- MX: Distant metastasis cannot be assessed
- M0: No distant metastasis
- M1: Distant metastasis

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37

Non-Neoplastic Hepatobiliary Disease

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CONTENTS

I. Viral Hepatitis 37-3
- Grading and Staging of Viral Hepatitis 37-3
- Hepatitis A 37-4
- Hepatitis B 37-4
- Hepatitis C 37-6
- Hepatitis D 37-7
- Hepatitis E 37-7
- Hepatitis F 37-7
- Hepatitis G 37-7
- Human Immunodeficiency Virus Infection (HIV) and AIDS 37-8
- Epstein-Barr Virus Infection 37-8
- Cytomegalovirus Infection 37-9
- Herpes Simplex Virus Infection 37-9

II. Nonviral Infections 37-10
- Bacterial Infection 37-10
  - Pyogenic Bacterial Infection 37-10
  - Brucellosis 37-10
  - Salmonellosis 37-10
- Recurrent Pyogenic Cholangiohepatitis 37-10
- Syphilis 37-11
- Mycobacterium Infection 37-12
  - Tuberculosis 37-12
  - Mycobacterium avium-intracellulare (MAI) Infection 37-12
  - Leprosy 37-12
- Rickettsial Infection 37-12
- Fungal Infection 37-12
  - Histoplasmosis 37-12
  - Coccidioidomycoses 37-13
- Parasite Infection 37-13
  - Amebic Abscess 37-13
  - Malaria 37-14
  - Hydatid Cyst 37-14
  - Clonorchiasis 37-14
  - Schistosomiasis 37-15

III. Drugs and Toxins 37-16
- General Features 37-16
- Pure Hepatocellular Necrosis 37-16
  - Common Example: Acetaminophen 37-16
  - Other Drugs 37-16
- Acute Hepatitis 37-16
  - Common Example: Isoniazid 37-16
  - Common Example: Phenytoin 37-16
  - Common Example: Halothane 37-16
  - Other Drugs 37-16
- Chronic Hepatitis 37-16
  - Common Example: Nitrofurantoin 37-16
  - Other Drugs 37-17
- Cholestasis and Duct Injury 37-17
  - Common Example: Oral Contraceptives 37-17
  - Other Drugs 37-17
- Fibrosis 37-17
  - Common Example: Methotrexate 37-17
  - Other Drugs 37-17
- Steatosis 37-17
  - Macrovesicular 37-17
  - Microvesicular 37-17
- Vascular Abnormalities 37-17
  - Peliosis-like Lesions 37-17
  - Sinusoidal Dilatation 37-17
  - Veno-Occlusive Disease 37-17
  - Vasculitis 37-17

Granulomas 37-17
Neoplasms 37-17
Liver Cell Adenoma 37-17
Hepatocellular Carcinoma 37-17
Cholangiocarcinoma 37-17
Angiocarcinoma 37-17

IV. Steatohepatitic Liver Disease....37-18
Acute Alcoholic Liver Disease....37-18
Steatosis 37-18
Steatohepatitis....37-18
Chronic Alcoholic Liver Disease 37-19
Progressive Perivenular Fibrosis....37-19
Cirrhosis 37-19
Total Parenteral Nutrition....37-20
Non-Alcoholic Steatohepatitic Liver Disease 37-20
Jejunoileal Bypass 37-20
Obesity and Diabetes Mellitus 37-20
Acute Fatty Liver of Pregnancy 37-20

V. Vascular Disorders....37-21
Hepatic Venous Outflow Obstruction....37-21
Congestive Heart Failure 37-21
Budd-Chiari Syndrome....37-21
Veno-Occlusive Disease 37-21
Hypotensive Anoxia 37-22
Inflammatory Vascular Lesions 37-22
Pyelphlebitis 37-22
Polyarteritis....37-23
Miscellaneous Vascular Disorders 37-23
Peliosis Hepatis....37-23
Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)....37-23
Idiopathic Portal Hypertension (Non-Cirrhotic Portal Fibrosis) 37-23

VI. Cholestasis and Biliary Tract Disorders 37-23
Acute Mechanical Duct Obstruction 37-23
Chronic Mechanical Duct Obstruction 37-24
Primary Biliary Cirrhosis 37-24
Primary Sclerosing Cholangitis 37-25
Intrahepatic Cholestasis 37-26
Postoperative Cholestasis 37-26
Intrahepatic Cholestasis of Pregnancy 37-26
Paucity of intrahepatic bile ducts 37-26

VII. Developmental, Hereditary, and Metabolic Liver Disease 37-26
Cystic Liver Disease....37-26
Solitary Unilocular Cyst 37-26
Infantile Polycystic Disease 37-27
Adult Polycystic Disease 37-27
Congenital Hepatic Fibrosis 37-28
Bile Duct Dilatation 37-28
Choledochal Cyst (Extrahepatic) 37-28
Caroli's Syndrome (Intrahepatic) 37-28
Extrahepatic Biliary Atresia 37-29
Idiopathic Paucity of Intrahepatic Bile Ducts 37-29
Alagille's Syndrome 37-29
Hereditary Hyperbilirubinemias....37-30
Dubin-Johnson Syndrome 37-30
Other Hereditary Hyperbilirubinemias 37-30
Progressive Intrahepatic Familial cholestasis 37-31
Benign Recurrent Intrahepatic cholestasis....37-32
Cystic Fibrosis....37-32
Alpha-1-Antitrypsin Deficiency....37-32
Genetic Hemochromatosis 37-33
Copper Storage Disorders 37-34
Wilson's Disease....37-34
Indian Childhood Cirrhosis 37-35
Amyloidosis 37-36
Porphyrias....37-36
Porphyria Cutanea Tarda 37-36
Erythropoietic Protoporphyria 37-37
Sickle Cell Anemia....37-38
Other Storage Disorders....37-38

VIII. Miscellaneous Conditions 37-39
Autoimmune Hepatitis 37-39
Granulomatous Liver Disease 37-39
Sarcoidosis 37-40
Inflammatory Bowel Disease....37-40
Neonatal Giant Cell Hepatitis 37-41
Reye's Syndrome 37-41
Toxemia of Pregnancy 37-42

IX. Disorders of the Gallbladder 37-42
Acute Cholecystitis 37-42
Chronic Cholecystitis and Biliary Colic 37-42
Cholelithiasis 37-42
Choledocholithiasis 37-43
Post-Cholecystectomy Syndrome 37-43

X. Suggested Reading....37-43

VIRAL HEPATITIS

Introduction

- Liver involved by both hepatotropic and non-hepatotropic viruses:
  - Commonest hepatotropic viruses are hepatitis A, B,C, E and the delta agent
  - Commonest non-hepatotropic viruses affecting liver are CMV, EBV, herpes and adenovirus
- Acute hepatitis characterized by lobular changes that are more or as marked as portal inflammation:
  - Lobular inflammation, necrosis, apoptotic bodies, hepatocyte degeneration and Kupffer cell prominence, giving an appearance of "lobular disarray" **(Figures 1–4)**
  - Portal inflammation present to variable degree but overshadowed by lobular changes
- Chronic hepatitis characterized predominantly by portal inflammation and destruction of limiting plate (interface hepatitis or piecemeal necrosis) **(Figure 5)**:
  - Lobular changes not as prominent as in acute hepatitis
- Determination of hepatitis requires knowledge of clinical and serological data:
  - All hepatotropic viral hepatitides show similar histology on H&E stain; exceptions are
  - hepatitis B if the biopsy shows ground glass cells **(Figure 6)**
  - hepatitis C may be suggested by the triad of mild bile duct destruction, mild fatty change and portal lymphoid follicles/aggregates **(Figure 7,8)**
  - Immunohistochemical stains available for hepatitis B and delta agent

Grading and Staging of Viral Hepatitis

- Grade reflects the degree of inflammatory activity:
  - Old terms are chronic persistent hepatitis, chronic active hepatitis, and chronic lobular hepatitis; these terms have become obsolete
  - Main determinants of grade are degree of lobular hepatocellular necrosis and degree of periportal hepatocyte necrosis (piecemeal necrosis or interface hepatitis)
  - Histological activity index of Knodell et al. is widely used in clinical trials and assesses grade and stage by adding numerical values for periportal and lobular necrosis, portal inflammation, and fibrosis
  - Simplified schemes exist and are more appropriate in daily patient care settings, using semiquantitative numeric values
  - Most practical is a grading system using "none, minimal, mild, moderate, and severe" as descriptive terms
  - Both chronic hepatitis B and C are amenable to grading, with hepatitis B showing much greater range of disease activity than hepatitis C

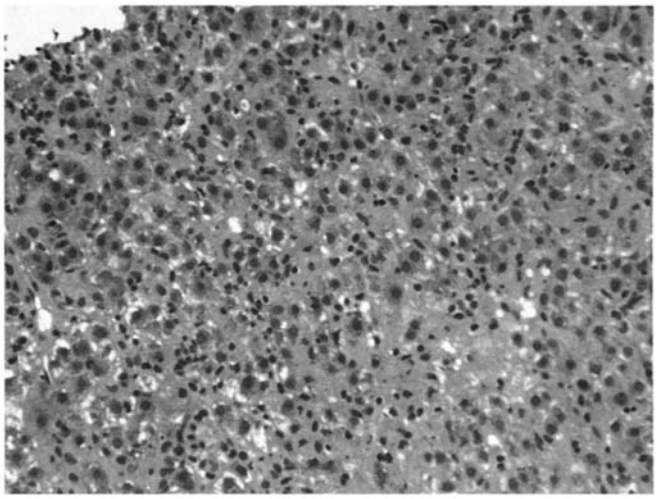


Fig. 1. Acute hepatitis showing "lobular disarray" caused by lobular inflammation, Kupffer cell prominence, necrosis, apoptotic bodies and cell degeneration.

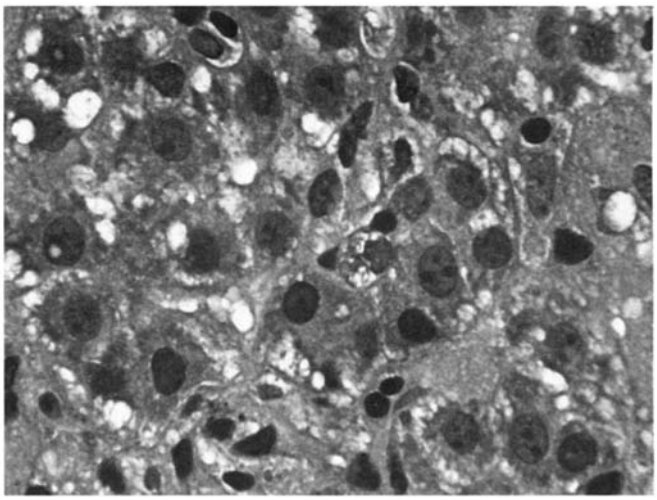


Fig. 2. Acute hepatitis showing cellular degeneration and necrotic hepatocytes.

- Stage refers to the degree of fibrosis, presumably subsequent to prior necroinflammatory insults:
  - Staging requires appropriate stains for connective tissue (Masson's trichrome)
  - Detailed staging systems have been proposed, but most practical is:
    - Fibrosis restricted to portal tracts (stage 1)
    - Periportal fibrosis and rare portal-portal septa (stage 2)
    - Numerous septa leading to architectural distortion (stage 3)
    - Bridging fibrosis with nodular regenerative nodules (stage 4); stage 4 represents cirrhosis

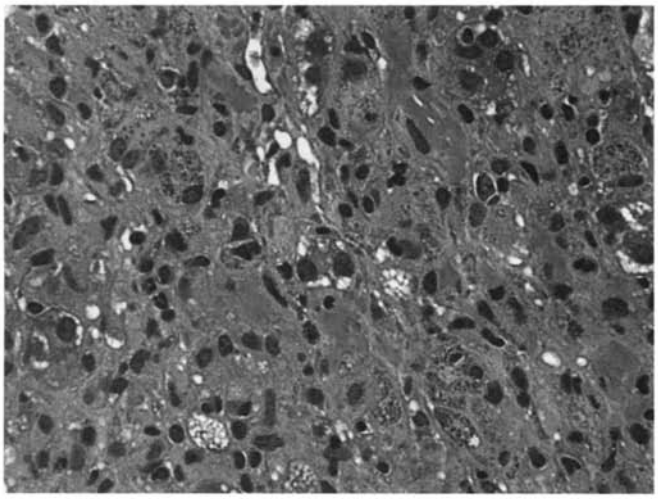


Fig. 3. Acute hepatitis with areas of parenchymal collapse containing pigment laden macrophages.

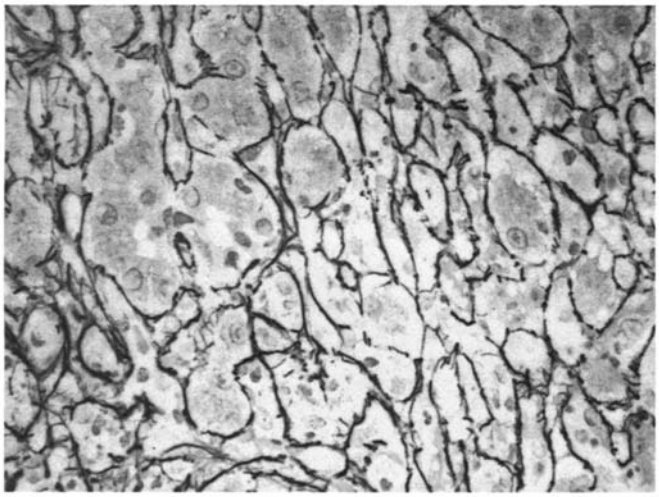


Fig. 4. Reticulin stain in acute hepatitis showing collapse of parenchymal architecture.

Hepatitis A

Clinical

- Picornavirus (non-enveloped ssRNA) icosahedral, 27 nm; not directly cytopathic
- 1-month incubation period, antibodies appear 2 weeks later; IgG indicates exposure in the past, IgM is marker for acute infection; may persist for 1 year
- Most cases anicteric, self-limited illness
- Fatalities in <0.5%; no chronic carrier state
- Interferon treatment in selected cases of fulminant hepatitis A

Microscopic

- Inflammation involves portal, periportal, and lobular areas; plasma cells predominate

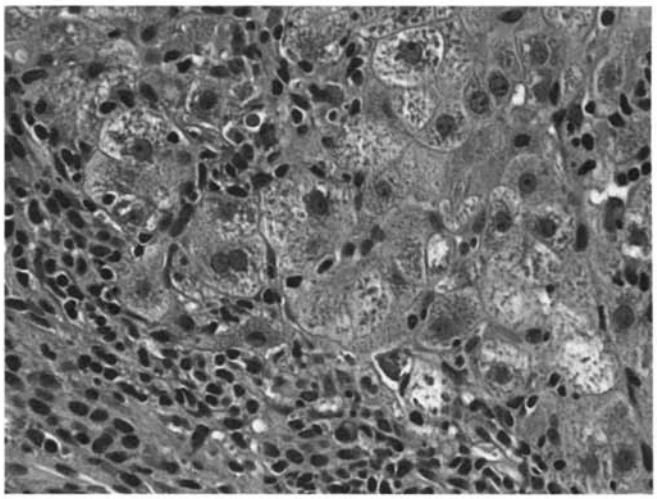


Fig. 5. Chronic hepatitis showing interface hepatitis (piecemeal necrosis) with a mononuclear inflammatory cell infiltrate destroying hepatocytes at the limiting plate. Several necrotic hepatocytes are seen surrounded by lymphocytes.

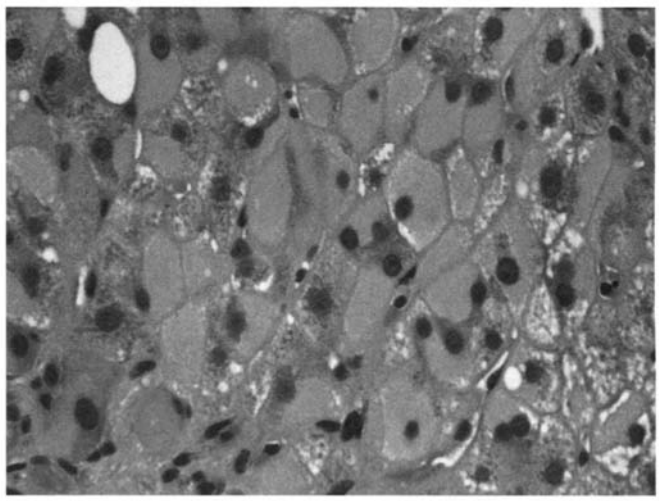


Fig. 6. Ground glass hepatocytes in chronic hepatitis B infection. The ground glass appearance results from accumulation of surface antigen in endoplasmic reticulum.

- Variable perivenular cholestasis; may predominate in some patients

Differential Diagnosis

- Hepatitis E
- Drug-induced hepatitis
- Autoimmune hepatitis

Hepatitis B

Clinical

- The most common viral hepatitis worldwide; endemic in the developing world

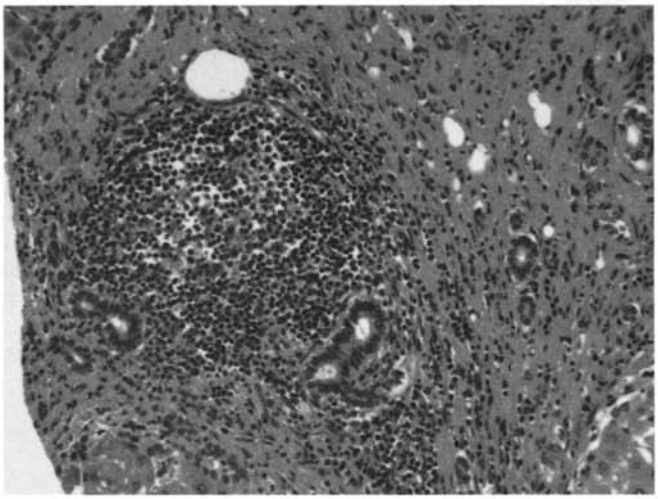


Fig. 7. Chronic hepatitis C infection showing lymphoid follicles in portal tracts.

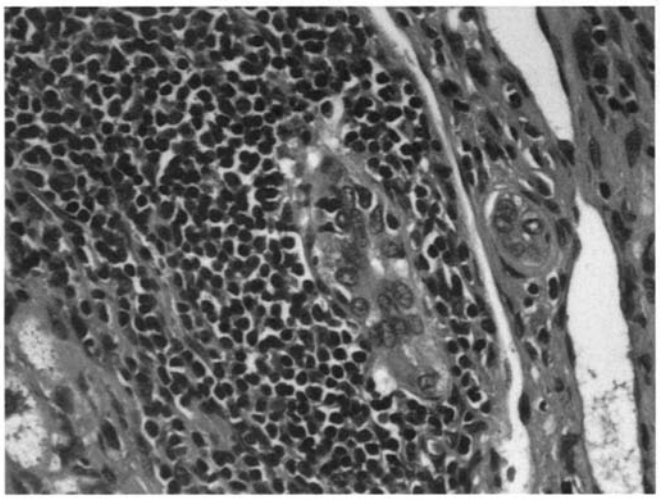


Fig. 8. Chronic hepatitis C infection showing epithelial damage in bile ducts surrounded by lymphoid aggregate.

- Enveloped (42 nm) "Dane particle," hexagonal inner core with circular dsDNA genome
- Not directly cytopathic; injury secondary to inflammation
- Present in blood near the end of the incubation period; transmission by blood or sexual contact
- Most cases are subclinical, 10% with fulminant hepatitis or chronic disease; host factors are probably the most important determinant of the individual clinical course
- Increased risk for hepatocellular carcinoma
- HBsAg appears first, followed shortly by HBeAg, which disappears with the arrival of IgM anti-HBc (beginning of symptoms) and later anti-HBe; HBsAg lost after approximately 2 months; 1–4 month "window period" before anti-HBs develops

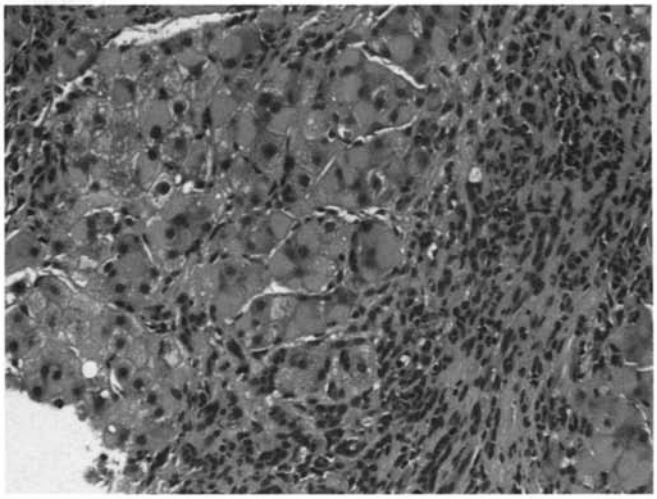


Fig. 9. Severe interface hepatitis in chronic hepatitis B infection; the inflammatory infiltrate is seen extending for a considerable distance beyond the limiting plate into the lobule.

- Persistence of HBeAg indicates persistent infection and likely progression to chronic hepatitis
- Active immunization is successful in preventing the disease

Microscopic (Acute Hepatitis B)

- Lobular predominant inflammation with highly varying degrees of degeneration (hepatocellular ballooning, necrosis) and regenerative changes
- Number of ground glass hepatocytes inversely proportional to degree of inflammation
  - Ground glass cells represent cytoplasmic aggregates of excess HBsAg admixed with smooth endoplasmic reticulin, which distend the cytoplasm and displace the nucleus peripherally)

Microscopic (Chronic Hepatitis B)

- Varying degrees of portal, periportal and lobular inflammation **(Figure 9)**
- Varying degrees of fibrosis (stage)
- Steatosis not a feature (in contrast to hepatitis C)
- Frequently associated with scattered ground glass hepatocytes; number of cells inversely proportional to degree of lobular inflammation
- Grading is useful and may predict the likelihood of progression to cirrhosis, dying from disease, and responding to therapy; however, the histologic grade is inter-related with replication status and host response:
  - Grading may not be useful in a patient with non-replicating disease
- Staging for prognostic purposes, prediction of therapy response to alpha interferon, confirmation of cirrhosis, and monitoring of disease progression

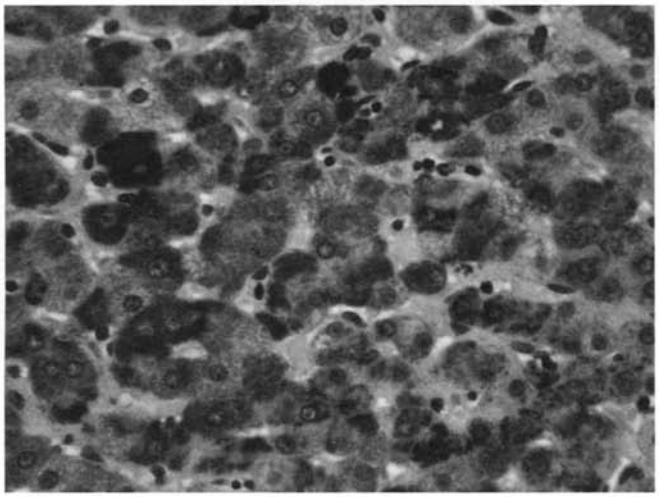


Fig. 10. Immunohistochemical stain for hepatitis B surface antigen shows cytoplasmic positivity.

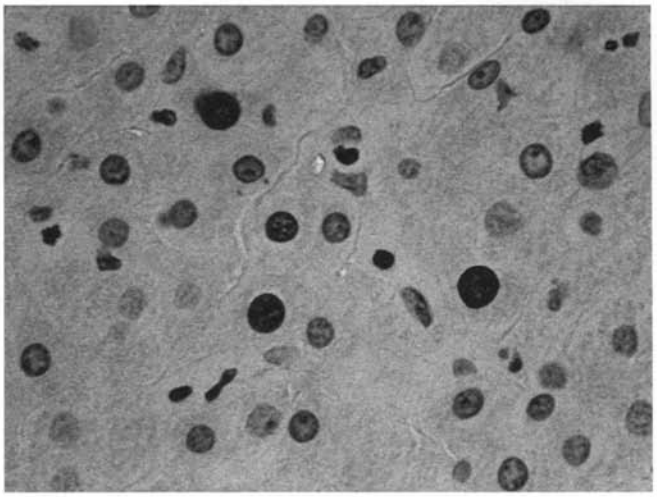


Fig. 11. Immunohistochemical stain for hepatitis B core antigen shows nuclear positivity.

Special Studies

- HBsAg and HBcAg are not uncommonly negative in acute hepatitis B and may be positive in chronic hepatitis B
- Cytoplasmic HbsAg+ (associated with or without core formation) **(Figure 10)**
- Nuclear HbcAg+ (indicative of active viral replication); when cytoplasmic HBcAg is also demonstrable, even greater degree of viral replication likely **(Figure 11)**
- Membranous HbsAg+ (indirect evidence of active viral replication)

Differential Diagnosis

- Other viral hepatitis
- Drug-induced hepatitis
- Autoimmune hepatitis

Hepatitis C

Clinical

- Enveloped ssRNA flavivirus, directly cytopathic; major cause for post-transfusion (before 1991) and "sporadic" non-A, non-B hepatitis; large cumulative medical burden with high costs per case
- Prevalence from 0.5% (Great Britain) to 40% (Cameroon)
- Six genotypes with 40 subtypes exist:
  - An individual patient may harbor several subtypes (quasispecies)
  - Genotypes 1a, 1b, 2a, 2b, and 3a are common in Western Europe and the United States
  - Genotype 4 is common in Africa and the Middle East
- Incubation time is 6–7 weeks; acute infection goes unrecognized in 90%; 90% of infected individuals carry the virus indefinitely
- Relatively indolent course over many years; more severe cases with certain virus genotypes; presence of cirrhosis often underestimated clinically
- Major complications include significant fatigue (50% at 10 years), cirrhosis (25% at 20 years), and hepatocellular carcinoma (5% at 30 years); HCV infection is the leading cause for liver transplantation
- Diagnosis by enzyme immunoassay; confirmation by recombinant immunoblot assay
- Interferon alpha is the only established treatment, but only about 25% of infected individuals benefit; genotype 1b responds less well; liver transplantation for end-stage liver disease
- Recurrence after liver transplantation, but less rapid progression compared to hepatitis B recurrence
- Vaccines difficult to develop currently are not available

Microscopic (Acute Hepatitis C)

- Lobular hepatitis similar to hepatitis A or B, but bridging necrosis is rare; rarely biopsied
- Significant portal inflammation and lymphoid aggregates are common
- Overall picture is similar to chronic hepatitis C; however, fibrosis is absent

Microscopic (Chronic Hepatitis C)

- Prominent portal and periportal inflammation with lymphoid infiltrates; lymphoid aggregates/follicles in 50%
- Some lymphocytic bile duct damage without ductopenia is common
- Lymphocytic piecemeal necrosis (interface hepatitis), lobular inflammation, and hepatocellular necrosis define disease activity (grade); these changes are common, but usually mild
- Macrovesicular steatosis, generally mild and non-zonal, is typical

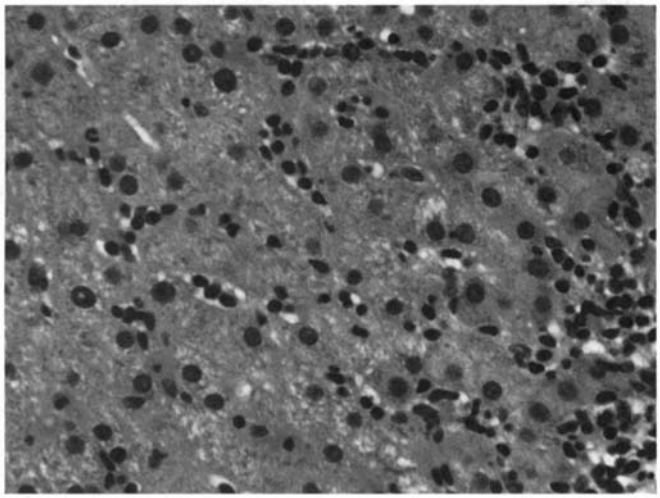


Fig. 12. Chronic hepatitis C infection showing sinusoidal lymphocytosis; the lymphocytes have been described as having a "string of beads" appearance.

- Increase in sinusoidal lymphocytes and macrophages ("string of beads") is common **(Figure 12)**
- Grading continues to be important in assessing disease activity because other reliable surrogate markers are not available:
  - Grading also plays a role in prognosis assessment and the predication of response to alpha interferon
- Staging predicts time to development of cirrhosis, response to medical therapy, rate of disease progression in untreated patients, and efficacy of therapy

Special Studies

- Immunohistochemical and/or in situ identification of HCV are technically possible but remain challenging; no diagnostic role in the non-transplant setting
- HCV RNA levels and HCV genotype can help predict response to alpha interferon

Differential Diagnosis

- Other viral hepatitis
- Steatohepatitis of other causes
- Drug-induced hepatitis
- Autoimmune hepatitis

Hepatitis D

- Very small RNA virus contained in hepatitis B virus protein envelope (HBs antigen), which is needed for entry into hepatocytes; defective virus requires the presence of HBV to replicate
- Worldwide distribution, with significant geographic variation; highest in South America
- HDV infection as coinfection at the time of HBV acquisition or as superinfection of chronic hepatitis B; wide range of clinical course
- Microscopic features in the range of those observed in hepatitis B
- Increases the severity of acute and chronic HBV infection and decreases the risk of becoming an HBV carrier
- Sexual and vertical transmission less common than in hepatitis B
- Detection by serologic testing or RT-PCR (method of choice); treatment with interferon is of uncertain benefit; prevention relies on hepatitis B prevention
- Liver transplantation is a valid treatment option; risk of allograft re-infection is much less than in typical hepatitis B case

Hepatitis E

Clinical

- RNA virus (calicivirus), endemic and/or epidemic in the developing world
- Transmission by fecal-oral route (contaminated water)
- Clinically indistinguishable from hepatitis A; incubation period is 2–9 weeks; commonly produces cholestasis
- Microscopically resembles acute hepatitis
- Cholestatic form shows centilobular cholestasis and gland-like transformation of hepatocytes
- Mild clinical course with resolution in a few weeks, however, high mortality in pregnancy (20%)
- Detection by serologic testing or by PCR; no specific treatment
- Prevention by prudent travel hygiene and sanitation

Hepatitis F

- Hepatitis F used for various undesignated viruses causing hepatitis
- Few cases from France, with subsequent experimental transmission to primates
- Cases from England of a hemorrhagic hepatitis related to a toga-like virus
- Virology, epidemiology, hepatotropicity, and clinical significance uncertain

Hepatitis G

- Also known as GBV-C
- Role as a true hepatitis virus uncertain
- Flavivirus, distant relative of HCV
- Identified by PCR, indicating current infection; immunoassay is in development; once antibodies are formed, HGV RNA is no longer present
- Nature, prevalence, risk factors, and preventive measures are unclear at this point
- Transmission is through blood transfusions, mother to child, and intravenous drug users
- Two percent of healthy blood donors test positive for HGV RNA

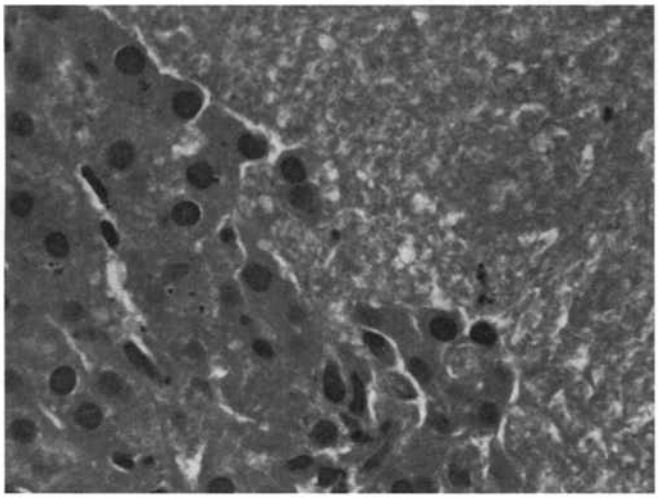


Fig. 13. Pneumocystis infection in a patient with HIV showing the typical pink frothy material characteristic of this infection.

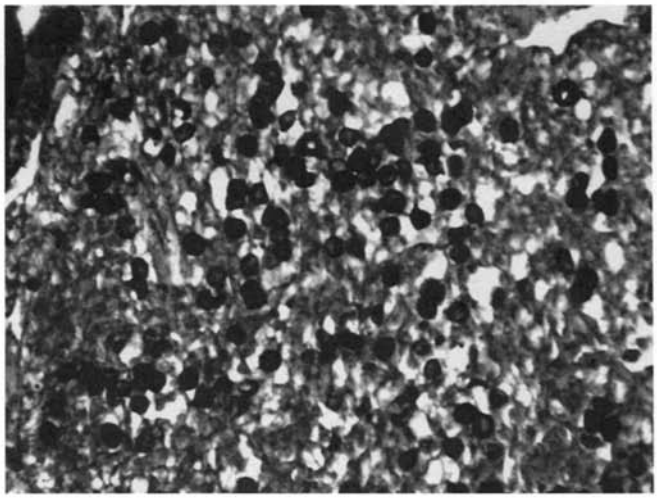


Fig. 14. Methanamine silver stain showing round and semi-lunar yeast forms of pneumocystis carinii in a patient with HIV infection.

- Co-infection with HBV or HCV is common, but no worsening of hepatitis B or C
- HGV may be a "virus looking for a disease"; likely does not cause acute hepatitis, but may be a co-factor in chronic hepatitis in certain risk groups

Human Immunodeficiency Virus Infection and AIDS

Clinical

- Majority of patients with AIDS reveal liver function abnormalities, secondary to associated infections, neoplasms, and drug toxicity **(Figure 13)**
- Prognosis related to AIDS stage
- Coinfection with hepatitis B and C is common

Microscopic

- Lymphocytic depletion in portal tracts in 50% of all cases
- Kupffer cells are main hepatic target for HIV
- Changes secondary to opportunistic infections (granulomas, multimicrobial AIDS cholangiopathy)
- Kaposi's sarcoma, lymphoma

Special Stains

- Ziehl-Nielsen stain (*M. tuberculosis*, *M. aviumintracellulare*)
- Methenamine silver (fungal organisms) **(Figure 14)**

Differential Diagnosis

- Other immunocompromising conditions

Epstein-Barr Virus Infection

Clinical

- Causes infectious mononucleosis; U.S. incidence twice that of acute viral hepatitis

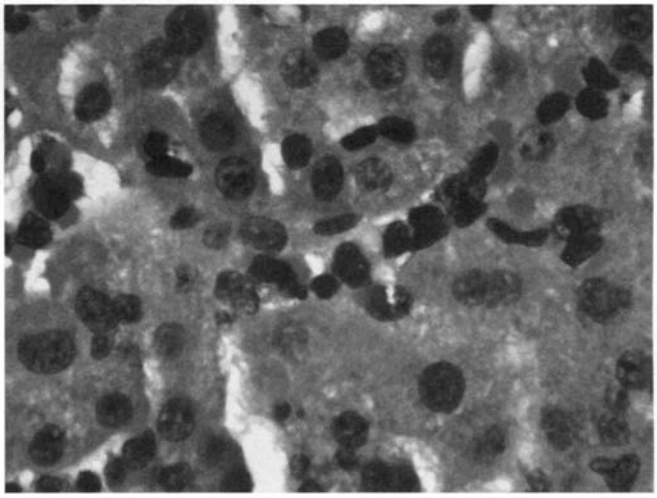


Fig. 15. Involvement of the liver by Epstein-Barr virus showing large atypical lymphocytes in "Indian file" arrangement in hepatic sinusoids.

- Five-week incubation period; 50% of cases clinically asymptomatic
- Liver involvement in 90% (elevated LFTs), jaundice only in 5%
- Immunocompromised patients may show signs of infection for years, no permanent liver damage

Microscopic

- Portal tract expansion by marked lymphoid infiltration; some lymphocytes are large and atypical, with circulating atypical lymphocytes in sinusoids (Indian file) **(Figure 15)**
- Cord-sinus pattern is intact, only minimal hepatocellular changes; no fibrosis **(Figure 16)**

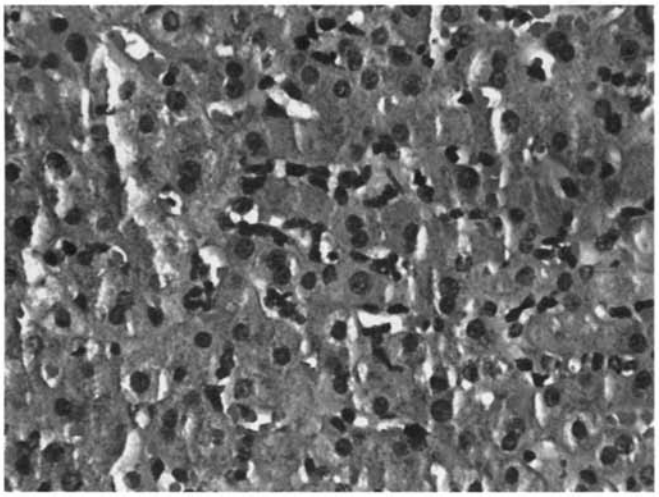


Fig. 16. Involvement of the liver by Epstein-Barr virus showing sinusoidal lymphocytosis without hepatocyte damage, necrosis or fibrosis.

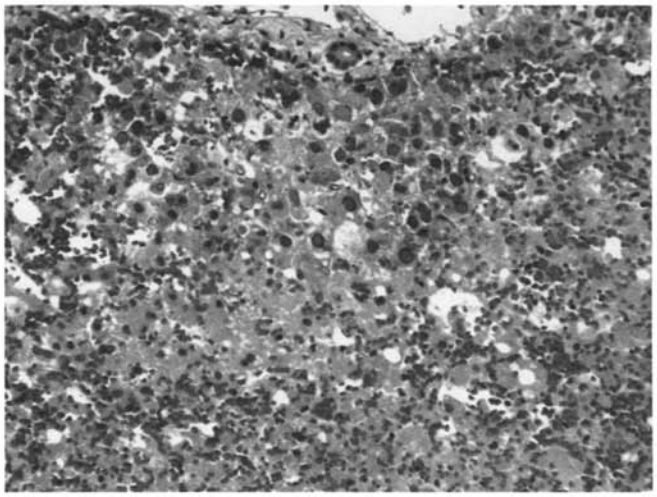


Fig. 17. Herpes simplex hepatitis showing areas of hemorrhagic necrosis.

Special Studies

- "Monospot" test is sensitive and specific
- EBV-specific antibodies confirm diagnosis

Differential Diagnosis

- Acute viral hepatitis
- CMV hepatitis
- Drug-induced hepatitis
- Lymphocytic leukemia

Cytomegalovirus Infection

Clinical

- Latent infection with subsequent reactivation in immunosuppression
- May be acquired from blood transfusions or congenital infection; multiorgan damage
- Clinically mild and self-limiting; rare cases of fatal liver failure in immunocompromised individuals

Microscopic

- Large intranuclear amphophilic inclusions with surrounding halo (owl's eye) are diagnostic, but generally only seen in immunocompromised individuals
- Mimics infectious mononucleosis when present in immunocompetent individuals
- Neonatal form with portal fibrosis, giant cells, and cholangitis

Special Studies

- CMV-specific serum antibodies

Immunohistochemistry

- CMV antigen as nuclear staining pattern in hepatocytes and bile duct epithelium

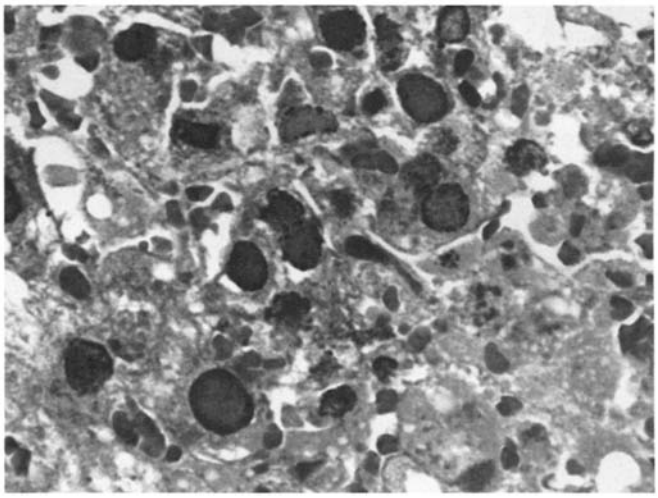


Fig. 18. Herpes simplex hepatitis showing amphophilic ground glass intranuclear inclusions of herpes simplex virus.

Differential Diagnosis

- Acute viral hepatitis
- EBV hepatitis
- Drug-induced hepatitis
- Lymphocytic leukemia

Herpes Simplex Virus Infection

Clinical

- Immunocompromised patients only
- Type 1 oral, type 2 genital; both may involve the liver
- Marked elevation of LFTs; disseminated intravascular coagulation common
- 90% fatality with symptomatic hepatic necrosis

Microscopic

- Coagulative necrosis and hemorrhage in large areas; no zonal distribution **(Figure 17)**
- Glassy, basophilic intranuclear inclusions; multinucleated cells with inclusions **(Figure 18)**

Special Studies

- HSV-genome sequencing after PCR-amplification distinguishes type 1 and 2

Immunohistochemistry

- Herpes virus

Differential Diagnosis

- Varicella-zoster
- Vaccinia
- Eclampsia

NONVIRAL INFECTIONS

Bacterial Infection

Pyogenic Bacterial Infection

Clinical

- Pyogenic abscesses from trauma, septicemia, and direct extension from other foci
- Malaise, pain, fever, hepatomegaly
- Treatment with antibiotics, aspiration, and culture for diagnosis
- Prognosis related to underlying condition

Microscopic

- Acute and chronic portal inflammation with cholestasis and microabscesses in parenchyma
- Liver cell necrosis, parenchymal inflammation with increased sinusoidal neutrophils

Special Stains

- Gram
- PAS (*Entamoeba histolytica*)

Differential Diagnosis

- Extrahepatic biliary obstruction
- Amebic abscess

Brucellosis

Clinical

- Brucella (gram negative coccobacillus), acquired by close contact with infected animals
- Fever, chills, hepatosplenomegaly, lymphadenopathy
- Diagnosis by culture from tissue (bone marrow); 5% fatality rate if untreated

Microscopic

- Granulomatous hepatitis with Kupffer cell hyperplasia
- Rarely microabscesses

Special Studies

- Tissue culture for diagnosis

Differential Diagnosis

- Typhoid fever
- Tularemia
- Drug-induced granulomatous changes
- Acid-fast bacilli or fungal organisms

Salmonellosis

Clinical

- S. typhi/paratyphi/typhimurium—food poisoning
- Hepatomegaly in 30%; jaundice infrequent
- Diagnosis by culture (blood, stool)
- 15% mortality if untreated; biliary tract disease as complication
- Chronic carrier state in 3%; gallbladder is reservoir for organisms

Microscopic

- Marked Kupffer cell hypertrophy and hyperplasia
- "Typhoid nodules" (focal necrosis and inflammatory aggregates) randomly seen in parenchyma
- Portal inflammation

Special Studies

- Culture for diagnosis, Gram-organisms in Kupffer cells

Differential Diagnosis

- Brucellosis
- Reticuloendothelial neoplasms

Recurrent Pyogenic Cholangiohepatitis

Clinical

- Frequently seen in the Far East; pathogenesis uncertain
- Clonorchis sinensis is present in 50%; biliary cultures are positive for enteric bacteria
- Recurrent symptoms of acute cholangitis
- Biliary calculi and sludge are present; left lobe is predominantly affected

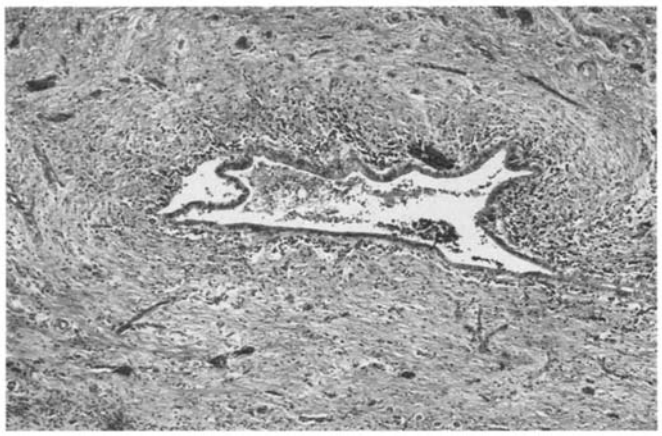


Fig. 19. Recurrent pyogenic cholangitis showing periductal inflamamtion, fibrosis and epithelial damage.

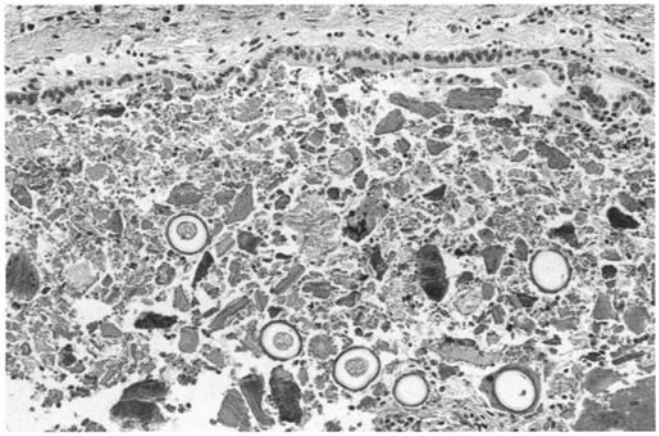


Fig. 20. Same case as shown in **Fig. 19.** Several ducts were dilated and contained bile sludge along with eggs of Ascaris lumbricoides.

- Complications include pancreatitis, liver abscess, fistulas, septicemia, cholangiocarcinoma, and portal vein thrombosis
- Prognosis related to complications

Microscopic

- Intrahepatic duct dilatation with surrounding inflammation and abscess formation
- Cholestasis, fibrosis, intrahepatic calculi, sludge **(Figures 19,20)**

Differential Diagnosis

- Extrahepatic obstruction
- Primary sclerosing cholangitis
- Caroli's disease

Syphilis

Clinical

- Treponema pallidum—liver involvement in three stages; consequences of tertiary disease determine prognosis:

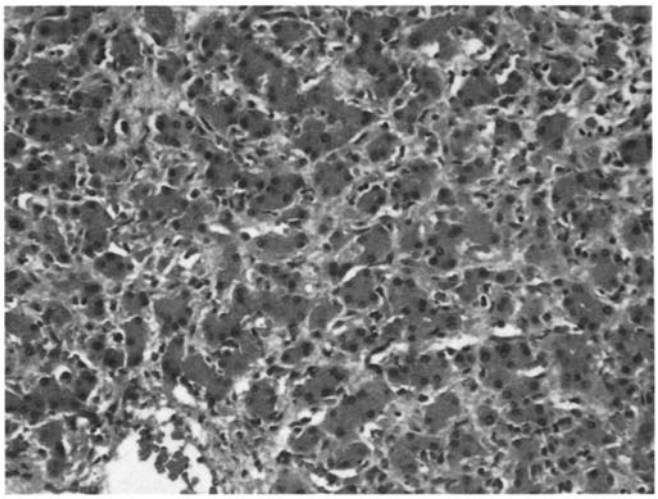


Fig. 21. Congenital syphilis showing marked sinusoidal fibrosis in the absence of inflammation, necrosis and fibrosis.

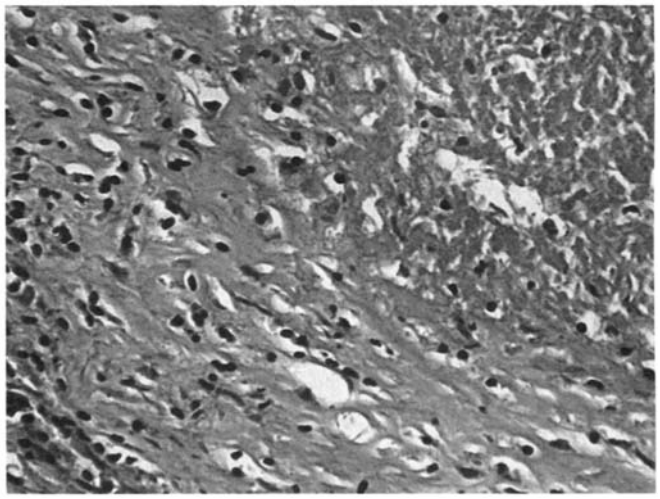


Fig. 22. Tertiary syphilis showing gumma with central necrosis surrounded by fibrosis.

  - Congenital syphilis (liver disease years after birth)
  - Secondary syphilis (10% of infected patients, non-specific liver disease)
  - Tertiary syphilis (Hepar lobatum—deeply scarred liver secondary to fibrosed gumma)

Microscopic

- Congenital: Severe portal and interstitial fibrosis with focal necrosis; no regeneration **(Figure 21)**
- Secondary: Scattered epithelioid granulomas and small vessel vasculitis typical
- Tertiary: Gumma formation and obliterative endarteritis, dense scar formation, and amyloid deposition **(Figure 22)**

Special Studies

- Darkfield microscopy
- Immunohistochemistry
- Silver stain (congenital, some secondary stage cases)

Differential Diagnosis

- Neonatal giant cell hepatitis
- Brucellosis/salmonellosis
- Drug-induced granulomatous hepatitis

Mycobacterium Infection

Tuberculosis

Clinical

- Hepatic involvement in 25% (chronic forms), 70% (acute primary pulmonary disease) to 95% (miliary tuberculosis)
- High index of suspicion because necrotizing granulomas, stained organisms, or positive culture are rather uncommon on liver biopsy
- Non-specific liver disease at presentation; severe hepatic dysfunction is rare; liver disease is almost never responsible for mortality

Microscopic

- Well-defined portal and parenchymal epithelioid granulomas with Langerhans' giant cells
- Necrotizing granulomas rare, seen with active organism growth
- Macrovesicular steatosis

Special Studies

- Ziehl-Neilsen stain (commonly negative)

Differential Diagnosis

- Sarcoidosis
- Other granulomatous reactions

Mycobacterium-avium intracellulare (MAI) Infection

Clinical

- Slowly growing nontuberculous organism; disseminated infection in immunocompromised individuals
- Hepatic involvement in 50%, with non-specific liver disease
- Treatment response in AIDS and other immunocompromised patients dismal

Microscopic

- Less circumscribed, usually non-necrotizing granulomas in portal tracts and parenchyma, with foamy histiocytes in immunocompromised patients
- No zonal distribution of granulomas

Special Studies

- PAS
- Acid-fast stain

Differential Diagnosis

- Tuberculosis
- Gaucher's disease
- Histiocytosis X
- Neoplasms

Leprosy

Clinical

- *M. leprae*, an estimated 20 million people infected (tropical climate); hepatic granulomas in >50%
- Systemic amyloidosis is a frequent complication
- Difficult to eradicate; morbidity from nerve destruction

Microscopic

- Tuberculoid type (granulomas), lepromatous type (granulomas and foamy histiocytes), types
- Portal inflammation

Special Studies

- Fite stain for acid-fast bacilli
- Silver stains (non-viable organisms)

Differential Diagnosis

- Sarcoidosis
- Tuberculosis

Rickettsial Infection

Clinical

- *Coxiella burnetti* (Q fever) and *R. rickettsii* (Rocky Mountain spotted fever)
- Liver involvement in 85%; antibiotics curative

Microscopic

- Granulomatous hepatitis with focal necrosis; fibrin ring around fat vacuoles (fibrin ring granulomas) **(Figure 23)**
- Portal inflammation and macrovesicular steatosis
- Prominent Kupffer cell hyperplasia

Differential Diagnosis

- Bacterial infections
- Lymphomas
- EBV infection

Fungal Infection

Histoplasmosis

Clinical

- Histoplasma capsulatum, highly endemic in Ohio and Mississippi River Valleys and in South America
- Birds are main carriers; asymptomatic infection in 90%

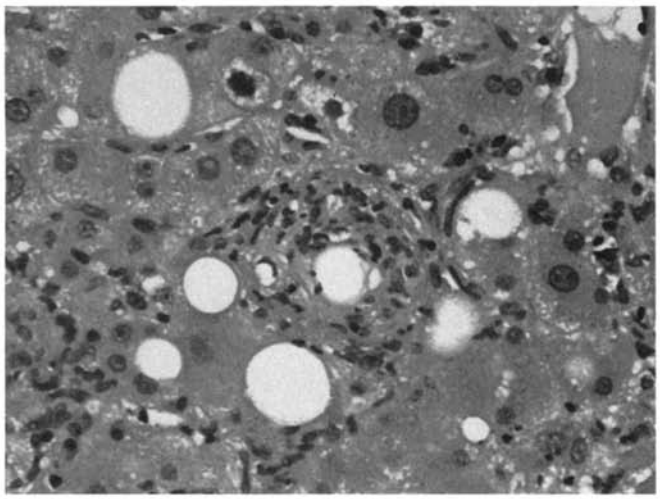


Fig. 23. Rickettsial heaptitis showing a fat vacoule surrounded by a fibrin ring—the "fibrin ring granuloma".

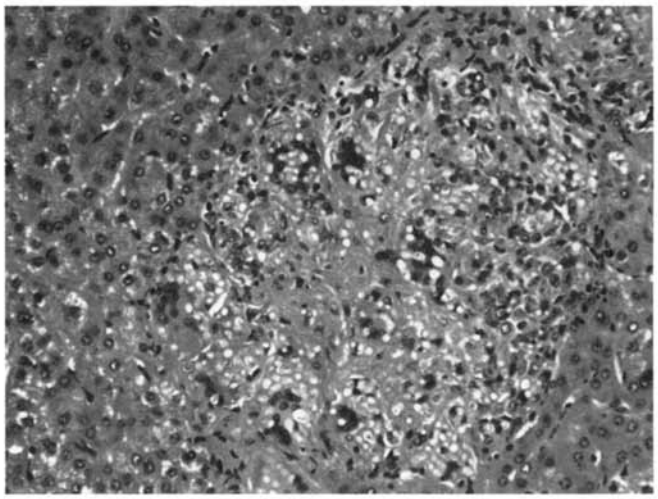


Fig. 24. Histoplasmosis of the liver with an early granuloma containing numerous organisms.

- Immunocompromised individuals with disseminated disease and liver involvement
- Mortality is high in untreated symptomatic disease

Microscopic

- Parenchymal granulomas, some necrotizing, often calcified in late stages **(Figure 24)**
- Organisms (2–5 mm with crescent appearance) in Kupffer cells and histiocytes **(Figure 25)**
- Abundant organisms and scant granulomas in immunocompromised patients

Special Studies

- PAS
- Silver stain

Differential Diagnosis

- Tuberculosis
- Sarcoidosis
- Leishmaniasis

Coccidioidomycoses

Clinical

- Coccidiodes immitis, endemic in southwestern United States and South America
- Usually benign, self-limited pulmonary infection
- Immunocompromised individuals with disseminated disease and liver involvement
- Mortality high in untreated symptomatic disease

Microscopic

- Epithelioid granulomas with multinucleated giant cells containing the organisms (20–200 mm spherules with 2 mm wall); no calcifications seen

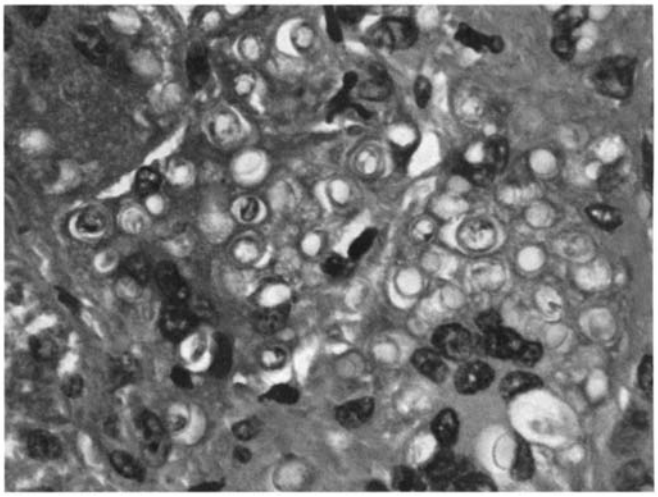


Fig. 25. A high power view of **Figure 24** showing 2–5 micron non-budding yeast forms of histoplasmosis.

- Portal inflammation

Special Studies

- PAS
- Silver stain

Differential Diagnosis

- Tuberculosis
- Sarcoidosis
- Blastomycosis

Parasite Infection

Amebic Abscess

Clinical

- Access of *Entamoeba histolytica* into the portal system from the intestine

- Usually single abscess, 8–12 cm diameter
- Gradual clinical onset with fever and pain; amebic serology is positive
- Responds to treatment; complications include dissemination or rupture

Macroscopic

- Abscess (cyst) formation with fibrous capsule

Microscopic

- Only minimal inflammatory reaction in cyst and wall
- Trophozoites identifiable at periphery (round to oval, 20–60 mm, spherical nuclei and eosinophilic cytoplasm, phagocytosed red blood cells)

Special Studies

- Immunostaining possible
- PAS

Differential Diagnosis

- Pyogenic abscess
- Necrotic tumor mass

Malaria

Clinical

- Plasmodium species, 100 million cases per year worldwide
- Liver involvement by adherence to liver venules and ischemic necrosis
- Liver forms of the organism responsible for late relapses
- Malaria symptoms plus hepatosplenomegaly; jaundice possible
- Increased mortality with *P. falciparum* species

Microscopic

- Dark pigment (hemozoin) in Kupffer cells **(Figure 26)**
- Perivenular necrosis
- Sinusoidal congestion with parasite-filled Kupffer cells and red blood cells

Special Studies

- Prussian blue; hemozoin is negative
- Immunostaining for the organism possible

Differential Diagnosis

- Disorders with hemosiderin deposition in Kupffer cells
- Schistosomiasis

Hydatid Cyst

Clinical

- Echinococcus species, transmitted by dog feces
- Usually single cyst, slowly enlarging (up to 25 cm), often palpable

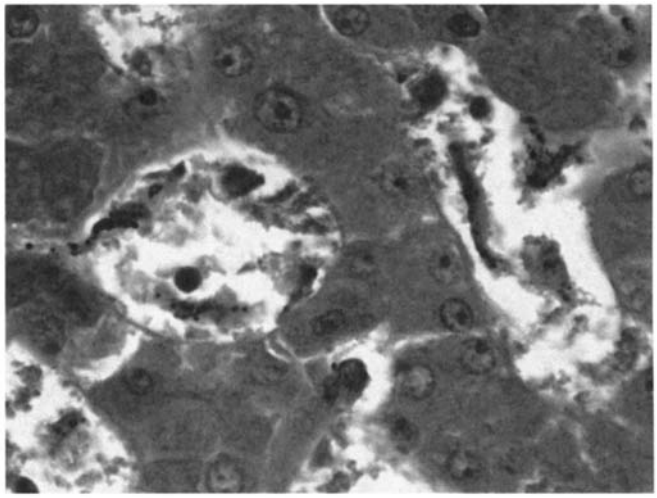


Fig. 26. Malaria showing marked deposition in Kupffer cells of hemozoin, that appears as a dark brown pigment on H&E stain.

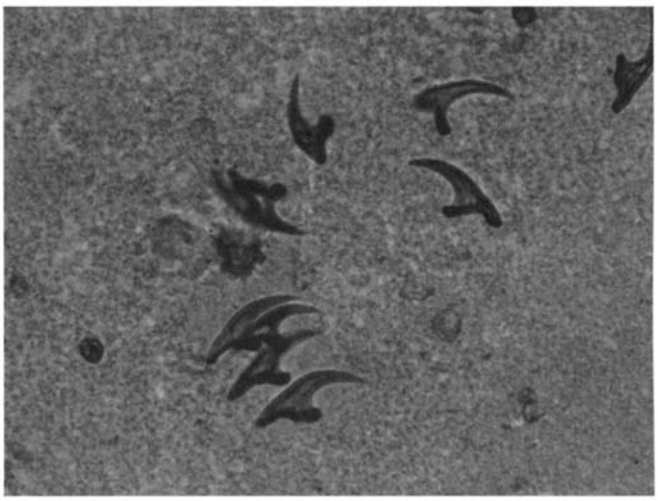


Fig. 27. Hooklets from the sediment of a hepatic hydatid cyst.

- Complications include biliary obstruction, cholangitis, superinfection, and anaphylaxis
- Prognosis usually good, if treated (surgical resection and/or parasiticidal drugs)

Macroscopic

- Unilocular or multilocular, endogenous (*E. granulosus*) or exogenous (*E. multiloculare*) daughter cyst formation
- Calcifications common

Microscopic

- Cyst wall with thin inner germinal layer and outer layer of dense hyalinized/calcified tissue with surrounding inflammation
- Scolices and hooklets present within the cyst **(Figure 27)**



Fig. 28. Clonorchis sinensis in a large bile duct that shows proliferation of small peribiliary glands.

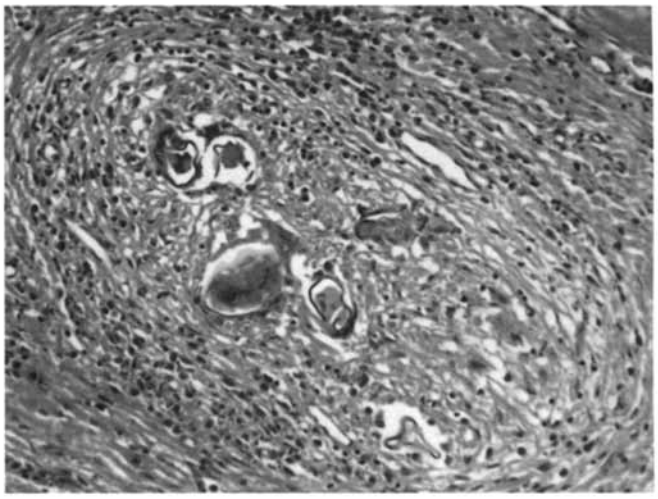


Fig. 29. Schistosomiasis showing several eggs surrounded by an intense granulomatous inflammation.

Differential Diagnosis

- Amebic abscess

Clonorchiasis

Clinical

- Clonorchis sinensis, common infection in the Far East, humans as definitive host; parasite rests in major intrahepatic ducts
- Usually asymptomatic; severe infections cause recurrent pyogenic cholangitis with typical symptoms
- Complications include duct obstruction, cholangitis, and cholangiocarcinoma; prognosis with treatment good

Macroscopic

- Hepatomegaly with grey and pale blue subcapsular cysts (dilated ducts with parasites)

Microscopic

- Organism in bile ducts **(Figure 28)**
- Proliferation of small glands around affected bile ducts
- Ductular proliferation in portal tracts

Differential Diagnosis

- Mechanical duct obstruction
- Recurrent pyogenic cholangiohepatitis

Schistosomiasis

Clinical

- Schistosoma species, infection through skin in infested waters; liver disease by *S. mansoni* and *S. japonicum*
- Mortality due to portal hypertension in chronic disease (granulomatous reaction to organism eggs in portal circulation)

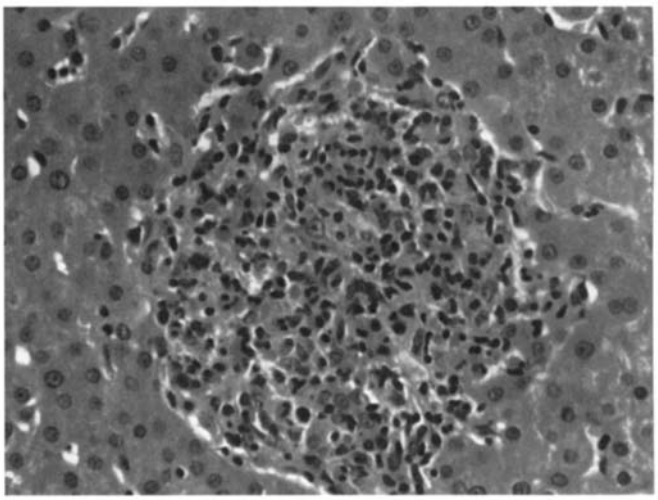


Fig. 30. Schistosomiasis showing an intense eosinophilic inflammation. Deeper sections showed a schistosoma egg within this infiltrate.

Microscopic

- Granulomatous and/or eosinophilic portal inflammation surrounding parasite eggs **(Figures 29,30)**
- Variable degrees of lamellar fibrosis (pipe-stem lesion)

Special Studies

- Acid-fast+

Differential Diagnosis

- Granulomatous lesions of other etiologies
- Portal fibrosis

DRUGS AND TOXINS

General Features

- Drugs and other chemical toxins account for <5% of cases of jaundice, hepatitis, or chronic liver disease, but are an important cause of more severe types of hepatic injury
- Drugs produce an array of hepatic lesions that mimic all known hepatobiliary diseases and pose a diagnostic challenge for clinicians and pathologists
- Diagnosis is circumstantial, with positive rechallenge being the only factor that unequivocally implicates a particular agent after consideration of the temporal relationships between drug ingestion and liver disease and exclusion of other hepatobiliary disorders
- Liver biopsy can lend support to the diagnosis; early detection is critical
- Protocol screening of patients with liver function tests and/or biopsy is recommended for certain drugs, but efficiency and cost-effectiveness are mostly unknown and controversial

Pure Hepatocellular Necrosis

Common Example: Acetaminophen

- Large dose (>10 g) results in liver cell necrosis with rapid development of liver failure; typically suicidal
- N-acetylcysteine (repletes glutathione) administration up to 10 hours after ingestion prevents catastrophic outcome; transplantation is life-saving, but controversial
- Coagulative-type necrosis, perivenular; uniform liver involvement **(Figure 31)**
- Marked midzonal and portal regeneration after 1 week

Other Drugs

- Periportal (zone 1): Ferrous sulfate, phosphorus
- Midzonal (zone 2): Beryllium, dioxane, disulfiram, sulfasalazine, indomethacin
- Perivenular (zone 3): Aflatoxin B1, chloroform, carbon tetrachloride, halogenated hydrocarbons, phalloidin, other alkaloids
- Diffuse: Trinitrotoluene, tetrachlorethane, piroxicam, cimetidine, carbamazepine

Acute Hepatitis

Common Example: Isoniazid

- Incidence of acute hepatitis and abnormal liver function tests in patients over 35 years of age is 3% and 30%, respectively; 10% of symptomatic patients die of hepatic failure; overall mortality is 0.1%
- Subacute hepatic injury or overt hepatic injury 2–11 months after treatment initiation
- Drug withdrawal resolves the problem in 70% of all cases; supportive treatment, liver transplantation
- Diffuse hydropic change, focal necroses, and periportal inflammation

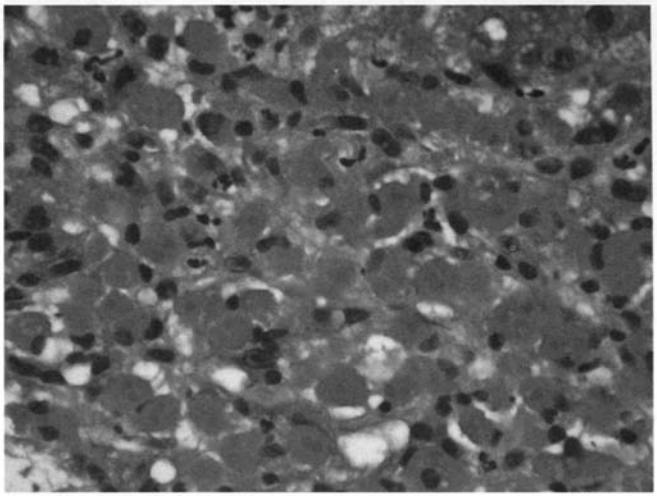


Fig. 31. Acetaminophen toxicity showing coagulative necrosis in acinar zone 3 in which hepatocytes have lost their nuclei but maintain their structure.

Common Example: Phenytoin

- Incidence of acute hepatitis is 1%; hepatotoxicity is caused by hypersensitivity
- Clinical presentation like viral hepatitis plus rash and eosinophilia
- Prompt reproducibility upon rechallenge; excellent prognosis
- Features resembling viral hepatitis and EBV infection with "Indian filing" of sinusoidal lymphocytes

Common Example: Halothane

- Incidence of acute hepatitis is 1:9,000; mortality rate is 1:40,000
- Clinical symptoms after 1–14 days of exposure; abrupt onset; jaundice
- Re-exposure triggers a more severe response
- Supportive treatment or liver transplantation
- Similar features as phenytoin and isoniazid, plus perivenular stromal collapse after repeated exposure

Other Drugs

- Alpha-methyldopa, diclofenac, tetracyclins, indomethacin, nitrofurantoin, phenylbutazone, rifampin, sulfasalazine

Chronic Hepatitis

Common Example: Nitrofurantoin

- Latent period is >6 months, probable autoimmune etiology (ANA+, SMA+)
- Jaundice, fatigue, fever
- Drug withdrawal results in resolution

- Periportal inflammation, diffuse liver cell necrosis, portal fibrosis, hydropic change, cholestasis

Other Drugs

- Alpha-methyldopa, aspirin, chlorpromazine, diclofenac, tetracyclins, disulfiram, isoniazid, methotrexate, propylthiouracil, sulfonamides

Cholestasis and Duct Injury

Common Example: Oral Contraceptives

- Overall incidence 1:10,000 users, symptomatic within 1–6 months
- Gradual onset of hepatitis/cholestasis symptoms
- Cessation of the drug induces remission
- Hepatocellular cholestasis, perivenular dilated canaliculi
- Other hepatic structures relatively normal

Other Drugs

- Pure cholestasis: Anabolic steroids
- Cholestatic hepatitis: Azathioprine, chlorpromazine, cimetidine, erythromycin, 6-mercaptopurine, flucloxacillin, nitrofurantoin, penicillin, sulfonamides, tamoxifen, verapamil
- Acute cholangitis: Allopurinol, chlorpromazine, hydralazine
- Biliary cirrhosis: Ajmaline, chlorpromazine, methyl testosterone, sulfonylurea, tolbutamide

Fibrosis

Common Example: Methotrexate

- Liver cell injury is dose-dependent (cumulative dose >2–4 g) and "predictable"
- Insidious onset of hepatosplenomegaly and ascites
- Surveillance liver biopsies recommended in long-term treatment
- Portal fibrosis and sinusoidal collagen deposition
- Prominent diffuse hepatocellular disarray and dysplasia

Other Drugs

- Aflatoxin, copper, disulfiram, alpha-methyldopa, isoniazid

Steatosis

Macrovesicular

- Bleomycin, L-asparaginase, methotrexate, steroids, cisplatin, sulfasalazine, warfarin, indomethacin, tamoxifen, amiadarone **(Figure 32)**

Microvesicular

- Aflatoxin, aspirin, phalloidin, tetracycline, valproic acid

Vascular Abnormalities

Peliosis-like Lesions

- Anabolic steroids, phalloidin, vitamin A

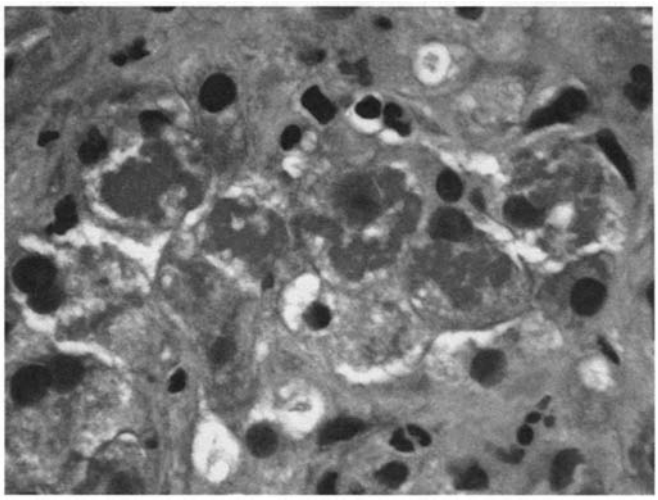


Fig. 32. Amiadarone toxicity showing numerous Mallory hyalin in damaged hepatocytes.

Sinusoidal Dilatation

- Oral contraceptives

Veno-Occlusive Disease

- Aflatoxin, azathioprine, busulfan, mitomycin C, oral contraceptives, tamoxifen, vinyl chloride, vitamin A

Vasculitis

- Allopurinol, chlorthiazide, penicillin, phenylbutazone, phenytoin, sulfonamides

Granulomas

- Non-necrotizing epithelioid or inflammatory types possible
- Usually random distribution
- May be associated with mild non-specific inflammatory changes
- Common examples include allopurinol, alpha-methyldopa, carbamazepine, hydralazine, penicillin, phenylbutazone, phenytoin, quinidine, and sulfonamides

Neoplasms

Liver Cell Adenoma

- Anabolic steroids
- Oral contraceptives controversial

Hepatocellular Carcinoma

- Aflatoxin, anabolic steroids, mycotoxins, thorotrast, vinyl chloride

Cholangiocarcinoma

- Thorotrast, vinyl chloride

Angiosarcoma

- Anabolic steroids, copper sulfate, diethylstilbestrol, thorotrast, vinyl chloride

STEATOHEPATITIC LIVER DISEASE

Acute Alcoholic Liver Disease

Steatosis

Clinical

- Most common hepatic abnormality in alcoholics (>90%); may occur in many other clinical conditions (*see* differential diagnosis)
- Degree of steatosis somewhat proportional to alcohol intake and dietary protein
- Hepatomegaly as the only clinical sign, demonstrable by ultrasound and CT; steatosis may appear focal
- Asymptomatic if steatosis only; completely reversible in 8 weeks if abstinent from alcohol

Microscopic

- Macrovesicular steatosis, more prominent perivenular
- Parenchymal lipogranulomas
- No significant inflammation

Differential Diagnosis

- Obesity
- Diabetes mellitus
- Jejunoileal bypass
- Drugs
- Malnutrition

Steatohepatitis

Clinical

- Chronic alcohol consumption; similar histology can be seen in non-alcoholics (non-alcoholic steatohepatitis, aka "NASH") in generally milder form clinically and histologically
- Wide range of possible presenting symptoms, including nausea, vomiting, hepatomegaly, fever, jaundice, ascites, and hepatic encephalopathy
- Occurs usually after several years of heavy drinking; one-third of patients have significant fibrosis/cirrhosis at presentation
- Cessation of alcohol intake and supportive treatment as the only therapeutic option; worsening of clinical symptoms 2–4 weeks after abstinence possible
- High mortality or definite progression to cirrhosis if drinking problem continues

Microscopic

- Variable macrovesicular steatosis, may be marked
- Ballooning change of hepatocytes, most prominent perivenular **(Figure 33)**
- Neutrophilic infiltrate around damaged hepatocytes
- Amorphous, eosinophilic material in many affected hepatocytes (Mallory hyalin) **(Figure 34)**

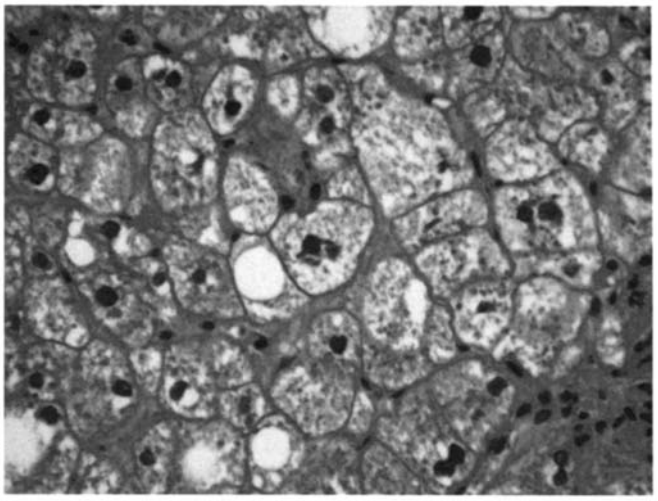


Fig. 33. Steatohepatitis showing ballooning change of hepatocytes.

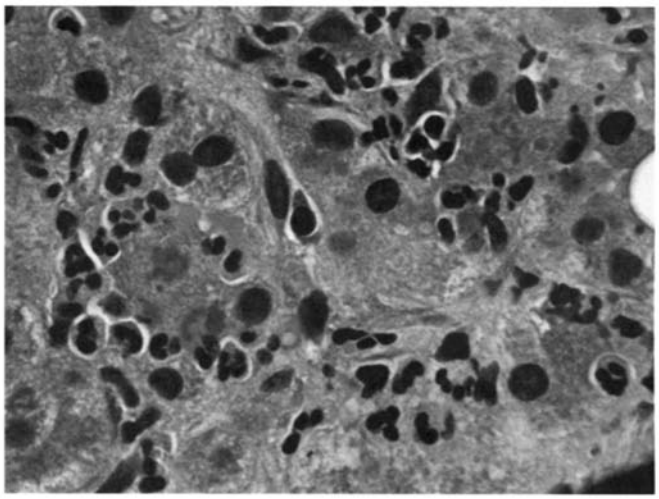


Fig. 34. Steatohepatitis showing neutrophilic infiltrate and Mallory hyalin which appears as amorphous, eosinophilic material in hepatocytes.

- Varying degrees of fibrosis, usually perivenular; later stages also bridging **(Figures 35,36)**
- Cholestasis possible
- Histologic variants include alcoholic foamy degeneration and acute sclerosing hyaline necrosis

Special Studies

- Masson's trichrome **(Figures 35,36)**
- Reticulin **(Figure 37)**
- PAS diastase

Differential Diagnosis

- Wide range of differential diagnoses (*see* steatosis)
- Search for other etiologies after exclusion of alcohol

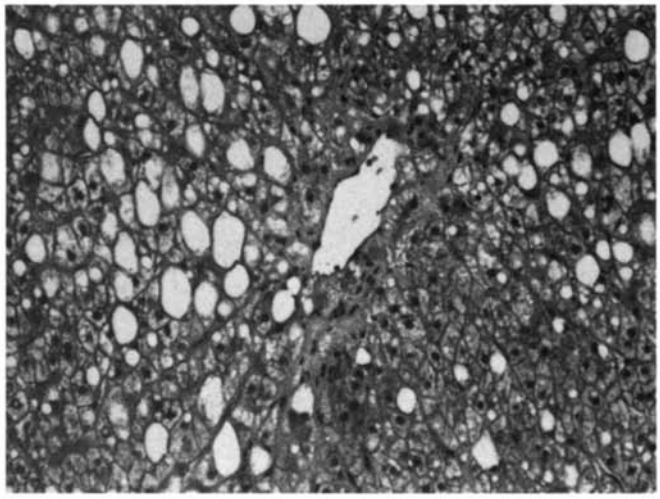


Fig. 35. Steatohepatitis showing macrovesicular steatosis, perivenular and pericellular fibrosis (Masson's trichrome).

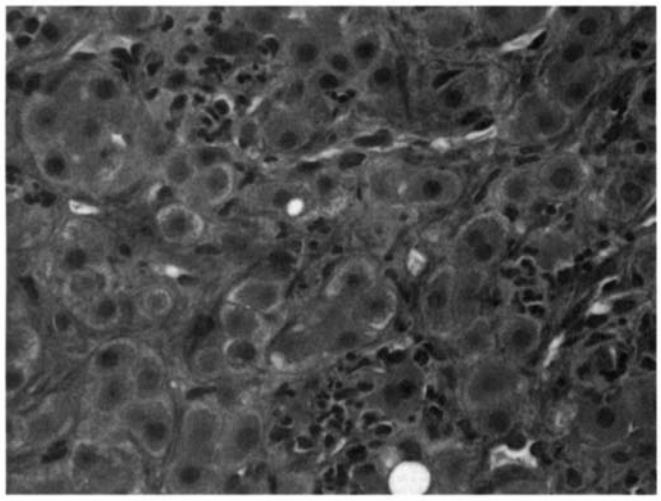


Fig. 36. Steatohepatitis showing extensive pericellular fibrosis (Masson's trichrome).

Chronic Alcoholic Liver Disease

Progressive Perivenular Fibrosis

Clinical

- Precirrhotic stage of chronic alcoholic liver disease
- Differs from the "usual" perivenular fibrosis in alcoholics by denseness and degree of perivenular fibrosis and by absence of regenerative nodules
- Patients present with jaundice and ascites, which is resistant to diuretics
- Uniform liver involvement with severe venous outflow obstruction, subsequent clinical features of portal hypertension, and concomitant cirrhosis
- Treatment and prognosis similar to cirrhosis

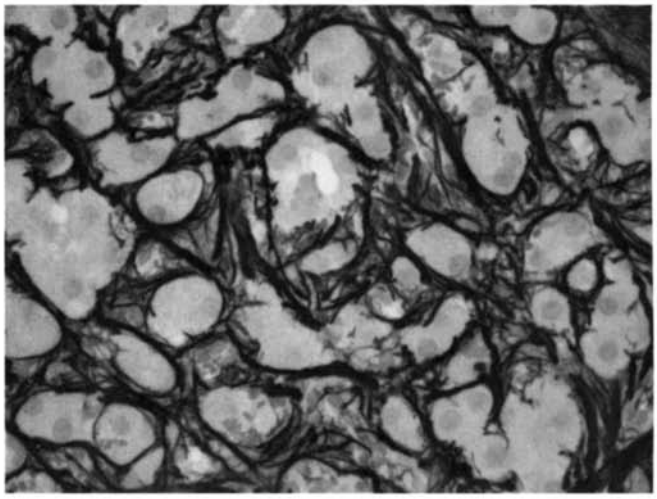


Fig. 37. Reticulin stain in steatohepatitis showing an increase in pericellular reticulin fibres.

Microscopic

- Dense sclerosis of perivenular zones
- Pericellular fibrosis of varying degrees
- Only minimal portal fibrosis
- Minimal or absent regeneration

Special Studies

- Masson's trichrome

Cirrhosis

Clinical

- Initial presentation in 40% of cases of alcohol-induced liver disease
- Several years of heavy drinking required; only a subset of chronic drinkers develop cirrhosis; dietary factors may play a role (protein intake)
- Women have a much lower threshold
- Active drinker has micronodular cirrhosis (nodules between 1–4 mm in size); with abstinence, regeneration occurs and nodules become larger
- Laboratory tests may be normal unless acute liver disease or decompensation is present
- Hepatomegaly in early stages; later, atrophic livers predominate
- Hepatocellular carcinoma in 5% to 10%
- Management similar to cirrhosis from other causes; abstinence does not influence survival in the cirrhotic stage; however, it is required for consideration of liver transplantation
- One-year survival after onset of gastrointestinal hemorrhage or ascites = 30% to 50%; 5-year survival after portacaval shunting = 25%; transplantation is curative

Microscopic

- Fibrous septa bridging central venules to central venules
- Pericellular fibrosis
- Micronodules or regenerative nodules if abstinent
- Varying degrees of inflammation, steatosis, cholestasis

Special Studies

- Masson's trichrome

Differential Diagnosis

- Cirrhosis of other etiologies

Total Parenteral Nutrition

Clinical

- Steatosis due to imbalances in lipoprotein and fatty acid synthesis with subsequent cholestasis
- Jaundice develops after 4–40 days of total parenteral nutrition, resolves with normal oral food intake; cirrhosis with long-standing TPN
- Gallstones and sludge develop frequently
- Disease mechanism in neonates and infants more complex; 2% mortality from liver failure

Microscopic

- Variable degrees of macrovesicular steatosis
- Perivenular cholestasis and portal bile ductular proliferation
- Giant cell transformation of hepatocytes in the neonate

Differential Diagnosis

- Extrahepatic biliary atresia
- Choledochal cyst
- Neonatal giant cell hepatitis

Non-Alcoholic Steatohepatitic Liver Disease

Jejunoileal Bypass

Clinical

- Procedure done for morbid obesity, 5% will develop hepatic failure months after surgery, with high mortality unless normal anatomy is restored
- Significant fibrosis and cirrhosis in 7% within 1–2 years

Microscopic

- Acute: significant macrovesicular steatosis, perivenular collagen deposition in sinusoids, with liver cell necrosis
- Chronic: well-circumscribed regenerative nodules with fibrosis/cirrhosis; no significant inflammation

Special Studies

- Masson's trichrome

Differential Diagnosis

- Drugs
- Obesity
- Diabetes mellitus
- Acute alcohol-induced liver disease

Obesity and Diabetes Mellitus

Clinical

- Liver function test abnormalities in 35% of patients with diabetes mellitus
- Typically overweight women, even in the absence of diabetes mellitus
- Cirrhosis more frequent in diabetics; weight loss as therapy

Microscopic

- Significant diffuse macrovesicular steatosis
- Glycogenated nuclei more commonly in the diabetic
- Minimal inflammatory changes, mild portal bile duct proliferation
- Micronodular cirrhosis in chronic cases

Special Studies

- Masson's trichrome

Differential Diagnosis

- Jejunoileal bypass
- Acute alcohol-induced liver disease

Acute Fatty Liver of Pregnancy

Clinical

- Young women in their first pregnancy, third trimester
- Rare disorder (<1:10,000 deliveries), etiology unknown
- Non-specific symptoms followed by jaundice
- Supportive treatment with termination of pregnancy; good prognosis with early recognition; overall mortality = 10% to 20%

Microscopic

- Marked microvesicular steatosis, less prominent periportal
- Minimal inflammation and necrosis

Special Studies

- Fat stains

Differential Diagnosis

- Drugs
- Alcohol-induced foamy degeneration
- Reye's syndrome

VASCULAR DISORDERS

Hepatic Venous Outflow Obstruction

Congestive Heart Failure

Clinical

- Serum LFTs usually mildly elevated or normal; jaundice almost never seen
- Chronic right-sided heart failure may cause phlebosclerosis
- "Cardiac cirrhosis" (long-standing congestion) takes years to develop; no regenerative nodules seen
- Treatment of heart disorder resolves liver disease; mortality due to cardiac complications

Microscopic

- Acute: perivenular sinusoidal dilatation and congestion
- Chronic: perivenular sinusoidal dilatation, liver cell atrophy, perivenular fibrosis and bridging fibrosis in long-standing disease

Special Studies

- Masson's trichrome

Differential Diagnosis

- Budd-Chiari syndrome
- Cirrhosis, non-cardiac

Budd-Chiari Syndrome

Clinical

- Hepatic venous outflow obstruction
- Causes include membranous obstruction of large hepatic veins (South Africa, Japan, India) and fibrous obliteration of major hepatic veins (Western countries), malignancy, trauma, infection, and radiation
- Clinical presentation with symptoms of acute to chronic liver failure; laboratory tests similar to cirrhosis
- Outcome and complications similar to cryptogenic cirrhosis (chronic forms), acute Budd-Chiari syndrome with poor prognosis

Microscopic

- Acute: severe perivenular sinusoidal dilatation, congestion and hemorrhage **(Figures 38,39)**
- Chronic: perivenular and sinusoidal fibrosis with bridging in late stages

Special Studies

- Masson's trichrome

Differential Diagnosis

- Cardiac congestion
- Drug effect
- Cirrhosis

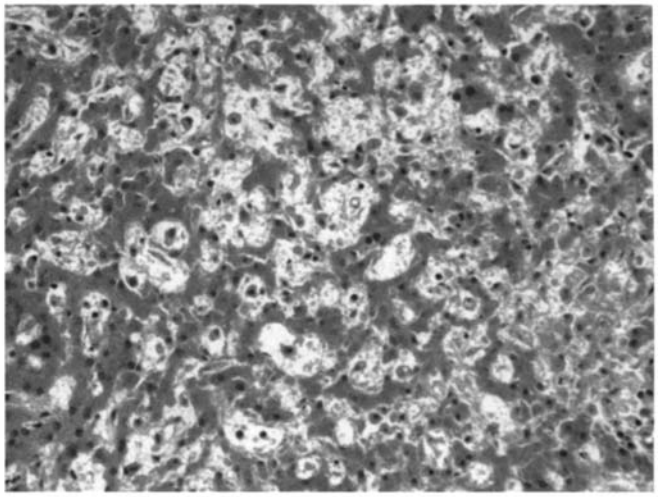


Fig. 38. Centrilobular sinusoidal dilatation and congestion with hepatic plate atrophy in a patient with Budd-Chiari syndrome.

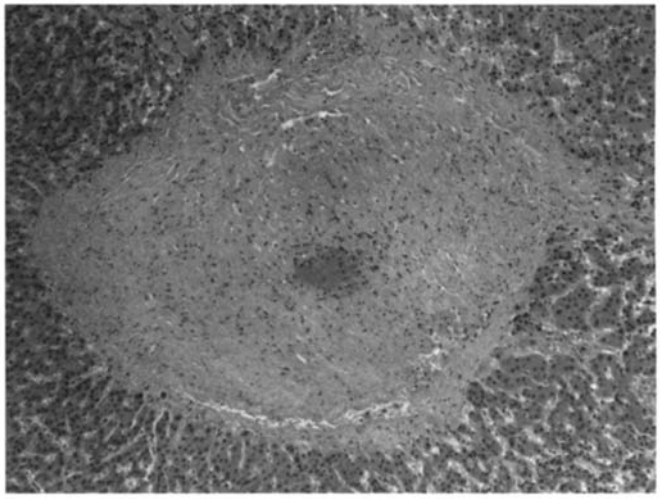


Fig. 39. An occluded sublobular hepatic vein in a patient with Budd-Chiari syndrome.

Veno-Occlusive Disease

Clinical

- Acute (hepatic failure) and chronic (insidious liver disease) presentations
- Direct hepatic vein endothelial damage with fibrin deposition
- Causes include radiation, chemotherapy, graft-versus-host disease in bone marrow transplantation, and alcoholic liver disease
- Endemic in the West Indies (tea with toxic alkaloids)
- Symptomatic treatment as in chronic liver disease, liver transplantation

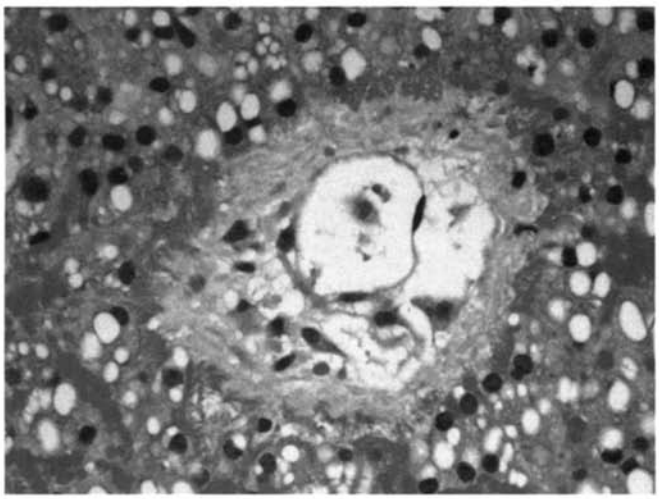


Fig. 40. Veno-occlusive disease showing intimal thickening and partial occlusion of a central venule in a patient on chemotherapy for leukemia. The remaining liver biopsy shows centrilobular congestion and necrosis.

Microscopic

- Acute: fibrous obliteration of terminal hepatic venules, sinusoidal dilatation and congestion **(Figure 40)**
- Chronic: liver cell atrophy, perivenular and sinusoidal fibrosis, no changes in larger hepatic veins

Special Studies

- Masson's trichrome

Differential Diagnosis

- Budd-Chiari syndrome
- Right-sided heart failure

Hypotensive Anoxia

Clinical

- Hepatic arterial blood flow directly related to cardiac output; only severe hypotension leads to extensive liver cell necrosis; usually varying degrees of mild ischemic necrosis throughout the liver; rarely significant hepatic dysfunction
- Full recovery from a single hypotensive episode; prognosis related to underlying problem

Microscopic

- Liver cell coagulative necrosis, prominent in perivenular zones, later perivenular collapse

Special Studies

- Reticulin

Differential Diagnosis

- Drug-induced liver injury
- Viral hepatitis

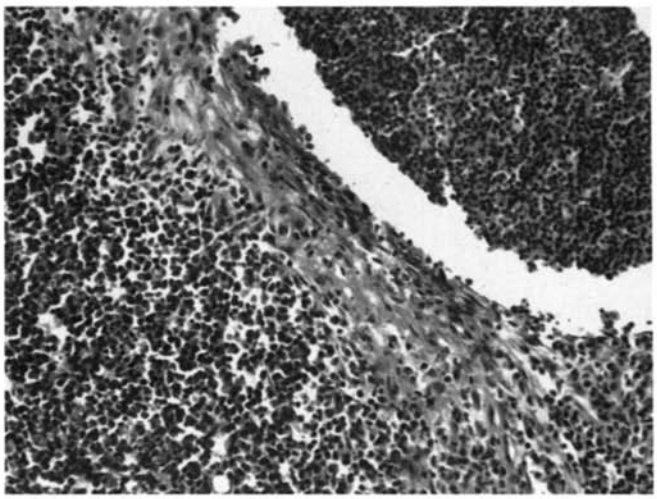


Fig. 41. Thrombophlebitis showing purulent infiltrate within the wall and lumen of a large portal vein.

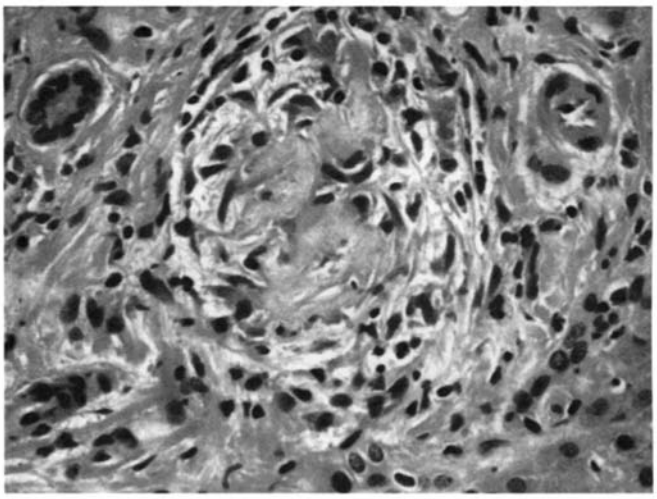


Fig. 42. Same patient as in **Fig. 41** showing a portal venule replaced by fibrous scar. The hepatic arteriole and bile ductule are seen on either side of the scarred venule.

Inflammatory Vascular Lesions

Pylephlebitis

Clinical

- Portal vein inflammation secondary to intra-abdominal suppurative infection (appendiceal, diverticular, or pelvic abscess)
- High mortality if infection cannot be eradicated; hepatic abscesses common complication

Microscopic

- Periportal neutrophilic infiltrate and vasculitis, thrombosis, microabscesses, fibrosis in later stages **(Figures 41,42)**

Differential Diagnosis

- Acute cholangitis
- Neoplasm-related thrombosis
- Graft rejection following liver transplantation

Polyarteritis

Clinical

- Necrotizing vasculitis of small arteries, immune-mediated
- Hepatic involvement (60% of all cases) may be symptomatic
- Thrombosis with infarction and aneurysms as complications
- Immunosuppression and plasmapheresis are therapeutic options

Microscopic

- Fibrinoid necrosis of arteries with mixed inflammatory infiltrate
- Secondary thrombosis

Differential Diagnosis

- Infarction from other causes
- Pylephlebitis

Miscellaneous Vascular Disorders

Peliosis Hepatis

- *See* Chapter 31

Hereditary Hemorrhagic Telangiectasia (Osler-Weber-Rendu Disease)

Clinical

- Autosomal dominant disorder, capillary arterio-venous malformations
- Number of lesions increases with age; liver involvement usually not symptomatic

Microscopic

- Dilated and enlarged portal vessels and arterio-venous malformations
- Variable degrees of fibrosis

Differential Diagnosis

- Idiopathic portal hypertension
- Primary biliary cirrhosis
- Cirrhosis of other etiology

Idiopathic Portal Hypertension (Non-Cirrhotic Portal Fibrosis)

Clinical

- Rare in Western countries; common in India and Japan
- Primary vascular disease, insidious onset with non-specific laboratory findings
- Portal hypertension with typical complications and symptomatic treatment
- Prognosis better than in cirrhosis

Microscopic

- Portal fibrosis, increased dilated vessels, no inflammatory changes, no bile duct anomalies
- No consistent portal-venous fibrosis pattern

Differential Diagnosis

- Osler-Weber-Rendu disease
- Primary biliary cirrhosis
- Drugs/toxins
- Alcohol-induced liver disease

CHOLESTASIS AND BILIARY TRACT DISORDERS

Acute Mechanical Duct Obstruction

Clinical

- Common causes include choledocholithiasis, neoplasms, acute pancreatitis, postoperative iatrogenic duct stricture, and abdominal trauma
- Clinical presentation with Charcot triad (pain, fever, jaundice), due to secondary cholangitis
- Relief of obstruction and antibiotics, otherwise development of chronic stages

Microscopic

- Perivenular cholestasis
- Dilatation of bile ducts with or without bile plugs
- Portal edema, proliferation of bile ductules associated with neutrophilic infiltrate
- Bile lakes (leakage from damaged interlobar ducts) and bile infarcts (toxic effect of bile to hepatocytes) are diagnostic, but not readily seen on biopsy

Differential Diagnosis

- Acute alcoholic liver disease
- Pylephlebitis
- Toxic shock syndrome
- Septicemia
- Primary sclerosing cholangitis

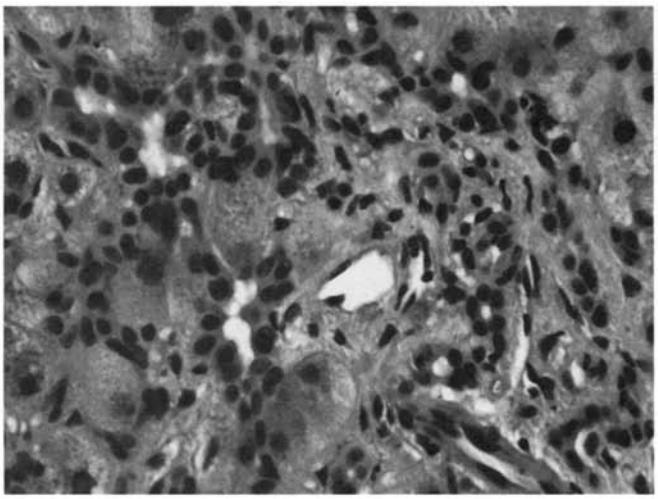


Fig. 43. Proliferation of bile ductules in a patient with long-standing biliary obstruction. Portal and periportal fibrosis were seen on trichrome stain.

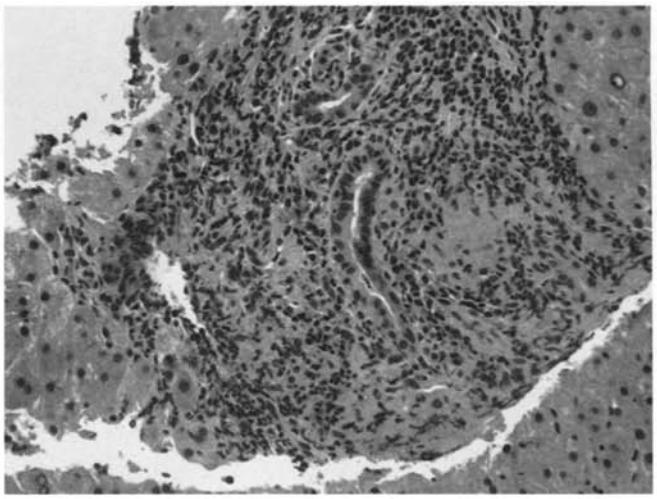


Fig. 44. Granulomatous inflammation is present around a damaged bile duct in primary biliary cirrhosis ("florid duct lesion").

Chronic Mechanical Duct Obstruction

Clinical

- Common causes include chronic pancreatitis, neoplasms, parasitic infection, extrahepatic biliary atresia, and chronic stages of acute etiologies
- Partial chronic obstruction commonly results in abscess formation and septicemia
- Recurrent cholangitic episodes with fibrosis/cirrhosis
- Interval to biliary cirrhosis is 4–7 years (common duct stricture or choledocholithiasis), 6 months in neonates with extrahepatic biliary atresia
- Cirrhotic patients are usually asymptomatic; no hepatocellular carcinoma risk
- Relief of obstruction reverses liver changes in non-cirrhotic patients

Microscopic

- Proliferation of bile ductules with bile plugs, with or without neutrophilic infiltrate **(Figure 43)**
- Cholestasis, acute cholangitis, bile lakes, and bile infarcts are sometimes seen, but are not as common as in acute obstruction
- Bile ducts may be decreased or absent in late stages
- Portal fibrosis with bridging fibrosis/ cirrhosis in late stages

Differential Diagnosis

- Primary biliary cirrhosis
- Primary sclerosing cholangitis
- Drug-induced reactions

Primary Biliary Cirrhosis

Clinical

- Chronic progressive bile duct destruction leading to biliary cirrhosis; typically granulomatous cholangiodestructive lesions
- Prevalence of 20–240 cases per million population; rarely in Africa or India
- Exact etiology uncertain; likely pathogenesis combination of autoimmune and microbiological factors
- Presentation with pruritus (50%), fatigue and pain (25%), and hepatic decompensation (25%); portal hypertension may develop before onset of cirrhosis; cholestatic liver function tests positive
- Commonly associated is sicca syndrome, also thyroid disease, arthralgia, sclerodactyly, and Raynaud's disease; only weak HLA association (DR8)
- Increased serum immunoglobulins, many autoantibodies
- Anti-mitochondrial autoantibodies (M2-subtype) are specific and are found in 96% of all cases, recognizes a mitochondrial antigen PDC-E2 expressed aberrantly on small intrahepatic bile ducts
- Mayo prognostic index is most widely used (serum bilirubin, albumin, age, edema, and prothrombin time); median survival time from diagnosis = 3–10 years (stage-dependent)
- Symptomatic treatment for pruritus, lethargy, and osteopenia; ursodeoxycholic acid slows development of cirrhosis; liver transplantation life-saving

Microscopic

- Non-suppurative destructive, granulomatous cholangitis ("florid duct lesion") and lymphocytic cholangitis **(Figures 44,45)**
- Duct loss (ductopenia) in later stages
- Mild lobular inflammation with granulomas may be seen
- Pseudoxanthomatous swelling, copper deposition, and Mallory's hyaline in periportal hepatocytes in later stages, reflecting bile acid (cholate) stasis

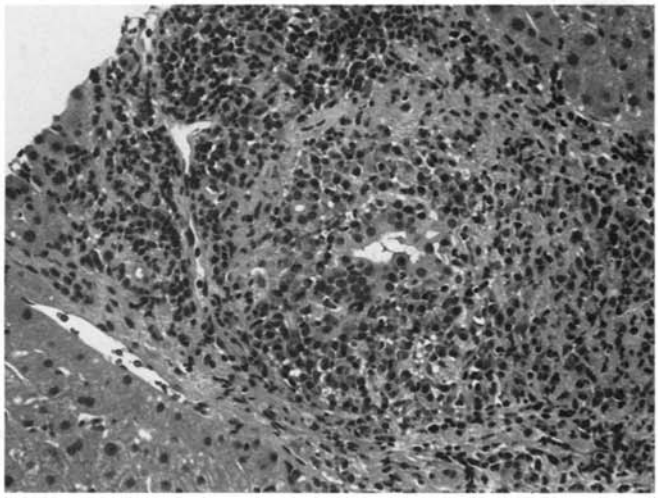


Fig. 45. Primary biliary cirrhosis showing lymphoplasmacytic inflammation around damaged bile ducts.

- Four stages (Scheuer staging scheme):
  - Florid duct lesion
  - Ductular proliferation
  - Portal and periportal fibrosis
  - Cirrhosis
- Recurs in allograft; incidence of recurrence increases with duration of follow-up; characterized by granulomatous cholangitis and presence of PDC-E2 in biliary epithelium; recurrent disease is indolent

Differential Diagnosis

- Sarcoidosis
- Graft-versus-host disease
- Chronic hepatitis C
- Primary sclerosing cholangitis

Primary Sclerosing Cholangitis

Clinical

- Slowly progressive (10–15 years) cholestatic disease with resulting biliary cirrhosis; prevalence is 2–7 per 100,000 population
- Etiology unknown; implicated factors include chronic portal bacteremia, toxic bile acid metabolites, chronic viral infections, and ischemic vascular changes
- Male predominance (75%); average age at diagnosis = 40 years
- Typically associated with inflammatory bowel disease (70%); usually chronic ulcerative colitis
- Associated with HLA B8/DR3 haplotype; antineutrophil nuclear and cytoplasmic antibodies (ANCA) are usually +
- Presentation with one or more of progressive fatigue, pruritus, or jaundice in 75%, cholestatic liver function tests

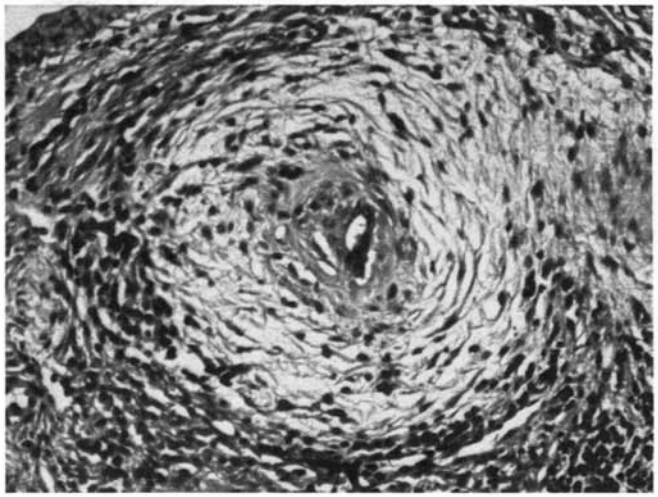


Fig. 46. Primary sclerosing cholangitis showing concentric fibrosis around duct showing marked epithelial damage and constriction of lumen.

- Diagnosis with liver biopsy and cholangiogram via ERCP ("beaded" appearance caused by strictures and intervening dilatations)
- Median survival time from diagnosis = 9–11 years; no association with bowel disease stage
- D-penicillamine, methotrexate, ursodeoxycholic acid, steroids, and other immunosuppressants have not shown definite beneficial treatment effects
- Complications include fat-soluble vitamin deficiencies, metabolic bone disease, recurrent bacterial cholangitis (frequent), cholelithiasis (30%), bile duct strictures (20%), and cholangiocarcinoma (10% to 15%)
- Liver transplantation treatment of choice; fourth leading cause for liver transplantation in the United States; liver transplantation for diagnosed cholangiocarcinoma experimental
- Recurrent disease in approximately 8% at 3–5 years after transplantation

Microscopic

- Disease of large bile ducts, therefore pathognomic lesions may not be seen on liver biopsy
- Concentric periductal fibrosis ("onion-skin" appearance) and inflammation, ductular proliferation **(Figure 46)**
- Fibrous obliterative cholangitis (bile duct scars), ductopenia **(Figure 47)**
- Four stages, analogous to PBC, but not as well defined

Differential Diagnosis

- Sarcoidosis
- Graft-versus-host disease
- Chronic hepatitis C
- Primary biliary cirrhosis
- Alcohol-, drug-, and autoimmune-induced hepatitis

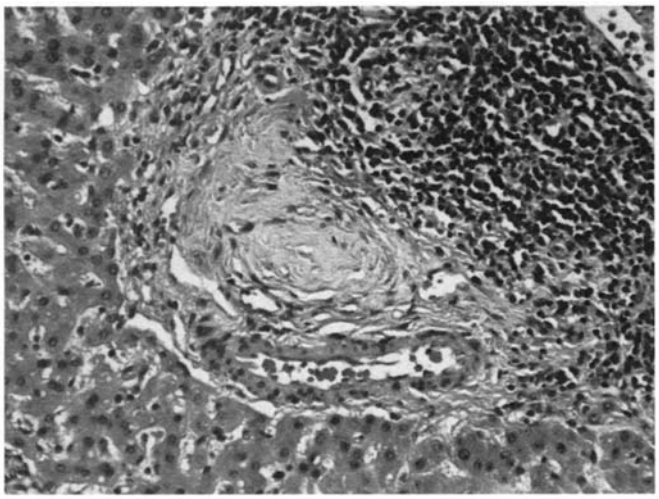


Fig. 47. Primary sclerosing cholangitis showing bile duct scar.

Intrahepatic Cholestasis

Postoperative Cholestasis

Clinical

- Benign, infrequent surgical complication (0.2% of elective procedures); more common after cardiac surgery
- Occurs 1–2 days after prolonged surgical procedures, secondary to bilirubin overload (hemolysis, transfusions) and temporary decrease in liver function
- Prognosis related to surgical complications

Microscopic

- Cholestasis within perivenular hepatocytes and dilated canaliculi
- Minimal inflammation only, bile ducts normal in number; no fibrosis

Differential Diagnosis

- Drugs
- Septicemia
- Early acute duct obstruction
- Intrahepatic cholestasis of pregnancy
- Benign recurrent intrahepatic cholestasis

Intrahepatic Cholestasis of Pregnancy

Clinical

- Third trimester, 2% to 5% of all pregnancies; higher prevalence in Chile and Sweden
- Some association with PFIC III/MDR3 mutation; mutation of MDR3 present in some patients; seen in families of patients with PFIC III
- Mild jaundice, disappears after delivery; recurrence in 50% of subsequent pregnancies
- Etiology might be secondary to liver dysfunction from gonadal and placental hormones
- No consequences (other than pruritus) for the mother; increased risk of fetal distress and stillbirth
- Apparent interplay between genetic predisposition and exogenous factor(s) (e.g., selenium deficiency)
- Ursodeoxycholic acid improves maternal pruritus and fetal prognosis

Microscopic

- Cholestasis within perivenular hepatocytes and dilated canaliculi
- Minimal inflammation only, bile ducts normal in number; no fibrosis
- Giant cell transformation of hepatocytes possible

Differential Diagnosis

- Drugs
- Septicemia
- Early acute duct obstruction
- Postoperative cholestasis
- Benign recurrent intrahepatic cholestasis

Paucity of Intrahepatic Bile Ducts

- Associated with a number of inherited/ metabolic conditions or acquired conditions
- Alpha-1 antitrypsin deficiency, inborn errors of bile acid metabolism, Turner's syndrome, trisomy 17, trisomy 21
- Viral hepatitis, drugs, allograft rejection, graft vs host disease
- Idiopathic forms (*see* below)

DEVELOPMENTAL, HEREDITARY, AND METABOLIC LIVER DISEASE

Cystic Liver Disease

Solitary Unilocular Cyst

Clinical

- Congenital and developmental forms; may arise from aberrant bile ducts
- Usually asymptomatic, incidental finding; rarely rupture or compression symptoms
- Surgical excision if symptomatic

Macroscopic

- Well-circumscribed
- Usually small; may contain several liters of fluid

Microscopic

- Cyst wall lined by flat or cuboidal epithelium
- Well-demarcated from hepatic parenchyma by collagen capsule; contains serous or mucinous fluid

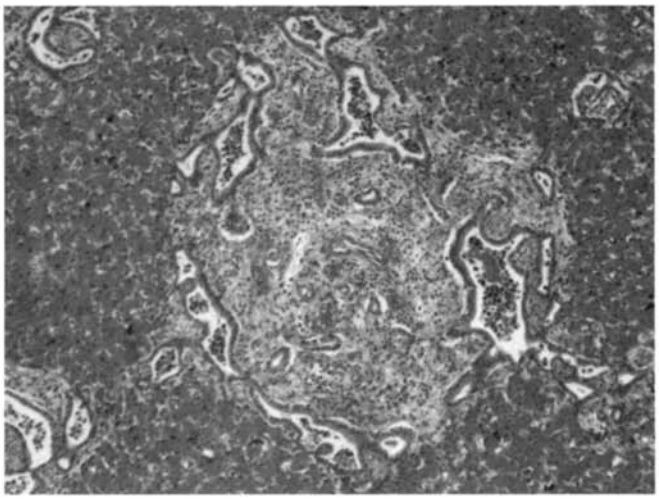


Fig. 48. Juvenile polycystic liver disease shows irregularly shaped, dilated and anastomosing biliary channels without cyst formation.

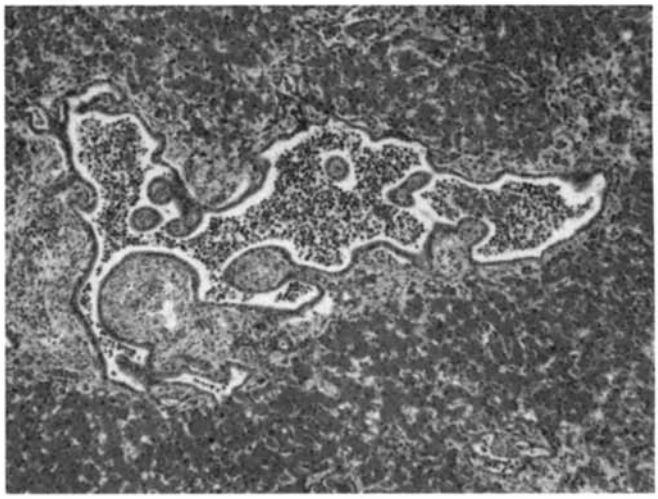


Fig. 49. Juvenile polycystic liver disease, showing irregularly shaped dilated biliary channel.

Differential Diagnosis

- Caroli's syndrome
- Cystadenoma

Infantile Polycystic Disease

Clinical

- Associated with autosomal recessive polycystic kidney disease (ARPKD)
- Early presentation with portal hypertension
- Increasing microcystic changes
- Death from associated chronic renal failure and hypertension

Microscopic

- Dilated, anastomosing, and proliferating bile ducts and prominent vascular channels; true cyst formation is uncommon **(Figures 48,49)**
- Biliary channels extend into lobules
- Portal fibrosis

Differential Diagnosis

- von Meyenburg complexes
- Congenital hepatic fibrosis

Adult Polycystic Disease

Clinical

- Associated with autosomal dominant polycystic kidney disease (ADPKD), 3 gene mutations known
- PKD1 gene on 16p13, 90% of cases, encodes polycystin
- PKD2 gene on 4q21-23, encodes polycystin 2
- Multisystem disease with cysts and connective tissue abnormalities, polycystic renal disease in 50%, cerebral aneurysms in 10% of patients
- May be asymptomatic; or present with hepatomegaly, abdominal discomfort/pain, difficulty in breathing

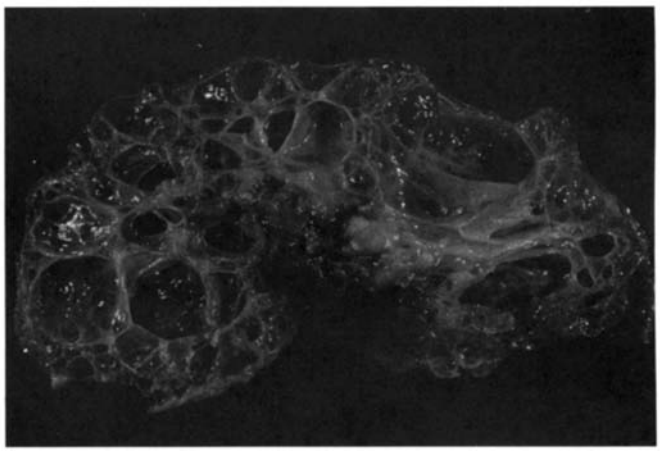


Fig. 50. Adult polycystic liver disease showing severe hepatomegaly and cysts of varying sizes.

- May be complicated by infection or cholangiocarcinoma
- Cysts enlarge with age, hepatic expression of disease influenced by age, female gender, pregnancy and severity of renal lesion and function

Macroscopic

- Variable, diffuse liver involvement, with cyst sizes of 1 mm to several centimeters, may cause massive hepatomegaly **(Figure 50)**
- Clear to yellow cyst fluid

Microscopic

- Cyst wall lined by flat or cuboidal epithelium
- Less well-defined fibrous walls with mild chronic inflammation

Differential Diagnosis

- von Meyenburg complexes
- Congenital hepatic fibrosis

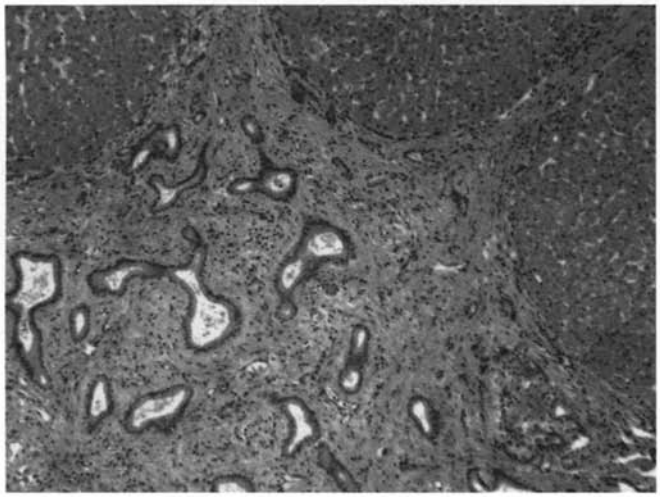


Fig. 51. Congeital hepatic fibrosis showing dilated malformed bile ducts in broad fibrous septa that lack inflammation.

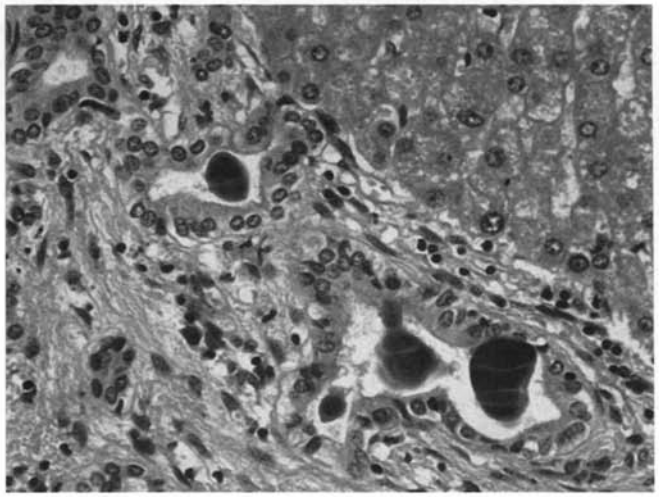


Fig. 52. Congenital hepatic fibrosis showing dilated biliary channels containing bile casts that occur typically at the interface of fibrous bands with hepatic nodules.

Congenital Hepatic Fibrosis

Clinical

- Rare autosomal recessive disorder, part of the cystic disease complex; associated renal cystic disease in 50%
- Adolescents present with complications of portal hypertension; shunt procedures often helpful
- Death from esophageal varices bleeding or renal failure; not hepatic failure

Microscopic

- Marked fibrosis with broad bands dividing hepatic parenchyma into irregular nodules
- Fibrous bands contain small bile ducts; interrupted circular arrangement of bile ducts resembling ductal plate malformation **(Figure 51)**
- Small dilated ducts containing bile plugs often present at the edge of fibrous bands and nodules **(Figure 52)**
- No regenerative nodules or inflammation

Bile Duct Dilatation

Choledochal Cyst (Extrahepatic)

Clinical

- Congenital but may present at any age, 20% within the first year of life; adults present with mild
- Obstructive jaundice, children with progressive biliary disease
- Malformation of pancreato-biliary system with damages by pancreatic juice, subsequent expansion and cyst formation likely
- often associated with other duct anomalies; female predominance
- Increased incidence of cholangiocarcinoma
- Surgical therapy with complete resection and hepaticojejunostomy

Macroscopic

- Cysts vary in size, may contain up to 5 liters of bile **(Figure 53)**
- Saccular or fusiform shapes possible

Microscopic

- Fibrotic cyst wall with chronic inflammation and sometimes abundant mucinous glands **(Figure 54)**
- Secondary cholestasis with duct proliferation, cholangitis, and biliary cirrhosis in long-standing cases

Differential Diagnosis

- Recurrent pyogenic cholangiohepatitis
- Extrahepatic biliary atresia

Caroli's Syndrome (Intrahepatic)

Clinical

- Diffuse or multifocal segmental dilatation of ducts with interspersed normal areas
- Often associated with other duct anomalies; may present at any age, predominantly adolescents
- Hepatomegaly and jaundice, progressive biliary disease with cirrhosis
- Increased incidence of cholangiocarcinoma
- Surgical therapy with complete resection of affected segments or liver transplantation in severe cases

Microscopic

- Dilated ducts with columnar or cuboidal epithelium
- Portal fibrosis of varying degrees with superimposed acute inflammation and microabscesses
- Lobular cholestasis

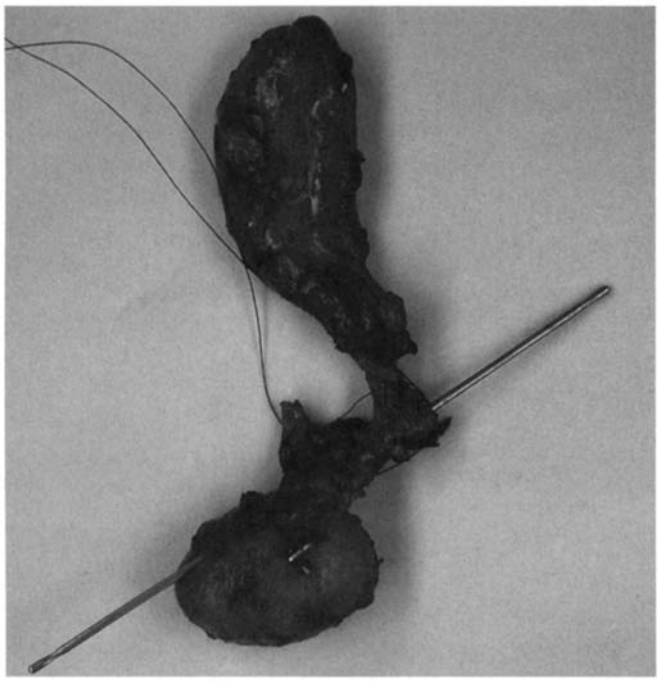


Fig. 53. Choledochal cyst appearing as a saccular dilatation of the common bile duct.

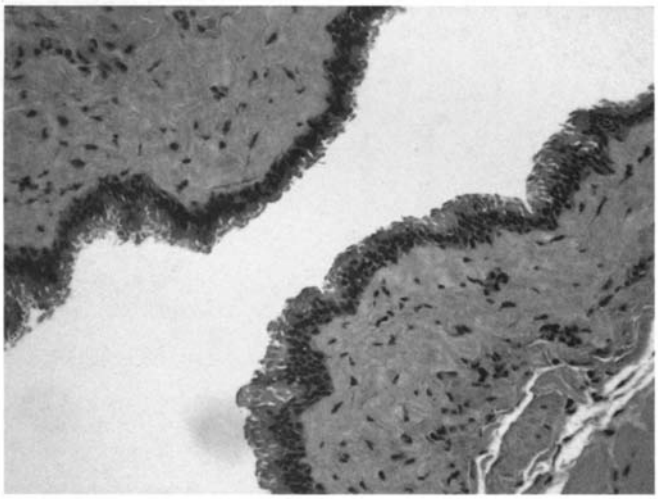


Fig. 54. Choledochal cyst in **Fig. 53** shows a fibrotic wall lined by tall columnar epithelium.

Differential Diagnosis

- Recurrent pyogenic cholangiohepatitis
- Extrahepatic biliary atresia

Extrahepatic Biliary Atresia

Clinical

- Probably in utero acquired disorder (viral infection?); incidence is 1:15,000 births

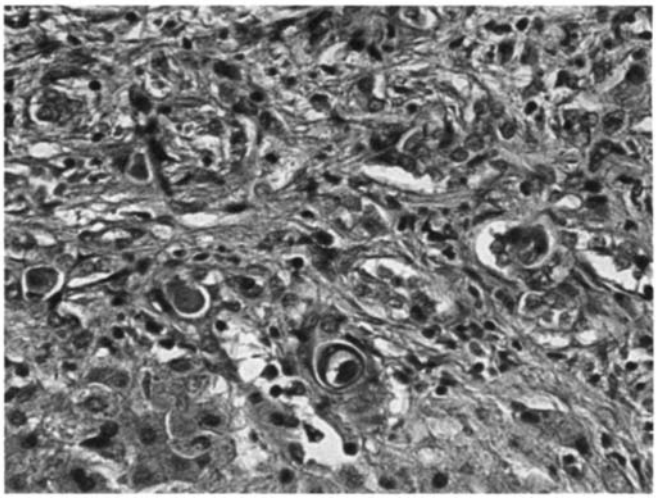


Fig. 55. Extrahepatic biliary atresia showing proliferation of bile ductules that contain bile casts.

- Usually complete involvement of extrahepatic duct system; minority of cases have partial atresia or hypoplasia
- Jaundice develops 1–2 weeks after birth; dark urine, acholic feces, hepatomegaly
- Mortality is 50% in 1 year if untreated; biliary cirrhosis develops rapidly
- Kasai procedure (hepato-portoenterostomy) is beneficial for several years in most cases; most will subsequently require liver transplantation

Microscopic

- Marked bile ductular proliferation, neutrophilic infiltrate, bile ductal dilatation with bile plugs **(Figure 55)**
- Prominent perivenular cholestasis
- Acute and chronic portal infiltrate
- Paucity of bile ducts in late stages
- Portal fibrosis and biliary cirrhosis
- Multinucleated giant cell transformation of hepatocytes

Differential Diagnosis

- Choledochal cyst
- Neonatal giant cell hepatitis

Idiopathic Paucity of Intrahepatic Bile Ducts

- Non-syndromic (isolated) or syndromic (Alagille's syndrome—also previously referred to as intrahepatic biliary atresia)

Alagille's syndrome

Clinical

- Paucity of intrahepatic bile ducts, pulmonary stenosis, ocular posterior embryotoxon, vertebral arch deformities, triangular facies
- 1:70,000 live births

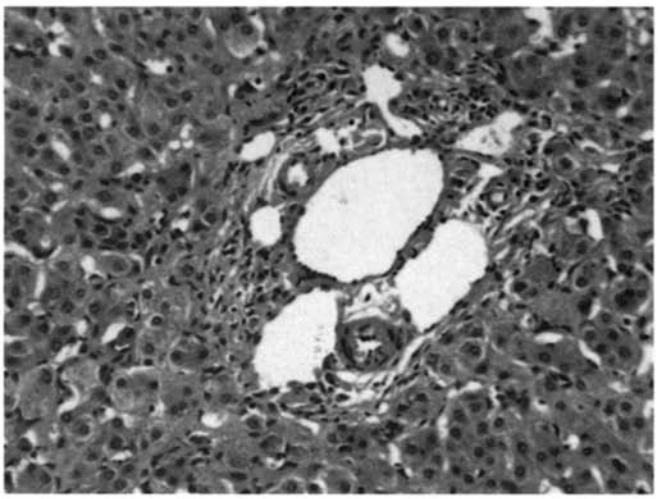


Fig. 56. Alagille's syndrome showing absence of bile ducts in small portal tracts without significant inflammation.

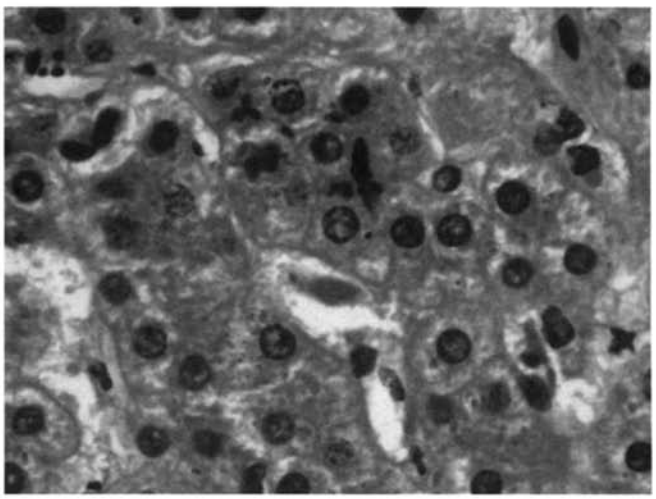


Fig. 57. Alagille's syndrome showing canalicular cholestasis in the lobules without inflammation.

- Gene mapped to 20p12—mutations of JAGGED 1, important for development of intrahepatic bile ducts through JAGGED/NOTCH interactions
- Jaundice and severe pruritus within the first 3 months; elevated serum bile acids
- Cirrhosis uncommon; minimal fibrosis, if at all
- Liver transplantation as definitive treatment, depending on the overall situation

Microscopic

- Portal tracts with decreased to absent interlobular bile ducts **(Figure 56)**
- Intralobular cholestasis, most prominent perivenular **(Figure 57)**
- Minimal chronic portal inflammation, not directed toward bile ducts
- Minimal fibrosis in portal tracts, if at all

Differential Diagnosis

- Alpha-1-antitrypsin deficiency
- Neonatal giant cell hepatitis
- Extrahepatic biliary atresia
- Progressive familial intrahepatic cholestasis

Hereditary Hyperbilirubinemias

Dubin-Johnson Syndrome

Clinical

- Autosomal recessive, absence of canalicular multispecific organic anion transporter (CMOAT)
- Conjugated hyperbilirubinemia
- Chronic intermittent episodes of jaundice, precipitated by stress, trauma, infection, or pregnancy
- No specific therapy; avoidance of precipitating factors, phenobarbital

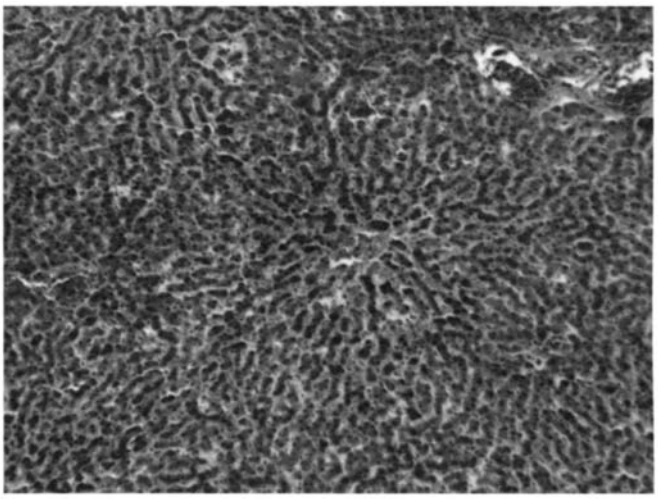


Fig. 58. Dubin-Johnson syndrome showing pigment deposition in the perivenular region.

Microscopic

- Granular, dark brown pigment in hepatocytes, more prominent around canaliculi and perivenular **(Figures 58,59)**
- Portal tracts normal, no inflammation

Differential Diagnosis

- Drugs
- Lipofuscin in the elderly

Other Hereditary Hyperbilirubinemias

Clinical

- Crigler-Najjar syndrome:
  - Autosomal recessive, very rare, inability to conjugate bilirubin, glucuronyltransferase deficiency (complete

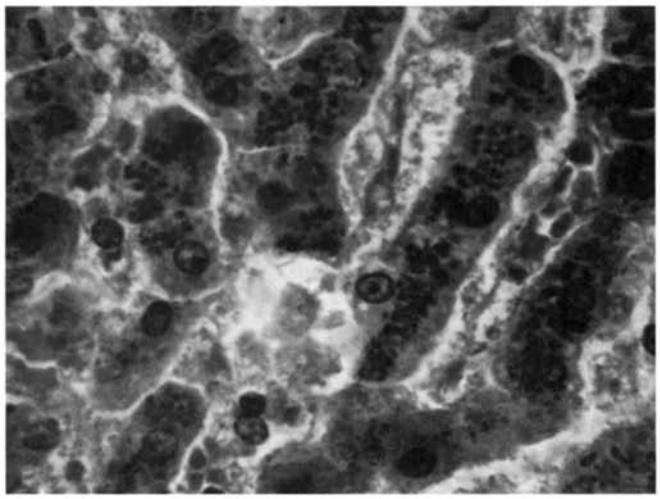


Fig. 59. Dubin-Johnson syndrome showing a brown, coarse granular pigment that localizes to the pericanalicular membrane of hepatocytes.

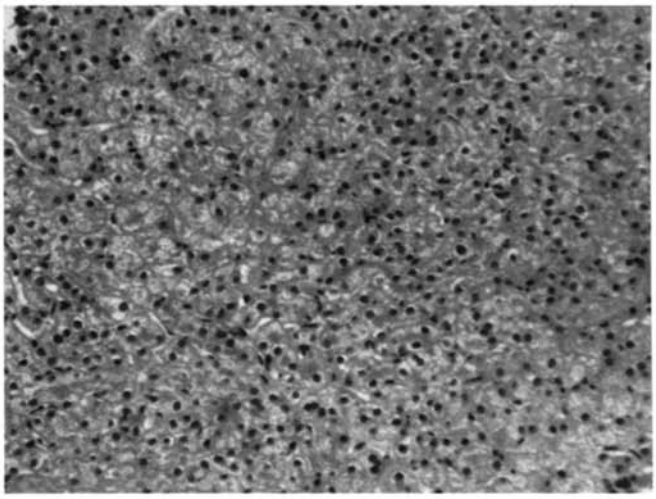


Fig. 60. Crigler-Najjar syndrome showing occasional bile canalicular plugs without inflammation, necrosis or fibrosis.

or partial), gene localised to chromosome 2, unconjugated bilirubin increased
  - Presentation as neonate; death within 2 years (complete deficiency); life expectancy = 40–50 years (partial deficiency)
- Gilbert's syndrome
- Inability to conjugate bilirubin, transglucuronidation deficiency, unconjugated bilirubin increased:
  - Presentation from neonates to adolescents; jaundice precipitated by stress, alcohol, infection, or trauma; normal life expectancy
- Rotor's syndrome:
  - Autosomal recessive, inability to secrete conjugated bilirubin, conjugated and unconjugated bilirubin increased
  - Presentation in childhood; fluctuation of jaundice; normal life expectancy

Microscopic

- Overall, the hepatic morphology is not distinctive
- Occasional canalicular bile plugs (Crigler-Najjar syndrome) **(Figures 60,61)**
- Rarely mild increase in lipofuscin in hepatocytes (Gilbert's syndrome)

Progressive Intrahepatic Familial Cholestasis

Clinical

- Currently classified into 3 types; more types probably exist
- All autosomal recessive involving various transporter molecules in the bile canaliculus:
  - Type I PFIC — aka Byler's syndrome:
    - Chromosome 18q21-22—gene is FIC-1, P-type ATPase
    - Typical granular bile (Byler's bile) on EM

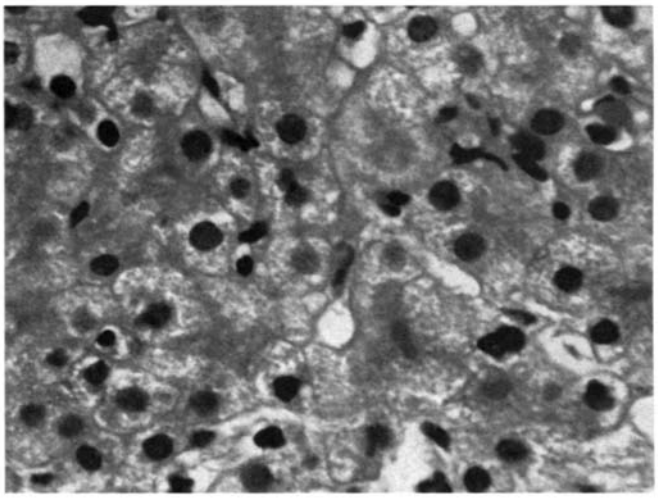


Fig. 61. Crigler-Najjar syndrome, showing canalicular bile plugs.

  - Type II PFIC:
    - Chromosome 2q24—bile salt export protein (BSEP)
  - Type III PFIC:
    - Chromosome 7q21—multidrug resistant 3 gene (MDR3), phospholipid transporter
- Presents with diarrhea and foul-smelling stools, progression to jaundice within 1 year
- Poor prognosis, death from hepatic failure and portal hypertension within 10 years
- Cholestasis of pregnancy in type III
- Eight nerve deafness in type I
- Various medical therapies, biliary diversion, liver transplantation

Microscopic

- Type I: bland cholestasis; typical granular bile on EM
- Type II: cholestasis, giant cell transformation, bridging fibrosis and cirrhosis
- Type III: cholestasis, ductular proliferation and bridging fibrosis

Differential Diagnosis

- Alpha-1-antitrypsin deficiency
- Neonatal giant cell hepatitis
- Extrahepatic biliary atresia
- Idiopathic paucity of intrahepatic ducts

Benign Recurrent Intrahepatic Cholestasis

Clinical

- Deficiency of FIC-1, shares a common defect on chromosome 18q21-22 with type I PFIC
- Recurrent events of pruritus and jaundice throughout life; begins in childhood
- Intervals (months to years) of entirely normal liver function between bouts
- Might represent immunological dysfunction triggered by environmental agent
- No adverse long-term outcome

Microscopic

- Cholestasis within perivenular hepatocytes and dilated canaliculi
- Minimal inflammation only, bile ducts normal in number; no fibrosis

Differential Diagnosis

- Drugs
- Septicemia
- Early acute duct obstruction
- Intrahepatic cholestasis of pregnancy
- Postoperative cholestasis

Cystic Fibrosis

Clinical

- Autosomal recessive disorder, incidence = 1:2,000 births; carrier frequency is 5%
- Gene localized to chromosome 7q31, encodes CF transmembrane receptor protein (CFTR)
- Liver disease due to viscous mucus production with bile duct plugging, cholestasis, and biliary fibrosis
- 10% develop cirrhosis by age 25, microgallbladder in 20%
- Death from pulmonary complications

Microscopic

- Biliary type fibrosis and cirrhosis **(Figure 62)**
- Proliferation and dilatation of bile ductules with intraluminal eosinophilic secretions **(Figure 63)**

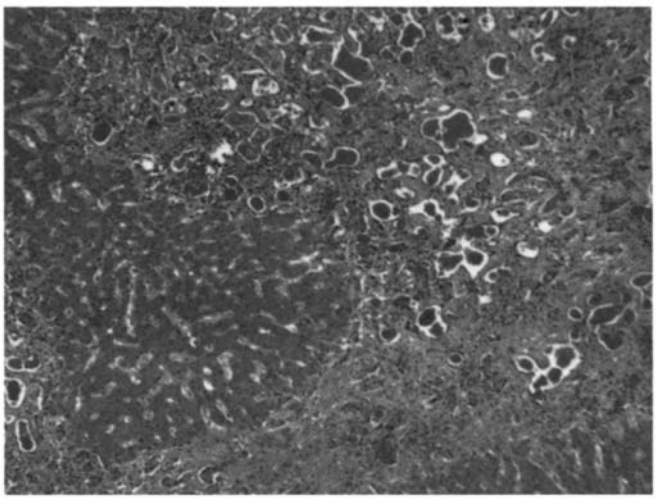


Fig. 62. Cystic fibrosis showing cirrhosis with proliferating, dilated ducts containing an eosiniophilic, slightly orange-staining material.

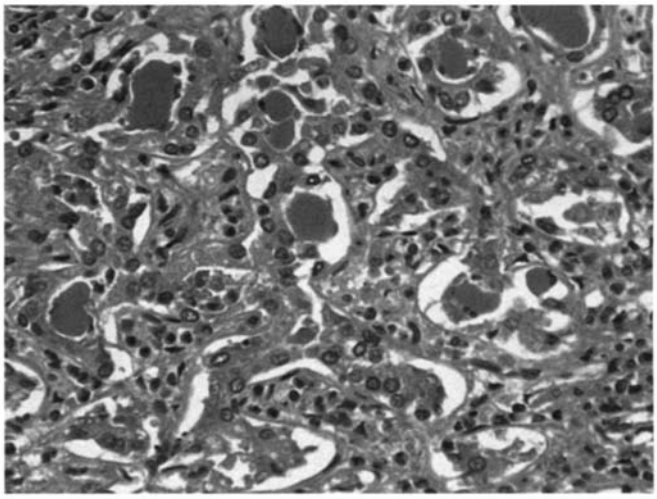


Fig. 63. Cystic fibrosis, with proliferating bile ductules containing eosinophilic material.

Differential Diagnosis

- Extrahepatic biliary obstruction

Alpha-1-Antitrypsin Deficiency

Clinical

- Normal alpha-1-antitrypsin (acute phase glycoprotein) inhibits neutrophilic proteases
- Common type of alpha-1-antitrypsin deficiency (PiZZ) due to a point mutation (Glu342Lys) in the alpha-1-antitrypsin gene, resulting in accumulation of the abnormal protein in the endoplasmatic reticulum of hepatocytes (typical globules seen microscopically); mechanisms of liver damage unclear

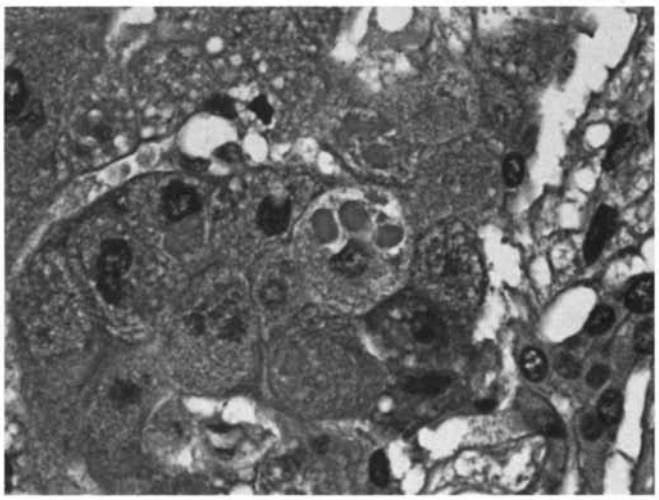


Fig. 64. Alpha-1 antitrypsin deficiency shows eosinophilic cytoplasmic globules in periportal hepatocytes.

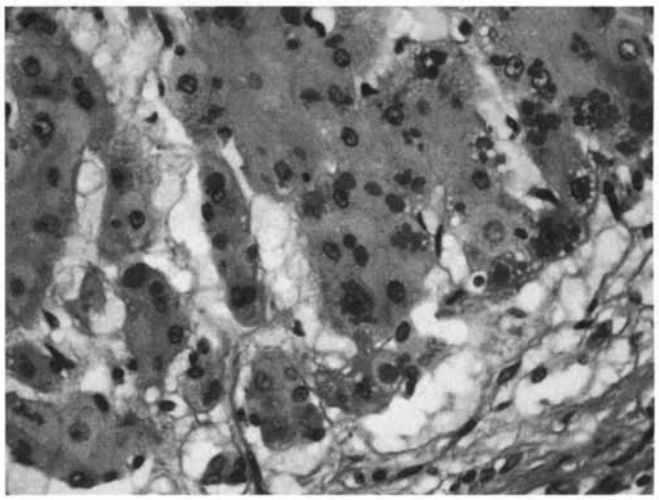


Fig. 65. Alpha-1 antitrypsin globules stain with PAS and are resistant to digestion by diastase.

- Phenotypes are PiMM (normal), PiZZ (homozygote), and PiMZ (heterozygote); other rare phenotypes exist
- Most common cause for liver disease in children, often ductopenic, affecting 1 in 1,700 life births; only a subgroup develops clinically significant liver disease (10% of homozygotes)
- Clinical presentation as early as neonates, with jaundice, hepatosplenomegaly, and ductopenia, but can occur at any age, with adults presenting as (non-ductopenic) cirrhosis; increased risk for cirrhosis and hepatocellular carcinoma
- Diagnosis by phenotyping of alpha-1-antitrypsin in the serum
- Risk or predisposition of heterozygotes (MZ-phenotype) to liver injury is less than that of the ZZ-phenotype, but likely an uncommon cause of cirrhosis and a potentiator of fibrosis when co-existing with other liver disease(s)
- Treatment includes avoidance of smoking (potentiates associated pulmonary disease), supportive and symptomatic measures for liver disease management, and liver transplantation

Microscopic

- Periportal hepatocytes with abundant round eosinophilic cytoplasmic inclusions **(Figure 64)**
- Mixed micro-and macronodular cirrhosis (adults); biliary cirrhosis in children
- Smaller, less numerous cytoplasmic inclusions in the heterozygote
- Associated giant cell transformation of hepatocytes in children
- Initial bile duct proliferation; later stages show paucity of ducts in children
- Only mild portal mononuclear inflammatory infiltrate

Special Studies

- PAS with diastase+ globules **(Figure 65)**
- Alpha-1-antitrypsin immunohistochemistry

Differential Diagnosis

- Giant cell hepatitis
- Extrahepatic biliary atresia
- Paucity of ducts syndrome
- Drug- and alcohol-induced liver disease

Genetic Hemochromatosis

Clinical

- Incidence = 1–2:1,000; male predominance; needs to be distinguished from other (secondary) iron overload conditions
- Failure to regulate iron absorption, resulting in severe iron overload; exact mechanism still unknown
- Associated with two missense mutations (Cys282Tyr and His63Asp) in the HFE gene on chromosome 6p21.3 coding for an MHC class I-like molecule
- Homozygosity for Cys282Tyr in 80% to 90% of patients with typical hemochromatosis
- Compound heterozygotes (Cys282Tyr and His63Asp) comprise 5%; 5% to 10% of patients are wild-type for both loci, suggesting yet another genotype
- Presentation with signs of liver damage, abdominal pain, skin pigmentation, diabetes, and cardiomegaly (25%) or asymptomatic until late (75%)
- Many patients identified through abnormal serum iron studies; sensitivity and specificity of iron laboratory studies rather low
- Liver biopsy to establish diagnosis; hepatic iron index (hepatic iron contents in mmol/g dry weight divided by

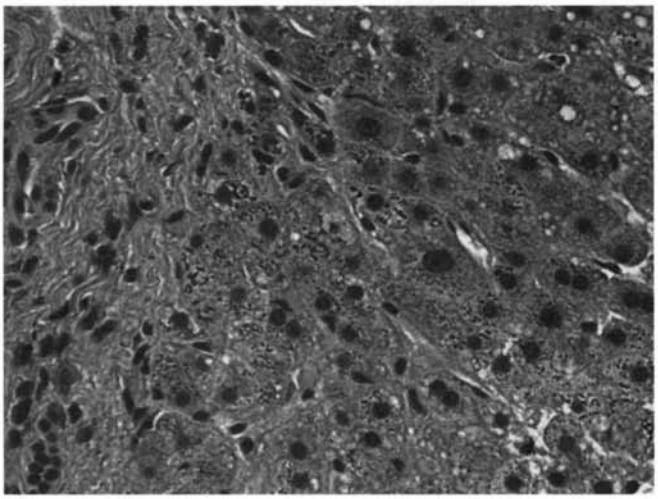


Fig. 66. Hemachromatosis showing hemosiderin deposition in periportal hepatocytes.

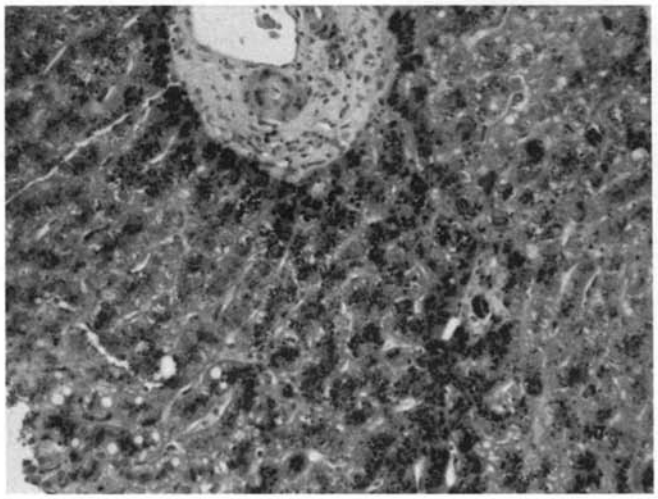


Fig. 67. Hemachromatosis showing hemosiderin deposition in periportal hepatocytes (Prussian blue stain).

age) >1.9 typically associated with homozygous hemochromatosis, although exceptions exist (exogenous iron overload, cirrhosis in particular)

- PCR-based diagnosis of Cys282Tyr and/or His63Asp highly specific
- Family screening recommended; treatment of choice is multiple phlebotomy until development of iron-limited hematopoiesis, then maintenance phlebotomy as required

Microscopic

- Extensive hemosiderin pigment (iron) deposition in cytoplasm of periportal hepatocytes (early) and eventually all hepatocytes (late) **(Figure 66)**
- Subsequent portal fibrosis and cirrhosis
- Kupffer cell hyperplasia
- Only mild inflammation

Special Studies

- Prussian blue **(Figure 67)**
- Masson's trichrome

Differential Diagnosis

- Hemosiderosis from other etiologies
- Alcohol-induced liver disease

Copper Storage Disorders

Wilson's Disease

Clinical

- Autosomal recessive disorder of copper metabolism with highly variable presentation
- Incidence of 2:100,000; carrier frequency 1/100
- Altered gene is on chromosome 13q, codes for a copper-transporting adenosine triphosphatase
- Hepatic copper accumulation causes hepatocellular necrosis, periportal inflammation, and fibrosis/cirrhosis; patients present at various stages of chronic liver disease
- Acute episodes (sudden copper release into circulation) associated with hemolysis
- Later stages develop corneal and brain deposits of copper with severe neurologic deficits; liver damage presents usually before neurologic deficit; early diagnosis is crucial
- Presence of Kayser-Fleischer rings (cornea) and low serum ceruloplasmin is sufficient for diagnosis
- High index of suspicion; after exclusion of other liver diseases, measurement of hepatic copper contents is mandatory in patients with liver biopsy (+ if >250 mg/g dry weight)
- Treatment is D-penicillamine and/or zinc; death in untreated cases; liver transplantation should be offered

Microscopic

- Histology is not specific and may resemble chronic hepatitis or steatohepatitis
- Non-specific inflammatory changes of variable degrees in early stages
- Constellation of microvesicular steatosis, ballooning change, glycogenated nuclei, anisonucleosis and binucleation very suggestive **(Figure 68,69)**
- Copper is variably demonstrable and is predominantly periportal but may be inapparent by special stains, especially in early stages
- Later stages show micro- and macronodular cirrhosis, steatosis, cholestasis, and hepatocellular copper deposits

Special Studies

- Rhodanin stain (copper, orange-red)
- Orcein (copper binding protein, black-brown)

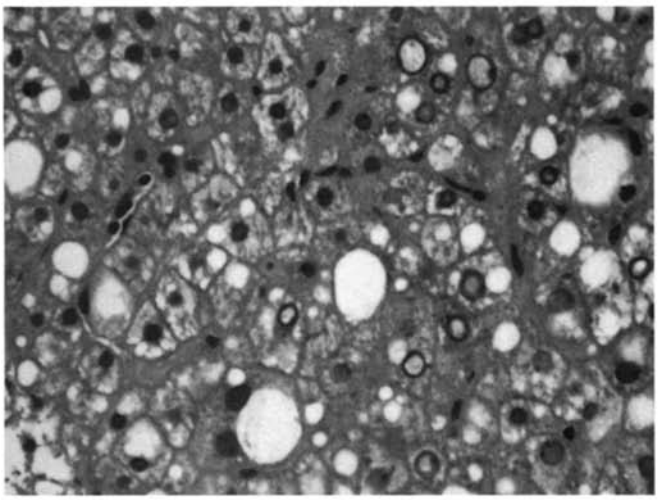


Fig. 68. Wilson's disease showing macro and microvesicular steatosis, glycogenated nuclei, anisonucleosis and binucleation.

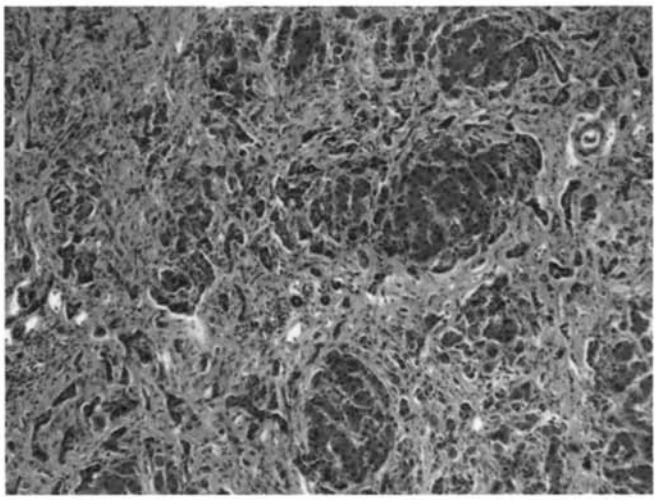


Fig. 70. Indian childhood cirrhosis showing micronodular cirrhosis without any regenerative activity in the nodules.

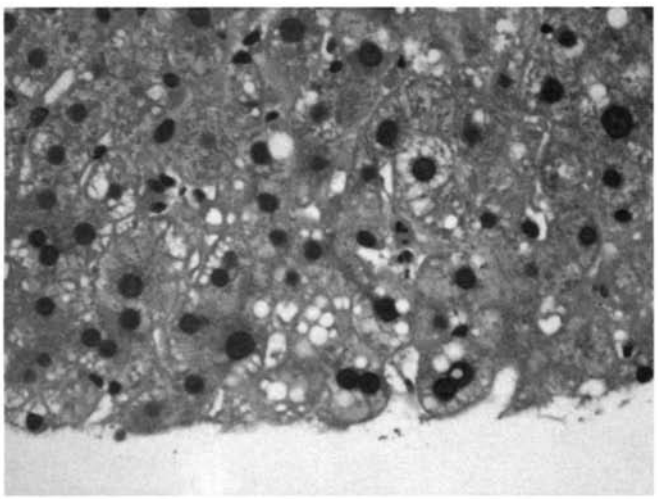


Fig. 69. Wilson's disease.

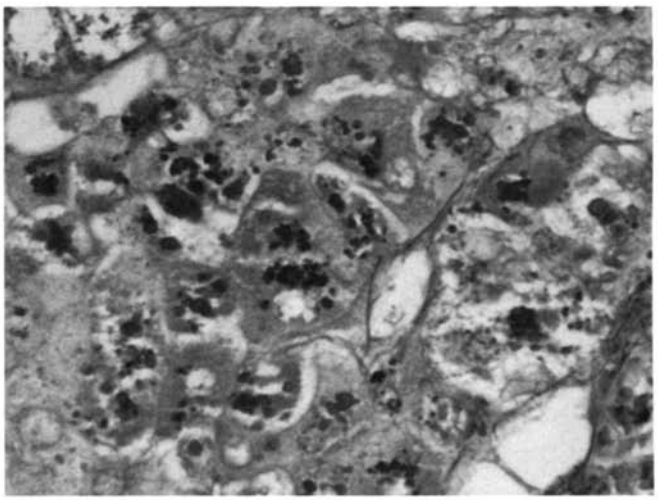


Fig. 71. Indian childhood cirrhosis showing accumulation of coarse granules of copper-associated protein (Orcein stain).

Differential Diagnosis

- All major chronic liver diseases
- Drugs (chlorpromazine)
- Indian childhood cirrhosis

Indian Childhood Cirrhosis

Clinical

- Hepatic disorder of predominantly Indian children with familial predisposition; rare case reports of patients in other geographic regions
- Probably related to excessive dietary ingestion of copper
- Clinical presentation as young children (1–5 years) with gradual progression to micronodular cirrhosis
- Alpha-fetoprotein levels elevated from birth
- Death within 1–2 years of diagnosis, if untreated
- Early initiation of penicillamine treatment offers regression of hepatic disease

Microscopic

- Extensive fibrosis/cirrhosis with Mallory bodies in hepatocytes **(Figure 70)**
- Mild portal mononuclear inflammatory infiltrate
- Increased copper and copper-binding protein **(Figure 71)**

Differential Diagnosis

- Metabolic defects with fibrosis/cirrhosis
- Alpha-1-antitrypsin deficiency

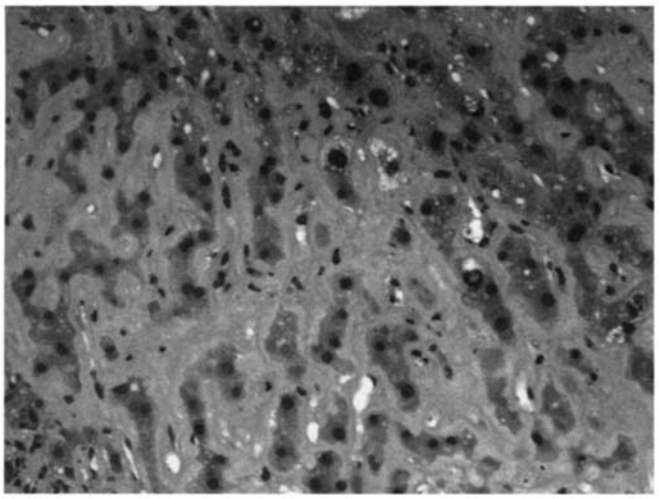


Fig. 72. Amyloid appears as an amorphous, eosinophilic material that deposits initially in the space of Disse and eventually causes atrophy of the hepatic plates.

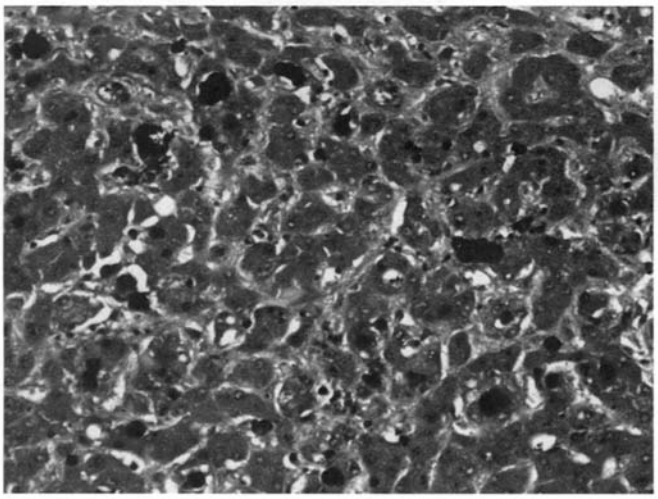


Fig. 73. Erythropoietic protoporphyria showing deposition of a dark brown pigment.

Amyloidosis

Clinical

- Systemic amyloidosis in 0.5% at autopsy; 50% liver involvement
- Primary (familial) amyloidosis is rare; high index of suspicion; liver transplantation may become necessary
- Secondary amyloidosis frequently related to systemic diseases (multiple myeloma, connective tissue diseases, infections)
- Hepatomegaly, rarely severe liver problems
- Underlying diseases determine the prognosis

Microscopic

- Perivascular or perisinusoidal, deposition begins in space of Disse **(Figure 72)**

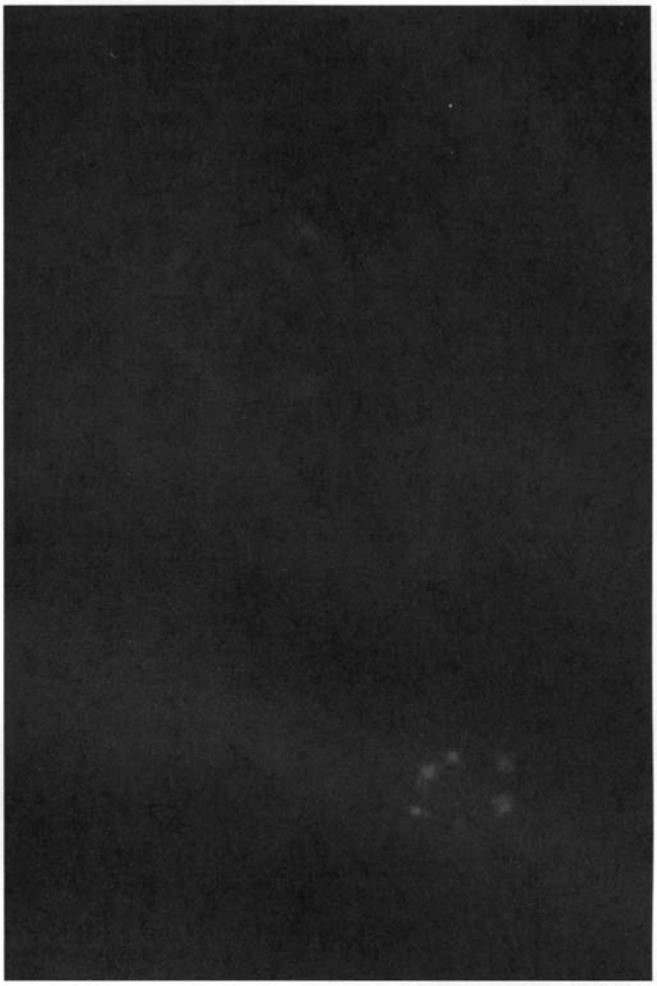


Fig. 74. Erythropoietic protoporphyria. Under polarized light, the pigment is birefringent and shows Maltese cross profiles.

- Massive deposition leads to compression and atrophy of liver cell plates

Special Studies

- Congo red+
- Immunohistochemistry with antibodies for specific subtypes (AL kappa, lambda, AA, transthyretin, beta-2 microglobulin)

Differential Diagnosis

- Collagen or fibrin depositions
- Intracellular inclusions

Porphyrias

Porphyria Cutanea Tarda

Clinical

- Uroporphyrinogen decarboxylase deficiency, autosomal dominant inheritance
- Incidence = 5:100,000, manifests after the age of 35

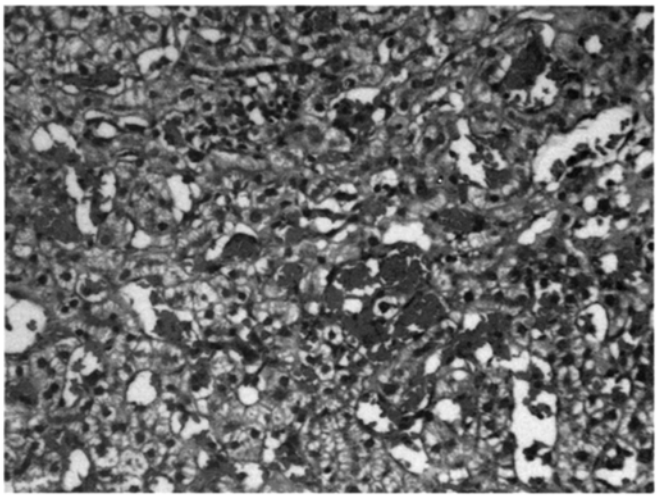


Fig. 75. Sickle cell disease showing dilated and congested sinusoids due to the accumulation of sickled red blood cells.

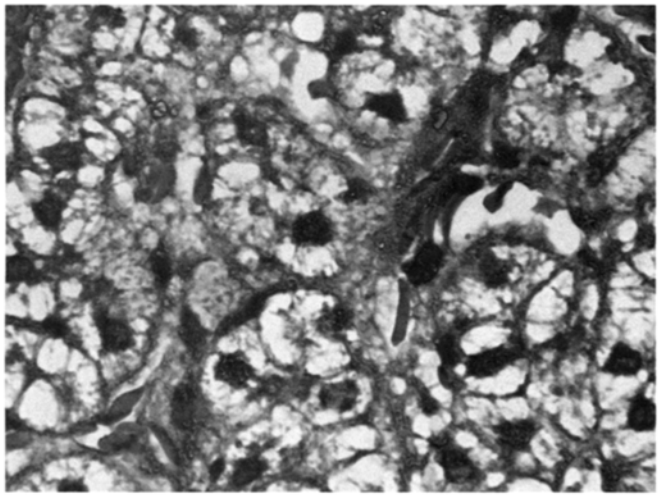


Fig. 76. Sickle cell disease showing sickle-shaped red cells in congested sinusoids.

- Associated with chronic alcoholic liver disease in 90% of all cases; liver involvement manifests late, usually cirrhosis present
- Overall prognosis is good

Microscopic

- Massive uroporphyrin deposits in hepatocytes, causing prominent red autofluorescence on frozen sections and birefringent cytoplasmic inclusions
- Macrovesicular steatosis, cirrhosis in 20%, increased iron

Special Studies

- Prussian blue

Differential Diagnosis

- Iron overload
- Chronic alcoholic liver disease

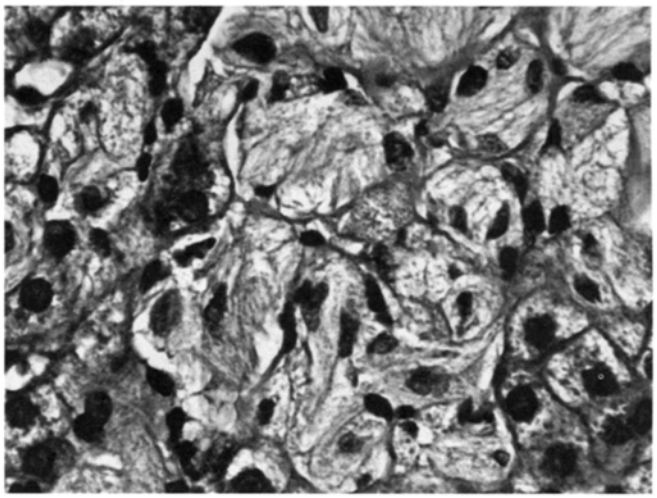


Fig. 77. Gaucher's disease shows deposition of the abnormal glucocerebroside in Kupffer cells that have a striated "wrinkled tissue paper" appearance.

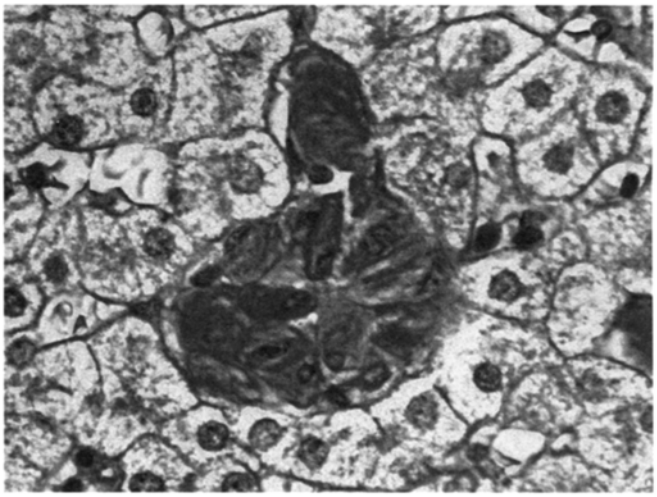


Fig. 78. The storage cells of Gaucher's disease are highlighted by PAS stain following diastase digestion.

- Diabetes mellitus
- Other porphyrias

Erythropoietic Protoporphyria

Clinical

- Deficiency in ferrochelatase
- Liver involvement with cirrhosis is rare

Microscopic

- Dark brown pigment in almost all liver elements **(Figure 73)**
- Orange-red autofluorescence on frozen sections and birefringent cytoplasmic inclusions **(Figure 74)**

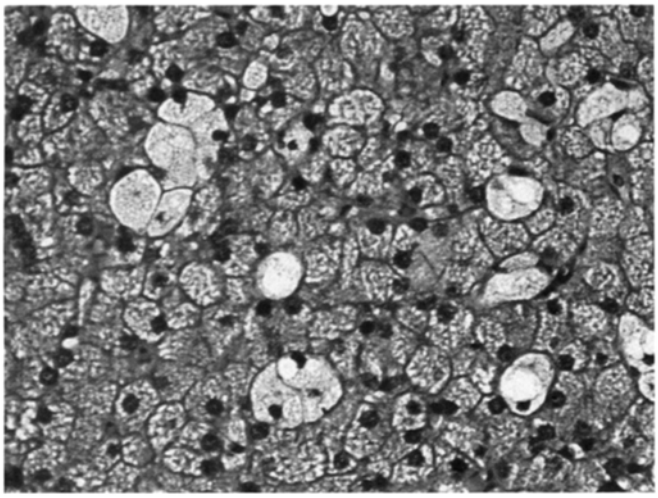


Fig. 79. Niemann-Pick disease showing accumulation of the abnormal glucocerebroside in both hepatocytes and Kupffer cells; the storage cells have a foamy appearance.

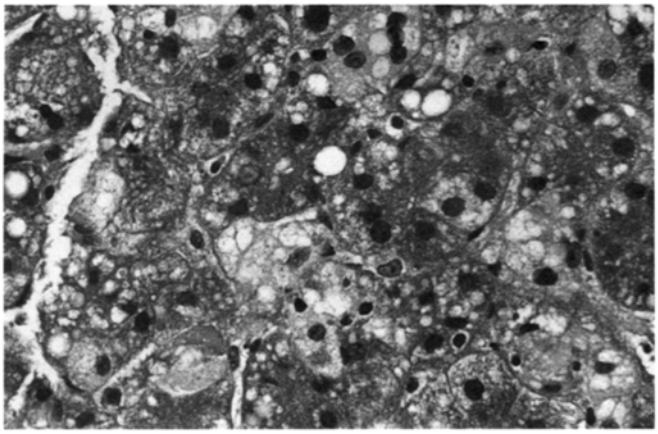


Fig. 80. The storage cells of Niemann-Pick disease showing a faintly basophilic appearance on PAS stain.

- Fibrosis/cirrhosis possible; varying degrees of chronic inflammation with focal necrosis

Differential Diagnosis

- Iron overload
- Other porphyrias

Sickle Cell Anemia

Clinical

- Liver involvement in 2%, typically anoxic-type necrosis due to sickling of RBC's in the homozygote
- Hyperbilirubinemia predominantly due to hemolysis, gallstones in 50% of all cases
- Overall prognosis not liver-related

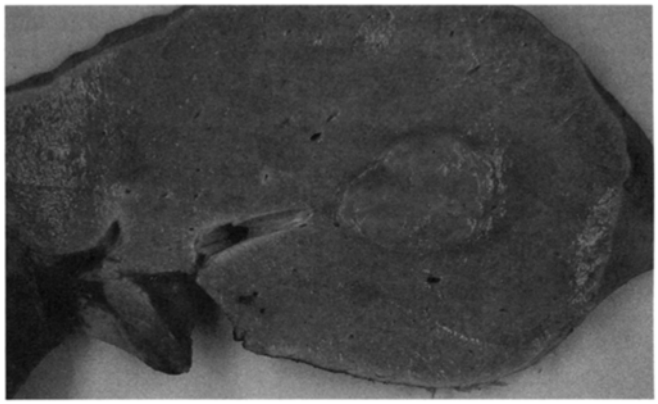


Fig. 81. Von Gierke's disease showing hepatomegaly and a pale yellowish appearance of the liver. A hepatocellular carcinoma is seen.

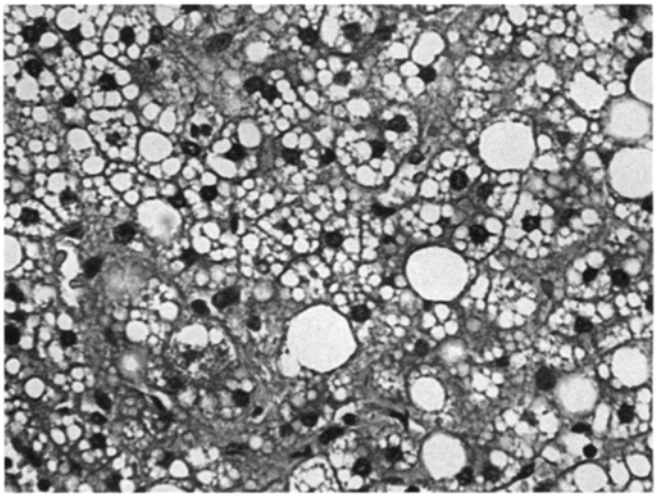


Fig. 82. Von Gierke's disease showing macro and microvesicular steatosis.

Microscopic

- Sickling of RBC's with fibrin deposition in dilated sinusoids, most prominent perivenular; focal necroses and hemosiderin deposits **(Figures 75,76)**
- Extramedullary hematopoiesis in 50% of all cases, secondary to hemolytic anemia

Differential Diagnosis

- Disseminated intravascular coagulation
- Passive congestion
- Acute viral hepatitis

Other Storage Disorders

- Glucocerebrosidoses e.g., Gaucher's—striated appearance of storage cells **(Figures 77,78)**; Niemann-Pick—lightly basophilic foamy appearance of storage cells **(Figures 79,80)**

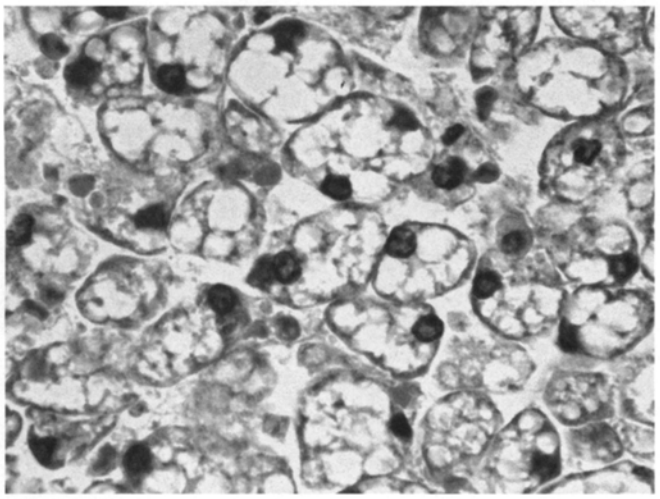


Fig. 83. Pompe's disease, a glycogen storage disease showing microvesicular steatosis.

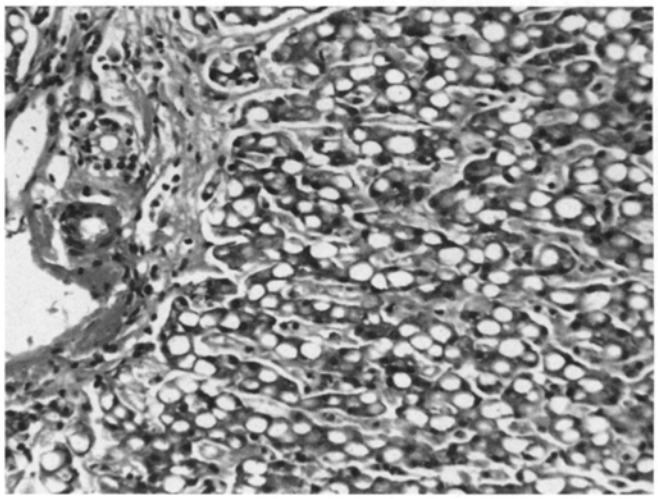


Fig. 84. Hurler's disease, a mucopolysaccharidoses, shows vacuolated hepatocytes.

- Glycogen storage diseases e.g., von Gierke's—microvesicular steatosis, cirrhosis, hepatocellular adenoma and caracinoma **(Figures 81,82)**; and Pompe's—cytoplasmic glycogen deposits **(Figure 83)**, fibrosis/cirrhosis in types III and IV
- Mucopolysaccharidoses e.g., Hurler's—small lipid droplets in liver cells, Kupffer and Ito cells, fibrosis **(Figure 84)**
- Lipid and cholesterol storage disorders—small fat droplets in hepatocytes, foamy macrophages with cholesterol deposits
- Glycosphingolipidoses e.g., Fabry's—hypertrophy of portal macrophages, Kupffer cells
- Gangliosidoses e.g., Tay-Sachs—laminated inclusions in hepatocytes only by electron microscopy

MISCELLANEOUS CONDITIONS

Autoimmune Hepatitis

Clinical

- Younger to middle-aged females predominantly affected; clinical presentation often with jaundice and hepatosplenomegaly
- Immunologic diseases are present in half of all cases; serum IgG is usually elevated
- Autoantibodies are present, including ANA (nuclear components), SMA (smooth muscle); LKM (liver kidney microsomal), LMA (liver membrane), LSP (liver-specific lipoprotein). These autoantibodies are sensitive, but not specific markers
- AMA (antimitochondrial antibodies) are not seen, as opposed to findings in primary biliary cirrhosis
- May overlap with other chronic liver diseases
- Treatment is with corticosteroids; many cases present with fibrosis or early cirrhosis
- Prognosis is good in responding patients; liver transplantation for unresponsive cases

Microscopic

- Portal inflammation with prominent plasma cells
- Lymphoplasmacytic piecemeal necrosis during active disease; often severe in untreated patients **(Figures 85,86,87)**
- Irregular distribution of lobular inflammation and hepatocellular necrosis of variable severity
- Minimal inflammation in treated or spontaneously inactive cases
- Varying degrees of portal fibrosis or cirrhosis

Special Studies

- Serum autoantibody assays

Differential Diagnosis

- Viral hepatitis
- Drug-related liver disease

Granulomatous Liver Disease

General Features

- Granulomas are present in approximately 5% of all liver biopsy specimens
- Causes include systemic disease (70%), primary liver diseases (5%), and unknown etiologies (25%)

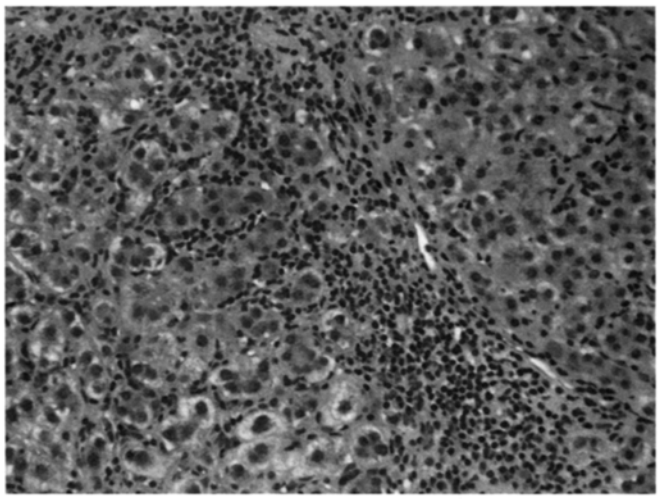


Fig. 85. Autoimmune hepatitis showing severe interface activity.

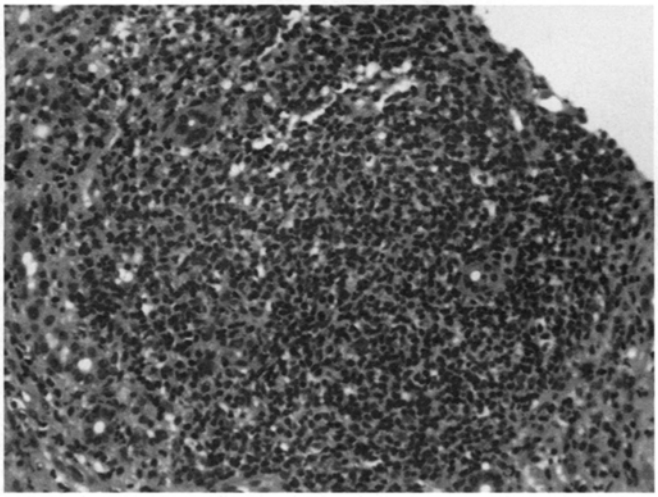


Fig. 86. Autoimmune hepatitis showing lymphoid aggregates in portal tracts.

- Tuberculosis and sarcoidosis are the most common causes worldwide
- Associated conditions: infections, hypersensitivity reactions to drugs, neoplasms, foreign body material in iv-drug users, and primary biliary cirrhosis
- Two major morphologic types:
  - Inflammatory, poorly defined (CMV-infection, drugs)
  - Epithelioid, well-demarcated (tuberculosis, sarcoidosis)
- Other types include lipogranulomas and fibrin ring granulomas

Sarcoidosis

Clinical

- Liver involvement in 60% to 90% of all cases; clinically significant liver problems are rare

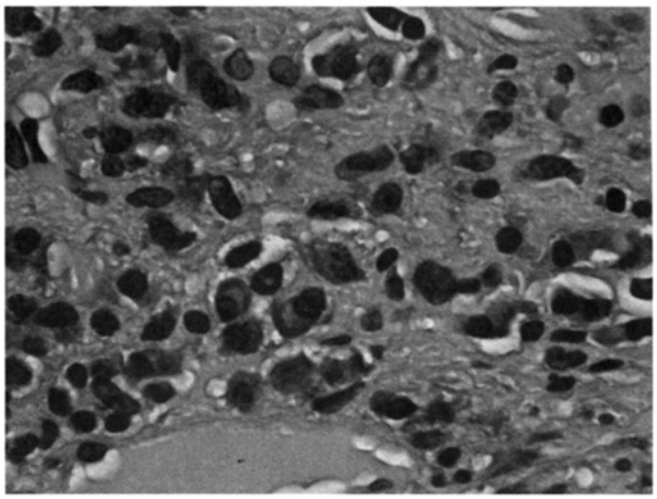


Fig. 87. Autoimmune hepatitis showing an inflammatory infiltrate rich in plasma cells.

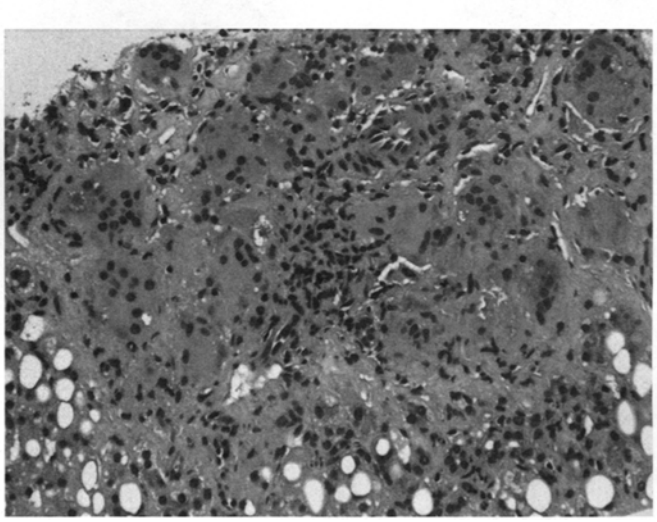


Fig. 88. Hepatic sarcoidosis showing large, non-necrotising granulomas without prominent lymphocytic inflammation ("naked" granulomas) in portal and periportal areas.

- Variable number of granulomas in early stages; fibrosis and rarely total resolution in later stages
- Minority of cases progress to portal hypertension due to portal granulomas and fibrosis
- Prognosis is generally good; pulmonary fibrosis determines clinical outcome

Microscopic

- Non-necrotizing epithelioid granulomas, most prominent portal/periportal but also lobular **(Figure 88)**
- Multinucleated giant cells with asteroid bodies **(Figure 89)**
- Late stages, granulomas sclerosed with intersegmentation of granulomas typical, bridging fibrosis and cirrhosis
- Loss of intrahepatic bile ducts

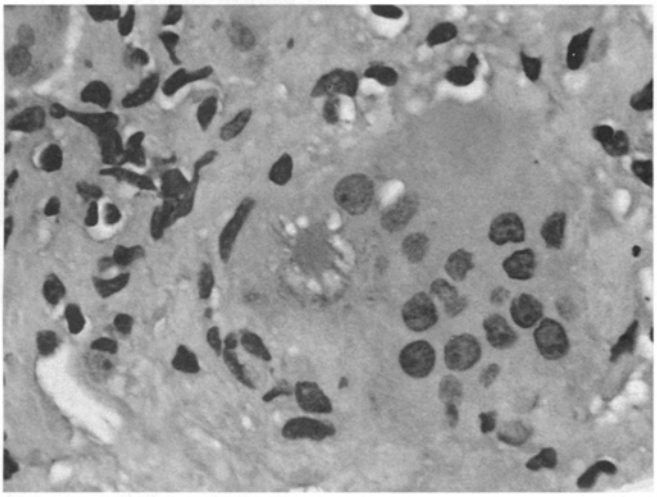


Fig. 89. Hepatic sarcoidosis showing an asteroid body within a giant cell.

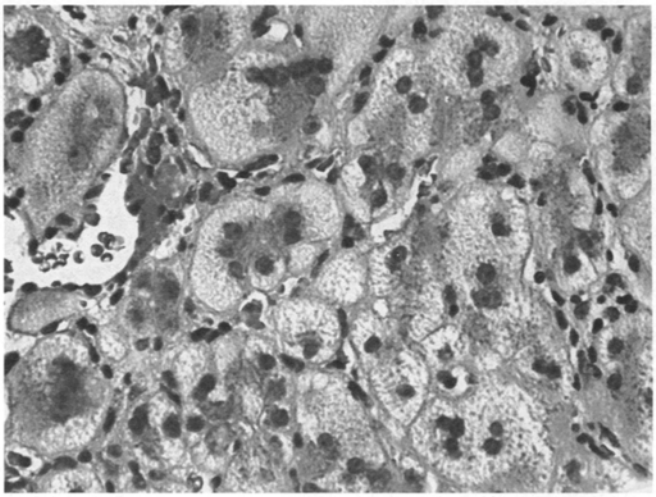


Fig. 90. Neonatal hepatitis showing multinucleated syncytial giant cells.

Special Studies

- Masson's trichrome
- Ziehl-Nielsen
- Methenamine silver

Differential Diagnosis

- Granulomas of other causes (tuberculosis, drug-induced)
- Primary biliary cirrhosis

Inflammatory Bowel Disease

- 50% of patients with chronic ulcerative colitis or Crohn's disease exhibit hepatic dysfunction of varying degrees; 5% develop clinically significant liver disease, most often primary sclerosing cholangitis
- Non-specific reactive changes with mild elevations in serum LFTs and asymptomatic clinical course represent the majority of cases
- Primary sclerosing cholangitis (5%) with cirrhosis (1%) and cholangiocarcinoma (1%) are relatively common complications of chronic ulcerative colitis
- Chronic hepatitis C and autoimmune hepatitis in 1% to 2% of all cases
- Colon resection for inflamatory bowel disease does not influence the course of primary sclerosing cholangitis

Neonatal Giant Cell Hepatitis

Clinical

- Non-specific reaction pattern with conjugated hyperbilirubinemia, normal biliary tree, chronic inflammation, and syncytial giant cell transformation of hepatocytes by cell fusion and/or mitotic inhibition
- Most common associated disorder is alpha-1-antitrypsin deficiency; other metabolic, biliary, or infectious etiologies; half of all cases have no known cause
- Overall prognosis variable; underlying liver disease (if known) determines clinical cause and outcome

Microscopic

- Syncytial giant cell transformation of hepatocytes; typically diffuse distribution with lobular disarray **(Figure 90)**
- Lymphocytic chronic inflammation and normal bile ducts; some cholestasis possible

Special Studies

- Immunostains and/or PAS-diastase to rule out alpha-1-antitrypsin deficiency

Differential Diagnosis

- Extrahepatic biliary atresia
- Alpha-1-antitrypsin deficiency

Reye's Syndrome

Clinical

- Children, usually younger than 5 years
- Acute encephalopathy and diffuse microvesicular steatosis; other organs also with fatty change; generalized mitochondrial problem is likely
- Often associated with viral upper respiratory tract infection and aspirin exposure
- Supportive treatment, severe liver disease uncommon, responds to aggressive management; 25% mortality

Microscopic

- Uniform distribution of microvesicular steatosis without significant inflammation

- Microvesicular fat also accumulates in proximal tubules of the kidney, in myocardium, and in skeletal muscle
- May lead to zonal or massive hepatic necrosis

Special Studies

- Fat stains
- Electron microscopy shows enlarged pleomorphic mitochondria with swollen matrix

Differential Diagnosis

- Metabolic storage disorders
- Drugs/toxins

Toxemia of Pregnancy

Clinical

- Responsible for 5% of jaundice during pregnancy, usually in third trimester
- Vasospasms and/or disseminated intravascular coagulation as initiating event
- Treatment supportive with termination of pregnancy

Microscopic

- Periportal fibrin deposition along sinusoids
- Hemorrhage and ischemic hepatocellular necrosis
- Fibrin thrombi in portal veins

DISORDERS OF THE GALLBLADDER

Acute Cholecystitis

- Usual cause is cystic duct or Hartmann's pouch occlusion by a gallstone; rarely occlusion by neoplasm; secondary bacterial infection
- Acalculous cholecystitis may occur after polytrauma, burns, or major surgery; may also complicate hemolysis, typhoid fever, brucellosis, or pancreatitis
- Presentation with initial biliary colic, but continuous pain; vomiting, fever; mild jaundice possible; elderly patients may present pain-free and afebrile
- Inflammatory laboratory parameters +; LFTs may be abnormal; ultrasonography diagnostic
- Treatment includes antibiotics and semi-elective cholecystectomy after 2–3 days of medical treatment
- Complications include empyema, gangrene, abscess, and peritonitis

Chronic Cholecystitis and Biliary Colic

- Chronic cholecystitis is due to stones in the gallbladder; poor correlation between clinical features and pathologic findings
- Gallbladder wall is typically thickened; the mucosal surface becomes flattened and may ulcerate; microscopically there is fibrosis and variable chronic inflammatory infiltrate; Rokitansky-Aschoff sinuses (mucosal diverticula) usually present
- Various reactive and hyperplastic mucosal changes frequently develop; several polyps and tumor-like conditions can be seen (*see* Chapter 31)
- Extensive wall calcifications lead to a "porcelain gallbladder"
- Biliary colic episodes are common symptoms with sudden onset of pain (which is not colicky despite its name) after certain meals
- Oral cholecystography and ultrasound are diagnostic; ultrasound is more sensitive (stones 1–3 mm in size identifiable)
- Pain relief in acute attacks, followed by elective cholecystectomy, possibly laparoscopic; mortality rate = 0% to 1%, four times higher if choledocholithotomy is performed

Cholelithiasis

- Most common disorder of the biliary system; gallstones are usually designated as cholesterol stones, mixed stones, or pigment stones **(Figure 91)**
- Continuous spectrum of stone composition:
  - Only 20% are pure cholesterol or pigmented stones
  - 10% to 20% of stones contain enough calcium to be radio-opaque
- Prevalence varies considerably:
  - Rare in Africa and among Eskimos
  - Common in Western countries
  - Very high frequency among American Pima Indians suggests genetic predisposition along with lifestyle factors
  - Incidence is increasing worldwide
- Gallstones become more common with age; females two to three times more often affected than males; risk factors also include obesity, high calorie diet, and long-term parenteral nutrition
- Pigment stones arise when excess unconjugated bilirubin leads to precipitation of calcium bilirubinate; they are especially common in the Far East, equal frequency in men and women; associated with hemolytic anemia, cirrhosis, and cholangitis; occur also in the absence of known risk factors
- Gallstones are found in most patients with carcinoma of the gallbladder and in 50% of patients with acute pancreatitis



Fig. 91. Large faceted gallstones in a patient with cholelithiasis.

- Dissolution therapy only indicated in patients with small (<1.5 cm), cholesterol-rich stones; chenodeoxycholic acid most widely used; recurrence when therapy is stopped
- Cholecystectomy as definite treatment in symptomatic patients; only 20% of patients with gallstones develop symptoms
- Complications include biliary colic, acute cholecystitis, acute pancreatitis, and biliary obstruction; rarely, gallbladder carcinoma, fistules, or gallstone ileus

Choledocholithiasis

- 10% of patients with cholecystolithiasis, incidence increases with age
- Majority of bile duct stones have migrated from the gallbladder and may increase in size in the bile duct; primary bile duct stones are rarer and typically associated with partial biliary obstruction due to strictures; primary duct stones are usually single, ovoid, soft, and conform to the bile duct
- Secondary hepatic changes dependent on degree of obstruction, time present, and amount of biliary infection
- Episodes of obstructive jaundice or pancreatitis; recurrent symptoms after cholecystectomy; Charcot's triad (pain, obstructive jaundice, fever)
- Ultrasound and/or ERCP for diagnosis
- Complications include acute cholangitis and septicemia
- Treatment of choice is ERCP-based stone extraction or cholecystectomy with bile duct exploration

Post-Cholecystectomy Syndrome

- Describes residual recurrent pain or discomfort in the upper abdomen following cholecystectomy; 30% of patients are affected, 2% to 5% with severe symptoms
- Extrabiliary causes include reflux esophagitis, peptic ulceration, chronic pancreatitis, irritable colon, and functional pain
- Major biliary causes include retained common bile duct stones and biliary stricture
- Debated causes include long cystic duct remnant, papillary stenosis, adhesions, and traumatic neuromas
- Pain typical of organic biliary disease may arise in the absence of demonstrable biliary calculi; pain mechanism poorly understood; dysmotility of gallbladder and sphincter of Oddi suspect
- Treatment includes searching for definable cause, ERCP, cholecystectomy, or sphincterotomy; only 50% of patients benefit from surgical intervention

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38

Neoplasms of the Liver and Biliary System

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CONTENTS

I. Tumors of the Liver and Intrahepatic Bile Ducts 38-2
Benign Epithelial Tumors 38-2
Liver Cell Adenoma 38-2
Bile Duct Adenoma 38-2
Hepatobiliary Cystadenoma 38-3
Biliary Papillomatosis 38-3
Malignant Epithelial Tumors 38-4
Hepatocellular Carcinoma 38-4
Fibrolamellar Carcinoma 38-8
Hepatoblastoma 38-8
Cholangiocarcinoma 38-10
Hepatobiliary Cystadenocarcinoma 38-12
Miscellaneous Malignant Epithelial Tumors 38-12
Benign Mesenchymal Tumors 38-13
Hemangioma 38-13
Infantile Hemangioendothelioma 38-13
Angiomyolipoma 38-13
Miscellaneous Benign Mesenchymal Tumors 38-15
Malignant Mesenchymal Tumors 38-15
Angiosarcoma 38-15
Epithelioid Hemangioendothelioma 38-15
Undifferentiated Sarcoma 38-16
Embryonal Rhabdomyosarcoma 38-17
Miscellaneous Malignant Mesenchymal Tumors 38-17
Hematopoietic Neoplasms 38-17
Primary Malignant Lymphoma 38-17
Secondary Hematopoietic Neoplasms 38-18
Metastases 38-18
Tumor-like Lesions 38-18
Cysts 38-18
Focal Nodular Hyperplasia 38-18
Nodular Regenerative Hyperplasia 38-19
Mesenchymal Hamartomas 38-19
Biliary Hamartoma (von Meyenburg Complex) 38-19
Peliosis Hepatis 38-20
Inflammatory Pseudotumor 38-20

II. Tumors of the Gallbladder and Extrahepatic Bile Ducts 38-21
Benign Epithelial Tumors and Lesions 38-21
Polyps 38-21
Hyperplasia and Metaplasia 38-22
Papillary Hyperplasia 38-22
Hepatobiliary Cystadenoma 38-22
Adenoma 38-22
Malignant Epithelial Tumors 38-22
Carcinoma of the Gallbladder 38-22
Carcinoma of the Extrahepatic Bile Ducts 38-23
Miscellaneous Malignant Epithelial Tumors 38-23
Benign and Malignant Non-Epithelial Tumors 38-23
Tumor-like Lesions 38-23
Adenomyoma 38-23

IV. Suggested Reading 38-24

TUMORS OF THE LIVER AND INTRAHEPATIC BILE DUCTS

Benign Epithelial Tumors

Liver Cell Adenoma

Clinical

- Occurs most commonly in women of reproductive age taking oral contraceptive steroids with a causal link related to dose, duration of use, and patient's age
- Absolute risk of <3 per 100,000 oral contraceptive users per year for women under 30 years of age; may be higher for older women; overall incidence decreasing
- Also occurs in adult men and children treated with anabolic/androgenic steroids
- Spontaneous regression after discontinuation of the drug is rare, as are instances of malignant transformation
- Clinical presentation (depending on tumor size) with episodic right upper quadrant pain and discomfort, or with severe abdominal pain, hemorrhage, and shock
- Surgical resection indicated in most cases
- No production of excess alpha-fetoprotein

Macroscopic

- Usually solitary, occasionally pedunculated; can arise anywhere in the liver
- Bulging mass with dilated blood vessels over its surface; up to 30 cm in size
- Cut surface soft, well-demarcated, usually spherical, seldom encapsulated
- Yellow-tan-brown color spectrum; frequent necrosis and hemorrhage
- Not associated with cirrhosis; remaining liver is usually normal

Microscopic

- Made up purely of hepatocytes arranged in plates two to three cells thick, never more; separated by inconspicuous, endothelial-lined sinusoids **(Figures 1,2)**
- Tumor cells generally larger than hepatocytes; uniform nuclei; cytoplasm may be pale or clear; mitoses are absent or rare
- Bile may be present as cytoplasmic droplets or plugs in distended canaliculi
- Often very vascular with large, tortuous arteries and veins
- Fibrous septae without bile ducts; hepatic reticulin around individual hepatocytes **(Figure 3)**
- Peliosis more common in anabolic/androgenic steroid users
- Rare features are epithelioid and giant cell granulomas, steatohepatitic changes, and extramedullary hematopoiesis

Differential Diagnosis

- Focal nodular hyperplasia
- Well-differentiated hepatocellular carcinoma
- Hepatocellular carcinoma arising in liver cell adenoma

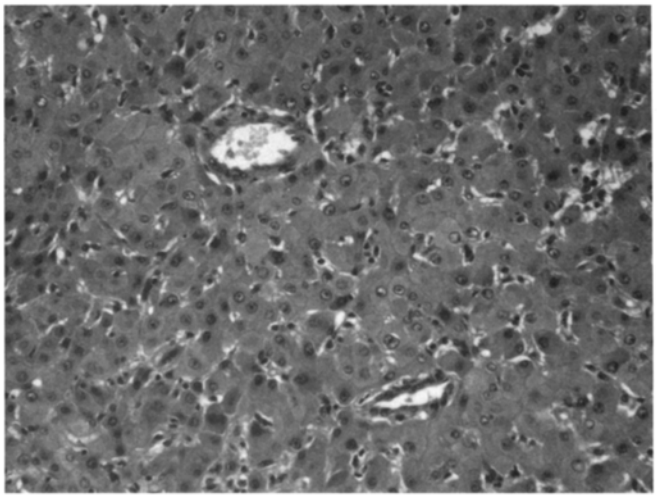


Fig. 1. Hepatic adenoma showing hepatocytes arranged as 2 or 3 cell thick plates with thick-walled arterioles scattered within the lesion. The tumor cells are slightly larger than normal hepatocytes and have regular nuclei.

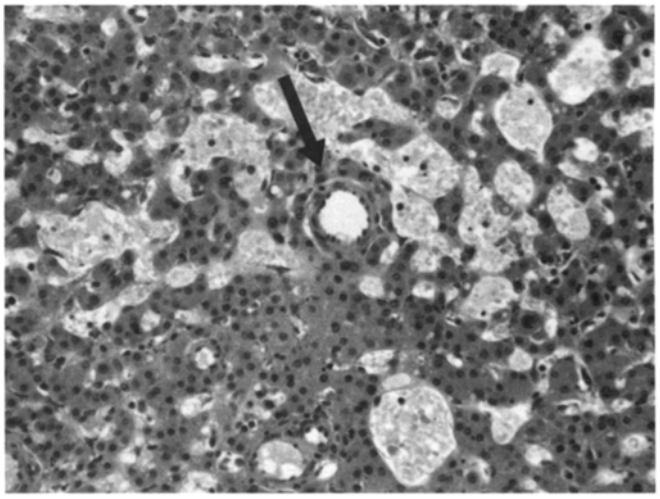


Fig. 2. Areas of sinusoidal dilatation are commonly seen within hepatic adenomas. Arrow points to a thick-walled arteriole.

Bile Duct Adenoma

Clinical

- Common (up to 30%) incidental finding at laparotomy or autopsy
- May be mistaken for metastases grossly, especially at surgery for abdominal tumors

Macroscopic

- Solitary, small, subcapsular, white, firm; without encapsulation

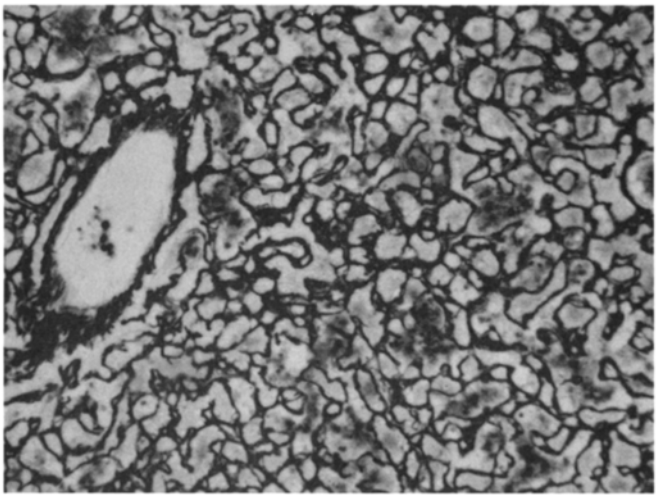


Fig. 3. Reticulin stain of a liver cell adenoma shows reticulin fibres around individual hepatocytes.

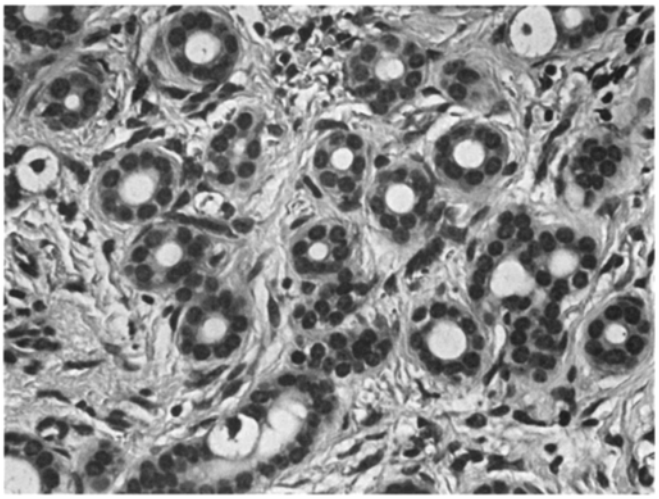


Fig. 4. Bile duct adenoma consists of small benign tubules with regular nuclei and no mitoses in a fibrous stroma.

Microscopic

- Small tubules set in a fibrous stroma with lymphocytes **(Figure 4)**
- Single layer of cuboidal cells; possible mucin secretion; no bile in lumen
- Normal portal tracts often included **(Figure 5)**
- Considerable nuclear atypia and desmoplasia may be present, not to be mistaken for metastatic carcinoma, especially in frozen sections **(Figures 6,7)**
- May actually represent peribiliary gland hamartomas

Differential Diagnosis

- Biliary hamartoma (von Meyenburg complexes)
- Mesenchymal hamartoma

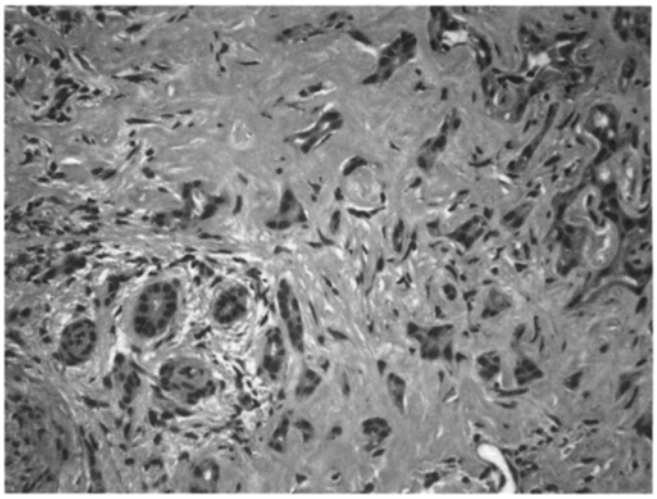


Fig. 5. Bile duct adenoma with a portal tract within the lesion (left lower corner).

Hepatobiliary Cystadenoma

Clinical

- Rare, resembling cystadenomas of the pancreas or ovary
- Middle-aged women; usual presentation with pain and discomfort
- Slow growth; tends to become symptomatic with increasing size
- Surgical resection always indicated, malignant transformation possible

Macroscopic

- Always multilocular, usually >10 cm **(Figure 8)**
- Contains clear to cloudy mucinous fluid
- Inner surface usually smooth, sometimes trabeculated, or with small projections

Microscopic

- Epithelium is mucinous, simple columnar; may become atrophic and cuboidal; occasionally shows intestinal metaplasia with goblet cells **(Figures 9,10)**
- May contain cellular, "ovarian-type" stroma in women ("ovarian" type); estrogen and/or progesterone receptor positive **(Figures 9,11)**
- Invasion, indicative of malignant transformation, should be sought through extensive sampling

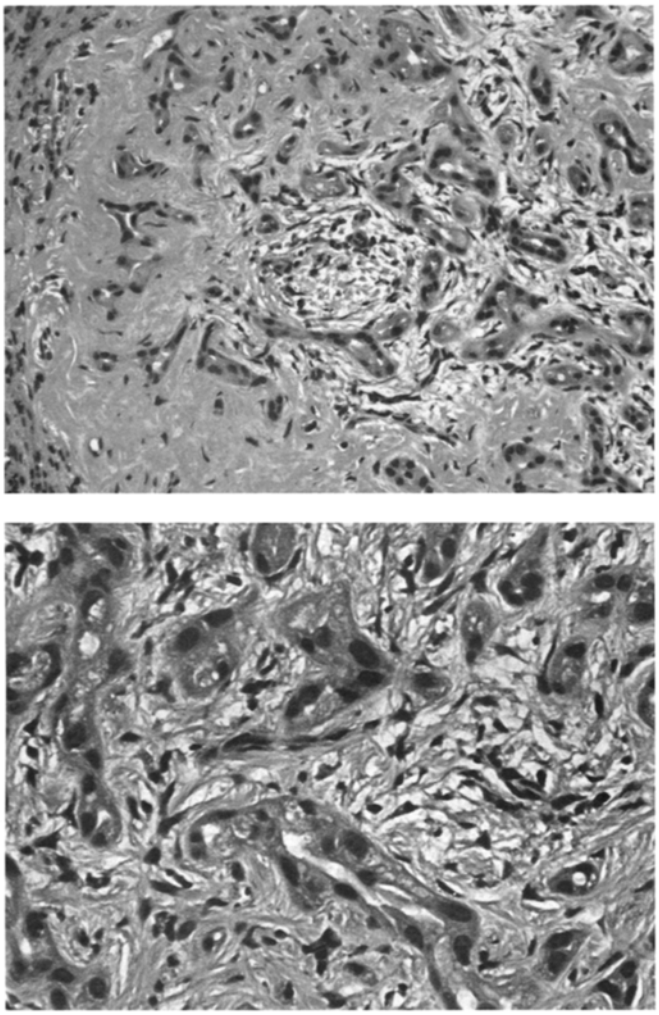
Differential Diagnosis

- Developmental cysts
- Cystadenocarcinoma

Biliary Papillomatosis

Clinical

- Rare; middle-aged patients
- Numerous lesions of intra- and extrahepatic bile ducts
- Clinical course always progressive; high mortality



Figs. 6.7. Bile duct adenoma showing considerable nuclear atypia and desmoplasia. The lesion was detected while the patient was undergoing Whipple's excision for pancreatic carcinoma.

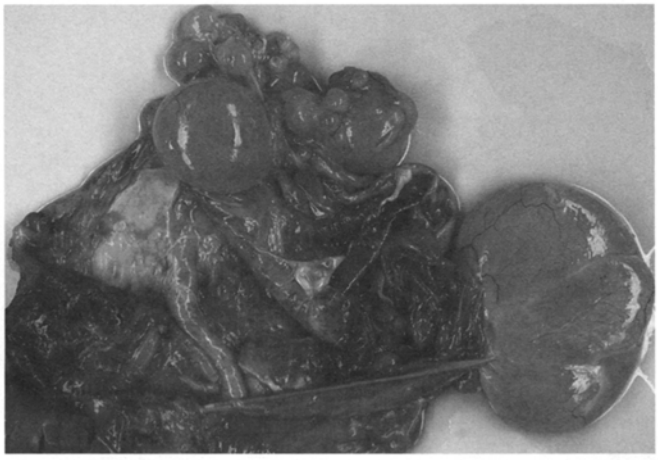


Fig. 8. Hepatobiliary cystadenoma showing a multiloculated cystic lesion. An opened cyst in the foreground shows smooth inner wall without any excrescences.

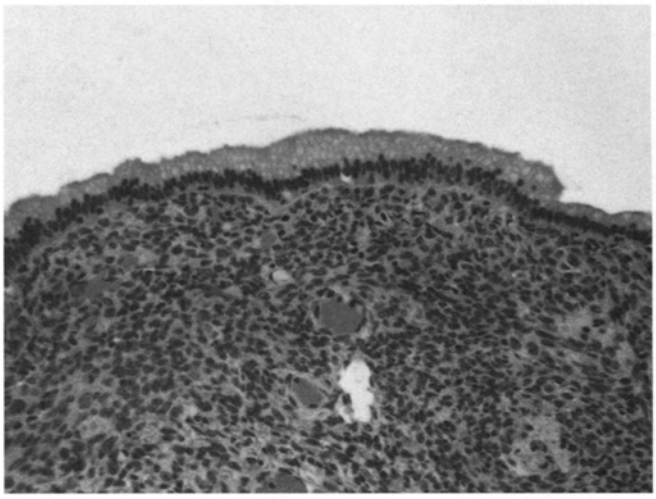


Fig. 9. Hepatobiliary cystadenoma lined by a single layer of columnar mucinous cells with underlying ovarian-type stroma.

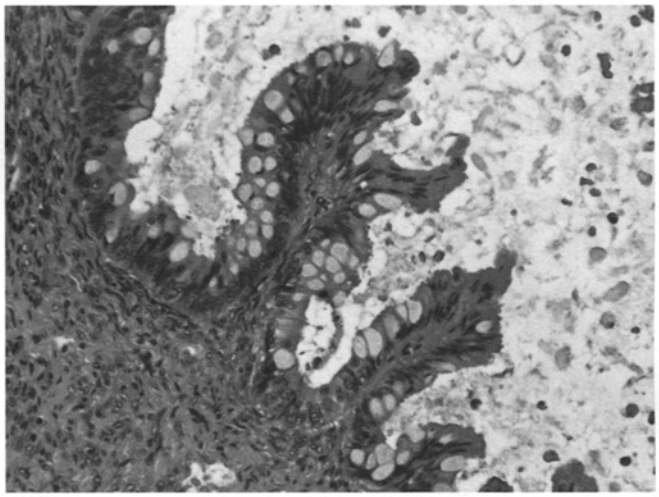


Fig. 10. Hepatobiliary cystadenoma lined by intestinal epithelium with goblet cells.

Macroscopic

- Dilated major bile ducts with friable papillary excrescences

Microscopic

- Mucus-secreting columnar epithelial cells with thin fibrovascular stalks
- Atypia and focal invasion possible

Malignant Epithelial Tumors

Hepatocellular Carcinoma

Clinical

- Geographic variation in incidence (per 100,000 population and year):
  - 20–150 in most of Africa and South-East Asia

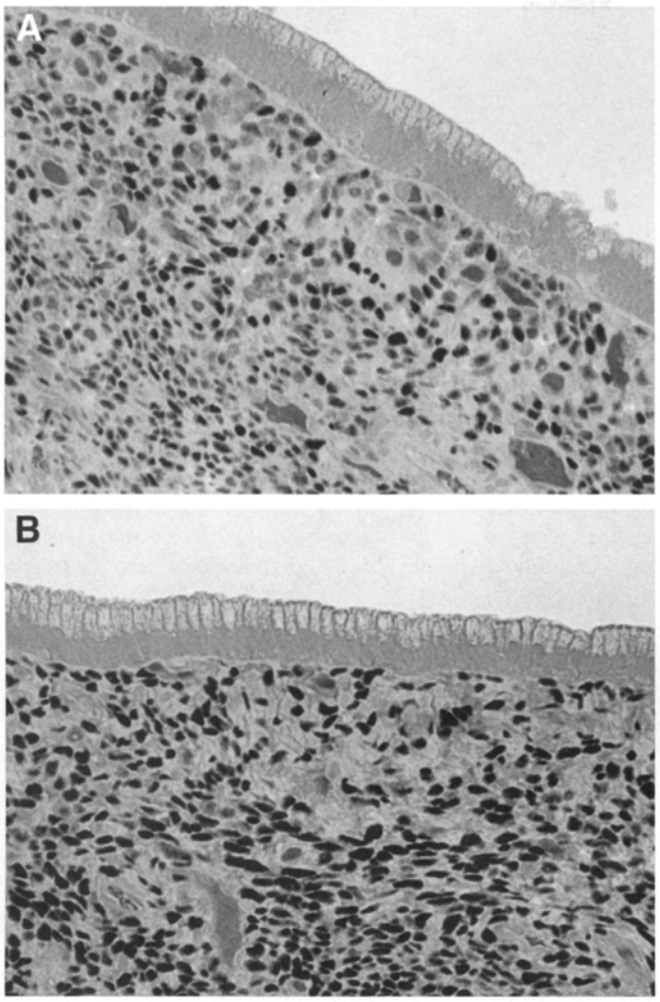


Fig. 11. Immunohistochemical stains show estrogen **(A)** and progesterone **(B)** receptor positivity in the ovarian-type stroma of a hepatobiliary cystadenoma.

  - <5 in Europe, North and South America, and Australia
  - 5–20 in Japan, North Africa, and Middle East
- More frequent in men; racial variations in incidence related to geographic prevalence of hepatitis B infection
- Common predisposing factors include:
  - Chronic liver diseases with cirrhosis as the common denominator
  - Most important factor is chronic hepatitis B (HBV DNA integration into host genome with subsequent malignant transformation)
  - Aflatoxin B1 exposure (molds) with molecular "fingerprint" in the p53 gene (G>T transversion at codon 249)
  - Rare predisposing factors include type-1 tyrosinemia, familial ataxia-telangiectasia, and hepatic porphyrias
- Xenobiotics weakly associated with hepatocellular carcinoma include organochloride pesticides, poly-chlorinated biphenyls, thorotrast, and vinyl chloride

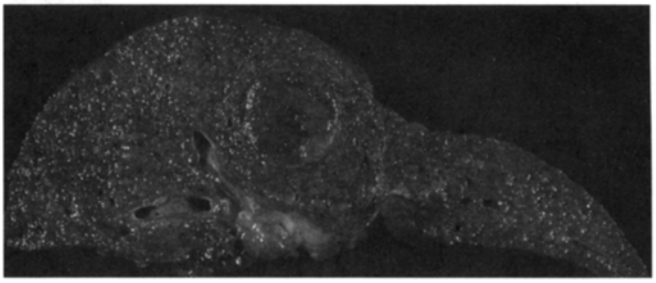


Fig. 12. Hepatocellular carcinoma seen as a soft green-yellow nodule arising in a cirrhotic liver.

- Clinical presentation:
  - Middle-to-early old age patients with long-standing cirrhosis and rapidly developing liver failure (low incidence areas)
  - Young adults presenting with pain, weight loss, or hemorrhage (high incidence areas)
- Significantly elevated serum AFP may be diagnostic, but is only moderately sensitive; imaging studies better sensitivity but may miss small lesions, especially in a cirrhotic background
- Lymph node metastases are common and treatment results are poor
- Most patients die within months of presentation, although better results are seen with small and incidental tumors

Macroscopic

- Most hepatocellular carcinomas arise on background of cirrhosis **(Figure 12)**
- Soft, yellow-green or reddish masses of varying size; three basic patterns encountered (multinodular, solitary massive, or diffuse)
- For symptomatic individuals, most common is a large mass surrounded by several "satellite" nodules; multinodular appearance may be difficult to distinguish from cirrhosis; diffuse patterns are rare
- Tumor thrombi in veins are common, as is spontaneous rupture of larger masses

Microscopic

- Most characteristic pattern recapitulates normal liver architecture with trabeculae and intervening sinusoids **(Figures 13,14)**
- Common cytological features are hepatocyte-like appearance of tumor cells with increased nucleo-cytoplasmic ratio, slightly more basophilic cytoplasm than normal liver cells and prominent nucleoli
- Presence of bile is diagnostic of hepatocellular carcinoma
- Inclusions are common (eosinophilic intranuclear, hyaline cytoplasmic, pale cytoplasmic)
- Several histologic and cytologic variants are recognized that commonly occur in combinations; these variants as

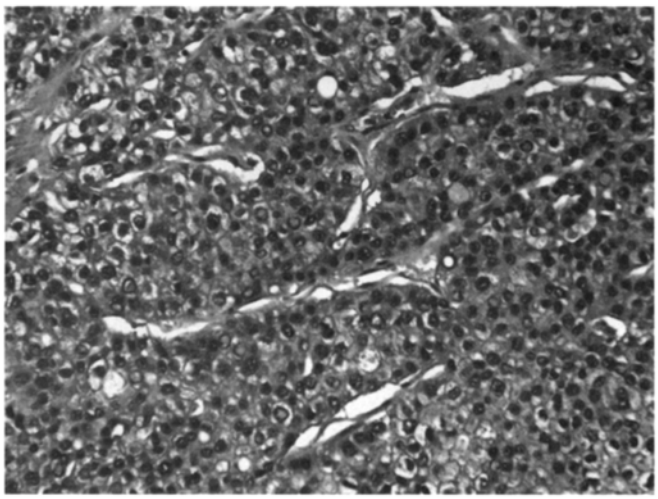


Fig. 13. Hepatocellular carcinoma showing a macrotrabecular pattern consisting of hepatocytes arranged as thick trabecula separated by sinusoids.

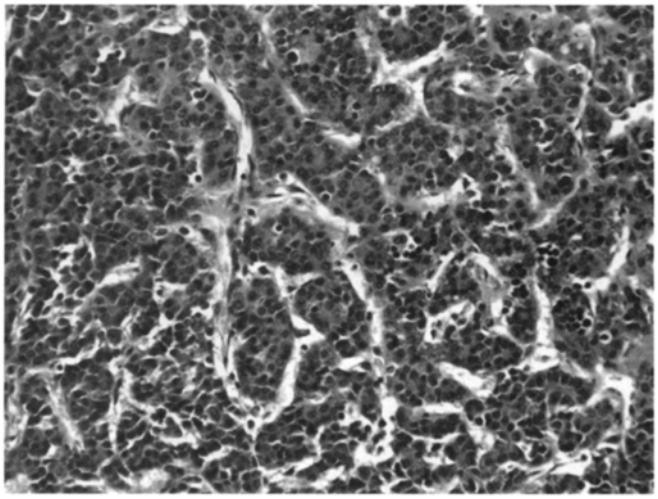


Fig. 14. Hepatocellular carcinoma showing a microtrabecular pattern consisting of slender trabecula separated by sinusoids.

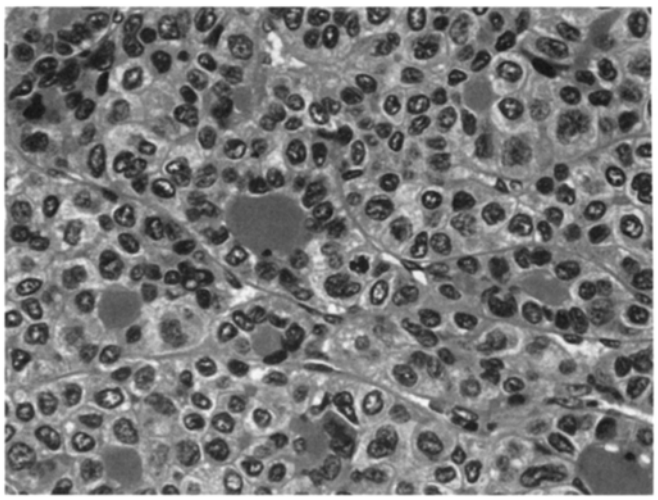


Fig. 15. Hepatocellular carcinoma showing pseudoglandular pattern with eosinophilic secretions within the gland-like structures.

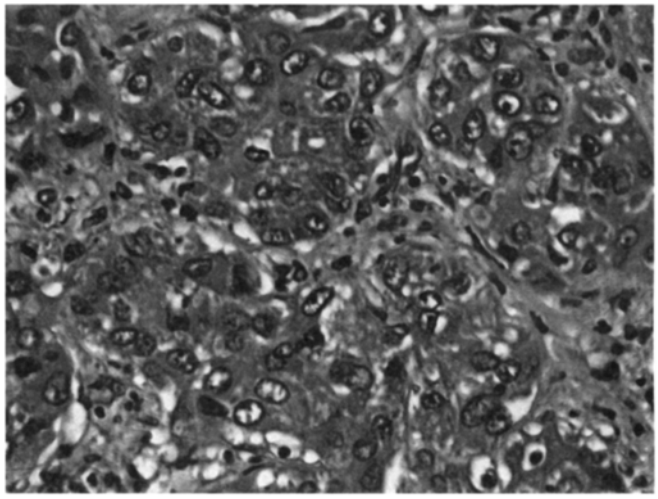


Fig. 16. Poorly differentiated heaptocellular carcinoma growing in a solid pattern.

well as histologic grade are of little or no clinical or biological significance

- Major histological patterns include trabecular, pseudo-glandular, and solid growth **(Figures 15,16)**
- Less common patterns include clear cell, steatohepatitis-like, inflammatory, anaplastic giant cell, and spindling, clear cell **(Figures 17–20)**
- Microscopic variability gives rise to confusion with cholangiocarcinoma or metastatic lesions. This can largely be avoided by remembering the most frequent architectural characteristic: resemblance to normal liver plates; presence of bile and absence of mucin diagnostic of hepatocellular carcinoma **(Figures 21,22)**
- Fine-needle aspirations yield a low rate of false+, but a rather high false– rate. Helpful features include investment of malignant cells by endothelial cells and presence of bile.

Special Stains

- Reticulin (decreased) **(Figure 23)**
- PAS (clear cell variant)
- Mucin (absent in hepatocellular carcinoma)
- Trichrome (cytoplasmic inclusions)

Immunohistochemistry and In Situ Hybridization

- Alphafetoprotein+ (in 25%)
- Keratin variable, Mucin–
- Albumin mRNA in situ hybridization+
- Hepatocyte-specific antigen (HSA)+
- Polyclonal CEA and CD10+ (canalicular pattern)

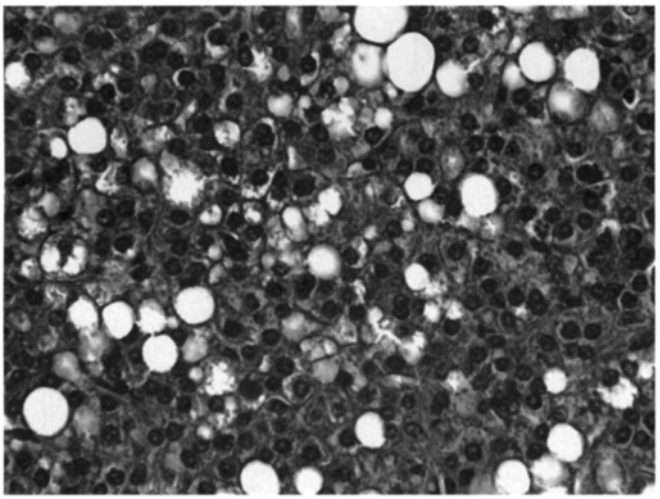


Fig. 17. Hepatocellular carcinoma showing macrovesicular fatty change.

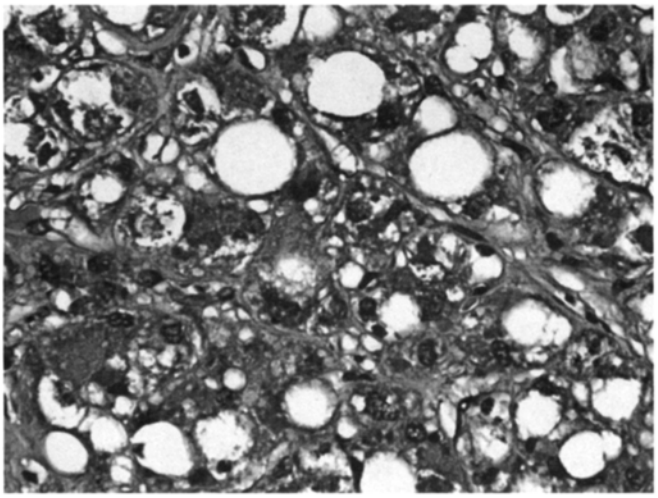


Fig. 18. Hepatocellular carcinoma showing steatohepatitis-like areas with fatty change and Mallory hyalin.

Variants

- Pedunculated hepatocellular carcinoma (better prognosis as surgically resectable)
- Minute (small, encapsulated) hepatocellular carcinoma (15% of all liver cell cancers from South-East Asia) with better prognosis

Differential Diagnosis

- Liver cell adenoma
- Cholangiocarcinoma
- Metastatic tumors
- Mixed hepatocellular carcinoma and cholangio–carcinoma

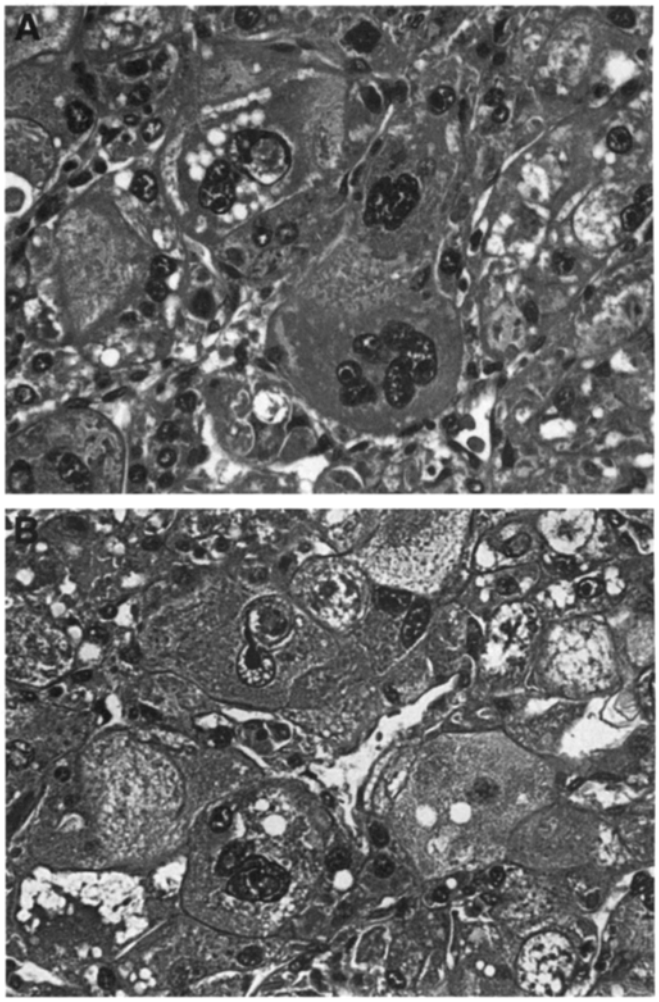


Fig. 19. Hepatocellular carcinoma with bizzare, multinucleated giant tumor cells **(A,B)**.

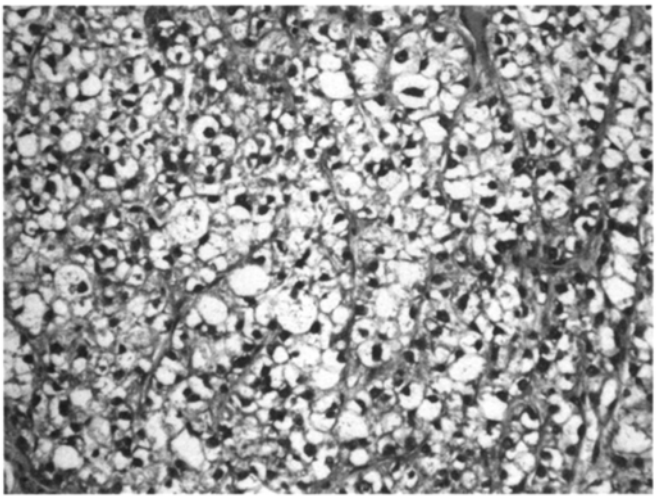


Fig. 20. Hepatocellular carcinoma with a clear cell pattern.

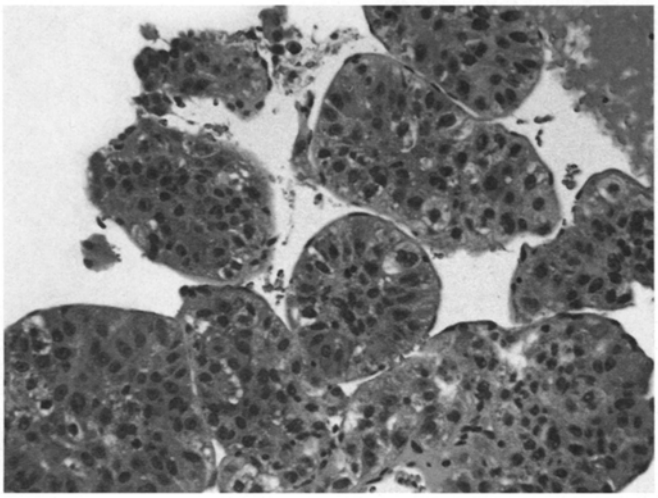


Fig. 21. Hepatocellular carcinoma from a fine needle aspiration specimen showing the characteristic covering of tumor groups by an endothelial lining.

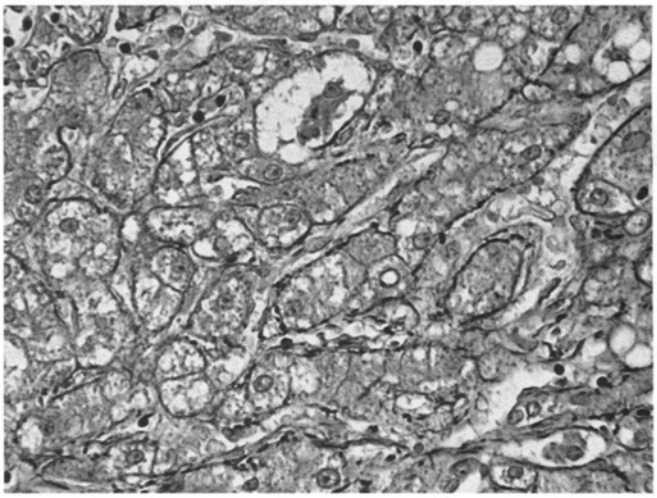


Fig. 23. Reticulin staining of hepatocellular carcinoma shows scant reticulin fibres within the tumor.

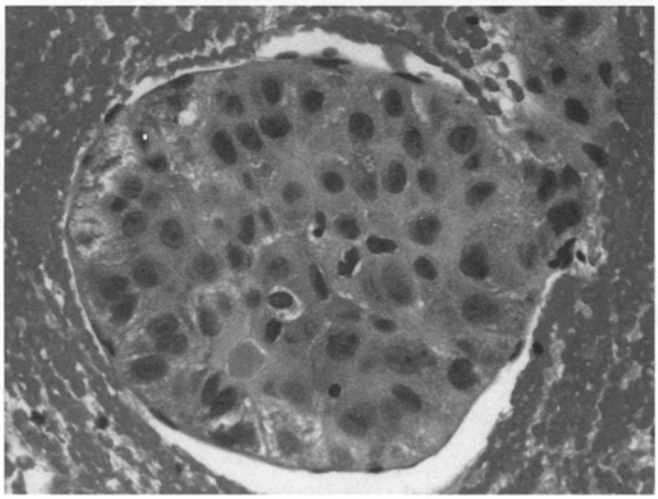


Fig. 22. Hepatocellular carcinoma showing presence of bile which is a definitive diagnostic feature for this tumor.

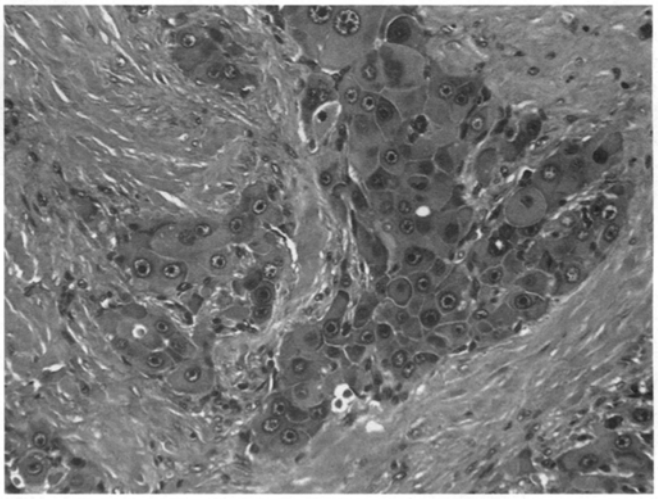


Fig. 24. Fibrolamallar carcinoma consists of sheets of tumor cells separated by lamellar fibrosis.

Fibrolamellar Carcinoma

Clinical

- Vast majority occur in patients between 18 and 45 years of age; rarely (if ever) in elderly
- Presentation with abdominal pain, malaise, and weight loss; a mass is usually readily palpable
- Patients do not have cirrhosis; hepatitis B infection infrequent
- Frequently localized to the liver at diagnosis; often resectable
- Slow progression; 5-year survival 10% to 50%

Macroscopic

- Well-defined, solitary mass; lobular arrangement with interconnecting fibrous septae or central scar; small satellite nodules possible
- Metastases to regional lymph nodes and lungs in late stages

Microscopic

- Three major criteria: macronucleoli, abundant eosinophilic cytoplasm (abundant mitochondria), and lamellar (plate-like) fibrosis **(Figures 24,25)**
- Cytoplasmic globules and "pale bodies" common; bile production may be seen; occasionally fat **(Figures 26,27)**

Immunohistochemistry and In Situ Hybridization

- Polyclonal CEA outlines bile canaliculi
- Usually alphafetoprotein–
- Albumin in situ hybridization usually +

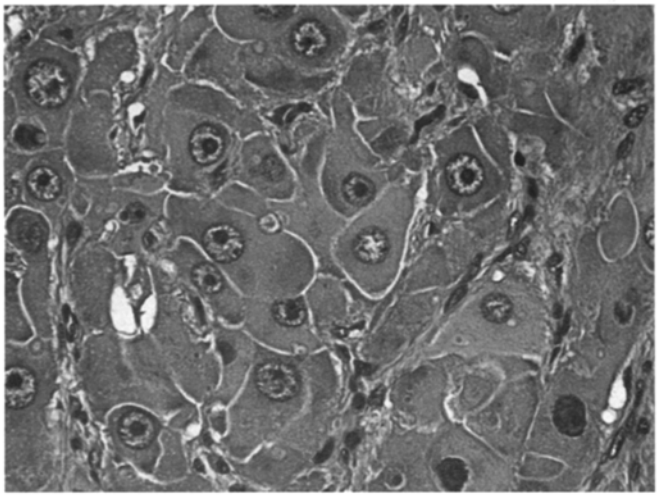


Fig. 25. Fibrolamellar carcinoma consists of large tumor cells with abundant eosinophilic cytoplasm and large eosinophilic nucleoli.

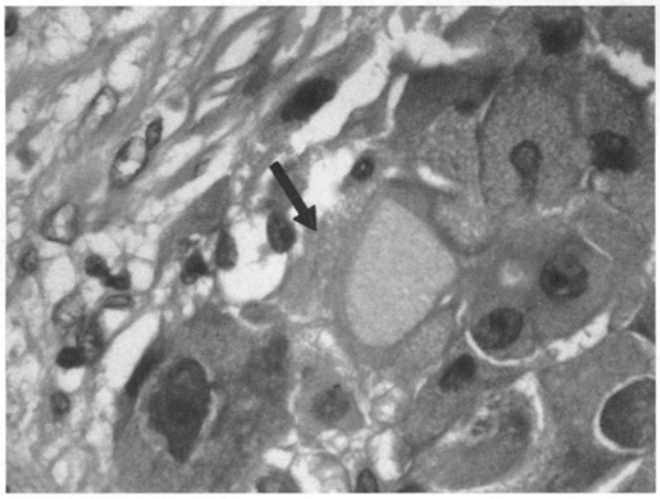


Fig. 26. Fibrolamellar carcinoma with pale bodies.

Hepatoblastoma

Clinical

- Children <5 years old; peak incidence in the first 2 years of life; rare cases in adolescents and young adults
- Incidence worldwide identical; nephroblastoma: neuro-blastoma:hepatoblastoma = 6 : 3 : 1
- 1/3 of patients with congenital anomalies (familial colonic polyposis, nephroblastoma, Down's syndrome, or other malformations)
- Presenting features include failure to thrive, weight loss, and rapidly enlarging upper abdominal mass with markedly elevated serum levels of alphafetoprotein
- Primary treatment is surgical resection, pre-operative chemo/radiotherapy decreases tumor size and makes it surgically resectable

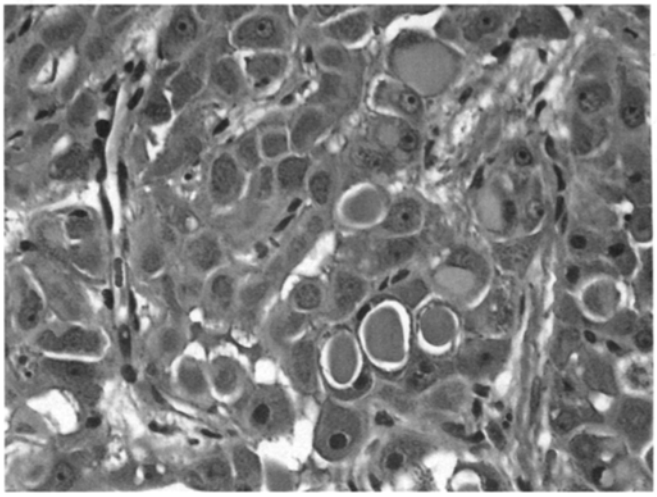


Fig. 27. Fibrolamellar carcinoma with intracytoplasmic eosinophilic inclusions.

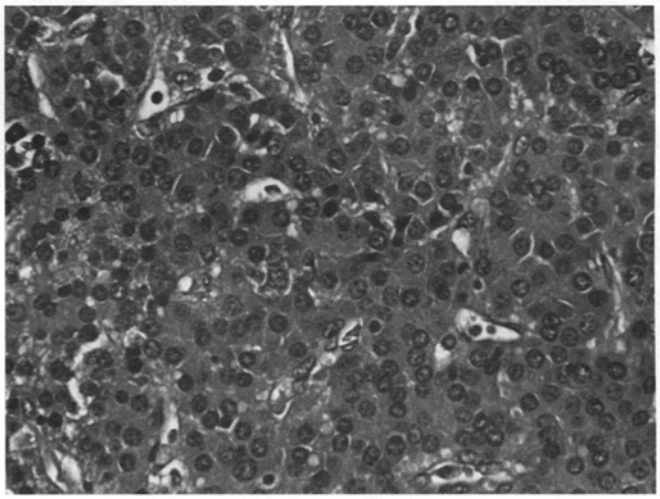


Fig. 28. Hepatoblastoma showing fetal type hepatocytes with slightly increased nucleo-cytoplasmic ratio, eosinophilic cytoplasm and central, round, regular nuclei.

- Poor prognosis in age <1 year, large size, vital structures involved, predominance of small anaplastic cells (uniformly fatal) or macrotrabeculae (chemotherapy resistance)

Macroscopic

- Single, large mass (up to 25 cm)
- Variegated gross appearance, according to histologic components present
- Often necrosis, cystic change, hemorrhage
- Non-cirrhotic

Microscopic

- Epithelial component of several types:
  - Large, polygonal fetal-type cells with oval nuclei, single nucleoli, and granular or clear cytoplasm organized into irregular plates with bile canaliculi and sinusoids **(Figures 28,29)**

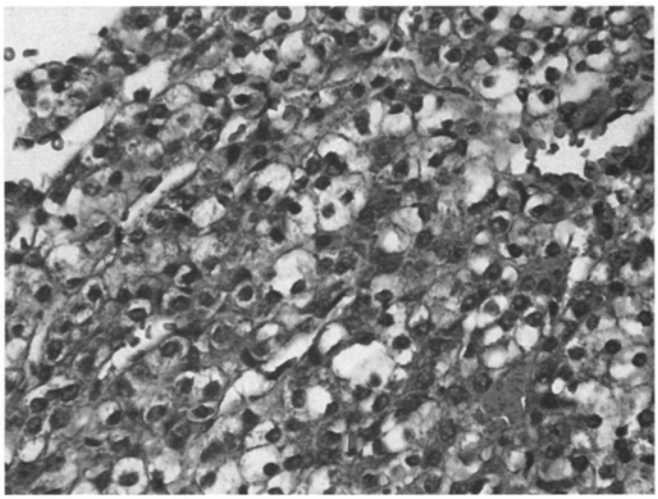


Fig. 29. Fetal areas of hepatoblastoma often consists of cells with clear cytoplasm.

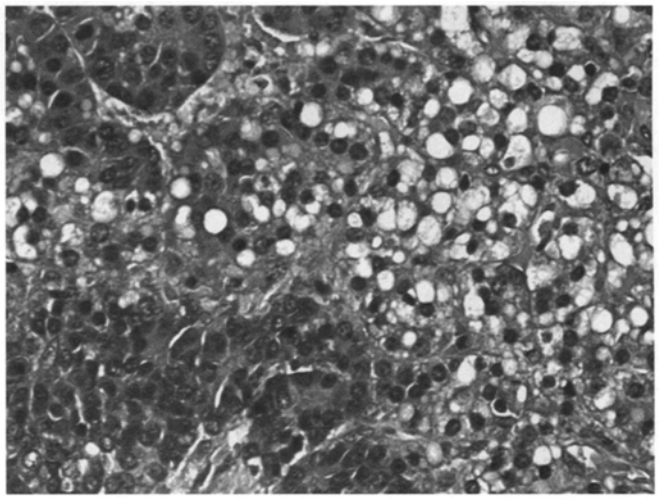


Fig. 31. Hepatoblastoma with admixture of fetal and embryonal patterns.

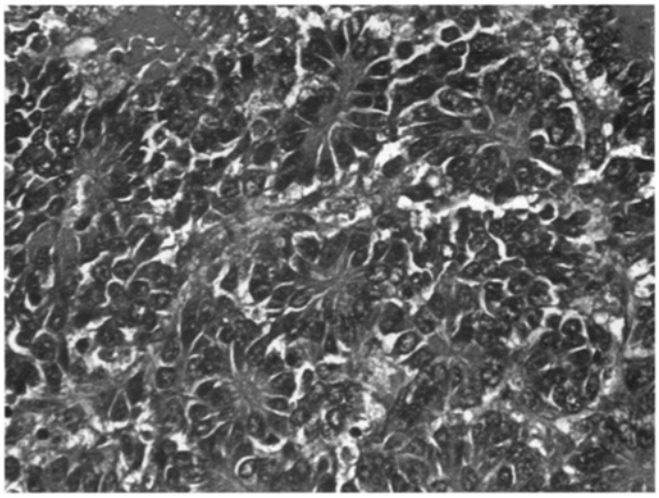


Fig. 30. Hepatoblastoma showing areas that resemble embryonal hepatocytes with pseudo-rosetting.

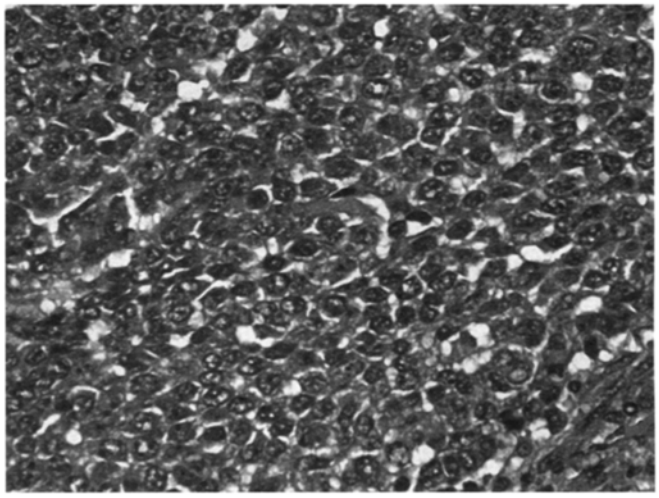


Fig. 32. Hepatoblastoma with anaplastic (small cell) component.

- Smaller, darkly staining embryonal-type cells with scant cytoplasm, aggregating into cords, ribbons, or rosette-like clusters; fetal and embryonal areas are often intermixed **(Figures 30,31)**
- Anaplastic small cells (small blue cell or neuroblastoma type) **(Figure 32)**
- Macrotrabecular component (resembles hepatocellular carcinoma)

♦ First two components are invariably present in varying proportions

♦ Mesenchymal component with osteoid or undifferentiated spindle cell mesenchyme, admixed with epithelial components **(Figure 33)**

♦ Extramedullary hematopoiesis common; intestinal glands and squamous metaplasia may be seen

Immunohistochemistry and In Situ Hybridization

♦ Alphafetoprotein+ (fetal and embryonal cells), beta-hCG+ (giant cells), vimentin+ (anaplastic cells), albumin in situ hybridization+, HSA+

Variants

♦ Teratoid hepatoblastoma (presence of cartilage, striated muscle, neural tissue)

Cholangiocarcinoma

Clinical

♦ Tumor arises in ducts proximal to the liver hilum

♦ Associated with liver flukes (*Clonorchis sinensis:* Hong Kong, Canton; *Opisthorchis viverrini:* Thailand), hepatolithiasis, primary sclerosing cholangitis, congenital anomalies, and Thorotrast exposure **(Figure 34)**

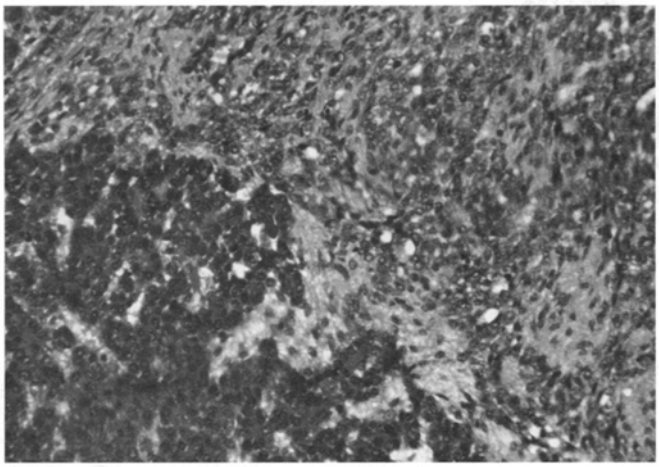


Fig. 33. Hepatoblastoma with admixture of epithelial and mesenchymal elements; the latter is seen as an undifferentiated spindle cell component.

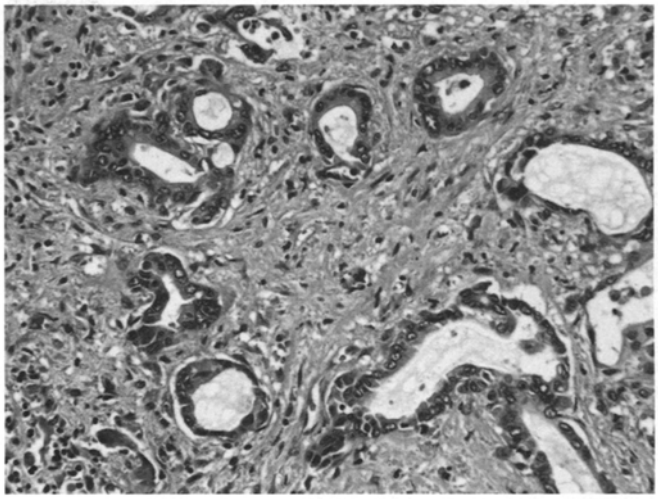


Fig. 35. Cholangiocarcinoma showing irregularly shaped glands with pleomorphic nuclei in a desmoplastic stroma.

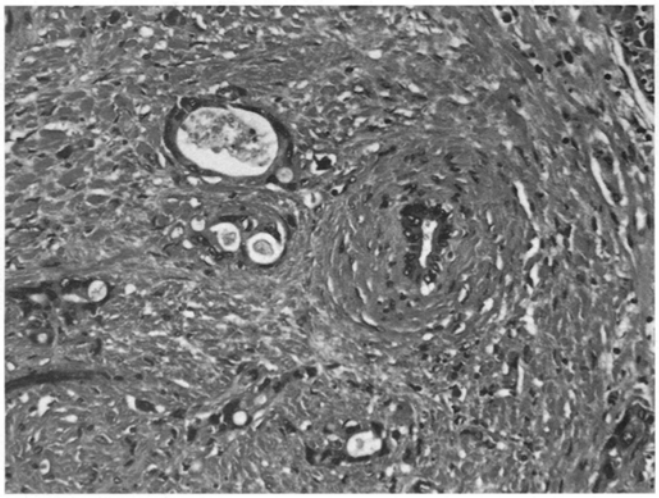


Fig. 34. Cholangiocarcinoma and a duct with concentric periductal fibrosis in a patient with PSC.

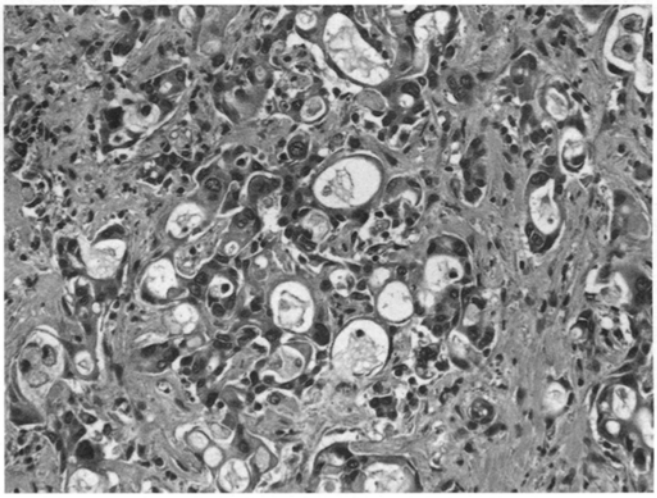


Fig. 36. Cholangiocarcinoma with signet ring cells and mucin production.

- No association with cirrhosis, HBV infection, or mycotoxins
- Patients in fifth and sixth decade present at late stage with pain, weakness, and weight loss
- Serum AFP usually normal, CEA elevated
- Frequently *ras*-mutations (possibility for carcinoma-screening)
- Metastases common (regional lymph nodes, later hematogenous spread)
- Frequently not resectable; prognosis very poor

Macroscopic

- Solitary, sometimes multinodular grey-white, firm mass with predominantly central sclerosis and calcifications; finger-like extensions from main mass (lymphatic spread)
- Characteristically avascular
- Growth into major bile ducts or blood vessels rarely seen

Microscopic

- Well- to moderately differentiated tubular adeno-carcinoma in abundant fibrous stroma; PAS or mucin stains+ **(Figure 35)**
- Many different architectural growth patterns possible, with no biological or clinical significance **(Figure 36)**
- Remaining liver frequently shows bile duct hyperplasia, atypical hyperplasia, and carcinoma in situ adjacent to the tumor
- Tumors associated with stones, cysts, or anomalies may be squamous

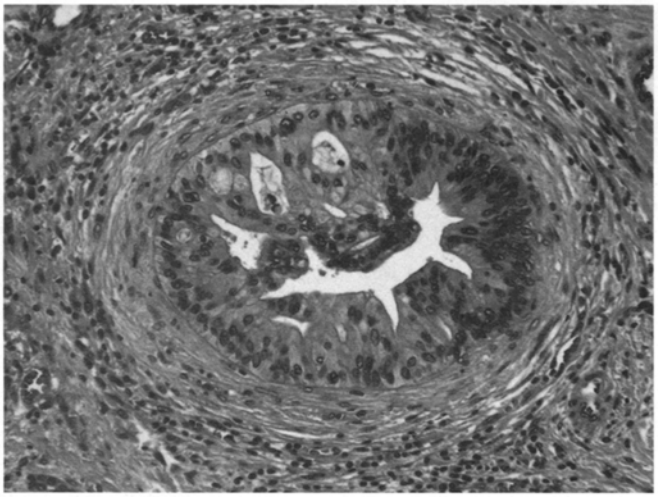


Fig. 37. Severe dysplasia in ducts with concentric periductal fibrosis in a patient with PSC and cholangiocarcinoma.

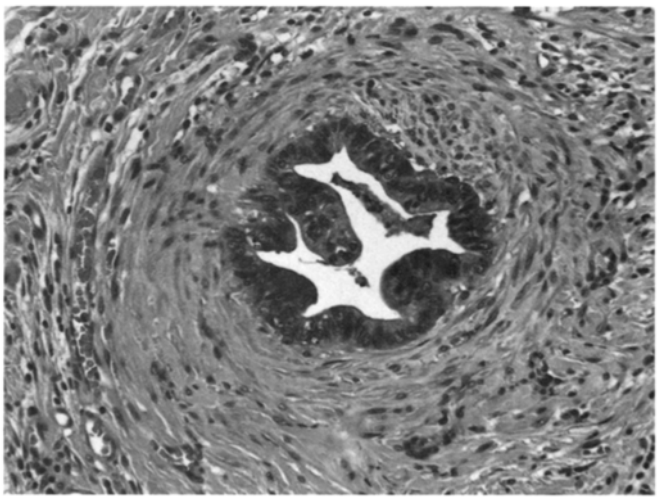


Fig. 38. Severe dysplasia in a patient with PSC and cholangiocarcinoma.

- Distinction from metastases requires demonstration of carcinoma in situ in adjacent ducts; not possible in needle biopsies **(Figures 37,38)**

Immunohistochemistry

- Mucin+ **(Figure 39)**
- Alphafetoprotein–
- EMA+
- CEA+ (cytoplasmic pattern)
- Keratin+

Variants

- Hilar adenocarcinoma (Klatskin tumor) with slower growth and better prognosis (arises from the main hepatic duct or lobar branches with early jaundice as presenting symptom)

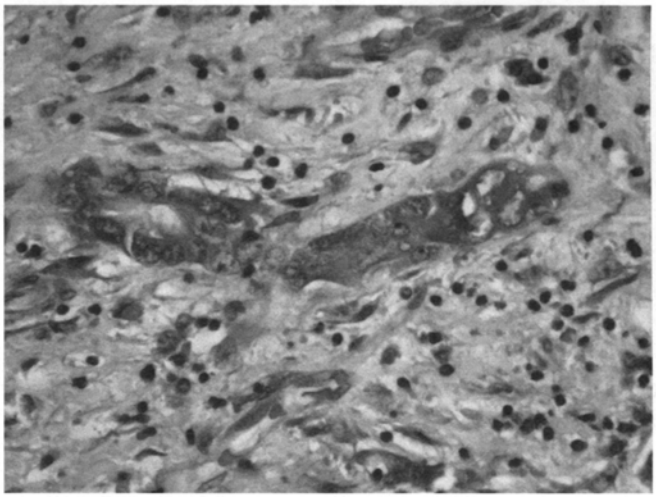


Fig. 39. Mucin positivity in cholangiocarcinoma (Mucicarmine stain).

Differential Diagnosis

- Metastatic adenocarcinoma
- Hepatocellular carcinoma
- Atypical benign bile duct proliferation in hepatolithiasis or malformations

Hepatobiliary Cystadenocarcinoma

Clinical

- Very rare malignant counterpart of hepatobiliary cystadenoma; "borderline" tumors are described
- Majority in middle-aged women; no symptoms until very large
- Usually grows well-defined; surgery often possible with good prognosis

Macroscopic

- Similar to hepatobiliary cystadenoma

Microscopic

- Similar to hepatobiliary cystadenoma, but with invasion **(Figure 40)**
- Significance of high-grade dysplasia and solid intracystic masses independent of invasion unclear

Immunohistochemistry

- Similar to cholangiocarcinoma

Differential Diagnosis

- Hepatobiliary cystadenoma
- Carcinoma arising in developmental cysts

Miscellaneous Malignant Epithelial Tumors

- Mixed hepatocellular carcinoma/cholangiocarcinoma rarely seen
- Adenosquamous or squamous carcinomas in association with stones, cysts, or anomalies

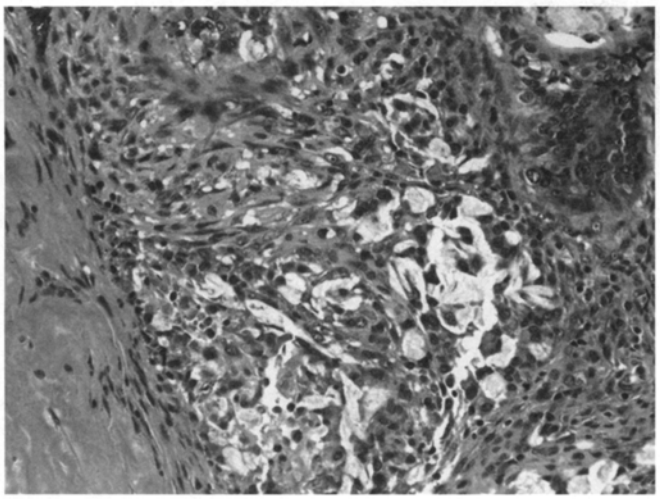


Fig. 40. Stromal invasion in a hepatobiliary cystadenocarcinoma.

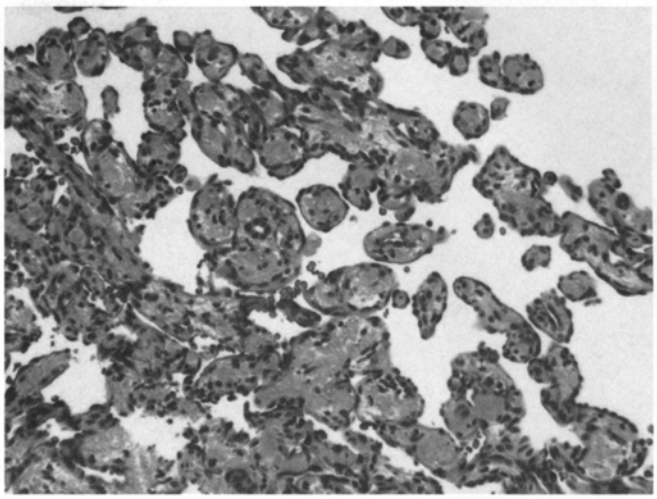


Fig. 41. Cavernous hemangioma consists of anastomosing vascular channels lined by flattened, inconspicuous endothelial cells.

- Mucoepidermoid carcinoma of salivary gland type
- Primary carcinoid tumor
- Neuroendocrine carcinoma

Benign Mesenchymal Tumors

Hemangioma

Clinical

- Most common benign liver tumor; mostly incidental finding in all ages and both sexes
- Usually solitary and <5 cm; remain stable or involute
- "Giant" hemangiomas >10 cm are symptomatic with pain and discomfort
- Resection only if symptoms or rare complications (rupture, thrombocytopenia) occur

Macroscopic

- Subcapsular, flat, circumscribed; may be pedunculated
- Red-blue color
- Usually collapse upon sectioning
- May show fibrosis and calcification; large lesions have a central scar

Microscopic

- Cavernous vascular spaces with flattened endothelium **(Figure 41)**
- Fibrous septae, thrombosis, and calcifications common

Differential Diagnosis

- Peliosis hepatis
- Angiosarcoma
- Hereditary hemorrhagic telangiectasia

Infantile Hemangioendothelioma

Clinical

- Most common mesenchymal liver tumor in infancy (first 6 months of life), often associated with cutaneous hemangiomas
- Presenting features include hepatomegaly, mass, failure to thrive, and high output cardiac failure (A-V shunting in the tumor), complications (rupture, thrombocytopenia) are rare
- Tumor tends to regress gradually over a few months
- Treatment (surgery, embolization, steroids) sometimes required, overall very good prognosis

Macroscopic

- Usually multinodular or diffuse growth
- Spongy, red-brown with scarring

Microscopic

- Intricate maze of vascular channels lined by prominent endothelial cells with variable appearance **(Figure 42)**
- Thrombosis and infarction common
- Small bile ducts present throughout the lesion **(Figure 43)**
- Nuclear atypia, multilayering, and endothelial hypertrophy possible

Differential Diagnosis

- Angiosarcoma
- Hemangioma

Angiomyolipoma

Clinical

- Middle age, female predominance
- May be solitary or multiple

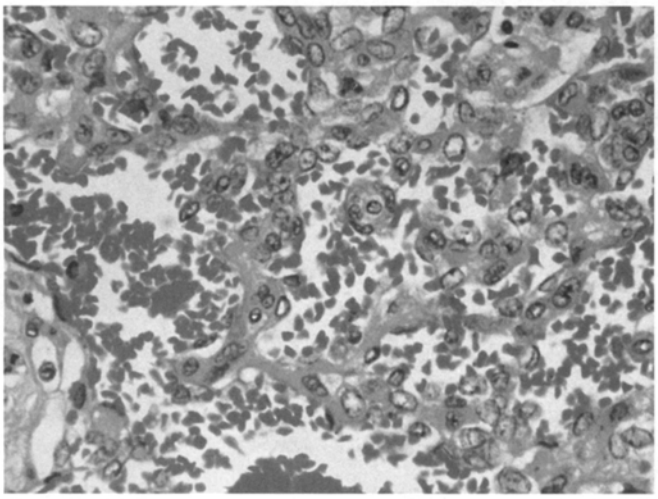


Fig. 42. Infantile hemangioendothelioma showing anastomosing vascular channels lined by plump, prominent endothelial cells.

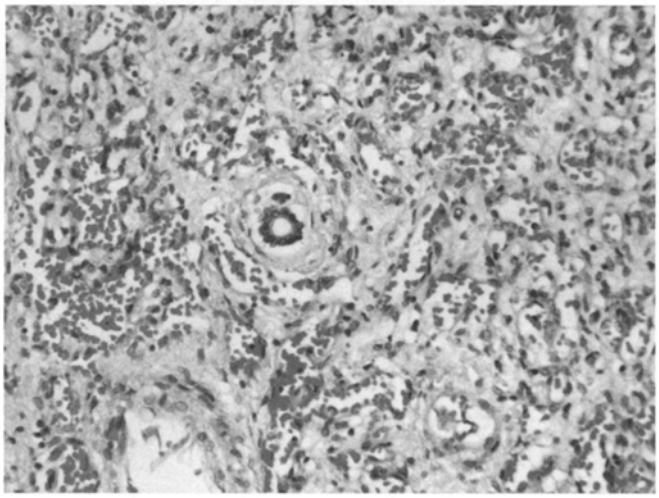


Fig. 43. Infantile hemangioendothelioma with interspersed normal bile ducts.

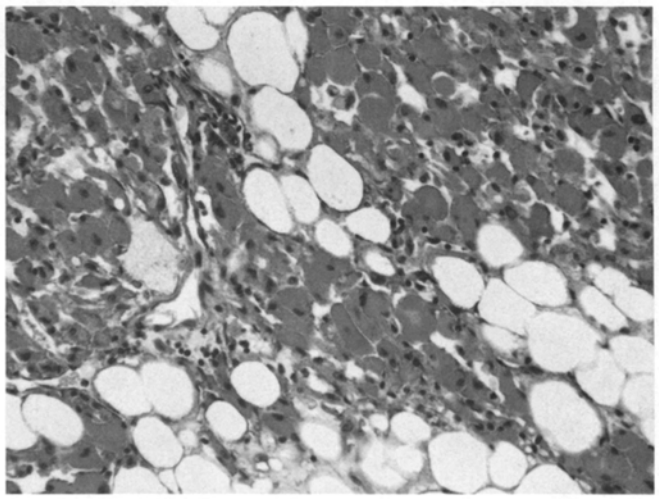


Fig. 44. Angiomyolipoma showing an admixture of lipomatous and myoid elements.

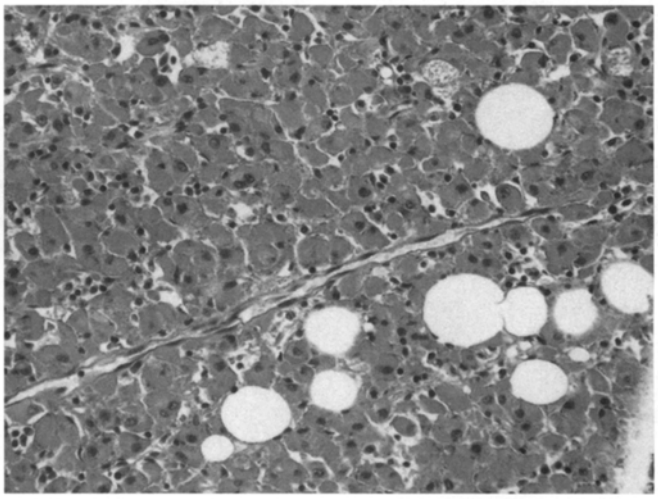


Fig. 45. Angiomyolipoma dominated by epithelioid myoid cells with low nucleo-cytoplasmic ratio, abundant eosinophilic cytoplasm and small regular nuclei.

- Associated with tuberous sclerosis, these patients also have renal angiomyolipomas

Macroscopic

- Non-encapsulated
- May be soft and yellow or firm and tan depending on whether the lipomatous or myoid component predominates
- No necrosis, hemorrhage

Microscopic

- Combination of fat, muscle and vessels in various proportions **(Figure 44)**
- May be classified as lipomatous (>70%), myomatous (<10% fat), angiomatous or inflammatory pseudotumor-like types
- Fatty component consists of mature adipose tissue, no lipoblasts
- Vessels are thick walled and surrounded by mantle of smooth muscle, rich capillary network throughout
- Myoid component takes on variety of appearances: solid, trabecular, polygonal and epithelioid shape (may predominate), clear or oncocytic, and may cause diagnostic difficulty **(Figure 45)**

Immunohistochemistry

- Desmin, smooth muscle actin+ in smooth muscle cells
- HMB 45+ in smooth muscle cells, diagnostic

Differential Diagnosis

- Leiomyosarcoma



Fig. 46. Angiosarcoma appearing as a spongy, hemorrhagic mass in a non-cirrhotic liver.

- Malignant fibrous histiocytoma
- Inflammatory pseudotumor

Miscellaneous Benign Mesenchymal Tumors

- Lymphangioma/lymphangiomatosis
- Lipoma
- Hibernoma
- Leiomyoma
- Granular cell tumor
- Chondroma
- Solitary fibrous tumor
- Hamartoma

Malignant Mesenchymal Tumors

Angiosarcoma

Clinical

- Most common sarcoma arising in the liver (annual incidence 0.25 per million), with peak age incidence sixth and seventh decade
- Strongly associated with exposure to Thorotrast (radioactive contrast medium used in 1920–1955) and vinyl chloride monomer (molecular fingerprint in the p53 gene, similar to aflatoxin); also associated with chronic arsenic exposure
- Clinical presentation with abdominal pain, hemorrhage, jaundice, and coagulopathy
- Death within 6 months of diagnosis; no treatment successful

Macroscopic

- Ill-defined, spongy nodules with hemorrhage; usually throughout the liver at autopsy **(Figure 46)**
- Metastases (regional and distant) in 20%

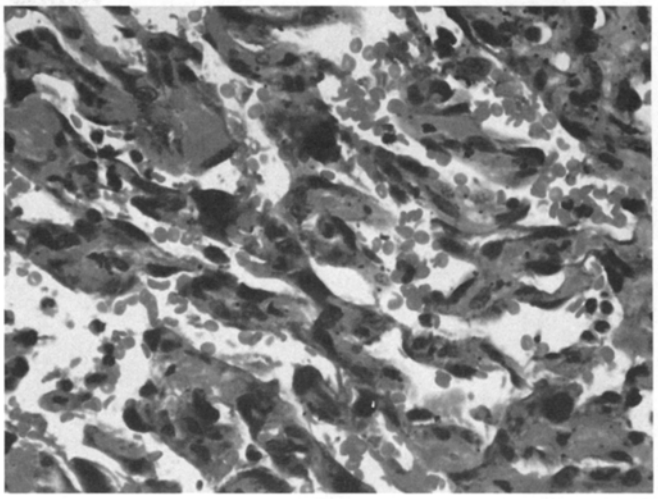


Fig. 47. Angiosarcoma consists of anastomosing vascular channels lined by malignant endothelial cells with hyperchromatic, pleomorphic nuclei.

Microscopic

- Angiosarcoma with characteristic scaffold-like (tectorial) growth on liver cell plates; the latter atrophy and disappear as the tumor progresses
- Solid masses are rarely seen; typical features are large, cavernous spaces with coarse reticulin pattern
- Pleomorphic, elongated nuclei; scanty cytoplasm; vascular invasion; necrosis; and hemorrhage **(Figure 47)**

Immunohistochemistry

- Factor VIII+, CD31+, and CD34+

Differential Diagnosis

- Hemorrhagic liver cell carcinoma
- Vascular leiomyosarcoma
- Diffuse metastatic disease in sinusoids
- Kaposi's sarcoma
- Epithelioid hemangioendothelioma

Epithelioid Hemangioendothelioma

Clinical

- Rare tumor; wide age range (second to eighth decade of life)
- Vague clinical presentation with malaise, weight loss, and upper abdominal discomfort
- Surgical resection or liver transplantation possible
- Histology is unreliable to predict clinical outcome
- Prognosis better than angiosarcoma; with a substantial percentage of long-term survivors

Macroscopic

- Solitary or multiple firm, fibrous masses

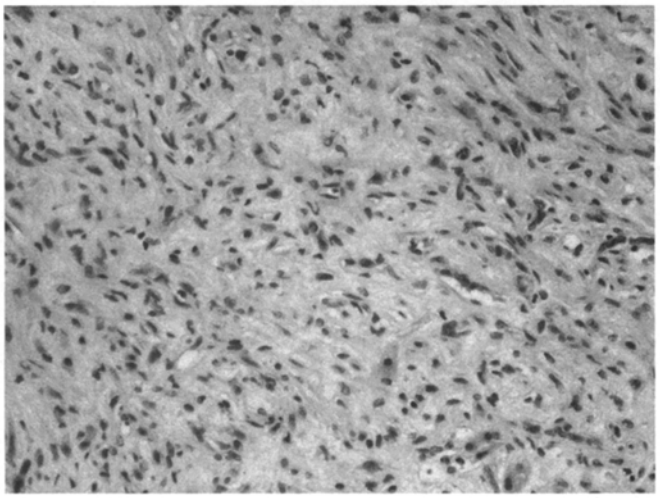


Fig. 48. The center of an epithelioid hemangioendothelioma consists of myxoid paucicellular tissue containing spindle tumor cells.

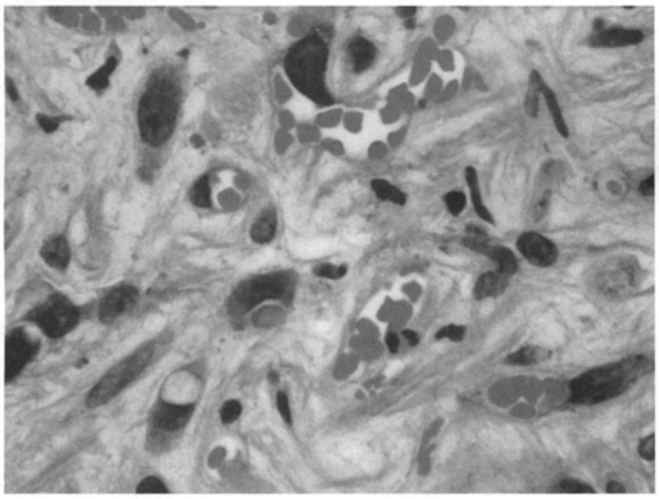


Fig. 49. Single cells with intracytoplasmic lumina (signet ring cells) are characteristic of epithelioid hemangioendothelioma, especially when the lumina contain red blood cells.

Microscopic

- Mildly pleomorphic cells with epithelioid appearance infiltrating sinusoids at the periphery of the tumor and replacement of liver parenchyma in cords toward the center of the lesion **(Figure 48)**
- Fairly abundant connective tissue stroma; light blue (vaguely "chondroid" in appearance) or pink with hematoxylin and eosin
- Tumor center is fibrous, hyalinized, and often calcified, with scanty tumor cells
- Tumor cells may have intracytoplasmic vascular lumina (visible as large vacuoles, "signet ring" appearance) **(Figure 49)**

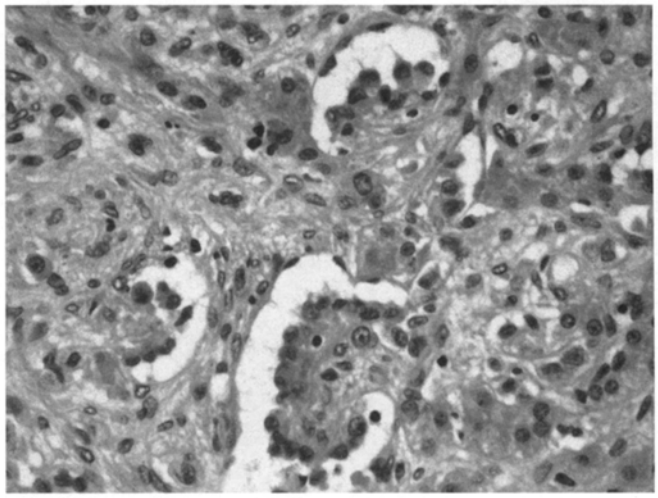


Fig. 50. At the periphery of the lesion, epithelioid hemangioendothelioma tends to infiltrate sinusoids producing papillary tufts and glomeruloid structures.

- Tumor cells may form papillary tufts within vascular channels or sinusoidal spaces **(Figure 50)**

Immunohistochemistry

- Factor VIII+, CD31+, and CD34+
- Keratin may be +

Differential Diagnosis

- Angiosarcoma
- Hemorrhagic hepatocellular carcinoma
- Diffuse metastatic disease in sinusoids
- Cholangiocarcinoma

Undifferentiated Sarcoma

Clinical

- Third most common malignant liver tumor in children
- Age usually 6–10 years; rarely in adults
- Presenting with weight loss and abdominal swelling
- Large, hypodense, avascular mass on imaging
- Prognosis very poor; 5-year survival with aggressive chemotherapy = 15%

Macroscopic

- Soft, globular, large mass, usually in the right lobe
- Cut surface variegated; solid and cystic areas; necrosis and hemorrhage common
- Thin pseudocapsule usually present

Microscopic

- Loosely arranged, spindle-shaped, pleomorphic cells **(Figures 51,52)**
- Compact areas with more rounded nuclei possible
- Abundant mucopolysaccharide matrix

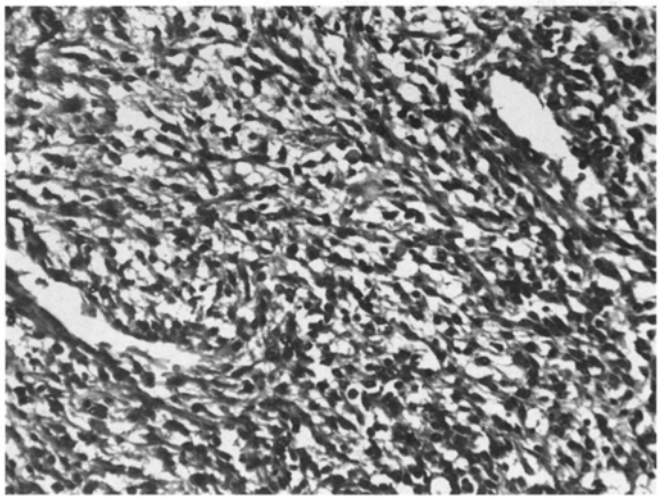


Fig. 51. Undifferentiated sarcoma consisting of sheets of undifferentiated spindle cells.

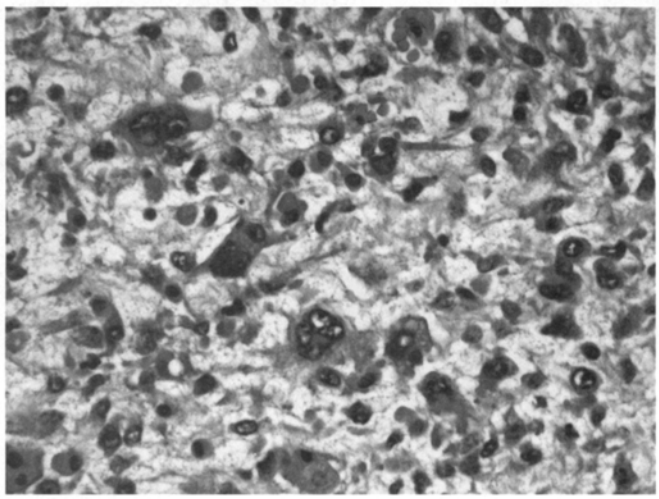


Fig. 52. Undifferentiated sarcoma showing plump, epithelioid cells, some multinucleated within a myxoid stroma.

- Dilated, benign-appearing bile ducts and PAS+ diastase-resistant globules characteristic

Immunohistochemistry

- Wide range of mesenchymal differentiation in individual cases
- Vimentin uniformly+, keratin may be focally+

Differential Diagnosis

- Rhabdomyosarcoma
- Metastatic tumors

Embryonal Rhabdomyosarcoma

Clinical

- Children <5 years of age; rarely in adults
- Obstructive jaundice, fever, and weight loss
- Tumor arises from major bile ducts at the hilum
- Treatment and prognosis similar to undifferentiated sarcoma

Macroscopic

- Gelatinous, grape-like (botryoid) masses with biliary epithelium-covered projections into bile duct lumina

Microscopic

- "Cambium" layer of dark, round cells beneath the surface and spindle cells in a loose myxoid stroma elsewhere; numerous mitoses
- "Typical" cross-striated structures seldom seen

Immunohistochemistry

- Actin+, myosin+, myoglobin+, and desmin+

Differential Diagnosis

- Undifferentiated sarcoma

Miscellaneous Malignant Mesenchymal Tumors

- Rare as primary liver tumors, usually in middle and old age
- Presentation in advanced stage
- Wide range of mesenchymal differentiation in individual cases; most common are fibrosarcoma, malignant fibrous histiocytoma, and leiomyosarcoma
- Slow progression, with poor prognosis
- Rule out metastatic lesions

Hematopoietic Neoplasms

Primary Malignant Lymphoma

Clinical

- Wide age range with biphasic age/incidence pattern (children/adolescents and older adults) and male predominance
- Clinical presentation with pain, mass, or hepatomegaly; B-symptoms in 50%
- Some associated with hepatitis B virus infection or AIDS
- Surgical resectability provides good prognosis; aggressive radiochemotherapy offers clinical benefit

Macroscopic

- Mostly solitary or multifocal; some cases with diffuse infiltration pattern
- Fish-flesh appearance on cut section

Microscopic

- All are non-Hodgkin's lymphomas, usually high-grade
- May be of B- or T-cell lineage, the latter typically of the diffuse type
- Destructive nature of the infiltrate and monoclonality best clues for the diagnosis

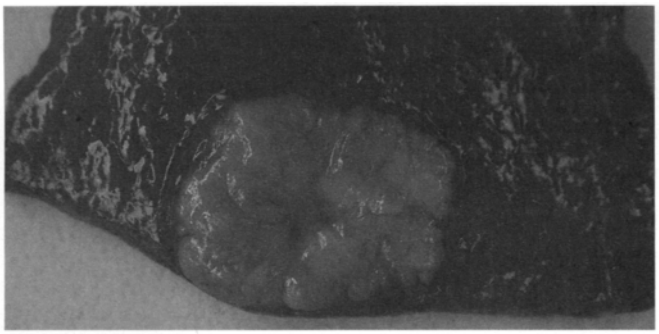


Fig. 53. Focal nodular hyperplasia consisting of a well-circumscribed, lobulated lesion with a central stellate scar and arising in a non-cirrhotic liver.

Differential Diagnosis

- Metastatic carcinoma
- Metastatic malignant melanoma
- Inflammatory pseudotumor
- Chronic hepatitis

Secondary Hematopoietic Neoplasms

- Hodgkin's lymphoma
- Non-Hodgkin's lymphoma
- Leukemias
- Multiple myeloma
- Histiocytosis
- Mast cell disease

Metastases

- Common site for metastases, particularly from lung, breast, and GI tract
- Diffuse infiltrate may resemble primary liver tumor
- Metastases may be missed by needle biopsy; characteristic triad in adjacent liver (proliferating bile ducts, leukocytes, and sinusoidal dilatation) may be helpful clues to sampling error
- Resection beneficial if few isolated lesions

Tumor-Like Lesions

Cysts

- Multiple intrahepatic cysts occur in polycystic disease and Caroli's disease (*see* chapter 30), and are developmental in origin
- Solitary, non-neoplastic and non-parasitic cysts rare
- Ciliated hepatic foregut cysts are reported with differentiation toward bronchial structures

Focal Nodular Hyperplasia

Clinical

- Thought to be a vascular malformation with A-V anastomoses and localized overgrowth of all liver constituents
- Occurs in both sexes at all ages, but most commonly in young women

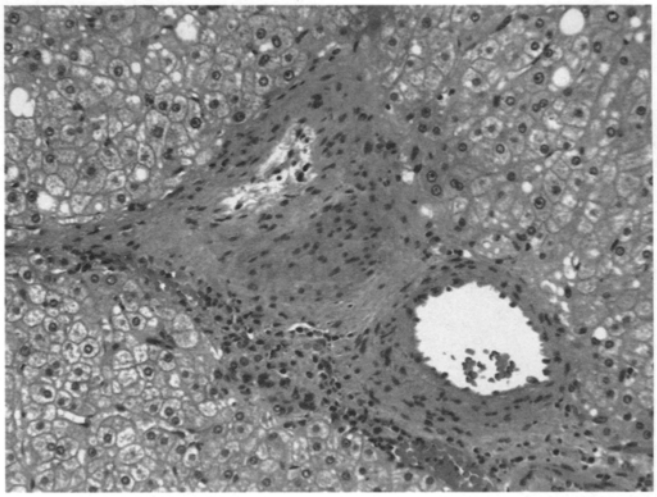


Fig. 54. Focal nodular hyperplasia showing atypical vessels with eccentric thickening of their walls.

- Incidental finding, rarely symptomatic (pain, palpable mass)
- Occasionally large (up to 15 cm), sometimes pedunculated
- Association with oral contraceptives controversial
- Treatment usually not necessary; surgery only for symptomatic lesions

Macroscopic

- Usually solitary, <5 cm in size
- Well-circumscribed fibrous mass with bulging of the cut surface
- Multiple yellow-brown nodules of liver parenchyma separated by fibrous septae **(Figure 53)**
- Central scar typical

Microscopic

- Central stellate scar with thick-walled vessel that lacks internal elastic lamina, usually show eccentric thickening of their walls; no bile ducts; variable inflammation **(Figure 54)**
- Incomplete septa radiating from central scar; composed of fibrous tissue, variable inflammation, no bile ducts, and often prominent proliferating ductules (cholangioles)
- Regenerative nodules of hepatic parenchyma with occasionally increased glycogen and/or fat; bile, Mallory's hyaline uncommon

Differential Diagnosis

- Liver cell adenoma
- Mesenchymal hamartoma

Nodular Regenerative Hyperplasia

Clinical

- Occurs in both sexes and at all ages
- Associated with a large number of a variety of extrahepatic diseases (usually vascular, connective disease or circulatory abnormality)

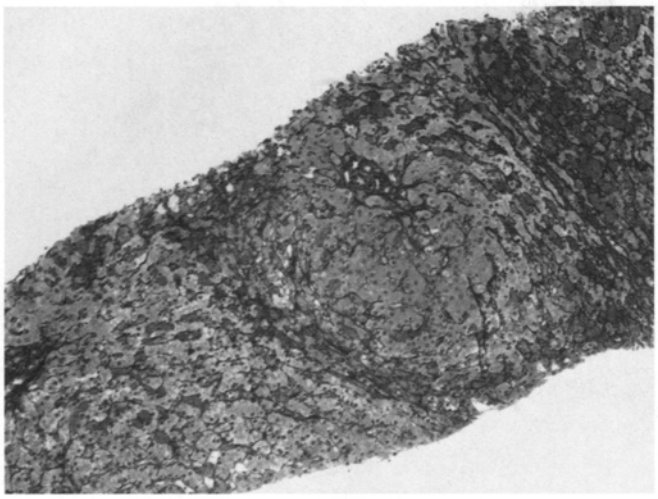


Fig. 55. Reticulin stain of nodular regenerative hyperplasia showing alternate areas of parenchymal atrophy and hyperplasia creating nodular liver architecture in the absence of fibrosis.

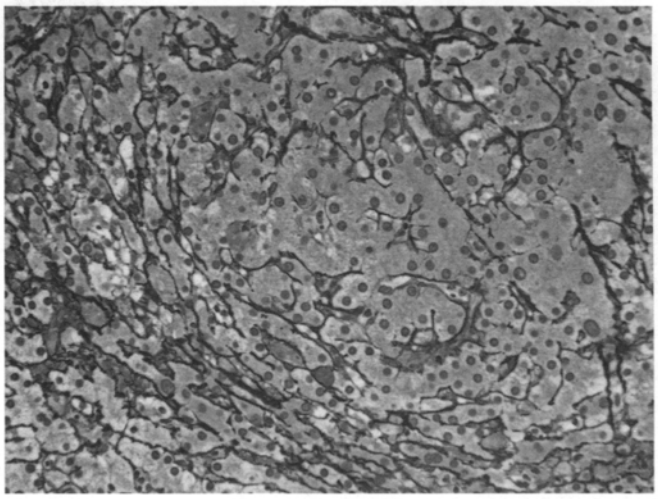


Fig. 56. Reticulin stain of nodular regenerative hyperplasia.

- May be a secondary, non-specific tissue adaptation to uneven distribution of total hepatic blood flow
- Not a preneoplastic condition
- Usually incidental finding; may cause non-cirrhotic portal hypertension or intraperitoneal hemorrhage
- Diagnosis by liver biopsy difficult; most cases seen at autopsy or laparotomy

Macroscopic

- Numerous nodules (0.1–1 cm) throughout the liver
- May spare portions of the liver ("partial nodular transformation")
- Rare cases with large (up to 10 cm) nodules

Microscopic

- Nodules composed of hepatocytes, expansile with distortion, but not effacement of the hepatic architecture
- Plates with two to three liver cells in thickness, with atrophic intervening parenchyma, best seen on reticulin stain **(Figures 55,56)**
- No fibrous septae; normal portal structures remain evenly distributed
- Obliterative portal venular changes may be seen

Differential Diagnosis

- Liver cell adenoma, if large nodules present

Mesenchymal Hamartomas

Clinical

- Considered to be localized abnormality of ductal plate development preceding birth, with subsequent enlargement (fluid accumulation)
- Almost exclusively in young children (median = 15 months of age)
- Progressive abdominal enlargement as presenting feature; surgical resection curative

Macroscopic

- Large (>1 kg) multicystic mass with soft, smooth surface and gelatinous contents
- Solid areas are fibrous, myxoid, or liver-like

Microscopic

- Haphazard and variable admixture of normal liver structures
- Predominant component is loose, edematous mesenchymal tissue **(Figures 57,58)**
- Dilated lymphatic channels and blood vessels; randomly scattered bile ducts and hepatocyte nodules

Differential Diagnosis

- Focal nodular hyperplasia
- Liver cell adenoma

Biliary Hamartoma (von Meyenburg Complex)

Clinical

- Very common, clinical importance lies in being grossly suspected of being metastates during abdominal surgery
- Often multiple, throughout the liver
- Part of the spectrum of ductal plate malformation (localized)

Macroscopic

- Small1 (<0.5 cm) whitish nodules

Microscopic

- Small, irregular, occasionally dilated ducts in a fibrous stroma **(Figure 59)**

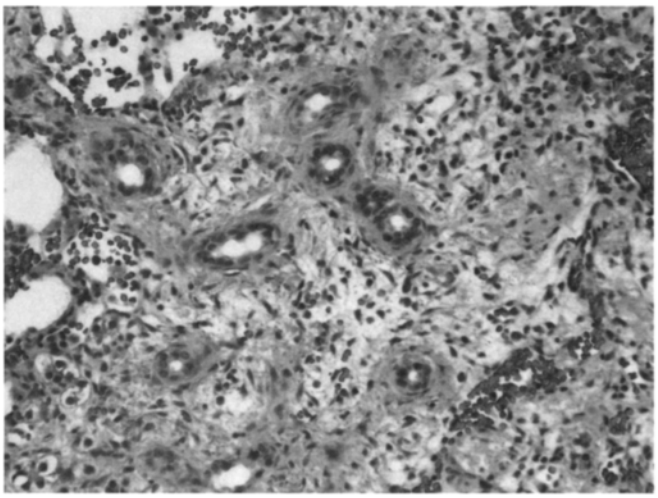


Fig. 57. Mesenchymal hamartoma containing haphazardly arranged bile ducts and blood vessels in a loose myxoid stroma.

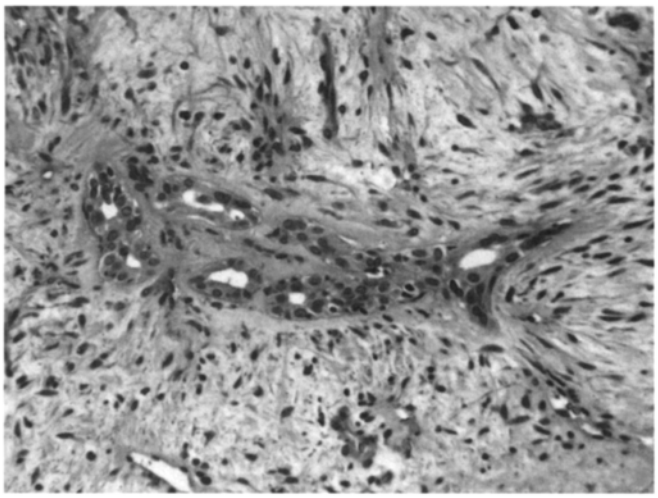


Fig. 58. Mesenchymal hamartoma containing irregular ductal structures in a loose myxoid stroma.

- May contain bile
- No significant cytologic atypia or mitosis

Differential Diagnosis

- Bile duct adenoma:
  - More compressed ducts, less fibrous stroma
  - Lumens may contain mucin (not bile)

Peliosis Hepatis

Clinical

- Often associated with exposure to anabolic steroids and various drugs, as well as in transplant and AIDS patients
- Also seen in liver cell adenomas induced by anabolic steroids
- Similar lesions described in spleen, lungs, and lymph nodes

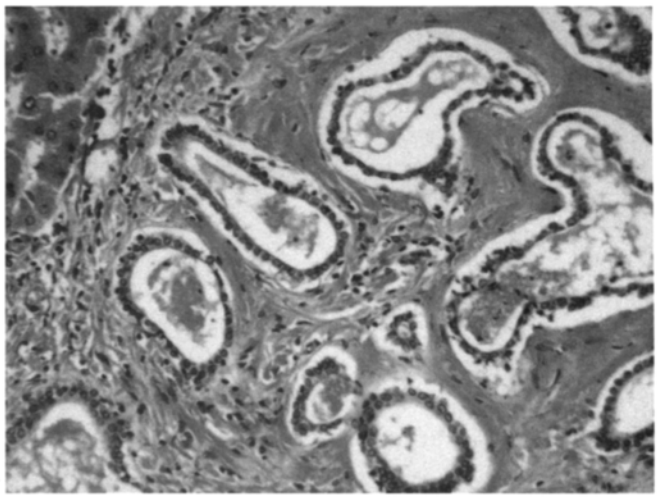


Fig. 59. Von Mayenburg complex consisting of dilated ducts containing eosinophilic material in a fibrotic stroma.

- Pathogenesis unknown (endothelial cell injury?)
- May present with liver failure, portal hypertension, or severe hemorrhage

Macroscopic

- Multiple, blood-filled spaces throughout the liver
- Size from 1 mm to several cm

Microscopic

- Blood-filled spaces with "capsule" of fibrin/early collagen; may have endothelial lining

Differential Diagnosis

- Bacillary peliosis hepatis ("bacillary angiomatosis") in AIDS

Inflammatory Pseudotumor

Clinical

- Rare lesion, similar to those occurring in multiple other sites of the body
- Usually young adults; several causes proposed, including ascending cholangitis, autoimmune processes, and ischemia; rare cases may be true neoplasms
- Many synonyms (e.g., plasma cell granuloma and inflammatory myofibroblastic tumor), reflecting the wide range of histologic patterns
- Presentation with intermittent fever, pain, and weight loss
- Inflammatory laboratory markers +, alkaline phosphatase elevated
- Almost always mistaken for malignancy by radiography
- Surgery is curative, but not necessary; lesions usually regress after steroid treatment or spontaneously

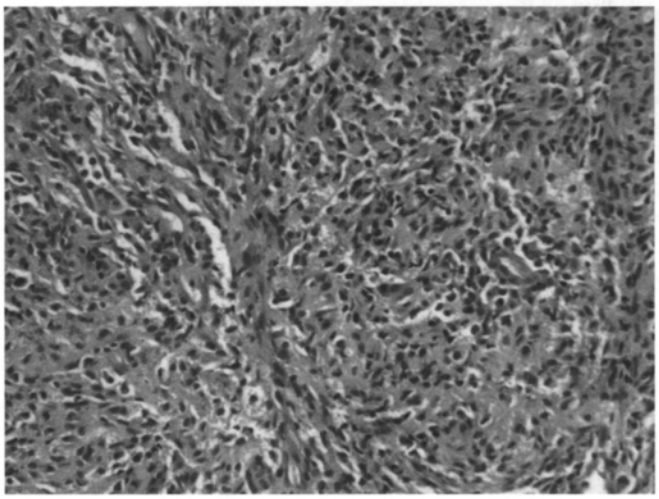


Fig. 60. Inflammatory pseudotumor consisting of spindle cells in a whorled arrangement.

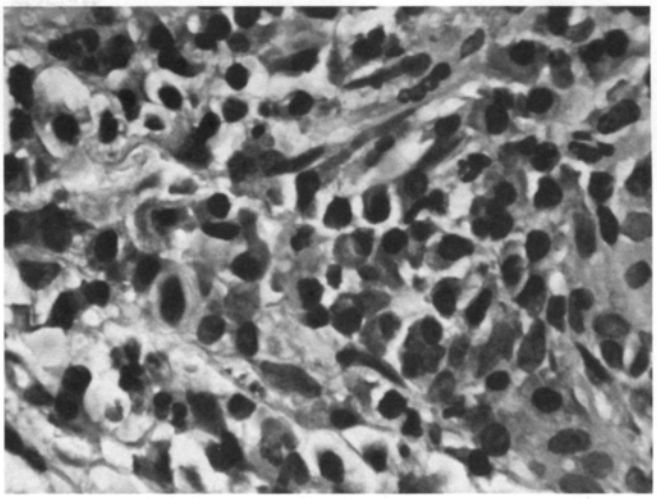


Fig. 61. Inflammatory pseudotumor showing numerous plasma cells.

Macroscopic

- Tumor-like lesion, solitary or multiple, up to 25 cm in size; may invade adjacent structures

Microscopic

- Mixture of spindle fibroblastic/myofibroblastic cells and inflammatory cells **(Figure 60)**
- Sclerosis and whorled pattern commonly present
- Nuclear atypia (reactive)
- Inflammatory cells include combination of polyclonal plasma cells (usually predominate), eosinophils, macrophages **(Figures 61,62)**

Immunohistochemistry

- Plasma cells are polyclonal for kappa/lambda light chains

Differential Diagnosis

- Malignant lymphoma
- Malignant fibrous histiocytoma

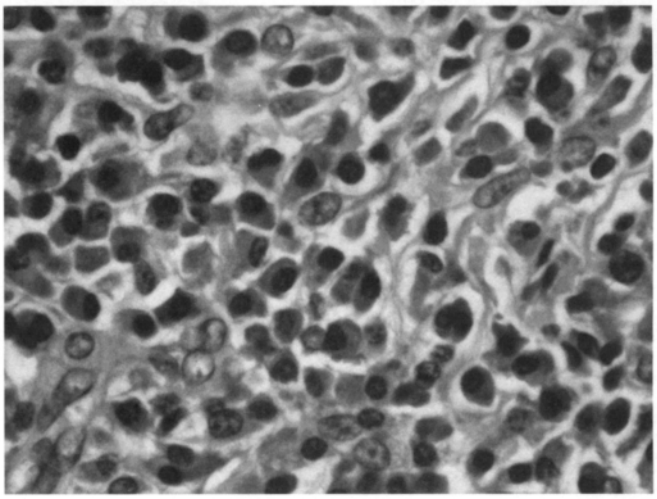


Fig. 62. Inflammatory pseudotumor showing a mixture of plasma cells and eosinophils.

TUMORS OF THE GALLBLADDER AND EXTRAHEPATIC BILE DUCTS

Benign Epithelial Tumors and Lesions

Polyps

- Lymphoid polyps:
  - Benign, sessile, or pedunculated hyperplastic lymphoid lesions covered by normal biliary epithelium
  - 2–4 mm in size
  - Older age group
- Granulation tissue polyps:
  - Contain numerous small vascular channels with inflammatory cells
  - Overlying epithelium typically denuded
  - <1 cm in size
  - Associated with acute and chronic cholecystitis
- Fibrous polyps:
  - Larger in size, detectable by ultrasonography, with abundant edematous connective tissue stroma and only scattered glands/ducts
  - Covered by normal biliary epithelium
- Cholesterol polyps:
  - Small pedunculated yellow structures filled with lipid-laden macrophages and covered by normal gallbladder epithelium

- Represent 50% of all gallbladder polyps
- Usually *not* associated with cholesterolosis

Hyperplasia and Metaplasia

- Nodular hyperplasias of pseudopyloric glands:
  - Sessile, small nodules
  - Often seen adjacent to adenomas and carcinomas
  - Tall, mucin-producing cells and Paneth cells
  - Relatively poor demarcation
  - Dysplasia possible
- Intestinal metaplasia:
  - Characterized by replacement of the normal surface epithelium by intestinal-type cells
  - Dysplastic changes seen
  - Process may be focal, segmental, or diffuse
  - May co-exist with adenomas and carcinomas

Papillary Hyperplasia

- Primary papillary hyperplasia:
  - Can be focal, segmental, or diffuse in gallbladder and/or extrahepatic bile ducts
  - Papillary structures
  - No intestinal-type cells, no dysplasia
- Secondary papillary hyperplasia:
  - Typically associated with cholecystitis and cholelithiasis
  - Numerous crowded mucosal folds lined by tall columnar cells with mucin, interspersed goblet- and Paneth cells
- Biliary papillomatosis

Hepatobiliary Cystadenoma

- *See* page 31-2

Adenoma

- Rare (0.5%) lesions, usually not precancerous
- Occasionally in association with familial polyposis coli or Gardner's syndrome
- Typically incidental findings (gallbladder) may be symptomatic with jaundice, cholangitis, or hemobilia (common bile duct)
- Usually <2 cm in size; sessile or pedunculated; solitary
- Tubular, papillary, or mixed architectural patterns; pyloric-type or colonic mucosa common **(Figure 63)**
- Paneth cells or neuroendocrine elements possible; variable degrees of dysplasia seen
- Differential diagnosis includes adenocarcinoma, biliary cystadenoma, and biliary papillomatosisere

Malignant Epithelial Tumors

Carcinoma of the Gallbladder

Clinical

- Fourth most common malignant neoplasm of the GI tract

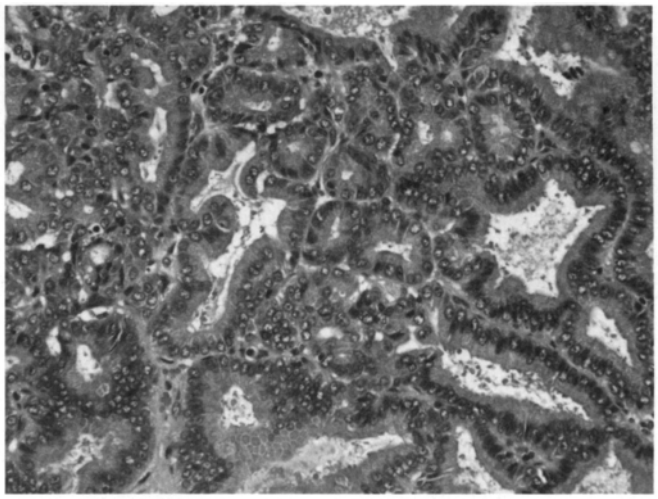


Fig. 63. Tubular adenoma arising in a gallbladder that appears very similar to the intestinal counterpart.

- Main etiological association with gallstones/chronic inflammation
- Gallstones are present in 80% to 90% of all cases
- Arise from flat dysplasia, not adenoma
- Usually incidental discovery during surgery, but with metastatic spread to lymph nodes and the liver bed in 50% to 70%
- Distant metastases to liver, peritoneum, and lungs
- Curable if confined to the gallbladder, without muscular invasion
- Overall 5-year survival = 5% to 10%

Macroscopic

- Usually diffuse thickening of the gallbladder wall
- Polypoid neoplasms rare

Microscopic

- Typical adenocarcinoma in 85%, usually tubular type
- Commonly associated with hyperplasia, or antral or intestinal metaplasia
- Dysplasia or carcinoma in situ in adjacent mucosa
- Perineural invasion common

Immunohistochemistry

- CEA+, keratin+

Variants

- Intestinal, mucinous, signet ring types
- Clear cell and aggressive oat cell carcinoma
- Adenosquamous and pure squamous cell carcinoma
- Undifferentiated (spindle cell) carcinoma

Differential Diagnosis

- Dysplasia extending into the cystic duct, Luschka's ducts, and Aschoff-Rokitansky sinuses
- Adenoma/cystadenoma
- Adenomyoma

Carcinoma of the Extrahepatic Bile Ducts

Clinical

- Less common than, and different from, gallbladder carcinoma
- Older individuals; cholelithiasis less commonly associated
- Choledochal cysts prone to malignant transformation
- Obstructive jaundice, cholangitis, and hemobilia as presenting symptoms
- Resectability and prognosis poor, with better results for distal lesions
- Metastatic spread to lymph nodes and liver frequent at diagnosis

Macroscopic

- Appearance as diffuse segmental thickening, stricture, or small polyp

Microscopic

- Similar to gallbladder carcinoma
- May be associated with metaplasia, dysplasia, or adenoma

Immunohistochemistry

- Monoclonal CEA+ (cytoplasmic)

Differential Diagnosis

- Non-neoplastic fibrous stricture
- Primary sclerosing cholangitis

Miscellaneous Malignant Epithelial Tumors

- Carcinosarcoma/undifferentiated spindle cell carcinoma
- Carcinoid tumor
- Metastatic tumors (breast, stomach, pancreas)

Benign and Malignant Non-Epithelial Tumors

- Granular cell tumor
- Malignant melanoma
- All others are exceedingly rare, including: lipoma, hemangioma, neurofibroma, paraganglioma, leiomyo-rhabdomyosarcoma, MFH, and malignant lymphoma

Tumor-Like Lesions

Adenomyoma

Macroscopic

- Anywhere in the gallbladder or extrahepatic bile ducts
- Localized, segmental, or diffuse **(Figure 64)**

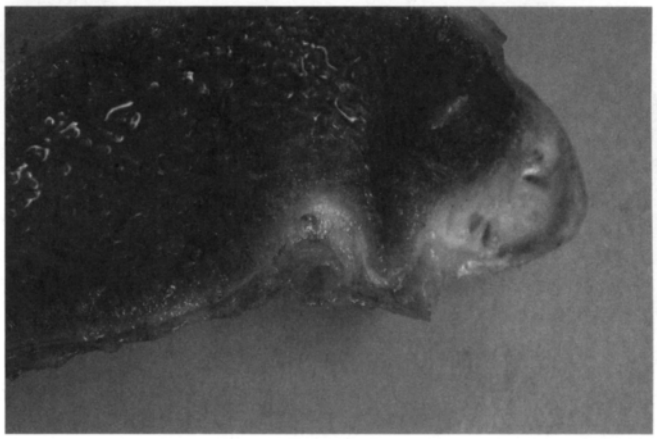


Fig. 64. Adenomyoma in the wall of a gallbladder appears as a fibrous lesion with slit-like spaces.

Microscopic

- Branching, ductal, or cystic glandular structures; no dysplasia
- Hyperplastic smooth muscle cell stroma
- Lumina with mucus, bile, or stones
- Granulomatous inflammation with fibrosis around ruptured glands
- T: Primary Tumor:
  - Tx: Primary tumor cannot be assessed
  - T0: No evidence of primary tumor
  - T1: Solitary tumor without vascular invasion
  - T2: Solitary tumor with vascular invasion or multiple tumors none more than 5 cm
  - T3: Multiple tumors more than 5 cm or tumor involving a major branch of the portal or hepatic vein
  - T4: Tumor with direct invasion of adjacent organs other than gallbladder or with perforation of visceral peritoneum
- N: Regional Lymph Nodes:
  - Nx: Regional lymph modes cannot be assessed
  - N0: No regional lymph node metastasis
  - N1: Regional lymph node metastasis
- M: Distant Metastasis:
  - Mx: Distant metastasis cannot be assessed
  - M0: No distant metastasis
  - M1: Distant metastasis

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Index

Abrasion, 103
Abscess, bacterial infection, neuropathology, 406–407
Abscess, fungal infection, neuropathology, 407
Absidia species, 189
Acanthamoeba corneal ulcer, 843
Acanthamoeba species, 211
Acetaminophen, 131
Acetones, 127–130
Acetylsalicylic acid (Aspirin), 131–132
Achalasia, 1288
Achondroplasia, 50–51
Acinar cell carcinoma, 146, 325, 1360–1363
Acinar cell cystadenoma, 1361
Acinetobacter baumannii, 173
Acinic cell carcinoma, 146, 306, 774–75, 775t
Acne keloidalis nuchae, 631–32
Acquired progressive lymphangioma, 573
Acquired renal cystic disease, 1145–1146
Acral A-V tumor, 572
Acral-lentiginous melanoma, 581
Acrochordons, 565
Acrodermatitis enteropathica, 66–67
Actinic keratosis (senile, solar), 537
Actinomyces, 183–84, 267
Actinomycosis, 183–184, 936, 1022
Acute disseminated encephalomyelitis (ADEM), 405
Acute EBV infection, 487
Acute inflammatory demyelinating polyneuropathy (AIDP), 405
Acute megakaryoblastic leukemia (AMkL), 505
Acute myeloid leukemia (AML), 20–22, 479, 500–507
Acute promyelocytic leukemia (APML), 501–502
Acute tubular necrosis (ATN), 1138–1139
Adamantinoma, 706
Adamantinomatous craniopharyngioma, 389–390
Addison's disease *See* Primary adrenal insufficiency
Adenocarcinoma, 146
  of anal duct/gland, 1344
  with atrophic features, prostate, 1240–1241
  benign lesions of, prostate, 1222–1228
  bladder, 1208–1210
  colon, 322
  early invasion (microinvasion), uterus, 1032–1033
  esophagus, 1296
  gastrointestinal tract, 1337–1338
  glomeruloid features, prostate, 1240
  in-sit (AIS), uterus, 1032
  lung, 946–948
  microvacuolated cytoplasm, prostate, 1241
  nasal cavity, paranasal sinuses, and nasopharynx, 822
  neuroendocrine differentiation, prostate, 1239
  putative precursor of, prostate, 1228–1231
  respiratory cytology, 301–303
  of skin appendage, 1012
  specific variants, gastrointestinal tract, 1337
  with spindle cell metaplasia, breast, 988
  staining characteristics of, 302t
  stomach, 321, 1306–1308
  uterus, 1033
Adenocarcinomas, 1034, 1222–1228
Adenofribroma, 1036, 1056–1057, 1063
Adenoid basal carcinoma, uterus, 1034–1035
Adenoid cystic carcinoma, 146, 1241–1242
  breast, 986–987
  larynx and trachea, 828
  lung, 945–946
  nasal cavity, paranasal sinuses, and nasopharynx, 820–821
  salivary gland, 306, 775–777
  skin, 551
  uterus, 1034
Adenoma, 146
  breast, 972–973
  extrahepatic bile duct, 1434
  gallbladder, 1434
  prolactin producing, 419
  stomach, 1306
Adenomatoid hyperplasia, 805
Adenomatoid tumor
  epididymis, 1267
  fallopian tube, 1064–1065
  odontogenic, 810
  ovary, 1091
  uterus, 1055–1056
Adenomatous polyp, 322
Adenomyoepithelioma, 994–995
Adenomyoma, 1036, 1056, 1435
Adenomyosis, uterus, 1042
Adenosarcoma, uterus, 1036, 1057
Adenosine deaminase, 68
Adenosis, 969, 1016, 1224–1225
Adenosquamous carcinoma
  breast, 988
  esophagus, 1297
  lung, 949
  prostate, 1239–1240
  uterus, 1034
Adenovirus, 204, 935
Adipocyte-derived tumors and proliferations, 554–555
Adipose neoplasms, 146
Adipose tissue tumors, 317
Adrenal aplasia, 657
Adrenal cortical
  carcinoma, 669–671
  hyperplasia, 660–661
  neoplasms, 146
  rests.
    ovary, 1072
    testis, 1250
Adrenal gland
  cysts, 657
  cytomegaly, 657–658
  heterotopia, 656–657
  leukodystrophy, 658
  medullary hyperplasia, 662–663
Adrenal insufficiency (Addison's disease), 659–660
Adrenoleukodystrophy, 69, 417
Adult rhabdomyoma, 735
Adult T-cell leukemia/lymphoma (ATLL), 315, 449–450, 520–521
Aerobic, facultatively anaerobic (or microaerophilic) bacteria, 158–163
Agenesis of corpus callosum, 412–413
Aggressive angiomyxoma, 755, 1013
Aggressive digital papillary adenoma/adenocarcinoma, 547–548
AIDS. *See* HIV/AIDS
Airway inflammation-lymphocytic bronchitis/bronchiolitis, 942
Airways and obstructive diseases, 920–923
Alagille's syndrome, 1397–1398
Albinism, 57, 576
Alcohol, malnutrition, 415
Alcoholic liver disease, 1386–1387
Alcoholism, chronic, 96–97
Alcohols, 127–130
Algor mortis (body cooling), 91
Allergic fungal sinusitis, 814–815
Alopecia, 630–632
  areata, 630
  non-scarring, 630
  scarring, 630–632
  syringoma-like proliferations associated with, 545–546
Alpha-hemolytic streptococci (Viridan streptococci), 163
Alpha-1-antitrypsin deficiency, 1400–1401
Alport syndrome, 53, 1134
Alternaria species, 198–199
Alveolar
  adenoma, lung, 942–943
  rhabdomyosarcoma, 736
  soft part sarcoma, 147, 755–756
Alzheimer's disease (AD), 398
Amalgam tattoo, 805
Amebic abscess, 1381–1382
Amebic meningoencephalitis, 410
Ameloblastic carcinoma, 811
Ameloblastic fibroma, 810
Ameloblastoma, 809
Amiodarone (antiarrhythmic drug)- induced changes, 299
Amitriptyline, 131
Amphetamines, 129–130
Amplification, 31
Amyloid, breast, 972
Amyloidoma, 753
Amyloidosis, 525–526
  eyelid, 858–859
  glomerular diseases, 1126–1127
  heart, 899–900
  hepatobiliary disease, 1404
Amyotrophic lateral sclerosis (ALS), 402–403
Anaerobic bacteria and diseases, 177
Analgesics, 131–132

Anal intraepithelial neoplasia (AIN), 1342
Anaphylaxis, 98–99
Anaplastic carcinoma, 310, 648–649
Anaplastic large cell lymphoma (ALCL), 27, 315–316, 454–455, 519–520
Ancylostoma duodenale, 221
Androblastoma, 1088–1089
Androgen deprivation therapy, prostate, 1244–1245
Androgenetic alopecia, 630
Anemia of chronic disease, bone marrow, 529
Anencephaly, 410
Aneurysmal bone cyst (ABC), 690–691
Aneurysms, 910
Angelman syndrome, 42–43
Angiocentric lymphomas, 956–957
Angiodysplasia, 1329
Angiofibroma, 566
Angioimmunoblastic T-cell lymphoma, 453
Angioinvasive forms, 407–408
Angiokeratoma, 570, 901, 1008
Angioleiomyoma, 559
Angiolipoma, 554, 729
Angiolymphoid hyperplasia, 570
Angioma serpiginosum, 571
Angiomatoid MFH, 560–561, 726
Angiomatosis, 573, 739, 996
Angiomyofibroblastoma, 1008–1009
Angiomyolipoma (AML), 327
  kidney, 1168–1169
  liver and biliary system, 1425–1427
Angiomyxoma, 755
Angiosarcoma
  bone and joints, 702
  breast, 997
  cardiac, 908
  hepatobiliary disease, 1385
  liver and biliary system, 1427
  lung, 953–954
  skin, 574–575
  soft tissue, 319, 741–742
  spleen, 485
Angistrongylus species, 225
Anisakis species, 225
Anorchidism, 1249
Anovulation, glandular and stromal breakdown associated with, 1040
Anoxic encephalopathy (global ischemic injury), 393–394
Antidepressants, 131
Antigen receptor gene rearrangements as markers of clonality, 16
Antipsychotics, 131
Antracycline cardiotoxicity, 900–901
Anus, 1342–1344
Aortic
  dissection, 95
  stenosis, 93, 897
  valve stenosis, 902
APC resistance testing, benefits/limitations, 12
Aphthous stomatitis, 805
Apical periodontal cyst, 807
Aplasia, thymic, 872
Aplastic anemia (AA), bone marrow, 530–531
Apocrine
  carcinoma, 314, 552–553, 984
  derived tumors and proliferations, 551
  intraductal carcinoma, 978
  nevus, 551
Apoplexy, 419
Appendix, 1330–1331
Aqueductal stenosis, 411
Arias-stella reaction, 273, 1025, 1039
Arnold-Chiari (Chiari II) malformation, 410–411
Arrythmogenic right ventricular cardiomyopathy (ARVD), 899
Arsenic poisoning, 132, 415–417
Arteriosclerosis, 396, 908–909
Arteriovenous malformation (AVM), 397
Arthritides, 683–685
Arthropod bite reaction, 624
Asbestos-related reactions, 930
Ascaris lumbricoides (roundworm), 221–222
Aspergillosis, 300, 938–939
Aspergillus species, 188–189
Aspermatogenesis, 1254–1255
Asphyxia, 115–122
Aspirin. *See* Acetylsalicylic acid
Asthma, 300, 921–922
Astrocytoma, 334, 368–370, 368t, 370t
Ataxia-telangiectasia, 46
α-thalassemia, 54
Atherosclerosis, 908, 1140
Atherosclerotic aneurysm of the abdominal aorta, 910
Atmospheric pressure changes, 122–123
Atresia, 1288
Atrial septal defect (ASD), 897
Atrophy, prostate, 1226
Atypia, 1024, 1193t
Atypical adenomatous hyperplasia (AAH), 944, 1230–1231
Atypical basal cell hyperplasia (ABCH), prostate, 1223
Atypical chronic myeloid leukemia (aCML), 513
Atypical lipomatous tumor (ALT), 731
Atypical small acinar proliferation (ASAP), 1231–1232
Autoerotic asphyxia, 118
Autosomal polycystic kidney disease (ADPKD), 1143–1145

Babesia microti, 211
Bacillary angiomatosis, 737
  lymph node, 460–461
  skin, 570–571
  spleen, 488
Bacillus anthracis (etiologic agent of anthrax), 163–164
Bacillus cereus, 164
Bacteremia, 158, 173, 179
Bacteria, 158–187
Bacterial infections
  cervicitis, 1022
  hepatobiliary disease, 1378
  neuropathology, 406–407
  ovary, 1071
  penis, 1274–1276
  ulcers, eye, 843
  vaginosis, 267
Bacteroides fragilis group, 182–183
Balanitis, 1276–1277
Balanoposthitis, 1276
Balantidium coli, 211–212
Barbiturates, 130
Barotrauma, 123
Barrett's esophagus, 321, 1292–1293, 1294t
Bartholin's glands, carcinoma of, 1012
Bartonella, 185–186, 488
Basal cell adenocarcinoma, 773–774
Basal cell adenoma, 768, 1223
Basal cell carcinoma (BCC), 316, 543–544, 1012
Basal cell hyperplasia (BCH), prostate, 1223
Basal cell nevus syndrome (Gorlin syndrome), 77
Basal cell proliferations, prostate, 1222–1223
Basaloid adenomas/canalicular adenoma, differential characteristics, 765t
Basaloid follicular hamartoma, 542
Basaloid squamous cell carcinoma, 813–814, 827, 1031
Batholin's duct cyst, 1005
B-cell acute lymphoblastic leukemia (B-ALL), 507
B-cell lymphoma of MALT, 1340–1341
B-cell lymphoproliferative disorders, 435t, 514–518
B-cell prolymphocytic leukemia (B-PLL), 24, 435, 515
Becker's nevus, 558, 576
Beckwith-Wiedemann syndrome, 44, 658
Behcet's disease, 1003
Benign nephrosclerosis, kidney, 1139
Benign ovary, 1071–1075
Benign papillary mesothelioma, 1268
Benign prostatic hyperplasia (BPH), 1222–1225
Berry aneurysm of cerebral arteries, 910
Berry (saccular) aneurysm, 396–397, 397
Berylliosis, 931
Bethesda System (2001), 266, 276
Bile duct
  adenoma, 1414–1415
  cells, 322
  dilatation, 1396–1397
  hamartoma, 322
Biliary
  cirrhosis, primary, 1392
  colic, 1410
  hamartoma (von Meyenburg complex), 1431–1432
  papillomatosis, 1415–1416
Binswanger's disease, 396
Biphasic neoplasms, 991t
Biphasic tumors, breast, 990–993
Bizarre parosteal osteochondromatous proliferation (Nora's lesion), 697
B-K mole, 578
Black adenoma, 146–147
Black thyroid nodule, 308
Blastic hematolymphoid malignancies, paraffin section immunophenotype of, 433t
Blastic NK-cell lymphoma, 452
Blastomyces dermatitidis, 191
Blastomycosis
  lung, 940
  respiratory cytology, 300–301
  spleen, 488
Blood vessels, pathology of, 908
Bloom syndrome, 45–46
Blue nevi, skin, 577
Blue nevus, uterus, 1037
B-lymphoblastic leukemia (B-ALL)/lymphoblastic lymphoma (B-LBL), 431–432
Bone, cytology, 319–320
Bone cysts, 689–691
Bone-forming lesions, 691–696
Bone infections, 681–683
Bone marrow
  anemias, 528–530
  general considerations, 495
  infections, 528
  reactive conditions, treatment changes, 530–531
  storage diseases, 527
  transplantation (BMT), 254–257
Bordetella pertussis, 174
Botryomycotic abscesses, 158

Botulism, 180–181
Bowenoid papulosis, 540, 1279
Bowen's disease *See* Squamous cell carcinoma *in situ*
Brachial cleft cyst, 306–307
Brain death syndrome ("respirator brain"), 394
Brainstem avulsion, 109
Branchial cleft cysts, 535–536
Breast, cytology, 310–314
Brenner tumor
  ovary, 326, 1082–1083
  vagina, 1015
Bronchial
  asthma, 97–98
  brushings, 298
  washings, 298
Bronchiectasis, 921
Bronchiolitis
  cellular, 923
  constrictive (obliterative), 923
  follicular, 923
  obliterans *vs* cryptogenic organizing pneumonia, 247t
  respiratory (smokers'), 922
Bronchiolo-alveolar carcinoma, 148, 948
Bronchoalveolar lavage (BAL), 298
Bronchocentric granulomatosis, 922
Bronchogenic cysts, 870, 918
Bronchopulmonary dysplasia, 919
Bronhogenic cyst, skin, 536
Brucella species, 174–175
Brugia malayi, 224
β-thalassemia, 54–55
Bubonic plague, 170
Budd-Chiari syndrome, 1389
Buerger's disease. *See* Thromboangiitis obliterans
Bullet track: low velocity missles, 392
Bullous keratopathy, 840–841
Bullous pemphigoid (BP), 587–588
Bullous systemic lupus erythematosus (BSLE), 590–591, 601
Burkholderia, 173
Burkitt's lymphoma/leukemia (BL), 26, 315
  bone marrow, 508
  gastrointestinal tract, 1341
  lymph node, 447–448
  spleen, 474
Burns *See* Local hyperthermia

CADASIL (Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy), 396
Café-au-lait spot, 576
Calcifying aponeurotic fibroma, 719
Calcifying epithelial odontogenic tumor (Pindborg tumor), 810
Calcifying odontogenic cyst (Gorlin cyst), 807–808
Calcium pyrophosphate crystal deposition disease (pseudogout, chondrocalcinosis), 684–685
Calymmatobacterium granulomatis, 187
Campanacci's disease (osteofibrous dysplasia), 706
Campylobacter jejuni, 171–172
Canalicular adenoma, 768–769
Cancer
  bladder specimens, 1196t, 1200t
  breast, 30, 77–78
  urinary bladder, 1184–1191
Candida albicans, 199–200, 267
Candida species, 199–200, 1290
Candidiasis
  lung, 939
  oral cavity, 798
  respiratory cytology, 301
  vulva, 1004
Capillaria philippinensis, 225–226
Capillary hemangioma (Infantile hemangioendothelioma), 737
Carbohydrate metabolism disorders, 63–64
Carbon dioxide, 120
Carbon monoxide, 121–122, 396, 415
Carcinoid, 327
  atypical, 303
  bladder, 1215
  heart disease (CHD), 902
  islet cell tumors, 148
  ovary, 1086
  stomach, 1311–1312
  thymic, 880–881
  tumorlet, 949–950
  tumors, 1338–1339, 1338t
  typical/atypical, 303, 950
  uterus, 1035
Carcinoid, uterus, 1035
Carcinoma
  with basaloid features, 784t
  with chondroid metaplasia, 988
  duct collecting, 328, 1163–1164
  ex-pleomorphic adenoma, 769–770
  fallopian tube, 1063
  hymic, 879–880
  papillary, 1092
  with pleomorphic, sarcomatoid, and sarcomatous elements, 949
  secretory, 985
  serous, 1048–1049
  thyroid, 673
  undifferentiated
    bladder, 1206
    nasopharynx, 150
    salivary gland, 781
    uterus, 1035, 1049
  see also Small cell carcinoma
Carcinosarcoma, 1036, 1064
  bladder, 1213–1214
  salivary gland, 770–771
  uterus, 1058
  vagina, 1017
Cardiac neoplasms, 905–908
Cardiac rhabdomyoma, 734
Cardiac transplantation, 903–905
Caroli's syndrome (intrahepatic), 1396–1397
Carotid body tumor *See* Paraganglioma
Carotid Sleeper Hold (Lateral Vascular Neck Restraint), 117–118
Cartilage, cytology, 319–320
Cartilagenous lesions, 696–701
Castleman's disease, 428, 888–889, 955
Cat scratch disease, 314, 430
Cavernous angioma ("Cavernoma"), 397–398
Cavernous hemangioma, 737–738
Cavernous lymphangioma, 569
C. botulinum, 180–181
C cell hyperplasia, 641–642
CD30+ lymphoproliferative disorders: lymphomatoid papulosis; CD30+ large, T-cell lymphoma, 584
Celiac disease, 1321–1322
Cell surface (plasmalemma), 144–146
Cell tumors, 147t
Cellular angiofibroma, 1008
Cellular neurothekeoma, 557, 748
Cellular rejection, 237, 904
Cementoblastoma, 810–811
Cemento-osseous dysplasia, 808
Central cemento-ossifying fibroma, 811
Central corneal ulcers, 842
Central nervous system, 333–335, 364–365, 365t
Central neurocytoma, 379
Central pontine myelinolysis (CPM), 415
Cephalic histiocytosis, 564
Cerebellar degeneration, 415
Cerebral
  amyloid angiopathy (CAA), 397
  contusion, 107–109
  edema, 363
  infarct, 393, 394t
  malaria, 410
  swelling, 109
Cerebrospinal fluid (CSF), cytology, 333–335
Cerebrovascular disease, 96
Cervical intraepithelial neoplasia (CIN), 1029–1030
Cervical squamous cell carcinoma (SCC), 272
Cervicitis, 1022–1024, 1022
Cestodes (tapeworms), 220–221
Chalazion, 857–858
Chancroid (soft chancre), 1275
Charcot's joints *See* Neuropathic arthropathy
Charot-Marie-tooth disease, 50
Chemical asphyxia, 120–122
Chemicals, 133
Chemotherapy-induced atypia, 299
Cherry angiomas, 572
Cherubism, 809
Chief cell hyperplasia, 651–652
Chlamydial cervicitis, 1022
Chlamydia trachomatis, 268
Choke hold (Shime-Waza), 117
Choking, 118–120
Cholangiocarcinoma, 148, 323, 1422–1424
Cholangitis, primary, 1393
Cholecystitis, 1410
Choledochal cyst (extrahepatic), 1396
Choledocholithiasis, 1411
Cholelithiasis, 1410–1411
Cholestasis
  and biliary tract disorders, 1391–1394
  and duct injury, 1385
  post-operative, 1394
  of pregnancy, intrahepatic, 1394
Chondroblastoma, 319, 698–699
Chondroid
  chordoma, 707
  syringoma (benign mixed tumor), 547
  tumors, 148
Chondroma, 319, 697–698
Chondromyxoid fibroma, 699
Chondro-osseous tumors, 752–753, 752t
Chondrosarcoma, 700–701
  bone and cartilage, 320
  and its variants, 700–701
  jaws, 812
  larynx and trachea, 828–829
Chop wound, 115
Chordoma, 707
Chorioamnionitis, 1102–1103
Choriocarcinoma
  mediastinum, 884
  ovary, 1084–1085
  placenta, 1100–1101

testis, 1262
Choroid plexus neoplasms, 377–378
Choroid plexus papilloma, 334, 377
Chromoblastomycosis, 199
Chromophobe renal cell carcinoma, 328, 1161–1163
Chromosomal disorders, 39–46
Chromosomal sarcomas, 29t
Chromosome breakage syndromes, 45–46
Chronic
bronchitis, 921
bullous disease of childhood *See* Linear IgA bullous dermatosis
cellular rejection, 237
cervicitis, 1022
endometritis, 1041
eosinophilic leukemia (CEL), 499
follicular cervicitis, 269
follicular conjunctivitis, 847–848
gastritis, 321
gliosis, 363
granulomatous inflammation, eye, 838–840
histiocytic intervillositis (massive chronic intervillositis), 1112–1113
idiopathic myelofibrosis (CIMF), 497–498
inflammation and coagulation, placenta, 1111–1114
lymphocytic leukemia (CLL), 23–24
bone marrow, 514–515
lymph node, 433–434
spleen, 471–472
multifocal recurrent osteomyelitis, 682
myelogenous leukemia (CML), 495–497
myelomonocytic leukemia (CMML), 512–513
myeloproliferative diseases (CMPD), 19–20
myeloproliferative disorders, 495–500
neutrophilic leukemia, 499
nongranulomatous inflammation, eye, 837–838
osteomyelitis, 681–682
pancreatitis, 324
papillary conjunctivitis, 848
pyelonephritis, 1137–1138
rejection, cardiac transplantation, 905
salpingitis, 1060
sclerosing sialadenitis of submandibular gland (Küttner's tumor), 789
spongiotic dermatitis, 613
thyroiditis, 308
vascular rejection, 237, 942
Churg-Strauss syndrome, blood vessels, 912
Churg-Strauss syndrome (allergic angiitis granulomatosis), lung, 932
Cicatricial pemphigoid, 588
Cigarette smoking, 299
Ciliated cell change (tubal metaplasia), uterus, 1043
Ciliocytophthoria, 300
Cingulate (subfalcine) herniation, 364
Circumscribed astrocytomas, 370–373
Cirrhosis, 1387–1388, 1403
Clark's nevus, 578
Classical Hodgkin lymphoma (CHL), 27
Clear cell
acanthoma, 539–540
adenocarcinomas, 148, 1034
carcinoma
bladder, 1210–1211
breast, 985
kidney (CCSK), 1153–1154
odontogenic, 811–812
ovary, 326
renal, 148, 327–328, 1157–1159
uterus, 1049
vagina, 1016
metaplasia, 969
sarcoma, 148, 750–751, 1150
tumor
benign, lung, 957–958
myomelanocytic, bladder, 1216
ovary, 1081–1082
Clonality, 12, 15–18
Clonorchiasis, 1383
Clonorchis sinensis, 227
Clostridial cellulitis, 178
Clostridial myonecrosis (gas gangrene), 177–178
Clostridial suppurative myositis, 178
Clostridium, 177–180, 179–180
Clumped cytoid bodies and shaggy deposition of fibrinogen along the basement membrane zone, 603
Coal worker's pneumoconiosis (CWP), 930
Coarctation of aorta, 897
Coats' disease, 840
Cobalt, 132
Cocaethylene, 128–129
Cocaine, 128–129
Coccidioides immitis, 191–193
Coccidioidomycosis, 300, 488, 939
Colitis
collagenous, 1325
diversion, 1325–1326
ischemic, 1328–1329
lymphocytic, 1325
microscopic, 1325
radiation, 1326–1327
Collagenous spherulosis, 971
Colloid carcinoma, pancreas, 1354–1355
Colloid cyst of third ventricle, 98
Colloid nodule, 308–309
Colon, cytology, 321–322
Colonic *versus* ovarian carcinoma, 1080t
Comedocarcinoma, 1240
Comedonal cyst, 535
Common melanocytic nevi, 578
Comparative genomic hybridization (CGH), 14
Complex choristomas, 846
Complex sclerosing lesion/radial scar, 970
Condyloma, 235, 1015, 1028, 1191, 1278, 1342
Congenital, 1135
adrenal hyperplasia (adrenogenital syndrome), 658–659
anomalies, 918–920, 1177
and bicuspid aortic valves, helpful distinguishing features of, 902t
dyserythroblastic anemias (CDA), 530
epulis, 557
gingival granular cell tumor, 802
glaucoma, diseases associated with, 836t
heart disease, 897
hydrocephalus, 410–411
infection, 1111–1112
mesoblastic nephroma (CMN), 1152–1153
nephrotic syndrome, 1135–1136, 1136t
nevus, 579
pneumonia, 162
pulmonary airway malformation, 918–919
self-healing reticulohistiocytosis, 563–564
Congestive heart failure, 1389
Conjunctiva, 846–851
Conjunctival
cysts, 846–847
inflammation, 847–849
intraepithelial carcinoma, 849
papillomas, 849
Conjunctivitis, 847
Connective tissue disorders, 51–53
Contact dermatitis, 613–614
Contact ulcer, 825–826
Contrecoup contusion, 107–108
Contusion, 103–104
Copper storage disorders, 1402–1404
Corbus' disease. *See* Balanitis, gangrenous
Corbus' disease, 1277
Cornea, 840–846
Corneal degenerations and dystrophies, 840–846
Corneal ulcers, 842
Corpora amylacea, 300
Corpus luteum cyst, 325–326, 1073
Cortical
adenoma, 663–666
contusion, 392
dysplasia, 412
granuloma (hyaline scar), 1074
hyperplasia, 661
infarcts, 1141
Corticobasal (ganglionic) degeneration (CBD), 402
Corticotrophic (ACTH) adenomas, 418
Corynebacterium diphtheriae, 164–165
Corynebacterium jeikeium (formerly Group "JK" bacilli), 165
Coup contusion, 107
Cowden's syndrome (Multiple hamartoma syndrome), 79
Cowper's glands, 1227–1228
Craniopharyngioma, 334, 389–390, 419
Craniorachischesis, 410
Creola bodies, 299
Crescentic glomerulonephritis, 1124–1125
Creutzfeldt-Jakob disease (CJD), 204, 401
Cribriform carcinoma, prostate, 1240
Cri du Chat syndrome, 43
Crohn's disease, 1323–1325
Crooke's hyaline change, 418
Cryoglobulinemic glomerulonephritis, 1127–1129
Cryptococcosis, 300, 940
Cryptococcus neoformans, 200
Cryptogenic organizing pneumonia (COP)/ bronchiolitis obliterans organizing pneumonia (BOOP), 924
Cryptorchidism, 1249
Cryptosporidium parvum, 212
Crystal arthropathies, 684–685
C. tetani, 181–182
Cushing's syndrome, 418
Cutaneous
ciliated cyst, 536
entrance wound, 110
exit wounds, 111
lymphoid hyperplasia (lymphocytoma cutis), 625
lymphomas, classification of, 581
meningothelial heterotopias/meningiomas, 558
myxoid cyst *See* Digital myxoma
neoplasms and developmental anomalies, 535–553
Cyclospora cayetanensis, 213
Cylindroma, 549–550
Cystadenoma, 106, 326
Cystic
fibrosis, 56–57, 1348–1349, 1400
granulosa cell tumor, 326
hygroma, 569
lesions
eyelid, 858

inflammatory, 790–792
mediastinum, 870–872
neoplastic or developmental, 535–537
salivary gland, 790–792
vulva, 1005–1006
liver disease, 1394–1396
lymphangioma, ovary, 1091
lymphoid hyperplasia (HIV+ subjects), 789–790
neoplasms, salivary gland, 790
nephroma, 1169–1170
partially differentiated nephroblastoma, 1151–1152
pleuropulmonary blastoma of childhood, 955
tumor of the atrioventricular node, 907
Cysticercosis, 409, 414
Cystinosis, 65–66
Cystinuria, 65
Cystitis
acute, 1177–1178
BCG-induced, 1180
chronic, 1178–1179
cystica, 1186
cytoxan-induced hemorrhagic, 1182
eosinophilic, 1184
granulomatous, 1179–1181
interstitial, 1182–1183
radiation, 1181–1182
special variants of, 1182–1184
treatment-induced, 1181–1182
tuberculous, 1179–1180
urinary bladder, 1177–1184
Cyst of müllerian origin, 1091
Cysts
esophagus, 1289
liver, 322, 1430
non-hematopoietic lesions, 481
peritoneum, 1091
thymic, 871–872
types of, 1289t
Cytogenic karyotyping, 12
Cytokeratin 7 and 20 immunostaining in various cancers, common patterns of, 1203t
Cytokine effects, bone marrow, 531
Cytologic/histologic variants, 366
Cytologic smear, evaluation of, 296
Cytomegalovirus, 32–34, 1005
esophagus, 1291
infection, hepatobiliary disease, 1377
lung, 934
lymph node, 426
microbiology, 204
neuropathology, 408–409
Cytoplasm, 136–144
Cytotoxic edema, 363

Dabska's tumor (malignant endovascular papillary angioendothelioma), 573
Dacryocystitis, 861
Dacryolithiasis, 861–862
DAG *See* diffuse antral-predominant gastritis
Dandy walker malformation, 411
Death, cardiovascular causes of, 93–96
Death, non-vascular causes of, 96–97
Decidual cells, 269–270
Decidual reaction, uterus, 1040
Decomposition, 91
Decompression sickness, 123
Decoy cells, 329
Decreased atmospheric pressure, 122–123
Dedifferentiated liposarcoma, 731–732
Deep penetrating nevus, 579
Defense wound, 115
Degenerations, conjunctiva, 846
Deletion syndrome, 22q, 43–44
Dematiaceous fungi, 198–199
Demyelinating disorders, 404–405
Demyelinating viral infections, 405
Dendritic cells neoplasms, 27
De novo carcinogenesis, 235
De-novo osteosarcoma, 692–694
Dentigerous cyst, 807
Dentinogenic ghost cell tumor (included here given similarity to Gorlin cyst), 808
Dermal analogue tumor (membranous adenoma), 768
Dermal nerve sheath myxoma, 748
Dermatitis herpetiformis (DH), 602
Dermatofibroma, 317–318, 567–568, 724–725
Dermatomyofibroma, 566
Dermatomyositis, 604, 619
Dermatopathic lymphadenopathy, 430
Dermatophytes, 197–198
Dermatophytosis, 618
Dermatoses, 626–627
Dermoid cyst
immunodermatology, 535
oral cavity, 805
testis, 1262
Desmoplastic fibroma, 704
Desmoplastic tumor, 148, 757–758
Desquamative interstitial pneumonitis (DIP), 924–925
Destructive malformations, 412
Diabetes mellitus, 98, 839, 1126, 1348
Decidual pseudopolyp and decidualization, 1027
Diffuse
alveolar damage (DAD)/acute interstitial pneumonia (AIP), 923–924
antral-predominant gastritis, 1303
axonal injury, 108–109
idiopathic pulmonary neuroendocrine cell hyperplasia, 945
(infiltrative) astrocytomas, 366–370
large b-cell lymphoma, stomach, 1311
large B-cell lymphoma (DLBLC), 315, 445–446, 478, 518
large cell lymphoma, 25, 886–887
mesangial sclerosis, 1135–1136
neurofibroma, 747
panbronchiolitis, 923
Digital fibrokeratoma, 566
Digital mucous cyst, 537
Digital myxoma (cutaneous myxoid cyst), 755
Digital pacinian neuroma, 745
Dilated cardiomyopathy, 94
Dilated pore of Winer, 541
Dimorphic fungi, 191–197
Diphyllobothrium latum, 220
Direct immunofluorescence (DIF), 587
Dirofilarial (dog heart worm) granulomas, 940
Dirofilaria species, 226
Discoid lupus erythematosus (DLE), 599–600
Disease classification of, 868t
Dissecting cellulitis, 631
Dissection, blood vessel, 910–911
Disseminated fungal infection, 798–799, 825
Diverticulae, 1289, 1289t, 1300, 1327
Diverticulosis, urinary bladder, 1187–1188
DNA diagnostic methodologies, 5–9, 12
Doderlein bacilli (lactobacillus acidophilis), 268
Dog heart worm. *See* Dirofilarial granulomas
Dowling-Degos disease, 575–576
Down Syndrome, 39–40, 413. *See also* Trisomy
Dracunculus medinensis, 222
Drowning, 122
Drugs and toxins, hepatobiliary disease, 1384–1386
Drug toxicity, 237
Dry drowning, 122
Dubin-Johnson syndrome, 1398
Duchenne/Becker muscular dystrophy (DMD/BMD), 49–50
Ductal
adenocarcinoma, 324–325
carcinoma, 312–314, 1351–1353
cysts, conjunctiva, 847
(endometrioid) adenocarcinoma, prostate, 1238
intraepithelial neoplasia (DIN), 975–978
neoplasia, pre-invasive, 1355–1359
Duct ectasia (periductal mastitis), 971
Dural metastases, 387
Duret (secondary brainstem) hemorrhage, 364
Dysembryoplastic neuroepithelial tumor (DNT) (WHO Grade I), 381
Dysfunctional uterine bleeding, 1040–1041
Dysgenetic cysts, 790–791
Dysgerminoma, 151, 327, 1083–1084
Dysplasia, 321
thymic, 872
Dysplastic nevus, 578

Eccrine
angiomatous hamartoma, 568–569
-derived tumors and proliferations, 545–553
duct carcinoma, 550
poroma, 548–549
spiradenoma, 550
syringofibroadenoma, 546
Echinococcus, 220, 488
Ectomesenchymoma, 737
Ectopic
decidual reaction, 1015, 1074, 1094
pregnancy, 1061–1062
prostatic tissue, 1190, 1228
supernumerary ovary, 1072
Eczematous dermatitis, 613–615, 617
Edward syndrome. *See* Trisomy
Edward syndrome, 40–41, 413
Effusion lymphoma, effusion, 26
Ehlers-Danlos syndrome, collagen related, 52–53
Ejaculatory ducts, 1227
Elastofibroma, 566, 716
Elisa, 587
Embolism, 102
Embryonal
rhabdomyosarcoma, 735–736, 1429
tumors, 382–385
Embryonal carcinoma, 148
mediastinum, 884
ovary, 1084
testis, 1260
Emphysema, 920–921
Emphysematous vaginitis, 1015
Empty Sella syndrome, 420
Encephalitis, 408
Encephalocele, 410
Endocarditis, 173
infectious, 902–903
non-infectious, 903
Endocardium valves, 901–903
Endocervical
adenocarcinoma, 274–275, 275t
cells, 273

polyps, 1028
transformation zone component (TZ), 267
Endocervical cells, 274
Endocervicosis, 1093, 1187
Endocrine carcinoma (small cell), poorly differentiated, 1363
Endocrine neoplasm, pancreas, 1361–1363
Endometrial
adenocarcinoma, 276–277
carcinoma, 1044–1047
cells, cytologically normal, 275–276
cellular changes (metaplasias), 1042
cycle, 1038–1039
cytology, 275–294
hyperplasia, 1044–1045
intraepithelial carcinoma, 1045–1046
polyps, uterus, 1043
stromal and related tumors, 1053–1054, 1055t
Endometrial cells, 276
Endometrioid
adenocarcinoma, 1016, 1034
carcinoma, 326, 1047–1048
polyp, 1063
tumors, 151
tumors, ovary, 1080–1082
Endometriosis
ovary, 1075, 1091
skin, 537
uterus, 1027
vulva, 1009
Endometriotic cyst, 326, 1091
Endometritis, 1041
Endometrium, 1038–1040, 1039
Endopthalmitis, 837
Endosalpingiosis, 537, 1093
End-stage scarring alopecia, 632
Entamoeba histolytica, 213, 268
Enteritis, 1319, 1329
Enterobius vermicularis (pinworm), 222, 268
Enterococcus species, 162–163
Enterocolitis, 1319
Enterohemorrhagic *E. coli* (O157:H7), 1320
Enteropathy-type T-cell lymphoma, 450
Entrance wound, 392
Entrapment (environmental suffocation), 119
EORTC Classification, 581–582
Eosinophilic granuloma (pulmonary histiocytosis-X/Langerhans' cell granulomatosis), 927
Eosinophilic pneumonia, 926–927
Eosinophils cellulitis (Wells' syndrome), 626
Ependymomas, 334, 375–376
Epidermal
cyst, 306, 535, 1006
tumors and proliferations, 537–541
Epidermoid cyst, 1262, 1365
Epidermolysis bullosa acquisita (EBA), 589–590
Epididymis, 1251, 1267–1269
Epidural hematoma, 392
Epidural hemorrhage, 106
Epilepsy, 97
Epithelial
cell abnormalities, 266
inclusion glands/cyst in ovarian cortex, 1074
malignancy in different salivary gland sites, frequency of, 765t
-myoephithelial carcinoma, 779–780
neoplasms and developmental anomalies, 535–553
sarcoma, vulva, 1014
tumors
fallopian tubes, 1062–1064
lung, 946
salivary glands, 763–783
uterus, 1027–1035, 1043–1049
Epithelial salivary gland tumors, incidence of, 764t
Epithelioid
hemangioendothelioma, 702, 1427–1428
immunodermatology, 573
lung, 952–953
soft tissue, 740–741
hemangioma, 738–739
sarcoma, 148, 568, 756
immunodermatology, 573
lung, 952–953
soft tissue, 740–741
Epstein-Barr virus (EBV), 204–206, 905, 1376–1377
Erdheim-Chester disease, 708
Eruptive histiocytoma, 564
Eruptive vellus hair cyst, 536
Erysipelas, 161
Erythema multiforme, 604
Erythema nodosum, 627–628
Erythroleukemia, 505–506
Erythropoietic protoporphyria, 1405–1406
Escherichia coli, 168–169
Esophageal cyst, 870–871
Esophagitis, 1289–1291
caustic (corrosive), 1289–1290
eosinophilic, 1290
infectious, 1290–1291
pill-induced, 1290
radiation, 1290
Esophagus, 1288–1299
cytology, 320–321
non-neoplastic anomalies, 1288–1289
Essential thrombocythemia (ET), 498
Ethanol (drinking alcohol), 127
Ethidium bromide (EtBr) staining of gels, 30
Ethylene glycol, 128
Ewing's sarcoma, 148, 320, 706–707
Exit wound, 392
Exstrophy, 1177
Extaspinal (soft tissue) ependymoma, 751
External hordeolum or stye, 858
External otitis, chronic, suppurative, 173
Extrarenal rhabdoid tumor, 757
Extrahepatic bile ducts, 1433–1435
Extrahepatic biliary atresia, 1397–1398
Extramedullary hematopoiesis (EMH), 478–479
Extramedullary plasmacytoma, 883
Extranodal lymphoma, 438–440, 450
Extraskeletal sarcoma, 752–753
Extra-uterine metastatic adenocarcinoma, 277
Extrinsic allergic alveolitis (hypersensitivity pneumonitis), 926
Eye
acute inflammation, 837
diseases that affect multiple structures in the, 835–840
inflammation of the, 836–840
tumors of the, 851–857
Eyelids, 857–861

Fabry disease, 75–76, 1131–1132
Factor V Leiden, 11–12
Failed corneal graft, 843
Fallopian tube, secondary tumors, 1065
Fallopian tubes, 1015, 1060–1066
Familial
adenomatous polyposis, 76–82
cancer syndromes, 76–83
hypophosphatemic rickets, 64–65
medullary thyroid carcinoma (FMTC), 80–81
Fanconi anemia, 45
Fasciitis, 565, 714–715
Fasciola hepatica, 227
Fasciolopsis buski, 227
Fatal familial insomnia (FFI), 402
Fat embolism, 102, 109
Fat necrosis, 311, 972
Ferruginous bodies, 300
Fetal Alcohol syndrome, 415
Fetal/perinatal insults, 413
Fetal rhabdomyoma, 735
Fetal thromboocclusive lesions, 1110–1111
Fetal vascular obstruction (fetal thrombotic vasculopathy), changes consistent with, 1110
Fibrillary glomerulonephritis, 1125
Fibroadenoma, 311, 990–992
Fibrocystic changes, 311, 967
Fibroepithelial polyp, 1009, 1027–1028
Fibroepithelioma of pinkus, 544
Fibrofolliculoma, 543
Fibrohistiocytic lesions, 317–318, 704–705
Fibrohistiocytic tumors, 722–727, 723t
Fibroid polyp, inflammatory, 1301–1302
Fibrolamellar carcinoma, 1420
Fibroma, 149
cardiac, 906–907
ovary, 1087–1088
of tendon sheath, 565, 716
Fibromatoses, 719–721
Fibromatosis
breast, 973–974
colli, 718
skin, 566
soft tissue, 317
Fibromuscular dysplasia, 909, 1140–1141
Fibrosarcoma, 149
bone, 740
soft tissue, 318, 568, 721–722
Fibrosing mediastinitis, 870
Fibrosis, hepatobiliary disease, 1385
Fibrothecoma, 326, 1087
Fibrous
dysplasia (FD, Jaffe-Lichtenstein syndrome), 705–706
and fibro-histiocytic tumors, lung, 951
hamartoma of infancy, 566, 717–718
histiocytoma, 149, 560, 704
lesions, 317–318, 704
papule, 566
proliferations and tumors, 564–568
thyroiditis (Riedel's thyroiditis), 637–638
tumors, 714–722, 715t, 890
Fibrous histiocytoma, 722–723
Fibroxanthoma, 562, 726
FIGO staging of the vulva and vagina, 1018
Fine needle aspiration (FNA), 299
Firearms injuries, 110–114
Fissure, 1342
Fistula, 1342
5q- syndrome, 511–512
Fixed drug eruption, 621
Flat urothelial lesions with atypia, 1192–1194
Florid cystitis glandularis, 1186–1187
Flourescence *in situ* hybridization (FISH), 12–13
FLT3 abnormalities, 22
Flukes *See* Trematodes
Fluoxetine (Prozac), 131
Foamy gland carcinoma. *See* Adenocarcinoma with microvacuolated cytoplasm

Focal "adrenalitis," 657
Focal nodular hyperplasia, 322, 1430
Focal segmental glomeruloscerlosis, 1119–1120
Folic acid deficiency, 269
Follicle cysts, ovary, 1072
Follicular
  adenoma, 643–644
  carcinoma, 310, 647–648
  cervicitis, 1022
  cyst, 325
  degeneration syndrome (central centrifugal scarring alopecia), 631
  dendritic cell, 149, 482
  hyperplasias, 425–428, 427t
  infundibulum, tumor of the, 541–542
  lesions, differential diagnosis of, 309t
  lymphoma, 24–25
    bone marrow, 516–517
    lymph node, 440–443
    spleen, 472–473
  neoplasm favor benign, 309
Folliculitis decalvans, 632
Forensic entomology, 91–92
Fox-Fordyce disease, 1003
Fracture contusion, 108
Fractures, 104–105
Fragile X syndrome, 47, 413
Francisella turlaensis, 175, 176
Freckle (ephelid), 575
Freons, 133
Friedreich's ataxia, 48, 404
Frontotemporal lobar degeneration (FTLD), 398
Fuchs' adenoma, eye, 857
Fuchs' dystrophy, 844
Fumarylacetoacetic acid hydrolase (FAH), 59
Fundic gland polyp, 1301
Fungal diseases, uterus, 1024
Fungal infection
  hepatobiliary disease, 1380–1381
  lymph node, 431
  neuropathology, 407–410
  penis, 1276
Fungal osteomyelitis, 683
Fungi, 188–204
Funiculitis, 1269
Fusarium species, 189
Fusobacterium genus, 182–183

Galactosemia, 64
Galatokinase deficiency, 64
Gallbladder, 1410–1411, 1433–1435
γ-Hydroxybutyrate (GHB), 130–131
Ganglion, 379, 755
Ganglioneuroblastoma, 673, 882
Ganglioneuroma
  adrenal gland, 668–669
  gastrointestinal tract, 1337
  mediastinum, 882
  soft tissue, 318–319, 748
Gangliosidosis, 71–72
Gas gangrene *See* Clostridial myonecrosis
Gastric
  antral vascular ectasia (GAVE), 1303
  emptying, 91
  marginal zone B-cell lymphoma, stomach, 1310–1311
  tumors, 2002 TNM classification of, 1312t
  ulcer, 321, 1306
Gastritis, 1303–1306
  acute hemorrhagic, 1305
  autoimmune, 13041306
  granulomatous, 1305
  lymphocytic, 1305
Gastroenteric cyst, 871
Gastroenteritis (by itself), 172
Gastroesophageal reflux disease (GERD), 1291–1292
Gastrointestinal
  autonomic nerve (GAN) tumor, 149
  lymphoma, 1340
  specific bacterial infection, 1319–1320
  stromal tumors (GIST), 28, 149, 1309–1310, 1339–1340, 1340t
Gastropathy, 1301
Gaucher disease, 73–74, 689
Gene expression profiling with microarray, 14–15
Gene rearrangements, 15–18
Genetic lesions associated with specific diseases, 19–27
Genital rhabdomyoma, 735
Geographic tongue, 539, 805
Germ cell tumors, 883–884
  fallopian tube, 1065
  mixed, testis, 1262–1263, 1265–1266
  neuropathology, 390
  ovary, 1083–1086
  testis, 1257–1263
  uterus, 1037, 1059
Germinal centers, progressive transformation of, 427–428
Germinoma, 334–335
Gerstmann-Sträussler-Scheinker disease (GSS), 402
Gestational trophoblastic disease, 1098–1102
Giant cell
  arteritis/aortitis, 911
  carcinoma, osteoclastic, pancreas, 1353–1354
  fibroblastoma, 566–567, 725
  granuloma, 800–801, 808
  lesions, 703–704, 808–809
  reparative granuloma, 704
  tumor, 703–704
    jaws, 808
    osteoclastoma, 703
    tendon sheath, 319, 565, 743
Giant condyloma, 1284, 1342
Giant lymph node hyperplasia (Castleman's disease), 955
Giardia lamblia, 213
Gingival cyst/lateral periodontal cyst, 813
GI tract, 1328t, 1340t
Gitter cells, 363
Glandular cell abnormalities, 273–275
Glandular tumors and precursor lesions, uterus, 1032–1034
Glassy cell carcinoma variant, uterus, 1034
Glaucoma, 835–836, 836t
Glioma of the optic nerve (pilocytic astrocytoma of the optic nerve), 865
Gliosis (reactive astrocytosis), 363
Glomerular diseases, 1119–1137
Glomeruloid hemangioma, 572–573
Glomerulonephritides characterized by immune-type dense deposits, 152–153
Glomerulonephritis by predominant clinical manifestations, 1120t
Glomerulopathies, 152–154
Glomus tumor
  bone and joints, 702
  skin, 575
  soft tissue, 742
  stomach, 1312
Glycogen acanthosis, 1288
Glycogen storage diseases, 63–64, 900
Gnathostoma species, 226
Gonadal dysgenesis, 1071
Gonadoblastoma, 1089, 1265–1266
Gonadotrophic (FSH/LH) adenomas, 419
Gonorrhea, 1274–1275
Goodpasture's disease (anti-basement membrane antibody disease [ABMA]), 929
Gorham's disease (massive osteolysis), 702
Gorlin cyst *See* Calcifying odontogenic cyst
Gorlin syndrome. *See* Basal cell nevus syndrome
Gout and gouty arthritis, 684
Graft *vs* host disease, 604, 620
Gram-negative bacilli, 168–176, 182–183
Gram-negative cocci, 176–182
Gram-positive bacilli, 163–168, 183–184
Gram-positive cocci, anaerobic, 183
Granular cell tumor, 149
  breast, 974
  cytopathology, 318
  esophagus, 1297–1298
  neuropathology, 419
  oral cavity, 802
  skin, 556–557, 958
  soft tissue, 748–749
  vulva, 1008
Granular dystrophy, 844
Granulocytic sarcoma, 887–888, 998
Granuloma
  annulare, 625
  bone marrow, 531
  fungal infection, 407
  hepatobiliary disease, 1385
  inguinale, 1275
Granulomatous
  lesions, differential diagnosis of, 933t
  mastitis, 971
  mediastinitis (localized fibrosing mediastinitis), 869–870
  prostatitis, 1221–1222
  prostatitis, etiology of, 1221t
  salpingitis, 1060–1061
  slack skin, 585
  thyroiditis (de Quervain's), 636–637
Granulosa cell proliferation, 1074
Granulosa cell tumor, 149, 326, 1086–1087, 1265
Graves' disease, 639–640, 864
Gray matter, 411–413
Group staging criteria, 1299t, 1312t
Growth hormone adenoma, 418–419
Guillain-Barré syndrome (GBS), 405
Gunshot wounds, 392
Guttate psoriasis, 616
Gynandroblastoma, 1089
Gynecologic cytology, 268–269
Gynecomastia, 312, 968
Gyral defects, 411–412

Haemophilus influenzae, 174
Hairy cell leukemia, 24, 150, 437–438, 474–475, 517–518
Halo nevus, 579–580
Haloperidol (Haldol), 131
Hamartoma, 481, 943, 973
Hamartomatous polyp, 1332–1333
Handguns, 110–114
Hanging, 116
Hantavirus, 206–207
Hantavirus pulmonary syndrome, 935–936
Hard metal pneumoconiosis (CWP), 930–931

Hartnup disease, 65
Hashimoto's thyroiditis, 308, 638–639
Head, gunshot wounds of, 111–112
Head and neck, 304–307
Head injuries, 105–106
  blunt, 392
  closed, 392
  complications of, 109
  open, 392
Heart, pathology of, 897–908
Heart disease, atherosclerotic, 93
Heart transplantation, 242–245
Heat loss, mechanism of, 125
Helicobacter pylori, 172, 1303
Helminths, 220–221
Hemangioblastoma (WHO Grade I), 388–389
Hemangioendothelioma, 485, 1425
Hemangioma, 957, 1425
  bladder, 1212
  cavernous, capillary, 483, 571–572
  deep, 571–572
  hobnail, 572
  infantile, 571–572
  liver, 322
  mediastinum and thymus, 890
  salivary gland tumors in children, 785
  solitary, 701–702
  superficial, 571–572
Hemangiopericytoma, 149, 386–387
  breast, 996–997
  musculoskeletal, 702
  skin, 575
  soft tissue, 742–743
  tumor of the nasal cavity, 818–819
Hematologicdisorders, 54–56
Hematology, molecular diagnosis in, 10–12
Hematopoietic
  disorders, 502t
  neoplasms, 12–27, 1266–1267, 1430
  tumors, 1017, 1365
Hemochromatosis, 10, 67–68, 900, 1401–1402
Hemopericardium, 901
Hemophagocytic syndrome (HPS), 429, 481, 526
Hemophilia, 55–56
Hemophilic pseudotumor, 702
Hemorrhagic telangiectasia (Osler-Weber-Rendu disease), hereditary, 1391
Hemorrhoids, 1342
Hemosiderin-laden macrophages, 299–300
Hepatic encephalopathy, 415
Hepatic fibrosis, congenital, 1396
Hepatic venous outflow obstruction, 1389–1390
Hepatitis, 207, 1372–1376, 1384–1385, 1407, 1409
Hepatobiliary cystadenocarcinoma, 1424
Hepatobiliary cystadenoma, 1415
Hepatobiliary disease, 1379–1385, 1389–1391
Hepatoblastoma, 323, 1421–1422
Hepatocellular
  adenoma, 149, 322
  carcinoma, 323, 1385, 1416–1419
  necrosis, pure, 1384
Hepatocytes, 322
Hepatoid carcinoma, 1090
Hepatosplenic T-cell lymphoma, 450–451, 476, 521
Hereditary hemochromatosis, 10–11
Hereditary
  hemochromatosis (HH), 10–11
  hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome), 570
  liver disease, 1394–1407
  nephritis, 1134–1135
  neuropathy with liability to pressure palsies, 50
  non-polyposis, colon cancer, 78–79
  Polyposis syndromes and gastric manifestations, 1302t
Herniation, 108
Herniation syndrome, 364
Herpes gestationis (pemphigoid gestationis), 588
Herpes simplex virus (HSV)
  cytopathology, 267–277
  esophagus, 1291
  infection, 1004, 1023, 1377–1378
  keratitis, 843
  lung, 934–935
  neuropathology, 408
  1 and 2 (HSV), 207
  oral cavity, 798
  penis, 1276
Heterotopic
  gastric mucosa ("inlet patch"), 1289
  meningeal lesions (ectopic meningioma), 749
  nasal glioma, 558, 749
  ossification, 679
  pancreas, 1300
  thyroid, 635
Heterozygotes, 12
Hibernoma, 555, 730
Hide and Die syndrome, 124
Hidradenitis suppurativa, 1004
Hidradenocarcinoma (malignant nodular hidradenoma), 548
Hidradenoma papilliferum (HP), 552, 1008
Hidroacanthoma simplex (intraepidermal poroma), 548
Hidrocystoma, 537
High-grade prostatic intraepithelial neoplasia (HGPIN), 1228–1230
High grade squamous intraepithelial lesion (HSIL), 271–272
High-grade surface osteosarcoma, 695
Hilar Leydig cell hyperplasia, 1074
Hilus cell tumor, 149, 150
Hippocampal necrosis, 394
Histiocytic and dendritic neoplasms, 27
Histiocytic and macrophage disorders, bone marrow, 526–527
Histiocytic cells neoplasms, 27
Histiocytic lymph node tumors, 426, 459–460
Histiocytoid carcinoma, 984
Histiocytosis X (Langerhans' cell histiocytosis), 419
Histology clues, sellar/suprasellar pathology, 417
Histoplasma capsulatum, 193
Histoplasmosis, 300, 488, 939, 1380–1381
HIV/AIDS, 207–208, 408, 426, 488, 1130, 1376
Hobnail hemangioma *See* Targetoid hemosiderotic hemangioma
Hodgkin lymphoma (HL), 316, 426, 455–459, 477, 523–524
Hodgkin's disease (HD), thymus, 884–885
Holoprosencephaly, 410
Homocystinuria, 60–61
Homozygotes, 12
Hordeolum, 858
Hormone administration, effects of, 1040
Hortaea werneckii, 196
Hospital gangrene *See* Necrotizing fasciitis
Human papilloma virus (HPV), 208, 798, 1004, 1023–1024
Human t-cell lymphotropic virus 1 and 2 (HTLV), 208
Humoral rejection (hyperacute rejection), 903–904
Humoral ("vascular") rejection, 904
Huntington's disease (HD), 48, 401
Hürthle cell, 309, 644–645, 649
Hyaline arteriosclerosis, 908–909
Hyaline fungi, 188–191
Hybrid cyst, 537
Hydatid cyst, 1382–1383
Hydatidiform mole, 1098–1099
Hydranencephaly, 412
Hydrocele, 1268
Hydrocephalus, 363–364
Hydrocystomas ("water cysts"), 858
Hydrogen cyanide, 121
Hydrogen sulfide, 121
Hymenolepis species, 220
Hyperacute rejection, 237
Hyperbilirubinemias, 1398–1400
Hypereosinophilic syndrome (HES), 499
Hyperkeratosis (HK), 269, 826
Hyperkeratotic squamous papilloma, 818
Hyperparathyroidism, 686–687
Hyperplasia, 314, 1032, 1184, 1222, 1226, 1434
Hyperplastic arteriolosclerosis, 909
Hyperplastic polyp (HPP), 321, 1300–1301, 1333
Hyperreactio luteinalis, 1073
Hypertensive
  cardiovascular disease, 93
  heart disease, 899
  intracerebral hemorrhage, 397
  vascular disease, 908–909
Hypertrophic
  cardiomyopathy, 94
  pyloric stenosis, 1299–1300
  scar and keloid, 564–565
Hypoglycemic brain injury, 396
Hypospermatogenesis, testis, 1254
Hypotensive anoxia, 1390
Hypothalamic hamartoma, 419–420
Hypothermia, local, 123–124
Hypoxic ischemic encephalopathy, 109

Idiopathic
  dilated cardiomyopathy, 898–899
  granulomatous mastitis, 971
  granulomatous orchitis, 1253
  guttate hypomelanosis, 576
  hypertrophic cardiomyopathy, 898
  inflammatory bowel disease, 1322–1325
  interstitial pneumonias, 924–926
  Parkinson's disease (IPD), 398–401
  paucity of intrahepatic bile ducts, 1397
  portal hypertension (non-cirrhotic portal fibrosis), 1391
  pulmonary hemosiderosis, 929
"Id" reaction, 615
IgA nephropathy (IgAN), 1122–1123
IgA pemphigus, 596–597
IgH PCR for B-cell clonality determinations, 17
Ileal conduit, 329
Immersion hypothermia, 124
Immune-mediated disease, oral cavity, 799–800
Immune thrombocytopenic purpura (ITP), 531
Immunoblastic reaction, 429
Immunobullous diseases, 587–602
Immunocytoma (marginal zone lymphoma), 582
Immunodermatology, 587–607
Immunoglobulin and T-cell receptor gene rearrangements, 15, 15t
Immunophenotypic distinction between Hodgkin lymphoma and anaplastic large cell lymphoma, 459t

Immunosuppression, 234
Impetigo, 161
Incised wound, 115
Inclusion body fibromatosis (infantile digital fibromatosis), 718
Inclusion cysts and Walthard nests, 1062
Increased atmospheric pressure, 123
Indeterminate cell histiocytosis, 564
Indirect immunofluorescence (IIF), 587
Infantile
  digital fibroma/fibromatosis, 566
  fibromatosis (desmoid-type), 718–719
  lobar emphysema, 919–920
  myofibromatosis, 718
  Nephrotic syndrome. 1135–1136
  Refsum disease, 69
Infarcted appendix epiploica, 1093
Infections, 267–268
  contaminants, 268
  larynx and trachea, 825
  nasal cavity, sinuses, and nasopharynx, 814–815
  organisms, 267–268
  uncommon, ovary, 1071
Infectious
  lesions, vulva, 1004
  mononucleosis, 315, 429, 487
  processes, respiratory, 300–301
  sinusitis, other forms of, 815
Infectious pyelonephritis (ascending or hematogenous infection), 1137
Infertility, 1253–1256
Infiltrating carcinoma, 980–998, 981t
Infiltrative diseases. 899–900
Inflammatory
  bowel disease, 1409
  carcinoma, breast, 986
  disorder, gastrointestinal tract, 1319–1327
  fibrous polyp, 1334–1337
  hepatobiliary disease, 1409
  lesions
    appendix, 1330
    miscellaneous, ovary, 1071
    ovary, 1071
    prostate, 1221–1222
    vulva, 1003–1004
  myofibroblastic tumor
    lung, 959
    soft tissue, 721
    spleen, 482–483
    urinary bladder, 1188–1189
  non-neoplastic lesions, 800–802, 816–817, 825–882
  pancreas, 1349–1351
  pseudopolyp, 1333
  pseudotumor, 1093
    liver and biliary system, 1432–1433
    lung, 951
    lymph node, 462
    orbit, 862–864
    spleen, 481–482
  vascular lesions, hepatobiliary disease, 1390
Inflammatory disease, gastrointestinal tract, 1319
Infraclavicular, primary malignancy and parotid and parotid node metastasis, 787t
Injuries
  blunt force, 103–110
  electrical, 126–127
  physical, 101–127
  road traffic, 105
  sharp force, 114–115
  toxic, 415–417
Insular carcinoma, 648
Interdigitating dendritic cell neoplasm, 149
Interface dermatitis, 618–621
Internal hordeolum, 858
Interstitial diseases, 923–931
Interstitial pattern, 625–626
Intervillous thrombus (fetomaternal hemorrhage), 1107–1108
Intestinal ischemia, 1327–1328
Intestinal polyps, 1332–1337
Intra-abdominal desmoplastic small round cell tumor, 1092–1093
Intracerebral hemorrhage (apoplexy), 96
Intracortical osteosarcoma, 695
Intracranial hemorrhage, 106–107, 396–397
Intracystic papillary carcinoma, 312
Intraductal
  carcinoma with secretory features, 978
  clear cell carcinoma, 978
  epithelial proliferations, breast, 975–980
  hyperplasia (IDH), 976t
  oncocytic papillary neoplasms, 1358
  papillary mucinous neoplasms, 1357–1358
  papilloma, 312, 989–990
  papillomatosis, 990
  signet ring carcinoma, 978
  spindle cell carcinoma, breast, 978–979
Intrahepatic bile ducts, tumors of the, 1414–1433
Intrahepatic cholestasis, 1394, 1399–1400
Intralobar nephrogenic rests (ILNR), 1148
Intramuscular hemangioma, 739
Intramuscular myxoma, 754–755
Intraosseous ganglion, 689–690
Intraosseous well-differentiated osteosarcoma, 694
Intratubular germ cell neoplasia, unclassified (IGCNU), testis, 1258
Intrauterine devices, changes related to, 1042
Intravascular large B-cell lymphoma, 26
Intravascular lymphoma, 398
Intravascular lymphomatosis (angiotropic lymphoma), 957
Intravascular papillary endothelial hyperplasia (Masson's hemangioma), 571
Intravenous leiomyomatosis, 733
Intraventricular hemorrhage, 413
Instrument artifact and lithiasis, 329
Invasive carcinoma, 312–314
Invasive fungal sinusitis, 815
Invasive squamous cell carcinoma (ISCC), vulva, 1011–1012
Inverted follicular keratosis, 538
Inverted papilloma, 1204–1205, 1228
Iron deficiency anemia, bone marrow, 528–529
Irregular shedding, uterus, 1041
Ischemic fasciitis (atypical decubital fibroplasia), 715–716
Ischemic heart disease, 898–899
Ischemic injury, 1138, 1328
Islet cell tumors, 325
Isopropyl (rubbing alcohol), 127
Isospora belli, 213–214
Isovaleric acidemia, 61–62
IUD-associated change, 269

Jaffe-Lichtenstein syndrome. *See* fibrous dysplasia
Jaws, 806–813
JC virus, 409
Jejunoileal bypass, 1388
Juvenile
  hyaline fibromatosis, 718
  hypertrophy, breast, 968
  myelomonocytic leukemia, 513–514
  nephrophthisis (medullary cystic disease), 1145
  xanthogranuloma, 561, 723
Juxtaarticular myxoma, 755
Juxtaglomerular cell tumor, 1169

Kaposiform hemangioendothelioma, 573, 739–740
Kaposi's sarcoma, 319, 461, 574, 740, 953
Kawasaki's disease (Mucocutaneous Lymph Node syndrome), 911
Keloid scar, 717
"Keratinizing dysplasia," 272
Keratitis, 173, 842
Keratoacanthoma, 541, 1012
Keratoconus, 845–846
Kernicterus, 413
Kidney, 327–328, 1139–1146
Kidney transplantation, 237–242
Kikuchi-Fujimoto disease, 431
Kitamura's reticulate hyperpigmentation, 576
Klebsiella pneumoniae, 171
Klinefelter syndrome (XXY), 41
Krabbe disease, 74–75
Küpffer cells, 322
Kuru, 402
Küttner's tumor *See* Chronic sclerosing sialadenitis of submandibular gland

Labor pneumonia, 160
Laceration, 104
Lacrimal tumors, 862
Lactating adenoma, 973
Lactational changes, 311, 969
Lafora's disease (myoclonic epilepsy), 404
Laminar/pseudolaminar necrosis, 394
Langerhans' cell histiocytosis (LCH), 149, 320, 459, 526, 563, 708
Large B-cell lymphoma, 583
Large cell
  acanthoma, 540
  carcinoma
    neuroendrocrine, 303, 828, 950–951
    salivary gland, 782
    undifferentiated, 303, 948–949
  cutaneous T-cell lymphoma, 585
  neoplasms, 456t
Large granular lymphocytic (LGL) leukemias, 449, 476–477, 521–522
Large solitary luteinized follicle cyst of pregnancy and puerperium, 1073
Laryngeal nodule/polyp, 825–826
Laryngocele, 825
Larynx and trachea, 825–829
Lattice dystrophy, 845
Lead, 132
Lead poisoning, 417
Lecithin cholesterol acyltransferase (LCAT) deficiency, 1132
Legionella pneumophila, 173–174
Legionnaires' disease, 936
Leiomyoma, 1064
  bladder, 1212
  esophagus, 1297
  eye, 857
  soft tissue, 732–733
  stomach, 1310
  uterus, 1035, 1050
  vulva, 1009
Leiomyomatous peritonealis disseminata, 1093
Leiomyosarcoma
  bladder, 1213

prostate, 1242–1243
skin, 559–560
soft tissue, 319, 734
spermatic cord, 1270
uterus, 1035
vagina, 1017
variants, uterus, 1053
Leishmaniasis, 488
Leishmania species, 214–215
Lennert lymphoma. *See* Lymphoepithelial cell variant
Lentiginous melanosis, 1277
Lentigo maligna melanoma, 581
Lentigo simplex, 578
Leprosy, testis, 1252–1253
Leptothrix, 268
Lesch-Nyhan, 68
Lesions
benign
anus, 1342
breast, 311–312
cystic, neck, 792t
discolored, vulva, 1006–1007
hyperplastic, lung, 955
liver, 322
lymphoepithelial, 789
non-neoplastic, vagina, 1014–1015
respiratory, 299–300
squamous cell, uterus, 1027–1028
thyroid, 307–309
urinary bladder, 329–330, 1184–1191
uterus, 1028–1029
hemorrhagic, placenta, 1107–1109
lacrimal drainage system and lacrimal glands, 861–862
miscellaneous, 805–806, 813, 823–824
peritoneum, 1093
pre-invasive, lung, 944
reactive, 486–490
spermatic cord, 1269–1270
tumor-like
liver and biliary system, 1430–1433, 1435
salivary glands, 787–790, 788t
vascular, 995–997
bone and joints, 701–703
capillary microangioma, 1267
gastrointestinal tract, 1327–1330
Leukemia, 17, 390–391, 1266–1267
Leukemia cutis, 586
Leukemias of ambiguous lineage, 507
"Leukoaraiosis," 396
Leukodystrophies, 417
Leukoedema, 539
Leukoplakia, oral cavity, 802
Leydig cell tumor, 150, 1263
Lichenoid dermatitis, 604
Lichenoid drug, 604, 621
Lichenoid keratosis (lichen planus-like keratosis), 537–538
Lichen planopilaris, 631
Lichen planus, 603–604, 620, 799–800, 1006
Lichen sclerosus, 627, 1006, 1277
Lichen simplex chronicus (LSC), vulva, 617, 1003
Li-Fraumeni syndrome, 79–80
Light chain cast nephropathy (myeloma kidney), 1139
Light chain deposition disease, glomerular diseases, 1127
Lightning, 126–127
Ligneous conjunctivitis, 848–849
Limbal (epibulbar) dermoids, 846
Lineage determination, 12
Linear epidermal nevus, 539
Linear IgA bullous dermatosis (chronic bullous disease of childhood), 591–593
Lingual thyroid, 805
Lipid degeneration, 845
Lipid-laden macrophages in bronchial lavage, 300
Lipid-rich carcinoma, breast, 984–985
Lipid (steroid) cell tumors, ovary, 1089
Lipoblastoma, 554, 730
Lipoblastomatosis, 554
Lipodermatosclerosis (lipomembranous panniculitis, sclerosing panniculitis), 628
Lipodystrophy, 1133–1134
Lipofibromatous hamartoma of nerve, 554
Lipoma, 146
lung, 944
skin, 554
soft tissue, 317, 727–729
thymus, 889
Lipomatosis, 554, 730
Lipomatous hypertrophy of the interatrial septum, 907
Lipomatous tumors, 727–732, 728t
Liposarcoma, 146
mediastinum, 890
skin, 555
soft tissue, 317, 731
spermatic cord, 1270
Liposclerosing myxofibrous tumor (LSMTF), 704
Lissencephaly/pachygyria, 411
Listeria monocytogenes, 165
Littoral cell angioma, 484–485
Liver
cell adenoma, 1385, 1414
cytology, 322–324
disease, 1394–1408
reactive/regenerative changes, 322
tumors of the, 1414–1433
Liver transplantation, 247–252
Loa loa, 224
Lobar hemorrhage, 397
Lobular capillary hemangioma, 737, 817–818
Lobular carcinoma, 312–313
Lobular intraepithelial neoplasia (LIN), 979–980
Localized fibrous tumor of the pleura, 961
Long QT syndrome (LQTS), 93–94
Low-grade B-cell lymphoma of MALT type, 887
Low grade myofibroblastic sarcoma, 721
Low grade squamous intraepithelial lesion (LSIL), 271
Lung
cytology, normal cellular components of, 298
infections, 934–941
injury, acute, 923–924
Lung fluke. *See* Paragonimiasis
Lung transplantation, 245–247, 941–942
Lupus erythematosus, 604, 618–619, 630–631
Lupus panniculitis (lupus profundus), 629
Lupus variants, immunobullous diseases, 599
Luteal phase, inadequate, 1040–1041
Lymphadenitis, 314
Lymphangiogram effect, 428
Lymphangio (leio) myomatosis, 928
Lymphangioma, 483–484, 569, 701–702, 889–890, 1365
Lymph node, 314–316, 425, 429
Lymphoblastic leukemia/lymphoma (ALL/LBL), 22–23, 475, 507–509
Lymphoblastic lymphoma (LBL), thymus, 885–886
Lymphocyte Hodgkin lymphoma, 458–459
Lymphocytic
hypophysitis, 420
interstitial pneumonitis (diffuse lymphoid hyperplasia), 955
leukemia, 150
mastitis (diabetic mastopathy, fibrous mastopathy), 972
thyroiditis (painless thyroiditis), 638
Lymphocytic leukemia/lymphoma (ALL/LBL), 334
Lymphoepithelial carcinoma, 150, 782, 782t, 813
Lymphoepithelial cell variant (Lennert lymphoma), 454
Lymphoepithelial cyst, 805, 1364–1365
Lymphoepithelioma-like carcinoma, 828, 1032, 1205, 1240
Lymphogranuloma venereum (LGV), 430, 1005, 1276
Lymphoid
hematopoietic tumors, 1037, 1065
hyperplasias, 425–431, 872–873
lesions, 997–998
neoplasms, 474–478, 1310–1311
tumors, 866
Lymphoma, 150, 469–474
bladder, 1215
breast, 997–998
cardiac, 908
central nervous system, 390–391
common variants of, 315–316
cutaneous follicular center cell, 582
diagnosis, 17
esophagus, 1298
lesion, uterus, 1027
leukemia, 277, 1059, 1090
liver and biliary system, 1429–1430
lung, 955–957
malignant (WHO classification), 425
mucosa associated lymphoid tissue (MALT), 955–956
neuropathology, 390–391
prostate, 1243
salivary gland, 784, 785t
stomach, 321
testis, 1266
Lymphomatoid granulomatosis, 956–957
Lymphomatoid papulosis (LyP), 585t, 623–624
Lymphoplasmacytic lymphoma, 24, 435–436, 472, 515–516
Lymphoproliferative disorders, 518–523, 581–587, 884–889, 957
Lymphoproliferative lesions, 955
Lysergic acid diethylamide (LSD), 130
Lysosomal storage diseases/disorders, 69–76, 417

Macrophage/microglial reactions, 363
Macroscopic, esophagus, 1289
Macular dystrophy, 845
MAG *See* Multifocal intestinalized pangastritis
Malabsorptive disorder, gastrointestinal tract, 1319–1327
Malakoplakia, 936, 1180, 1253
Malaria, 488, 1382
Malassezia furfur, 196
Male breast, carcinoma of the, 987
Malignancy, mimics of, urinary bladder, 329–330
Malignant
(anaplastic) meningioma, 386
chondroid syringoma, 547
cylindroma, 549–550
eccrine spiradenoma, 550

fibrous histiocytoma (MFH), 318, 562, 704–705, 726–727, 952
hyperthermia, 125
lesions, 323–324, 330–331
lymphoma
eye, 857
lymph node, 315, 425–426, 431–459
nasal cavity, paranasal sinuses, and nasopharynx, 819–820
melanoma, 150
eye, 851–852
nasal cavity, paranasal sinuses, and nasopharynx, 821–822
oral cavity, 804–805
skin, 316, 580–581
uterus, 1037
vagina, 1017
vulva, 1013
mesothelioma, 960–961, 1092, 1268
myoepithelioma (myoepithelial carcinoma), 995
neoplasms
jaws, 811–813
nasal cavity, paranasal sinuses, and nasopharynx, 819–823
oro/hypopharynx, 813
salivary glands, 306
nephrosclerosis, 1140
pilomatricoma, 544
tumors
epithelial, 787, 1009, 1015–1017, 1063–1064
gastrointestinal tract, 1337–1342
lung, 945–949
mesenchymal, 890
mixed Müllerian, 277, 1081
non-epithelial, 1013
peripheral nerve sheath, 151, 318, 558, 749, 750, 882
prostate, 1232–1244
serous, 1078–1079
triton, 737
trophoblastic, 1100–1102
Malignant melanoma, 580
MALT lymphomas, 24
Mammary ductal proliferations, 976t
Mansonella perstans. 224
Mantle cell lymphoma (MCL), 25, 315, 443–445, 473, 517, 1341
Maple syrup urine disease, 60
Marfan syndrome, fibrillin related, 51–52
Marginal zone hyperplasia versus marginal zone lymphoma, 487t
Marginal zone lymphoma (MZL), 24, 516, 582
Marihuana, 130
Marijuana smoking, habitual, 299
Masses and tumor-like lesions, lung, 959–960
Massive ovarian edema, 1075
Massive perivillous fibrinoid deposition (maternal floor infarction), 1113–1114
Massive retinal gliosis, 840
Masson's tumor. *See* Papillary endothelial hyperplasia
Mast cell tumor, lung, 957
Mastitis, lung, 971
Mastitis/periareolar abscess, 971
Mastocytoma, 626
Mastocytosis, 27, 626
Metastases from distal sites, 890
Maternal arteriopathies and preeclampsia, 1106
Maturation arrest, 1255
Mature B-cell neoplasms, 23, 425, 433–448
Mature cystic teratoma, 326
Mature peripheral T-cell lymphoma/leukemia, 26–27
Mature T-cell and NK-cell neoplasms, 425–426, 448–455
Measles, 208, 935
Mechanical asphyxia, 120
Mechanical duct obstruction, 1391–1392
Meconium and subacute hypoxia, 1104–1106
Mediastinal parathyroid lesions, 873–874
Mediastinal (thymic) large B-cell lymphoma, 25–26, 446–447
Mediastinal tumors, 878t
Mediastinitis, 869
Medullary carcinoma, 310, 313, 649–651, 983–984, 1355
Medulloblastoma, 335, 382–383
Medulloepithelioma, 857
Megaloblastic anemia, bone marrow, 529–530
Melanoacanthoma, 806
Melanocytic nevi, 1007
Melanocytic proliferations, 576–580
Melanocytic proliferations and pigmentary disorders, 575–587
Melanocytic tumors, uterus, 1037
Melanoma, 1299, 1344
Melanotic neuroectodermal tumor of infancy, 812
Melanotic paraganglioma, 1058
Melasma, 575
Membranoproliferative (mesangiocapillary) glomerulonephritis (MPGN), 1123
Membranous nephropathy (MN), 1121
Meningioma, 385–386
Meningiomas, 150, 307, 335, 385, 386t, 865–866
Meningitis, 160, 162, 406–407
Menke's disease, 67
Mercury, 132
Merkel cell carcinoma, 150, 316, 553
Merkel cell tumor, 1014
Mesenchymal
chondrosarcomas, 812
cystic hamartoma, 944
hamartoma, 1431
lesions, 705–709
neoplasms, kidney, 1168–1169
tumors
benign (low-grade), mediastinum, 889–890
fallopian tube, 1064–1065
lung, 951–952
mediastinum, 889–890
pancreas, 1365
salivary glands, 784–785
uterus, 1035–1036, 1050–1056
Mesial temporal sclerosis (MTS; hippocampal sclerosis), 414
Mesodermal stromal polyp (pseudosarcoma botryoides), uterus, 1027
Mesonephric adenocarcinoma, 1016, 1034
Mesonephric (Gartner's duct) cyst, 1006
Mesonephric remnants and mesonephric hyperplasia, 1026–1027
Mesothelial
cells, 332t
hyperplasia, 331–332, 1091
metaplasia, 1091
tumors, fallopian tube, 1064–1065
Mesothelial cells, 331–332
Mesothelioma, 150, 302t, 332, 960t
Metabolic bone disease, 685–689
Metabolic disorders, 58–69, 416t, 417
Metabolic liver disease, 1394–1407
Metachromatic leukodystrophy, 75
Metal metabolism disorders, 66–68
Metals, 132–133
Metanephric tumor family, 1166–1168
Metaphyseal fibrous defect (non-ossifying fibroma), 705
Metaplasia
esophagus, 1292
gallbladder, 1434
intestinal, 1186
nephrogenic, bladder, 1185
nephrogenic, prostate, 1226
prostate, 1225–1226
urinary bladder, 1184–1186
Metaplastic carcinomas, 314, 987–988
Metaplastic changes, breast, 968
Metaplastic papillary tumor, 1063
Metastases, 391, 528, 787, 1430
Metastasizing leiomyoma, benign, 960
Metastasizing pleomorphic adenoma, 771
Metastatic
adenocarcinoma, 323–324, 332–333
bone disease, 709
carcinoid, 324
carcinoma, 304, 310, 335
disease, 485, 528, 812
esophagus, 1299
malignancy from infraclavicular primary to submandibular gland, 787t
tumors, 857, 890, 1090, 1094
Methane, 121
Methanol, 127, 396, 415
Methotrexate toxicity, 417
Methylmalonic acidemia, 63
Microadenomatous hyperplasia (primary pigmented nodular adrenocortical disease), 661–662
Microaerotolerant, histotoxic species, 179–180
Microbiology, molecular diagnosis in, 30–34
Microcalcifications, lung, 967
Microcystic adnexal carcinoma, 550–551
Microdeletion syndromes, 42–45
Microfilaria (tissue roundworms), 224–228
Microglandular adenosis (MGA), 970
Microglandular endocervical hyperplasia, 1025–1026
Microglandular hyperplasia, 273
Microglial activation (rod cells, microglial nodules), 363
Microinvasive breast carcinoma, 978
Microscopic hemangioma, breast, 996
Microsporidia, 215–216
Microvenular hemangioma, 572
Migrational/gyral defects, 411–412
Milia, 535
Miller-Dieker syndrome, 44–45
Minimal change disease (MCD), 1119
Minimal residual disease, 12
Minute pulmonary meningothelial-like lesion (minute pulmonary chemodectoma), 958
Mitochondrial disorders, 83–84
Mitral regurgitation, 903
Mitral stenosis, 903
Mitral valve prolapse, 94–95
Mixed carcinoid-adenocarcinoma, gastrointestinal tract, 1337
Mixed carcinomas, pancreas, 1364
Mixed cell adenocarcinoma, uterus, 1049
Mixed cellularity Hodgkin lymphoma (MCHL), 457–458
Mixed endometrial stromal and smooth muscle tumor, 1054

Mixed epithelial and mesenchymal tumors, 1036, 1056–1058
Mixed epithelial and stromal tumor, kidney, 1170–1171
Mixed epithelial mesenchymal tumors, fallopian tube, 1064
Mixed epithelial neoplasms, kidney, 1169–1171
Mixed oligoastrocytoma, 375
Mixed tumor, malignant, 769–771
Molecular determination of clonality of non-lymphoid malignancies, 18
Molecular pathology assays, guidelines for rational use of, 18
Mollaret meningitis, 334
Molluscum contagiosum, 208–209, 268, 1004, 1276
Mönckeberg's medial calcific sclerosis, 909
Mondor's phlebitis, 1277
Mongolian spot, 576
Monoclonal gammopathy of undetermined significance (MGUS), 525
Monomorphic adenomas, types of, 765t
Morbilliform drug eruption, 620, 621
Morphea, 627
Morphologic classification, 1119t
Morton's neuroma (localized interdigital neuritis), 745
Motor neuron disease, 402–403
Mountain sickness, 122–123
Mucinous
  adenocarcinoma, 1033–1034, 1048, 1238–1239, 1337
  change, uterus, 1043
  (Colloid) carcinoma, breast, 313, 983
  cystadenocarcinoma, 326
  cystadenoma, 326, 943
  cystic neoplasms, pancreas, 324, 1355–1356
  eccrine carcinoma, 551
  metaplasia, 969, 1225
  tubular carcinoma, 1164
  tumors, 151, 1079–1080
Mucocele, 791–792, 791t, 816, 967–968
Mucocutaneous Lymph Node syndrome. *See* Kawasaki's disease
Mucoepidermoid carcinoma, 306, 551, 777, 945
Mucolipidoses, 70–71
Mucopolysaccharidoses, 69–70, 71t, 689
Mucopolysomal disorders, 417
Mucormycosis (phycomycosis), 939
Mucor species, 189
Mucosal melanotic macules, 576
Mucosal neuroma, 745
Mucous extravasation phenomena (mucocele/ranula), 801
Mucous membrane (cicatricial) pemphigoid, 800
Mucus gland adenoma, 943
Multiple endocrine neoplasia type 1, 80
Müllerianosis, 1187
Müllerian papilloma, 1014, 1028–1029
Multicentric reticulohistiocytosis, 561–562
Multifocal intestinalized pangastritis, 1304
Multifocal osteosarcoma, 694
Multi-infarct dementia, 396, 398
Multilocular cystic renal cell carcinoma, 1159–1160
Multilocular peritoneal inclusion cysts (multicystic benign mesothelioma), ovary, 1091–1092
Multilocular thymic cyst (acquired [reactive] process), 872
Multiple endocrine neoplasia types 2A, 2B (MEN2A and MEN2B), 80–81
Multiple follicular cysts, ovary, 1072–1073
Multiple pregnancy, 1114–1115
Multiple sclerosis (MS), 404–405
Multistep carcinogenesis: the colorectal cancer (CRC) paradigm, 28–29
Multisystem atrophy (MSA), 402
Musculoskeletal neoplasms, 689–709
Musculoskeletal neoplasms, staging of, 709
Mutational analysis, 13
Mycobacterial tuberculosis (TB), 936–937
Mycobacterium
  avium-intracellulare, 488
  infection, 1380
  species, 184
Mycoplasma pneumoniae, 938
Mycosis fungoides (MF)
  bone marrow, 520
  with follicular mucinosis, 584
  lymph node, 452–453
  skin, 583–584
Mycotic ulcers, 843
Myelocytic (granulocytic sarcoma) leukemia, 149
Myelodysplastic/myeloid proliferative diseases, 20, 512–514
Myelodysplastic syndromes, 480, 509–512, 511t
Myeloid dysplastic syndrome (MDS), 20
Myelolipoma, 666
Myelomeningocele, 410
Myelomonocytic leukemia, 149
Myeloproliferative disorders (MPD), 479–480, 495, 499
MYH-associated polyposis, 76–77
Myiasis, 228
Mycobacteria, 1275
Myocardial ischemia (approximate), sequence of certain microscopic changes in, 898t
Myocarditis, 94, 900
Myocardium, 898–901
Myoclonic epilepsy *See* Lafora's disease
Myoepithelial carcinoma, 771–772
Myoepithelial lesions, 994–995, 995t
Myoepithelioma, 763–765
Myoepitheliosis, breast, 994
Myofibroblastoma, 974
Myofibroma/myofibromatosis, 566
Myositis, 565, 715
Myositis ossificans, 679, 752
Myospherulosis, 816
Myotonic dystrophy, 48
Myxoid liposarcoma, 732
Myxoid medial degeneration, 909–910
Myxoma, 754–755, 905–906, 1089

Nabothian cyst, 1026
Naegleria fowleri, 216
Nail-Patella syndrome, 1132–1133
Nasopalatine cyst, 806
Nasopharyngeal angiofibroma, 819
Nasopharyngeal carcinoma, 307, 823
Natural killer (NK) leukemias and lymphomas, bone marrow, 522–523
Navicular cells, 269
Near drowning, 122
Necator americanus, 221
Neck compression, 116–118
Necrobiosis lipoidica, 625
Necrotic pseudoxanthomatous nodule, 1094
Necrotizing
  capillaritis, 932
  fasciitis (gangrene), 161–162
  granulomatous lymphadenitis, 314, 425, 430–431
  non-granulomatous lymphadenitis, 425, 431
  sarcoid granulomatosis (NSG), 932
  sialometaplasia, 788, 801–802
Neisseria gonorrhoeae, 176
Neisseria meningitidis, 176–177
Nelson's syndrome, 418
Nematodes (roundworms), 221–224
Neonatal adrenoleukodystrophy, 69
Neoplasia, 1351–1360, 1351–1365
Neoplasiatransplantation pathology, 235–237
Neoplasms, 146–152
  benign
    jaws, 809
    larynx and trachea, 826
    nasal cavity, paranasal sinuses, and nasopharynx, 817–819
    oral cavity, 802
    urothelial, 1191–1192
    vascular, 571–573
  of the bladder, 1191–1212
  breast, 972–975
  B/T-cell, 425, 431–433
  epithelial, breast, 972–973
  hepatobiliary disease, 1385
  mediastinal, 873–874
  mesenchymal, 387
  metastatic to heart, 908
  not limited to thymus, 882–890
  ovary, 1076–1077
  pre-invasive ductal, 1357t
  pre-malignant/malignant, 802–805, 826–829
  serous membrane, ovary, 1091
  soft tissue, 554–568
  testis, 1257–1267
  thymus, 874–881
  thyroid gland, 643–651
  ultrastructural features of, 146–152
Neoplastic
  adenomas, 1334–1337
  epithelial, 1293
  lung disease, 942–961
  mesenchymal, 1297–1298
  miscellaneous tumors, esophagus, 1298–1299
  stomach anomalies, 1299–1312
Neoplastic lesions
  benign, salivary glands, 305–306
  head and neck, 307
  respiratory, 301–303
  thyroid, 309–310
Nephroblastomatosis, 1148
Nephroblastoma (Wilms' tumor), 1148–1150
Nephrogenic rests, 1148
Nephrotoxic injury, kidney, 1138–1139
Nerve sheath myxoma (NSM), 557
Nerve sheath tumors, 882
Nesidioblastosis, 1348
Neural-derived tumors and proliferations, 555–558
Neural tube defects, 410
Neural tumors, 318–319, 744–751, 745t
Neurilemoma (schwannoma), 974–975
Neuroaxonal dystrophy, 404
Neuroblastoma
  adrenal gland, 671–673
  mediastinum, 882
  soft tissue, 318
  staging, 1151
Neurodegenerative disorders, the minimalist's approach, 399t
Neuroectodermal tumors, uterus, 1058
Neuroendocrine
  carcinoma, 822

derived tumors, 553
neoplasm, 150
tumors, 949–961, 1035
Neurofibroma, 746
bladder, 1212–1213
mediastinum, 882
skin, 555
soft tissue, 318
Neurofibromatosis type 1 (von Recklinghausen), 57–58
Neurofibromatosis type II, 58
Neurogenic tumors, 882, 954–955
Neuroleptic Malignant syndrome, 125–126
Neuroma, circumscribed, 745
Neuronal tumors, derivations/definitions used in, 379
Neuropathic arthropathy (Charcot's joints), 684
Neuropathology
anoxic disorders, 393–398
chromosomal syndromes, 413
general reactions to injury, 363–364
gliomas, 364–379
glioneuronal neoplasms, 379–385
infectious diseases, 404–410
inflammatory diseases, 404–410
ischemic disorders, 393–398
malformations, 410–413
meningeal neoplasms, 385–388
neurodegenerative disorders, 398–404
neuronal neoplasms, 379–385
non-glial neoplasms, 388–391
pediatric, 410–414
seizure, 410–414
sellar/suprasellar pathology, 417–420
toxic/metabolic disorders, 415–417
trauma, 392–393
vascular disorders, 393–398
Neuropathy, 415
Neurosarcoidosis, 406
Neurosyphilis, 407
Nevus
anemicus, 569
atypical, 578
comedonicus, 539
depigmentosus, 576
flammeus, 568
of ito and ota, 577
lipomatosus superficialis, 555
sebaceous, 544–545
New variant CJD (nvCJD), 401
Nicotine stomatitis, 806
Niemann-Pick, type C (NP-C), 73
Niemann-Pick, types A and B, 73
NIH GIST, workshop classification, proposed, 1310t
Nipple lesions, 993–994
NK-cell neoplasms, 27
Nocardia species (nocardiosis), 165–166
Nocardiosis, 165
Nocardiosis, lung, 936
Nodal marginal zone B-cell lymphoma, 440
Nodal marginal zone lymphoma, spleen, 474
Nodal MZL, 24
Nodular fasciitis, 317, 565, 714
Nodular fibrous periorchitis, 1269
Nodular goiter, 308–309
Nodular hidradenoma (clear cell hidradenoma, solid-cystic hidradenoma, and eccrine acrospiroma), 548
Nodular hyperplasia, 640–641
Nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL), 27, 455, 477–478, 523–524
Nodular lymphoid hyperplasia (pseudolymphoma), 955
Nodular malignant melanoma, 581
Nodular or diffuse infiltrates, 625–626
Nodular regenerative hyperplasia, 1430–1431
Nodular sclerosis Hodgkin lymphoma, 457
Nodular vasculitis (erythema induratum), 628
Non-gynecologic cytology, overview, 296–298
Non-Hodgkin's lymphoma, 708
Noninfectious granulomatous inflammation, ovary, 1071
Non-necrotizing granulomatous lymphadenitis, 315
Nonneoplastic disease, reactive, 808
Non-neoplastic diseases, 613, 918–942, 967–972
Non-neoplastic disorders, 790t, 869–874
Non-neoplastic hyperplasias, 1300–1303
Non-neoplastic lesions
fallopian tubes, 060–1062
head and neck, 306–307
salivary glands, 305
testis, 1249–1256
thymus, 872–873
uterus, 1022–1027, 1041–1043
Non-odontogenic cysts/pseudocysts, jaws, 806–813
Nonopportunistic infection, 234
Non-tuberculous mycobacteria, 937–938
Nontyphoidal *Salmonella* infections, 169–171
Nonviral infection, hepatobiliary disease, 1378–1383
Nora's lesion *See* Bizarre parosteal osteochondromatous proliferation, 697
Nuchal fibroma, 717
Nucleic acid isolation and purification, 30
Nucleus, 136
Null cell (IP-) adenomas, 419
Nummular dermatitis (nummular eczema), 614

Obesity and diabetes mellitus, 1388
Obstruction of airway, 118–120
Odontogenic disorders, 807–808, 811
Olfactory neuroblastoma, 307, 821
Olfactory neuroblastoma (WHO Grade III), 384
Oligodendroglioma, 373, 375
Onchocerca volvulus, 224–225
Onchocerciasis, 842
Oncocytic carcinoma, 772
Oncocytic cyst, 825
Oncocytoma, 150, 327, 666–667, 765–767, 1155–1157
Oncocytosis, 788
I-cell disease, 70
Opiates, 129
Opportunistic infection, 234
Optically clear nuclei, 1040
Oral cavity, 537, 566, 798–806
Orbital tumors, 862–866, 863t
Orchidoepididymitis, granulomatous, 1251–1253
Organic acidemias, 61–63
Organophosphates, 133
Oro/hypopharynx, 813–814
Osler-Weber-Rendu syndrome *See* Hereditary hemorrhagic telangiectasia
Ossifying fibroma, 800
Ossifying fibromyxoid tumor, 755
Osteitis (sclerosing osteomyelitis), 682
Osteoarthritis (OA), 683–684
Osteoblastic neoplasms (osteoma, osteoblastoma, osteosarcoma), 150–151
Osteoblastoma, 691–692
Osteochondritis "juvenilis," 681
Osteochondroma (osteocartilaginous exostosis), 696–697
Osteochondromyxoma, 699–700
Osteoclast-like giant cells, carcinoma with, 985–986
Osteogenesis imperfecta, 51, 52t, 688–689
Osteoid osteoma, 691
Osteoma cutis, 752
Osteomyelitis, 158, 173, 681
Osteonecrosis (avascular, aseptic, ischemic necrosis), 680–681, 688
Osteoporosis, 685–686
Osteosarcoma, 320, 692, 812
Ovarian
cancer, 77–78
cysts, 1091
cytology, 325–327
fibromatosis, 1075
neoplasms, immunohistochemical profiles in, 1076t
Remnant syndrome, 1072
surface epithelial neoplasms, 151
thecal metaplasia, 662
tumors, 1089, 1268–1269
Ovary, 1071–1090

Pachygyria, 411
Pagetoid reticulosis, 584
Paget's disease, 687–688, 993, 1010–1011
Painless thyroiditis *See* lymphocytic thyroiditis
Palisaded encapsulated neuroma, 556, 806
Palisaded myofibroblastoma, 461, 733
Palisading granulomatous dermatitis, 625
Palpable hemangioma, 996
Pancreas, 1348, 1365–1366
acinar metaplasia, stomach, 1300
and islet cell transplantation, 253–254
cytology, 324–325
in metabolic and other medical disorders, 1348–1349
neoplasia, 1354t, 1359–1363, 1362t
tumors, 1365
Pancreatitis, 324, 1349–1350
Pancreatoblastoma, 1364–1365
Panmyelosis with myelofibrosis, 506
Panniculitis, 627–629
Panophthalmitis, 837
Papillary
adenoma, 942, 1155
carcinoma, 309, 645–647, 990, 1284
craniopharyngioma (WHO Grade I), 390
cystadenoma, 1267
cystadenoma lymphomatosum, 305–306
eccrine adenoma, 547
endocervicitis, 1022
endothelial hyperplasia (Masson's tumor), 737
fibroelastoma, 906
hyperplasia, 1434
lesions, breast, 989
renal cell carcinoma, 328, 1160–1161
serous adenocarcinoma, 277
serous cystadenocarcinoma, 326
squamous cell carcinoma, 814, 828, 1031–1032
urethritis, proliferative, 1228
urothelial tumors, non-invasive, 1194–1197
Papilloma, 106, 990, 1191–1192
Papillomatosis, 942, 1277–1278
Pap test, adequate, 266–267
Paracoccidioides brasiliensis, 193–196
Paracortical hyperplasias, 425, 429
Paradoxical undressing, 124
Paraganglia, prostate, 128
Paraganglioma, 151

bladder, 1215
head and neck cytology, 307
heart, 907
mediastinum, 882–883
neuropathology, 381–382
Paragonimiasis (lung fluke), 941
Paragonimus westermani, 227–228
Parakeratosis (PK), 269
Paraneoplastic encephalomyelitis, 406
Paraneoplastic pemphigus, 597–599, 604
Paraphimosis, 1277
Paraproteinemia, 1126–1129
Parasites, 211–228, 409–410
Parasitic diseases, 1024
Parasitic infections, 1276
Parathyroid gland, 651–656
Paratubal cysts, 1062
Parosteal osteosarcoma, 695–696
Paroxysmal nocturnal hemoglobinuria (PNH), 530
Parvovirus B19, 209
Patau syndrome. *See* Trisomy
Patau syndrome, 40, 413
Patent ductal artery (patent ductus arteriosis, PDA), 897
Pathogen detection, PCR *vs* culture and/or serology, 31
Paucity of intrahepatic bile ducts, 1394
Pearly penile papules, 566
Pediatric fibrous tumors, 717–719
Pediatric interstitial Lund disease, 920
Peliosis, spleen, 483
Peliosis hepatis, 1433
Pemphigus, 593
erythematosus, 596
foliaceus, 594–596
variants, 593
vulgaris, 593–594, 800
Penetrating wound, 392
Penicillium marneffei, 189–191
Penile intraepithelial neoplasia, 1278
Penis
benign conditions, 1274–1278
cancer, 1279–1284
congenital anomalies, 1274
inflammatory conditions, 1274–1278
putative precursor lesions of the, 1278–1279
Peptostreptococci, 183
Perforating wound, 392
Pericardial cyst (coelomic cyst), 871
Pericardial effusion, 901
Pericarditis, 901
Pericardium, 901
Periductal stromal sarcoma, 992
Perifollicular fibroma, 543
Perilobar nephrogenic rests (PLNR), 1148
Perinatally acquired pneumonia, 162
Perineurioma, 557–558, 747–748
Periosteal osteosarcoma, 695
Peripheral separation (marginal abruption), 1109
Peritoneal fluid, cytology, 331–333
Peritoneal leiomyomatosis, 733
Peritoneum, 1090–1094
Perivascular dermatitis, 621–623
Perivascular infiltrate, 623–625
Perivascular tumors, 575, 742–743, 1054–1055
Perivenous encephalomyelitis, 405
Periventricular leukomalacia (PVL), 413
Perivenular fibrosis, progressive, 1387
Peroxisomal disease, 69
Peroxisomal disorders, 417
Persistent hyperplastic primary vitreous, 835–836
Peutz-Jeghers syndrome, 81
Peyronie's disease, 1277
Phacoantigenic endophthalmitis, 839
Phaeohyphomycosis, 199
Phakomatosis pigmentovascularis, 568
Pharyngitis, 161
Phencyclidine (PCP), 130
Phenothiazine, 131
Phenylketonuria (PKU), 58–59
Pheochromocytoma, 151, 667–668
Phimosis, 1277
Phthisis bulbi, 840
Phycomycosis, 300
Phyllodes tumor, 314, 992, 1243
Pick's disease (lobar atrophy), 401
Piebaldism, 576
Piedraia hortae, 196–197
Pigmented spindle cell nevus of reed, 578
Pigmented terminal hair cyst, 536
Pilar and pilosebaceous-derived tumors, 541–545
Pilar sheath acanthoma, 541
Pilocytic astrocytoma (WHO Grade I), 370–371
Pilocytic gliosis, 363
Piloleiomyoma (pilar leiomyoma), 559
Pilomatrixoma (calcifying epithelioma of Malherbe), 316, 543
Pindborg tumor *See* Calcifying epithelial odontogenic tumor
Pineal parenchymal tumors, 379–380
Pineoblastoma, 380
Pineocytoma, 379–380
Pinguecula, 846
Pinworm *See* Enterobius vermicularis
Pituitary adenoma, 419
Pituitary adenomas, 417–419
Pityriasis, 615–617
Pityriasis lichenoides et varioliformis acuta (PLEVA), 623
Placenta, 1102–1114
Plague, 170
Plasma cell, 524–526
neoplasms, 26, 438
vulvitis, 1003
Plasmacytoma
breast, 998
immunodermatology, 583
lung, 957
testis, 1266
Plasmodium species, 216–217
Pleomorphic
adenoma, 305, 763, 973
fibroma, 565
lipoma, 554, 730
lipsarcoma, 732
rhabdomyosarcoma, 736–737
small/medium-sized cutaneous T-cell lymphoma, 585–586
xanthoastrocytoma (PXA) (WHO Grade II-III), 371–372
Pleura, tumors of the, 960–961
Pleural fluid, cytology, 331–333
Plexiform fibrohistiocytic tumor, 561, 725–726
Plexiform neurofibroma, 747
Plexogenic arteriopathy, 933
Pneumoconiosis, 929
Pneumocystis jiroveci, 201–203, 940
Pneumocystitis carinii (PCP), 301
Pneumomediastinum, 874
Pneumonia, 299
Poliomyelitis, 409
Polyarteritis, 912, 1391
Polyarteritis nodosa (PAN), 629, 912
Polycystic disease, 1395
Polycystic ovarian disease (POCD), 1072–1073
Polycythemia vera (PV), 497
Polyembryoma, 1084
Polymerase chain reaction (PCR), 5–6
detection of IgH and TCR, 16–17
dHPLC screening assay, 8
as microbiologic detection tool, 30
PCR-RFLP assay, 6–7
polymerase chain reaction (PCR)-FRET, 7
products, detection of, 30
semi-automated, product detection, 31
tests for infectious agents, 31
Polymicrogyria, 411
Polymorphic reticulosis, 956–957
Polymorphous low grade adenocarcinoma, 306
Polyomavirus, 209
Polyorchidism, 1249–1250
Polypoid adenomyoma, 1056
Polyps, gallbladder, 1433–1434
Polyps, nasal cavity, paranasal sinuses, and nasopharynx, 816–817
Pompholyx (dyshidrotic eczema), 614
Pontomedullary transection (brainstem avulsion), 392
Porencephaly, 412
Porocarcinoma (malignant eccrine poroma), 549
Porphyrias, 604–606, 1404–1406
Porphyromonas species, 182–183
Positional asphyxia, 120
Post-atrophic hyperplasia, prostate, 1226
Post-cholecystectomy syndrome, 1411
Post-infectious glomerulonephritis (PIGN), 1123–1124
Post-inflammatory hyperpigmentation, 575
Post-inflammatory pigment alteration, 622
Post-mortem chemistry, 92
Post-streptococcal glomerulonephritis, 161
Post-surgical granuloma, 1180
Post-transplantation infection cytomegalovirus, 905
Post-transplant lymphoproliferative disorder, 236
Pox virus *See Molluscum contagiosum*
Prader-Willi syndrome, 43
Pregnancy
luteoma, 1073
related changes, 269–270, 1039
Prevotella species, 182–183
Priapism, 1277
Primitive neuroectodermal tumor (PNET), 151, 318, 756–757, 1017
Proctitis, radiation, 1326–1327
Progressive multiform leukoencephalopathy (PML), 409
Prolactinoma (lactotrophic adenoma), 418
Prolymphocytic leukemia (PLL), 475
Propionic acidemia, 62–63
Prostate
cancer, 1237t
immunohistochemical profiles of, 1225t, 1236t
treatment effects, 1244–1245
Prostatic adenocarcinoma, 1232–1242
Prostatic urethral polyp, 1228
Prostatitis, 1221
Prosthetic valves, 903
Prothrombin G20210A mutation, 12
Prototheca wickerhamii, 203
Protozoa, 211–220
Protozoal diseases, uterus, 1024
Psammocarcinoma, 1079
Pseudallescheria/scedosporium, 191

Pseudoangiomatous hyperplasia, 995–996
Pseudocyst, 324, 1091, 1350–1351
Pseudo-hurler polydystrophy, 70–71
Pseudo-hyperplastic pattern of carcinoma, 1241
Pseudo-Kaposi's sarcoma, 571
Pseudo-membranous colitis, 1320
Pseudomonas, 173
Pseudomyxoma peritonei, 1094
Pseudopelade (idiopathic scarring alopecia), 632
Pseudo-tumors, inflammatory, 790
Psoriasiform dermatitis, 616–618
Psoriasis vulgaris, 616–618
Psychoactive drugs, 130–131
Pterygium, 846
Pulmonary
  allograft rejection, histologic grading of, 941–942
  alveolar proteinosis, 928
  amyloidosis, 959
  capillary hemangiomatosis, 934
  disease, 165
  Hodgkin's disease, 957
  hyalinizing granuloma, lung, 959
  hypertension, 933–934
  infarct, 299
  lymphangiomatosis, 919
  manifestations of graft *vs* host disease, 256t
  neuroendocrine tumors, 303
  sequestration, 918
  stenosis, 897
  thromboembolism, 95–96
  veno-occlusive disease, 933
Purine metabolism disorders, 68
Purkinje cell necrosis (cerebellar cortex), 394
Pustular psoriasis, 616
Pyelonephritis, 1137
Pylephlebitis, 1390–1391
Pyogenic granuloma, 570
Pyogenic infection, 1378–1379
Pyogenic osteomyelitis, 681–683

Quantitative RT-PCR, 13

Rabies, 209–210, 409
Radiation, 269, 299, 1245
Rasmussen's encephalitis, 414
Rathke's cleft cyst, 419
Real-time quantitative reverse transcription PCR, 8
Reflex sympathetic dystrophy (algodystrophy), 680
Reflux esophagitis, 320
Refractory anemia (RA), 509–511
Regressed tumor, testis, 1263
Renal
  cell carcinoma (RCC), 1157–1166
  Cholesterol microembolism syndrome, 1142
  dysplasia, 1143
  epithelial neoplasms, 1157t
  medullary carcinoma, 1164
  neoplasms, 1148–1171, 1169–1171
  neuroblastoma, 1150
  peripheral neuroectodermal tumor (PNET), 1150–1151
  synovial sarcoma, 1150
Renomedullary interstitial cell tumor (medullary fibroma), 1168
Renovascular hypertension (renal artery stenosis), 1140–1141
Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), 922–923
Respiratory cytology, 298–304
Respiratory syncytial virus, 210, 935
Restrictive cardiomyopathy, 94
Rete ovarii (rete adenoma/cyst), 1074
Reticulohistiocytoma, 561–562, 723–724
Retiform hemangioendothelioma, 573
Retinoblastoma (RB), 81–82, 335, 384–385, 854–855
Retinopathy of prematurity (retrolental fibroplasia), 835
Retroplacental hemorrhage, 1108–1109
Revolvers, 110–111
Reye's syndrome, 1409–1410
Rhabdoid tumor of kidney, 1150, 1154–1155
Rhabdomyoma, cardiac, 907
Rhabdomyomatous mesenchymal hamartoma, 734
Rhabdomyosarcoma
  alveolar and embryonal, 151
  bladder, 1213
  nasal cavity, paranasal sinuses, and nasopharynx, 822–823
  orbit, 864–865
  soft tissue, 319, 735
  spermatic cord, 1269–1270
Rheumatic fever, 161
Rheumatic heart disease, acute, chronic, 901–2
Rheumatoid arthritis (RA), 426–427, 685
Rheumatoid nodule, 625
Rheumatoid pleuritis/pericarditis, 332
Rhinosporidium seeberi, 203–204
Rhinosporiosis, 849
Rhizopus species, 189
Rhodococcus equi, 166–168
Rickets and osteomalacia, 686
Rickettsial infection, 1380
Rickettsia rickettsii, 186–187
Rifles, 114
Rigor mortis (rigidity), 90
Ring abscess, 842
Ring ulcer, 842
Ritter disease, 158
Rocky mountain spotted fever (RMSF), 186–187
Rosai-Dorfman disease, 459–460
Roundworms *See* Nematodes
Ruptured berry aneurysm, 96

Salivary duct carcinomas, 306, 777–779, 778t
Salivary duct cysts, 806
Salivary gland, secondary cysts, 791
Salivary glands, 304–306, 787t
  carcinomas, 783t
  cysts, 304–307, 790
  tumors, 764t, 784t, 785–787, 786t
Salmonella typhi (Typhoid fever), 169–170
Salmonellosis, gastrointestinal tract, 1319
Salpingitis, 1060
Salpingitis isthmica nodosa, 1061
Sandfly vector (phlebotomus), 186
Sandhoff disease, 72–73
Sarcocystis, 217
Sarcoidosis
  conjunctiva, 849
  hepatobiliary disease, 1408–1409
  lung, 927–928
  nasal cavity, paranasal sinuses, and nasopharynx, 816
  repiratory cytology, 300
  testis, 1253
Sarcomas, 28
  botryoides, 1013, 1017
  ovary, 1089
  salivary glands, 785t
  soft tissue fibrous tumors, 715
  spermatic cord, 1269–1270
  thymic, 881
  undifferentiated
    endometrial, 1054
    liver and biliary system, 1428–1429
Sarcomatoid carcinoma, 804, 827–828, 1211, 1240
Sarcoptes scabiei, 228
S. aureus endocarditis, 158
Scabies, penis, 1276
Scalp injuries, external, 105
Scarlet fever, 161
Schamberg's disease, 622
Schistosoma species, 228
Schistosomiasis, 1180–1181, 1383
Schwannoma, 151
  breast, 974
  head and neck cytology, 307
  mediastinum, 882
  skin, 555–556
  soft tissue, 318, 745–746
Scleroderma, 626–627, 1329–1330
Sclerotic fibroma, 565
Sclerotic ulegyria, 412
Scuba diving, 122
Sebaceous gland
  adenoma, 545, 768
  carcinoma, 545, 773, 860
  epithelioma, 545
  hyperplasia, 545
  lymphadenoma, 767
  metaplasia, esophagus, 1293
Seborrheic dermatitis, 615
Seborrheic keratosis, 538, 1006–1007
Seizure-associated pathology, 413–414
Selective neuronal necrosis, 394
Seminal vesicles, 1227
Seminoma, 15, 884, 1258–1260
Senile seminal vesicle amyloidosis, 1227
Septicemia, 158, 172–173
Septic spleen, 487
Sertolic cell tumor, 151, 1264–1265
Sexual development, abnormalities of, ovary, 1071
Sézary syndrome (SS), 452–453, 520, 584–585
Shaken baby syndrome (SBS), 109–110
Shigella species (cause bacillary dysentery), 169
Shigellosis, 1319
Shotguns, 112–114
Sialadenitis, 305, 788
Sialadenosis, 305, 788
Sialoblastoma, 785
Sialolithiasis, 787–788
Sickle cell anemia, 55, 1406
Signet ring cell carcinoma, prostate, 1239
Silent corticotroph adenoma, 418
Silicone reaction, breast, 971–972
Silicosis, 929–930
Simple cyst, kidney, 327
Single-gene disorders, 46–58
Sinonasal neoplasm, 804t
Sinonasal papilloma, 818
Sinonasal undifferentiated carcinoma (SNUC), 821
Sinus histiocytosis, 998
Sinus histiocytosis with massive lymphadenopathy (SHML), 459–460
Sinus hyperplasias, 425, 428
Sinusitis, 814
Sinusoidal dilatation, 1385
Sjögren's syndrome, 789
Skeletal angiomatosis, 701–702
Skeletal disorders, 50–51
Skeletal muscle tumors, 734–737, 735t

Skeletal trauma and other common conditions, 679–681
Skene's duct cyst, 1005–1006
Skin
  adnexal tumors, 994
  cytology, 316
  pigmentary disorders of the, 575–576
Skull fracture, 105–106, 392
Small B-cell lymphoproliferative disorders, 436t
Small bowel transplantation, 257–258
Small cell carcinoma, 303–304
  anus, 1344
  bladder, 1211
  esophagus, 1297
  gastrointestinal tract, 1337
  larynx and trachea, 828
  lung, 890, 948
  ovarian hypercalcemic type, 151–152
  ovary, 1090
  prostate, 1239
  pulmonary type, 151
  salivary gland, 781
  uterus, 1035, 1049
Small cell osteosarcoma, 694
Small lymphocytic lymphoma (SLL), 23–24, 315, 433–434, 471–472
Smallpox *See Variola major*
Small vessel disease/deep infarcts, 396
Smith-Magenis syndrome, 44
Smoke inhalation, 124–125
Smokeless tobacco-induced keratosis, 806
Smooth muscle hamartoma, 558
Smooth muscle tumors, 558–560
  classification of, 733t
  leiomyosarcoma, 952
  soft tissue, 732–733, 732–734
  uncertain malignant potential (STUMP), 1052–1053
  uterus, 1035, 1050–1052
Smothering, 118–119
Soft tissue
  chondroma, 752
  cytology, 317–319
  neoplasms, 554–568
  tumors, bladder, 1212–1214
Solar lentigo, 577
Solid-pseudopapillary neoplasm, 325, 1363–1364
Solitary Rectal Ulcer syndrome (SRUS), 1326
Solitary unilocular cyst, 1394–1395
Southern blotting, 5, 13, 16, 31
Specimen adequacy terminology/reporting, 266–267
Spectral karyotyping (SKY), 13–14
Sperm granuloma, 1267
Sphingolipidoses, 71–76
Spider angioma (nevus araneus), 569
Spina bifida occulta, 410
Spinal and bulbar muscular atrophy (SBMA, Kennedy disease), 49
Spinal cerebellar ataxia (SCA), 49
Spinal cord, subacute combined degeneration of, 415
Spinal cord trauma, 392–393
Spinal muscular atrophy (SMA), 50, 51t, 404
Spindle cell
  carcinoid, 303
  carcinoma, kidney, 1164
  hemangioendothelioma, 573
  hemangioma, 739
  lesions of lymph nodes, 426, 460–462
  lesions of the bladder, 1203t
  lipoma, 554, 729–730
  nodule, post-operative, 1015, 1027, 1188
Spinocerebellar ataxia (SCA), 404
Spirometra species (sparganosis), 220
Spironolactone bodies, 146
Spitz nevus (spindle and epithelioid cell nevus), 579
Spleen
  autoimmune conditions, 489–490
  examination and evaluation of the, 468
  general considerations, 468–469
  hyperplasias, 486
  infections, 487–488
  lymphoid neoplasms, 469–478
  myeloid and related disorders, 478–481
  non-hematopoietic lesions, 481–485
  red blood cell disorders, 486–487
  storage diseases, 488–489
  systemic disorders, 489
  vascular disorders, 483t, 486
Splenic disorders, 490
  ectopia, 469
  gonadal fusion, 1250
  inflammatory pseudotumor, 482t
  marginal zone lymphoma (SMZL), 436–437, 469–471
  MZL, 24
  rupture, 469
Splenomegaly, 468–469, 488
Spongiform encephalopathies (SE), 401
Spongiotic dermatitis, 613–616, 613
Spontaneous splenic rupture: associations and etiologies, 470t
Sporothrix schenckii, 196
Sporotrichosis, 939
Sputum, 298
Squamotransitional cell carcinoma, 1032
Squamous cell abnormalities, 270–272
Squamous cell carcinoma (SCC)
  anus, 1342–1343
  basaloid type, 1282
  bladder, 1207–1208
  Bowen's disease, 540
  breast, 987
  esophagus, 321, 1294–1296
  head and neck, 307
  invasive, 849, 1030–1031
  jaws, 811
  keratinizing/non-keratinizing, 301, 1031
  larynx and trachea, 827
  lung, 946
  microbiology, 152
  nasal cavity, paranasal sinuses, and nasopharynx, 819
  oral cavity, 803
  oro/hypopharynx, 813
  papillary, 804
  penis, 1279–1285
  primary, 781
  prostate, 1239–1240
  sarcomatoid (spindle cell) subtype, 1284
  skin, 316, 540
  uterus, 1031–1032, 1049
  vagina, 1016
Squamous cell hyperplasia, vulva, 1006
Squamous cell papilloma, bladder, 1192
Squamous cells, atypical (ASC), 270–271
Squamous differentiation (squamous metaplasia), uterus, 1043
Squamous dysplasia/carcinoma *in situ*, 802–803, 826–827, 944
Squamous hyperplasia, penis, 1278
Squamous intraepithelial lesions (SIL), 271
Squamous metaplasia
  breast, 969
  prostate, 1225
  urinary bladder, 1184–1185
Squamous papilloma
  esophagus, 1293–1294
  eyelids, 859
  urinary bladder, 1191
  uterus, 1028
Squamous tumors, 810, 1029–1031
Squamous vestibular papillomatosis, 1008
Stab wound, 115
Stafne defect, 813
Staphylococcal scalded skin syndrome (Ritter disease), 158
Staphylococcus aureus, 158–159
Staphylococcus epidermidis and other coagulase-negative staphylococci (CNS), 159–160
Stasis dermatitis, 615–616
Steatocystoma, 535
Steatohepatitic liver disease, 1386–1389
Steatohepatitis, 1386
Steatosis, 322, 1385
Steele-Richardson-Olszewski disease, 402
Stein-Leventhal syndrome, 1072
Stenotrophomonas maltophilia, 173
Stickler syndrome, 53
Stomach, 321, 1299–1312
Strangulation, 116–117
Streptococcus, 161–162
Stroke *See* Cerebral infarct
Stromal
  hyperplasia, 1074, 1222
  luteoma, 1089
  scarring, eye, 841
  tumor, 1088
Strongyloides stercoralis, 222–223
Struma ovarii, 1085–1086
Strychnine, 133
Subacute cutaneous lupus erythematosus (SCLE), 600–601
Subacute gliosis, 363
Subacute lymphocytic thyroiditis, 308
Subacute sclerosing panencephalitis (SSPE), 409
Subacute spongiotic dermatitis, 613
Subacute thyroiditis, 308
Subarachnoid hemorrhage (SAH), 107, 392, 396–397
Subareolar abscesses, 311
Subcutaneous
  lymphoma, 451–452, 586
  morphea, 628
  mycoses, 198–199
Subdural hematoma, 106–107, 392
Subependymal giant cell astrocytoma (SEGA), 372–373
Subependymoma, 376–377
Subscapular hemorrhage, 105
Sudden death from natural disease, 92–101
Sudden infant death syndrome (SIDS), 99–101
Superior limbic keratoconjunctivitis, 847
Surface nodular/papillary stromal proliferation, 1074
Sweet's syndrome, 623
Swimmer's ear *See* external otitis
Sympathetic uveitis, 838–839
Syncytiotrophoblasts, 270
Synovial sarcoma, 152, 319, 568, 743–744, 890
Syphilis, 617, 1379–1380

lymph node, 427
penis, 1275–1276
vulva, 1005
Syphilitic keratitis, 842
Syringobulbia, 413
Syringocystadenoma papilliferum, 551–552
Syringoid eccrine carcinoma (eccrine epithelioma), 550
Syringoma, 546
Syringomatous adenoma, 993–994
Syringomyelia, 413
Systemic hyper/hypothermia, 124–126
Systemic lupus erythematosis (SLE), 431, 601–602, 1129–1130
Systemic mastocytosis, 480–481, 500

Taenia species, 220–221
Tailgut cyst (retrorectal cystic hamartoma), 1094
Takayasu's disease, 911–912
Tamoxifen, 1040
Tancho's nodule and paraffinoma, 1277
Tapeworms *See* Cestodes
T-cell
acute lymphoblastic leukemia (T-ALL), 508–509
histiocyte rich variant, 446
lymphoma, 453–454, 522, 1341–1342
prolymphocytic leukemia (T-PLL), 448–449, 518–519
receptor gene arrangements, 15
Telangiectatic osteosarcoma, 568–575, 694
Telogen effluvium, 630
Temporal arteritis (giant cell arteritis), 912–913
Teratoma, 883–884
mature/immature, 883, 1037
ovary, 1085–1086
testis, 1261–1262
Terminal duct carcinoma (TDC), 778t, 780
Tersinia enterocolitica, 170
Testicular neoplasia, overview of, 1257t
Testicular torsion and infarct, 1250
Testicular "tumor" of Adrenogenital syndrome (TTAGS), 1266
Testis, 1249–1251
Tetanus, 181–182
Tetralogy of Fallot, 897
Thallium, 133
Thermal injuries, 123–126
Thin Glomerular Basement Membrane syndrome, 1134–1135
Thrombic arteriopathy: pulmonary infarction, 934
Thromboangiitis obliterans (Buerger's disease), 913
Thromboembolic diseases, 1141–1143
Thromboembolism, 102
Thrombophlebitis, 629
Thrombosis, venous, 11–12
Thrombotic microangiopathy, 1142
Thymolipoma, 881
Thymoma, 152, 874–879
Thyroglossal duct cyst, 306, 536, 635–636
Thyroid gland, 635–651
carcinoma, 673
cytology, 307–310
neoplasms, 643–651
non-neoplastic conditions, 635–643
tumors, 643t
Thyroiditis, 308, 308, 636
Thyrotrophic adenoma/hyperplasias, 419
Tissue roundworms *See* Microfilaria
T-lymphoblastic leukemia/lymphoma (T-ALL/T-LBL), 432–433
TNM classification
bladder cancer, 1216
colorectal adenocarcinoma, 1344
FIGO staging system, 1038, 1059–1060, 1066
larynx, 829–830
lip/oral cavity, 829
lung cancer, 961–962
orbit sarcoma, 865
pancreatic tumors, 1366
penile cancers, 1285
prostate cancer, 1245
retinoblastoma, 855–857
salivary gland, 792
skin melanoma, 607–608
testicular tumors, 1270
thymoma, 891
uvea melanoma, 852–853
TNM classification of carcinoma
breast, 998
conjunctiva, 849–851
esophageal tumors, 1299t
eyelid, 860–861
lacrimal gland, 862
ovarian, 1094
skin, 608
TNM staging of renal cell carcinoma, 1171–1172
Tonsillar herniation, 364
Tonsillitis, 161
Tori, 813
Torulopsis, 200–201
Total parental nutrition, 1388
Toxic diffuse hyperplasia (Graves' disease), 309
Toxic epidermal necrolysis, 618
Toxicology, 127–133
Toxic shock syndrome (TSS), 158
Toxocara canis (visceral larva migrans), 226–227
Toxoplasma gondii, 217, 941
Toxoplasmosis, 409–410, 426, 905
Tracheobronchopathia osteoplastica, 960
Tracheoesophageal fistula/esophageal atresia, types of, 1288t
Transbronchial FNA, 299
Transitional cell carcinoma (TCC), 152, 1049, 1083
Transitional cell metaplasia, 1025
Transitional cell tumors, 1082–1083
Transplantation, 233–237, 258
Transport disorders, 64–66
Transposition of great arteries, 897
Transudate and exudate, comparison between, 332t
Trauma, mechanical, 101–102
Traumatic asphyxia, 120
Traumatic bone cavity, jaws, 806–807
Traumatic neuroma, 556, 744–745
Traumatic ulcerative granuloma with stromal eosinophilia, 801
Trematodes (flukes), 227–228
Trichilemmal cyst, 536
Trichilemmoma, 542
Trichinella spiralis, 223
Trichoadenoma, 542
Trichoblastoma, 543
Trichodiscoma, 543
Trichoepithelioma, 543
Trichofolliculoma, 541
Trichomonas vaginalis, 217–219, 267
Trichosporon beigelii, 197
Trichotillomania, 630
Trichuris trichiura (whipworm), 224
Tricyclic antidepressants, 131
Trinucelotide repeat disorders, 46–50, 47t
Trisomy, 39–41, 413
Trophoblastic disease, 1065
Trophoblastic tumor, 1101–1102
Tropical Sprue syndrome, 1322
True thymic hyperplasia, 872
Trypanosoma species, 219–220
T(12;21)(p13;q22), 23
Tubal metaplasia, 273, 1024–1025
Tubal prolapse, 1062
Tubercular osteomyelitis, 682
Tuberculosis (TB)
bone marrow, 528
hepatobiliary disease, 1380
lymph node, 430
neuropathology, 407
pleural and peritoneal fluid, 332
spleen, 487
uterus, 1022–1023
Tuberous sclerosis, 58, 414
Tuboendometrioid metaplasia, 1025
Tubular adenoma, 552, 972–973, 1015
Tubular carcinoma, 313, 970t, 982–983
Tubular hyalinization, 1256
Tubulocystic carcinoma, kidney, 1165
Tubulointerstitial diseases of the kidney, 1137–1139
Tubulointerstitial nephritis, 1138
Tubulovillous adenoma, vagina, 1015
Tufted angioma (tufted angioblastoma), 572
Tularemia, 175, 430
Tumoral calcinosis, 753
Tumors
anus, 1342–1344
appendix, 1331
benign, 1008, 1015
epithelial, 942–943, 1062–1063
lung, 942–944
mesenchymal, 943–944, 973–975
mixed (spindle cell epithelioma), vagina, 1015
serous, 1077
borderline, 1063, 1076–1078
histogenesis, 754t, 957–958
immunohistochemical analysis of, 784t
molecular diagnostics of, 28–30
neuroendocrine differentiation, 951
pancreas, 324
salivary gland, 784–787, 945
serus, 151, 1077–1079
sex cord stromal, 1058, 1086–1089, 1263–1266
soft tissue, 753–758
solitary fibrous, 717, 1091
supraclavicular, 787t
surface epithelial-stromal, 1076, 1076t
sympathetic nervous system, 882
synovial, 743–744, 744t
teratoid/rhabdoid, 383–384
thynic, 881
thyroid gland, 643t
urothelial, 1198t
uterine, 1037, 1051t, 1066
vaginal, 1017–1018
Tunga penetrans, 228–229
Tunics, lesions of, 1267–1269
Tunnel clusters, 1026
Turberculosis, 301
Turner syndrome, 41–42
Typhoid fever, 169–170
Tyrosinemia type 1, 59–60

Ulcerative colitis, 1322–1323
Ulcerative jejunoileitis, 1322

Uncal (transtentorial) herniation, 364
Unicameral bone cyst (UBC), 689
Unilocular thymic cyst (developmental origin), 871–872
Unsatisfactory specimen, 267
Urachal abnormalities, 1177
Urachal remnant, 1093
Urea cycle disorders, 61, 61t
Urethral polyp, 1189–1191
Urinary bladder, 328–331, 1201t
Urinary tract infection, 173
Urothelial
  adenocarcinoma, 331
  atypia of unknown significance, 1192–1193
  carcinoma, 330–331, 1194–1207, 1242
  cells, 329
  dysplasia, 1193–1194
  hyperplasia, 1184
  metaplasia, 1225–1226
  papilloma, 1191, 1228
  tumors, 1198t
Urticaria, 606–607, 622
Usual interstitial pneumonia (UIP), 925
Uterine gas gangrene, 178–179
Uterus, 1022–1060, 1043

Vacuolar myelopathy of AIDS, 408
Vagina, 1014–1018
Vaginal adenosis (VA), 1014–1015
Vaginal intraepithelial neoplasia (VAIN), 1015–1016
Varicella-Zoster virus (VZV), 210
Varices, 1292–1293
Varicocele, prostate, 1250–1251
Variola major (smallpox), 210–211
Vascular, 931–934
  malformations, 397–398, 952
  proliferations, 568–575
  stasis, 1111
  tumors
    classification of, 738t
    eye, 857
    immunocompromised patients, 703
    low-grade malignancy, 573–575, 739–740
    related conditions, 952–955
    soft tissue, 737–743
Vascularization, 841
Vascular lesions, breast, 996
Vascular rejection, 237, 941–942
Vasculitides, 931–932
Vasculitis
  blood vessel, 911–913
  breast, 996
  gastrointestinal tract, 1329
  GI tract, types of, 1330t
  immunodermatology, 607
  kidney, 1142–1143
  neuropathology, 398
  non-infectious, 911–913
Vasitis nodosa, 1269
Vasogenic edema, 363
Veno-occlusive disease, 1385, 1389–1390
Venous infarcts, 396
Venous lake, 569
Ventricular septal defect (VSD), 897
Verruciform xanthoma, 801
Verrucous carcinoma (VC)
  larynx and trachea, 827
  oral cavity, 803–804
  penis, 1282–1284
  skin, 540–541
  uterus, 1031
  vulva, 1012
Verrucous leukoplakia, 803
Verumontanum mucosal gland hyperplasia, 1226–1227
Vesicular dermatophytosis, 615
Vibrios, gastrointestinal tract, 1319
Vibrio vulnificus, 172–173
Villitis of unknown etiology (VUE), 1112
Villous adenoma, bladder, 1015, 1211–1212
Viral exanthem, 620
Viral hepatitis, 1371–1378
Viruses, 204–211
Vitiligo, 576
Von Brunn's nests, 1186
Von Hippel-Lindau (VHL), 82
Von Willebrand disease, 56
Vulva, 1003–1014
Vulva condyloma accuminata, 1004
Vulva intraepithelial neoplasia (VIN), 1009–1010
Vulva vestibulitis, 1003

Waldenström macroglobulinemia, 435–436
Walthard nest, 1093
Warthin's tumor, 305–306, 767, 772–773
Warty carcinoma, 1031, 1282, 1284t
Warty dyskeratoma, 538–539
Water cysts. *See* Hydrocystomas
Waterhouse-Friederichsen syndrome, 98
Watershed (borderzone) infarct, 394
Webs and rings, esophagus, 1288
Wegener's granulomatosis, 913, 931–932
Well-differentiated liposarcoma (WDLS), 731
Wells' syndrome *See* Eosinophils cellulitis
Wernicke-Korsakoff syndrome, 415
Western immunoblotting, 587
Whipple's disease, 407, 428–429, 1320–1321
Whipworm See *Trichuris trichiura*
White sponge nevus, 539
William syndrome, 45
Wilms' tumor, 82–83, 328
Wilson's disease, 66, 1402–1403
Wind hypothermia, 124
Worldwide transplants as of 2001, 233t
Wound infections, 172
Wuchereria bancrofti, 225

Xanthelasma, 562-563, 859
Xanthoma, 562–563, 724
Xeroderma pigmentosum, 46

Yeasts, 199–201
Yersinia, 170–171, 430
Yersiniosis, 1319–1320
Yolk sac tumor
  mediastinum, 884
  ovary, 1084
  testis, 1260–1261
  uterus, 1037
  vagina, 1017
  vulva, 1014

Zellweger syndrome, 69
Zollinger-Ellison syndrome, 1302
Zoonotic roundworms, 225–227
Zygomycetes, 300