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Lung

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CONTENTS

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

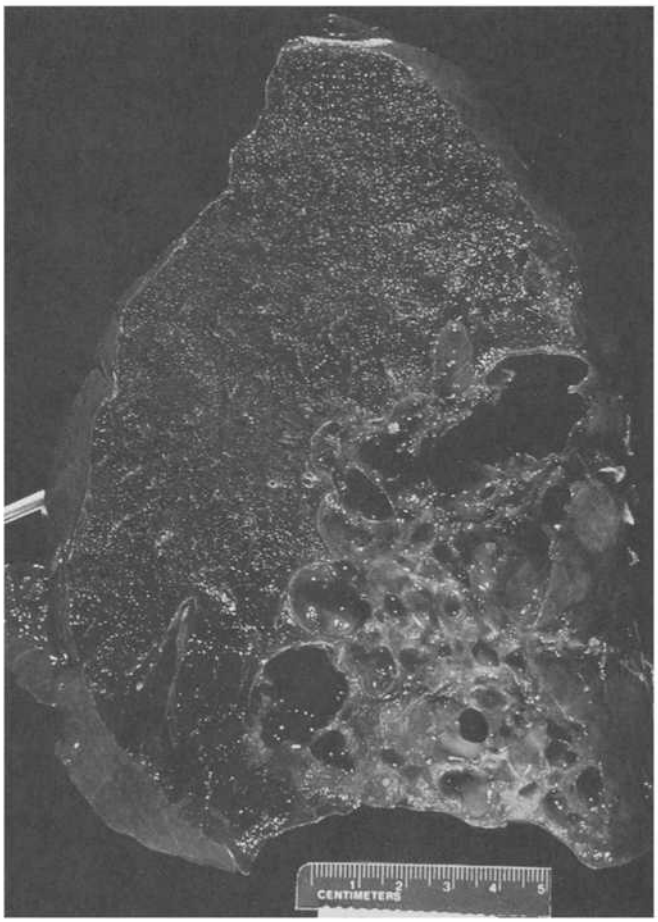


Fig. 1. Intralobar sequestration.

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

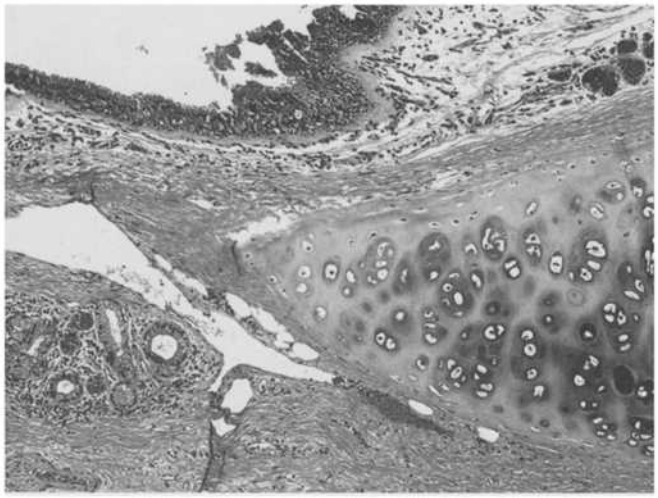


Fig. 2. Bronchogenic cyst.

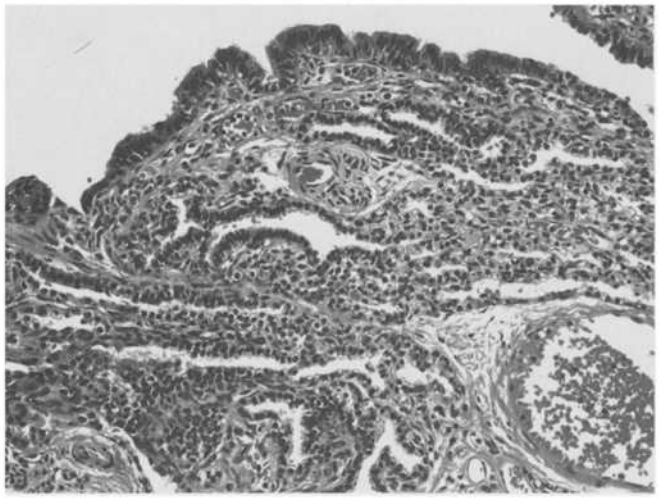


Fig. 3. Type I Congenital cystic adenomatoid malformation.

- 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

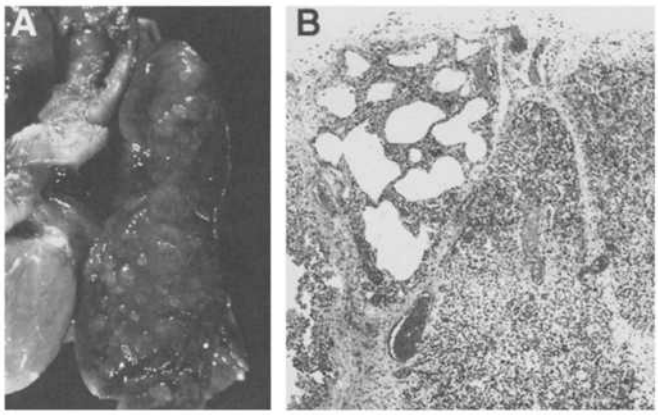


Fig. 4. Bronchopulmonary dysplasia **(A,B)**.

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

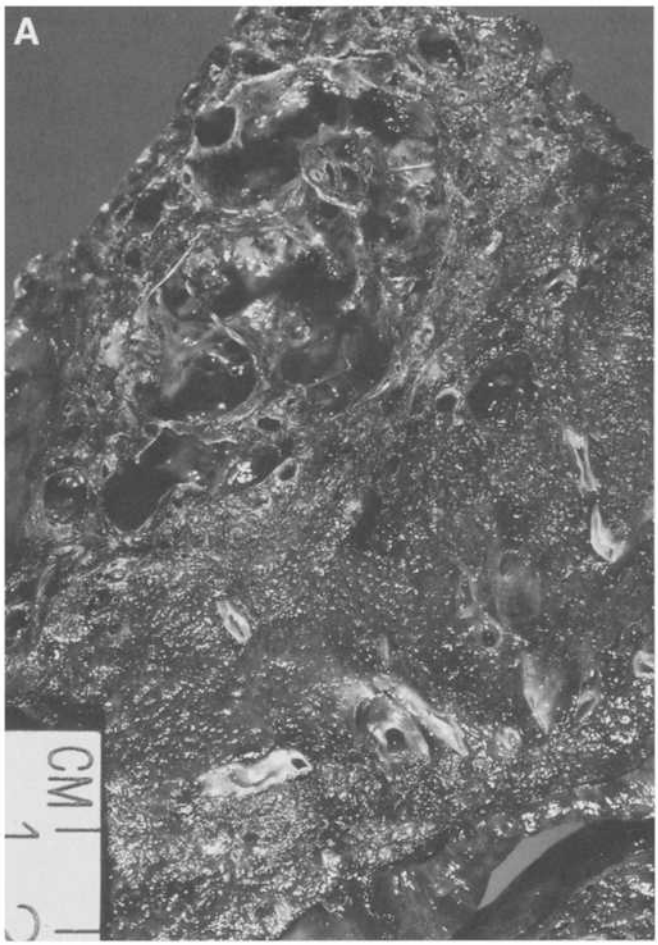


Fig. 5. Emphysema: **(A,B)** centrilobular; **(C)** panacinar.

  - 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

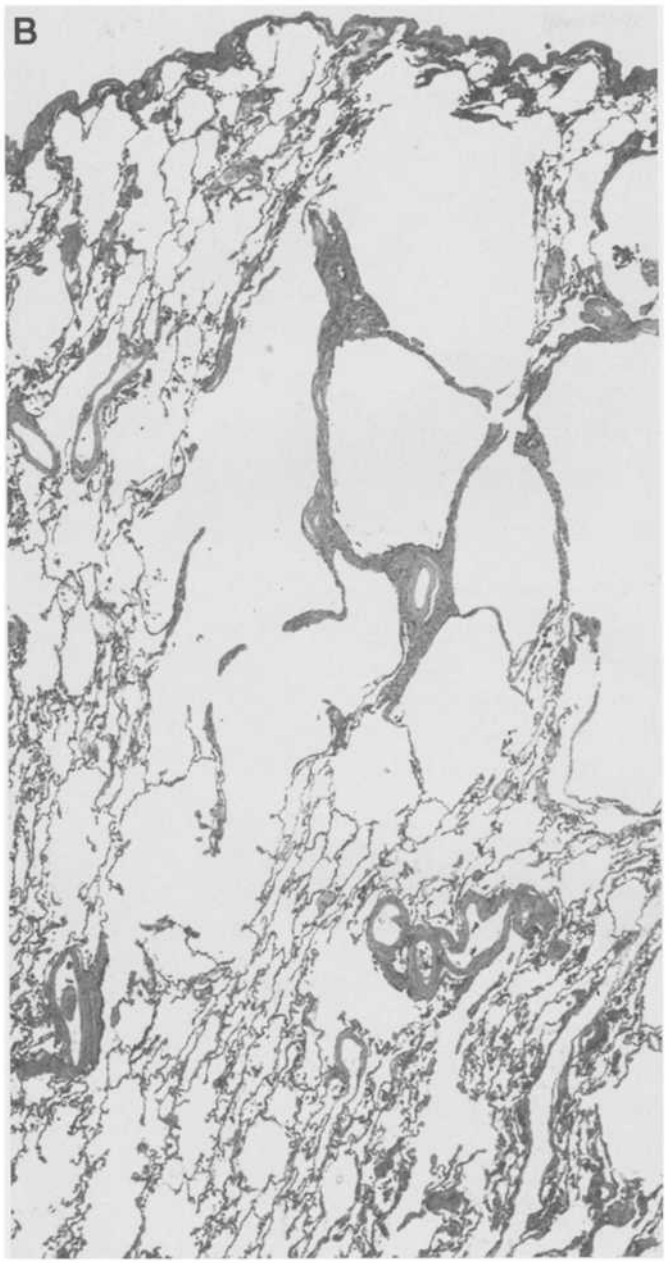


Fig. 5. (*Continued*)

- 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

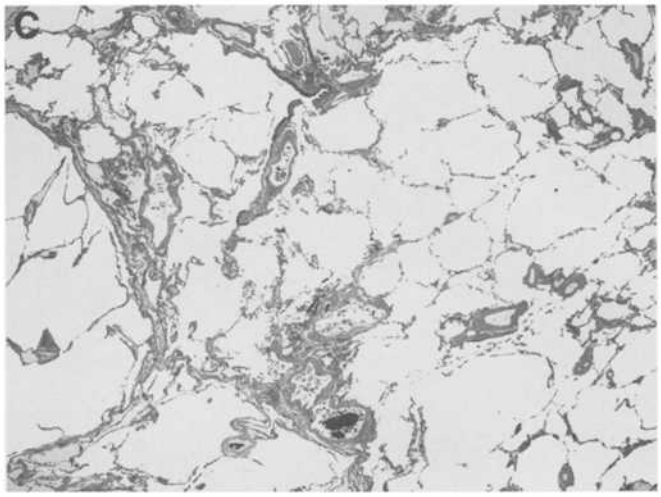


Fig. 5. (*Continued*)

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)

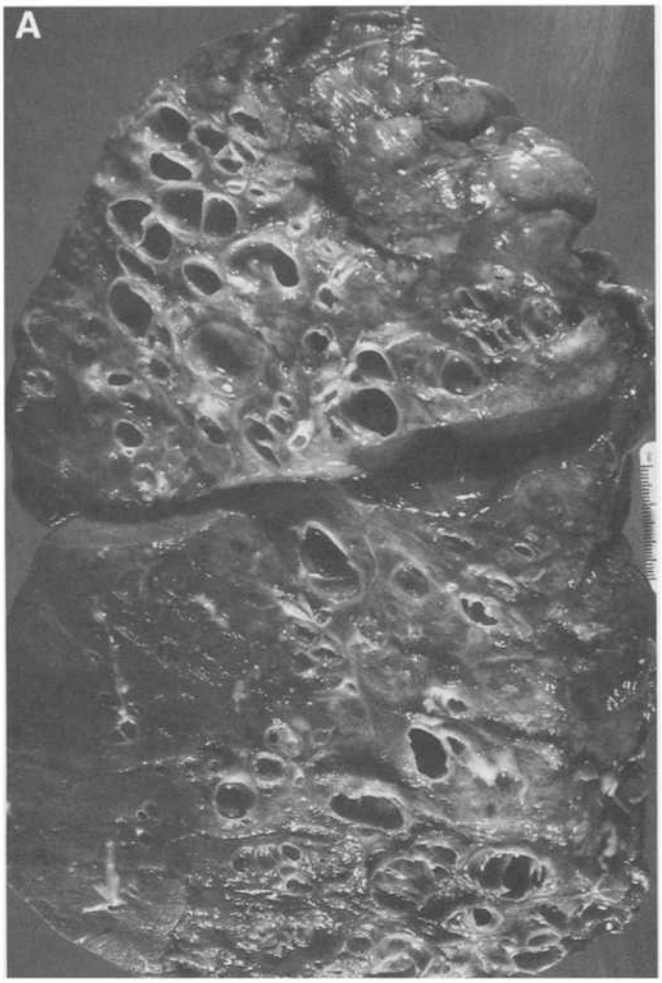
Asthma

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



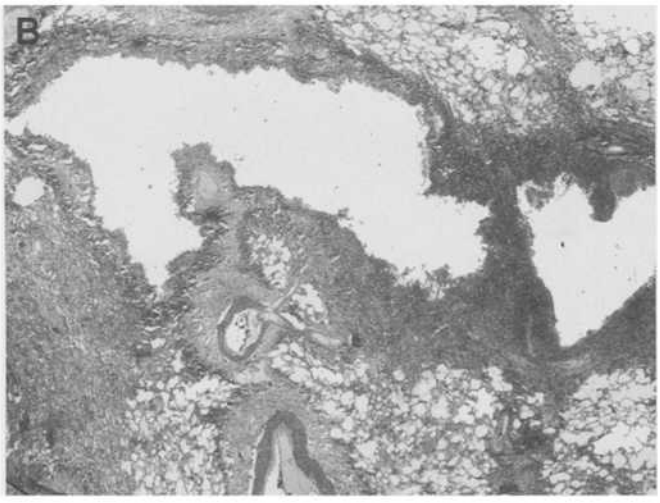


Fig. 6. Bronchiectasis **(A,B)**.

Microscopic

- Thickened basement membranes; mucous plugs; goblet cell hyperplasia
- Submucosal gland hypertrophy; may show eosinophilic infiltrate

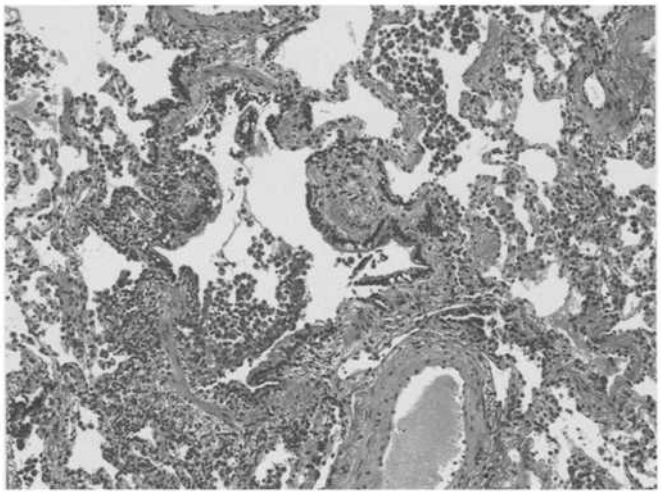


Fig. 7. Respiratory bronchiolitis.

- 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

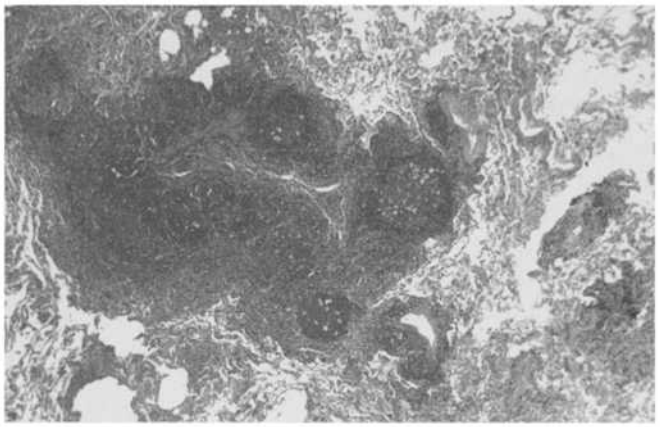


Fig. 8. Follicular bronchiolitis.

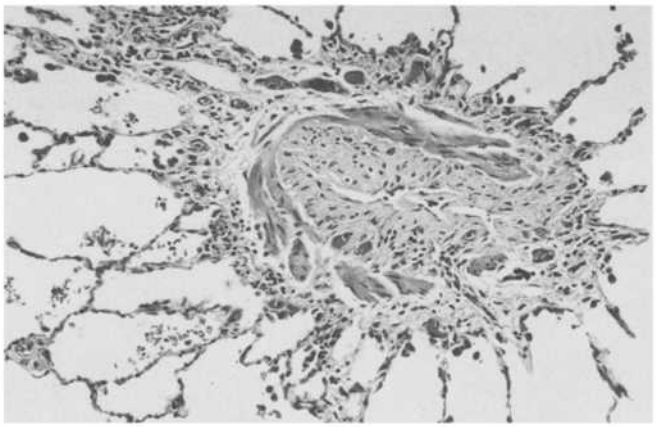


Fig. 9. Constrictive (oblierative) bronchiolitis.

- 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

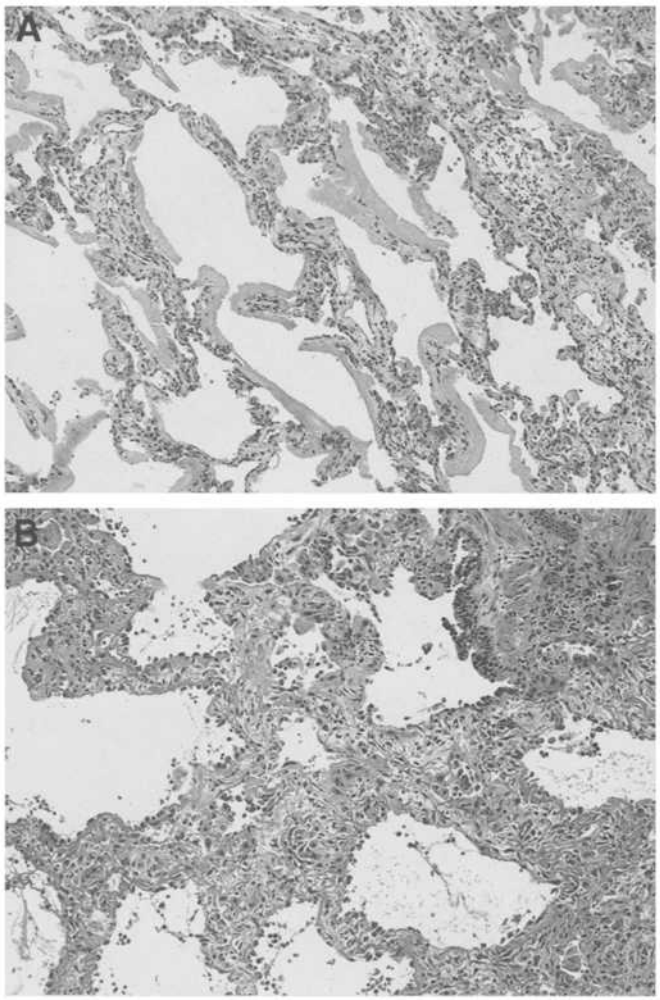


Fig. 10. Acute diffuse alveolar damage **(A,B)**.

- 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

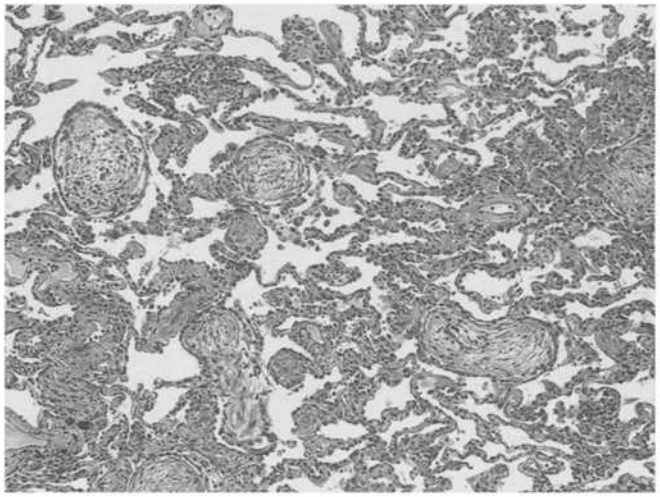


Fig. 11. Brochiolitis obliterans organizing pneumonia (BOOP).

*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

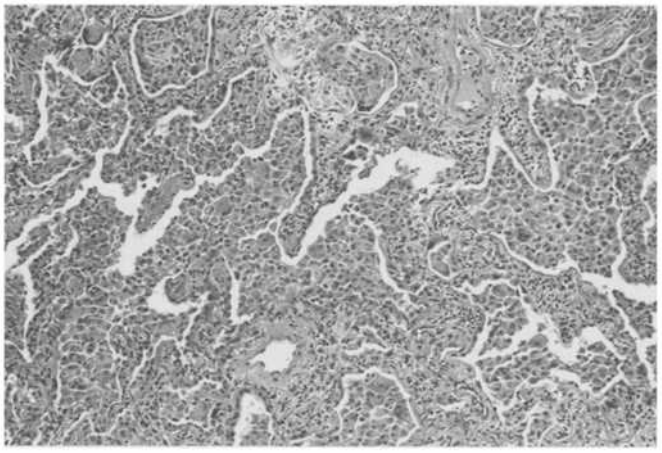


Fig. 12. Desquamative interstitial pneumonitis.

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

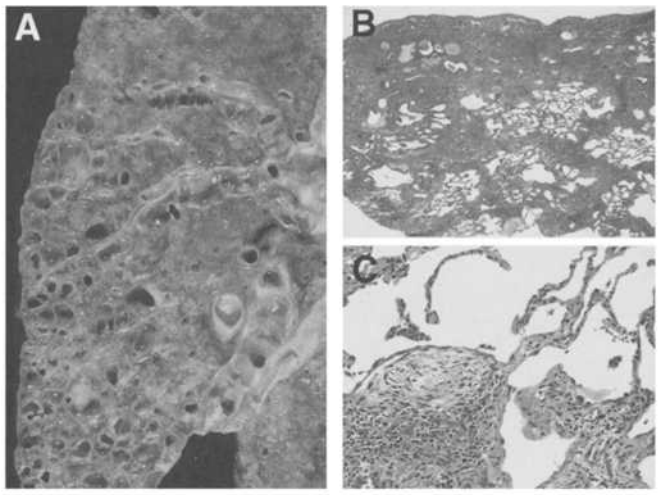


Fig. 13. Usual interstitial pneumonia with honeycomb changes **(A,B)** and fibroblastic foci **(C)**.

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

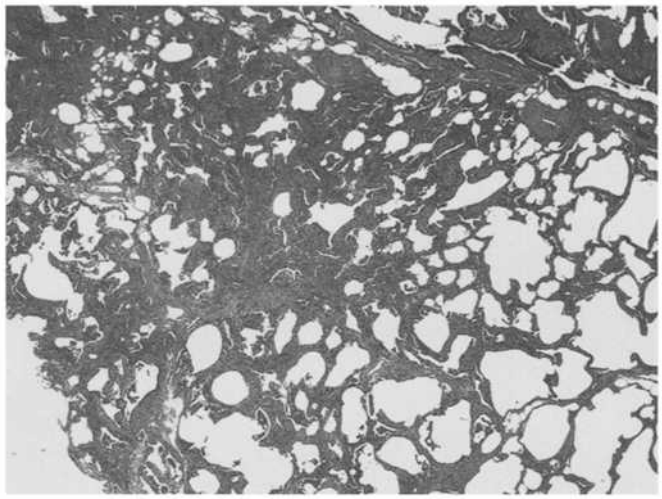


Fig. 14. Non-specific interstitial pneumonia.

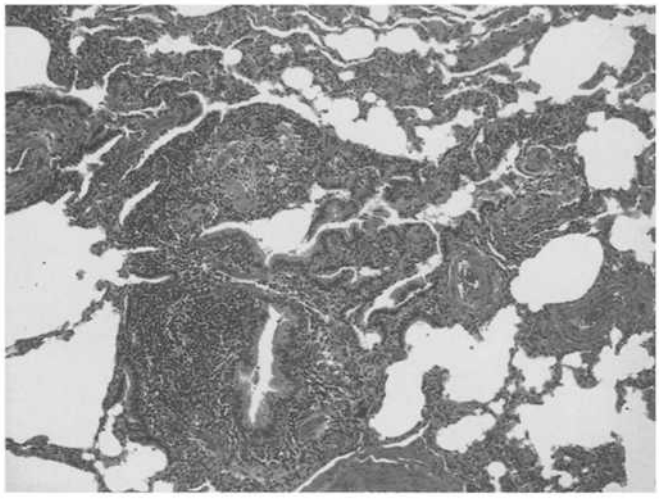


Fig. 15. Extrinsic allergic alveolitis/hypersensitivity pneumonitis.

- 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

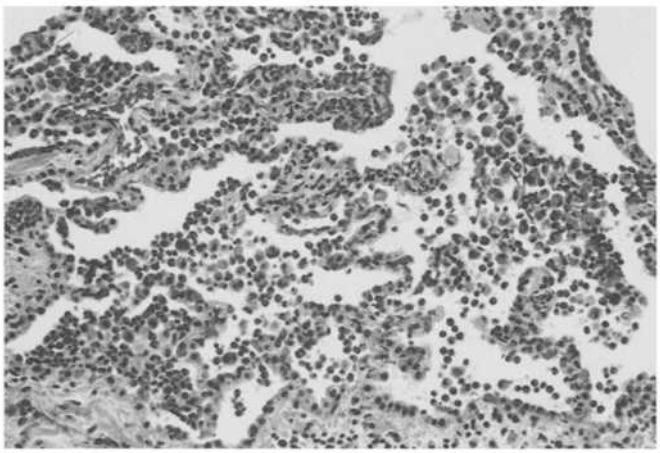


Fig. 16. Eosinophilic pneumonia.

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)

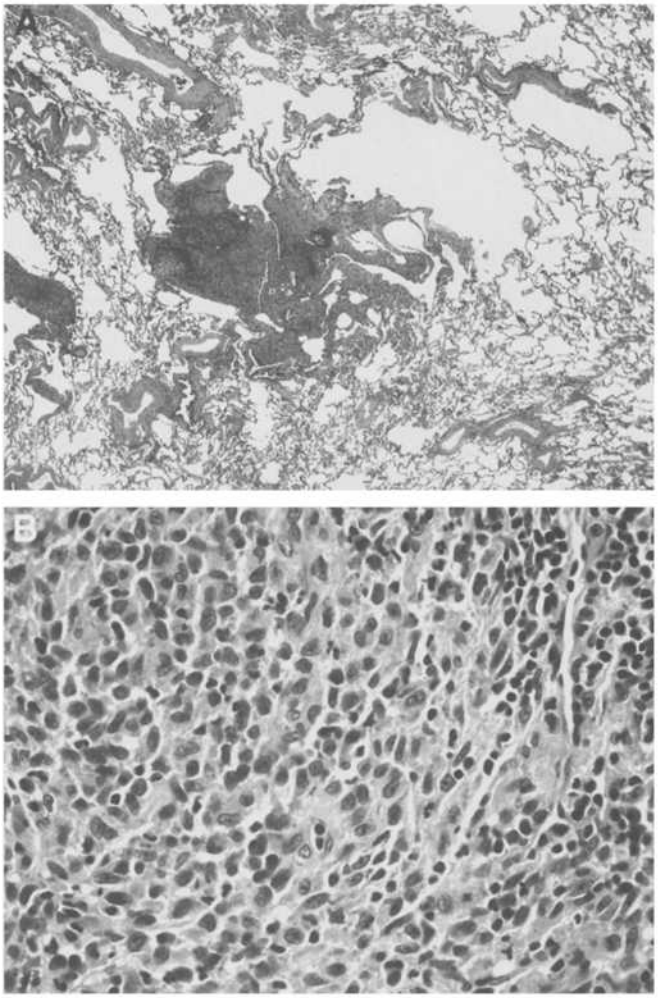


Fig. 17. Pulmonary histiocytosis-X (eosinophilic granuloma) **(A,B)**.

- 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

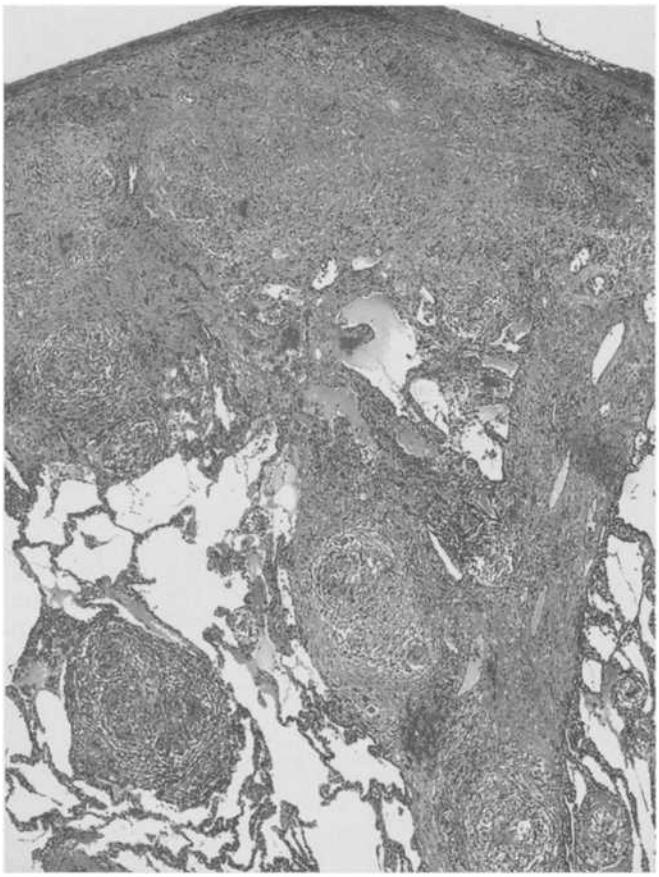


Fig. 18. Sarcoidosis.

- 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

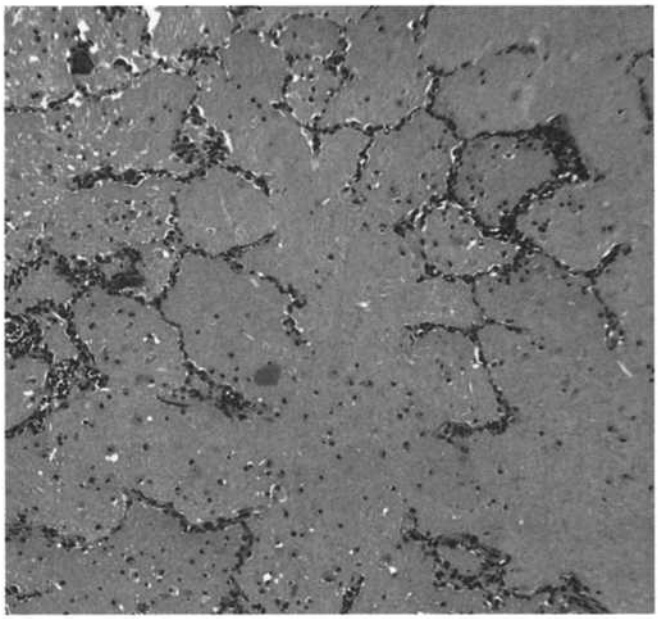


Fig. 19. Pulmonary alveolar proteinosis.

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

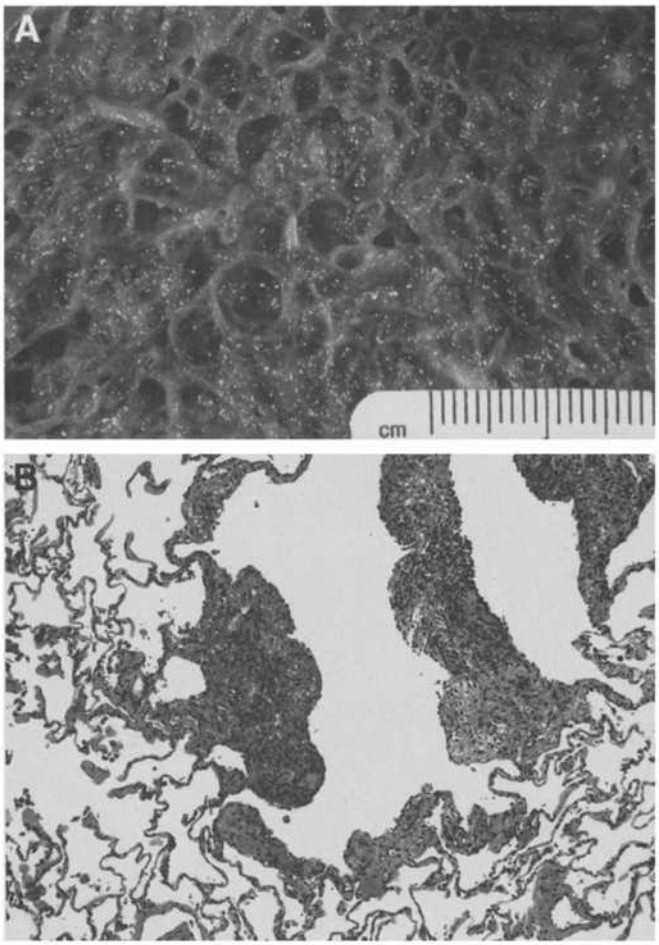


Fig. 20. Lymphangioleiomyomatosis **(A,B)**.

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

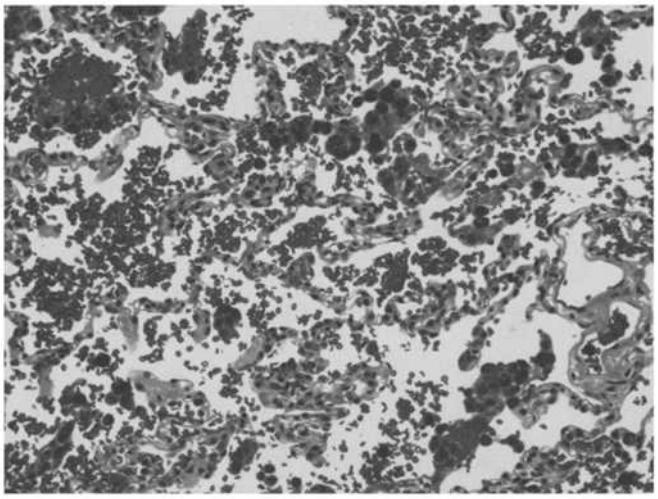


Fig. 21. Idiopathic pulmonary hemosiderosis.

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

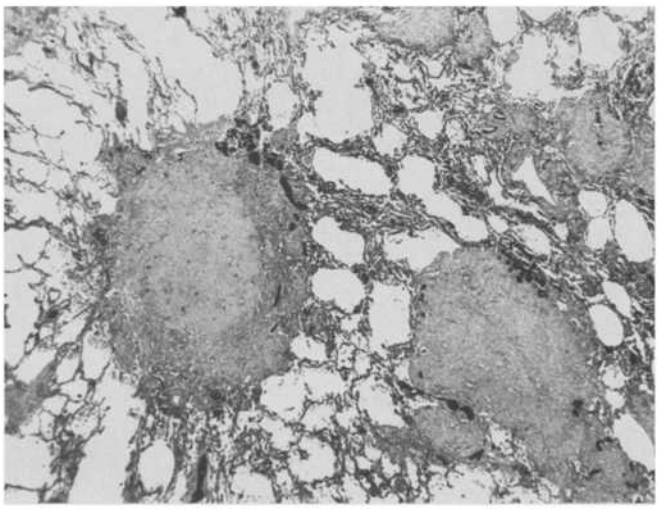


Fig. 22. Silicotic nodule.

- 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

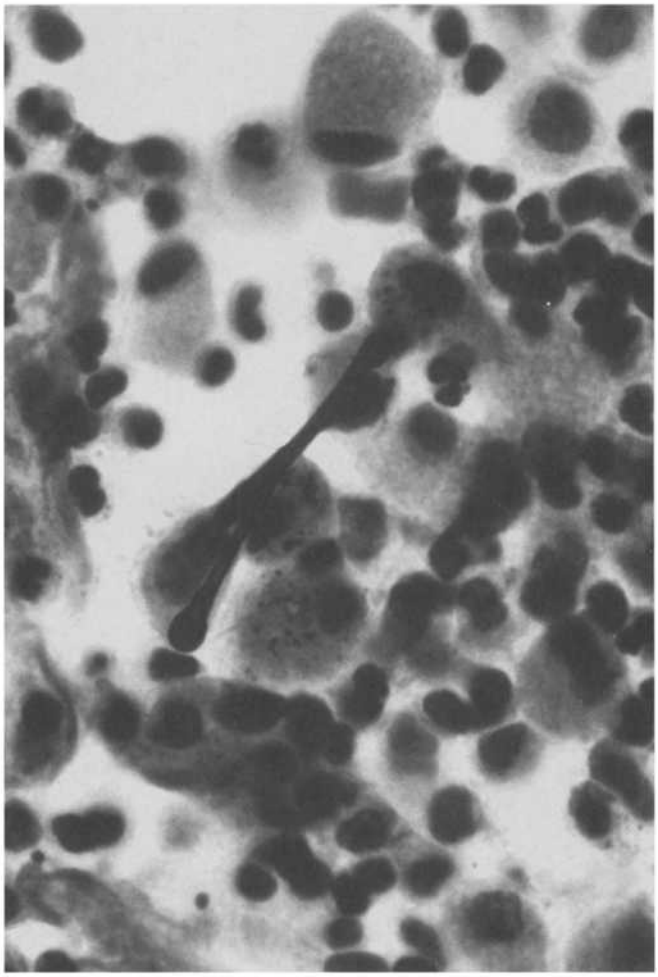


Fig. 23. Asbestos-related reactions—ferrugninous body.

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

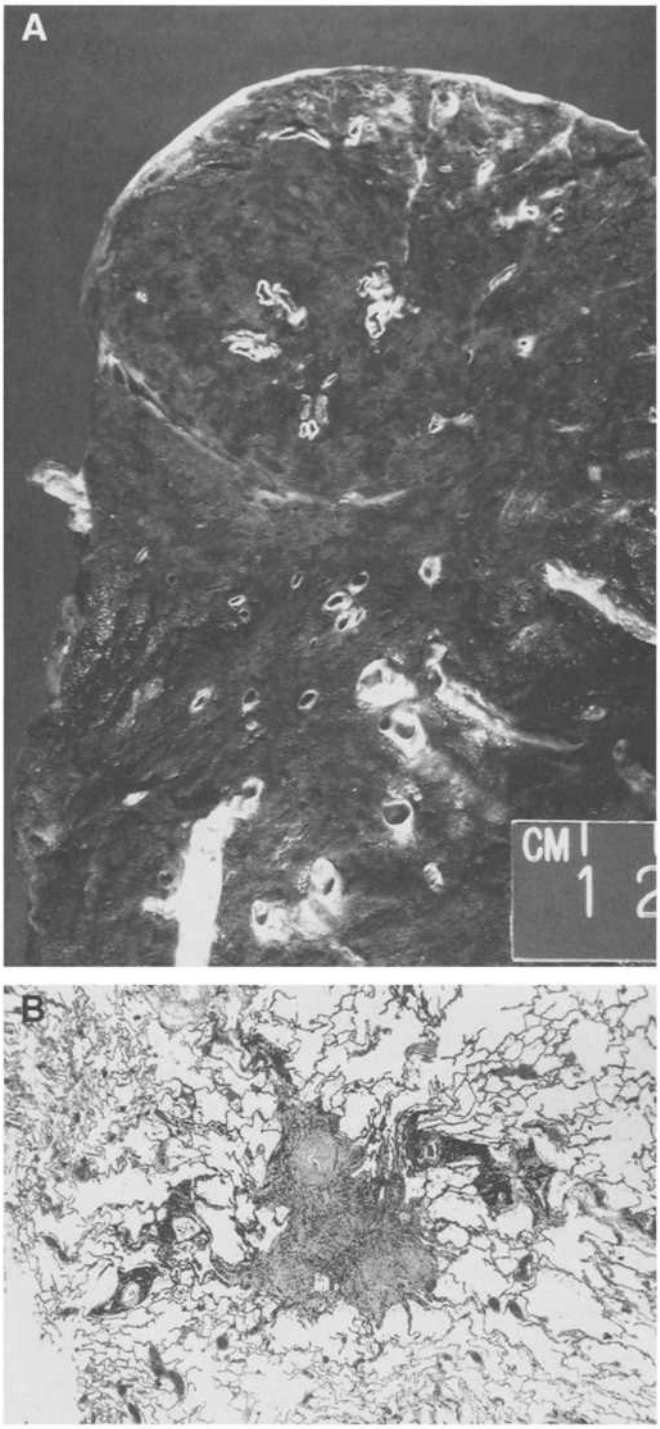


Fig. 24. Progressive massive fibrosis/Coal worker's pneumonconiosis (**A,B**).

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

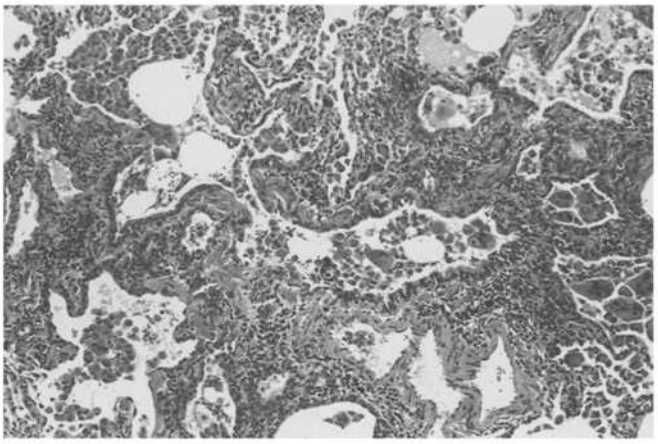


Fig. 25. Hard metal pneuomoconiosis/giant cell pneumonitis.

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

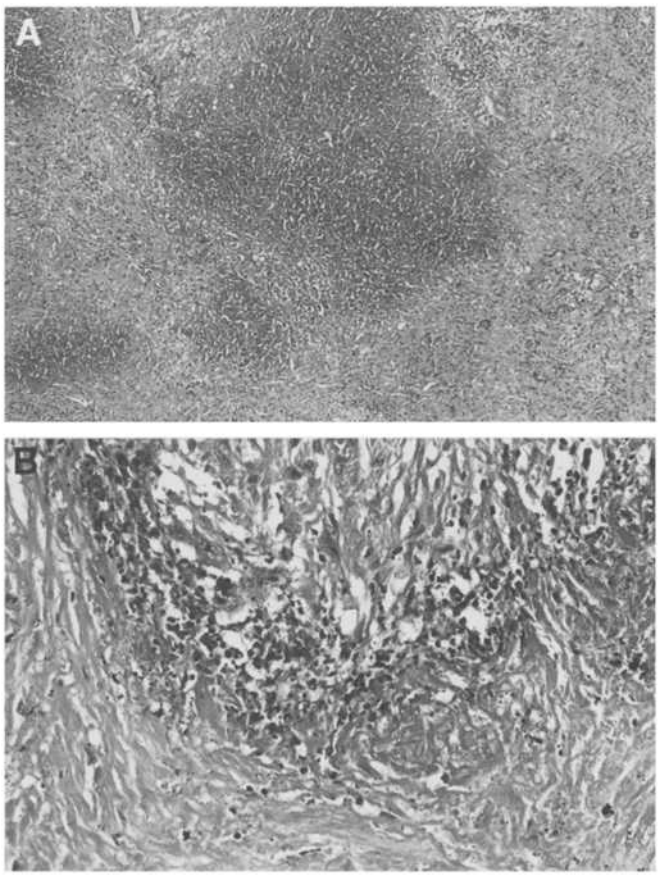


Fig. 26. Wegener's granulomatosis: **(A)** eographic necrosis; **(B)** collagenous necrosis.

- 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.*

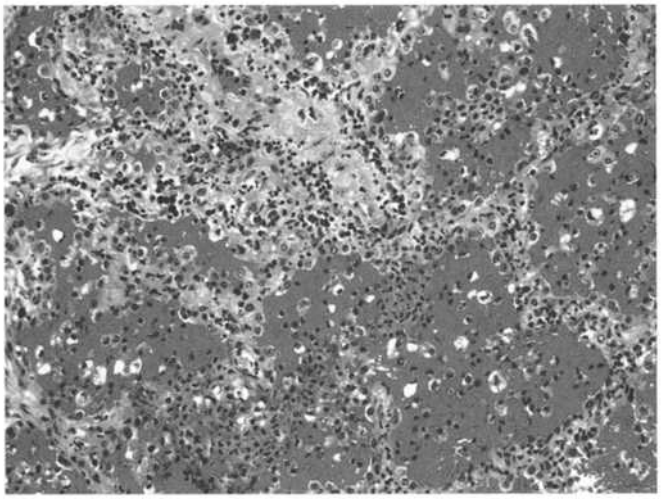


Fig. 27. Necrotizing capillaritis.

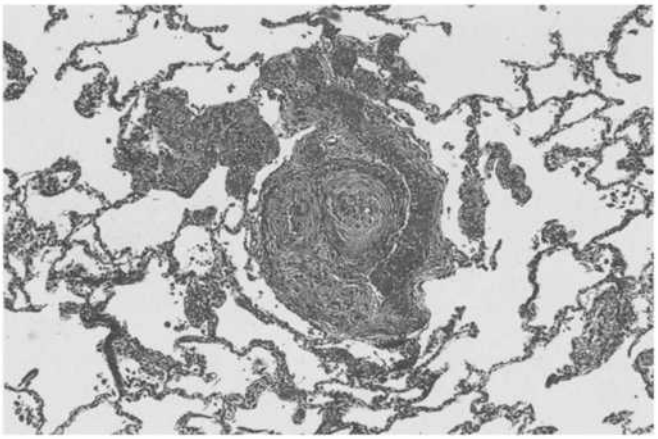


Fig. 28. Pulmonary hypertension plexogenic arteriopathy.

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

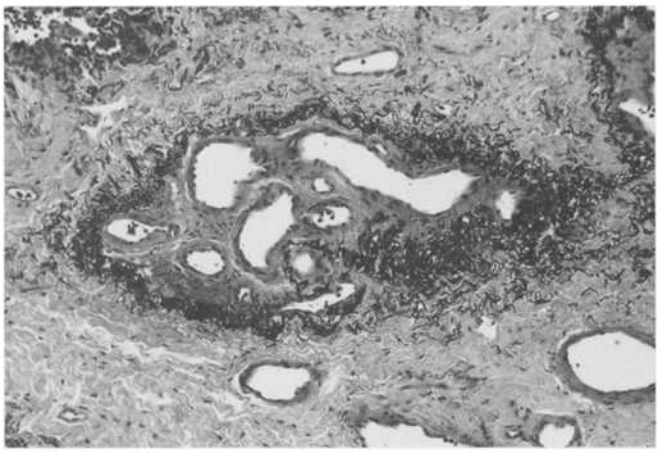


Fig. 29. Pulmonary veno-occlusive disease (PVOD).

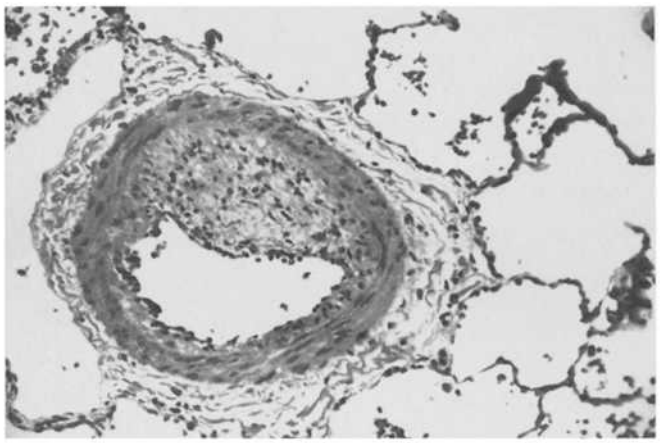


Fig. 30. Thrombotic arteriopathy.

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

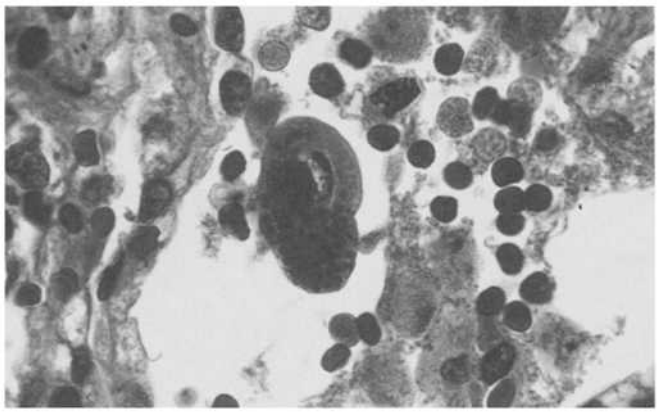


Fig. 32. Cytomegalovirus (CMV) inclusion in alveolar macrophage.

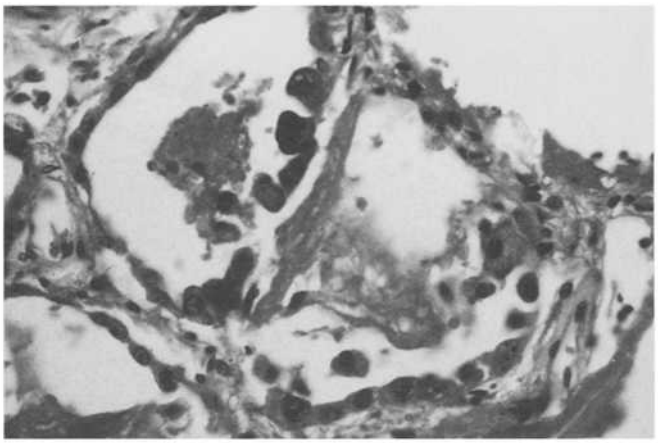


Fig. 33. Adenovirus infection.

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

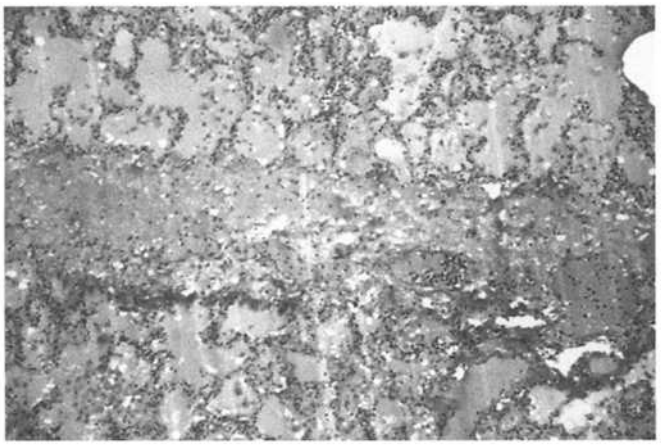


Fig. 34. Hantavirus pulmonary syndrome.

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+

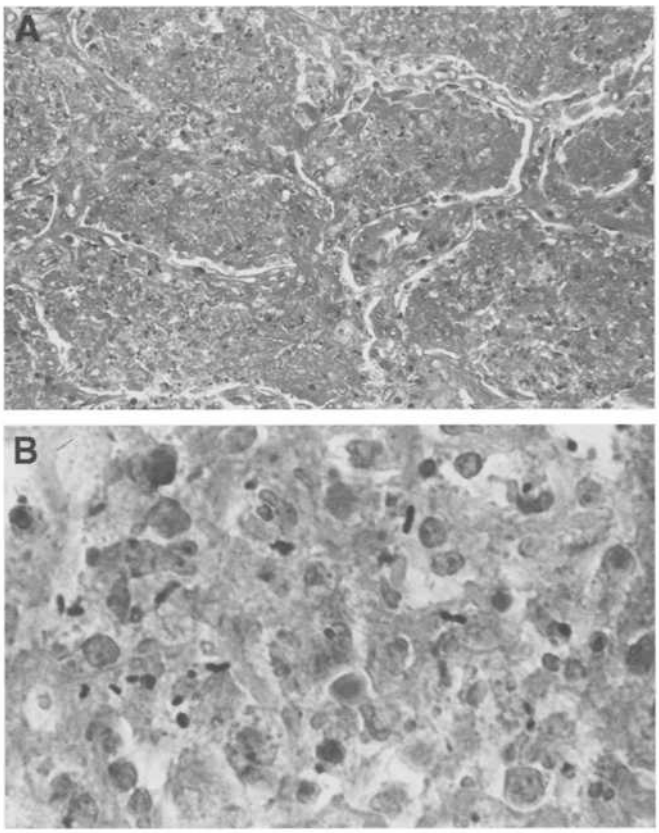


Fig. 35. Legionnaires' disease **(A)**. The organisms are highlighted by Dieterle stain **(B)**.

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,

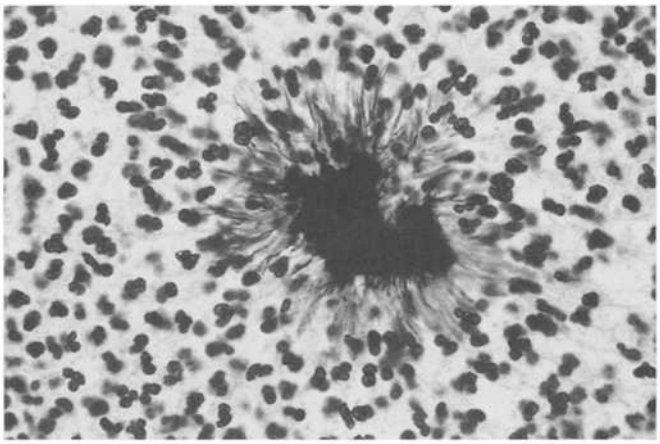


Fig. 36. Actinomyces Gram stain.

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*

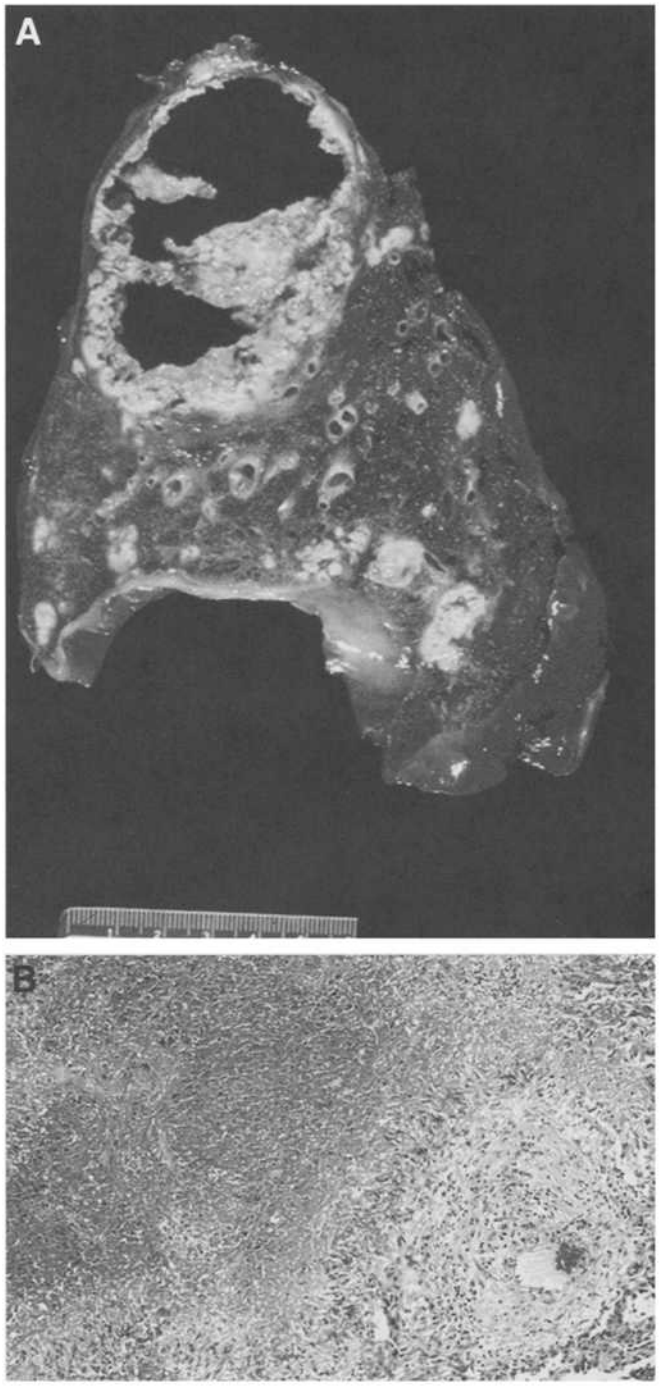


Fig. 37. Mycobacterial tuberculosis. **(A)** apical cavitary lesion; **(B)** Mycobacterial necronizing granuloma.

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

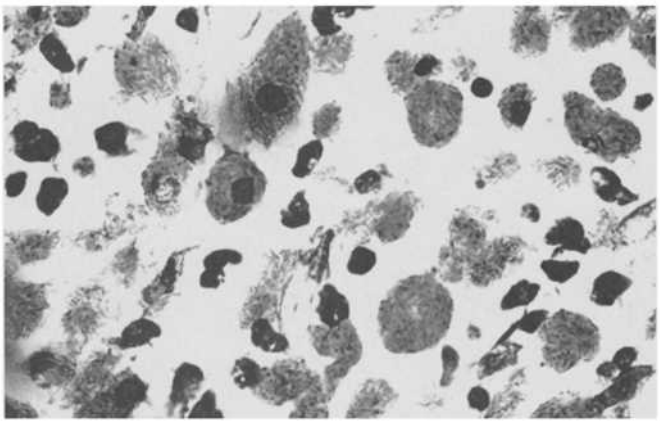


Fig. 38. Mycobacterium avium complex (MAI) in an AIDS patient.

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

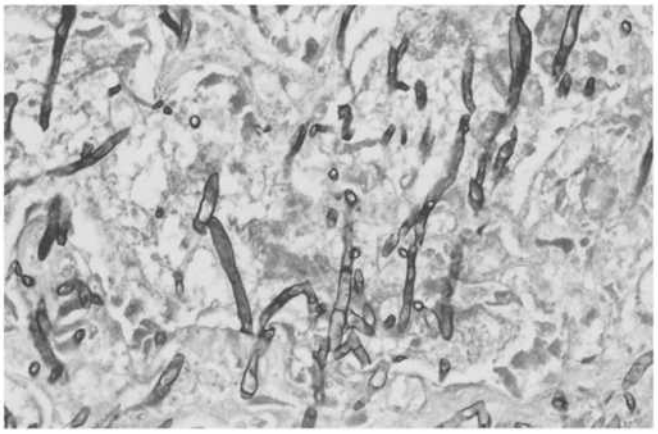


Fig. 39. Aspergillus fungal hyphae, silver stain.

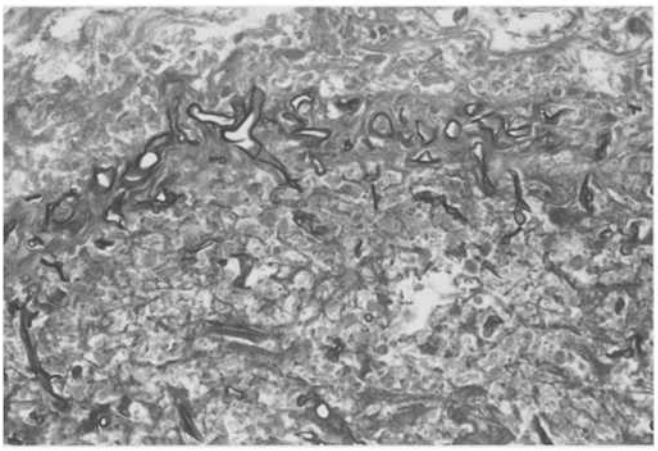


Fig. 40. Mucormycosis.

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

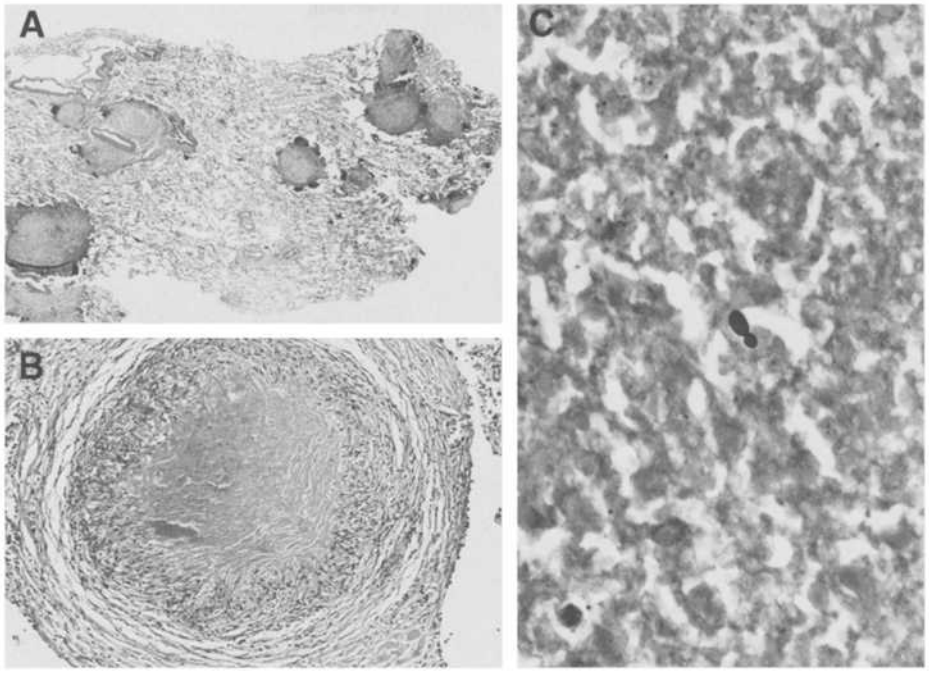


Fig. 41. Histoplasmosis. Necrotizing granuloma over airways **(A,B)**. Histoplasma capsulatum **(C)**.

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

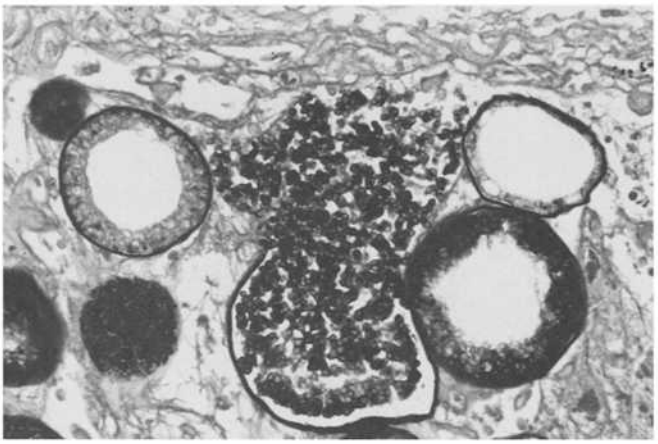


Fig. 42. Coccidioides immitis.

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

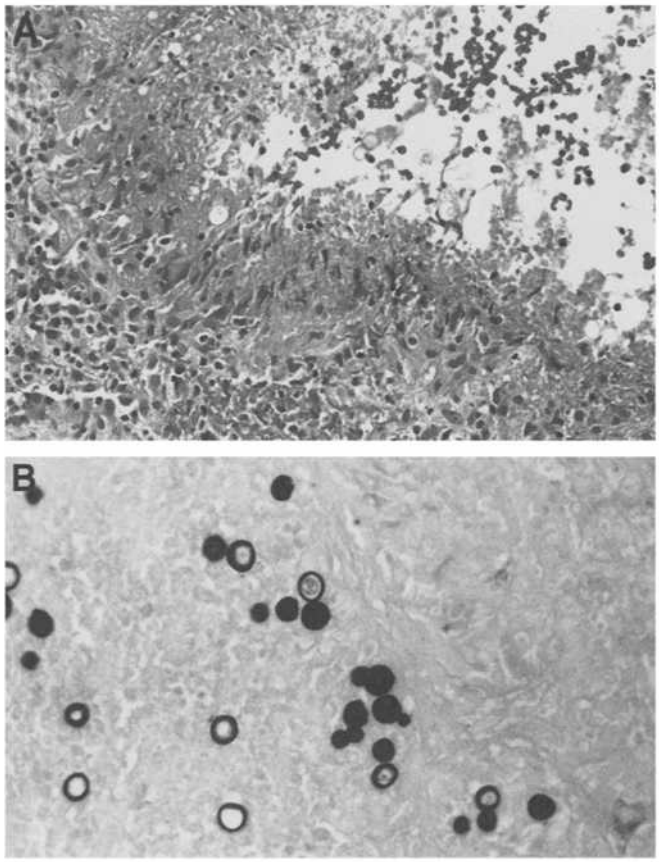


Fig. 43. Blastomycosis. Necrotizing granuloma **(A)**. Blastomyces dermatitides **(B)**.

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

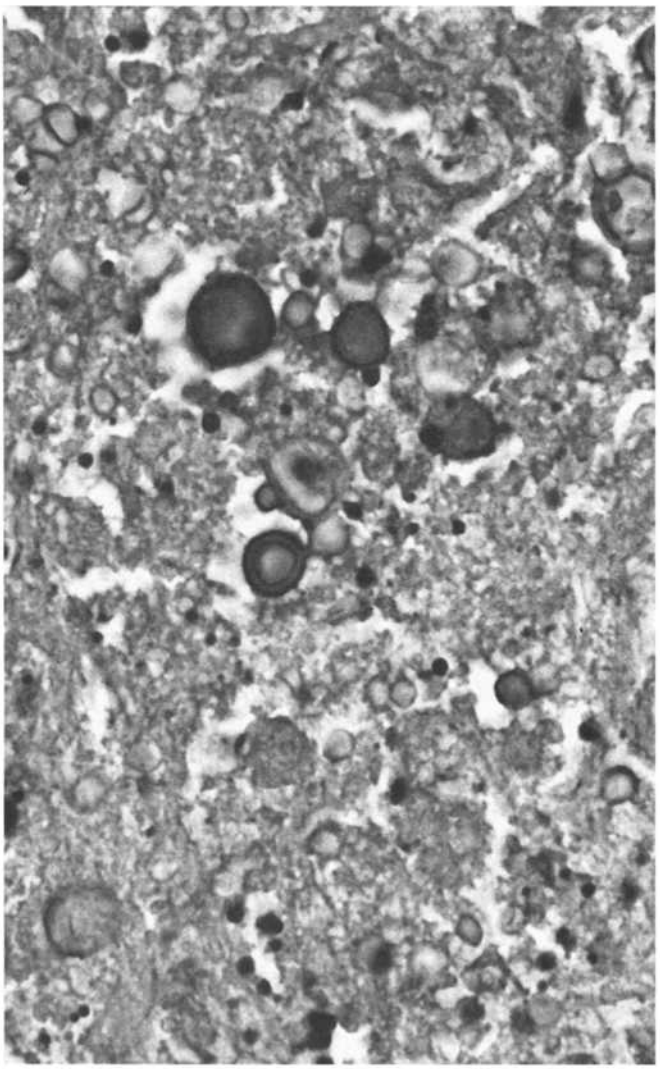


Fig. 44. Cryptococcus neoformans.

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

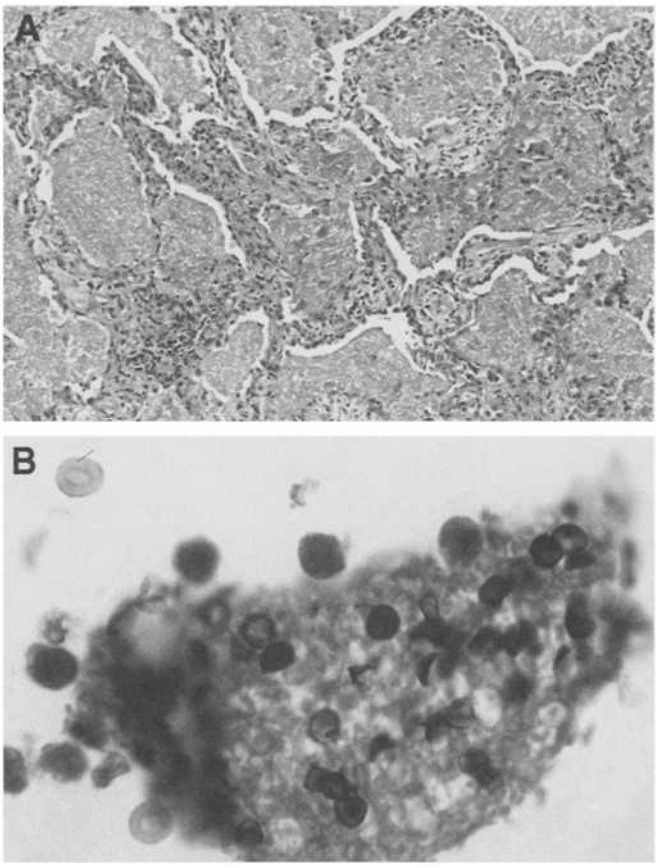


Fig. 45. Pneumocystis carinii pneumonia (PCP). Pneumocystis carinii organisms highlighted by silver stain **(B)**.

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)

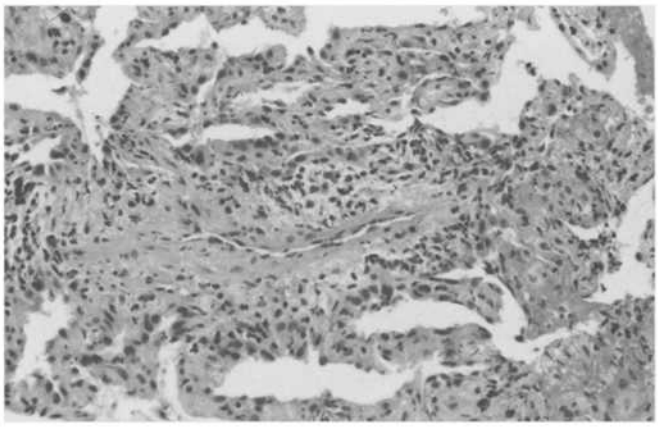


Fig. 46. Minimal acute vascular rejection of pulmonary allograft.

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;

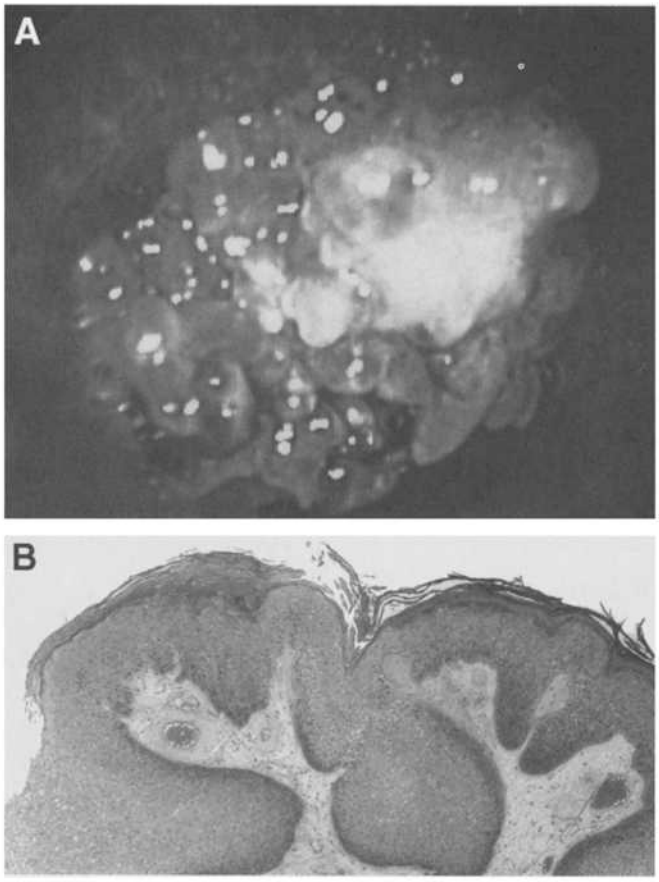


Fig. 47. Squamous papillomatosis **(A,B)**.

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

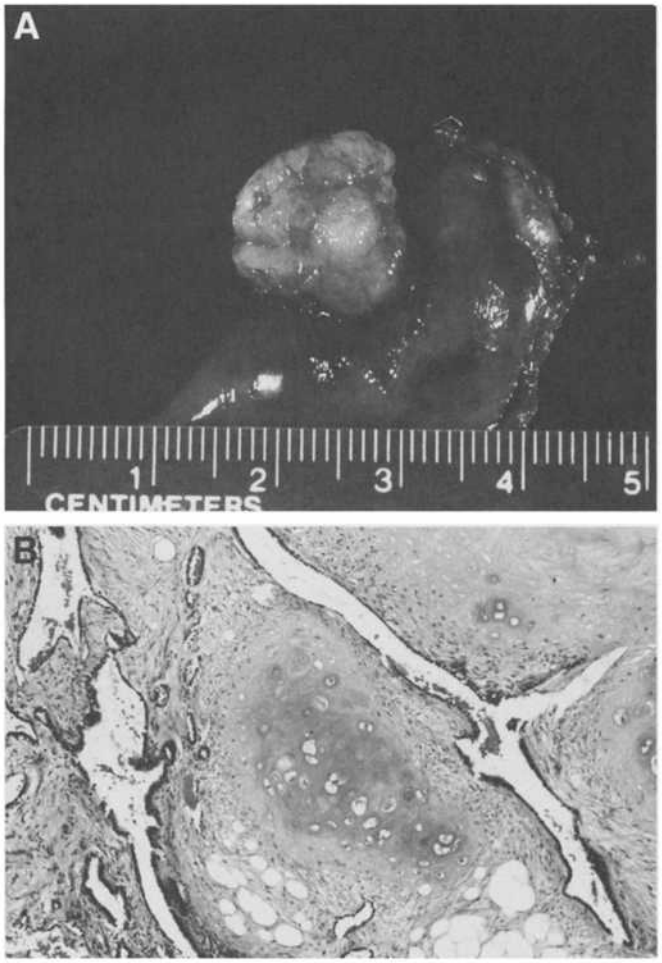


Fig. 48. Hamartoma (**A,B**).

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

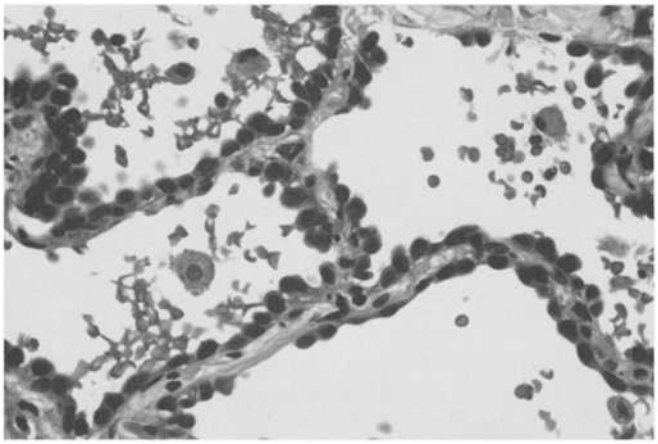


Fig. 49. Atypical adenomatous hyperplasia.

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

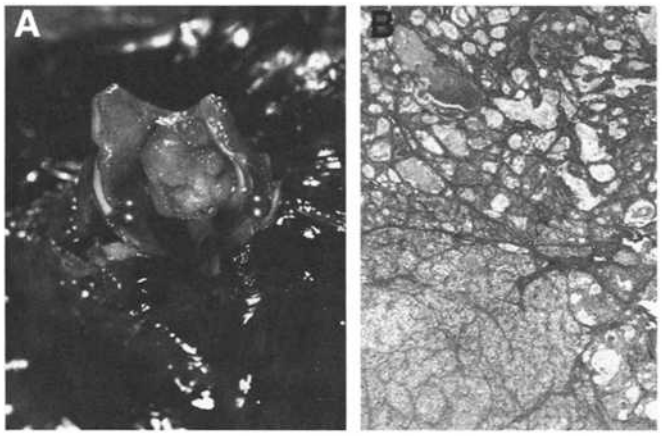


Fig. 50. Mucoepidermoid carcinoma (**A,B**).

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

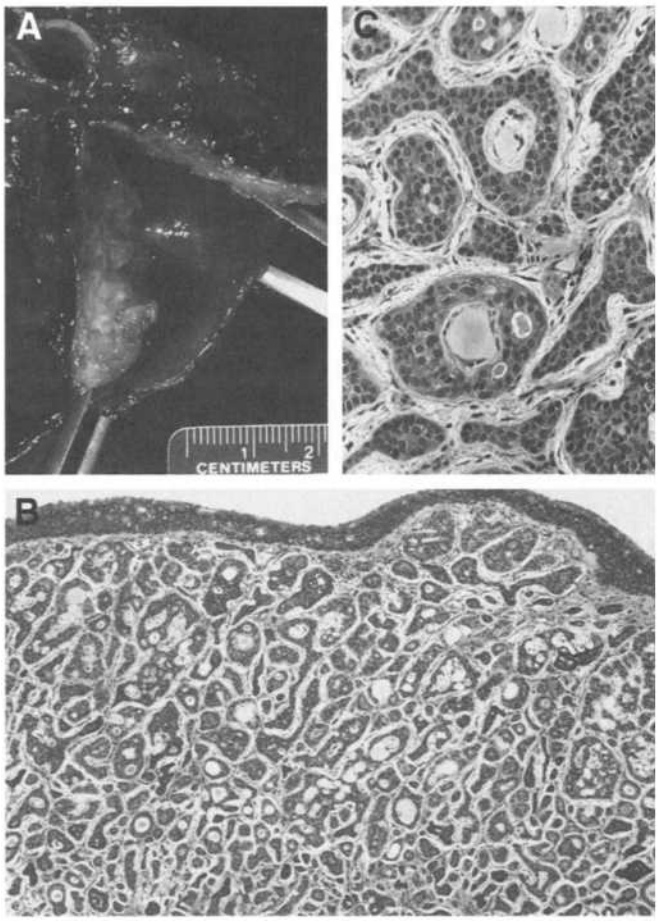


Fig. 51. Adenoid cystic carcinoma (**A–C**).

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

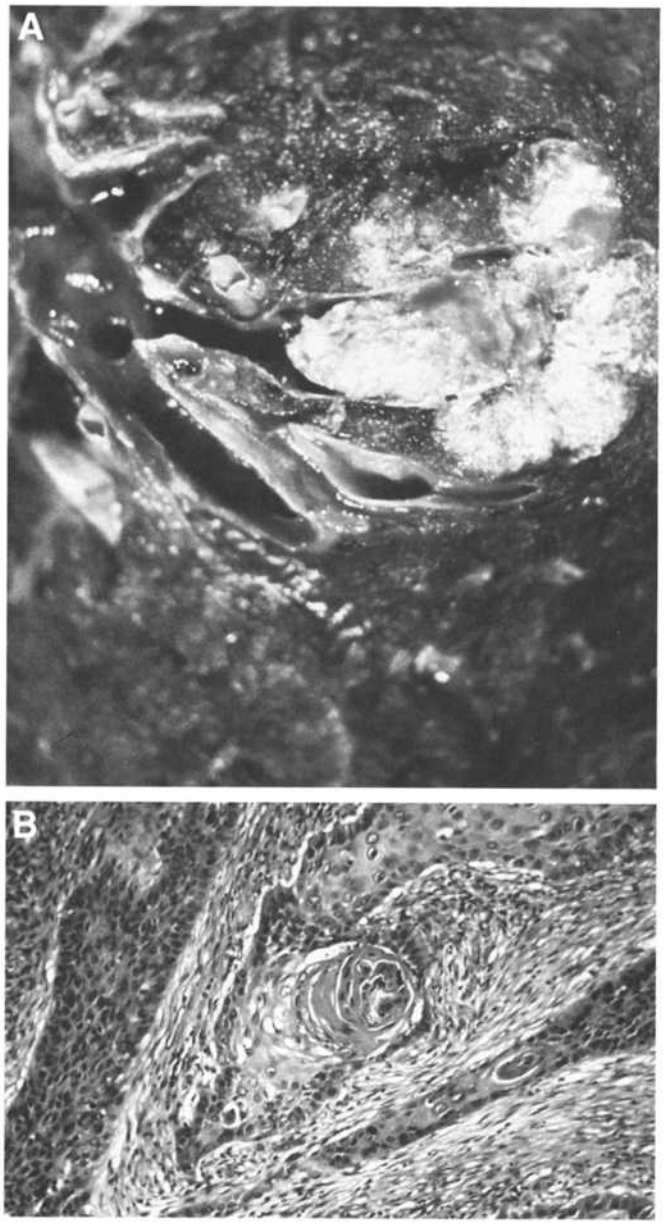


Fig. 52. Squamous cell carcinoma **(A,B)**.

- 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

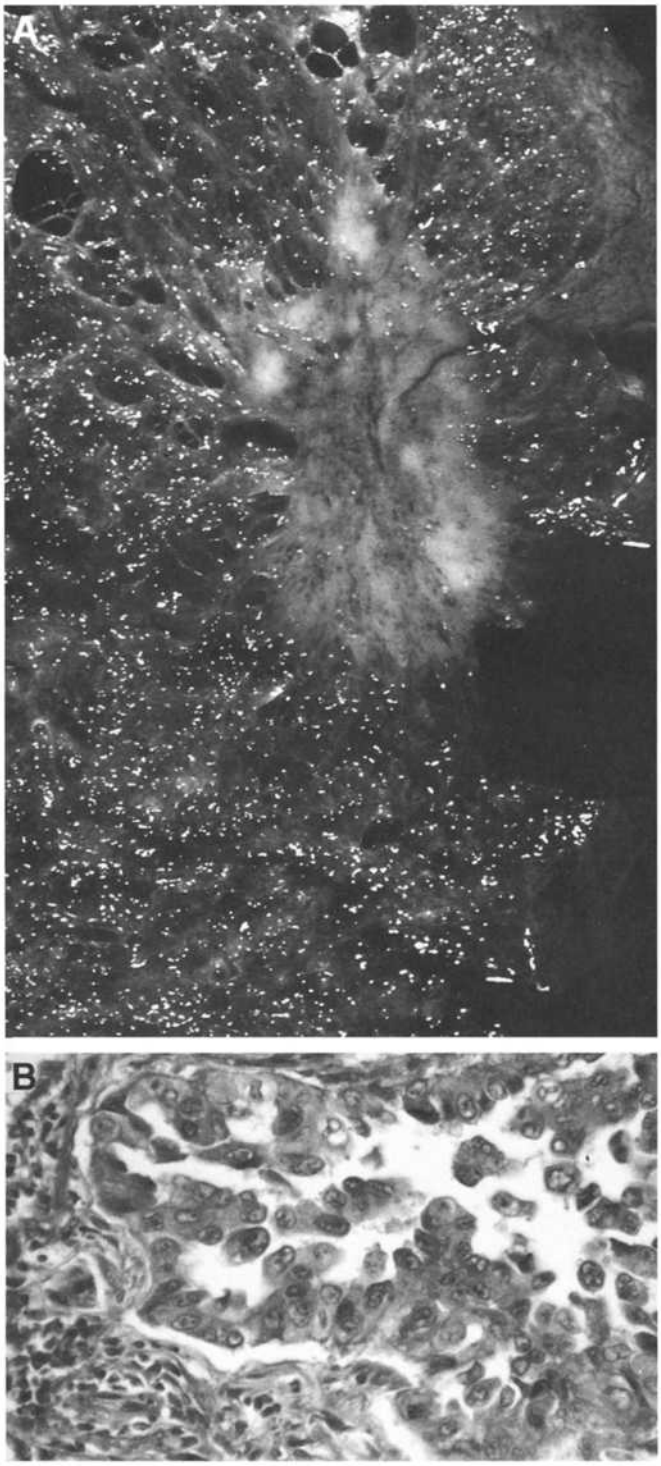


Fig. 53. Adenocarcinoma: **(B)** acinar type.

- Bronchioloalveolar
- Solid

♦ Bronchioloalveolar carcinoma is considered a subtype of adenocarcinoma **(Figure 54)**:

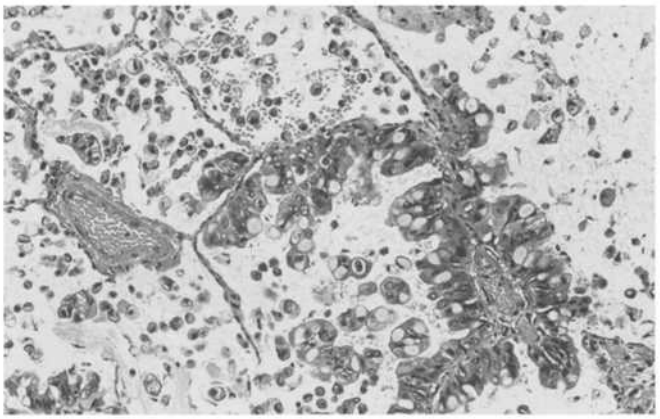


Fig. 54. Bronchioloalveolar adenocarcinoma.

- 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:

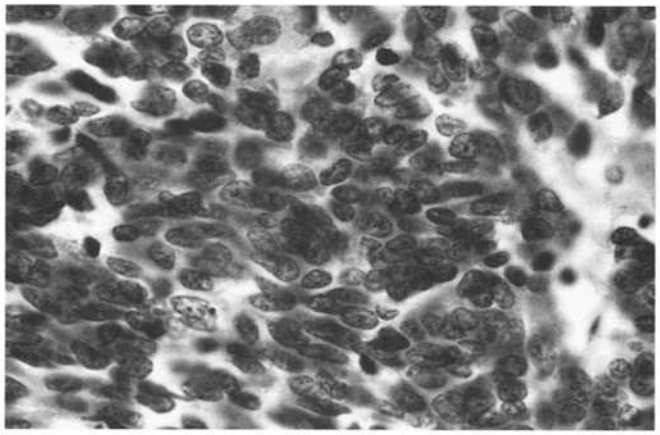


Fig. 55. Small cell carcinoma.

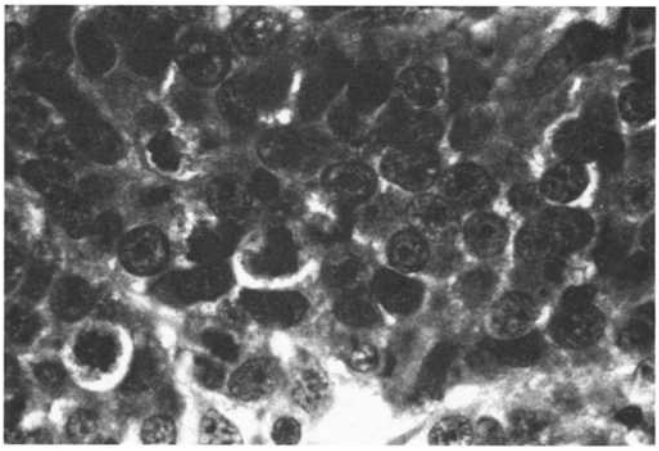


Fig. 56. Large cell undifferentiated carcinoma.

- 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)

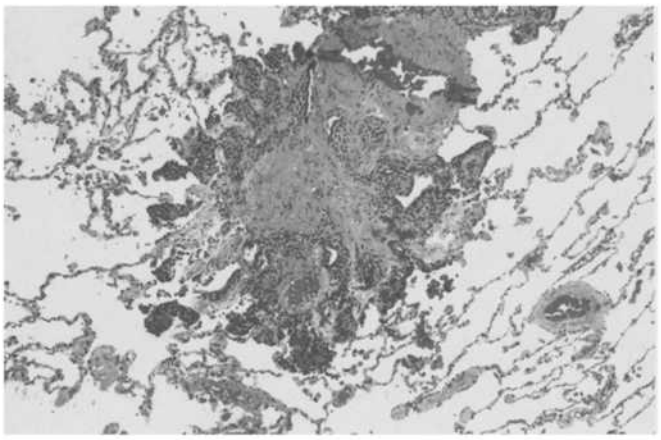


Fig. 57. Carcinoid tumorlet.

  – 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

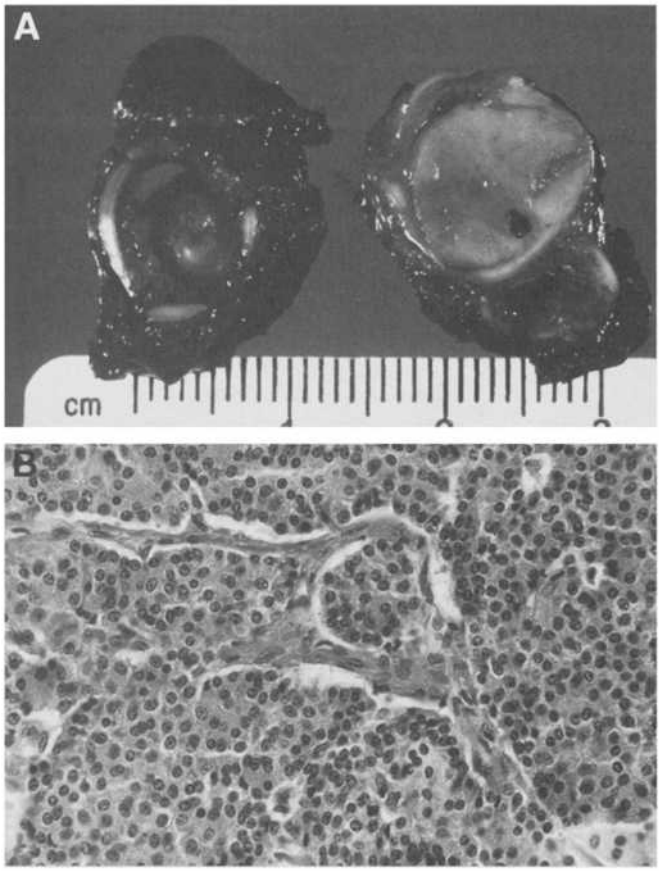


Fig. 58. Typical carcinoid **(A,B)**.

- 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

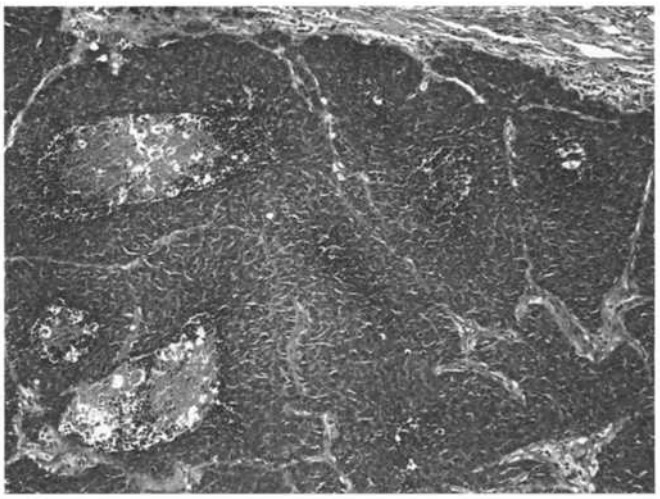


Fig. 59. Large cell neuroendocrine carcinoma.

- 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

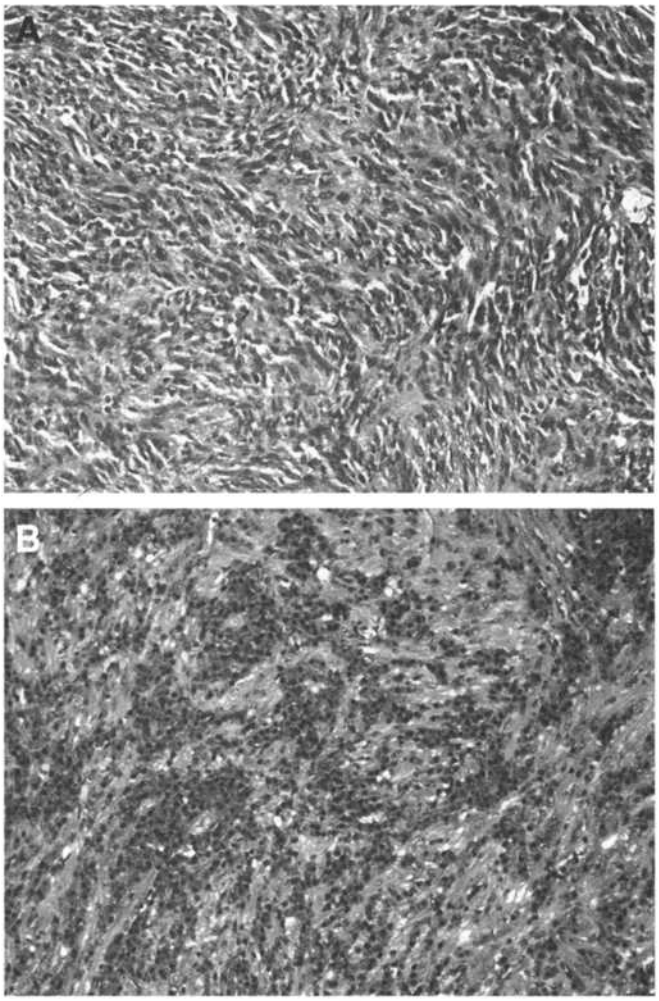


Fig. 60. Inflammatory pseudotumor: **(A)** fibrohistocytic subtype; **(B)** plasma cell granuloma subtype.

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

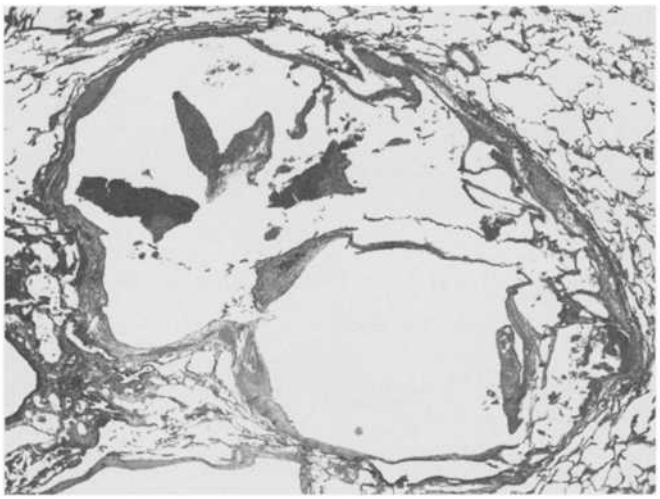


Fig. 61. Arteriovenous malformation.

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

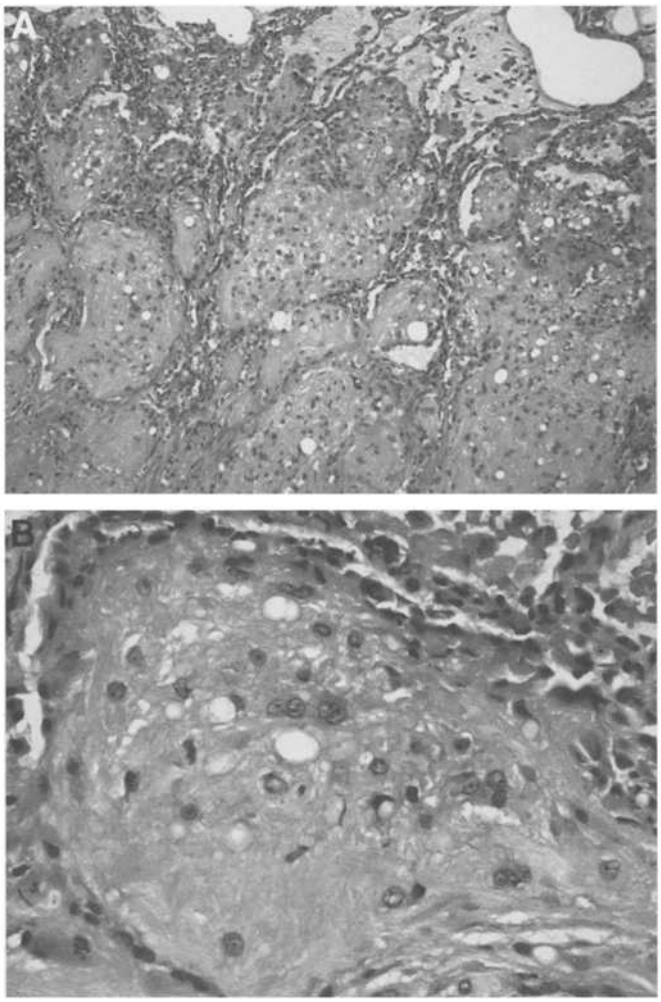


Fig. 62. Epithelioid hemagioendothelioma (intravascular bronchioloalveolar tumor) **(A,B)**.

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

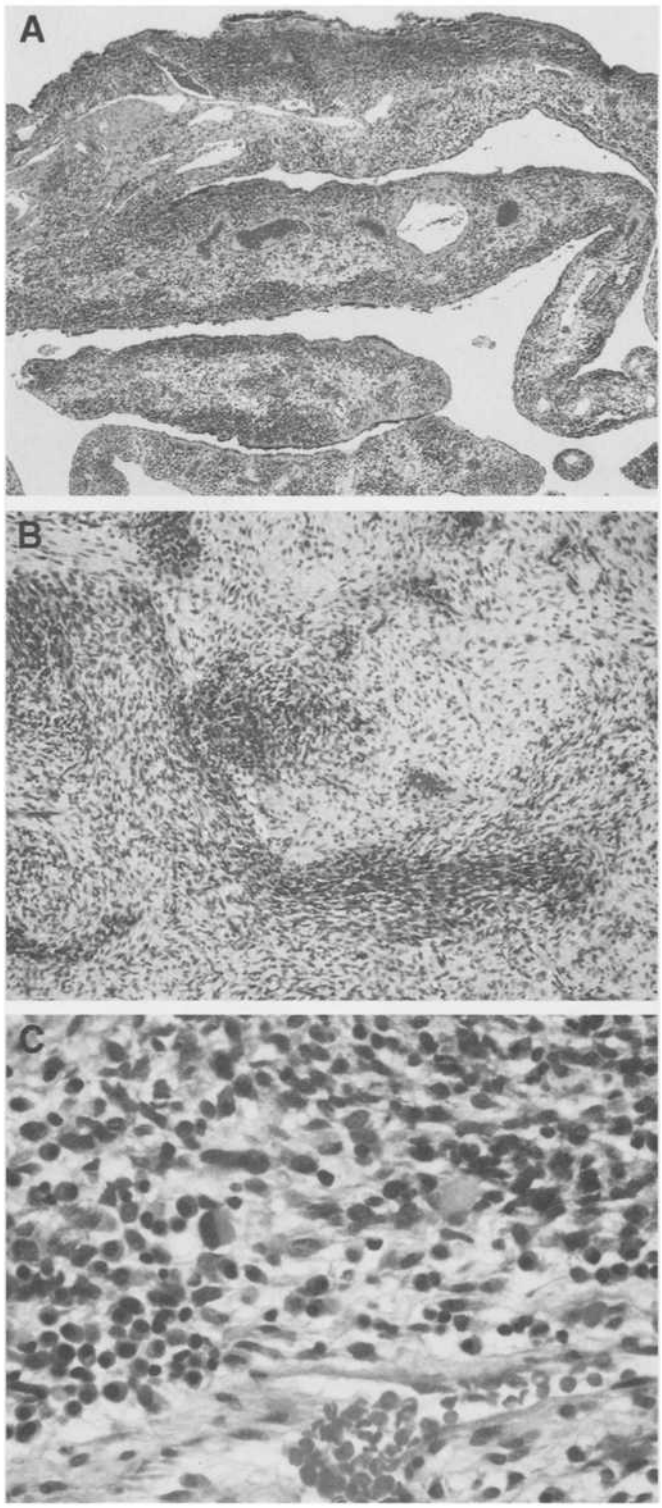


Fig. 64. Pleuropulmonary blastoma. **(A)** Characteristic multicystic lesion with compact small-cell proliferation beneath respiratory epithelium. **(B)** Solid area with blastematous and sarcomatous foci. **(C)** Foci of rhabdomyosarcoma are common.

- 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

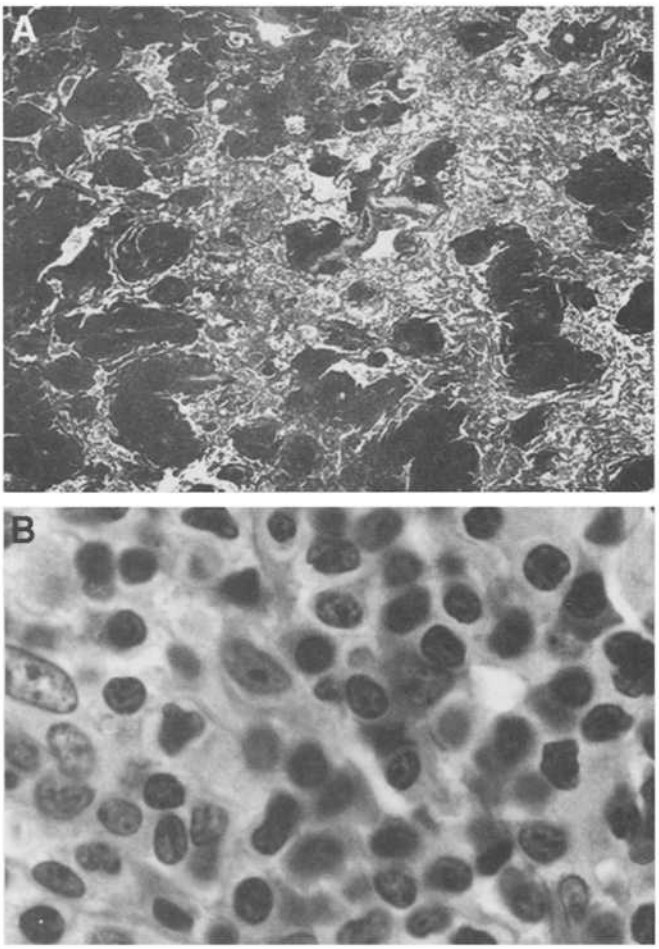


Fig. 65. Marginal zone lymphoma of the BALT type.

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

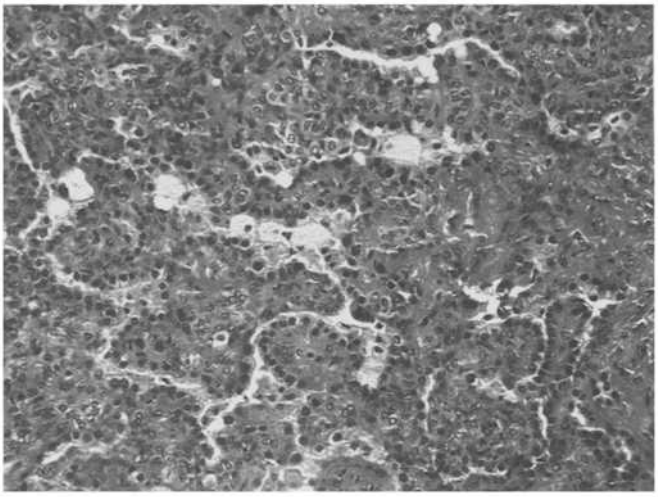


Fig. 66. Sclerosing hemangioma.

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

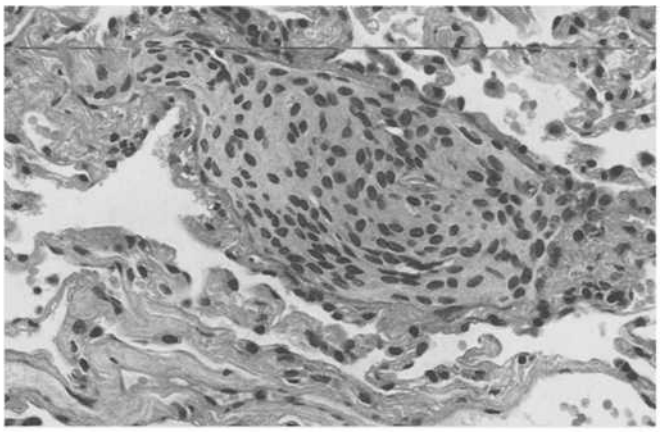


Fig. 67. Pulmonary meningothelial-like lesion (chemodectoma).

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

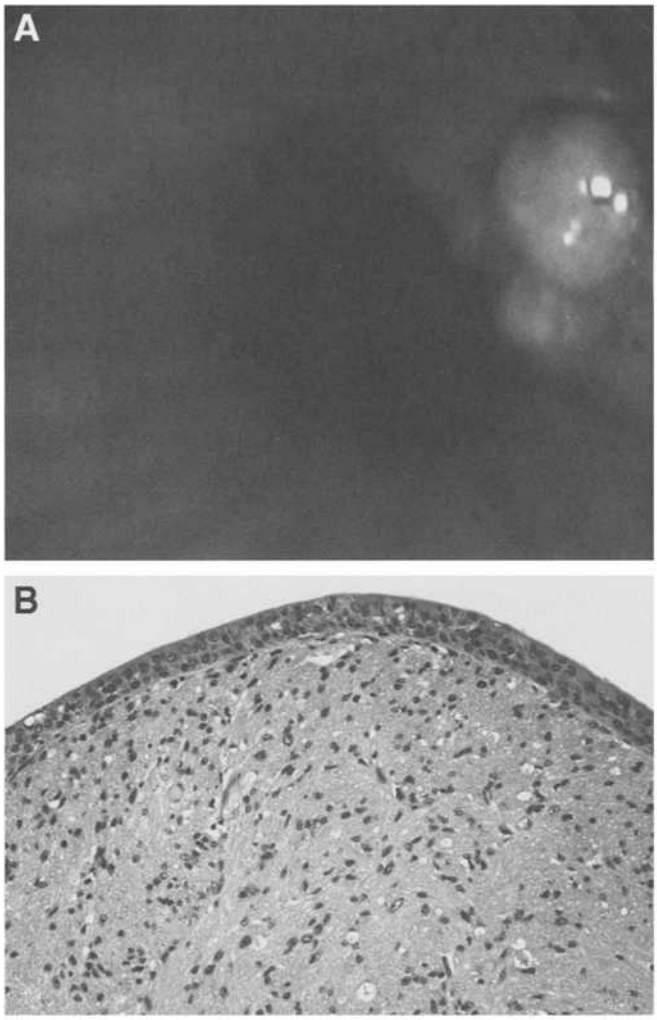


Fig. 68. Granular cell tumor (**A,B**).

- 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

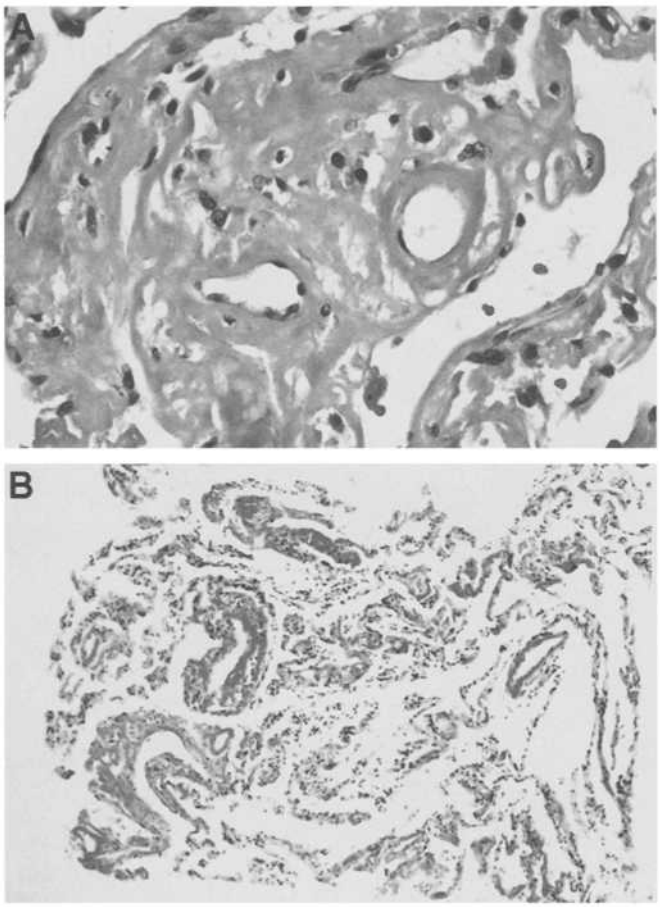


Fig. 69. Amyloidosis. **(B)** Congo red stain.

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+

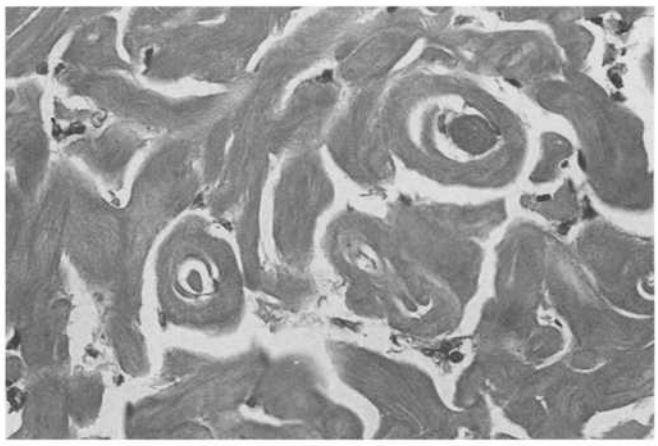


Fig. 70. Pulmonary hyalizing granuloma.

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+

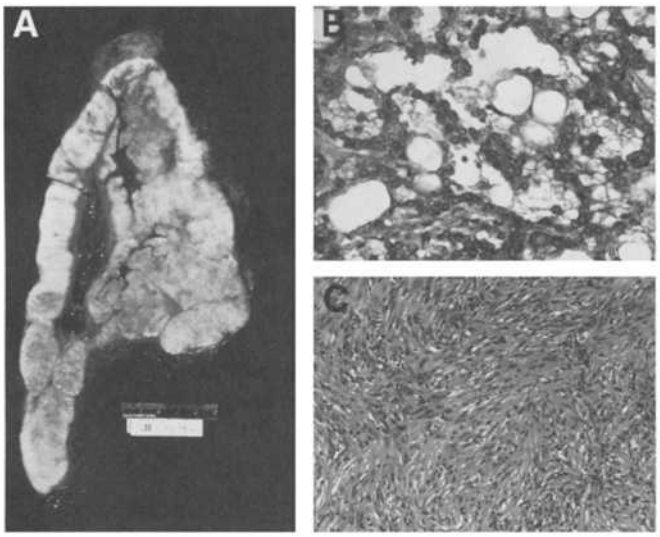


Fig. 71. Malignant mesothelioma. **(A)** Gross appearance; **(B)** epithelioid type; **(C)** sarcomatoid type.

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

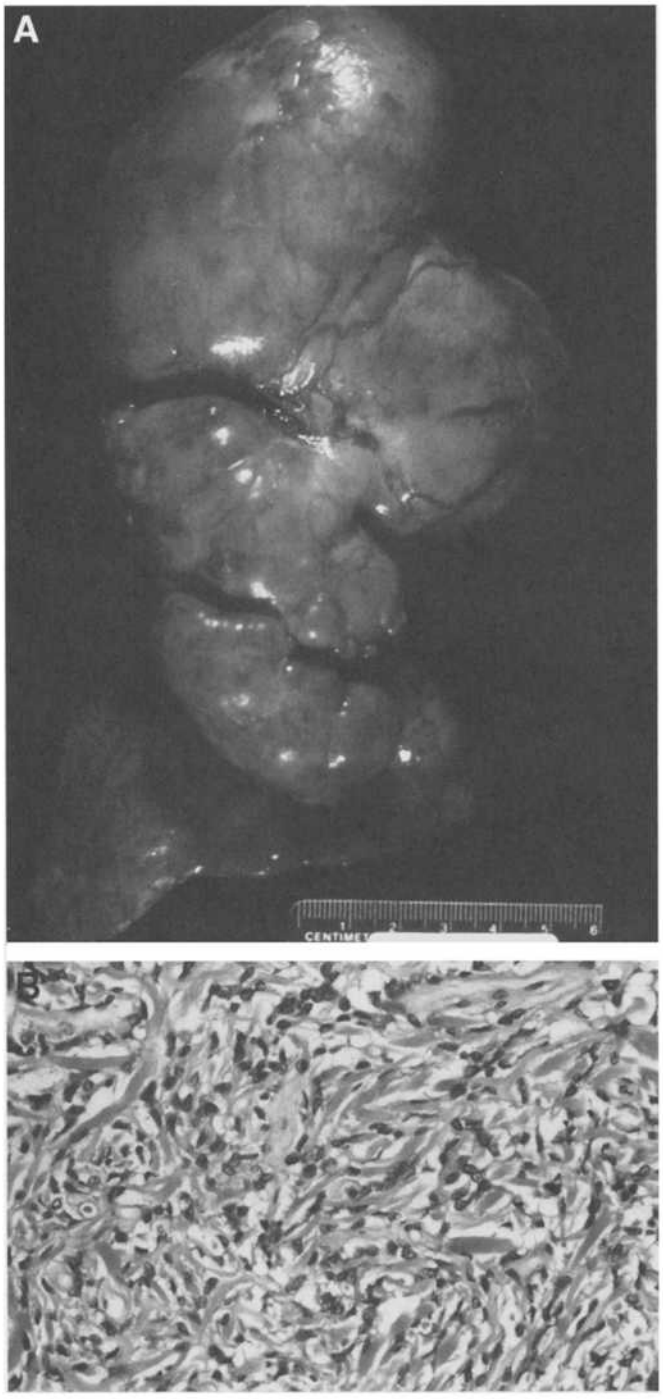


Fig. 72. Solitary fibrous tumor of the pleura **(A,B)**

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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