# 28

# Lung and Pleura

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CONTENTS





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# NONNEOPLASTIC DISEASES OF THE LUNG

## Congenital Anomalies and Pediatric Lesions

### Pulmonary Sequestration

#### *Intralobar*

#### *Clinical*

- 90% lower lobes; 55% on left; M:F = 1.1:1
- 50% over 20 years; usually presents with recurrent infections

#### *Macroscopic (Fig. 28.1)*

- Firm, cystic area within lobe
- Systemic arterial supply from elastic artery from thoracic aorta or below the diaphragm
- Venous return via normal pulmonary veins
- 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

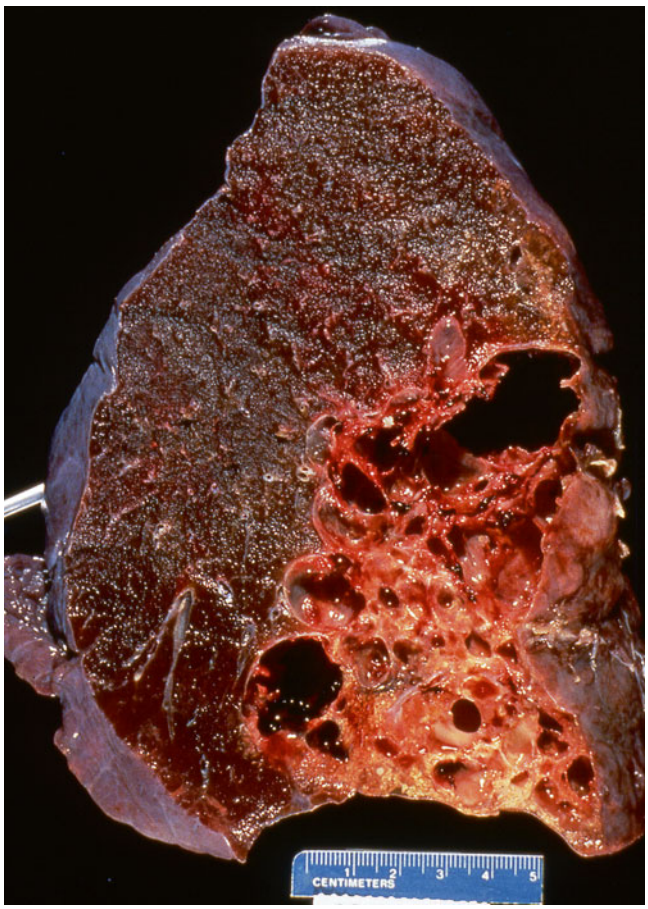


Fig. 28.1. Intralobar sequestration. Lower segment of lobe shows end-stage changes with marked, fibrosis, and remodeled airways.

#### *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 and pectus excavatum (funnel chest)

#### *Macroscopic*

- Spongy, pyramidal mass outside of normal pleura; invested by own pleura
- Systemic anomalous arterial supply; venous drainage through systemic or portal systems

#### *Microscopic*

- May appear normal; may resemble congenital pulmonary airway malformation (CPAM)

## Bronchogenic Cysts

#### *Clinical*

- Supernumerary lung buds from foregut; commonly found in subcarinal or middle mediastinum location
- Usually incidental findings on chest imaging

#### *Macroscopic*

- Usually unilocular cysts with smooth margins; no communication with tracheobronchial tree

#### *Microscopic (Fig. 28.2)*

- Respiratory epithelium with smooth muscle, cartilage, and submucosal glands
- Squamous metaplasia, purulent exudate, chronic inflammation, and fibrosis if infected

#### *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

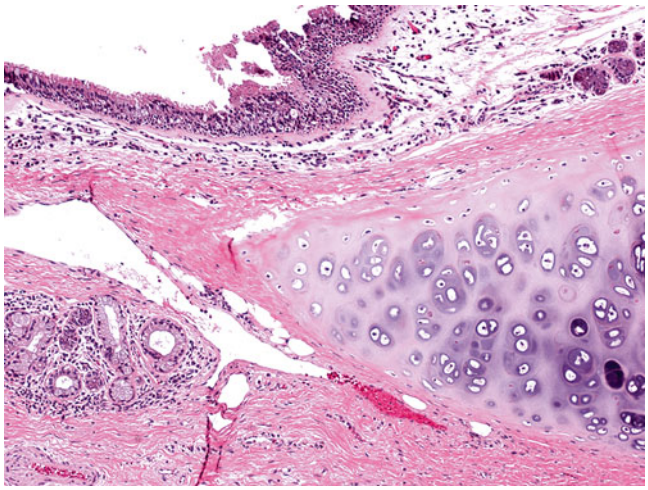

Fig. 28.2. Bronchogenic cyst. Cyst lining contains normal ciliated respiratory epithelium submucosal glands (*lower left*) and hyaline cartilage, features seen in normal bronchials.

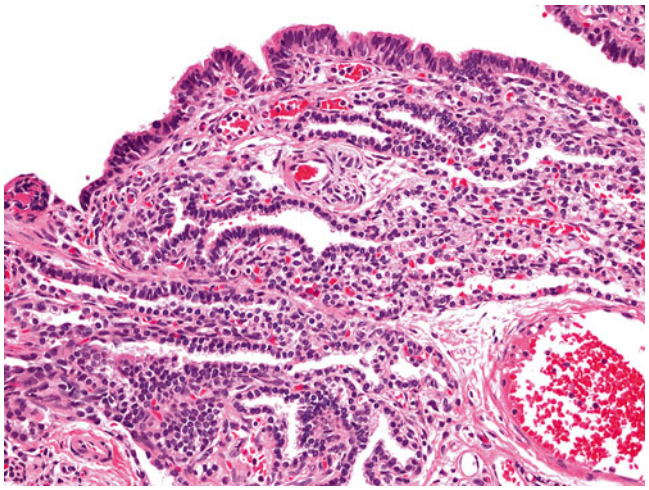

Fig. 28.3. Type I congenital pulmonary airway malformation. Pseudostratified respiratory-like epithelium and, in some areas, are more cuboidal epithelium line the cyst spaces. There are mixed inflammatory cells within the interstitium.

### *Macroscopic*

- Five types of lesion
  - Type 0 – Malformation of proximal tracheobronchial tree; acinar dysplasia or dysgenesis
  - Type I
    - Most frequent type (>65% of CPAMs)
    - One or more large cysts; cured with surgical removal
    - May progress to lepidic type adenocarcinoma in older children/adults
  - Type II
    - Multiple, small, uniform cysts 0.5–2.0 cm; poor prognosis
    - Rhabdomyomatous dysplasia is a rare subgroup
  - Type III – Spongy tissue; no cysts; large bulky lesion with mediastinal shift; poor prognosis
  - Type IV – Large (up to 7 cm) thin-walled cystic lesions usually in periphery of lobe

### *Microscopic (Fig. 28.3)*

- Type 0 – Bronchial-like structure with respiratory epithelium, smooth muscle, and cartilaginous plates
- Type I – Pseudostratified, primitive epithelium; cartilaginous islands; may progress to lepidic adenocarcinoma
- Type II – Ciliated cuboidal or columnar epithelium
- Type III – Randomly distributed bronchial-like structures with ciliated cuboidal epithelium
- Type IV – Thinned type I and type II alveolar lining cells

### *Differential Diagnosis*

- Extralobar sequestration
  - Located outside of pleura
  - Have a separate arterial blood supply

## Diffuse Pulmonary Lymphangiomatosis

### *Clinical*

- Occurs in young children; presents with wheezing and dyspnea; slowly progressive
- Sporadic

### *Macroscopic*

- Firm, lobulated lung

### *Microscopic*

- Proliferation of dilated, endothelial-lined spaces; may have smooth muscle in walls
- Expands pleura and interlobular septa

### *Differential Diagnosis*

- Lymphangioleiomyomatosis
  - Occurs only in women of reproductive years
  - Smooth muscle is HMB45+
- Lymphangiectasis
  - Dilated channels but not increased number
  - Can be a component of chromosomal disorders (Turner or Down syndrome)

## Bronchopulmonary Dysplasia (BPD)

### *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, and retractions and may have an associated pulmonary hypertension

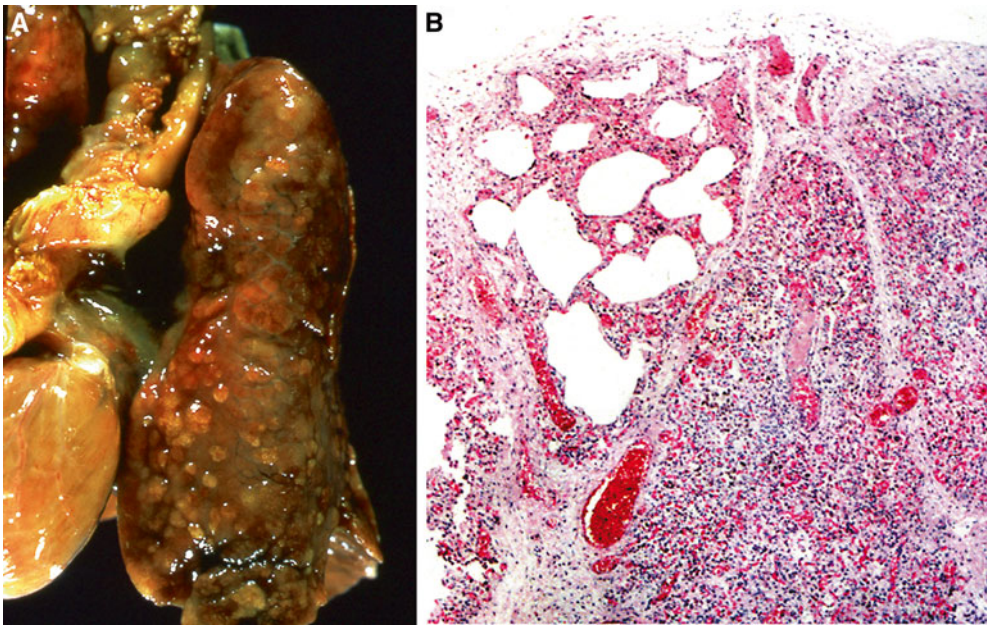


Fig. 28.4. Bronchopulmonary dysplasia (**A**, **B**). Late BPD shows a cobblestoning gross appearance (**A**) due to underlying alternating areas of overdistension and fibrosis (**B**). Courtesy of Beverly Dahms M.D., Case Western Reserve University.

### *Macroscopic (Fig. 28.4A)*

- Early BPD in nonsurfactant-treated infants resembles RDS with firm, congested, and heavy lungs
- Late BPD has pleural cobblestoning caused by underlying parenchymal areas that alternate between overdistension and fibrosis

### *Microscopic (Fig. 28.4B)*

- Early BPD has hyaline membranes with necrotizing bronchiolitis, atelectasis, and interstitial edema
- Late BPD has lobules which alternate between interstitial fibrosis and distension. Lobules with distension have constrictive bronchiolitis as a sequela of the necrotizing bronchiolitis from the early BPD

### *Differential Diagnosis*

- Early BPD is similar to DAD
- Late BPD has features of emphysema, interstitial fibrosis, and constrictive bronchiolitis

## Infantile (Congenital) Lobar Emphysema

### *Clinical*

- Most frequent lung malformation
- Lobar overinflation within the first 6 months of life; presents with respiratory distress
- M:F = 1.8:1

### *Macroscopic*

- Lung is overinflated
- Most commonly found in the left upper lobe

### *Microscopic*

- Alveolar ducts and alveoli are distended (classic form)
- Absolute increase in the number of alveoli (hyperplastic form)

### *Differential Diagnosis*

- Congenital pulmonary airway malformation, type IV
- Congenital lobar inflation
  - Normal number of alveoli

## Interstitial Pulmonary Emphysema

### *Clinical*

- Occurs in two forms:
  - Acute interstitial pulmonary emphysema (AIPE)
  - Persistent interstitial pulmonary emphysema (PIPE)
- Found in infants over ventilated and in infants of low birth weight
- Incidence decreased with the use of synthetic surfactant and high-frequency oscillatory ventilation
- Complications include pneumothorax, pneumomediastinum, and pneumopericardium

### *Macroscopic*

- AIPE: Spherical cysts in interstitial air spaces
- PIPE: Irregular and channel-like cysts in interstitial air spaces

### *Microscopic*

- Air within the connective tissue and possibly the lymphatics, of the perivascular and interlobular septa
- Cysts formed have no lining
- Adjacent parenchyma may display changes of hyaline membrane disease (HMD) of bronchopulmonary dysplasia (BPD)

- AIPE: No fibrosis or giant cell reaction in cyst wall
- PIPE: Fibrosis and giant cell reaction in cyst wall

### *Differential Diagnosis*

- Pulmonary lymphangiectasis or lymphangiomatosis may mimic microscopically, but antibody D2-40 will label lymphatic endothelium and help to distinguish

## Pediatric Interstitial Lung Disease

### *Clinical*

- Interstitial lung disease presenting in the pediatric popular (<18 years of age) is quite rare
- In children <2 years of age, the term childhood interstitial lung disease in infancy (chILD) is used
- Causes of chILD include surfactant dysfunction mutations, including surfactant protein B and surfactant protein C, ABCA3, and TTF1 (NKX2.1) gene mutations, and storage disorders

### *Macroscopic*

- Varies depending upon interstitial disease involvement; consolidation, fibrosis, and hemorrhage

### *Microscopic*

- Desquamative interstitial pneumonia (DIP) and lymphocytic interstitial pneumonia (LIP) are most commonly seen
- DIP in children is not linked to smoking
- PAP, chronic interstitial pneumonia usually seen in surfactant gene mutation-related chILD

### *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 (panlobular)
    - Alpha-1-protease inhibitor deficiency (ZZ); lower lobes most affected
    - Can be seen in talc IV drug abuse and in Ritalin use
  - Localized (distal acinar)
    - May contribute to spontaneous pneumothoraces and bullae formation in tall, asthenic male adolescent
  - Paracicatricial (irregular) emphysema
    - Most common type; around area of fibrosis

### *Macroscopic*

- May manifest as bullae-alveolar spaces >1 cm or blebs-representing airspaces made by dissection through connective tissue

### *Microscopic*

- Alveolar wall destruction distal to terminal bronchioles
- No fibrosis
- Four major types
  - Centrilobular (proximal acinar): proximal part of acini (Fig. 28.5A, B)
  - Panacinar: acini are uniformly involved (Fig. 28.5C)
  - Localized: peripheral acinar involved
  - Paracicatricial emphysema: emphysema adjacent to fibrosis

### *Differential Diagnosis*

- Congenital lobar overinflation
  - No destruction of alveoli
- Honeycomb lung
  - Fibrosis with metaplastic columnar epithelium

## Large Airway Disease

### Chronic Bronchitis

### *Clinical*

- "Blue bloater"
- Most common etiology is cigarette smoking

### *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 upper lobe

### *Microscopic*

- Thickened basement membranes; mucous plugs; goblet cell hyperplasia
- Submucosal gland hypertrophy; may show eosinophilic infiltrate
- Smooth muscle hypertrophy
- Curschmann spirals, Charcot–Leyden crystals, Creola bodies

### *Differential Diagnosis*

- Chronic bronchitis

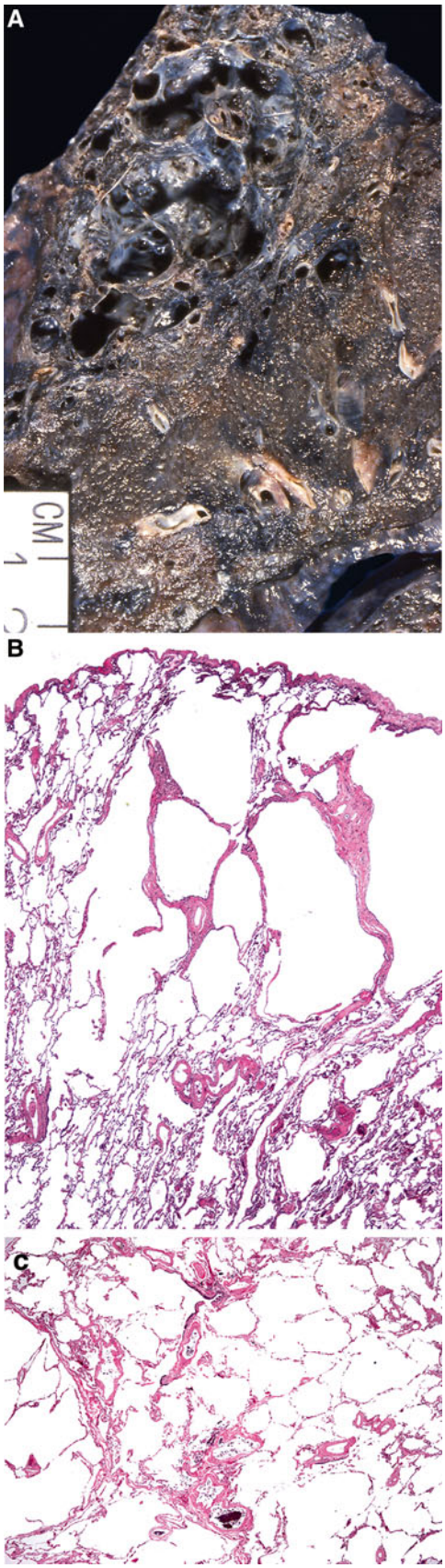


Fig. 28.5. Emphysema (**A**, **B**, centrilobular; **C**, panacinar). *Upper*

– Histology very similar to asthma, except found only in smokers

### *Bronchiectasis*

#### *Clinical*

- Causes include postinflammatory, postobstructive; seen in setting of cystic fibrosis, ciliary disorders, immunologic deficiencies, and idiopathic
- Recurrent pneumonias with productive cough; hemoptysis; recurrent fevers
  - Cystic fibrosis

#### *Macroscopic (Fig. 28.6A)*

- Diffuse or localized enlarged, fibrotic cartilaginous airways; dilated airways extend to pleural surface; commonly filled with mucopurulent material

#### *Microscopic (Fig. 28.6B)*

- 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

## Small Airway Disease

### *Respiratory Bronchiolitis (Smoker's)*

#### *Clinical*

- Incidental findings in smokers

#### *Microscopic (Fig. 28.7)*

- Pigmented macrophages within terminal bronchioles and surrounding alveoli
- Mild chronic inflammation, fibrosis

### *Follicular Bronchiolitis*

#### *Clinical*

- Rare small airway disease; usually associated with collagen vascular diseases, including Sjögren disease and rheumatoid arthritis, and with immunodeficiencies

#### *Microscopic (Fig. 28.8)*

- Marked chronic inflammatory infiltrate surrounding small bronchioles; germinal centers are frequent; acute inflammatory cells within lumen can be seen
- Can be considered part of Diffuse Lymphoid Hyperplasia (see DLHP/LIP below)

**Fig. 28.5** (continued) lobe tissue destruction with bulla formation is characteristic of centrilobular emphysema (**A**). In this form, alveolar wall area destroyed in the area surrounding the bronchovascular area at the proximal and center of the respiratory lobule (**B**). In panacinar emphysema, tissue destruction results in a more even loss of alveolar walls throughout the lobule (**C**).

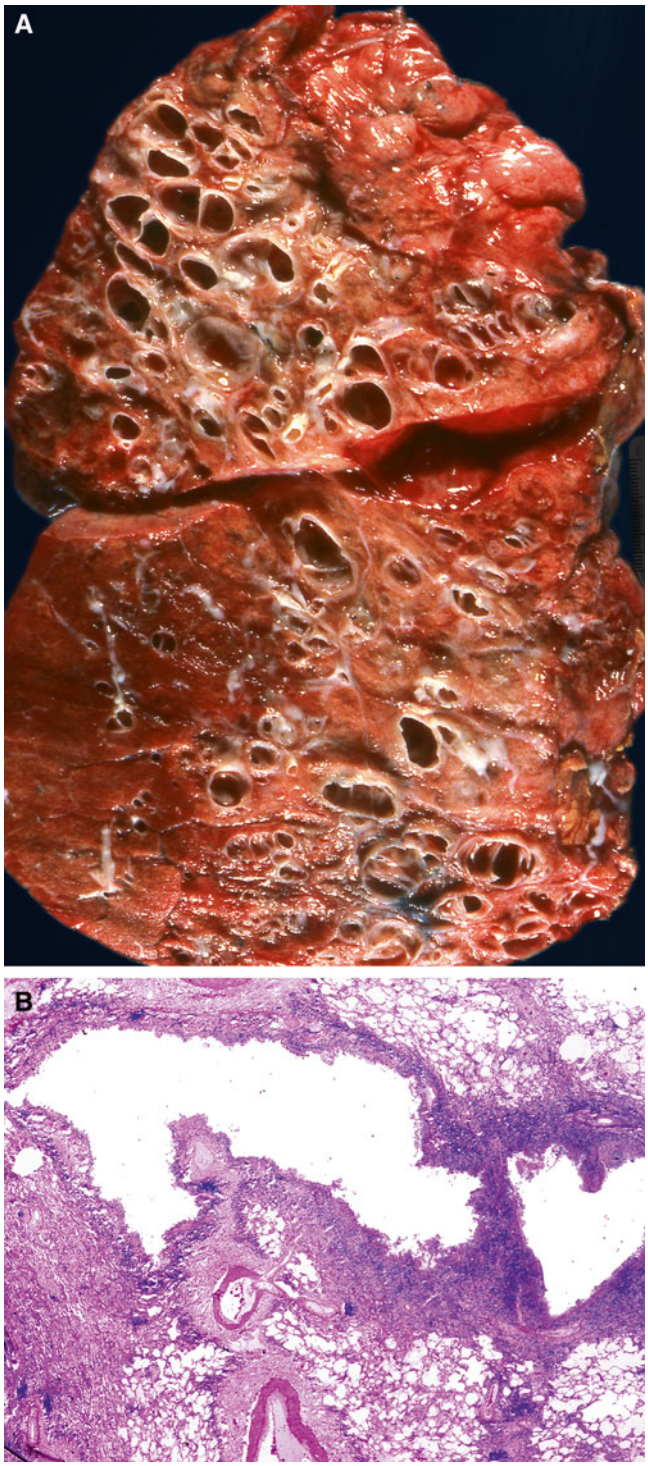


Fig. 28.6. Bronchiectasis. Diffuse airway enlargement, fibrosis, and remodeling occur in this lung with cystic fibrosis (**A**). The airways are irreversibly distended and surrounded by a lymphoplasmacytic infiltrate. The overlying respiratory epithelium many times shows a metaplastic squamous epithelium (**B**).

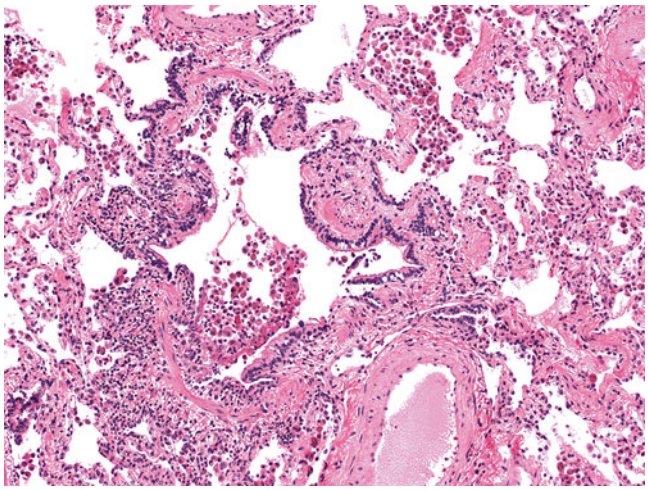

Fig. 28.7. Respiratory bronchiolitis. Pigmented macrophages accumulate around a small airway with chronic remodeling changes consisting of increased smooth muscle and mild fibrosis.

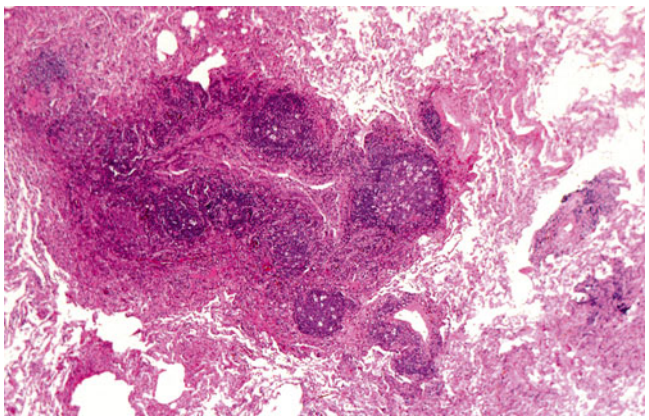

Fig. 28.8. Follicular bronchiolitis. A marked chronic inflammatory infiltrate with germinal centers surrounds small airways.

### *Constrictive (Obliterative) Bronchiolitis*

#### *Clinical*

- Complication of lung or bone marrow transplantation; drug toxicity; connective tissue disease and idiopathic disease

#### *Microscopic (Fig. 28.9)*

- Bronchiolar and peribronchiolar fibrosis with narrowing and eventual obliteration of the lumen; may be preceded by a lymphocytic bronchiolitis

### *Diffuse Panbronchiolitis*

#### *Clinical*

- Seen almost exclusively in Japan; association with HLA BW54
- Etiology unknown; erythromycin offers some benefit

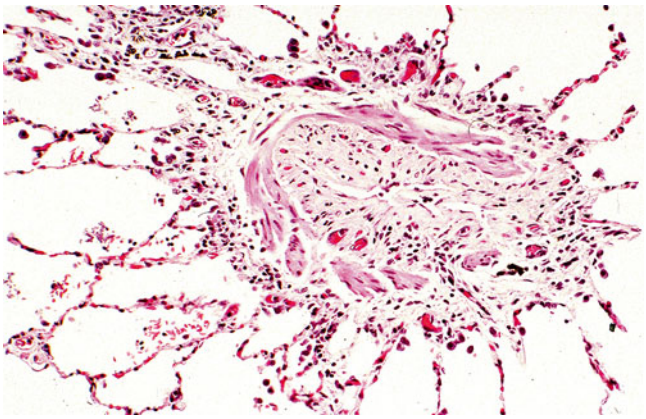

Fig. 28.9. Constrictive (obliterative) bronchiolitis. Collagenous-type fibrosis narrows and eventually obliterates the lumen of the small airways.

### *Microscopic*

- Dense peribronchiolar infiltrate with characteristic foamy macrophages within the walls of the small bronchioles

## Interstitial Diseases

### Acute Lung Injury

#### *Diffuse Alveolar Damage/Acute Interstitial Pneumonia*

### *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/gray diffuse consolidation

### *Microscopic (Fig. 28.10A, 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, reepithelialization and organization within airways.
  - Acute and organizing thrombi within vessels are common

### *Differential Diagnosis*

- Organizing pneumonia including cryptogenic organizing pneumonia (COP)/bronchiolitis obliterans organizing pneumonia (BOOP)
  - More subacute clinical course.

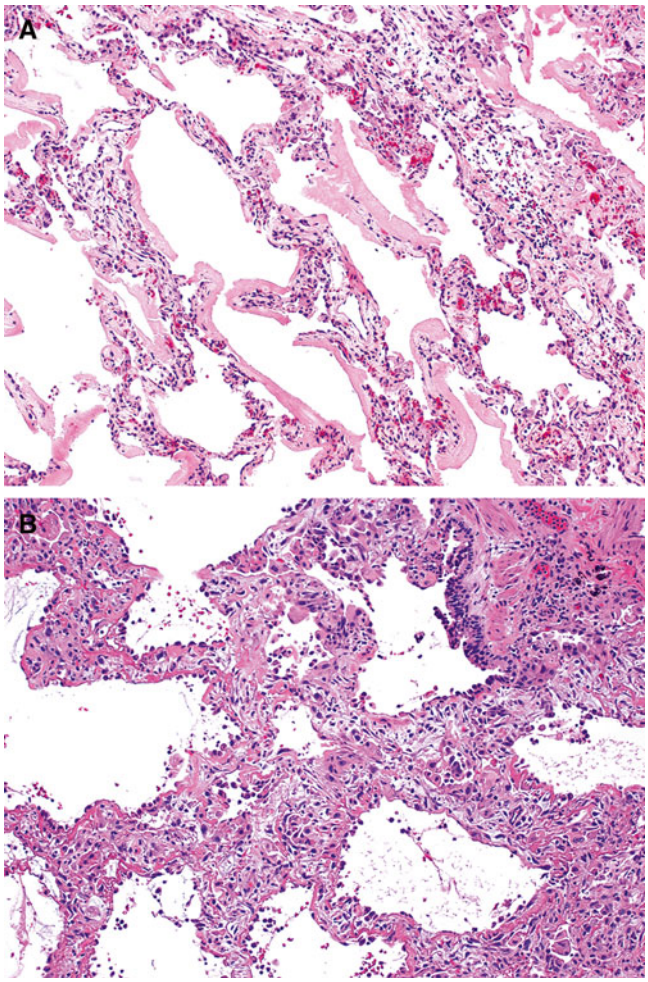


Fig. 28.10. Acute and organizing diffuse alveolar damage. Hyaline membranes in the alveolar spaces (**A**) and are eventually organized into and widen the interstitium (**B**).

  - Process is patchy around bronchioles.
  - Hyaline membranes are not seen.
  - Organization is intraluminal.

#### *Organizing Pneumonia (COP)/Bronchiolitis Obliterans Organizing Pneumonia (BOOP)*

### *Clinical*

- A general term found in three clinical scenarios: postinfection repair process, systemic diseases such as collagen vascular disease (bronchiolitis obliterans organizing pneumonia (BOOP)), and idiopathic (cryptogenic organizing pneumonia (COP))
- Subacute onset of cough, dyspnea, and fever; multiple patchy airspace opacities, usually bilateral, on chest imaging
- Treated with steroids; excellent prognosis

### *Microscopic (Fig. 28.11)*

- Temporally uniform injury
- Patchy, immature fibroblastic proliferations within bronchiolar lumina and peribronchiolar airspaces; usually sharply demarcated with adjacent normal parenchyma

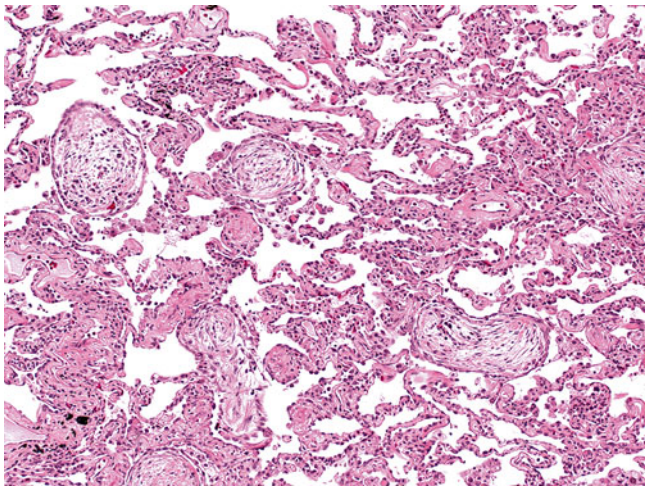

Fig. 28.11. Cryptogenic organizing pneumonia (COP)/bronchiolitis obliterans organizing pneumonia (BOOP). Organizing fibrosis in the form of fibroblastic proliferation is present within the bronchiolar and alveolar airspaces. The adjacent alveolar walls are relatively unremarkable.

- 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 heterogeneous injury.
  - Interstitial fibrosis is predominantly subpleural and paraseptal with scattered fibroblastic foci.
  - Collagen deposition honeycomb foci can be found.

## Idiopathic Interstitial Pneumonias

### *Respiratory Bronchiolitis-Associated Interstitial Lung Disease (RB-ILD)*

### *Clinical*

- Smokers' disease
- Dyspnea, cough, mild restrictive defects
- Chest imaging usually normal; may present as interstitial infiltrates

### *Microscopic*

- Finely granular-pigmented macrophages accumulate within lumens of distal bronchioles and surrounding alveoli
- Mild chronic inflammation and fibrosis

### *Differential Diagnosis*

- Desquamative interstitial pneumonia
  - Mild interstitial fibrosis
- Pulmonary Langerhans cell histiocytosis (PLCH)
  - Characteristic nodules with Langerhans cells (S-100 protein+, CD1a+)
  - Peribronchiolar-based Langerhans cells

### *Desquamative Interstitial Pneumonitis (DIP)*

### *Clinical*

- Usually in middle-aged adults, 90% are smokers; insidious onset of dyspnea
- Chest imaging: bilateral, lower lobe, ground-glass opacities
- Favorable response to corticosteroids
- Mean survival = 12 years

### *Microscopic (Fig. 28.12)*

- Striking pigmented macrophages within alveolar spaces; type II pneumocyte hyperplasia with subtle interstitial fibrosis
- Diffuse process; temporally uniform

### *Differential Diagnosis*

- DIP-like reaction of UIP
  - Temporally heterogeneous pattern of injury
- Pulmonary Langerhans cell histiocytosis (PLCH)
  - Patchy distribution; predominantly bronchiolar
  - Tightly packed macrophages (Langerhans cells)
  - Can be found in patients <40 years old
- Respiratory bronchiolitis-associated interstitial lung disease
  - No interstitial fibrosis
  - Less macrophage accumulation and more airway centered

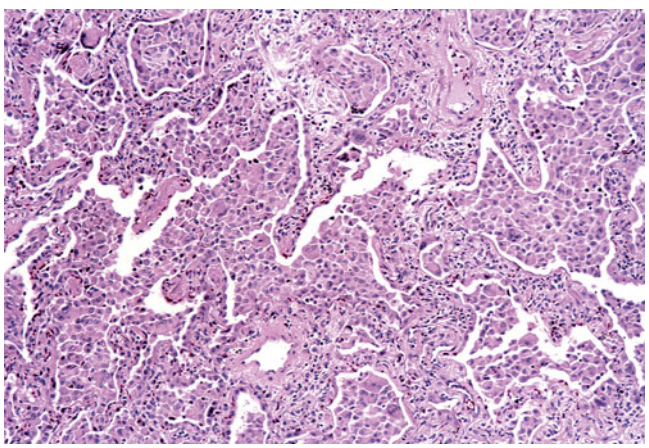

Fig. 28.12. Desquamative interstitial pneumonitis. Abundant pigmented macrophages fill the alveolar spaces. Reactive type II pneumocytes line the alveolar walls.

## Usual Interstitial Pneumonitis

### Clinical

- Insidious onset of dyspnea with chronic, progressive downhill course
- Most patients are 40–70 years old; collagen vascular diseases are commonly present
- 60% of patients die; mean survival 3 years

### Macroscopic (Fig. 28.13A)

- Honeycomb changes most advanced at bases and periphery

### Microscopic (Fig. 28.13 B, C)

- Temporally heterogeneous 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 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 are common
- Vascular changes of intimal fibroplasia and medial hypertrophy are common

### Differential Diagnosis

- DIP
  - Macrophage accumulation is diffused.
  - Injury is temporally uniform
- COP/BOOP
  - Injuryis temporally uniform
  - Clinical course is subacute
  - Fibroblastic foci are more pronounced
  - Areas of dense collagen deposition are absent
- Nonspecific interstitial pneumonia/fibrosis (NSIP)
  - Injury is temporally uniform

## Nonspecific Interstitial Pneumonia/Fibrosis

### Clinical

- Dyspnea and cough over several months; bilateral interstitial infiltrates on chest imaging
- Middle-aged adults; underlying connective tissue disease is common; idiopathic
- Cellular form is usually steroid responsive with good prognosis
- Fibrotic form may act similar to UIP

### Microscopic (Fig. 28.14)

- Two types
  - Cellular

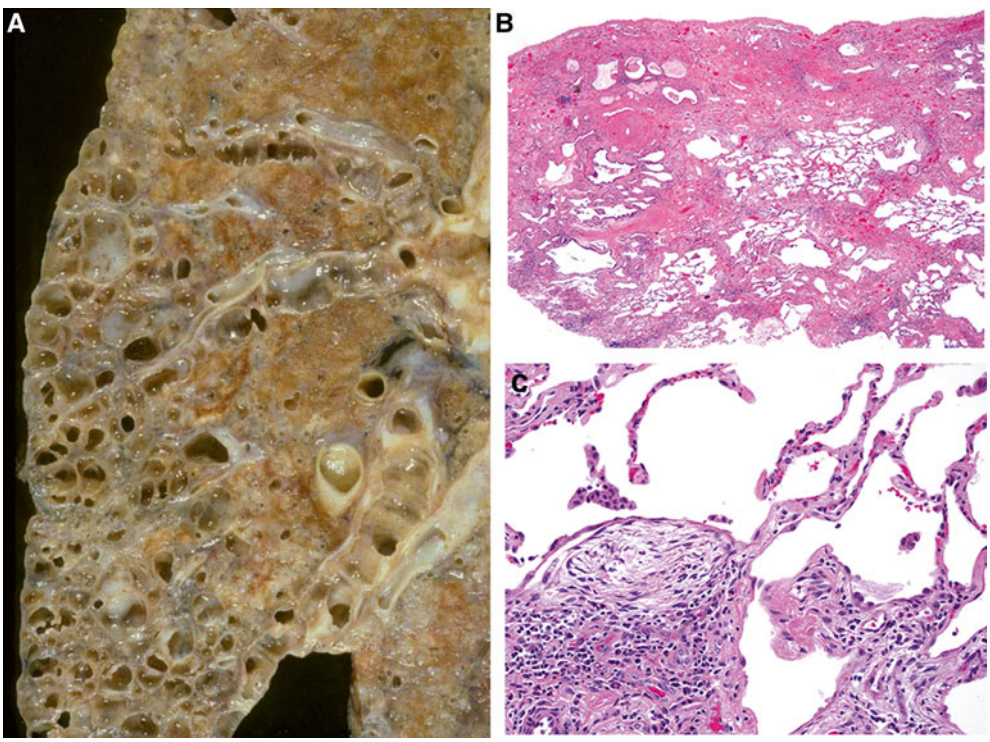


Fig. 28.13. Usual interstitial pneumonia with honeycomb changes (**A**, **B**) and fibroblastic foci (**C**). Honeycomb airspaces filled with mucous are present in the base of the lobe (**A**). The chronic inflammation and fibrosis in this pattern of injury have a variegated low-power appearance (**B**) with characteristic fibroblastic foci intervening between the normal and the fibrotic areas of the lung (**C**).

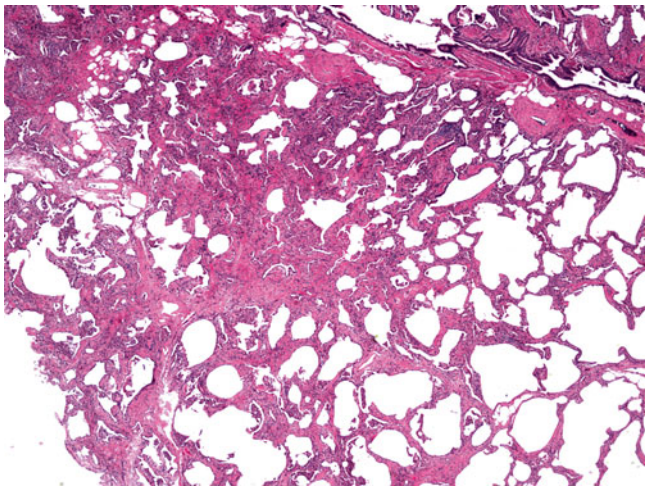

Fig. 28.14. Nonspecific interstitial pneumonia. A chronic, lymphocytic infiltrate is present in the alveolar walls, and the overall lung architecture is preserved in this cellular type of NSIP.

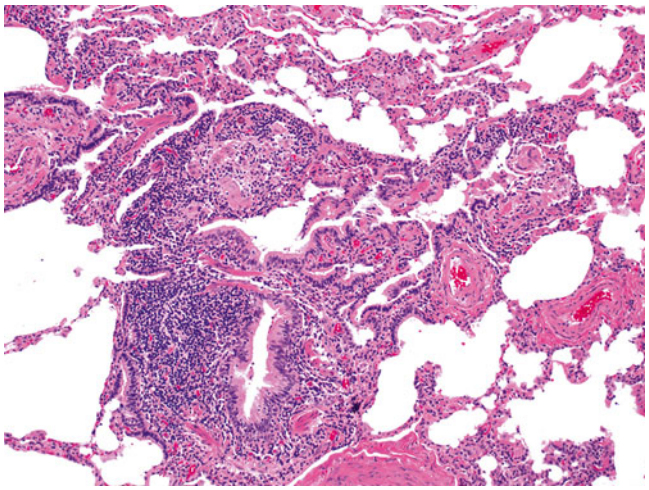

Fig. 28.15. Extrinsic allergic alveolitis/hypersensitivity pneumonitis. A prominent cellular bronchiolitis along with an interstitial pneumonitis is a major component.

- Interstitial chronic inflammation with lymphocytes and plasma cells
- Preserved lung architecture

– Fibrosing
- Patchy or diffuse temporally uniform interstitial fibrosis

### *Differential Diagnosis*

♦ Usual interstitial pneumonia
– Injury is temporally heterogeneous with fibroblastic foci
– Collagen deposition and honeycomb changes are seen
– Diffuse Lymphoid hyperplasia/Lymphocytic interstitial pneumonia here

## *Extrinsic Allergic Alveolitis (Hypersensitivity Pneumonitis)*

### *Clinical*

♦ Insidious onset of dyspnea with dry cough, fatigue, and malaise
♦ Exposure source not identified in 67% of cases diagnosed by pathology; diffuse interstitial infiltrates on chest X-ray
♦ Corticosteroids help after exposure has been eliminated

### *Microscopic (Fig. 28.15)*

♦ Triad of features: interstitial pneumonitis; chronic bronchiolitis with areas of organizing pneumonia and ill-formed, non-necrotizing granulomas or giant cells in parenchyma

### *Differential Diagnosis*

♦ Usual interstitial pneumonia
– Injury is temporally heterogeneous.
– Granulomas usually not seen
♦ Sarcoidosis
– Interstitial pneumonia, if present, is very mild.
– Granulomas are well formed in lymphatic distribution
♦ Lymphoid interstitial pneumonia
– Pathology is more diffusely distributed.
– Does not have areas of organizing pneumonia.

## *Eosinophilic Pneumonia*

### *Clinical*

♦ Four clinical categories:
– Simple: Loeffler 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, parasites, inhalants, and idiopathic)

### *Microscopic (Fig. 28.16)*

♦ Filling of alveolar spaces with eosinophils and variable number of macrophages
♦ Eosinophilic abscesses and necrosis of cellular infiltrate; organizing pneumonia is common
♦ Features of DAD have been seen in acute form; mild, nonnecrotizing vasculitis of small arterioles and venules common

### *Differential Diagnosis*

♦ Churg–Strauss syndrome
– Necrotizing granulomatous vasculitis is present
♦ Pulmonary Langerhans cell histiocytosis (PLCH)
– Infiltrate is interstitial and usually peribronchiolar.
– Seen only in smokers
♦ Desquamative interstitial pneumonitis
– Eosinophilic abscesses and necrosis of infiltrate rarely seen
– Vasculitis not seen

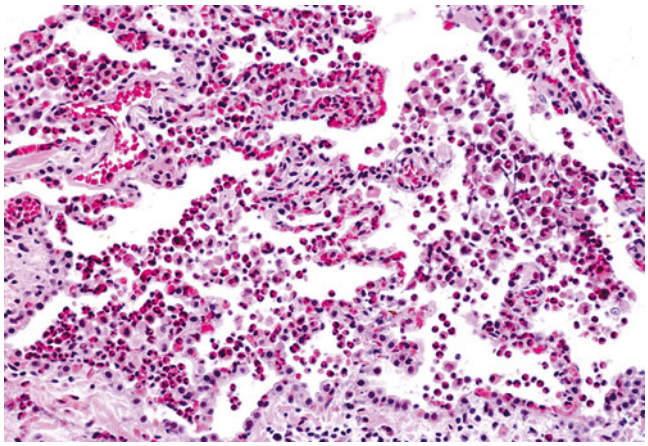

Fig. 28.16. Eosinophilic pneumonia. There are abundance eosinophils with scattered alveolar macrophages that fill the alveolar spaces.

## Pulmonary Langerhans Cell Histiocytosis

### Clinical

- Occurs almost exclusively in smokers; M:F=4:1; symptoms may be minimal; fourth decade
- Chest imaging: multiple, bilateral nodules 0.5–1.0 cm in upper lung lobes with cystic lesions

### Microscopic (Fig. 28.17A, B)

- Discrete, nodular/stellate lesions; bronchiolocentric
- Langerhans cell: convoluted (kidney-bean) nuclei

### Immunohistochemistry

- Langerhans cells: S100+, CDla+, HLR-DR+

### Electron Microscopy

- Birbeck granule ("tennis racket" morphology)

### Differential Diagnosis

- DIP
  - Interstitial lesion
- Respiratory bronchiolitis-associated interstitial lung disease
  - Does not destroy bronchiole
  - Minimal fibrosis
  - No Langerhans cells

## Sarcoidosis

### Clinical

- Most common in young, African-American female (20–35 years old)
- Deficient T-cell response (cutaneous T-cell anergy and decreased helper T cells)
- Associations: functional hypoparathyroidism; hypercalciuria ± hypercalcemia; erythema nodosum; uveitis
- Kveim test: granulomatous reaction following injection of human spleen extract
- Serum ACE (angiotensin-converting enzyme)

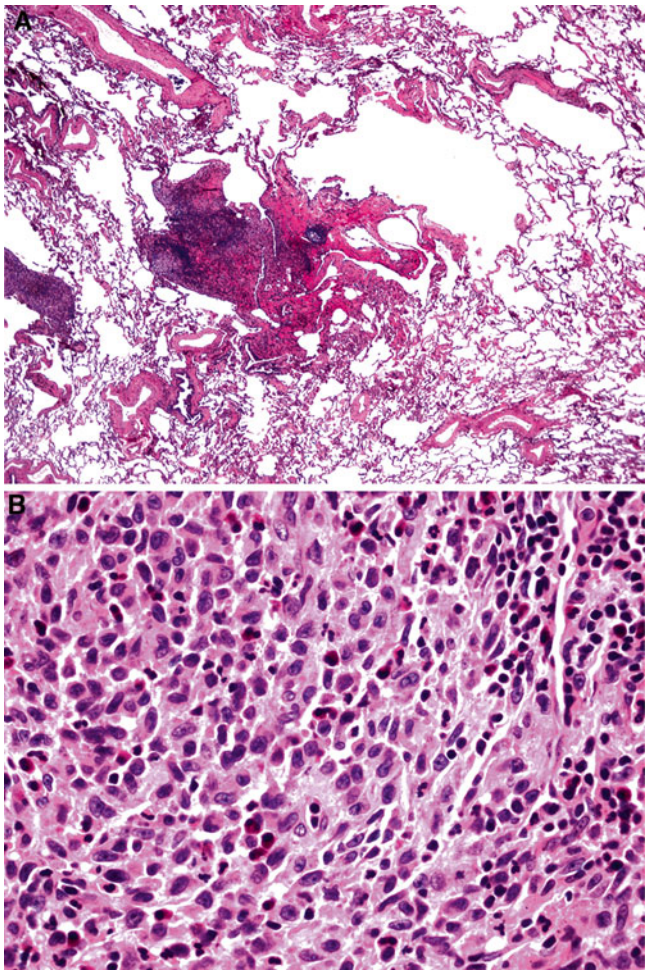


Fig. 28.17. Pulmonary Langerhans cell histiocytosis (eosinophilic granuloma). The cellular phase of this disease shows prominent bronchiolocentric inflammation that has a somewhat stellate shape (**A**); histiocytes with a kidney-bean-type appearance are present (**B**).

- 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: End-stage fibrosis with honeycombing

### Microscopic (Fig. 28.18)

- Interstitial noncaseating granulomata distributed in lymphatic and bronchovascular pathways; vascular and pleural involvement common

### Differential Diagnosis

- Chronic berylliosis
  - Elevated beryllium levels on tissue quantitation
  - Clinical history of beryllium exposure
- Extrinsic allergic alveolitis

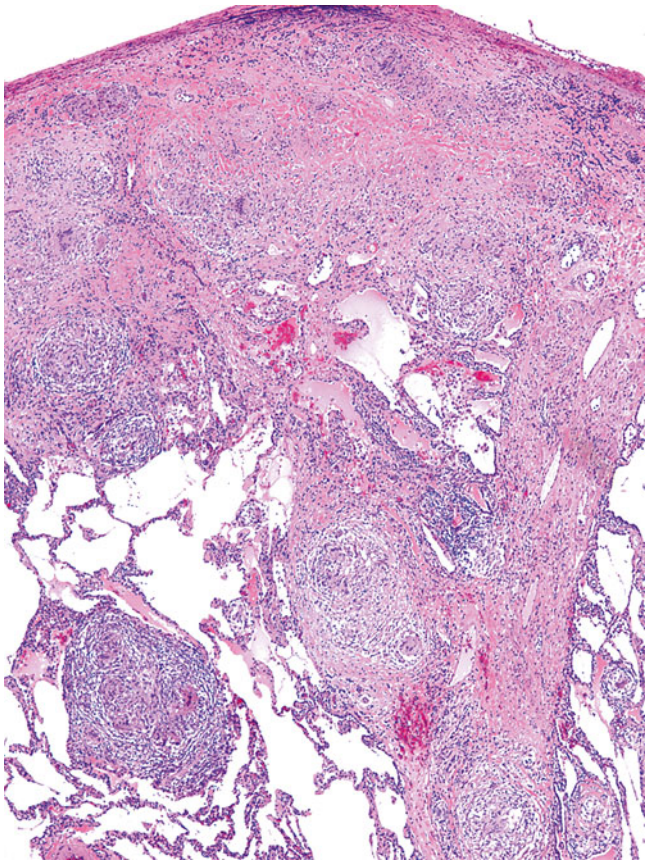

Fig. 28.18. Sarcoidosis. Predominantly nonnecrotizing granulomas with giant cells follow the subpleural and interlobular septa in a lymphatic type distribution.

  - Ill-formed granulomata; interstitial distribution
  - Accompanying interstitial pneumonia

### Pulmonary Alveolar Proteinosis

#### Clinical

- Etiologies: dusts, drug, immunodeficiency, leukemia, kaolin
- Bronchoalveolar lavage: treatment of choice
- Idiopathic or associated with infection
- Anti-GM-CSF circulating antibody found in idiopathic variant

#### Microscopic Features (Fig. 28.19)

- Accumulation of granular eosinophilic material in alveoli; PAS+ material

#### Electron Microscopy

- Lamellar body

#### Differential Diagnosis

- Pulmonary edema
  - Interstitial/septal edema
- Mycobacterial, nocardial, or *Pneumocystis* pneumonia
  - Positive special stains or microbiologic cultures

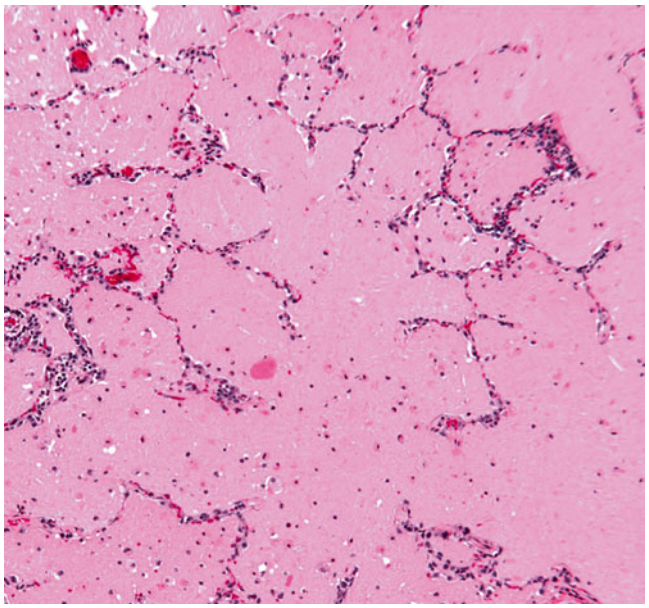

Fig. 28.19. Pulmonary alveolar proteinosis. An eosinophilic material fills the alveolar spaces; the alveolar walls are essentially unremarkable.

### Anti-Basement Membrane Antibody [ABMA] Disease (Goodpasture syndrome)

#### Clinical

- M: F=9:1; bimodal distribution of presentation (peaks at 30 and 60 years)
- Smokers; DRw15, DQw6
- Cytotoxic, antibody-mediated, immune reaction; antibodies to type IV collagen in serum cross-react to both kidney and lung
- Hemoptysis, anemia, azotemia, and diffuse lung infiltrates

#### Microscopic

- Extensive intra-alveolar hemorrhage; nonspecific type II pneumocyte hyperplasia
- Small vessel vasculitis may be present
- Iron encrustation of elastic fibers within interstitium and vessels may be present
- Mild interstitial fibrosis can be seen

#### Immunofluorescence:

- Linear staining of glomerular and pulmonary basement membranes for IgG

#### Differential Diagnosis

- Other causes of small vessel vasculitis
  - Absence of ABMA in tissue by immunofluorescence
- Idiopathic pulmonary hemosiderosis
  - Child and adolescent.
  - Immunofluorescent linear pattern is absent.
  - No acute hemorrhage.

### Idiopathic Pulmonary Hemosiderosis

#### Clinical

- Exclusively in children <16 years; M:F = 1:1
- Hemoptysis, hypoxemia, chest infiltrates; iron deficiency anemia
- *Stachybotrys chartarum* may be an etiologic agent
- Poor prognosis with death in majority at 2–5 years

#### Microscopic (Fig. 28.20)

- Intra-alveolar hemorrhage without capillaritis; alveolar wall thickening and type II pneumocyte hyperplasia
- Bronchoalveolar lavage with hemosiderin-laden macrophages in large numbers

#### Differential Diagnosis

- ABMA Disease
  - Linear immunofluorescence pattern (IgG)
  - Kidney involvement

## Pneumoconioses

- A nonneoplastic 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 bronchovascular bundles, in subpleural and interseptal areas

#### Microscopic (Fig. 28.21)

- Discrete foci of concentric layers of hyalinized collagen; dust-filled histiocytes are abundant; birefringent particles usually present
- When necrosis is present, consider complicating infection by mycobacterial tuberculosis

#### Differential Diagnosis

- Inactive mycobacterial or fungal infections
  - Giant cells and palisading histiocytes are 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 (Fig. 28.22)

- Marked interstitial fibrosis with minimal inflammatory infiltrate; UIP-like reactions common
- Presence of asbestos bodies, fibrosis, and exposure history is needed for definitive diagnosis
- Hyalinizing pleural plaques, pleural fibrosis, and rounded atelectasis can also be seen

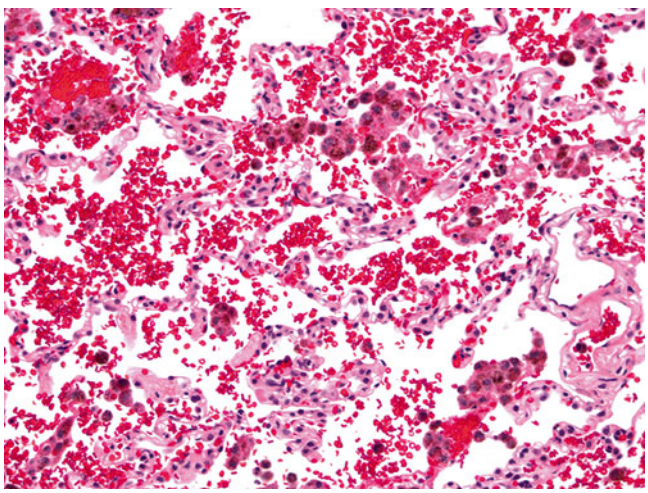

Fig. 28.20. Idiopathic pulmonary hemosiderosis. Hemosiderin-laden macrophages are abundant adjacent to mildly thickened alveolar septa with type II pneumocytes.

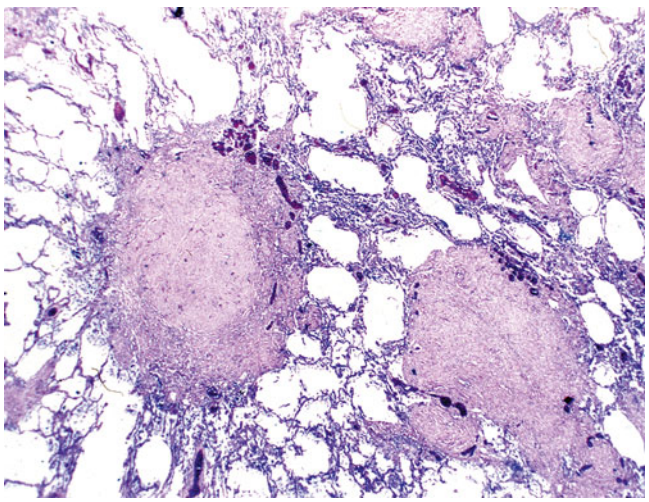

Fig. 28.21. Silicotic nodule. Multiple hyalinized nodules are adjacent to bronchioles.

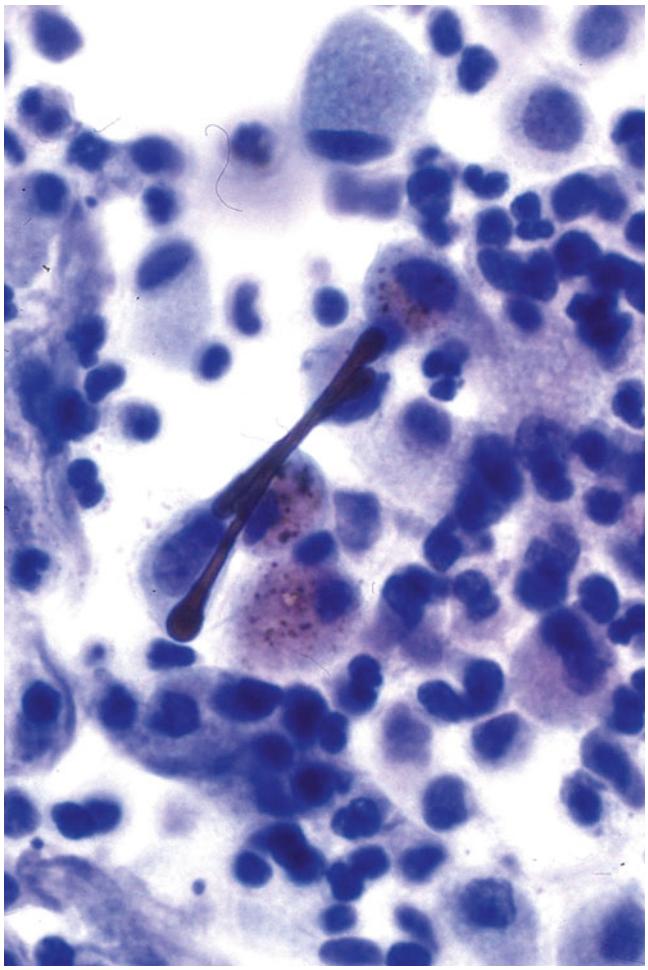

Fig. 28.22. Asbestos-related reactions – ferruginous body. Asbestos fiber within the core surrounded by a proteinaceous iron-containing coat takes on a dumbbell shape.

### *Differential Diagnosis*

- Usual interstitial pneumonia
  - Temporally heterogeneous
  - Lack of asbestos bodies

## *Coal Worker's Pneumoconiosis (CWP)*

### *Clinical*

- Simple: single nodule, <2 cm
- Complicated: >2 cm, including progressive massive fibrosis
- Caplan syndrome: rheumatoid nodule with CWP (progressive massive fibrosis)

### *Macroscopic (Fig. 28.23A)*

- Dense fibrosis and anthracosis, predominantly upper and middle lobes

### *Microscopic (Fig. 28.23B)*

- Hyalinized nodule with anthracotic pigment in lung and lymph nodes
- Macules adjacent to bronchioles; may have centrilobular emphysema

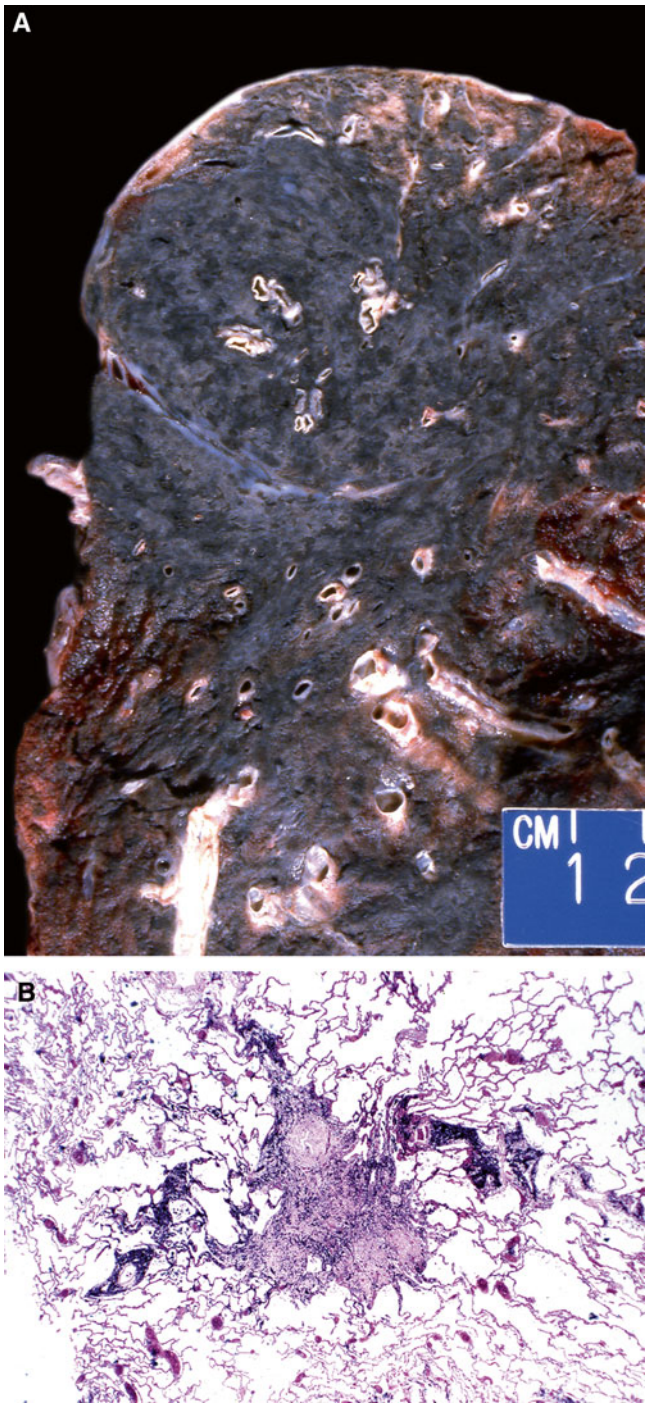


Fig. 28.23. Progressive massive fibrosis/coal worker's pneumoconiosis. Black/tan mass involves majority of the upper lobe (**A**); hyalinized nodule adjacent to the airway with emphysema (**B**).

## *Hard Metal Pneumoconiosis*

### *Clinical*

- Exposure to tungsten carbide and cobalt, usually in grinding, drilling, cutting, or sharpening
- Dyspnea with restrictive pulmonary function tests

### *Microscopic (Fig. 28.24)*

- Giant cell interstitial pneumonitis with interstitial fibrosis, peribronchiolar giant cells, and DIP-like reaction
- Giant cells are multinucleated and commonly engulf other inflammatory cells

### *Differential Diagnosis*

- Viral bronchiolitis/pneumonitis
  - No history of tungsten carbide/cobalt exposure
- Hypersensitivity pneumonitis
  - Increased interstitial and peribronchiolar inflammatory infiltrate
  - Nonnecrotizing granulomas

## Berylliosis

### *Clinical*

- Acute: Massive exposures produce acute respiratory distress syndrome-like pictures
- 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*

- Nonnecrotizing granulomas in a lymphatic distribution

### *Differential Diagnosis*

- Sarcoidosis
  - No history of beryllium exposure
- Infections (mycobacterial or fungal)
  - Necrotizing granulomas
  - More airway distribution

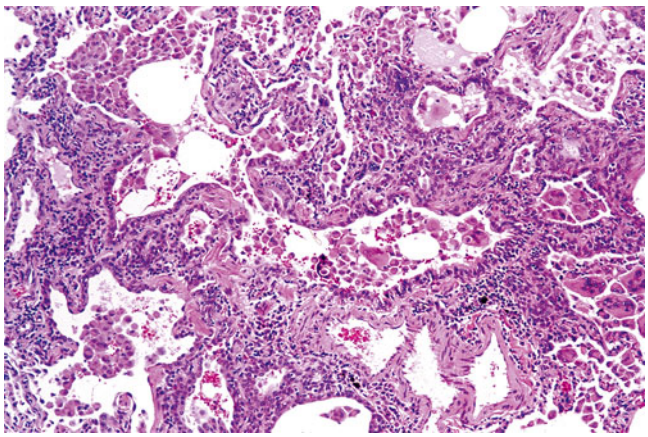

Fig. 28.24. Hard metal pneumoconiosis/giant cell pneumonitis. Peribronchiolar infiltrate with macrophages and scattered giant cells and prominent smooth muscle is seen in small airways.

# Vascular Conditions

## Vasculitides (Also See Chapter XX)

## Granulomatosis with Polyangiitis (GPA)

### *Clinical*

- Triad: upper airway, lower airway (lung), and kidney; saddle nose; rarely lung only (so-called limited)
- 40% of patients in remission are c-ANCA+ (anti-proteinase 3); 90% of patients with active disease are c-ANCA+
- Chest imaging: multiple well-demarcated peripheral nodules, lower lobes; rarely as a solitary pulmonary lobule

### *Microscopic (Fig. 28.25)*

- Triad: parenchymal (basophilic) necrosis, vasculitis, granulomatous inflammation
- 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

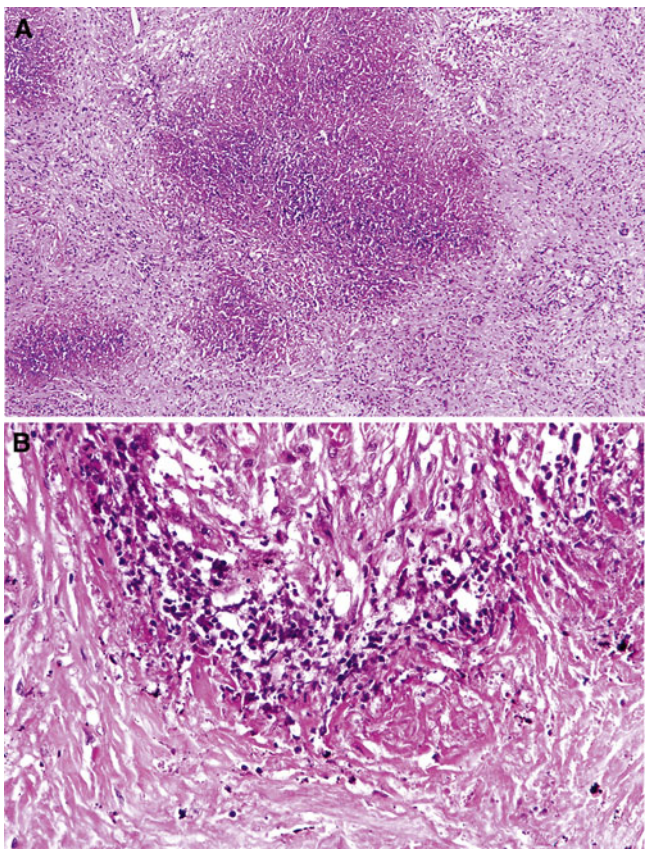


Fig. 28.25. Granulomatosis with polyangiitis. (**A**) Geographic necrosis. (**B**) Collagenous necrosis. A large area of basophilic necrosis (**A**) is lined by histiocytes and scattered giant cells (**B**).

Table 28.1. **Differential Diagnosis of Granulomatous Lesions**

| | *NSG* | *GPA* | *Infection* | *Churg–Strauss syndrome* | *Rheumatoid nodule* |
|---|---|---|---|---|---|
| Sarcoidal granuloma | ++ | – | ++ | + | – |
| Vasculitis | ++ | ++ | +/– | ++ | – |
| Necrosis | ++ | ++ | ++ | ++ | + |
| Hilar adenopathy | +/– | – | ++ | – | – |
| Cavitation | + | ++ | + | ++ | + |
| Asthma/peripheral eosinophilia | – | – | – | + | – |
| Tissue organismal stains (fungal/mycobacterial) | – | – | + | – | – |

### *Differential Diagnosis (Table 28.1)*

- Lymphomatoid granulomatosis
  - Atypical cytology
- Granulomatous infections
  - Well-formed, nonnecrotizing granulomas
  - Eosinophilic necrosis
- Rheumatoid nodules
  - Found only in the setting of clinical rheumatoid arthritis
  - Usually subpleural
- Necrotizing sarcoid granulomatosis
  - Well-formed nonnecrotizing granulomas in lymphatic distribution in lung adjacent to necrobiotic nodule

## *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 28.1)*

- Chronic eosinophilic pneumonia
  - Nongranulomatous
- Allergic bronchopulmonary aspergillosis
  - Bronchocentric
- Drug-induced vasculitis
- Polyarteritis nodosa
  - Rarely involves the lung
- Granulomatosis with polyangiitis
  - Geographic necrosis

## *Necrotizing Sarcoid Granulomatosis (NSG)*

### *Clinical*

- F:M = 2.2:1; variable age presentation; cough, chest pain, weight loss, fever
- No systemic vasculitis
- Chest imaging: bilateral lung nodules, usually lower lobe; hilar adenopathy is present in <10% of cases

### *Microscopic*

- Lymphoplasmacytic or granulomatous vasculitis; parenchymal necrosis without necrotizing vasculitis; numerous caseating sarcoid-like granulomas

### *Differential Diagnosis (Table 28.1)*

- Granulomatosis with polyangiitis (GPA)
  - No sarcoidal granulomas
- Infection:
  - Vasculitis not a prominent component
  - Positive 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 erythematosus, Wegener granulomatosis, Henoch–Schönlein purpura, cryoglobulinemia, Behçet disease, drug reactions (sulfonamides), and Goodpasture disease

### *Microscopic (Fig. 28.26)*

- Focal necrosis of alveolar septa with neutrophilic infiltration, capillary fibrin thrombi, and interstitial hemorrhage/hemosiderosis
- Often associated with foci of DAD

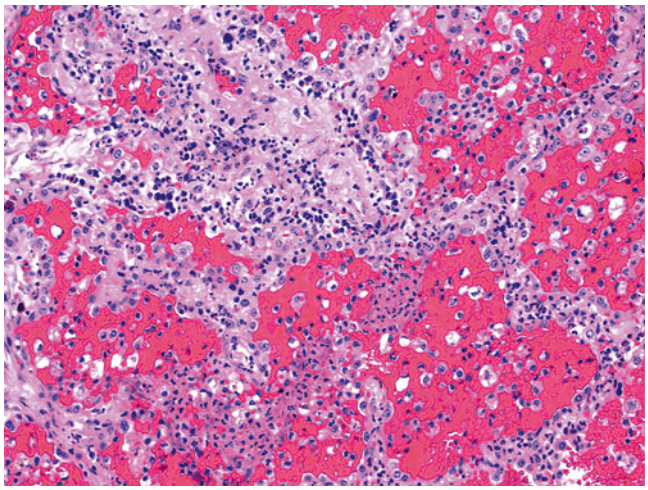

Fig. 28.26. Necrotizing capillaritis. A neutrophilic infiltrate involves the alveolar septa capillaries.

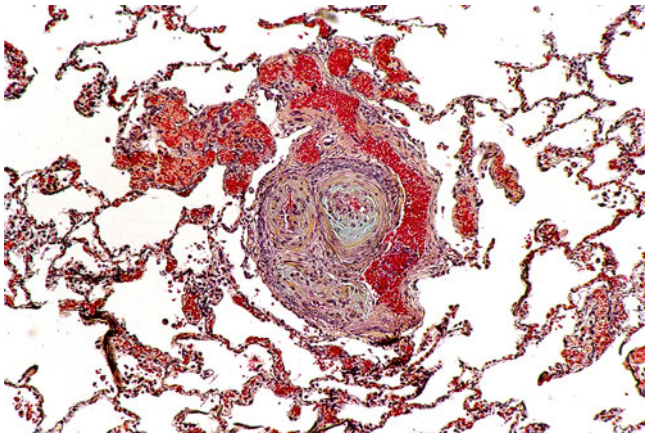

Fig. 28.27. Pulmonary hypertension – plexogenic arteriopathy. A plexogenic lesion contains a remodeled artery wall with abnormal vascular spaces lined by myofibroblasts.

### *Differential Diagnosis*

- Acute hemorrhagic bronchopneumonia
  - Neutrophils predominate in alveolar space

## Pulmonary Hypertension

### *Pulmonary hypertension (PH)*

### *Clinical*

- Idiopathic pulmonary hypertension
  - F:M 1.7:1
- Familial (FPAH)
  - Germline mutations in BMPR2 (chromosome 2q31-32)
- Associated with:
  - Collagen vascular disease
  - Congenital cardiac shunts
  - Portal hypertension
  - HIV infection
  - Drugs and toxins
  - Aminorex fumarate

### *Microscopic (Fig. 28.27)*

- Pathologic changes from low grade to high grade
  - Muscularization of pulmonary arteries
  - Cellular intimal proliferation
  - Intimal concentric laminar fibrosis
  - Plexiform lesions
  - Plexiform and angiomatoid lesions
  - Necrotizing arteritis

### *Pulmonary Veno-Occlusive Disease with Secondary Pulmonary Arterial Hypertension*

### *Clinical*

- Rare form of pulmonary hypertension; 33% occur in children
- Causes: drug toxicity, especially chemotherapeutics, viral infections

### *Microscopic (Fig. 28.28)*

- Congestive changes with hemosiderin-laden macrophages
- Pulmonary hypertensive changes
- Intimal fibrosis and thrombosis of veins; recanalization is common

### *Pulmonary Capillary Hemangiomatosis*

### *Clinical*

- Rare cause of pulmonary hypertension; most patients between 20 and 40 years old

### *Microscopic*

- Abnormal proliferation of capillary-like vessels in alveolar septa; patchy hemosiderin
- May have secondary venous changes with intimal fibrosis

### *Thrombotic Arteriopathy*

### *Clinical*

- Sudden shortness of breath with pleuritic pain

### *Macroscopic (Fig. 28.29)*

- Hemorrhagic wedge-shaped peripheral lesions

### *Microscopic (Fig. 28.30)*

- Eccentric intimal fibrosis; colander lesions common; widespread small vessel thrombi

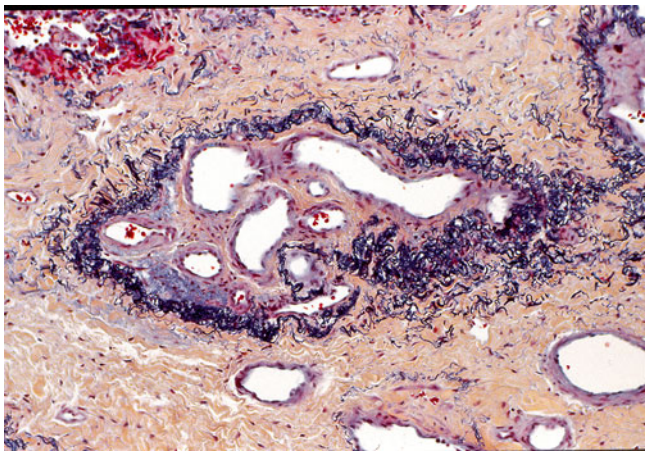

Fig. 28.28. Pulmonary veno-occlusive disease (PVOD). A vein containing prominent intimal fibrosis and recanalization (colander lesion) is characteristically found in this disease.

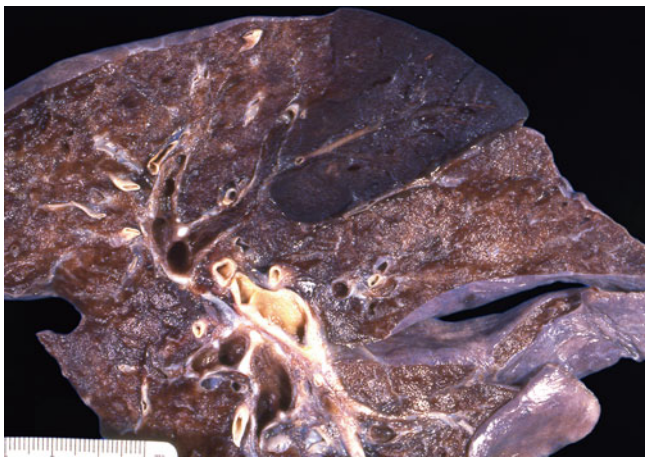

Fig. 28.29. Pulmonary infarction. A wedge-shaped hemorrhagic area represents a recent, hemorrhagic infarction of the lung.

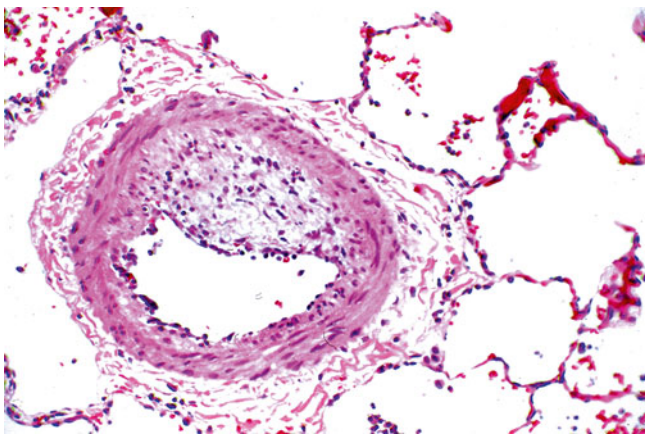

Fig. 28.30. Thrombotic arteriopathy. An eccentric pattern of intimal fibroplasia is seen in this form of pulmonary hypertensive disease.

- Plexogenic lesions are rarely found (probably represents plexogenic arteriopathy with superimposed thrombi)
- Ischemic necrosis and surrounding areas of organization and hemosiderin pigment

### *Differential Diagnosis*

- Necrotizing pneumonia

## Infections (Also See Chapter XX)

### Viral

#### *Cytomegalovirus*

#### *Clinical*

- Found almost exclusively in immunocompromised patients

#### *Microscopic (Fig. 28.31)*

- Diffuse interstitial pneumonitis and nodular (miliary) pneumonia
- Cytopathic changes: cytomegaly (2–3 times normal cell); amphophilic/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; immunocompromised patient, inhalation injuries, and chronic obstructive pulmonary disease patient
- Laryngotracheobronchitis, bronchopneumonia

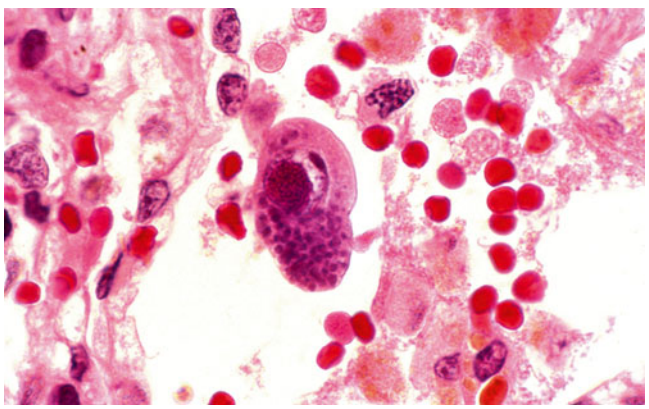

Fig. 28.31. Cytomegalovirus (CMV) inclusion in alveolar macrophage. Both nuclear and cytoplasmic inclusions can be seen in this enlarged alveolar macrophage infected by CMV.

### *Microscopic (Fig. 28.32)*

- 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 the 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

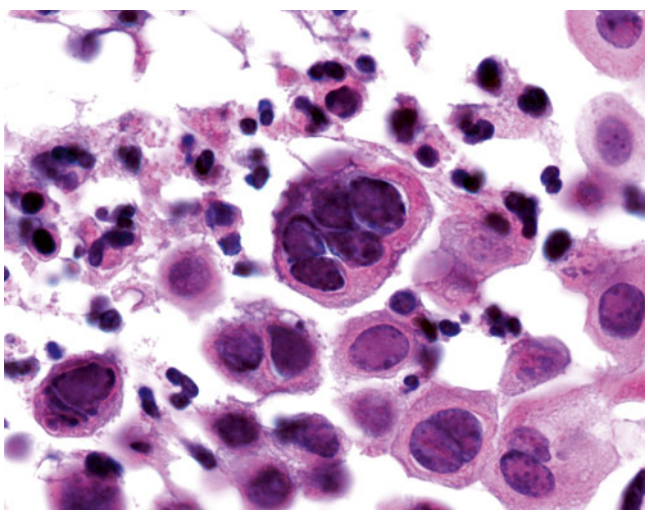

Fig. 28.32. Herpes inclusion in alveolar macrophage. Cowdry type A inclusions with eosinophilic nuclei with a halo separating the inclusion from the nuclear membrane.

## Adenovirus

### *Clinical*

- Generally found in children; can cause fulminant pneumonia in immunosuppressed patients

### *Microscopic (Fig. 28.33)*

- 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 neutrophils
- 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

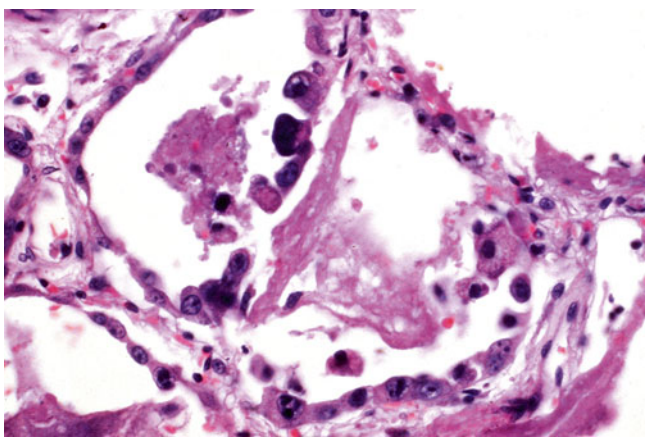

Fig. 28.33. Adenovirus infection. *Dark*, intranuclear inclusions are found in the "smudge" cells.

- Host: deer mice
- Diagnosis usually made by culture or serologies; biopsy rarely done for diagnosis

### *Microscopic (Fig. 28.34)*

- Pulmonary edema and pleural effusions; early DAD
- Influenza, parainfluenza virus, varicella

## Bacteria

### *Legionnaires Disease*

#### *Clinical*

- First recognized in large outbreak at the 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 (Fig. 28.35A, B)*

- Acute bronchopneumonia with characteristic intra-alveolar exudate of neutrophils, macrophages, and karyorrhectic debris

#### *Special Studies*

- Small, pleomorphic Gram-negative bacillus; cultured in modified Mueller–Hinton agar
- Dieterle 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

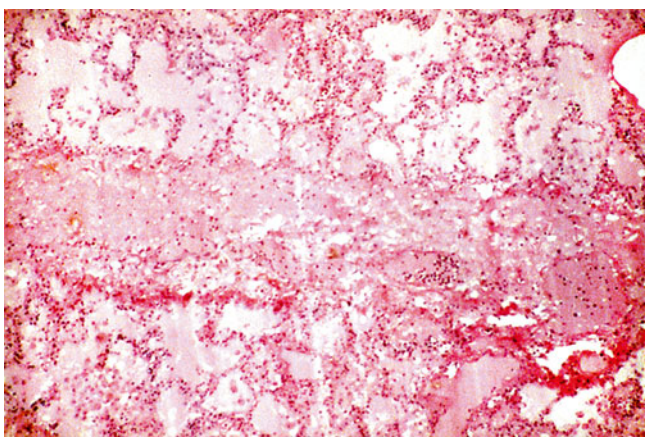

Fig. 28.34. Hantavirus pulmonary syndrome. Fluid-filled alveolar spaces and interstitial edema are present.

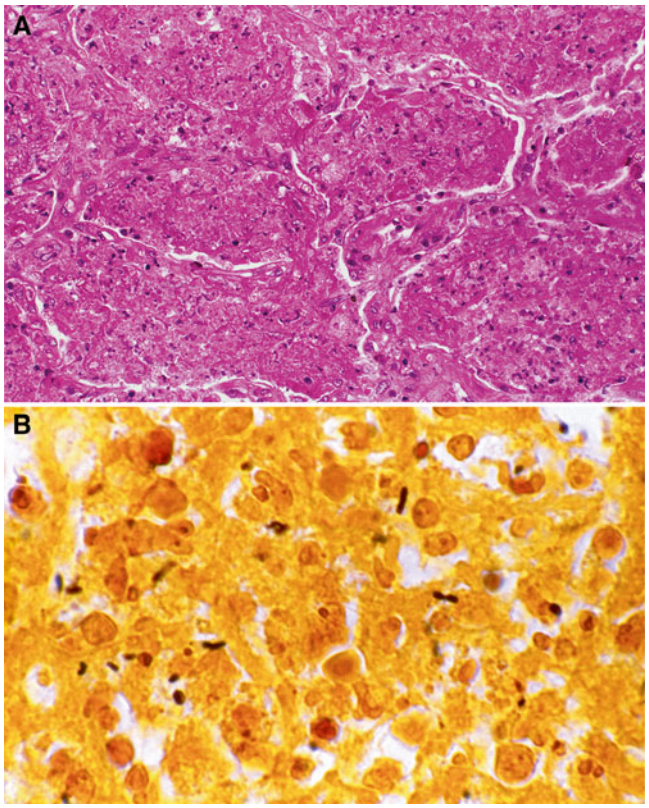


Fig. 28.35. Legionnaires disease. A prominent intra-alveolar exudate with degenerating inflammatory cells (**A**) is present; the organisms, pleomorphic Gram-negative bacilli, are highlighted by Dieterle stain (**B**).

- Silver stain is best for diagnosis: fine, filamentous organisms – may be very difficult to find
- Weakly acid-fast (Fite stain) and Gram-positive

### *Actinomycosis*

#### *Clinical*

- Aspiration of oral or tonsillar organisms; patients with poor dentition or repeated tonsillitis

#### *Microscopic (Fig. 28.36)*

- Abscess in the lung or mediastinum; sulfur granules found with palisading eosinophilic proteinaceous halo – Splendore–Hoeppli reaction

### *Malakoplakia*

#### *Clinical*

- Nodular lesions in immunocompromised patients, particular HIV-infected individuals; *Rhodococcus equi* is a common etiologic agent

#### *Microscopic*

- Chronic infiltrate with plasma cells and lymphocytes with sheets of histiocytes containing abundant Michaelis–Gutmann bodies

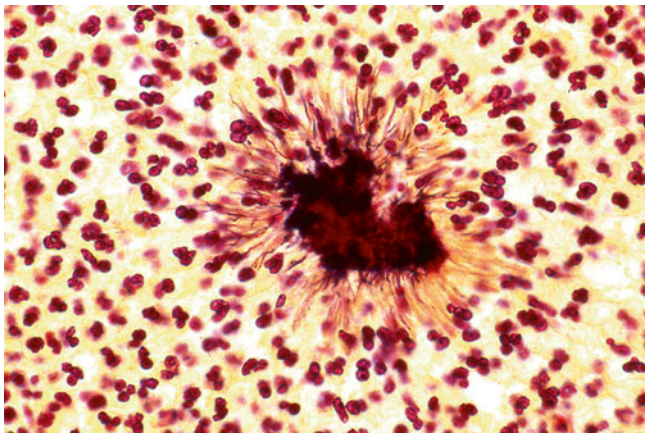

Fig. 28.36. Actinomyces. Gram-positive sulfur granules are seen in this Splendore–Hoeppli reaction.

## Mycobacterial Infections

### Mycobacterial Tuberculosis

#### Clinical

- High-risk factors include elderly, immigrants, lower socioeconomic groups, aboriginal races, HIV infection, silicosis, diabetes mellitus, hemodialysis, gastrectomy, nutritional deficiency, intravenous 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 (Fig. 28.37A)

- Primary TB
  - Ghon focus: single subpleural nodule, above or below interlobar fissure and enlarged 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 (Fig. 28.37B)

- Primary/postprimary TB
  - Necrotizing grnulomatous 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

### Nontuberculous Mycobacteria

- Most common are *Mycobacterium avium–intracellulare* complex and *M. kansasii*

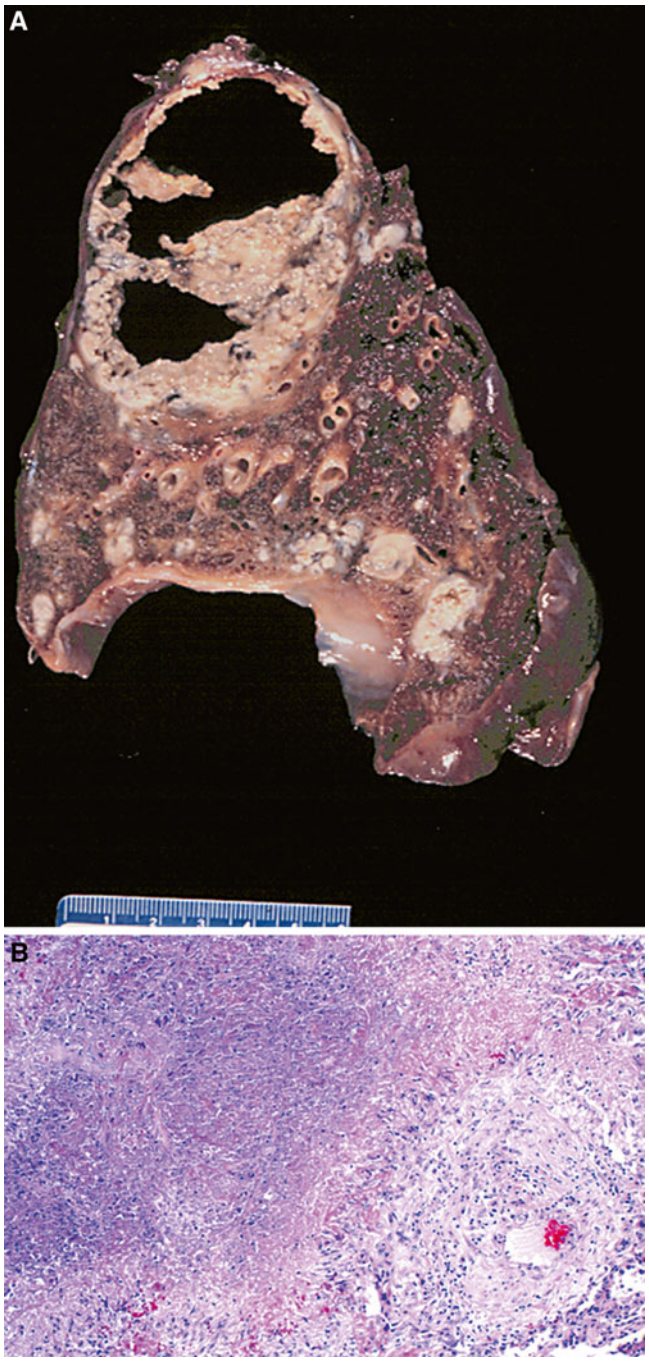


Fig. 28.37. Mycobacterial tuberculosis. A cavitating apical lesion (**A**) and necrotizing granulomas (**B**) are seen.

#### Clinical

- Opportunistic infections in HIV-infected patients
- Other risk factors COPD, bronchiectasis, pneumoconioses
- Also found in patients without underlying lung disease (nonsmoking women)

#### Macroscopic

- Can cause upper lobe cavitary lesion

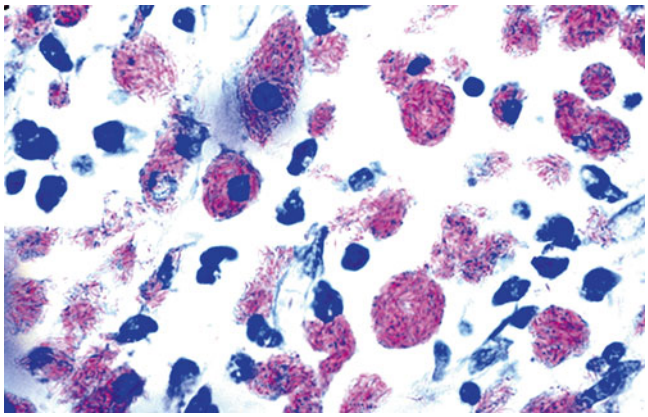

Fig. 28.38. *Mycobacterium avium* complex (MAI) in an AIDS patient. Abundant acid-fast bacilli are present within alveolar macrophages.

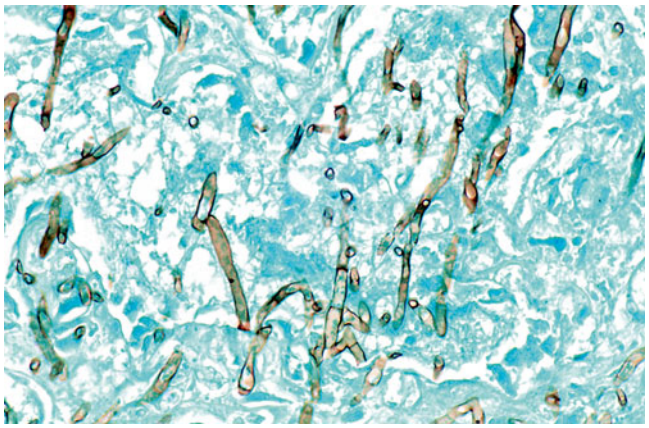

Fig. 28.39. *Aspergillus* fungal hyphae. A *silver stain* highlights the septated hyphae with acute angle branching.

- Noncavitating 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 (Fig. 28.38)
- Auramine-rhodamine immunofluorescence stain: more sensitive

### *Differential Diagnosis*

- Granulomatosis with polyangiitis (Table 28.1)
  - 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; fourfold titer increase is diagnostic of infection
- Stains on Giemsa stain; DNA probe is the best way to find organisms in tissue

## Fungal

### *Aspergillosis (Fig. 28.39)*

- *Aspergillus*: thick-walled hyphae, septated and 45° branching; oxalic acid/calcium oxalate crystals seen in *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

### *Differential Diagnosis*

- Mucormycosis
  - Nonseptate, larger, right angle branching
  - Culture needed to be distinguished, especially if aspergillosis 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 (Fig. 28.40)*

- Nonseptate hyphae 10–25 microns wide; irregular right angle branching; pleomorphic, collapsing walls; necrotizing bronchopneumonia with infarction

### *Differential Diagnosis*

- Aspergillosis
  - Septate, right angle branching

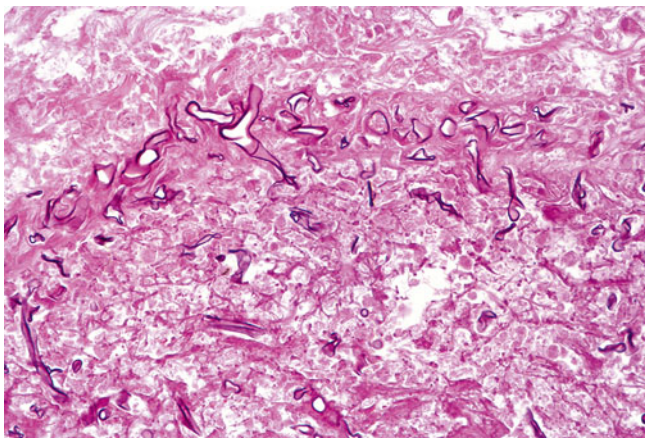

Fig. 28.40. Mucormycosis. Nonseptate hyphae with a ribbon-like morphology are present within infarcted lung tissue.

## *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 the kidney

## *Histoplasmosis*

### *Clinical*

- Can be seen in normal host; commonly found in Mississippi and Ohio River Valley; bird and bat feces

### *Microscopic (Fig. 28.41A–C)*

- Necrotizing granulomas, similar to *M. tuberculosis*; yeast forms 2–5 microns; usually degenerating forms are seen; budding is unusual but seen

## *Coccidioidomycosis*

### *Clinical (Fig. 28.42)*

- Can be seen in normal host; southwest USA, dry arid climate (San Joaquin Valley fever); inhaled arthrospores develop into spherules
- *C. immitis* usual organism; complement fixation tests positive in 90% patients

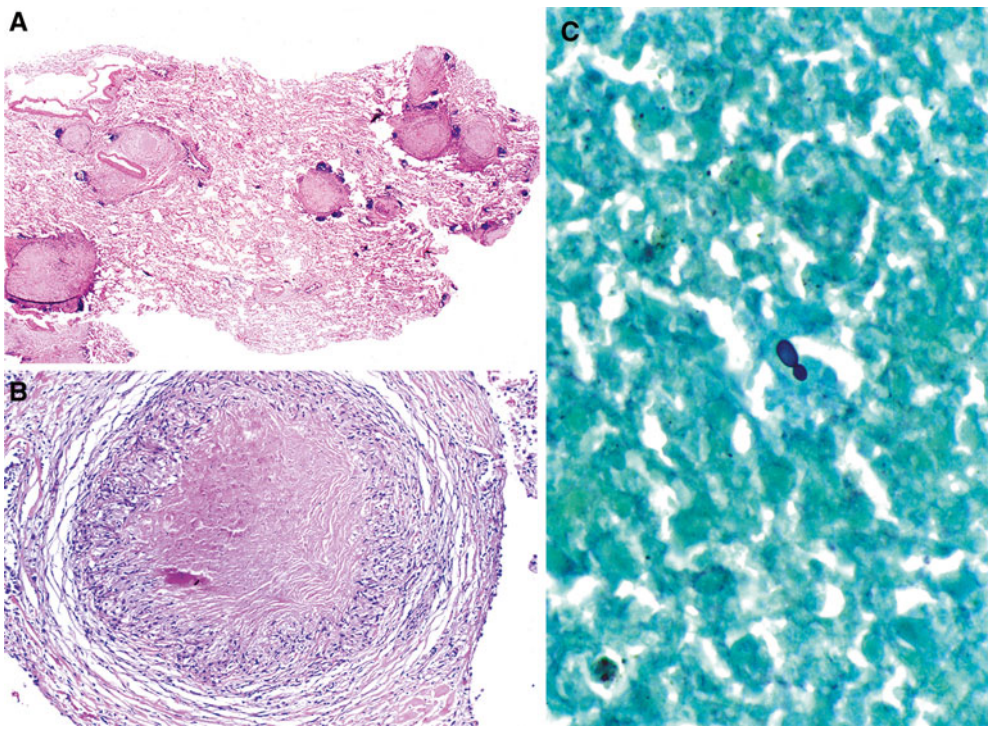


Fig. 28.41. Histoplasmosis. Necrotizing granulomas are present over the majority of airways (**A**) and usually show abundant central necrosis (**B**). Present within the area of necrosis are budding yeast forms of *Histoplasma capsulatum* (**C**).

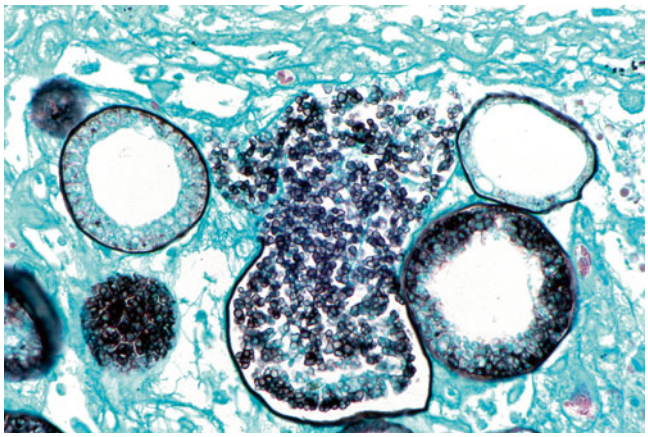

Fig. 28.42. *Coccidioides immitis.* A silver stain highlights large spherules containing endospores that spill out into infected lung tissue.

### *Microscopic*

- 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* usually organism; found in straw, moss, timber, and plants

### *Microscopic*

- Single, necrotizing lesion; significant hilar adenopathy

## *Blastomycosis*

### *Clinical*

- Can be seen in normal host; *Blastomyces dermatitidis*, soil-growing fungus
- North America around Mississippi and Ohio rivers and Southeast (Georgia)

### *Microscopic (Fig. 28.43A, B)*

- Necrotizing granulomas with central microabscess multinucleated giant cells; yeast forms: broad-based budding
- Bronchial lesions are common; bronchial stenosis 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 (Fig. 28.44)*

- Granulomatous lesions with acute inflammation; pleomorphic yeast forms (2–10 microns); single bud

### *Special Studies*

- Silver +; mucicarmine + capsule

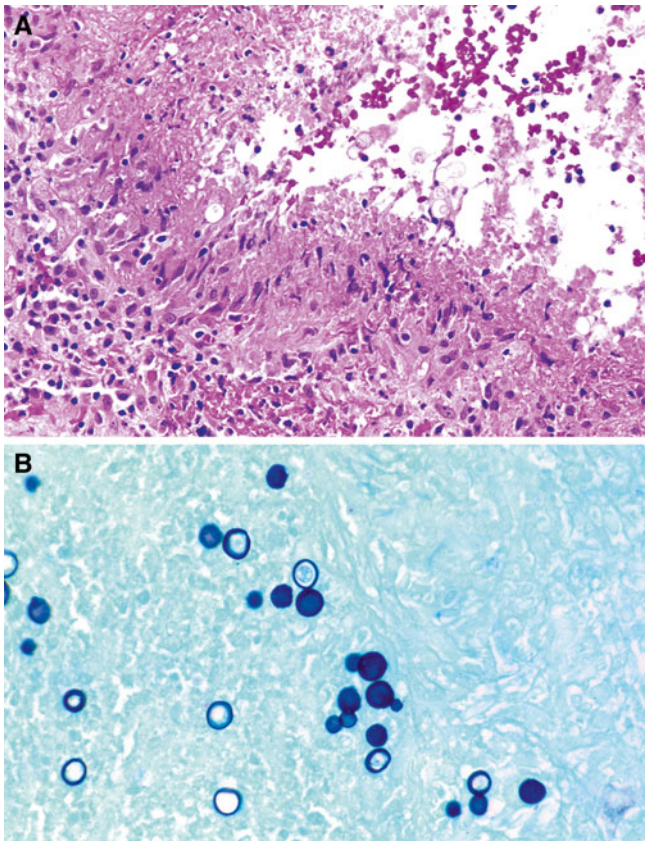


Fig. 28.43. Blastomycosis. Loosely formed necrotizing granuloma (**A**) is characteristic of this infection; a silver stain highlights the broad-based budding of *Blastomyces dermatitidis* (**B**).

## Protozoan

## Pneumocystis jiroveci *Pneumonia*

### *Clinical*

- Immunocompromised host, especially AIDS; insidious onset; bilateral infiltrates

### *Microscopic (Fig. 28.45)*

- Frothy, eosinophilic intra-alveolar exudate with faint blue dots
- Mild chronic interstitial pneumonitis
- Unusual reactions include granulomatous inflammation, diffuse alveolar damage, alveolar proteinosis, calcifications, and tissue invasion

### *Special Studies*

- Cyst (5–8 microns) is best seen on methenamine silver stain
- Trophozoite (1–2 microns) is best seen on Giemsa stain

### *Differential Diagnosis*

- Pulmonary alveolar proteinosis
  - Negative methenamine silver stain
    - Minimal interstitial reaction
    - PAS+

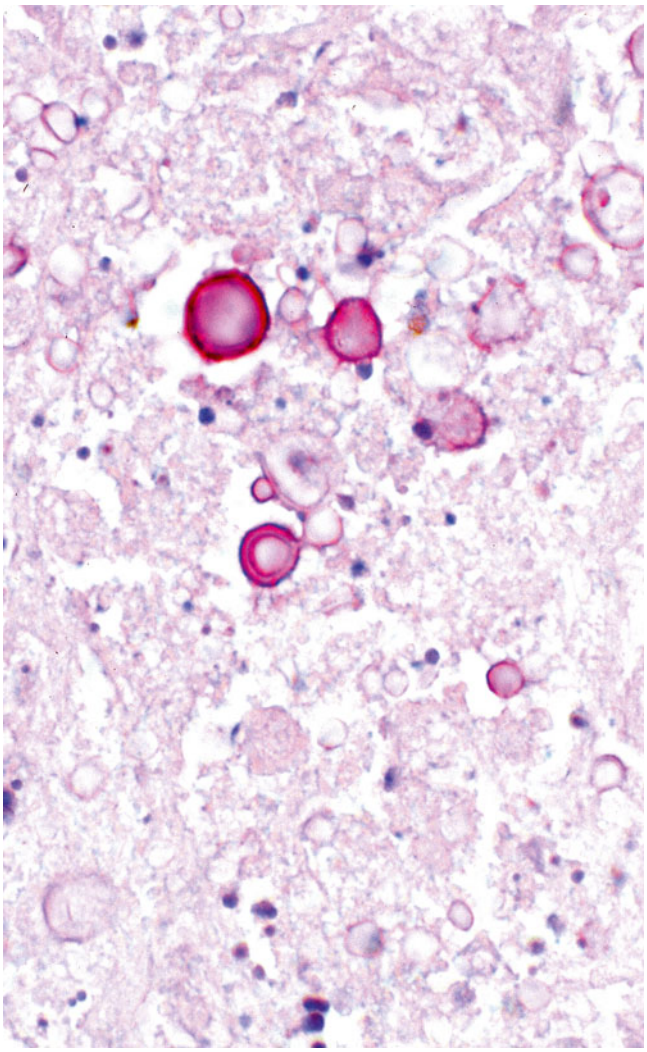

Fig. 28.44. *Cryptococcus neoformans.* A *mucin stain* highlights the presence of a capsule and budding commonly found in this yeast.

### *Dirofilarial (Dog Heart Worm) Granulomas*

#### *Clinical*

- *Dirofilaria immitis*, dog heart worm; adult worm resides in the 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 the center of infarct
- 100–200 microns; thick cuticle with longitudinal ridges

### Toxoplasma gondii *Pneumonia*

#### *Clinical*

- Immunocompromised host, especially AIDS and neonate; cats are carriers

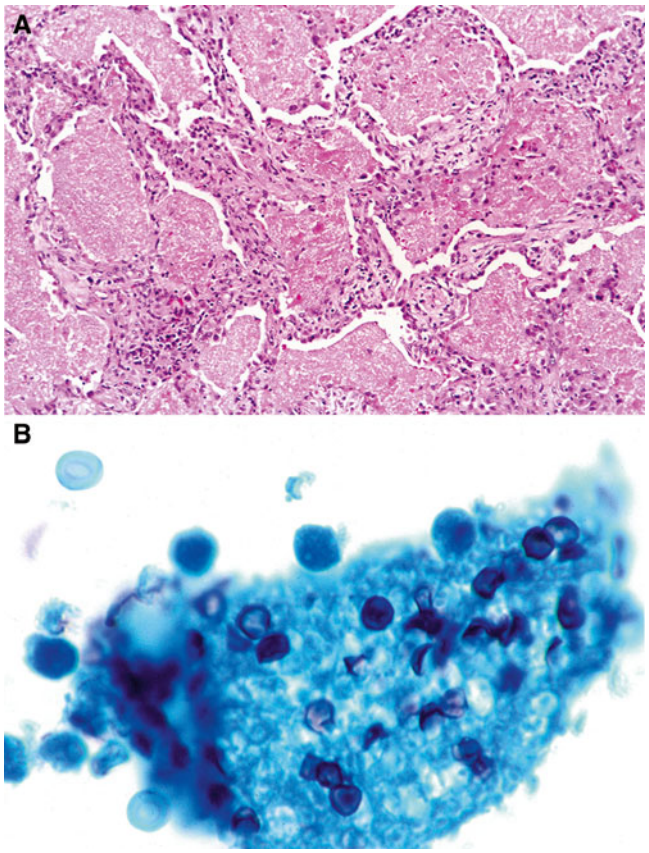


Fig. 28.45. *Pneumocystis jiroveci* pneumonia (PCP). A "frothy" intra-alveolar exudative is present with prominent type II pneumocytes (**A**). *Pneumocystis jiroveci* organisms are highlighted by a silver stain (**B**).

- 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 are helpful for identification of cysts

### Paragonimiasis *(Lung Fluke)*

#### *Clinical*

- Endemic in South America, Africa, India, 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 XX)

### Histologic Grading of Pulmonary Allograft Rejection

### *Acute Cellular Rejection (Fig. 28.46)*

- 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 endotheliitis; 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-Lymphocytic Bronchitis/Bronchiolitis*

- Grade B0: None
- Grade B1R: Low grade
- Grade B2R: High grade
- Grade BX: Not gradable

### *Chronic Airway Rejection/Bronchiolitis Obliterans*

- Grade C0: None
- Grade C1: Present

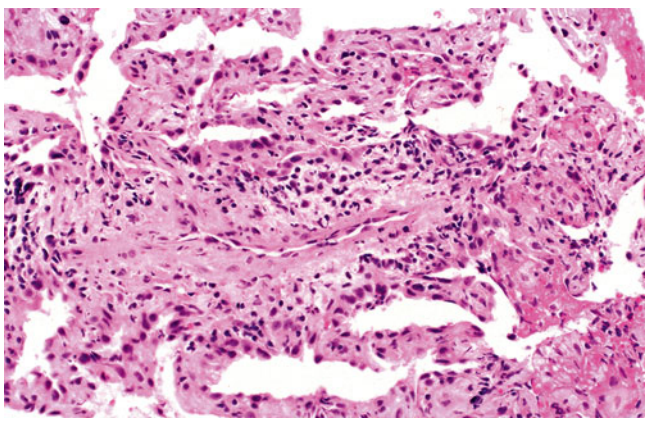

Fig. 28.46. Minimal acute vascular rejection of pulmonary allograft. A scattering of mononuclear cells surrounds a small vessel and is difficult to distinguish from low power.

### *Chronic Vascular Rejection-Accelerated Graft Sclerosis*

- Fibrointimal thickening of arteries and veins of uncertain clinical significance

### *Antibody-Mediated Rejection (AMR)*

### *Clinical*

- Progressive respiratory failure, pulmonary edema, and opacification of allograft

### *Microscopic*

- Diffuse alveolar damage
- Pulmonary hemorrhage with capillaritis

### *Special Studies*

- Deposition of IgG and complement (C4d) in the alveolar septa

### *Differential Diagnosis*

- Ischemia-reperfusion injury with acute lung injury
  - No vasculitis or capillaritis is seen.
  - Negative lymphocyte cross-match.

## Masses, Tumorlike Lesions, and Deposition Diseases

### Amyloidosis

### *Clinical*

- Patients have monoclonal proteins in serum or urine
- Associated diseases include multiple myeloma, lymphoid interstitial pneumonitis, low-grade lymphomas, and Sjögren syndrome

### *Macroscopic*

- Five types: nodular, diffuse, alveolar-septal, senile, and tracheobronchial
- Waxy, hard irregular nodules

### *Microscopic (Fig. 28.47)*

- Amorphous, eosinophilic material in vessels, in 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–

### Pulmonary Hyalinizing Granuloma

### *Clinical*

- Asymptomatic; adults
- 60% have serologic evidence of autoimmunity

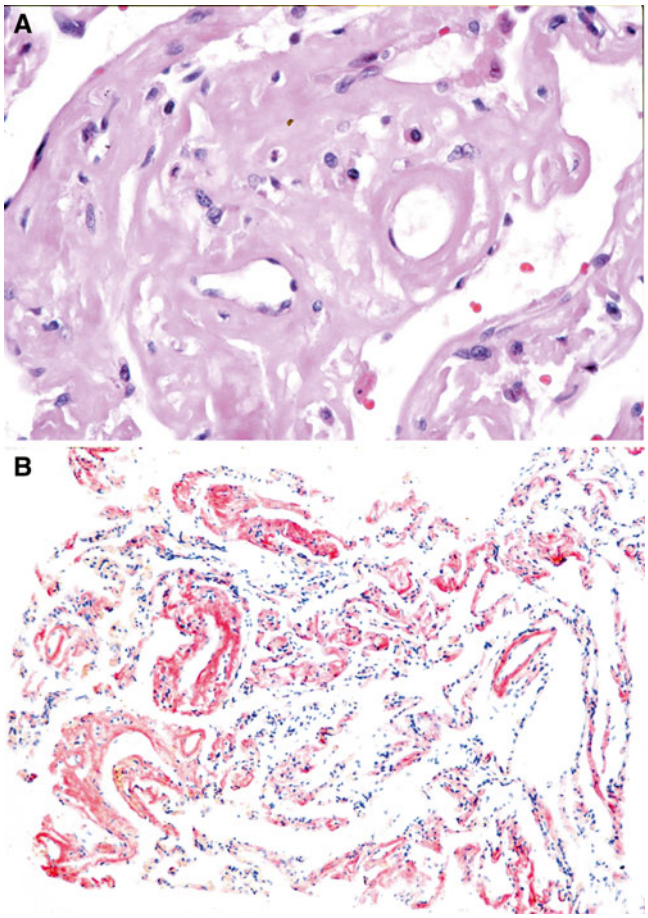


Fig. 28.47. Amyloidosis. Amorphous eosinophilic material is present surrounding vessels and within alveolar septa (**A**). A *Congo red stain* reveals "apple-green" birefringence under polarized light (**B**).

### *Macroscopic*

- Bilateral nodules; white/gray "cotton balls"

### *Microscopic (Fig. 28.48)*

- Lamellar collagen in storiform or whorled array – "donuts"; mild lymphoplasmacytic infiltrate

### *Differential Diagnosis*

- Nodular amyloidosis
  - Congo red stains for apple-green birefringence
- Hyalinized infectious granulomas
  - Collagen arranged in parallel around center

## Tracheobronchopathia Osteoplastica

### *Clinical*

- Middle-aged or elderly men with hoarseness, stridor, hemoptysis; possible relationship to tracheal amyloidosis

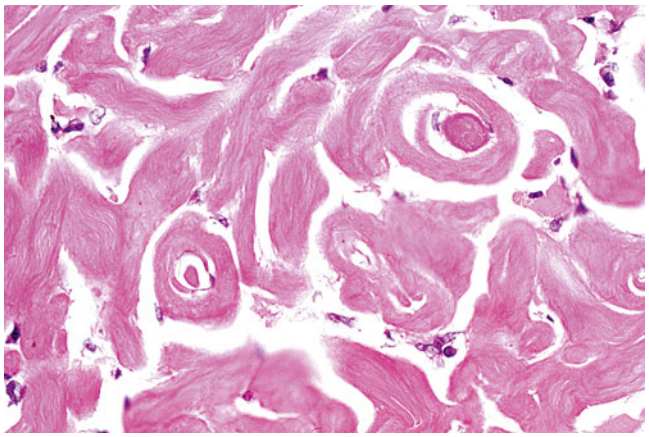

Fig. 28.48. Pulmonary hyalinizing granuloma. Thick bundles of collagen in storiform arrays are present.

### *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*

- Gray/white lobulated mass; shells out from lung parenchyma

### *Microscopic*

- Well-differentiated smooth muscle; may have type II epithelial inclusions
- ≤5 mitoses/50 hpf

### *Differential Diagnosis*

- Hamartoma
  - Bronchial epithelium
- Metastatic leiomyosarcoma
  - >5 mitoses/50 hpf
  - Primary sarcoma
  - Usually multiple lesions

## Light Chain Deposition Disease

### *Clinical*

- Found predominantly in patients with underlying plasma cell dyscrasia or other B-cell neoplasms such as lymphomas, Waldenstrom macroglobulinemia, and chronic lymphocytic leukemia
- Prognosis is poor usually because of its association with hematologic malignancies

### *Macroscopic*

- Bilateral pulmonary nodules with tan, well-circumscribed morphology
- Grossly similar to nodular amyloidosis
- May have a reticulonodular or interstitial pattern

### *Microscopic*

- Amorphous eosinophilic material, similar to amyloid, but consists of nonamyloid immunoglobulin light chains
- PAS+ and refractile blue on Giemsa
- Negative by polarization with all amyloid stains
- Consist of immunoglobulin light chains, most commonly kappa type

### *Differential Diagnosis*

- Nodular amyloidosis
  - Congo red stains for apple-green birefringence
- Hyalinized infectious granulomas
  - Collagen arranged in parallel around center
- Pulmonary hyalinizing granuloma
  - No kappa or lambda restriction on light chain

## IgG4-Related Lung Disease

### *Clinical*

- Multisystem disorder characterized by fibroinflammatory disease in many organs including the pancreas, bile duct, salivary gland, lacrimal gland, liver, kidney, and aorta
- Elevated peripheral blood IgG4 levels
- Steroid responsive

### *Macroscopic*

- Parenchymal nodules and infiltrates
- Tracheobronchial involvement
- Pleural nodules
- Mediastinal lymphadenopathy with fibrosing mediastinitis

### *Microscopic (Fig. 28.49)*

- Lymphoplasmacytic infiltrate with collagenous-type fibrosis, which can have a storiform pattern
- Characteristic phlebitis that can be obliterative
- Plasma cells present though exact number (per 10 hpf) still debated
  - Should represent majority of inflammatory cells present

### *Differential Diagnosis*

- Nodular amyloidosis
  - Congo red stains for apple-green birefringence
- Hyalinized infectious granulomas
  - Collagen arranged in parallel around center

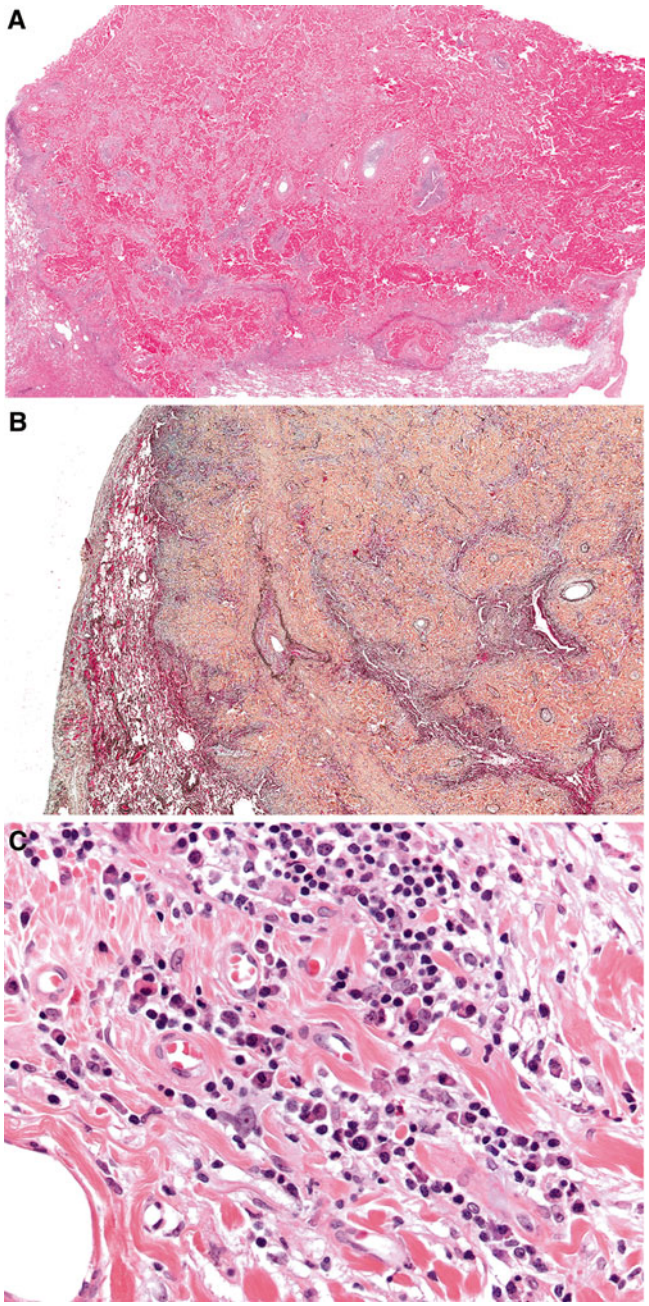


Fig. 28.49. IgG4-related lung disease. Fibroinflammatory nodule with hyalinized collagen and scattered foci of chronic inflammatory cells (**A**). A Movat stain reveals a vein within nodule with intimal fibroplasia consistent with characteristic phlebitis (**B**). Foci of chronic inflammatory cells show scattered plasma cells (**C**).

- Pulmonary hyalinizing granuloma
  - Few plasma cells and no phlebitis
- Nodular light chain disease
  - Kappa or lambda restriction of light chain

# 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 (Fig. 28.50A)

- Multiple lobulated excrescences in bronchioles; distal bronchiectasis common

##### Microscopic (Fig. 28.50B)

- Fibrovascular cores with cytologically bland nonkeratinizing squamous epithelium; koilocytic changes are common; mucous-secreting, transitional, or intermediate cells are sometimes interspersed

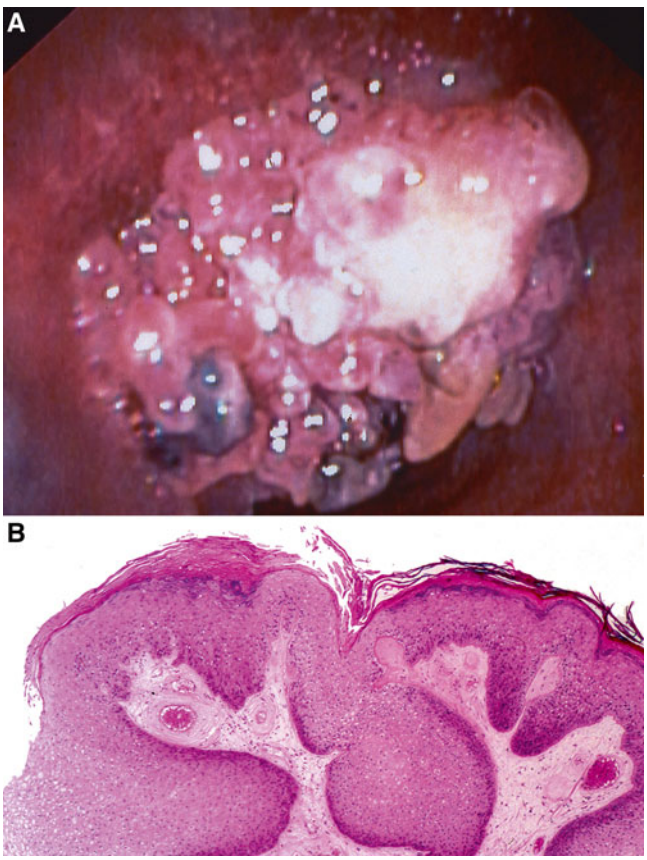


Fig. 28.50. Squamous papillomatosis. A tan-lobulated mass is present in the trachea (**A**) and microscopically shows cytologically bland squamous epithelium with some superficial keratinization (**B**).

##### Differential Diagnosis

- Papillary squamous cell carcinoma
  - Marked cytologic atypia with increased dyskeratosis and hyperkeratosis
  - Invasion into adjacent tissue

#### Papillary Adenoma of Type II Cells

##### Clinical

- Asymptomatic, "coin lesion" radiographically

##### Microscopic

- Circumscribed lesion of branching, papillary fronds lined by cytologically bland columnar cells; no mitoses, necrosis, or infiltrative pattern; intranuclear inclusions common

##### Differential Diagnosis

- Metastatic papillary carcinoma
  - Rule out primary ovarian, thyroid, kidney, colon, and breast
- Sclerosing hemangiomas
  - More variegated histologic patterns including solid, sclerosing, papillary, and hemorrhagic, two cell types, cuboidal and polygonal
- Papillary adenocarcinoma
  - Cytologic atypia, mitoses, infiltrative growth

#### Alveolar Adenoma

##### Clinical

- Solitary nodule in women

##### Microscopic

- Multicystic, well-circumscribed with ectatic spaces filled with eosinophilic material; flat lining cells; interstitium contains collagenous matrix with myofibroblasts

##### Differential Diagnosis

- Lymphangioma
  - Endothelial-lined spaces; cytokeratin negative

#### Mucous 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
- Solid and cystic gelatinous surfaces

##### Microscopic

- Cystic, mucous-filled glands with cytologically bland, mucus-secreting epithelium; oncocytic metaplasia can be seen

### Differential Diagnosis

- Low-grade mucoepidermoid carcinoma
  - Intermediate cells
- Adenocarcinomas
  - Cytologic atypia, necrosis, mitoses, lack of large cystic spaces

## Mucinous Cystadenoma

### Clinical

#### Rare

- Nodule in adult smokers
- Usually asymptomatic

### 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

- Mucinous adenocarcinomas
  - No fibrous cyst wall
- Mucinous cystadenocarcinoma
  - Invasive growth into surrounding lung

## Sclerosing Hemangioma

### Clinical

- Female predominance (80% found in women); asymptomatic

### Macroscopic

- Gray/red circumscribed mass; 50% are in lower lobes

### Microscopic (Fig. 28.51)

- Variegated architectural patterns including solid, papillary, sclerotic, and hemorrhagic
- Cell types:
  - Small cuboidal surface cells with dark round nuclei.
  - Polygonal/round, larger stromal cells.
  - Inflammatory cells, including mast cells, may be numerous

### Immunohistochemistry

- Surface and stromal polygonal cells: TTF1, EMA, and CK7 positive

### Differential Diagnosis

- Adenocarcinoma, in situ, papillary, or solid predominant
  - One cell population, cytologic atypia, infiltrative growth
- Epithelioid hemangioendothelioma
  - CD31, CD 34, and ERG positive; TTF1 negative
- Carcinoid tumor
  - Neuroendocrine markers positive; TTF1 variable staining

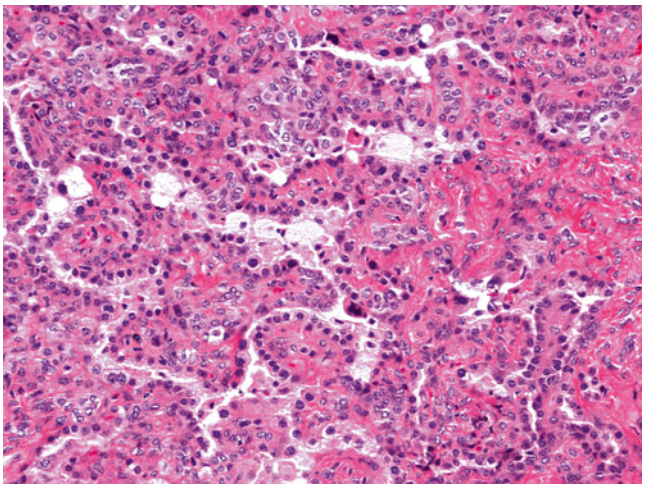

Fig. 28.51. Sclerosing hemangioma. Cuboidal cells are seen lining solid and papillary areas.

# Benign Mesenchymal Tumors

## Hamartoma

### Clinical

- Central endobronchial: cough, obstructive pneumonia
- Parenchymal: usually asymptomatic

### Macroscopic (Fig. 28.52A)

- Well-circumscribed white, bulging nodules of cartilaginous consistency
- Calcium or bone may be present

### Microscopic (Fig. 28.52B)

- Usually composed predominantly of cartilage; fat, smooth muscle, and fibromyxoid tissue can be seen
- Surrounded by clefts of benign ciliated or nonciliated epithelium, entrapped metaplastic epithelium

### Cytogenetics

- 6p21 rearrangement activates high mobility group gene (HMGI-Y)

### Differential Diagnosis

- Bronchial chondromas as seen in young women with Carney triad (pulmonary chondromas, gastric epithelioid tumors, and extra-adrenal paragangliomas)
  - Usually connected to airway cartilage
- Benign metastasizing leiomyoma
  - Fat, cartilage, and other fibromyxoid elements are not seen
- Intrapulmonary solitary fibrous tumor
  - Stromal cells are CD 34 and STAT-6 positive.

## Lipoma

### Clinical

- Usually arise in central bronchi; lead to obstruction, wheezing, and bronchiectasis

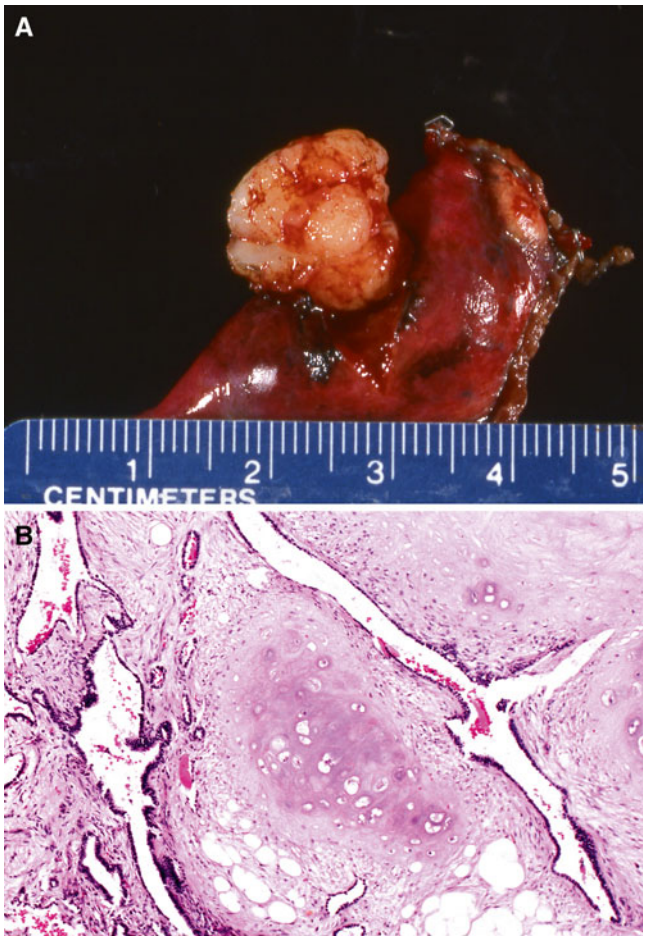


Fig. 28.52. Hamartoma. A well-circumscribed white nodule (**A**) extrudes from the underlying lung parenchyma and contains cartilage, adipose tissue, and benign entrapped respiratory epithelium (**B**).

- Large variant completely enveloping bronchus can be sequela of chronic bronchiectasis

### *Macroscopic*

- More frequent in left main bronchus than on the 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

### *Macroscopic*

- Small cysts with connections to bronchioles

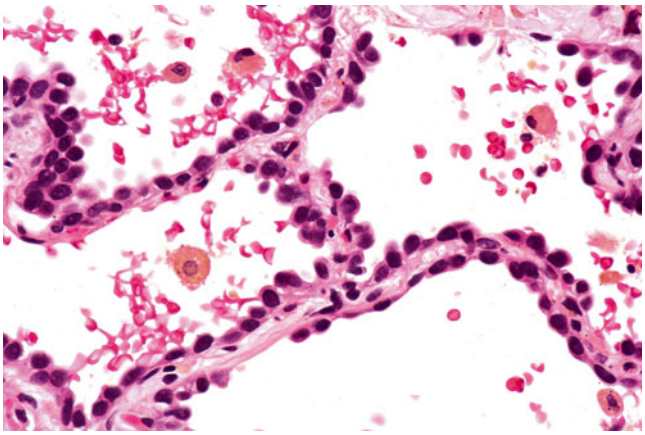

Fig. 28.53. Atypical adenomatous hyperplasia. A cuboidal epithelium contains hyperchromatic cells with cytologic atypia.

### *Microscopic*

- Normal respiratory or cuboidal epithelium; underlying primitive mesenchymal cells
- Hypertrophic arteries within mesenchyme

### *Differential Diagnosis*

- Pulmonary sequestration
- Congenital pulmonary airway malformation (congenital cystic adenomatoid malformation)
- Cystic bronchiectasis
  - None of the above contains primitive mesenchymal cells beneath epithelium
- Metastasis
  - Primary sarcoma (many of the reported cases have been metastases from uterine neoplasms)

## Epithelial Preinvasive 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
- Carcinoma in situ: entire mucosal involvement by dysplasia without invasion through basement membrane

### Atypical Adenomatous Hyperplasia

### *Microscopic (Fig. 28.53)*

- Focal lesions, by definition < 5mm
- Mild/moderately atypical alveolar cuboidal cells lining alveolar walls; mitoses rare

### *Differential Diagnosis*

- Adenocarcinoma in situ
  - Larger than 5 mm, greater nuclear atypia, mitoses

### Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia

#### *Clinical*

- Dyspnea and cough with an obstructive pattern on pulmonary function tests
- Multiple centrilobular nodules

#### *Microscopic*

- Multiple airways involved
- Hyperplasia: increased number of neuroendocrine cells contained within the basement membrane
- Carcinoid tumorlet: nests of neuroendocrine cells within the airway wall associated with fibrosis and remodeling

#### *Differential Diagnosis*

- Neuroendocrine cell hyperplasia and carcinoid tumorlets secondary to chronic inflammatory pulmonary diseases

## Malignant Tumors

### Tumors of Salivary Gland Type

#### Mucoepidermoid Carcinoma

#### *Clinical*

- 50% are in patients less than 30 years old; symptoms of large airway obstruction/irritation

#### *Macroscopic (Fig. 28.54A)*

- Tan/pink endobronchial nodule, most common in main or lobar bronchi
- Mucoid surface with underlying cystic areas; can ulcerate on surface

#### *Microscopic (Fig. 28.54B)*

- Mucin-secreting, squamous, and intermediate cells
- Similar grading criteria to salivary glands using mitoses (>4/10 hpf), nuclear pleomorphism, intracystic component (>25%), characteristic of invasive front (broad islands versus small infiltrating nests), lymphovascular invasion, perineural invasion, and necrosis (Brandwein)

#### *Molecular*

- Rearrangement of MAML2 gene present [t(11;19)(q21;p13)]

#### *Differential Diagnosis*

- Bronchial mucous gland adenoma:
  - No intermediate or squamous cells
- Adenosquamous cell carcinomas
  - Peripheral lesions with adjacent in situ carcinoma.
  - Intermediate cells are absent; usually keratinization is seen.

#### *Adenoid Cystic Carcinoma*

#### *Clinical*

- Most common salivary gland type tumor of the lower respiratory tract
- Lower trachea, main stem bronchi or lobar bronchi
- Large airway obstruction/irritation
- Recurrence is common

#### *Macroscopic*

- Tan/gray tumors intrude bronchial wall with sessile or annular lesions; can spread submucosally along bronchial wall and diffusely involve adjacent airways

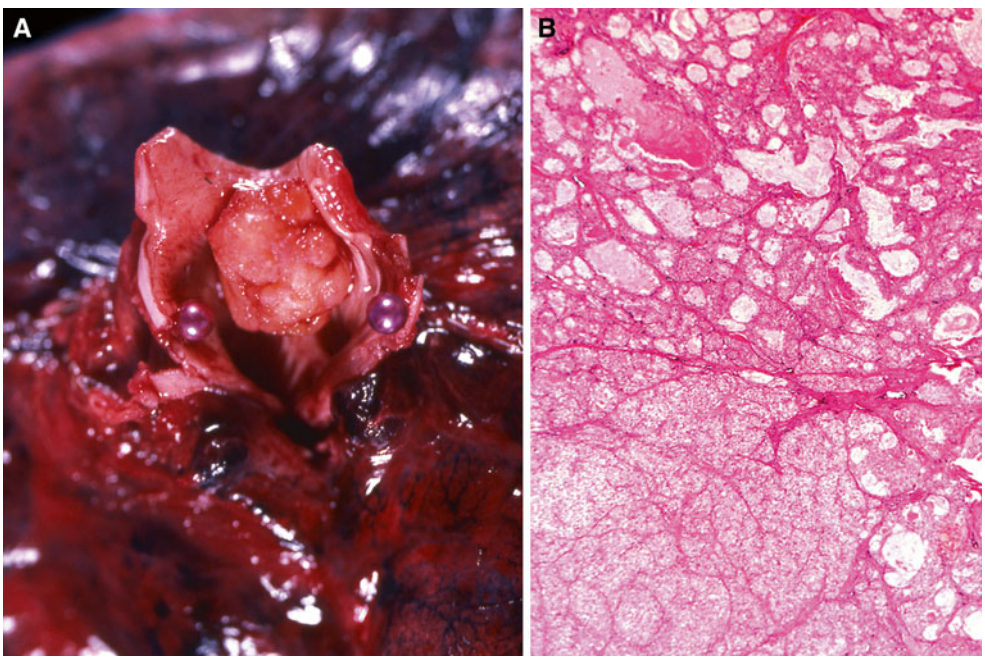


Fig. 28.54. Mucoepidermoid carcinoma. A tan polypoid endobronchial nodule is present in a proximal bronchus (A); microscopic features include both squamous and mucin-producing cells and more solid areas of intermediate cells (B).

### *Microscopic (Fig. 28.55A–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
  - Epithelial and myoepithelial cells; mesenchymal chondromyxoid component; no cribriform or cylindromatous areas, no perineural invasion
- Adenocarcinomas
  - Cytologic atypia, mitoses, necrosis

## Epithelial Tumors

### *Squamous Cell Carcinoma*

### *Clinical*

- 67% central; more common in men; second most common primary pulmonary carcinoma; strong association with smoking
- Paraneoplastic syndrome: hypercalcemia due to parathormone-related protein secretion by tumor

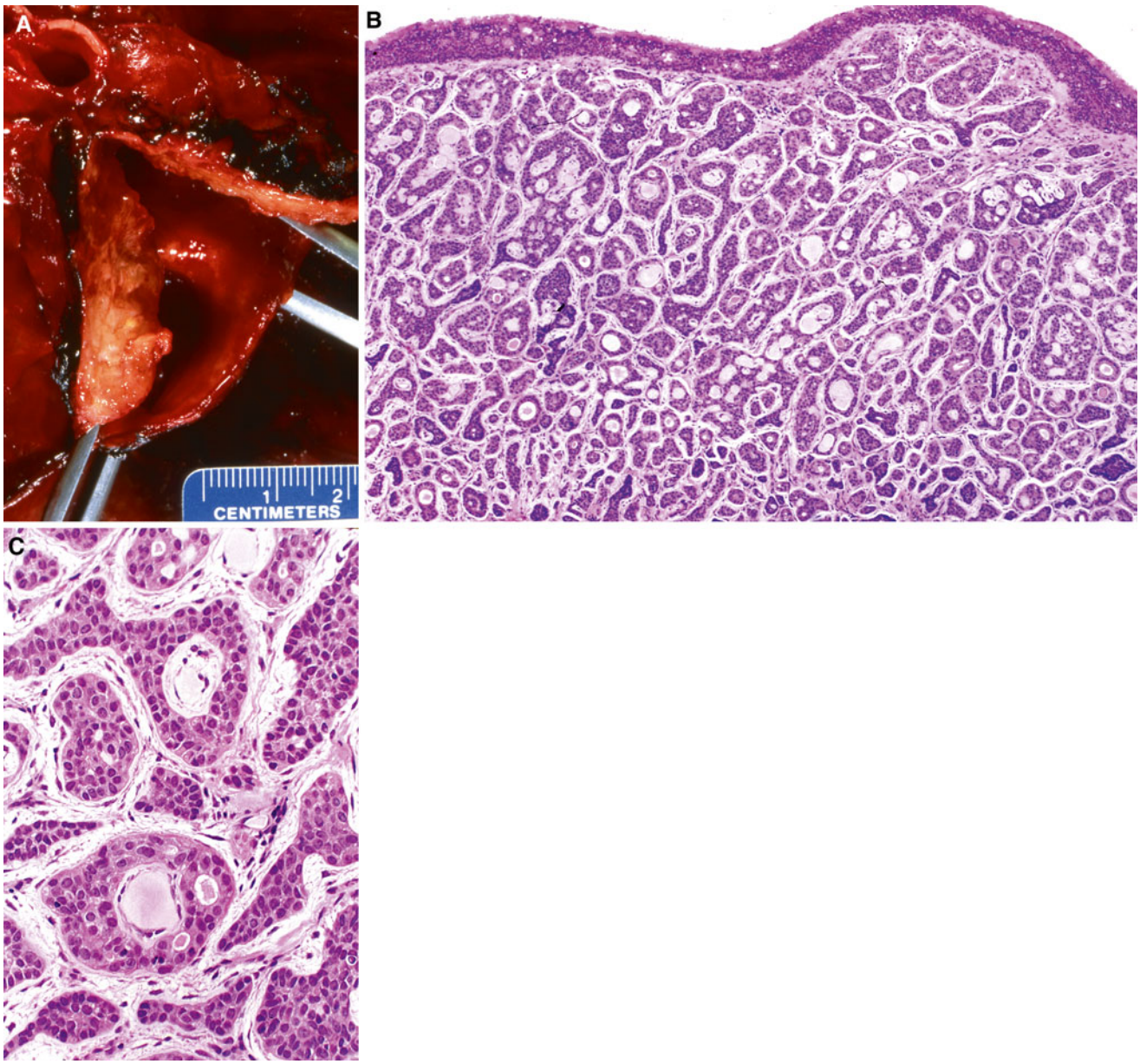


Fig. 28.55. Adenoid cystic carcinoma. A tan/white tumor mass thickens a bronchial wall (**A**); well-formed glands (**B**) with hyperchromatic cells and prominent basal lamina material are characteristic (**C**).

### *Macroscopic (Fig. 28.56A)*

- Solid necrotic masses, commonly cavitate

### *Microscopic (Fig. 28.56B)*

- Squamous differentiation with intercellular bridges and/or keratinization (keratin pearls)
- Well, moderate, and poorly differentiated based on degree of squamous differentiation
- Spindle cells, osteoclastic-type tumor giant cells, and clear cell changes can be seen
- Histologic variants: papillary, clear cell, basaloid

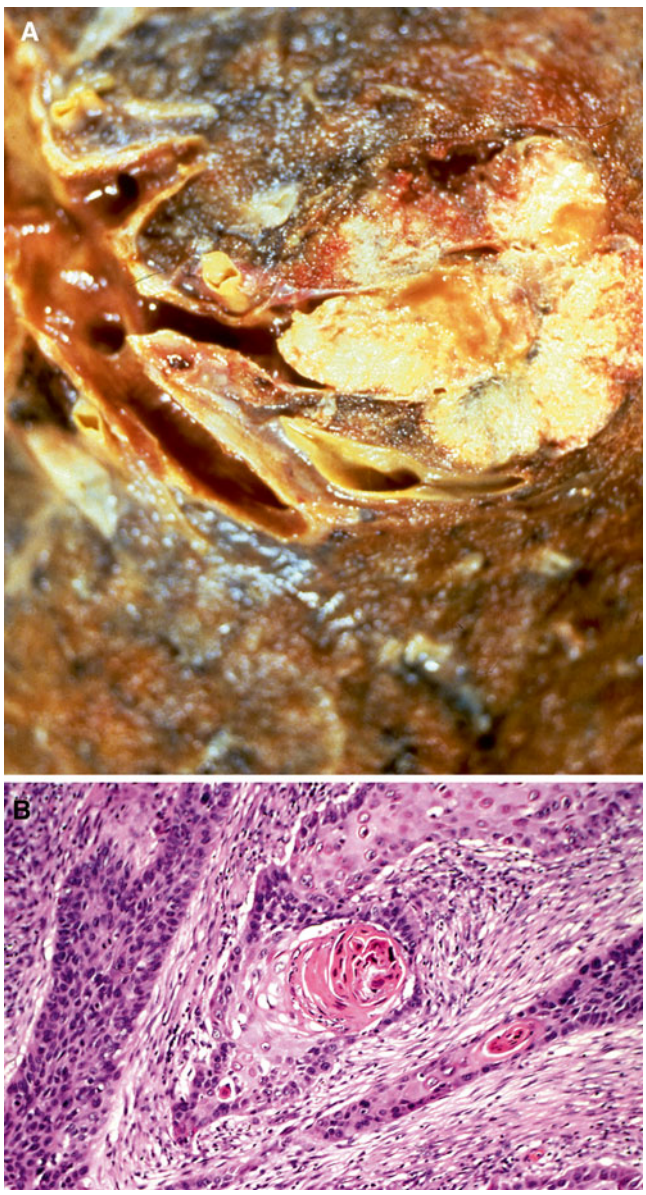


Fig. 28.56. Squamous cell carcinoma. A proximal, obstructing, cavitating tumor is present in a proximal airway (**A**). Malignant squamous cells and prominent keratinization are present (**B**).

### *Differential Diagnosis*

- Squamous dysplasia
  - Lack stromal invasion
- Adenosquamous carcinoma and mucoepidermoid carcinoma
  - Glandular component
- Small cell carcinoma
  - Cells with little cytoplasm; increased N/C ratio, lack nucleoli, nuclear molding, and crush artifact seen in small biopsies; no squamous differentiation

## *Adenocarcinoma*

### *Clinical*

- Most common primary pulmonary carcinoma; most common lung cancer in women
- Paraneoplastic syndrome: Hypertrophic pulmonary osteoarthropathy
- Associated with smoking; however, smoking history is more variable than in other pulmonary carcinomas

### *Macroscopic (Fig. 28.57A)*

- More commonly peripheral
- Adenocarcinoma in situ: ill-defined area of lung firmness
- Invasive adenocarcinoma: dense desmoplastic "scarred" center with a rim of firm, abnormal-looking lung

### *Microscopic (Fig. 28.57B)*

- Adenocarcinoma in situ: neoplastic cells lining alveolar septa without basement membrane disruption, invasion into underlying stroma, or lymphatic or pleural invasion (lepidic growth)
- Minimally invasive adenocarcinoma: adenocarcinoma measuring less than 3.0 cm with predominant lepidic pattern and an invasive focus of <0.5 cm
- Invasive adenocarcinoma: Adenocarcinoma with an invasive focus of >0.5 cm or any adenocarcinoma measuring more than 3.0 cm
- Multiple growth patterns, classified according to predominant component
  - Acinar predominant
  - Papillary predominant
  - Solid predominant
  - Micropapillary predominant
- Mucinous (colloid) adenocarcinoma
  - Adenocarcinoma in situ
  - Minimally invasive adenocarcinoma
  - Invasive adenocarcinoma
- Uncommon variants
  - Well-differentiated fetal adenocarcinoma: ribbons of neoplastic cells with nuclear stratification resembling embryonal lung tubules
  - Signet ring cell adenocarcinoma

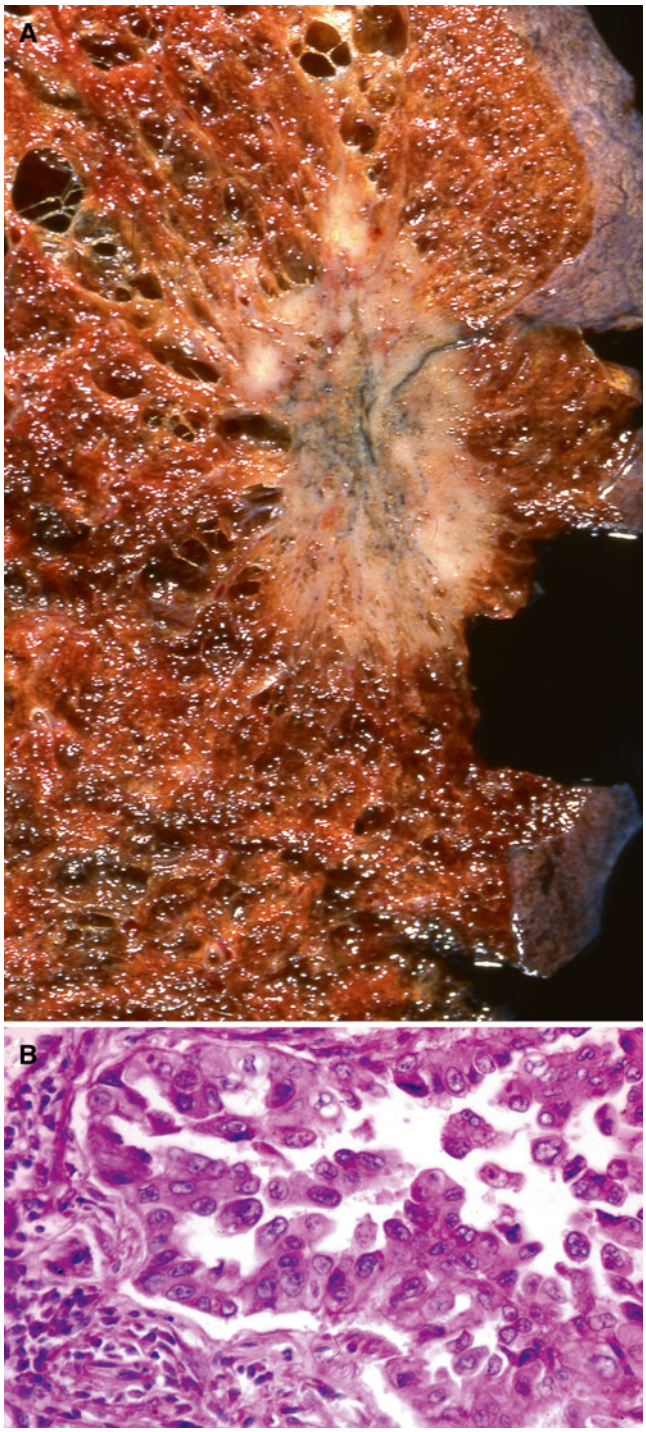


Fig. 28.57. Adenocarcinoma. A peripheral tan/white tumor mass arises adjacent to the pleural surface (**A**) Histologically, in this acinar variant, the tumor contains malignant glands with marked atypical epithelium (**B**).

- Clear cell adenocarcinoma
- Enteric-type adenocarcinoma: histologically and immunophenotypically similar to conventional colorectal adenocarcinoma

### *Immunohistochemistry*

- TTF1 positive >80%, Napsin-A: positive (80%), p63 negative or focally positive, cytokeratin 7 positive, and cytokeratin 20 +/–

### *Electron Microscopy*

- Short microvilli with glycocalyx and rootlets

### *Molecular*

- Epidermal growth factor receptor (EGFR) mutations
  - Most commonly seen in nonsmokers, nonmucinous adenocarcinomas
  - Different mutations convey sensitivity or resistance to treatment with EGFR-tyrosinase kinase inhibitors
- KRAS mutations: most commonly seen in smokers
  - Alk-1 rearrangements
  - ROS-1
  - RET-1

### *Differential Diagnosis*

- Reactive alveolar proliferation
  - Heterogeneity of cell types, low N/C ratio, gaps between atypical cells, inflammatory changes present
- Atypical adenomatous hyperplasia
  - Mild to moderate cytologic atypia, no invasion
  - Focal lesion <0.5 cm
- Alveolar cell adenoma
  - Focal lesion, <0.7 cm, lack cytologic atypia
- Metastatic adenocarcinoma
  - Renal: TTF1, CK7, and CK20 negative; Napsin-A may be positive
  - Breast: CK7 and GATA3 positive; CK20, TTF1, and Napsin-A negative
  - Gastrointestinal tract: CK7 variable; CK20 positive; CDX2 positive; TTF1 and Napsin-A negative
  - Mullerian tract: PAX8 and CK7 positive; estrogen receptors strongly positive; TTF1, Napsin-A, and CK20 negative

## *Adenosquamous Carcinoma*

### *Clinical*

- <4.0% of lung carcinomas
- Strong association with smoking

### *Microscopic*

- Squamous cell carcinoma and adenocarcinoma components; each should be at least 10%

### *Differential Diagnosis*

- Adenocarcinoma with metaplastic squamous changes
  - Bland squamous component
- Squamous cell carcinoma with entrapped bronchial epithelium
  - Bland glandular epithelium
- High-grade mucoepidermoid carcinoma

- Lack carcinoma in situ, may contain areas of low-grade mucoepidermoid carcinoma, intermediate cells, lacks keratinization; goblet cells comprise the glandular component.

### Large Cell Undifferentiated Carcinoma

#### Clinical

- Strongly associated with smoking; may be peripheral or central

#### Macroscopic

- Central or peripheral solid usually necrotic mass; typically large with pleural invasion

#### Microscopic (Fig. 28.58)

- Sheets and nests of poorly differentiated atypical cells, usually with extensive necrosis; large nuclei with prominent nucleoli; lack definitive evidence of squamous or glandular differentiation
- Giant cell, clear cell, or spindle cell changes can be present
- Variants: 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
  - S100, HMB45, Melan-A, and SOX-10 positive; cytokeratin negative
- Large cell lymphoma (including anaplastic type)
  - Cytokeratin negative; CD45 positive; CD30 positive

### Sarcomatoid Carcinomas

#### Clinical Features:

- Strong association with smoking; may be peripheral or central

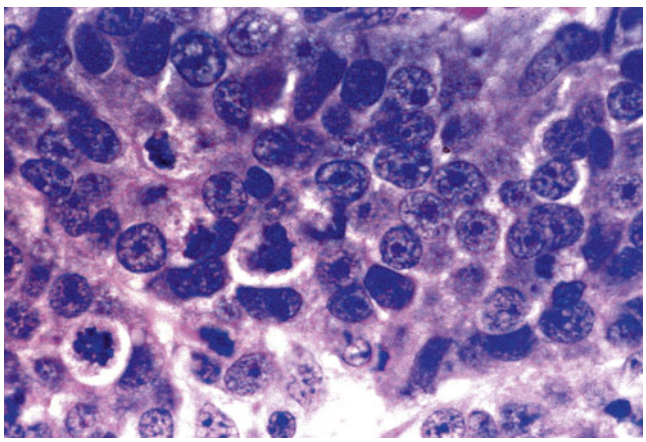

Fig. 28.58. Large cell undifferentiated carcinoma. Pleomorphic cells show undifferentiated architecture with no squamous or glandular features.

#### Macroscopic Features

- Solitary and well circumscribed

#### Microscopic features

- Non-small cell carcinomas associated with sarcoma or sarcoma-like elements; carcinoma component can be squamous cell carcinoma, adenocarcinoma, or large cell carcinoma
- Pleomorphic carcinoma: neoplastic spindle cells and/or giant cells present

### Spindle Cell Carcinoma

- Tumor Entirely Composed of Neoplastic Malignant Spindle Cell
- Giant cell carcinoma: tumor entirely composed of neoplastic malignant giant cells
- Carcinosarcoma: carcinoma with malignant heterologous component including osteosarcoma, chondrosarcoma, and/or rhabdomyosarcoma
- Pulmonary blastoma: carcinoma component similar to well-differentiated fetal adenocarcinoma; sarcomatoid component usually with embryonic differentiation

#### Immunohistochemistry

- Cytokeratin elements can be negative

#### Differential Diagnosis

- Sarcomas, primary or metastatic:
  - Cytokeratin negative, clinical history important

## Neuroendocrine Tumors

### Typical and Atypical Carcinoid

#### Clinical

- May present with postobstructive changes
- Most common in adults; can occur in children

#### Macroscopic (Fig. 28.59A)

- Central or peripheral
- Central lesions have endobronchial component with postobstructive changes distally
- Peripheral lesions are usually subpleural
- Tan/yellow mass, highly vascularized

#### Microscopic (Fig. 28.59B)

- Bland neuroendocrine cells with round to oval monotonous nuclei with finely granular chromatin and inconspicuous nucleoli
- Can have spindle cell morphology
- Organoid, trabecular, insular, palisading ribbon, and/or rosette-like arrangement
- Stromal changes include bone, cartilage, dense fibrosis, amyloid
- Typical carcinoid: <2 mitoses/10 hpf, no necrosis
- Atypical carcinoids: 2–10 mitoses/10 hpf and/or necrosis

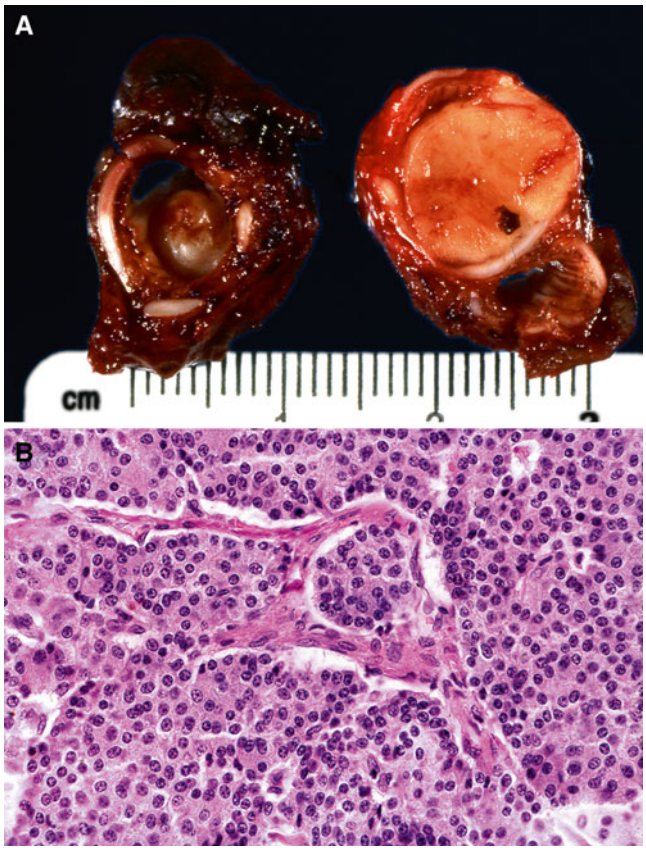


Fig. 28.59. Typical carcinoid. A central, tan polypoid lesion is present in a proximal airway (**A**). Bland epithelial cells with finely granular chromatin are seen (**B**).

### *Differential Diagnosis*

- Adenocarcinoma:
  - Cytologic atypia, gland formation, or mucin secretion
  - Metastatic carcinoma, spindle cell carcinoma (spindle cell lesions)

## *Small Cell Carcinoma*

### *Clinical*

- 20–25% of all lung cancer; strong association with smoking
- Locally advanced neoplasm with early distant metastasis
- Paraneoplastic syndromes: inappropriate antidiuretic hormone (IADH), Cushing syndrome,
- Eaton–Lambert syndrome, encephalomyelitis; subacute sensory neuropathy syndrome

### *Macroscopic*

- 70% of cases present as a perihilar mass with extensive mediastinal lymph node involvement

### *Microscopic (Fig. 28.60)*

- Small cells (size less than 3 resting lymphocytes) with scant cytoplasm

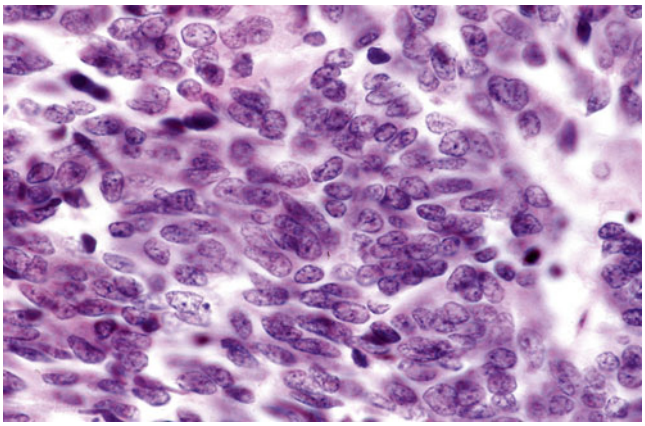

Fig. 28.60. Small cell carcinoma. Fusiform nuclei with prominent nuclear molding and abundant mitoses are present.

- Round to spindled nuclei; faint or absent nucleoli; usually extensive necrosis present
- Combined small cell carcinoma variant: small cell carcinoma and non-small cell carcinoma components (each present at least 10%)

### *Immunohistochemistry*

- Chromogranin, synaptophysin, CD56, and CD57 usually positive but negative in 25% of cases; cytokeratin may be negative; TTF1 positive; Napsin-A negative; p63 negative, p40 negative

### *Cytogenetics*

- 3p deletions

### *Differential Diagnosis*

- Non-small cell carcinoma, including large cell neuroendocrine carcinoma
  - Larger nuclei, prominent nucleoli, lower N/C ratio, lack of nuclear molding

## *Large Cell Neuroendocrine Carcinoma*

### *Clinical*

- Strong association with smoking

### *Macroscopic*

- Can extensively replace lung; central or peripheral; can be multinodular

### *Microscopic (Fig. 28.61)*

- 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*

- Neuroendocrine differentiation should be confirmed by immunohistochemistry
- Chromogranin, synaptophysin, CD56, CD57, Bombesin variably positive; CEA positive; cytokeratin positive

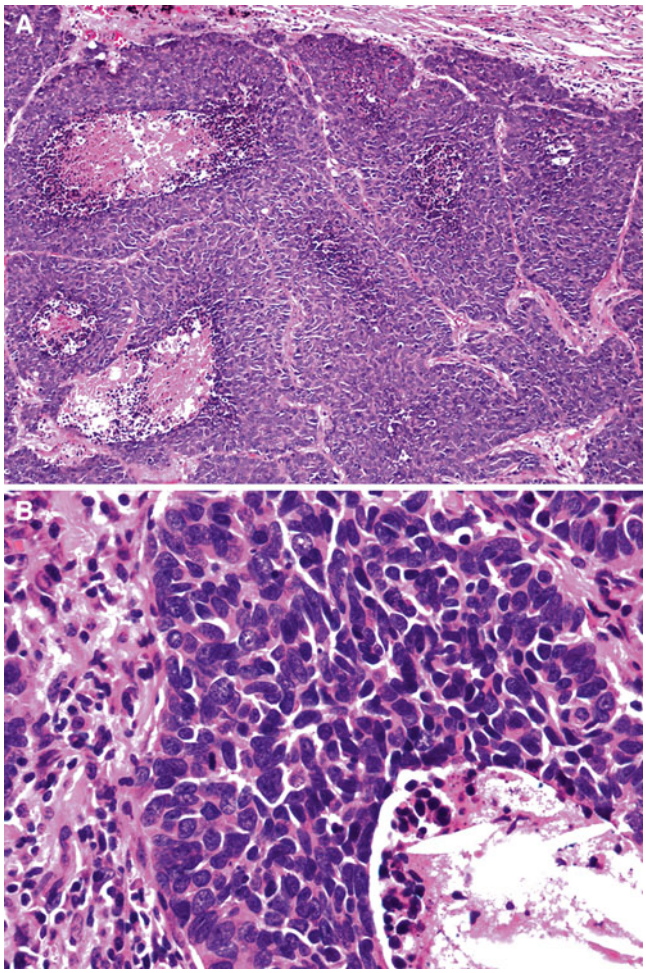


Fig. 28.61. Large cell neuroendocrine carcinoma. An organoid architecture with comedo-type necrosis is seen.

### *Differential Diagnosis*

- Small cell carcinoma
  - Smaller nuclei, no nucleoli, increased nuclear/cytoplasmic ratio
- Atypical carcinoid
  - Less cytologic atypia, 2–10 mitoses/10 hpf
- Large cell undifferentiated carcinoma
  - No evidence of neuroendocrine differentiation by light microscopy or immunohistochemical

## Mesenchymal Tumors

### Fibrous and Fibrohistiocytic Tumors

#### *Inflammatory Myofibroblastic Tumor*

### *Clinical*

- 60% occur under the age of 40; most common benign tumor in children
- Usually asymptomatic, incidental finding
- Solitary, peripheral mass

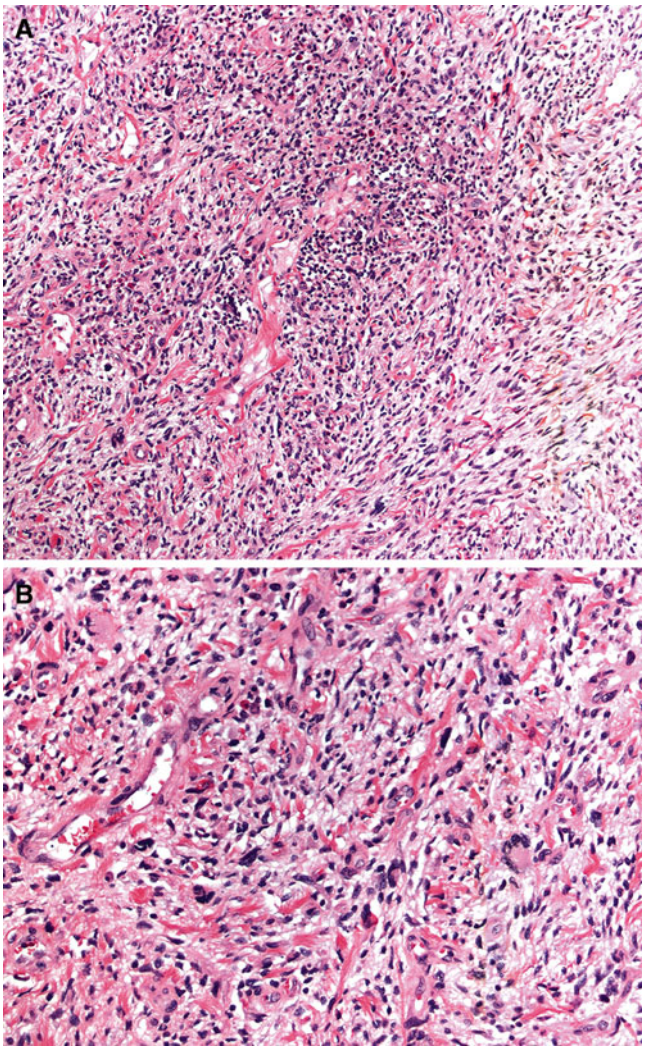


Fig. 28.62. Inflammatory myofibroblastic tumor. A prominent myofibroblasts and fibroblasts are present with scattered giant cells in the fibrohistiocytic variant (**A**). Touton giant cells and mitoses can be seen (**B**).

### *Macroscopic*

- Round, well-circumscribed rubbery tumor; can penetrate pleura or extend into adjacent mediastinal structures; white to yellow, xanthomatous in color
- Calcification and foci of necrosis can be seen

### *Microscopic (Fig. 28.62)*

- Spindle cells admixed with plasma cells, lymphocytes, and macrophages in variable proportions; Touton giant cells and xanthoma cells can be seen

### *Immunohistochemistry*

- Spindle cells variably positive for smooth muscle actin, muscle-specific actin, and desmin; anaplastic lymphoma kinase (ALK) positive

### *Molecular:*

- Rearrangements of 2p22–24 (*ALK*) gene

### *Differential Diagnosis*

- Depends on the predominant cell population
- Inflammatory sarcomatoid carcinoma
  - Atypical spindle cells, positive for epithelial markers
- Malignant fibrous histiocytoma
  - Increased cytologic atypia, cellularity, and necrosis
  - Mitotic rate >3/50 hpf
- Solitary fibrous tumor
  - Spindle cells are CD34, Bcl-2, and STAT-6 positive.
  - Primary or metastatic sarcoma.

## *Malignant Fibrous Histiocytoma*

### *Clinical*

- 60–70 years old; primary is rare; always consider metastatic lesion

### *Macroscopic*

- Usually solitary mass (2–10 cm); peripheral location; rarely intrabronchial

### *Microscopic Features*

- 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
  - Keratins and CEA positive
- Inflammatory myofibroblastic tumor, 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 mass; most are parenchymal
- Propensity for hilar region

### *Microscopic*

- Malignant spindle cells, smooth muscle actin positive

### *Differential Diagnosis*

- Leiomyoma
  - <5 mitoses/50 hpf, no cytologic atypia, no significant necrosis
- Benign metastasizing leiomyoma
  - History of uterine leiomyoma
  - Multiple nodules
  - Well-differentiated smooth muscle without mitoses/necrosis/cytologic atypia
- Lymphangioleiomyomatosis
  - Seen exclusively in women
  - Multifocal, benign-modified smooth muscle lining cystic spaces; smooth muscle actin and melanocytic markers positive

## *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

## *Epithelioid Hemangioendothelioma*

### *Clinical*

- Multiple nodules in young women (M:F = 1:4)
- Over 50% patients are <40 years old; can be seen in children
- Concomitant multifocal disease can be seen in the bone, soft tissue, and liver

### *Macroscopic*

- Discrete, firm white, circumscribed nodules (1–2 mm); may resemble cartilage

### *Microscopic (Fig. 28.63A, B)*

- Cytologically bland cells with round nuclei and small nucleoli; intracytoplasmic vacuoles present, some may contain red blood cells; endothelial differentiation
- Myxoid to densely collagenized stroma that may resemble cartilage or amyloid; hypocellular center

### *Immunohistochemistry*

- Factor VIII, CD34, CD31, and ERG positive; epithelial markers negative

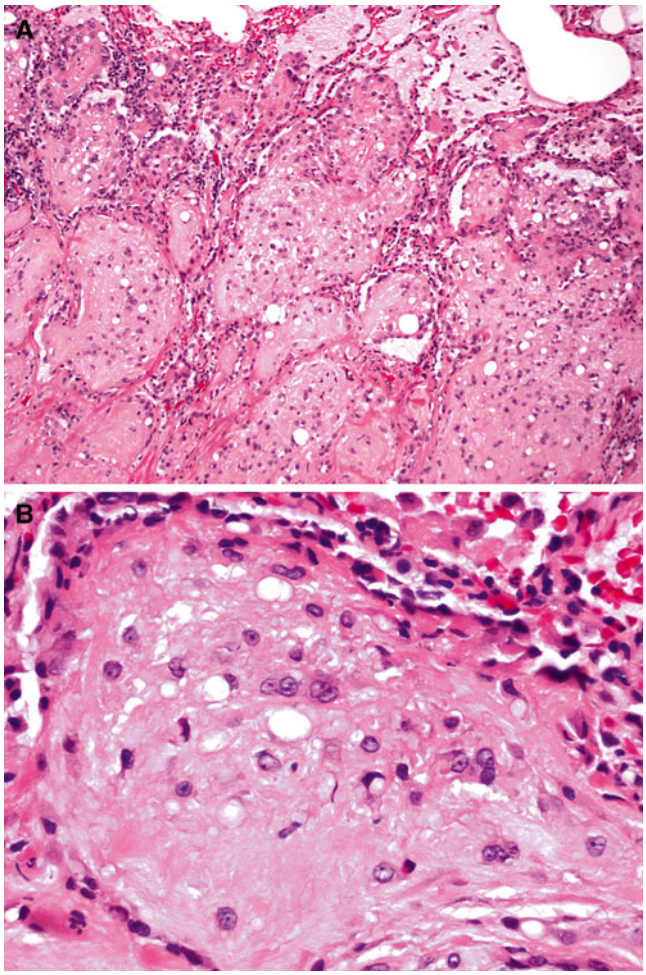


Fig. 28.63. Epithelioid hemangioendothelioma. An eosinophilic matrix is present (**A**), and cells are cytologically bland with intracytoplasmic lumina formation (**B**).

### *Molecular*

- Rearrangements involving *WWTR1* and *CAMTA1* genes [t(1;3)(p36;q25)]

### *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+
- Hamartoma
  - Usually solitary
  - Entrapped epithelium is cytokeratin+
- Angiosarcoma
  - Marked cytologic atypia
  - Predominantly intravascular

## *Kaposi 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 proliferating around vascular channels containing red blood cells
- Hemosiderin and plasma cells present

### *Immunohistochemistry*

- Spindle cells are CD34, CD31, and ERG positive; HHV8 positive

### *Differential Diagnosis*

- Angiosarcoma
  - Marked cytologic atypia
  - Not usually found in immunocompromised patients
- Benign granulation tissue
  - Lack red blood cells within 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 periarterial involvement is common; epithelioid variant may be cytokeratin positive; vascular markers (CD31, CD34, and ERG) positive

### *Differential Diagnosis*

- Kaposi sarcoma
  - Lack cytologic atypia
- Metastatic sarcoma
  - Primary lesion (e.g., heart or pulmonary artery)

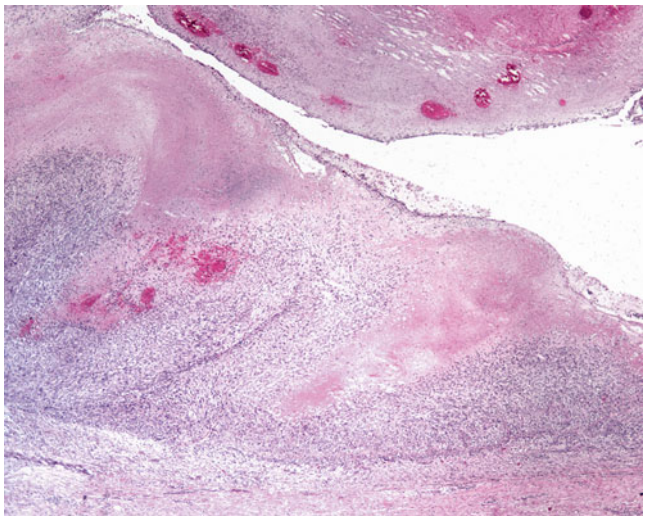

Fig. 28.64. Pulmonary artery sarcoma. Undifferentiated spindle and epithelioid cells with areas of prominent necrosis in a polypoid mass in the pulmonary artery.

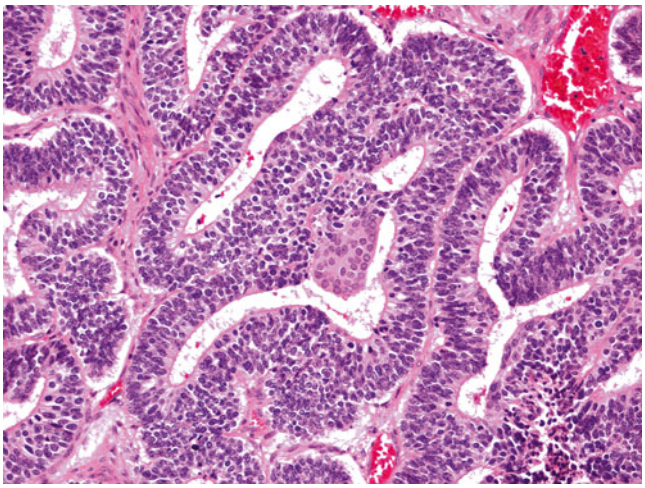

Fig. 28.65. Pleuropulmonary blastoma.

- Primary/metastatic carcinoma
  - Epithelia markers positive, vascular markers negative

### Other Vascular Tumors

- Pulmonary artery and vein sarcomas (Fig. 28.64)
  - Polypoid mass involving pulmonary vessels.
  - 80% involve pulmonary trunk
- Hemangiopericytomas
  - 10% of all primary hemangiopericytomas occur in the lung.
  - Poor prognosis associated with >5 cm and increased mitotic rate

### Pleuropulmonary Blastoma of Childhood

#### Clinical

- Found in children
  - Type I: <1 year of age
  - Type II: <3 years of age
  - Type III: <4 years of age
- Survival depends upon type
  - Type I: >80% 5 year survival
  - Types II and III: 40% 5-year survival

#### Macroscopic

- Type I: Unilocular cyst
- Type II: Solid and cystic
- Type III: Tan/white solid

#### Microscopic (Fig. 28.65)

- Type I: 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
- Types II and III: Mixture of sarcomatous and blastomatous elements

#### Differential Diagnosis

- Pulmonary blastoma
  - Adult
  - Smoking history
- Congenital cyst
  - No malignant mesenchyme

## Lymphoproliferative Lesions of the Lung

### Benign/Hyperplastic Lesions

#### Nodular Lymphoid Hyperplasia (Old Term "Pseudolymphoma")

#### Clinical

- Adults; 30–80 years; most are asymptomatic
- Can be associated with autoimmune diseases such Sjögren syndrome, lupus erythematosus
- May have polyclonal hypergammaglobulinemia

#### Macroscopic

- Most are solitary masses but can present as multinodular lesions
- Rarely >5 cm

#### Microscopic

- Polymorphous infiltrates of lymphocytes and plasma cells; germinal centers commonly seen; necrosis is rare; organizing pneumonia can be seen at the periphery of the lesion

### *Differential Diagnosis*

- Extranodal marginal zone B-cell lymphomas of mucosa-associated lymphoid tissue (MALT)
  - Lymphoepithelial lesions; granulomatous inflammation and amyloid can be seen; airway and vascular invasion; monoclonality demonstrated by immunohistochemistry and/or molecular studies

**Diffuse Lymphoid Hyperplasia (See Lymphocytic Interstitial Pneumonitis)**

### *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), and drug-induced lung disease

### *Macroscopic*

- Firm, consolidated lung

### *Microscopic*

- Dense, diffuse lymphoplasmacytic infiltrates in alveolar walls (LIP)
- Germinal centers around airways (follicular bronchiolitis)
- 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
  - Areas of organization
  - Prominent bronchiolitis

## *Lymphomas (See also Chapter 9)*

**Extranodal Marginal B-cell Lymphoma of the Mucosa-Associated Lymphoid Tissue (MALT)**

### *Clinical*

- Adults: 60 years; over half cases are symptomatic
- B symptoms uncommon
- Over 20% have monoclonal serum gammopathy
- Radiology shows localized infiltrate or solitary lesion in 50%

### *Macroscopic*

- Single or multiple nodules
- Commonly fleshy, nonnecrotizing mass; infiltrative growth pattern
- Large mass lesions can be seen

### *Microscopic (Fig. 28.66A, B)*

- Dense cellular infiltrates of lymphocytes, monocytoid/centrocytic cells, plasma cells, and large transformed lymphocytes

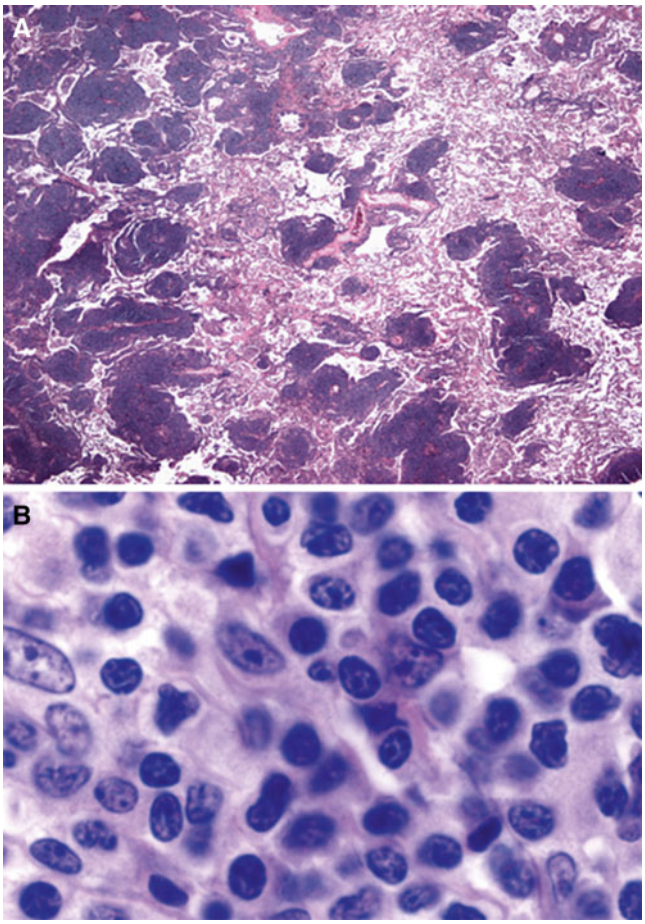


Fig. 28.66. Marginal zone lymphoma of the BALT type. Prominent lymphoid aggregates are present throughout, usually with a lymphatic distribution (**A**). A monotonous population of lymphocytes with centrocyte cytoplasmic clearing is seen (**B**).

- Lymphatic distribution usually appreciated at the edge of the lesion
- Germinal centers are commonly seen; lymphoepithelial lesions can be seen
- Airway, vascular, and pleural invasion is common

### *Immunohistochemistry*

- CD20 positive B cells with a smaller population of CD3 positive T cells
- Light chain restriction usually, but not always, seen by immunohistochemistry

### *Molecular Studies*

- Immunoglobulin (Ig) PCR shows clonal B-cell rearrangements
- Cytogenetic abnormalities include translocations involving the MALT1 gene and the API2 gene [t(11;18)(q21;q21)] or the IGH gene [t(14;18)(q32;q21)] and trisomies of chromosomes 3 and 18

### *Differential Diagnosis*

- Nodular lymphoid hyperplasia
  - Heterogeneous and polyclonal population
  - Solitary nodule
- Diffuse lymphoid hyperplasia
  - Heterogeneous and polyclonal population
  - No bronchial, vascular, or pleural invasion
- Secondary pulmonary involvement by chronic lymphocytic leukemia
- Peripheral white blood cell count consistent with chronic lymphocytic leukemia

## *Lymphomatoid Granulomatosis (LYG)*

### *Clinical*

- Average age: 40–50 years; most present with multiple lung nodules
- Skin and CNS involvement is frequent
- Immunodeficiency is a risk factor
- Poor prognosis

### *Macroscopic*

- Multiple nodules of parenchymal consolidation; may have central necrosis

### *Microscopic*

- Variable combinations of large atypical cells with numerous small- to intermediate-sized lymphocytes and some histiocytes
- Angiocentric pattern

Cell population may be heterogeneous; grading according to degree of cytologic atypia and number of EBV+ cells

- Grade 1: <5 EBV+ cells.
- Grade 2: 5–20 EBV+ cells; usually necrosis is present.
- Grade 3: numerous EBV+ cells

### *Immunohistochemistry*

- Atypical cells CD20 and EBV positive
- Small and intermediate lymphocytes are positive for T-cell markers

### *Molecular Studies*

- Immunoglobulin rearrangements (B cell)

### *Differential Diagnosis*

- Necrotizing granulomatous infections
  - No atypical cells; EBV negative; well-formed granulomas may be present
- Wegener granulomatosis
  - Giant cells and neutrophilic microabscesses
  - No atypical cells; EBV negative
- Extranodal marginal B-cell lymphoma of MALT
  - Predominantly lymphatic distribution
- Hodgkin disease
  - Classic Reed–Sternberg cells; classic background of lymphocytes and eosinophils
- Large cell lymphoma
  - Distinction from high-grade LYG may be arbitrary.

#### Posttransplant 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*

- Lymphomatoid granulomatosis
  - 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 Disease

- Usually involves lung by direct extension from mediastinum
  - Primary lung involvement is rare.
  - Multiple nodules are common.
  - Histologic features of HD elsewhere.

# Tumors of Perivascular Epithelioid Cell (PEC) Differentiation

## *Lymphangioleiomyomatosis*

### *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 40% of women with tuberous sclerosis complex (TSC-LAM)
- Nontransmissable sporadic form (S-LAM) in 3–5 women/1 million
- Classified as "low-grade malignant neoplasm" in National Cancer Institute
- Angiomyolipomas (MLs) can occur in the kidney

### *Macroscopic (Fig. 28.67A)*

- Randomly distributed cystic airspaces with thin walls

### *Microscopic (Fig. 28.67B)*

- Haphazard proliferation of smooth muscle in lymphatics, blood vessels, bronchioles, and alveolar septa

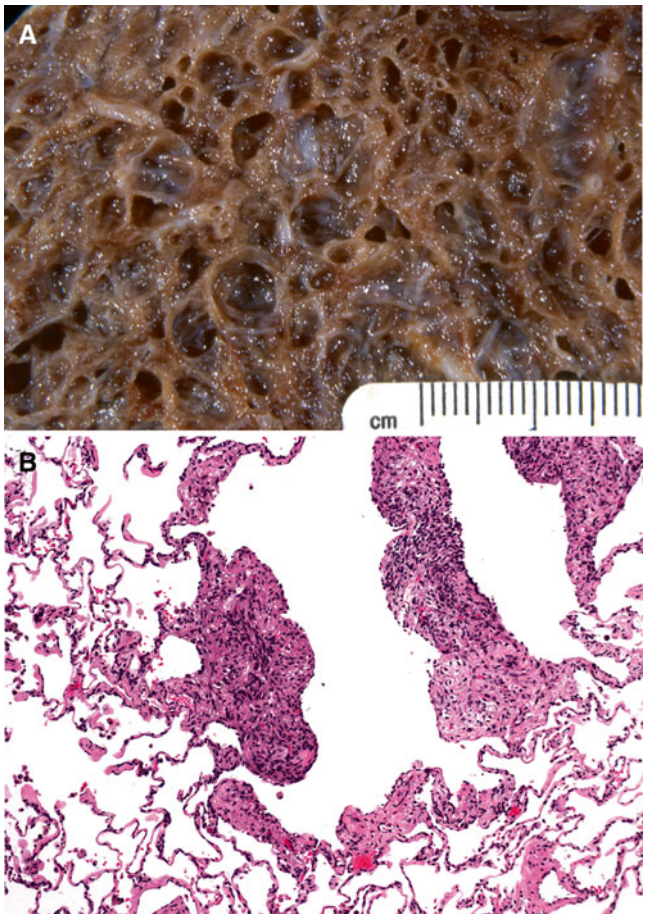


Fig. 28.67. Lymphangioleiomyomatosis. *Brown/red* cysts are characteristic of the gross appearance (**A**). Spindle-shaped cells infiltrate predominantly around veins and bronchioles (**B**).

- Hemosiderin-laden macrophages accumulate in the alveoli, especially in subpleura

### *Immunohistochemistry*

- HMB45, SOX-10 and Cathepsin K are positive

### *Differential Diagnosis*

- Benign metastasizing leiomyoma
  - Discrete nodules; some contain entrapped pulmonary epithelium
- UIP with honeycomb changes
  - Small lungs, lower lobe predominant
  - Chronic inflammatory changes and fibrosis
  - Older age group; men and women

## *Benign Clear Cell (Sugar) Tumor*

### *Clinical*

- Incidental mass on chest X-ray; asymptomatic

### *Macroscopic*

- Well-circumscribed red/tan mass; shell out from surrounding lung

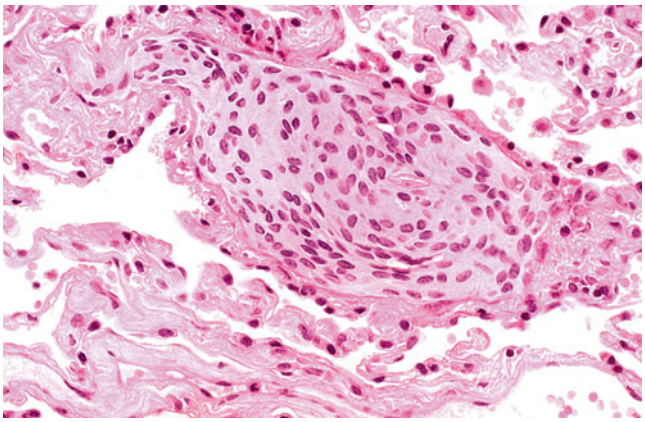

Fig. 28.68. Pulmonary meningothelial-like lesion (chemodectoma). Spindle cells form a "Zellballen" pattern.

### *Microscopic*

- Round cells with abundant granular eosinophilic to clear cytoplasm
- Abundant glycogen (PAS positive, PAS after diastase pretreatment negative)
- Dilated sinusoidal-like thin-walled blood vessels without a muscular coat

### *Immunohistochemistry*

- HMB45, Melan-A, tyrosinase, cathepsin K and SOX-10 positive; smooth muscle actin positive; desmin and S100 variably positive; cytokeratin negative; CEA negative

### *Differential Diagnosis*

- Primary lung cancer with clear cell change
  - Infiltrative growth, cellular atypia, and melanocytic markers negative
- Renal cell carcinoma
  - PAX-8 positive, HMB45, Cathepsin K negative
  - Multiple, thick-walled vessels

## Miscellaneous Tumors

## *Minute Pulmonary Meningothelial-Like Lesion (Pulmonary Chemodectoma)*

### *Clinical*

- Incidental microscopic finding usually in resection specimens for other causes; female predominance

### *Microscopic (Fig. 28.68)*

- Spindle or oval-shaped cells; perivenular location
- Zellballen pattern

### *Immunohistochemistry*

- EMA positive; cytokeratin and neuroendocrine markers negative

### *Differential Diagnosis*

- Carcinoid tumorlets
  - Associated with bronchioles
  - Neuroendocrine markers positive
- Angiomatoid lesions of pulmonary hypertension
  - Associated with arteries/arterioles
  - CD34 and CD31 positive

## *Granular Cell Tumor*

### *Clinical*

- Schwann cell lineage
- Usually solitary mass of trachea or bronchus; can be multiple
- Also found in the skin, breast, esophagus, and rectum; respiratory tract may be metastatic lesion
- Primary lung lesions may metastasize

### *Macroscopic (Fig. 28.69A)*

- Sessile or polypoid lesion with smooth surfaces; grow in walls of airways

### *Microscopic (Fig. 28.69B)*

- Large polygonal to fusiform cells with granular foamy cytoplasm and eccentrically located nuclei
- Squamous metaplasia of overlying respiratory epithelium

### *Immunohistochemistry*

- S-100 protein and neuron-specific enolase positive; cytokeratin negative

### *Electron Microscopy*

- Osmophilic inclusions

### *Differential Diagnosis*

- Oncocytic carcinoid
  - Neuroendocrine markers positive

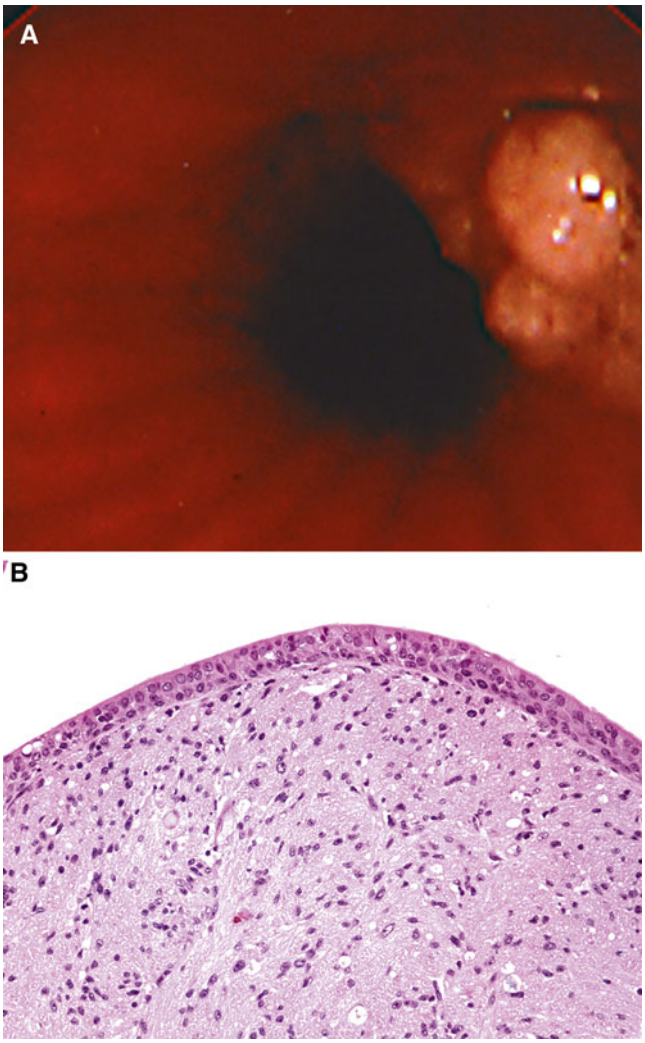


Fig. 28.69. Granular cell tumor. A *tan/pink* sessile mass is present in the bronchi (**A**). Bland granular-type epithelioid cells with foamy cytoplasm are present (**B**).

# TUMORS OF THE PLEURA

## Tumors of the Pleura

### Malignant Mesothelioma

### *Clinical*

- Asbestos is the most frequent association; M>F
- Crocidolite and amosite asbestos fibers more carcinogenic than chrysotile fibers

### *Macroscopic (Fig. 28.70A)*

- Nodular and plaque-like masses diffusely involving pleura including fissures; may encase the lung entirely

### *Microscopic Features (Fig. 28.70B, C)*

- Epithelial
  - Polygonal cells with eosinophilic cytoplasm, well-defined cytoplasmic borders, and central round to oval nuclei.
  - Usually mild to moderate nuclear atypia but marked pleomorphism may occur.
  - Tubulopapillary, glandular, and solid patterns.
  - May contain myxoid matrix in the background.
  - Deciduoid, clear cell, small cell, and signet ring cell features can be seen
- Sarcomatoid
  - Spindle cells with mild to moderate atypia with fascicular growth and patternless pattern
- Desmoplastic variant: hypocellular lesions; neoplastic spindle cells with abundant collagen deposition

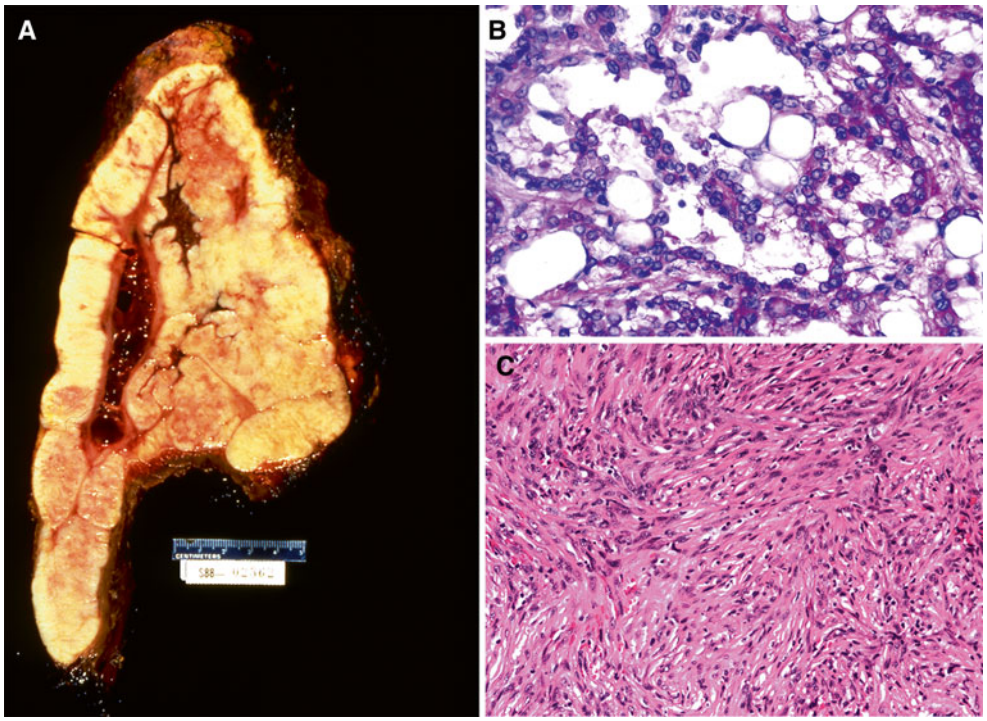


Fig. 28.70. Malignant mesothelioma. The tan/white tumor infiltrates the pleura and compresses the underlying lung parenchyma (A). An epithelioid variant (B) and spindle cell variant (C) can be seen.

- Mixed epithelial and sarcomatoid

### *Histochemistry and Immunohistochemistry*

- (See Table 28.2)

### *Molecular Features*

- Deletions of 9p21 (locus containing $p16^{INK}$ and $p14^{ARF}$ genes)

### *Differential Diagnosis*

- Benign mesothelial proliferations
  - No invasion into underlying tissues; cellular "zonation"; associated inflammatory changes
- Pleural plaque
  - Orderly arrangement of spindle cells and collagen; no nodular or frankly sarcomatous growth; no invasion of underlying tissues
- Epithelial type: adenocarcinoma (see Table 28.2)
- Sarcomatoid type: primary or metastatic sarcoma
  - Cytokeratin negative; clinical history

## Localized Fibrous Tumor of the Pleura

### *Clinical*

- Most are incidental masses
- Hypoglycemia due to insulin-like growth factor

### *Macroscopic (Fig. 28.71A)*

- Usually pedunculated; can be intrapulmonary
- Well-circumscribed solid mass with whorled and fibrous-like appearance

### *Microscopic (Fig. 28.71B)*

- Spindle cells arranged in short storiform fascicles or in a patternless pattern alternating with hyalinized collagenized areas
- Hemangiopericytoma-like areas present
- Entrapped mesothelium and alveolar epithelium form linear epithelial inclusions at the periphery of the tumor
- Features of aggressive behavior:
  - Hypercellular areas
  - >4 mitoses/10 hpf
  - >10 cm
  - Nuclear pleomorphism
  - Necrosis
  - Parietal pleura location
  - Sessile growth
  - Local tumor recurrence following surgical resection
  - Associated pleural effusion
  - Invasion of adjacent structures

### *Immunohistochemistry*

- CD34 and STAT-6 positive; bcl-2 variably positive; cytokeratin negative

### *Differential Diagnosis*

- Other spindle cell lesions including synovial sarcoma, schwannoma, inflammatory myofibroblastic tumor, and spindle cell carcinoma

**Table 28.2. Ancillary Tests for Diagnosis of Mesothelioma Versus Adenocarcinoma***

| | *Mesothelioma, epithelial type* | *Adenocarcinoma* |
|---|---|---|
| *Histochemical Stains* | | |
| Periodic and Schiff with diastase digestion | (–) | (+):40–50% |
| Mucicarmine | (–) | (+):50% |
| Alcian Blue or colloidal iron | (+) | (+) |
| Alcian Blue or colloidal iron with hyaluronidase digestion | (–) | (+) |
| *Immunohistochemistry* | | |
| Cytokeratin 5/6 | (+) | (–) |
| Cytokeratin 7 | (+) | Variable (organ dependent) |
| Carcinoembryonic antigen | (–) | (+) |
| Leu M1 (CD-15) | (–) | (+) |
| Ber EP4 | (–) | (+) |
| B72.3 | (–) | (+) |
| TTF1 | (–) | Lung (+) |
| Calretinin1 | Epithelial (+) | (–) |
| | Sarcomatoid (–/+) | |
| WT-1 | Epithelial (+) | (–) |
| | Sarcomatoid (–/+) | |
| D2-40 | (+) | (–) |
| *Electron microscopy* | – Long, branching villi, length/diameter ≥10:1 | – Small microvilli |
| | – Perinuclear intermediate filaments | – Well-developed rootlets |

*(+) and (-) signs indicate usual results.*

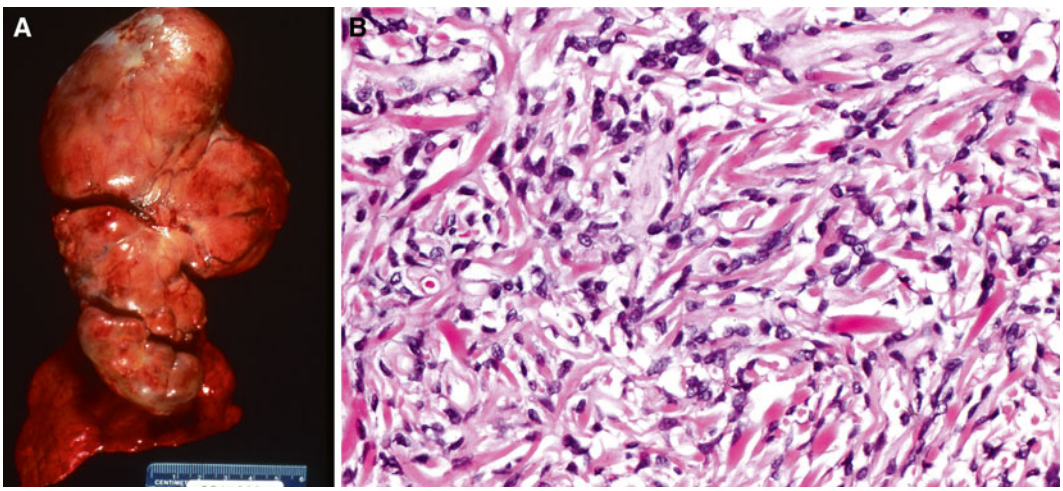


Fig. 28.71. Solitary fibrous tumor of the pleura. A large, tumor mass arises from the visceral pleura surface and extends into the pleural space (**A**). The tumor cells are spindled with storiform architecture and can have intervening strands of collagen (**B**).

## TNM CLASSIFICATION OF CANCER (2010 REVISION)

### *Lung*

Primary Tumor (T)

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.

T0 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).

T1a Tumor 2 cm or less in greatest dimension.

T1b Tumor more than 2 cm but 3 cm or less in greatest dimension.

T2 Tumor with any of the following features of size or extent:

>3 cm in greatest dimension

Involves main bronchus, ≤2 cm distal to the carina

Invades visceral pleura

Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung

T2a Tumor more than 3 cm but 5 cm or less in greatest dimension.

T2b Tumor more than 5 cm but 7 cm or less in greatest dimension.

T3 Tumor more than 7 cm or one that directly invades any of the following – parietal pleura, chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, 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 or separate tumor nodule(s) in the same lobe.

T4 Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, or tumor separate tumor nodule(s) in different ipsilateral lobe.

### Regional Lymph Nodes (X)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastasis.

N1 Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension.

N2 Metastasis in ipsilateral mediastinal and/or subcarinal lymph nodes(s).

N3 Metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s).

### Distant Metastasis (M)

MX Presence of distant metastasis cannot be assessed.

M0 No distant metastasis.

M1 Distant metastasis present.

M1a Separate tumor nodule(s) in a contralateral lobe or tumor with pleural nodules or malignant pleural (or pericardial) effusion.

M1b Distant metastasis. Pleura. IMIG Staging System for Diffuse Malignant Pleural Mesothelioma.

### Primary Tumor (T)

TX Primary tumor cannot be assessed.

T0 No evidence of primary tumor.

T1 Tumor involves ipsilateral parietal pleura, with or without mediastinal pleura or diaphragmatic pleura involvement.

T1a Tumor involves ipsilateral parietal (mediastinal, diaphragmatic) pleura.

T1b Tumor involves also visceral pleura.

T2 Tumor involves each of the ipsilateral pleural surfaces with at least one of the following:

Invasion of diaphragmatic muscle

Direct involvement of lung parenchyma

T3* Tumor involves all of the ipsilateral pleural surfaces, with at least one of the following:

Invasion of the endothoracic fascia

Extension into mediastinal fat

Solitary, completely resectable focus of tumor extending into the soft tissues of the chest wall

Nontransmural involvement of the pericardium

T4** Tumor involves all of the ipsilateral pleural surfaces, with at least one of the following:

Diffuse or multifocal extension in the chest wall, with or without rib destruction

Transdiaphragmatic extension to the peritoneum

Direct extension to mediastinal organ(s)

Direct extension to the contralateral pleura

Direct extension to the spine

Direct extension to the internal surface of the pericardium with or without pericardial effusion or tumor involving the myocardium

*T3 *Describes locally advanced but potentially resectable tumor.*

***T4* *Describes locally advanced, technically unresectable tumor.*

### Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed.

N0 No regional lymph node metastases.

N1 Metastases in the ipsilateral bronchopulmonary and/or hilar lymph nodes(s).

N2 Metastases in the subcarinal lymph node(s) and/or the ipsilateral internal mammary or mediastinal lymph node(s).

N3 Metastases in the contralateral mediastinal, internal mammy, or hilar lymph node(s) and/or the ipsilateral or contralateral supraclavicular or scalene lymph node(s).

### Distant Metastasis (M)

MX Distant metastases cannot be assessed.

M0 No distant metastases.

M1 Distant metastases.

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