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Normal Anatomy

Grossly the lungs are subdivided into lobes, three on the right (upper, middle, and lower) and two on the left (upper and lower). Each lobe is supplied by a dedicated lobar bronchus with a companion artery and vein that subdivides into bronchopulmonary segments. Bronchopulmonary segments are of special importance to thoracic surgeons because they are amenable to surgical excision in those patients for whom less than lobectomy is preferred. The cut surface of normal lung is characterized by connective tissue septa that subdivide the parenchyma into polygonal pulmonary lobules (Fig. 10.1).

The two main components of the lung interstitium are the alveolar walls and the extra-alveolar connective tissue affiliated with

bronchopulmonary bundles, interlobular septa, and visceral pleura.¹ The alveoli are normally covered primarily by type I pneumocytes with small attenuated nuclei and large cytoplasmic processes and cuboidal type II (granular) pneumocytes with a hobnail appearance; the latter produce surfactant and comprise the minority of alveolar lining cells in normal lungs but are the main proliferating component after alveolar injury.² The alveolar walls contain capillaries whose basement membrane fuses with that of the alveolar epithelium to constitute a single alveolar capillary membrane.²

The main types of bronchial and bronchiolar epithelial cells are basal cells, neuroendocrine cells, ciliated cells, serous cells, Clara cells, and goblet cells.^{1,2} Goblet and ciliated cells decrease in number as one approaches the terminal bronchioles, whereas the number

Abstract

This chapter provides an overview of non-neoplastic and neoplastic disorders of the lung following a brief overview of normal gross and microscopic anatomy. Non-neoplastic diseases include common and uncommon infections, other non-infectious granulomatous diseases, and diffuse diseases that are common sources of diagnostic difficulty in surgical and transbronchial lung biopsies. Neoplastic diseases include mainly malignant epithelial tumors with special emphasis on current diagnostic criteria and the role of immunohistochemical and molecular tools for both classification and management. The chapter concludes with a review of less common tumors that may frequently complicate differential diagnosis in both small and large specimens.

Keywords

Bronchopulmonary sequestration,
bronchiectasis,
granulomatous inflammation,
sarcoidosis,
granulomatosis with polyangiitis (Wegener's),
eosinophilic granulomatosis with polyangiitis (Churg-Strauss),
usual interstitial pneumonia,
nonspecific interstitial pneumonia,
diffuse alveolar damage,
organizing pneumonia,
hypersensitivity pneumonia,
Langerhans cell histiocytosis,
pulmonary alveolar proteinosis,
transplantation,
adenocarcinoma,
squamous cell carcinoma,
small cell carcinoma,
large cell neuroendocrine carcinoma,
carcinoid tumor,
pulmonary blastoma,
sclerosing pneumocytoma,
lymphomatoid granulomatosis,
lymphangioleiomyomatosis

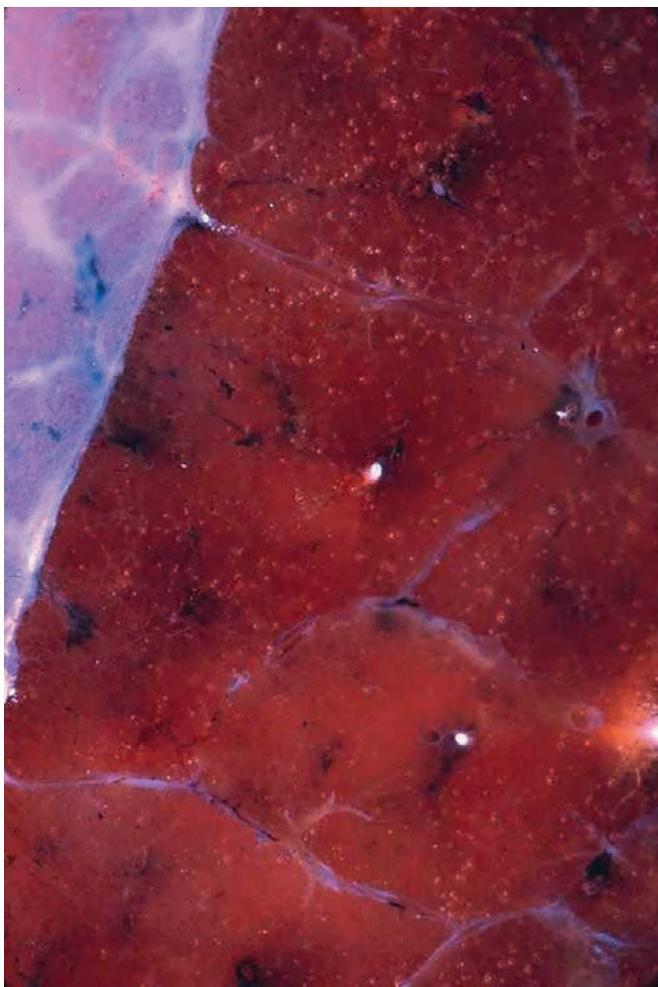


Figure 10.1 Gross appearance of cut surface of normal lung showing pulmonary lobules separated by connective tissue septa.

of Clara cells increases proportionally. Clara cells have a secretory function and represent the main progenitor cells after bronchiolar injury. They are recognized—whether in normal, reactive, or neoplastic conditions—by the presence of apical secretory granules that are periodic acid-Schiff (PAS) positive and diastase resistant and have a dense appearance ultrastructurally. Airway-associated neuroendocrine cells are part of the diffuse neuroendocrine system and are numerous in the fetus and neonate but very scanty and difficult to demonstrate in the adult.³

Small clusters of neuroendocrine cells located within the epithelium of bronchi and bronchioles (and sometimes also at the level of alveoli) are referred to as *neuroepithelial bodies*; their function is unknown.²

Submucosal glands are associated with the larger bronchi; they are composed of both serous and mucous cells and are invested by a myoepithelial cell layer. In older individuals, these glands may exhibit oncocytic changes.

Structures sometimes seen in alveolar spaces that are of no diagnostic significance include fresh red blood cells (usually the result of surgical trauma), alveolar macrophages that are frequently pigmented in smokers, corpora amylacea (common in elderly people), and blue bodies (composed primarily of calcium carbonate).⁴ The lungs of adult city dwellers often contain black anthracotic pigment (carbon); scattered birefringent silica crystals may also be found, a feature which, by itself, is not diagnostic of silicosis.

Megakaryocytes are a common incidental finding in the alveolar walls; the large, hyperchromatic, and distorted nuclei of these cells should not be misinterpreted as evidence of malignancy or viral infection.

Metaplastic bone is an age-related change sometimes seen in the bronchial cartilage; it may be accompanied by calcification and by bone marrow elements.

Lymph vessels follow the bronchovascular structures and are found mainly beneath the pleura and in septa, but not in alveolar walls. They drain to intrapulmonary peribronchial and hilar lymph nodes. The drainage is mainly cephalad, primarily through mediastinal lymph node groups, but also to abdominal lymph nodes.

Intrapulmonary lymph nodes may be found in the peribronchial region and occasionally as individual intraparenchymal nodules in the peripheral, subpleural lung.⁵ The vasculature of the lung derives from the pulmonary vessels and bronchial vessels, the latter belonging to the systemic circulation. Pulmonary arteries have both an internal and external elastic membrane, whereas pulmonary veins have a single (outer) elastic layer.

Ectopic tissues sometimes occur in otherwise normal lung or form localized abnormalities and comprise skeletal muscle⁶ (sometimes present extensively in the newborn lung, a condition known as rhabdomyomatosis⁷), neuroglial elements,⁸ pancreas,⁹ and adrenal cortex.¹⁰ Histologically normal thyroid tissue occurs only rarely in the lung; whether all such cases represent metastases from well-differentiated carcinomas remains controversial.^{11,12}

Non-Neoplastic Lesions

Biopsy

Lung biopsies performed to evaluate patients suspected of having non-neoplastic lung diseases come in many different shapes and sizes. Small closed biopsies are often done to minimize procedural risk and morbidity. The relative value of different procedures depends on the clinical and radiological setting. It is helpful, especially when interpreting smaller specimens, for the pathologist to know the clinical history and radiological findings before drawing a firm conclusion regarding the diagnosis. Basic facts such as patient age, whether or not the patient is immunocompromised, onset and tempo of disease progression (i.e. acute or chronic), localized versus diffuse radiological distribution of abnormalities, presence and degree of functional impairment, and occupational or travel history can be especially helpful in this regard.

The type of lung biopsy obtained is also important. Wedge biopsies have the highest sensitivity, specificity, and accuracy for nearly all non-neoplastic lung diseases, but smaller biopsies obtained through a bronchoscope using either a biopsy forceps (*transbronchial biopsy*) or a cryoprobe (*cryobiopsy*) are especially helpful in certain diseases like infections, sarcoidosis, diffuse alveolar damage (DAD), pulmonary alveolar proteinosis, eosinophilic pneumonia, and hypersensitivity pneumonia.¹³ Histologic findings that complicate interpretation of transbronchial biopsies include a 'holes' or 'bubbles' artifact that mimics the appearance of exogenous lipid pneumonia,¹⁴ procedure-related hemorrhage which is common, and mesothelial cells when the biopsy unintentionally captures pleural tissue.¹⁵ Multiple-step sections are extremely helpful in maximizing the diagnostic yield of transbronchial lung biopsies, especially in patients suspected of having sarcoidosis.^{16,17}

Surgical lung biopsies are especially useful in patients suspected of having idiopathic interstitial pneumonias, such as usual or nonspecific interstitial pneumonia (NSIP).¹⁸ The lingula and right middle lobes may be appropriate biopsy targets depending on the

radiological distribution of abnormalities.¹⁹ Areas of extreme scarring and honeycombing are likely to show only end-stage disease and therefore are not very informative. Ideally, samples should be obtained from two or three different areas.¹⁸ A formalin-filled syringe attached to a small (25-gauge) needle may be used to gently infuse fixative into wedge biopsies until fully expanded. A simpler approach is to remove the staple line before teasing apart the lung parenchyma and using a fresh scalpel blade to breadloaf the sample from the nonpleural surface.⁴ Routine submission of tissue for microbiologic studies has little value and is a procedure best reserved for patients in whom the clinical suspicion of infection is high.²⁰

Cystic Diseases

Cystic lung diseases may be congenital or acquired, and each of these categories can be further subdivided into localized and diffuse diseases. Some of the diffuse diseases in which cysts are a prominent radiological finding (e.g. lymphangioleiomyomatosis, Langerhans cell histiocytosis [LCH]) are reviewed elsewhere.

Congenital Cystic Diseases

Congenital cystic disease is a generic term for any cystic process of the lung thought to be already present at birth.²¹ Congenital cystic diseases are generally viewed as diseases of childhood, but they occasionally go undetected until adulthood.²² The most common types of congenital cystic disease encountered in surgical pathology include congenital lobar overinflation (i.e. congenital lobar *emphysema*), congenital cystic adenomatoid malformation (CCAM) also referred to as congenital pulmonary airway malformation (CPAM), bronchogenic cyst, and pulmonary sequestration.²³ A significant overlap exists between these entities, suggesting a common pathogenesis.²⁴ Some patients also have extrapulmonary anomalies. Congenital cystic diseases of the lung are frequently diagnosed *in utero* and are associated with excellent postnatal outcomes in the absence of fetal hydrops or other severe congenital abnormalities.^{25,26}

Congenital lobar overinflation (congenital lobar emphysema) occurs in young children. It affects only one of the upper lobes or the right middle lobe of the lung. Theories for its occurrence include mucosal folds, mucous plugs, and deficiencies in the bronchial cartilages. The pathologic change consists of massive overdistention of the alveolar spaces, not accompanied by tissue destruction. It is therefore not truly a cystic or an emphysematous process. Severe compression of the other pulmonary lobes may result from this lesion.

CCAM (CPAM) is characterized by the presence of variously sized intercommunicating cysts lined by cuboidal-to-ciliated pseudostratified columnar ('adenomatoid') epithelium (Figs. 10.2 to 10.4).^{23,25-27} Those that are not detected prenatally usually present with respiratory distress in early infancy due to compression of lung tissue and mediastinal shift. They are usually solitary and involve a single lobe. Some go undetected until later in life when they may be complicated by mucinous adenocarcinoma with lepidic-predominant (*bronchioloalveolar*) growth patterns.^{12,28} Three morphologic variants have been described based on size and number of cysts (Stocker types 1, 2, and 3).²⁷ These subcategories show significant histologic overlap limiting their value. They can be more simply divided into large (>2 cm) and small (<2 cm) cyst types, roughly corresponding to Stocker types 1 and 2, respectively.²³ Large cyst CCAMs can be unilocular or multilocular and show cystic spaces lined by ciliated respiratory epithelium. Mucinous columnar epithelium resembling gastric mucosa may be present in both the cyst wall lining and adjacent lung tissue. Small cyst CCAMs show a compact



Figure 10.2 Gross appearance of congenital cystic adenomatoid malformation of lung.

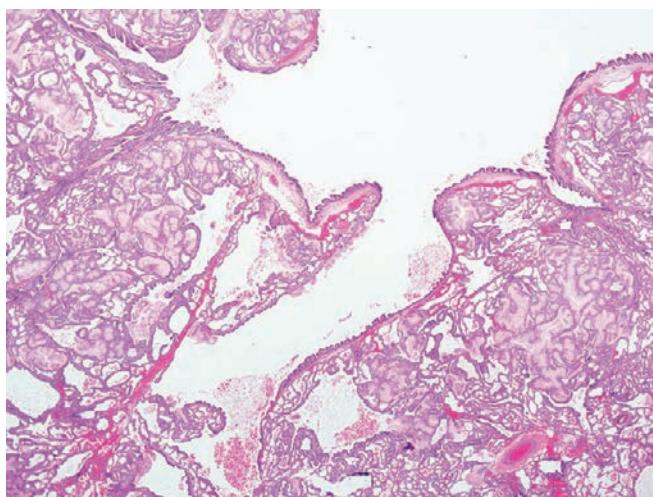


Figure 10.3 Microscopic appearance of large cyst (Stocker type 1) congenital cystic adenomatoid transformation. A large cystic air space is lined by ciliated respiratory epithelium and mucinous gastric-like epithelium is scattered throughout the adjacent lung parenchyma.

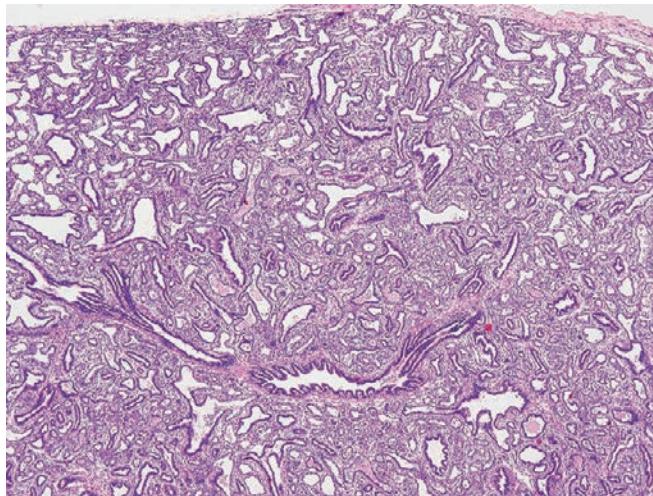


Figure 10.4 Microscopic appearance of small cyst (Stocker type 2) congenital cystic adenomatoid malformation. Microcystic air spaces lined by cuboidal epithelium are associated with tubular bronchiole-like structures lined by columnar respiratory epithelium.

arrangement of irregularly shaped microcystic spaces and variable numbers of tubular bronchiole-like structures that lack companion arteries. Mucinous epithelium is less common than in large cystic variants.

Acquired cystic diseases of the lung are a heterogeneous group of unrelated lesions that have in common the presence of cysts on computed tomography (CT) scans of the chest. **Emphysema** is the most common form of acquired cystic disease and is defined as an increase in the size of airspaces distal to the terminal bronchiole associated with destruction of their walls.²⁹ Emphysema is the most important morphologic substrate of chronic obstructive pulmonary disease, which in turn is a leading cause of disability and death. Emphysema is most commonly encountered as an incidental finding in surgical specimens excised for other reasons, in wedge resections following pneumothorax, as part of volume reduction surgery in patients with severe disease, or in explanted lungs from patients undergoing transplantation.³⁰⁻³² **Emphysematous bullae** are large (1 cm or greater) cystic spaces covered by a thin, stretched pleura. Giant bullae can result in an appearance vaguely reminiscent of chorionic villi, a change that has been designated as *placental transmogrification* (Fig. 10.5).³³ Symptoms may result from hemorrhage, infection, compression of adjacent lung, or pneumothorax. **Blebs** are formed by the rupture of an alveolus directly beneath the pleura and the escape of air into the areolar layer of the pleura, which results in interstitial emphysema. They are less than 1 cm in diameter. A bleb may rupture into the free pleural space, causing pneumothorax and *reactive eosinophilic pleuritic*, which is a common finding after pneumothorax of any cause.

Swyer-James (McLeod) syndrome, thought to be the result of repeated episodes of pulmonary infection, is characterized by the development of severe emphysema (occasionally accompanied by placental transmogrification), bronchiectasis, and/or bronchiolitis obliterans.³⁴

Pleuropulmonary blebs and cysts (usually basilar) can represent the pulmonary component of the **Birt-Hogg-Dubé syndrome**, a rare genodermatosis associated with an increased risk of renal and colonic neoplasia.^{35,36}

Chondroid cystic malformation associated with trisomy 8 mosaicism is a rare form of localized cystic lung malformation in which connective tissue septa contain cartilaginous islands.³⁷

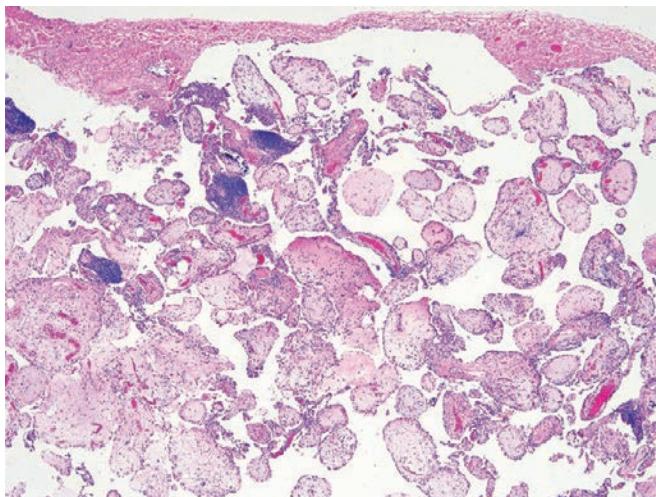


Figure 10.5 Microscopic appearance of placental transmogrification in which connective tissue papillae persist in a giant bulla resulting in an unusual histology that is reminiscent of chorionic villi.

Bronchopulmonary Sequestration

Bronchopulmonary sequestration is characterized by partial or complete separation of a portion of a lobe of the lung with a systemic arterial supply often affiliated with no connection to the functional components of the tracheobronchial tree (*bronchial atresia*).²³ The pathogenesis of sequestration remains controversial, but most authorities argue persuasively that they are developmental abnormalities rather than acquired lesions.²³

The **extralobar** variety develops from aberrantly located pulmonary mesenchyme as an extrapulmonary island of lung tissue enveloped by its own pleural covering. Extralobar sequestrations can be located at any level from the thoracic inlet to the diaphragm, or even within the abdominal cavity (Fig. 10.6).²³ About 90% of cases occur in the left side. Other congenital malformations, especially diaphragmatic hernias, occur in approximately 20% of patients. On occasion, the sequestered lung communicates with the foregut. An association with polyhydramnios and edema has been observed. The arterial supply is usually by one or several small arteries from the aorta or one of its branches. The venous drainage is into the azygos system.

The **intralobar** variety is a more heterogeneous group for which the alternative term *bronchial atresia with systemic vascular connection* has been proposed.²³ Intralobar sequestrations are much more likely to be symptomatic. They are characteristically located within the lower lobe, especially in the posterior basal segment, and are also more commonly located in the left lung (Fig. 10.7). Grossly, the sequestered portion may present as a single cyst, as a multicystic area, or as a solid mass. The segment is supplied by a *large* artery arising from the aorta or one of its branches; this artery arises above the diaphragm in 75% of the patients and below the diaphragm in the remainder. Despite its origin, the artery is always of the elastic pulmonary type. Microscopically the findings are relatively nonspecific, reflecting the consequences of proximal bronchial atresia and comprise a combination of chronic inflammation and fibrosis. Key to diagnosis is the surgeon's identification of a large elastic artery representing the systemic vascular connection.



Figure 10.6 Extralobar type of pulmonary sequestration. The lung has a spongy appearance and is covered by normal pleura.



Figure 10.7 Intralobar type of pulmonary sequestration. As is often the case with this variety, there are extensive secondary inflammatory changes. (Courtesy of Dr. J Costa, New Haven, CT.)

Bronchiectasis

Bronchiectasis refers to the permanent dilation of bronchi usually associated with destruction of some elements of the bronchial wall and inflammatory changes that extend into the surrounding or distal lung parenchyma. It represents the end stage of a variety of unrelated disorders and can be divided into localized and diffuse forms.³⁸

Localized bronchiectasis often results from partial or total obliteration of the bronchial lumen by a neoplasm, foreign body, localized inflammatory process, inspissated mucus, or external compression (e.g. broncholithiasis due to a calcified lymph node) (Fig. 10.8). It can occur in any area of the lung and follows the branching pattern of the obstructed bronchus. If the source of obstruction is relieved at an early stage, the bronchiectatic changes will regress; otherwise, the secondary inflammatory and fibrotic changes will render the condition irreversible. Localized bronchiectasis is a common finding in patients with middle lobe syndrome, a condition characterized by fixed radiological abnormalities limited to the right middle lobe and/or lingula.³⁹

Diffuse bronchiectasis is a consequence of inflammation and postinflammatory destruction of airway walls that is usually the result of repeated episodes of infection. This is the form of bronchiectasis often seen in patients with cystic fibrosis (Fig. 10.9). Two other disorders associated with chronic sinonasal infection and frequent bronchiectasis are *Kartagener* or *immotile cilia syndrome (primary ciliary dyskinesia)*, associated with complete situs inversus and infertility, and *Young syndrome*, associated with infertility caused by azoospermia but lacking ultrastructural ciliary abnormalities.⁴⁰ The distribution of diffuse bronchiectasis depends on the underlying condition. For example, bronchiectasis patients with cystic fibrosis and allergic bronchopulmonary aspergillosis usually presents with upper lobe predominant disease.

Inflammation of the bronchial wall is a constant finding in bronchiectasis of any cause and usually includes a mixed infiltrate of both acute and chronic inflammatory cells. Lymphocytes often

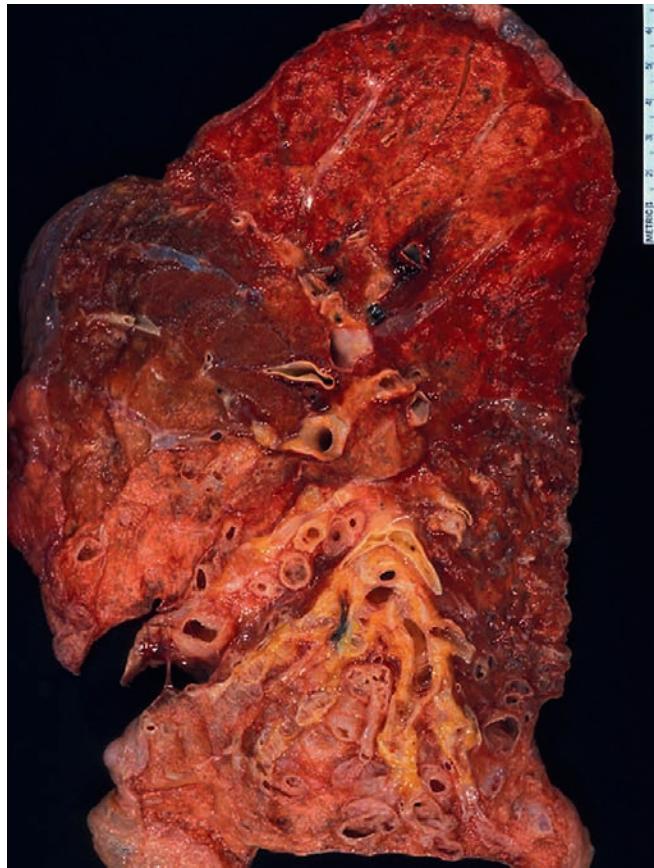


Figure 10.8 Localized bronchiectasis involving the lower lobe in a lung resected from a patient with a centrally obstructing endobronchial neoplasm.

predominate and typically include lymphoid aggregates with secondary germinal centers (i.e. lymphoid hyperplasia). Areas of ulceration are common, but the residual epithelium is usually ciliated and otherwise normal; squamous metaplasia can occur, but it is unusual. In a more advanced stage, granulation tissue develops in the lamina propria, the cartilage is fragmented or destroyed, and the muscle is erased or undergoes focal hyperplastic changes. The mucous glands persist longer than other structures. The bronchial arteries often become greatly enlarged, tortuous, and thick walled. Distal lung parenchyma, including smaller airways, usually shows a range of nonspecific postobstructive changes that may include organizing pneumonia. Multiple carcinoid tumorlets may occur in distal lung parenchyma and should not be confused with metastatic disease.⁴¹

Complications of bronchiectasis such as bronchopleural fistula with empyema, brain abscess, and amyloidosis are no longer frequent. Conservative medical treatment focused on prevention or suppression of infection and early treatment for acute exacerbations is sufficient to control the disease in most patients.³⁸ Surgical resection is limited primarily to patients with localized disease in whom hemorrhage and/or repeated pulmonary infections cannot be controlled with more conservative measures.⁴² Cystic fibrosis with respiratory failure is also an indication for double-lung transplants in highly selected patients.⁴³

Abscess

In the pre-antibiotic era, solitary lung abscesses often followed tonsillectomies and other ear, nose, and throat operations. Presently,



Figure 10.9 Diffuse bronchiectasis in lung resected from a patient with cystic fibrosis.



Figure 10.10 Bronchopneumonia with abscess formation in a 2-year-old boy secondary to aspiration of a foreign body (timothy grass inflorescence). The first recorded case of this condition seems to be that recorded in a book entitled *Some account of Lord Boringdon's accident on July 21st, 1817, and its consequences* as follows: 'In 1662, Armand de Boute, son of the Compte de Nogent, was seized with a violent fever, accompanied by a great difficulty in breathing, a dry cough, afterwards spotting of blood, sleeplessness, and great pain in the right side. A tumor at length appeared on that side, and a surgeon extracted from it an ear of barley almost entire which was quite green and had undergone no change.' (From Kissane JIM. *Pathology of Infancy and Childhood*. 2nd ed. St Louis, MO: Mosby; 1975.)

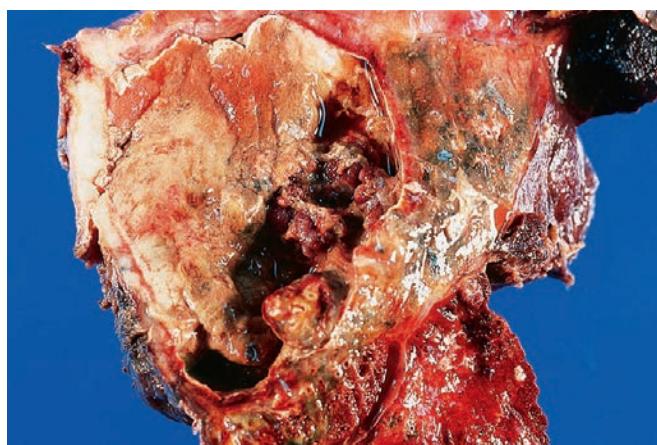


Figure 10.11 Large lung abscess.

most lung abscesses follow the aspiration of foreign material or are a complication of necrotizing pneumonia (Fig. 10.10).⁴⁴

The most common locations of lung abscesses in surgical series are the right lower lobe, the right upper lobe (particularly the subapical segment), and the left lower lobe, in that order of frequency (Fig. 10.11).⁴⁴ The apical segment of the lower lobes is particularly vulnerable in patients who must assume a supine position. Anaerobic organisms are the agents that are most commonly responsible. Chronic abscesses have thick fibrotic walls and are surrounded by areas of organizing pneumonia.

Lung abscesses in children are most commonly due to *Streptococcus* species, *Staphylococcus aureus*, and *Klebsiella pneumoniae*.⁴⁵

Complications of untreated lung abscesses include overgrowth of fungi (particularly *Mucor* and *Aspergillus*) in the cavity, spread of the process to other portions of the lung, massive hemorrhage, bronchopleural fistula with empyema, and brain abscess.

Intravenous antibiotics have been used successfully for the treatment of lung abscesses, particularly in children. For small unilocular abscesses, aspiration and drainage or partial resection of the lobe may be curative.⁴¹ For larger lesions, lobectomy is preferable because it is associated with a much lower probability of postoperative complications such as bronchopleural fistula and empyema.

Granulomatous Inflammation

A large number of diseases in which granulomatous inflammation is a dominant feature involve the lung; some of them simulate radiological and gross features of neoplastic processes.^{46,47} Microscopic examination is insufficient to establish a specific diagnosis in some patients; therefore it is important to submit a sample for culture and to perform stains for mycobacteria (Ziehl–Neelsen) and fungi (Gomori methenamine silver, GMS) in every case.⁴⁸

Tuberculosis

Tuberculosis is second only to HIV as a cause for fatal infection in the developing world and remains a major global public health challenge.⁴⁹ The prevalence of tuberculosis in the United States has fallen dramatically since the early 1990s and is now more commonly

diagnosed in foreign-born rather than native-born persons.⁵⁰ Tuberculosis in foreign-born persons is most commonly the result of reactivation of infection with multidrug-resistant organisms acquired before entry into the United States; secondary transmission accounts for fewer newly diagnosed cases.⁵¹ Most patients are diagnosed using a combination of skin testing, cultures, and other emerging techniques applied to sputum or blood.

Specimens harboring tuberculosis that are received in the pathology laboratory are usually from patients in whom some other diagnosis was suspected and may be a biopsy obtained with the fiberoptic bronchoscope, material procured via fine-needle aspiration, a surgical lung biopsy, or a resected lobe. There are still patients with pulmonary tuberculosis who fail medical therapy and therefore become candidates for therapeutic surgical intervention, but this is increasingly rare.⁵² Historical indications for pulmonary resection were summarized by Strieder et al. as follows⁵³:

1. Open cavity (with or without positive sputum) after a suitable period (4–6 months) on a satisfactory drug regimen
2. Residual caseous or fibrocaseous disease, with or without positive sputum
3. Irreversible destructive lesion, such as bronchostenosis or bronchiectasis
4. Recurrent or persistent hemorrhage, usually arising in a cavity or bronchiectasis
5. Thoracoplasty failure
6. Unexpandable lobe or lung, with associated chronic encapsulated tuberculous empyema
7. Suspected neoplasm.

The gross features of tuberculosis in tissue obtained for diagnosis differ from surgical specimens obtained from patients who have failed medical management in whom most of the resected tissue typically consists of inflamed, fibrotic, and otherwise nonfunctioning lung parenchyma (Fig. 10.12). Peribronchial tuberculous lymph nodes may infect the bronchial mucous glands by direct extension or penetrate the bronchial wall and erode into the lumen, especially when these nodes are calcified (i.e. broncholithiasis).

Tuberculous cavities removed in patients after prolonged antimicrobial therapy may show resolution into a stellate scar. In other



Figure 10.12 Massive destruction of lung parenchyma by tuberculosis.

patients the lesion stabilizes as a chronic open cavity that may harbor viable organisms in inspissated caseous material. Treated tuberculosis rarely resolves into a sterile cavity with a thin fibrous wall and a smooth surface that has no lining except for a short squamous segment at the point where the bronchus enters the cavity. Examination of these healed cavities for acid-fast organisms is invariably negative.

Tuberculomas, a term referring to localized conglomerates of necrotizing granulomatous infection due to *Mycobacterium tuberculosis* presenting as solitary lung nodules, are usually seen in adults and are a form of tuberculous reinfection. This is the form of tuberculosis most likely to be encountered by the surgical pathologist. Grossly, tuberculomas present as round, discrete, firm nodules (Fig. 10.13); they are usually solitary and located immediately beneath a white or slightly yellowish pleura. On section the lesions show central necrosis that may be complicated by calcification or cavitation. Microscopically, there is often central caseous necrosis characterized by paucicellular, granular, eosinophilic debris surrounded by a mixed inflammatory infiltrate that includes epithelioid and multinucleated giant cells with associated fibrosis (Fig. 10.14). Non-necrotizing granulomas are often present in the adjacent lung tissue. Specific pathogens cannot be reliably predicted on the basis of routine histologic finding in necrotizing granulomatous inflammation and frequently require special stains, cultures, or molecular studies for identification.⁴⁸ Organisms are usually present within the central zone of necrosis and can be demonstrated using Ziehl-Neelsen or other comparable stains for acid-fast bacilli (Fig. 10.15).⁵⁴ Highly sensitive molecular genetic techniques are available in a limited number of centers and may be helpful in highly selected cases.^{55,56}

Atypical Mycobacteriosis

A significant number of granulomatous infections of the lung are caused by 'atypical' or 'unclassified' mycobacteria, such as *M. avium* complex (MAC), *M. kansasii*, *M. xenopi*, and *M. abscessus*.⁵⁶ Many of these cases are seen in immunocompromised hosts and/or in patients with preexisting lung disease, including chronic obstructive lung disease, previous tuberculosis, pneumoconiosis, bronchiectasis, and lung carcinoma. Infection due to MAC in elderly women may resemble the middle lobe syndrome (Lady Windermere syndrome). *Hot tub*



Figure 10.13 Tuberculoma that presented as asymptomatic 3-cm solitary lung nodule.

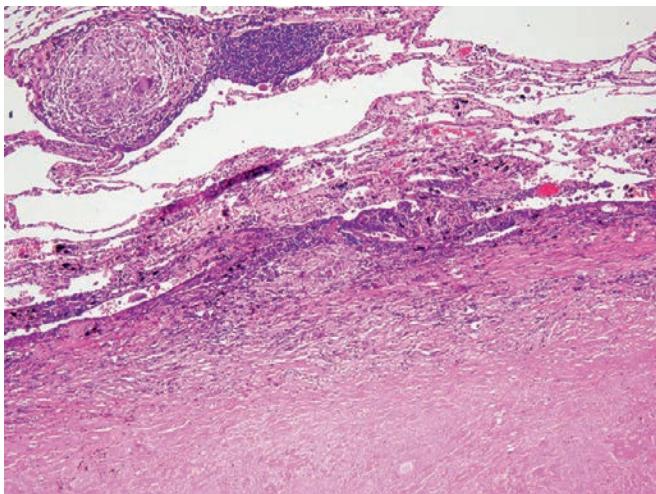


Figure 10.14 Tuberculosis. An area of caseous necrosis is bounded by a mixed inflammatory infiltrate that includes epithelioid and multinucleated histiocytes. A sarcoidal non-necrotizing granuloma accompanied the necrotizing granuloma.

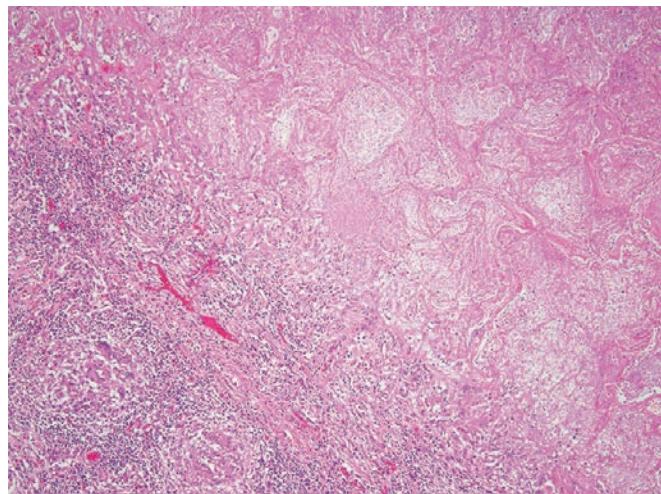


Figure 10.16 Atypical mycobacteriosis due to MAC. An area of necrosis showing 'infarct-like' features is surrounded by an inflammatory infiltrate that includes epithelioid and multinucleated histiocytes. Loose clusters of epithelioid and multinucleated giant cells also form non-necrotizing granulomas at the periphery. These histologic features are indistinguishable from those seen with other infectious granulomatous diseases including tuberculosis. Cultures from this case grew *M. avium* complex.

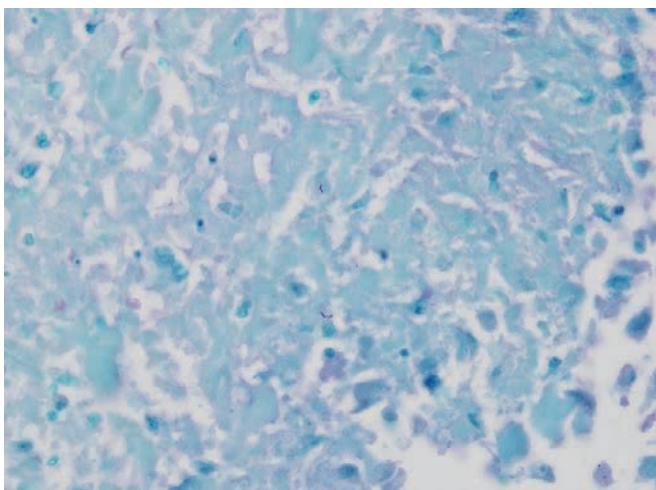


Figure 10.15 Tuberculosis. Ziehl-Neelsen stain demonstrating two acid-fast bacilli.



Figure 10.17 Coccidioidomycotic granuloma. The necrotic center is surrounded by fibrous tissue showing concentric lamination.

lung refers to a syndrome resembling hypersensitivity pneumonia resulting from exposure to hot tubs contaminated with nontuberculous mycobacteria.⁴⁶

Infections by atypical mycobacteria cannot be distinguished from tuberculosis on the basis of their gross or microscopic appearance (Fig. 10.16).⁴⁸ The diagnosis may be suspected from the appearance of the organisms in acid-fast preparations, since they tend to be longer (about 20 μm), thicker, more coarsely beaded, and much more bent than tubercle bacilli. However, positive identification of the organism by culture and/or polymerase chain reaction (PCR) techniques is necessary for precise speciation.⁵⁶

Other Granulomatous Infections

Granulomatous infections due to organisms other than tuberculous and nontuberculous mycobacteria likely to be encountered by surgical pathologists comprise mainly fungal infections that target immunocompetent as well as immunocompromised patients. Rates of disease for individual pathogens are linked to geographic variation

in prevalence of the organisms. In North America those most likely to present as necrotizing granulomatous inflammation in surgical specimens include histoplasmosis, blastomycosis, cryptococcosis, and coccidioidomycosis.⁴⁶ These same organisms have a worldwide distribution, causing disease in Central and South America, parts of Asia, Africa, and Europe.

Granulomatous fungal infections have highly variable clinical manifestations, often presenting as asymptomatic solitary pulmonary nodules (Fig. 10.17). The inflammation in each of these conditions frequently includes a combination of necrotizing and non-necrotizing granulomas with overlapping histologic features making it difficult to predict a specific pathogen on the basis of the histologic findings alone. Diagnosis is dependent on identifying the organisms for which special stains (e.g. GMS) are extremely helpful (Fig. 10.18). *Blastomyces dermatitidis* (Fig. 10.19), *Cryptococcus neoformans* (Figs. 10.20 and 10.21), and *Coccidioides immitis* (Fig. 10.22) are visible on routinely stained sections in which their distinctive morphologic features are sometimes seen to better advantage. *Histoplasma capsulatum* is usually not visible on routinely stained sections except in

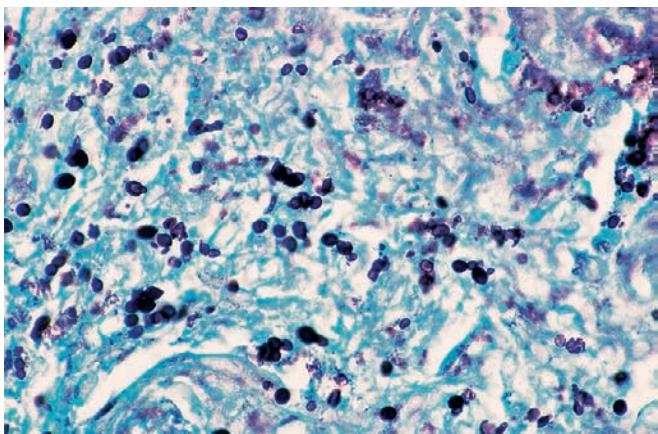


Figure 10.18 Pulmonary histoplasmosis. The organisms are demonstrated with the Grocott stain and are relatively small (1–5 μm) with a characteristic oval or teardrop shape.

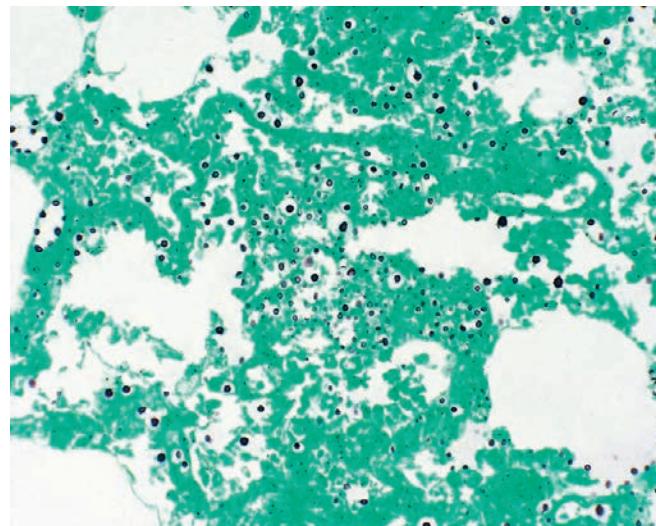


Figure 10.21 Microscopic appearance of cryptococcosis in a Grocott stain. Note the clear halo around the organisms.

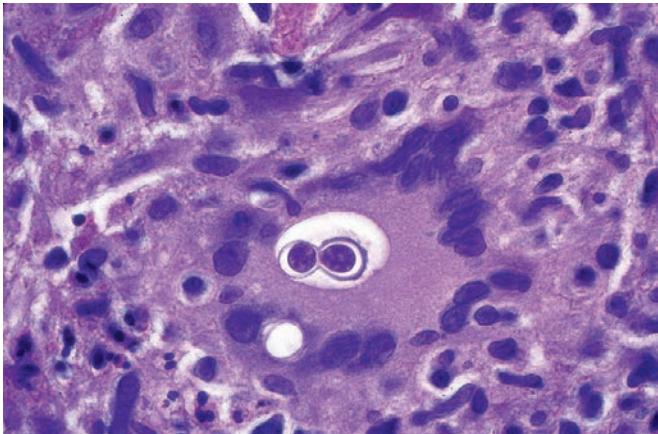


Figure 10.19 Pulmonary blastomycosis. Microscopic appearance of *B. dermatitidis* in a hematoxylin and eosin stain. The organisms are large (8–15 μm) with a doubly refractile wall and basophilic nucleus.

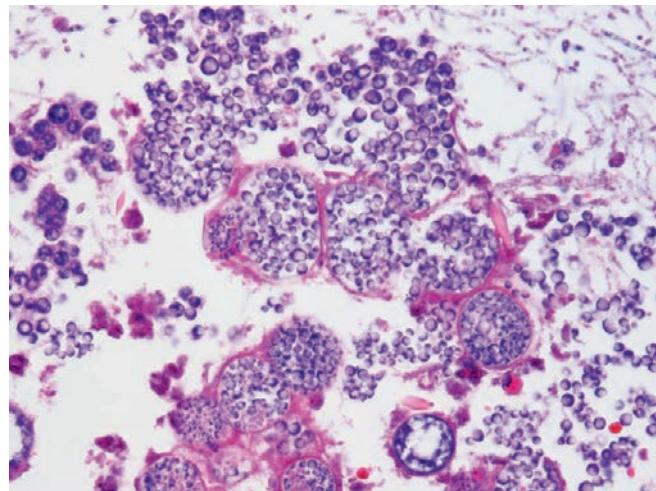


Figure 10.22 Microscopic appearance of *C. immitis* in a hematoxylin and eosin stain. Large (30–60 μm) intact and ruptured spherules contain much smaller (2–5 μm) endospores. In this example there are also mycelia (upper right) which is an uncommon finding.

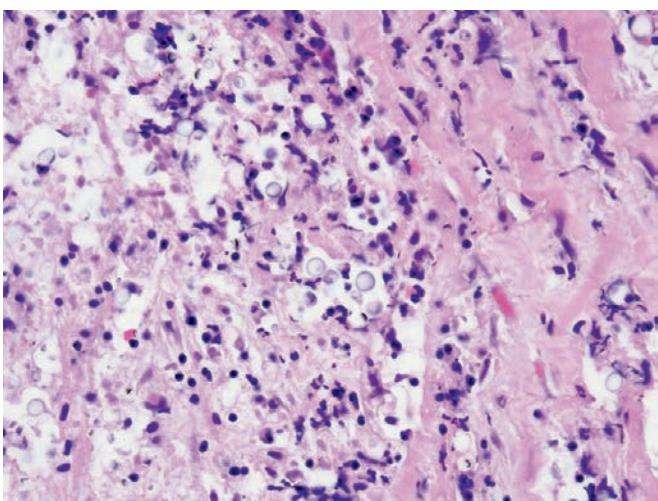


Figure 10.20 Pulmonary cryptococcosis. Microscopic appearance of *C. neoformans* in a hematoxylin and eosin stain. Variably sized, round, and occasionally fractured yeast are intermediate in size (4–7 μm) and have pale staining, thin walls with associated halos.

disseminated histoplasmosis in which numerous organisms parasitize dense infiltrates of histiocytes without well-formed granulomas (Fig. 10.23).

Dirofilaria of the lung usually presents as an incidental asymptomatic solitary nodule on chest radiographs or CT scans performed for other reasons, but it can also be multiple and/or symptomatic (Fig. 10.24). Microscopically, there is a histiocyte-rimmed necrotic nodule with marked eosinophilia containing fragments of *Dirofilaria immitis* (Fig. 10.25).⁵⁷

Sarcoidosis

Sarcoidosis can present in the thoracic cavity in various ways: moderate to marked perihilar lymph node involvement without pulmonary disease, diffuse pulmonary disease without radiographic evidence of node involvement, a combination of lymph node enlargement and diffuse pulmonary disease, pulmonary interstitial fibrosis, and

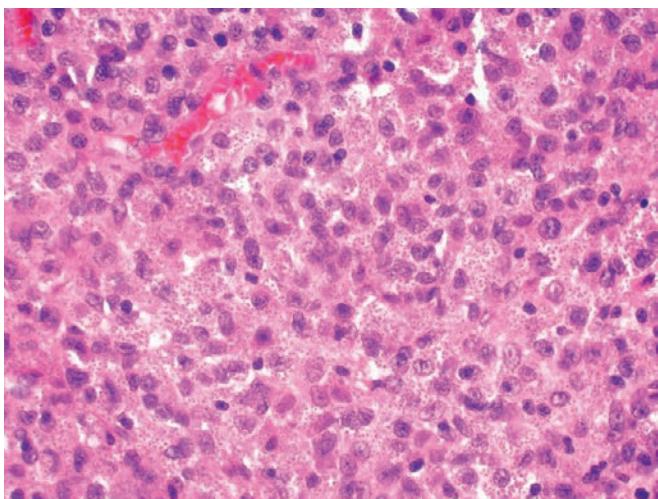


Figure 10.23 Disseminated histoplasmosis. Sheets of histiocytes demonstrate numerous organisms within their cytoplasm.



Figure 10.24 Sharply outlined lung infarct resulting from *Dirofilaria* infestation.

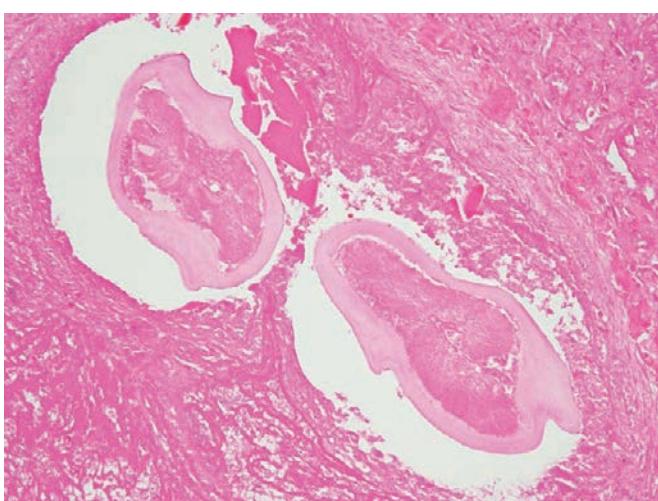


Figure 10.25 Microscopic appearance of *D. immitis* within the necrotic center of a dirofilarial nodule.

localized bronchostenosis with distal bronchiectasis and atelectasis.^{58–60} The great majority of cases fall into the first and third categories. The etiology of sarcoidosis remains controversial.

Microscopically, the hallmark of the disease is a compact non-caseating granuloma composed of epithelioid cells, Langhans giant cells, and lymphocytes (Fig. 10.26). These compact, well-formed granulomas are confined to the interstitium, where they tend to be distributed along lymphatic pathways and may coalesce to form macroscopic nodules (*nodular sarcoidosis*) (Fig. 10.27).

There are many variations in this morphologic theme. Circumferential fibrosis, central hyalinization, and diffuse interstitial fibrosis in late stage disease may render the diagnosis difficult.⁶¹ Small foci of necrosis having a bright eosinophilic ('fibrinoid') appearance may be found in the center of some granulomas. Intracellular and extracellular inclusions of several kinds may be seen, including birefringent calcium salts, but none is specific.⁶² The granulomas often surround bronchioles (but not large bronchi); because of this, transbronchial lung biopsy is positive in more than 80% of the cases.⁶³ Granulomas are also frequently present around and within

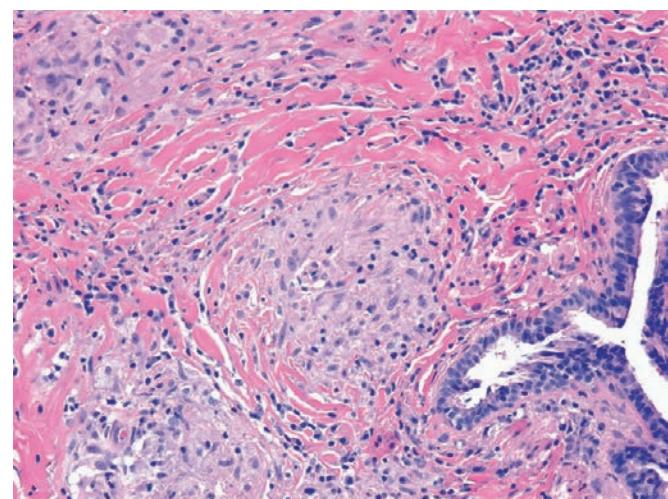


Figure 10.26 Sarcoidosis. Well-formed granuloma characteristic of sarcoidosis with characteristic collar of coarse collagen bundles.

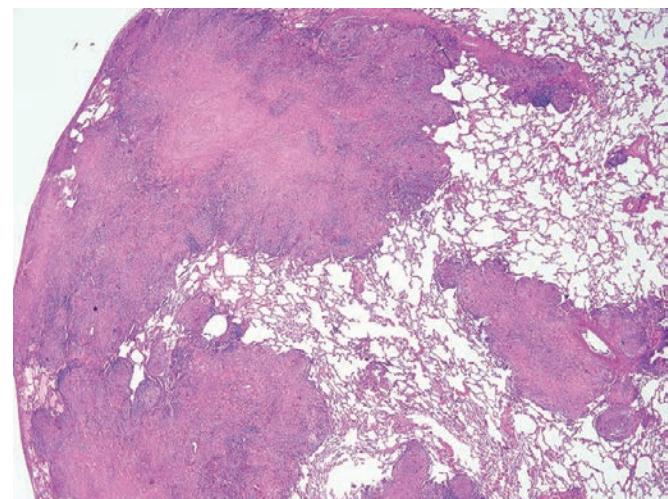


Figure 10.27 Sarcoidosis. Numerous granulomas with associated fibrosis form conglomerate nodules that expand visceral pleura, interlobular septa, and bronchovascular bundles in a characteristic 'lymphangitic' pattern.

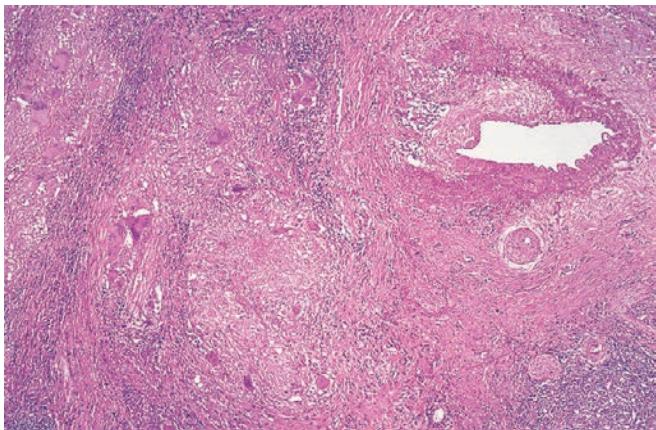


Figure 10.28 Necrotizing sarcoid granulomatosis. There is extensive involvement of large vessels by the inflammatory infiltrate, which has a necrotizing quality. Most authorities consider this a variant of nodular sarcoidosis.

blood vessel walls including predominantly pulmonary veins, and may contribute to pulmonary hypertension.⁶⁴ Vascular necrosis, however, is not a feature.

Necrotizing sarcoid granulomatosis is the name given by Liebow to a pulmonary disease characterized by extensive vascular granulomas that infiltrate and occlude pulmonary arteries and veins and are accompanied by widespread necrosis of lung tissue (Fig. 10.28). The preponderance of evidence strongly suggests that this is a variant of nodular sarcoidosis.⁶⁵ Response to steroid and immunosuppressive drugs is good, and excision of localized lesions is usually curative.⁶⁶

Granulomatosis With Polyangiitis (Wegener's)

Granulomatosis with polyangiitis (Wegener's), abbreviated GPA, is the term endorsed by a number of authoritative medical societies for the syndrome referred to historically as Wegener granulomatosis.⁶⁷ GPA is the best known member of the group of heterogeneous diseases designated by Liebow as *pulmonary angiitis and granulomatosis*. It is increasingly clear that this group comprises a number of totally unrelated entities, and it is therefore a term of historical interest but one that should not be retained for current disease classification. It is perhaps more useful to categorize GPA with the other antineutrophil cytoplasmic autoantibody (ANCA)-associated small vessel vasculitides: *microscopic polyangiitis* and *eosinophilic granulomatosis with polyangiitis (EGPA) (Churg–Strauss)*, an asthma-associated vasculitis referred to historically as Churg–Strauss syndrome.⁶⁸ ANCA characterized by a *cytoplasmic* (C-ANCA) staining pattern with immunofluorescence and/or corresponding antiproteinase three antibodies with the ELISA test are found in over 90% of classic cases of GPA and in about 60% of patients with limited disease and can be a useful adjunct in diagnostically challenging cases.⁶⁷

GPA is defined by a combination of necrotizing granulomatous inflammation and necrotizing vasculitis targeting small to medium size vessels.⁶⁸ Classic GPA is characterized by the triad of necrotizing angiitis, aseptic necrosis (involving both the upper respiratory tract and the lungs), and focal glomerulitis.⁶⁶ Other vessels may be involved, such as the temporal artery and cutaneous small vessels, resulting in tumefactive lesions at extrapulmonary sites.⁶⁹ If untreated, the disease runs an accelerated clinical course; however, it has proved quite responsive to cytotoxic drugs (particularly cyclophosphamide) as first line induction therapy.⁶⁹ Current treatment strategies for refractory disease and maintenance therapy include a growing list

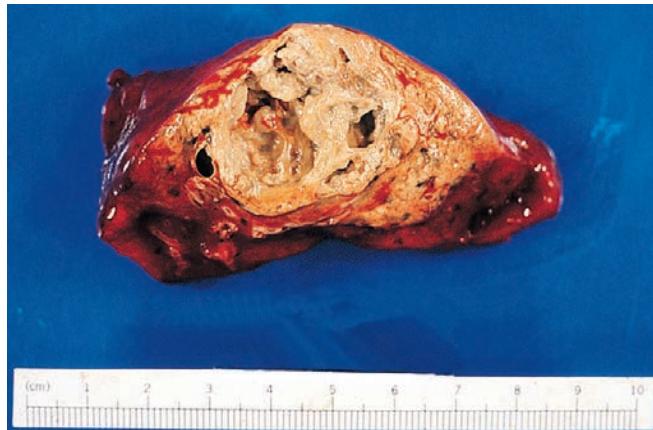


Figure 10.29 Granulomatosis with polyangiitis (Wegener's). The lesion is well circumscribed, with a granulomatous and partially necrotic appearance.

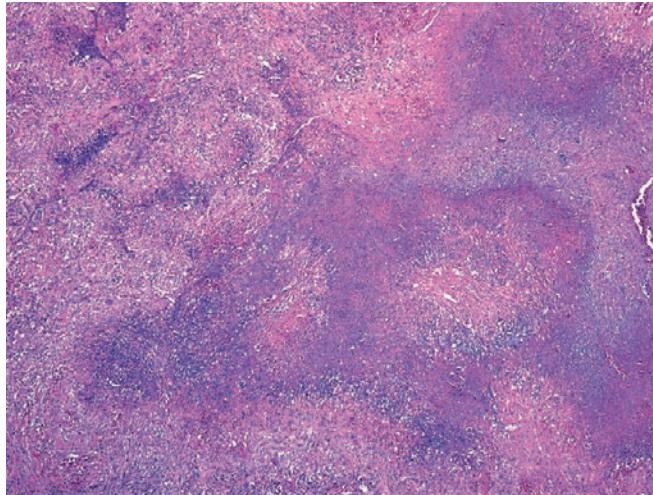


Figure 10.30 Granulomatosis with polyangiitis (Wegener's) demonstrating characteristic 'geographic' pattern of necrosis.

of novel agents such as rituximab which may selectively target vasculitis-associated changes while being relatively ineffective for granulomatous inflammation.⁷⁰

The lungs are commonly involved at the time of diagnosis in patients with GPA. The main morphologic change in the lungs is necrotizing granulomatous inflammation grossly resembling other localized necrotizing processes (Fig. 10.29). The necrotic zones have an irregularly shaped (*geographic*) configuration at low magnification and are occasionally centered on airway lumens, a phenomenon that when dominant is referred to as the *bronchocentric variant* (Figs. 10.30 and 10.31).⁷¹ The necrosis often has a characteristic 'dirty' basophilic appearance due to prominent karyorrhexis of neutrophils. Smaller granulomatous microabscesses with centrally necrotic zones containing nuclear dust surrounded by palisaded histiocytes and multinucleated giant cells are another distinctive form of granulomatous inflammation characteristic of GPA (Fig. 10.32). Well-formed non-necrotizing granulomas like those seen more commonly in granulomatous infections and sarcoidosis are generally not present in GPA.⁷² In addition to neutrophils and modified histiocytes, the mixed inflammatory infiltrate invariably includes eosinophils, lymphocytes, and plasma cells in various proportions. Eosinophils are common and when conspicuous account for descriptions of the

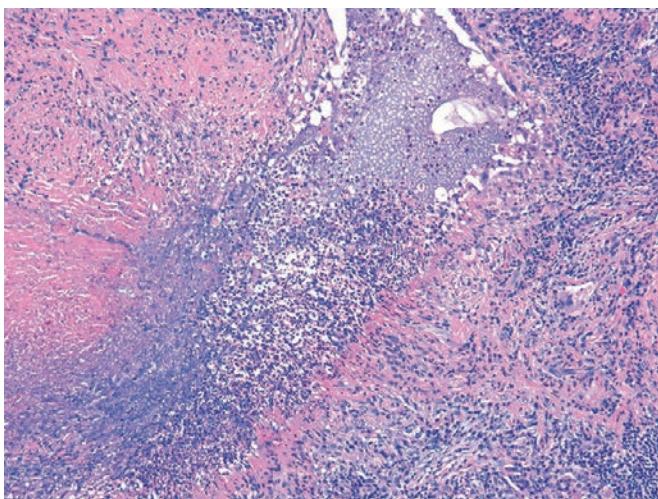


Figure 10.31 Bronchocentric variant of granulomatosis with polyangiitis (Wegener's) in which the necrosis is centered an airway lumen and the airway wall partially replaced by a granulomatous infiltrate comprising palisaded histiocytes.

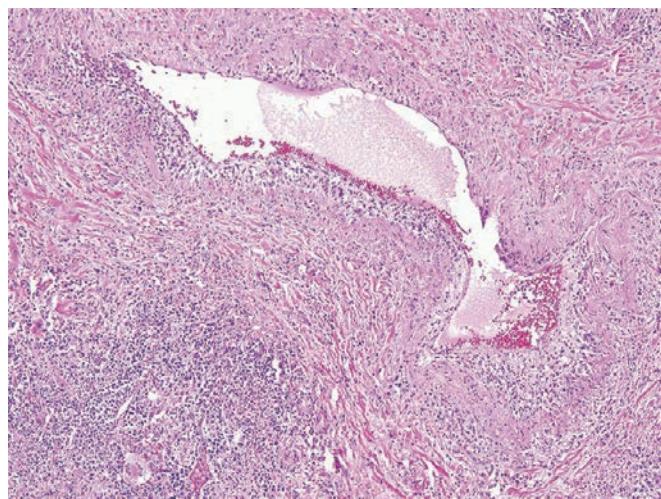


Figure 10.33 Granulomatosis with polyangiitis (Wegener's) showing characteristic pattern of patchy vessel wall inflammation and necrosis.

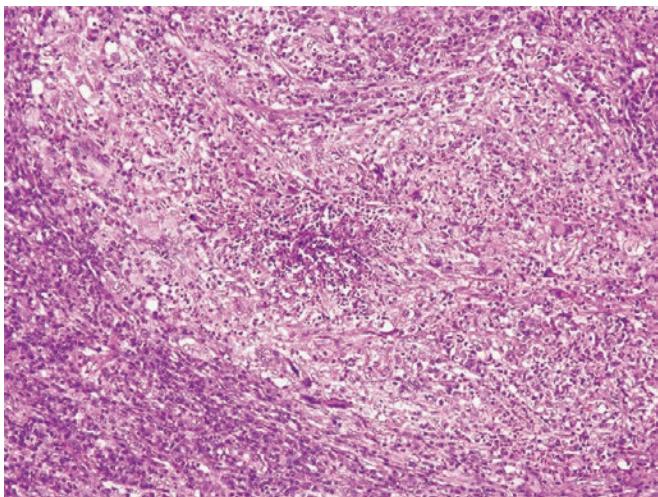


Figure 10.32 Granulomatous microabscess characteristic of granulomatosis with polyangiitis (Wegener's).

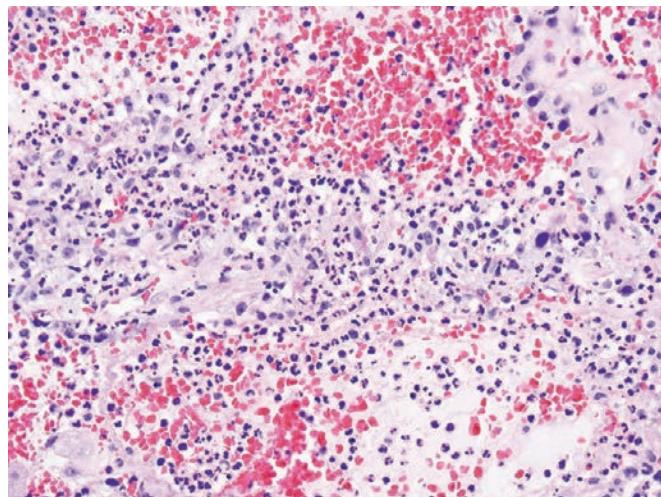


Figure 10.34 Capillaritis and alveolar hemorrhage in a patient with granulomatosis with polyangiitis (Wegener's).

*eosinophilic variant.*⁷³ Establishing the diagnosis with confidence requires a destructive leukocytolytic angiitis involving arteries and veins (Fig. 10.33).⁷³ The vasculitis is patchy in distribution characterized by abrupt transmural neutrophil-rich inflammatory infiltrates with associated karyorrhexis and vessel wall necrosis. Occasionally the necrotizing vasculitis includes granulomatous features in the form of multinucleated giant cells. In rare cases diffuse pulmonary hemorrhage with associated necrotizing capillaritis is a dominant feature, a combination of findings also seen in other vasculitic syndromes, including microscopic polyangiitis and systemic lupus erythematosus (Fig. 10.34).^{74,75} The diagnosis of GPA can be made or suggested in transbronchial biopsy specimens.⁷⁶

Limited (localized) GPA is confined to the lungs, more specifically with no renal involvement, and has a more protracted clinical course.⁷³ Steroids and cytotoxic drugs are highly effective. Grossly, there are multiple bilateral nodules, some round and others infarctlike, frequently located in the lower lobes. Microscopically, the disease is indistinguishable from the classic variety. Necrotizing vasculitis is a requisite for the diagnosis. However, it should be recognized that

vessels located within ordinary infectious granulomas can exhibit secondary inflammatory changes that mimic vasculitis.⁵⁴ Therefore the presence of angiitis *away* from the areas of necrosis and massive inflammation should be searched for to document the diagnosis. The diagnosis of GPA should be made with caution in granulomas that appear solitary by radiographic examination.⁷⁷

Eosinophilic Granulomatosis With Polyangiitis (Churg–Strauss)

EGPA (Churg–Strauss) is the current term for the disease referred to historically as Churg–Strauss syndrome.⁶⁶ EGPA is defined by a combination of necrotizing granulomatous inflammation, eosinophilia, and necrotizing vasculitis involving small and medium-size vessels. It presents a clinical picture of systemic vasculitis resembling polyarteritis nodosa but is associated with asthma, peripheral eosinophilia (up to 80%), and a higher incidence of pulmonary involvement.^{78–80} In some patients this asthma-associated vasculitis syndrome may be unmasked or exacerbated when

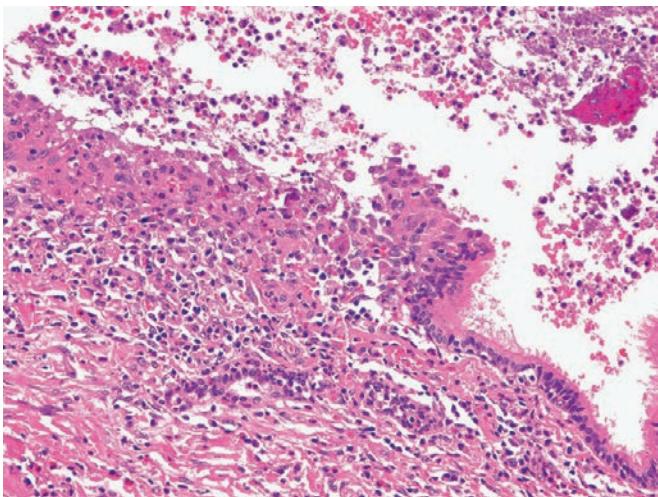


Figure 10.35 Bronchocentric granulomatosis in a patient with allergic bronchopulmonary aspergillosis. The bronchial wall is partially replaced by epithelioid histiocytes with associated eosinophilia.



Figure 10.36 Mucoid impaction of bronchi in a patient with allergic bronchopulmonary aspergillosis. Thick, tenacious secretions expand ectatic bronchi and in this patient formed a hilar mass for which clinical concerns included carcinoma.

transitioning from corticosteroids to steroid-sparing leukotriene receptor antagonists, such as montelukast, although the precise role that these agents have in the pathogenesis of vasculitis remains controversial.⁸¹

Microscopically, both the pulmonary and the extrapulmonary lesions are characterized by a prominent eosinophilic infiltrate, foci of necrosis (some associated with eosinophils and some unrelated to them), a granulomatous reaction around some of these necrotic foci, and necrotizing vasculitis. Finding all of these features in a single biopsy is uncommon, and therefore establishing the diagnosis on the basis of lung biopsy often requires careful correlation with other clinical and laboratory data. In lung biopsies, for example, the eosinophilic infiltrates often take the form of eosinophilic pneumonia, which is a relatively nonspecific finding in the absence of necrotizing granulomatous inflammation and/or necrotizing vasculitis. About 70% of patients will have a positive P-ANCA corresponding to an anti-myeloperoxidase (MPO) autoantibody by ELISA.⁷⁸

Bronchocentric Granulomatosis, Mucoid Impaction of Bronchi, and Allergic Bronchopulmonary Mycosis

Bronchocentric granulomatosis is a form of necrotizing granulomatous inflammation in which all or nearly all the granulomas are centered on bronchi and bronchioles, leading to their destruction. Broncho- or bronchiocentric necrotizing granulomatous inflammation is not specific to any one disease and can be seen in GPA as well as granulomatous infections. For that reason the term *bronchocentric granulomatosis* is generally limited to patients with **allergic bronchopulmonary aspergillosis**, a disease occurring almost exclusively in asthmatics and patients with cystic fibrosis in whom the bronchocentric granulomatosis (Fig. 10.35) is usually accompanied by eosinophilic pneumonia and mucoid impaction of bronchi.⁸² Globally allergic bronchopulmonary mycosis can be due to other fungi, such as *Candida albicans*, *Bipolaris*, and *Curvularia* organisms.⁸³

Mucoid impaction of bronchi is a process in which proximal ectatic bronchi become filled with thick inspissated mucus (Fig. 10.36). This change may cause localized radiological abnormalities for which diagnostic considerations include neoplasms. Occasionally

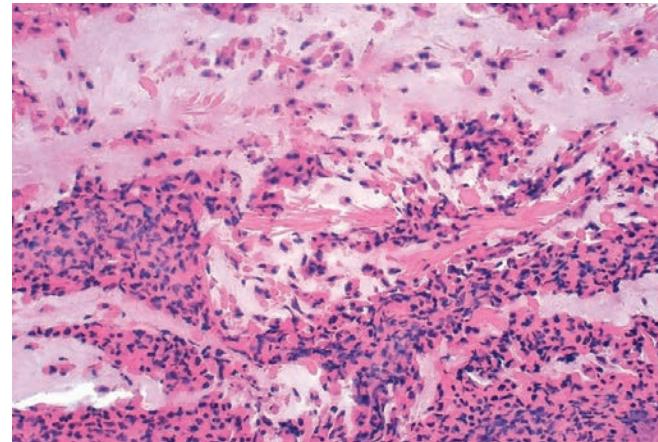


Figure 10.37 Mucoid impaction of bronchi showing the 'allergic mucin' typical of allergic bronchopulmonary aspergillosis including numerous Charcot-Leyden crystals.

patients expectorate these histologically distinctive plugs that comprise a combination of inspissated mucus, necrotic eosinophils, and Charcot-Leyden crystals distributed in a layered fashion resembling the rings of a tree (Fig. 10.37).

Other Granulomatous Inflammations

Granulomas are occasionally seen in other noninfectious conditions, including aspiration of particulates and drug abuse in which inorganic fillers common in the oral medications used instead for intravenous injection elicit a perivascular granulomatous response (Fig. 10.38). Occasionally granulomas are present in diffuse lung diseases other than sarcoidosis, including most commonly hypersensitivity pneumonia, lymphoid interstitial pneumonia, and related forms of lymphoid hyperplasia, and eosinophilic pneumonia.

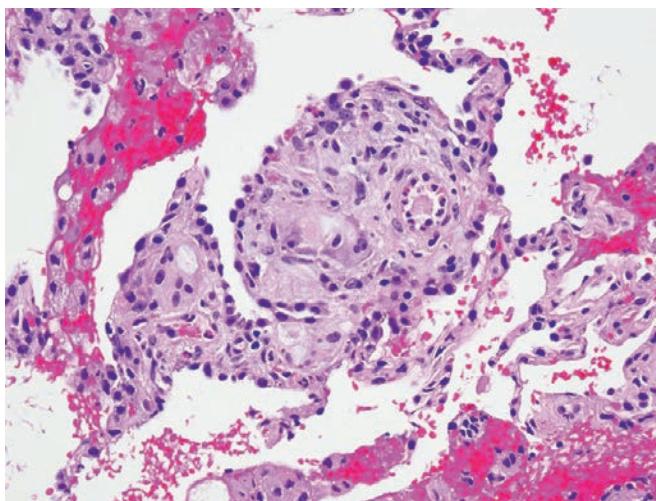


Figure 10.38 Drug abuser's lung in which perivascular granulomas include foreign body giant cells containing birefringent particulates, in this case a combination of talc and cellulose.

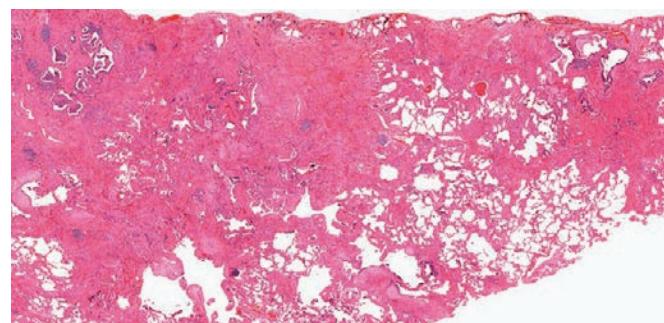


Figure 10.39 Usual interstitial pneumonia. Patchwork pattern of fibrosis with scarring and honeycomb change is characteristic.

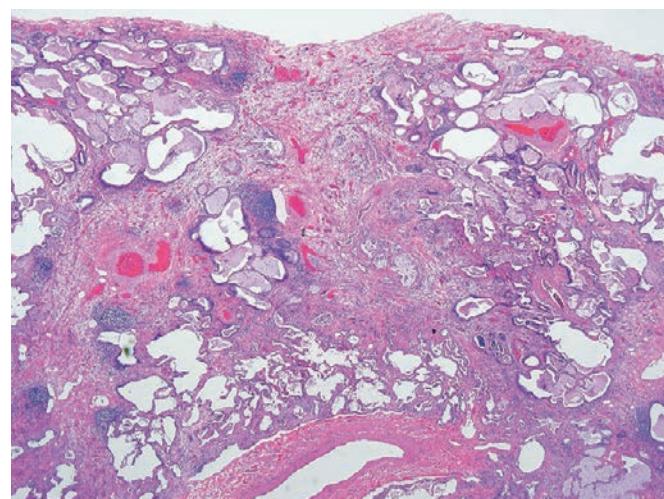


Figure 10.40 Usual interstitial pneumonia. Characteristic appearance of honeycomb change.

Table 10.1 Classification of idiopathic interstitial pneumonias¹⁸

Chronic fibrosing interstitial pneumonias	UIP NSIP
Smoking-related interstitial pneumonias	RBILD SRIF
Acute/subacute interstitial pneumonias	Diffuse alveolar damage Organizing pneumonia
Rare interstitial pneumonias	LIP Pleuroparenchymal fibroelastosis Unclassifiable interstitial pneumonia

LIP, Lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; RBILD, respiratory bronchiolitis-interstitial lung disease; SRIF, smoking-related interstitial fibrosis; UIP, usual interstitial pneumonia.

Diffuse Interstitial Lung Disease

This is a complex group of non-neoplastic pulmonary diseases that often require correlation of morphologic, clinical, and radiological findings. High-resolution computed tomography (HRCT) represents a major advance in this area, and a multidisciplinary approach provides at present the highest levels of diagnostic reproducibility.⁸⁴

Idiopathic interstitial pneumonias account for a substantial subset of the diffuse lung diseases that a surgical pathologist is likely to encounter and can be divided into *chronic fibrosing* interstitial pneumonias, *smoking-related* interstitial pneumonias, and the *acute or subacute* interstitial pneumonias (Table 10.1).¹⁸ The chronic fibrosing interstitial pneumonias comprise the largest category and account for over 80% of patients with idiopathic interstitial pneumonia who undergo surgical lung biopsy.⁸⁵⁻⁸⁸ The same range of histologic abnormalities also occur in patients with underlying connective tissue diseases, a distinction that hinges in large part on clinical and laboratory studies.

Usual interstitial pneumonia (UIP) is the most common of the idiopathic interstitial pneumonias, accounting for nearly two-thirds of patients who undergo biopsy for diffuse lung disease of unknown cause.⁸⁵⁻⁸⁸ Most patients with UIP fall into the clinical category of idiopathic pulmonary fibrosis (IPF), a syndrome that classically has

an insidious onset characterized by a combination of breathlessness and cough with a relentlessly progressive evolution, many of the patients dying of respiratory failure after 3–4 years.⁴ Acute exacerbation is increasingly recognized as a common final pathway in patients with underlying UIP and is characterized by sudden worsening of symptoms and more rapid progression of respiratory failure.⁸⁹ Some instances of UIP show a familial pattern indicating a heritable predisposition.⁹⁰ Others have underlying systemic connective tissue diseases, most commonly rheumatoid arthritis, scleroderma, and systemic lupus erythematosus.

Microscopically, UIP is a primarily interstitial fibrosing process. According to Katzenstein et al., the single most important feature that distinguishes UIP from the other interstitial pneumonias (including so-called NSIP) is the marked regional variation in the nature and degree of the fibrosis, with a distinct patchwork distribution and evidence of architectural derangement (Fig. 10.39).⁹¹⁻⁹³ The architectural derangement takes the form of scarring and *honeycomb change*, the latter referring to cystic spaces situated within distally collapsed, fibrotic lung (Fig. 10.40). Areas of fibrosis in UIP are often most advanced in peripheral, subpleural lung where it is frequently associated with smooth muscle hyperplasia. Small *fibroblast foci* are often sandwiched between surface epithelium and fibrotic scar and are composed of spindled fibroblasts and myofibroblasts organized in a vaguely linear fashion within a pale-staining stroma (Fig. 10.41).⁹¹ These findings are complicated by a superimposed pattern of acute lung injury that usually takes the form of organizing DAD in patients with acute exacerbation.⁹⁴ Less commonly patients

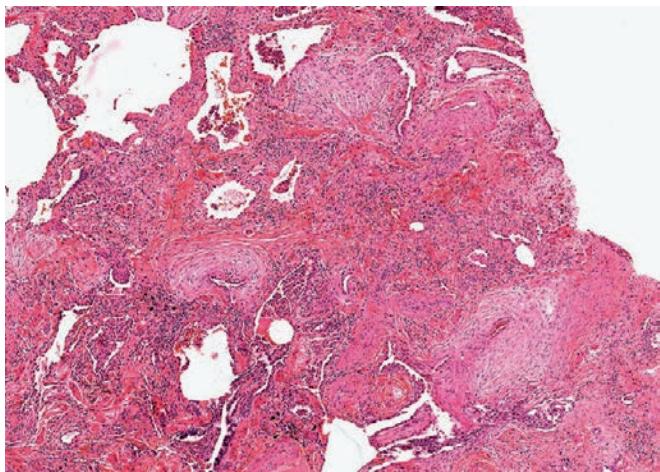


Figure 10.41 Usual interstitial pneumonia with prominent fibroblast foci. Fibroblast foci resemble organizing pneumonia except for their interstitial location.

with acute exacerbation show a combination of UIP and organizing pneumonia. Patchy changes resembling eosinophilic pneumonia have also been described in UIP and appear to have limited clinical significance.⁹⁵

Ultrastructural studies suggest that fibroblast foci are foci of abnormal wound healing in which activated mesenchymal cells migrate from the interstitial into the intraluminal compartment through defects in the basement membrane following epithelial necrosis, resolving through a disordered process of alveolar collapse, reepithelialization, and remodeling.^{96,97} Fibroblast foci are characteristic of UIP but are not specific and can be seen in other diffuse lung diseases. They are the consequence of aberrant activation of epithelial cells and fibroblasts in lungs with an aging phenotype leading to accumulation of extracellular matrix and architectural distortion.⁹⁸

NSIP/fibrosis is a term that was originally used for cases that could not be classified into any of the major categories of interstitial pneumonia, but which has now acquired an identity of its own.^{18,99,100} Patients with NSIP fall into several different categories, including a subset with underlying systemic connective tissue disorders in which NSIP is the most common form of diffuse fibrotic lung disease.¹⁰¹ NSIP is the second most common finding in patients with interstitial pneumonias of unknown cause ('idiopathic' NSIP).¹⁰⁰ In either circumstance patients with NSIP generally have a better prognosis than patients with UIP.¹⁰²

The main morphologic difference with UIP is that NSIP lacks the heterogeneous pattern of lung involvement characteristic of the former.^{18,85,91,99,102–104} The changes in NSIP may be patchy or diffuse but retain a degree of qualitative uniformity in areas of abnormality that set it apart from UIP. Interstitial structure including alveolar septa are expanded by an inflammatory infiltrate with ('fibrotic' NSIP) or without ('cellular' NSIP) collagen fibrosis (Fig. 10.43). Even with fibrosis, NSIP lacks the architectural derangement typical of UIP and instead is characterized by relative preservation of lung structure. Focal areas resembling NSIP can occur in otherwise classical UIP, which is why deciding that NSIP is a representative finding even in surgical lung biopsies requires careful correlation with clinical and radiological information.^{91,92,104}

Respiratory bronchiolitis is a common incidental finding in heavy smokers but in some instances accounts for a form of symptomatic diffuse lung disease referred to as **respiratory bronchiolitis-interstitial lung disease (RBILD)**.^{105,106} Histologically, respiratory

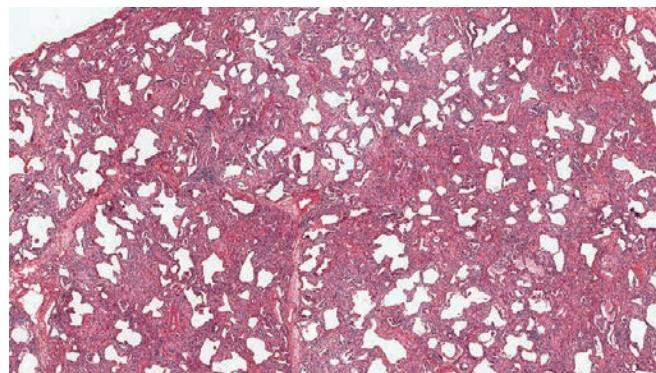


Figure 10.42 Nonspecific interstitial pneumonia demonstrating the diffuse uniform interstitial widening without the patchwork fibrosis or honeycomb change typical of UIP.

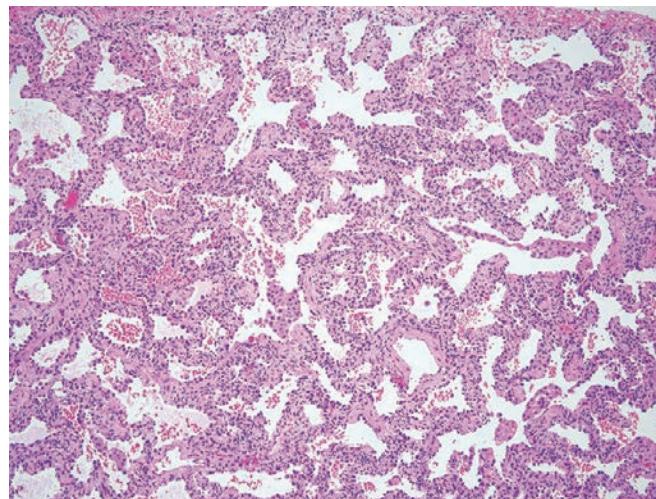


Figure 10.43 Cellular NSIP. Alveolar septa are uniformly expanded by cellular infiltrate with minimal fibrosis.

bronchiolitis is characterized by an accumulation of lightly pigmented alveolar macrophages within respiratory bronchioles spilling into neighboring alveoli (Fig. 10.44). The changes differ from the lesion referred to historically as desquamative interstitial pneumonia (DIP) in that the histiocytic accumulation is centriacinar instead of diffuse and lacks an associated interstitial pneumonia. Occasionally, RBILD is accompanied by mild, paucicellular fibrosis in the form of lamellar eosinophilic collagenous thickening of alveolar septa in a patchy, mainly subpleural distribution, a condition referred to as **smoking-related interstitial fibrosis (SRIF)** (Fig. 10.45) that is not to be confused with chronic fibrosing interstitial pneumonias such as UIP and NSIP.¹⁰⁷ The presence or absence of SRIF is not helpful in distinguishing patients with incidental respiratory bronchiolitis from those with RBILD, a distinction that is primarily dependent on clinical and radiological data. It is likely that SRIF in patients with symptomatic lung disease not attributable to COPD includes what would have been referred to historically as DIP.

DIP was defined historically by a filling of the alveolar spaces by large mononuclear cells, associated with relatively minor interstitial changes (Fig. 10.46).¹⁰⁸ Ultrastructurally, the cells that were originally thought to be desquamated pneumocytes have features of macrophages instead, making the term *DIP* a misnomer. Katzenstein and others have proposed that patients previously diagnosed as DIP are more properly categorized today as RBILD, SRIF or NSIP, and therefore

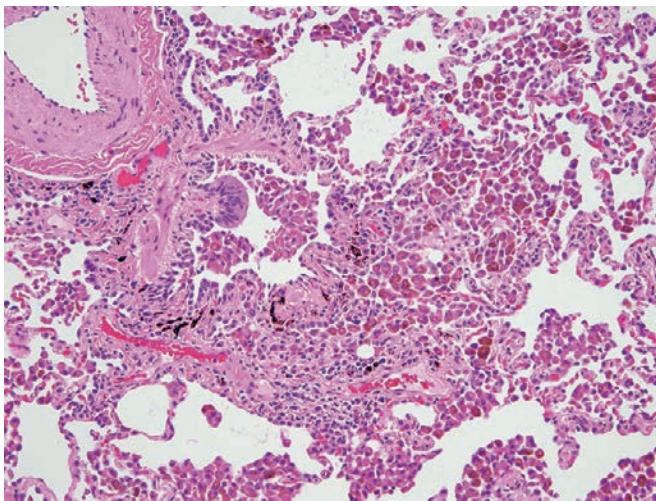


Figure 10.44 Respiratory bronchiolitis. Pigmented (smoker's) macrophages are clustered in the lumens of distal airways and peribronchiolar air spaces. The smoking-associated pigment is positive with Prussian-blue iron stains and should not be confused with hemosiderin.

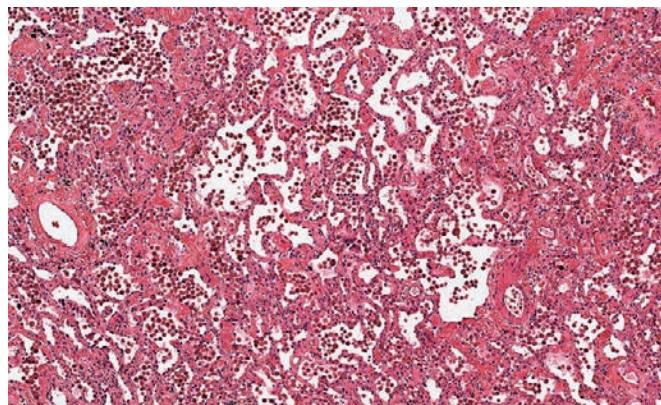


Figure 10.46 Desquamative interstitial pneumonia, an increasingly anachronistic term that should be abandoned in favor of the more modern alternatives NSIP, RBILD, or SRIF with considerable overlap between the latter two. Pigmented ('smoker's') macrophages identical to those illustrated in RBILD are more extensively distributed within alveolar spaces.

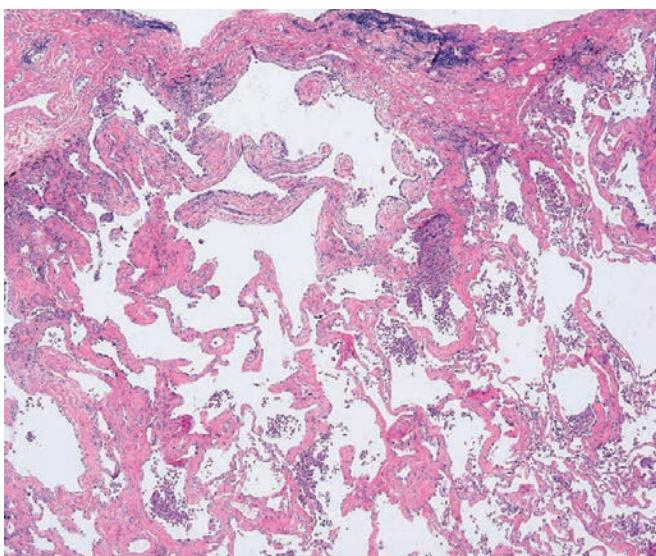


Figure 10.45 Smoking-related interstitial fibrosis. Subpleural septa are expanded by deeply eosinophilic collagen but without the patchwork distribution or honeycomb change characteristic of UIP. There is associated emphysema and respiratory bronchiolitis.

the term DIP should be abandoned (personal communication). Others have argued for continued use of the term, citing potentially important prognostic differences.¹⁰⁹ Whatever terminology one prefers for this uncommon group of overlapping conditions the important point is to avoid confusing them with UIP given that all of them have a better prognosis and frequently benefit from some combination of smoking cessation and steroids.¹¹⁰

DAD is usually diffuse and bilateral in patients with the acute respiratory distress syndrome (ARDS).¹¹¹ It may be caused by infectious agents (particularly viruses), inhalants (such as oxygen), drugs (especially chemotherapeutic agents), ingestants (such as kerosene or paraquat), shock, sepsis, radiation, and acute exacerbation of UIP.^{111,112} With the exception of pathogens detectable on routine histology or with special stains, the cause of DAD cannot be determined from the microscopic picture alone. The earliest stages consist

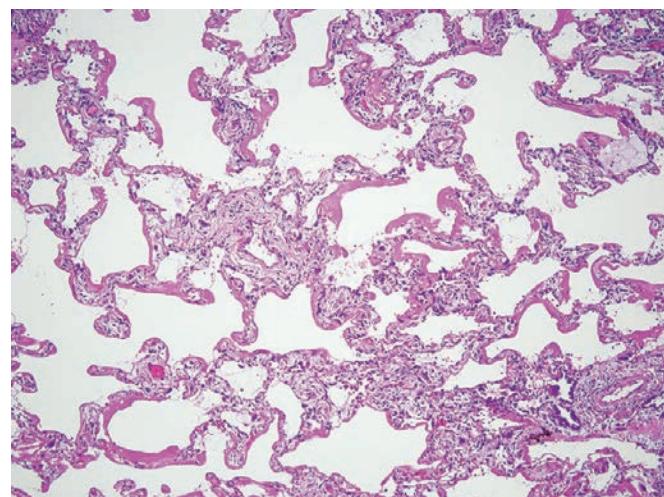


Figure 10.47 Diffuse alveolar damage in the acute phase with well-formed hyaline membranes.

of edema, intra-alveolar hemorrhage, and fibrin deposition. This is followed by hyaline membrane formation (most prominent 3–7 days after the injury), a sparse interstitial infiltrate, fibrin thrombi (inconstant), and hyperplasia of the alveolar lining cells (Fig. 10.47). These cells, which are mainly reparative type II (granular) pneumocytes, may exhibit atypia, mitotic activity, and cytoplasmic hyaline bodies. A distinctive form of squamous metaplasia in bronchiolar epithelium combined with cytologic atypia can be pronounced enough to mimic a squamous cell carcinoma.¹¹³ Foamy alveolar macrophages may also be present and may be more common in cases resulting from amiodarone.¹¹⁴ In a later (organizing) stage, there is interstitial and intraluminal proliferation of organizing fibroblasts and myofibroblasts associated with persistence of the hyperplastic lining cells and collapse of alveolar structures resulting in marked architectural remodeling (Fig. 10.48).⁹⁷

Acute interstitial pneumonia (AIP) is a rapidly progressive form of idiopathic interstitial pneumonia and is synonymous with the *Hamman–Rich syndrome*.^{115,116} By definition, there is no identifiable initiating event. The typical patient is a young adult who presents with dyspnea following an influenza-like illness. The prognosis is very poor, with most patients dying within 2 months of onset.

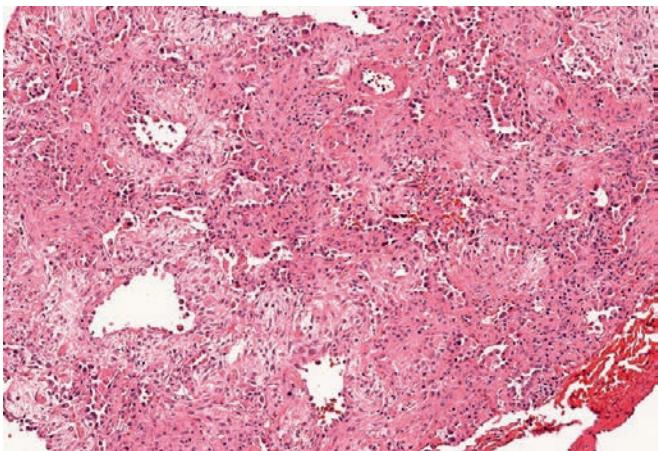


Figure 10.48 Diffuse alveolar damage in the organizing phase accompanied by alveolar collapse.

Microscopically, the appearance is equivalent to that of the organizing phase of DAD, the most striking feature being the interstitial expansion and distortion by organizing fibroblasts and myofibroblasts.

Organizing pneumonia, also termed bronchiolitis obliterans–organizing pneumonia (BOOP), is a nonspecific form of organizing acute or subacute lung injury that is associated with several conditions, including infections, inhalants (including silo-filler's lung), drugs, and collagen-vascular diseases. Organizing pneumonia occasionally occurs as a form of diffuse lung disease of unknown ('idiopathic') cause termed *cryptogenic organizing pneumonia* (COP), a syndrome referred to historically as idiopathic BOOP.^{18,117,118} COP is frequently grouped with the idiopathic interstitial pneumonias, but the clinical and radiological findings at presentation more closely mimic the features of infectious pneumonia. The onset is usually acute and characterized by cough, dyspnea, fever, and malaise. Less commonly COP presents as a solitary radiological opacity that may be asymptomatic and mimic the appearance of a neoplasm, a variant to which some have applied the term *focal organizing pneumonia* (Fig. 10.49).¹¹⁹ The prognosis is generally excellent; patients requiring treatment often improve with sustained corticosteroids but may relapse when their steroid dose is tapered.¹²⁰ Morphologically, the hallmark of organizing pneumonia in any clinical context is represented by fibroblastic plugs ('Masson bodies') filling air spaces (Fig. 10.50). These plugs have a typical elongated to serpiginous, bifurcating shape reflecting the configuration of distal bronchioles and alveolar ducts and are formed by spindle to stellate fibroblasts embedded in a pale-staining matrix. Other changes include clusters of foamy macrophages, a few scattered neutrophils, and thickening of alveolar septa in the areas of intraluminal fibrosis. It is characteristic for the process to have a patchy appearance on low-power examination, a feature of importance in the differential diagnosis with UIP (see earlier). The rare cases of COP with unfavorable outcome (steroid unresponsive) have shown scarring and remodeling of the lung parenchyma on microscopic examination, suggesting an underlying chronic fibrosing lung disease.¹²¹

Lymphoid (lymphocytic) interstitial pneumonia (LIP) is characterized by a lymphocytic infiltrate with associated lymphoid follicles, often admixed with histiocytes and plasma cells, that expands alveolar septa and peribronchiolar interstitium.^{122,123} Although included by some as a rare form of idiopathic interstitial pneumonia, LIP is a lymphoproliferative disorder analogous to reactive lymphoid hyperplasia that overlaps clinically, radiologically, and histologically with follicular bronchiolitis.¹²² A third of the cases have been



Figure 10.49 Hilar mass that was considered radiographically to be carcinoma but proved pathologically to be organized pneumonia.

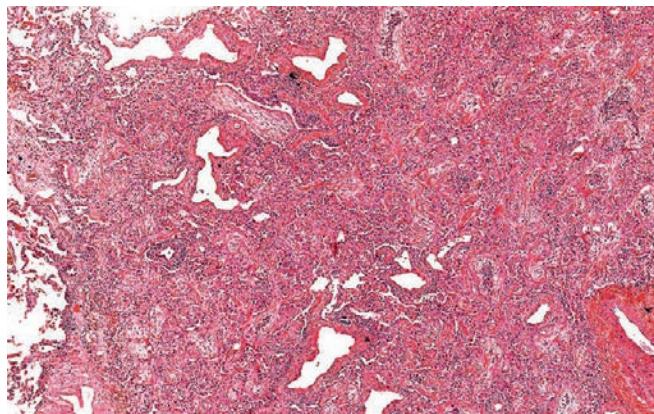


Figure 10.50 Cryptogenic organizing pneumonia showing characteristic intraluminal plugs of organizing fibroblasts and myofibroblasts. The central portion of some of the plugs show an infiltrate of chronic inflammatory cells, a nonspecific finding of no special significance.

associated with Sjögren syndrome, a circumstance in which distinction from marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT) may be challenging. Another large subset of cases are associated with underlying immunodeficiencies, including HIV infection and common variable immunodeficiency. Some of the cases have been incorporated into the ever-enlarging spectrum of IgG4 disease.¹²⁴ The radiological appearance is that of interlobular septal lines often accompanied by ground-glass opacities and cysts. Cysts occur especially in patients with underlying Sjögren's syndrome, including some with diffuse variants of MALT lymphoma, often with associated amyloid or non-amyloid light chain deposition.¹²⁵ Histologically alveolar septa are expanded by a cellular infiltrate

composed of a combination of lymphocytes and plasma cells with prominent peribronchiolar lymphoid follicles, many of them with secondary germinal centers (Fig. 10.51).^{123,126} Non-necrotizing granulomas accompany the infiltrates in some cases. Granulomas are especially common in patients with common variable immunodeficiency for which the term *granulomatous and lymphocytic interstitial lung disease* is sometimes used.¹²⁷

LIP overlaps with **follicular bronchitis and bronchiolitis**, a nonspecific inflammatory reaction in which reactive germinal centers are seen adjacent to airways in the absence of chronic obstructive pulmonary disease. Follicular bronchitis/bronchiolitis is a common secondary finding in bronchiectasis but also occurs as a primary lymphoproliferative disorder in the same clinical circumstances described for LIP.^{123,128}

Pleuroparenchymal fibroelastosis (PPFE) is a rare pattern of diffuse lung fibrosis with histologic features that overlap with the much more common *apical cap*, a localized form of fibroelastosis unique to the lung apices and superior segments of the lower lobes.¹²⁹ PPFE tends to preferentially affect the upper lobes and is exquisitely localized to peripheral subpleural parenchyma and bronchovascular bundles (Fig. 10.52).¹³⁰ PPFE is not a specific disease in that this pattern of fibrosis occurs in a number of clinical scenarios, including lung and stem cell transplants, drug-induced lung disease, and connective tissue disease.^{131,132} Importantly this form of peripheral fibroelastosis can also coexist with other forms of diffuse fibrotic lung disease, most importantly UIP.

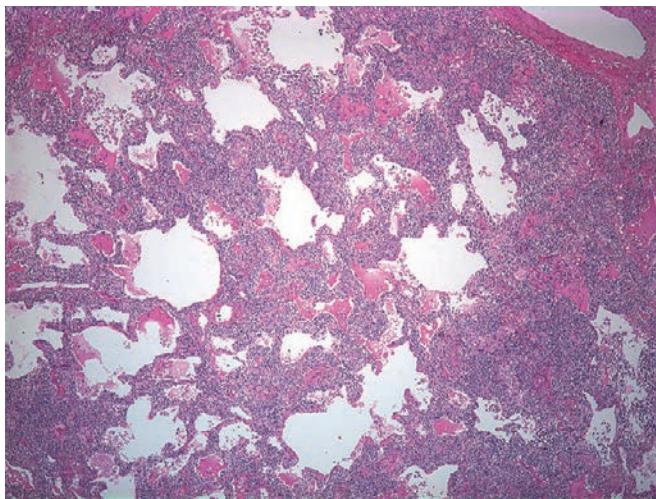


Figure 10.51 Lymphoid interstitial pneumonia in a patient with Sjögren syndrome.

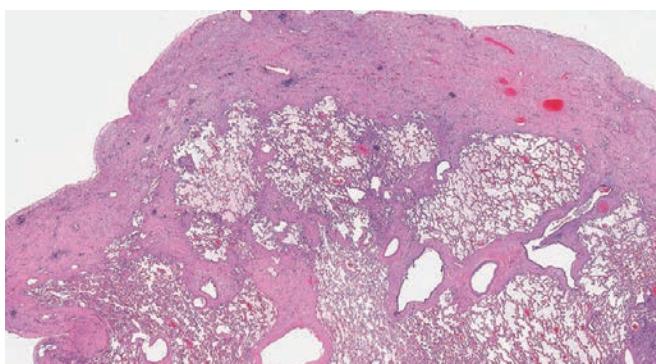


Figure 10.52 Pleuroparenchymal fibroelastosis.

Hypersensitivity Pneumonia (Extrinsic Allergic Alveolitis)

Hypersensitivity pneumonia (extrinsic allergic alveolitis) is the generic term given to an acute, subacute, or chronic inflammatory process representing a tissue reaction to an inhaled allergen.¹³³ Patients suffering from this condition have both cellular and humoral immune processes directed against the organic allergen. The most common offending antigens include thermophilic bacteria (e.g. farmer's lung, humidifier lung), molds (e.g. Japanese summer type hypersensitivity), and avian proteins (e.g. pigeon breeder's lung). In acute hypersensitivity pneumonia, fever and dyspnea develop a few hours after exposure to relatively high doses of the offending antigen. With repeated exposures, often to relatively low doses of an environmental antigen that may be unknown to the patient, a chronic fibrosing lung disease develops than can mimic many of the features of IPF.

Microscopically, classical hypersensitivity pneumonia is characterized by a combination of a cellular interstitial pneumonia that tends to be accentuated around airways (*bronchiolocentric*), equally cellular chronic bronchiolitis, and a distinctive pattern of granulomatous inflammation (Figs. 10.53 and 10.54). This combination of findings predicts for the diagnosis of hypersensitivity pneumonia even in patients for whom no exposure was known prior to lung biopsy.^{134,135} Fibrosis occurs in some patients and when advanced can closely mimic UIP or the fibrotic stage of NSIP; the presence of isolated giant cells, poorly formed granulomas, and/or Schaumann bodies in a peribronchiolar location should suggest the right diagnosis.¹³⁶ Fibrosis is associated with a generally poor prognosis.¹³⁷

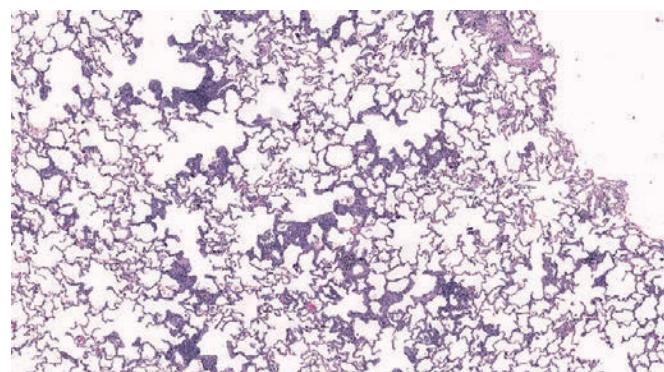


Figure 10.53 Hypersensitivity pneumonia showing patchy interstitial infiltrate of lymphocytes distributed in an exquisitely bronchiolocentric fashion.

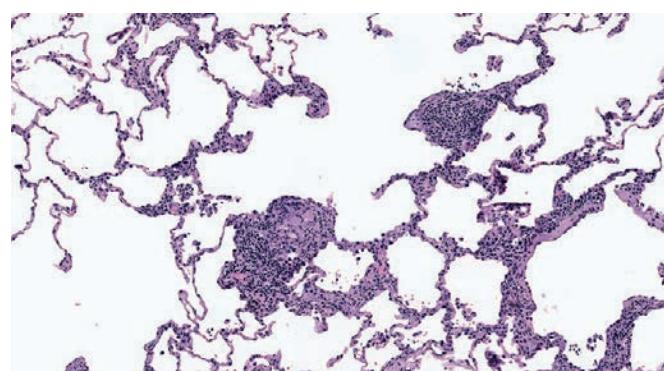


Figure 10.54 Hypersensitivity pneumonia with characteristic loose cluster of multinucleated giant cells in peribronchiolar interstitium.

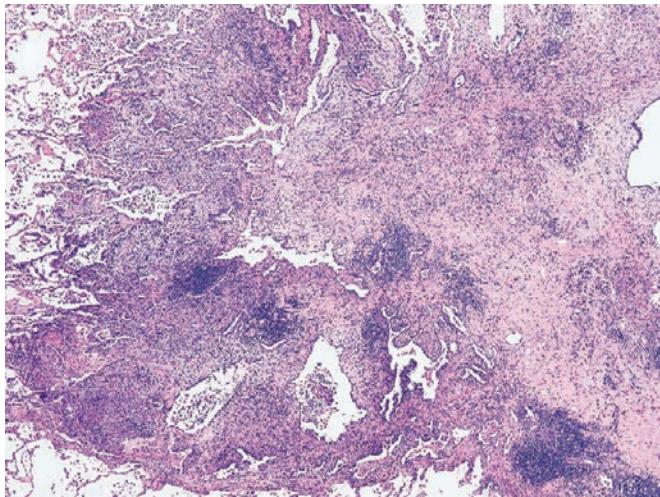


Figure 10.55 Langerhans cell histiocytosis.

Silo-filler's disease should be clearly separated from the aforementioned group, since it is a form of acute lung injury secondary to nitrogen dioxide inhalation and is characterized by the presence of DAD without granulomatous inflammation.¹³⁸

Langerhans Cell Histiocytosis and Other Histiocytic Disorders

Pulmonary LCH, referred to historically as Langerhans cell granulomatosis, histiocytosis X, and eosinophilic granuloma of the lung, is most commonly seen in the third and fourth decades of life.^{139–141} LCH occurs almost exclusively in cigarette smokers in whom it typically presents as a diffuse process and rarely as a solitary nodule.¹⁴² It predominates in the upper lobes and produces a combination of nodules and cavitary lesions or cysts. In approximately 20% of the patients, there is associated extrapulmonary involvement, usually as isolated lesions in bones or the pituitary region. Spontaneous pneumothorax is a common complication. In most patients with LCH of the lung, the disease resolves or stabilizes. A few patients develop progressive pulmonary disease that is ultimately fatal.

Microscopically, there is a compact interstitial infiltrate that expands peribronchiolar interstitium and is, composed of Langerhans cells, variable numbers of eosinophils, and other mononuclear inflammatory cells (Fig. 10.55). Langerhans cells are the essential element for the diagnosis; they have an abundant acidophilic cytoplasm and a vesicular nucleus, with typical grooves and indentations (caveat: similar grooves also can be seen in reactive mesothelial cells and alveolar macrophages) (Fig. 10.56). Immunohistochemical staining for S-100 protein, CD1a, or langerin can be very helpful in highlighting Langerhans cells and can also be applied to cells in bronchoalveolar lavage fluid.¹⁴³ The bronchiocentric nodules heal through a process of fibrosis that begins in the center eventually extending into peribronchiolar alveolar septa where it is accompanied by a characteristic pattern of scar emphysema (paracapillary air space enlargement). At this late fibrotic stage it may be very difficult to establish a microscopic diagnosis of LCH since the characteristic Langerhans cells may be absent (Fig. 10.57). Correlation with CT scans can be helpful in showing a pattern and distribution of cystic lung disease characteristic of LCH. In the healing stage, the disease may no longer be diagnosable microscopically.

Molecular studies using a variety of techniques suggest that there is a clonal proliferation of Langerhans cells in at least a subset of patients.^{144–147} Evidence of clonal evolution in pulmonary LCH

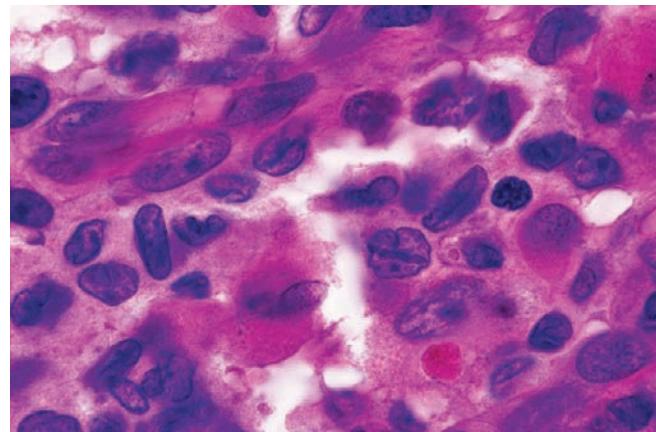


Figure 10.56 Prominent longitudinal grooves in the nuclei of Langerhans cells in a case of pulmonary Langerhans cell histiocytosis.

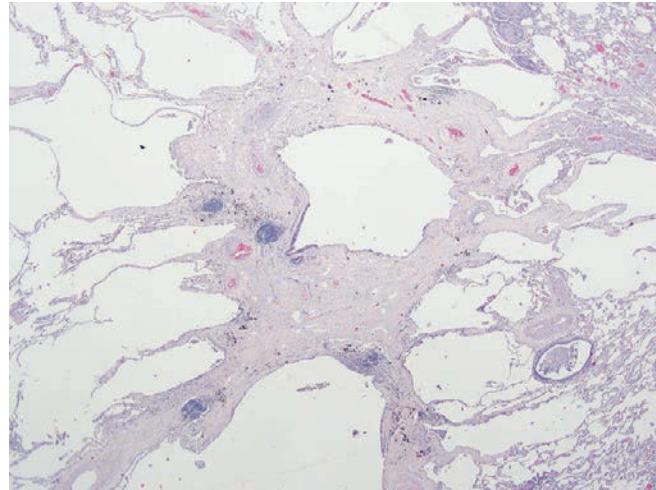


Figure 10.57 Fibrotic Langerhans cell histiocytosis showing characteristic stellate configuration and associated peripheral 'scar emphysema' (paracapillary air space enlargement).

includes *BRAF^{V600E}* mutations in 20%–50% of patients.^{145,147,148} Some of these patients may benefit from targeted therapy with vemurafenib.¹⁴⁹

Reactive eosinophilic pleuritis is a nonspecific response to pleural injury that may closely simulate LCH because of the mixture of eosinophils, mesothelial cells, and histiocytes (which can look very similar to Langerhans cells); in contrast to true eosinophilic granuloma, this lesion by itself does not show interstitial lung disease.¹⁵⁰ However, in some instances it may be accompanied by eosinophilic infiltration of the pulmonary vessels.¹⁵¹

Erdheim–Chester disease is another histiocytic disorder which can affect the lung, in conjunction with bones (the latter often in the form of symmetric osteosclerosis), soft tissues, and the central nervous system.^{139,152} Pulmonary involvement is typically septal (lymphatic) in distribution and characterized by an infiltrate of foamy histiocytes, lymphocytes, and Touton giant cells (Figs. 10.58 and 10.59). The histiocytes are consistently positive for CD68, sometimes reactive for S-100 protein, and negative for CD1a. Recent studies demonstrate *BRAF^{V600E}* mutations in more than half as well as recurrent mutations in *RAS* and *PIK3CA*, indicating that this is a myeloid neoplasm for which targeted therapy with vemurafenib is proving effective in a large number of patients.^{153–155}

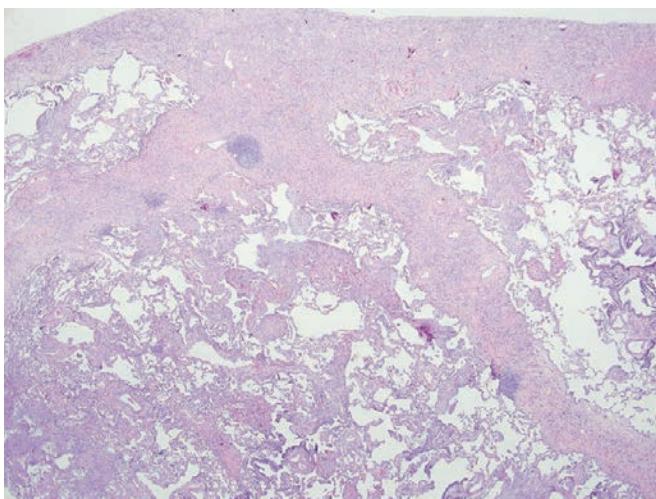


Figure 10.58 Erdheim–Chester disease.

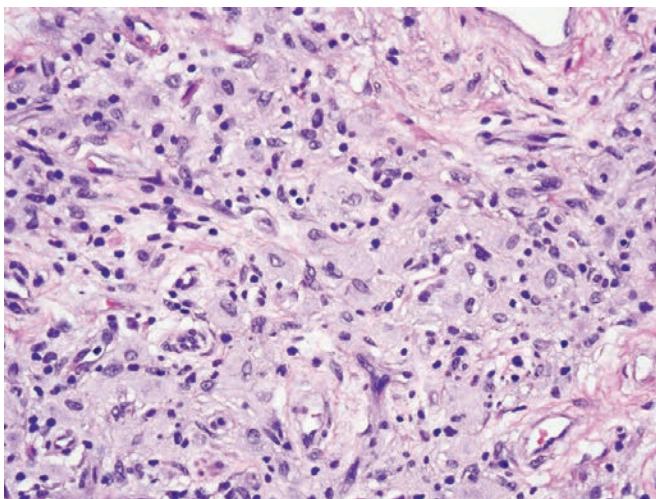


Figure 10.59 Erdheim–Chester disease involving the lung showing histiocyte-rich infiltrate.

Rosai–Dorfman disease (sinus histiocytosis with massive lymphadenopathy) is seen in the lung parenchyma only exceptionally, in contrast to its relatively frequent involvement of the upper respiratory tract.^{156–158} The histologic findings overlap with IgG4-related disease, which is a diagnostic pitfall requiring careful correlation with the clinical and radiological findings.^{159,160}

Pneumoconiosis

Pneumoconiosis is defined as the non-neoplastic reaction of the lungs to inhaled mineral or organic dust, exclusive of asthma, bronchitis, and emphysema.

Anthracosis is often applied as a general and relatively nonspecific term to black pigment with minimal associated fibrosis in the lungs of heavy smokers and residents of heavily polluted urban environments. Pigmented dust macules also occur in coal workers, however, in whom the term *anthracosis* has a specific and more narrow interpretation, and therefore the term is probably best avoided. *Coal worker's pneumoconiosis* may present either as 'coal nodules' (of little functional significance) or as progressive massive fibrosis (which results in pulmonary function abnormalities).^{161–163}

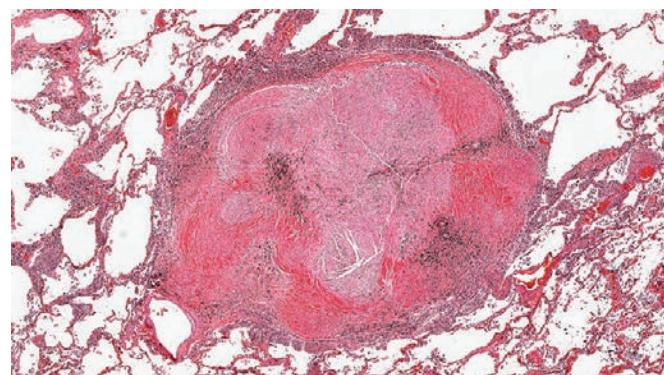


Figure 10.60 Simple silicosis showing classic, uncomplicated silicotic nodule.

Silicosis results from the deposition in the lung of particles of free crystalline silica (quartz, silicon dioxide). The lesions are characterized by micronodular scars with a characteristic pattern of central lamellar fibrosis distributed in a bronchiocentric pattern with a cellular periphery in which dust-laden macrophages predominate (Fig. 10.60). Complicated silicosis and progressive massive fibrosis result from fusion of nodules to form larger (≥ 1 cm) macroscopic nodules and masses. Larger nodules may undergo necrosis and cavitate as a result of ischemia, or more commonly superimposed mycobacterial infection; acid-fast stains should be performed when necrosis is identified. Silicotic nodules in patients with rheumatoid arthritis (*Caplan syndrome*) assume some of the morphologic changes characteristic of rheumatoid nodules, including central necrosis with palisaded histiocytes at the periphery.¹⁶⁴

Silica particles are best demonstrated under polarized light. They appear as weakly birefringent spicules with pointed ends, 5 μ m or less in length, and are usually accompanied by more brightly birefringent contaminants. They may be found intracellularly or extracellularly. It should be emphasized that the mere presence of silica particles in a lung specimen does not establish the diagnosis of silicosis. Such a diagnosis should be reserved for cases showing silica in association with characteristic silicotic nodules.¹⁶⁵

Mixed dust fibrosis is the term used for pneumoconioses resulting from mixed dust exposure, including silica and quartz. It affects foundry workers, arc welders, hematite miners, and boiler scalers. Most cases show a combination of dust macules and fibrotic nodules that may or may not include a minor component of silicotic nodules.¹⁶⁶

Asbestosis refers to diffuse lung fibrosis attributable to asbestos exposure. Aside from an incriminating occupational history, the clinical and radiological findings may be indistinguishable from other forms of diffuse fibrotic lung disease save for the presence of calcified pleural plaques on imaging studies. Histologic diagnosis requires a combination of diffuse interstitial fibrosis and asbestos bodies in ordinary 5- μ m sections.^{167–169} The histologic features closely mimic UIP, although there tends to be less inflammation, fewer fibroblast foci, and more visceral pleural fibrosis (Fig. 10.61).¹⁶⁹ The diagnosis of asbestosis in lung biopsy samples requires the identification of asbestos bodies, usually by conventional microscopy although special techniques can be helpful in a limited number of contexts.¹⁷⁰ The typical asbestos body is a long, thin, symmetric, beaded structure with bulbous ends (Fig. 10.62). It is usually straight, but it may be bent or branched. Its core is translucent, a key feature in separating asbestos bodies from other types of non-asbestos ferruginous bodies.¹⁷¹

Other pneumoconioses include siderosis (seen in iron workers, hematite miners, and welders), berylliosis, and disorders resulting

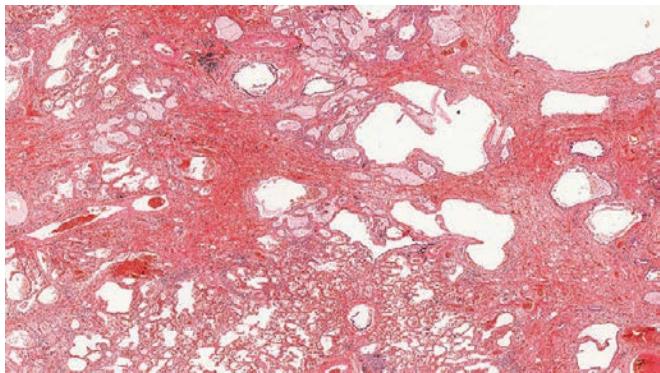


Figure 10.61 Asbestosis showing a pattern of fibrosis resembling UIP.

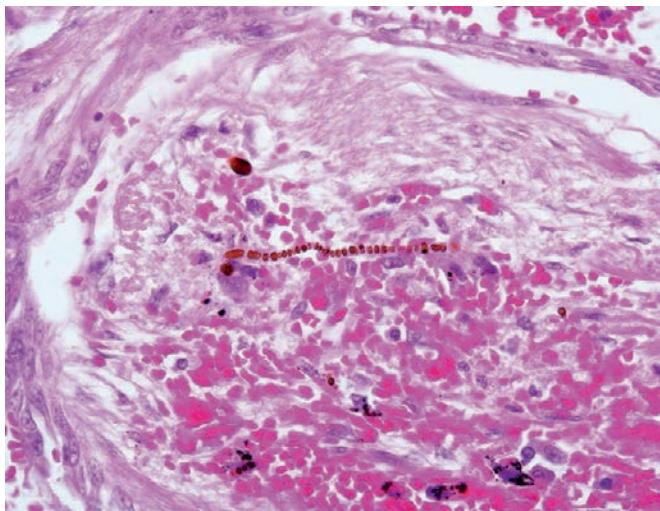


Figure 10.62 Asbestos body in a patient with asbestosis showing characteristic beaded appearance with central translucent core.

from talc and other silicates, aluminum, hard metals, and silicon carbide.

Lipoid Pneumonia

Lipoid pneumonia is often a complication of debilitating disease found as an incidental post mortem finding. However, the local expression of this process may be confused with a malignant neoplasm and consequently may become a surgical problem.

Lipoid pneumonia can be divided into two types: exogenous and endogenous. In the *exogenous* type, now seen only rarely, mineral oil from nasal sprays, laxatives, or other sources reaches the lung through the tracheobronchial tree (Fig. 10.63).¹⁷² Grossly, exogenous lipoid is well circumscribed and firm. Microscopically, coarse lipid vacuoles that vary markedly in size are present within the air spaces and the interstitial compartment where they are accompanied by a combination of inflammation and variable degrees of fibrosis. The inflammatory infiltrate includes multinucleated giant cells that surround and engulf the lipid vacuoles. Identifying the giant cell reaction is extremely helpful in separating exogenous lipoid pneumonia from the 'holes' (*pseudolipoid*) artifact common in both surgical and transbronchial lung biopsies.¹⁴ The much more common *endogenous* type is the consequence of bronchial obstruction by carcinoma or some other process resulting in accumulation of finely vacuolated lipid-laden macrophages in distal air spaces with infrequent involvement of the peribronchiolar interstitium. The gross distribution

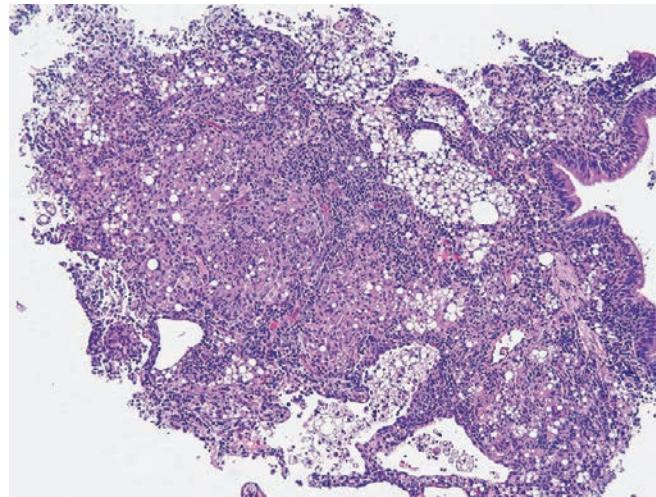


Figure 10.63 Exogenous lipoid pneumonia in a transbronchial biopsy from a patient suspected of having a malignancy.

of the abnormality depends on the level of the obstruction, frequently reflecting the lobar or segmental anatomy of the lung.

Aspiration Pneumonia

Aspiration pneumonia (other than the previously listed exogenous form of lipoid pneumonia) is often due to the aspiration of food and is a well-recognized complication in debilitated patients. Aspiration pneumonia is increasingly recognized as a cause for symptomatic or asymptomatic lung disease that can be multifocal or localized and bilateral or unilateral on radiographs or CT scans of the chest.^{173–175} When solitary, aspiration pneumonia can simulate a neoplastic process. Microscopically, the changes are mainly represented by BOOP, usually in combination with multinucleated giant cells, acute bronchopneumonia and/or bronchiolitis, and suppurative granulomas. The key finding is the presence of foreign material, most often food remnants or inorganic fillers (e.g. microcrystalline cellulose, crospovidone) commonly used in oral medications (Figs. 10.64 and 10.65).¹⁷⁴

Eosinophilic Pneumonia

Eosinophilic pneumonia is a histologically distinct pattern of tissue eosinophilia that may or may not be associated with peripheral eosinophilia (Fig. 10.66). Eosinophilic pneumonia is a common manifestation of drug-induced lung disease and can also occur as a component of a more complex combination of histologic findings in patients with EGPA (Churg–Strauss) and allergic bronchopulmonary aspergillosis. Changes overlapping with eosinophilic pneumonia have also been described in coccidioidomycosis, an important diagnostic consideration in endemic areas.¹⁷⁵ Patients in whom eosinophilic pneumonia is an unexplained primary pathologic abnormality fall into several different clinical categories.^{176,177} An acute self-limited form of *simple eosinophilic pneumonia*, characterized by fleeting pulmonary infiltrates accompanied by eosinophilia and lasting no more than a month, is commonly referred to as *Löffler syndrome*. *Tropical eosinophilic pneumonia*, as the term implies, is limited to patients living in the tropics where it is a well-recognized syndrome of pulmonary infiltrates with eosinophilia thought to be related to filarial infestations. Neither patients with simple or tropical eosinophilic pneumonia are likely to be biopsied.

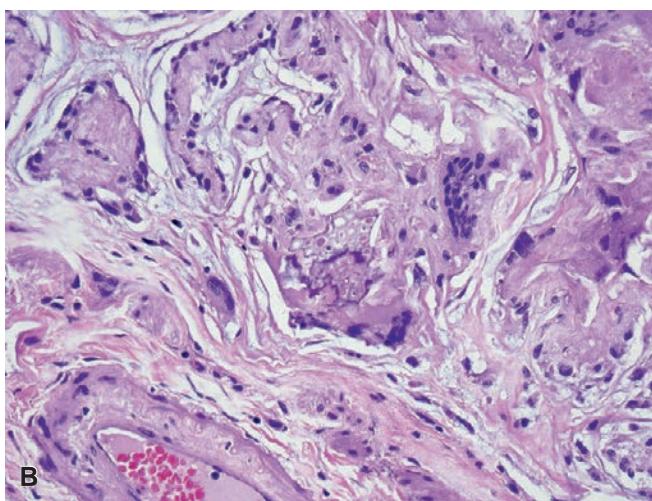
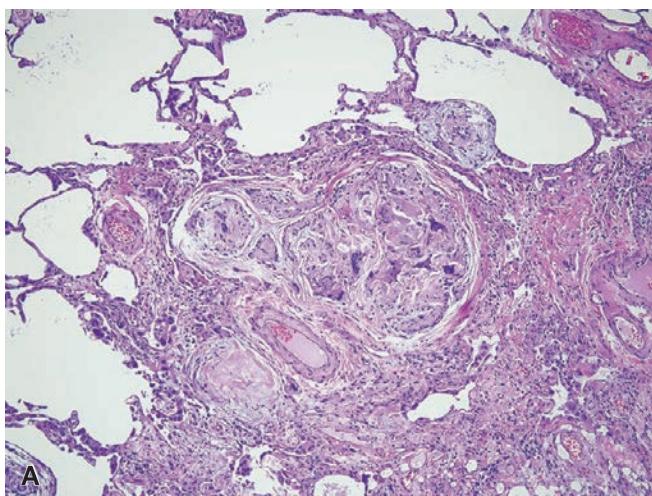


Figure 10.64 Aspiration pneumonia showing a combination of organizing pneumonia with granulomatous inflammation (A) and degenerated organic particulates typical of food (B).

Most patients with eosinophilic pneumonia discovered in a diagnostic lung biopsy have a respiratory syndrome characterized by a subacute or chronic onset referred to as *chronic eosinophilic pneumonia*.^{178,179} This is a disease that affects women more often than men, usually between the ages of 30 and 50 years. About half of patients have a history of asthma, and most have peripheral eosinophilia. Clinically, the onset is characterized by fever, weight loss, cough, and dyspnea. Chest roentgenograms and CT scans show a characteristic peripheral distribution of infiltrates in about half of patients. As in all other forms of eosinophilic pneumonia the most notable microscopic change is alveolar and interstitial infiltration by eosinophils and histiocytes often with an associated fibrinous exudate (see Fig. 10.66). Charcot-Leyden crystals may be found. Additional features may include mild angiitis, giant cells, and occasionally non-necrotizing granulomas, organizing fibroblasts, and myofibroblasts resembling organizing pneumonia, focal necrosis, mucous plugging, and bronchiolitis.

Acute eosinophilic pneumonia presents as acute respiratory failure, often with profound hypoxemia requiring intubation and mechanical ventilation.¹⁸⁰ As with other forms of eosinophilic pneumonia, however, patients respond quickly and dramatically to corticosteroid therapy. Histologically acute eosinophilic pneumonia shows histologic features that overlap eosinophilic pneumonia and DAD.

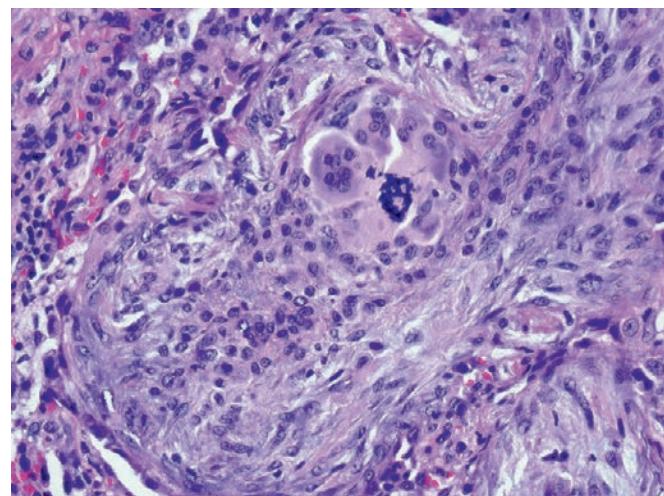


Figure 10.65 Aspiration pneumonia with organizing pneumonia and granulomatous inflammation in which a multinucleated giant cell contains crospondine, an inorganic filler used in oral medications.

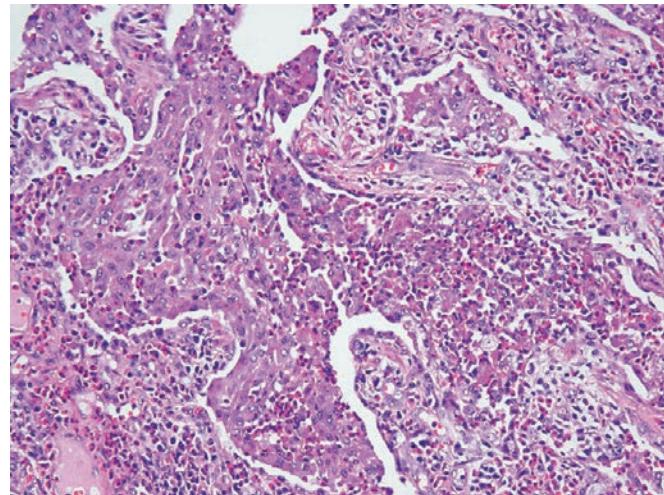


Figure 10.66 Eosinophilic pneumonia. Numerous mature eosinophils are admixed with histiocytes and granular pneumocytes.

Pulmonary alveolar proteinosis (alveolar lipoproteinosis) is a rare disorder characterized by a paucicellular granular air space exudate composed of a combination of surfactant lipids and proteins.¹⁸¹⁻¹⁸³ It affects men more commonly than women, usually in the fourth to fifth decades of life. Pulmonary alveolar proteinosis is rare in neonates in whom it is affiliated with mutations in surfactant protein or granulocyte macrophage-colony stimulating factor (GM-CSF) receptor genes. Conventional chest radiographs show bilateral perihilar infiltrates resembling pulmonary edema. CT scans show a characteristic but nonspecific combination of opacities and septal lines described as *crazy paving*. A large majority (90%) of adult patients with alveolar proteinosis have an autoimmune disorder characterized by high concentrations of neutralizing anti-GM-CSF autoantibodies. In a small subset of patients, pulmonary alveolar proteinosis is secondary to inhalational injuries (*acute silicoproteinosis*) or underlying hematological neoplasms. Whole-lung lavage is the mainstay of therapy. Inhaled or systemically administered GM-CSF and strategies aimed at reducing the levels of circulating anti-GM-CSF autoantibodies may also have value in patients with autoimmune pulmonary alveolar proteinosis.^{182,183}

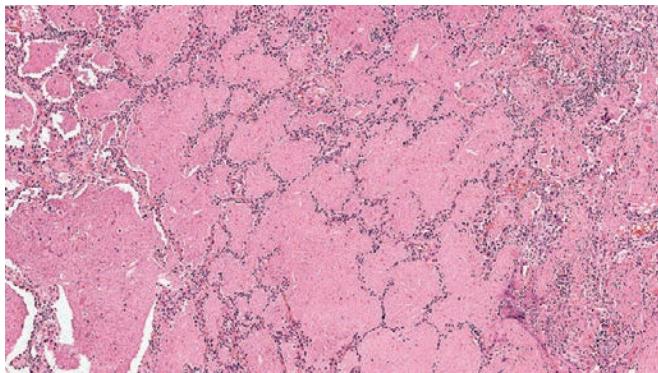


Figure 10.67 Filling of alveolar spaces by amorphous granular material in alveolar proteinosis.

Microscopically, the hallmark of the process is the accumulation of an amorphous eosinophilic (but sometimes basophilic) PAS-positive material of predominantly phospholipid nature in the alveolar lumina, associated with a minimal infiltrate of lymphocytes, macrophages, and desquamated pneumocytes. The air space exudate is usually affiliated with only mild interstitial abnormalities including a lymphocytic infiltrate with minimal associated fibrosis (Fig. 10.67). In patients who have underlying hematological disorders or are otherwise immunocompromised, alveolar proteinosis may be associated with infections such as nocardiosis, pneumocystis, histoplasmosis, cryptococcosis, aspergillosis, tuberculosis, or cytomegalovirus, making appropriate use of special stains and other microbiologic assays mandatory in this context.

Pulmonary Hemorrhage

Diffuse pulmonary (alveolar) hemorrhage is uncommon. Most patients are symptomatic and complain of a combination of dyspnea, cough, fever, chest pain, and/or hemoptysis. Vasculitic syndromes, anti-glomerular basement membrane disease (**Goodpasture syndrome**) and systemic connective tissue diseases are among the most common causes; affected patients often have concomitant glomerulonephritis (pulmonary-renal syndrome).¹⁸⁴ Patients with underlying vasculitides frequently have circulating ANCA (ANCA-associated vasculitides). In Goodpasture syndrome there is an associated glomerulonephritis, circulating antiglomerular basement membrane antibodies, and linear deposits of IgG along glomerular and alveolar basement membranes. Other less common causes of diffuse alveolar hemorrhage include congestive heart failure, occupational exposure to trimellitic anhydride, drug-induced hemorrhage, inhalational lung injury (e.g. crack cocaine), and various clotting disorders.¹⁸⁵ In some patients no underlying cause or immune-mediated disease is identified. Chest roentgenograms and CT scans usually show relatively nonspecific diffuse opacities. Surgical lung biopsies show alveolar hemorrhage, often associated with hemosiderin pigment and organizing pneumonia, with associated small vessel vasculitis (*necrotizing capillaritis*) in those with vasculitis syndromes (most commonly GPA [Wegener's], microscopic polyangiitis, or systemic lupus erythematosus) (Fig. 10.68).

Idiopathic pulmonary hemosiderosis is a rare condition that classically presents in children and young adults with dyspnea, cough, hemoptysis, and refractory anemia.¹⁸⁶ Children who present with diffuse pulmonary hemorrhage show the same range of underlying systemic diseases, including ANCA-associated vasculitides, as adults making idiopathic pulmonary hemosiderosis a diagnosis of exclusion. Down syndrome and celiac disease are common underlying conditions in children with idiopathic pulmonary hemosiderosis. Microscopically,

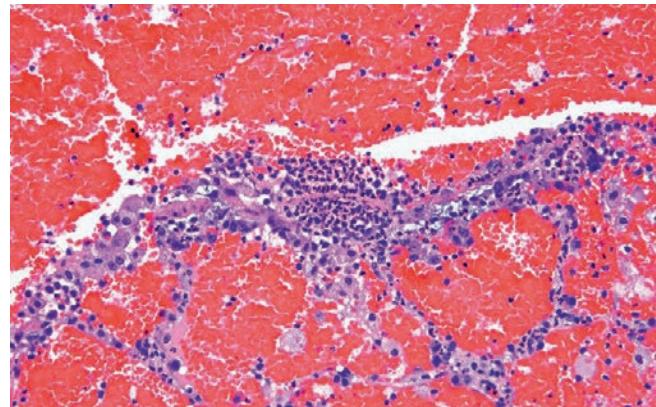


Figure 10.68 Diffuse alveolar hemorrhage with capillaritis in a patient with granulomatosis with polyangiitis (Wegener's).

large accumulations of hemosiderin-laden macrophages in the alveolar lumens are accompanied by hyperplastic alveolar pneumocytes lining thickened alveolar septa. Necrosis, vasculitis, granulomas, and lymphoid follicles do not occur, and there are no deposits of IgG on the alveolar basement membranes, an important distinction from Goodpasture syndrome.

Localized pulmonary hemorrhage is usually secondary to some underlying condition, such as a necrotizing primary or metastatic neoplasm, necrotizing infection, or bronchiectasis.¹⁸⁷ Hematoma of the lung can present as a distinct round mass that radiographically resembles a neoplasm; it usually develops as a result of nonpenetrating blunt trauma to the thorax.¹⁸⁸

Miscellaneous Infections

Improved microbiologic assays applied to various noninvasively acquired samples have diminished the role of tissue biopsies in establishing non-granulomatous infectious diagnoses in the lung. Despite these trends there remain a subset of pulmonary infections for which lung biopsy is occasionally required.

Pneumocystis jirovecii Pneumonia

Pneumocystis jirovecii pneumonia is an opportunistic fungal infection.^{189,190} Most cases are seen in individuals who are chronically debilitated and immunosuppressed, such as those receiving therapy for neoplastic disease or affected with AIDS. *Pneumocystis* remains the most prevalent opportunistic infection in AIDS patients. In severely immunocompromised patients, the infection may spread to extrapulmonary sites and become disseminated.

Bronchoalveolar lavage is the most commonly used method for diagnosing pneumocystis pneumonia. Lung biopsy is reserved for those patients in whom bronchoalveolar lavage is unsuccessful or in whom the diagnosis was not anticipated. Microscopically, the typical case is characterized by a foamy or honeycombed intra-alveolar exudate accompanied by a lymphoplasmacytic interstitial infiltrate (Fig. 10.69). However, these features may be inconspicuous or absent in some cases, which may exhibit instead epithelioid granulomas, focal multinucleated giant cells, marked interstitial fibrosis, vasculitis, a marked infiltrate of alveolar macrophages, calcifications, or DAD.^{191,192} Given the variability in the histologic findings associated with *P. jirovecii* pneumonia one should have a low threshold for performing special stains in potentially immunocompromised patients.

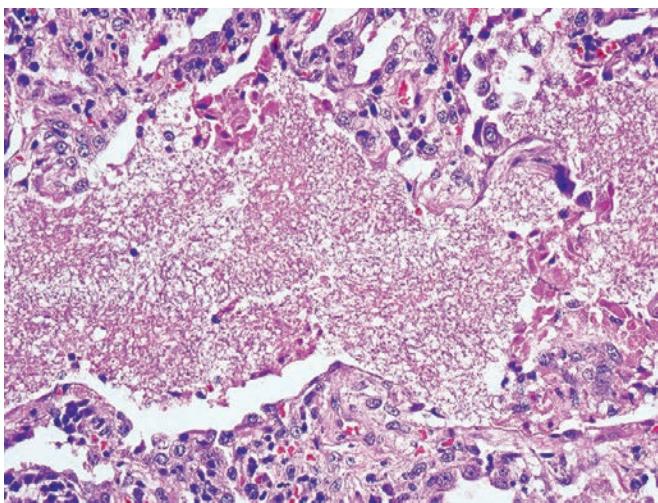


Figure 10.69 Frothy alveolar exudate in *P. jirovecii* pneumonia.

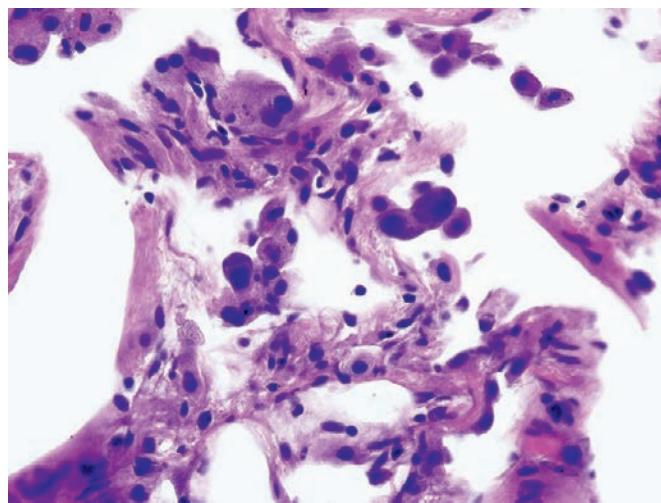


Figure 10.71 Cytomegalovirus infection with characteristic viral cytopathic changes in infected pneumocytes.

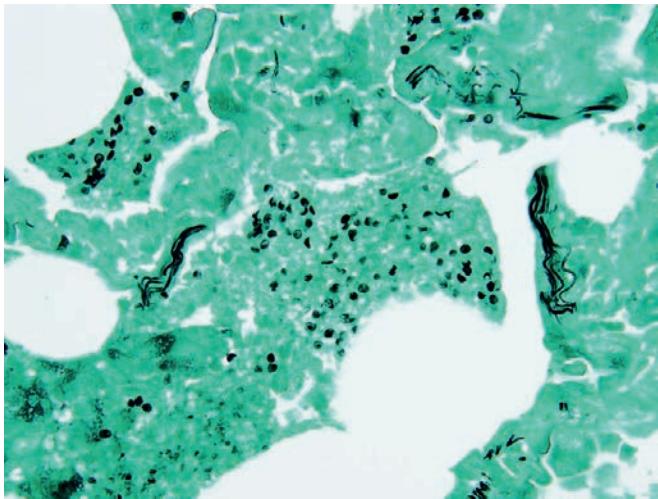


Figure 10.70 GMS stain showing *P. jirovecii* in frothy alveolar exudate.

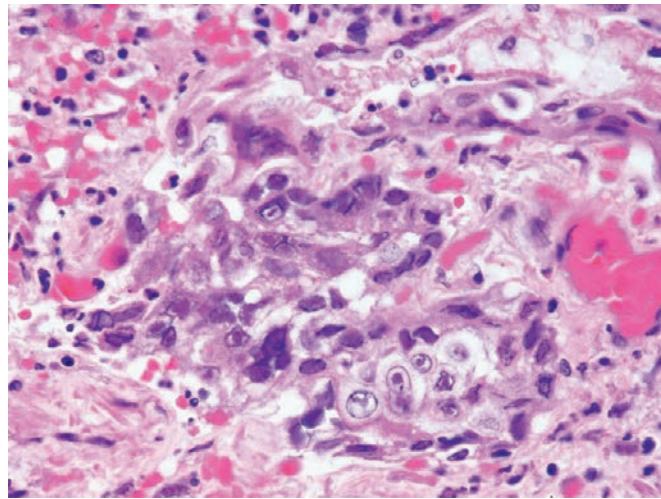


Figure 10.72 Intranuclear inclusions in herpes simplex pneumonia.

The diagnosis of pneumocystic pneumonia depends on identification of the organism.¹⁸⁹ Cytology and biopsy specimens should be cultured (to rule out the possibility of other infectious processes), imprints should be taken, and the rest of the sample processed routinely or subjected to frozen section examination. If *P. jirovecii* is present, the imprints are almost invariably positive. The most reliable stain for detecting the organism is GMS (Fig. 10.70). The cystic forms of the organism appear with the silver stain as round structures, up to 5 µm in diameter, containing single or paired discrete 'intracystic bodies' measuring 1–2 µm. Some of the cysts are crumpled and others are collapsed, with a crescentic shape. False-negative staining with GMS does occur, making careful interpretation of routinely stained sections and use of appropriate positive controls all the more important.¹⁹³ Immunoperoxidase techniques using monoclonal antibodies and PCR methods are also available.

Cytomegalovirus pneumonia is usually seen in immunocompromised patients, such as those with AIDS or lymphoid malignancies, transplant recipients, and those receiving cytotoxic drugs.¹⁹⁴ Radiographically, it may present in the form of small (2–4 cm) peripherally located nodules or consolidated opacities, as an acute miliary pattern, or as a diffuse interstitial process. Microscopically, a patchy mixed inflammatory infiltrate is seen in conjunction

with an air space exudate and hyperplasia of the alveolar epithelium. In the diffuse pattern, these changes may be associated with focal areas of hemorrhagic necrosis and DAD. Viral inclusion bodies are found in the nucleus and cytoplasm of alveolar macrophages, epithelial cells, and endothelial cells and can be detected in most but not all of the cases (Fig. 10.71). Cytoplasmic inclusions are stained with both PAS and GMS, a fact that may lead to a mistaken diagnosis of *P. jirovecii* pneumonia.¹⁹⁵

Herpes simplex pneumonia occurs in immunocompromised patients and immunocompetent patients requiring prolonged mechanical ventilation.¹⁹⁶ Microscopically herpes simplex pneumonia usually results in a necrotizing tracheobronchitis and bronchopneumonia that is frequently accompanied by DAD. Intranuclear viral inclusions can be found in airway epithelial cells at the edge of the necrotic areas (Fig. 10.72).

Adenovirus pneumonia also causes a necrotizing bronchiolitis and bronchopneumonia frequently accompanied by DAD, but differs from herpes simplex virus in that adenovirus pneumonia affects previously healthy immunocompetent as well as immunocompromised patients. The characteristic cytopathic changes include a combination of smudged nuclei and bricklike intranuclear inclusions in epithelial cells (Fig. 10.73).

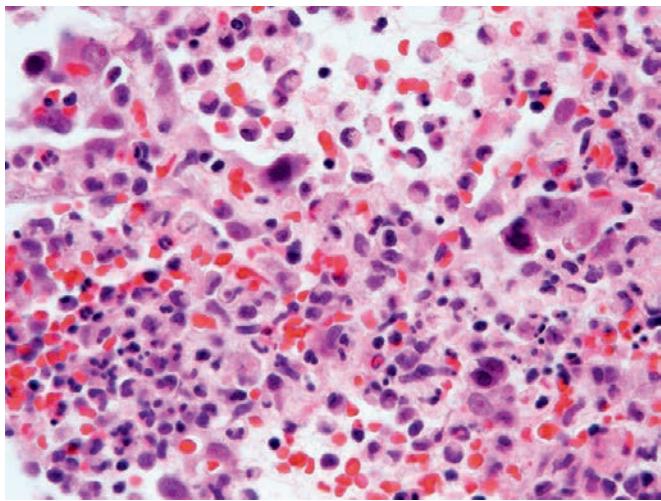


Figure 10.73 Adenovirus showing characteristic smudge cells.

Influenza pneumonia can result in a wide range of morphologic changes, most commonly a combination of necrotizing pneumonia and DAD.¹⁹⁷ Mild acute and organizing pneumonia can also occur. Unlike the previously described viral pneumonias there are no characteristic viral cytopathic changes, and diagnosis requires confirmatory cultures or serological studies. Similar changes occur in H1N1 influenza A and are often accompanied by pulmonary hemorrhage, vascular thrombosis, and hemophagocytosis in lung and extrapulmonary sites.¹⁹⁸

Severe acute respiratory syndrome (SARS) is an infectious condition caused by a coronavirus. It emerged from Guangdong Province in China in November 2002 and resulted in widely publicized outbreaks in Hong Kong, Vietnam, and Singapore. Microscopically, the predominant pattern is that of DAD, often associated with a fibrinous air space exudate resembling that described in acute fibrinous and organizing pneumonia.¹⁹⁹

Hantavirus pulmonary syndrome is a severe pulmonary disease caused by a previously unrecognized hantavirus.²⁰⁰ An outbreak has occurred in the southwestern United States. The usual morphologic finding is pulmonary edema and/or DAD with focal hyaline membranes.²⁰¹

Legionnaires' disease became an instant media sensation in 1976, when it occurred in a small epidemic form among persons attending a convention in a hotel in downtown Philadelphia.²⁰² It turns out that it is anything but a new disease; apparently, sporadic cases have been seen by the thousands over previous decades. Involvement of the hilar lymph nodes occurs in nearly half of autopsied patients, and in about one-fourth of the cases there is hematogenous spread to other organs. Occasionally, an open or transbronchial lung biopsy is performed in these patients. Microscopically, the process is characterized by intra-alveolar accumulation of neutrophils, macrophages, and fibrin as in other bacterial pneumonias.²⁰³ However, many cases also show a leukocytoclastic neutrophilic inflammatory infiltrate, small vessel vasculitis, and necrosis. The Dieterle silver impregnation stain has proved to be the most reliable for identifying the short gram-negative bacillus that is the etiologic agent. Immunostains are also available but carry a risk of falsely negative staining.

Nocardiosis is another opportunistic lung infection sometimes seen in transbronchial or surgical lung biopsies.^{204,205} Approximately half of the reported cases have occurred in patients who have a history of organ transplantation, immunosuppression, steroid



Figure 10.74 Gross appearance of hydatidosis of lung. (Courtesy of Dr. RA Cooke, Brisbane, Australia. From Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004.)

usage, or chemotherapy. Microscopically, the picture is that of a focal necrotizing bronchopneumonia with microabscesses and a peripheral inflammatory infiltrate that frequently includes palisaded histiocytes resulting in a vaguely granulomatous appearance. Gram and GMS stains show slender, slightly beaded, branching filamentous bacilli.

***Mycoplasma pneumoniae* pneumonia**, formerly known as *atypical pneumonia*, is dominated by upper respiratory tract symptoms and bronchiolitis with shifting pulmonary infiltrates. Disease is usually mild and self-limited, but in some patients *M. pneumoniae* causes pneumonia that may be severe and potentially life-threatening, especially in patients with underlying lung disease.²⁰⁶ Microscopically, the main change is a severe acute and chronic bronchiolitis with an acute inflammatory exudate in the lumens of small airways.²⁰⁷ The bronchiolitis may be accompanied by other changes including organizing pneumonia and, in severely ill patients, DAD.

Hydatidosis (echinococcosis) results from infestation by *Echinococcus granulosus* (which is usually cystic) and only rarely by *Echinococcus multilocularis* (which causes alveolar echinococcosis) (Figs. 10.74 and 10.75).¹²¹

Lung in AIDS

Pulmonary disease occurs frequently during the course of AIDS and may necessitate bronchoalveolar lavage, transbronchial biopsy, or less commonly surgical lung biopsy for appropriate management.^{208,209} Surgical lung biopsies are uncommon in AIDS patients but still have value in a highly selected subset of patients, especially those with noninfectious lung diseases.^{210,211} Opportunistic infections remain the most common abnormalities, including *Pneumocystis*

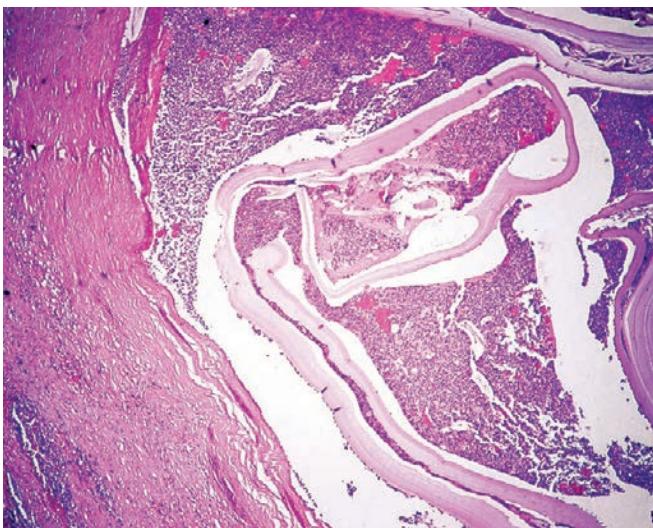


Figure 10.75 Microscopic appearance of pulmonary hydatidosis.

pneumonia, cytomegalovirus pneumonia, atypical mycobacteriosis and tuberculosis, candidiasis, invasive aspergillosis, toxoplasmosis, cryptococcosis, histoplasmosis, blastomycosis, *Rhodococcus equi*, and microsporidiosis.²¹² The histologic findings are generally similar to those affiliated with these pathogens in non-AIDS patients. *R. equi* causes a histologically distinct histiocyte-rich inflammatory response indistinguishable from malakoplakia.²¹³ Noninfectious pulmonary complications include neoplasms, most notably Kaposi sarcoma and lymphomas including lymphomatoid granulomatosis.^{214,215} Kaposi sarcoma can be an especially challenging diagnosis in transbronchial biopsies.²¹⁶ AIDS patients may get other nonlymphomatous lymphoproliferative lesions that are frequently lumped under the designation of lymphoid interstitial pneumonia.²¹⁷ Sometimes the morphologic changes are nonspecific and overlap with the idiopathic interstitial pneumonias.²¹⁸

Lung and Transplantation

Most late nonleukemic deaths after bone marrow transplantation are caused by infectious and noninfectious pulmonary diseases, including cytomegalovirus pneumonia, DAD, constrictive (obliterative) bronchiolitis, venoocclusive disease, and various forms of chronic interstitial pneumonia including PPFE.^{219–222} Regardless of the histologic findings, late-onset noninfectious pulmonary complications are highly related to, and likely a manifestation of, graft-versus-host disease.

Lung biopsies in patients who are status post lung transplantation are most commonly performed to evaluate allograft rejection for which the differential diagnosis is usually infection.²²³ Grading of acute and chronic rejection has been standardized by the International Society for Heart and Lung Transplantation, but rates of interobserver agreement remain low.^{224,225} Acute cellular rejection is recognized by the accumulation of perivascular and interstitial mononuclear inflammatory cells, often with associated eosinophils. Acute rejection is graded based on the intensity and extent of the inflammatory infiltrate, from A0 (negative) to A4 (severe).²²⁴ Perivascular and interstitial inflammation is often accompanied by a lymphocytic bronchiolitis that is also graded based on the intensity of the inflammatory infiltrate. Perivascular inflammation and bronchiolitis occur commonly in opportunistic infections, most importantly pneumocystis and cytomegalovirus, and therefore infection should be carefully

excluded before ascribing these changes to acute rejection.²²³ The pathology of acute antibody-mediated rejection has not yet been well defined.²²⁶ Chronic rejection is manifested by fibrosis narrowing the lumen of bronchioles (*obliterative bronchiolitis*), arteries, and veins and is graded on the basis of the airway changes as either absent (C0) or present (C1).

Vascular Diseases

The term pulmonary hypertension includes a variety of diseases that have different etiologies, but which may have similar clinical presentations, overlapping histologic findings, and variable responses to medical treatment.^{227,228} Histopathology plays a less important role in current classification schemes which define phenotypes based on a combination of clinical and physiological findings as well as an expanding list of biomarkers.²²⁷

Surgical lung biopsies are rarely performed to evaluate otherwise unexplained pulmonary hypertension. Various forms of primary pulmonary hypertension are more likely to be seen in explanted lungs from patients who undergo transplantation. The histologic features unique to pulmonary hypertension were extensively studied in historical studies of patients with congenital heart disease for whom histologic grading of pulmonary hypertension played an important role in determining the potential effectiveness of corrective surgery.^{229,230} Elastic tissue stains are very helpful in evaluating the status of arteries, veins, and smaller vessels. In patients with congenital heart disease vascular disease is considered reversible when the arterial lesions are restricted to medial hypertrophy, thickening of longitudinal intimal smooth muscle, post-thrombotic intimal fibrosis, or cellular intimal hyperplasia.²²⁹ Concentric-laminar intimal fibrosis of moderate or severe degree probably does not regress. Fibrinoid necrosis and/or plexiform (plexogenic) lesions are regarded as contraindications to surgery unless the nature of the defect is such that one lung is spared. An increase in the number of neuroendocrine cells has been detected in hypertensive pulmonary vascular diseases.²³¹ Many of the principles that link histopathologic findings to the severity of pulmonary hypertension in patients with congenital heart disease also apply to patients with primary pulmonary hypertension.^{232,233}

Pulmonary veno-occlusive disease (PVOD) accounts for about 10% of patients with idiopathic pulmonary arterial hypertension and affects men and women equally across a wide age range.²³⁴ Radiological findings are distinct compared with other forms of primary pulmonary hypertension and may overlap with the diffuse interstitial diseases.²³⁵ Pulmonary hypertension develops because of widespread occlusion of medium and small-sized branches of the pulmonary veins, accompanied by recanalization and pseudoangiomatous changes. Redundant alveolar septal capillary loops (*capillary hemangiomatosis-like change*) are common and overlap with **capillary hemangiomatosis**, a condition that some have advocated may be indistinguishable from PVOD.²³⁶ Arterial thickening and prominent hemosiderosis are also present. The etiology of idiopathic PVOD is unknown; identical changes are sometimes seen in patients with chronic venous hypertension resulting from primary cardiac disease which should always be excluded. PVOD has also been described as a consequence of drug toxicity and in bone marrow transplant patients with chronic graft-versus-host disease.

Arteriovenous malformations (aneurysms) are radiographically discernible, frequently multiple lesions that occur most often in the lower lobes (Figs. 10.76 and 10.77). Most are congenital, occurring most commonly in patients with hereditary hemorrhagic telangiectasia (Rendu–Osler–Weber syndrome). Because of the shunt, there may be bruits and cyanosis on physical examination accompanied by polycythemia and hypoxemia. Excision is curative. Others can be successfully managed using radiologically guided embolization. They

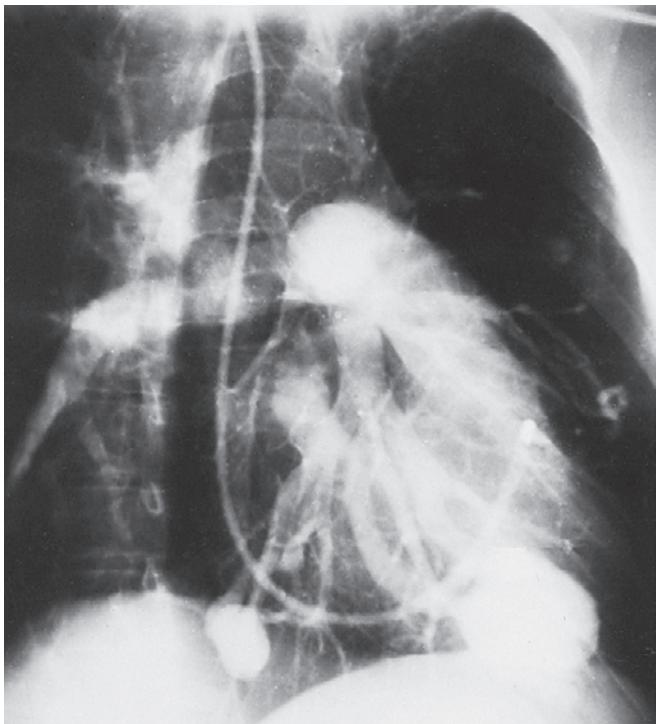


Figure 10.76 Angiogram of a 28-year-old man with multiple arteriovenous malformations. The patient had Rendu–Osler–Weber syndrome (hereditary hemorrhagic telangiectasia). After left lower lobectomy, oxygen saturation rose from 86% to 95%.



Figure 10.78 Typical wedge-shaped appearance of pleural-based pulmonary infarct. A large occluding thrombus is evident in the vessel leading to the area of the infarct.



Figure 10.77 Gross appearance of pulmonary arteriovenous malformation.

are made up of large vascular channels with arteriovenous communications. Microscopically, the vessels are abnormal, often showing deficiencies and excesses of muscle, which make it impossible to distinguish artery from vein.

Infarcts resulting from pulmonary thromboembolic disease are usually identified as such on the basis of radiological studies demonstrating a combination of thromboemboli and pleural-based triangular opacities. However, occasionally they simulate a malignant tumor and are either biopsied or resected (Fig. 10.78).²³⁷ Those that come to the attention of a surgical pathologist are less likely to demonstrate the characteristic wedge-shaped configuration on chest imaging studies and instead present as solitary or multiple nodules.²³⁷

Other Non-Neoplastic Diseases

Broncholithiasis is defined as the presence of calcified material within the lumen of a cartilaginous airway and is most commonly a complication of infectious granulomatous diseases (particularly tuberculosis and histoplasmosis) in which a calcified granuloma erodes into a bronchus.²³⁸ Less common causes include calcification of aspirated food or inspissated secretions in bronchiectasis.

Pulmonary hyalinizing granuloma usually presents in minimally symptomatic or asymptomatic adults with multiple, bilateral nodules or infiltrates that may mimic metastatic disease.^{239,240} Microscopically, the central portion is made up of hyalinized, keloid-like collagen. This is surrounded by a mixed inflammatory infiltrate comprising mainly lymphocytes, plasma cells, and a minor component of macrophages including rare multinucleated giant cells, the overall appearance simulating nodular amyloidosis (Fig. 10.79). However, special stains for amyloid are negative. Necrotic areas and non-necrotizing epithelioid granulomas are distinctly unusual in this condition, which is of importance in the differential diagnosis. Some patients have evidence of antecedent or concomitant granulomatous infection, but in most the pathogenesis is unknown. Pulmonary hyalinizing granuloma may be associated with sclerosing mediastinitis and/or retroperitoneal fibrosis, with recent evidence suggesting a link to the spectrum of IgG4-related sclerosing diseases.²⁴¹

Endometriosis of the lung may present with recurrent catamenial hemoptysis, or as asymptomatic nodules discovered on routine chest x-ray film.²⁴² Most of the reported cases have been located on the right side. The disease often extends to the pleural surface.²⁴³

Pulmonary alveolar microlithiasis is a rare disease characterized by the presence of microliths or calcospherites within the alveoli of an otherwise normal lung.²⁴⁴ The process is diffuse and bilateral,

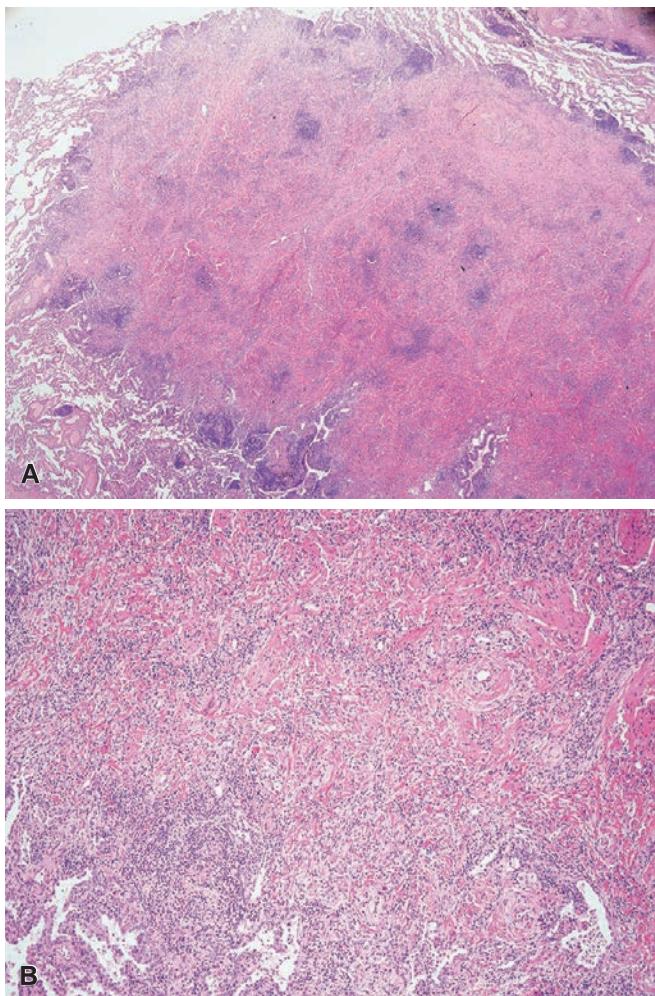


Figure 10.79 Pulmonary hyalinizing granuloma showing circumscribed nodule (A) with characteristic pattern of collagen fibrosis and inflammation (B).

and the clinical course is extremely long. The chest radiographic appearance is virtually diagnostic.²⁴⁵

Carcinoma

General and Clinical Features

Carcinoma of the lung has become very frequent since the 1930s. The American Cancer Society reported that in 2015 there were 221,200 new cases and 158,040 deaths from lung cancer in the United States. The only hopeful trend in this dreadful situation is the fact that the incidence rates overall are declining in the United States, having peaked in men in the mid-1980s and stabilized in women in the first two decades of the 21st century after steadily increasing through the 1980s and 1990s.²⁴⁵ The declining trend in men and steady increases in women have converged to a place of near parity across sexes, with a male to female ratio of 1:1. These trends are not unique to the United States and have been documented on multiple continents.²⁴⁶ More than 98% of the patients diagnosed in 2015 are projected to be 45 years of age or older, but cases have also been reported in young adults and adolescents.

Much has been written about the epidemic nature of lung carcinoma, the leading cause of cancer-related deaths. Many factors

thought in the past to be of pathogenetic importance—such as tuberculosis, tarring of roads, the 1918 influenza epidemic, anthracosis, and anthracosilicosis—are now considered to be totally unrelated to cancer or to account for only a minimal fraction of cases. Exposure to asbestos; polycyclic aromatic hydrocarbons; arsenic, nickel, and chromium compounds; bis(chloromethyl) ether (BCME); chloromethyl methyl ether (CMME); vinyl chloride; radiation (as seen in uranium workers and in people with high radon concentration in their houses); and other occupational agents undoubtedly account for some of the cases.²⁴⁷ This is particularly true for asbestos (thought to be responsible for about 5% of all lung carcinoma deaths) and for radon.²⁴⁸ However, the significance of all these factors pales by comparison with the role played by cigarette smoking, both in males and in females.²⁴⁵ This is true for all major histologic types of lung carcinoma. The fact that smokers living in urban areas and/or exposed to asbestos are at a higher risk for lung carcinoma than others suggests the potentiating effect of air pollution and asbestos on the carcinogenic effect of tobacco, a possibility that is supported by some experimental models.²⁴⁹ Significantly, in animals there is a nearly total absence of spontaneously occurring lung tumors that are histologically similar to smoking-related human lung cancers.²⁵⁰

The relationship of cigarette smoking with malignant, dysplastic, and metaplastic alterations of the tracheobronchial tree has also been thoroughly documented by the meticulous histologic observations of Auerbach et al.²⁵¹ and confirmed by others²⁵²; at autopsy, Auerbach et al. found an almost linear correlation between the severity of the changes and the amount of cigarette consumption. A similar relationship between smoking and lung cancer precursors has been suggested for marijuana and may be additive with tobacco use.²⁵³

Approximately 10%–15% of cases of lung carcinoma occur in never-smokers. Among them, three-fourths are women, and a high proportion of cases show an adenocarcinoma histology.²⁵⁴ Adenocarcinoma occurring in never-smoker women appears to be more prevalent in Asian populations.

Another factor thought to be related to the development of carcinoma is pulmonary fibrosis, through a preceding stage of atypical proliferation of the terminal bronchiolar epithelium. Malignant tumors arising at the site of scars resulting from bullets, other foreign bodies, and old granulomas have been well documented, although in most the cause-and-effect relationship between scar and cancer is uncertain at best.²⁵⁵ The relationship between lung carcinoma and diffuse fibrosis is more complicated. In a classic study of 153 consecutively resected lung tumors,²⁵⁶ 21% were associated with—and presumably preceded by—honeycombing and atypical epithelial proliferation. Most of these tumors were in the upper lobe, and one-third of them were adenocarcinomas. Others have documented a clear relationship between UIP and increased lung cancer risk, although the effect of fibrosis *per se* is confounded by the high prevalence of cigarette smoking in these patients.²⁵⁷ Carcinomas arising in UIP show disproportionate involvement of the lower lobes which mirrors the distribution of the fibrotic changes. Peripheral squamous cell carcinomas are over-represented in UIP patients and are especially common in older male smokers.^{258,259}

Atypical adenomatous hyperplasia of type 2 alveolar cells has emerged as an important potential precursor of adenocarcinoma in a subset of patients.^{260,261}

Rare examples of squamous cell carcinomas of the lung resulting from human papilloma virus (HPV)-driven malignant transformation of respiratory papillomatosis have been reported.^{262,263} On the whole, however, HPV does not seem to play an important role in the genesis of lung cancer.²⁶⁴

Lung carcinoma is multiple (either synchronous or metachronous) in about 2%–6% of patients^{265,266} and is associated with independent smoking-related cancer of the head and neck region in about 5%–15%

of patients.²⁶⁷ Molecular genetic studies have shown that a majority of multicentric lung tumors (whether synchronous or metachronous) show evidence of a common clonal origin.^{268,269} Despite the molecular evidence, patients thought to have multifocal synchronous or metachronous primary lung carcinomas on the basis of established histologic criteria have a substantially better prognosis than those with intrapulmonary metastases.²⁷⁰

Most lung cancers are in a relatively advanced stage by the time of diagnosis; about 60% are inoperable as a result of extensive locoregional spread and/or distant metastases. Symptoms and signs develop relatively late in the course of the disease, are often related to partial or complete bronchial obstruction, and may lead to confusion with a primary inflammatory process. Overall survivals remain low, with about 17% surviving 5 years in a large cohort (2005–2011) from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program.²⁷¹

The most common symptoms, in decreasing order of frequency, are cough, weight loss, pain, increased sputum production, hemoptysis, malaise, fever, and those resulting from paraneoplastic manifestations. Peripherally located lesions are clinically silent until they reach a sufficient size to ulcerate into a bronchus or to involve the pleural space. Carcinomas located in the superior pulmonary sulcus result in a clinical picture peculiar to their location, known as *Pancoast syndrome*.²⁷² This is characterized by pain in the distribution of the ulnar nerve and is often accompanied by Horner syndrome secondary to involvement of the sympathetic chain.

Sometimes lung carcinoma presents as a solitary pulmonary nodule ('coin lesion') on the chest x-ray film or CT scan of an asymptomatic individual. About 35%–50% of solitary pulmonary nodules in adults evaluated using modern imaging techniques represent lung carcinoma.²⁷³ The percentage is higher for patients older than 60 years and for noncalcified lesions. The incidence of malignancy in coin lesions exhibiting obvious calcification is less than 1%.

Lung neoplasms are sometimes associated with extrapulmonary manifestations (*paraneoplastic syndromes*) remote from the sites of primary or metastatic tumor.²⁷⁴ Although exceptions occur, there is a fairly good correlation between some morphologic parameters of the tumor and the systemic effect produced. These are summarized in Table 10.2. These manifestations are caused by the tumor's secretion of biologically active compounds. In the case of the *Lambert–Eaton syndrome* associated with small cell carcinoma, voltage-gated calcium channel autoantibodies have a pathophysiologic role. Additional substances that have been detected in some cases of lung carcinoma include amylase, calcitonin, CEA, alpha-fetoprotein (AFP), β -pregnancy-specific glycoprotein, and epidermal growth factor receptors (EGFRs). A preponderance of small cell carcinomas exists in this group; however, the correlation between the presence of a tumor marker and the histologic tumor type is generally poor.

Because of the generally late stage of clinically diagnosed lung carcinomas, screening efforts have been mounted over the years at a considerable cost to detect early and potentially curable cases in high-risk individuals.²⁷⁵ Until now, those efforts have been generally disappointing. At present, extensively publicized multi-institutional studies and a randomized controlled National Lung Screening Trial have indicated an opportunity to reduce lung cancer mortality through thoughtfully implemented screening programs applied to carefully selected high-risk populations. How to implement current screening recommendations in a cost-effective manner remains controversial.^{276–278} Parenthetically, the large majority of screening-detected carcinomas—whether solitary or multiple—were adenocarcinomas, including some with doubling times much longer than those historically associated with incident lung carcinomas reflecting the risk of overdiagnosis in this population.^{279,280}

Table 10.2 Systemic effects of lung carcinoma and their most commonly related tumor type²⁷⁵

SYSTEMIC EFFECT AND HORMONE RESPONSIBLE	TUMOR TYPE
Cushing syndrome (ACTH)	Small cell carcinoma Carcinoid tumor
Carcinoid syndrome	Carcinoid tumor Small cell carcinoma
Hyponatremia (ADH)	Small cell carcinoma
Hypercalcemia (parathyroid hormone-related protein)	Squamous cell carcinoma
Gynecomastia (hCG)	All tumor types
Clubbing of fingers and hypertrophic pulmonary osteoarthropathy	Unrelated to tumor type; mainly dependent on proximity to pleural surface
Mental syndromes (i.e. toxic confusional psychosis)	Small cell carcinoma
Cortical cerebellar degeneration	All tumor types
Encephalomyelitis	Small cell carcinoma
Sensory neuropathy	Small cell carcinoma
Myopathic–myasthenia syndrome (Lambert–Eaton syndrome)	Small cell carcinoma

Pathologic and Immunohistochemical Features

Several microscopic classifications of lung carcinoma exist. The one most widely used derives from the World Health Organization (WHO) Classification of Tumors developed in collaboration with the International Association for the Study of Lung Cancer (IASLC).²⁸¹ It includes the following major categories:

1. Adenocarcinoma
2. Squamous cell carcinoma
3. Neuroendocrine tumors (including small cell carcinoma, large cell neuroendocrine carcinoma, typical and atypical carcinoid tumors, and diffuse neuroendocrine cell hyperplasia)
4. Large cell carcinoma
5. Adenosquamous carcinoma
6. Sarcomatoid carcinoma (including pleomorphic, spindle cell and giant cell carcinoma, carcinosarcoma, and pulmonary blastoma).

Several studies have shown the reproducibility of this classification and the close correlation between biopsies and surgical specimens.²⁸³ The current WHO classification of lung tumors differs from its predecessors in including not only criteria based on routine light microscopy but also immunophenotypic criteria based on a limited number of commonly available immunostains.²⁸¹

Larger lung carcinomas often show a combination of histologic patterns which complicates classification. In a study of 100 consecutive cases of lung carcinomas in which either the entire tumor or 10 blocks were examined, just over half were composed of a single histologic type.²⁸⁴ The immunophenotypes of the main histologic tumor types are relatively stable and highly reproducible, although rare exceptions to the anticipated immunostaining patterns are well documented.^{283,285,286}

The relative frequencies of the various microscopic types of lung carcinoma have changed over the years. Adenocarcinomas are now the most common incident lung carcinoma while incidence rates for both squamous cell and small cell carcinoma have declined.²⁴⁶ The relative frequencies are also influenced by the utilization of immunostains for histologic classification which has sharply reduced those cases assigned to the category of large cell carcinoma.²⁸⁷

The histochemical, immunohistochemical, ultrastructural, and molecular genetic features of lung carcinoma are discussed with the respective histologic categories. Suffice it to say here that the most important generic immunomarkers of lung carcinomas are the following:

- **Keratins.** They are present in all types of lung carcinoma, but the expression of individual keratins is dependent upon the tumor subtype.²⁸⁸
- **TTF-1.** Thyroid transcription factor 1, which is consistently expressed in normal type 2 pneumocytes and Clara cells, has emerged as one of the most useful markers of epithelial lung tumors.^{289,290} It is expressed in over 80% of the adenocarcinomas, a similar proportion of small cell carcinomas, and in a much smaller percentage of the other lung carcinoma types.²⁸⁵ Given relatively high sensitivity and specificity, the current WHO classification scheme proposes positive staining for TTF-1 (or napsin A) as a criterion for classifying otherwise poorly differentiated non-small cell carcinomas as adenocarcinomas. 'False-positive' results sometimes occur when staining in non-neoplastic respiratory epithelial cells is mistakenly attributed to neoplastic squamous cells, a diagnostic trap especially important to remember when interpreting small biopsies.²⁹¹ Detection of TTF-1 in metastases in brain or other extrapulmonary sites is also very helpful in identifying lung as a likely primary site. There is only one major caveat: as its name indicates, the other tissue in which TTF-1 is consistently expressed is the thyroid epithelium. TTF-1 staining has also been described at low frequencies, and usually with a very focal distribution, in small cell carcinomas originating in nonpulmonary sites such as the prostate and bladder and in adenocarcinomas of the breast, colon, ovaries, and endometrium.²⁸⁹
- **Napsin A.** Napsin A is an aspartic proteinase involved in the maturation of surfactant protein B. It is detected in the cytoplasm of type II pneumocytes and alveolar macrophages. It is a highly sensitive marker for pulmonary adenocarcinomas (positive in about 80% of cases) and thus is a useful adjunct in TTF-1 negative tumors.²⁹² Napsin staining is also seen in a subset of renal cell carcinomas and tall cell variants of papillary thyroid carcinomas.²⁹³ Like TTF-1, napsin stains non-neoplastic respiratory epithelial cells that may be intimately admixed with neoplastic squamous cells, a potential diagnostic trap that complicates interpretation.²⁹⁴
- **p63 & p40 (Δ Np63).** p63 comprises a family of variants (isoforms) including transcriptionally active tumor suppressor genes and transcriptionally inactive oncogenes. The p63 antibody most commonly used for tissue diagnosis is a 'pan-p63' marker while p40 is a nontransactivated isoform (Δ Np63) with greater specificity for squamous/basal-type epithelium.²⁹⁵ Both are diffusely positive in nearly all squamous cell carcinomas from any site, including the lung, but p63 is less specific in that focal staining is also seen in a third or more of lung adenocarcinomas.²⁹⁶ The current WHO classification of lung tumors suggests that diffuse staining for p63 or p40 should be used as a criterion for classifying TTF-1 negative poorly differentiated non-small cell lung carcinomas as squamous cell carcinomas.

A selected immunohistochemical profile of the major types of lung carcinoma, extracted from the literature by Pandit et al.,²⁹⁷ is shown in Table 10.3. A practical approach for classifying poorly differentiated non-small cell carcinomas that are difficult to classify

Table 10.3 Immunohistochemical profile of the major types of lung carcinoma

	TTF-1 (%)	CD56 (%)	CK5/6 (%)	34 β E12 (%)
Adenocarcinoma	77	3	0	46
Squamous carcinoma	7 ^a	6	100	97
Small cell carcinoma	88	95	0	12

^aOrdonez and others hypothesize that TTF-1 (and napsin A) staining in squamous cell carcinomas is limited to non-neoplastic respiratory epithelium.^{292,295}
TTF-1, Thyroid transcription factor 1.

on the basis of routine histology alone that also preserves tissue for molecular testing in small biopsies or cytologies is a combination of TTF-1 and either p63 or p40. Adding immunostains for high-molecular-weight keratins (CK5/6 rather than 34 β E12 given greater specificity) and napsin A may have value in cases for which TTF-1 and p63/p40 are insufficient.^{290,298} Low rates of discordance with final classification of resected tumors are explained primarily by the impact of sampling rather than fidelity of immunostaining profiles.

Blood vessel and/or lymphatic invasion is seen in about half of resected non-small cell carcinomas and is more frequent in larger tumors.²⁹⁹ The prognostic significance of vascular and/or lymphatic invasion remains somewhat controversial but both tend to predict a greater likelihood of recurrence and shorter survival and should be included in pathology reports for resected lung carcinomas.^{300,301} Visceral pleural invasion occurs in about 20% of resected non-small cell carcinomas and also predicts for shorter overall survival in otherwise early stage node-negative lung carcinomas.³⁰² Aside from being a prognostic factor, visceral pleural invasion is also important in upstaging (stage IB) small (≤ 3.0 cm) node-negative tumors that might otherwise be considered earlier stage (stage IA) carcinomas.³⁰³

Adenocarcinoma

Adenocarcinomas comprise over half of all lung carcinomas in females and nearly 45% of those in males.³⁰⁴ Incidence rates for adenocarcinoma are higher than for other microscopic type of lung cancer, to the extent that it is now the most common form.²⁴⁶ In data collected from two large national databases in the United States for the period 2004–2009, adenocarcinomas were 1.7 times more common than squamous cell carcinomas and 2.5 times more common than small cell carcinomas.³⁰⁵

Grossly, invasive adenocarcinomas usually present as poorly circumscribed gray–yellow peripheral lesions (Fig. 10.80). They may be single or multiple. If they secrete abundant mucin, they have a gelatinous, glairy appearance. Cavitation is unusual. About 65% of the cases are located peripherally, and often about the visceral pleura at the time of excision, resulting in pleural fibrosis or 'puckering' (Fig. 10.81). Occasionally, a small peripheral adenocarcinoma spreads massively into the pleural space and coats both pleural layers so as to closely simulate the appearance of diffuse mesothelioma (*pseudomesotheliomatous carcinoma*) (Fig. 10.82).³⁰⁵ Adenocarcinomas only rarely present as endobronchial polypoid masses (Fig. 10.83).³⁰⁶

Adenocarcinomas occasionally arise in association with a peripheral scar, including apical caps.³⁰⁷ In a classic series of 82 'scar cancers' reviewed by Auerbach et al.,³⁰⁸ 72% were adenocarcinomas and 18%

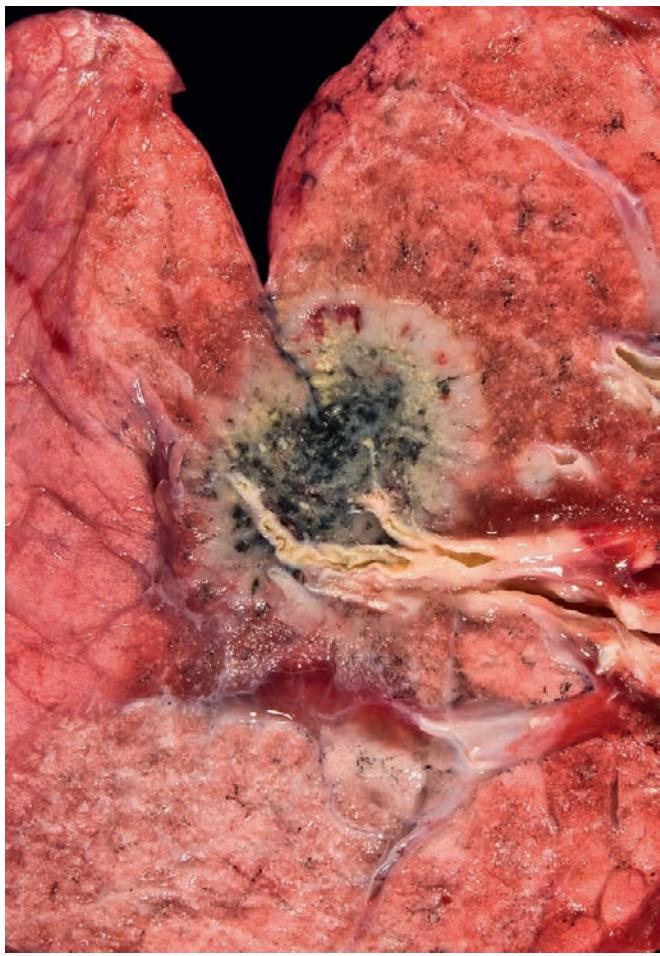


Figure 10.80 Typical peripheral location of pulmonary adenocarcinoma, in this case puckering and retracting visceral pleura. (Courtesy of Dr. J. Carvalho, Minneapolis, MN.)

were squamous cell carcinomas, the rest being assigned to the category of large cell undifferentiated carcinomas at a time that immunostains were not used to subclassify poorly differentiated non-small cell lung carcinomas. There were no small cell carcinomas. A number of studies have proposed that many (most?) of these peripheral cancers do not arise from preexisting scars but instead reflect scar formation by the tumor through various combinations of desmoplasia, infarcts, alveolar collapse, and fibroelastosis.³⁰⁹⁻³¹¹

Microscopically, adenocarcinomas exhibit a wide range of differentiation, from well-differentiated *in situ* adenocarcinomas formerly termed *bronchioloalveolar carcinoma* to poorly differentiated solid adenocarcinomas that would have been previously classified as large cell carcinoma. The two morphologic signs of glandular differentiation that define adenocarcinoma, often found together, are formation of tubules or papillae and/or secretion of mucin. On occasion, lung adenocarcinoma cells exhibit prominent eosinophilic intracytoplasmic globules that are distinct from mucin globules.³¹² Immunoreactivity for pneumocyte markers, most commonly TTF-1 and/or napsin A, is also sufficient to establish the diagnosis of adenocarcinoma in poorly differentiated carcinomas that lack glandular histology or mucin secretion, assuming no compelling histologic features (e.g. keratinization) to suggest an alternative.^{261,313}

Adenocarcinomas are histologically heterogeneous with many of them showing a combination of growth patterns. Identifying the predominant growth pattern may have prognostic value in predicting

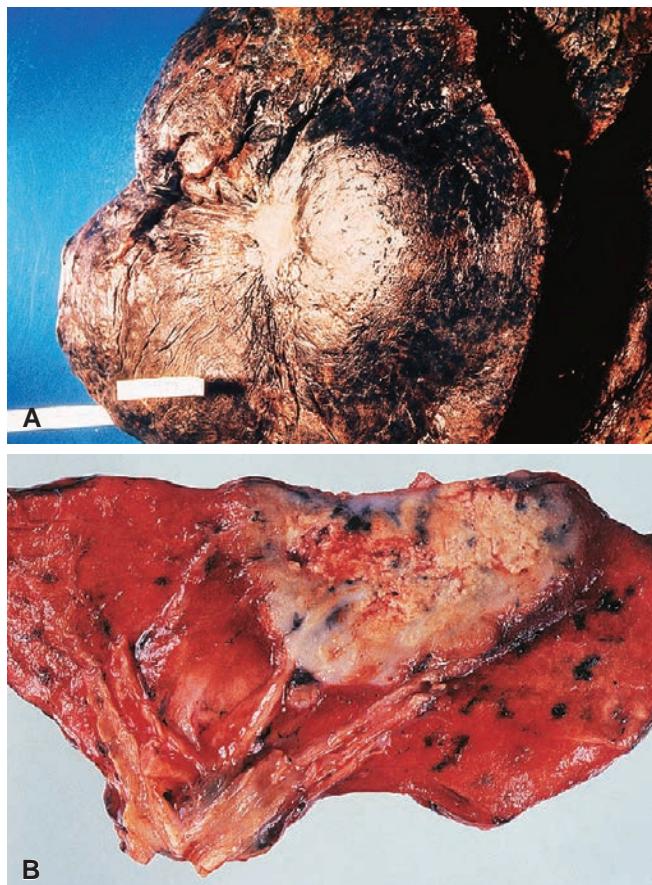


Figure 10.81 **A** and **B**, Outer aspect and cut section of two pulmonary adenocarcinomas showing pleural retraction.

the likelihood of disease-free survival depending on the stage of disease. In patients with small (≤ 3.0 cm) node-negative tumors, noninvasive (*in situ*), minimally invasive (≤ 0.5 cm of invasive carcinoma), and *lepidic* predominant adenocarcinomas (a group of well-differentiated adenocarcinomas referred to in previous iterations of lung tumor classifications as *bronchioloalveolar carcinoma*) (Fig. 10.84) are affiliated with an excellent prognosis.³¹⁴ Most early-stage lesions that lack evidence of invasion are composed of nonmucinous columnar cells, although there are rare examples of *in situ* and minimally invasive adenocarcinomas in which bland, mucinous columnar cells comprise the neoplastic population. Frankly invasive stage 1 adenocarcinomas in which a *lepidic* (*bronchioloalveolar*) growth pattern comprises at least 50% of the tumor without other adverse histologic findings (i.e. angiolymphatic and/or visceral pleural invasion, a focal micropapillary growth pattern) are affiliated with the same excellent prognosis described for *in situ* and minimally invasive adenocarcinomas.³¹⁵ Indeed some have shown that the presence of even a minor *lepidic* (*bronchioloalveolar*) component is associated with better survival compared with adenocarcinomas that lack this distinctive well-differentiated growth pattern.³¹⁶ Micropapillary (Fig. 10.85) and solid (Fig. 10.86) adenocarcinomas are more likely to be affiliated with higher-stage disease and portend a poor prognosis.^{314,316} The presence of even a minor micropapillary component is worth noting in pathology reports as it implies a more aggressive tumor with greater potential for recurrence and distant relapse.³¹⁷ Conventional acinar (Fig. 10.87), papillary (Fig. 10.88), and invasive mucinous (Fig. 10.89) adenocarcinomas are affiliated with an intermediate prognosis.³¹⁴ Rare variants of adenocarcinoma

include *signet ring cell adenocarcinoma* (Fig. 10.90),³¹⁸ *invasive mucinous carcinoma* (see Fig. 10.89) which includes cases formerly classified as mucinous bronchioloalveolar carcinomas and overlaps with descriptions of colloid carcinoma and cystadenocarcinomas,³¹⁹ *adenocarcinoma with enteric (goblet cell)*³²⁰ and *hepatoid*³²¹ differentiation, *adenocarcinoma with rhabdoid features*,³²² *microcystic adenocarcinoma*³²³ (a pattern that overlaps with cribriform carcinomas³²⁴), and *adenocarcinoma with massive lymphocytic infiltration*.³²⁵

It should be remembered that a lepidic growth pattern (lining of tumor cells along alveolar walls) is not unique to primary adenocarcinomas of the lung and also occurs in metastatic tumor types,

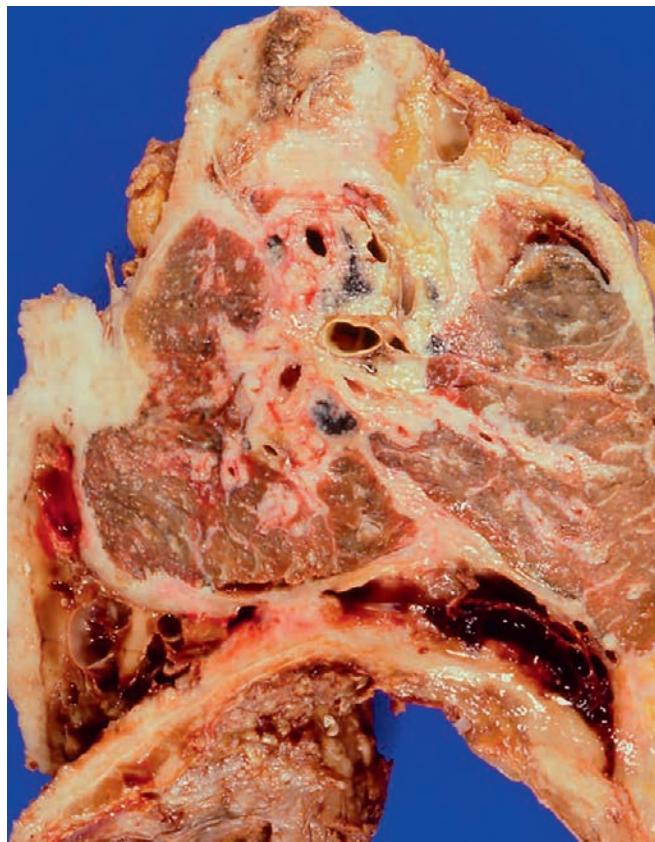


Figure 10.82 Peripheral adenocarcinoma of lung spreading diffusely to pleural surfaces and closely simulating the gross appearance of malignant mesothelioma. Note metastases in intrapulmonary peribronchiolar lymph nodes.

including those arising from breast and thyroid which may also be TTF-1 positive.³²⁶ The frequency of TTF-1 staining in adenocarcinomas arising from sites other than lung and thyroid (e.g. breast, colon, pancreaticobiliary tract, ovary, endometrium) is heavily dependent on the antibody clone that is used; of the most commonly used commercially available antibodies 8G7G3/1 (Dako) is less sensitive but more specific than SPT24 (Leica/Novocastra) which is more

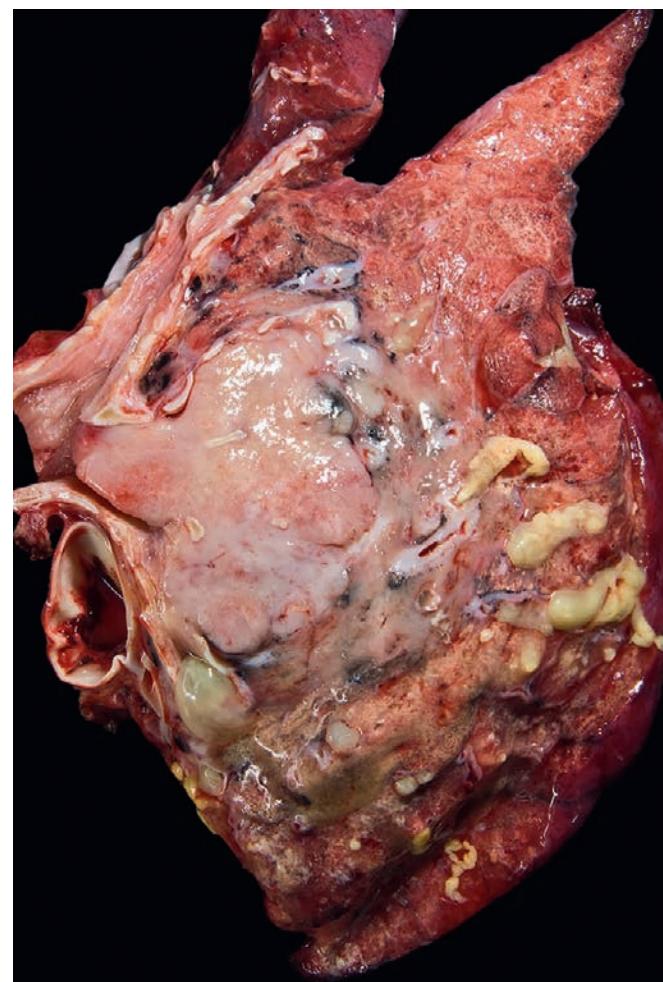


Figure 10.83 Endobronchial polypoid adenocarcinoma with post-obstructive bronchiectasis and obstructive 'golden' (endogenous lipid) pneumonia. (Courtesy of Dr. J. Carvalho, Minneapolis, MN.)

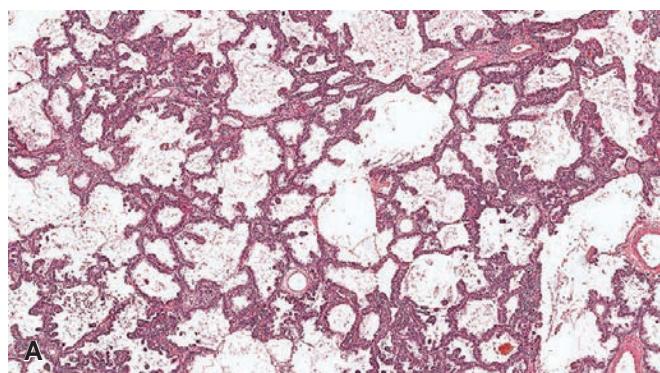
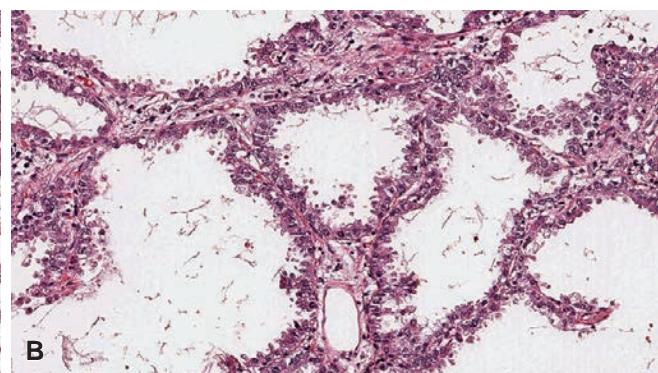


Figure 10.84 Lepidic (bronchioloalveolar) growth pattern that predominated in this minimally invasive adenocarcinoma. Overall architecture is preserved (**A**) with neoplastic nonmucinous columnar cells distributed along interstitial surfaces (**B**).



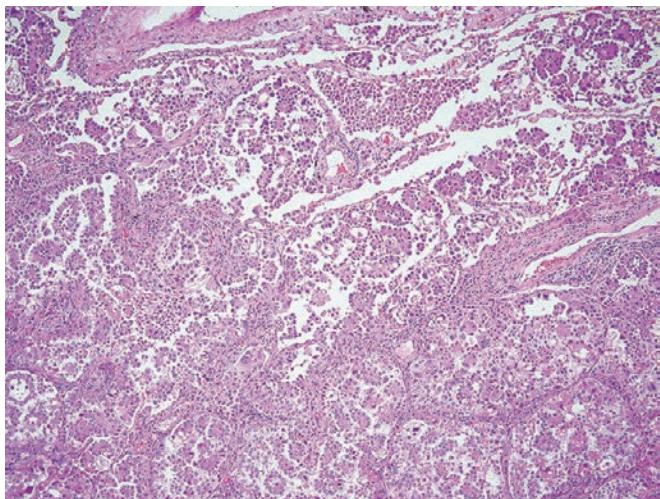


Figure 10.85 Micropapillary adenocarcinoma.

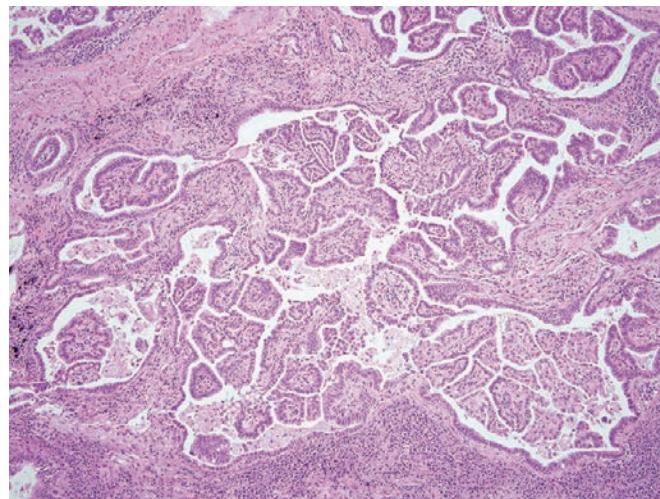


Figure 10.88 Papillary adenocarcinoma.

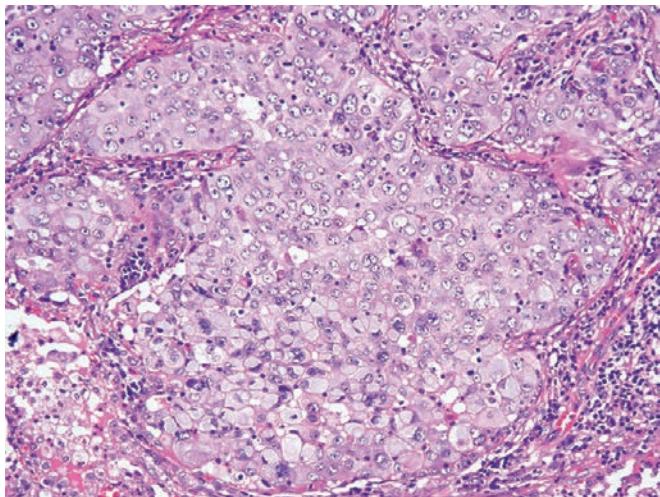


Figure 10.86 Solid adenocarcinoma indistinguishable from large cell carcinoma except for focal positivity with a mucin stain and an immunostain for TTF-1.

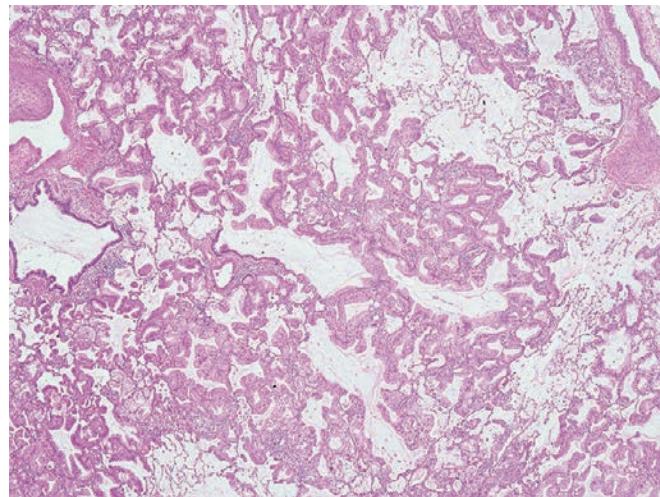


Figure 10.89 Invasive mucinous adenocarcinoma.

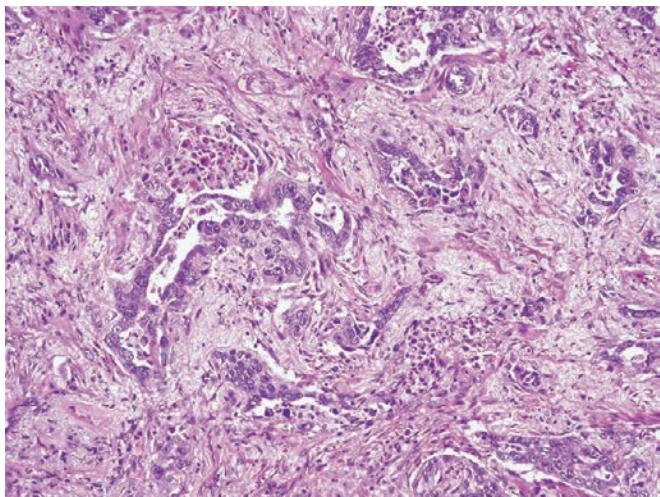


Figure 10.87 Acinar adenocarcinoma with desmoplastic stromal response.

likely to show unanticipated TTF-1 staining in tumors from other sites.³²⁷

Pagetoid spread within the mucosa of large bronchi has been reported only rarely in primary adenocarcinomas of the lung.³²⁷

Immunohistochemically, adenocarcinomas of the lung are usually positive for low-molecular-weight keratins (sometimes with coexpression of vimentin³²⁸), EMA, CEA, secretory components, MOC-31, Ber-EP4, TAG-72, BG-8, and various members of the MUC family.³²⁹ Expression of keratin 7 has been taken as evidence of glandular differentiation in lung carcinoma but is not specific and occurs in a substantial number of squamous cell carcinomas.³²⁶ TTF-1 and napsin A are positive in most cases, as previously summarized. The usual negativity for CDX2 is helpful in the differential diagnosis with metastatic colorectal adenocarcinoma, but this does not apply to a subset of lung adenocarcinomas with enteric differentiation, including some mucinous carcinomas.^{319,330} Similarly, their usual negativity for estrogen receptors (ERs) is helpful in the differential diagnosis with metastatic breast carcinoma but is not an absolute criterion given that focal ER positivity occurs in fewer than 10% to nearly 30% of lung adenocarcinomas, depending on the antibody used.³³¹ In about half of cases there is positivity for surfactant

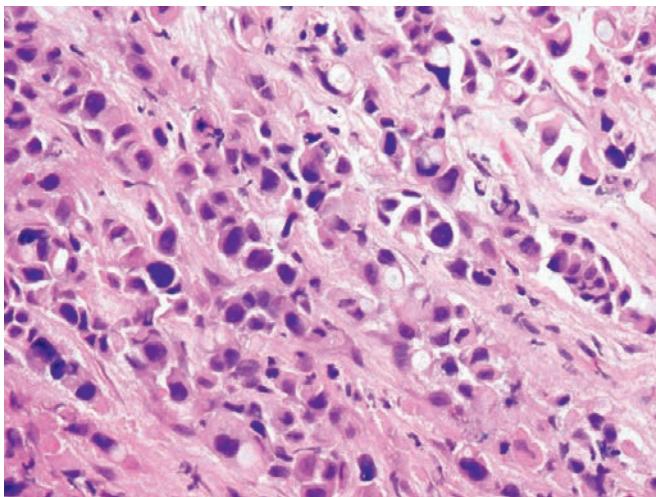


Figure 10.90 TTF-1- and mucin-positive primary pulmonary adenocarcinoma with signet ring cells.

apoprotein (PE-10), a feature of potential utility in the differential diagnosis with other types of primary lung carcinoma and with metastatic adenocarcinoma, although its value as a diagnostic tool has been largely supplanted by TTF-1 which is more sensitive and specific.³³² Lung adenocarcinomas also show consistent expression of Lewis X and Y blood group antigens, a feature that may be of some differential diagnostic value in separating benign from malignant epithelial proliferations.³³³ Adenocarcinomas with Clara cell differentiation are immunoreactive for DC-LAMP, a molecule normally expressed in mature dendritic cells that is also expressed in endometrial adenocarcinomas.³³⁴

Pulmonary adenocarcinomas, like other histologic types of non-small cell carcinomas, harbor multiple genetic and epigenetic alterations.^{335,336} TP53 mutations, most commonly in the form of point mutation and sometimes homozygous deletion, are found in about 50% of cases.³³⁷ Mutations in KRAS were second in frequency to TP53 in the large comprehensive molecular profiling of lung adenocarcinomas performed by The Cancer Genome Atlas (TCGA) Research Network and were associated with cigarette smoking, as were high fractions of C greater than A nucleotide transversions (*transversion-high*) in individual genes and genome wide.³³⁶ The detection of KRAS oncogene activation in lung adenocarcinomas from former and current smokers suggests that KRAS mutations constitute an early and irreversible event in the development of smoking-related adenocarcinomas. Other driver mutations demonstrated in TCGA analysis of lung adenocarcinomas included EGFR (14%), BRAF (10%), PIK3CA (7%), MET (7%), RIT1 (2%); tumor-suppressor genes STK11 (17%), KEAP1 (17%), NF1 (11%), RB1 (4%), and CDKN2A (4%); chromatin-modifying genes SETD2 (9%), ARIDIA (7%), and SMARCA4 (6%); RNA-splicing genes RBM10 (8%) and U2AF1 (3%); and MGA (8%), a gene encoding a protein important in the MYC pathway.³³⁶ KRAS and EGFR mutations are also present in *atypical adenomatous hyperplasia*, a putative adenocarcinoma precursor defined as a small (≤ 0.5 cm) localized proliferation of mildly to moderately atypical nonmucinous columnar cells without significant associated inflammation and/or fibrosis.³³⁷ EGFR mutations are mutually exclusive of KRAS mutations and occur at a significantly higher frequency in adenocarcinomas from East Asians than from non-Asians, from women than from men, and from never-smokers than from ever-smokers.^{338,339} The importance and details of *molecular* testing for specific abnormalities is discussed in a subsequent section on treatment.

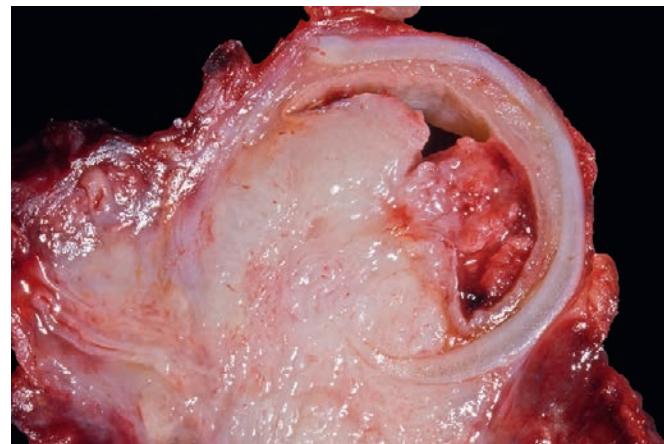


Figure 10.91 Intraluminal bronchial growth of squamous cell carcinoma. (Courtesy of Dr. J. Carvalho, Minneapolis, MN.)

There is a rapidly growing list of molecular abnormalities other than single gene mutations that play important roles in the pathogenesis of lung adenocarcinomas. Specific translocations of the *ALK* (anaplastic lymphoma kinase) gene, with the usual fusion partner (*EML4*) also from the 2p chromosome (i.e. inversion), occur in fewer than 10% of lung adenocarcinomas, depending on the population studied.³⁴⁰ *ALK*-translocated pulmonary adenocarcinomas show the following characteristics: occurrence in never-smokers or light smokers, younger patient age, and lack of mutations in the *EGFR*, *KRAS*, and *TP53* genes.³⁴¹⁻³⁴³ These tumors tend to show a solid growth pattern, often with signet ring cell morphology.³⁴²⁻³⁴⁴ There has been great interest and enthusiasm in this minor subset of adenocarcinomas because inhibitors that target *ALK* tyrosine kinase yield objective responses in nearly three-fourths of patients and longer progression-free survival on average compared with standard chemotherapy.³⁴⁵ Given the potential impact of these sorts of targeted approaches to therapy, molecular testing for *EGFR* mutations and *ALK* rearrangements (a list that has expanded to include other potentially targetable genetic and epigenetic abnormalities in many laboratories) are now endorsed by multiple pathology organizations and the American Society of Clinical Oncology as the standard of care for selected patients with adenocarcinoma of the lung.^{346,347}

Squamous Cell Carcinoma

Squamous cell carcinomas are the second most common form of lung carcinoma, accounting for a third of incident lung cancers in males and 20%–25% of lung cancers in females.³⁰⁴ Most cases are centered in segmental bronchi (Fig. 10.91) and therefore present as hilar or perihilar masses in chest radiographs and CT scans. The bronchial mucosa adjacent to the tumor usually shows squamous metaplasia and sometimes carcinoma *in situ*, occasionally extending several centimeters from the main mass. Rarely, squamous cell carcinoma presents as an endobronchial polypoid mass with only minimal spread beyond the bronchial wall.³⁴⁸ As a consequence of their tendency to involve central airways, exfoliated malignant cells are more commonly identified in sputum or brushing cytology specimens than for other types of lung carcinoma. Signs of bronchial obstruction, such as obstructive pneumonia or atelectasis, are found in approximately half of the patients presenting with centrally located tumors. The tumors have a special tendency to undergo central necrosis with cavitation (Fig. 10.92). Calcification is unusual. Squamous cell carcinomas can also be found peripherally and even subpleurally.^{349,350} When they do, they may fill the alveolar lumens

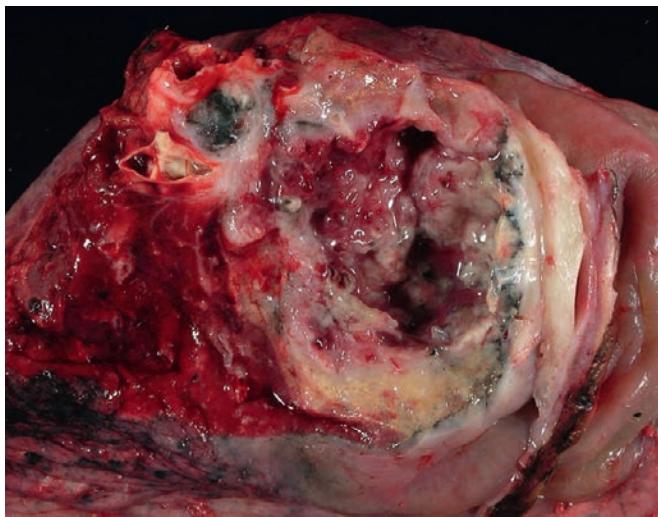


Figure 10.92 Large squamous cell carcinoma associated with central cavitation.

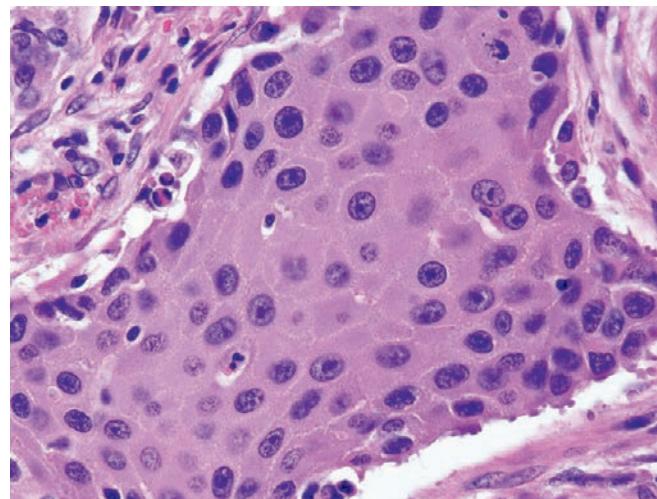


Figure 10.94 Microscopic appearance of squamous cell carcinoma with intercellular bridges.

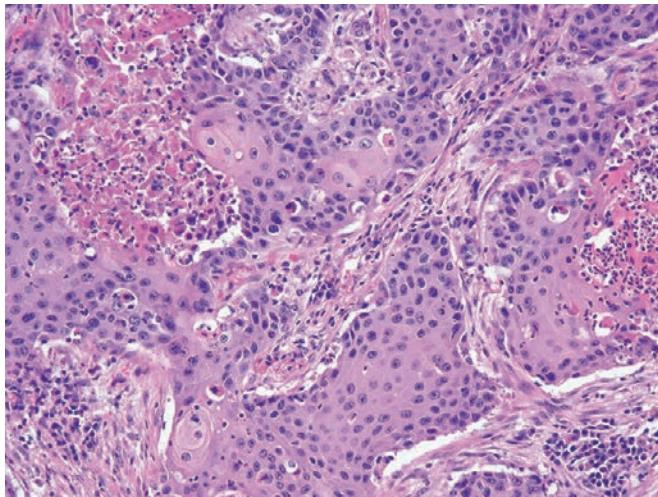


Figure 10.93 Microscopic appearance of squamous cell carcinoma with keratinization and necrosis.

in a lepidic-like fashion, mimicking a growth pattern more typically associated with adenocarcinomas.³⁵¹ A predominant alveolar space-filling growth pattern in small, early stage, peripheral tumors may predict a more favorable outcome in squamous cell carcinomas much as a lepidic growth pattern does in adenocarcinomas.³⁵²

Microscopically, the diagnosis of malignancy is based on cell atypia and invasion, and the diagnosis of squamous cell type on the detection in hematoxylin and eosin sections of keratinization and/or intercellular bridges (Figs. 10.93 and 10.94).³⁵³ Keratin formation may be seen in isolated cells or, more commonly, in the form of 'keratin pearls.' Isolated necrotic cells should not be confused with keratinized cells. Strong, diffuse staining for markers of squamous differentiation such as CK5/6 (high-molecular-weight cytokeratins) and/or p63 or p40 is also sufficient to classify an otherwise nonclassifiable poorly differentiated non-small cell carcinoma as a squamous cell carcinoma.³⁵³

The finding of an occasional intracytoplasmic mucin droplet in an otherwise typical squamous cell carcinoma should not lead to a reclassification of the tumor. Only when at least 10% of the sampled tumor comprises a histologically distinct

matous component is the designation of *adenosquamous carcinoma* justified.³⁵⁴

Other morphologic features that can be encountered in squamous cell carcinoma include oncocytoid appearance of the tumor cells (due to increased mitochondrial density); giant cell foreign body reaction to keratin; palisaded granulomas; and extensive infiltration by neutrophils and other inflammatory cells. Further subclassification into *small cell*, *clear cell*, and *papillary variants* is of limited value beyond describing the range of histologic features that may complicate differential diagnosis.

The exception is *basaloid squamous cell carcinoma*, a poorly differentiated carcinoma analogous to the homonymous tumor arising in the upper aerodigestive tract (see Chapter 4) with a characteristically lobulated growth pattern and peripheral palisading of neoplastic cells (Fig. 10.95A).³⁵⁵ A subset of these tumors show focal and abrupt keratinization; more commonly they are nonkeratinizing carcinomas with a pattern of diffuse immunoreactivity for p63 and/or p40 characteristic of squamous differentiation (see Fig. 10.95B). Immunostains are also positive for antibodies directed against high-molecular keratins such as CK5 or CK5/6 but are negative for TTF-1. Focal staining for neuroendocrine markers is seen in a minority of basaloid squamous cell carcinomas. This is an important subgroup of centrally occurring carcinomas characterized by an aggressive clinical course similar to that seen with other same stage poorly differentiated squamous cell carcinomas.^{356,357}

Squamous cell carcinomas are graded into well, moderately, and poorly differentiated on the basis of the amount of keratinization present. Electron microscopic examination shows abundant tonofilaments, complex desmosomes, and basal lamina formation (Fig. 10.96).

Immunohistochemically, there is consistent staining for low- and high-molecular-weight keratins as well as p63 and p40, as previously outlined. Of the most commonly available antibodies directed against high-molecular-weight keratins, CK5/6 shows greater specificity than 34βE12 and is the antibody of choice for distinguishing squamous cell carcinomas from adenocarcinomas in the lung.²⁸⁴ GATA3 is positive in only about 10% of squamous cell carcinomas of the lung, which may be helpful in distinguishing lung primaries from cutaneous and urothelial metastases.³⁵⁸ Desmocollin-3 and glyican-3 are additional proteins more commonly expressed in squamous cell carcinomas than adenocarcinomas for which there are commercially available antibodies.^{359,360}

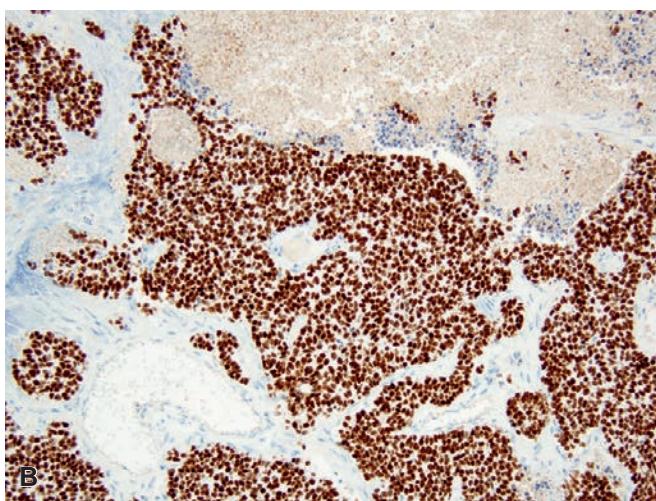
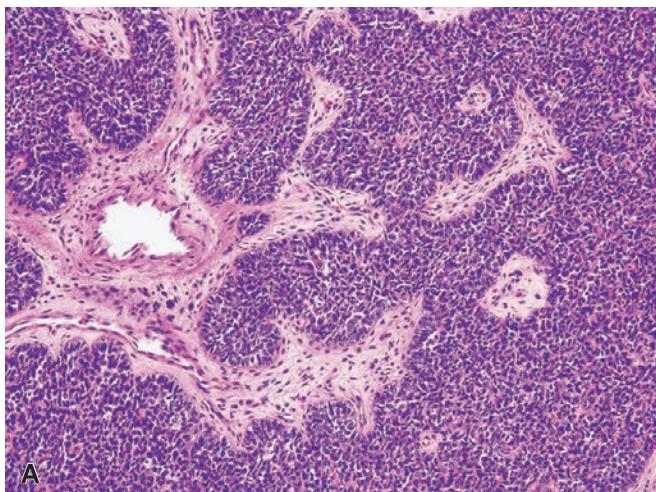


Figure 10.95 Basaloid squamous cell carcinoma with characteristic lobulated growth pattern (A) and diffusely positive staining for p63 (B).

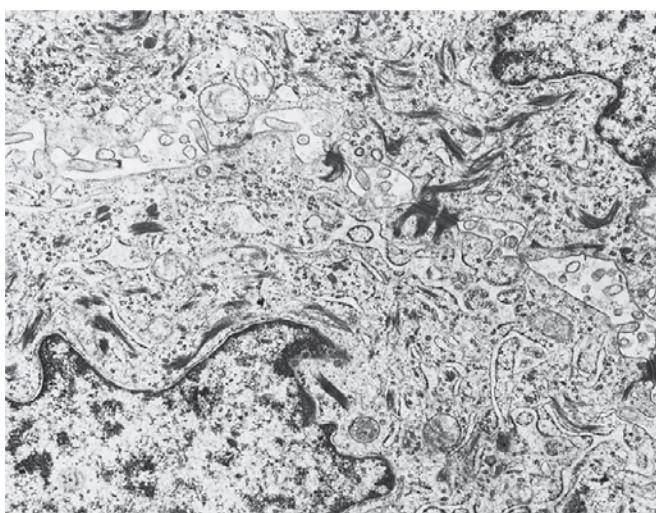


Figure 10.96 Squamous cell carcinoma of lung. Neoplastic cells with numerous tonofilaments, some of them attached to desmosomes. This is characteristic of squamous differentiation (x16,850).

HPV has been documented in a minority of squamous cell carcinomas and in some adenocarcinomas, with a prevalence that is highly variable depending in large part on geographic origin.³⁶¹ HPV 16 and 18 are the most commonly detected high-risk genotypes, but their role in carcinogenesis remains uncertain.^{264,362}

At the genetic level, the most common alterations are somatic mutations in *TP53* and inactivation of *CDKN2A* through epigenetic silencing, inactivating mutations, and homozygous deletion.³⁶³ Other frequently altered genes include a subset involved in squamous differentiation (*SOX2*, *TP63*, *NOTCH1*, *NOTCH2*, *ASCL4*, *FOXP1*) and another group that regulate the oxidative stress response (*KEAP1*, *CUL3*, and *NFE2L2*).³⁶³

Neuroendocrine Tumors

Neuroendocrine lung tumors include two high-grade variants, *small cell carcinoma* and *large cell neuroendocrine carcinoma*, an intermediate-grade category termed *atypical carcinoid tumors*, and low-grade *typical carcinoid tumors*. *Tumorlets* and *diffuse neuroendocrine cell hyperplasia* are two overlapping lesions more likely to present as diffuse multifocal disease in contrast to the other neoplasms included in this category. Small cell carcinoma and large cell neuroendocrine carcinoma are high-grade neuroendocrine carcinomas for which there are low rates of interobserver agreement even among experts in consistently separating one from the other.³⁶⁴ This may be of limited significance given overlapping natural histories in clinical studies, overlapping immunophenotypes, and emerging molecular profiling studies showing that they tend to cluster together but are separate and distinct from atypical and typical carcinoid tumors.^{365,366}

Small cell carcinoma comprises 10%–20% of incident lung cancers in the United States.³⁰⁴ Incidence rates in men and women have been converging toward parity since the 1980s and early 1990s.²⁴⁶ Small cell carcinoma, like squamous cell carcinoma, shows a very strong dose-dependent association with cigarette smoking; nearly all affected patients are current or former smokers.³⁶⁷ Small cell carcinoma is disseminated (stage III or IV) at the time of diagnosis in around 90% of patients; 10% have limited stage disease for which therapeutic options may include surgical excision.^{368,369}

Small cell carcinoma is typically a lesion of the central portions of the lung, but occasionally it is found in a peripheral location. Grossly, the tumor is white-tan, soft, friable, and extensively necrotic. When centered in a large bronchus (the usual situation), it may involve it in a circumferential fashion and/or spread widely beneath the normal mucosa (Fig. 10.97). The bronchus may be totally occluded in the late stages, but pure or predominant endobronchial involvement is unusual.

Microscopically, small cell carcinoma should be viewed as a distinctive tumor type rather than as an undifferentiated form of lung cancer. The histologic pattern is generally solid or sheetlike, combined with other growth patterns commonly affiliated with neuroendocrine differentiation including a nested or organoid architecture, often with peripheral palisading of neoplastic cells, ribbons, trabeculae, and rosettes or pseudorosettes.³⁷⁰ Necrosis is common and is usually extensive.

The 'pure' form of small cell carcinoma is characterized by small round or oval cells resembling lymphocytes (Fig. 10.98).³⁷¹ The nuclei are finely granular and hyperchromatic, nucleoli are inconspicuous, mitoses are frequent, and the cytoplasm is so scanty as to be almost unrecognizable in routine preparations. In some instances the cells have a spindle shape. Nuclear 'molding,' a change first described in cytologic smears, can also be appreciated in microscopic preparations and is a consequence of scant cytoplasm relatively free of intermediate filaments. In rare cases, small cell carcinomas that are otherwise typical may contain scattered giant tumor cells.³⁷² A very common



Figure 10.97 Small cell carcinoma of the lung. The tumor is growing diffusely along the wall of a lobar bronchus and its branches.

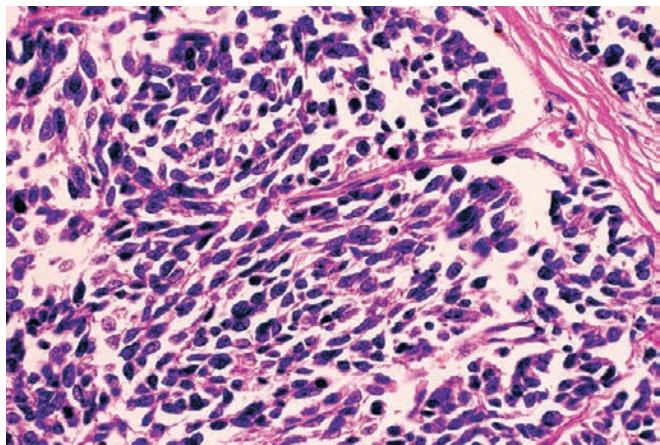


Figure 10.98 Small cell carcinoma showing cells with darkly staining oval to spindle nuclei and extremely scanty cytoplasm.

artifact, particularly prominent in small biopsy specimens, is elongation of the nuclei, with deformation, clumping, and diffusion of the chromatin (Fig. 10.99). If present throughout the specimen, it may make the diagnosis impossible on a biopsy specimen, although correlation with corresponding cytology specimens is often very

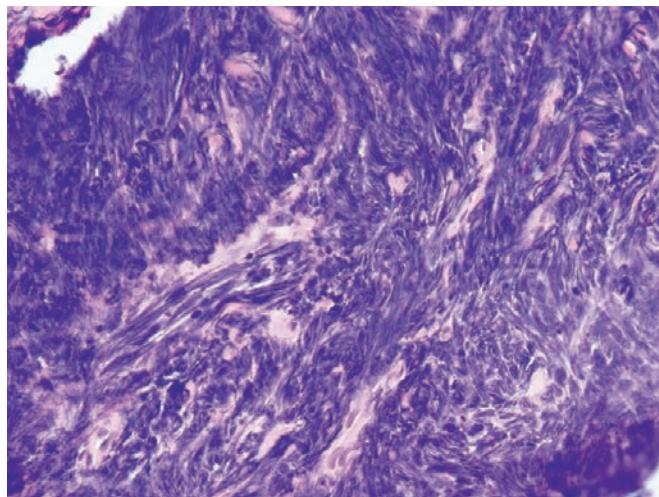


Figure 10.99 Small cell carcinoma in bronchial biopsy with extensive crush artifact making diagnosis all but impossible in this field.

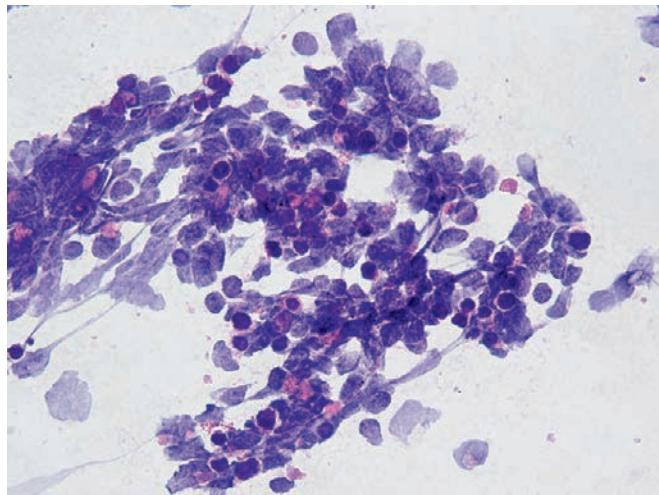


Figure 10.100 Small cell carcinoma smear from endobronchial ultrasound-guided fine-needle aspiration of subcarinal lymph node.

helpful (Fig. 10.100).³⁷³ Another artifact, often referred to as the *Azzopardi effect*, that is sometimes seen in small cell carcinomas is chromatin diffusion and encrustation of blood vessel walls, which appear strongly hematoxyphilic (Fig. 10.101).

Interestingly, the classic appearance of small cell carcinoma is seen almost exclusively in small biopsies. In specimens obtained from lymph node or distant metastases or from the rare resection specimens of the primary tumor, the tumor cells are usually larger and with more abundant cytoplasm.³⁷⁰ This suggests that some degree of artifactual shrinkage is at least partially responsible for the 'small cell' phenotype which may contribute to the challenge in separating from large cell neuroendocrine carcinoma.

Historical subclassifications of small cell carcinoma were primarily based on cytologic criteria, subdividing small cell carcinomas into *oat cell*, *intermediate cell*, and *mixed small and large cell* categories. These classification schemes lacked reproducibility and had no consistent clinical or biologic significance, instead reflecting a range of cytologic heterogeneity in these high-grade neuroendocrine carcinomas heretofore too narrowly defined.^{374,375} Both the 2004 and 2015 WHO tumor classification schemes regard small cell carcinoma as a single entity that, like all other forms of lung

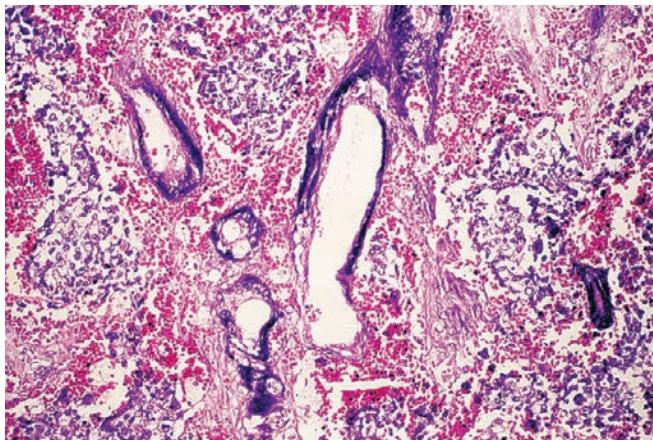


Figure 10.101 Small cell carcinoma with extensive necrosis associated with hematoxyphilic staining of the vessel walls (so-called 'Azzopardi effect').

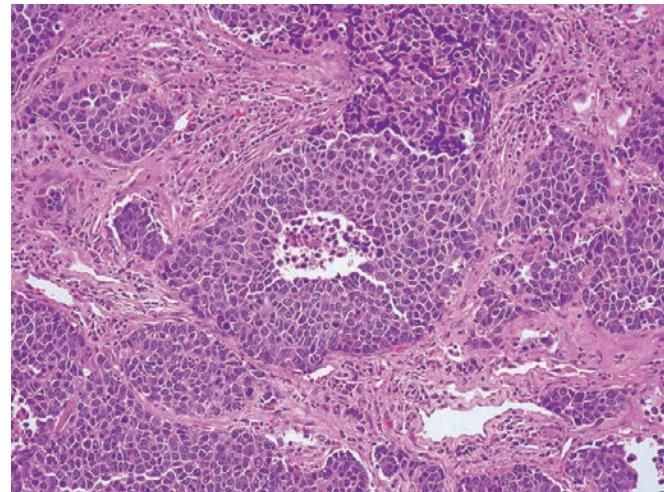


Figure 10.103 Large cell neuroendocrine carcinoma with a nested ('organoid') growth pattern, characteristic pattern of necrosis and numerous mitoses.

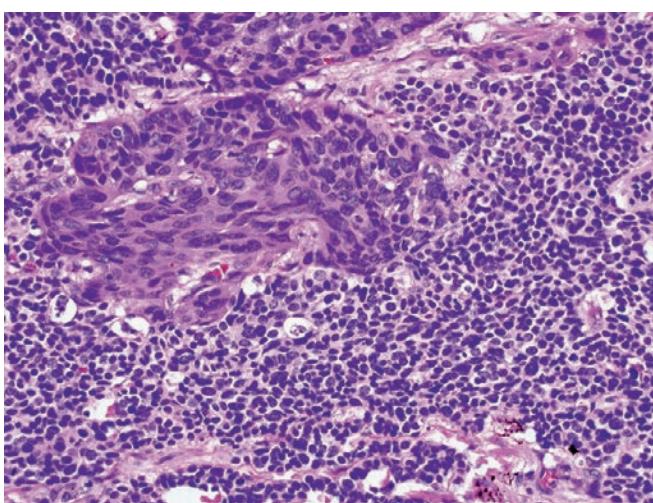


Figure 10.102 Combined small cell-squamous cell carcinoma.

carcinoma, can present in a 'pure' form or admixed ('combined') with other cell types.³⁷¹ **Combined small cell carcinoma** is uncommon and is defined as a small cell carcinoma combined with a second component comprising squamous cell carcinoma, adenocarcinoma, or rarely variants of sarcomatoid carcinoma (Fig. 10.102).

The key factor in determining whether a lung tumor belongs to the small cell category or not, in either a pure or a combined form, is not the detection of neuroendocrine differentiation (as discussed in the following paragraph) or the nuclear size, but rather the chromatin and nucleolar patterns as determined by light microscopic examination of routinely stained material.³⁷³ The chromatin should be finely dispersed, without prominent clumps; more importantly, nucleoli should be inconspicuous or absent altogether.

Immunostains are of limited value in establishing a diagnosis of small cell carcinoma but are frequently useful to narrow the differential diagnosis, especially in small biopsies.³⁷³ Nearly all small cell carcinomas are positive for keratins, especially low-molecular-weight keratins.^{373,376,377} This is useful in distinguishing small cell carcinoma from lymphoma, a tumor that can mimic the clinical, radiological, histologic, and cytologic features of small cell carcinoma. Immunostains can be especially helpful in separating small cell carcinoma from basaloid variants of squamous cell carcinoma given that small cell carcinomas are usually negative or show only focal staining of isolated tumor cells for high-molecular-weight cytokeratins

(e.g. 34 β E12 and CK5/6), p63, and p40.³⁷⁷ TTF-1 is positive in about 80%–90% of small cell carcinomas, another feature that distinguishes small cell carcinomas from basaloid squamous cell carcinoma.³⁷⁸ The proliferation rate, as measured with Ki-67 (MIB-1), is almost 100%, a key finding in the differential diagnosis with carcinoid and atypical carcinoid tumor on small biopsies.³⁷⁹ Stains for neuroendocrine markers are of limited value because as many as 40% of small cell carcinomas may be negative for synaptophysin and chromogranin. CD56 is more sensitive but less specific. At the same time nearly a third or more of conventional non-small cell carcinomas show evidence of neuroendocrine differentiation using a three-antibody panel (chromogranin, synaptophysin, and CD56 or CD57).³⁸⁰

At the molecular genetic level, small cell carcinoma is characterized by a deletion in chromosome 3 (p14–p23) in almost 100% of cases, mutation of TP53 in over 80%, inactivating mutations of the RB gene in over half, and amplification of MYC, SOX2, and FGFR1 in a minority.^{381,382} Mutations in KRAS and EGFR are rarely found.³⁸²

Large cell neuroendocrine carcinoma is another form of high-grade neuroendocrine carcinoma with substantial histologic, immunophenotypic, molecular, and clinical overlap with small cell carcinoma. Like small cell carcinoma it is strongly associated with a history of heavy cigarette smoking. Large cell carcinoma is defined by a neuroendocrine architecture under the microscope (i.e. organoid, trabecular, peripheral palisading, and rosette-like structures), relatively large cells with prominent nucleoli and variably abundant cytoplasm, a high (>10 mitoses per 2 mm²) mitotic rate, necrosis, and immunohistochemical evidence of neuroendocrine differentiation (Fig. 10.103). The neuroendocrine architecture distinguishes large cell neuroendocrine carcinoma from other high-grade non-small cell carcinomas that happen to have neuroendocrine differentiation, the mitotic rate separates it from atypical carcinoid tumors, and the combination of prominent nucleoli and more abundant cytoplasm is what separates large cell neuroendocrine carcinoma from small cell carcinoma. Cell size by itself is of limited value given considerable overlap with small cell carcinoma.³⁸³

Carcinoid Tumor

Carcinoid tumors comprise less than 1% of primary lung cancers.³⁸⁴ Pulmonary carcinoid tumors are separated into *typical* and *atypical* categories based on a combination of necrosis and mitotic rate.

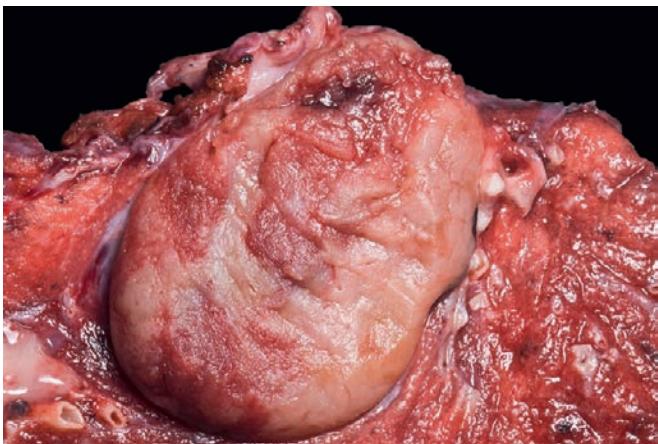


Figure 10.104 Central carcinoid tumor showing well-circumscribed quality situated within a large bronchus. (Courtesy of Dr. J. Carvalho, Minneapolis, MN.)

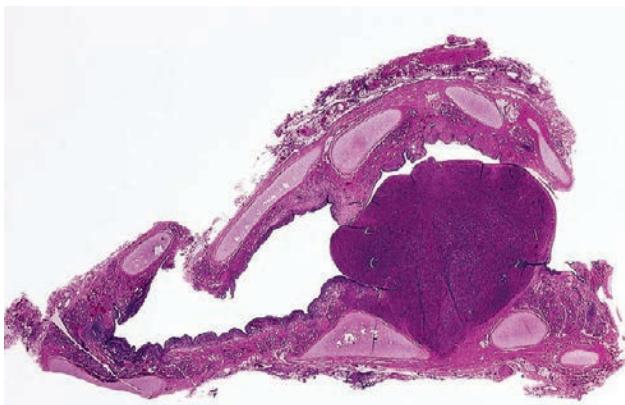


Figure 10.105 Whole mount of central carcinoid tumor showing polypoid endobronchial growth.

Typical carcinoid tumor is the most common of the neuroendocrine lung tumors, known in the distant past as bronchial adenoma.³⁸⁵ It usually presents as a slow-growing, solitary polypoid mass within a major bronchus (Figs. 10.104 and 10.105); because of its location and highly vascular stroma, hemoptysis and postobstructive pulmonary infection are common. About one-fourth of typical carcinoid tumors occur peripherally and are more likely to be detected as asymptomatic solitary lung nodules. Most cases occur in adults, but they can also develop in children, in whom they are the most common primary malignant lung neoplasm.³⁸⁶ The gender incidence is almost equal in adults and children. Most cases are endocrinologically silent at the clinical level. However, patients with carcinoid syndrome and elevated urine 5-HIAA have been documented. ACTH-secreting typical and atypical carcinoid tumors are also a rare but important potential cause of Cushing syndrome.³⁸⁷

Grossly, typical carcinoid tumors are predominantly endobronchial neoplasms with an intact, nonulcerated mucosal surface and limited infiltration through the bronchial wall to the surrounding parenchyma. Marked invasion of adjacent lung parenchyma is uncommon, however, and more commonly signifies an atypical carcinoid tumor.³⁸⁸ Peripheral tumors are grossly nonencapsulated but well circumscribed, variegated gray to tan-brown, and focally hemorrhagic nodules with no anatomic relationship to a bronchus (Fig. 10.106).



Figure 10.106 Peripheral carcinoid tumor showing characteristic subpleural location and well-circumscribed configuration.

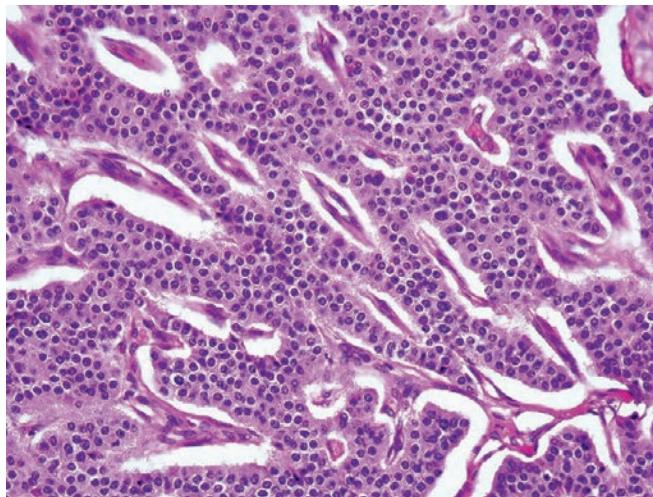


Figure 10.107 Carcinoid tumor showing characteristic architecture and cytology.

Microscopically, carcinoid tumors are well circumscribed with limited invasion of adjacent lung tissues.³⁸⁸ They are composed of intermediate-size uniform cells having central nuclei, small nucleoli, and a moderate amount of finely granular cytoplasm (Fig. 10.107). Occasionally, prominent nuclear (*endocrine-type*) pleomorphism comprising a combination of hyperchromasia and anisonucleosis is seen in the absence of necrosis or mitoses; this feature by itself is not sufficient to place the tumor in the atypical carcinoid category. Neoplastic cells form compact nests, ribbons, and festoons³⁸⁵; pseudopapillary or a true papillary growth pattern is rare.³⁸⁹ Small glands with a rosette-like appearance are only rarely present. Vascularity is pronounced and is the reason that bronchoscopists may choose not to biopsy endobronchial lesions with the gross appearance of a carcinoid. Tumor cells may be seen within lymph vessels in or around the tumor, a finding of no prognostic significance.

Microscopic variants of carcinoid tumor are relatively uncommon but may complicate differential diagnosis. Spindle cell carcinoid tumors are composed predominantly of spindle cells that may closely simulate the appearance of nonepithelial tumors, including smooth muscle neoplasms and monophasic synovial sarcoma (Fig. 10.108).

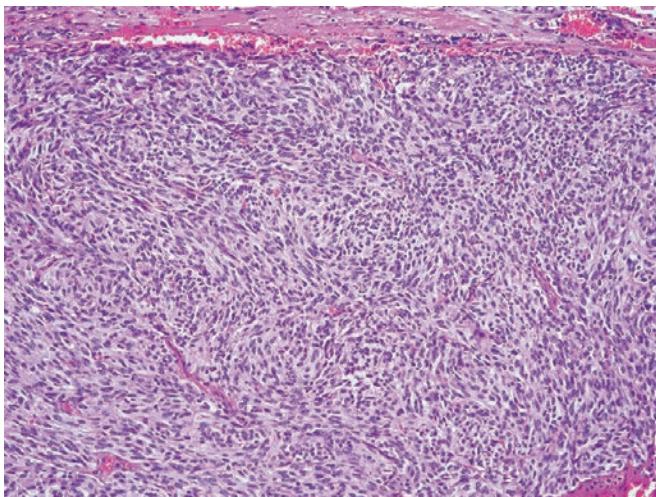


Figure 10.108 Spindle cell appearance of peripheral carcinoid tumor, which may simulate a mesenchymal neoplasm.

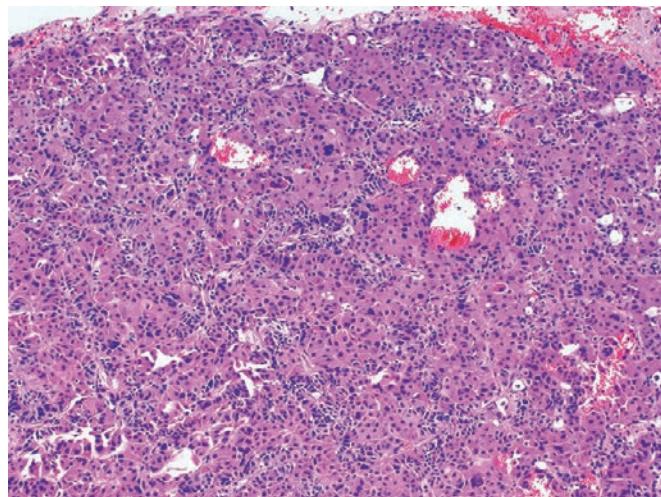


Figure 10.110 Oncocytic variant of carcinoid tumor.

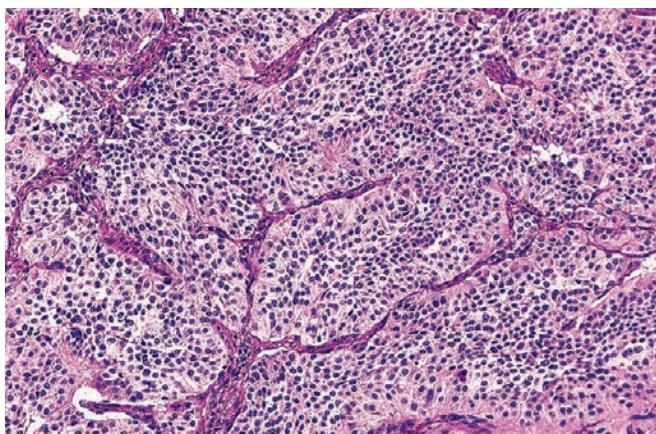


Figure 10.109 Central carcinoid tumor with paraganglioma-like pattern of growth.

The arrangement of the cells is less orderly and the nuclei smaller and more hyperchromatic with finely divided chromatin and higher N:C ratios sometimes mimicking small cell carcinoma.³⁹⁰ Spindle cell carcinoids are more commonly peripheral in location, frequently presenting as asymptomatic solitary nodules, but can also occur centrally. As in the case of more classical appearing carcinoid tumors, spindle cell carcinoids may acquire paraganglioma-like features, including the presence of S-100 protein-positive sustentacular cells (Fig. 10.109).³⁹¹ Oncocytic variants are less common but may be confused with higher-grade lesions, given the tendency toward nuclear pleomorphism and prominent nucleoli (Fig. 10.110).³⁹² In exceptional cases, carcinoid tumors contain melanin granules in the tumor cells ('melanotic carcinoid tumor').³⁹³ The stroma in carcinoids can be heavily sclerotic or hyalinized and may exhibit focal calcification or ossification.³⁹⁴

Immunohistochemically, there is variable but usually positive reactivity for keratin and a broad array of neuroendocrine markers, including neuron-specific enolase, chromogranin A and B, synaptophysin, CD56, and neurofilaments.³⁸⁴ In addition, many peptide hormones have been detected in individual tumors, sometimes in combination. In addition to many neuroendocrine-type markers, carcinoid tumors display immunoreactivity for the transcription factor TTF-1 in over half of the cases (higher in the peripheral

type).^{378,395-397} whereas they are consistently negative for CDX2 and PAX8, thus rendering these three markers important tools for the differential diagnosis between primary and metastatic carcinoid tumors in the lung from the gastrointestinal tract and pancreas, respectively.^{398,399} Carcinoid tumors with a prominent nesting pattern of growth may acquire a 'paraganglioid' appearance, which is accentuated by the presence of S-100 protein-positive sustentacular cells at the periphery of the nests (see Fig. 10.109).

Carcinoid tumors demonstrate a low mutation burden compared with other higher-grade primary lung neoplasms and usually lack the TP53 and RB1 mutations more common in high-grade neuroendocrine lung tumors. Comprehensive molecular profiling has demonstrated mutually exclusive driver mutations in genes affecting histone methylation (MEN1/PSIP1) and ATP-dependent chromatin-remodeling (ARID2, SETD1B and STAG1).⁴⁰⁰

From a diagnostic viewpoint, central carcinoid tumors are easily identifiable with the bronchoscope in the majority of cases. Bronchoscopic biopsy is usually positive, although severe hemorrhage may result because of the marked vascularity of the tumors. The microscopic diagnosis is generally easy, although small samples with crush artifact can be confused with small cell carcinoma, as we have seen on several occasions. A Ki-67 (MIB-1) immunostain can be very useful in this circumstance, since it will be positive in nearly all cells of a small cell carcinoma but usually in less than 10% of the cells of a typical carcinoid.^{379,401}

The treatment is surgical.⁴⁰² Removal through the bronchoscope is not sufficient because of the potentially infiltrative nature of the tumor. Depending on the location of the tumor along the bronchial tree and the status of the distal lung, the operation may be a segmental bronchial resection, a lobectomy (the usual procedure), or a pneumonectomy. Metastases to regional lymph nodes occur in about 5% of the cases and are usually limited to N1 nodes, a finding that has no impact on the generally excellent prognosis affiliated with typical carcinoid tumors.⁴⁰³

Atypical carcinoid tumor not only exhibits the overall architectural, ultrastructural, and immunohistochemical features of carcinoid tumor, but also exhibits atypical features in the form of increased mitotic activity (2–10 mitoses per 2 mm²) and/or foci of necrosis (Fig. 10.111).⁴⁰⁴ These have been referred to as *atypical carcinoid tumors*. Like their typical counterparts, they express various neuroendocrine and neural markers with the same relative frequencies⁴⁰⁵ and may be occasionally accompanied by amyloid deposition in the stroma.⁴⁰⁶ Historically, atypical carcinoid tumors were thought to represent a

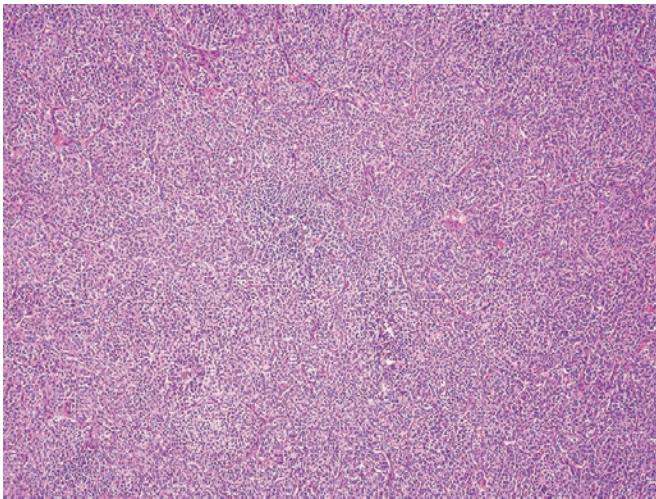


Figure 10.111 Atypical carcinoid tumor.

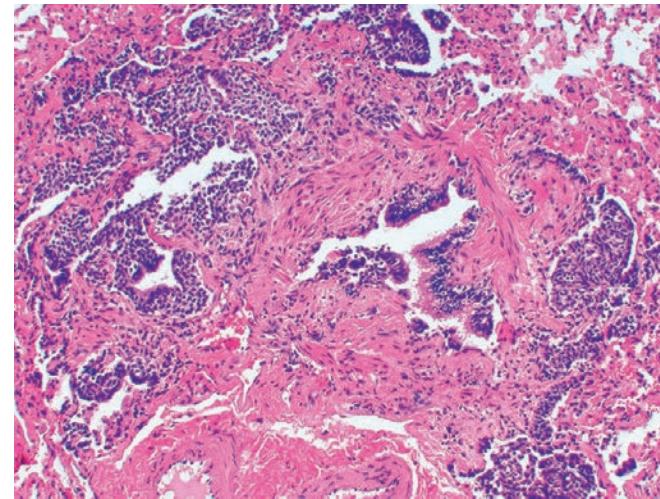


Figure 10.112 So-called pulmonary tumorlet.

link between typical carcinoid tumor and small cell carcinoma. There is now strong molecular evidence against it,^{365,366,400} but there is no question that, for prognostic and therapeutic purposes, typical carcinoid tumors should be sharply separated from the atypical variety given marked differences in natural history and survival.^{388,404,407} In one surgical series the incidence of lymph node metastases for atypical carcinoid was just over 35%, as opposed to an incidence of about 9% for the typical carcinoid.⁴⁰⁸ The authors concluded that the treatment for surgical candidates should be more aggressive and not substantially different from that for ordinary lung carcinoma of non-small cell type, including conventional resection and radical mediastinal lymphadenectomy.^{408,409} In this large series, the 5-year survival of atypical carcinoid was 78% and dropped to 60% in those with nodal involvement. Features of adverse prognostic significance are female gender, large tumor size, nodal involvement, higher mitotic rates, marked invasion into adjacent lung parenchyma, and lymph vessel invasion.^{388,407,408}

The role of Ki-67 staining in routinely separating carcinoid tumors of the lung into meaningful groups is unresolved. In several studies subclassification using current WHO mitotic rate cutoffs outperformed Ki-67 labeling index in predicting disease progression and survival.^{410,411} Others have argued that Ki-67 staining is more reproducible than current histologic criteria for grading neuroendocrine lung tumors and separating them into prognostically useful categories.^{412–414}

Tumorlet (carcinoid tumorlet) is the term given to a nodular proliferation of small spindle cells seen in relation to bronchioles, often in association with bronchiectasis and other conditions associated with scarring including intralobular sequestration (Fig. 10.112). Tumorlets are frequently multiple and in rare cases are affiliated with a *diffuse* proliferation of airway-associated neuroendocrine cells in a condition referred to as *diffuse idiopathic pulmonary neuroendocrine hyperplasia* (DIPNECH) (Fig. 10.113).⁴¹⁵ Cases with multiple tumorlets may also be affiliated with one or more carcinoid tumors, thus mimicking the radiological appearance of metastatic disease in patients being followed for other malignancies.⁴¹⁶ Exceptionally, one may find tumorlet-like nests of neuroendocrine cells in intrathoracic lymph nodes, a finding that should not be misconstrued as evidence of metastatic disease.⁴¹⁷

Pulmonary tumorlets closely resemble spindle cell carcinoid tumors, differing mainly in size, distribution, and histologic context. An arbitrary size criterion of 0.5 cm has been used to distinguish between tumorlet and carcinoid tumor given their overlapping histologic and cytologic features. The fact that at the cytogenetic

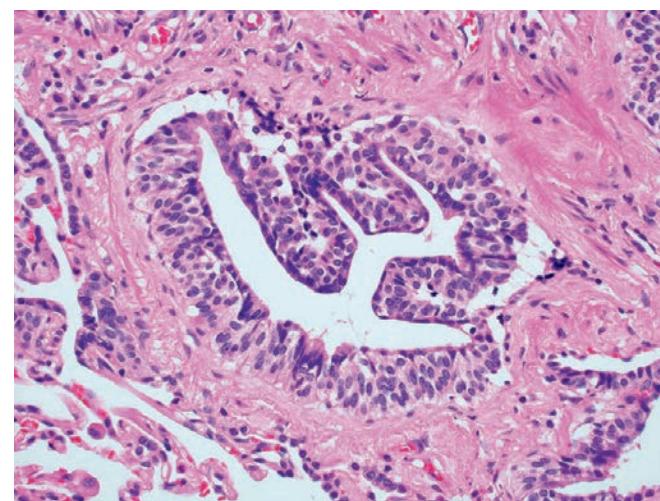


Figure 10.113 Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia in a patient with multiple carcinoid tumorlets.

level tumorlets generally lack the 11q13 allelic imbalance that is characteristic of carcinoid tumors suggests a different molecular pathogenesis for the two lesions and provides a potential tool for their distinction.⁴¹⁸

The behavior of tumorlet is generally benign, although isolated instances of metastatic behavior have been reported. The main practical importance is that they can be misdiagnosed radiographically and microscopically for lung metastases, especially in patients with a history of breast carcinoma.^{416,419}

Large Cell Carcinoma

Large cell carcinomas are pleomorphic malignant epithelial tumors without cytologic, histologic, or immunophenotypic features of adenocarcinoma, squamous cell carcinoma, small cell carcinoma, or large cell neuroendocrine carcinoma.⁴²⁰ The tumor cells are large, at least in comparison with those of small cell carcinoma, and demonstrate marked nuclear pleomorphism and variably abundant cytoplasm mimicking other pleomorphic poorly differentiated tumors, such as melanoma and lymphoma (Fig. 10.114). Many high-grade

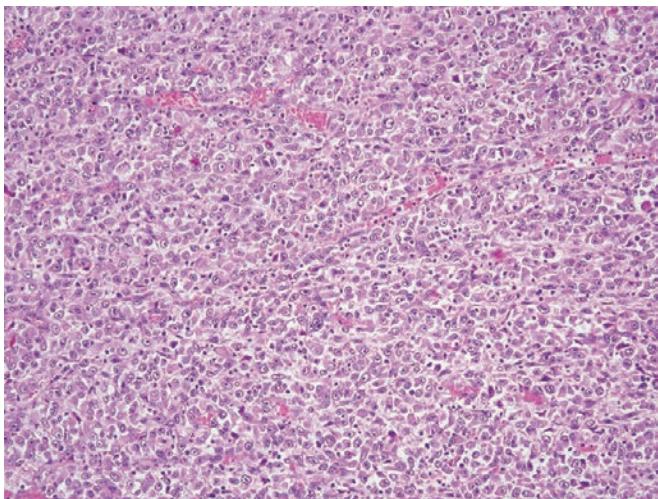


Figure 10.114 Large cell carcinoma.

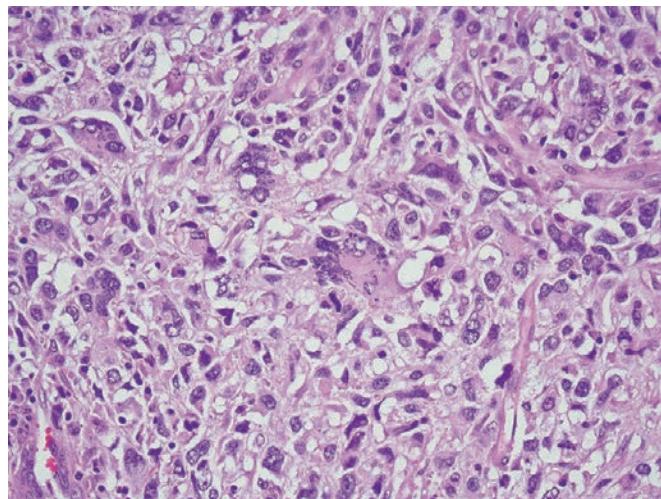


Figure 10.116 Prominent neoplastic giant cells in a sarcomatoid ('giant cell') carcinoma.

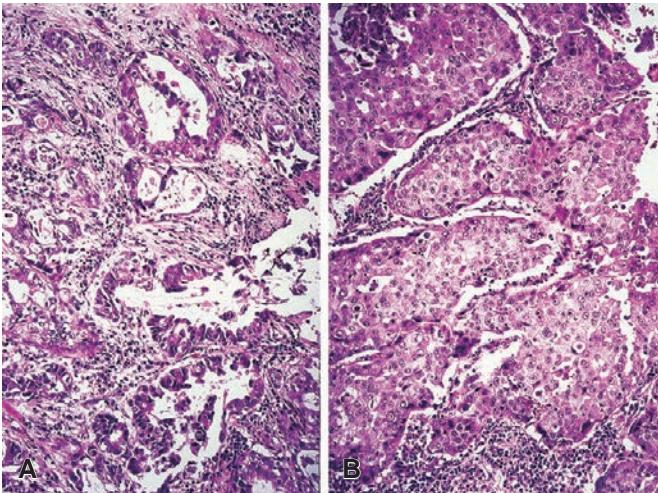


Figure 10.115 Adenosquamous carcinoma of lung showing an admixture of glandular (A) and squamous (B) components in the same tumor.

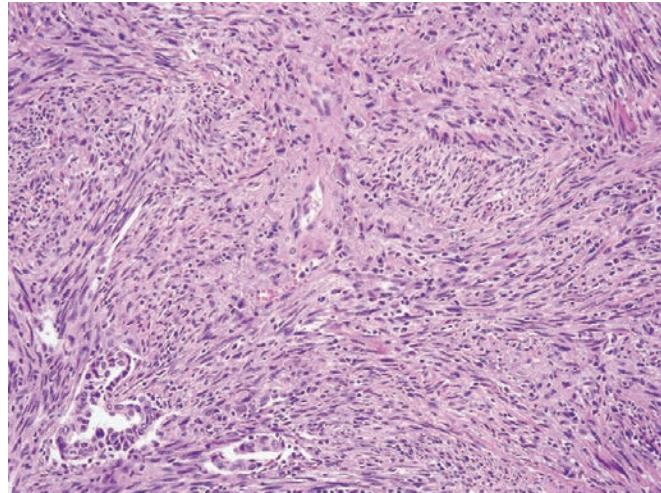


Figure 10.117 Prominent spindle cells in a sarcomatoid ('spindle cell') carcinoma.

non-small cell carcinomas historically assigned to this category are now considered poorly differentiated adenocarcinomas and squamous cell carcinomas based on the results of immunohistochemical and molecular studies. This applies to previously included variants like basaloid carcinomas, lymphoepithelioma-like carcinomas, clear cell carcinomas, and large cell carcinomas with rhabdoid phenotype.^{421,422} Large cell neuroendocrine carcinoma has been recategorized with other neuroendocrine lung tumors. As a consequence large cell carcinomas represent a smaller and smaller subset of lung carcinoma types. Large cell carcinomas accounted for only 4% of lung carcinomas in a review of two large national databases accruing incident cases from 2004 to 2009, and declined from a rate of six cases per 100,000 person-years in the 1990s to about 1 case per 100,000 person-years in 2010 in another study.²⁴⁶

Adenosquamous Carcinoma

The term adenosquamous carcinoma is used for lung tumors in which distinct areas of squamous and glandular differentiation are found in the same neoplasm, each accounting for at least 10% of

the sampled tumor (Fig. 10.115).³⁵⁴ Squamous cell carcinomas having occasional mucin-producing cells or adenocarcinomas with minute foci of squamous differentiation are named according to their predominant component. Thus defined, adenosquamous carcinomas account for less than 5% of lung cancers. Most of the cases are located peripherally and often are associated with a scar, suggesting a closer relationship with adenocarcinoma than with squamous cell carcinoma.

Sarcomatoid Carcinoma and Carcinosarcoma

As in other organs, there exists in the lung a family of carcinomas having sarcoma-like features referred to generically as *sarcomatoid carcinomas*.⁴²³⁻⁴²⁵ Further subtyping of these tumors is of limited biologic or clinical significance and is dependent upon minor variations in their microscopic appearance and the histogenetic biases of the observer. When composed predominantly of tumor giant cells, they have been designated as *giant cell carcinomas* (Fig. 10.116). When predominantly composed of spindle cells but still identifiable as epithelial on morphologic, ultrastructural, or immunohistochemical

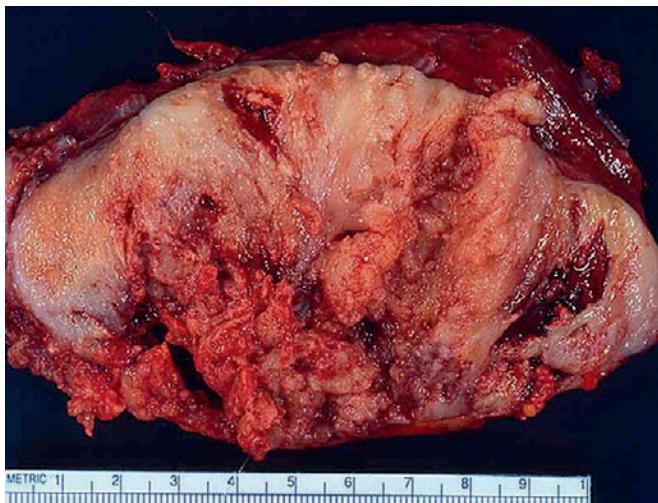


Figure 10.118 Sarcomatoid carcinoma with extensive necrosis.

grounds, they have been called *spindle cell carcinomas* (Fig. 10.117). Some authors have applied the term *pleomorphic carcinoma* to tumors in which there are both giant cell and spindle cell components, often in combination with a more histologically classic component of adenocarcinoma, squamous cell carcinoma, or undifferentiated non-small cell ('large cell') carcinoma. When the carcinomatous and sarcoma-like components are segregated and the latter demonstrates heterologous elements (e.g. chondrosarcoma, osteosarcoma, rhabdomyosarcoma), the term *carcinosarcoma* has been used. Studies of large series of cases with morphologic, immunohistochemical, and molecular techniques have rendered apparent the fact that these represent various manifestations of the same biologic phenomenon, by which neoplastic cells derived from pluripotent stem cells lose in part or completely their epithelial phenotype and acquire characteristics of mesenchymal cells, a phenomenon sometimes referred to as epithelial–mesenchymal transition.^{426,427}

Grossly, these tumors can appear either as intraparenchymal or endobronchial polypoid masses that are frequently large and partially necrotic (Fig. 10.118).⁴²⁵ Microscopically, the identifiable epithelial elements, when present, may show squamous differentiation, glandular differentiation, or be undifferentiated, thus resembling large cell carcinoma (Fig. 10.119). The sarcoma-like component may be nondescript, or resemble chondrosarcoma, osteosarcoma, rhabdomyosarcoma, or angiosarcoma. Osteoclast-like giant cells can be present, resulting in histologic features resembling those seen in giant cell tumor of bone. As indicated, the interface between the carcinomatous and the sarcoma-like components can be indistinct or sharp. Bronchoscopic or needle biopsy may show one or both elements.

The immunostains traditionally used to support the presence of epithelial differentiation in sarcomatoid carcinomas, albeit in a less than specific fashion, are pankeratin, EMA, and p63.⁴²⁸ Immunostains for TTF-1 are also useful in a surprising number of cases of sarcomatoid lung carcinomas.⁴²³ There remain a minority of cases in which immunostains may fail to show convincing evidence of epithelial differentiation in sarcomatoid components. In this circumstance, knowledge of the radiological distribution of disease is helpful given that sarcomatoid carcinomas often present as large, bulky solitary lung masses with or without intrathoracic adenopathy.

The prognosis of this tumor is poor, overlapping with same-stage poorly differentiated non-small cell carcinomas of other histologic subtypes.⁴²⁹

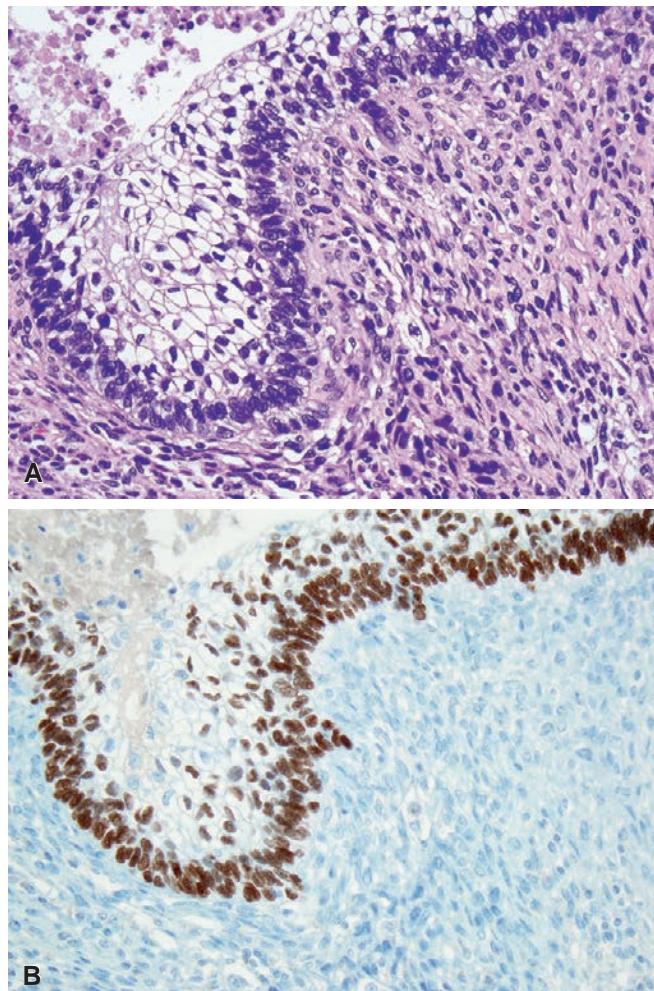


Figure 10.119 Sarcomatoid ('pleomorphic') squamous cell carcinoma showing a spindle cell component and an epithelial component with squamous differentiation demonstrating clear cell change (A); staining for p63 was limited to the squamous component (B).

Pulmonary Blastoma

Pulmonary blastoma typically presents in adults, in contrast to blastomas of other organs. Pulmonary blastoma should not be confused with *pleuropulmonary blastoma* (PPB), a pediatric malignancy with a totally different presentation and morphologic appearance (see p. 428). Pulmonary blastoma usually presents as a peripherally located, solitary, well-circumscribed, large mass grossly resembling other sarcomatoid carcinomas (Fig. 10.120).⁴³⁰ Microscopically, it is characterized by the presence of a well-differentiated adenocarcinomatous component in a cellular stroma composed of undifferentiated small ('blastematos') spindle cells (Fig. 10.121).⁴³¹ The overall appearance resembles fetal lung between 10 and 16 weeks' gestation and is also reminiscent of Wilms tumor.⁴³² The glandular cells often show subnuclear and supranuclear cytoplasmic vacuoles and variably abundant cytoplasmic glycogen. Solid balls of cells with abundant acidophilic cytoplasm ('morules') are common, mimicking the appearance of endometrioid adenocarcinomas; curiously, the nuclei in these formations often have a ground-glass (optically clear) appearance, said to be due to the accumulation of biotin.⁴³³ Taken on its own the epithelial component is indistinguishable from *fetal adenocarcinoma* (referred to historically as *pulmonary endodermal tumor resembling fetal lung*) (Fig. 10.122), the only difference being the



Figure 10.120 Pulmonary blastoma forming a large well-circumscribed necrotic mass.

associated primitive appearing stroma in pulmonary blastoma.⁴³⁴ Both the stromal component and the epithelial component may show divergent or heterologous differentiation, including skeletal muscle, cartilage, or bone in the former and intestinal, yolk sac, and malignant melanoma in the latter. Like other forms of sarcomatoid carcinoma, classical pulmonary blastoma is an aggressive tumor with greater than 50% mortality at 2 years and median survivals of less than 6 months in a small retrospective cohort.⁴³⁰

The occasional presence of combined or transitional forms between pulmonary blastoma and sarcomatoid carcinoma/carcinosarcoma (particularly the latter form) and their similar immunohistochemical and ultrastructural features suggest that they are histogenetically overlapping entities and that in a given case the distinction may not be possible.⁴³⁵ More recently mutations in the β -catenin gene have been identified in fetal adenocarcinoma as well as the epithelial and stromal components of pulmonary blastoma, suggesting that activation of the Wnt signaling pathway may be a distinguishing feature.⁴³⁶ β -Catenin mutations are associated with aberrant nuclear and cytoplasmic localization of β -catenin by immunohistochemistry, a potentially useful diagnostic tool for separating pulmonary blastoma from other forms of sarcomatoid carcinoma.

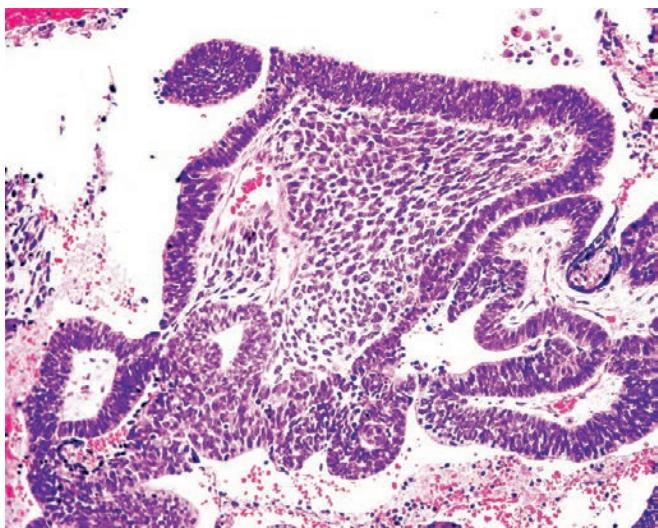


Figure 10.121 Pulmonary blastoma showing typical biphasic pattern of growth and 'fetal' appearance of the epithelial component.

Carcinoma Precursors

Dysplasia and carcinoma *in situ* are the precursors of invasive squamous cell carcinoma. It has been known for a long time that squamous cell carcinomas of the lung have a long preclinical stage in which the lesion progresses from various degrees of dysplasia (mild, moderate, and severe) to carcinoma *in situ*, microinvasive carcinoma, and frank invasive carcinoma.⁴³⁷ This progression is neither obligatory nor linear, making it difficult to assess the risk for developing an invasive carcinoma based solely on histologic grading of preinvasive lesions.⁴³⁸ Detailed morphologic studies of very early cases have demonstrated that most potentially significant squamous cell carcinomas arise unifocally in a segmental bronchus (Fig. 10.123).⁴³⁹ Grossly, the bronchial mucosa may show slight irregularities in the form of granularity, papillation, and loss of rugae, or it may appear unremarkable. Microscopically, the diagnostic criteria are similar to those applied for this diagnosis elsewhere, including a full-thickness change with an intact basement membrane. There is often extension into the ducts of the submucosal glands, a change that may be difficult to distinguish from broad-based early submucosal invasion. The presence of stromal desmoplasia favors the latter. The proliferative index, as measured with Ki-67 (MIB-1), parallels the morphologic changes.⁴⁴⁰ Genetically, early events include loss of heterozygosity at 3p and 9p in squamous metaplasia and dysplasia, followed by TP53 mutations in carcinoma *in situ*, and aberrant coexpression of p53 and EGFR.^{441,443}

The terms 'early invasive' and 'intramucosal' carcinoma have been used somewhat interchangeably (and somewhat inaccurately) to designate tumors exhibiting superficial invasion of the stroma that does not extend to the level of the bronchial cartilage; most of these are well-differentiated to moderately differentiated tumors (Fig. 10.124).⁴⁴⁴ The majority of screening-detected early squamous cell carcinomas show extensive surface involvement with little invasion ('creeping' type); a minority show more deep invasion through the bronchial wall without longitudinal extension along the mucosal surface ('penetrating' type).⁴⁴⁵ The observation that penetrating growth patterns are underrepresented in occult squamous cell carcinomas suggests that they may be more rapidly growing and therefore more likely to present as clinically and radiologically significant tumors.

Atypical adenomatous hyperplasia is thought to be the pre-invasive precursor of nonmucinous BAC and of some peripheral

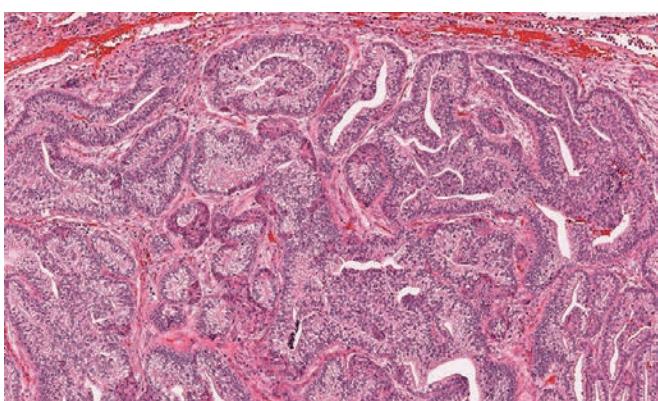


Figure 10.122 Fetal adenocarcinoma (pulmonary endodermal tumor) resembling fetal lung. In contrast to pulmonary blastoma, a mesenchymal component is absent.

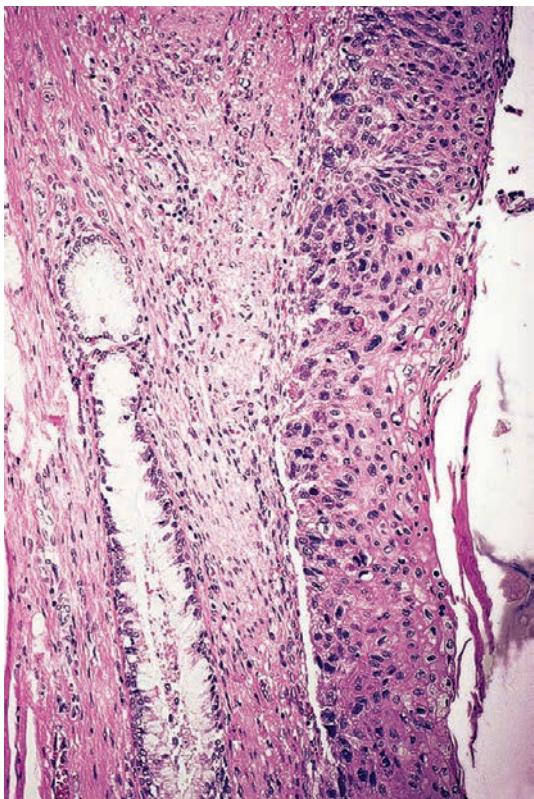


Figure 10.123 Carcinoma in situ of bronchial mucosa.

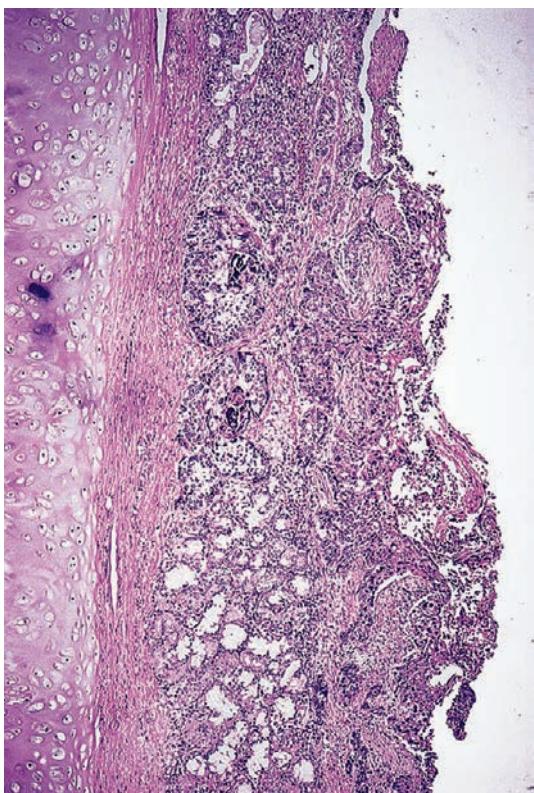


Figure 10.124 Early invasive squamous cell carcinoma of bronchial mucosa.

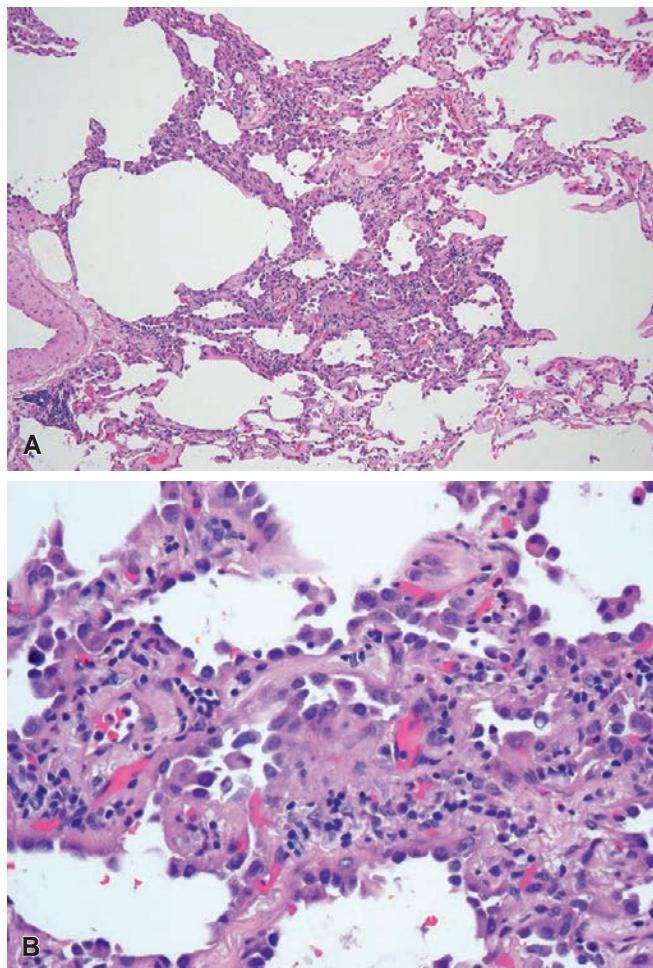


Figure 10.125 Low (A) and high (B) magnification view of atypical adenomatous hyperplasia.

adenocarcinomas.²⁶² Atypical adenomatous hyperplasia represents localized proliferations of mildly atypical nonmucinous columnar cells forming small (generally no larger than 5 mm) peripheral nodules in the absence of underlying inflammation or fibrosis (Fig. 10.125). The nodules of atypical adenomatous hyperplasia can be solitary or multiple and are seen more commonly in resected adenocarcinomas (around 15%–20%) than in resected squamous cell carcinomas (fewer than 5%) and occur more commonly in women than in men.^{446–450} Importantly, the finding of atypical adenomatous hyperplasia in resected lung carcinomas has no impact on outcomes.^{447,451}

Genetically, atypical adenomatous hyperplasia resembles adenocarcinoma in demonstrating mutually exclusive KRAS and EGFR mutations but differs in that the frequency of the two is markedly different, at least in Asian populations, with KRAS mutations more common in atypical adenomatous hyperplasia and EGFR mutations more common in adenocarcinoma.⁴⁵² This difference is aligned with experiments in genetically engineered mice in whom KRAS mutations affecting respiratory epithelial cells is commonly affiliated with atypical adenomatous hyperplasia rather than adenocarcinoma, while the reverse is true for EGFR mutations.^{453,454}

Frozen Section

Frozen section is an important procedure in debatable lesions of the lung and has its greatest value in peripherally located lesions.

In patients with resectable lung carcinoma, bronchoscopic and/or cytologic examination combined with percutaneous image-guided needle biopsy will yield a diagnosis in the majority of the cases. There remain a number of patients who will undergo surgery for suspected cancer without a definite preoperative diagnosis. For peripheral lesions, it is better to excise them entirely with a margin of normal lung. This is usually in the form of a wedge excision. Frozen section is then done. Sometimes, the lesion proves to be a benign process such as a hamartoma, organizing pneumonia, or granulomatous inflammation, in which case no additional surgery is necessary. If it is carcinoma, the surgeon will decide whether to proceed to completion lobectomy, an especially important decision as less-than lobectomy becomes an increasingly viable option for managing patients with early stage screening-detected lung cancers.⁴⁵⁵

Frozen sections are an accurate method for diagnosing small pulmonary nodules, the chief potential pitfalls being the distinction of carcinoid tumors from other lesions and of early noninvasive or minimally invasive adenocarcinomas from atypical adenomatous hyperplasia and non-neoplastic reactive atypia.⁴⁵⁶ Stromal hyalinization, an organoid growth pattern, and spindle cell cytology can be helpful in supporting a diagnosis of carcinoid tumor at the time of frozen section, while a desmoplastic stroma, nuclear pleomorphism, irregular nuclear contours and a mitotic rate above 5 per 10 high powered fields should suggest alternatives.⁴⁵⁷ Accurate diagnosis of small *in situ* or minimally invasive adenocarcinomas at the time of frozen section is especially challenging in smaller (less than 1 cm) lesions and may benefit from more extensive sampling, correlation with findings on CT scans of the chest, and inflation of lung specimens with diluted embedding medium.^{458,459} Observation of multiple growth patterns, variation in cell size, extensive atypia involving at least three-fourths of the area of interest, macronucleoli, and atypical mitoses are features that favor well differentiated adenocarcinomas over reactive atypia.⁴⁶⁰ It is important that pathologists exercise caution in making a diagnosis of well-differentiated adenocarcinoma in the face of significant inflammation and fibrosis. Uncommon tumors, like sclerosing pneumocytoma, can be accurately diagnosed in most cases, especially when frozen section includes careful examination of the gross specimen.⁴⁶¹

Two important contributions of frozen section to the surgical handling of lung carcinoma are the mapping of hilar and mediastinal lymph nodes and the evaluation of the bronchial margin. The latter is particularly valuable for central tumors, particularly those of salivary gland-type, and is less valuable in more peripheral tumors.^{462,463}

Spread and Metastases

Centrally located lung cancer spreads by direct extension proximally and distally along the bronchus of origin and may reach the trachea at the level of the carina. It also grows into the lung parenchyma, from where it may reach the mediastinum or pleura. The latter event may result in seeding in both pleural layers and extension into the chest wall and diaphragm. Pleural effusion is very common under these circumstances. Occasionally, the entire pleural space is seeded in a fashion mimicking mesothelioma (see Fig. 10.82). Invasion of blood vessels is very common (over 80% of the cases); sometimes, this may lead to extensive tumor emboli and *cor pulmonale*, an uncommon phenomenon reported with not only primary lung adenocarcinomas but also metastatic adenocarcinomas, for which breast and stomach are the most commonly reported sites.⁴⁶⁴ It has been postulated that tumor cells also spread through air spaces, with seeding through the air passages and development of secondary deposits at some distance from the main mass.⁴⁶⁵ Indeed observation of spread through air spaces in otherwise low-stage adenocarcinomas

may predict for a greater likelihood of locoregional and distant relapse.

Lymph node metastases occur first in the interlobar and hilar region, then in the mediastinal and lower cervical (supraclavicular) groups, and less commonly in axillary and subdiaphragmatic sites. Skip metastases occur in as many as 25% of patients and may reflect the frequency with which micrometastases are clinically and radiologically occult.⁴⁶⁶ The site of resection, mediastinal lymph nodes, and supraclavicular fossa remain common sites of locoregional relapse after surgical resection independent of nodal status at the time of diagnosis.

Distant metastases are more common in liver, other areas of lung, adrenal, bone and bone marrow, kidney, and central nervous system.⁴⁶⁷ Less common sites include the gastrointestinal tract, pancreas, thyroid, spleen, ovary, pituitary gland, skin, and skeletal muscle. Brain metastases seem to be more common in adenocarcinoma and may be the first manifestation of the disease.⁴⁶⁸ The presence of distant metastases at the time of initial diagnosis is particularly high in small cell carcinoma, although the small subset of patients who present without clinical evidence of locoregional or distant spread may benefit from stage-appropriate surgery.^{368,469}

Treatment

The standard therapy for operable non-small cell carcinoma of the lung is complete surgical excision through video-assisted thoracoscopic surgery or thoracotomy. The excision can be in the form of pneumonectomy, lobectomy, bilobectomy, or less than lobectomy in highly selected patients, depending on the location and type of the tumor. The first successful lung resection for squamous cell carcinoma was performed by Dr. Evarts A. Graham at Barnes Hospital in St. Louis, Missouri, in 1933. The patient, a physician, died 30 years later of an unrelated disease (Fig. 10.126). Ironically, he survived Dr. Graham, who died as a result of lung carcinoma. As illustrated by this historical patient, surgical therapy is regarded as sufficient in cases of early stage disease, whereas a combined modality therapy is usually applied to patients who present with higher tumor stage.

Radiation therapy can effectively control the local growth of lung cancer and sometimes results in long-term survival⁴⁷⁰; however, like surgery, it fails to cure most patients, mainly because as many as 50% of them have distant metastases when diagnosed or shortly following the initial diagnosis. It also has a limited impact on rates of recurrence in the cases showing microscopic evidence of involvement of the bronchial margin. The role of radiation therapy seems to be greater, whether given alone or as a preoperative measure, for tumors of the superior pulmonary sulcus (Pancoast tumor), as an adjunctive measure in the treatment of small cell carcinoma, and when administrated as adjuvant therapy in combination with chemotherapy.

A significant advance in the treatment of lung cancer is exemplified by the success story of tyrosine kinase inhibitors (such as gefitinib, erlotinib, afatinib), which is a showcase of the new paradigm in targeted therapy for cancer. Analysis of several phase III clinical trials has demonstrated that tyrosine kinase inhibitors outperform standard combination chemotherapy in patient with advanced stage non-small cell lung carcinomas harboring *EGFR*-activating mutations.⁴⁷¹ The same effect has been demonstrated using crizotinib, a small molecule inhibitor of ALK, MET, and ROS1 kinases, as first line therapy in patients with advanced stage non-small cell carcinomas positive for *ALK* translocations.³⁴⁵ Promising results have also been demonstrated in a phase I trial of crizotinib in patients with *ROS1* rearrangements who have failed conventional therapy.⁴⁷² These results are the exemplars for the rapidly evolving field of precision ('personalized') medicine and serve as the underpinnings for current recommendations

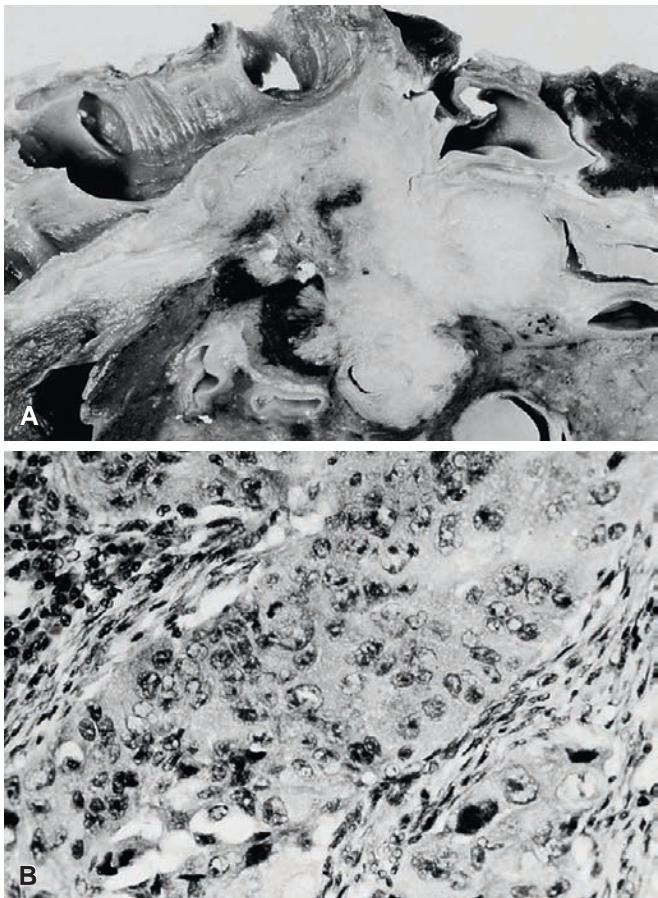


Figure 10.126 **A**, Squamous cell carcinoma of lung resected by Dr. Evarts A. Graham in 1933. Note extension into surrounding lung and involvement of two regional lymph nodes. The patient died in 1962 without evidence of cancer. **B**, Poorly differentiated squamous cell carcinoma shown in **A**.

regarding routine application of molecular testing in patients with advanced or recurrent non-small cell carcinomas.³⁴⁶ Given that small biopsies with insufficient tissue remain a key impediment to molecular testing in these patients it is increasingly important that surgical pathologists remain stewards of these precious patient assets, minimizing utilization of immunostains unlikely to add substantial value and focusing instead on preservation of tissue for the sorts of testing likely to impact important decisions regarding treatment.³³⁹ This is an important paradigm shift in the role of surgical pathologists in not only diagnosing but also managing patients with lung cancer. This shift will apply to a larger and larger pool of patients as new molecular targets are identified in not only adenocarcinomas but also squamous cell carcinomas for which immunotherapy (nivolumab) has already been approved as a potential therapy, although the role of companion diagnostics relevant to surgical pathology is less clear.⁴⁷³

Prognosis

The long-term prognosis of lung carcinoma remains disappointingly poor, with limited improvement having been made in recent years in long-term survival rates. In a recent review of data from the United States collected in the SEER program, 1-year survival rates had increased from 34.4% in 1975–1977 to 44.7% in 2006–2009. But overall 5-year survival rates remained low, at 18.2% for non-small cell lung carcinomas and 6.3% for small cell carcinoma.⁴⁷⁴

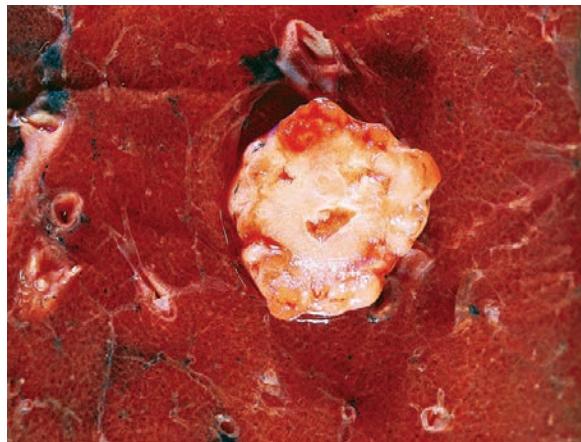


Figure 10.127 Lobulated shape and shiny cut surface of pulmonary hamartoma. (Courtesy of Dr. RA Cooke, Brisbane, Australia. From Cooke RA, Stewart B. *Colour Atlas of Anatomical Pathology*. Edinburgh: Churchill Livingstone; 2004.)

The prognosis of lung carcinomas has been related to a large number of factors, tumor stage chief among them including tumor size and presence or absence of visceral pleural and lymphatic space invasion in those with apparently localized node-negative disease who undergo resection with curative intent.^{475,476} Older age, male gender, and low performance status at the time of diagnosis also influence natural history and prognosis.⁴⁷⁷ Subtyping or grading of non-small cell carcinomas may have value, particularly in cases of early-stage adenocarcinoma in which solid and micropapillary growth patterns predict for lower rates of disease-specific survival.⁴⁷⁸

A burgeoning list of biomarkers suggests a complex interplay of factors that may affect outcome, including selected genetic markers. For example, KRAS mutations have been associated with lower overall survival rates in patients with earlier stage (stage I–IIIa) adenocarcinomas.⁴⁷⁹ Survival of patients with activating EGFR mutations who are treated with tyrosine kinase inhibitors is influenced by the specific type of mutation, with cases characterized by deletions in exon 19 surviving longer than cases with L858R point mutations.⁴⁸⁰ ALK-rearranged cases are overrepresented in patients who present with advanced-stage disease, suggesting that it may predict for a subset of more aggressive adenocarcinomas that tend to affect younger nonsmokers.³⁴²

Other Primary Tumors

Hamartoma

Hamartoma is the most common benign neoplasm encountered in surgical pathology and generally occurs in adults and is more common in males.⁴⁸¹ It is usually solitary but can be multiple. Its most common location is the peripheral lung parenchyma just beneath the pleura, and it presents in most instances as an asymptomatic solitary pulmonary nodule. Endobronchial hamartomas account for only about 10% of cases and are more likely to present with cough or symptoms related to obstruction.⁴⁸² Hamartomas are usually small, measuring less than 2.0 cm on average. Radiographically, a characteristic popcorn pattern of calcification is seen in two-thirds of the cases.⁴⁸³ Grossly, it is sharply delineated and lobulated (Fig. 10.127). The cut surface is characterized by glistening nodules of cartilage separated by ill-defined clefts. A less common presentation is as a polypoid mass inside a large bronchus (Fig. 10.128).⁴⁸³

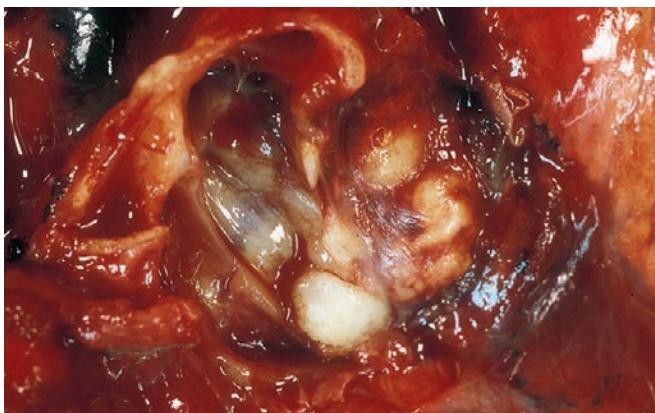


Figure 10.128 Endobronchial hamartoma.

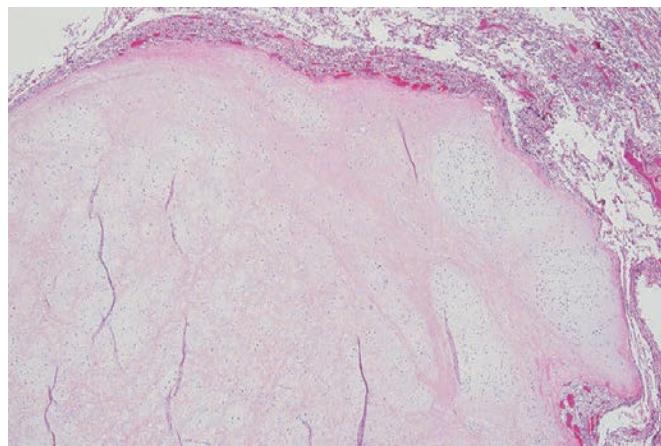


Figure 10.130 Pulmonary chondroma.

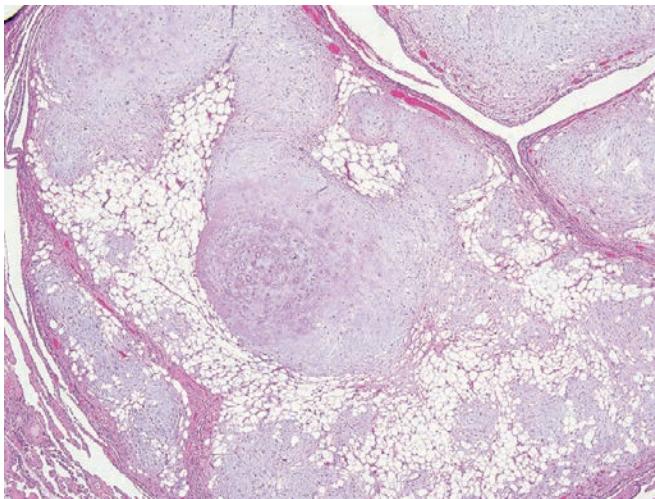


Figure 10.129 Pulmonary hamartoma showing intermingling of hyaline cartilage, fat, myxoid stroma, and non-neoplastic respiratory epithelium.

Microscopically, hamartoma is made up of normal cartilage arranged in islands, fat, smooth muscle, a characteristic myxoid stroma, and clefts lined by ciliated or nonciliated respiratory epithelium (Fig. 10.129). Any one of these components can predominate in any individual tumor, resulting in a range of histologies that include leiomyomas and lipoma. Sometimes exaggerated invagination of non-neoplastic epithelium results in a pattern resembling so-called *placental transmogrification*, characterized by the formation of placental villus-like papillations.⁴⁸⁴

Immunohistochemically, some of the spindle cells of this lesion have features of myoepithelial cells, such as positivity for actin and S-100 protein. The spindle cells in myxoid areas are unique in expressing glial fibrillary acidic protein (GFAP), a finding they have in common with fetal cartilage.⁴⁸⁵ There is also common expression of ER, progesterone receptor (PR), and androgen receptor (the latter only in males), most of it in the myoepithelial-like cells.⁴⁸⁶ We have seen two salivary gland-type tumors with a myoepithelial cell component and a well-differentiated liposarcoma arising from pulmonary hamartoma.^{487,488}

Hamartomas are acquired nonepithelial neoplasms characterized by clonal rearrangements of chromosome 6p21 (implicating the *HMGA1* gene) or chromosome 12q14–15 (implicating the *HMGA2* gene).^{489,490}

The treatment of hamartoma is in the form of conservative surgery usually performed as a diagnostic procedure: wedge resection or

enucleation of peripheral lesions and sleeve resection of endobronchial lesions.

Carney has identified a nonfamilial syndrome ('Carney triad') in which pulmonary chondromas (usually multiple) are associated with gastric epithelioid leiomyosarcomas (most of which would be currently categorized as gastrointestinal stromal tumors, [GISTs]), and functioning extra-adrenal paragangliomas.⁴⁹¹ Pulmonary chondromas differ from the usual hamartomas in being purely cartilaginous with a more sharply circumscribed fibrous pseudocapsule without entrapped, invaginated epithelium (Fig. 10.130).⁴⁹² Pulmonary chondromas also show a broader range of cellularity and cytologic atypia in the neoplastic cartilage.

Paraganglioma and Other Neural Neoplasms

Paragangliomas have been exceptionally described in the lung, presenting as solitary (usually peripheral but sometimes endobronchial) masses.⁴⁹³ Their histologic appearance is identical to that of paragangliomas in other sites. The differential diagnosis with carcinoid tumor may be extremely difficult, even after applying electron microscopic and immunohistochemical techniques, and this had led some authors to doubt the very existence of pulmonary paragangliomas. The presence of ribbons, festoons, rosettes, and positivity for mucin, CEA, and especially keratin, favor carcinoid, whereas a prominent 'Zellballen' pattern throughout the tumor and the presence of a population of S-100 protein-positive sustentacular cells at the periphery of the nests favor paraganglioma.⁴⁹⁴ Excision is usually curative, but metastasizing cases have also been reported.

Other neural tumors that have been described in the lung include *ganglioneuroblastoma*⁴⁹⁵ (one combined with carcinoid tumor⁴⁹⁶) and *gangliocytic paraganglioma*^{497,498} (one associated with Cushing syndrome⁴⁹⁹). It is difficult to escape from the suspicion that these are histogenetically closely related tumors that have been interpreted and named just a little differently. A single example of a purported primary pulmonary ependymoma has been reported.⁵⁰⁰

Minute Meningothelial Nodules and Meningioma

Meningothelial-like nodule (MLN) is the term currently preferred for a curious, usually clinically inconsequential pulmonary lesion originally misinterpreted as pulmonary paraganglioma (chemodectoma).^{501,502} It is generally seen as an incidental finding in surgically

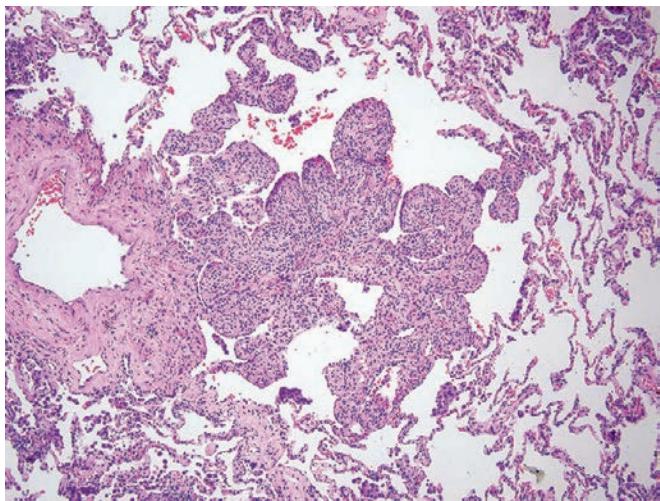


Figure 10.131 Incidentally discovered meningotheelial-like nodule.

excised lungs, the lesions presenting as one or more 1–3 mm tan-yellow nodules randomly distributed within the interstitium (Fig. 10.131).⁵⁰² Occasionally, the lesions are disseminated and bilateral, associated with symptoms of restrictive pulmonary disease.⁵⁰³ Ultrastructural studies have shown a total lack of neurosecretory granules or other features suggestive of neuroendocrine differentiation. The cells have instead an appearance similar to that of normal arachnoidal cells and the cells of meningioma.⁵⁰⁴ Immunohistochemically, they are negative for keratin and positive for vimentin, EMA, CEA, CD56, and PR, a profile again similar to that of meningotheelial cells.⁵⁰² Their genotypic features, however, are different from those of CNS meningiomas⁵⁰⁵ and more in keeping with a reactive than a neoplastic process.

True *meningioma* of lung presenting as a primary solitary nodule has also been described,⁵⁰⁶ including a chordoid⁵⁰⁷ and a malignant variety.⁵⁰⁸ These should be distinguished from 'benign metastasizing meningioma,' a rare but well-documented occurrence.^{509,510}

Sclerosing Pneumocytoma

Sclerosing pneumocytoma, referred to historically as *sclerosing hemangioma*, is a distinctive lesion that occurs mostly in younger adult females, usually detected as an asymptomatic small, solitary nodule on a chest radiograph or CT scan.^{511–516} On serial films, the lesion is found to be stable or, at the most, very slow growing. Grossly, it is a well circumscribed but not encapsulated, solid peripheral, subpleural mass with a variegated tan, yellow, and frequently hemorrhagic cut surface (Fig. 10.132). Microscopically, sclerosing pneumocytoma is characterized by a combination of architectural and cytological heterogeneity, with growth patterns that may be solid, papillary, sclerosing, and hemorrhagic, resulting in a variegated appearance at low magnification (Fig. 10.133). At higher magnification the cytologic heterogeneity results from a combination of bland interstitial round cells that represent the neoplastic population and incorporated non-neoplastic respiratory epithelial cells that line papillary surfaces in a manner analogous to that seen with other slowly growing lesions such as hamartoma (Fig. 10.134).

The histogenesis of this lesion has been highly controversial since its description as an entity, which has been variously proposed to be of endothelial, histiocytic, mesothelial, and epithelial nature.⁵¹⁴ Immunohistochemically, there are two distinct components. One

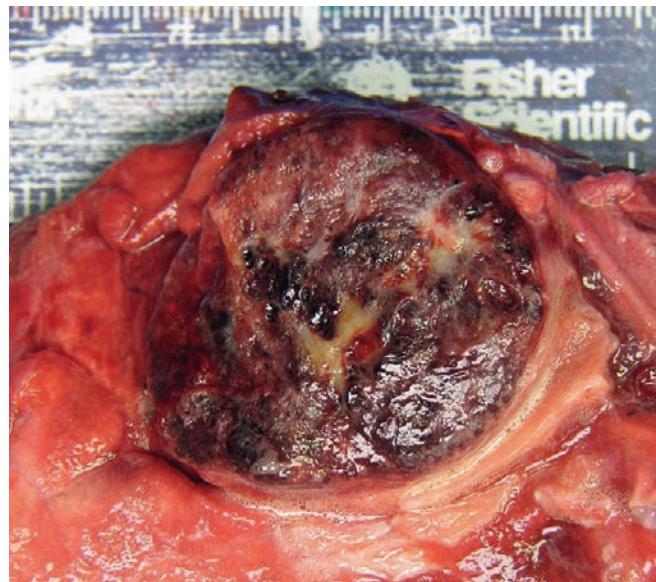


Figure 10.132 Sclerosing pneumocytoma. Yellow solid areas alternate with foci of fresh hemorrhage and fibrosis. (Courtesy of Dr. J. Carvalho, Minneapolis, MN.)

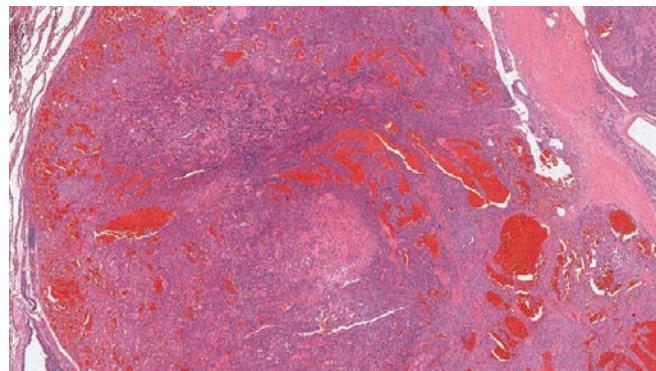
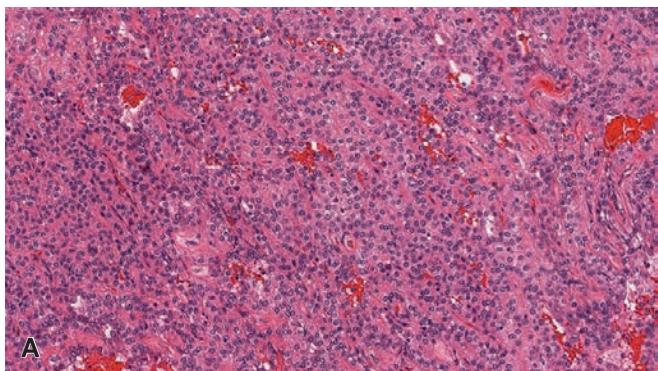


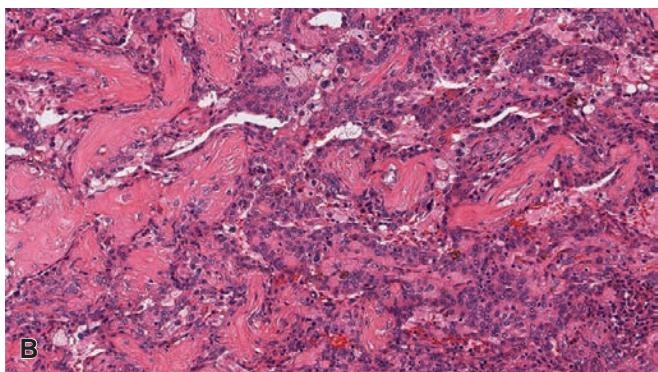
Figure 10.133 Sclerosing pneumocytoma. A variety of growth patterns is appreciated on low-power examination resulting in a characteristic variegated appearance.

(referred to as *surface cells*) is of clearly epithelial nature and reactive for EMA, keratin, CD15, Ber-EP4, apocrine epithelial antigen, surfactant apoprotein, TTF-1, napsin A, and ER beta.^{511–513,516–521} Some of these reactivities correspond to those of type 2 pneumocytes, as supported by the ultrastructural finding of a microvillous-like folding of the cell membrane and lamellar inclusions. The second—and numerically more prominent—component (referred to as *round or stromal cells*) is negative for many of these markers except EMA, ER beta, and TTF-1, features that suggest an origin from primitive respiratory epithelium. The similar pattern of allelic loss that has been found between sclerosing hemangioma and bronchioloalveolar carcinoma also suggests an origin from the terminal lobular unit.⁵²² These observations served as the drivers for adoption of the term *sclerosing pneumocytoma* in the most recent WHO classification scheme.⁵²³

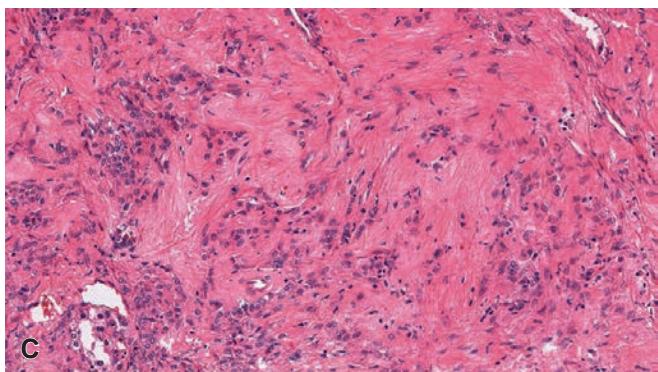
From a clinical standpoint, sclerosing hemangioma is a benign lesion cured by conservative surgery. There are rare reports of local lymph node deposits, but these patients have done well without evidence of distant metastases or tumor-related death.^{512,524}



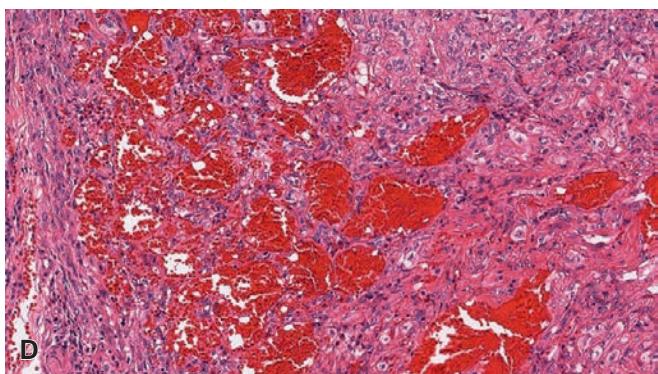
A



B



C



D

Figure 10.134 Sclerosing pneumocytoma. Higher-magnification views of tumor illustrated in Fig. 10.133 show solid (A), papillary (B), sclerotic (C), and hemorrhagic (D) areas. Areas of solid growth (A) show neoplastic round cells while papillary areas (B) show non-neoplastic bronchiolar epithelium lining papillary surfaces.

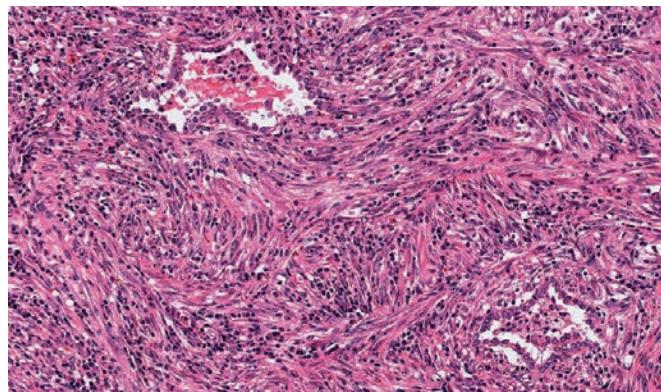


Figure 10.135 Inflammatory myofibroblastic tumor. Elongated myoid cells are heavily infiltrated by plasma cells. Incorporated non-neoplastic respiratory epithelium results in a 'pseudobiphasic' appearance.

Inflammatory Pseudotumor and Inflammatory Myofibroblastic Tumor

There is a group of pulmonary lesions presenting as more or less circumscribed nodules, having as a common denominator the presence of large numbers of mononuclear inflammatory cells. Wide variations on this basic theme occur from case to case or even within the same case and are responsible for the many names and histogenetic interpretations that this group of lesions has received. In addition to inflammatory cells, these variations include vascular proliferation, fibrosis that may take the form of organizing pneumonia, hyalinization, myxoid change, fat accumulation with the formation of xanthoma cells, hemosiderin deposition and proliferation of non-neoplastic respiratory epithelial cells.

It seems likely that within the heterogeneous group of lesions diagnosed as inflammatory pseudotumor is a subset with a reasonably distinct morphologic appearance for which the term *inflammatory myofibroblastic tumor* has been proposed.⁵²⁵ In this condition, the predominant element is a spindle cell with immunohistochemical and ultrastructural features (actin reactivity, cytoplasmic filaments) consistent with those of myofibroblastic cells, or—alternatively—the cells of the accessory immune system known as fibroblastic (myoid) reticulum (dendritic) cells.^{526,527} These are accompanied by a heavy mononuclear infiltrate in which plasma cells often predominate and are intimately admixed with the spindle cells in a fashion reminiscent of that seen in other reticulum (dendritic) cell tumors (Fig. 10.135). The consistent finding of chromosomal rearrangements involving 2p23 (harboring the *ALK* gene), including *EML4-ALK* inversions analogous to those described in adenocarcinomas, in about half of these lesions supports the neoplastic nature of this subset.⁵²⁸ Other kinase fusions involving *ROS1* and *RET* occur in a smaller number of cases, bringing to two-thirds the total number of inflammatory myofibroblastic tumors that may be amenable to treatment with appropriately targeted kinase inhibitors.⁵²⁹ Interestingly this applies mainly to inflammatory myofibroblastic tumors in children in whom sensitizing kinase fusions are more common and less so to those diagnosed in adults in whom kinase fusions are rare. HHV8 has been detected in only rare cases.^{526,530}

Most cases diagnosed as inflammatory pseudotumors of the lung occur in adults, but a good number of those rich in plasma cells ('plasma cell granulomas') are seen in children. Actually, they constitute the most common isolated primary lesion of the lung in patients under 16 years of age. The majority present as asymptomatic solitary, small peripheral nodules, yellow and firm, covered by an intact pleura. In rare instances there is extension to the pleura or

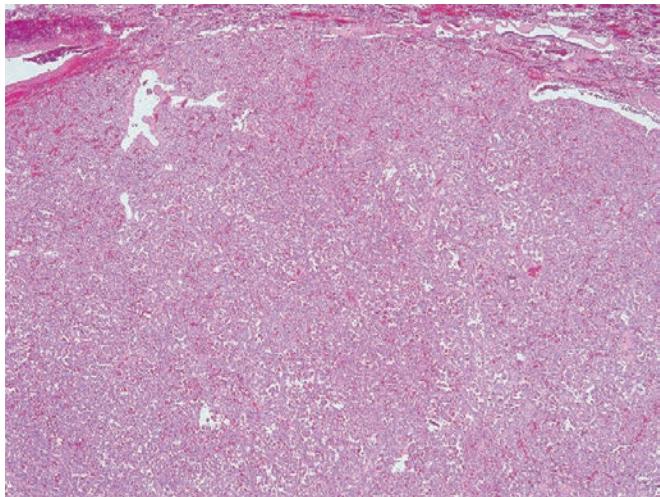


Figure 10.136 Capillary hemangioma presenting as solitary mass in a child.

mediastinum. Other cases present as polypoid endobronchial masses and may lead to distal inflammatory changes. Interestingly, some cases show many IgG4-positive plasma cells, suggesting an immune-mediated pathogenesis or at least overlap with IgG4-related sclerosing disease. There is emerging evidence that the presence of significantly increased IgG4-positive plasma cells is a feature that distinguishes inflammatory pseudotumor, a non-neoplastic proliferation, from inflammatory myofibroblastic tumor.⁵³¹⁻⁵³³

Surgical excision is usually curative, but some aggressive examples have been described, especially when the appearance corresponds to that of an inflammatory myofibroblastic tumor.

Vascular Tumors

Vascular tumors of the lung are extremely rare. **Bona fide hemangioma** is seen more commonly in children; it can be either endobronchial or parenchymal and should not be equated with the lesion formerly referred to as sclerosing hemangioma (now termed sclerosing pneumocytoma), a nonvascular lesion. Microscopically, most are of the capillary type (Fig. 10.136).⁵³⁴

Hemangiomatosis, which is by definition multifocal or diffuse, presents with symptoms and signs of pulmonary hypertension (*pulmonary capillary hemangiomatosis*) accompanied by radiological findings more typical of diffuse interstitial lung disease.⁵³⁵ The histologic findings include not only the 'capillary hemangiomatosis-like change' previously described in PVOD, but also nodular proliferation of capillary size vessels that infiltrate the interstitium and vessel walls in a manner more characteristic of a neoplastic process.²³⁶

Hemangiopericytoma (including its *lipomatous variant*) has been described as a primary lung tumor, but most such cases would be placed in other categories at present, particularly cellular solitary fibrous tumor. A particularly notorious trap is the misdiagnosis of a solitary lung metastasis of endometrial stromal sarcoma as a hemangiopericytoma.⁵³⁶

Glomus tumor can exceptionally involve the lung, its appearance being similar to that of its more common cutaneous and soft tissue counterparts.^{537,538} Most of the few reported cases presented as asymptomatic peripheral nodules with a median diameter of 2.0 cm but with a broad size range (1.1–6.5 cm). Symptomatic endobronchial tumors are even more rare but mimic the appearance of carcinoid tumor at bronchoscopy (Fig. 10.137). It can also be confused with carcinoid tumor histologically; immunostains are helpful with negative



Figure 10.137 Endobronchial glomus tumor.

staining for cytokeratins and neuroendocrine markers in glomus tumors that are instead positive for smooth muscle actin and desmin. Three reports of malignant glomus tumors (*glomangiosarcoma*) included follow-up in two; one died a year and a half after surgery and the other was alive with disease 5 years after resection.⁵³⁷

Kaposi sarcoma primary in the lung is usually a manifestation of AIDS but can also occur in immunocompetent individuals.²¹⁷ The distribution of the disease typically follows lymphatic channels.

Angiosarcoma can present as a single mass or as diffuse pulmonary infiltrates as an expression of a primary lung malignancy but in most patients represents metastatic disease of nonpulmonary origin for which potential primary sites include the heart and great vessels.⁵³⁹ A subset of patients with metastatic angiosarcoma may have a clinical presentation that mimics diffuse alveolar hemorrhage syndromes.⁵⁴⁰

Lymphangioma and **diffuse lymphangiomatosis** are extremely rare; both of these conditions are more common in children but occasionally present in adulthood.^{541,542}

Epithelioid hemangioendothelioma is the term for the neoplastic process originally described in the lung as *intravascular bronchioloalveolar tumor* (IV-BAT) that typically presents as multiple nodules.⁵⁴³ Many of the patients are young adults, and females outnumber males by 3–4:1.⁵⁴³⁻⁵⁴⁵ Microscopically, the most common growth pattern is multiple centrally hyalinized and/or necrotic nodules in which there are variably conspicuous acidophilic endothelial cells that may resemble epithelium, histiocytes, or decidualized stromal cells. The surprisingly bland neoplastic cells are distributed individually, in small solid cords, and in a vaguely lobulated pattern often as a thin rim surrounding an eosinophilic or basophilic ('chondroid') mass of hyalinized stroma, which is sometimes calcified (Figs. 10.138 and 10.139). These polypoid formations fill alveoli and occasionally bronchioles. The walls and lumen of both arteries and veins may also be occupied by tumor, even at a distance from the main mass, as the tumor spreads in a lymphangitic pattern. Grading into low and intermediate grades based on mitotic rate, necrosis, and nuclear pleomorphism can separate them into subsets that differ in prognosis, but that together are better than high-grade epithelioid angiosarcoma.⁵⁴⁶ Unusual growth patterns include rare reports of solitary nodules and diffuse pleural disease mimicking mesothelioma.⁵⁴⁷ Although originally interpreted as a variant of bronchioloalveolar carcinoma, ultrastructural and immunohistochemical studies have shown that the tumor is composed of endothelial cells and that it represents the pulmonary version of epithelioid hemangioendothelioma. Neoplastic cells are positive for vascular markers such as

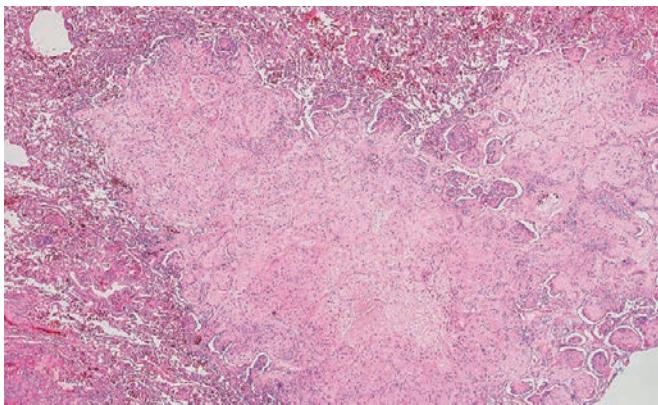


Figure 10.138 Epithelioid hemangioendothelioma. Nodular intra-alveolar aggregates of tumor cells are seen enclosing an amorphous eosinophilic material.

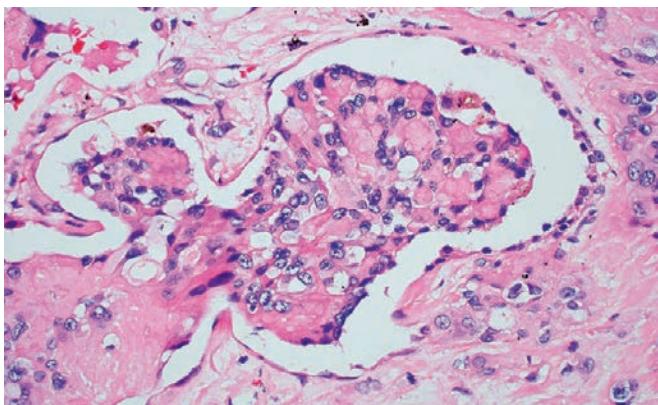


Figure 10.139 Prominent intracytoplasmic lumen formation and cytoplasmic intranuclear pseudo-inclusions in epithelioid hemangioendothelioma.

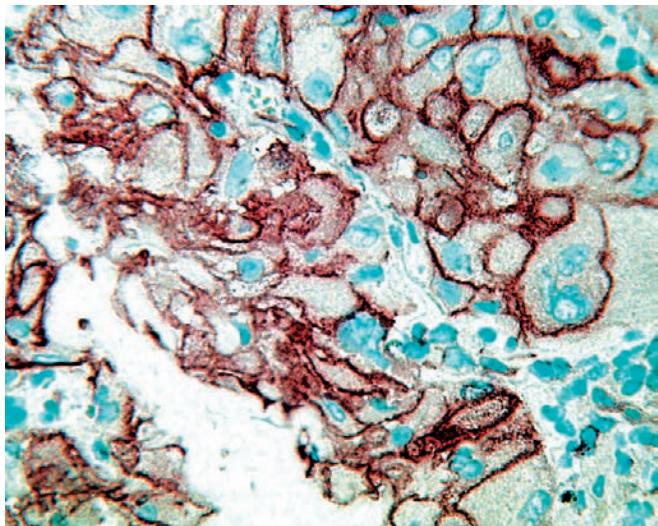


Figure 10.140 Strong immunoreactivity for CD31 in epithelioid hemangioendothelioma.

CD31, ERG, and CD34 but can also be positive for keratins, a potential diagnostic trap (Fig. 10.140).^{546,548} Thoracic epithelioid hemangioendotheliomas, like their soft tissue counterparts, show recurrent translocations corresponding to *WWTR1-CAMTA1* and *YAP1-TFE3* gene fusions. Nuclear expression of CAMTA1 in tumors with

WWTR1-CAMTA1 fusions (85%–90%) and strong nuclear staining for TFE3 in the minority with *YAP1-TFE3* fusions is relatively specific and offers another diagnostically useful immunostain.⁵⁴⁹

The tumor grows in a very slow but progressive fashion, with a tendency to remain restricted to the thoracic cavity. Some patients die as a result of pulmonary insufficiency. Poor prognostic factors at the time of diagnosis include respiratory symptoms and/or pleural effusion, and intermediate histologic grade.^{544–546} Most of these tumors are primary in the lung, but others with an identical appearance have been interpreted as metastases from epithelioid hemangioendotheliomas located elsewhere, particularly liver.

Epithelioid hemangioma (angiolymphoid hyperplasia with eosinophilia) has been reported in the lung.⁵⁵⁰ As in other sites in which it is more frequent, its neoplastic versus inflammatory nature remains controversial.

Lymphoid Tumors and Tumorlike Conditions

The lung can be involved by various types of lymphoproliferative processes, either secondarily or as the only manifestation of the disease.^{551,552} Secondary lung involvement can be peribronchial/ perivascular, nodular alveolar, interstitial, pleural, or (more commonly) a combination of them. **Leukemic involvement** of the lung is found at autopsy in 30%–40% of the chronic lymphocytic forms, in about 15%–20% of the chronic myelogenous types, and in over 60% of the adult acute forms, but most of them do not result in clinical manifestations.^{553–556} Occasionally, however, significant pulmonary impairment results from the infiltrate of chronic lymphocytic leukemia acquiring a selective bronchiocentric distribution.⁵⁵⁵ In rare cases, acute myeloid leukemia presents with widespread pulmonary nodules or infiltrates (*myeloid sarcoma*).^{557,558}

For purposes of discussion, lymphoproliferative disorders presenting in the lung can be divided into four main categories: extranodal marginal zone lymphomas of MALT lymphoma, lymphomas of conventional type spanning the spectrum of phenotypes and histologies including intravascular large B-cell lymphoma, lymphomatoid granulomatosis, and Hodgkin lymphoma.

Small lymphocytic proliferations forming pulmonary nodules are often difficult to interpret. This broad and historically nebulous category comprises predominantly MALT lymphomas, the most common form of primary pulmonary lymphoma.⁵⁵⁹ Most patients are in the sixth and seventh decades of life and asymptomatic at the time of diagnosis, the lesion presenting as a solitary nodule or infiltrate on a chest x-ray film or CT scan without associated lymphadenopathy. Underlying autoimmune diseases (especially Sjögren syndrome) and monoclonal gammopathies are common.⁵⁵⁹ MALT lymphomas may also complicate pulmonary lymphoid hyperplasia in patients with common variable immunodeficiency.⁵⁶⁰

Grossly, they appear as a relatively well-defined but unencapsulated mass, which on cut surface has a homogeneous white to gray appearance (Fig. 10.141). Microscopic features are similar to those described in other extranodal marginal zone lymphomas and include a tumefactive infiltrate of small lymphocytes, monocyteid B cells, and plasma cells with associated germinal centers scattered throughout and variably well-developed lymphoepithelial complexes (Fig. 10.142). Occasional cases have associated amyloid; in fact, most cases of nodular amyloidosis in the lung are MALT lymphomas in which amyloid deposits overrun the clonal lymphoplasmacytic infiltrate.⁵⁶¹ Histologically indistinguishable nodules composed of non-amyloid light chain may also complicate MALT lymphoma.⁵⁶² Nodular hyperplasia is extremely uncommon but the main differential diagnosis for MALT lymphoma.^{552,563} Features in favor of malignancy are the monomorphic nature of the infiltrate; the presence of plasmacytoid features with associated intranuclear Dutcher bodies;



Figure 10.141 Gross appearance of a MALT lymphoma in a surgical lung biopsy.

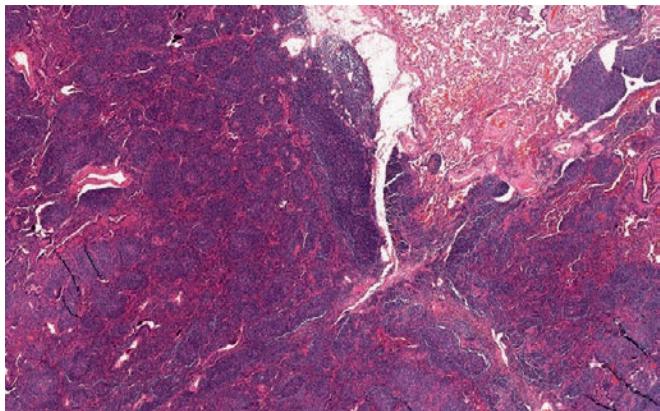


Figure 10.142 MALT lymphoma of lung showing a tumefactive and vaguely nodular configuration on the left with extension along lymphatic pathways on the right.

the presence of amyloid in the stroma; the invasion of bronchial cartilage, wall of large vessels, or visceral pleura; a lymphangitic pattern of infiltration at the periphery; and light chain restriction and/or clonal rearrangements of the immunoglobulin heavy chain gene.^{552,559}

Amyloidosis of the lung can be divided into four categories on the basis of distribution: nodular (for which previous comments regarding overlap with MALT lymphoma are relevant), tracheobronchial, diffuse alveolar septal (usually in patients with systemic disease), and vascular (never a serious clinical problem when it occurs in isolation).⁵⁶⁴ Radiographically, lesions in the first and second categories can be solitary or multiple and can simulate granulomatous infection or a metastatic neoplasm. Diffuse alveolar septal amyloidosis may lead to a severe impairment of lung function, a diffuse infiltrate on radiographic examination, and a poor prognosis. The amyloid material is mostly made up of AL protein. There are rare reports of localized deposits of non-amyloid light chain forming nodules that are indistinguishable from amyloidosis in routinely stained sections.⁵⁶² *Crystal storing histiocytosis* is a related condition resulting from massive accumulation of crystallized immunoglobulin in the cytoplasm of non-neoplastic histiocytes. The disease, which is usually a manifestation of a MALT lymphoma or plasma cell neoplasm, can be localized to the lung or other sites, or systemic.⁵⁶⁵

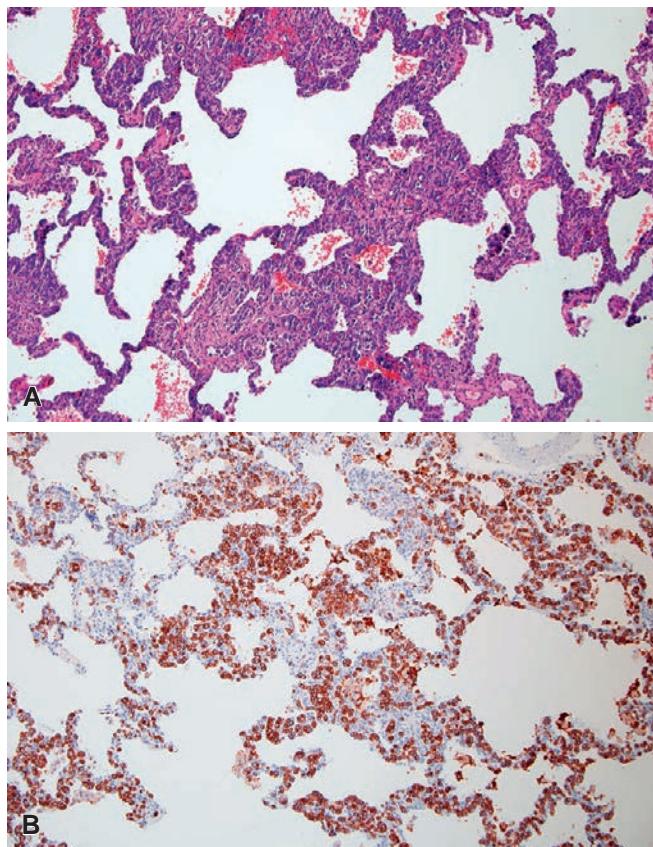


Figure 10.143 **A**, Intravascular lymphoma in a patient with unexplained breathlessness. **B**, An immunostain for CD20 shows neoplastic large B cell exquisitely localized to alveolar septal capillaries.

Plasmacytoma should be used as a diagnostic term only for neoplastic lesions composed entirely of neoplastic, light chain restricted plasma cells. Plasmacytic tumors with a lymphoid component should be classified with the MALT lymphomas; it is likely that some of the tumors previously regarded as primary pulmonary plasmacytomas were instead MALT lymphomas.⁵⁶⁶ CD56 can be a helpful immunostain in distinguishing MALT lymphomas from plasmacytomas, as it tends to be positive in the latter and negative in the former.⁵⁶⁶ Plasmacytomas of lung may be intraparenchymal or endobronchial, may be associated with nodal or bone involvement, and may exhibit production of light chain protein,⁵⁶⁷ which may appear in the tissue in the form of diffuse or nodular deposits that resemble amyloid but are not congophilic.⁵⁶⁸

Large cell lymphoma of conventional type presents as a large mass, sometimes occupying most of a lobe, and is often accompanied by foci of necrosis.⁵⁶⁹ Occasionally the pattern of growth is predominantly endobronchial. Microscopically, a monomorphic infiltrate of large lymphoid cells is present. Most cases are diffuse large B-cell lymphomas, with rare examples resembling primary mediastinal large B-cell lymphoma.⁵⁷⁰ Intravascular lymphoma is a form of extranodal large B-cell lymphoma that sometimes presents with lung involvement, often in symptomatic patients with minimally abnormal imaging studies (Fig. 10.143)^{571,572}; central nervous system, skin, and bone marrow are other commonly affected sites. Anaplastic large cell lymphomas can also occur in the lung.⁵⁷³

Lymphomatoid granulomatosis, originally included by Liebow in his *pulmonary angitis and granulomatosis* group,⁵⁷⁴ is now placed among the B-cell lymphoproliferative disorders.⁵⁷⁵ It usually presents

in middle age with bilateral rounded mass densities, which radiographically may resemble metastases.^{576,577} Cases of lymphomatoid granulomatosis and similar atypical lymphoproliferative processes have been reported in immunosuppressed transplant recipients in whom it represents a form of post-transplant lymphoproliferative disorder, and in HIV-infected patients.²¹⁶ The key microscopic picture is the presence of a polymorphic infiltrate comprising a combination of plasma cells, small lymphocytes in which T-cells predominate, immunoblasts, and atypical large lymphoid cells, with a tendency to form centrally necrotic nodules and to involve the walls of pulmonary vessels as transmural, circumferential infiltrates (Fig. 10.144). The multinucleated giant cells and necrotizing vasculitis of GPA (Wegener) are not present. Lymphomatoid granulomatosis can be graded according to the relative proportion of atypical large cells (grades 1–3), although the criteria proposed and the relationship to prognosis are inconsistent.^{576,578,579}

Extrapulmonary involvement occurs in over a third of the cases.⁵⁷⁷ The most common sites are the skin (particularly in the lower extremities) and central nervous system. Other less commonly involved sites include kidneys, liver, spleen, adrenal glands, heart, and gastrointestinal tract. The histologic appearance is similar in all of these sites. In rare cases the microscopic changes of lymphomatoid granulomatosis are seen in an extrapulmonary site in the absence of pulmonary involvement.

It has become increasingly evident that both the morphologic features of lymphomatoid granulomatosis and its clinical course are more in keeping with a malignant than a reactive process and that it is common for large cell lymphomas of the lung to exhibit vascular infiltration. Accordingly, lymphomatoid granulomatosis is currently viewed as a primary EBV-related lymphoproliferative disease that either

is or has a great tendency to become malignant lymphoma.^{575,577} On the basis of combined immunohistochemical and *in situ* hybridization studies, most cases of lymphomatoid granulomatosis represent a proliferation of EBV-infected B cells associated with a prominent T-cell reaction with prominent vascular involvement.^{580–583}

Response to steroids is poor, but multidrug chemotherapy induces complete remission in about half of cases.⁵⁸⁴ Novel treatments including a combination of immunotherapy and chemotherapy have been effective in some cases.⁵⁸⁵ Despite treatment advances, lymphomatoid granulomatosis remains an aggressive disease with relatively high disease-related mortality.⁵⁷⁷

Hodgkin lymphoma involving the lung parenchyma is usually associated with nodal involvement, direct extension from the mediastinum (thymus) being frequent in the nodular sclerosis form. However, rare cases of primary pulmonary Hodgkin lymphoma have been well documented.^{586–588} They are reported with slightly greater frequency in women over a broad age range and usually appear as solitary or multiple nodular lesions on chest x-rays and/or CT scans.^{586–588} Endobronchial involvement can also occur, either in the form of a plaquelike infiltrate or as a polypoid mass.

Salivary Gland-Type Tumors

Several types of epithelial tumor with patterns analogous to those of salivary gland neoplasms occur in the lung, probably arising from submucous bronchial glands. Most of them are located within the trachea or the main cartilaginous bronchi.⁵⁸⁹

Adenoid cystic carcinoma is the most common type. It is usually centered in the major bronchi (Fig. 10.145) and often involves the trachea, although peripheral examples are also on record.⁵⁹⁰ Metastases to regional lymph nodes occur in a minority of cases.^{589,591} The histologic, immunohistochemical, and cytogenetic findings are indistinguishable from those described for adenoid cystic carcinomas arising in extrathoracic salivary glands (see Chapter 6), including a characteristic t(6;9)(q22–23;p23–24) translocation resulting in fusion of the *MYB* oncogene and *NFIB* transcription factor in about half of cases.⁵⁹¹ TTF-1 and napsin A staining have been reported in lung metastases from extrapulmonary primaries but is rare in primary pulmonary adenoid cystic carcinomas, making these stains of little value in separating primary from metastatic tumors.⁵⁹² The primary treatment is surgical excision. Irradiation therapy may induce marked regression, but it is not curative. The total duration of the disease is long, but the ultimate prognosis is poor.⁵⁸⁹

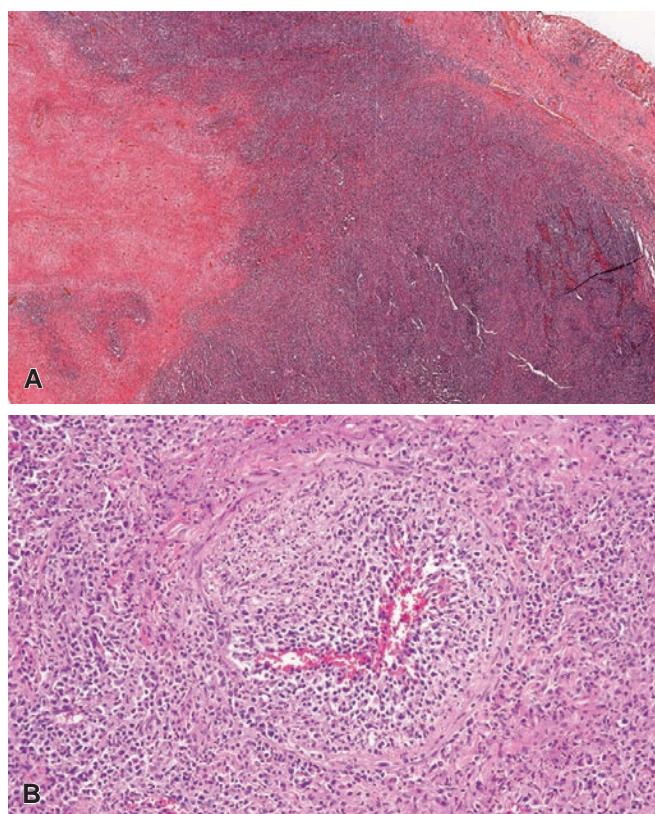


Figure 10.144 Lymphomatoid granulomatosis showing polymorphic infiltrate forming centrally necrotic nodule (A) and characteristic angioinvasive growth pattern (B).



Figure 10.145 Adenoid cystic carcinoma presenting as an endobronchial mass invading adjacent lung parenchyma.



Figure 10.146 Endobronchial growth of mucoepidermoid carcinoma.

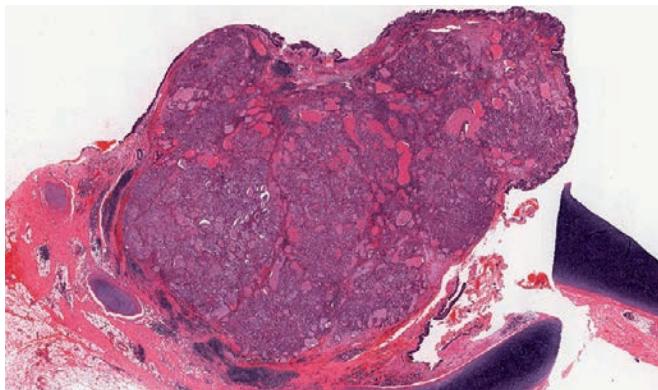


Figure 10.147 Endobronchial mucoepidermoid carcinoma showing characteristic low-grade histology.

Mucoepidermoid carcinomas of the lung affect males and females equally across a broad age range, including children, and usually present as an exophytic endobronchial mass (Fig. 10.146).^{589,593,594} They can be divided into low-grade and high-grade varieties, like their salivary gland counterparts.⁵⁹⁴ High-grade variants are rare and not easily separated from adenosquamous carcinoma. As in their more common extrathoracic salivary gland location, they are composed of a combination of mucus-secreting cells, squamous cells, and cells of intermediate type (Fig. 10.147). Rarely, they are accompanied by a heavy lymphoplasmacytic infiltrate.⁵⁹⁵ Immunohistochemical stains show a profile identical to that described in mucoepidermoid carcinomas arising in other sites (see Chapter 6), including negative staining for TTF-1 and napsin A.⁵⁹³ Pulmonary mucoepidermoid carcinomas demonstrate the same t(11;19)(q21;p13) translocation of the *mucoepidermoid carcinoma translocated 1* (*MECT1*) and *mammalian mastermind-like 2* (*MAML2*) genes resulting in the *MECT1–MAML2* fusion oncoprotein unique to all mucoepidermoid carcinomas of salivary gland origin.⁵⁹⁶

Low-grade mucoepidermoid carcinoma has a low malignant potential, characterized mainly by local invasion and a relatively good prognosis.^{589,593,594,597} The rare cases of high-grade mucoepidermoid carcinoma have a stage-dependent prognosis resembling that seen with other forms of high-grade non-small cell carcinoma.⁵⁹⁴ These tumors, like adenoid cystic carcinomas, lack the sensitizing *EGFR* mutations that occur in a subset of conventional lung adenocarcinomas.⁵⁹⁸

Cases of lung carcinoma with adenosquamous features, a suggestion of myoepithelial cell differentiation (such as positivity for

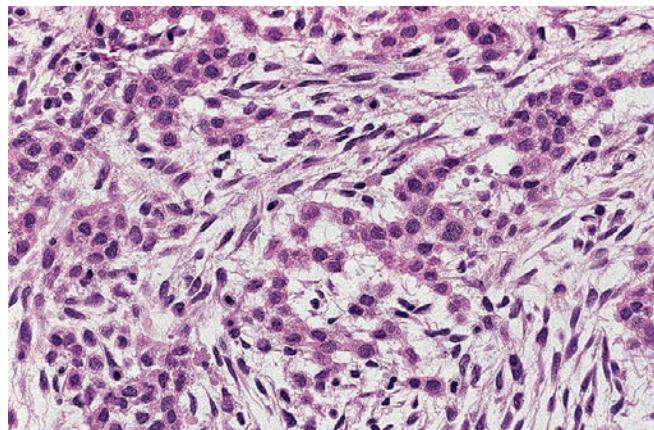


Figure 10.148 Myoepithelioma of lung. This particular tumor had arisen from a typical hamartoma.

S-100 protein), and amyloid-like stroma made up of basement membrane material have been reported and may represent a unique subset of lung carcinomas with features resembling salivary gland neoplasms.⁵⁹⁹

Other less common tumors belonging to this rather generic category of salivary gland or salivary gland-like neoplasms include:

- **Pleomorphic adenoma** (benign mixed tumor)⁶⁰⁰
- **Malignant mixed tumor**^{600,601}
- **Myoepithelial tumors**
 - Epithelial–myoepithelial carcinoma⁶⁰²
 - Pneumocytic adenomyoepithelioma⁶⁰³
 - Myoepithelioma arising in hamartoma (Fig. 10.148)⁴⁸⁷
- **Acinic cell carcinoma**⁶⁰⁴
Combined with typical carcinoid tumor⁶⁰⁵
- **Oncocytoma**.⁶⁰⁶ This tumor, which can be malignant, is analogous to oncocytomas of salivary gland origin and should be distinguished from oncocytic neuroendocrine tumors and adenocarcinomas, a task that may require immunohistochemical evaluation^{392,607}

PEComatous Tumors

Clear cell tumor ('sugar tumor') is analogous to PEComas arising in other nonpulmonary sites. In the lung, these rare tumors present as a round or ovoid solitary peripheral lung nodule usually measuring no more than 2 cm in greatest dimension.⁶⁰⁸ It usually occurs in adults, but it has also been reported in children.⁶⁰⁹ Microscopically, it is made up of large cells with clear to eosinophilic granular cytoplasm crowded with glycogen granules (Fig. 10.149). Some cells have a 'spidery' appearance. Fat is absent. Mitoses are not seen. There is scanty intervening stroma, but thin-walled vessels may be prominent, as well as extracellular amorphous eosinophilic material (sometimes calcified).

Immunohistochemically, clear cell tumors of the lung show the same expression of melanogenesis-associated markers affiliated with PEComas elsewhere, including staining for HMB-45, S-100 protein, and cathepsin B accompanied by focal and inconstant positivity for actin, neuron-specific enolase, and synaptophysin.^{608,610} By electron microscopy, most of the glycogen is membrane bound in lysosome-like organelles.⁶⁰⁸ Intracytoplasmic filaments may be present. Dense-core granules compatible with premelanosomes have been found in a few of the cells; in rare cases, well-developed melanosomes occur.⁶⁰⁸ Basal lamina often surrounds the tumor cells.

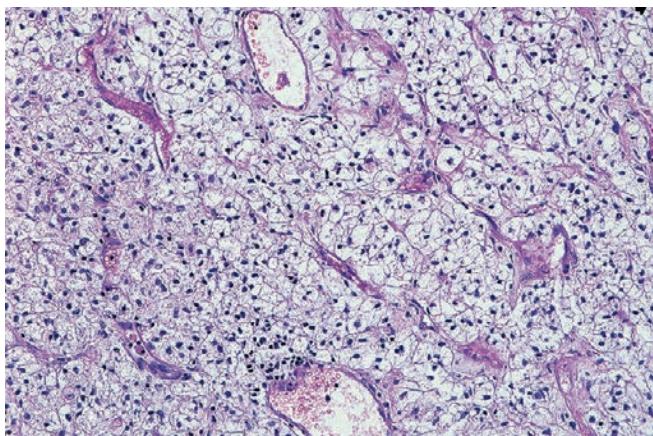


Figure 10.149 Clear cell tumor (PEComa) of lung. Medium-sized clear cells grow in a solid pattern, separated by a prominent vasculature.

The histogenesis of this tumor has been a source of great controversy. Pericytes, smooth muscle cells, neuroendocrine cells, Clara cells, and epithelial cells have all been proposed at one time or another. The HMB-45 immunoreactivity, occasional detection of melanosomes, and other similarities with renal angiomyolipoma suggest that it belongs to a family of tumors thought to be derived from perivascular epithelioid cells (so-called PEComas), a family of tumors that includes lymphangioleiomyomatosis.^{611–613}

Lymphangioleiomyomatosis involves both lungs, usually presenting as diffuse cystic lung disease in young women who present with spontaneous pneumothorax and/or pulmonary symptoms, most commonly dyspnea on exertion.^{614,615} It occurs only very rarely in men.^{616,617} Some patients are affected by tuberous sclerosis (including nearly all of the rare cases reported in men), renal angiomyolipomas, and PEComas of uterus and other sites.^{614,618} Grossly, early cases may simply suggest emphysematous changes, whereas more advanced cases show widespread cystic spaces separated by thick, whitish-gray septa (Fig. 10.150). The microscopic features include a combination of cystic spaces associated with interstitial spindled and epithelioid cells with cytologic characteristics typical of other PEComatous lesions (Fig. 10.151). These findings are often accompanied by hemosiderosis, an especially conspicuous feature in more advanced disease.⁶¹⁹ The proliferating ('LAM') cells are immunoreactive for HMB-45 and other melanocytic markers such as melan-A and microphthalmia transcription factor (MiTF) in a patchy distribution with more widespread staining for smooth muscle markers (e.g. smooth muscle actin, desmin) as well as ER and PR. LAM cells are also immunoreactive for β -catenin, which may be a more sensitive marker than HMB-45.⁶²⁰ LAM cells demonstrate the same complement of mutations in tumor suppressor genes *tuberous sclerosis complex* (TSC) 1 or TSC2 as other PEComatous lesions with clonal identity across sites in cases with multiorgan involvement, including some who develop recurrent pulmonary disease after lung transplant.⁶²¹ These observations suggest that lymphangioleiomyomatosis is a low-grade metastasizing neoplasm. Transplantation and, more recently, sirolimus are the mainstays of therapy for cases of lymphangioleiomyomatosis.⁶²² The prognosis of lymphangioleiomyomatosis is variable, but survivals measured in decades are the rule rather than the exception.⁶²³ Respiratory symptoms and/or pleural disease (i.e. pneumothorax or chylous effusion) at presentation predict shorter transplant-free survivals.

Muscle Tumors

Leiomyoma presenting as a primary solitary pulmonary mass is rare.⁶²⁴ Peripheral lesions are more common and typically present

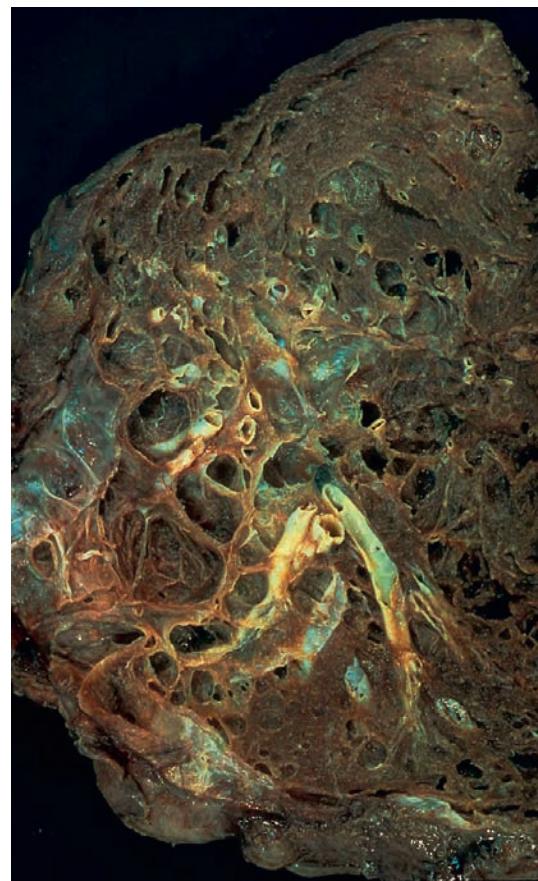


Figure 10.150 Explanted lung showing lymphangioleiomyomatosis in a woman whose pretransplant diagnosis was emphysema.

as asymptomatic nodules; endobronchial lesions are more likely to be affiliated with findings related to postobstructive bronchiectasis and pneumonia. Multiple EBV-associated leiomyomas and leiomyosarcomas involving the lungs and gastrointestinal tract have been described in HIV-infected children and in MEN 1 patients.^{625,626}

Occasionally, a middle-aged asymptomatic or minimally symptomatic female is seen with multiple small pulmonary nodules composed of well-differentiated smooth muscle, sometimes enclosing epithelial-lined clefts in a condition referred to most commonly as *benign metastasizing leiomyoma* (Fig. 10.152).⁶²⁷ Concomitant or preexistent uterine smooth muscle tumors are invariably present. In most cases the pulmonary nodules likely represent clonally related metastases from well-differentiated uterine smooth muscle neoplasms.

Leiomyosarcoma primary in the lung does occur both in adults and children,⁶²⁸ but in the presence of a malignant smooth muscle tumor in the lung—even if solitary—the chances are overwhelming that the lesion is metastatic. Most are intraparenchymal masses, some associated with an endobronchial component. Leiomyosarcomas arising from the pulmonary veins can invade secondarily the lung parenchyma.⁶²⁹

Some cases originally reported as congenital leiomyosarcomas have been reinterpreted as *myofibroblastic tumors* and have been found to be characterized by an indolent clinical course.⁶³⁰

Rhabdomyosarcoma can present in its *pleomorphic* form in the lungs of adults (exceptionally rare)⁶³¹ or as an expression of the *embryonal* variety in the lungs of children. In children, it tends to occur against a background of cystic changes and blends with the PPBs having a prominent rhabdomyoblastic component (see later).⁶³²

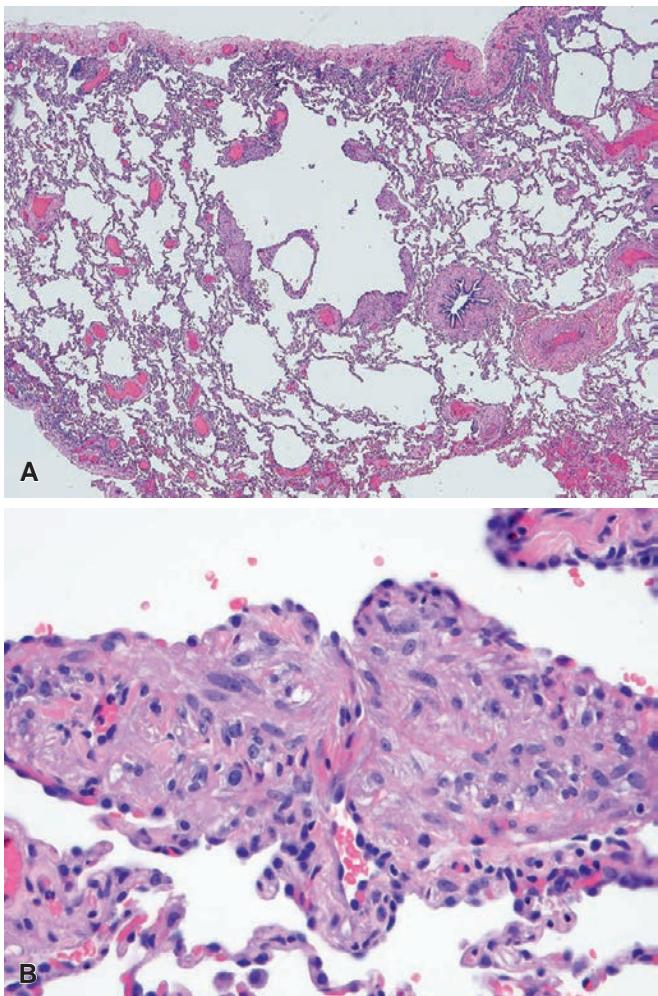


Figure 10.151 Lymphangioleiomyomatosis in which cystic space (A) is associated with loose interstitial aggregates of lesional smooth muscle-like (LAM) cells (B).

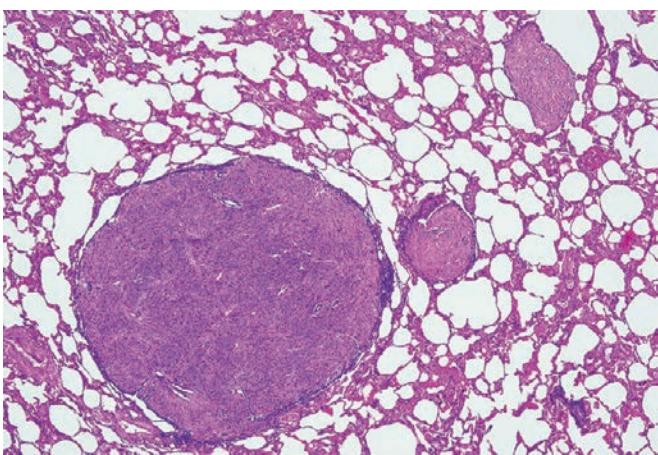


Figure 10.152 Benign metastasizing leiomyoma.

Pleuropulmonary Blastoma

PPB is a dysontogenetic (embryonal, blastomatous) malignant pediatric neoplasm that is pulmonary and/or pleural based.⁶³³ It is unrelated to pulmonary blastoma, which is described elsewhere in this chapter as a histologically distinct form of high-grade sarcomatoid

carcinoma in adults. PPB is characterized histologically by an admixture of primitive blastomatous and sarcomatous elements.^{634,635} The latter may exhibit evidence of skeletal muscle and cartilaginous differentiation. An epithelial component is either lacking or present only in the form of benign-looking, presumably entrapped epithelium. A three-type system has been proposed for this entity, type I tumors being predominantly cystic and type III tumors almost entirely solid. Care should be exercised to avoid underdiagnosing type I tumors as a developmental cystic malformation.⁶³⁶ Mutations of the *DICER1* gene have been detected in about two-thirds of cases.⁶³⁴ The behavior of this tumor is potentially aggressive, particularly for the more solid forms (i.e. types II and III).^{634,637}

The recently described fetal lung interstitial tumor may or may not be related to the cystic form of (type I) PPB.⁶³⁸

Miscellaneous Primary Tumors

Squamous papillomas account for about 70% of solitary lung papillomas, the others showing glandular or mixed types of epithelial lining cells.⁶³⁹ Squamous papillomas are more common in men and more likely to be associated with cigarette smoking and HPV infection. The prognosis for solitary papillomas is excellent independent of the epithelial type.⁶³⁹ Multiple squamous papillomas may involve the lower respiratory tract in patients with recurrent respiratory papillomatosis and are more likely to be associated with an aggressive course including progression to squamous cell carcinoma.⁶⁴⁰

Granular cell tumor can present either as a polypoid endobronchial mass with signs of bronchial obstruction or as an asymptomatic peripheral lung nodule.⁶⁴¹ Most are solitary, but multicentric lesions have been described.

Benign lung tumors other than those already mentioned are rare and include intrapulmonary thymoma,⁶⁴² schwannoma,⁶⁴³ ganglioneuroblastoma,⁶⁴⁴ endobronchial blue nevus,⁶⁴⁵ microcystic fibromyxoma,⁶⁴⁶ ciliated mucnodular papillary tumor (a benign or low-grade tumor frequently associated with *BRAF-V600E* or *EGFR* mutations)^{647,648} and lipoma (endobronchial, peripheral, and atypical),^{649–651} a lesion probably related to the more conventional hamartoma described elsewhere in this chapter. We have seen a case of *multifocal microcysts and papillary cystadenoma* of the lung associated with striking vascular proliferation in a patient with von Hippel–Lindau disease, and a similar case has been reported.⁶⁵²

Solitary fibrous tumor, although usually pleural based (see Chapter 11), can be entirely intrapulmonary and should therefore be considered in the differential diagnosis of spindle cell tumors of this organ.⁶⁵³

Synovial sarcoma is now recognized as one of the most common types of primary pulmonary sarcoma. The large majority are of the monophasic spindle type, a relatively high percentage (higher than in the soft tissue) are poorly differentiated, and extremely few are biphasic (Fig. 10.153).⁶⁵⁴ Sometimes they are cystic and present with recurrent pneumothorax.⁶⁵⁵

Primary sarcomas of lung other than those already mentioned are rare. Fibrosarcoma affecting pediatric age patients,⁶⁵⁶ so-called undifferentiated pleomorphic sarcoma (previously termed malignant fibrous histiocytoma),⁶⁵⁷ low-grade fibromyxoid sarcoma (including the related hyalinizing spindle cell tumor with giant rosettes),⁶⁵⁸ chondrosarcoma⁶⁵⁹ (including the mesenchymal variety⁶⁶⁰), osteosarcoma,⁶⁶¹ malignant peripheral nerve sheath tumor (including malignant triton tumor),⁶⁶² Ewing sarcoma/PNET,⁶⁶³ desmoplastic small cell tumor,⁶⁶⁴ and follicular dendritic cell tumor/sarcoma⁶⁶⁵ have been described in the lung. Primary pulmonary myxoid sarcoma is a more recently described form of lung sarcoma that tends to target younger adults and has a characteristic *EWSR1-CREB1* fusion (Fig. 10.154).⁶⁶⁶ Primary pulmonary myxoid sarcoma shares morphologic and molecular

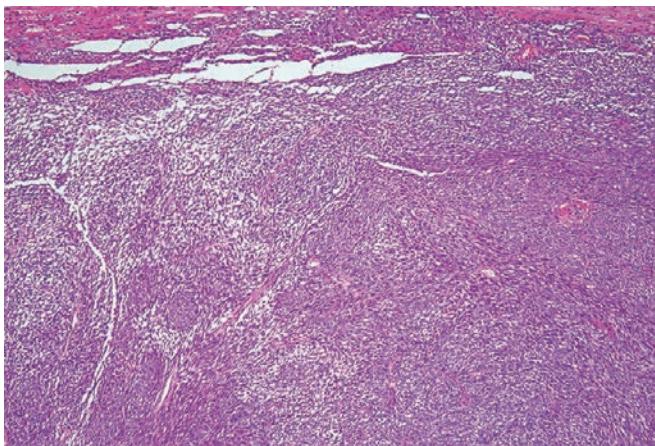


Figure 10.153 Primary monophasic synovial sarcoma of lung. Some areas have a fibroblastic appearance, whereas in others the cells are slightly plumper, although still lacking an identifiable epithelial organization. There was focal immunoreactivity for keratin.

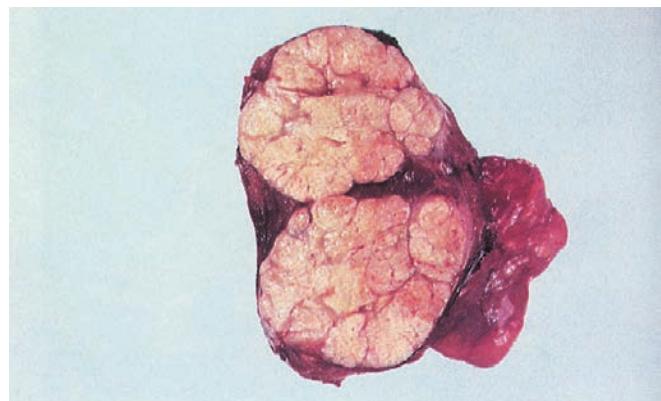


Figure 10.155 Metastatic renal cell carcinoma to lung. The lesion is well circumscribed, multinodular, and golden yellow.

Metastatic Tumors

The lung is a very common site of metastatic disease, sometimes as the only expression of distant tumor spread. Most metastases are multiple, bilateral, sharply outlined, and rapidly growing; this is particularly true for metastases from some types of carcinoma (breast, gastrointestinal tract, and kidney), sarcomas, and melanomas. They range from miliary nodules to 'cannonball' lesions and are more common in the lower lobes. Other metastases (particularly from carcinomas of stomach, breast, pancreas, and prostate) tend to present as widespread neoplastic involvement of the pulmonary perivascular and peribronchial lymphatics (so-called *lymphangitic carcinomatosis*), which may result in severe dyspnea and pulmonary hypertension (*tumor-related thrombotic pulmonary microangiopathy*), sometimes in the absence of chest x-ray abnormalities.⁶⁷⁷

In other instances the metastases present as isolated nodules and may simulate the appearance of primary tumors (Figs. 10.155 to 10.159). Central cavitation can occur in them; this is particularly common in squamous cell carcinomas of the upper aerodigestive tract and adenocarcinomas of colorectal origin.

Another type of lung metastasis that can be confused with a primary tumor results from the penetration of intraparenchymal or nodal deposits into the wall of a major bronchus and their presentation as polypoid endobronchial masses mimicking primary lung carcinomas.⁶⁷⁸ The most common primary sites of origin for endobronchial metastases are breast, large bowel, kidney, stomach, prostate, and melanoma and in some cases is the first manifestation of malignancy.

The differential diagnosis between primary and metastatic lung carcinoma can be difficult and sometimes impossible. Multiplicity of lesions and extensive lymphatic permeation favor a metastasis. The presence of atypical or *in situ* changes in the bronchial mucosa adjacent to a squamous cell carcinoma, and of honeycombing and atypical hyperplasia of bronchiolar epithelium in the parenchyma surrounding an adenocarcinoma, favor a primary tumor. However, it should be remembered that many metastatic cancers to the lung (particularly from large bowel and pancreas) can line the alveolar walls in a 'lepidic' fashion, simulating well differentiated adenocarcinomas of the lung.⁶⁷⁹ One of least common forms of metastatic lung involvement by adenocarcinomas from the gastrointestinal tract is the form associated with pseudomyxoma peritonei which accounts for rare reports of parenchymal deposits resembling primary colloid carcinomas.⁶⁸⁰

Immunohistochemical staining may provide great assistance in some situations as summarized earlier in this chapter. Depending on suspected extrapulmonary primary sites, TTF-1 and napsin A can

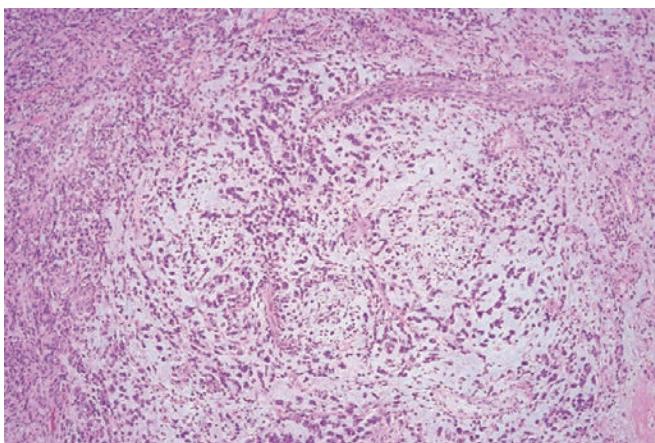


Figure 10.154 Primary pulmonary myxoid sarcoma with a *EWSR1-CREB1* fusion.

features with *angiomatoid fibrous histiocytoma*, leading some to conclude that they may be overlapping entities.⁶⁶⁷ In the presence of any of these tumors, all efforts should be made to rule out the possibility of a primary tumor elsewhere and/or of a primary lung carcinoma with a sarcoma-like appearance. This applies particularly to the cases reported as *rhabdoid tumor* or *rhabdoid sarcoma* of lung, most of which are dedifferentiated forms of lung carcinoma.³²³

Malignant melanoma primary in the lung is yet another tumor type that should be diagnosed with great caution. Although reasonably convincing examples exist (supported by the presence of a 'junctional' bronchial component),⁶⁶⁸ the large majority represent metastatic deposits from known or occult primaries.

Germ cell tumors of choriocarcinomatous, yolk sac, and other (nonseminomatous) types allegedly primary in the lung have been described.⁶⁶⁹⁻⁶⁷¹ They need to be distinguished from pulmonary metastases of gonadal germ cell tumors⁶⁷² and from primary lung carcinomas with germ cell-like features, both of which are much more common. Lung carcinomas have the capacity to secrete a number of proteins more commonly associated with germ cell tumors including the alpha subunit of hCG⁶⁷³ and AFP,^{674,675} the latter particularly in association with rare cases of adenocarcinoma resembling hepatocellular carcinoma (*hepatoid adenocarcinoma*⁶⁷⁶).

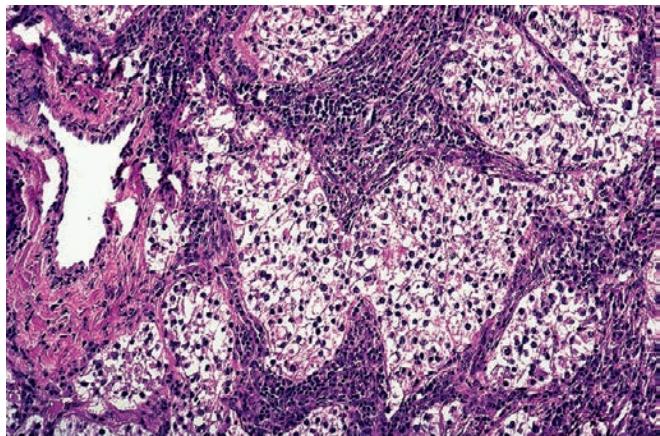


Figure 10.156 Renal cell carcinoma of clear cell type metastatic to lung.

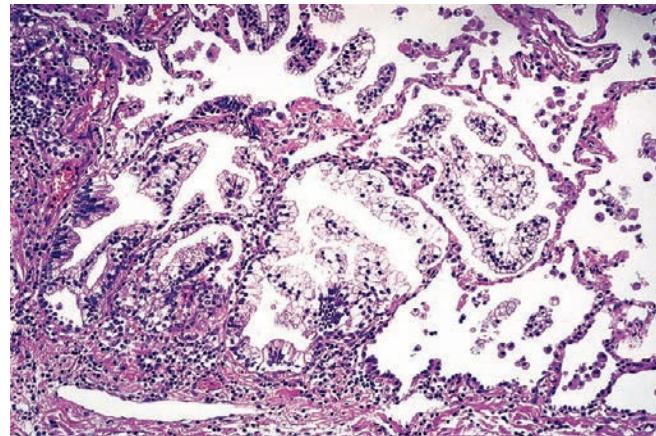


Figure 10.159 Metastatic prostatic adenocarcinoma simulating the appearance of a well differentiated lepidic-predominant adenocarcinoma of the lung.

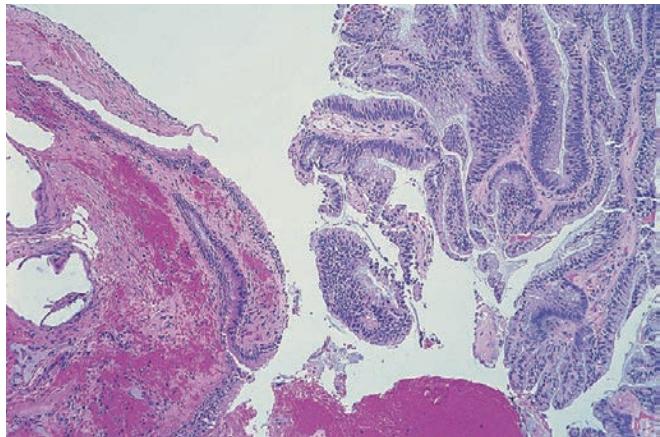


Figure 10.157 Well-differentiated colonic adenocarcinoma metastatic to lung, diagnosed in a bronchial biopsy.

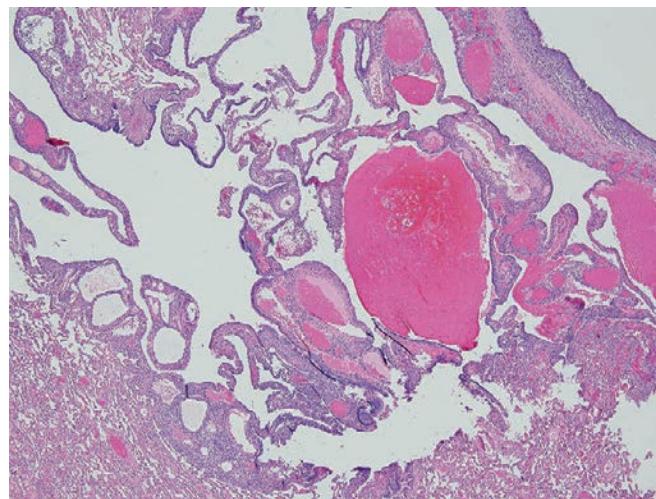


Figure 10.160 Metastatic cellular fibrous histiocytoma of cutaneous origin (cystic fibrohistiocytic tumors) forming multiple bilateral cystic masses in a young woman with a preoperative diagnosis of lymphangioleiomyomatosis.

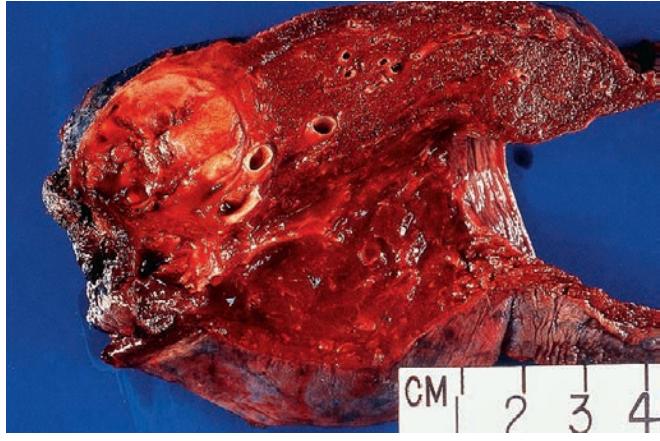


Figure 10.158 Malignant melanoma metastatic to lung.

be especially helpful in supporting pulmonary origin, while staining for PAX8, GATA3, and other selected markers often signify origin from elsewhere.

Among the sarcomas, there are some that are notorious for their ability to simulate primary lung processes. Some metastatic spindle cell sarcomas grow extensively along bronchi and vessels, a pattern that Liebow referred to as *pulmonary sarcomatosis*. Some metastatic angiosarcomas masquerade either as primary vascular tumors or as

diffuse pulmonary hemorrhage.^{540,681} Among uterine tumors, well-differentiated leiomyosarcomas are well known for their ability to simulate leiomyomatous hamartomas, and endometrial stromal sarcomas have often been confused with primary hemangiopericytomas, spindle carcinoid tumors, and other lung primary neoplasms. The fact that the interval between the removal of the original tumors and the appearance of the (often single) lung metastasis can be measured in years or decades contributes to the potential diagnostic pitfall.⁵³⁶ Another potential diagnostic pitfall pertains to cystic metastases from low-grade nonepithelial tumors (Fig. 10.160), such as cutaneous fibrous histiocytomas (cystic fibrohistiocytic tumors⁶⁸²), dermatofibrosarcoma protuberans, and low-grade smooth muscle tumors, that may mimic other forms of cystic lung disease such as lymphangioleiomyomatosis or LCH.

When the pulmonary metastatic foci are few (*oligometastases*) and sharply circumscribed, they may be amenable to surgical excision (metastasectomy).⁶⁸³⁻⁶⁸⁵ Poor prognostic signs are multiplicity and size of metastases and presence of extrapulmonary disease. A particularly aggressive approach has been taken toward lung metastases in children, often including some combination of metastasectomy, radiation, and chemotherapy. Five-year survival rates of 25%–40% have been obtained, which is a remarkable achievement.⁶⁸⁶

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