22 Lungs

Normal Histology

The lungs consist of principally four compartments: the large airways (bronchi), small airways and airspaces (bronchioles and alveoli), interstitium, and vessels. As in most organs, inflammatory processes tend to preferentially involve one or two compartments, so identifying the most affected area is key to the differential diagnosis. Normal histologic features include the following:

- *Bronchi*: The bronchi are lined with ciliated or columnar epithelium with scattered goblet cells. Goblet cell metaplasia is an indication of irritation, such as in bronchitis or asthma. Squamous cell metaplasia is common in smokers. Under the epithelium you should find seromucinous (salivary-type) glands, cartilage, smooth muscle, and branches of the bronchial arteries (Figure 22.1).
- *Bronchioles*: Bronchioles should have a cuboidal epithelium without goblet cells (Figure 22.2). The Clara cells are probably secretory and reserve cells, but they are difficult to see. There is no cartilage.
- *Alveoli*: The alveoli are the terminal air sacs and therefore have extremely thin walls (see Figure 22.2); in atelectasis, a common biopsy artifact, it is difficult to pick out the collapsed airspaces. Normally they are lined by nearly invisible flat type I epithelium. The presence of a cuboidal epithelium indicates type II hyperplasia (surfactant and reserve cells, which are normally sparse), seen in chronic inflammation or repair. Alveolar macrophages are often scattered throughout but macrophages packing the alveoli is pathologic (see later discussion of desquamative interstitial pneumonia).
- *Vessels*: Pulmonary arterioles run with bronchioles and have two elastic layers on Movats stain (train track appearance). Veins run in interlobular septa and have one irregular elastic lamina. Lymphatics run with arteries, veins, and in pleura.

Movats stain is a standard supplemental stain for nonneoplastic lung. On this pentachrome stain, you will see elastic laminae highlighted as black fibers (useful for identifying pleural involvement by tumors as well), hyaluronic acid or mucin in aqua blue, mature collagen in yellow, smooth muscle in dull red, and fibrinoid necrosis (as in vessels) as bright red (Figure 22.3). This stain is very useful for identifying fibroblast foci in bronchiolitis obliterans–organizing pneumonia (discussed later) because they stand out as turquoise swirls on low power. Established interstitial fibrosis will be yellow.

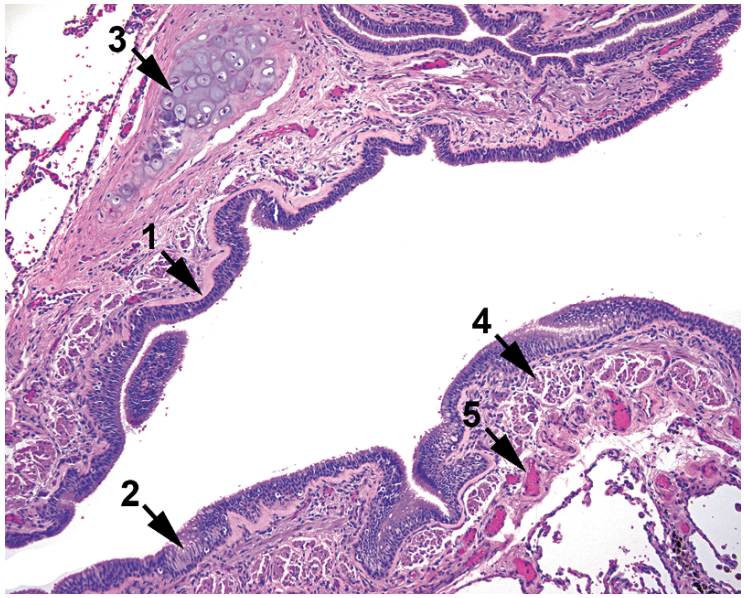

Figure 22.1. Normal bronchus. The bronchus is lined by ciliated columnar epithelium (1), foci of goblet cells (2), cartilage (3), and smooth muscle (4). The small arteries seen here (5) are branches of the bronchial artery, which carries oxygenated blood from the left ventricle.

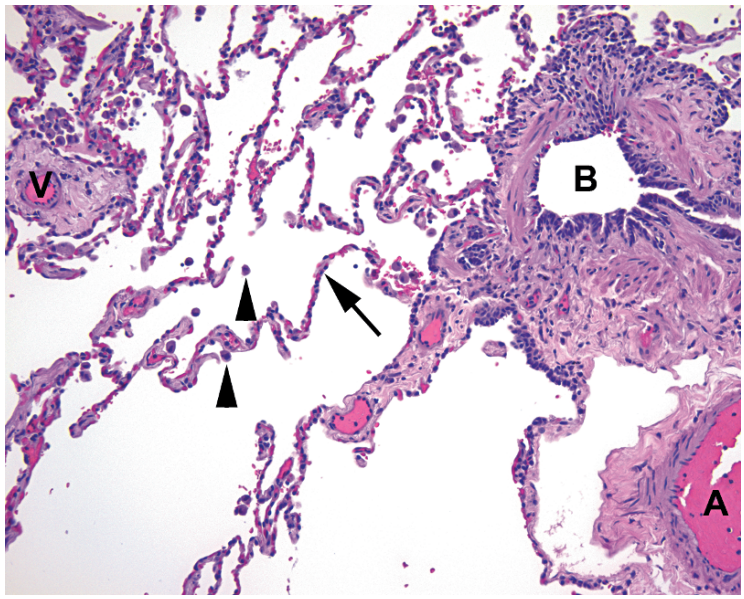

Figure 22.2. Bronchioles and alveoli. The small bronchiole (B) seen here is lined by a cuboidal epithelium and smooth muscle. The large adjacent arteriole (A) is a branch of the pulmonary artery. The veins or venules (V) run in septa. The alveolar walls (arrow) are normally lined with flat type I epithelium, of which only the nuclei are visible. Alveolar macrophages (arrowheads) are common.

A Brief Introduction to Nonneoplastic Lung

In nonneoplastic lung, within each of the four compartments you are usually looking for something that does not belong. Examples of things that do not belong include heavy mononuclear cell infiltrates (lymphocytes and macrophages), neutrophils (other than in capillaries), eosinophils, granulomas, fibrosis and fibroblast foci, and substances such as amyloid, edema fluid, and asbestos. Table 22.1 lists differential diagnoses organized by what you see and in which compartment.

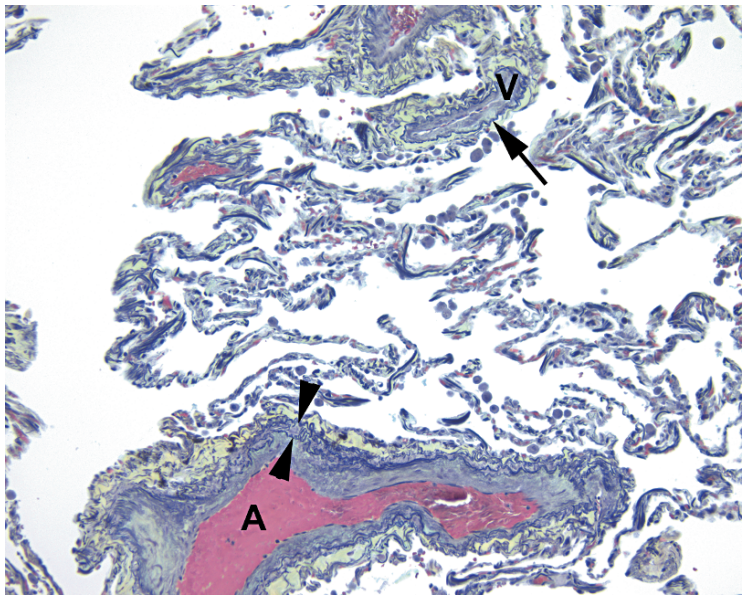

FIGURE 22.3. Movats stain. The pulmonary arteries (A) have two elastic layers (arrowheads), while the veins (V) have one (arrow). The collagen lining the vessels is pale yellow-green in this stain.

TABLE 22.1. Differential diagnoses.

	Large and small airways	Alveoli	Interstitium/septa	Vessels
Lymphocytes and mononuclear cells	Atypical/viral pneumonia EAA RB-ILD (macrophages)	Atypical/viral pneumonia DIP (macrophages) EAA	DAD (late or organizing)/AIP EAA NSIP, CIP, and LIP *Pneumocystis carinii* pneumonia UIP LCH (histiocytes)	
Neutrophils	Bronchopneumonia BCG	Bronchopneumonia	ACIP	Wegener's granulomatosis
Eosinophils	Asthma and ABPFD CEP BCG	Loeffler's syndrome CEP Churg-Strauss syndrome EAA	CEP	Churg-Strauss syndrome
Granulomas	BCG TB and fungus	TB and fungus	EAA Sarcoid Rheumatoid nodules	Churg-Strauss syndrome Invasive aspergillosis Sarcoid Wegener's granulomatosis
Fibrosis and fibroblast foci	BOOP OB	BOOP	DAD (late or organizing)/AIP DIP Pneumoconioses Sarcoid Systemic disease (RA, SLE) UIP	Pulmonary hypertension
Other substances (mucus, exudates, etc)	Asthma Chronic bronchitis	Early DAD (HM) Goodpasture's syndrome (heme) PAP (exudate) *P. carinii* pneumonia (foam)	Pneumoconioses (refractile material) Lymphangioleiomyomatosis (smooth muscle)	Amyloidosis DAD (fibrin thrombi)

ABPFD, allergic bronchopulmonary fungal disease; ACIP, active chronic interstitial pneumonitis; AIP, acute interstitial pneumonitis; BCG, bronchocentric granulomatosis; BOOP, bronchiolitis obliterans–organizing pneumonia; CEP, chronic eosinophilic pneumonia; CIP, chronic interstitial pneumonia; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; EAA, extrinsic allergic alveolitis (hypersensitivity pneumonitis); HM, hyaline membranes; LCH, Langerhans cell histiocytosis; LIP, lymphocytic interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OB, obliterative bronchiolitis; PAP, pulmonary alveolar proteinosis; RA, rheumatoid arthritis; RB-ILD – respiratory bronchiolitis–interstitial lung disease; SLE, systemic lupus erythematosus; TB, tuberculosis; UIP – usual interstitial pneumonia.

Response to Injury in the Lung

It is useful to think of the three phases of injury response in the lung: acute, subacute, and chronic. *Acute injury*, which may be from infection, trauma, toxins, drugs, or a transfusion reaction, manifests as *diffuse alveolar damage*. Clinically this pattern correlates with acute respiratory distress syndrome. Idiopathic diffuse alveolar damage, when no known precipitating factor can be identified, is called *acute interstitial pneumonitis*. The histologic picture is a nonspecific indication of injury and includes interstitial edema and hemorrhage, hyaline membrane formation, type II hyperplasia, and fibrin thrombi (Figure 22.4). There should be a uniform and diffuse appearance throughout the field of view (although it may be patchy grossly).

When the initial injury begins to resolve, you see the organizing phase, which consists of new fibroblast foci forming in alveoli and bronchioles. These are the swirling nodules of stellate fibroblasts that appear myxoid on H&E stain and aqua on Movats stain (Figure 22.5). They are also the hallmark of *bronchiolitis obliterans–organizing pneumonia* (BOOP), the pattern of *subacute injury* response. It can be impossible to distinguish a primary BOOP from a resolving acute injury without the clinical context. It is also seen as a component of many other disease processes, but as a primary disease it is simply "idiopathic BOOP." Obliterative bronchiolitis is a related lesion that is really only seen in transplant patients, and is a form of either rejection or graft-versus-host disease.

Chronic and repetitive injury to the lung is like a scab on the skin that gets repeatedly picked off; there are multiple cycles of damage and repair, and the end result is chronic inflammation and fibrosis. The final common pathway of many diseases, or end-stage lung, is called honeycomb lung. A specific pattern of chronic injury that may lead to honeycomb lung is *usual interstitial pneumonia*. Usual interstitial pneumonia is a nonspecific pattern; *idiopathic pulmonary fibrosis* is the name given to idiopathic usual interstitial pneumonia.

Usual interstitial pneumonia should be *temporally heterogenous*, which means you should see evidence of all stages of injury (acute, subacute, and chronic). There is prominent interstitial fibrosis, which outlines large and angular distorted airspaces (Figure 22.6), but there should also be fibroblast foci. The airspaces are lined by plump, reactive, and scary looking type II pneumocytes. There is diffuse chronic inflammation, as well as pockets of acute inflammation.

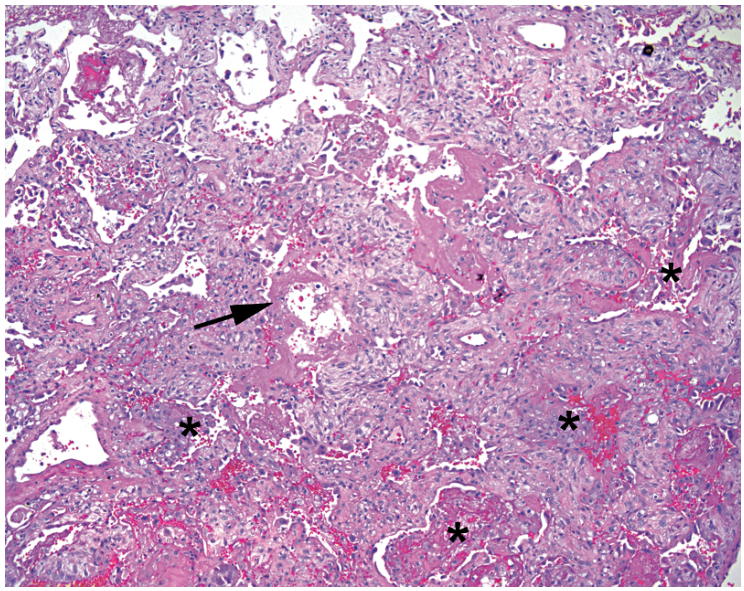

Figure 22.4. Diffuse alveolar damage. The alveolar spaces are full of fluid and blood (asterisk), which in some areas is beginning to coalesce into thick pink hyaline membranes (arrow). The interstitial spaces are thickened due to edema.

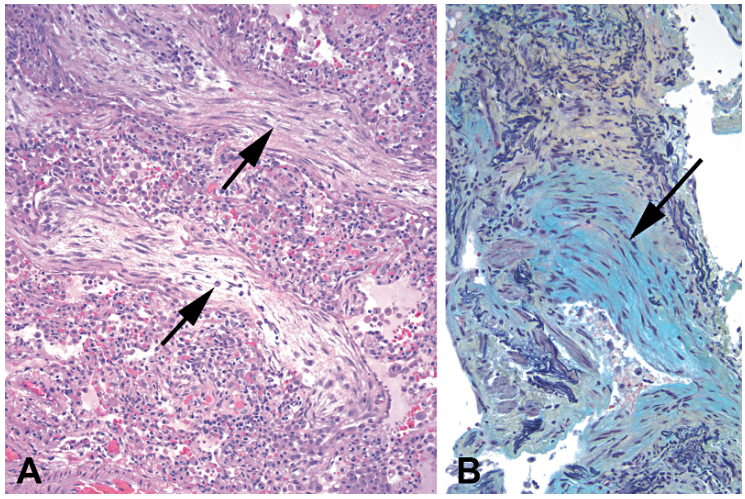

Figure 22.5. Fibroblast foci. **(A)** By H&E stain, these myxoid swirls of new fibroblasts are pale and streamy (arrows). **(B)** On Movats stain, they are turquoise (arrow).

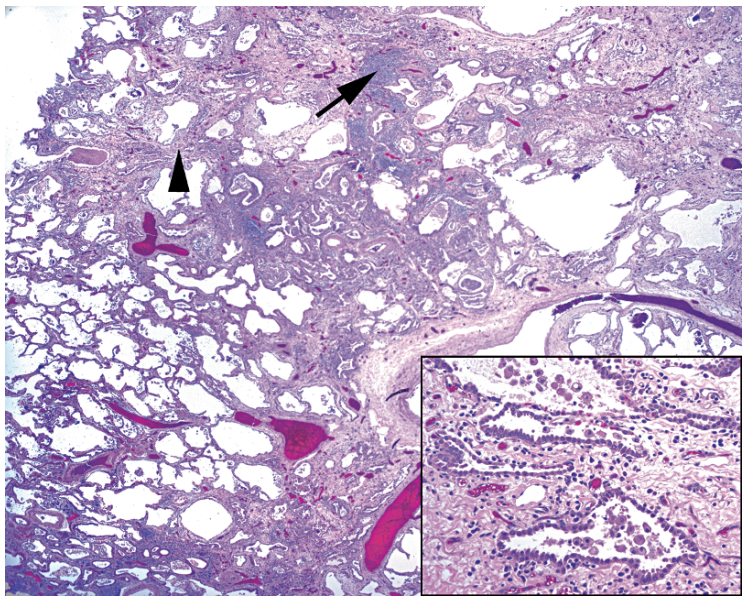

Figure 22.6. Usual interstitial pneumonia. The interstitial spaces are thickened and fibrotic (arrowhead), and there is abundant chronic inflammation (arrow). **Inset**: The scarred down, irregularly shaped, residual alveolar spaces are lined with type II pneumocytes, which protrude into the lumen and may have atypical nuclei.

Allergic Disease

There are two forms of allergic response in the lung: IgE-mediated disease and cell-mediated hypersensitivity reactions. Diseases in the first category include asthma, allergic bronchopulmonary fungal disease, bronchocentric granulomatosis (allergy to *Aspergillus*), and the eosinophilic pneumonias.

The prototypical cell-mediated hypersensitivity disease is *extrinsic allergic alveolitis*. It can have many causes and many appearances. This includes all the "(undesirable-job-here)'s lung" and "(exotic-pet-name) fancier's lung" diseases (e.g., "formalin lung" and "lizard-lover's lung"). Eosinophils do *not* feature prominently in extrinsic allergic alveolitis. The classic histologic

triad includes (1) patchy chronic interstitial pneumonia, especially peribronchiolar; (2) poorly formed small nonnecrotizing granulomas; and (3) foci of BOOP.

Diseases of Smokers

Smokers get a spectrum of interstitial lung diseases, including desquamative interstitial pneumonitis (DIP), respiratory bronchiolitis, Langerhans cell histiocytosis, and probably usual interstitial pneumonia. They also get obstructive lung disease, which includes chronic bronchitis and emphysema. DIP is a disease process in which alveolar macrophages pack the alveoli; it is usually associated with smoking, but a DIP pattern may be seen in other processes as well.

Note that Langerhans cell histiocytosis, also called *eosinophilic granuloma*, does not have traditional granulomas and may not always have eosinophils. What it does have is collections of histiocytes, identified by their pale nuclei with folds and creases (or by immunostains). This disease may occur systemically in the pediatric population, but in adults (which are 50% of cases) it is an isolated pulmonary disease of smokers.

Neoplastic Lung

Dysplasia and Carcinoma In Situ

The terms *dysplasia* and *carcinoma in situ* are not often used in pulmonary pathology. There are at least two types of epithelium that can be evaluated, the respiratory (columnar) and the squamous metaplastic. For the respiratory epithelium, the presence of cilia is a reassuring sign that all is well (Figure 22.7). However, chronically injured or irritated airspaces can get type II cell hyperplasia. On the slide, this appears as plump cuboidal to columnar eosinophilic cells, with enlarged nuclei, lining the airspaces. If this occurs as a prominent change within a small focus (less than 10 mm), it is analogous to dysplasia and is called *atypical adenomatoid hyperplasia* (Figure 22.8). Presumably these foci can go on to become bronchioloalveolar carcinoma, which is essentially adenocarcinoma in situ. Like dysplasia in other organs, these processes can be multifocal.

For squamous epithelia, although squamous dysplasia exists and is analogous to other organs, in practice it is not often caught on biopsy. Similarly, squamous carcinoma in situ

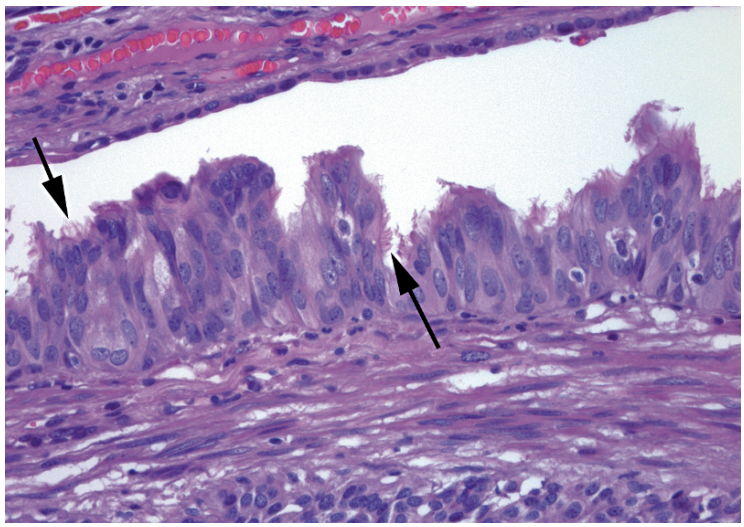

Figure 22.7. Reactive bronchial epithelium overlying a carcinoid tumor. Although the epithelium is very proliferative and has enlarged and crowded nuclei, the presence of cilia (arrows) indicates that these cells are benign.

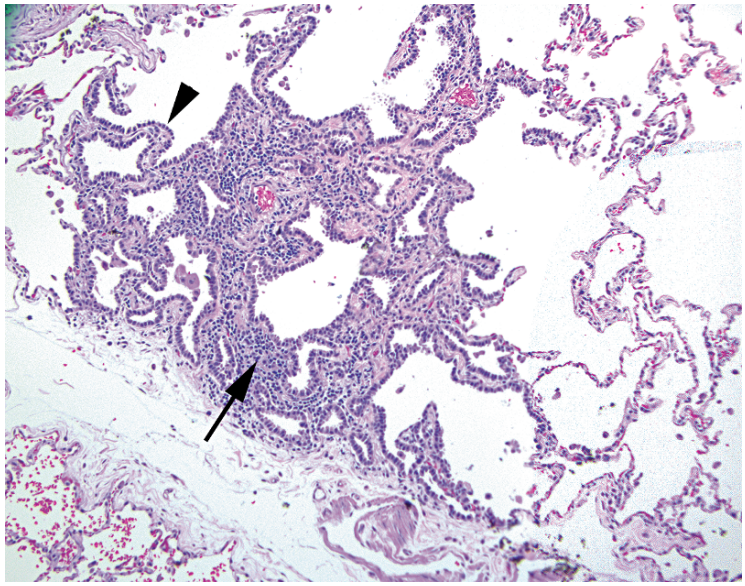

Figure 22.8. Atypical adenomatoid hyperplasia. In this tiny, limited focus, there is interstitial inflammation (arrow) and prominent type II hyperplasia (arrowhead). The adjacent alveolar walls are unremarkable.

exists in the bronchi just as in the larynx or oropharynx but is usually seen at the periphery of squamous cancers instead of as the sole finding in a biopsy specimen.

Carcinoma

Most lung biopsies in the neoplastic category are performed because a mass lesion was detected on radiology. Dysplasia and carcinoma in situ generally are not mass forming, so once you have ruled out a granulomatous process (those can form nodules), you are trying to identify the neoplasm. The most common lesions are discussed below. However, keep in mind than in lung, most tumors are a mix of tumor types or variants (pluripotent stem cells?), so you must sample well, name the tumors for their major components, and ignore small foci of different morphologies. *Non–small cell* is sort of a wastebasket term used to mean *adenocarcinoma* or *squamous cell carcinoma*, which can be grouped like that because their clinical behavior is similar.

Squamous carcinoma arises from squamous metaplasia, often in the major bronchi, and therefore is often central or hilar. The most recognizable form is the well to moderately differentiated keratinizing variety, with its pink, dense cytoplasm, keratin whorls, and distinct cell borders (Figure 22.9). It is graded on the typical well, moderately, or poorly differentiated scale. However, there are trickier variants, including the following:

- Nonkeratinizing
- Basaloid: blue and palisading, with a dense syncytial look (see Figure 22.9)
- Small cell: similar to small cell neuroendocrine, but with uglier nuclei and no neuroendocrine staining
- Spindle cell or sarcomatoid: densely cellular spindly pattern, resembling a sarcoma (Figure 22.10)
- Clear cell (adenocarcinoma can also have clear cells)
- Intrabronchial papillary: architecture like a papilloma, but malignant

Adenocarcinoma arises from multiple cell types and therefore can vary in morphology. Patterns include acinar, tubular, papillary, and solid, and they may be mucinous or nonmucinous. If you see gland formation or mucin production, it is almost certainly adenocarcinoma (Figure 22.11), and then you must decide if it is primary or metastatic.

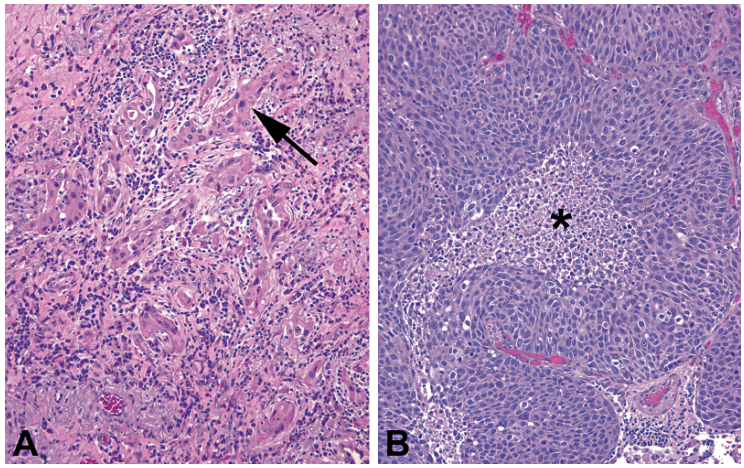

FIGURE 22.9. Squamous cell carcinoma. **(A)** Moderately differentiated squamous cell carcinoma, with irregular nests of cells with highly pleomorphic nuclei and bright pink, dense cytoplasm (arrow). Keratin pearls may also be seen in more well-differentiated tumors. **(B)** Basaloid squamous cell carcinoma, with rounded nests of very blue tumor cells with high nuclear to cytoplasmic ratio and a high mitotic rate. Central necrosis (asterisk) is common.

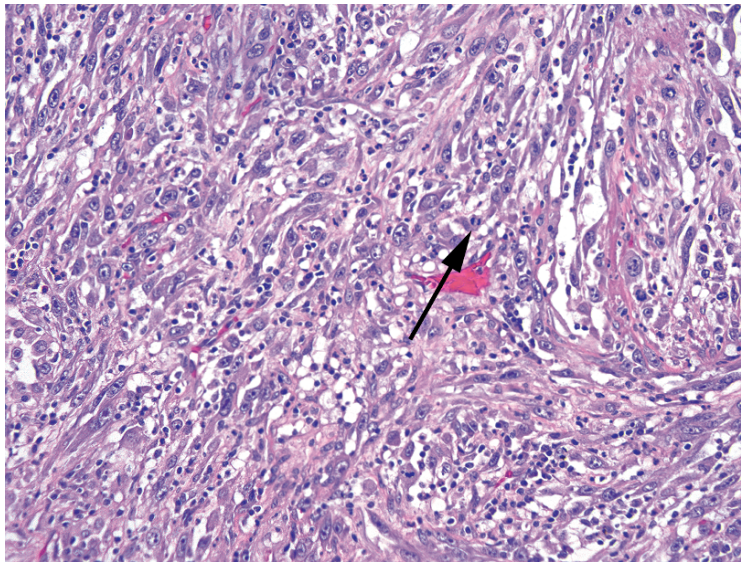

FIGURE 22.10. Sarcomatoid carcinoma. Sheets of spindled cells with large nuclei and prominent nucleoli are visible. Mitoses (arrow) are common. These cells should be positive for cytokeratin stains, confirming their epithelial origin.

As described earlier, *bronchioloalveolar carcinoma* (BAC) is the in situ form of adenocarcinoma. BAC in pure form appears to have a better prognosis than other non–small cell cancers, but, surprisingly, it still behaves, and is managed like, a full-fledged carcinoma. BAC may be mucinous (probably arising from goblet cell metaplasia) or nonmucinous. Of the two, the nonmucinous type has a better prognosis and is more often solitary.

BAC takes the form of columnar and usually eosinophilic cells growing along the bronchial and alveolar walls, outlining the structure of the airspaces (Figure 22.12). By definition, there must not be evidence of stromal invasion (irregularly shaped back-to-back glands, single cells, desmoplasia). BAC is often found at the periphery of invasive tumors, so this diagnosis should

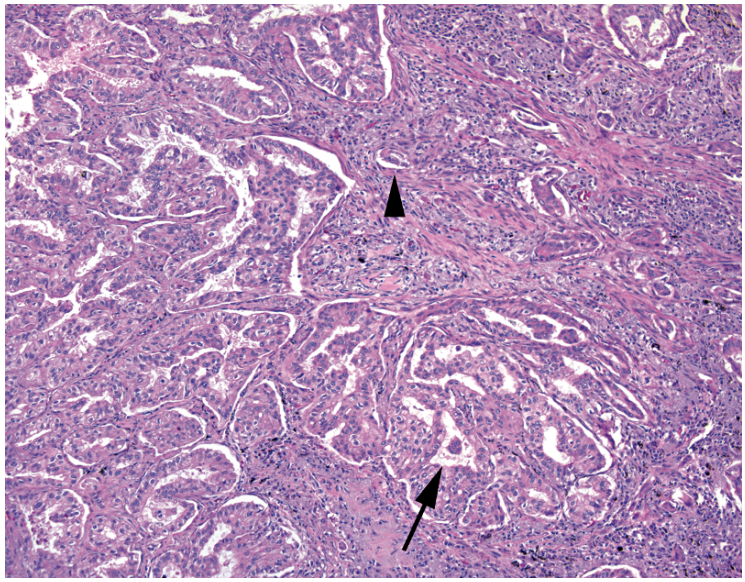

FIGURE 22.11. Adenocarcinoma. In some areas this tumor is forming cribriform glandular spaces (arrow), and in others small malignant glands or single cells are seen embedded in a desmoplastic stroma (arrowhead), confirming invasion.

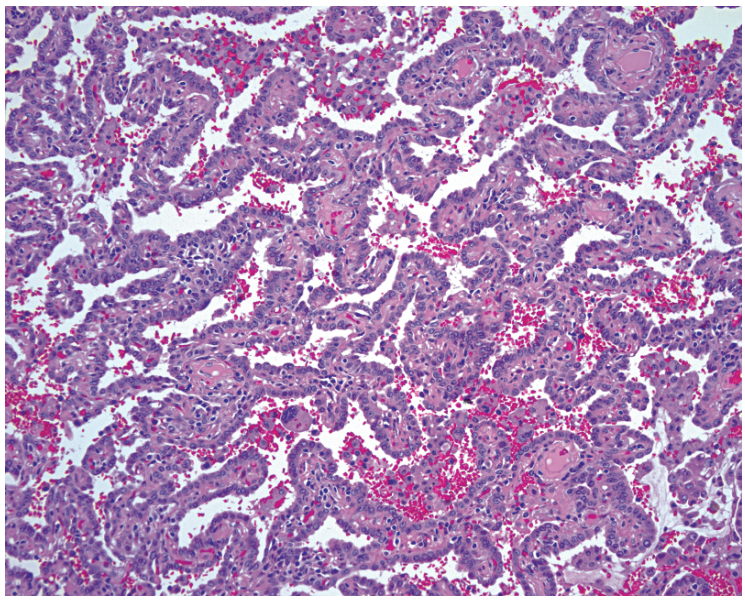

FIGURE 22.12. Bronchoalveolar carcinoma. The malignant cells line the alveolar walls but do not invade the stroma.

not be made on a biopsy specimen or frozen tissue or until the entire tumor has been sampled. This rule applies to most "improved-prognosis variant" tumors in pathology: you had better not label something as a good-prognosis tumor unless the entire lesion is of that type. A "BAC pattern" refers to a growth pattern of an invasive tumor that mimics BAC.

Large cell undifferentiated carcinoma arises when adenocarcinoma dedifferentiates into a very ugly tumor with no recognizable glandular features. It can also acquire pleomorphic or giant cell features. Another variety is the lymphoepithelioma-like carcinoma (scattered large

malignant cells in a sea of lymphocytes). Neuroendocrine carcinoma can have large-cell morphology; this is discussed below.

Neuroendocrine Tumors

The neuroendocrine spectrum is broad and confusing in the lung. Rosai's *Surgical Pathology* has a nice categorization of the tumor types, which includes the following:

- *Carcinoid*: A carcinoid is a well-differentiated (but not benign) neoplasm with classic neuroendocrine features, including epithelial-to-spindled architecture, regular round nuclei with fine chromatin, and no nucleoli (Figure 22.13). Despite the appearance, carcinoids can metastasize to lymph nodes.
- *Atypical carcinoid*: Atypical carcinoids are carcinoids with (1) increased mitoses, 2–10 per 10 high-power fields; (2) hyperchromatic nuclei; or (3) necrosis.
- *Small cell carcinoma*: Small cell carcinoma is a high-grade neuroendocrine neoplasm with small cell morphology, including solid-to-trabecular-to-tubular patterns, hyperchromatic finely granular (denim-blue) nuclei, no nucleoli, syncytial appearance with nuclear molding, mitoses/apoptosis/necrosis, and streaming crush artifact (Figure 22.14). Small cell carcinoma may be found in combination with other carcinomas.
- *Large cell neuroendocrine*: A large cell neuroendocrine tumor is a high-grade neuroendocrine neoplasm with some neuroendocrine features, either architectural or nuclear, and positive neuroendocrine immunostains. Note that the "large cell" refers to the presence of cytoplasm, not larger nuclei per se.
- *Non-small cell carcinoma with neuroendocrine features*: Per Rosai, this lesion looks like non–small cell by any criteria, but you happen to accidentally demonstrate that it is chromogranin positive.

Other Lesions (Incomplete Listing)

- Hamartoma: A hamartoma is a tumor-like mass composed of a disorganized mixture of the normal elements found in that organ. It is not clonal and therefore not really a neoplasm. In the lung, these are often masses of cartilage, fat, smooth muscle, and epithelium.

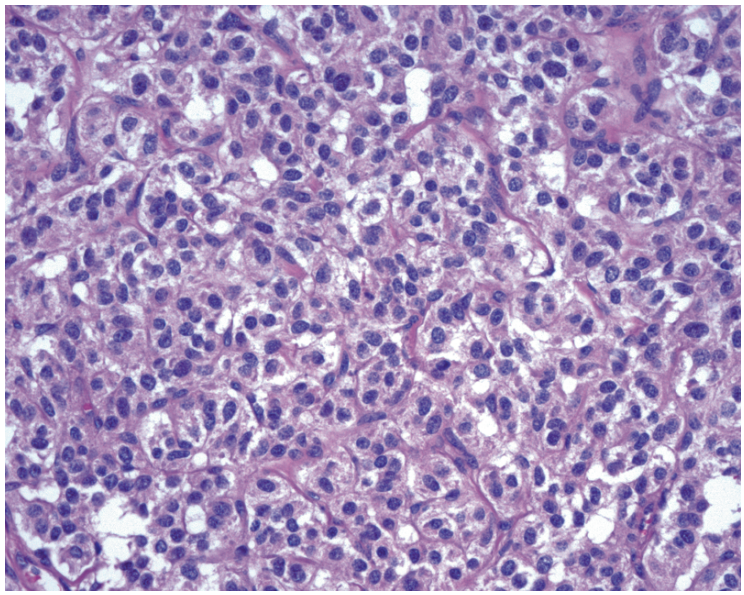

Figure 22.13. Carcinoid. This high-power view of an intrabronchial carcinoid shows a nested and trabecular pattern of cells with oval nuclei and typical "neuroendocrine" chromatin, meaning finely textured and speckled, without nucleoli or prominent nuclear membranes.

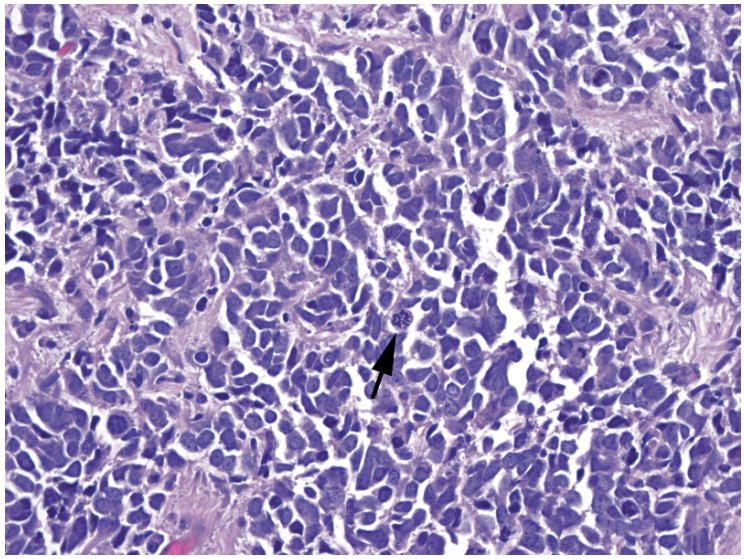

Figure 22.14. Small cell carcinoma. Sheets of nuclei appear molded together with interlocking shapes due to the near absence of cytoplasm. The chromatin, like low-grade neuroendocrine neoplasms, is uniform and lacks nucleoli. Necrosis and mitoses (arrow) are common.

- Salivary neoplasms: The seromucinous glands around the bronchi can give rise to any of the traditional salivary gland neoplasms.
- Carcinosarcoma: Carcinosarcoma is a truly biphasic malignant lesion, with a recognizable epithelial component (carcinoma) and a separate recognized form of sarcoma, such as osteosarcoma or chondrosarcoma. This is different from the sarcomatoid carcinoma, which is a pure carcinoma that has acquired spindle cell morphology.
- Pulmonary blastoma: Pulmonary blastoma is a form of carcinosarcoma in adults in which the epithelial component resembles fetal lung and the stromal component may be composed of adult-type sarcomas or immature mesenchymal tissue.
- Pleuropulmonary blastoma: Pleuropulmonary blastoma is an embryonal-type sarcoma of infancy, intrathoracic but often extrapulmonary, which may have cartilage and rhabdomyoblastic elements but not a carcinoma component.