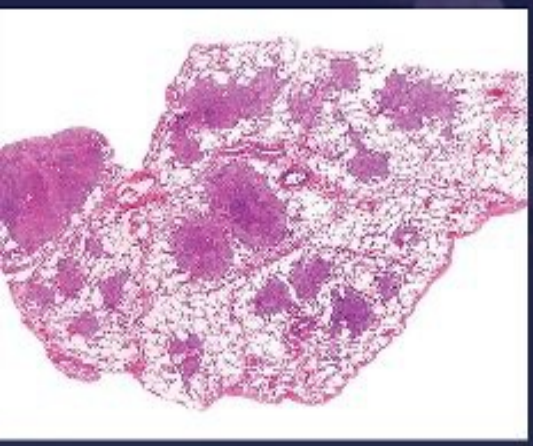
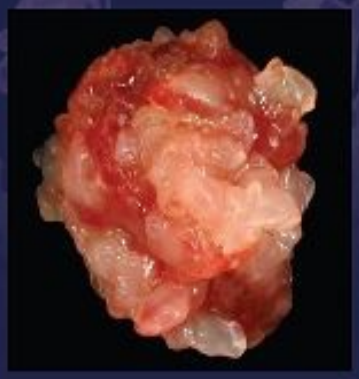
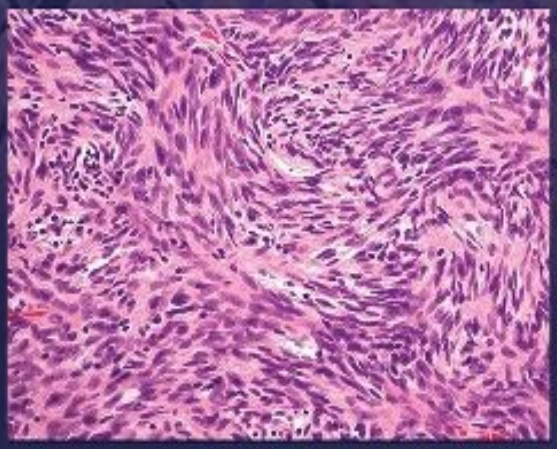
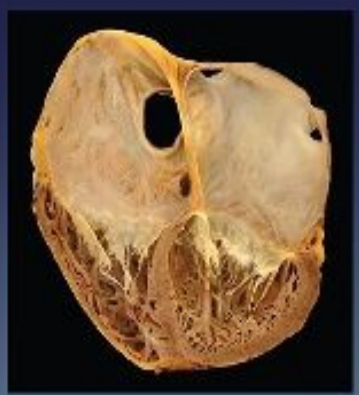
Practical Thoracic Pathology

Diseases of the Lung, Heart & Thymus



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Wolters Kluwer

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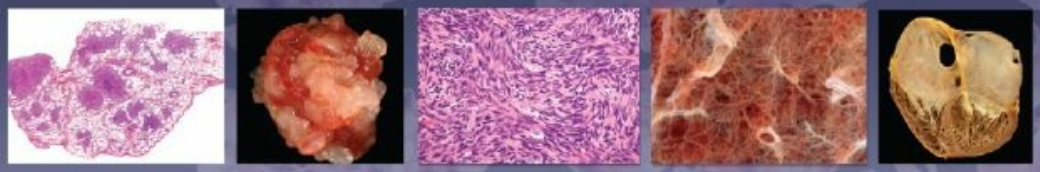

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To my family, to the clinicians and radiologists who help me make reasonable diagnoses, to my pathology colleagues, and to the many patients whose illnesses are described and depicted in this book.
Allen P. Burke

To all who have guided me along this journey, my teachers and mentors, my friends and colleagues, my residents and fellows, my family and parents, and above all my husband.
Marie-Christine Aubry

To Bill Edwards for his constant mentorship, support, and encouragement. To my wife, Brooke – a wellspring of patience and optimism. And our children, Emma and Joseph – sources of endless joy.
Joseph J. Maleszewski

To my wife Anna – it's a privilege to share my life and love with you. And to my children Alexander and Julia – your growth provides a constant source of joy and pride.
Borislav A. Alexiev

To Iusta, a woman of love and letters. To Andre and Igor: may they always have strong lungs and warm hearts.
Fabio R. Tavora

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Preface

Major changes mark the second edition of “Practical Cardiovascular Pathology.” Since the publication of the first book, we decided to expand the volume to include the lung and thymus. Much of this desire derived from our involvement in teaching residents and fellows in lung and mediastinal pathology as well as cardiac pathology. Our efforts in maintaining up-to-date lectures on new classifications in neoplastic and nonneoplastic lung disease led to the development of many of the chapters in the first section. Of course this book is a much larger undertaking than the last, requiring additional editors. We are indebted to MC Aubry and Joe Maleszewski for their huge contributions. Without their help, and the help of Bob Alexiev, this new volume would not have been thinkable. We also expanded the individual author list to include dozens of experts, tapping on expertise from Mayo Clinic, Baltimore, New York, and Brazil from a variety of institutions. In this area also we are grateful to our Mayo coeditors for seeking out the necessary breadth of expertise.

Our goal in this second edition is to fill a niche in the market for a pathology text that has reasonable depth, fits in one volume, and includes all structures in the thorax except the esophagus and bony structures. A semantic issue involving the title is the use of the word “thymus” instead of “mediastinum.” Although all areas of the mediastinum were covered except the esophagus, “thymus” was chosen as tumors and conditions of the thymus were emphasized in the second section.

Areas of recent developments in pulmonary pathology is an in-depth assessment of updated classifications of interstitial lung disease and carcinomas of the lung, with an intent to remain unbiased in discussing pros and cons of divergent approaches. Similarly for the thymus, we wanted to objectively present different points of view for the classification of epithelial tumors. In the case of carcinomas of the lung and thymus, and mesotheliomas of the pleura, the TNM classification (as of the time this book is in press) is in transition, but the upcoming staging, which should be published later this year or next, is presented in the chapters devoted to these entities with comparison to the current staging system.

The subject of the genetics of lung cancer is a moving target, and any review will be somewhat out-of-date as soon as the ink dries and the book is in press. Nevertheless, this important area is presented in some depth with the practicing pathologist in mind, focusing on current guidelines for genetic testing and what likely lies ahead.

The interpretation of nonneoplastic lung disease in general is facilitated by correlation with imaging studies and is greatly improved with interaction and mutual learning from our radiology colleagues, whom we frequently consult before committing to a diagnosis. How often are we led astray by incomplete clinical information, and only pointed to the correct diagnosis by obtaining imaging and clinical data? We are indebted in this book to Seth Kligerman, for his contributions to imaging in interstitial lung disease, as well as a separate chapter on the subject. Many of the chapters in the lung section include sections of radiologic findings and explain radiologic findings that correlate with pathologic diagnosis.

One objective in formulating this book was ease of use as a reference text. In the lung volume, there is a first section that introduces a “pattern” diagnosis approach, which provides differential diagnoses that are addressed in individual chapters in following sections. The result is a certain degree of redundancy, with numerous cross-references, which we believe will facilitate location of diagnostic entities in the differential diagnosis of a particular histologic finding.

The cardiac section (which formed the entire first edition) has been significantly changed with extensive reorganization of the material. The classification system of cardiomyopathy, for example, is complex and largely dependent on clinical and genetic material and has changed significantly over the past 10 years. For this reason, this sections was completely rewritten. Furthermore, the understanding of genetics of cardiomyopathy and sudden death has evolved tremendously. Because cardiovascular pathology requires knowledge of clinical cardiology, the cardiac volume discusses clinical correlation even more than the pulmonary and mediastinal sections. Our goal in the heart section was to maintain the “practical” nature of the first edition, while updating the material and making it even more relevant to day-to-day pathologic practice as a reference text.

We hope that residents, community pathologists, forensic pathologists, and academic pathologists who occasionally review thoracic pathologic materials find this volume to be a practical reference source for difficult and not-so-difficult diagnostic problems. Because of the depth of many of

the chapters, we would also hope that some subspecialty pathologists may also find the book of use. We hope this book helps practicing pathologists and those in training in the difficult areas of thoracic pathology, by providing a reference that answers in a more efficient or usable way than what is currently available.

Allen P. Burke
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Joseph J. Maleszewski
Borislav A. Alexiev
Fabio R. Tavora

Contents

SECTION TWELVE: BENIGN LUNG TUMORS

SECTION THIRTEEN: CARCINOMAS OF THE LUNG

SECTION TWO: THYMIC CARCINOMAS AND NEUROENDOCRINE TUMORS

SECTION THREE: NON-NEOPLASTIC LESIONS OF THE THYMUS

SECTION FOUR: NON-NEOPLASTIC LESIONS OF THE MEDIASTINUM

SECTION FIVE: GERM CELL TUMORS

SECTION SIX: HEMATOLOGIC NEOPLASMS

SECTION SEVEN: SOFT TISSUE TUMORS OF THE MEDIASTINUM

PART 3
Heart

SECTION ONE: GENERAL TOPICS

SECTION TWO: THE HEART IN SYSTEMIC DISEASE

SECTION THREE: ISCHEMIC HEART DISEASE

SECTION FOUR: CARDIOMYOPATHIES AND ENDOCARDIAL DISEASE

SECTION TEN: DISEASES OF THE THORACIC AORTA

PART 1
Lung

SECTION ONE
APPROACH TO DIAGNOSIS

1 Normal Anatomy and Histology, Specimen Processing, Pathologic Reporting, and Artifacts

Allen P. Burke, M.D., and Joseph J. Maleszewski, M.D.

Pulmonary Anatomy and Histology

General Features and Development

The respiratory system broadly includes the acini, which are primarily responsible for gas exchange, and the airways and blood vessels that deliver the gases and blood, respectively, to such.

The lungs begin development as bilateral and symmetric structures; they acquire asymmetry through development and therefore ultimately exhibit sidedness (situs). Pulmonary sidedness is determined by the position of the morphologic right and left lungs, which is largely driven by the relative position of the pulmonary arteries and bronchi. In normal sidedness (situs solitus), the right mainstem bronchus is short and eparterial, meaning that the right pulmonary artery travels anterior to the right upper and intermediate bronchi. The left upper lobe bronchus is longer and hyparterial, passing inferior to the left pulmonary artery (Fig. 1.1).

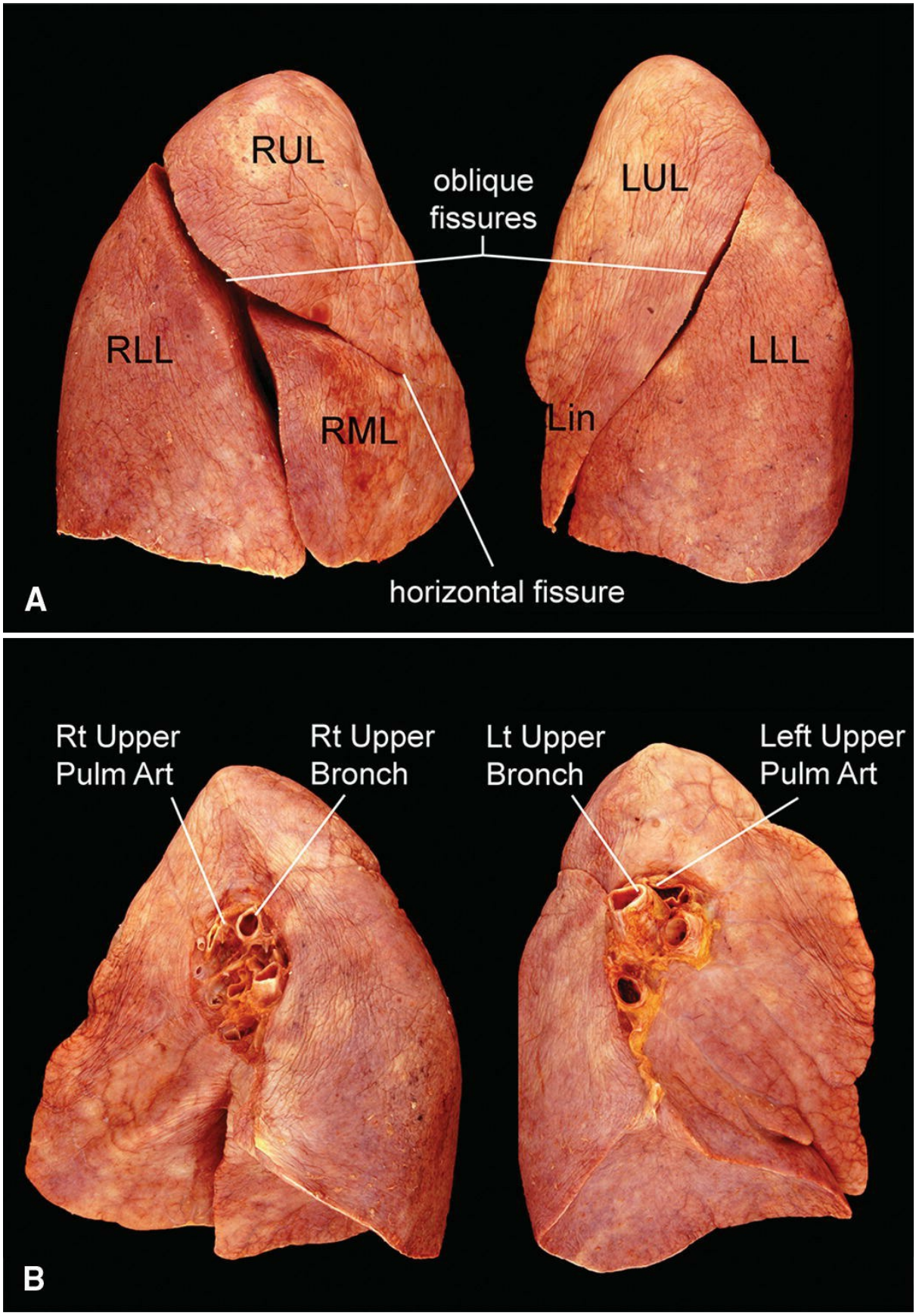


FIGURE 1.1 Gross pulmonary anatomy. **A.** Normal lobation pattern. **B.** Normal relationship of the pulmonary artery and

bronchus. A morphologic right lung shows the pulmonary artery anterior to the upper lobe bronchus, while a morphologic left lung shows the pulmonary artery superior to the upper lobe bronchus.

Airways

Airways can be categorized by structure/size (large cartilaginous and small noncartilaginous) and by function. The latter categorization divides airways into those that are responsible for transmitting gas to and from the units of gas exchange (conducting airways) and those that actually contain gas exchange units (respiratory airways). Regardless of classification, the airways begin at the trachea and end at the respiratory bronchiole.

The trachea enters the thoracic inlet, just distal to the larynx, along with vascular structures, esophagus, muscles, vagus and phrenic nerves, and thoracic duct. The trachea divides into the right and left bronchi, with a more acute angle to midline on the right (20 degrees) than on the left (35 degrees), leading to a propensity for aspirated material to enter the right bronchus. In addition to transmitting air to and from the acini, they also provide an important protective role, both immunologic and physical, with their lymphoid, epithelial, and mucociliary structures.

The airways are lined by respiratory epithelium, under which is the muscular layer. The bronchi have a cartilaginous and fibrous layer under the muscularis and mucus glands between the muscularis and cartilage (submucosa). The respiratory epithelium consists of mucus-secreting goblet cells, ciliated cells, scattered neuroendocrine cells, and a basal layer. Additionally, there is a population of pulmonary brush cells, which differ ultrastructurally from ciliated cells, thought to be involved in fluid absorption.[1] The ciliated cells are important in mucous transit and the clearance of particulate matter from the airways back to the environment. Ultrastructurally, the cilia consist of nine doublets that surround a central pair (Fig. 1.2). Dynein arms (inner and outer) join the peripheral doublets, and radial spokes connect the peripheral doublets to the central pair. Identification of these normal structures is critical in the evaluation for primary ciliary dyskinesia.

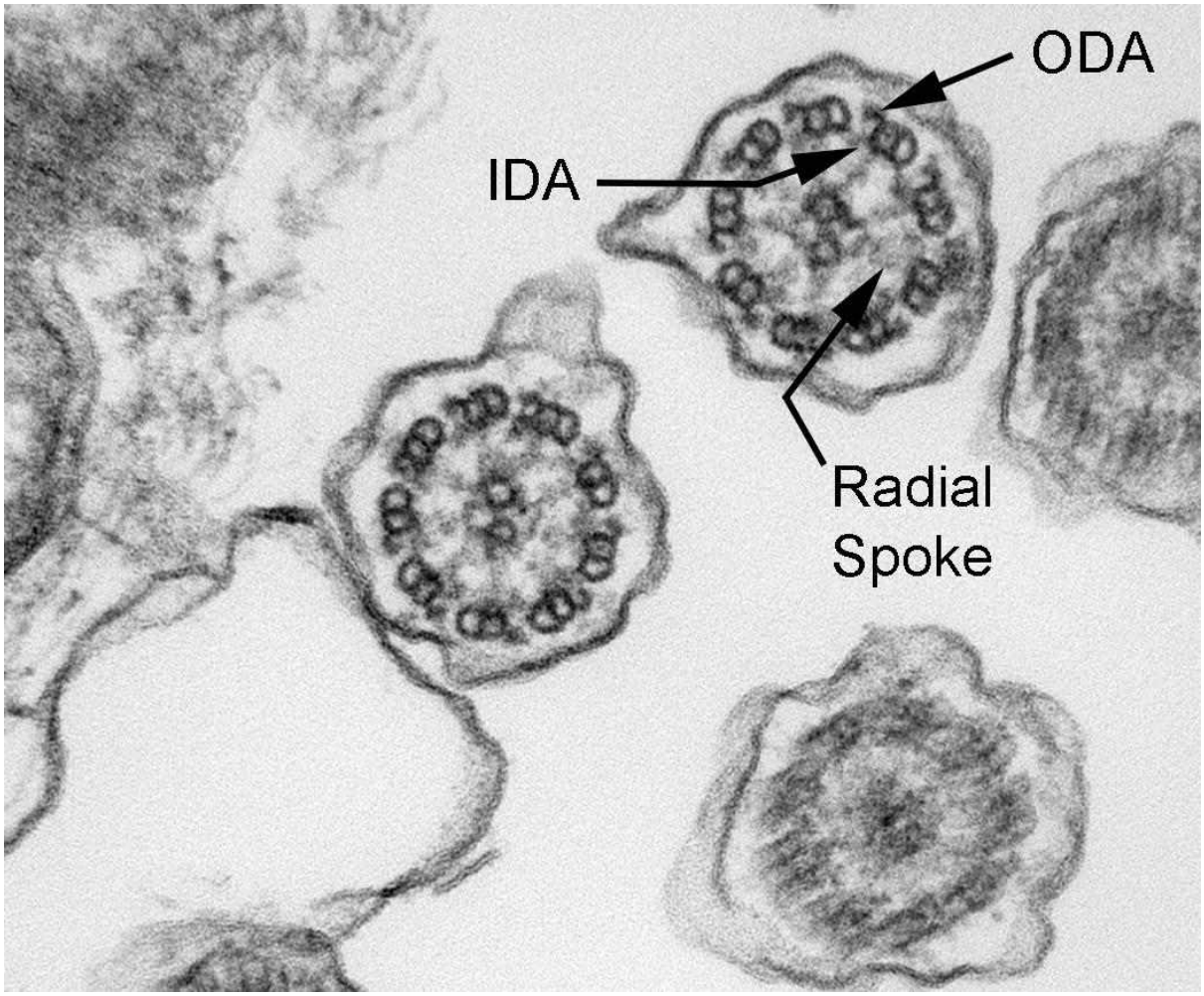


FIGURE 1.2 Ciliary ultrastructure. Nine outer doublets radiate around a central pair and are connected to such via radial spokes. Inner dynein arms (IDA) and outer dynein arms (ODA) are visible extending from the outer doublets. Absences or abnormalities of these dynein arms are the most common morphologic finding in cases of primary ciliary dyskinesia.

All epithelial cells express cytokeratins, including cytokeratin 7; in addition, the basal cells express p40 and p63. TTF-1 expression is limited to respiratory bronchioles, which contain Clara cells (surfactant-producing cells), and to alveolar lining cells (pneumocytes). In general, the number of goblet and ciliated cells decreases in the distal airways, and the respiratory bronchioles are composed primarily of basal and Clara cells.

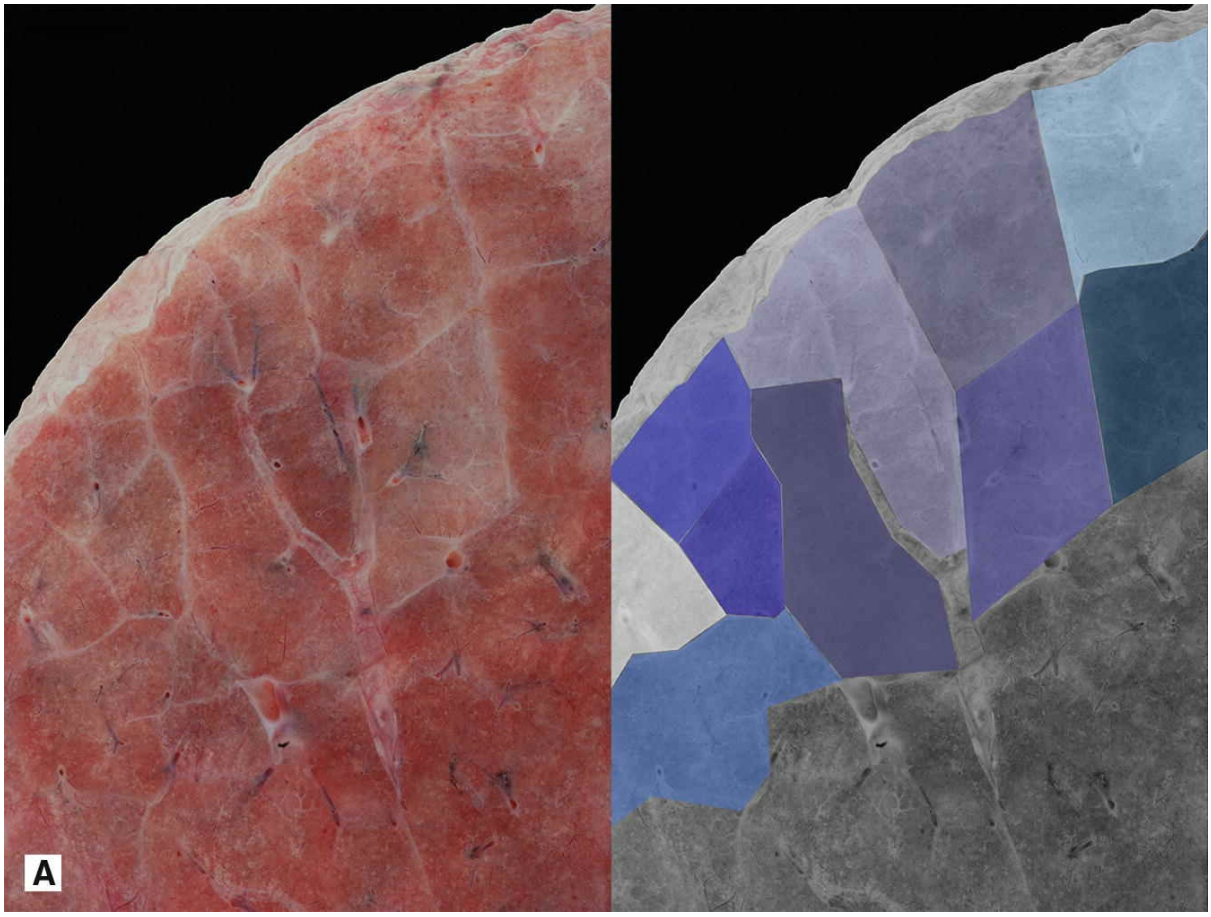
Lobation and Lung Segments

The left and right lung lobes are separated by interlobar fissures, usually one on the left and two on the right (Fig. 1.1). Oblique fissures, on each right and left lung, divide the upper and lower lobes and travel from the upper lateral to lower medial lungs. A horizontal fissure on the right separates the upper and middle lobes. Incomplete development or absence of the horizontal fissure is a common variant, resulting in a two-lobed right lung.[2] This is why lung laterality is best assigned by the relationship of the bronchus and pulmonary artery, rather than lobation.

There are 19 bronchopulmonary segments: 10 on the right and 9 on the left, owing to fusion of the apical and posterior segments of the left upper lobe (Table 1.1). Secondary pulmonary lobules (Fig. 1.3), the smallest unit recognized by high-resolution computed tomography (CT), are 1.0- to 2.5-cm polyhedral collections of acini (see below) served by terminal bronchioles. They are bounded by the pleura and the interlobular septa.

TABLE 1.1 Lung Segments

Lobe	Segments
Right upper	Apical
	Posterior
	Anterior
Right middle	Lateral
	Medial
Right lower	Superior
	Medial basal
	Anterior basal
	Lateral basal
	Posterior basal
Left upper	Apicoposterior
	Anterior
	Superior lingular
	Inferior lingular
Left lower	Superior
	Medial basal
	Anterior basal
	Lateral basal
	Posterior basal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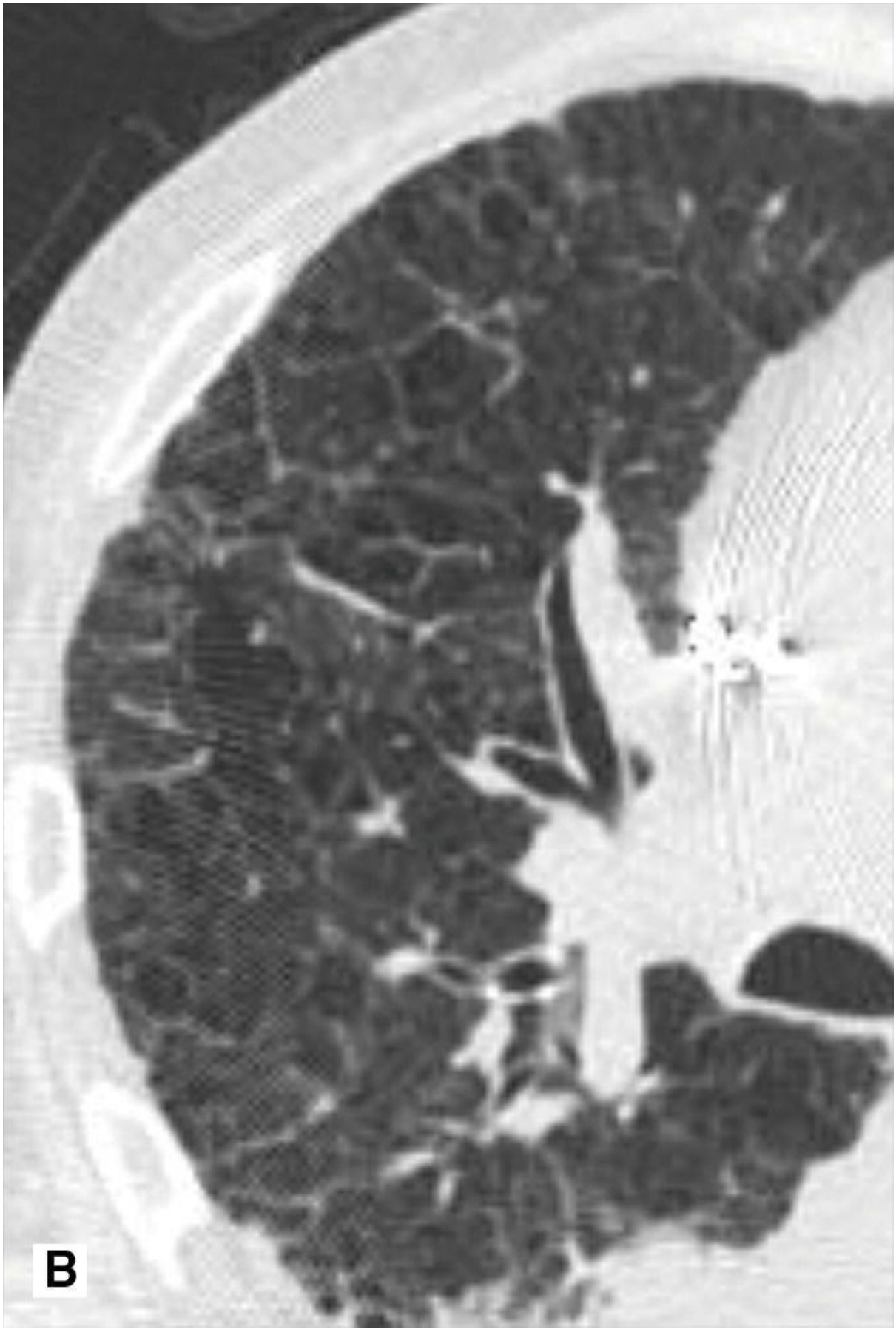

FIGURE 1.3 Secondary pulmonary lobules. **A.** These

polygonal lobules are bounded by the interlobular septa and pleura. **B.** The secondary lobules (sometimes called "pulmonary lobule") are the smallest recognizable organizational unit identified by high-resolution CT scan (seen here in this case of pulmonary venoocclusive disease).

Alveoli

Each secondary lobule contains between 10 and 15 acini (the functional units), which include all the alveoli containing structures distal to the terminal bronchiole. The alveoli are the sac-like structures involved in gas exchange and receive air from the upstream airways. The alveoli themselves measure ~200 μm across. Some alveolar sacs arise directly from respiratory bronchioles without connections through primary lobules.

The histologic features in two dimensions do not readily allow for distinction between the various alveolar compartments. Respiratory bronchioles may be seen adjacent to alveoli, whereas bronchioles are generally seen on cross section.

The lining cells of the terminal bronchioles and alveoli are composed of TTF-1–positive Clara cells in the former and pneumocytes in the latter. Mature type I pneumocytes are flattened, attenuated squamous cells with abundant cytoplasm, and small nuclei are generally not visible in normal sections and cover over 95% of the alveolar surface. They are attached to one another by desmosomes and occluding junctions. Pneumocytes with the ability to regenerate are type II pneumocytes, which have surfactant production capability. They are cuboidal and cover a much smaller surface area (<5%), despite the fact that they are actually more numerous than type I pneumocytes.

Approach to Histologic Evaluation of Peripheral Lung Tissue

When evaluating lung tissue, starting at low magnification helps to characterize the overall architecture and pattern of any pathology. Identification of bronchovascular bundles, small airways, interlobular septa, alveolar septa, and pleural surfaces should also be done at this time (Figs. 1.4 to 1.7). Patterns of pathology can help to establish a differential diagnosis.

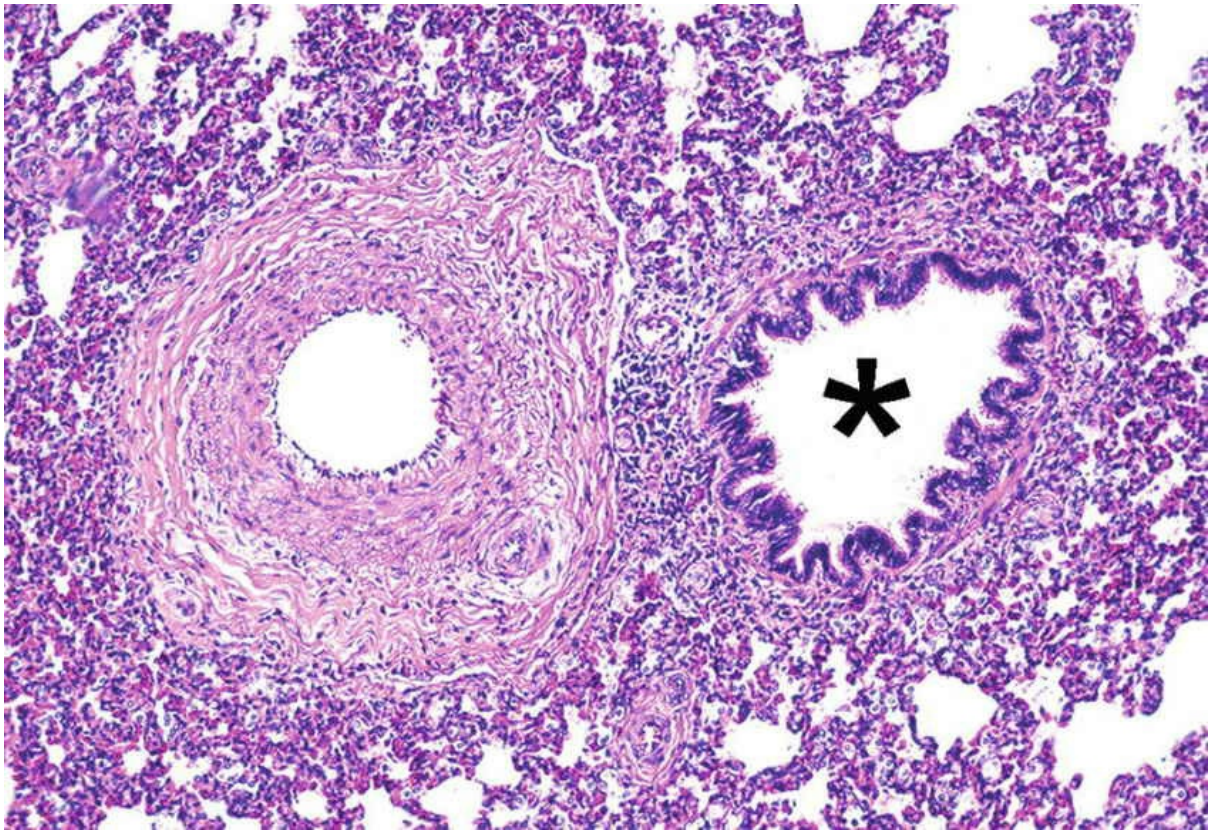

FIGURE 1.4 Bronchovascular bundle. The airways (*asterisk*) travel with muscular pulmonary arteries and are of similar caliber.

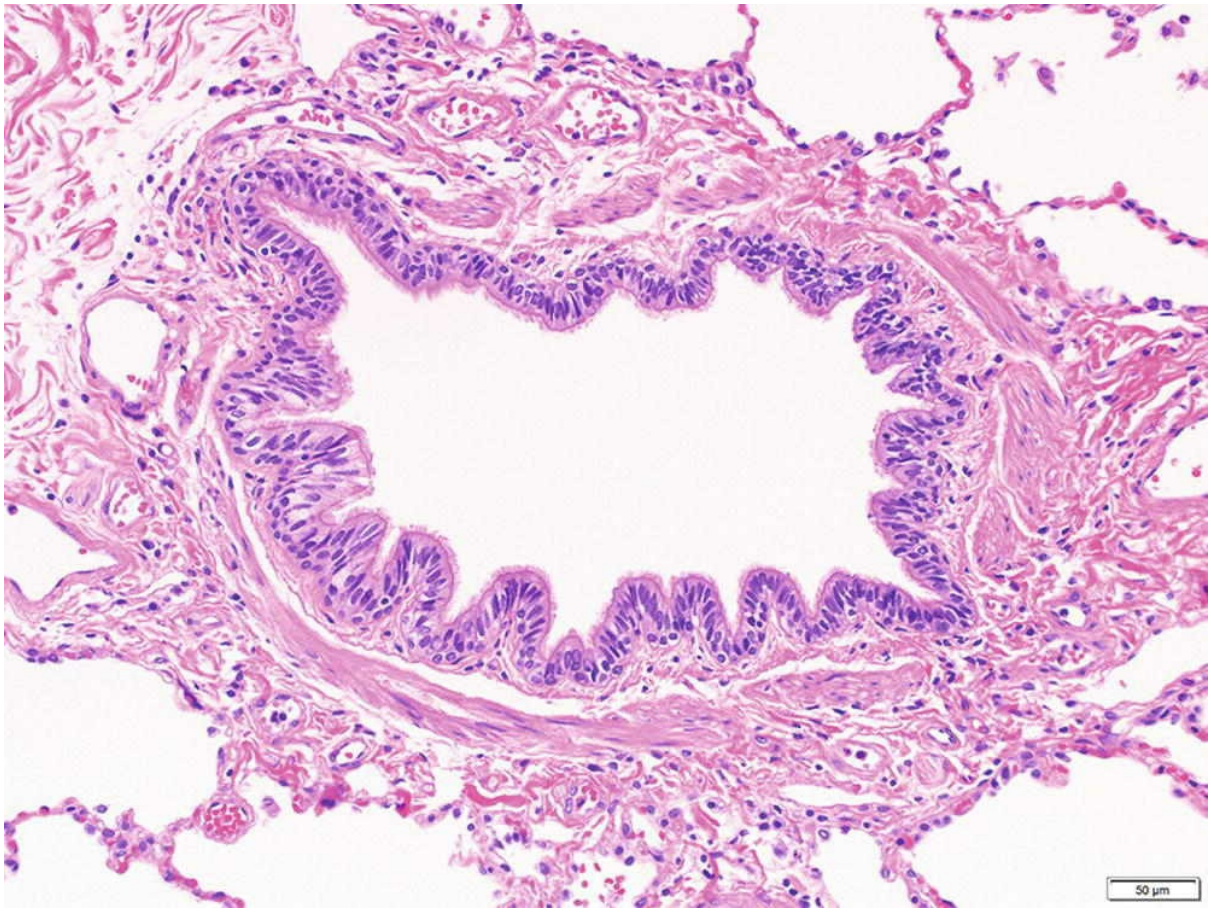

FIGURE 1.5 Cross section of bronchiole. In this transbronchial biopsy, there was a complete cross section of a bronchiole. Often, only tangential or partial sections are present. Note the normal serrated border in the collapsed state. There is little inflammation and collagen between the respiratory epithelium and muscle wall (lamina propria).

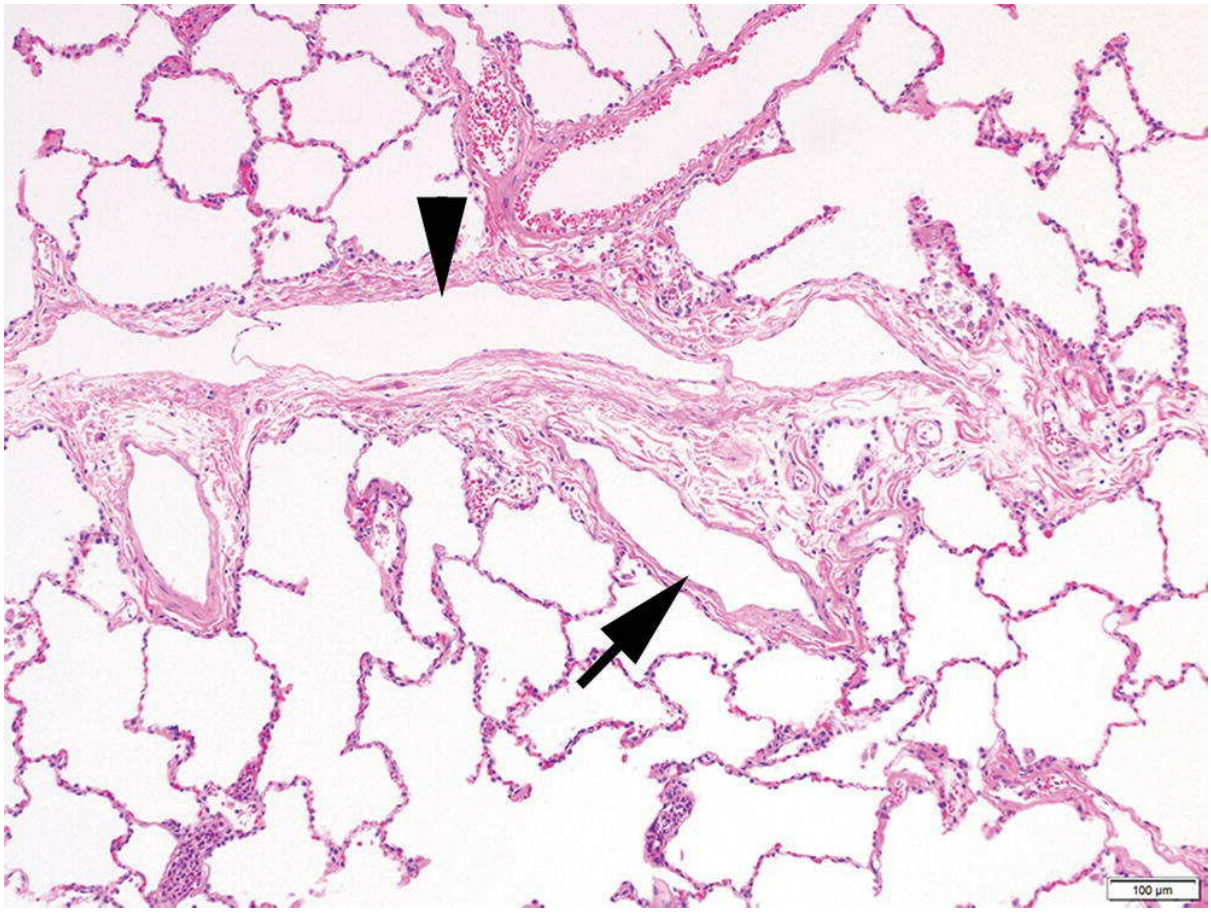

FIGURE 1.6 Interlobular septum. Normally, there are fine sparse collagen bundles and small thin-walled lymphatics (*arrowhead*) and veins (*arrow*) within the septum.

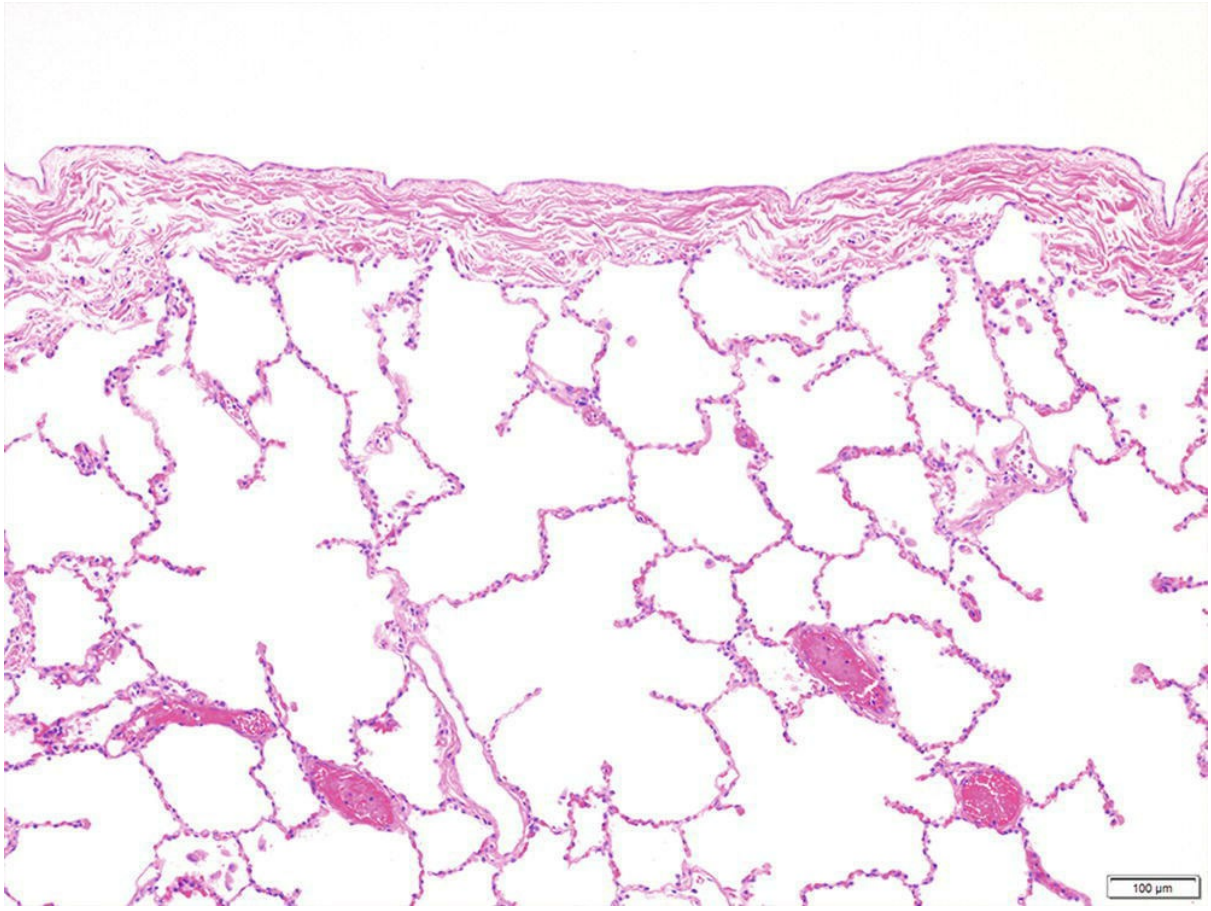

FIGURE 1.7 Pleura. The pleural surface is relatively thin, composed of collagen, elastin, and a mesothelial lining.

Bronchiolocentric processes occur around the bronchioles, while angiocentric lesions occur around the adjacent muscular pulmonary arteries. Septal and paraseptal patterns of disease/injury follow the interlobular septa that bound the pulmonary lobules. Lymphatics are present along the pleura, bronchovascular bundles, and interlobular septa, which will all tend to be involved in diseases with a lymphatic distribution. Consolidative processes will fill the airspaces and make the lung look more “solid.” Finally, diffuse interstitial diseases can involve virtually all of the nonairspace regions of the pulmonary microanatomy. Although the limits of the secondary lobules cannot usually be clearly seen in normal lung, the parenchyma around the bronchovascular bundles is generally centrilobular or centriacinar and that alveoli near pleural surfaces or lobular septa are peripheral.

Pulmonary Arteries

The pulmonary trunk branches into the right and left pulmonary arteries.

The right pulmonary artery, longer than the left, travels beneath the aortic arch before entering the lung hilum. The arteries divide into lobar and segmental branches, with names similar to the bronchopulmonary segments that they feed. The bronchial arteries arise from the thoracic aorta just distal to the arch, directly either from the aorta or from the intercostal arteries, and usually with one on the right and two on the left.

Histologically, pulmonary arteries are identified adjacent to the bronchi and in bronchovascular bundles toward the periphery. Normally, there is little intima, and the media is thin (10% or less of the diameter of the artery) (Fig. 1.8). There may be concentric intimal thickening (or hyalinosis) as a result of aging or increased arterial pressures. Typically, the artery is similar in diameter to the accompanying airway. The proximal arteries accompanying the bronchi (main pulmonary arteries and lobar arteries) are elastic, with concentric elastic lamellae, seen best on elastic stains. There is a gradual transition to muscular arteries accompanying segmental bronchi and bronchioles. Muscular pulmonary arteries have a distinct internal and external elastic lamina, unlike bronchial arteries, which tend to have only a distinct internal elastic membrane with a more fragmented external elastic membrane (like all other systemic muscular arteries).

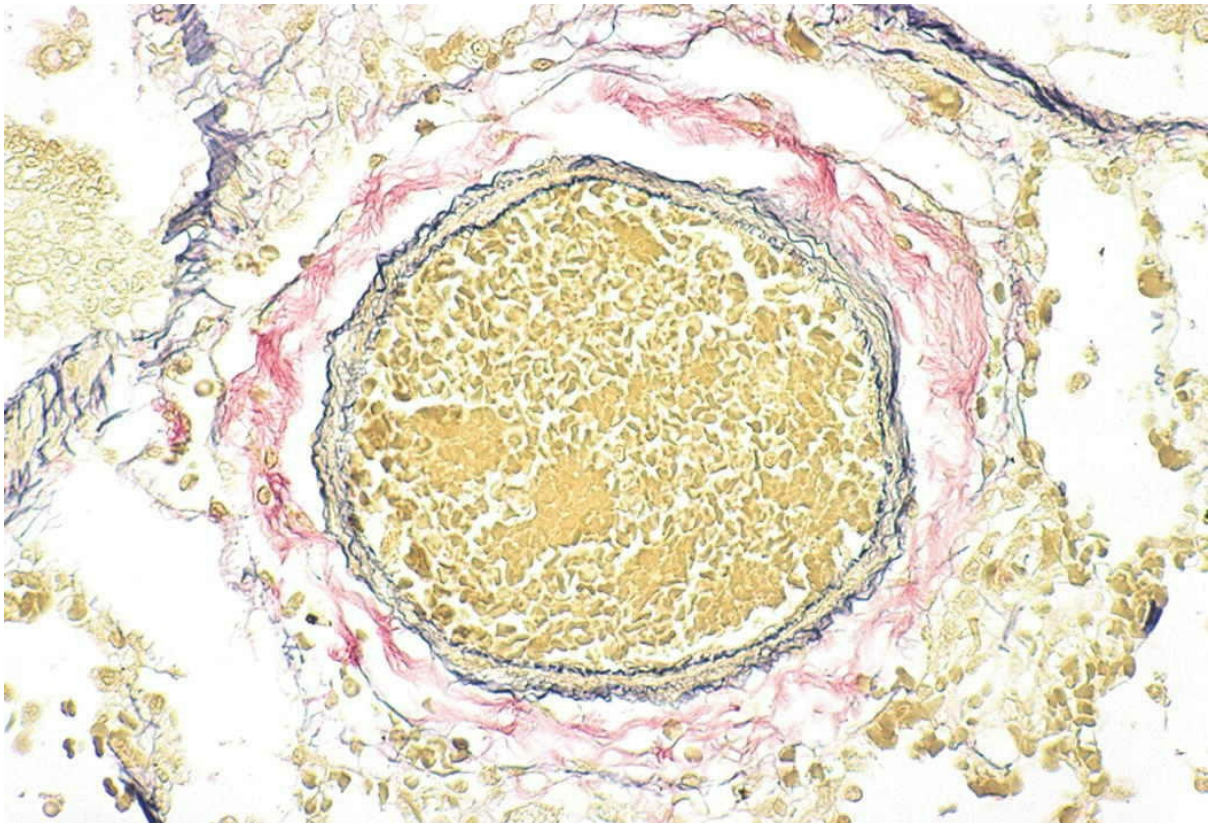

FIGURE 1.8 Muscular pulmonary artery. The media is <10% of the total vessel diameter and is bounded by defined internal and external elastic membranes.

Pulmonary Veins

The pulmonary veins travel in the interlobular septa. The media of the veins is less organized than the discrete media of the arteries and frequently contains smooth muscle bundles rather than layers. There is more elastic tissue in the adventitia in veins, compared to arteries. There is no discrete internal and external elastic lamina. With increased pulmonary venous pressure, there may be accentuation of the elastic tissue, with a thicker inner elastic layer mimicking an internal elastic lamina (so-called arterialization of veins). Like in arteries, aging and interstitial lung disease may cause hyalinization or intimal thickening of the wall in distal veins.

Types of Specimens, Processing, and Reporting

Transbronchial Forceps Biopsy

The most frequent tissue sampling of lung parenchyma is performed by transbronchial biopsy, which was first introduced in the early 1960s with a rigid bronchoscope, and later in the 1970s with flexible bronchoscopy. Risks include bleeding and pneumothorax, with thrombocytopenia and mechanical ventilation considered to be relative contraindications. The tissue is obtained via forceps biopsy, and is blind, as the catheter is advanced as far as possible. For this reason, biopsies for focal lesions are generally performed under fluoroscopy, and CT guidance is also possible.[3] Optimally, 4 to 10 fragments are obtained, with higher numbers recommended for focal lesions (Fig. 1.9).[4] Fragments are usually about 3 mm, unless jumbo forceps with rigid bronchoscopy are used, which may increase the diagnostic yield in interstitial lung disease. Concomitant suction catheter aspiration can result in higher diagnostic yields.[5] Histologic samples are generally from peripheral lung, as opposed to endobronchial biopsies. A sample of histologic findings in pathologic reporting is presented in Table 1.2. There are no specific processing requirements; shaking the container to minimize specimen atelectasis has

anecdotally been recommended, similar to larger specimens (Fig. 1.10A).[6]

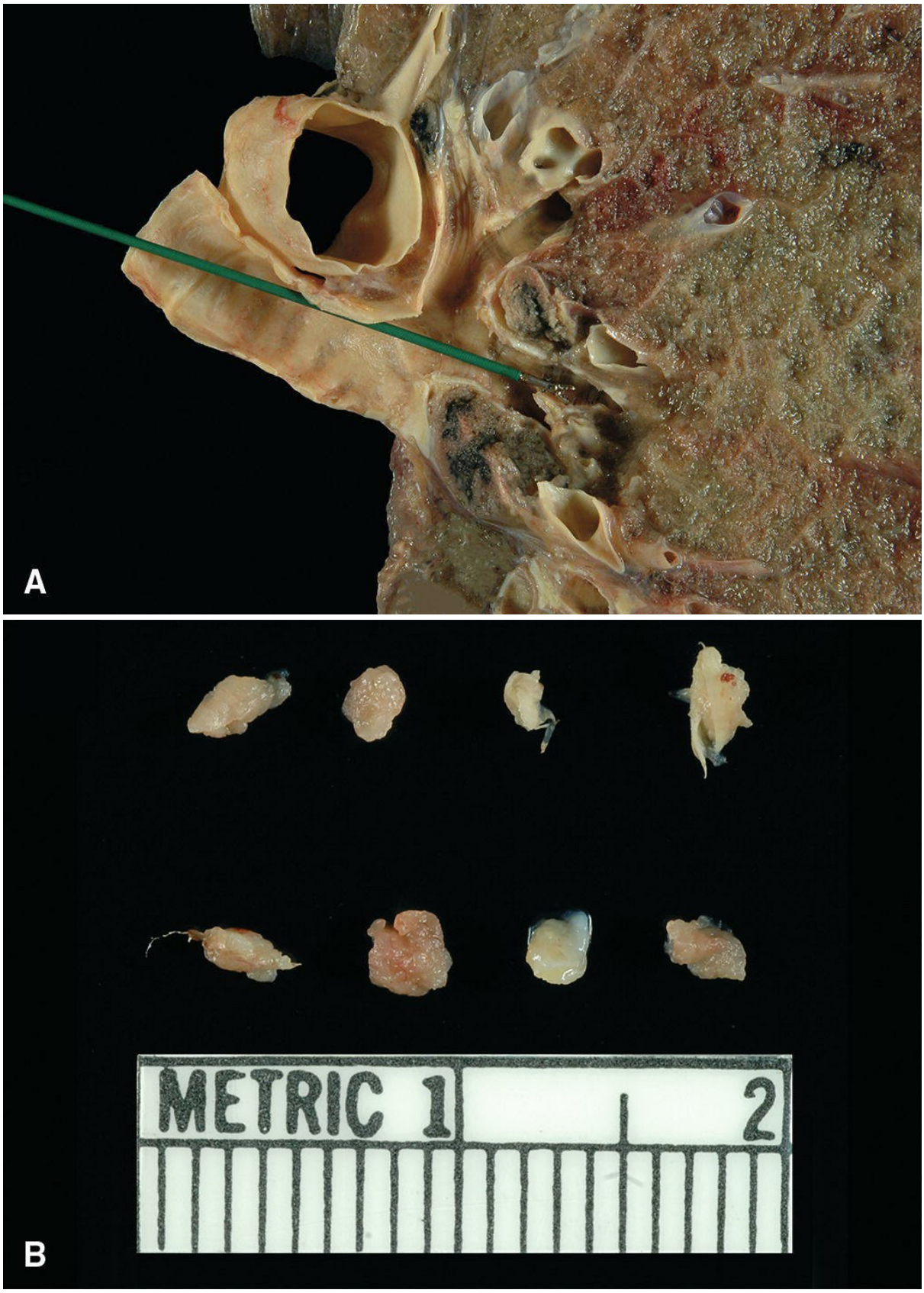

FIGURE 1.9 Transbronchial biopsy (forcep method). **(A)** The bioptome is placed into the airway and is lodged peripherally before **(B)** 6 to 8 samples are taken.

TABLE 1.2 Pathologic Reporting of Nonneoplastic Transbronchial Biopsies in Native Lung Biopsies

Number of Tissue Fragments	Number with Lung Parenchyma, Number with Airway
Alveolar spaces	Intra-alveolar fibrin (not procedure related), indicative of acute lung injury
	Acute inflammation (airway, intra-alveolar)
	Histiocytes (intra-alveolar vs. interstitial); type (foamy, anthracotic pigment, iron pigment, fine dusty pigment, vacuolated)
	Eosinophils
	Organizing pneumonia
	Proteinaceous material (pulmonary alveolar proteinosis)
	Mucus (exclude adjacent neoplasm vs. mucus plugging with extravasation)
	Edema fluid
Alveolar septa	Mononuclear inflammation (note distribution relative to bronchovascular bundles and venules)
	Acute inflammation (note relation with hemorrhage and possible capillaritis)
	Organizing pneumonia
	Pneumocytes (normal, reactive, viral inclusions)
	Smooth muscle cell hyperplasia or fibrosis
	Hyaline membranes
	Vacuolated pneumocytes (suggestive of amiodarone exposure)
Bronchovascular bundles	Granulomas (well or poorly formed and location)
	Squamous metaplasia (especially endobronchial biopsies)
	Vascular changes (intimal thickening, thrombi)
Interlobular septa	Edema
	Fibrosis
	Thickened veins
	Venous recanalization

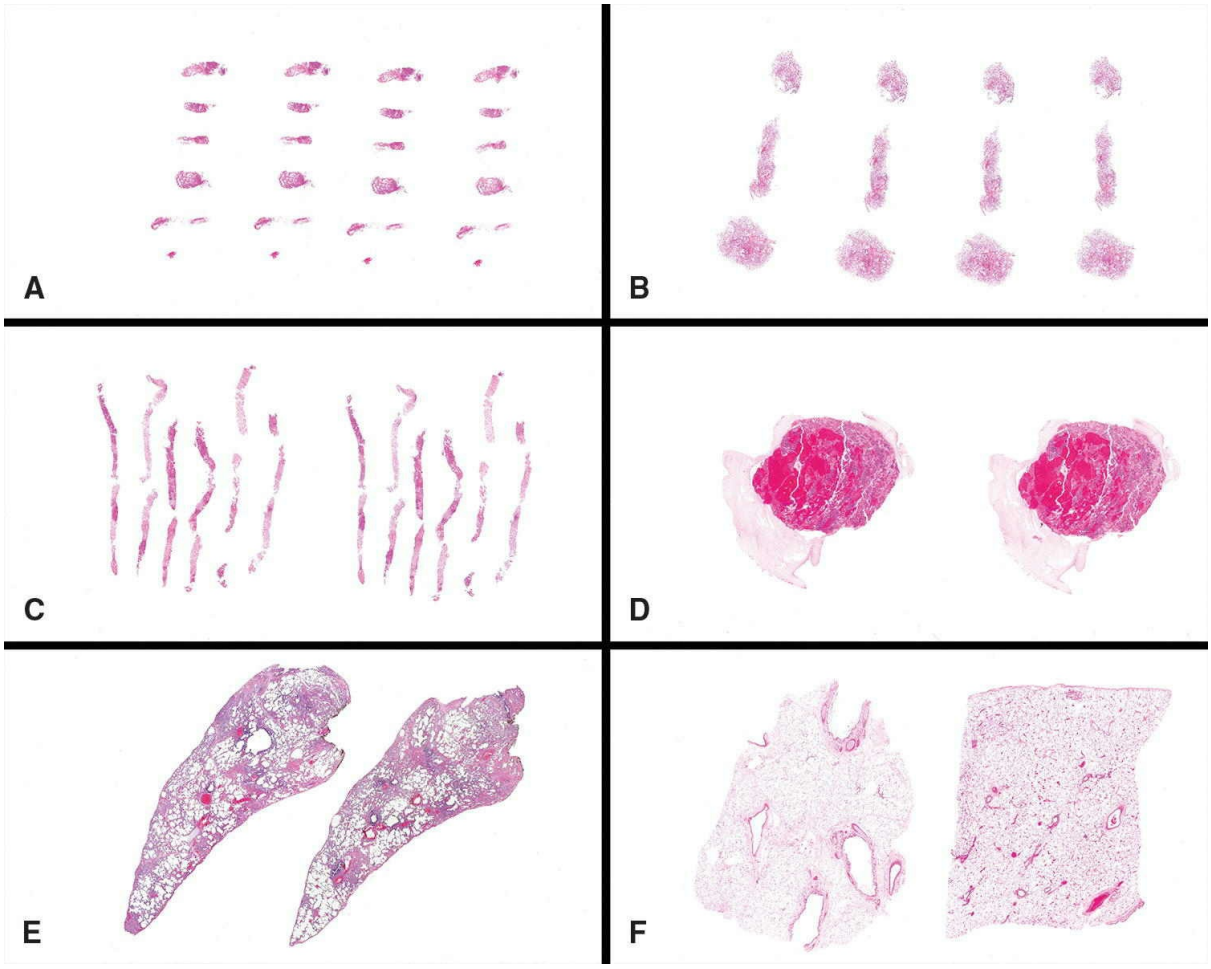

FIGURE 1.10 Relative sizes of lung specimens sampled for histology. **A.** Transbronchial forcep biopsy. **B.** Transbronchial cryobiopsy. **C.** Needle core biopsy. **D.** Bronchoalveolar lavage (BAL) cell block. **E.** Surgical wedge resection. **F.** Pneumonectomy, lobectomy, or autopsy.

Transbronchial Cryobiopsy

This relatively new technique relies on utilization of a bronchoscopically delivered cryoprobe that transbronchial freezes the subjacent parenchyma. The stuck on tissue is then retracted with the cryoprobe. It has the advantages, over forcep biopsy, of less crush artifact, better architectural preservation, and larger samples (Fig. 1.10B). Some studies have reported more hemorrhage with this modality than traditional forcep methods.[7] Preliminary studies suggest that this technique can have additional utility in the diagnosis of interstitial lung diseases, which typically necessitated surgical (wedge) lung biopsy (see below).[8]

Endobronchial Biopsy

Endobronchial biopsies are generally performed with the same bronchoscope as transbronchial biopsies, but are used for proximal lesions, which are directly visualized through the bronchoscope. In such samples, alveolated parenchyma may be absent/scant with the specimen largely limited to bronchial mucosa and submucosa. The presence of the various layers present (respiratory epithelium, lamina propria, muscularis mucosa, submucosa with mucus glands, cartilage) should be mentioned in the pathology report, along with pathologic alterations.

Transthoracic Core Biopsies

These are usually performed under CT guidance for tumors or masses. Tissue sampling is critical in obtaining tumor for potential molecular markers; therefore, procedures to minimize sectioning of paraffin blocks are paramount. Typically, a 17- or an 18-gauge needle is used to produce multiple tissue cores (Fig. 1.10C).[9] Common complications include pneumothorax (most of which resolve spontaneously) and hemoptysis.

Cytologic Specimens

In many cases of transbronchial biopsy, concomitant cytologic specimens are obtained, especially in the evaluation of masses or nodules. These include bronchial washes, brushes, and needle aspirates of either central tumors or mediastinal lymph nodes, which can be sampled via bronchial and esophageal endoscopy (Fig. 1.10D). It is a matter of choice whether to combine samples into one case accession or separate biopsies from cytologic specimens obtained in one bronchoscopic session.

Bronchoalveolar lavage (BAL) is often performed as an adjunct to diagnosis of inflammatory lung disease as well as malignancies. Typically, about 100 mL is infused, either in an affected area or right middle lobe or lingula in diffuse disease, which is most easily accessed in a supine patient. Total numbers of leukocytes are expressed per unit volume with a differential count, and organisms are identified by routine special stains. BAL is useful for the diagnosis of cytomegalovirus, herpes, pneumocystis, and fungal infections and may be useful in the diagnosis of sarcoidosis, hypersensitivity pneumonitis, and idiopathic pulmonary fibrosis, although the findings are nonspecific. Pneumoconioses may be diagnosed by the identification of silicates or asbestos bodies.

Wedge Biopsies

Open lung biopsy is commonly used for the diagnosis of most forms of interstitial lung disease and is generally performed by minimally invasive techniques, such as video-assisted thoracoscopic surgery (VATS) (Fig. 1.10E). In order to minimize the artifact of specimen atelectasis, injection of the parenchyma with formalin using a needle is often recommended. Inking the pleura is generally not necessary, unless there is a possibility of extension through the pleura in cases of peripheral lung cancer resection.[10] The histologic assessment of margins for tumor may be difficult in cases of stapled parenchymal resection margins.[10,11] Careful removal of staples with assessment of the margin is recommended. Cytologic assessment of margins has also been espoused before removing the staples.[12]

In the case of wedge biopsies for interstitial lung disease, it is recommended that multiple regions (upper and lower lobes) be sampled, such that the distribution of the process can be ascertained. Reporting of biopsies for interstitial lung disease involves enumeration of histologic patterns of injury (to be discussed in the following chapters), with the formulation of a clinicopathologic diagnosis following the acquisition and integration of radiographic and clinical data (see Chapter 16).

Lobectomy

In lobectomy specimens, the pathologist or assistant should attempt to distend the tissue from a vascular or airway at the surgical margin, which should be assessed in cases of tumor for staging purposes. The size and nature of nodules and relationship and distance to pleural and resection margins should be recorded. Any peribronchial lymph nodes should be evaluated. The total number of lymph nodes obtained for cancer resections is critical for staging, and peribronchial nodes in lobectomies need to be carefully dissected and counted.

Pneumonectomy

Complete lung resections are performed for proximal lung cancers, certain infections, and during allotransplantation in patients who are surgical candidates with adequate respiratory reserve in the contralateral lung (Fig. 1.10F). Optimally, the lung should be distended with formalin to prevent specimen atelectasis, and all lymph nodes must be submitted for histologic assessment. Vascular and bronchial margins are necessary for tumor

staging in the case of resection for malignancy.

Pleural Surfaces

The state of the pleura is important to describe, including the presence of adhesions, fibrosis, puckering, exudates, anthracosis, and “cobblestoning” (retraction caused by interstitial fibrosis). It is especially important in cancer resections to note any puckering, which could represent visceral pleural invasion, and the presence of shaggy tissue or obvious portions of chest wall (skeletal muscle or bone). It is useful to refer to the operative summary to determine if a part of endothoracic fascia was resected near a tumor, because an additional margin is thus created. Pleural surfaces need not be inked if there is underlying tumor, as the intact pleura is not a margin. However, if there is attached chest wall, then determination of margins with inking is essential in determining the proper tumor stage.

Autopsy

In order to assess histologic changes at autopsy, perfusion fixation is especially important, because of the added effect of autolysis on postmortem atelectasis. In general, it is not difficult to directly deliver formalin into the trachea or individually in the mainstem bronchi to distend the distal parenchyma. With adequate distention of the lungs, fixation is generally sufficient within a few minutes following clamping of the trachea or bronchi. Optimal visual inspection of the lungs occurs by placing the lungs with the hilum up and performing serial parasagittal sections with a sharp knife at ~1 cm intervals.

Histologic Artifacts

Specimen Atelectasis

Specimen atelectasis refers to collapse of the alveolar spaces after biopsy or resection, or postmortem. This effect can be minimized by gentle agitation of small specimens or formalin injection/distension of larger specimens. With practice, it is possible to distinguish alveolar collapse from areas of consolidation (Fig. 1.11). Cytokeratin staining can occasionally be useful in this regard. Specimen atelectasis also makes especially difficult the distinction between in situ and invasive low-grade adenocarcinoma (Chapter 74).

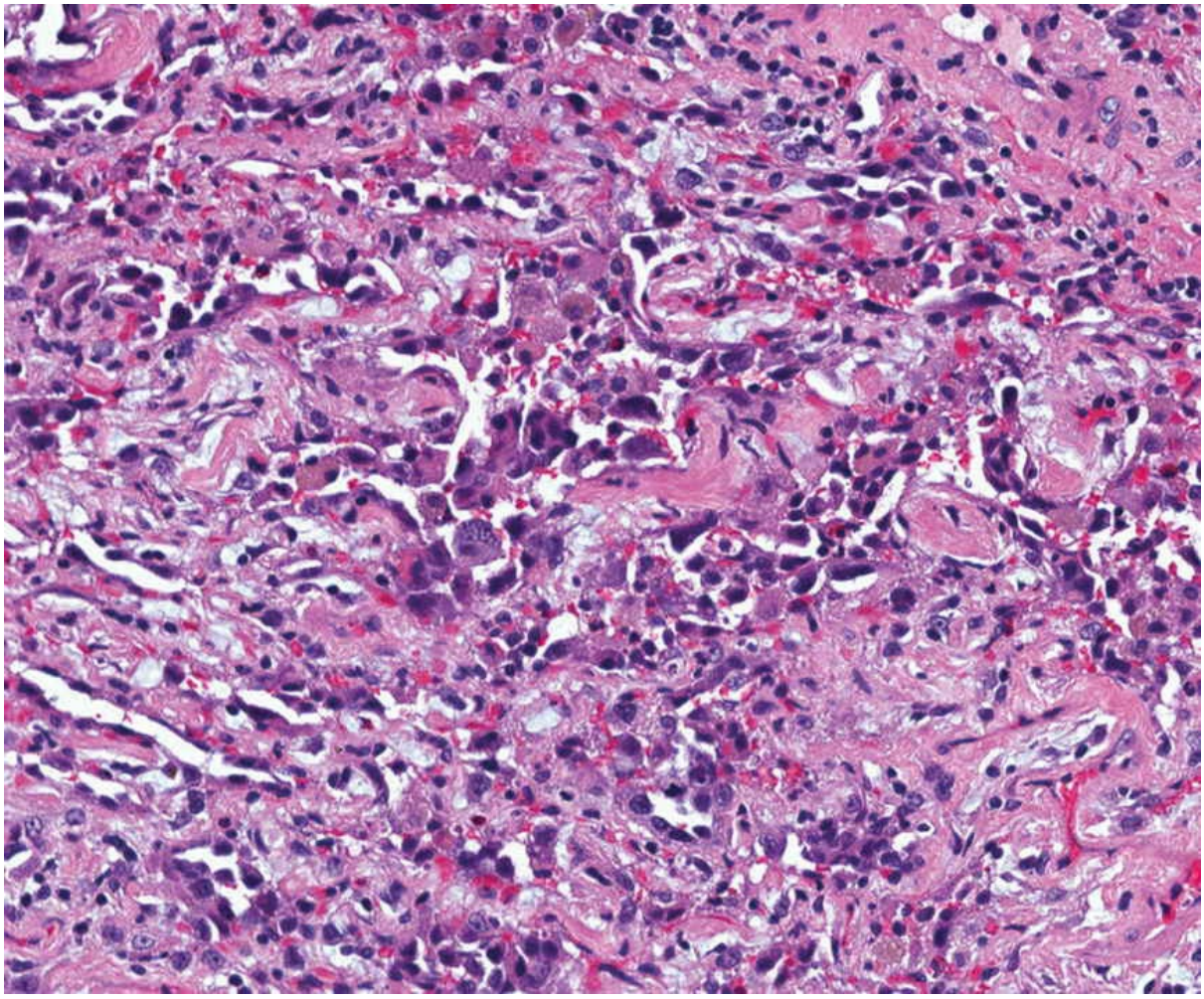

FIGURE 1.11 Specimen atelectasis. If the airspaces are not expanded, the alveolar structures collapse, making interpretation difficult. In this case, alveolar septal inflammation and reactive pneumocytes are discernable, allowing a diagnosis of subacute lung injury.

Procedural Fibrin Versus Acute Lung Injury

It may be difficult to distinguish procedural hemorrhage with fibrin coagulation from acute lung injury and pathologic deposition. In general, procedural hemorrhage will demonstrate intact red blood cells and fine fibrillar fibrin strands indicative of recent formation (Fig. 1.12). Organization will also be absent in procedure-related changes.

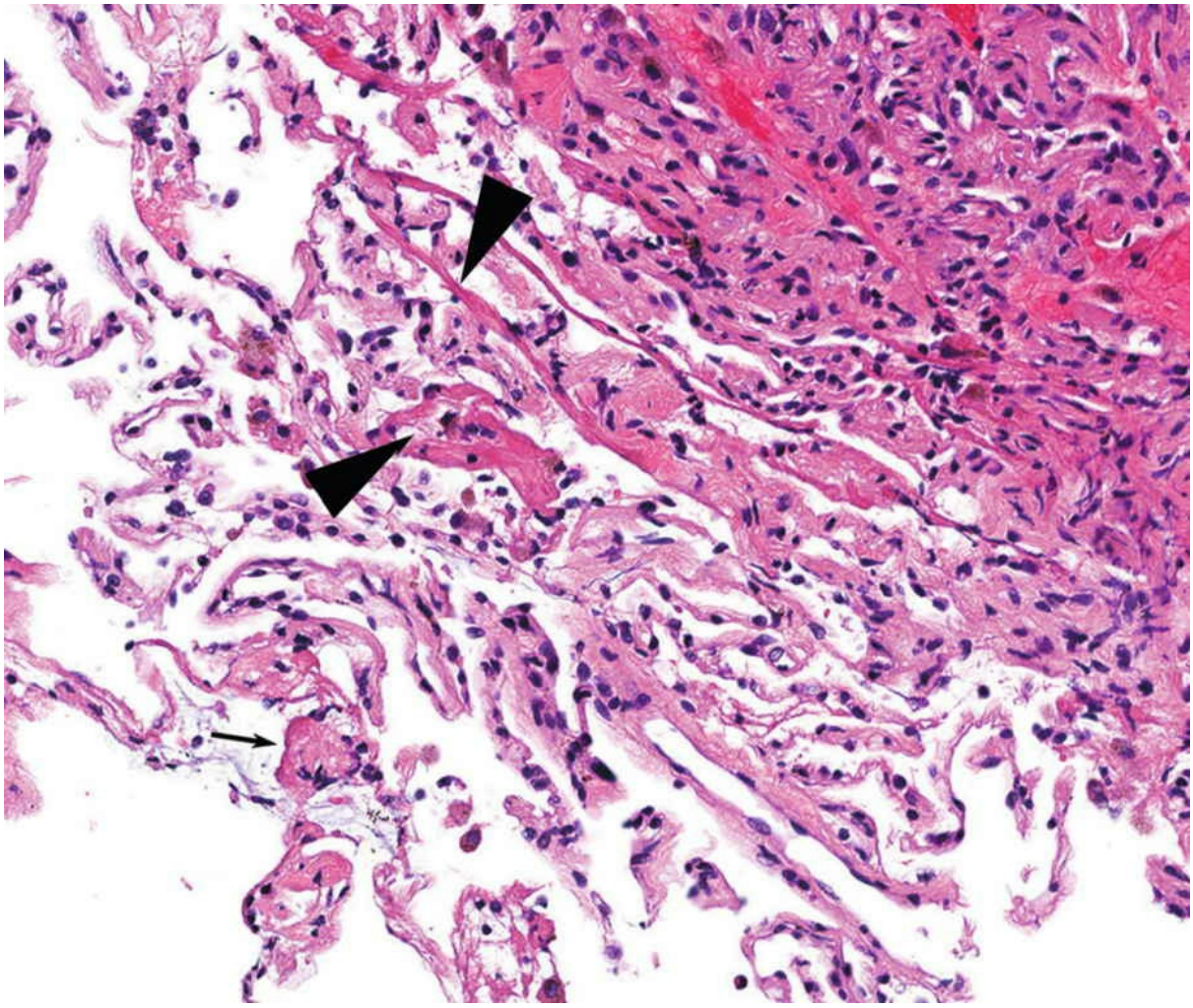

FIGURE 1.12 Procedural fibrin. There are intact fibrin strands (*arrowheads*) and scattered erythrocytes. In the absence of pneumocyte hyperplasia or other findings, the fibrin is likely due to the forceps trauma.

Vascular Tunneling

A common artifact in lung biopsies is procedural intussusception of vessels, especially arteries, mimicking intimal thickening (Fig. 1.13).

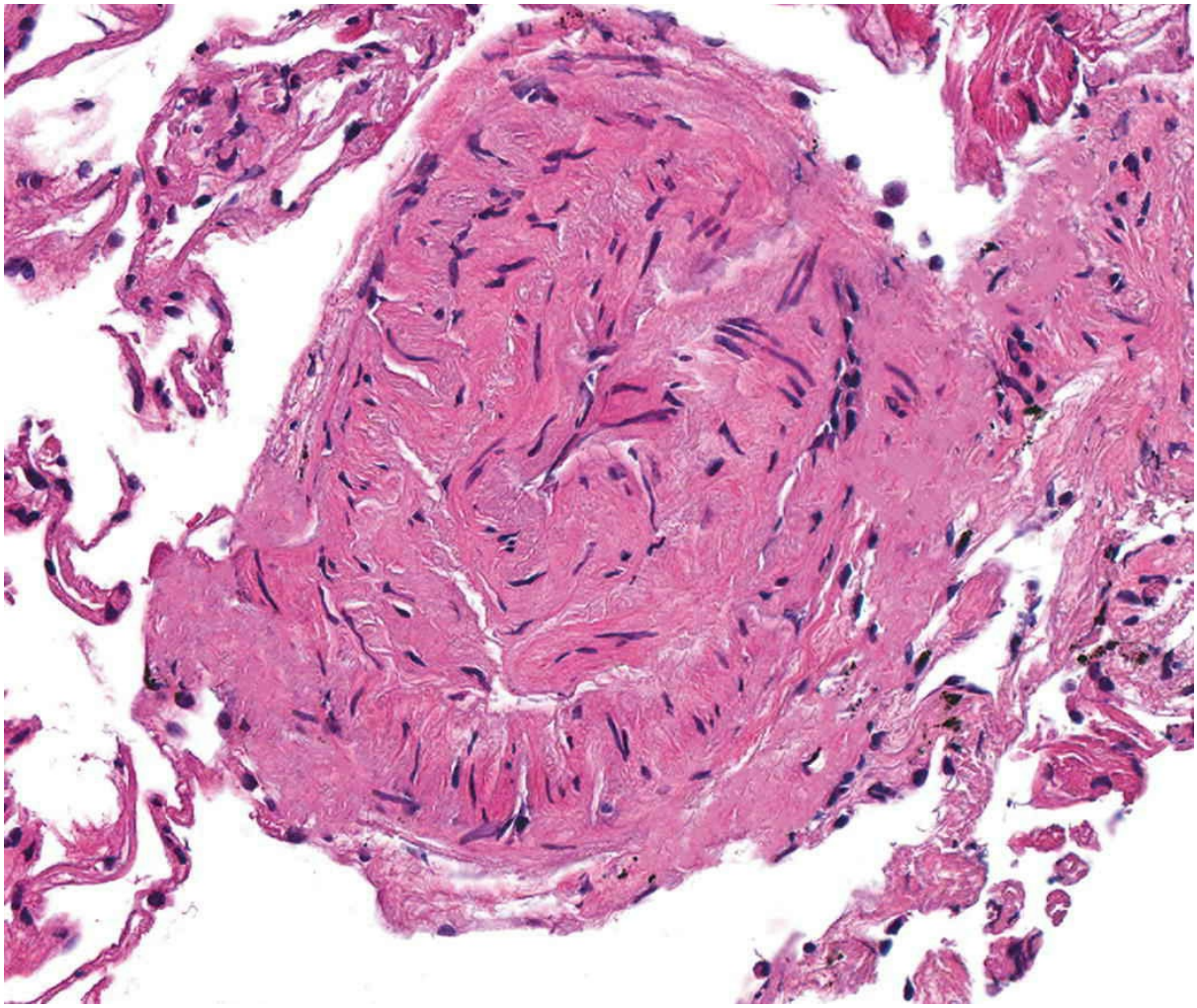

FIGURE 1.13 Arterial telescoping. Artifactual intussusception of normal arteries may result in an appearance mimicking intimal thickening.

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2 Pathologic Changes Involving Alveolar Septa and Interstitium

Allen P. Burke, M.D., and Fabio R. Tavora, M.D., Ph.D.

Inflammation

The most common type of inflammation in the alveolar septa is a mixture of mononuclear cells, including lymphocytes (usually predominantly T cells), macrophages, and plasma cells. If a pattern is recognizable, it is important to mention if it appears bronchiolocentric (Figs. 2.1 and 2.2) or perivascular (Fig. 2.3). There is often reactive pneumocyte hyperplasia, which indicates organizing lung injury of various causes and stages. The organizing lung injury may show discrete areas of organizing pneumonia.

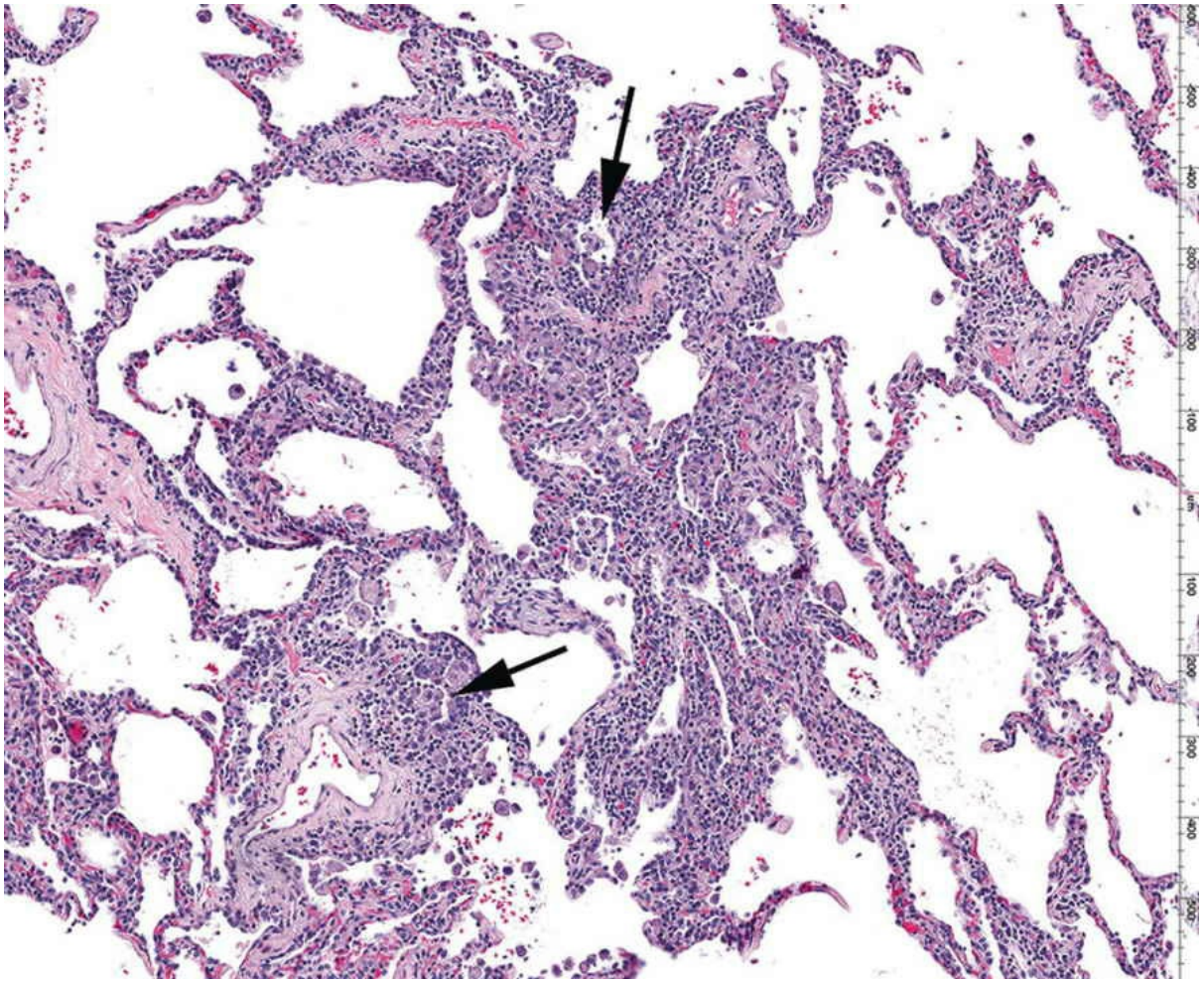

FIGURE 2.1 Chronic interstitial inflammation, peribronchiolar. The bronchioles are difficult to discern in the inflammation and are identified by their perivascular location (*arrows*). The patient's ultimate clinicopathologic diagnosis was nonspecific interstitial pneumonia with areas of organizing pneumonia.

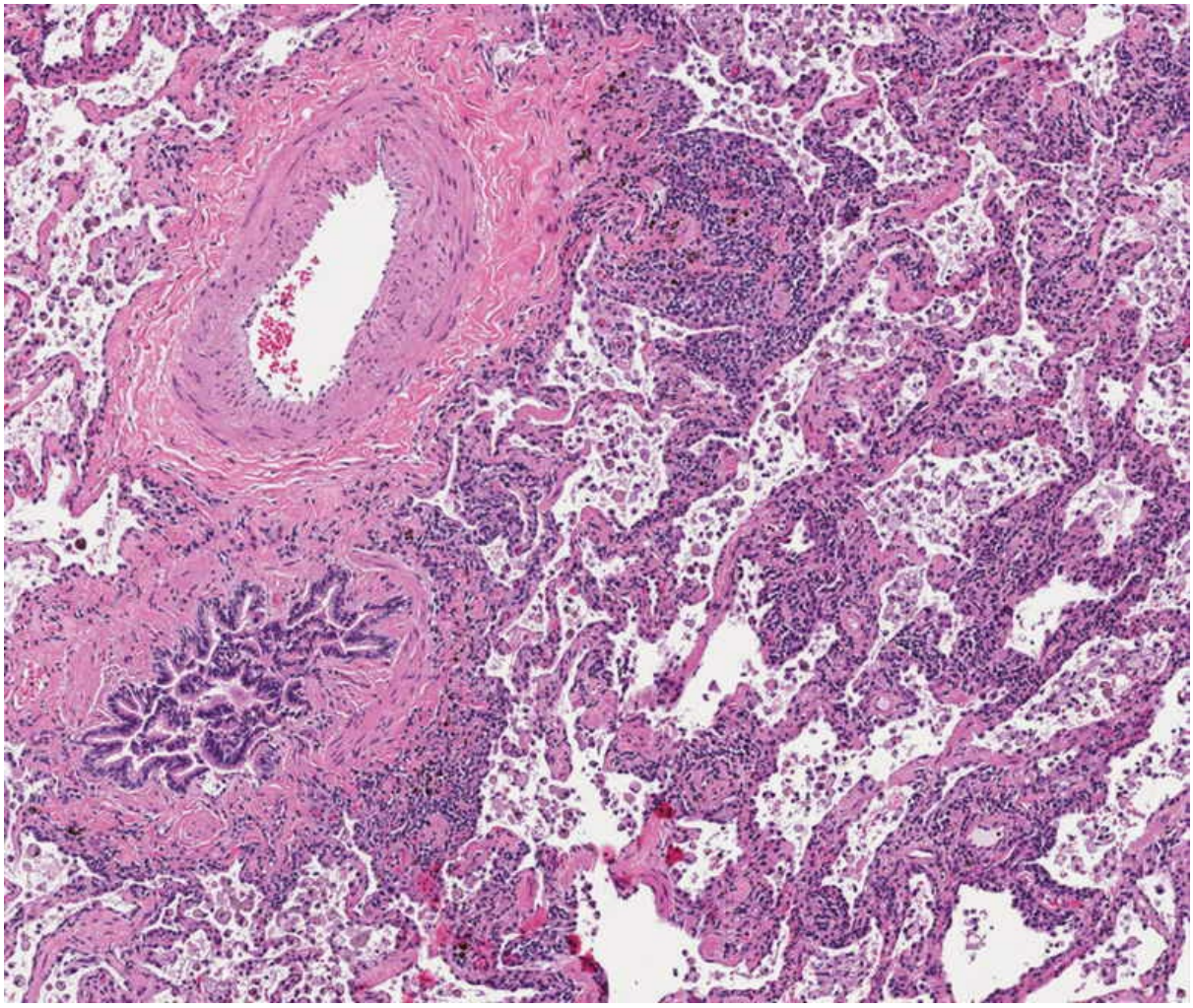

FIGURE 2.2 Chronic interstitial inflammation, peribronchiolar. There is a large bronchovascular bundle on the left. The ultimate diagnosis was probable hypersensitivity pneumonitis.

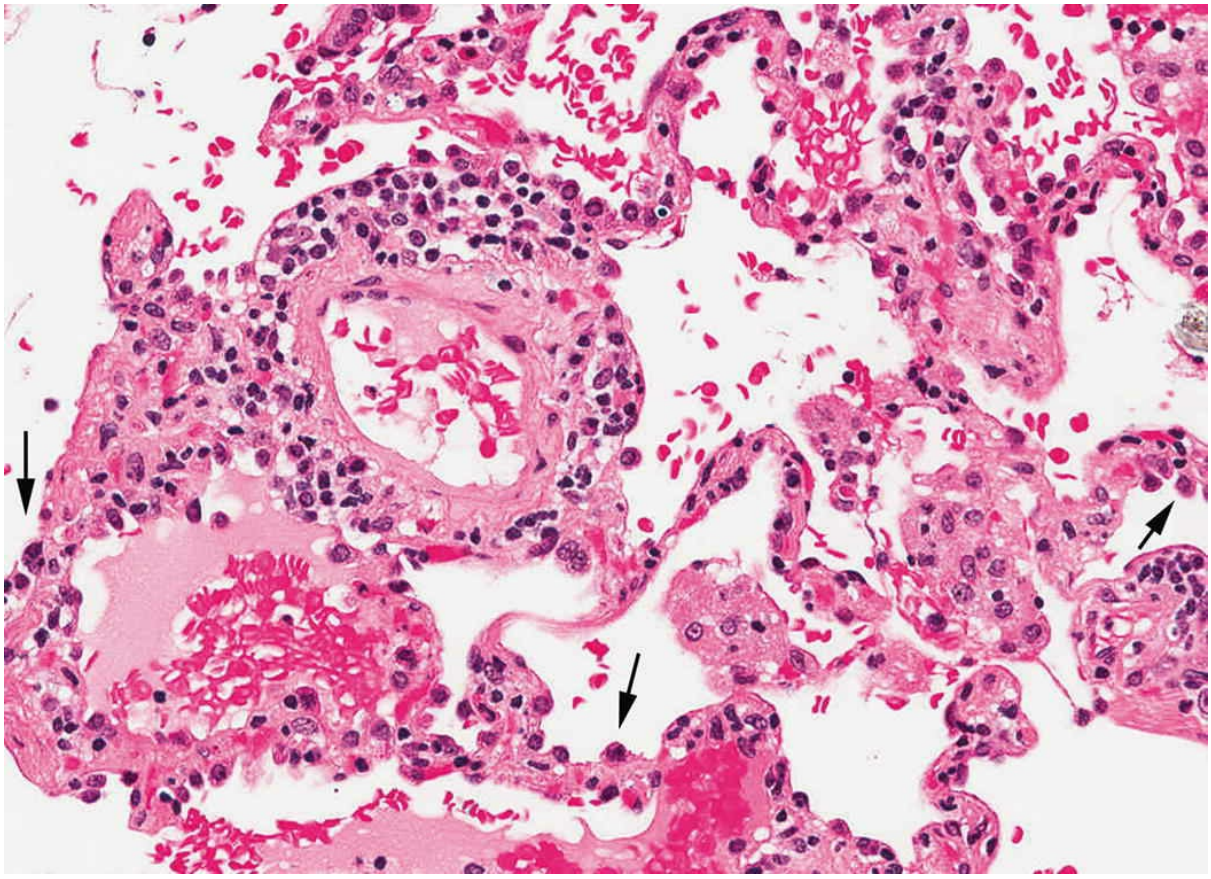

FIGURE 2.3 Chronic interstitial inflammation interstitial and perivascular. There is mild reactivity to alveolar lining cells (*arrows*). The patient had an undifferentiated connective tissue syndrome and interstitial cellular infiltrates that responded to steroids. The clinicopathologic diagnosis was interstitial pneumonia associated with rheumatoid arthritis.

The differential diagnosis of chronic interstitial pneumonitis (a nonspecific pattern of diagnosis) is outlined in Table 2.1.

TABLE 2.1

Pattern, High Magnification	Pattern, Lower Magnification/ Accompanying Features	Possible Clinicopathologic Diagnoses
Chronic interstitial inflammation[a]	Predominantly peribronchiolar	Hypersensitivity pneumonitis (poorly formed granulomas, OP) Chronic bronchiolitis, including infectious NSIP COP
Chronic interstitial inflammation[a]	Indeterminate pattern, perivascular	Infection Organizing diffuse alveolar damage (often with loose fibrosis) NSIP COP Drug reaction Autoimmune lung injury in CTD (i.e., lupus pneumonitis) Alloimmune lung injury
Capillaritis		Autoimmune (MPA, lupus and other CTD, Goodpasture) Early infarction Infection
Interstitial inflammation with fibrosis	With or without OP	NSIP Autoimmune CTD Drug reaction Organizing lung DAD (may have areas of loose fibrosis mimicking OP)

[a]Reactive pneumocytes are common and are a result of alveolar injury of various causes.

OP, organizing pneumonia; COP, cryptogenic organizing pneumonia; CTD, connective tissue disease; MPA, microscopic polyangiitis; NSIP, nonspecific interstitial pneumonia.

Neutrophilic inflammation is less common and may be seen in infection

(Fig. 2.4) and in areas close to an infarction. It is a hallmark of autoimmune injury (capillaritis, Fig. 2.5) and may be seen in alloimmune injury as well (antibody-mediated rejection).

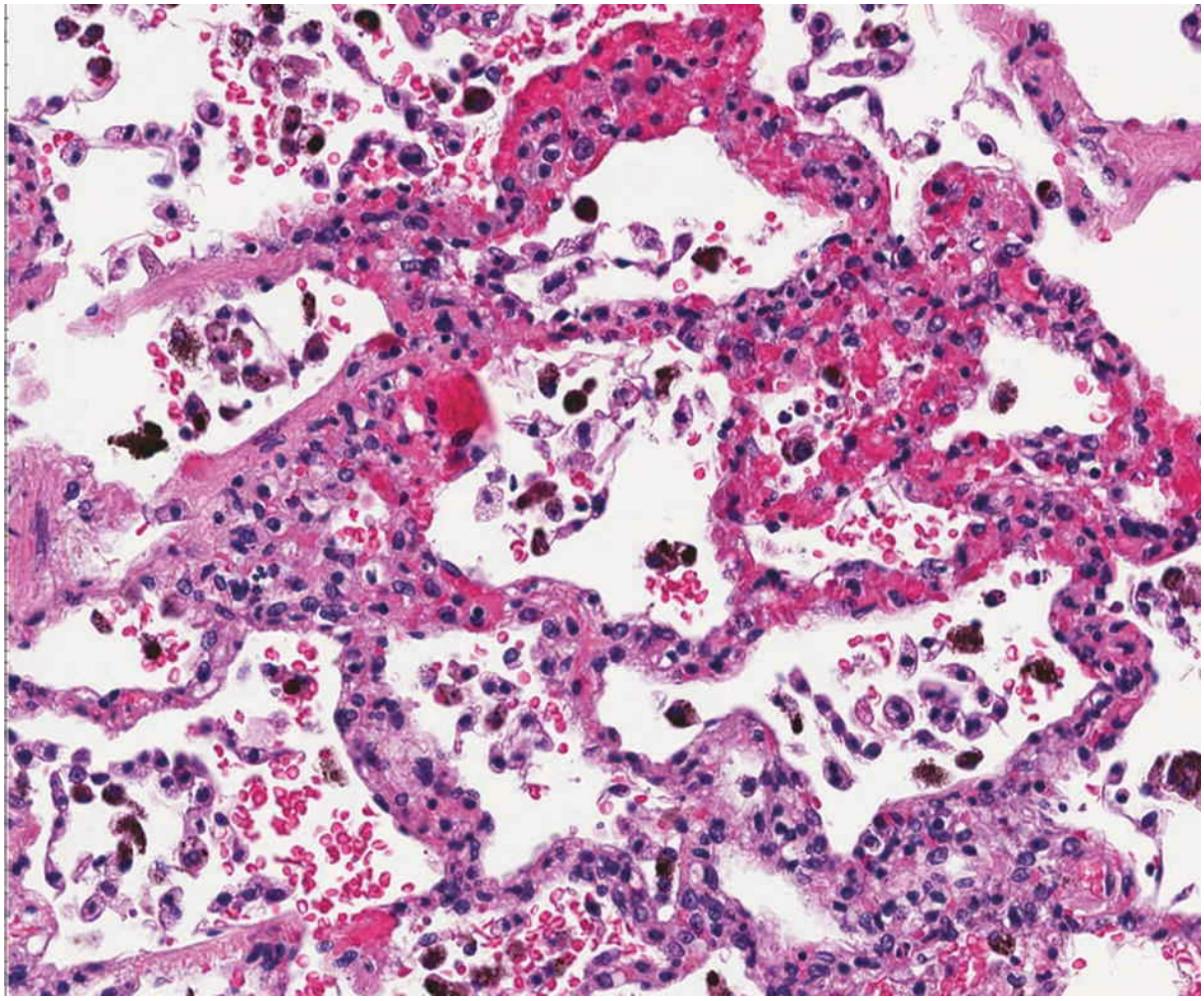

FIGURE 2.4 Acute interstitial inflammation. There is acute and chronic alveolar septal inflammation with early necrosis and alveolar hemosiderin macrophages. The patient had fungal sepsis and areas of hematogenous spread of *Aspergillus* in the lung. The findings could represent early infarct from angioinvasive aspergillosis with resulting capillary congestion.

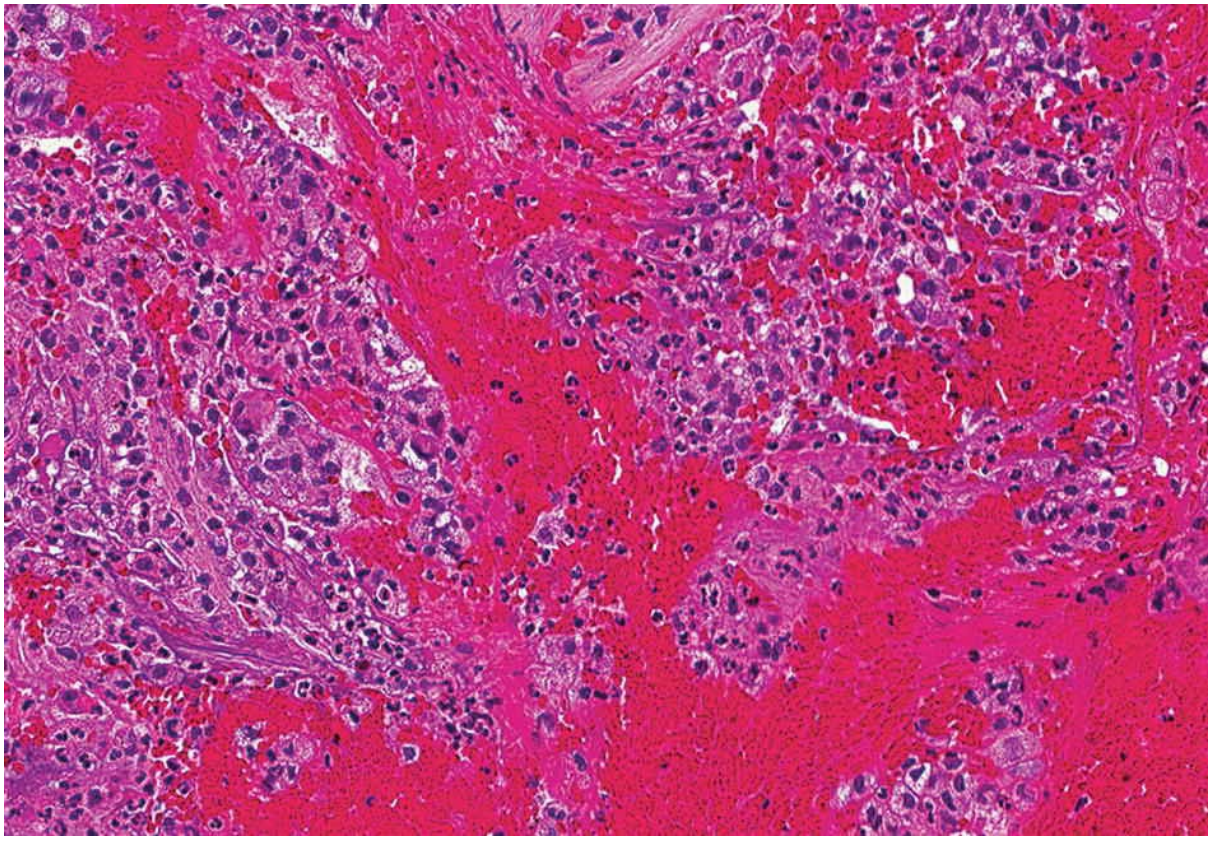

FIGURE 2.5 Acute interstitial inflammation, capillaritis. The patient had acute lung injury secondary to microscopic polyangiitis, ANCA-positive.

Other components of interstitial inflammation may include eosinophils, seen in allergic or in eosinophilic pneumonia and to a lesser degree in hypersensitivity pneumonitis.

Fibroblasts and Collagen

Chronic inflammation may progress to interstitial fibrosis in a variety of settings, including interstitial pneumonias, organizing lung injury, and hypersensitivity pneumonitis. Initially, there are fine strands of collagen in a cellular matrix (Fig. 2.6), which may become more collagenized or form localized areas with organizing pneumonia (Fig. 2.7). Type II pneumocyte hyperplasia is typical when there is early collagen deposition. Denser collagen may occur with organizing diffuse alveolar damage (Fig. 2.8) or smoking-related fibrosis. Dense acellular collagen, often with “naked” granulomas, is typical of sarcoidosis, although the scarring is not typically within alveolar capillaries.

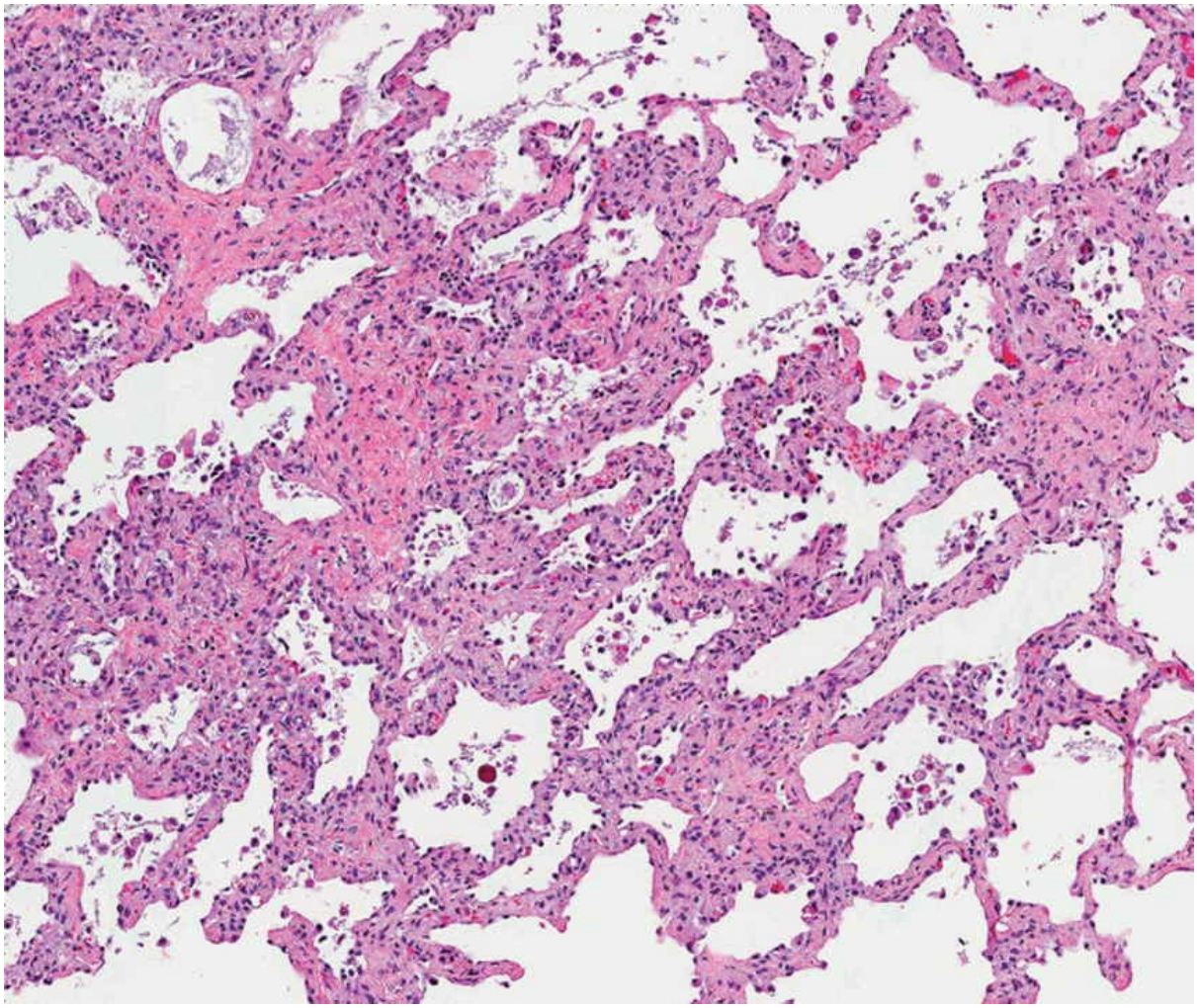

FIGURE 2.6 Chronic interstitial inflammation with type II pneumocyte hyperplasia and early fibrosis. The clinicopathologic diagnosis was hypersensitivity pneumonitis in a patient with birds as pets.

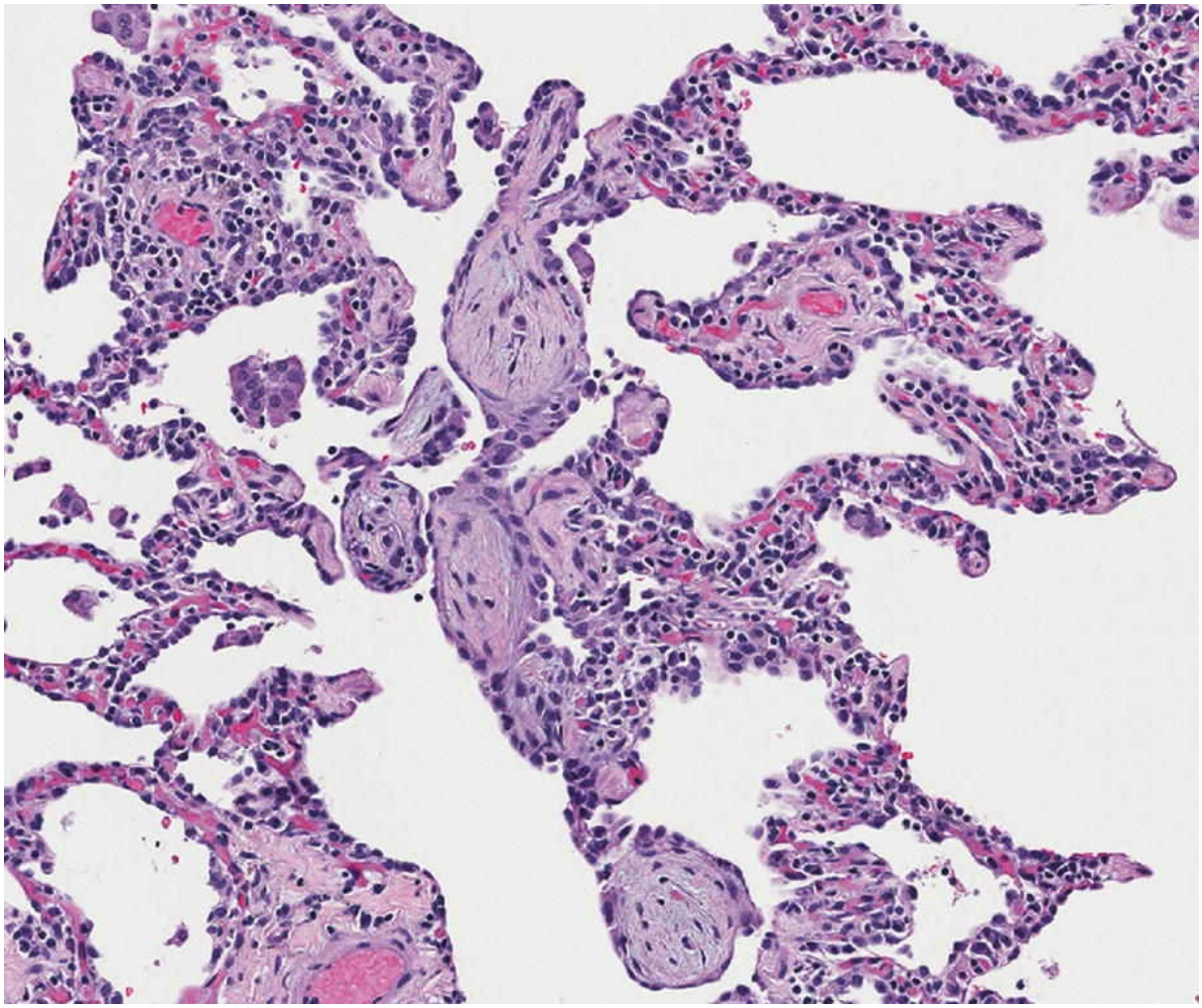

FIGURE 2.7 Chronic interstitial inflammation with patchy organizing pneumonia. The clinicopathologic diagnosis was cryptogenic organizing pneumonia.

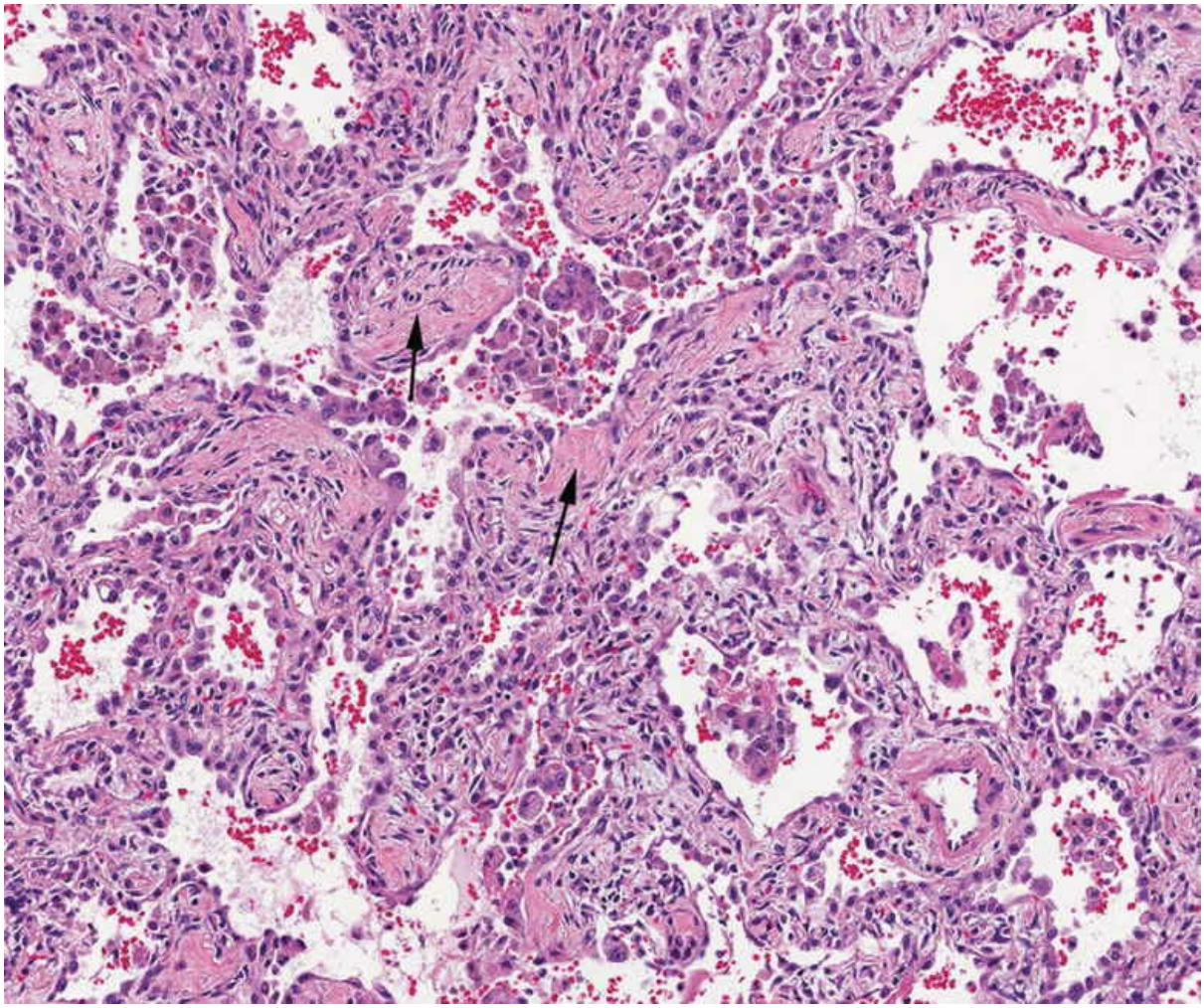

FIGURE 2.8 Diffuse interstitial inflammation with focal fibrosis (*arrows*) and diffuse type II pneumocyte hyperplasia. The clinicopathologic diagnosis was organizing diffuse alveolar damage.

Elastosis

Elastosis is an extremely common finding especially in localized reactions to tumors and pneumothorax. Caps of elastosis in the apices (“apical caps”) are present in most lungs of older people. When diffuse, the term “pleuroparenchymal fibroelastosis” is used. Elastosis does not typically demonstrate an alveolar septal distribution but is associated with alveolar collapse and loss of normal architecture.

Smooth Muscle Cells