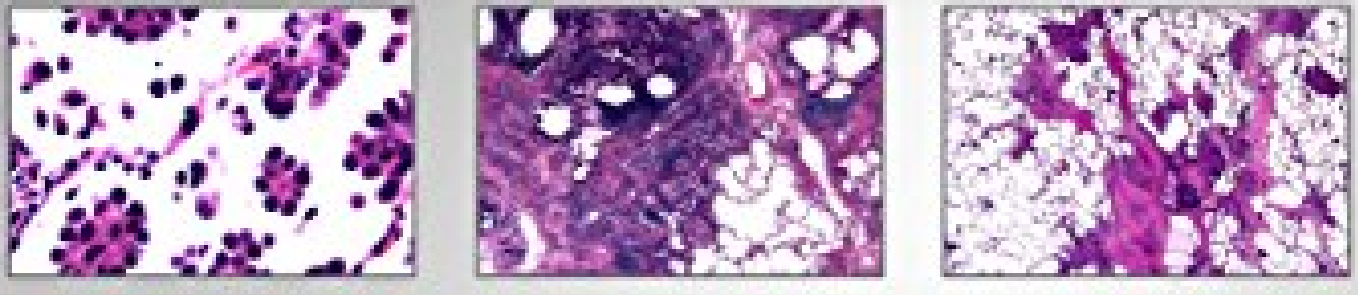
Dani S. Zander
Carol F. Farver

Pulmonary Pathology

SECOND EDITION



a volume in the series
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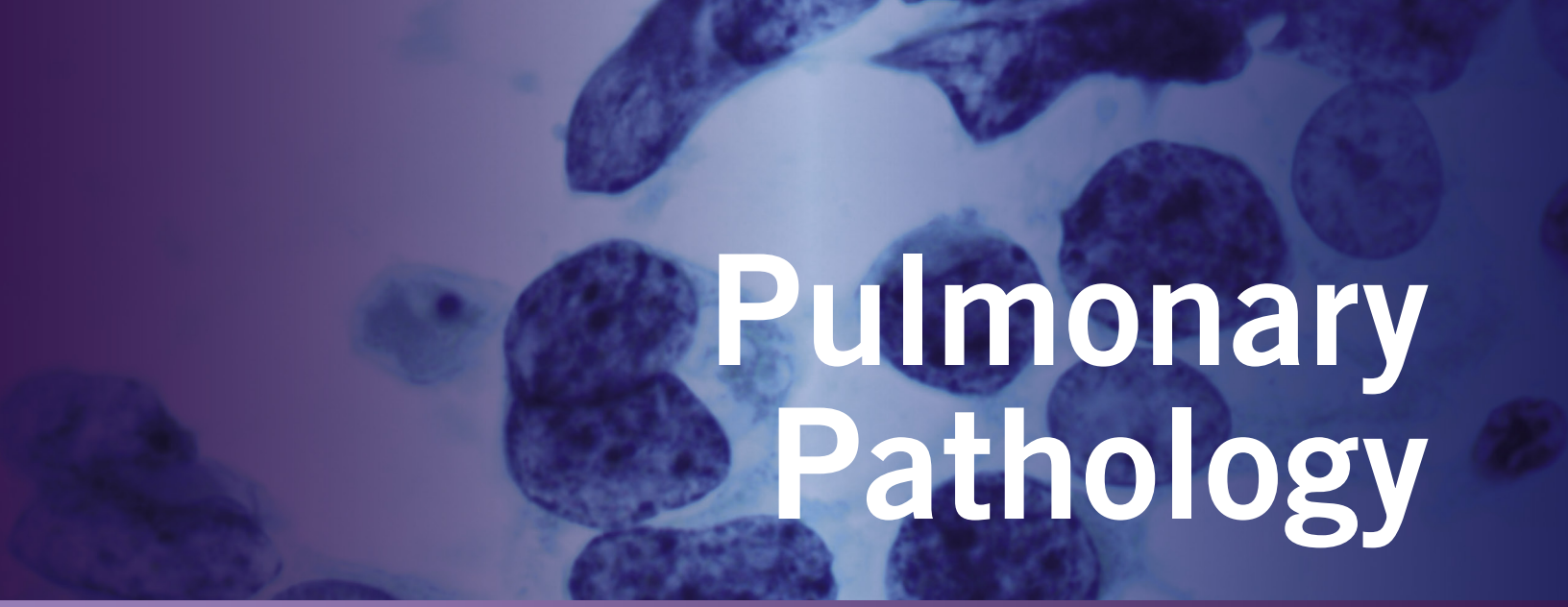

Pulmonary Pathology

SECOND EDITION

A Volume in the Series Foundations in Diagnostic Pathology

edited by

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PULMONARY PATHOLOGY, SECOND EDITION
A Volume in the Series Foundations in Diagnostic Pathology

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–Dani S. Zander, MD

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–Carol F. Farver, MD

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FOREWORD

Surgical pathology, with all of its subspecialties, has become enormously complex. It is impossible for a single individual to master all of the skills and knowledge required to perform the numerous tasks required of a surgical pathologist. Providing a correct diagnosis is challenging enough, but the standard of care has far surpassed merely providing an accurate pathologic diagnosis. Pathologists are asked on a daily basis to provide large amounts of ancillary information, both diagnostic and prognostic, often based upon their observations of small amounts of tissue, a task that is daunting even for the most experienced pathologist.

General surgical pathology textbooks are very useful resources, but by necessity they cannot possibly cover many of the detailed aspects that pathologists need to know and include in their daily reports. For this reason, *Foundations in Diagnostic Pathology* was developed. This series of books is designed to cover all of the major areas of surgical pathology, and each volume is focused on one major topic. The goal of every book in this series is to provide the essential information that any practicing pathologist, whether general or subspecialized, in training or in practice, would find useful in the evaluation of virtually any type of specimen.

Dr. Dani Zander and Dr. Carol Farver, experienced and world-renowned pulmonary pathologists, have edited an outstanding book covering the essential aspects of pulmonary pathology. I truly know of no other book that so effectively gets to the core of what practicing surgical pathologists want and need to know about this difficult topic. The list of contributors is most impressive and includes nationally and internationally recognized pulmonary pathologists who were exceedingly generous in providing their expertise and time to the creation of this book. By design, there is uniformity in the organization of these chapters, each of which includes practical information and numerous photomicrographs that emphasize the essential diagnostic points. There is, at every turn, integration of ancillary diagnostic techniques including immunohistochemistry and genetic and molecular diagnostic testing, which of course are essential to the modern practice of pulmonary pathology, particularly as it relates to pulmonary carcinomas. This edition is organized into 36 chapters covering the range of nonneoplastic and neoplastic pulmonary disorders. Each chapter is written by a leader in this field, and their practical knowledge is an essential part of each of these chapters.

I would like to extend my deepest appreciation to Drs. Zander and Farver and all of the authors who have contributed to this outstanding edition of the *Foundations in Diagnostic Pathology* series. This second edition significantly improves on what was already an outstanding volume in this series, and I am completely confident that you will enjoy this edition of the *Foundations in Diagnostic Pathology* series.

John R. Goldblum, MD

PREFACE

With a sense of excitement, gratitude, and responsibility, we are happy to present the second edition of *Pulmonary Pathology.* In the eight years since our first edition, the field has made the anticipated move toward a more molecular world, but the original aim of this book remains the same—to provide students and practitioners of pulmonary pathology the necessary tools to confidently interpret lung and pleural pathology. Since the first edition, this diagnostic tool set has expanded for both neoplastic and nonneoplastic lung diseases. Neoplastic lung pathology now requires a greater number of immunohistochemical and molecular studies as diagnoses for many tumors now require more specificity for new, more sophisticated therapies based on targetable mutations—ie, non-small cell carcinoma is no longer enough! Although nonneoplastic lung pathology currently has fewer therapies linked to these molecular events, research underway suggests opportunities for future intervention. Nonetheless, improvements in prognosis and therapy for this group of diseases have occurred through advances in radiologic technologies and physiologic assessments, demanding from pathologists a greater clinical knowledge of each entity, as multidisciplinary consensus diagnoses become the standard.

Despite all of these advances, morphology remains the most useful tool for the lung pathologist. Thus in this new edition, the emphasis remains on the morphologic features of each entity with enhanced descriptions of known entities and detailed morphologic descriptions of new entities, all informed by new observations since the first edition. As in the previous edition, these diagnostic tools are presented in a richly illustrated, templated approach characteristic of the *Foundations* series with ample clinical information to enhance the practical application of this pathology in our everyday practice. We are grateful to Dr. John Goldblum, our Editor-in-Chief, for his continued support of this volume in the *Foundations* series and to the editorial staff at Elsevier for making it happen. To the talented authors who have brought extraordinary expertise to each chapter—thank you for your time, your friendship, and for all that you have taught us and the readers who will consult your works throughout the years. Finally, to our readers—it is a privilege to bring you this new edition, and we hope that it will play at least some small part in encouraging your interest and ongoing learning in pulmonary pathology.

Dani S. Zander, MD
Carol F. Farver, MD

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1

Normal Anatomy, Tissue Artifacts, and Incidental Structures

Douglas B. Flieder

NORMAL ANATOMY

The lungs occupy most of the volume of the thoracic cavity. The average weights of male and female lungs are approximately 850 grams and 750 grams, respectively. The right lung is composed of ten distinct segments comprising three lobes (upper, middle, and lower), and the left lung has ten segments organized into two lobes (upper and lower). Each lobe is covered with pleura (visceral pleura) and separated from the other lobes by fissures. At the microscopic level, the lungs feature distinct yet integrated components, including conducting airways, distal airspaces, blood vessels and lymphatics, and other cellular constituents (Table 1.1).

AIRWAYS

Not only do conducting airways form the passageways through which air enters and exits the lungs, but they also warm, humidify, and aid in sterilizing incoming air. The trachea bifurcates into the left and right mainstem bronchi, which bifurcate into additional bronchi that undergo further bifurcations into smaller bronchi and then bronchioles. Airways in adult lungs usually undergo 23 divisions to finally merge with the gas exchange units, the alveoli.

Airways are classified as either bronchi or bronchioles. Bronchi have cartilaginous walls and measure more than 0.1 cm in diameter, whereas bronchioles measure less than 0.1 cm in diameter and lack cartilage. In the mainstem bronchi, hyaline cartilage is C-shaped, but as the airways enter the lung tissue, the cartilage becomes discontinuous. As the bronchial diameter decreases, the cartilage plates become smaller. Unlike bronchioles, bronchi also have submucosal salivary-type glands with both serous and mucous cells (Fig. 1.1).

Terminal bronchioles are the smallest pure conducting airways; about 30,000 terminal bronchioles are found within the lungs. The terminal bronchioles bifurcate into respiratory bronchioles, whose walls consist partially of alveoli (Fig. 1.2). Bronchioles also give rise to alveolar ducts, which terminate in alveolar sacs.

Airways are composed of mucosa, submucosa, muscularis propria, and adventitia. Bronchial epithelium lines the airway lumen and includes pseudostratified ciliated columnar epithelial cells, interspersed goblet cells and neuroendocrine cells, and underlying basal cells. The ciliated respiratory epithelial cells and goblet cells are specialized cells that function in mucociliary clearance mechanisms. Goblet cells secrete mucus, which is important for trapping inhaled particles, and the cilia propel the mucus and entrapped particles toward the pharynx, where they can be eliminated. Bronchi also feature basal cells, pluripotential reserve cells that can regenerate a damaged bronchial mucosa. Scattered neuroendocrine cells are also interspersed in the respiratory epithelium. Clusters of neuroendocrine cells can occasionally be found at airway bifurcations and are termed *neuroepithelial bodies*. Neuroendocrine cells may not be recognizable in routine hematoxylin and eosin-stained tissue sections but can be highlighted by immunohistochemical staining using antibodies directed against chromogranin or synaptophysin antigens. Neuroendocrine cells may play a role in lung development and/or ventilation/perfusion regulation.

In bronchioles, goblet cells are replaced by nonciliated columnar cells with prominent apical cytoplasm (Clara cells). Clara cells produce surfactant-like material, accumulate and detoxify inhaled toxins, and serve as progenitor cells for regeneration of damaged bronchiolar epithelium.

All airways feature a basement membrane composed of type III collagen and underlying elastic fibers and smooth

TABLE 1.1

Structural and Cellular Components of the Lungs

Bronchi

Epithelium
- Ciliated columnar epithelial cells
- Goblet cells
- Basal cells
- Neuroendocrine cells

Subepithelial connective tissue
Submucosal serous and mucinous acini with myoepithelial cells
Smooth muscle
Hyaline cartilage
Autonomic nervous system components
Vasculature and lymphatics

Bronchioles

Epithelium
- Ciliated columnar epithelial cells
- Clara cells

Subepithelial connective tissue
Smooth muscle
Autonomic nervous system components
Vasculature and lymphatics

Alveoli

Epithelium
- Type I pneumocytes
- Type II pneumocytes

Alveolar macrophages
Interstitium
- Fibroblasts
- Myofibroblasts
- Monocytes/macrophages
- Mast cells
- Collagen and elastic fibers

Alveolar capillaries
- Endothelial cells
- Pericytes

Interlobular septa

- Connective tissue
- Veins and lymphatics

Visceral pleura

- Mesothelial cells
- Connective tissue with blood vessels and lymphatics

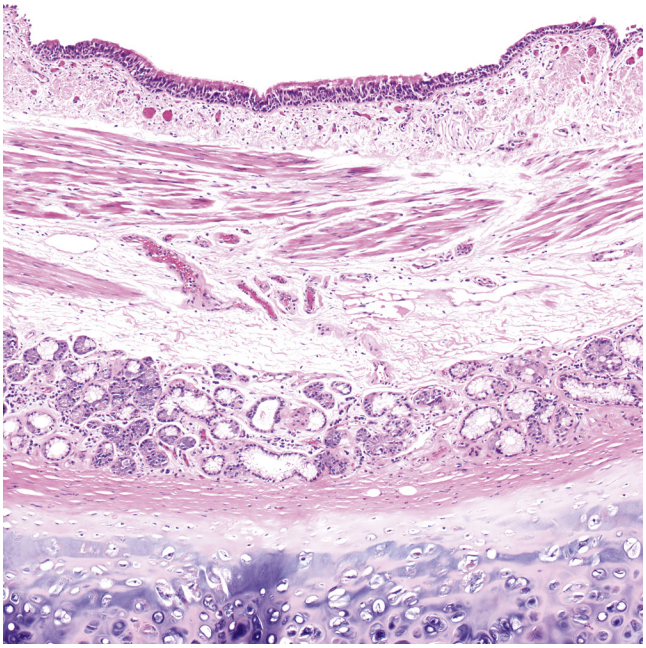

FIG. 1.1

Bronchus. The bronchial wall features pseudostratified ciliated columnar epithelium with goblet cells, submucosal seromucinous glands, bronchial vessels and lymphatics, smooth muscle, and hyaline cartilage.

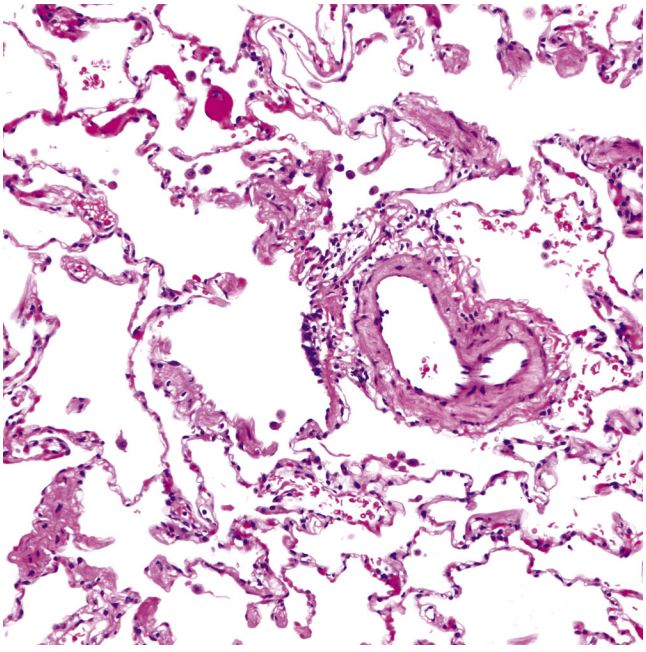

FIG. 1.2

Respiratory bronchiole and peribronchiolar structures. The respiratory bronchiole travels with a small branch of the pulmonary artery. This airway opens into an alveolar duct, as well as individual alveolar sacs. Scattered intraalveolar macrophages are a common finding and may be increased in smokers.

muscle bundles. Airways are richly innervated by parasympathetic and sympathetic nerves. Blood vessels and lymphatics also course through the airway submucosa.

GAS EXCHANGE UNITS

An average lung from a man contains approximately 300 million alveoli and 140 m^2 of gas-exchanging alveolar surface. Several terminal bronchioles and associated airspaces form each pulmonary lobule, which is bounded by a fibrous septum (Fig. 1.3). The lobules function semiautonomously, with neural controls to regulate air and blood flow. Lobules consist of up to 30 individual gas exchange compartments termed *acini.* An acinus is an anatomic unit that consists of multiple respiratory bronchioles, alveolar ducts, and alveoli that are supplied by a single terminal bronchiole.

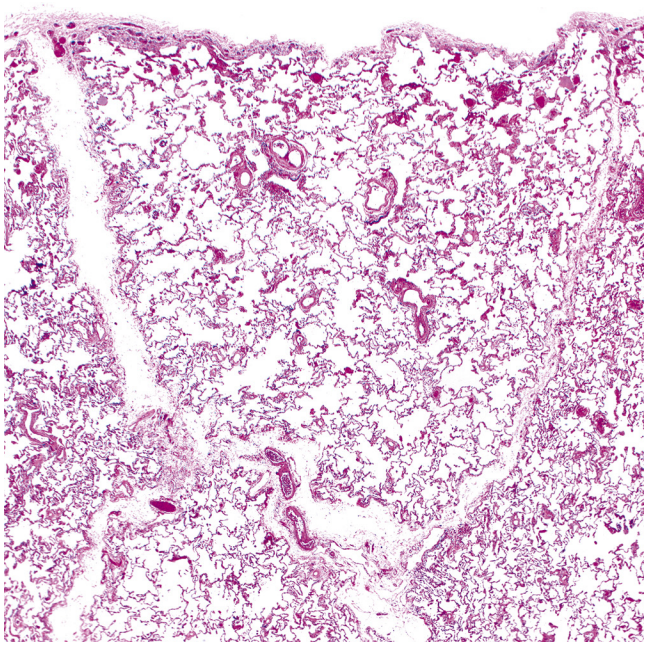

FIG. 1.3

Pulmonary lobule. The pulmonary lobule is bounded by interlobular septa and visceral pleura, which contain inconspicuous pulmonary veins and lymphatics.

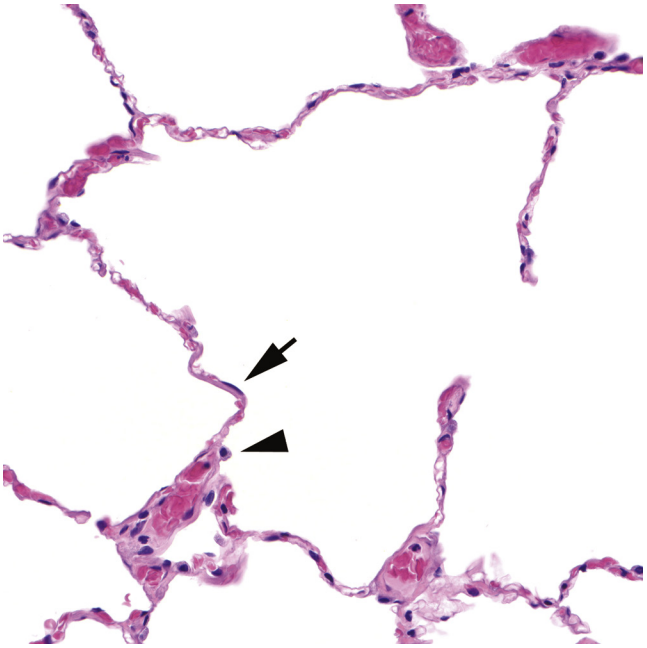

FIG. 1.4

Alveoli. Alveolar walls seem to consist only of capillaries and are lined by flattened type I cells *(arrow)* and occasional type II cells *(arrowhead).* The airspace is free of debris or cells.

Individual alveolar sacs are lined by two types of epithelium joined by well-formed tight junctions (Fig. 1.4). Type I pneumocytes have flattened nuclei and inconspicuous cytoplasm. They constitute 40% of the lining cells, yet cover 90% of the alveolar surface due to their abundant (up to 50 microns long) and thin (as little as 0.1 micron thick) cytoplasm. Type I pneumocytes facilitate O_2 and CO_2 exchange across their cytoplasm. Type II pneumocytes are cuboidal cells with large basally located nuclei, variably prominent nucleoli, and granular or vacuolated cytoplasm. These epithelial cells constitute 60% of the alveolar lining cells but cover only 5% of the airspace surface. In addition to secreting surfactant, a phospholipid that lowers surface tension and prevents alveolar collapse at low intraalveolar pressures, type II pneumocytes are alveolar stem cells capable of dividing and terminally differentiating into type I cells after alveolar injury.

Communications between alveoli are not present at birth but appear shortly thereafter and increase in number throughout life. Pores measuring up to 10 microns in diameter, termed *pores of Kohn,* are rarely seen in histologic sections. They may contain surfactant or be open and involved in collateral ventilation. Pores larger than 15 microns, between alveoli, are called *fenestrae* and are considered abnormal. Communications between terminal bronchioles and alveoli, termed *canals of Lambert,* also aid in collateral ventilation and are prominent in diseased airways as respiratory epithelium covers alveolar walls, so-called *lambertosis*.

Pulmonary capillaries in alveolar walls are vitally important for gas exchange. Incredibly, the intricate alveolar capillary meshwork yields an air–blood interface of 125 m^2, a surface area approximately 70 times that of the skin. At many points, the basal lamina underlying type I pneumocytes fuses with the basal lamina underlying pulmonary capillary endothelial cells. Endothelial cells are easily recognized in histologic sections and participate in regulating gas, water, and solute transport, converting angiotensin I to angiotensin II, inactivating bradykinin, and taking part in a variety of other metabolic functions.

Alveolar walls also contain small numbers of mesenchymal cells, including fibroblasts, smooth muscle cells, pericytes, and myofibroblasts. The mesenchymal cells maintain the septal elastic and collagen fibers and proteoglycans, and the contractile cells control capillary blood flow. Scattered mast cells and occasional lymphocytes and monocytes are also normally present, but large numbers of inflammatory cells in the alveolar interstitium indicate a pathologic process.

VASCULATURE

The lungs have dual blood supplies. The bronchial circulation is part of the systemic circulation and has a high pressure and high oxygen content. Bronchial arteries most often arise from the descending aorta and "feed" the bronchial tree as far as the respiratory bronchiole. Branches also nourish most of the mediastinal visceral pleura. Large bronchial arteries can be seen in the bronchial adventitia and usually demonstrate only one elastic lamina: the internal elastic lamina. Bronchial veins travel in the bronchial adventitia and feed into either the azygos or hemiazygos vein, or they empty into the pulmonary venous system.

The pulmonary circulation originates from the right ventricle. The main pulmonary arteries branch into lobar arteries and enter the lungs with the lobar bronchi. The arteries branch in tandem with the airways and additionally feature right-angle bifurcations in order to reach peribronchiolar alveoli. It is useful to keep in mind that arteries accompanying airways in histologic sections should have approximately the same diameters as the airways. Differences indicate the existence of a pathologic process. Compared with systemic arteries, pulmonary arteries feature more elastic and less smooth muscle, resulting in relatively increased luminal diameters. Two or more elastic laminae are found in arteries greater than 0.1 cm in diameter; yet as arteries become smaller, the smooth muscle layer becomes thinner and the elastic lamina fuse and fragment. Pulmonary venules are inconspicuous but coalesce to form small veins within the interlobular septa. These lobular veins converge into larger veins at subsegmental septa and eventually join the bronchi and pulmonary arteries at the segmental level. The large veins proceed to the hilum and drain oxygenated blood into the left atrium for systemic distribution.

LYMPHATICS AND IMMUNE EFFECTOR CELLS

Two separate inconspicuous lymphatic systems drain extracellular fluid, debris, and inflammatory cells from the lung. A centriacinar system resides within the bronchovascular bundles, starting at the level of the respiratory bronchioles. Lymphatics associated with pulmonary arteries extend deeper into the acinus than those associated with airways, but the two components of this system intersect often as they course through the lung to the hilum. The peripheral acinar system associated with pulmonary veins begins at the edge of the acinus and tracks through the interlobular septa and pleura. Although the two lymphatic systems communicate at lobar, lobular, and pleural boundaries, they drain separately into hilar lymph nodes. The right lung and left lower lobe usually drain into the right thoracic duct, the remainder of the left lung drains into the left thoracic duct, and interconnecting mediastinal lymphatic channels allow for cross-drainage. Flat endothelial cells line lymphatic channels, and larger lymphatics contain adventitial smooth muscle and collagen. Alveolar walls do not have lymphatics; yet the interstitial space is capable of draining extracellular fluid.

Small submucosal lymphoid aggregates are termed *bronchus-associated lymphoid tissue* (BALT) and are most commonly seen at bronchial bifurcations and near respiratory bronchioles. Whereas these structures have little known significance in children, the presence of BALT in adults suggests a pathologic process. Approximately 60% of the lymphoid cells are B-cells, generally small lymphocytes with a centrocyte-like appearance, and the remainder are T-cells. There are occasional HLA-DR$^+$ interdigitating cells and follicular dendritic cells. Germinal centers can form in the BALT. Overlying attenuated epithelium, so-called *lymphoepithelium,* facilitates antigen processing. Lymphoid aggregates involving other locations in the lung should be considered abnormal.

Intrapulmonary lymph nodes are found in all age groups but are more common in tobacco smokers and individuals with occupational exposures to asbestos and nonfibrous silicates. Two-thirds are solitary, and most measure less than 2.0 cm in diameter. The lymph nodes usually lie in subpleural areas, along interlobular septa or within the major fissures of the lung, and resemble normal lymph nodes with the additional frequent findings of anthracosilicotic pigment deposition and silicotic nodules.

Alveolar macrophages are bone marrow–derived phagocytes that enter the airspaces from the systemic circulation. Resident interstitial monocytes also contribute to alveolar macrophages. After engulfing debris, macrophages can persist in the alveolar sacs or be eliminated from the lung, primarily via airway clearance mechanisms. When particle burdens are very high and macrophages are overwhelmed, particles accumulate in the visceral pleura, alveolar septa, and connective tissues around airways. Particles derived from tobacco smoke and air pollution are particularly prominent around respiratory bronchioles.

PLEURA

The visceral pleura has five layers. A single layer of mesothelial cells without a basement membrane rests on a submesothelial layer of loose connective tissue approximately as thick as the mesothelial cell layer. The third layer is a well-defined elastic layer, and the fourth is the interstitial or loose connective tissue layer containing lymphatics, blood vessels, and collagen. The final layer is composed of elastic fibers and fibrous tissue that merges with the underlying lung. This architecture is often disturbed in settings of inflammatory or neoplastic disorders. Parietal pleura is similar to visceral pleura, but the layers are less distinct. The mesothelial cells lie on a connective tissue plane containing a single elastic layer and scattered blood vessels and lymphatics. The parietal pleura interdigitates with chest wall adipose tissue overlying dense collagen. This endothoracic fascia fuses with either skeletal muscle or rib periosteum. It should be noted that the presence of fat in a pleural biopsy does not necessarily indicate that a biopsy is from the parietal pleura, because fatty metaplasia of visceral pleura and subpleural lung tissue is a common finding in many disease states.

ARTIFACTS

Variations in normal histology and tissue distortions resulting from specimen procurement often present challenges for pathologists evaluating lung specimens (Table 1.2). Tissue from apical segments of lung features larger alveoli and fewer blood vessels than basal segment specimens and often shows fibrosis and elastosis (“apical cap”). Visceral pleura

TABLE 1.2

Common Artifacts in Lung Tissues

Atelectasis and mechanical compression
Can mimic:
Interstitial fibrosis
Exogenous lipoid pneumonia
Can mimic or obscure malignancies, especially small cell carcinoma (crush artifact)
Overinflation
Can mimic:
Lymphatic dilatation
Emphysema
Can wash out intraalveolar cells
Procedure-associated hemorrhage
Can mimic pulmonary hemorrhage syndromes
Mechanical displacement of tissue
Can mimic malignancy
Air-dry artifact
Sponge artifact (due to use of sponge in processing)

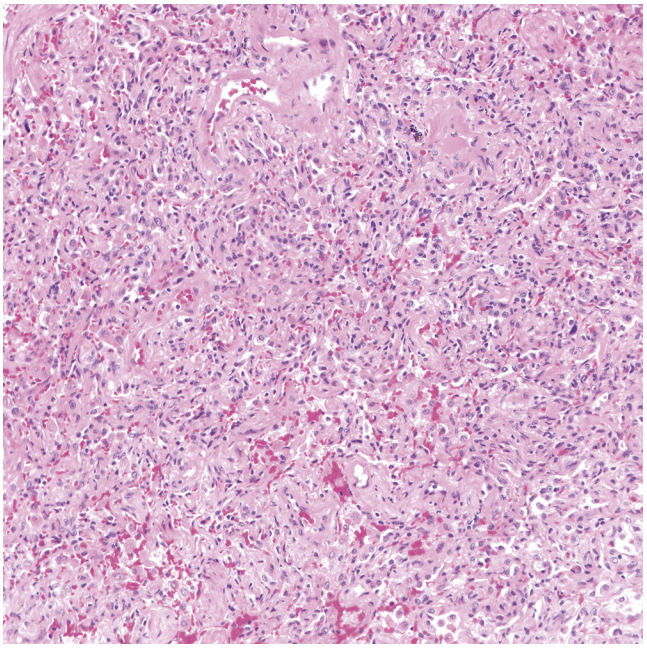

FIG. 1.5

Artifactual atelectasis. Artifactual atelectasis can interfere with morphologic interpretation of lung samples. This biopsy is actually unremarkable but could be misconstrued as showing a fibrosing process. Surgical lung biopsies and resection specimens are frequently compressed during surgery or in the pathology laboratory, but specimen inflation with formalin can improve one's ability to assess tissue architecture and evaluate for subtle pathologic changes.

is thicker at the lung bases and in fissures than over smooth lung surfaces. Lung tips, especially the lingula and right middle lobe tips, often demonstrate nonspecific scarring and honeycomb change even in individuals without clinical pulmonary disease. Subbronchial alveolar septa are thicker and slightly fibrotic, so samples from these regions should not be overinterpreted as representing fibrosing interstitial lung disease. Age-associated changes, including bronchial wall submucosal elastosis, bronchial seromucinous gland hyperplasia or oncocytic metaplasia, intimal thickening of vessel walls, senile vascular sclerosis, and alveolar space enlargement (senile emphysema), do not represent pathologic processes.

Biopsy and resection specimens may feature atelectasis secondary to compression associated with the biopsy procedure (Fig. 1.5). Atelectatic areas may not be interpretable, and one should be wary of attempting to diagnose interstitial lung diseases in these samples. Compression can produce a rounding of alveoli, suggesting lipoid change and a diagnosis of exogenous lipoid pneumonia. The absence of alveolar macrophages and fibrosis, however, should argue against this diagnosis. Injection of formalin into surgical lung biopsies can be done to inflate them and facilitate evaluation of interstitial abnormalities. Overinflation of lung tissue, however, can expand interlobular septa and pulmonary lymphatics or overexpand alveoli, leading to erroneous considerations of lymphangiectasia and emphysema. Surgical clamping of lung tissue may also lead to septal edema and distortion of alveolar spaces not unlike that produced by pathology laboratory–induced specimen overinflation.

Lung specimens extensively handled by surgeons may feature visceral pleural mesothelial cell sloughing with dense intracapillary neutrophils and surface fibrin strands. Due to biopsy procedures, lobules may fill with blood, but in the absence of hemosiderin-laden macrophages, intraalveolar fibrin, and/or alveolar septal neutrophils, a pulmonary hemorrhage syndrome is unlikely. Smoker's macrophages contain tan-brown pigment that will stain with an iron stain, but the particles are finer than coarse hemosiderin.

Transbronchial biopsies can also show procedure-related artifacts. Crush artifact is common in endoscopic biopsies, particularly those obtained from small cell carcinomas and lymphoid processes. Caution is advised when making a diagnosis on severely crushed tissue (Fig. 1.6), and well-preserved, diagnostic areas should be sought to ensure the accuracy of the interpretation. Circumferential strips of bronchial wall with partially denuded respiratory epithelium should be recognized as such, and clumps of displaced ciliated epithelium with prominent goblet cells should not be mistaken for malignancy.

INCIDENTAL FINDINGS

A large variety of incidental findings can be seen in the lung and can involve any anatomic compartment. Some abnormalities discovered unexpectedly may have clinical relevance (eg, granuloma containing mycobacteria, pulmonary embolus), and although incidental, these findings can represent important diagnostic entries. Most incidental findings, however, do not have potential clinical significance, and the main importance of recognizing many of these entities lies in not confusing them with meaningful pathologic processes (Table 1.3, Figs. 1.7–1.9).

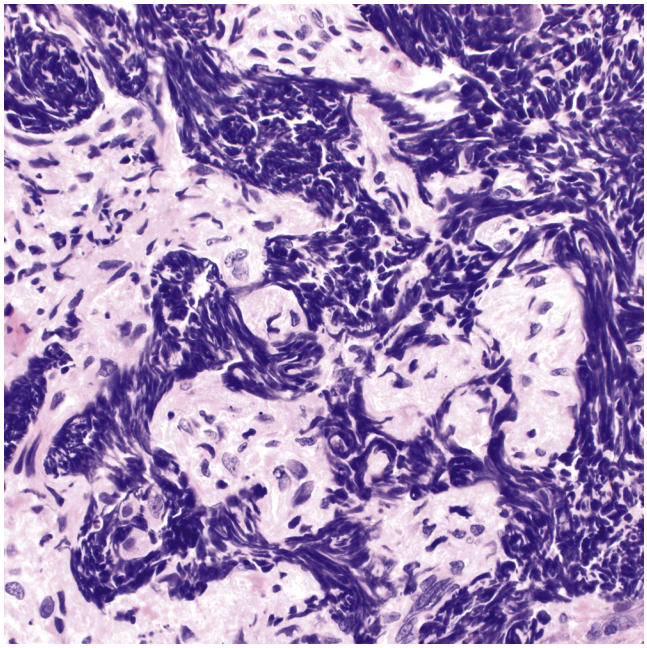

FIG. 1.6

Crush artifact. Crush artifact interferes with morphologic assessment. Small cell carcinomas are particularly susceptible to this artifact, but other benign and malignant processes can also show this change. In this case the concomitant cytology specimen and immunohistochemical stains were diagnostic of malignant lymphoma.

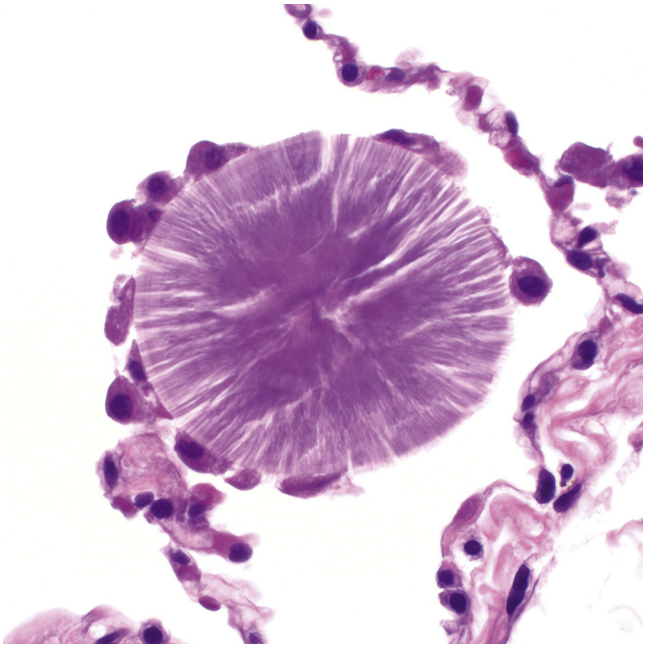

FIG. 1.7

Corpus amylaceum. Corpora amylacea are common incidental findings in airspaces. These spherical structures, 30 to 200 microns in diameter, are composed of glycoproteins and may have prominent radiations. Although they are periodic acid-Schiff (PAS)-positive, they should not be mistaken for fungal organisms.

TABLE 1.3

Common Incidental Findings in Lung Tissues

Large airways

Ossification of bronchial cartilage
Oncocytic metaplasia of bronchial submucosal glands
Bronchial submucosal elastosis

Alveolar parenchyma

Scar
Apical cap
Focus of smooth muscle hyperplasia
Metaplastic bone
Corpora amylacea
Blue body
Schaumann's body
Asteroid body
Mallory's hyaline-like material in type II pneumocytes
Ferruginous body
Foreign body, including aspirated material
Cholesterol cleft
Carcinoid tumorlet
Minute meningothelial-like nodule
Isolated granuloma
Anthracotic pigment deposit
Calcium oxalate crystal
Silicotic nodule

Vascular

Megakaryocyte
Small embolus
Calcification of elastic fibers
Senile venous sclerosis

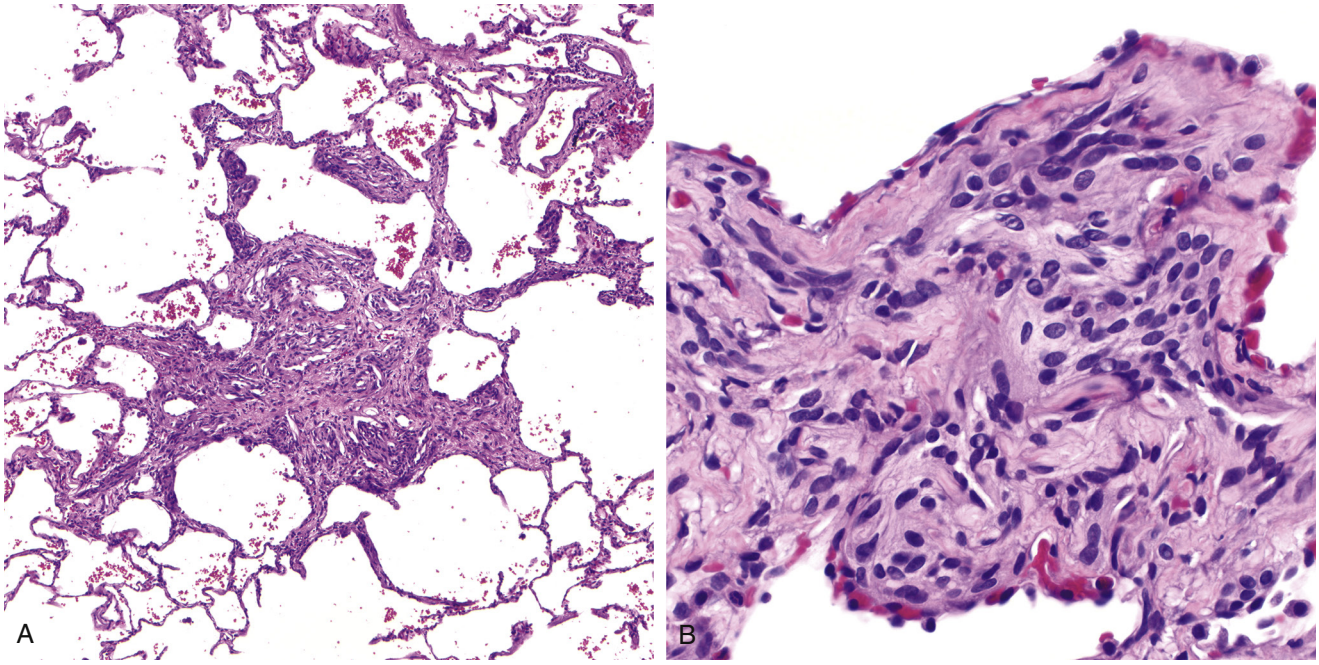

FIG. 1.8

Minute meningothelial-like nodule. (A and B) Minute meningothelial-like nodules usually measure less than 3 mm and are nodular perivenular interstitial proliferations of meningothelial-like cells. They consist of nests and streams of cells with uniform oval nuclei, homogeneous chromatin, and lightly basophilic cytoplasm. Intranuclear inclusions can be seen, and cells show immunoreactivity with anti-epithelial membrane antigen (EMA) antibodies. These common incidental proliferations should not be confused with malignancy.

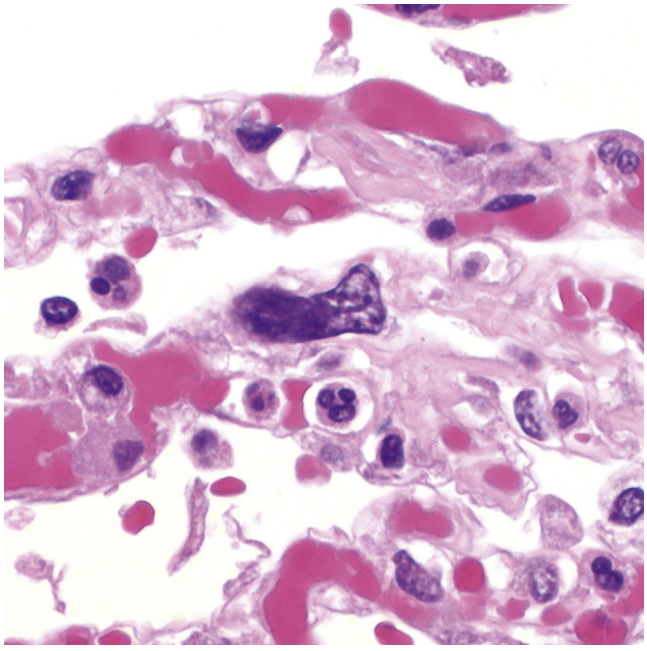

FIG. 1.9

Megakaryocyte. Megakaryocytes travel through the pulmonary circulation and can be mistaken for metastatic tumor cells or virally infected cells. They can be especially prominent in settings of significant blood loss and acute inflammatory conditions.

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2

The Uses and Abuses of the Lung Biopsy

■ Anthony A. Gal ■ Carol F. Farver

■ INTRODUCTION

The lung biopsy is widely recognized as a valuable tool for the diagnosis and management of diverse pulmonary disorders. The various procedures currently in use, such as the open lung biopsy (OLBx), video-assisted thoracoscopic surgery (VATS) biopsy, and transbronchial lung biopsy (TBBx) and cryobiopsy (TBLC), can be diagnostic when performed under appropriate circumstances and if evaluated by the pathologist with several caveats in mind. Although the morphologic findings seen in lung biopsy specimens may represent a specific disease entity, in many circumstances these changes may be nonspecific findings that will need to be correlated with the clinical and radiographic presentations.

■ HISTORY

The lung biopsy is a relatively new tool for the diagnosis of lung diseases. Although rigid bronchoscopy was introduced just before the end of the 19th century, it was primarily used for visualization of the large airways without pathologic confirmation. Later refinements in procedures led to its use for the evaluation of central lesions, but peripheral lesions were poorly visualized and seldom biopsied.

In the early 1960s, refinements in optical technology led to the first flexible fiber-optic bronchoscope. The introduction of this new equipment and its application in a variety of clinical situations led to increased use of the TBBx. Henceforth, numerous studies examined the role of fiber-optic bronchoscopy and the diagnostic yield of TBBx in a spectrum of clinical settings.

In the past decade, TBLC offers another novel technique for obtaining larger tissue volumes than the conventional TBBx (Fig. 2.1). During the bronchoscopic procedure, a cryoprobe rapidly freezes lung tissue samples, which are further processed as other biopsies. The TBLC provides more tissue that allows for better evaluation of lung parenchyma, small bronchioles, and blood vessels and may prove to be useful in various clinical settings. However, its current use is limited to very few centers, and its potential for more widespread use remains uncertain.

After World War II, major advances in surgical technique, anesthesia, and antibiotic therapy led to the development of the OLBx. Although this procedure is valuable for enabling diagnosis of many lung diseases, thoracotomy with OLBx is associated with significant morbidity and mortality. This procedure has now been largely replaced by VATS, which allows the thoracic surgeon to procure tissue via a less invasive means and potentially minimize postoperative complications. In capable hands, several studies have shown that the ability to procure tissue via VATS is equivalent to that of open thoracotomy. It is currently the standard of practice for obtaining lung tissue for the evaluation of interstitial lung diseases, primary lung cancer, and other mass lesions.

■ EFFICACY OF THE TRANSBRONCHIAL LUNG BIOPSY AND CRYOBIOPSY

In common practice, the TBBx is performed by the bronchoscopist in the hopes of arriving at a definitive diagnosis and avoiding the use of a more invasive procedure such as an OLBx or VATS biopsy. Various cytologic specimens, such as bronchial washings, bronchial brushings, and bronchoalveolar lavages, are usually also collected during the bronchoscopy procedure to improve overall diagnostic yield. Although TBBx can be a highly effective tool for the diagnosis of certain lung diseases, its role in most other

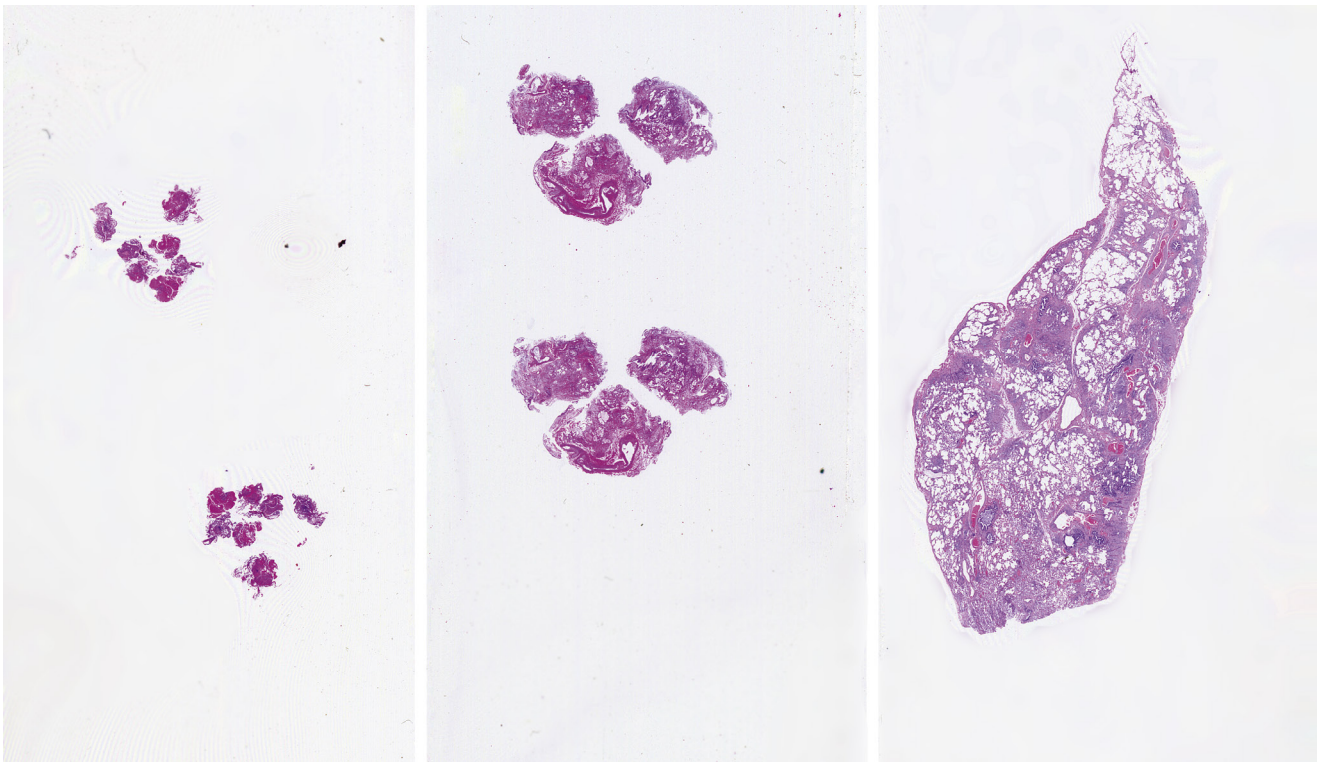

FIG. 2.1
Comparison of transbronchial, cryobiopsy, and open lung biopsy. *(Courtesy of Venerino Poletti, MD, Dipartimento Toracico, Ospedale G.B. Morgagni, Forlì, Italy.)*

circumstances is quite limited. Moreover, although TBLC has been used in the setting of interstitial lung diseases, cancer and nodular lesions, lung transplantation, and immunocompromised patients, it is premature to say whether this technique is superior to other current methods to obtaining lung tissues. Irrespective of technique, the prudent pathologist should not fall into the trap of being forced into rendering a diagnosis from bronchoscopically derived tissues outside of certain clinical and pathologic settings.

The TBBx is particularly effective for the diagnosis of primary lung carcinomas; the addition of cytologic specimens increases the overall yield. The TBLC may be particularly useful for large exophytic endobronchial tumors, but it can also be utilized for peripheral lesions. Other less common primary lung tumors, such as the carcinoid, sclerosing hemangioma, or bronchial gland tumors, could be potentially diagnosed by TBBx or TBLC in appropriate circumstances. These biopsies are less effective, however, in the setting of metastasis to the lungs, particularly when the mass is solitary and peripheral in location. Because the morphologic features of metastases can sometimes mimic those of a primary lung carcinoma, the pathologist should always consider whether a given neoplasm could represent a metastasis and order immunohistochemical stains as needed to facilitate the differential diagnosis.

Bronchoscopic biopsies can also provide useful information in certain nonneoplastic lung diseases. Sarcoidosis can often be diagnosed by TBBx, endobronchial biopsies, and TBLC, assuming that other granulomatous disorders have been excluded. However, the presence of nonnecrotizing granulomas in a tissue biopsy should lead to the consideration of a broader differential diagnosis (Fig. 2.2). For uncommon disorders such as pulmonary alveolar proteinosis or lymphangioleiomyomatosis, the TBBx may be diagnostic, but histochemical and immunohistochemical stains should be employed for confirmation. In immunocompromised patients, certain opportunistic infections such as *Pneumocystis jirovecii* and viral and fungal infections can be diagnosed by TBBx. In lung transplant recipients, TBBx and TBLC are highly effective for the diagnosis of acute allograft rejection, sometimes effective for detecting obliterative bronchiolitis, and less effective for some of the other entities that occur in this clinical setting, such as posttransplant lymphoproliferative disorders.

Although hemorrhage in most lung biopsies is usually a result of the biopsy procedure, certain pathologic and clinical scenarios should prompt consideration of other explanations. The presence of diffuse alveolar hemorrhage with necrotizing capillaritis and hemosiderin deposition may suggest a diagnosis of an antineutrophil cytoplasmic antibody–related lung disease or another autoimmune disorder. In practice, unfortunately, it can be difficult to separate small vessel vasculitis from nonspecific neutrophilic margination during the biopsy or

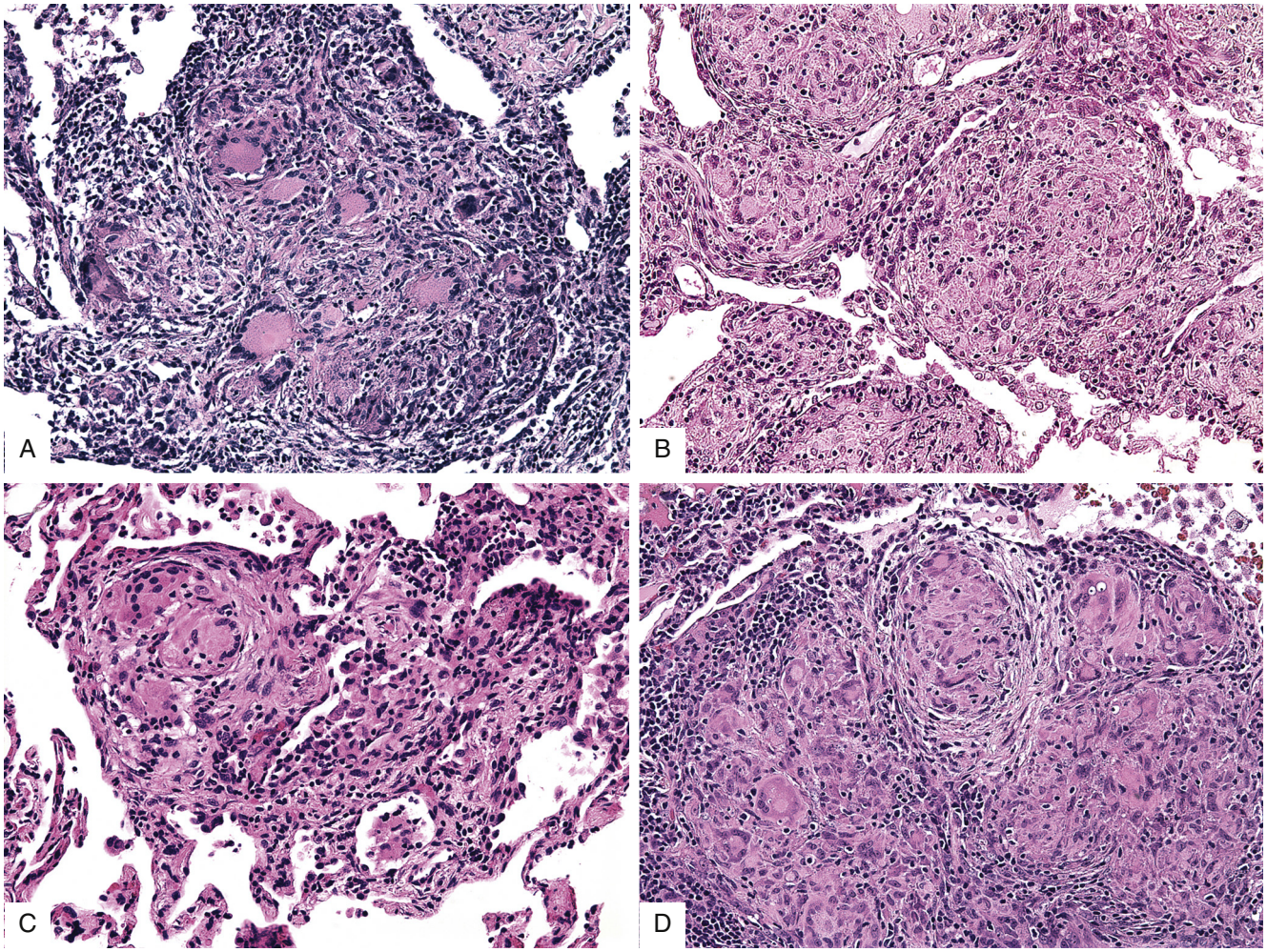

FIG. 2.2

Nonnecrotizing granulomas in biopsy specimens. The presence of a nonnecrotizing granuloma should lead to the consideration of several disease processes, which can have similar morphologies: (A) Sarcoidosis. (B) Berylliosis. (C) Chronic hypersensitivity pneumonitis. (D) Tuberculosis.

an early bronchopneumonia. Alternatively, the finding of bland alveolar hemorrhage in the absence of small vessel vasculitis could suggest antibasement membrane disease (Goodpasture's syndrome), and in the appropriate clinical settings, other studies (immunofluorescence staining of tissues, serologic studies for antibasement membrane antibodies) can be pursued.

For many other nonneoplastic disorders, it is unlikely that the TBBx will be adequate for diagnosis. In pulmonary granulomatosis with polyangiitis (GPA), it is essential to find both the necrotizing granulomata and vasculitis; however, it is quite exceptional to receive adequate tissue with all of the key pathologic findings in small biopsy specimens. Moreover, caution is advised because vasculitis-like changes can be seen in blood vessels that are adjacent to necrotizing granulomas due to various infectious disorders. In organizing pneumonia, TBBx may not sample diagnostic areas of the patchy process, whereas the TBLC may provide a better sample. When the biopsy shows tissue eosinophilia, it may not be possible to further characterize this infiltrate. For lymphoproliferative disorders, the biopsy may not provide sufficient tissue to separate lymphoid interstitial pneumonia from low-grade malignant lymphoma or other disorders in this category.

Whereas the TBBx has limitations (sample size, sampling artifacts, representativeness) that make it less useful for the diagnosis and classification of the diffuse idiopathic interstitial lung diseases, the TBLC has shown promise in this clinical setting (Fig. 2.3), and VATS biopsies are almost always diagnostic, provided that appropriate areas are sampled. There is some variation in practice regarding the choice and sequencing of biopsy procedures, however. Some clinicians attempt to use TBBx as a "first step" diagnostic procedure, that is, to rule out certain diseases that may be diagnosed by TBBx, such as malignancies or granulomatous diseases, before proceeding to a VATS biopsy for definitive diagnosis of the idiopathic interstitial pneumonia. Others may not perform a TBBx before proceeding to a VATS biopsy if an interstitial lung disease is suspected.

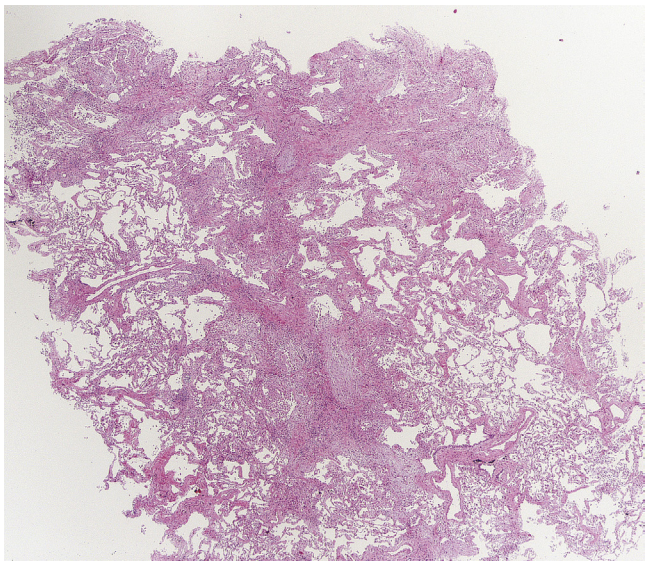

FIG. 2.3

Cryobiopsy in usual interstitial pneumonia. This cryobiopsy discloses patchwork fibrosis with fibroblastic foci. *(Courtesy of Alberto Cavazza MD, Unità Operativa di Anatomia Patologica, Reggio Emilia, Italy.)*

PROBLEMS WITH LUNG BIOPSY

ISSUES OF TISSUE

The morphologic changes that are present in lung biopsies of inflammatory diseases are seldom specific for a single entity and can be the result of various causes. This is particularly the case with interstitial lung diseases, in which there are overlapping pathologic findings. For example, each of the key histologic features seen in usual interstitial pneumonia (UIP) (ie, fibroblast foci, variation in degree and extent of fibroconnective tissue, honeycomb changes, variable chronic interstitial inflammation) are not specific for UIP and may not be present in limited biopsy samples (Fig. 2.4). Alternatively, when a nonspecific feature such as chronic interstitial inflammation is seen in a biopsy, it may or may not be of diagnostic significance. Other features, such as blood, edema, fibrosis, or chronic bronchiolitis, are commonly present in specimens, and it may be difficult to decide whether these changes have true pathologic significance.

As would be expected, tissues procured by rigid or fiberoptic bronchoscopy typically yield a limited number of lung tissue fragments. Moreover, the TBLC typically samples a single site and most frequently the peripheral subpleural zone of the lung. Whereas a small biopsy may be sufficient for the diagnosis of malignancy, it may not be sufficient for other disorders. For example, in the setting of lung transplantation, it has been suggested that at least five pieces of alveolated lung tissue containing more than 100 alveoli be present for a proper evaluation. Further, TBBx does not allow for the evaluation of architectural features at low power that is essential in differentiating the various interstitial lung diseases.

Larger surgical specimens such as OLBx and VATS biopsies generally provide more generous tissue samples, but there may also be problems in obtaining adequate lung tissue for diagnosis. Specimens taken from the lingula or from other areas of markedly fibrotic lung may not be representative of the underlying disease process. For this reason, biopsies of interstitial lung diseases should ideally be obtained from at least two sites, increasing the probability of sampling a site of active (not advanced or end-stage) disease.

A number of artifacts may occur in lung biopsies (Chapter 1), potentially interfering with interpretation. Inflation techniques can be used to obviate artifactual atelectasis in OLBx and VATS biopsies. A small-gauge needle is inserted into the lung to inflate the lung with formalin. This procedure expands the alveolar spaces and eliminates collapse. For the frozen section, this technique can be easily modified by using a slightly larger-gauge needle; the optimal cutting temperature (OCT) compound embedding medium can inflate the small sample, and this technique will facilitate cryo-sectioning and avoid atelectasis (Fig. 2.5).

INTERPRETIVE ISSUES

The histologic evaluation and interpretation of lung biopsies can be a challenging task for the pathologist. There are several explanations for this, including the level of experience and confidence level of the pathologist, the quality and number of specimens evaluated, and whether appropriate clinical, radiographic, or other pertinent information is readily available. Yet even when the sample is sufficient and information is available, there still remains substantial variation in the interpretation of lung biopsies.

A presurgical biopsy by TBBx, TBLC, or cytology of a primary lung carcinoma frequently results in accurate tumor classification. In most instances, the tumor can be readily classified as either “small cell carcinoma” or “nonsmall cell carcinoma.” However, further classification into pathologic subgroups of nonsmall cell lung cancer (ie, squamous cell carcinoma, adenocarcinoma, or large cell carcinoma) may not always be feasible. Reproducibility studies of lung tumor pathologic classification have demonstrated significant problems in interobserver and intraobserver variability. Nonetheless, accurate classification as a specific type of nonsmall cell lung cancer has become even more important in recent years because of the need to perform additional genetic studies on some tumor types and the targeted therapies available for specific types of nonsmall cell lung cancers.

There are many potential pitfalls in making an accurate diagnosis of a pulmonary neuroendocrine tumor in small bronchoscopically derived biopsies. A carcinoid can be misdiagnosed as small cell carcinoma, and vice versa. Not infrequently, small cell carcinoma in TBBx exhibits significant crush artifact or a subpopulation of larger cells, which makes it difficult to separate from other entities in the differential

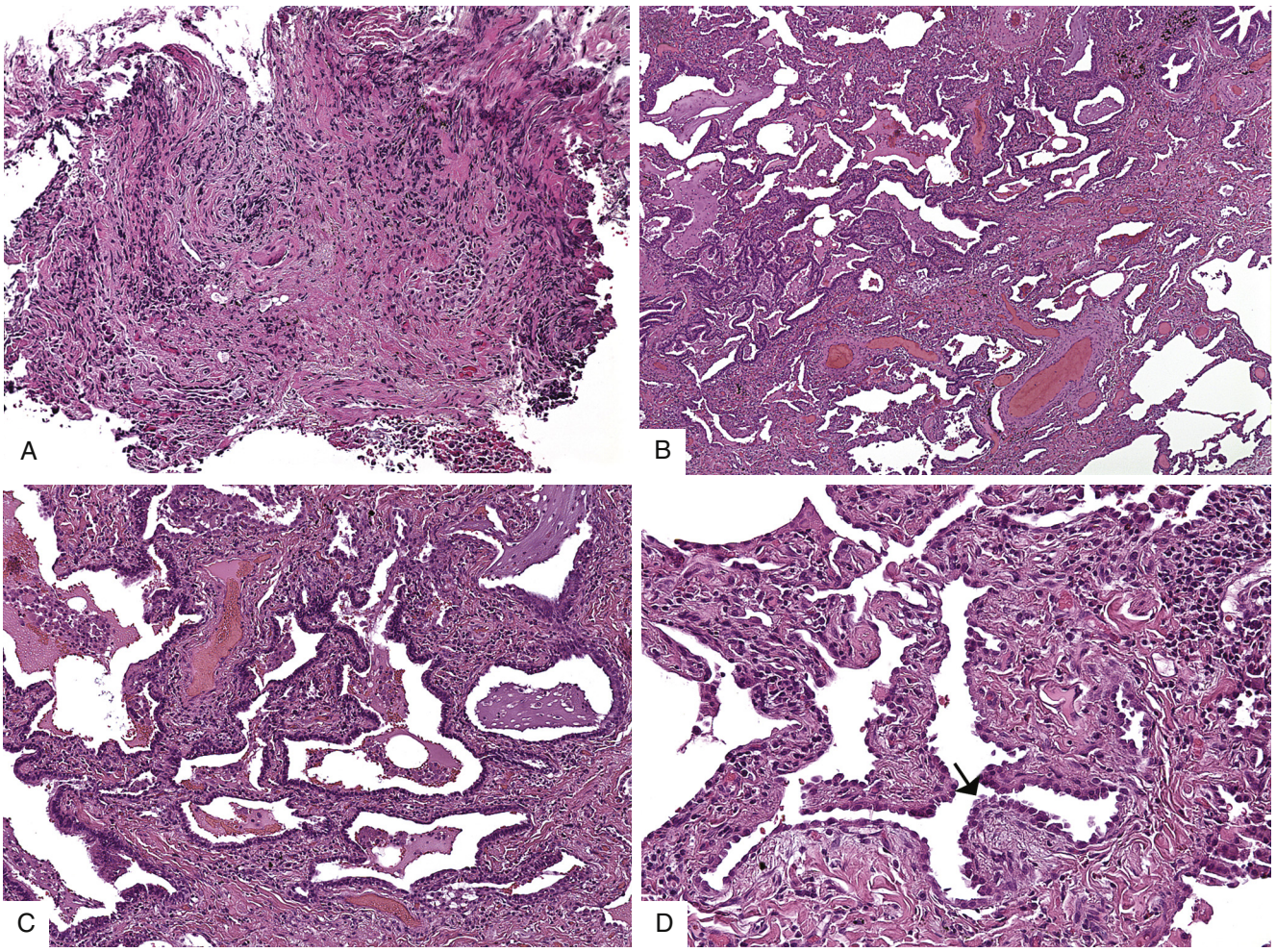

FIG. 2.4

Limited use of transbronchial biopsy in idiopathic pulmonary fibrosis. (A) The transbronchial biopsy discloses some fibrosis but is otherwise nondiagnostic. (B) The subsequent open lung biopsy discloses low-power architectural features of usual interstitial pneumonia (UIP). (C) Honeycomb change, which is an important feature in diagnosing UIP, is visible in the open lung biopsy, but was not seen in the transbronchial biopsy. (D) The fibroblastic focus, which consists of young basophilic collagen underneath the alveolar epithelium, is evident at the arrow in the open lung biopsy. This feature was also not appreciated in the transbronchial lung biopsy.

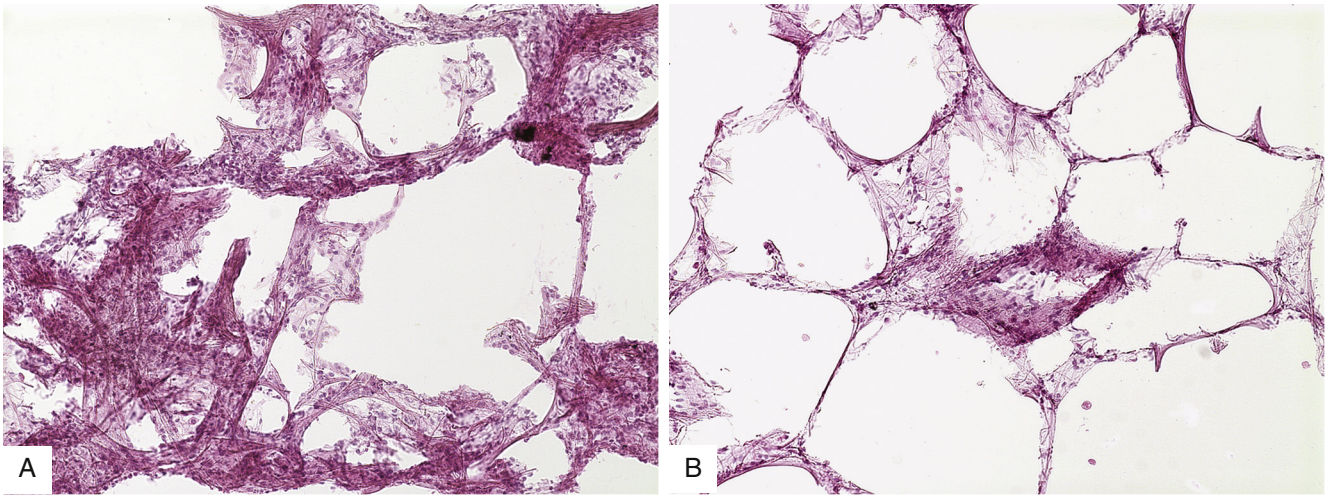

FIG. 2.5

Inflation of lung during frozen section. (A) This piece of lung is structurally normal, but the sectioning artifact and artifactual atelectasis could lead to a misinterpretation of pulmonary fibrosis. (B) Injecting the lung tissue with OCT-embedding material prevents the artifactual atelectasis and facilitates cryosectioning.

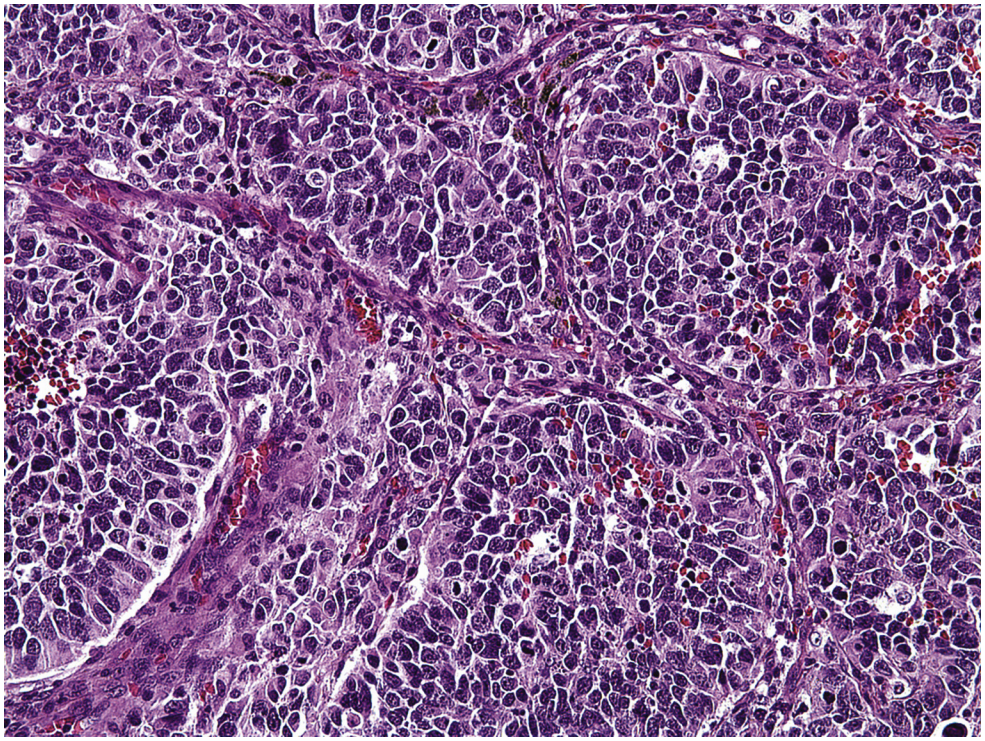

FIG. 2.6

Problematic high-grade neuroendocrine carcinoma of the lung. Classification of this high-grade neuroendocrine carcinoma is difficult: large cell neuroendocrine carcinoma versus combined small cell carcinoma with large cell neuroendocrine carcinoma.

diagnosis (Fig. 2.6). Small cell carcinoma and basaloid squamous cell carcinoma can be difficult to separate based on morphology. Judicious use of immunohistochemical stains (keratins, TTF-1, p40, MIB-1, or other neuroendocrine markers) may be helpful in some examples. Correlation of the biopsies with cytology specimens is strongly recommended for problematic cases.

Another significant example of interobserver variability in lung pathology is in the classification of the diffuse interstitial lung diseases. Among pulmonary pathologists who have expertise in interstitial lung diseases, there is a high degree of diagnostic accuracy for some disorders (ie, sarcoidosis), but poorer degrees of concordance for others (ie, usual interstitial pneumonia versus nonspecific interstitial pneumonia). Resolution of problematic cases frequently necessitates close correlation with the clinical and radiologic findings. Multidisciplinary diagnostic conferences can be an excellent resource for facilitating an integrated diagnosis.

CONCLUSION

Bronchoscopic biopsies offer a low-risk approach to acquiring tissue that is more likely to be diagnostic in some clinical settings than others. Transbronchial cryobiopsies may offer a way of acquiring more lung tissue without the necessity of a surgical biopsy, although this procedure is still being evaluated for more widespread use. Open lung and VATS biopsies are sensitive, and specific tests that should be utilized when a specific diagnosis cannot be gleaned from less invasive procedures and from available clinical and radiographic data. It cannot be overemphasized that the morphologic findings must be correlated with the clinical and radiographic presentations. First-hand knowledge of the indications and limitations of lung biopsies is necessary for proper patient care and diagnosis.

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3

A Pattern-Based Approach to Diagnosis

■ Diana N. Ionescu ■ Maxwell L. Smith ■ Kevin O. Leslie

■ INTRODUCTION

Each of us follows well-established patterns as we go about our daily lives, and in turn we interact with our world through the recognition of patterns: in the people we know, the places we live, and the structures that form our physical environment. Similarly, the specialty of anatomic pathology relies heavily on pattern recognition, especially given the observational nature of this medical discipline. The experienced anatomic pathologist quickly recognizes the pattern of disease and, without dwelling on the initial overview, very often has already moved on instinctively to glean additional qualitative and quantitative information to arrive at a diagnosis. This initial observation forms the basis for this chapter and the basic patterns of pulmonary disease that will be discussed here. In addition, we will explore how specific morphologic findings contribute to the construction of a specific diagnosis or limited differential diagnosis.

The lung is an organ open to the environment, and with every breath it is exposed to a large number of potential injuries. Despite superb dynamics and adaptability, the lung responds to injury with a limited repertoire of inflammatory and reparative reactions. These reactions can be grouped based on their acuity (eg, acute, subacute, and chronic) and by the distribution of abnormalities spatially or in relation to underlying lung anatomy (eg, alveolar space filling, nodule formation). Some lung diseases are characterized by quite subtle changes at the microscopic level, and these are grouped together as a pattern we refer to as *minimal changes* (at scanning magnification). Through these foundation patterns, we present a practical approach to pulmonary pathology.

A journey through the true three-dimensional microanatomy of the lung, even today, is still mainly an imaginative one. A histology slide prepared from lung tissue presents the lung anatomy in two dimensions. To the inexperienced eye, the structure appears at first overly simple; yet translating what is seen in two dimensions to its corollary in three-dimensional anatomy takes considerable practice and repeated exposure. As a reasonable starting point, a schematic representation may be helpful (Fig. 3.1). This

relationship is also very important in correlating the histopathology with the radiologic changes, particularly those seen in high-resolution computed tomography (HRCT) scans. A radiology–pathology correlation of anatomic distribution in lung pathology is summarized in Table 3.1.

In this chapter we will present these six patterns by describing the essential elements that each of them comprise, followed by a diagnostic algorithm by which individual disease entities within each pattern can be discerned.

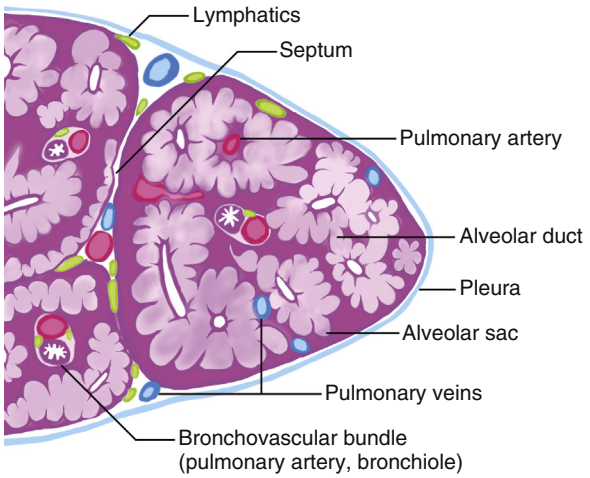

FIG. 3.1

Schematic representation of microscopic lung anatomy. *(Courtesy of Hailey J. Smith.)*

TABLE 3.1
Anatomic Distribution in Diffuse Lung Disease

Histologic	Radiologic (HRCT)
Bronchocentric/bronchiolocentric	Centrilobular
	Bronchovascular
Angiocentric	Bronchovascular (arterial)
	Interlobular septal (venous)
Pleural/subpleural	Pleural/subpleural
Lymphatic	Bronchovascular
	Interlobular septal
	Pleural/subpleural
Peripheral acinar	Subpleural peripheral distribution (paraseptal)
Septal	Septal (interlobular septal)
Random nodular	Random nodular
Parenchymal consolidation	Consolidation
Diffuse interstitial	Diffuse interstitial, ground-glass attenuation
Mixed and unclassified	Mixed/unclassifiable

HRCT, High-resolution computed tomography.
From Leslie KO, Colby TV, Swenson SJ. Anatomic distribution and histopathologic patterns of interstitial lung disease. In: Schwarz M, King T, eds. *Interstitial Lung Disease*. 4th ed. Hamilton: Ontario; B.C. Dekker, Inc., 2003.

This pattern-based diagnostic approach is most helpful in the assessment of surgical wedge lung biopsies for nonneoplastic disease—the most difficult and challenging samples in pulmonary pathology. By following the pattern-based approach, we can be certain that all histologic entities from the most common to the most esoteric are acknowledged and, therefore, unlikely to be missed.

Detailed clinical and radiologic features of the specific lung diseases, along with treatment and prognosis, are presented throughout the chapters of this book. Here we will emphasize the pathologic features helpful in narrowing the differential diagnosis and provide cross-references to other chapters for more detailed discussion wherever appropriate.

ACUTE LUNG INJURY (PATTERN 1)

ACUTE LUNG INJURY (PATTERN 1)—FACT SHEET AND PATHOLOGIC FEATURES

Definition

- Lung biopsies are diffusely involved by interstitial and alveolar edema, intraalveolar fibrin, and reactive type II cell hyperplasia

Potential Etiologies

- Infections
- Sepsis
- Shock, trauma
- Radiation
- Drugs or toxins
- Aspiration
- Many others (see other chapters)

Histologic Characteristics

- Edema: interstitial and alveolar
- Reactive type II pneumocytes
- Hyaline membranes or fibrin deposition in alveoli
- Variably present:
  - Necrosis
  - Neutrophils
  - Eosinophils
  - Siderophages
  - Vacuolated macrophages

ELEMENTS OF THE PATTERN

The lung biopsy is involved by varying amounts of alveolar wall edema, intraalveolar edema, and fibrin and has reactive pneumocytes (Fig. 3.2). Acute lung injury typically has a short clinical evolution and often a rapid onset of symptoms. When the pattern of diffuse lung injury is noted, the biopsy should be searched for specific histologic features that will help suggest a more specific etiology. Infectious diseases should always lead the differential diagnosis in Pattern 1, and therefore special stains for organisms are a requirement, along with close correlation with clinical history and microbiologic findings.

I. ACUTE LUNG INJURY WITH EDEMA, FIBRIN, AND REACTIVE PNEUMOCYTES

Many systemic medical conditions can affect the lung, especially cardiovascular diseases, but also shock, trauma, sepsis, etc. Many of these conditions are rarely biopsied, and when they are, it is to assess the presence, extent, and severity of the lung injury and to exclude the possibility of atypical infection. The earliest changes seen in acute lung injury are interstitial (alveolar septal) edema, followed by intraalveolar edema and fibrin, and then accumulation of cellular alveolar debris. A search for necrosis or granulomas is essential in this setting.

II. ACUTE LUNG INJURY WITH HYALINE MEMBRANES

Hyaline membranes are accumulations of proteinaceous alveolar exudates at the periphery of the alveoli. These become adherent to the alveolar septa and are seen to outline the alveolar spaces (Fig. 3.3). The diagnosis of diffuse alveolar damage (DAD) is appropriate when hyaline membranes are present. As the time between the insult and the biopsy becomes longer, the hyaline membranes become more organized (cellular) and distinct (thicker), a phenomenon seen 3 to 7 days after injury. During this phase, fibrin thrombi can be seen in the small pulmonary arteries, and the interstitium shows a mononuclear cell inflammatory infiltrate. When reactive type 2 cell hyperplasia is seen, the injury is usually about 1 week old, and the proliferative phase of DAD has started. This phase is characterized by fibroblastic proliferation, seen mainly in the interstitium, but also in the alveoli (Fig. 3.4). By the late proliferative phase, most hyaline membranes have been reabsorbed. Mitotic activity can be prominent, and immature squamous metaplasia can be seen. Acute lung injury is often a repetitive event (ie, drugs, ongoing infections, or sepsis disease manifesting in the lung), and therefore changes characteristic of the exudative and proliferative phases of DAD can be seen in the same biopsy.

III. ACUTE LUNG INJURY WITH FIBRIN AND ORGANIZATION ONLY

A new entity has recently been described with some similarities to DAD, termed *acute fibrinous and organizing pneumonia (AFOP)*. AFOP lacks hyaline membranes but is rich in fibrinous alveolar exudates (Fig. 3.5). By definition, AFOP lacks evidence of infection or extravascular eosinophils as might be expected of acute eosinophilic pneumonia (EP).

Among lung infections, viral infections are a recognized trigger of DAD (Chapter 13). Bacterial and fungal infections can also occasionally present as DAD, either in the setting of a pneumonia or a systemic infection (sepsis).

IV. ACUTE LUNG INJURY WITH NECROSIS

Necrosis in the setting of acute lung injury can be seen in infections, infarction, and acute aspiration. Necrosis can involve lung parenchyma alone or occur with necrosis of airway epithelium (Fig. 3.6).

Influenza, herpes simplex, varicella-zoster, and adenovirus pneumonias are all infections characterized by DAD

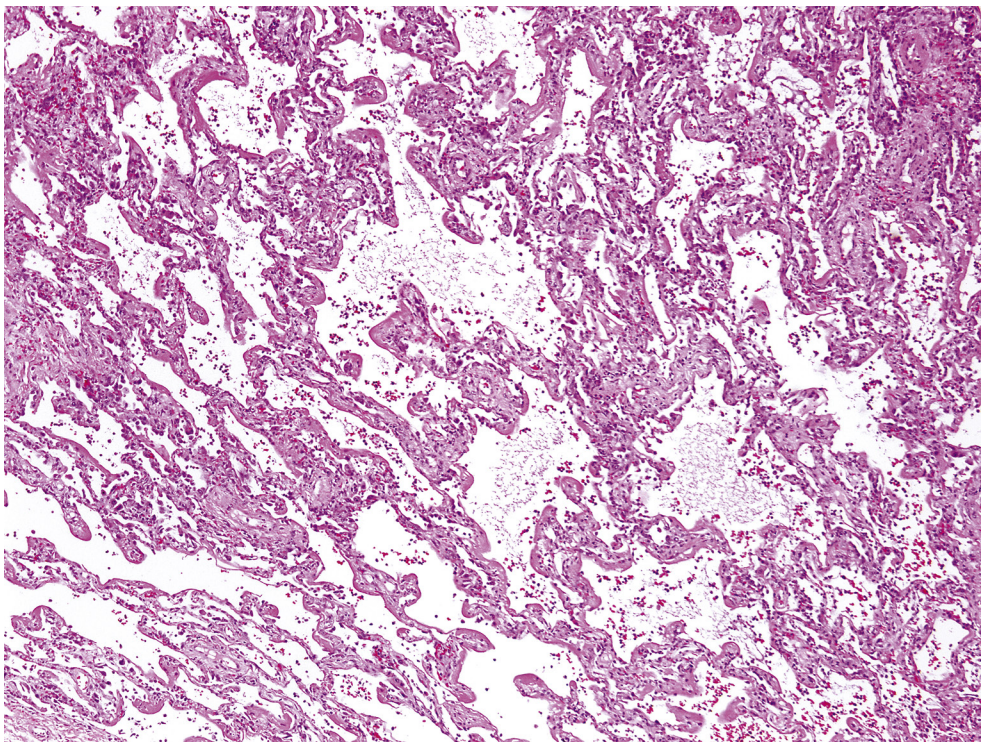

FIG. 3.2

Acute lung injury (Pattern 1). The lung biopsy demonstrates alveolar wall edema, intraalveolar edema and fibrin, and reactive pneumocytes.