PATTERN RECOGNITION SERIES
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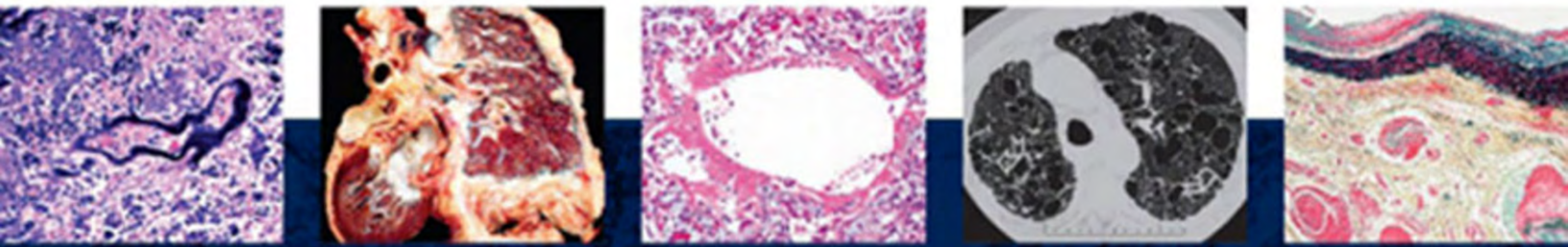
Practical Pulmonary Pathology

A Diagnostic Approach

Third Edition



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Practical Pulmonary Pathology

A Diagnostic Approach

Third Edition

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This work is dedicated to my wife, Peggy, and our children, Katie and Amy, whose support and tolerance over the years have made this work possible. I am also thankful for my good fortune in knowing Dr. Tom Colby, longtime friend, colleague, and mentor, and for the hundreds of pathologists and pulmonologists whose patients have provided me with insight and inspiration over the years.
—KOL

Many thanks are due to my wife, Jane, and my children, Morgan, Robert, and Kellyn, for generously giving of their time with me so that edition three could be completed. In addition, I would like to dedicate the current text to the memory of Philip E. Bernatz, MD (1921–2010), who was a wonderful mentor, colleague, and friend.
—MRW

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Series Preface

It is often stated that anatomic pathologists come in two forms: "Gestalt"-based individuals who recognize visual scenes as a whole and match them unconsciously with memorialized archives; and criterion-oriented people who work through images systematically in segments and tabulate the results—internally, mentally, and quickly—as they go along in examining a visual target. These approaches can be equally effective, and they are probably not as dissimilar as their descriptions would suggest. In reality, even "Gestaltists" subliminally examine details of an image, and, if asked specifically about particular features of it, they are able to say whether one characteristic or another is important diagnostically.

In accordance with these concepts, in 2004 we published a textbook titled *Practical Pulmonary Pathology: A Diagnostic Approach* (PPPDA). That monograph was designed around a *pattern-based* method, wherein diseases of the lung were divided into six categories on the basis of their general image profiles. Using that technique, one can successfully segregate pathologic conditions into diagnostically and clinically useful groupings.

The merits of such a procedure have been validated empirically by the enthusiastic feedback we have received from users of our book. In addition, following the old adage, "imitation is the sincerest form of flattery," since our book came out, other publications and presentations have appeared in our specialty and have used the same approach.

After publication of the PPPDA text, representatives at Elsevier, most notably William Schmitt, were enthusiastic about building a *series* of texts around pattern-based diagnosis in pathology. To this end we have recruited a distinguished group of authors and editors to accomplish that task. Because a panoply of patterns is difficult to approach mentally from a practical perspective, we have asked our contributors to be complete and yet to discuss only principal interpretative images. Our goal is to eventually provide a series of monographs that, in combination with one another, will allow trainees and practitioners in pathology to use salient morphologic patterns to reach with confidence final diagnoses in all organ systems.

As stated in the introduction to the PPPDA text, the evaluation of dominant patterns is aided secondarily by the analysis of cellular composition and other distinctive findings. Therefore, within the context of each pattern, editors have been asked to use such data to refer the reader to appropriate specific chapters in their respective texts.

We have also stated previously that some overlap is expected between pathologic patterns in any given anatomic site; in addition, specific disease states may potentially manifest themselves with more than one pattern. At first, those facts may seem to militate against the value of pattern-based interpretation. However, pragmatically, they do not. One can often narrow diagnostic possibilities to a very few entities using the pattern method, and sometimes a single interpretation will be obvious. Both of those outcomes are useful to clinical physicians caring for a given patient.

It is hoped that the expertise of our authors and editors, together with the high quality of morphologic images they present in this Elsevier series, will be beneficial to our reader-colleagues.

Kevin O. Leslie, MD
Mark R. Wick, MD

Preface

It has been 12 years since *Practical Pulmonary Pathology: A Diagnostic Approach* (PPPDA) was first published. We are happy to report that the original version of this book was warmly received, with a distribution of approximately 8000 copies. Readers seemed to find our pattern-based approach to be a useful one in the daily practice of anatomic pathology, judging by the direct feedback we received. We also were honored when PPPDA won the 2005 Textbook of the Year Award from the Royal Society of Medicine and Royal Society of Authors.

In light of these successes, and in view of the fact that hospital pathology continues to grow rapidly in scope and complexity, we decided to prepare a second and now third edition of our book. Several features are new to this edition. A new chapter (Chapter 2) on pulmonary function for pathologists has been added, authored by renowned pulmonary and critical care specialist Dr. Emre Noth. This chapter succeeds and compliments the second edition chapter on chest imaging patterns authored initially by international expert radiologists Drs. Maffessanti and Dalpiaz, now updated under the sole authorship of Dr. Dalpiaz. Both of these chapters help round out the pathologist's understanding of lung diseases and are critical to the book. Inevitably there have been additions to, and revisions of, the prior text because of advances in our understanding of the pertinent disease processes. Corresponding references have been added, and they are current through 2016. Moreover, many illustrative photomicrographs have been changed in an effort to improve the visual presentation of the topics discussed. Finally, self-assessment questions tied to all the chapters in the current book have been compiled and are available online. It is hoped that these questions will be useful to pathologists in their maintenance of certification and as a reflection of their mastery of the information in the book.

As before, we begin with the general patterns of disease and then add key morphologic findings that assist the reader in focusing on appropriate sections of the book where similar findings are discussed. This approach is facilitated by a structural overlay that limits the patterns. We have found that six general patterns occur, and these are best appreciated at scanning magnification with the microscope. We could begin at an even lower "magnification" using the high-resolution computed tomogram (CT), and this is what our radiology colleagues commonly do as they assemble a differential diagnosis based on observed findings in this medium (see Chapter 4). However, in practice, the CT images may not be readily available to the pathologist at the time the biopsy is interpreted, so for our six pathology patterns, we begin with a tissue section mounted on a glass slide. To help the pathologist in practice correctly identify diseases within patterns, we have included a simple worksheet that emphasizes the importance of knowing the clinical, imaging, and pathologic features in order to arrive at the most appropriate diagnostic category (page xvi).

An overview of the six patterns is presented, and each pattern is then illustrated in the pages that follow. Most of the patterns were devised to navigate the diffuse lung diseases commonly referred to as *interstitial lung diseases* or *ILD*. Given the tumefactive nature of neoplasms, these are heavily represented in Pattern 5 (Nodules), but some nonneoplastic diseases, such as sarcoidosis, nodular infections, granulomatosis with polyangiitis, and certain pneumoconioses, may also manifest as a nodular pattern. Rarely, neoplasms can present as diffuse interstitial lung disease clinically and radiologically.

A basic knowledge of the two-dimensional structure of the lung is essential for accurately assessing patterns of disease. We assume that the reader is familiar with basic lung anatomy by the time a diagnostic problem is being evaluated in the patient care setting, but a brief review is always helpful (see Chapter 1).

Once the overriding or dominant pattern is recognized, the diagnostician assesses the cellular composition and any other distinctive findings that accompany the pattern. In the case of a tumor forming a nodular mass, the presence of prominent spindled cells, or large granular cells, or clear cells provides a direction for creating a differential diagnosis. Within each pattern, we have attempted to use such qualifying elements to direct the reader to the appropriate chapter for further study, reasonably confident that the answer will lie within. For the unusual finding not identified in the list for a given pattern, the reader is directed to the appendix where we have assembled a "visual encyclopedia" of distinctive findings and artifacts.

Naturally, overlap occurs between patterns, and this too can be a useful guide to the correct diagnosis. For example, some infections are both *nodular* and have *airspace filling* (e.g., botryomycosis, aspiration pneumonia), whereas others are characterized by *acute lung injury* and *diffuse airspace filling* (e.g., pneumococcal pneumonia, pneumocystis pneumonia.) In fact, some diffuse inflammatory conditions in the lung

may manifest five of the six patterns in different areas of the same biopsy (e.g., rheumatoid lung). Nevertheless, as more and more information is accrued from the biopsy, the differential diagnosis becomes more limited. In some cases it may be necessary to include several possibilities in the final diagnosis, especially for the nonneoplastic diseases where the effect of ancillary data not available at the time of diagnosis may be very large.

Once again, we are grateful to all of the authors who generously and diligently updated their chapters in the third edition of PPPDA. In addition, many thanks are due to our colleagues at the Mayo Clinic and the University of Virginia for their strong support of this project. Finally, this work could not have reached fruition without the valuable help of our editor, William Schmitt of Elsevier, and the editorial and production expertise of Laura Schmidt and Amanda Mincher.

Kevin O. Leslie, **MD**
Mark R. Wick, **MD**

Pattern-Based Approach to Diagnosis

A fundamental truth about medical textbooks is that they are often not read from beginning to end once a student of medicine has progressed beyond the basic medical school curriculum. In the practice of medicine, textbooks are more commonly used as references for learning about a disease or entity that a clinician suspects a patient may have based on history, physical findings, and imaging/laboratory data gleaned from an initial screening evaluation. The disease-based textbook is analogous to a dictionary or encyclopedia, both of which are much easier to use if a person already has a good idea of what he or she is investigating.

Today, the vast majority of diagnosis-oriented medical textbooks continue to exist as compendia of individual diseases, more or less grouped by the anatomic compartment or structure affected (e.g., brainstem diseases, bile duct diseases, glomerular diseases) or a common mechanism if one is discernible (e.g., inflammatory diseases, neoplastic diseases). Typically, the discussion of each disease begins with a historical introduction, continues with the characteristics of the disease, and ends with the treatment and prognosis. This book is no different, but the authors have added this introductory material as a tool to help navigate the contents. The approach is based on the premise that six primary histopathologic patterns exist for all lung diseases. Identifiable using the low-magnification microscope objective lens, these patterns serve as the introductory image of the disease process. (In truth, chest imaging with high-resolution computed tomography is an even better place to begin—see Chapter 4). Once the primary pattern is recognized, the histopathologist must collect additional findings from the biopsy specimen. With the primary pattern and secondary attributes in hand, a cogent differential diagnosis can be proffered. This process is significantly enhanced by knowledge of the clinical presentation and imaging characteristics, but if these are not available when the slides are being examined, they can still be useful for narrowing the differential diagnosis after the histopathology has been evaluated. A detailed analysis of the use of clinical, radiologic, and histopathologic data in the evaluation of the diffuse medical lung diseases (often referred to as *interstitial lung diseases*, or *ILDs*) is available for the interested reader (open access file for download).*

A basic knowledge of the two-dimensional structure of the lung is essential for accurately assessing patterns of disease. We assume that the reader is familiar with basic lung anatomy by the time a diagnostic problem is being evaluated in the patient care setting, but a brief review is always helpful (see Chapter 1). An overview of the six major patterns is provided (see Table 1), followed by illustrations of each pattern. The pattern-based approach presented here was devised mainly to assist in the interpretation of the diffuse lung diseases, commonly referred to as *ILDs*. Given the tumefactive nature of neoplasms, these are heavily represented in Pattern 5 (Nodules), but some nonneoplastic diseases, such as sarcoidosis, nodular infections, granulomatosis with polyangiitis, and certain pneumoconioses, may also manifest a nodular pattern. Rarely, neoplasms can present as diffuse ILD clinically and radiologically (e.g., lymphangitic carcinoma, intravascular lymphoma). Within each of the major patterns, the authors have provided the reader with the appropriate chapters and relevant pages in the book for further study, reasonably confident that the answer (or approach) to a particular diagnostic problem will be present. There are diagnostic considerations for which no specific chapter or page number is provided. Some of these may require reference to another source. For the distinctive or unusual finding not identified in the list for a given major pattern, the reader is directed to the Appendix, where the authors have assembled a "visual encyclopedia" of distinctive findings and artifacts encountered in the course of microscopic evaluation.

As every diagnostic pathologist knows, overlap occurs between diseases, and sometimes this overlap can be useful in establishing the correct diagnosis. For example, some infections both are nodular (Pattern 5) and have airspace filling (e.g., botryomycosis, aspiration pneumonia), whereas others are characterized by acute lung injury and diffuse airspace filling (e.g., pneumococcal pneumonia, pneumocystis pneumonia). In fact, some diffuse inflammatory conditions of the lung may manifest all of the six patterns in different areas of the same biopsy (e.g., rheumatoid lung). In some cases, it may be necessary to include several possibilities in the final diagnosis, especially for the nonneoplastic diseases, where the effect of ancillary data not available at the time of diagnosis may be very large. The exposition begins with Pattern 1 (Acute Lung Injury) because this is the pattern that dominates all others and is most often the reason a biopsy was performed at all.

*See Leslie KO: My approach to interstitial lung disease using clinical, radiological and histopathologic patterns. *J Clin Pathol.* 2009;62(5):387–401. The Worksheet for the Pattern-Based Approach to Lung Disease, located on page xvi, is a printable form for organizing these data.

Worksheet for the Pattern-Based Approach to Lung Disease

Patient Information

Age: _____ Gender: Male Female

Disease Onset

Acute (hours to days) Subacute (weeks to a few months) Chronic (months to years)

Character of Infiltrate(s) on CT Scan

Nodular Ground glass Consolidation Reticular Honeycombing

Biopsy Information

Transbronchial biopsy Cytology specimen Surgical wedge biopsy

Lung Pathology Pattern

Pattern 1 (Acute Lung Injury)
With hyaline membranes (DAD)
With necrosis (infection)
With fibrin and organization only (infection, CVD, drug, EP)
With siderophages (infection, CVD, drug, EP)
With background fibrosis (acute on chr disease ddx)
With vasculitis (infection, DAH, CVD, drug, EP)
With eosinophils (infection, drug, EP)

Pattern 2 (Fibrosis)
With temporal heterogeneity (UIP)
With diffuse septal fibrosis (NSIP ddx)
With granulomas (sarcoid, chr HP)
With acute lung injury (acute on chr disease ddx)
With honeycombing only (many causes)
With pleuritis (CVD)

Pattern 3 (Cellular Infiltrates)
With lymphocytes and plasma cells (NSIP ddx)
With neutrophils (infection, DAH, drug)
With fibrin and organization (infection, CVD, drug)
With granulomas (infection, HP, hot tub, drug, LIP ddx)
With background fibrosis (NSIP ddx, chr drug)
With vasculitis (infection, CVD, DAH)
With pleuritis (CVD)

Pattern 4 (Alveolar Filling)
With macrophages (EP, SRILD, aspir)
With granulomas (infection, hot tub, aspir)
With giant cells only (aspir, EP, hard metal)
With neutrophils (infection, aspir, DAH capil)
With eosinophilic material (PAP, PAM, edema)
With blood only (artifact)
With blood + siderophages (DAH, IPH, smoker)
With OP (infection, drug, CVD, COP)

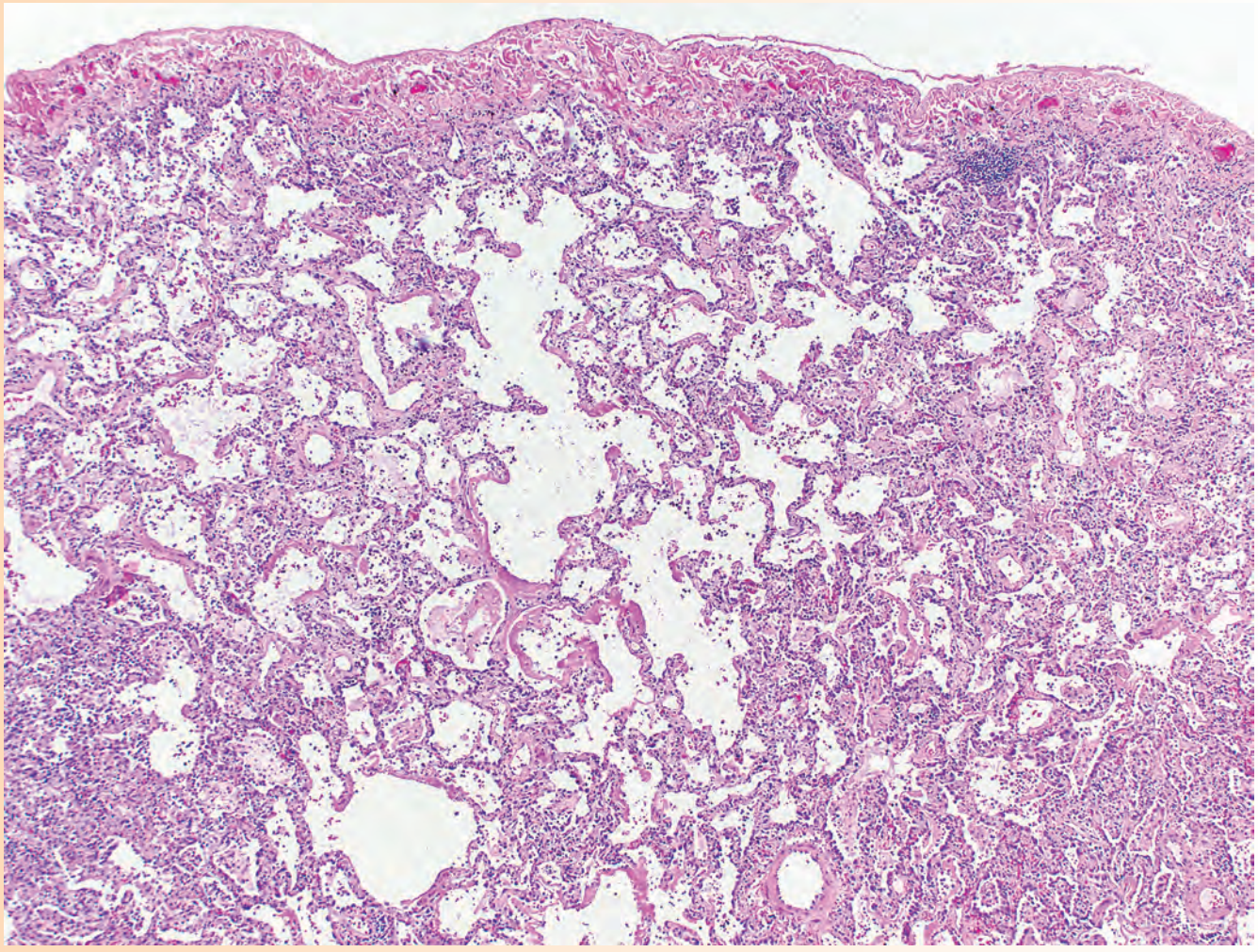
Pattern 5 (Nodules)
With granulomas (infection, sarcoid, aspir)
With lymphoid cells (lymphoma, PLCH, GPA)
With necrosis (infection, tumor, infarction)
With atypical cells (virus, tumor, EP)
With OP (infection, aspir, idiop nod OP)
With vasculitis (infection, GPA)
With stellate scars (PLCH)

Pattern 6 (Minimal Changes)
With small airways disease (OB)
With vascular disease (PHT, VOD)
With cysts (PLCH, LAM)
With no specific findings (sampling)

aspir, Aspiration; chr, chronic; *COP,* cryptogenic organizing pneumonia; *CVD,* collagen vascular disease; *DAD,* diffuse alveolar damage; *DAH,* diffuse alveolar hemorrhage; *DAH capill,* diffuse alveolar hemorrhage with capillaritis; *ddx,* differential diagnosis; *drug,* drug toxicity; *EP,* eosinophilic pneumonia; *GPA,* granulomatosis with polyangiitis; *hard metal,* cobalt-associated hard metal disease; *hot tub,* "hot tub" lung; *HP,* hypersensitivity pneumonitis; *idiop,* idiopathic; *IPH,* idiopathic pulmonary hemosiderosis; *LAM,* lymphangioleiomyomatosis; *LIP,* lymphoid interstitial pneumonia; *nod,* nodular; *NSIP,* nonspecific interstitial pneumonia; *OB,* obliterative bronchiolitis (constrictive bronchiolitis); *OP,* organizing pneumonia; *PAM,* pulmonary alveolar microlithiasis; *PAP,* pulmonary alveolar proteinosis; *PHT,* pulmonary hypertension; *PLCH,* pulmonary Langerhans cell histiocytosis; *smoker,* changes related to cigarette smoking; *SRILD,* smoking-related interstitial lung disease; *UIP,* usual interstitial pneumonia; *virus,* viral infection; *VOD,* venoocclusive disease.

Pattern	Diseases to Be Considered
Acute lung injury	Diffuse alveolar damage (DAD) Infection Eosinophilic pneumonia Drug toxicity Certain systemic connective tissue diseases Diffuse alveolar hemorrhage Irradiation injury Idiopathic (acute interstitial pneumonia) Acute hypersensitivity pneumonitis Acute pneumoconiosis Acute aspiration pneumonia Idiopathic acute fibrinous and organizing pneumonitis
Fibrosis	Usual interstitial pneumonia (UIP) Collagen vascular diseases Chronic eosinophilic pneumonia Chronic drug toxicity Chronic hypersensitivity pneumonitis Nonspecific interstitial pneumonia (NSIP) Smoking-related interstitial lung disease (ILD)/advanced Langerhans cell histiocytosis Sarcoidosis (advanced) Pneumoconioses Erdheim-Chester disease Hermansky-Pudlak syndrome Idiopathic pleuroparenchymal fibroelastosis Idiopathic airway-centered fibrosis
Chronic cellular infiltrates	Hypersensitivity pneumonitis Nonspecific interstitial pneumonia (NSIP) Systemic connective tissue diseases Certain chronic infections Certain drug toxicities Lymphocytic and lymphoid interstitial pneumonia Lymphomas and leukemias Lymphangitic carcinomatosis
Alveolar filling	Infections Airspace organization (organizing pneumonia) Diffuse alveolar hemorrhage Desquamative interstitial pneumonia (DIP) Respiratory bronchiolitis-associated ILD Alveolar proteinosis Dendriform (racemose) calcification Alveolar microlithiasis Mucostasis and mucinous tumors
Nodules	Infections (mycobacterial and fungal, primarily) Primary and metastatic neoplasms Granulomatosis with polyangiitis Sarcoidosis/berylliosis Aspiration pneumonia Pulmonary Langerhans cell histiocytosis
Nearly normal biopsy	Chronic small airways disease (as constrictive bronchiolitis) Vasculopathic diseases Lymphangioleiomyomatosis (LAM) Other rare cystic diseases

Pattern 1 Acute Lung Injury



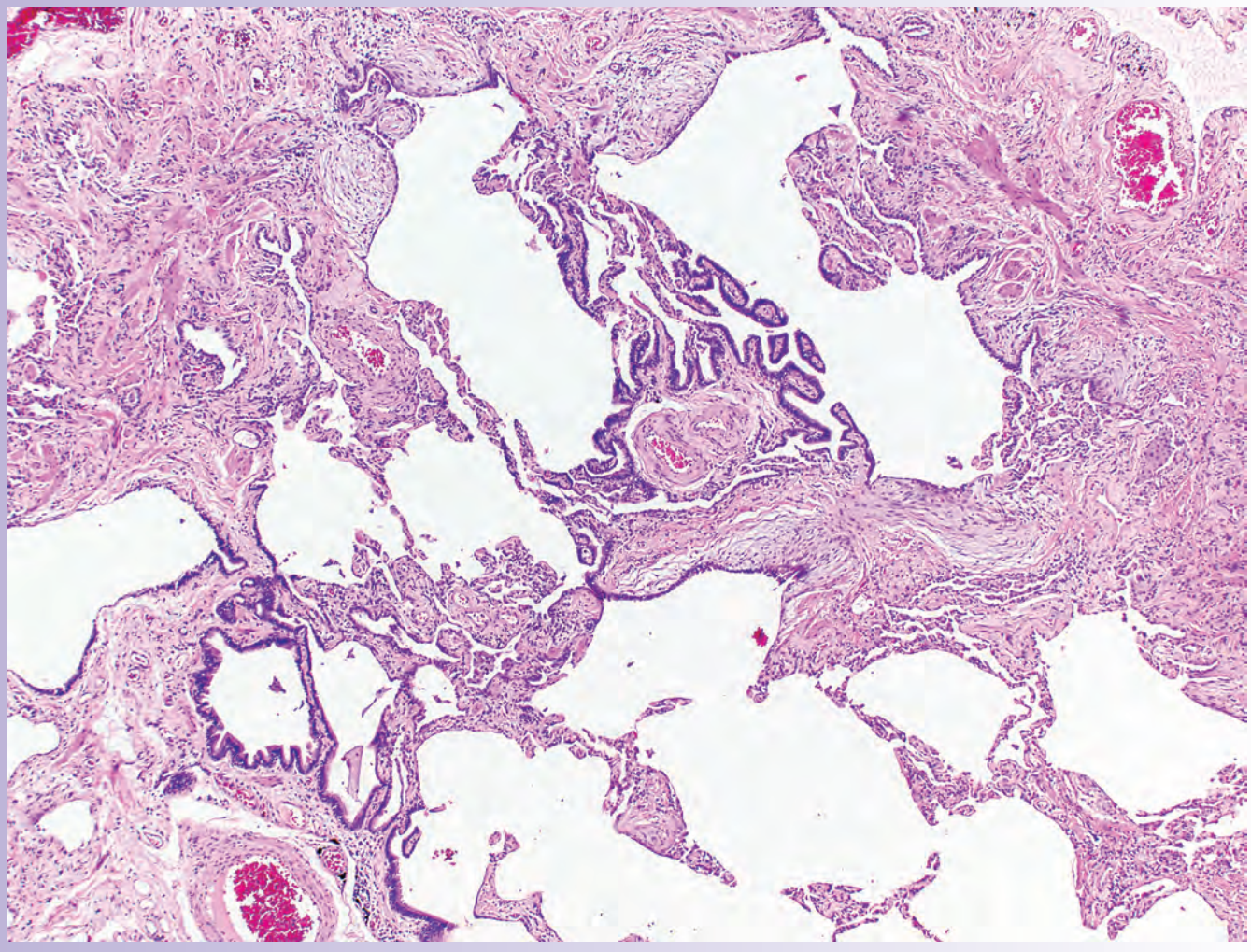
Elements of the pattern: The lung biopsy shows patchy or diffuse edema, fibrin, and reactive type 2 cell hyperplasia. The dominance of noncellular, protein-rich material imparts an overall red or pink appearance to the biopsy at scanning magnification (in routine hematoxylin-eosin stained sections).

Special stains for organisms are required for all lung specimens that show acute injury.

Pattern 1 Acute Lung Injury

Additional Findings	Diagnostic Consideration	Chapter:Page
Hyaline membranes	Diffuse alveolar damage	Ch. 5:110; Ch. 6:125
Necrosis in parenchyma	Infection Some tumors Infarct	Ch. 6:130 Ch. 17:586 Ch. 11:390
Necrosis in bronchioles	Infections Acute aspiration	Ch. 6:133; Ch. 9:312 Ch. 9:306
Fibrin in alveoli	Diffuse alveolar damage Drug toxicity Connective tissue disease Infection	Ch. 6:128 Ch. 6:136 Ch. 6:134 Ch. 6:133; Ch. 7:203
Eosinophils in alveoli	Eosinophilic lung diseases	Ch. 6:139; Ch. 8:255
Siderophages in alveoli	Diffuse alveolar hemorrhage Drug toxicity Infarct	Ch. 6:140; Ch. 11:393 Ch. 11:394 Ch. 7:152; Ch. 11:390
Fibrinous pleuritis	Connective tissue diseases Eosinophilic pneumonia Pneumothorax	Ch. 6:134 Ch. 6:139 Ch. 8:276
Neutrophils	Infections Capillaritis in diffuse alveolar hemorrhage	Ch. 6:143 Ch. 11:395
Atypical cells	Acute lung injury Viral infections Leukemias Intravascular lymphoma	Ch. 6:142 Ch. 6:143 Ch. 16:528 Ch. 16:548
Fibrin + vacuolated macrophages	Infection Drug toxicity Connective tissue diseases	Ch. 7:174 Ch. 6:136 Ch. 6:136

Pattern 2 Fibrosis



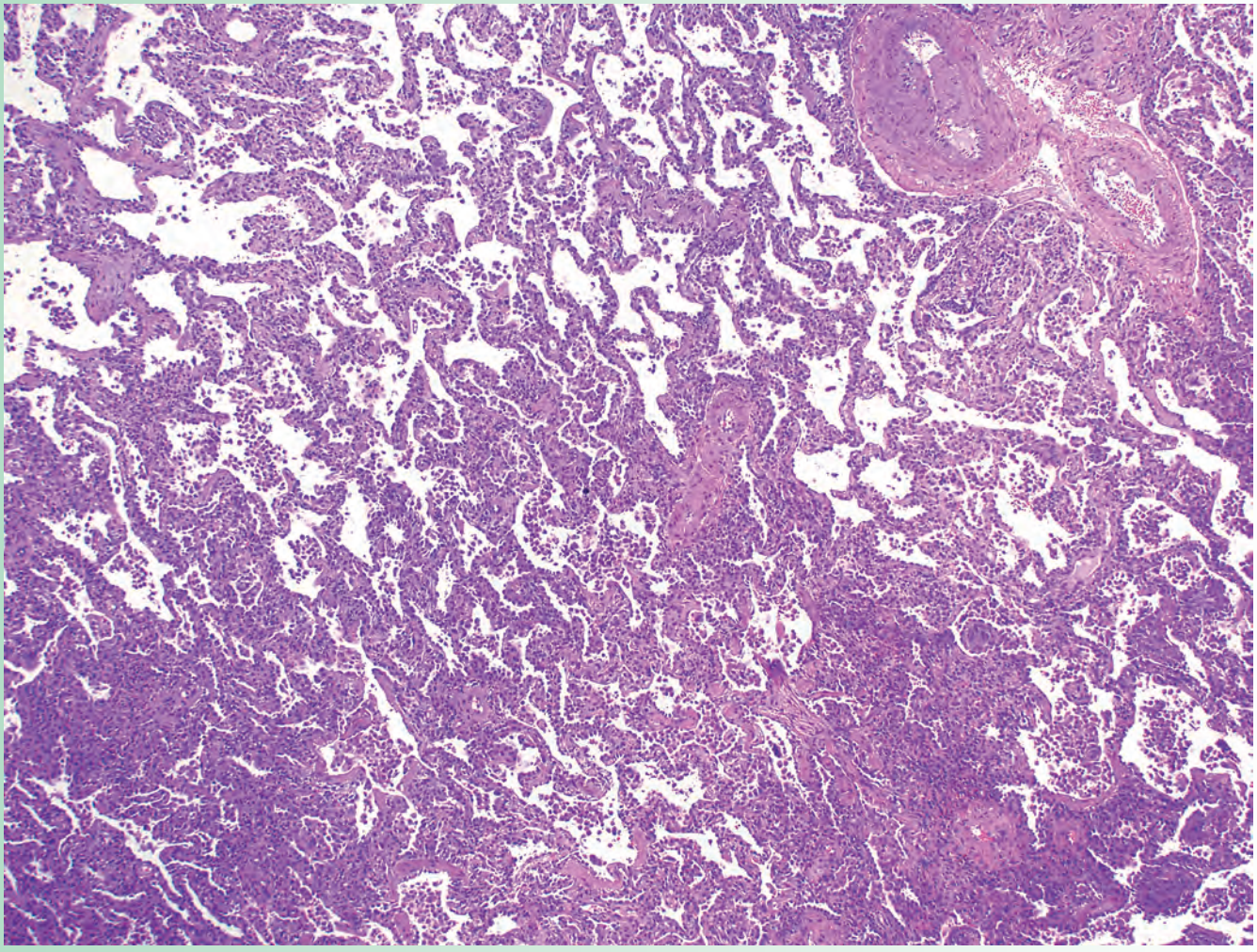
Elements of the pattern: The lung biopsy is involved by variable amounts of fibrosis. As in Pattern 1, the biopsy tends to be more pink than blue at scanning magnification, as a result of collagen deposition (in routine hematoxylin-eosin stained sections). Some fibrosis patterns are accompanied by chronic inflammation that may impart a blue tinge to the process, or even dark blue lymphoid aggregates.

Significant lung fibrosis is always associated with some degree of structural remodeling. Avoid diagnosing "fibrosis" on transbronchial biopsies.

Pattern 2 Fibrosis

Additional Findings	Diagnostic Consideration	Chapter:Page
Hyaline membranes	"Acute on chronic" disease	Ch. 5:110
	Infection on fibrosis	Ch. 6:128
	Drug toxicity on fibrosis	Ch. 6:136
	Connective tissue disease in "exacerbation"	Ch. 6:140
	Acute exacerbation of idiopathic pulmonary fibrosis (IPF)	Ch. 8:234
Microscopic honeycombing	Usual interstitial pneumonia (UIP)	Ch. 8:229
	Hypersensitivity pneumonitis	Ch. 8:269
	Connective tissue disease	Ch. 8:247
Prominent bronchiolization	Pulmonary Langerhans cell histiocytosis	Ch. 8:272
	Respiratory bronchiolitis ILD	Ch. 8:240
	Connective tissue diseases	Ch. 8:247
	Chronic hypersensitivity pneumonitis	Ch. 8:269
	Small airways disease	Ch. 9:317
	Chronic aspiration	Ch. 8:267; Ch. 9:312
Uniform alveolar septal fibrosis	Connective tissue diseases	Ch. 8:247
	Postirradiation	Not specifically addressed
Peripheral lobular fibrosis	UIP/IPF	Ch. 8:229
	Erdheim Chester disease	Ch. 8:276
	Rosai-Dorfman disease	Ch. 19:650
	Chronic eosinophilic pneumonia	Ch. 8:255
Siderophages in alveoli	Chronic cardiac congestion	Ch. 5:114
	Chronic venous outflow obstruction	Not specifically addressed
	Chronic hemorrhage in connective tissue disease	Ch. 8:250
	Chronic hemorrhage in bronchiectasis	Ch. 11:390
	Pneumoconiosis	Ch. 10:339
	Pulmonary Langerhans cell histiocytosis	Ch. 8:272
	Smoking-related interstitial lung disease	Ch. 8:243
	Chronic renal dialysis	Not specifically addressed
	Idiopathic pulmonary hemosiderosis	Ch. 11:395
Fibrinous pleuritis	Connective tissue disease	Ch. 8:247
	Eosinophilic pleuritis in pneumothorax	Ch. 8:276; Appendix:770
Prominent nonnecrotizing granulomas	Sarcoidosis	Ch. 8:266
Many vacuolated cells	Chronic airway obstruction	Ch. 8:272
	Drug toxicity	Ch. 8:289
	Hermansky-Pudlak syndrome	Ch. 8:279
	Genetic storage diseases	Ch. 5:120
Prominent chronic inflammation	Nonspecific interstitial pneumonia (NSIP)	Ch. 8:235
	Rheumatoid arthritis and other connective tissue diseases	Ch. 8:247
Airway-centered scarring	Pulmonary Langerhans cell histiocytosis	Ch. 8:272
	Pneumoconiosis	Ch. 9:320
	Chronic hypersensitivity pneumonitis	Ch. 8:269
	Connective tissue diseases	Ch. 8:247
	Idiopathic airway-centered fibrosis	Ch. 8:288
	Idiopathic pleuroparenchymal fibroelastosis	Ch. 8:246
	Chronic aspiration	Ch. 8:267; Ch. 9:312

Pattern 3 Chronic Cellular Infiltrates

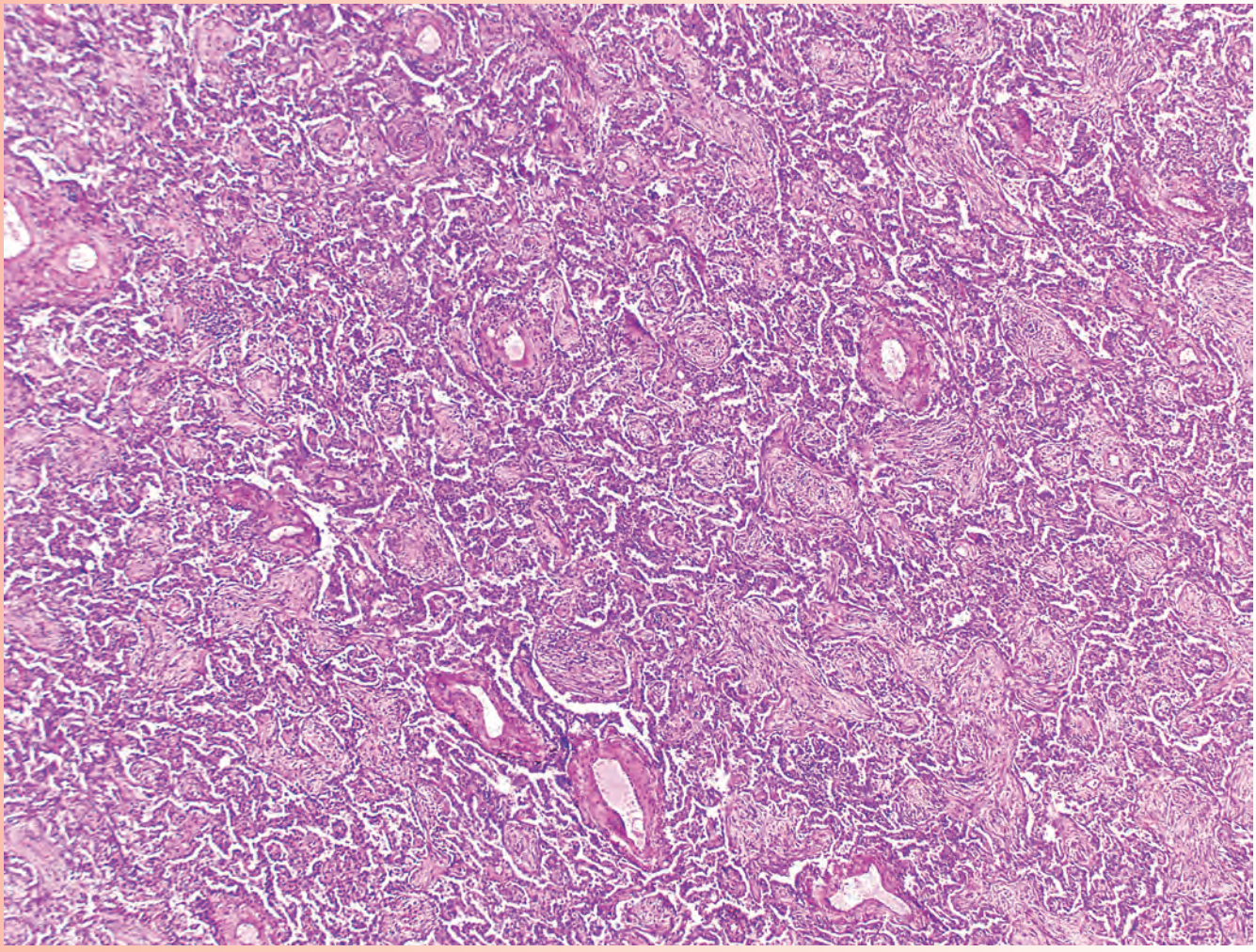


Elements of the pattern: The lung biopsy is dominated by interstitial chronic inflammation and variable reactive type 2 cell hyperplasia. The dominance of mononuclear infiltrates may impart an overall blue appearance to the biopsy at scanning magnification (in routine hematoxylin-eosin stained sections).

Pattern 3 Chronic Cellular Infiltrates

Additional Findings	Diagnostic Consideration	Chapter:Page
Hyaline membranes	"Acute on chronic" connective tissue disease	Ch. 6:134
	Drug toxicity	Ch. 6:136
	Diffuse alveolar hemorrhage	Ch. 11:393
Necrosis in parenchyma	Viral and fungal infections	Ch. 7:178, 199
	Aspiration	Ch. 7:161; Ch. 9:306
	Infarction in antiphospholipid syndrome	Ch. 8:251
Necrosis in bronchioles	Viral infections	Ch. 7:199
	Aspiration	Ch. 7:161; Ch. 9:306
Poorly formed granulomas (small and nonnecrotizing)	Hypersensitivity pneumonitis (subacute)	Ch. 8:269
	Atypical mycobacterial infection	Ch. 8:270
	"Hot tub" lung	Ch. 7:175
	Lymphoid interstitial pneumonia	Ch. 8:244
	Drug toxicity	Ch. 8:259
Well-formed necrotizing granulomas	Infections	Ch. 7:177
	Rare drug reactions	Not specifically addressed
	Necrotizing sarcoidosis	Ch. 11:383
	Middle lobe syndrome	Ch. 9:303
Eosinophils in alveoli	Eosinophilic lung diseases	Ch. 6:139; Ch. 8:255
	Smoking-related lung diseases	Ch. 8:243
Siderophages in alveoli	Diffuse alveolar hemorrhage	Ch. 11:393
	Chronic cardiac congestion	Ch. 5:114
	Drug toxicity	Ch. 8:259
Fibrinous/chronic pleuritis	Connective tissue diseases	Ch. 8:247
	Thoracic trauma/infection	Ch. 8:248
	Pancreatitis-associated pleuritis	Not specifically addressed
Patchy organizing pneumonia	Drug toxicity	Ch. 8:259
	Connective tissue diseases	Ch. 8:247
	Infections	Ch. 8:239
	Cryptogenic organizing pneumonia	Ch. 8:237
	Diffuse alveolar hemorrhage	Ch. 11:393
	Aspiration	Ch. 7:161; Ch. 9:306
Atypical cells	Viral infections	Ch. 7:199
	Lymphangitic carcinoma	Ch. 8:246
Multinucleated giant cells	Hard metal disease	Ch. 10:354
	Mica pneumoconiosis	Ch. 10:347
	Hypersensitivity pneumonitis	Ch. 8:269
	Intravenous drug abuse	Ch. 8:263
	Drug toxicity	Ch. 8:259
	Aspiration pneumonia	Ch. 7:161; Ch. 9:306
	Eosinophilic pneumonia	Ch. 6:139; Ch. 8:255
Dense mononuclear infiltration	Lymphomas	Ch. 16:542
	Lymphoid interstitial pneumonia	Ch. 8:244
	Connective tissue diseases	Ch. 8:247
	Hypersensitivity pneumonitis	Ch. 8:269
	Certain infections (the atypical pneumonias)	Ch. 7:162
Lymphoid aggregates/germinal centers	Connective tissue diseases	Ch. 8:247
	Diffuse lymphoid hyperplasia	Ch. 8:245; Ch. 16:537
	Lymphoid interstitial pneumonia	Ch. 8:244
	Follicular bronchiolitis	Ch. 9:308

Pattern 4 Alveolar Filling

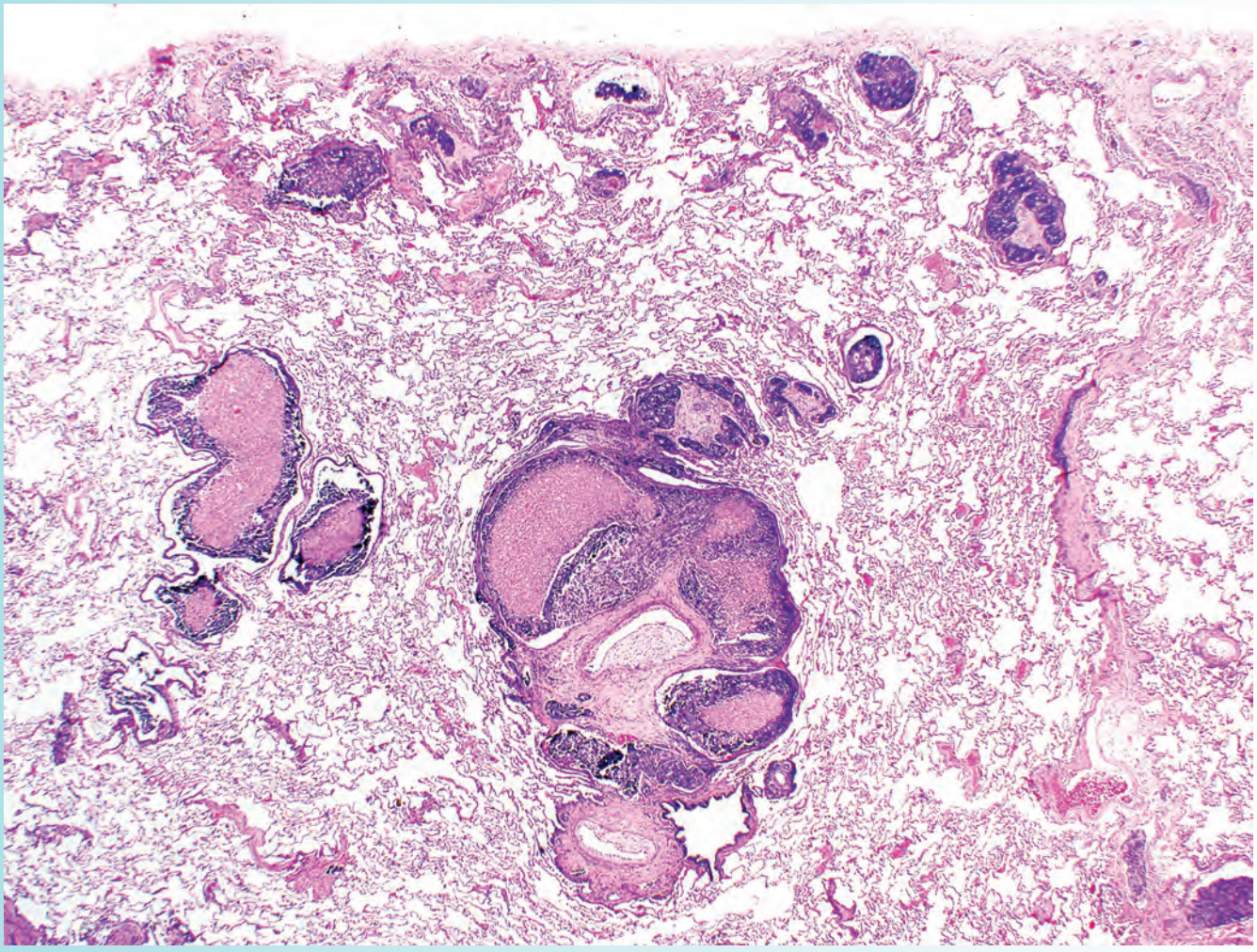


Elements of the pattern: The dominant finding is alveolar spaces filled with cells or noncellular elements.

Pattern 4 Alveolar Filling

Additional Findings	Diagnostic Consideration	Chapter:Page
Hyaline membranes and fibrin	Organizing diffuse alveolar damage	Ch. 6:125; Ch. 7:162
Necrosis and neutrophils	Bacterial infection Viral and fungal infection	Ch. 7:159 Ch. 7:178, 199
Organizing pneumonia	Organizing infection Drug toxicity Cryptogenic organizing pneumonia	Ch. 7:159 Ch. 8:259 Ch. 8:237
Fibrin and macrophages	Eosinophilic pneumonia, poststeroid Drug toxicity Connective tissue diseases Malakoplakia-like reaction	Ch. 6:139; Ch. 8:255 Ch. 8:259 Ch. 8:247 Ch. 7:160
Eosinophils and macrophages	Eosinophilic lung diseases	Ch. 6:139; Ch. 8:255
Siderophages and fibrin	Diffuse alveolar hemorrhage	Ch. 11:393
Mucin	Mucostasis in small airways disease Bronchioloalveolar carcinoma Cryptococcus infection	Ch. 9:317 Ch. 17:576 Ch. 7:184
Bone/calcification	Dendriform calcification Metastatic calcification Pulmonary alveolar microlithiasis	Ch. 8:240; Appendix:774 Appendix:774 Ch. 8:280
Atypical cells	Bronchioloalveolar carcinoma Herpesvirus infections Acute eosinophilic pneumonia Carcinomas and sarcomas	Ch. 17:576 Ch. 7:203 Ch. 6:139; Ch. 8:255 Not specifically addressed
Proteinaceous exudates	Edema Pulmonary alveolar proteinosis (PAP) PAP reactions Pneumocystis pneumonia	Ch. 6:126 Ch. 8:283 Ch. 8:283 Ch. 7:191
Multinucleated giant cells	Hard metal disease Eosinophilic pneumonia Granulomatosis with polyangiitis Aspiration pneumonia	Ch. 10:354 Ch. 6:139; Ch. 8:255 Ch. 11:367 Ch. 7:161; Ch. 9:306
Polypoid mesenchymal bodies resembling chorionic villi	Bullous placental transmogrification	Appendix:779

Pattern 5 Nodules



Elements of the pattern: One, or many, nodules of variable size and shape. An interface between the nodular lesion and more normal lung should be discernible. In the case of very large nodules encompassing the entire specimen, radiologic imaging can be used as part of the definition.

Pattern 5 Nodules

Additional Findings	Diagnostic Consideration	Chapter:Page
Large neoplastic lymphoid cells	Malignant lymphoma	Ch. 16:542
Small lymphoid cells without germ centers	Mucosa-associated lymphoid tissue (MALT) lymphoma, low grade	Ch. 16:542
Small lymphoid cells with germ centers	Follicular bronchiolitis	Ch. 16:534
	Diffuse lymphoid hyperplasia	Ch. 16:534
	Intraparenchymal lymph node	Not specifically addressed
Giant multinucleated neoplastic cells	Sarcomatoid carcinoma	Ch. 15:467
	Large cell undifferentiated carcinoma	Ch. 17:583
	Primary and metastatic sarcomas	Ch. 15:476
	Primary or metastatic pleomorphic carcinomas	Ch. 15:467
	Primary or metastatic melanoma	Ch. 15:500
	Giant cell tumor (primary or metastatic)	Ch. 15:467
Primitive small round neoplastic cells	Small cell carcinoma	Ch. 14:453
	Malignant lymphoma	Ch. 16:542
	Small cell squamous carcinoma	Ch. 17:581
	Metastatic tumors	Ch. 18:597
	Ewing sarcoma	Ch. 18:625
	Primitive neuroectodermal tumor	Ch. 14:459
	Small cell osteosarcoma	Ch. 18:621
	Neuroblastoma	Ch. 14:460
	Pleuropulmonary blastoma (with cysts)	Ch. 15:513
Spindled or fusiform neoplastic cells	Primary sarcomatoid carcinoma	Ch. 15:467
	Primary and metastatic sarcomas	Ch. 15:476
	Lymphangioleiomyomatosis (with cysts)	Ch. 8:276
	Inflammatory myofibroblastic tumor	Ch. 19:646; Ch. 20:692
	Benign metastasizing leiomyoma	Ch. 15:482; Ch. 20:681
	Localized fibrous tumor	Ch. 15:485
	Extraabdominal desmoid tumor	Ch. 20:703
Large pink epithelioid neoplastic cells	Poorly differentiated primary carcinomas	Ch. 17:583
	Large cell undifferentiated carcinoma	Ch. 17:583
	Metastatic carcinomas	Ch. 18:606
	Metastatic sarcomas	Ch. 18:617
	Epithelioid hemangioendothelioma	Ch. 15:482
	Melanoma (primary or metastatic)	Ch. 15:497
Large clear epithelioid neoplastic cells	Primary clear cell adenocarcinoma	Ch. 17:581
	Primary squamous carcinoma	Ch. 17:581
	Large cell carcinoma (primary)	Ch. 17:583
	Sugar tumor	Ch. 20:705
	Perivascular epithelioid cell tumor (PEComa)	Ch. 20:689
	Metastatic clear cell carcinoma	Ch. 18:609
	Metastatic clear cell sarcoma	Ch. 18:632
Large basophilic epithelial cells with peripheral palisade	Large cell undifferentiated carcinoma	Ch. 17:583
	Large cell neuroendocrine carcinoma	Ch. 14:450
	Basaloid large cell lung carcinoma	Ch. 17:583
	Basaloid squamous carcinoma	Ch. 17:583
	Certain metastatic tumors	Ch. 17:584

Table continues on following page.

Pattern 5 Nodules—Cont'd

Additional Findings	Diagnostic Consideration	Chapter:Page
Glands or tubules, malignant	Primary adenocarcinoma	Ch. 17:576
	Metastatic adenocarcinoma	Ch. 18:606
	Carcinoid tumor (primary or metastatic)	Ch. 14:443
	Synovial sarcoma (primary or metastatic)	Ch. 15:491
	Fetal-type primary adenocarcinoma	Ch. 15:472
	Carcinosarcoma (primary or metastatic)	Ch. 15:467
Glands or tubules, benign or mild atypia	Alveolar adenoma	Ch. 20:679
	Adenoma of type II cells	Ch. 20:684
	Pulmonary sclerosing hemangioma	Ch. 20:695
	Hamartoma	Ch. 19:643
	Micronodular pneumocyte hyperplasia	Ch. 8:282
	Adenomatoid tumor	Ch. 20:689
Malignant heterologous elements (cartilage, bone, skeletal muscle)	Carcinosarcoma	Ch. 15:467
	Metastatic teratocarcinoma	Ch. 15:516
	Metastatic sarcoma	Ch. 15:467
Distinct keratinization	Primary squamous cell carcinoma	Ch. 17:581
	Squamous metaplasia of terminal airways	Ch. 6:126, 130
	Basaloid squamous cell carcinoma	Ch. 17:583
	Adenosquamous carcinoma	Ch. 17:583
	Metastatic squamous cell carcinoma	Ch. 17:581
Pigmented cells	Cellular phase of Langerhans cell histiocytosis	Ch. 8:273
	Primary or metastatic melanoma	Ch. 15:497
	Melanotic carcinoid tumor	Ch. 15:499
	Metastatic angiosarcoma (hemosiderin)	Ch. 15:498
Malignant with dominant necrosis	Small cell carcinoma	Ch. 14:453
	Sarcomatoid carcinoma (primary or metastatic)	Ch. 15:467
	High-grade malignant lymphoma	Ch. 16:542
Benign with necrosis	Necrotizing infections	Ch. 6:128, 133; Ch. 9:312
	Bacterial	
	Fungal	
	Mycobacterial	
	Viral	
	Granulomatosis with polyangiitis	Ch. 11:367
	Churg-Strauss syndrome	Ch. 11:367
	Lung infarct	Ch. 11:385
Benign with dominant organizing pneumonia	Nodular organizing pneumonia	Not specifically addressed
	Aspiration pneumonia	Ch. 7:161; Ch. 9:306
Benign with well-formed granulomas	Granulomatous infection	Ch. 7:178
	Fungal	
	Mycobacterial	
	Bacterial (botryomycosis)	
	Sarcoidosis/berylliosis	Ch. 7:177
	Certain pneumoconioses	Ch. 10:335
	Aspiration pneumonia	Ch. 7:161; Ch. 9:306
	Necrotizing sarcoidosis	Ch. 11:383
Benign with stellate airways centered lesions and variable fibrosis	Pulmonary Langerhans cell histiocytosis	Ch. 8:272
	Certain inhalational injuries	Ch. 8:263
	Pneumoconioses	Ch. 10:335