Diagnostic Atlas of Non-Neoplastic Lung Disease
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A Practical Guide for Surgical Pathologists

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Lest we forget whence we came….

This book is dedicated to Dr. Averill A. Liebow (1911–1978), on whose works modern pulmonary pathology is based.
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List of Abbreviations

ABPA  allergic bronchopulmonary aspergillosis
ABPFD allergic bronchopulmonary fungal disease
AFB  acid-fast bacilli
AFOP  acute fibrinous and organizing pneumonia
AIP  acute interstitial pneumonia
AIS  adenocarcinoma in situ
ANA  antinuclear antibody
ANCA  antineutrophil cytoplasmic antibody
ARDS  acute respiratory distress syndrome
BALT  bronchial-associated lymphoid tissue
BCG  bronchocentric granulomatosis
BML  benign metastasizing leiomyoma
BMPR2  bone morphogenetic protein receptor 2
BOOP  bronchiolitis obliterans–organizing pneumonia
BPD  bronchopulmonary dysplasia
CBO  constrictive bronchiolitis obliterans
chILD syndrome  children’s interstitial lung disease syndrome
CMV  cytomegalovirus
CNS  central nervous system
COP  cryptogenic organizing pneumonia
CPI  chronic pneumonitis of infancy
CSS  Churg–Strauss Syndrome
CT  Computed tomography
CWP  coal worker’s pneumoconiosis
DAD  diffuse alveolar damage
DIP  desquamative interstitial pneumonia
DIPNECH  diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
EBER  EBV-encoded small RNA
EBV  Epstein–Barr virus
EG  eosinophilic granuloma
EGPA  eosinophilic granulomatosis with polyangiitis
EMA  epithelial membrane antigen
FM  fibrosing mediastinitis
GGO  ground glass opacity
GIP  giant cell interstitial pneumonia
GM-CSF  granulocyte-macrophage colony stimulating factor
GMS  Gomori methenamine silver stain
GPA  granulomatosis with polyangiitis
### LIST OF ABBREVIATIONS

- **GPS** Goodpasture Syndrome
- **H and E** hematoxylin and eosin
- **HP** hypersensitivity pneumonia
- **HRCT** high-resolution computed tomography
- **IHC** immunohistochemistry
- **IIP** idiopathic interstitial pneumonia
- **ILD** interstitial lung disease
- **IPF** idiopathic pulmonary fibrosis
- **IPH** idiopathic pulmonary hemosiderosis
- **LAM** lymphangioleiomyomatosis
- **LCH** Langerhans cell histiocytosis
- **LIP** lymphoid interstitial pneumonia
- **LYG** lymphomatoid granulomatosis
- **MAC** mycobacterium avium complex
- **MALT** mucosal-associated lymphoid tissue
- **MERS** Middle East respiratory syndrome
- **MIB** mucoid impaction of bronchi
- **MLN** meningothelial-like nodule
- **MNPH** micronodular pneumocyte hyperplasia
- **MPA** microscopic polyangiitis
- **MPO** myeloperoxidase
- **NEHI** neuroendocrine cell hyperplasia of infancy
- **NSG** necrotizing sarcoid granulomatosis
- **NSIP** nonspecific interstitial pneumonia
- **OP** organizing pneumonia
- **PAM** pulmonary alveolar microlithiasis
- **PAP** pulmonary alveolar proteinosis
- **PAS** periodic acid-Schiff
- **PBM** peribronchiolar metaplasia
- **PCP** pneumocystis carinii pneumonia
- **PCR** polymerase chain reaction
- **PHG** pulmonary hyalinizing granuloma
- **PIG** pulmonary interstitial glycogenosis
- **PMF** progressive massive fibrosis
- **PPFE** pleuroparenchymal fibroelastosis
- **PPH** primary pulmonary hypertension
- **PR3** proteinase 3
- **PVOD** pulmonary veno-occlusive disease
- **RB** respiratory bronchiolitis
- **RBILD** respiratory bronchiolitis interstitial lung disease
- **REP** reactive eosinophilic pleuritis
- **RSV** respiratory syncytial virus
- **SARS** severe acute respiratory syndrome
- **SRIF** smoking-related interstitial fibrosis
- **TO** tracheobronchopathia osteochondroplastica
- **TSC** tuberous sclerosis complex
- **UIP** usual interstitial pneumonia
- **URT** upper respiratory tract
- **WG** Wegener granulomatosis
- **WHO** World Health Organization
Preface

The main purpose of this book is to provide pathologists with a practical guide for diagnosing non-neoplastic lung diseases. The emphasis is on those diseases likely to be diagnosed by lung biopsy or excision, and, thus, many common diseases usually diagnosed clinically or at autopsy are not included. Numerous photomicrographs are supplied to illustrate each disease, and the discussion is focused primarily on diagnostic features and differential diagnosis with inclusion of clinical findings only as they facilitate diagnosis.

The chapters are organized mainly according to a histologic pattern with the intent of allowing the pathologist to move easily from reviewing the microscopic slides to finding the areas of the book that offer a pertinent differential diagnosis. This approach is different from that of my previous book (Katzenstein and Askin’s Surgical Pathology of Non-Neoplastic Lung Disease, fourth edition, Elsevier, 2006), which emphasized disease process over pattern. It also differs in that it offers more in-depth histologic details with less discussion of the ancillary particulars of each disease. Some figures are duplicated from the previous book, but most are new. Reference lists are short and include only selected classic articles or new papers that contribute to diagnosis.

The face of pathology is changing, and it seems likely that molecular diagnostic techniques may supersede the histologic diagnosis of many diseases in the coming years. Accurate molecular diagnosis, however, ultimately depends on strong histologic criteria for diagnosis. Another aim of this book, therefore, is to provide a robust histologic basis on which modern molecular diagnostic technologies can be appropriately developed.

Anna-Luise A. Katzenstein, MD
Acknowledgments

This book could not have been completed without the support of Dr. Robert Corona, chairman of the Department of Pathology at SUNY Upstate Medical University. Likewise, Deborah Rexine in the Medical Photography Department was another key figure who printed; arranged and rearranged; added insets, circles, and arrows; and otherwise improved the quality of the photomicrographs. Her hard work and dedication along with her cheerful demeanor were much appreciated. The author also thanks Rich Winters, formerly with Demos, who helped get this project started, David D’Addona, acquisitions editor, and Norman Graubart who skillfully ushered it through, and Joseph Stubenrauch, managing editor, for careful oversight of the fine details of production.

Much of the material illustrated in the photomicrographs came from the author’s consultation file, and she would especially like to thank the many pathologists who trusted her for consultations throughout the years.
Normal Lung, Common Artifacts, and Incidental Findings

This chapter briefly reviews architectural landmarks in the lung that are important for understanding pathologic alterations and explains how they are used in formulating diagnoses. Commonly encountered artifacts and incidental lesions that may cause confusion in histologic interpretation are reviewed. Suggestions for the optimal handling of tissue specimens are also provided.

TOPICS

- Normal Lung Architecture
- Handling of Tissue Specimens
- Approach to Diagnosis
- Artifacts
  - Artifactual Collapse
  - Fresh Hemorrhage
  - Bubble Artifact
- Incidental Findings
  - Corpora Amylacea
  - Interstitial Megakaryocytes
  - Bone Marrow Emboli
  - Blue Bodies
  - Cytoplasmic (Mallory) Hyaline
  - Minute Meningothelial-Like Nodules (MLNs)
  - Entrapped Pleural Fragments
  - Nodular Histiocytic/Mesothelial Hyperplasia

NORMAL LUNG ARCHITECTURE

Detailed reviews of the microscopic anatomy of the lung can be found in other textbooks, but a few basic landmarks are important to remember when evaluating biopsy or surgical specimens:

- Pulmonary arteries and bronchioles course together, and are similar in size (Figure 1.1). This relationship helps one to confirm that a particular blood vessel is an artery, and it also confirms bronchiocentricity of an inflammatory process if the affected bronchiole is destroyed (see Figures 6.23 and 6.24).
- Terminal (membranous) bronchioles contain a full lining of ciliated respiratory tract epithelium and have a continuous smooth muscle layer in their walls (Figure 1.1).
- Respiratory bronchioles are partially lined by ciliated respiratory tract epithelium and open up into alveolar ducts (Figure 1.2).
- Small collections of chronic inflammation, bronchial-associated lymphoid tissue (BALT), are common in the walls of bronchioles and by themselves are not a significant abnormality.
- Smooth muscle bundles protrude along the interstitium at the mouth of alveolar ducts and are present along the wall of alveolar ducts (Figure 1.2B). They may appear hyperplastic in emphysema.
- Alveolar septa are thin, membranous structures within which only scattered nuclei, mostly from endothelial cells, can be seen (Figure 1.1B). Alveolar lining cells are generally not visible in normal lung, and when prominent are indicative of prior injury or interstitial lung disease.
FIGURE 1.1  Normal lung. (A) At low magnification, a terminal bronchiole (TB) is seen adjacent to a pulmonary artery. Note that the artery and the bronchiole are similar in size. The surrounding alveoli are normal. (B) Higher magnification of the alveolated parenchyma shows thin, membranous, alveolar septa containing only scattered nuclei mainly from capillary endothelium. Distinct alveolar lining cells are not visible. A few macrophages are scattered within the airspaces.

FIGURE 1.2  Normal lung. (A) A respiratory bronchiole (RB) is seen adjacent to a pulmonary artery in this field, and it opens into alveolar ducts (AD). (B) Higher magnification view of the RB shows its discontinuous smooth muscle layer, as well as the smooth muscle bundles (arrows) that are present at the mouth of the adjacent AD.
• Alveolar spaces may contain scattered alveolar macrophages, but numerous macrophages within contiguous alveoli are abnormal.

• Pulmonary veins course separately from arteries and are located within interlobular septa (see Figures 10.19 and 10.20).

• Interlobular septa are connective tissue structures that extend from the visceral pleura into portions of underlying lung, and they contain lymphatic spaces in addition to veins.

• Pulmonary lymphatic spaces are located within the bronchovascular bundles, interlobular septa, and the pleura. They are normally inconspicuous, but they may be artifically dilated in specimens that have been fixed by inflation.

HANDLING OF TISSUE SPECIMENS

Although some pathologists advocate inflating surgical biopsy specimens with formalin using a syringe and needle, we have never found this technique to be necessary. In fact, inflation has its own hazards, including overinflation of airspaces, dilution of airspace exudates, and dilatation of lymphatic spaces, and we do not recommend it. Rather, the most important step in handling these specimens is immersing them immediately after excision in formalin, because leaving them exposed to air promotes atelectasis. A second important step is to use a fresh, sharp blade and to section with a gentle sawing motion, being careful not to compress the specimen during cutting or with one’s fingers. All staples should be removed before sectioning and the sections made perpendicular to the pleura starting at the (soft) excision margin and extending to the (firmer) pleural surface.

For transbronchial biopsy specimens, as with surgical biopsies, the most important step is to put the tissue into formalin immediately, because the main cause of atelectasis in these specimens is exposure to air. It is frustrating to receive relatively large tissue fragments that are uninterpretable because of atelectasis, and the clinicians should be advised about correcting this problem.

Gentle sectioning with sharp knives should also be used on lobectomy or pneumonectomy specimens. These specimens may be inflated first with formalin through the bronchi and fixed for 1 to 2 hours before sectioning. Inflation is not necessary, however, but it can facilitate dissection and help one to precisely localize lesions to determine their relationship with bronchi and other structures.

Helpful Tip—Handling of Tissue Specimens

• Careful handling of the fresh tissue is the most important step in ensuring optimal microscopic interpretation: Do not allow the specimen to air dry, and do not unduly compress during sectioning.

APPROACH TO DIAGNOSIS

Histologic Examination

The lung can be considered broadly to consist of two main compartments: interstitium and airspace. The interstitium is the supporting structure of the lung and includes alveolar septa, tissue surrounding bronchovascular bundles, and interlobular septa. The airspaces include the lumens of bronchi and alveolar spaces and all structures in between. An important first step in examining lung for non-neoplastic disease is to assess which compartment is primarily involved by the disease process. Many diseases affect the interstitium or airspaces predominantly and are reviewed in Chapters 2, 3, and 4, whereas others may affect both compartments relatively equally (diffuse alveolar damage, Chapter 5). Not all conditions can be categorized in this way, however, as some destroy lung in a cross-country fashion, replacing normal architecture altogether (nodular infiltrates and necrotizing processes, Chapters 6, 7, 8, and 12), while others involve blood vessels or bronchioles primarily (Chapters 10 and 11) and largely spare the adjacent parenchyma. Of course, not every disease fits nicely into these patterns, but systematic examination of the specimen with regard to the predominant site of involvement is a good starting point in the evaluation. Determining the distribution of the process, whether mainly peribronchiolar, perivascular, lymphangitic, or random, provides additional important information for synthesizing a diagnosis.

Rarely, biopsies appear superficially normal; yet patients are said to have severe respiratory compromise. Although such specimens may have not adequately sampled an abnormal area, subtle vascular (pulmonary hypertension, Chapter 10) or bronchiole (constrictive bronchiolitis obliterans, Chapter 11) changes should be suspected and carefully excluded.

A number of common special stains are routinely used in evaluating lung biopsy or excision specimens. Organism stains are used when indicated by the histologic findings or a history of immunocompromise, and we recommend Ziehl–Neelsen or auramine–rhodamine stain for acid-fast bacilli, and Gomori methenamine
silver (GMS) stain for fungi. Elastic tissue stains can be helpful in evaluating blood vessels. Some pathologists advocate connective tissue stains, especially Trichrome, to evaluate fibrosis in interstitial lung disease. We have not found this stain to be either necessary or useful. In fact, we would advise against its use in small transbronchial biopsy specimens because it obscures underlying cellular details and wastes tissue that could have been used for additional H and E or other more helpful stains.

**Clinical Input**

A clinical history is always helpful in interpreting lung biopsies, but it does not have to be detailed, and is not necessary in all cases. Knowing the basic presenting manifestations, whether acute or chronic, the patient’s immune status, whether immunocompromised or immunocompetent, and whether the radiographic findings are localized or diffuse is sufficient in most cases. A more detailed clinical history with radiographic description can be elicited if needed in more difficult cases.

The clinical history should be viewed as a useful ancillary finding that not only helps the pathologist formulate a diagnosis, but, more importantly, may prevent him or her from making erroneous diagnoses. It is best, however, that pathologists examine the slides initially before the clinical situation is known and formulate a differential diagnosis based on the morphologic features alone. The clinical history then can be used to refine the pathologic differential diagnosis. Reviewing the clinical history before examining the microscopic slides is not recommended, however, as it steers the pathologist toward the clinical impression and it may prevent an unbiased evaluation of the pathologic findings.

### TABLE 1.1 Common Radiology Terms and Correlation With Pathology Findings

<table>
<thead>
<tr>
<th>Radiology Term</th>
<th>Chest CT Appearance</th>
<th>Pathology Correlates</th>
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<tbody>
<tr>
<td>Air bronchogram</td>
<td>Air-filled bronchus visible within consolidated lung</td>
<td>Occurs in airspace filling process</td>
</tr>
<tr>
<td>Consolidation</td>
<td>Dense opacification, often with air bronchograms, all</td>
<td>Acute pneumonia, organizing pneumonia, other airspace filling processes</td>
</tr>
<tr>
<td></td>
<td>other lung landmarks obscured, usually localized</td>
<td></td>
</tr>
<tr>
<td>Crazy paving</td>
<td>Thickened interlobular and intralobular lines within</td>
<td>Classically in alveolar proteinosis, also in other diseases</td>
</tr>
<tr>
<td></td>
<td>ground glass opacity, usually diffuse or multifocal</td>
<td>Active inflammatory process, either interstitial or airspace or both</td>
</tr>
<tr>
<td>Ground glass opacity (GGO)</td>
<td>Incomplete, hazy opacification in which bronchial</td>
<td>Corresponds to gross honeycombing, characteristic of usual interstitial pneumonia</td>
</tr>
<tr>
<td></td>
<td>and vascular structures are visible, localized or diffuse</td>
<td></td>
</tr>
<tr>
<td>Honeycomb change</td>
<td>Small uniform spaces with well-defined walls, often at</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lung periphery, associated with reticular opacities</td>
<td></td>
</tr>
<tr>
<td>Mosaic attenuation</td>
<td>Patchwork of regions of differing attenuation</td>
<td>Air trapping, as in small airways disease, or patchy interstitial disease</td>
</tr>
<tr>
<td>Reticular/reticulonodular</td>
<td>Thin linear densities, sometimes with tiny nodules,</td>
<td></td>
</tr>
<tr>
<td>infiltrates</td>
<td>usually diffuse</td>
<td></td>
</tr>
<tr>
<td>Traction bronchiectasis</td>
<td>Dilated bronchi within fibrotic lung and honeycomb change</td>
<td>Associated with parenchymal scarring and honeycomb change</td>
</tr>
</tbody>
</table>

**Radiographic Findings**

As mentioned earlier, superficial knowledge of the basic radiographic findings, whether localized or diffuse, is usually sufficient to interpret most lung biopsies. However, it helps pathologists to understand the radiology jargon to some extent, especially as additional, more detailed radiographic descriptions can contribute to diagnosis in pathologically difficult cases. Some common radiology terms and their significance are listed in Table 1.1.

### Helpful Tips—Approach to Diagnosis

- Examine the microscopic slides first and formulate a differential diagnosis based on pathologic findings before reviewing clinical information.
- Determine the predominant site of involvement, whether interstitial, airspace, or cross-country, but remember that diseases are only rarely strictly confined to a single compartment, and judgment is required to determine the predominant one.
- Consider pulmonary hypertension or constrictive bronchiolitis obliterans when biopsies from patients with severe respiratory compromise appear otherwise normal.
- Use clinical information to confirm the pathologic impression or to prevent an erroneous diagnosis, but do not be biased by the clinical history before looking at the slides.

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TABLE 1.2 Features That Distinguish Artifactual Changes From Actual Diseases

<table>
<thead>
<tr>
<th>Artifact</th>
<th>Potential Mimic</th>
<th>Distinguishing Features of Artifact</th>
</tr>
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<tbody>
<tr>
<td>Artifactual collapse</td>
<td>Interstitial fibrosis</td>
<td>Normal alveolar septa at the edge of the collapsed area without transition, absent alveolar pneumocyte hyperplasia</td>
</tr>
<tr>
<td>Intra-alveolar blood</td>
<td>Alveolar hemorrhage syndrome</td>
<td>Absent hemosiderin; absent hemoptysis, anemia clinically</td>
</tr>
<tr>
<td>Bubble artifact</td>
<td>Exogenous lipid pneumonia</td>
<td>Branching of bubbles, absent intracytoplasmic and interstitial bubbles, no foreign-body giant cells</td>
</tr>
</tbody>
</table>

ARTIFACTS

Several artifacts that mimic an actual disease may be encountered in biopsy specimens. Helpful features in their distinction are summarized in Table 1.2.

Artifactual Collapse

Artifactual collapse is commonly encountered because of improper fixation, air drying, or heavy-handed sectioning, and it can be avoided or diminished by careful specimen handling. Atelectasis is greatest in specimens containing normal or near-normal lung, whereas severely abnormal lung is least affected. Transbronchial biopsy specimens are especially prone to this artifact (Figure 1.3; see also Figure 1.25), but it can be seen in surgical specimens as well. In such cases, the question arises whether the abnormal area is collapsed normal lung or interstitial fibrosis. Examination of parenchyma adjacent to the collapsed areas usually answers the question, because normal alveolar septa directly abut the edge of collapsed areas, whereas a transition from abnormal to normal is seen in interstitial fibrosis. The presence of hyperplastic alveolar lining cells within the abnormal area is another helpful finding that supports interstitial fibrosis.

Fresh Hemorrhage

Fresh blood within airspaces is common in all types of lung biopsy specimens, although transbronchial biopsy specimens seem to be disproportionately affected by this artifact (Figure 1.4). The question arises in such cases whether the bleeding is caused by an underlying lung disease or whether it is secondary to the biopsy procedure. The presence of hemosiderin deposits is the most helpful feature in distinguishing these two possibilities. As hemosiderin takes about 3 days to form from blood breakdown, its presence indicates that the bleeding preceded the biopsy and therefore is “real.” In cases of early alveolar hemorrhage in which hemosiderin has not yet formed, knowledge of the clinical situation is helpful, as most patients with significant acute lung hemorrhage have hemoptysis and sometimes anemia. Often, also, in true alveolar hemorrhage, the airspaces are dilated and packed with blood in contrast to artifactual blood in which the airspaces retain their normal size and configuration. Sometimes, acute inflammation and necrosis of alveolar septa are seen and indicate acute capillaritis (see Chapters 4 and 6) in the etiology of the bleeding.

FIGURE 1.3 Artifactual collapse. In this field, from a transbronchial biopsy specimen, the entire central area is collapsed and uninterpretable. The sharp demarcation from the adjacent relatively normal parenchyma (right) is characteristic of artifactual collapse and differs from the gradual transition from abnormal to normal, seen around fibrotic areas. See also Figure 1.25.
Corpora Amylacea

Corpora amylacea are large, rounded amphophilic to eosinophilic structures that are found within alveolar spaces (Figure 1.6). They measure from 30 to 200 μm and may fill an entire alveolus. They are often surrounded by a rim of alveolar macrophages and occasionally elicit a foreign-body giant cell reaction. Usually, only scattered forms are present, but they can be numerous and even form small clusters. At higher magnification, they have a distinct lamellar morphology, and well-fixed cases also show spoke-like structures radiating from the center (Figures 1.6B and 1.7A). Frequently, inclusions are seen in their centers and include lightly stained geometric shapes, darkly pigmented structures, and birefringent crystalloid areas (Figure 1.7). Distortion related to fixation and sectioning, such as wrinkling resembling chatter, and partial loss of architecture are common, but close examination reveals the characteristic lamination at least focally (Figure 1.8).

Corpora amylacea have no known significance, and their origin is unknown. They are most prominent in older adults. As they are passive occupants of alveolar spaces, they may be entrapped in any abnormal process affecting the alveoli, and it is important not to confuse them with any aspirated foreign material, especially when they are entrapped in an area of organizing pneumonia (Figures 1.9 and 1.10). Attention to morphologic details at high magnification, especially the presence of lamination, should clarify the issue.
FIGURE 1.5  Bubble artifact. (A) At low magnification, the airspaces are filled with a cellular exudate in which numerous varying-sized, clear vacuoles often having odd shapes are present. (B) A higher magnification better demonstrates the varying-sized, often-budding clear vacuoles that are intermingled among intra-alveolar macrophages. The vacuoles are not present within macrophage cytoplasm, however, and foreign-body giant cells are absent. This 35-year-old smoker had severe respiratory bronchiolitis as well as Langerhans cell histiocytosis elsewhere.

Interstitial Megakaryocytes

Megakaryocytes are frequently observed within alveolar septa, and they may be numerous. They are characterized by large, darkly staining nuclei that are easily visible at low magnification (Figure 1.11). The nuclei are irregularly shaped, often elongated, curved, or branching, and sometimes multilobated, but cytoplasm is usually not visible (Figure 1.11). High magnification indicates that they are present within capillary lumens (Figure 1.12). Although they have no relevance to the diagnosis of an underlying lung disease, they tend to be more numerous in patients with febrile illnesses, sepsis, cardiovascular diseases, and underlying malignancies. They should not be confused with tumor cells or fungal organisms.

Bone Marrow Emboli

Bone marrow emboli are common findings in surgical lung biopsy specimens, and are of no known significance. The marrow varies from fatty and nearly acellular to cellular, and it contains the usual marrow components (Figure 1.13). Single or multiple arteries may be involved. Bone marrow emboli are most common at autopsy where they are usually attributed to broken ribs related to resuscitation attempts. The pathogenesis of marrow emboli following surgical lung biopsies is not known, but may be related to rib manipulation during surgery.

Blue Bodies

Blue bodies are round, often fragmented, blue-gray structures that may appear laminated and are found within alveolar macrophages (Figure 1.14; see also Figure 4.24). They stain weakly for iron, and are positive with the von Kossa stain for calcium. They are thought to represent breakdown products of cell metabolism and they are entirely nonspecific. Blue bodies occur under any condition in which there are large numbers of intra-alveolar macrophages, and

(text continued on page 11)
FIGURE 1.6 Corpora amylacea. (A) At low magnification, numerous corpora amylacea are seen within alveolar spaces in an area of otherwise normal lung. The photograph is from a random section of a lobectomy performed for tumor. (B) The classic concentric lamellae are seen in this corpus amylacea, which is partly rimmed by alveolar macrophages.

FIGURE 1.7 Corpora amylacea. In addition to the classic concentric lamellae, these corpora amylacea contain irregularly shaped central structures that appear clear in (A) and pigmented in (B). Note also the spoke-like structures radiating from the center in (A).
FIGURE 1.8 Sectioning-induced changes in corpora amylacea. (A) Wrinkles resembling chatter artifact and fragmentation are common. (B) Concentric lamellae can still be visualized focally at higher magnification in this distorted corpus amylacea.

FIGURE 1.9 Corpora amylacea in organizing pneumonia. (A) A corpus amylacea is entrapped within this area of organizing pneumonia and even surrounded by a multinucleated giant cell. Although the appearance may initially suggest aspiration pneumonia, the finding of the typical lamellar structure at high magnification (B) distinguishes corpora amylacea from foreign material.
FIGURE 1.10 Distorted corpora amylacea in organizing pneumonia. (A) Sometimes corpora amylacea are distorted and difficult to identify, as in this example from an area of organizing pneumonia. (B) Higher magnification shows oddly shaped central degeneration, but preservation of the characteristic ring structure allows diagnosis.

FIGURE 1.11 Megakaryocytes in the lung. (A) In this case of organizing diffuse alveolar damage (see Chapter 5), numerous darkly staining, irregularly shaped megakaryocytes (arrows) are visible in the interstitium. (B) and (C) are higher magnification views showing the characteristic densely stained elongated and branching nuclei of megakaryocytes.
**FIGURE 1.12** Megakaryocytes in the lung. (A) In this case of mild chronic interstitial fibrosis, several elongated and curved nuclei of megakaryocytes are seen within the thickened alveolar septa. As illustrated at higher magnification in (B) and (C), they are present within spaces indicative of capillaries. Note the bilobed megakaryocyte in (C).

**FIGURE 1.13** Bone marrow emboli. This small pulmonary artery is filled with bone marrow containing a mixture of normal marrow cells and fat in approximately equal proportions.

they should not be confused with inhaled or aspirated particles.

**Cytoplasmic (Mallory) Hyaline**

Cytoplasmic accumulation of amorphous, densely eosinophilic, globular material is sometimes encountered within alveolar lining cells (Figure 1.15; see also Figure 3.11). The involved cells are enlarged with reactive features, and the changes are usually visible at low magnification. Mallory hyaline has been described most often in usual interstitial pneumonia (see Chapter 3), but it occurs under other conditions as well, such as acute interstitial pneumonia (see Chapter 5) and asbestosis (see Chapter 9), for example, and should be considered a nonspecific finding.

The hyaline material resembles Mallory hyaline seen in alcoholic and other liver diseases, hence the name, but there is no correlation of the lung deposits with a history of liver disease or alcoholism. The structural composition is similar, however, consisting of intermediate keratin filaments.

**Minute Meningothelial-Like Nodules (MLNs)**

In the past, MLNs were termed chemodectomas because of a superficial resemblance to
FIGURE 1.14  Blue bodies. Numerous macrophages fill airspaces adjacent to interstitial fibrosis in this case of usual interstitial pneumonia (see Chapter 3) in a smoker. Even at low magnification (A), the large blue-gray structures are visible, and at higher magnification (B), they are seen to be present mainly within the macrophage cytoplasm. The inset in (A) is a high-magnification view showing the fragmented, focally laminated blue-gray appearance. See also Figure 4.24.

FIGURE 1.15  Cytoplasmic (Mallory) hyaline. (A) In this case of usual interstitial pneumonia, enlarged, reactive-appearing alveolar pneumocytes containing intracytoplasmic eosinophilic inclusions (circle) are visible at low magnification. The densely eosinophilic, rope-like, and somewhat blury appearance of the hyaline material is better appreciated at high magnification (inset). (B) At high magnification in this field, typical hyaline material is seen within multinucleated, reactive-appearing alveolar pneumocytes.
chemodectomas (paragangliomas) in other locations, and when neuroendocrine differentiation was found to be absent, the term “so-called chemodectoma” was applied. Subsequently, ultrastructural and immunohistochemical studies showed evidence of meningothelial differentiation, hence the current terminology. MLNs were previously lumped with carcinoid tumorlets under the heading “tumorlet,” a term that is now reserved for carcinoid tumorlets.

MLNs are common findings occurring in almost 15% of routine biopsy specimens, and they can be found in nearly one half of lobectomy specimens if extensively sampled. They are most common in adults older than 50 years, with women affected twice as often as men. They are uncommon in individuals younger than 20 years and are quite rare in children. They are often associated with chronic lung disease, but they have no known clinical significance.

At low magnification, MLNs appear as well-demarcated rounded- to stellate-shaped nodules in the interstitium, and they frequently are multiple (Figures 1.16 and 1.17). They average about 1.0 mm in size, but may vary from only a few cells to several millimeters (Figure 1.18). They are composed of uniform epithelioid cells with a moderate amount of eosinophilic cytoplasm and indistinct cell borders. Their nuclei are bland, round to oval shaped with homogeneous chromatin and occasional nuclear clearing. The cells usually form rounded clusters that are reminiscent of the “cell balls” characteristic of paragangliomas. Variable fibrosis may be present between the cell clusters, and hemosiderin deposition is occasionally seen. MLNs are randomly distributed throughout the lung, although many occur near or around blood vessels. They are usually present in areas of normal lung, but may be entrapped within scars or other processes, such as granulomas and even tumors (Figures 1.19 and 1.20).

Immunostaining is usually not necessary for diagnosis because the H and E appearance is so distinct, but the cells are typically positive for vimentin, epithelial membrane antigen (EMA), and progesterone receptors (Figure 1.21). It is important to note that the cells are negative for cytokeratin, synaptophysin,
FIGURE 1.17  Multiple MLNs. (A) At low magnification, two nodules are present within normal-appearing alveolated parenchyma. The inset is a high-magnification view showing the characteristic bland nuclei within abundant cytoplasm. (B) This intermediate magnification view highlights the stellate shape and the interstitial location of the cellular infiltrate. The lesions were incidental findings in a 63-year-old woman with organizing pneumonia elsewhere. MLN, meningothelial-like nodule.

FIGURE 1.18  Small MLN. (A) This MLN consists of a tiny cluster of meningothelial-like cells around a small artery. (B) Higher magnification shows the characteristic oval-shaped cells immediately adjacent to a small artery (top and bottom). MLN, meningothelial-like nodule.
FIGURE 1.19  Large MLN in scarred parenchyma. (A) At low magnification, small groups of cells are clustered together forming a fairly large MLN within an area of parenchymal scar. (B) Higher magnification shows the tightly grouped bland cells within stromal fibrosis. Note the nuclear chromatin clearing present in some cells (top right). MLN, meningothelial-like nodule.

FIGURE 1.20  Large MLN within honeycomb lung. (A) This example from a case of usual interstitial pneumonia shows a sizeable cellular area present within honeycomb change (bottom) and adjacent interstitial fibrosis (top). (B) Higher magnification of the area outlined by the square in (A) shows the typical bland oval-shaped cells. MLN, meningothelial-like nodule.
and chromogranin, thus distinguishing the lesion from neuroendocrine proliferations and other epithelial neoplasms. It is interesting to note that the cells may stain for CD56, a finding considered nonspecific in this setting.

Rarely, MLNs are so numerous that they cause interstitial changes radiographically as well as symptoms clinically, and the name diffuse meningothe- liomatosis (see Chapter 2) has been applied to this entity. Histologically, the lesions comprising this condition are indistinguishable from ordinary MLNs, except that they tend to be larger and they may be nearly confluent in places (see Figure 2.36). As ordinary MLNs are commonly multiple, diffuse meningothe liomatosis should only be considered in persons with clinical and radiographic evidence of interstitial lung disease and no other pathologic findings.

Carcinoid Tumorlets

Carcinoid tumorlets are small proliferations of neuroendocrine (Kulchitsky-like) cells that, by definition, measure less than 5 mm. They are most commonly associated with bronchiectasis, parenchymal scars, and peripheral carcinoid tumors. They are often multiple, but in the absence of supporting clinical features, a diagnosis of the rare entity, diffuse idiopathic neuroendocrine cell hyperplasia (DIPNECH, see Chapter 11), should not be considered.

Histologically, carcinoid tumorlets are usually found in the vicinity of bronchioles that may be obstructed or obliterated by the lesions, and the accompanying fibrosis is often prominent (Figure 1.22). The component cells are typically bland with salt-and-pepper nuclear chromatin features, and they are oval to spindle shaped. Neuroendocrine cell hyperplasia commonly accompanies carcinoid tumorlets and blends into them. It is characterized by a proliferation of neuroendocrine cells within and beneath the normal bronchiolar epithelium (Figure 1.23).

Because they are small and composed of bland epithelial cells, carcinoid tumorlets and MLNs may be confused, and in the older literature both were lumped together as “tumorlets.” Their differentiating features are contrasted in Table 1.3. Although not usually necessary, in questionable cases, immunostaining for chromogranin or synaptophysin will identify the neuroendocrine features of carcinoid tumorlets, which are absent in MLNs (Figure 1.24).

Entrapped Pleural Fragments

Bits of pleura are frequently sampled in transbronchial biopsy specimens especially in patients

![Immunostaining in MLNs](image_url)

**FIGURE 1.21** Immunostaining in MLNs. Positive staining is seen for vimentin (A), EMA (B), and progesterone receptor (C). EMA, epithelial membrane antigen; MLN, meningothe liomatous-like nodule.
FIGURE 1.22 Carcinoid tumorlet. (A) A stellate-shaped cellular nodule is present that partially replaces a bronchiole (Br, bottom). Stromal fibrosis is prominent in the upper portion of the lesion. (B) Higher magnification shows the characteristic uniform, oval to elongated epithelial cells that contain bland nuclei with a salt-and-pepper nuclear chromatin pattern. Note the compressed overlying ciliated bronchiolar epithelium on the right.

FIGURE 1.23 Carcinoid tumorlet and neuroendocrine cell hyperplasia. (A) This tumorlet has almost completely obstructed a small bronchiole identified by the residual smooth muscle layer on the left (arrows) and the adjacent pulmonary artery on the bottom. The residual bronchiole lumen at the top is partially filled by neuroendocrine cell hyperplasia. (B) Higher magnification of neuroendocrine cell hyperplasia, which forms beneath normal bronchiolar epithelium and protrudes into the lumen.
TABLE 1.3  Contrasting Features of MLNs and Carcinoid Tumorlets

<table>
<thead>
<tr>
<th>MLN</th>
<th>Carcinoid Tumorlet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clusters (&quot;cell balls&quot;) of bland, round to oval cells</td>
<td>Nests of bland oval to spindle-shaped cells. Neuroendocrine cell hyperplasia also often present.</td>
</tr>
<tr>
<td>Homogeneous nuclear chromatin, occasional clearing</td>
<td>Salt-and-pepper nuclear chromatin</td>
</tr>
<tr>
<td>Random distribution, often perivascular</td>
<td>Bronchiolar and peribronchiolar distribution, often associated with scarring</td>
</tr>
<tr>
<td>Negative IHC staining for cytokeratin, chromogranin, synaptophysin</td>
<td>Positive IHC staining for cytokeratin, chromogranin, synaptophysin</td>
</tr>
<tr>
<td>Positive IHC staining for vimentin, EMA, progesterone receptor</td>
<td>Usually negative IHC staining for vimentin, EMA, progesterone receptor</td>
</tr>
</tbody>
</table>

EMA, epithelial membrane antigen; IHC, immunohistochemistry; MLN, meningothelial-like nodule.

**FIGURE 1.24** Immunostaining in carcinoid tumorlet. (A) This carcinoid tumorlet is composed of the characteristic spindle-shaped cells containing a salt-and-pepper nuclear chromatin pattern (inset), and it partially replaces a bronchiole (bottom). (B) Immunostaining for chromogranin is strongly positive in the tumorlet.

With interstitial lung disease and peripheral nodules or infiltrates. Although usually small and inconspicuous, they can form solid clusters or gland-like structures that raise the possibility of a neoplasm, an especially challenging situation in biopsies taken for evaluation of clinically suspicious nodules.

Histologically, visceral pleural fragments consist of a mixture of mesothelial cells and variable surrounding fibrosis. They may appear as solid clusters, or they may form gland-like spaces, and mixtures of both patterns may be present (Figures 1.25 and 1.26). They can be found within the substance of the lung fragments as well as on the edge, and some fragments...
FIGURE 1.25  Entrapped pleura in transbronchial biopsy. (A) At low magnification, a cluster of epithelioid cells is present on the edge of this lung fragment. Note also the severe artifactual collapse that involves almost the entire piece of tissue except for a tiny area of relatively normal lung that abuts the collapsed portion (lower left). (B) At high magnification, the cells are relatively bland with abundant cytoplasm, and they stain strongly for calretinin (inset). This biopsy was from a 72-year-old woman with a 4.0-cm opacity suspicious for neoplasm. No changes were present to explain the opacity, and therefore the biopsy was considered nondiagnostic.

FIGURE 1.26  Visceral pleura in transbronchial biopsy. (A) In this case, the pleura comprises an entire tissue fragment, and the appearance superficially suggests tumor within a bronchial wall. Both a solid portion (top, shown at high magnification in [B]) and a gland-like configuration (center, shown at high magnification in [C]) are present. The cells contain relatively uniform, bland nuclei and abundant cytoplasm. This 78-year-old man underwent biopsy to evaluate bilateral infiltrates and hypoxia. Findings that would explain his presenting complaints were not present elsewhere.
may be detached. The component cells are usually bland and uniform, although there may be mild nuclear atypia, and they contain abundant cytoplasm. Often the typical hobnail shape of mesothelial cells is recognizable, and a papillary configuration may be present. It is most important to consider pleura in the differential diagnosis of bland-appearing or mildly atypical cellular proliferations in transbronchial biopsies in order to avoid misdiagnosing a neoplasm. In difficult cases, immunostaining can confirm the diagnosis because mesothelial markers (calretinin and WT-1) are positive, whereas stains for other lesions in the differential diagnosis (chromogranin, synaptophysin, TTF-1, etc.) would be negative. In addition to visceral pleura fragments, pieces of parietal pleura are also occasionally encountered. They are easier to identify, because they consist mainly of adipose tissue covered by a mesothelial layer (Figure 1.27), and their presence should be a clue to the identity of the visceral pleura fragments present elsewhere. It is interesting to note that the presence of pleura, even parietal pleura, on transbronchial biopsy specimens does not seem to correlate with postbiopsy pneumothorax.

Any abnormality affecting pleura may also be sampled on transbronchial biopsy specimens, including nonspecific inflammatory reactions and tumors. Nodular histiocytic/mesothelial hyperplasia is a reactive cellular process that is composed predominantly of clusters of histiocytes admixed with fewer mesothelial cells and lymphocytes. When sampled on transbronchial biopsy specimens, cellular aggregates of bland-appearing cells with abundant cytoplasm are present that may mimic a low-grade neoplasm (Figure 1.28). Immunohistochemistry will clarify the issue, showing a mixture of cytokeratin-negative, CD68-positive histiocytes and cytokeratin-positive, calretinin/WT-1-positive mesothelial cells (Figure 1.29).
FIGURE 1.28 Nodular histiocytic/mesothelial hyperplasia in a transbronchial biopsy. (A) A prominent, well-circumscribed cellular nodule is present within this lung fragment. (B) At higher magnification, the nodule is composed of bland-appearing epithelioid cells. Note the pigmented macrophages (respiratory bronchiolitis) present within airspaces in the lower right. The patient was a 74-year-old heavy smoking woman with weight loss and a suspicious mass radiographically.

FIGURE 1.29 Nodular histiocytic/mesothelial hyperplasia. Same case as in Figure 1.28. (A) Higher magnification shows the central bland epithelioid appearing cells with abundant cytoplasm as well as a rim of smaller cells with darker cytoplasm. Although initially thought to represent a low-grade neoplasm, immunostaining for CD68 was strongly positive in most of the cells (B), while calretinin (and cytokeratin, not shown) marked only surrounding smaller mesothelial cells (C). As this lesion and the respiratory bronchiolitis were incidental findings, the biopsy was considered nondiagnostic in this clinical setting.
**Helpful Tips—Incidental Findings**

- Corpora amylacea may be entrapped within any airspace filling process and may be surrounded by histiocytes. Look for characteristic lamination to distinguish them from foreign material.
- The most reliable distinguishing features of MLNs and carcinoid tumorlets on routine stains include nuclear chromatin appearance (homogeneous vs. salt and pepper) and location (often perivascular vs. bronchiolar).
- CD56 immunostaining may be positive in MLNs, but in the absence of positive chromogranin or synaptophysin staining should not be considered evidence of neuroendocrine differentiation.
- Entrapped pleural fragments should be considered in the differential diagnosis of any cluster of bland to mildly atypical, unusual-appearing epithelioid cells occurring in transbronchial biopsy specimens.

**SELECTED REFERENCES**

**Approach to Diagnosis**


**Incidental Findings**


Diffuse alveolar damage (DAD) and its clinicopathologic counterpart, acute interstitial pneumonia (AIP), are reviewed in a separate chapter because they represent a unique manifestation of acute lung injury, and their pathologic changes cannot be pigeonholed into interstitial or airspace predominant categories.

### TOPICS

- Diffuse Alveolar Damage (DAD)
- Acute Interstitial Pneumonia (AIP)

### DIFFUSE ALVEOLAR DAMAGE (DAD)

Diffuse alveolar damage (DAD) is a purely descriptive term for the spectrum of pathologic changes that follow acute lung injury. Most patients clinically manifest the acute respiratory distress syndrome (ARDS). Usually, the cause of the lung injury is known, but when it cannot be identified, the resultant idiopathic condition is known as AIP. It is discussed in the subsequent section, “Acute Interstitial Pneumonia.”

**Histologic Features**

- Hyaline membranes and/or fibroblast proliferation
- Epithelial hyperplasia and metaplasia, often with cytologic atypia
- Small arterial thrombi

The pathologic changes in DAD comprise roughly two stages: acute (early), occurring within the first week or so following injury, and organizing (proliferative, later), occurring after a week or two. In reality, as illustrated schematically in Figure 5.1, there is no sharp division between the two stages because features of both are often present together in a given case. Nonetheless, the approximate time interval following injury can be estimated from the relative proportion of abnormalities present.

The histologic hallmark of the **acute stage** is the presence of hyaline membranes. Although edema, both interstitial and intra-alveolar, is the earliest change in DAD, edema is difficult to recognize in routine sections and to separate from biopsy-related artifactual changes. Hyaline membranes develop a day or so following injury and become most prominent in 3 or 4 days. They appear as glassy, eosinophilic structures within airspaces that are plastered along alveolar septa (Figure 5.2). They comprise a mixture of fibrin and other serum proteins and usually appear fairly homogeneous, although they sometimes contain scattered bare nuclei or other cellular debris. Remnants of edema fluid and fibrinous exudates as well as some nuclear debris may be seen in alveolar spaces, but intra-alveolar inflammation is scant if present at all (Figure 5.3).

Alveolar septa are mildly thickened by edema or alveolar wall collapse. Occasional acute or chronic inflammatory cells may also be present within alveolar septa, but interstitial inflammation is usually not prominent. Alveolar pneumocyte hyperplasia begins...
The organizing stage of DAD is a reparative response to the injury and is characterized by interstitial fibroblast and myofibroblast proliferation along with alveolar pneumocyte hyperplasia. At low magnification, the process is characterized by hypercellular,
FIGURE 5.3  DAD, acute stage. (A) In this example, hyaline membranes are plastered against alveolar septa that are thickened by edema, scattered mononuclear inflammatory cells, and a few fibroblasts. (B) At higher magnification, occasional pyknotic nuclei and cellular debris are seen within the hyaline membranes and in alveolar spaces. The appearance fits with injury occurring 5 to 7 days previously. DAD, diffuse alveolar damage.

FIGURE 5.4  Alveolar pneumocyte hyperplasia in DAD. (A) At low magnification, hyaline membranes are seen lining thickened alveolar septa and there are areas of prominent alveolar pneumocyte hyperplasia (circle). These findings indicate injury occurring a week or more previously. (B) Higher magnification of the circled area shows the typical hobnail configuration of the hyperplastic alveolar pneumocytes, some of which are cytologically atypical. DAD, diffuse alveolar damage.
temporally uniform thickening of alveolar septa that varies from mild to marked (Figures 5.6 and 5.7). Spindle-shaped fibroblasts and myofibroblasts embedded within lightly staining, often myxoid stroma are prominent within the thickened alveolar septa and account for much of the cellularity. In addition to the spindled cells, remnants of entrapped, often collapsed alveoli lined by hyperplastic pneumocytes comprise a portion of the interstitial cellularity and contribute to the alveolar wall thickening. The entrapped pneumocytes can be highlighted with cytokeratin immunostaining, which shows more cells than appreciated on hematoxylin and eosin (H and E) stains (Figure 5.8). A mild chronic inflammatory cell infiltrate may be associated with the other changes but is usually a minor component, and collagen deposition is minimal. Remnants of hyaline membranes may still be seen along alveolar septa in places, but are not prominent (Figure 5.9). In advanced cases, the fibroblast proliferation may be so extensive that the parenchyma appears solid with only slit-like lumens of alveolar spaces remaining (Figure 5.10). As in the acute stage, fibrin thrombi are common in small arteries (Figure 5.5B).

Epithelial hyperplasia is often prominent in the organizing stage and includes squamous metaplasia in and around bronchioles in addition to alveolar pneumocyte hyperplasia (Figures 5.4, 5.9B, and 5.11). Cytologic atypia is common in both the alveolar epithelium and the squamous metaplasia areas, and it may be severe. The hyperplastic lining cells are often enlarged, irregular, and hobnail shaped with vesicular nuclei and prominent nucleoli, and they can cause false-positive cytology diagnoses (Figure 5.12). Mitotic figures are often present, and some may be atypical. Atypia in the squamous metaplasia is frequently present as well and may be so striking as to suggest invasive carcinoma (Figure 5.13). The location of the squamous metaplasia in and around bronchioles along with the associated DAD should indicate the correct diagnosis.

Occasionally, in severely hypoxemic patients, small infarcts are seen, usually in peripheral, subpleural parenchyma. They are likely caused by severe

(text continued on page 123)
FIGURE 5.6  Organizing DAD. (A) At low magnification, relatively uniform cellular thickening of alveolar septa is noted, and adjacent airspaces appear dilated. (B) At higher magnification, the interstitial thickening is due mainly to fibroblasts within lightly staining stroma. Scattered tiny, partially collapsed airspaces lined by hyperplastic pneumocytes are also present (arrows), and there is a hyaline membrane remnant (arrow head). These findings indicate injury occurring at least 2 weeks earlier. DAD, diffuse alveolar damage.

FIGURE 5.7  Organizing DAD. (A) At low magnification, striking interstitial thickening is appreciated with small residual airspaces in some areas and dilated airspaces in others. The thickened interstitium appears cellular. (B) Higher magnification of the circled area in (A) shows prominent entrapped and collapsed alveoli lined by hyperplastic pneumocytes (hobnail-shaped cells with eosinophilic cytoplasm, center top) that are present in the thickened interstitium in addition to fibroblasts. Mild chronic inflammation accompanies the changes as well. The findings indicate injury occurring at least 2 weeks previously. DAD, diffuse alveolar damage.
FIGURE 5.8  Cytokeratin immunostaining in organizing DAD. (A) At low magnification, numerous entrapped alveolar pneumocytes are highlighted within the thickened interstitium. (B) A higher magnification better illustrates the numerous small and often collapsed alveolar remnants (dark brown) within the background fibroblast proliferation. The light brown stained areas represent hyaline membrane remnants that have also been incorporated into the interstitium. DAD, diffuse alveolar damage.

FIGURE 5.9  Hyaline membrane remnants in organizing DAD. (A) Hyaline membrane remnants are seen along alveolar septa thickened by fibroblasts in this area of otherwise typical organizing DAD. A few mononuclear inflammatory cells are also present within airspaces. (B) Nearby, typical organizing DAD is present with prominent, entrapped, partially collapsed alveoli lined by hyperplastic pneumocytes in the thickened interstitium along with fibroblasts. Stars indicate adjacent alveolar spaces. DAD, diffuse alveolar damage.
FIGURE 5.10 Organizing DAD. (A) In this case, the fibrosis is so severe that the alveolated parenchyma appears almost solid. (B) A higher magnification shows the marked interstitial fibroblast proliferation with resultant reduction of airspaces to slit-like spaces. This severe fibrosis occurs after several weeks following injury. DAD, diffuse alveolar damage.

FIGURE 5.11 Squamous metaplasia in DAD. (A) Low magnification showing prominent epithelial proliferation around a bronchiole. (B) At higher magnification, the squamous differentiation is better appreciated, and there is mild atypia. DAD, diffuse alveolar damage.
FIGURE 5.12 Alveolar pneumocyte atypia in DAD. (A) In this example, some alveolar lining cells are enlarged and contain prominent nucleoli. (B) The alveolar pneumocytes in this example are more severely atypical with vesicular nuclei and prominent nucleoli as well as varying size and loss of orientation (top). Inset from another area shows an atypical mitotic figure in addition to cytologic atypia. DAD, diffuse alveolar damage.

FIGURE 5.13 Florid squamous metaplasia with atypia in organizing DAD. (A) Low and (B) high magnification of a squamous proliferation that is so marked that it may suggest invasive squamous cell carcinoma. DAD, diffuse alveolar damage.
hypoxemia, and the arterial thrombi may also be a contributing factor.

It is not uncommon to find areas of acute DAD superimposed on organizing DAD. Although remnants of hyaline membranes may be present in ordinary organizing DAD, combined acute and organizing DAD cases contain areas of well-formed hyaline membranes in a background of organizing DAD (Figure 5.14). The changes are indicative of ongoing or recurrent injury, and they should be diagnosed as acute and organizing DAD. For estimating the time of onset of injury, the most advanced changes should be used.

**Differential Diagnosis**

Very few entities enter the differential diagnosis of the acute stage of DAD because hyaline membranes are quite specific. As infections in immunocompromised persons, especially viral and pneumocystis, can cause acute DAD, a careful search for organisms should be undertaken in this setting.

The main lesion in the differential diagnosis of organizing DAD is organizing pneumonia (OP; see Chapter 4, Figures 4.1 to 4.5), as both are characterized by prominent fibroblast proliferation. Their main distinguishing features are contrasted in Table 5.1. In most cases, the diagnosis is not difficult, as OP involves predominantly the airspaces in peribronchiolar parenchyma, whereas organizing DAD is predominantly interstitial, involving distal parenchyma unrelated to bronchioles. The diagnosis may be difficult, however, when the OP areas are more diffuse causing loss of the peribronchiolar location and blurring of the distinction between airspace and interstitial involvement. The most helpful feature for identifying DAD in difficult cases is finding other changes indicative of acute lung injury, such as hyaline membrane remnants, alveolar pneumocyte hyperplasia, squamous metaplasia in bronchiolar epithelium, and fibrin thrombi. Knowledge of the clinical situation is also helpful, as most patients with DAD receive mechanical ventilation in contrast to most patients with OP.

The situation is further complicated in that focal areas of OP are frequently found in a background of otherwise typical organizing DAD. Even if OP areas are present in the background of organizing DAD, they are of no significance in this situation, and they
do not need to be diagnosed. The prognosis in such cases, unfortunately, is that of DAD (see subsequent section, “Clinical Features”), which is considerably worse than that of OP.

Although interstitial thickening is prominent in organizing DAD, chronic interstitial pneumonias are not strong considerations in the differential diagnosis because they are characterized by interstitial inflammation or collagen formation but not diffuse fibroblast proliferation. Also, they lack other features of acute lung injury. It should be remembered, however, that DAD can complicate other processes, including chronic interstitial pneumonias. This occurs especially in usual interstitial pneumonia (UIP) and is known as exacerbation of UIP (see Chapter 3, Figures 3.13 and 3.14), and it has been described in nonspecific interstitial pneumonia (NSIP) as well as in hypersensitivity pneumonia (Chapters 2 and 3). Therefore, slides should be carefully reviewed in order not to overlook an underlying or coexisting disease in cases of DAD.

**Etiology**

DAD is a manifestation of severe acute lung injury, and there are a large number of potential causes, of which the most common are listed in Table 5.2. Unfortunately, with only a few exceptions, the histologic findings in DAD are identical regardless of cause, and identification of the etiology rests on clinical investigation. Infection is an important treatable cause of DAD, and in immunocompromised persons special stains for organisms, especially pneumocystis, may be productive (Chapter 7). Viral infections that produce specific cytopathic changes are another example of histologically identifiable causes, although the most common viral pneumonias in immunocompetent persons (influenza and parainfluenza) have no specific markers (see Chapter 7).

In a few cases, reactive lymphocytes and plasma cells may be focally prominent in alveolar septa. This finding should suggest viral infection or underlying collagen vascular disease in the etiology. If significant chronic inflammation is a diffuse finding, however, exacerbation of an underlying chronic interstitial pneumonia (especially NSIP) is more likely.

**Pathogenesis**

Injury to alveolar epithelium and capillary endothelium is central to the cascade of events that produce DAD (Figure 5.15). Capillary endothelial damage results in leakage of plasma fluids into the interstitium

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**TABLE 5.1 Contrasting Features of Organizing DAD and OP**

<table>
<thead>
<tr>
<th>Features</th>
<th>Organizing DAD</th>
<th>OP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibroblast proliferation</td>
<td>Yes, interstitial, distal alveoli</td>
<td>Yes, airspace, peribronchial</td>
</tr>
<tr>
<td>Hyaline membrane remnants</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Epithelial hyperplasia/metaplasia</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Arterial thrombi</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Patient on ventilator</td>
<td>Usually</td>
<td>Not usually</td>
</tr>
</tbody>
</table>

DAD, diffuse alveolar damage; OP, organizing pneumonia.

**TABLE 5.2 Common Causes of DAD**

- Infection (viruses, pneumocystis, rickettsia, mycoplasma, Legionella, etc)
- Toxic inhalants (fumes, smoke, crack cocaine, other)
- Drug toxicity (chemotherapy, amiodarone, others, heroin)
- Ingestants (paraquat, kerosene, rapeseed oil)
- Shock
- Sepsis
- Aspiration
- Radiation therapy
- Exacerbation of UIP
- Collagen vascular disease (especially lupus, scleroderma, dermatomyositis, mixed connective tissue disease, rheumatoid arthritis)
- Hematopoietic stem cell or solid organ transplantation
- Idiopathic (AIP)

AIP, acute interstitial pneumonia; DAD, diffuse alveolar damage; UIP, usual interstitial pneumonia.
ACUTE INTERSTITIAL PNEUMONIA (AIP)

AIP, referred to in the past as Hamman-Rich disease, idiopathic DAD, or idiopathic ARDS, is an uncommon idiopathic interstitial pneumonia, and the only one that is associated with an acute onset and rapid clinical course. AIP is a clinical syndrome, and, therefore, knowledge of the clinical history is necessary for diagnosis.

**Clinical Findings**

AIP occurs in previously healthy individuals in whom there is no identifiable cause of lung injury. Persons of middle age are most commonly affected, but there is a wide age range, with occasional cases reported in children and the elderly. The onset is acute with severe dyspnea occurring over several days usually accompanied by fever. An antecedent flu-like syndrome with myalgias, arthralgias, fever, chills, and malaise is common. Bilateral ground glass opacification and/

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**Clinical Features**

DAD is characterized clinically by the acute onset of shortness of breath. Patients develop diffuse lung infiltrates and severe hypoxemia indicative of the acute respiratory distress syndrome (ARDS), and most require intubation with mechanical ventilation. Mortality rates are high, averaging 35% to 50% depending on the cause and patient age. Treatment is mainly supportive, although corticosteroids may be used in some cases.

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**Histologic Features**

- DAD, Organizing Stage

The histologic findings in AIP are indistinguishable from the organizing stage of DAD with interstitial fibroblast proliferation and alveolar pneumocyte hyperplasia as well as other features of acute lung injury (see Figures 5.6, 5.7, and 5.10). Surprisingly, however, well-formed hyaline membranes and other features of the acute stage of DAD are generally not found.

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**Helpful Tips—DAD**

- The “diffuse” in DAD refers to diffuse involvement (endothelium, epithelium, and interstitium) of a single alveolus rather than to involvement of the entire lung; therefore, finding some areas of normal lung microscopically should not detract from the diagnosis.
- Consider superimposed acute bacterial bronchopneumonia if neutrophils are prominent within alveolar spaces.
- In histologically difficult cases, knowledge of the clinical findings should help in diagnosis, as most patients with DAD are on a ventilator with features of ARDS clinically.
- Be cautious in diagnosing DAD in patients who are not receiving mechanical ventilation.
- DAD can complicate underlying more chronic lung diseases in which case both processes should be diagnosed.
or consolidation is found on chest CT examination. Respiratory failure with severe hypoxemia requiring mechanical ventilation (ARDS) rapidly ensues, and mortality is high, exceeding 70% in some series. Corticosteroid therapy may be used, although there is little evidence for a beneficial effect.

**Terminology: DAD Versus AIP**

DAD is a purely descriptive pathologic term that has no implications for etiology, whereas AIP refers to a specific clinical syndrome that is pathologically characterized by DAD and is of unknown etiology. The diagnosis of AIP, therefore, requires knowledge of the clinical setting and cannot be made from the pathologic findings alone. The situation is analogous to diagnosing cryptogenic organizing pneumonia versus organizing pneumonia (Chapter 4), idiopathic pulmonary fibrosis versus UIP (Chapter 3), or sarcoidosis versus non-necrotizing granulomatous inflammation. DAD should be the diagnosis in most cases, unless unequivocally supportive clinical history is provided.

**SELECTED REFERENCES**

**Diffuse Alveolar Damage (DAD)**


**Acute Interstitial Pneumonia (AIP)**


**Helpful Tips—AIP**

- Despite the term “acute” interstitial pneumonia, acute inflammatory cells are not a feature in AIP. Rather, the “acute” refers to the clinical onset and course and not to the histologic findings.
- Be cautious about considering AIP if the biopsy shows acute DAD, because almost all cases manifest organizing DAD.
- Diagnose AIP only in the appropriate clinical setting and after all other potential causes of DAD have been excluded.
- Do not diagnose AIP if evidence of an underlying chronic interstitial fibrosing process, especially honeycomb change, is present, since in that setting exacerbation of UIP (Chapter 3) is more likely.