ATLAS OF INTERSTITIAL LUNG DISEASE PATHOLOGY

Pathology with High Resolution CT Correlations

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Dedicated to the late Drs. Charles Carrington and William Thurlbeck

Andrew Churg

Dedicated to my family

Nestor L. Müller

Preface

Interstitial lung disease (ILD) is an extremely confusing topic, and this problem extends from clinicians to radiologists to pathologists. Confusion arises in part because of the sheer number of ILDs; clinicians can name more than 150 separate entities. From the point of view of the pathologist there are many fewer diagnosable patterns, but this phenomenon immediately raises the question of how to make those patterns correspond to clinically defined diseases, particularly so because, at first glance, there appears to be considerable morphologic overlap among these various conditions. A further source of confusion is that much of what is called "interstitial" lung disease is really characterized by processes that take place largely in the airspaces—bronchiolitis obliterans organizing pneumonia (BOOP) is a good example—or those that affect primarily small airways; for example, constrictive bronchiolitis.

However, we believe that the biggest problem for pathologists trying to deal with ILD is that the non-lung specialist will see relatively few such cases in a year, and turning to standard textbooks provides only limited help because textbooks by their very nature can supply only a few illustrations of any particular condition.

This Atlas is intended to address this problem by providing a large number of illustrations to give the practicing pathologist a feel for the morphologic spectrum of any given ILD and also to illustrate the various differential diagnoses of any particular condition, something that textbooks often do not provide. For this reason we have included some uncommon variants of relatively common ILD; for example, fibrosis in chronic eosinophilic pneumonia (CEP) and in BOOP, interstitial spread of Langerhans cell histiocytosis (LCH), and progression of desquamative interstitial pneumonia (DIP) to a picture of fibrotic nonspecific interstitial pneumonia (NSIP). We have also included some material on imaging in every chapter, because non-neoplastic lung disease in general and ILD in particular is very difficult to diagnose without clinical and especially radiologic information. Conversely, we hope that radiologists will find this volume to be helpful in understanding the pathologic changes behind the radiologic appearances. But this book is not intended as a general detailed text on clinical features, imaging, pathogenesis, treatment, and so on of ILD, and we have also purposely kept references to an absolute minimum. Rather the book is meant as a quick reference whereby one can look at a set of pictures and get a reasonable idea of whether and how well a particular case shows the diagnostic features of a particular disease.

Andrew Churg
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Contents

CHAPTER

1

General Approach to Interstitial Lung Disease: Clinical and Pathologic Considerations

Interstitial lung diseases (ILDs) constitute a very broad class of confusing entities. The number of possible pathologic patterns of ILD is far fewer than the number of corresponding clinical conditions, the latter estimated as 150 or greater.[1] Although some pathologic ILD patterns are morphologically fairly specific (e.g., lymphangioleiomyomatosis [LAM] or Langerhans cell histiocytosis [LCH]), many are reaction patterns with a broad range of etiologies; thus nonspecific interstitial pneumonia (NSIP) is an entity in itself, but a pattern of NSIP may be seen in collagen vascular diseases, hypersensitivity pneumonitis, and drug reactions, to name just a few. A further confusing feature of ILD is that the pathologic features of one ILD can appear in another: Small foci of bronchiolitis obliterans organizing pneumonia (BOOP) are common in hypersensitivity pneumonitis and in NSIP, while NSIP patterns can be seen focally in biopsies of usual interstitial pneumonia (UIP). Further confusion is sown by the use of alphabetic abbreviations, sometimes referred to facetiously as "alphabet soup" (Table 1.1).

The relative nonspecificity of many pathologic ILD patterns mandates that the pathologist obtains some sort of clinical information, and, even more important, learns something about imaging of ILD. The advent of high-resolution computed tomography (HRCT) has revolutionized the diagnosis of ILD; for some conditions such as sarcoid, UIP, LCH, or LAM, HRCT often provides a highly specific diagnosis. But even where HRCT is less specific, for example, when the radiologist sees a pattern of ground-glass opacities (GGOs, see below for definitions), this still provides important guidelines to pathologic diagnosis. For these reasons we have written this atlas as a book primarily directed to pathologic diagnosis, but with an emphasis on HRCT correlations as well.

The most important conclusion from the comments just made is that ILD usually cannot be diagnosed by sitting in one's office without any clinical and radiologic information, and the pathologist needs to get into the habit of talking to the clinician and radiologist about each case. Sometimes the clinician can only say that the patient has evidence of an ILD, but more often he or she can narrow the diagnosis to likely possibilities. Similarly, HRCT often allows the radiologist to narrow the diagnostic possibilities, and the pathologist may want to get into the habit of reviewing the HRCT images with the radiologist.

Table 1.1

Commonly used abbreviations for interstitial lung diseases

AIP	**Acute Interstitial Pneumonia**
BOOP	Bronchiolitis obliterans organizing pneumonia (when idiopathic also called COP [cryptogenic organizing pneumonia])
DAD	Diffuse alveolar damage
DIP	Desquamative interstitial pneumonia
HP	Hypersensitivity pneumonitis
LAM	Lymphangioleiomyomatosis
LCH	Langerhans cell histiocytosis
NSIP	Nonspecific interstitial pneumonia
OP	Organizing pneumonia pattern (morphologically = BOOP)
PAP	Pulmonary alveolar proteinosis
RBILD	Respiratory bronchiolitis with interstitial lung disease
UIP	Usual interstitial pneumonia

Table 1.2

General morphologic approach to interstitial lung disease

Is this is a malignancy; e.g., lymphangitic carcinoma, lymphoma?
Is this an infection (PCP, CMV)?
Is this an ILD with a defined specific feature; e.g., sarcoid?
Is this a form of idiopathic interstitial pneumonia; e.g., UIP?
Is this a localized artifact (scar, edge of another lesion, etc.)?
Is this a drug reaction or a collagen vascular disease?

That said, there is a general pathologic approach to a given case of ILD. As shown in Table 1.2, when there is no helpful clinical or radiologic information, the idea is to first eliminate things that are relatively easy for the pathologist to diagnose (tumors such as lymphangitic carcinomas or lymphomas that can mimic ILD pathologically or radiologically; infections such as cytomegalovirus [CMV] or pneumocystis that can produce a picture of ILD); then to eliminate diseases with distinctive features such as granulomas; then to consider diseases with fewer specific features and more low power architectural patterns such as the idiopathic interstitial pneumonias.

It is also useful to ask oneself whether the biopsy could be a bad sample; sometimes biopsies pick up the edge of lesions or even misleading lesions, and this can be very confusing; for example, a biopsy taken at the edge of BOOP can look like cellular NSIP (Chapter 5, Fig. 5.11), and nonspecific scars can mimic UIP (Chapter 6, Figs. 6.40 and 6.41). BOOP itself can be seen around mass lesions (tumors, abscesses, nodules of Wegener granulomatosis) that are not ILD (Chapter 5, Fig. 5.20). As pathologists we get small samples to work with while the radiologist has two whole lungs, and a radiologic consultation often solves those particular problems. Lastly, remember that when one encounters a strange ILD pattern, particularly a strange combination of patterns, drug reactions and collagen vascular diseases should be considered. Obviously within each of these categories there are lots of important details, and we will go through these details in this atlas.

CLINICAL FEATURES OF INTERSTITIAL LUNG DISEASE

There are a general set of clinical signs and symptoms that suggest ILD. Most patients with ILD present with shortness of breath that is often slowly progressive and frequently have nonproductive cough as well. Physical examination shows small lung volumes and so-called velcro rales (the sound of two pieces of velcro being ripped apart, also called crackles or dry rales) at the lung bases, the latter a finding characteristic of ILD.[1]

Pulmonary function tests in most forms of ILD demonstrate a restrictive impairment and impaired diffusing capacity, and in relatively early disease only the diffusing capacity may be abnormal. However, some ILD also have airflow obstruction, for example, in constrictive bronchiolitis (bronchiolitis obliterans, see Chapter 20).

Although these abnormalities are typical of ILD, they are generally not useful by themselves for determining the underlying disease. For that reason we will not emphasize signs, symptoms, or pulmonary function tests in the sections that follow, except where there are specific patterns that are helpful.

THE IDIOPATHIC INTERSTITIAL PNEUMONIAS

Anyone dealing with ILD will sooner than later encounter the term "idiopathic interstitial pneumonia." This name refers to a set of different lesions that, partly for historic reasons and partly for reasons of nomenclature, are often grouped together. There is a standard classification of these entities promulgated by the American Thoracic Society and European Respiratory Society[2] that is shown in Table 1.3.

Although we discuss all the entities in Table 1.3, we are going to largely ignore the concept of idiopathic interstitial pneumonias for several reasons: first, acute interstitial pneumonia (AIP) is idiopathic acute respiratory distress syndrome (ARDS), and ARDS is not generally viewed as an ILD; second, except for respiratory bronchiolitis-associated interstitial lung disease (RBILD) and desquamative interstitial pneumonia (DIP), these diseases have no relationship with each other and in fact they tend to be both radiologically and pathologically quite different; third, RBILD and DIP are actually not idiopathic but rather are smoking-related diseases; and fourth, because the clinical features, radiologic and pathologic features, and treatment and prognosis are so different, a diagnosis of "idiopathic interstitial pneumonia" has no meaning.

Table 1.3

The idiopathic interstitial pneumonias (so-called)

Idiopathic pulmonary fibrosis (IPF, equivalent to UIP)
Nonspecific interstitial pneumonia (NSIP)
Cryptogenic organizing pneumonia (COP, BOOP)
Acute interstitial pneumonia (AIP)
Respiratory bronchiolitis with interstitial lung disease (RBILD)
Desquamative interstitial pneumonia (DIP)

We believe it is much more useful to create other categories such as smoking-related diseases (RBILD, DIP, and LCH) where these exist as logical units or have some morphologic continuity, and to treat the remaining conditions as individual diseases.

The pathologist may encounter the term "fibrosing interstitial pneumonia." This is a general name for any kind of ILD that produces dense old fibrosis; for example, UIP, fibrotic NSIP, and chronic hypersensitivity pneumonitis all can be described as fibrosing interstitial pneumonias. Some processes such as fibroblast foci or acute exacerbations (see Chapters 4 and 6 for detailed definitions of these terms) can be seen with any form of fibrosing interstitial pneumonia. Occasionally "fibrosing interstitial pneumonia" is useful as a diagnostic term when the combination of biopsy, imaging, and clinical features do not allow a more exact classification. However, this should always be a diagnosis of last resort because it provides little treatment and prognostic guidance to clinicians.

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CHAPTER

2

Imaging in Interstitial Lung Disease

The two imaging modalities that are used almost routinely in the assessment of patients with interstitial lung disease (ILD) are the chest radiograph and high-resolution computed tomography (HRCT). The radiograph is inexpensive, has a very low radiation dose, and can provide useful information regarding the progression of disease and the presence of associated findings. In some cases, the presence of characteristic findings on the radiograph in the proper clinical context can be highly suggestive of a specific diagnosis. For example, in a patient with minimal or no symptoms and no exposure history, the presence of symmetric bilateral hilar and paratracheal lymphadenopathy with associated ILD in a predominantly upper lobe distribution is highly suggestive of sarcoidosis. In the majority of cases, however, because of the superimposition of shadows, the radiograph plays a limited role in the differential diagnosis of ILD.

HRCT can depict the normal and abnormal interstitium with anatomic detail similar to that of gross pathologic specimens and has become the imaging modality of choice in the evaluation of patients with suspected ILD. In some patients, in the proper clinical context and interpreted by experts, it can provide a highly specific diagnosis, as has been shown particularly in usual interstitial pneumonia (UIP), lymphangiomyomatosis (LAM), Langerhans cell histiocytosis (LCH), and sarcoidosis.[1] When the findings are less specific it provides an overall view of the pattern and distribution of disease throughout the two lungs and therefore is helpful to the pathologist to determine whether the findings seen on the biopsy specimen are truly representative of the overall process. HRCT is also helpful in determining the optimal surgical biopsy site. It is recommended that the surgeon discuss with the radiologist the best sites to be biopsied in order to sample active disease and to avoid areas of end-stage lung (honeycombing) that will be nondiagnostic.[2]

The two technical modifications of CT technique that are used to increase the spatial resolution and that define HRCT are thin sections (typically in the order of 1 mm) and image reconstruction with a high-spatial frequency (sharp) algorithm. The thinner the section, the greater the spatial resolution. Reconstruction of the image using a high-spatial frequency algorithm, rather than a standard algorithm, reduces image smoothing, making structures appear sharper and increasing spatial resolution. Currently the majority of CT scans of the chest are performed on multidetector scanners that provide a volumetric assessment of both lungs during a single breath hold. Although HRCT images can be obtained routinely in these scanners, in many centers the radiologists elect to reformat the images using thicker sections (typically 3 to 5 mm) and standard algorithms. These thick sections can be helpful in the assessment of various conditions, but they do not provide the spatial resolution necessary for the interpretation of findings in ILD.

The differential diagnosis of ILD on the chest radiograph and HRCT is based on the pattern and distribution of abnormalities and the presence of associated findings such as lymph node enlargement or pleural effusion. ILD results in six distinct radiologic patterns of abnormality: interlobular septal thickening, reticulation, cystic pattern, nodular pattern, ground-glass opacities (GGOs), and consolidation. Each of these patterns can be visualized on HRCT and correlated with specific histopathologic findings. The appearances on the chest radiograph, however, are frequently nonspecific and sometimes misleading.[3] For example, a reticular pattern on the radiograph may result from summation of smooth or irregular linear opacities, cystic spaces, or both. Furthermore, in approximately 10% of patients with ILD the chest radiograph is normal.[4] Because of the limitations of the radiograph the discussion of imaging findings in ILD will focus on HRCT.

PATTERNS OF ABNORMALITY AND DIFFERENTIAL DIAGNOSIS OF ILD ON HRCT

Interlobular Septal Thickening

Normally only a few interlobular septa can be seen on HRCT. The presence of numerous visible interlobular septa almost always indicates the presence of septal thickening by interstitial fluid, cellular infiltration, or fibrosis.

On HRCT, thickened interlobular septa are most readily seen in the lung periphery as lines 1 to 2 cm in length outlining part of or an entire pulmonary lobule and extending to the pleura roughly perpendicular to the pleural surface (Fig. 2.1). Within the central lung, thickened septa outlining lobules appear as polygonal arcades (Fig. 2.1).

The most common conditions in which interlobular septal thickening is the predominant or the only interstitial abnormality evident on HRCT are interstitial pulmonary

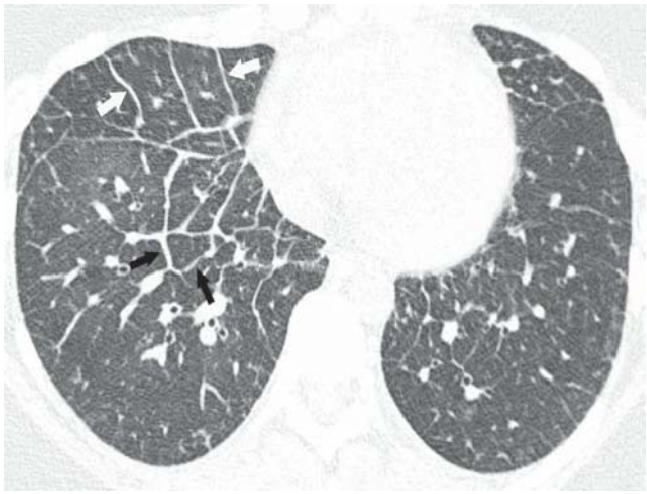

FIGURE 2.1. Interlobular septal thickening—HRCT shows thickened interlobular septa as lines 1 to 2 cm in length, separated by 1 to 2 cm, extending to the pleura (*white arrows*) and as polygonal arcades (*black arrows*) outlining secondary pulmonary lobules. The patient had interstitial pulmonary edema due to fluid overload. Lymphangitic carcinoma can also produce thickened interlobular septa (compare Fig. 2.2).

edema and lymphangitic carcinomatosis (Fig. 2.2). It should be noted, however, that septal thickening is also frequently seen in association with other findings. In these cases the differential diagnosis is more complex and influenced by the pattern and distribution of the associated findings and, most importantly, by the clinical history. For example, at least some thickening of the interlobular septa is commonly evident in patients with interstitial fibrosis. In these patients the septal thickening tends to be a minor finding, the predominant abnormality typically being a reticular pattern.

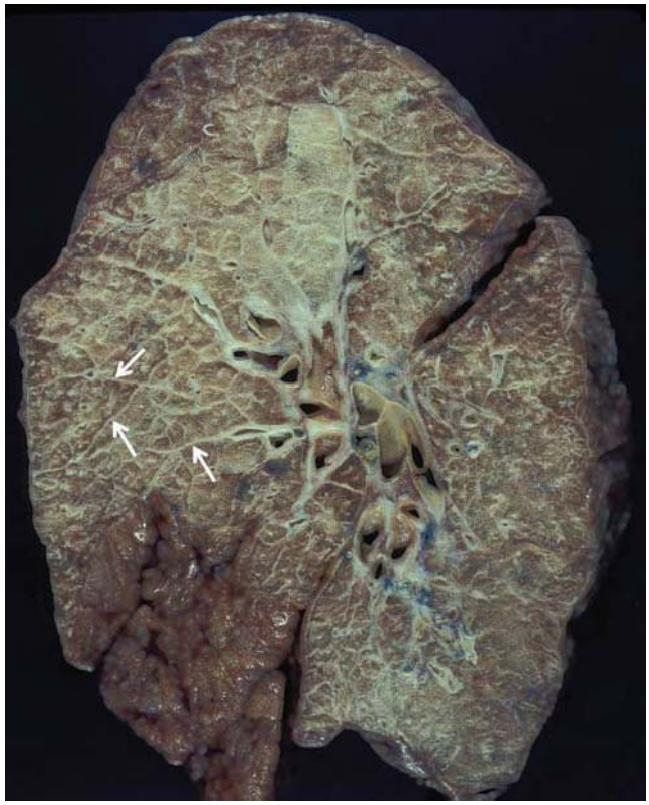

FIGURE 2.2. Interlobular septal thickening. Gross photograph of thickened interlobular septa (*arrows*) in a case of lymphangitic carcinoma.

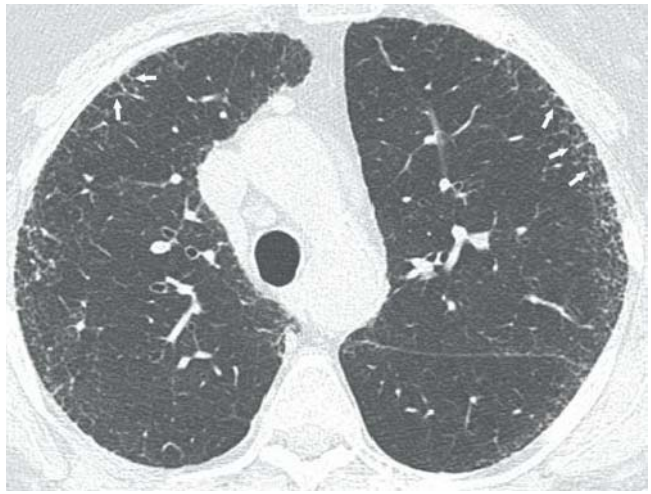

FIGURE 2.3. Reticular pattern. HRCT shows small interlacing irregular lines (*arrows*) separated by only a few millimeters in the periphery of both lungs. The patient had mild UIP.

Reticular Pattern (=Reticulation)

A reticular pattern is characterized by innumerable, interlacing linear opacities that suggest a mesh (Fig. 2.3).[5] It results from small irregular intralobular linear opacities separated by only a few millimeters. Reticulation typically reflects thickening of the interstitium within the secondary pulmonary lobule. It is most commonly caused by fibrosis but may also be seen in various other conditions. To suggest the presence of fibrosis it must be associated with distortion of the parenchymal architecture, traction bronchiectasis, and traction bronchiolectasis. Architectural distortion is characterized by abnormal displacement of bronchi, vessels, interlobar fissures, or interlobular septa. Traction bronchiectasis and bronchiolectasis respectively represent irregular bronchial and bronchiolar dilatation caused by surrounding retractile pulmonary fibrosis (Figs. 2.4 and 2.5).[5]

Cystic Pattern and Honeycombing

A cystic pattern on HRCT refers to the presence of multiple round, air-containing parenchymal spaces with well-defined walls (Fig. 2.6).[5] The definition on CT is therefore distinct from the histologic definition of a cyst as any round circumscribed space that is surrounded by an epithelial or fibrous wall. The HRCT term is commonly used to describe enlarged thin-walled airspaces seen in patients with LAM (Fig. 2.7) or LCH and to the thicker-walled honeycomb cysts seen in patients with end-stage fibrosis.

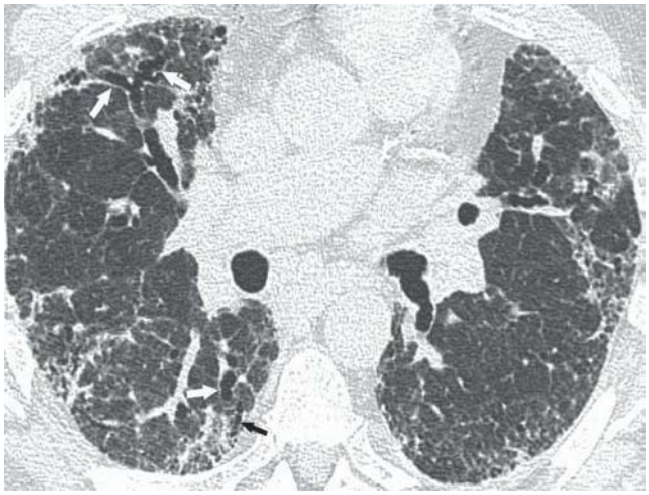

FIGURE 2.4. Reticular pattern with traction bronchiectasis and bronchiolectasis—HRCT demonstrates small interlacing irregular lines forming a reticular pattern mainly in the peripheral lung regions associated with irregular dilatation of the bronchi within areas of fibrosis (traction bronchiectasis) (*white arrows*). Dilated airways within a few millimeters from the pleura represent traction bronchiolectasis (*black arrow*). The patient had idiopathic pulmonary fibrosis with extensive interstitial fibrosis.

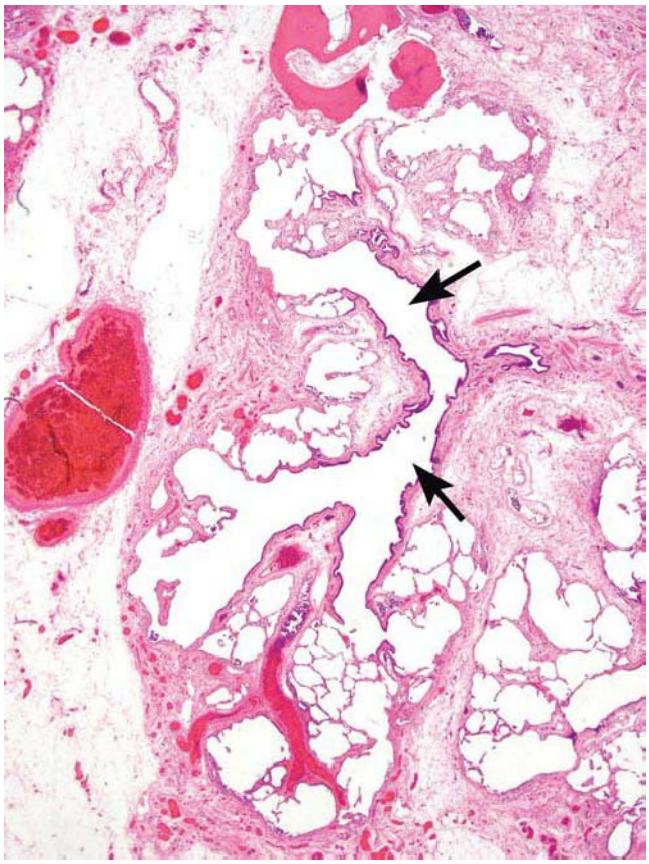

FIGURE 2.5. Microscopic appearance of traction bronchiolectasis (*arrows*) in a case of UIP. The dilated bronchioles are held open by surrounding fibrous tissue and do not narrow toward the periphery.

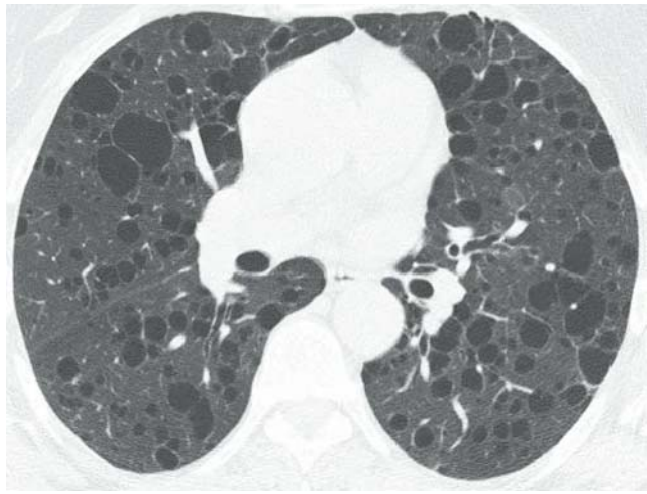

FIGURE 2.6. Cystic pattern. HRCT shows multiple bilateral circumscribed air-containing spaces ranging from a few millimeters to approximately 2 cm in diameter with fine smooth walls. The patient was a 55-year-old woman with LAM.

Honeycombing is characterized on HRCT by the presence of clustered cystic air spaces with well-defined walls and usually measuring 3 to 10 mm in diameter (Figs. 2.8 and 2.9).[5] It is usually predominantly subpleural and associated with other findings of fibrosis including reticulation, traction bronchiectasis, and traction bronchiolectasis.

Nodular Pattern

A nodular pattern in ILD is characterized by the presence of numerous round opacities measuring less than 1 cm in diameter. It results from expansion of the parenchymal interstitium by a roughly spherical cellular infiltrate,

FIGURE 2.7. Cystic pattern. Gross appearance of cysts in LAM.

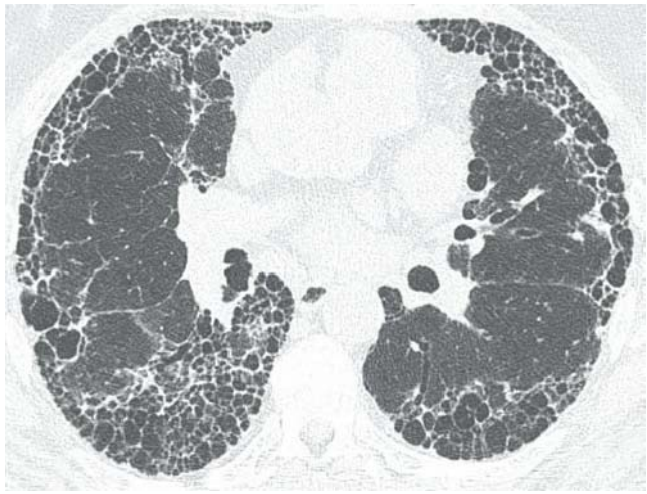

FIGURE 2.8. Honeycombing. HRCT demonstrates multiple clustered cystic air spaces with well-defined walls in the subpleural regions of both lungs. The patient had end-stage idiopathic pulmonary fibrosis.

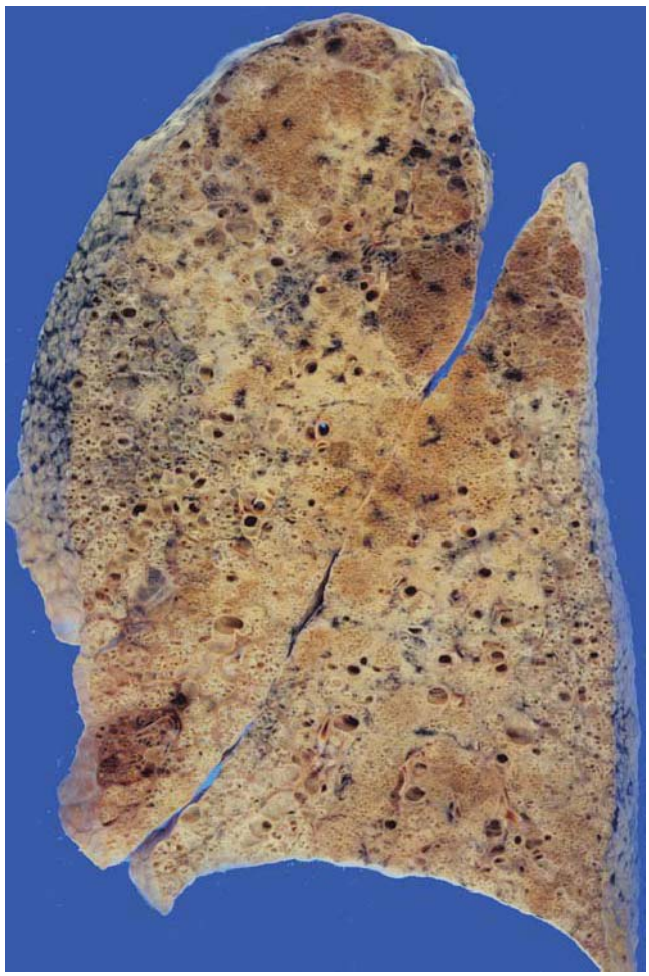

FIGURE 2.9. Gross appearance of UIP with honeycombing. There is extensive peripheral honeycombing appearing as fibrous-walled cysts under the pleura and in some areas extending deep into the lung parenchyma.

fibrous tissue, or both. On HRCT the distribution of the nodules can be classified into three types: perilymphatic, centrilobular, and random.[5]

A perilymphatic distribution on HRCT is characterized by a predominance along the lymphatic routes in lungs, that is, along the pleura, interlobular septa, and bronchovascular bundles (Fig. 2.10). ILDs characterized by a perilymphatic distribution include sarcoidosis (Fig. 2.11) and lymphangitic spread of cancer.

Centrilobular nodular opacities are recognized on HRCT by their typical location a few millimeters away from the pleura, interlobar fissures, interlobular septa, major vessels, and bronchi (Fig. 2.12). They reflect the presence of bronchiolocentric ILD or bronchiolitis. Centrilobular nodules are typically seen in hypersensitivity pneumonitis and in various forms of bronchiolitis including respiratory bronchiolitis, respiratory bronchiolitis with interstitial lung disease (RBILD), and infectious bronchiolitis.

Randomly distributed nodules are those with a haphazard distribution in relation to structures of the lung and secondary lobule. Small nodules in a random distribution are seen most commonly in miliary tuberculosis, miliary fungal infections, and hematogenous metastases.

Ground-Glass Pattern

A ground-glass pattern consists of a hazy increase in opacity without obscuration of the underlying vascular margins (Fig. 2.13).[5] If the vessels are obscured, the term consolidation is used. GGO reflects the presence of abnormalities below the resolution limit of CT. It is a common and nonspecific pattern that can result from partial filling of airspaces, interstitial thickening (due to fluid, cells, or fibrosis), partial atelectasis of alveoli, increased capillary blood volume, or a combination of these.

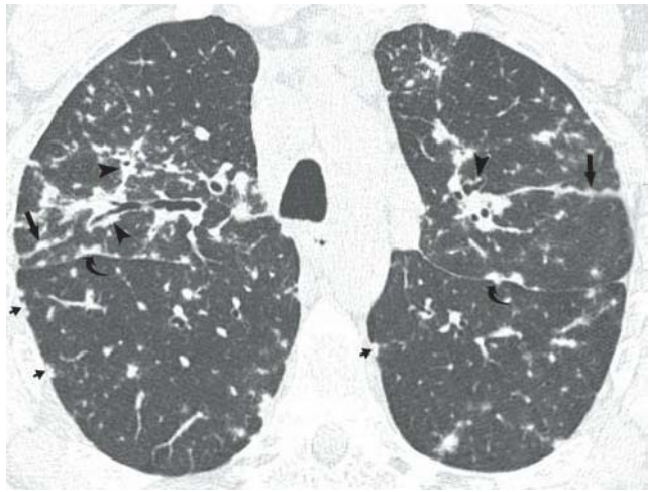

FIGURE 2.10. Nodular pattern in a perilymphatic distribution—HRCT shows bilateral small irregular nodules. The nodules are distributed mainly along the interlobular septa (*straight arrows*), interlobar fissures (*curved arrows*), costal pleura (*small arrows*), and along the bronchi (*arrowheads*) characterizing a perilymphatic distribution.

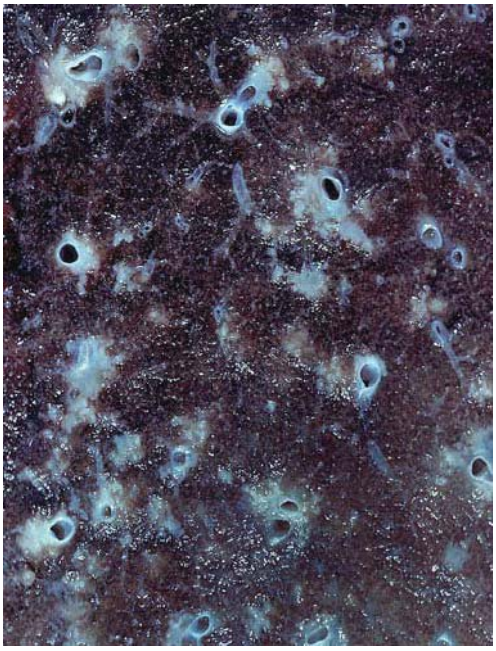

FIGURE 2.11. Gross appearance of sarcoid. Granulomas appear as small white nodules around the bronchovascular bundles.

Consolidation

Consolidation on HRCT refers to a homogeneous increase in pulmonary parenchymal attenuation that obscures the margins of vessels and airway walls (Fig. 2.14).[5] Usually it reflects histopathologic consolidation, that is, presence of exudate or material that replaces alveolar air, rendering the lung solid. However, it may occasionally also result from severe interstitial disease such as may occur in sarcoidosis (pseudoalveolar sarcoid).

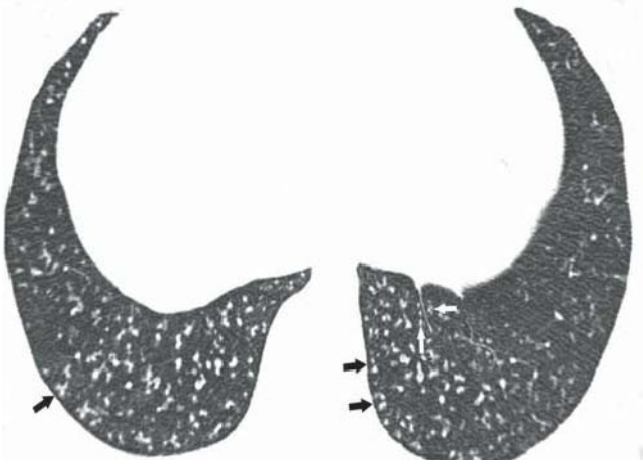

FIGURE 2.12. Nodular pattern in a centrilobular distribution—HRCT demonstrates small bilateral nodules that are clustered a few millimeters away from the pleura (*black arrows*) and the interlobular septa (*white arrows*) characterizing a centrilobular distribution. The patient was a 20-year-old woman with infectious bronchiolitis.

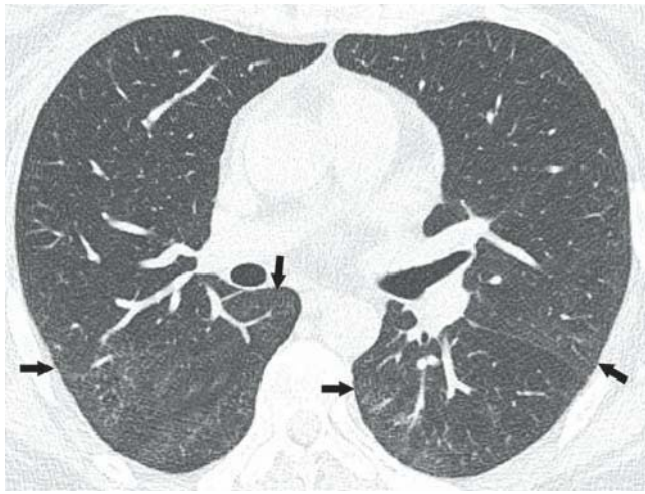

FIGURE 2.13. Ground-glass pattern—HRCT shows bilateral areas of hazy increase in opacity without obscuration of the underlying vascular margins involving the posterior lung regions (*arrows*). The patient was a 47-year-old woman with collagen vascular disease and NSIP.

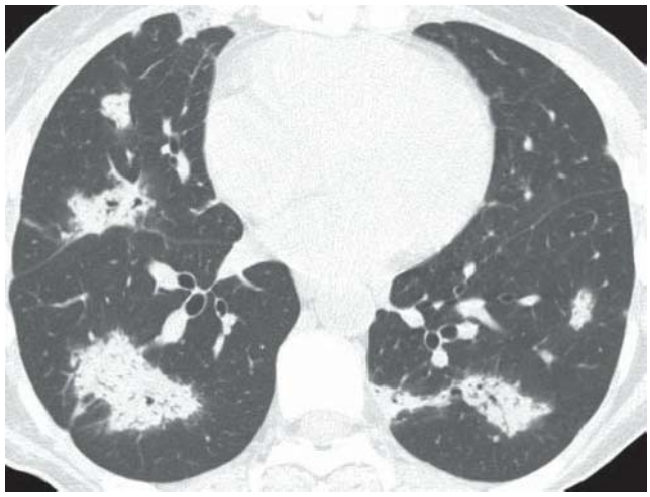

FIGURE 2.14. Consolidation—CT image demonstrates bilateral patchy areas of homogeneous increase in attenuation with obscuration of the underlying vessels. The patient was a 49-year-old woman with BOOP.

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CHAPTER

3

Biopsy Choices and Handling in Interstitial Lung Disease

TYPES OF BIOPSIES SUITABLE FOR EVALUATING ILD

Low-power architecture is the key to diagnosis in many interstitial lung disease (ILDs), and the diagnostic features of ILD may be scattered within the parenchyma. Thus the gold standard for ILD is the video-assisted thoracoscopic (VATS) or open lung biopsy (together often referred to as "surgical lung biopsies"), since these specimens provide large areas to examine. But to be of any use, VATS and open biopsies must be of an adequate size; we suggest that the smallest diameter of an adequate biopsy should be at least 2 cm, and with modern surgical staplers, it is common to receive biopsies of 7 or 8 cm in length.

Core needle biopsies are intended for the diagnosis of *mass* lesions and since, with the exceptions of nodular bronchiolitis obliterans organizing pneumonia (BOOP), and, arguably, Langerhans cell histiocytosis (LCH), ILDs are never mass lesions, core biopsies are not suitable for diagnosing ILD. Patterns that look like BOOP (see Chapter 5) (Fig. 3.1) or cellular nonspecific interstitial pneumonia (NSIP) (see Chapter 7) (Fig. 3.2) can sometimes be found in core biopsies but should be reported as nonspecific, since BOOP in this setting is most likely the edge of some other process and NSIP never forms a mass. For the same reason dense fibrosis in a core (Fig. 3.3) does not represent a fibrosing interstitial pneumonia such as usual interstitial pneumonia (UIP). We advise against reporting these patterns as BOOP or "interstitial fibrosis" because such diagnoses are easily misinterpreted as being specific.

Transbronchial biopsies in patients with putative ILD are a frequent cause of conflicts between clinicians and pathologists. Transbronchial biopsies have a limited role in this setting,[1] and can be divided into categories of high reliability–high yield (i.e., the diagnosis made on a transbronchial biopsy is accurate and the features of interest are sufficiently frequent in the lung that they are likely to be picked up on transbronchial biopsy); high reliability–low yield (the features of interest are specific if seen but are scattered in the lung [Figs. 3.4 and 3.5] and probably will not be picked up on a transbronchial biopsy); and low reliability (the features seen in the transbronchial biopsy are probably misleading).[2] These categories are summarized in Tables 3.1 to 3.3 and Figures 3.4 to 3.9.

These rules are not absolute and need to be interpreted in context. A pattern of BOOP is not unusual in transbronchial biopsies (Figs. 3.6 and 3.7), but BOOP is seen in many settings; whether it has any clinical meaning in a transbronchial biopsy requires consultation between the clinician, pathologist, and radiologist[1] (see Chapter 5). Occasionally hypersensitivity pneumonitis (HP) can be diagnosed on transbronchial biopsy (Figs. 12.38 and 12.39), but only if there are classic pathologic features and the clinical and radiologic features fit hypersensitivity pneumonitis. Similarly, the finding of diffuse alveolar damage (DAD) may be useful in cases of acute interstitial pneumonia (AIP), but again must be viewed cautiously because a sample showing BOOP or DAD in a transbronchial biopsy may have missed an adjacent important lesion.

Transbronchial biopsies that show just interstitial inflammation (Fig. 3.8) and/or interstitial fibrosis (Fig. 3.9) have no specificity[3] and may be very misleading (e.g., Fig. 3.8) and should be reported as nondiagnostic. We advise against using terms such as "chronic interstitial inflammation" or "interstitial fibrosis" in the diagnosis line because these words tend to be interpreted by clinicians as diagnostic of an ILD.

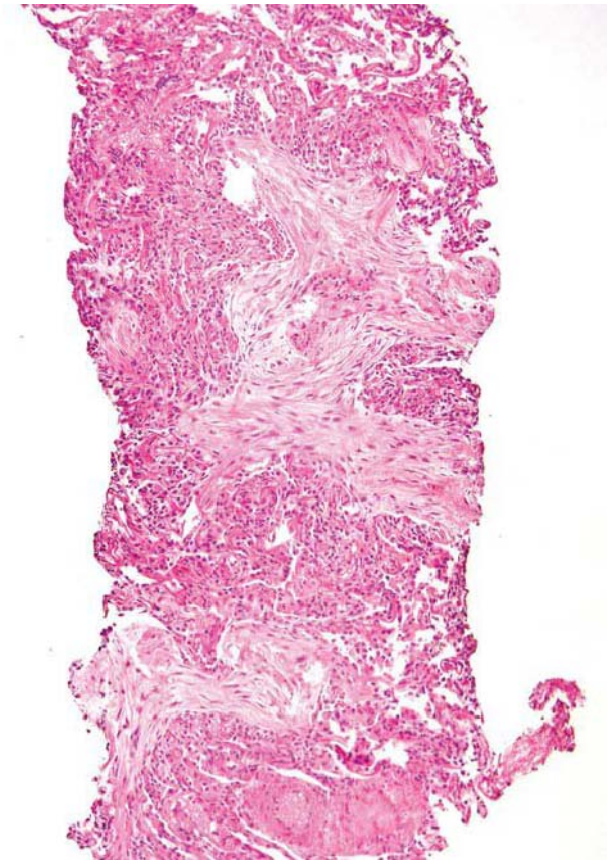
HANDLING VATS AND OPEN LUNG BIOPSIES

Collapsed lung parenchyma makes interpretation of surgical lung biopsies difficult (Figs. 3.10 and 3.11) and produces a false appearance of interstitial inflammation or can even mimic diffuse interstitial fibrosis (see Figs. 24.30 to

Table 3.1

High reliability—high-yield diagnoses on transbronchial biopsy

Malignancies
Transplant rejection
Sarcoid
Infections (with culture results)



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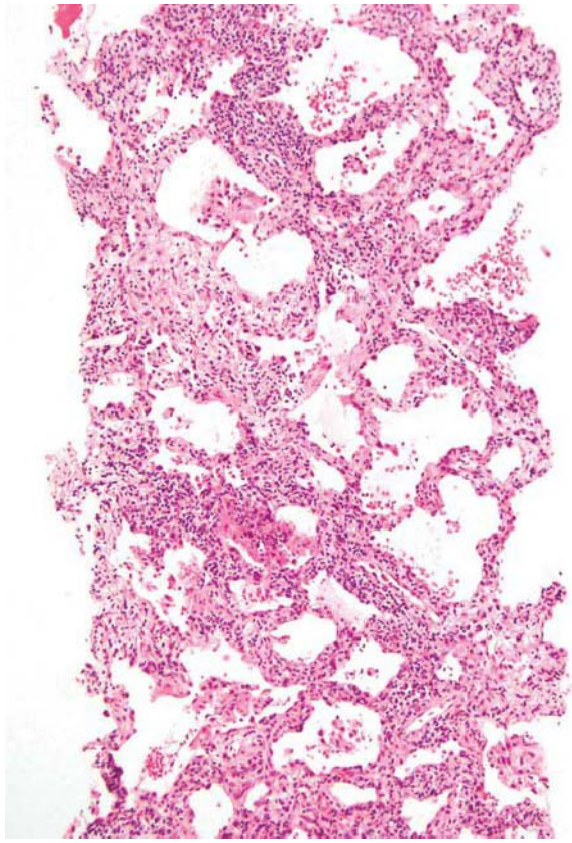

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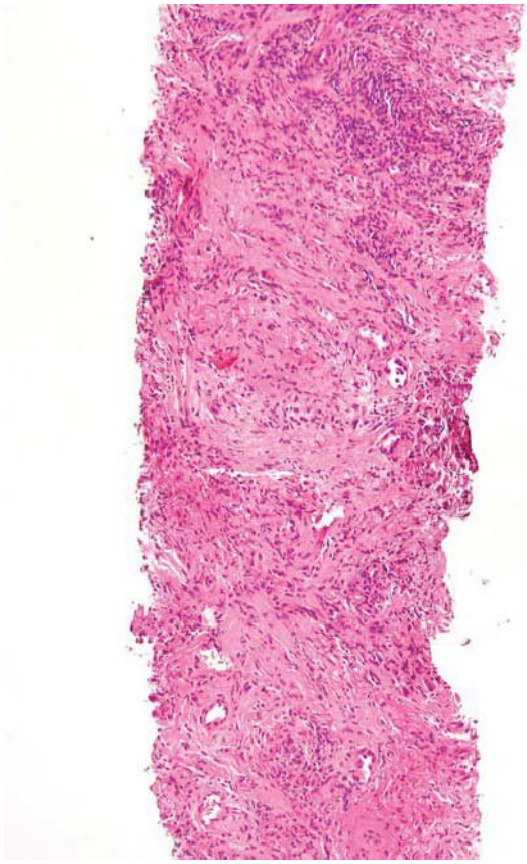


3.3

FIGURES 3.1 to 3.3. Mimics of ILD in core needle biopsies. Figure 3.1 shows a pattern of BOOP, Figure 3.2 shows a pattern mimicking cellular NSIP, and Figure 3.3 dense fibrosis with chronic inflammation. Core needle biopsies are designed for the diagnosis of mass lesions and none of the patterns illustrated here has any significance. We advise reporting these patterns as "nonspecific findings" to avoid misinterpretation.

Table 3.2

High reliability—low-yield diagnoses on transbronchial biopsy

LCH
Alveolar proteinosis
Lymphangioleiomyomatosis (LAM)
Chronic eosinophilic pneumonia
Any process in which a small but very specific feature is diagnostic

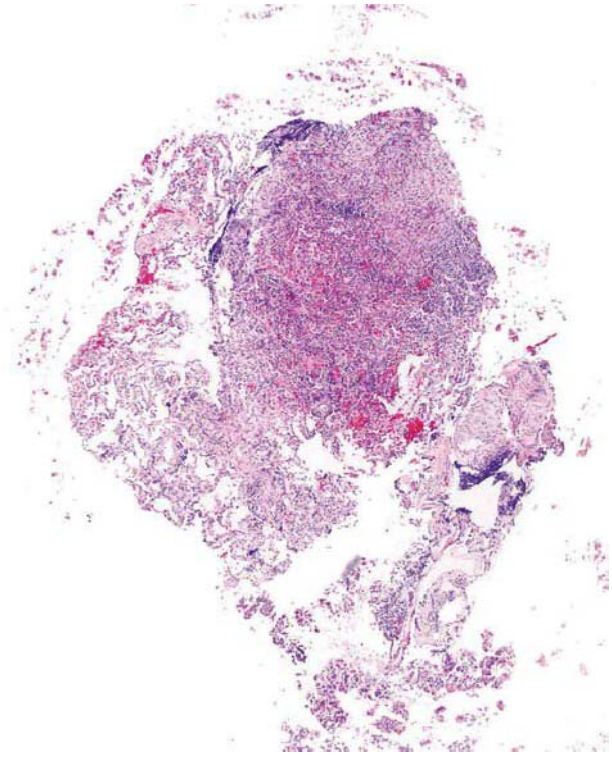
24.33). Collapse cannot be avoided in transbronchial biopsies and that is another reason for such biopsies being often unsuitable for diagnosing ILD. However, misinterpretation related to parenchymal collapse can be avoided by inflating VATS and open biopsies (Fig. 3.12), and we believe that all such biopsies should be routinely inflated with a fixative using a small syringe[4] (Table 3.4). The needle can be pushed through the pleura anywhere; if the biopsy encompasses an interlobular septum only a portion of the specimen may inflate, but simply moving the needle solves this problem. After inflation the whole specimen is put into the fixative.

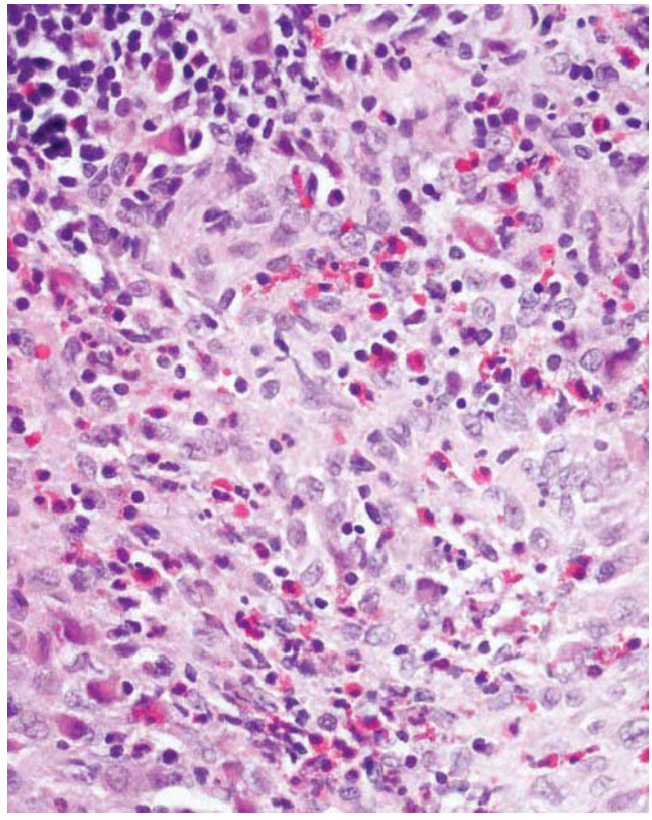
To use this technique the specimen must be received fresh from the operating room because even a short fixation will prevent subsequent inflation. After inflation, fixation time can be anything from 1 hour to overnight. Because low-power architecture is the key to the diagnosis of many ILDs, the biopsy should be cut to give the largest surface that can be blocked and cut; avoid mincing the biopsy into small fragments as small fragments obscure low-power architecture.

Table 3.3

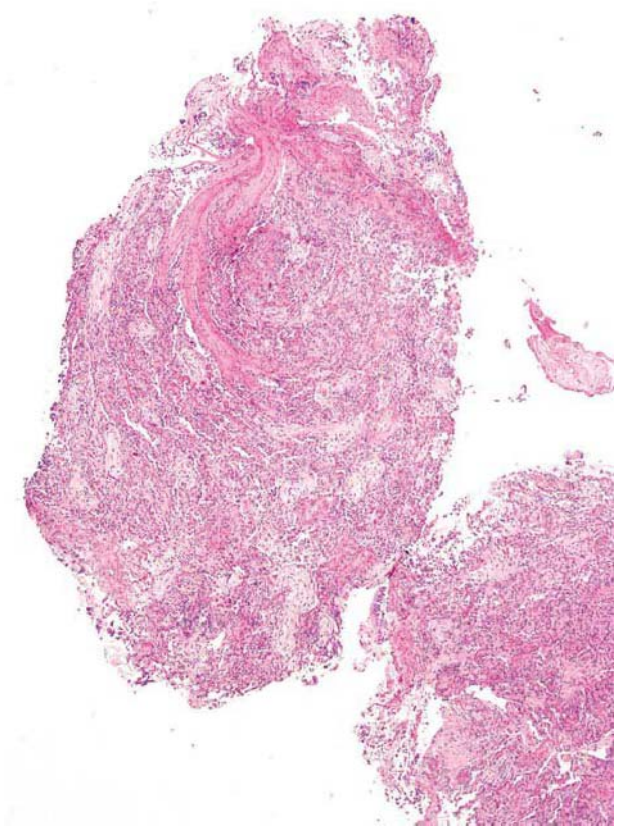
Low-reliability diagnoses on transbronchial biopsy

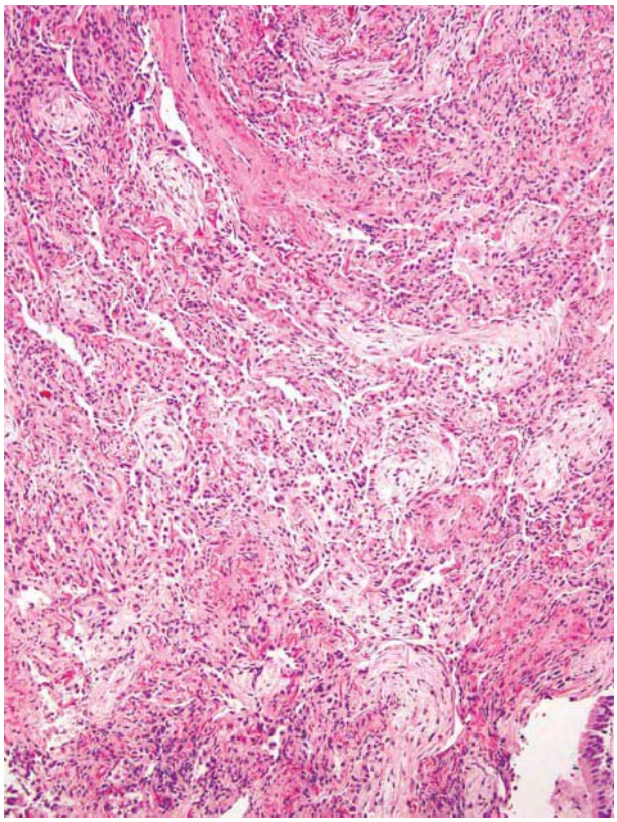
1. Idiopathic interstitial pneumonias
   - UIP
   - DIP/RBILD
   - NSIP
   - BOOP (occasionally accurate in correct clinical/radiologic setting)
2. Processes resembling idiopathic interstitial pneumonias
   - Some pneumoconioses such as asbestosis
   - Interstitial pneumonia-like drug reactions
3. HP
   - Occasionally diagnosis can be made on transbronchial biopsy in correct clinical/radiologic setting
4. ARDS/AIP
   - Occasionally diagnosis can be made on transbronchial biopsy in correct clinical/radiologic setting
5. Any process that depends on a low-power architectural diagnosis





FIGURES 3.4 and 3.5. Lower- and high-power views of LCH in a transbronchial biopsy. Transbronchial biopsy occasionally works for ILD when as here, a specific lesion is diagnostic if found.





FIGURES 3.6 and 3.7. Low- and high-power views of BOOP in a transbronchial biopsy. BOOP in a transbronchial biopsy may be diagnostic if the clinical and imaging findings fit, but more often it is a nonspecific reaction pattern that can be found as a part of other lesions.

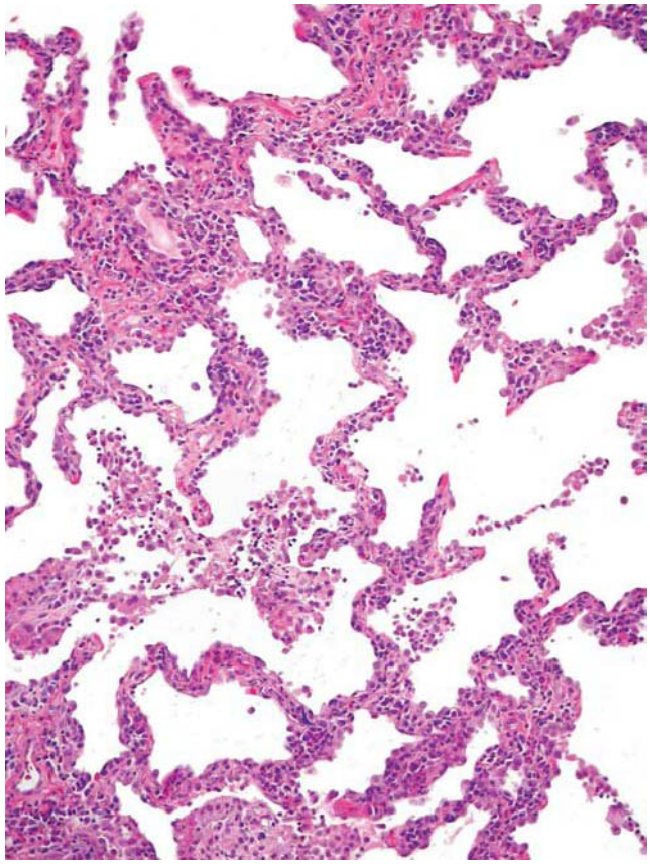


FIGURE 3.8. Chronic interstitial inflammation in a transbronchial biopsy. This finding is almost always nonspecific and should not be diagnosed as chronic interstitial inflammation. The present example is taken from the edge of a nodular lesion of Wegener granulomatosis, a condition that is not any form of ILD.

HANDLING FROZEN SECTIONS OF ILD BIOPSIES

In general we advise against frozen sections of ILD because they interfere with morphologic preservation. However, if a frozen section is absolutely necessary, for example, in putative AIP, the wedge should be inflated in a fashion similar to that described in Table 3.4, but with a 50:50 mixture of OCT™ or similar frozen section medium and saline (straight OCT will not go through a needle).[5] A portion of the specimen can then be frozen and cut, and the remainder placed directly into fixative. This approach avoids collapse artifacts, which are even more difficult to interpret in frozen sections than in paraffin sections.

HANDLING WEDGES AND WHOLE LOBES/LUNGS

Most large wedge biopsies are intended for the diagnosis of neoplasms, as are most lobectomies and pneumonectomies, excepting of course explanted lungs from

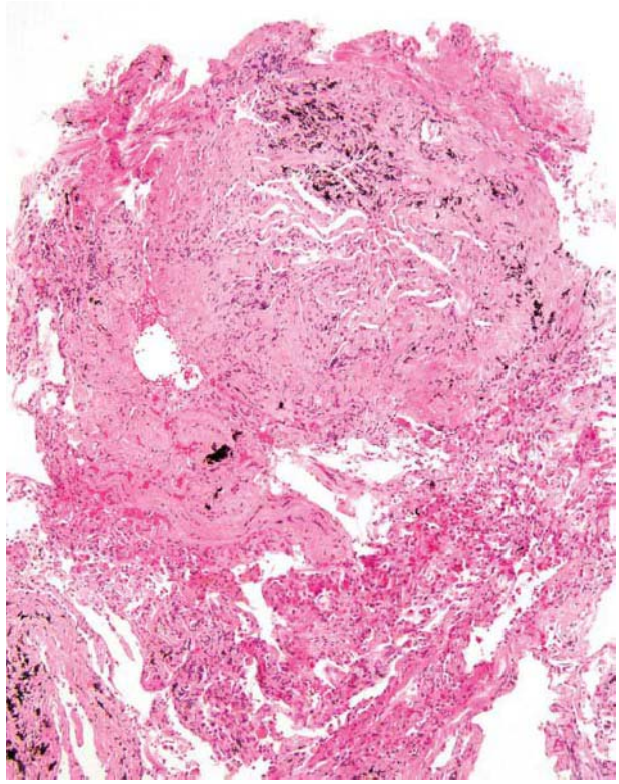
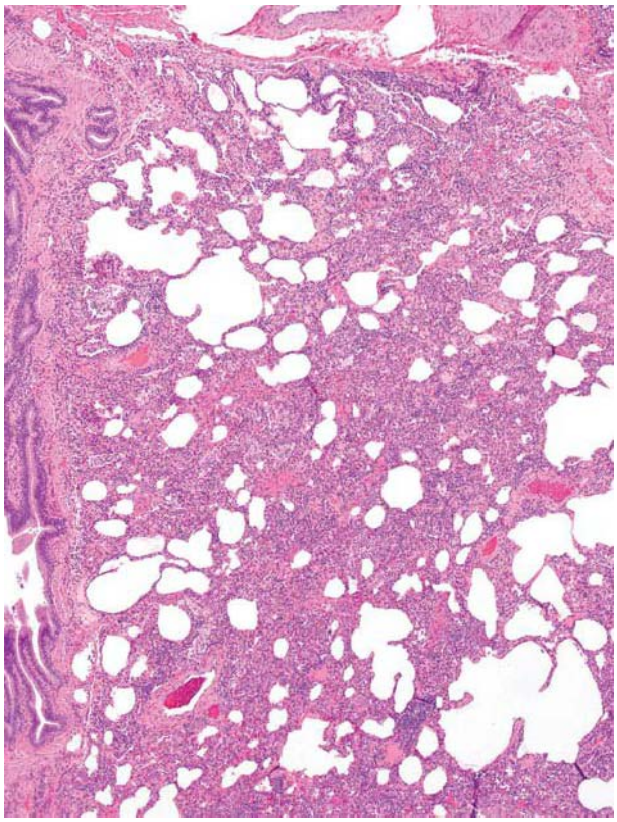
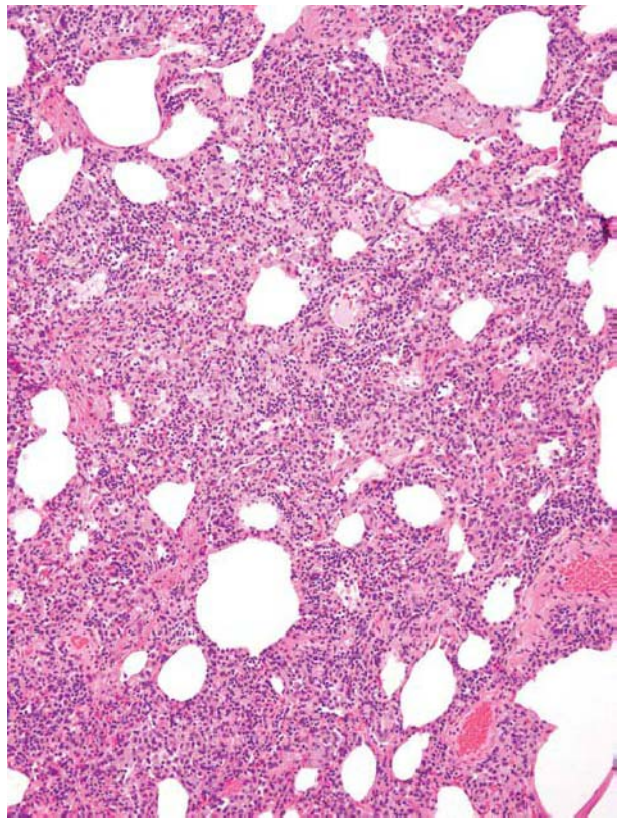


FIGURE 3.9. Fibrosis in a transbronchial biopsy. This finding is always nonspecific and should not be called "interstitial fibrosis" least it be misinterpreted as a form of ILD.





FIGURES 3.10 and 3.11. A completely collapsed surgical lung biopsy. The circular airspaces are a hint that the biopsy is collapsed (see Chapter 24). The biopsy is uninterpretable. We advise inflating all surgical lung biopsies using the method described in the text to avoid this problem.

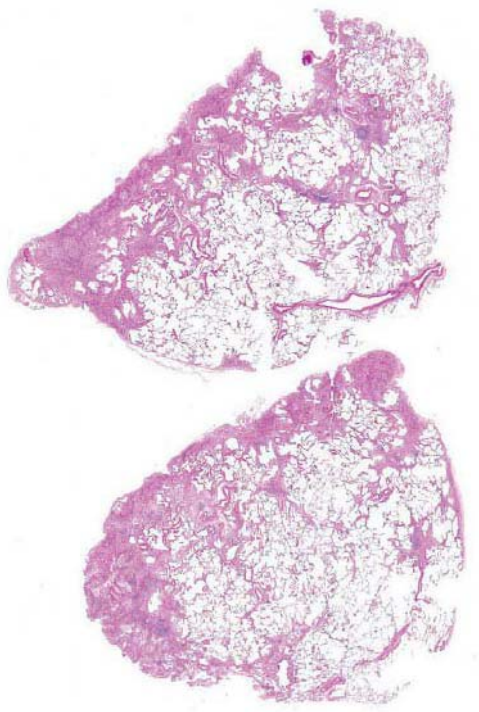


FIGURE 3.12. An inflated surgical lung biopsy. The diagnosis of UIP is readily apparent, even at scanning power.

TABLE 3.4

Procedure for inflating VATS and open lung biopsies

Specimen must be received fresh from the operating room
Inflate gently with fixative using a small syringe and small (20G or smaller) needle
Put inflated specimen into fixative for 1 hour minimum
Cut to give the largest blockable surface

transplantation. Such specimens may nonetheless harbor an ILD, and we believe that all should be inflated, whether for neoplastic or nonneoplastic lung disease, because collapse artifacts produce just as many interpretation problems in large as in small specimens. Where a suitable bronchus is present, inflation through the bronchus with a tube and plastic nipple connected to a tank of fixative works well; after inflation the bronchus is clamped and the whole specimen put into fixative. For wedges without a bronchus, a 50-cc syringe and a large bore (14G to 18G) needle can be used, putting the needle through the pleura in as many places as necessary to get the whole specimen inflated. No specific inflation pressure is required. Resected specimens generally should be fixed overnight and then breadloafed (e.g., Figs. 2.2 and 2.9).

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2. Churg A. Lung biopsy, lung resection, and autopsy lung specimens: handling and diagnostic limitations. In: Churg A, Myers J, Tazelaar H, et al., eds. *Thurlbeck's Pathology of the Lung*. 3rd ed. New York, NY: Thieme Medical Publishers; 2005:95–108.
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4. Churg A. An inflation procedure for open lung biopsies. *Am J Surg Pathol*. 1983;7:69–71.
5. Gianoulis M, Chan N, Wright JL. Inflation of lung biopsies for frozen section. *Mod Pathol*. 1988;1:357–358.

CHAPTER

4

Acute Interstitial Pneumonia

NOMENCLATURE ISSUES

To a clinician "acute lung injury" is a mild form of acute respiratory distress syndrome (ARDS). However, "acute lung injury" has been proposed by Katzenstein[1] as a way of referring to both diffuse alveolar damage (DAD) (the pathologic finding in acute interstitial pneumonia [AIP] and ARDS) and bronchiolitis obliterans organizing pneumonia (BOOP) (also called cryptogenic organizing pneumonia [COP] or just organizing pneumonia [OP]; see Chapter 5), and some pathologists diagnose "acute lung injury" on biopsies.

We advise avoiding the use of "acute lung injury" as a pathologic term. For one thing it confuses clinicians; for another, the clinical and radiologic features as well as prognosis and treatment of ARDS/AIP/DAD, and BOOP are quite different. Although there are some morphologic overlaps, for the most part DAD and BOOP can be separated microscopically (see below). In the relatively rare situation where the separation is unclear on biopsy, consultation with the radiologist usually solves the problem, since BOOP tends to appear predominantly as peribronchovascular and peripheral consolidation (Figs. 5.1 and 5.2), whereas DAD on imaging typically results in widespread ground-glass opacities (GGOs) and dependent consolidation (see section Imaging Features). The clinical story is different as well: DAD usually has an acute course, abrupt onset, and severe hypoxemia, whereas BOOP typically has a time course of a few weeks to a few months and is usually accompanied by systemic symptoms such as fever but modest levels of hypoxemia.

DEFINITION

Historically, AIP was first described by Hamman and Rich in the 1930s and for many years there was confusion between what was called "Hamman–Rich syndrome" and usual interstitial pneumonia (UIP).[2] The modern term acute interstitial pneumonia was coined by Katzenstein et al.[3]

AIP is simply idiopathic ARDS; that is, ARDS (pathologic DAD) in a patient who has no known predisposing cause. However, many patients ultimately diagnosed as AIP give a history of a preceding upper respiratory tract infection (URI), and it is likely that most cases of AIP are manifestations of a viral infection. Apart from the history, AIP cannot be separated on clinical, radiologic, or pathologic grounds from ARDS/DAD of any other cause (Table 4.1).

CLINICAL FEATURES

Patients with AIP present with severe hypoxemic respiratory failure, sometimes developing over a few weeks after a URI; however the severe shortness of breath typically develops over a few days. By definition, such patients do not have evidence of a (culture-provable) infection, nor do they have any other condition that would predispose to ARDS.

IMAGING FEATURES

The findings are those of DAD.[4] The acute or exudative phase is characterized on HRCT by the presence of bilateral GGOs and progressive consolidation (Fig. 4.1). There is often a sharp demarcation between areas of involved and apparently normal lung resulting in a geographic appearance.[4]

Table 4.1

Causes of a pathologic picture of DAD

Idiopathic = "acute interstitial pneumonia"
Infections
- Sepsis (usually Gram negative bacteria)
- Viral, fungal, pneumocystis pneumonias
- Severe bacterial pneumonia

Aspiration of gastric contents (acid)
Inhalation of toxic gases
- Smoke, oxygen, different fumes and chemicals

Shock
Lung trauma, head trauma
Metabolic disorders
- Pancreatitis, uremia

High exposure to a sensitizing agent
- Acute eosinophilic pneumonia

Drug reactions
Fat and amniotic fluid emboli
Collagen vascular disease (e.g., "lupus pneumonitis")
Near drowning
IV or lymphatic contrast material
Diffuse pulmonary hemorrhage (usually not associated with a clinical picture of ARDS)

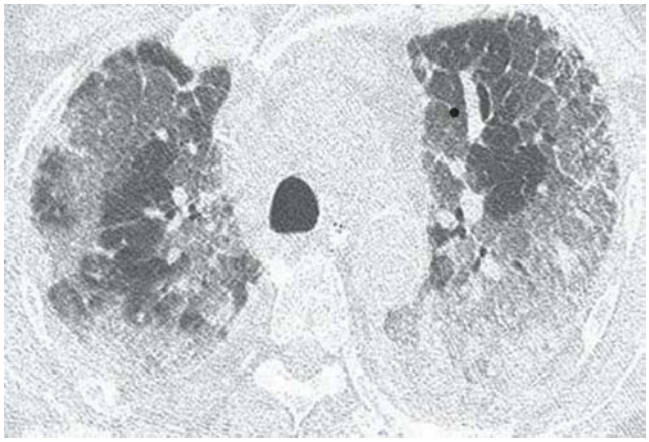


FIGURE 4.1. AIP. HRCT image at the level of the upper lobes demonstrates almost complete whiteout of both lungs. The abnormalities consist of extensive bilateral GGOs and patchy areas of consolidation involving mainly the dependent lung regions. The patient was an 86-year-old man.

The consolidation may be patchy or confluent and tends to involve mainly the dependent regions of the lower lobes (Fig. 4.1). Reticulation and bronchial dilatation develop in the proliferative phase. The fibrotic phase is characterized by GGOs associated with reticulation, traction bronchiectasis, and bronchiolectasis, and, in some cases, honeycombing.

PATHOLOGIC FEATURES

Although the original description of AIP[3] illustrated a pattern that mimicked an interstitial process (Figs. 4.12 and 4.13) (hence the name, and also the inclusion of AIP in lists of idiopathic interstitial pneumonias; see Chapter 1), cases of AIP can show any pathologic pattern seen in ordinary ARDS/DAD, and we have illustrated this chapter with both AIP and ARDS cases since they are morphologically indistinguishable.

At autopsy lungs from cases of AIP are typically very heavy, often more than 1,000 g each, very firm, and demonstrate effacement of the normal finely granular surface seen in fixed inflated and cut lungs (Fig. 4.2).

Microscopically AIP/DAD can be divided into the acute or exudative phase, the organizing or proliferative phase, and the fibrotic phase (Table 4.2). The acute phase is characterized by hyaline membranes (Figs. 4.3 and 4.4) and is readily recognized, but the organizing phase shows several patterns (Figs. 4.5 to 4.17) and can be confused with BOOP when the picture is one of granulation tissue plugs in respiratory bronchioles and alveolar ducts (Fig. 4.7). Table 4.3 offers some clues to separating DAD and BOOP in the equivocal case (Figs. 4.7 to 4.10). One helpful point is that in BOOP the granulation tissue plugs tend to have distinct borders and are usually separated from the underlying parenchyma, whereas in DAD the granulation tissue plugs often blend into the surrounding parenchyma (Figs. 4.8 and 4.9). However, organizing DAD can have areas that are indistinguishable from BOOP (Fig. 4.7).

FIGURE 4.2. Gross appearance of DAD at autopsy. Note the effacement of the normal surface granularity. This lung weighed more than 1,000 g, a common finding in DAD.

Table 4.2

Microscopic features of AIP (DAD)

Acute (exudative) phase (1–6 days after injury)

Necrosis of pneumocytes, endothelial cells
Hyaline membranes in alveolar ducts
Collapse of alveolar parenchyma
Diffuse alveolar hemorrhage in some cases

Organizing (proliferative) phase (as early as 2–3 days after injury but usually later)

Numerous morphologic patterns
Early
- Organization of hyaline membranes
- Formation of airspace granulation tissue
- Squamous metaplasia

Late
- Dense collagenization of airspace granulation tissue
- Alveolar duct ("ring") fibrosis
- "Interstitial pneumonia" pattern = interstitial-appearing granulation tissue secondary to parenchymal collapse

Fibrotic phase (usually after several weeks on respirator)

Cystic spaces with densely fibrotic walls

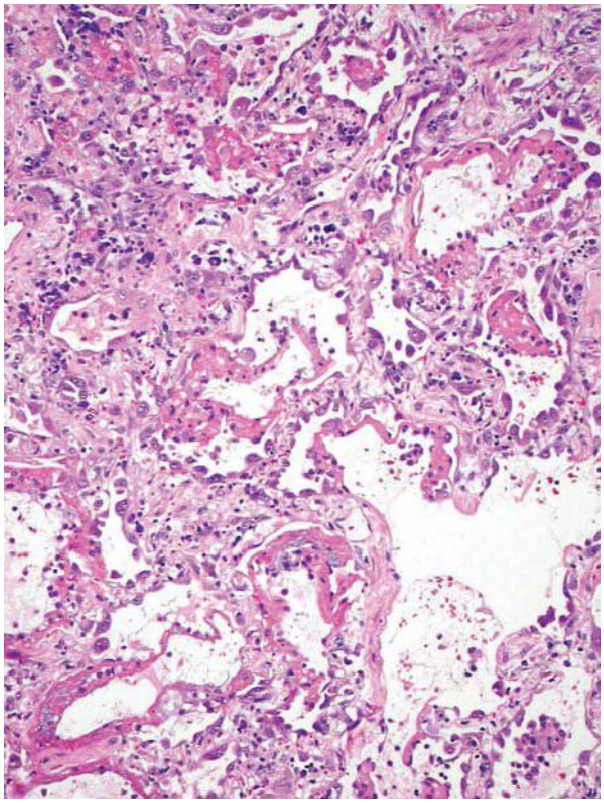


FIGURE 4.3. Exudative phase of DAD from the same case of AIP shown in Figure 4.1. Note the hyaline membranes and the very large reactive alveolar lining cells. There is parenchymal collapse. All the microscopic appearances illustrated in this chapter can be seen in DAD of any cause, including ARDS and AIP.

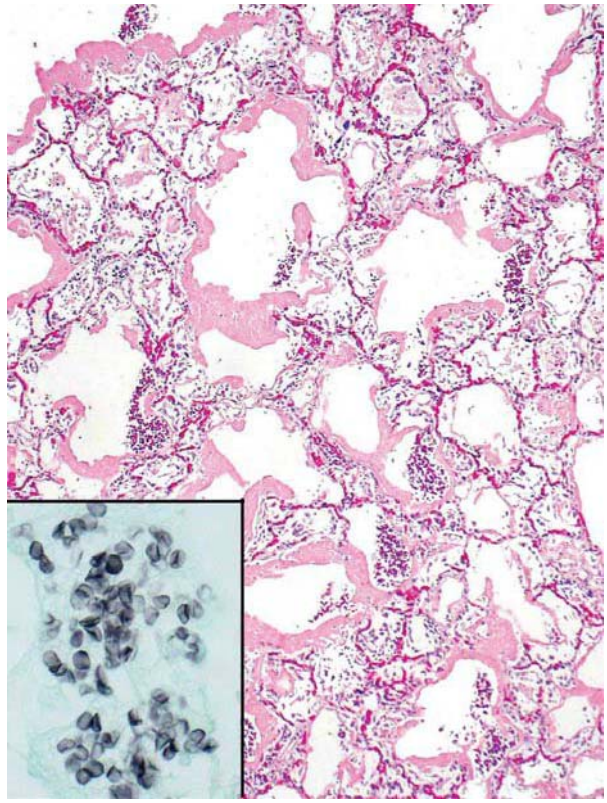


FIGURE 4.4. Early exudative phase of DAD with prominent hyaline membranes but no parenchymal collapse. This case was actually caused by pneumocystis (*inset*). We recommend staining all DAD cases with silver methenamine because pneumocystis produces no hint of its presence on H&E stain.

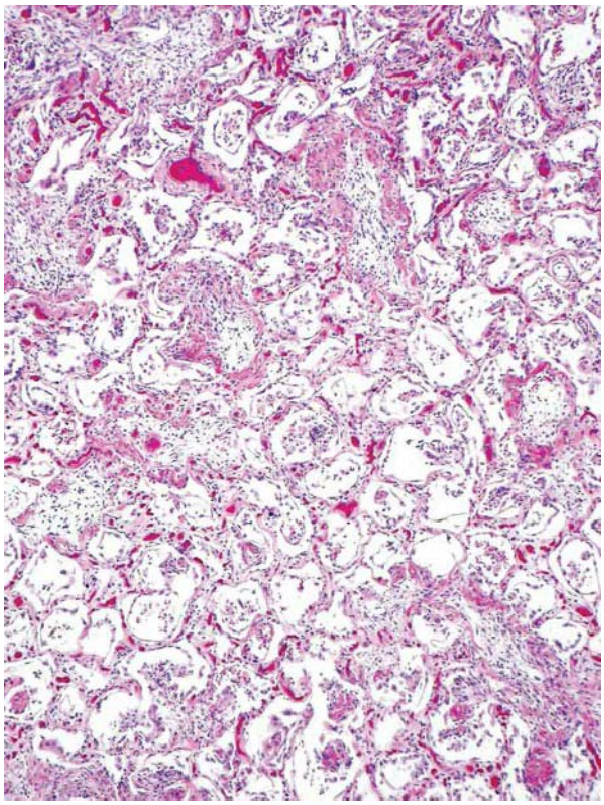


FIGURE 4.5. Early organizing phase of DAD with granulation tissue plugs in airspaces.

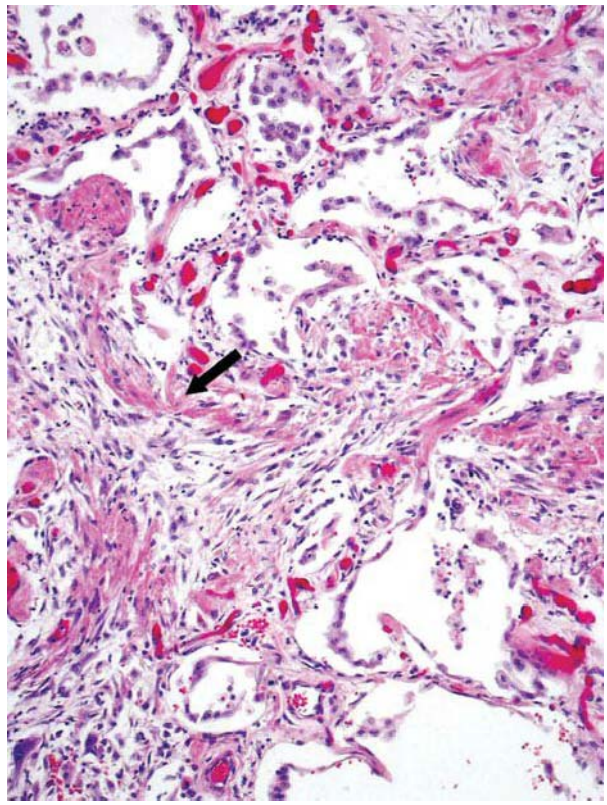
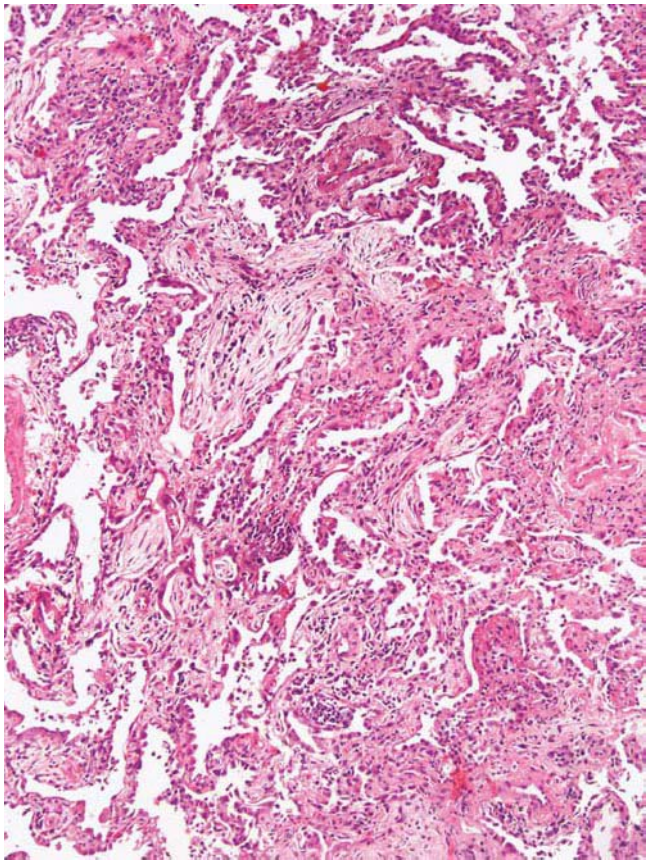


FIGURE 4.6. Higher-power view of Figure 4.5. Note the remnants of hyaline membranes in the granulation tissue (*arrow*).



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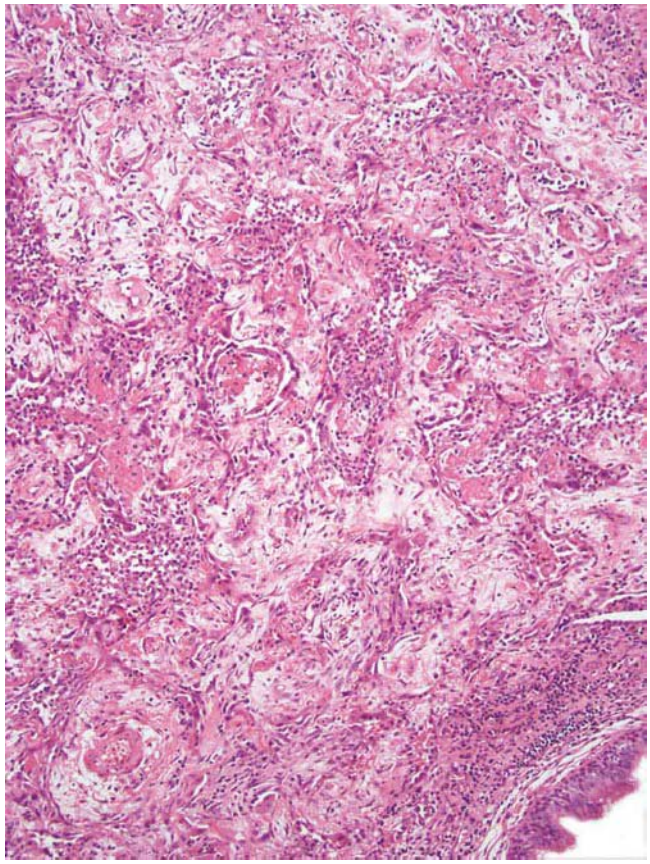

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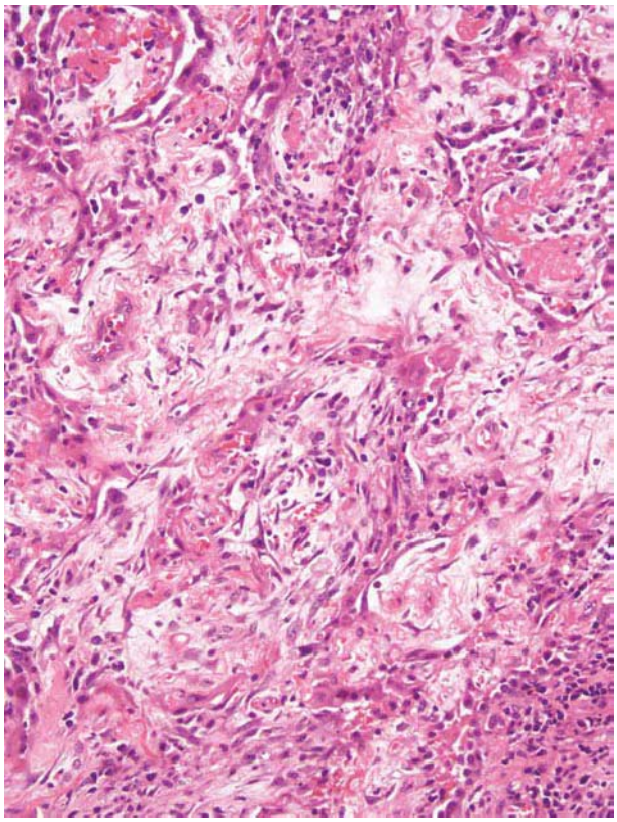

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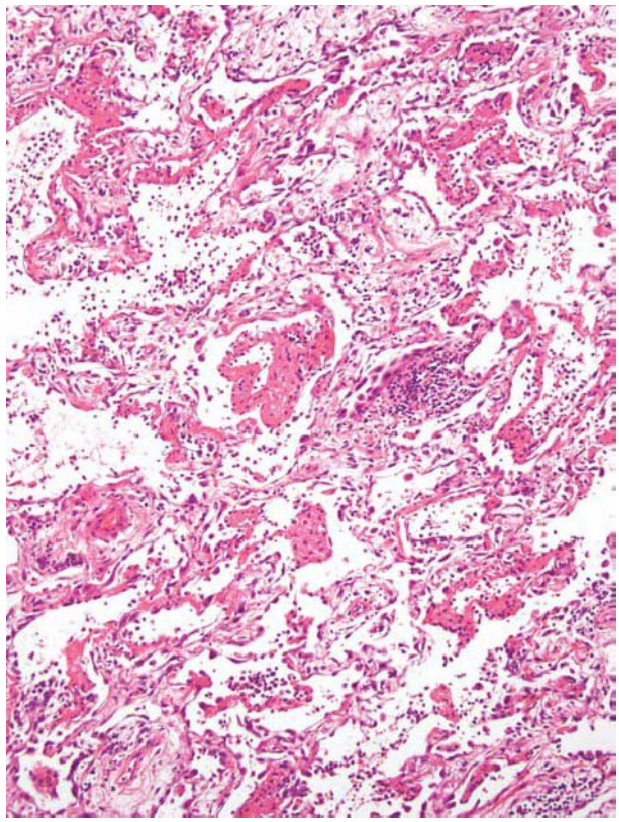


4.10

FIGURES 4.7. to 4.10. All from the same case. **Figure 4.7**: Organizing DAD with granulation tissue plugs in alveolar ducts. **Figure 4.7** is indistinguishable from BOOP (Chapter 5) but **Figures 4.8** and **4.9** show a pattern of organization (granulation tissue that fades off into the surrounding parenchyma) not seen in BOOP, and **Figure 4.10** shows hyaline membranes. Finding areas as in **Figure 4.8** or **Figure 4.10** is a useful way to sort out BOOP from organizing DAD.

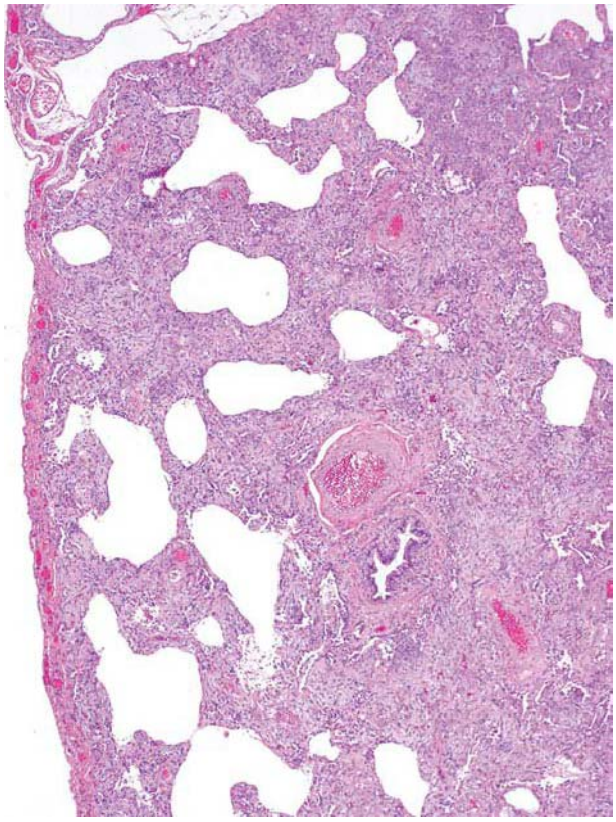


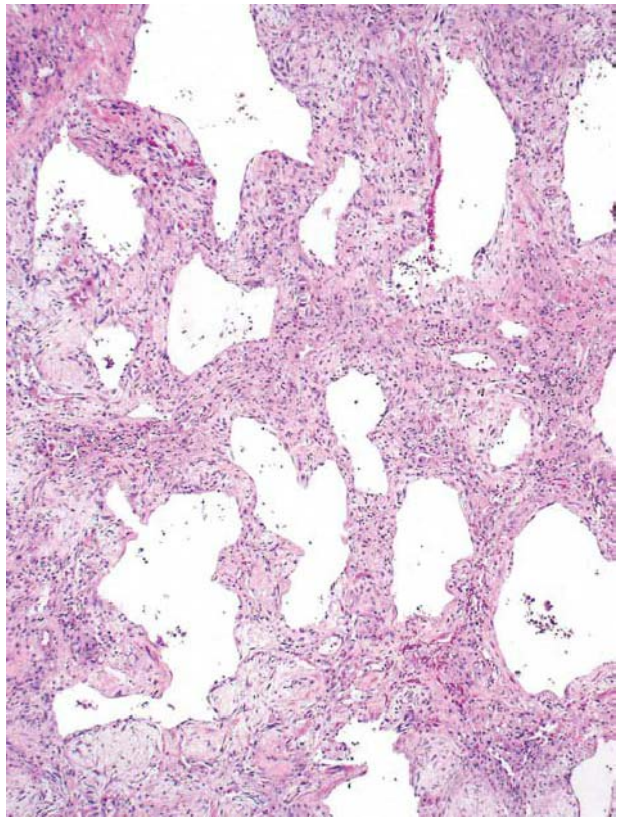
FIGURE 4.11. Parenchymal collapse in organizing DAD. This pattern is typical of DAD and helps to separate organizing DAD from BOOP.

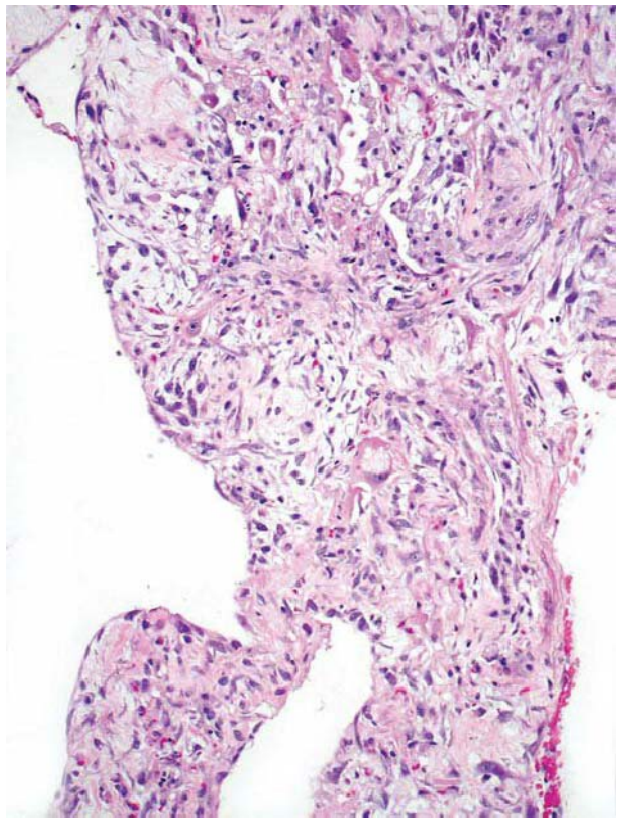
Despite the name, the granulation tissue in AIP/DAD is never really interstitial; rather this appearance is an artifact caused by parenchymal collapse (Figs. 4.12 and 4.13). Squamous metaplasia is rare in BOOP and is a good clue that one is dealing with organizing DAD (Fig. 4.18), as is collapse of the parenchyma leaving only the respiratory bronchioles and alveolar ducts open (Fig. 4.11).

The fibrotic phase appears grossly as lungs with fibrotic but fairly thin-walled cysts (Fig. 4.19) and microscopically as cysts with densely fibrotic walls (Fig. 4.20). This pattern is seen only after weeks on a respirator and is uncommon with modern respirator settings.

DETERMINATION OF ETIOLOGY

Frequently the clinician has a very good idea that the process in question is clinically AIP/ARDS, and a biopsy is performed in an attempt to find a specific and hopefully treatable etiology. Most of the time such biopsies simply show the features of DAD, but Table 4.4 provides a list of pathologic findings that may indicate etiology. Because pneumocystis can hide in DAD (Fig. 4.4), we suggest doing fungal/pneumocystis stains in all cases, even in patients who are not known to be immunocompromised.





FIGURES 4.12 and 4.13. "Interstitial" pattern in a case of organizing DAD. This is the pattern originally described by Katzenstein in AIP. The interstitial pattern is actually an artifact caused by parenchymal collapse.

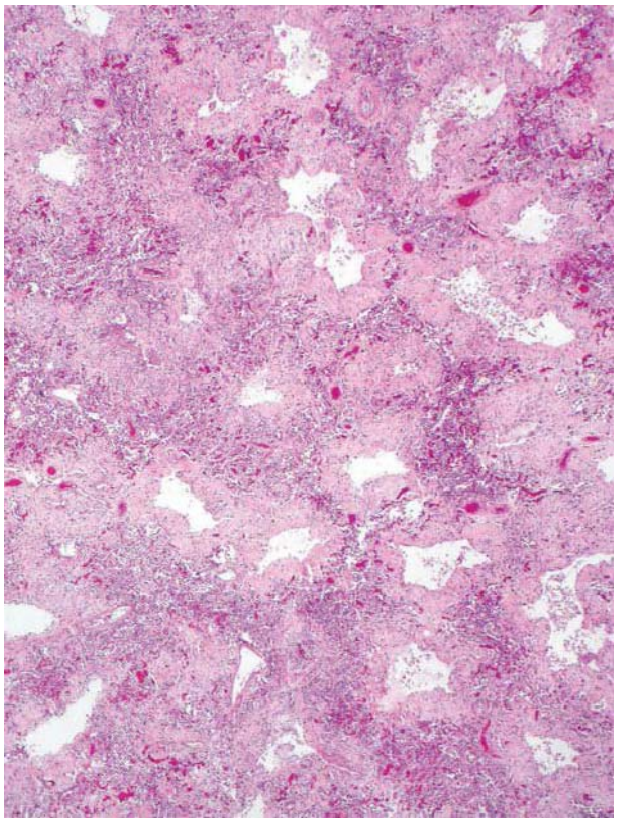


FIGURE 4.14. Organizing DAD with fibrosis of alveolar ducts. This is one of many patterns of organization of DAD.

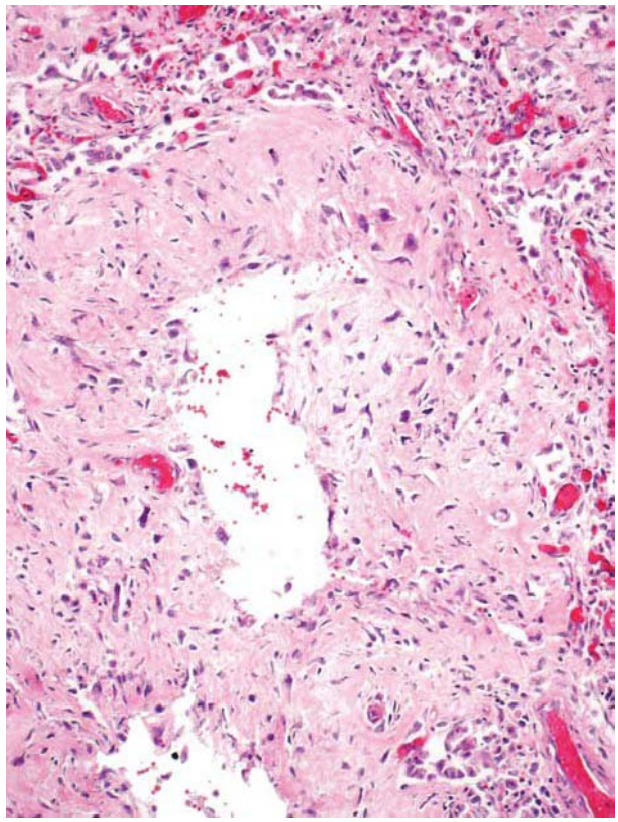


FIGURE 4.15. Higher-power view of Figure 4.12 showing dense fibrous tissue forming a ring around an alveolar duct. This process represents organization of hyaline membranes.

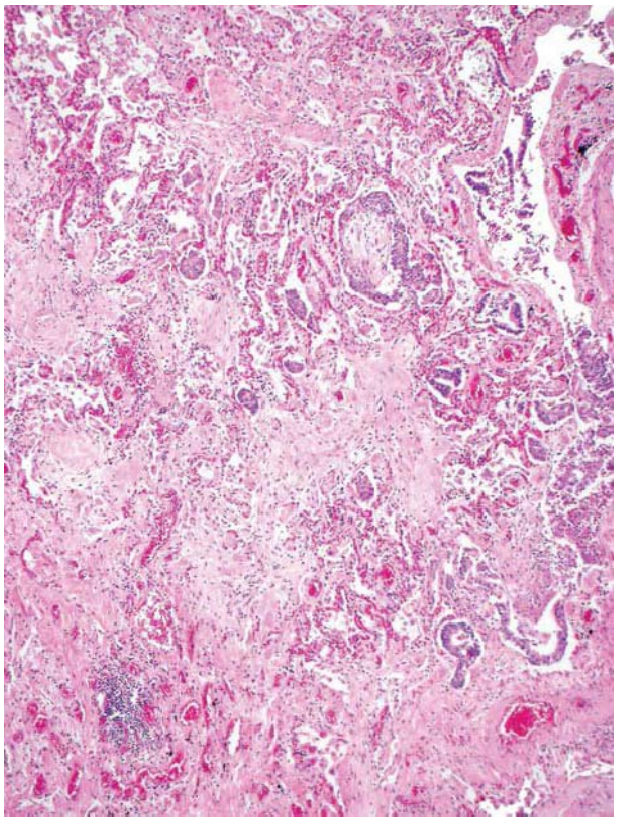


FIGURE 4.16. Organizing DAD showing dense airspace granulation tissue.

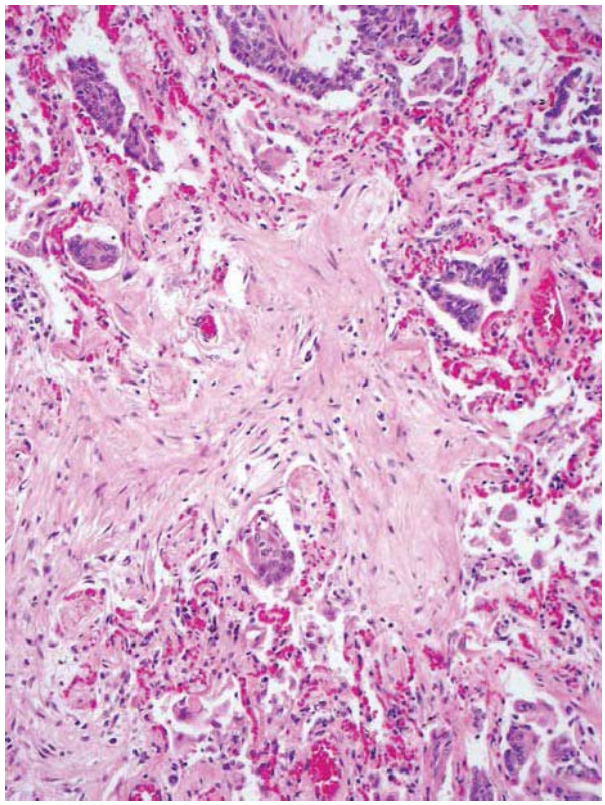


FIGURE 4.17. Higher-power view of Figure 4.13. Dense airspace granulation tissue is a pattern of organization of DAD and is rare in BOOP where the granulation tissue is typically much looser (see Chapter 5).

Table 4.3

Separation of organizing DAD (AIP/ARDS) from BOOP

Organizing DAD	BOOP
Parenchymal collapse with dilated respiratory bronchioles and alveolar ducts	No parenchymal collapse
Hyaline membranes or remnants often present	Hyaline membranes never present
Granulation tissue may merge into surrounding parenchyma	Granulation tissue usually separated from parenchyma
Granulation tissue may appear to be interstitial	Granulation tissue always purely in alveolar ducts and respiratory bronchioles
Granulation tissue may appear dense	Granulation tissue always loose
Granulation tissue may form dense rings around alveoli ducts	Alveolar duct rings never present
Squamous metaplasia often present	Squamous metaplasia rarely present

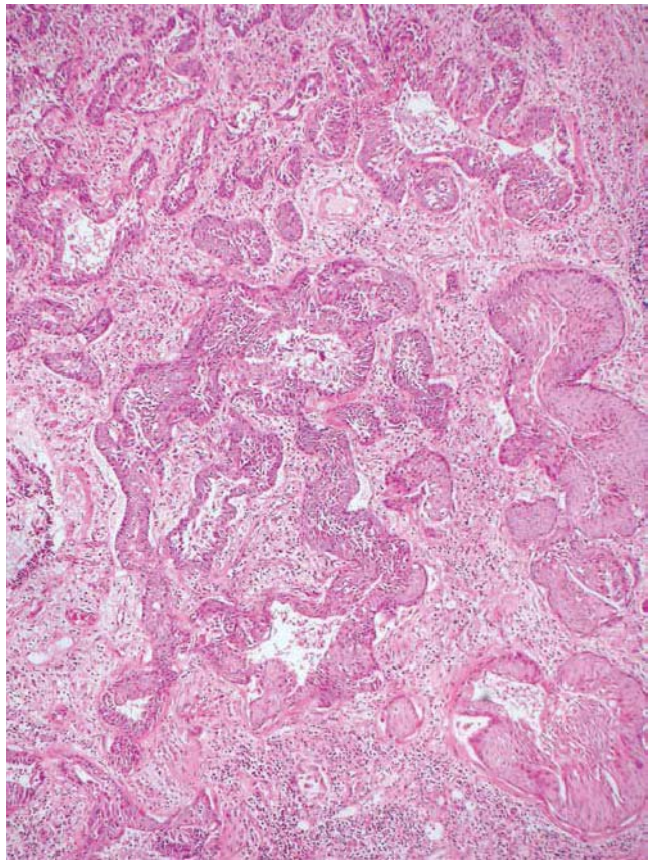


FIGURE 4.18. Extensive squamous metaplasia in organizing DAD. Squamous metaplasia in this setting can be cytologically very atypical, but the fact that the metaplastic epithelium follows the outline of alveolar ducts and does not form a mass lesion is evidence against a neoplastic process.

DIAGNOSTIC MODALITIES

Hyaline membranes may be picked up in transbronchial biopsies. Given a clinical and imaging setting of ARDS/AIP, a diagnosis of DAD can be allowed, but there is always a danger that such biopsies miss evidence of an etiologic agent. Organizing DAD can be very difficult to recognize in a transbronchial biopsy and the distinction from BOOP may be impossible. Video-assisted thoracoscopic surgery (VATS) biopsies are more useful in this regard.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of AIP/ARDS/DAD is shown in Table 4.5. Acute exacerbation of UIP is the development of new diffuse pulmonary infiltrates and new respiratory impairment in a patient with UIP. By definition the infiltrates cannot be caused by infection or heart failure.[5,6] On imaging acute exacerbations show diffuse GGOs and/or consolidation with evidence of underlying fibrosis (Fig. 4.21). Microscopically the acute process looks like DAD or BOOP superimposed on UIP (Figs. 4.22 to 4.25).[6]

In most cases of acute exacerbation the patient is known to have underlying UIP, but sometimes UIP presents for the first time as an acute exacerbation. The important microscopic clue to the diagnosis is the presence of old dense fibrosis (Figs. 4.22 and 4.24) something that is never part of DAD or BOOP. In a recent series of 58 cases of DAD on surgical lung biopsy, 12 turned out to be AIP and 7 acute exacerbations of UIP.[7]

Acute exacerbations also occur occasionally in other forms of fibrosing interstitial pneumonia including chronic hypersensitivity pneumonitis (Chapter 12), asbestosis (Chapter 22), fibrotic nonspecific interstitial pneumonia (NSIP) (Chapter 7), and desquamative interstitial pneumonia (DIP) (Chapter 8).[6] Additional discussion of acute exacerbations is provided in Chapter 6.

Diffuse hemorrhage is occasionally seen in acute DAD. However, it can also be a manifestation of vasculitis, and the DAD may be secondary to the hemorrhage. The presence of hemosiderin-laden macrophages, indicating that hemorrhage has been present for several days, and/or capillaritis is suggestive of vasculitis.

Eosinophils are ordinarily not seen in DAD, and their presence should raise a question of acute eosinophilic pneumonia (see Chapter 15 and Figs. 4.26, 4.27). This diagnosis is important not to miss because acute eosinophilic pneumonia is the only form of DAD that responds to steroids.[8]

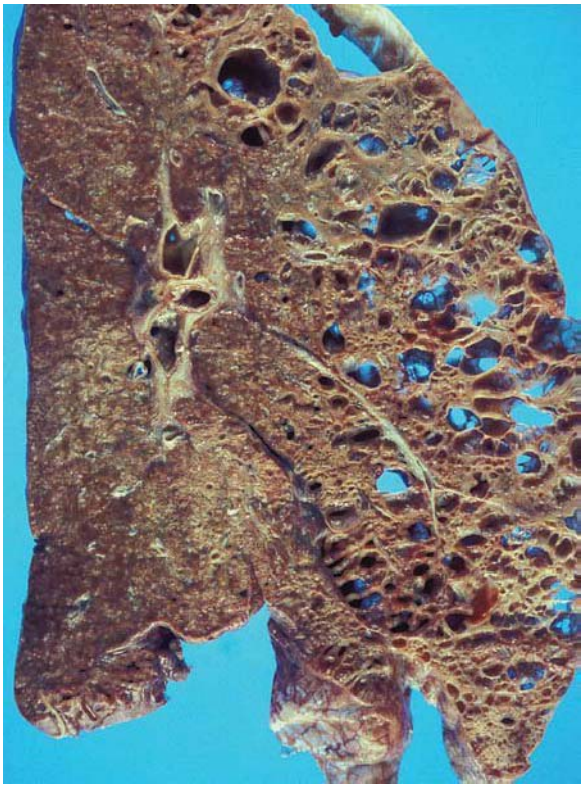


FIGURE 4.19. Fibrotic phase of organizing DAD. This type of lesion is seen only after weeks on a respirator and is rare in modern practice.

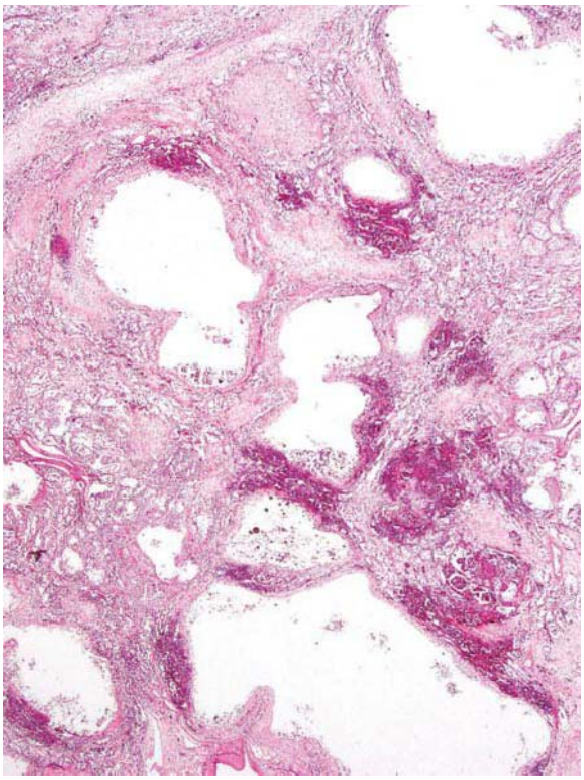


FIGURE 4.20. Microscopic appearance of case shown in Figure 4.16. Cystic spaces with dense fibrous walls somewhat mimic fibrotic NSIP (Chapter 7), but the spaces are larger than one finds in fibrotic NSIP.

Table 4.4

Morphologic findings that suggest a specific etiology of DAD

Visible infectious organisms (pneumocystis, viral inclusions)
Neutrophil collections (implication: infection)
Granulomas (implication: infection, aspiration, drug reaction)
Aspirated food particles
Fat or amniotic fluid emboli
Drug-associated changes (see Chapter 18)
  Foamy macrophages of amiodarone
  Granulomas: methotrexate, anti-TNF agents
Eosinophils = acute eosinophilic pneumonia (see Chapter 15)
Diffuse hemorrhage + capillaritis (implication: vasculitis)

Table 4.5

Differential diagnosis of AIP/ARDS/DAD and features that help in diagnosis

Acute stages

Acute exacerbation of UIP (presence of underlying old fibrosis) (Chapter 6)
Collagen vascular disease-associated ARDS (history/serology)
Drug-induced ARDS (history, occasional specific morphology) (Chapter 18)
Acute eosinophilic pneumonia (presence of eosinophils) (Chapter 15)
Infections (infectious agent by morphology or culture) (Fig. 4.4)
Diffuse hemorrhage (may be part of DAD, but presence of capillaritis implies underlying vasculitis)

Fibrotic stage

Fibrotic NSIP (Chapter 7)

PROGNOSIS

Early reports of AIP[3] indicated a very poor prognosis, but more recent data[9] suggest that survival may be as high as 80%. For ARDS, prognosis depends on the underlying condition; overall survival is currently 60% to 70% but patients with sepsis, advanced age, and multiorgan failure have a worse prognosis.

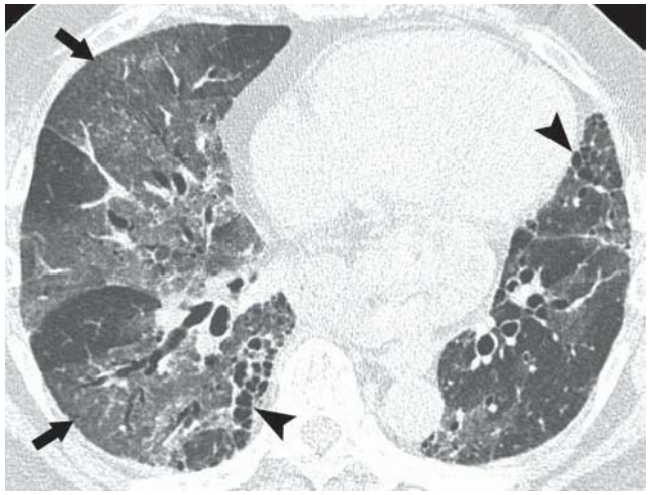


FIGURE 4.21. Acute exacerbation of UIP. HRCT shows extensive bilateral GGOs, patchy mild reticulation, and focal areas of honeycombing (*arrowheads*). Note that there is no definite evidence of fibrosis in the right middle lobe and lateral segment of the right lower lobe (*arrows*). A biopsy of these regions may therefore show only DAD without old fibrosis. The patient had acute exacerbation of UIP secondary to rheumatoid arthritis.

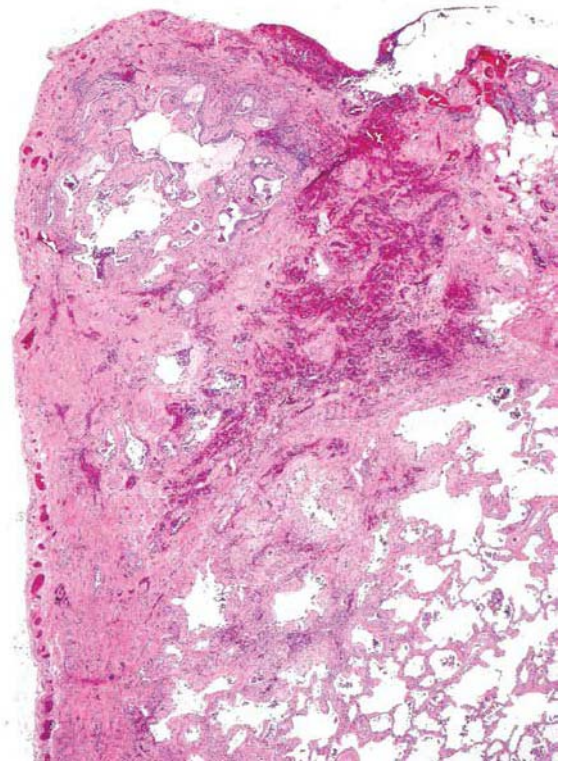


FIGURE 4.22. Acute exacerbation of UIP. This portion of the biopsy shows dense old fibrosis with honeycombing typical of UIP.

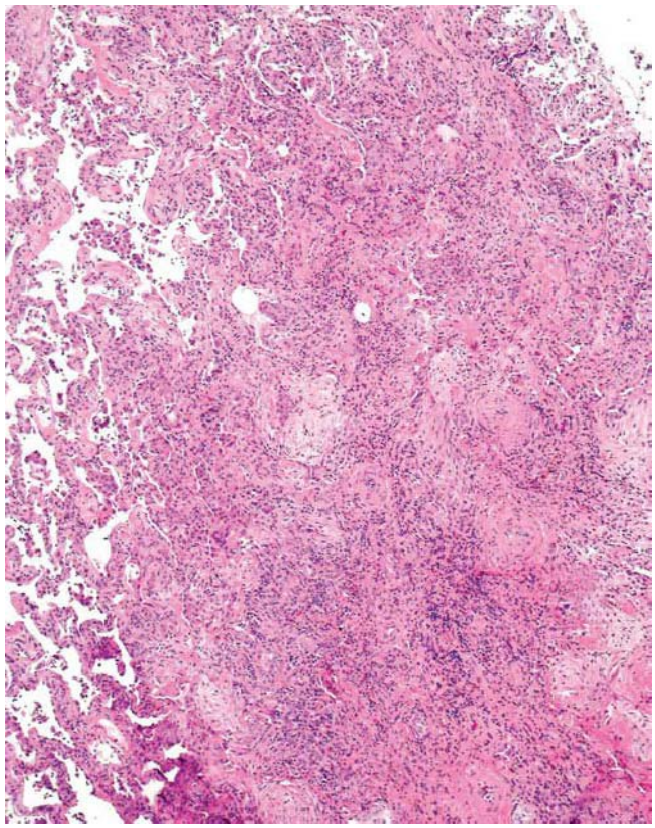


FIGURE 4.23. Acute exacerbation of UIP. Same case as in Figure 4.22. This portion of the biopsy shows organizing DAD. The combination of features in Figures 4.21 and 4.22 allows a diagnosis of acute exacerbation of UIP.

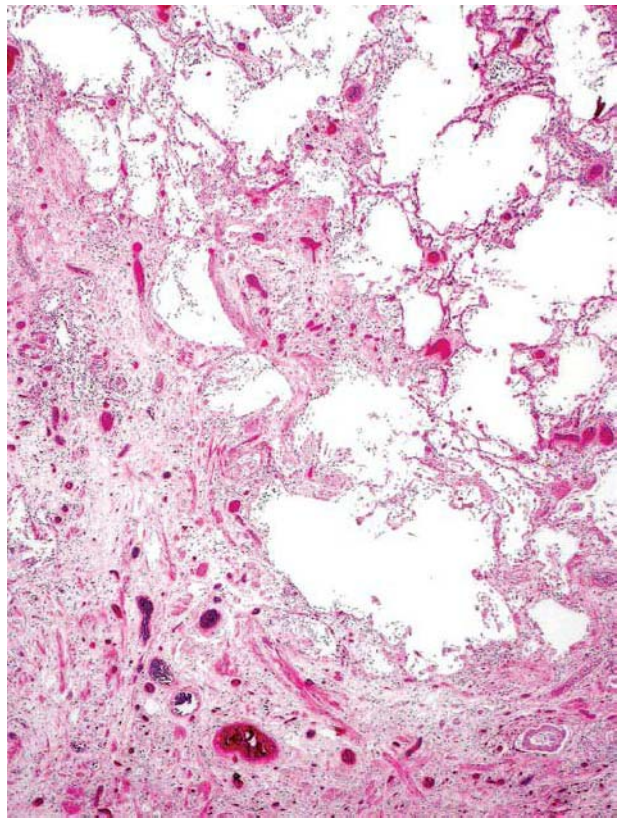


FIGURE 4.24. Acute exaceration of UIP in autopsy lung. This area shows a UIP pattern.

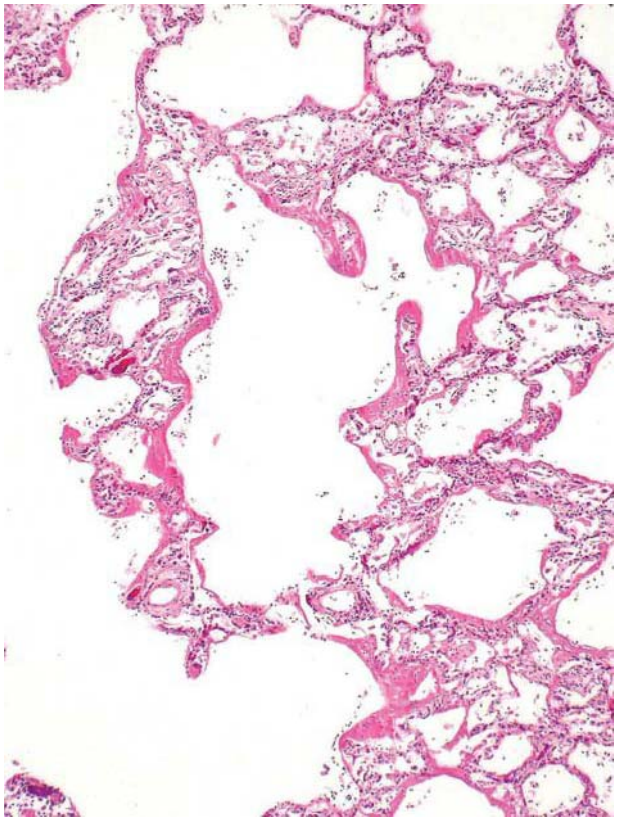
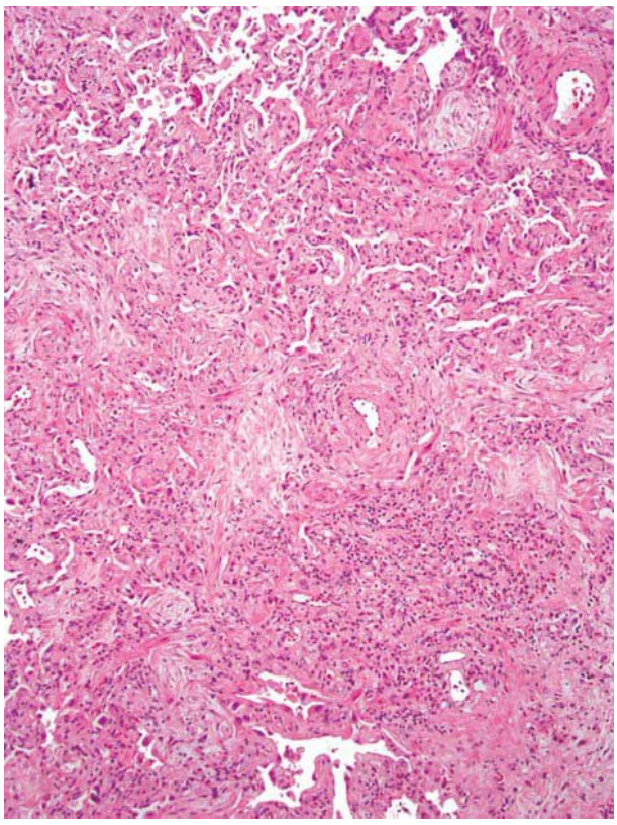
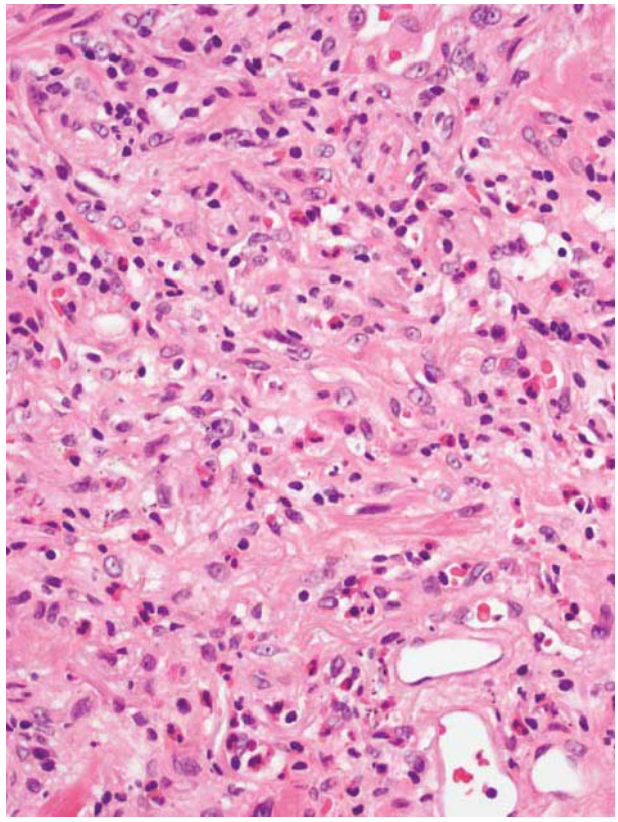


FIGURE 4.25. Same case as Figure 4.24. This area shows hyaline membranes. The combination of features in Figures 4.24 and 4.25 indicates a diagnosis of acute exacerbation of UIP.



FIGURES 4.26 and 4.27. Legend appears on next column



FIGURES 4.26 and 4.27. Acute eosinophilic pneumonia. Clinically the patient appeared to have ARDS. At low power (**Figure 4.26**) the appearance is that of organizing DAD, but high power shows numerous eosinophils, indicating that the correct diagnosis is acute eosinophilic pneumonia. Additional images of acute eosinophilic pneumonia can be found in Chapter 15.

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8. Tazelaar HD, Linz LJ, Colby TV, et al. Acute eosinophilic pneumonia: histopathologic findings in nine patients. *Am J Respir Crit Care Med*. 1997;155:296–302.
9. Suh GY, Kang EH, Chung MP, et al. Early intervention can improve clinical outcome of acute interstitial pneumonia. *Chest*. 2006;129:753–761.

CHAPTER

5

Bronchiolitis Obliterans Organizing Pneumonia

NOMENCLATURE ISSUES

The name bronchiolitis obliterans organizing pneumonia (BOOP) was popularized by the report of Epler et al.,[1] but is itself a modification of the term "bronchiolitis obliterans with interstitial pneumonia" (BIP) proposed by Liebow in the 1970s. The term "bronchiolitis obliterans" stems from the presence of granulation tissue plugs in the lumens of respiratory bronchioles, a process originally, but no longer, thought to be part of bronchiolitis obliterans (obliterative bronchiolitis, now called constrictive bronchiolitis, see Chapter 20), whereas the term "organizing pneumonia (OP)" reflects morphology that is identical to organizing bacterial pneumonia in the parenchyma.

The ATS/ERS classification of the idiopathic interstitial pneumonias[2] (see Chapter 2) suggested the term "organizing pneumonia" for the pathologic pattern, and "cryptogenic organizing pneumonia (COP)" rather than BOOP for the idiopathic disease. Although this phrase is correct in terms of etiology, our experience is that COP has not caught on and most clinicians are happy if they receive a diagnosis of BOOP.

Strictly speaking BOOP implies idiopathic BOOP, and BOOP of other etiologies, for example, BOOP around an abscess or a tumor or in hypersensitivity pneumonitis (HP) should be referred to as OP, but this usage can be confused for an infectious process and, again, most clinicians seem to understand the use of the term BOOP in this setting as well. Accordingly, we have used BOOP in this book, recognizing that the pathologic description needs to be used in clinical context.

We advise against reporting BOOP as "acute lung injury" because this term is confusing to clinicians and conveys no prognostic or treatment information (see Chapter 4 for a discussion).

CLINICAL FEATURES

Idiopathic BOOP often mimics the signs and symptoms of a community acquired pneumonia with fever, fatigue, cough, and shortness of breath; sometimes there is weight loss as well.[3,4] Often there is a history of a preceding upper respiratory tract infection (URI). In the majority of patients symptoms are present for less than two months and sometimes for only a few weeks.

BOOP that is part of another pathologic process is normally overshadowed by the primary lesion; for example, BOOP around an abscess will appear clinically as an abscess.

IMAGING FEATURES

The characteristic high-resolution computed tomography (HRCT) findings of BOOP consist of areas of consolidation that are usually bilateral and in 60% to 80% of cases have a predominately peribronchial and/or subpleural distribution[5] (Fig. 5.1). The subpleural predominance can mimic that of chronic eosinophilic pneumonia but consolidation in a peribronchial distribution is highly suggestive of BOOP.[6] The consolidation often also has a characteristic perilobular distribution; that is, along the periphery of the secondary lobules adjacent to the interlobular septa, resulting in a polygonal appearance[6] (Fig. 5.2). Although ground-glass opacities (GGOs) are present in the majority of cases they usually occur in association with areas of consolidation and are seldom the predominant finding.

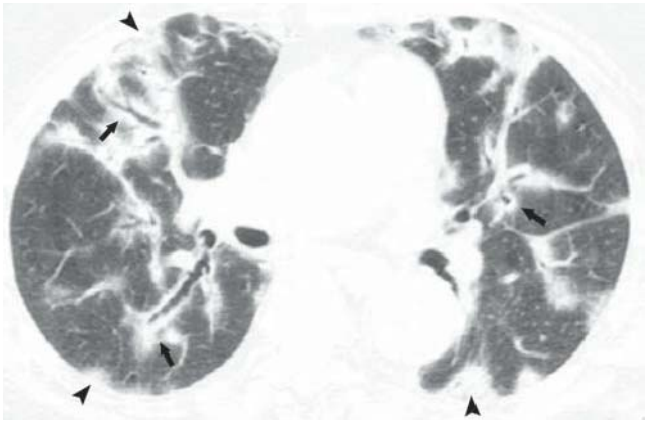


FIGURE 5.1. BOOP. HRCT demonstrates bilateral areas of consolidation in a peribronchial (*arrows*) and subpleural (*arrowheads*) distribution. The patient was an 81-year-old woman.

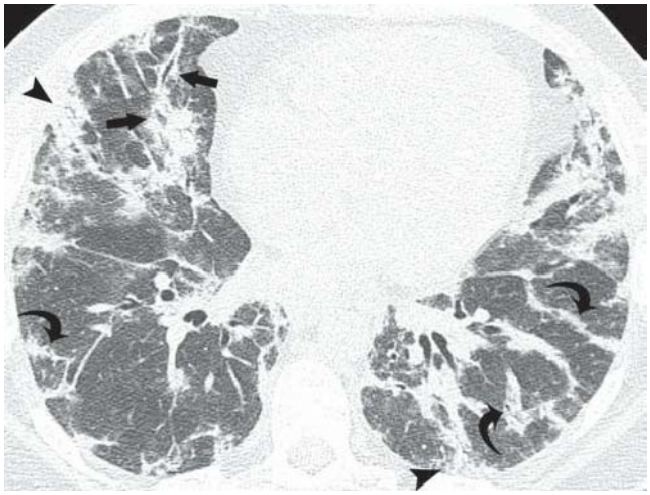


FIGURE 5.2. BOOP. HRCT shows bilateral areas of consolidation that involve mainly the subpleural (*arrowheads*), peribronchial (*straight arrows*), and perilobular (*curved arrows*) regions. The patient had BOOP secondary to polymyositis.

PATHOLOGIC FEATURES

Grossly BOOP appears as raised gray areas of lung that are more or less contiguous (Fig. 5.3) or less commonly as nodules (Fig. 5.4). The microscopic features of BOOP are summarized in Table 5.1 and illustrated in Figures 5.5 to 5.10; the fundamental finding is granulation tissue plugs in respiratory bronchioles and alveolar ducts with a mild accompanying chronic interstitial inflammatory infiltrate.

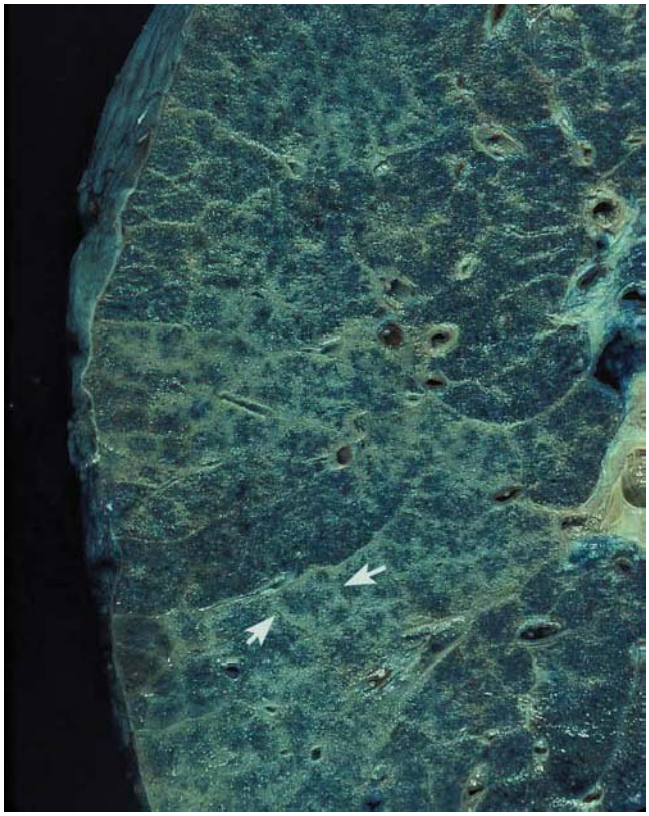


FIGURE 5.3. Gross appearance of BOOP. Note sparing of some lobules (*arrows*)—the same pattern as may be seen on CT.

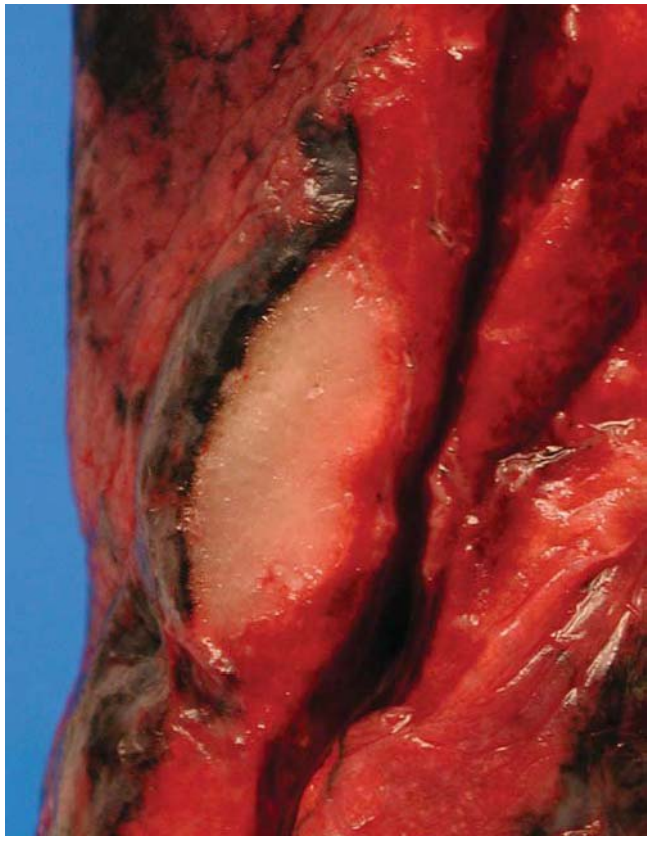


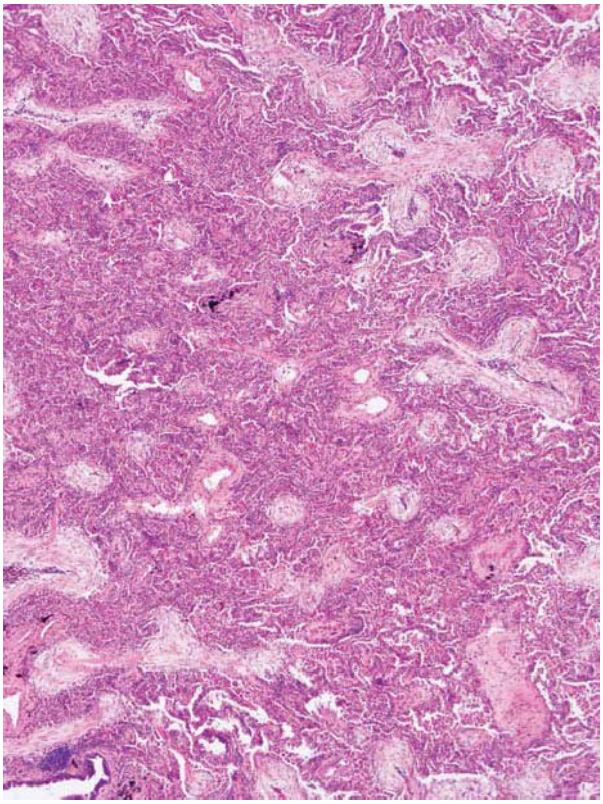
FIGURE 5.4. Gross appearance of nodular BOOP. (Case courtesy Dr. J. English.)

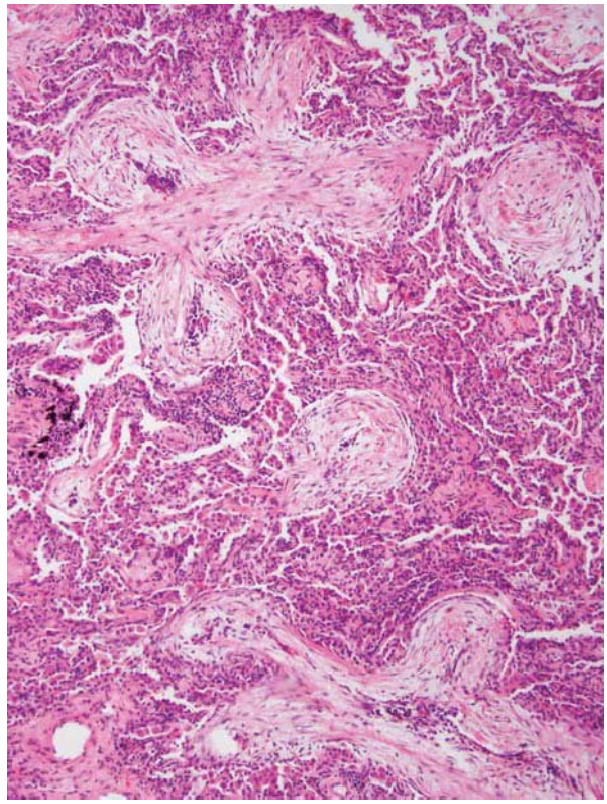
Two points that are important to note in idiopathic BOOP are the homogeneity of the process and the absence of underlying old fibrosis or architectural distortion. Idiopathic BOOP by definition cannot have another

Table 5.1

Pathologic features of BOOP

Granulation tissue plugs in respiratory bronchioles and alveolar ducts
Granulation tissue plugs typically are separated from the underlying lung tissue
Process often appears to spread from respiratory bronchioles
Variable interstitial infiltrate of chronic inflammatory cells
Reactive alveolar lining cells usually present
Process is temporally homogeneous
Underlying lung architecture preserved
No true old fibrosis or honeycombing





FIGURES 5.5 and 5.6. Low- and high-power microscopic views of BOOP. Note the absence of old fibrosis or architectural distortion. The high-power view shows the typical branching appearance of the granulation tissue plugs and the mild interstitial inflammatory infiltrate, something that is invariably present in BOOP.

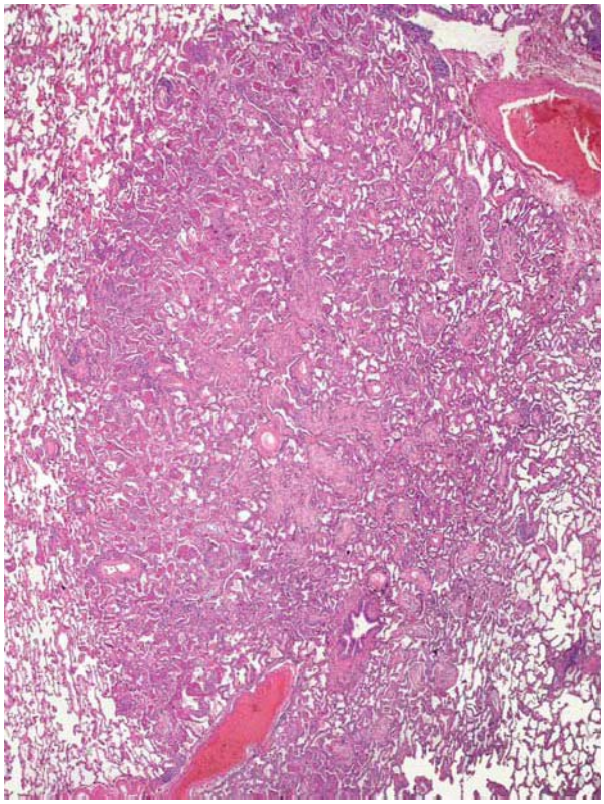
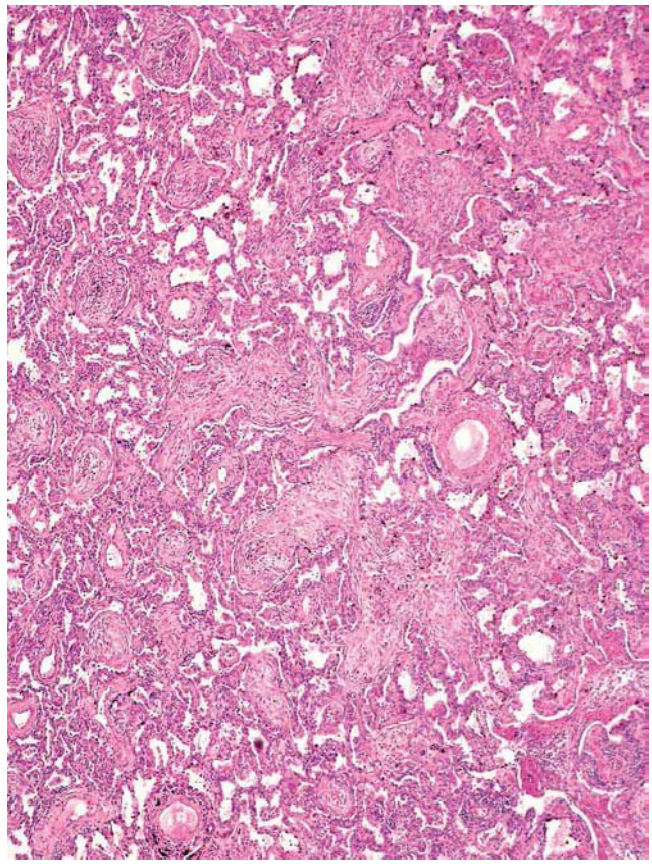
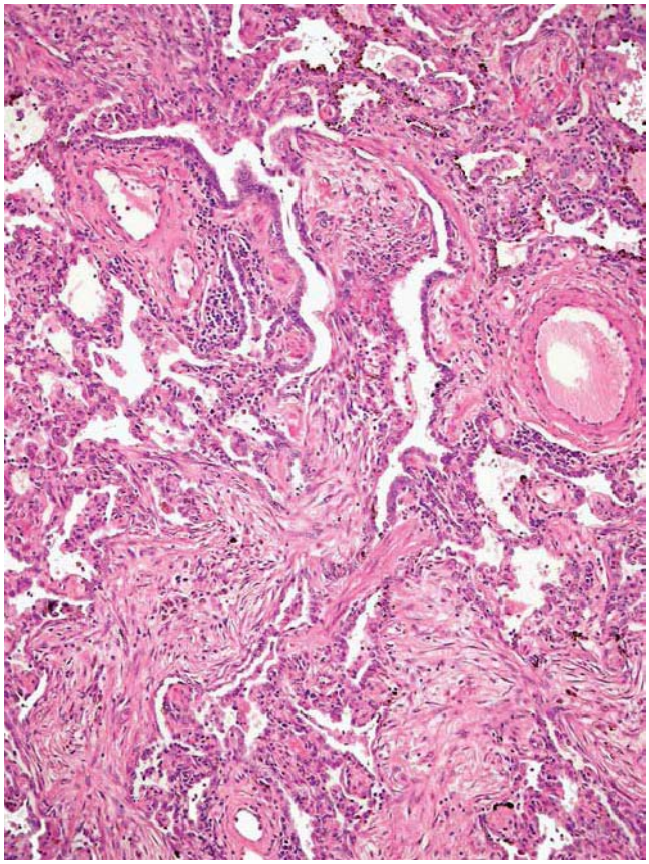
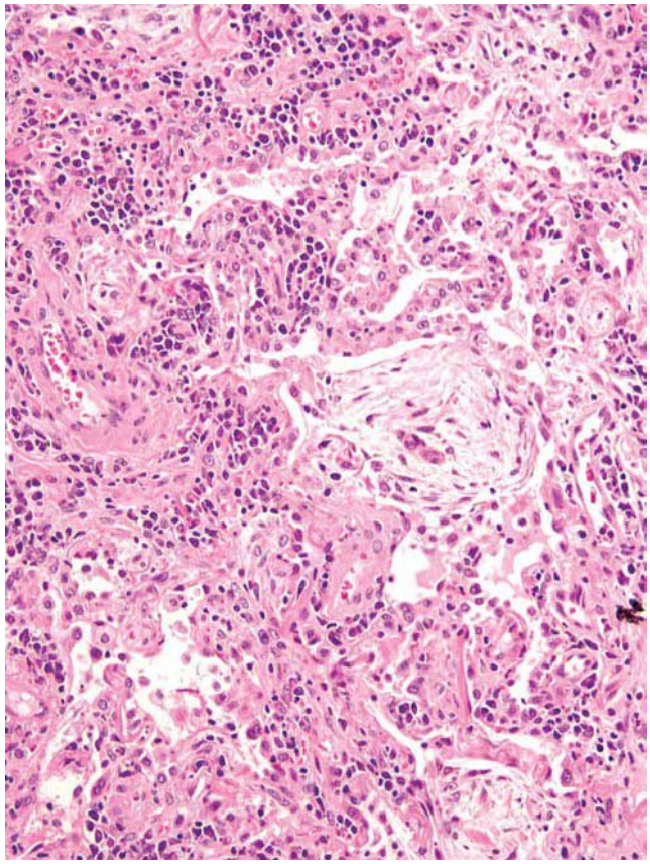


FIGURE 5.7. A low-power view of nodular BOOP. In nodular BOOP the process is sharply circumscribed and can appear as a nodule on imaging, whereas in most examples of BOOP the process fades off into the surrounding parenchyma.



FIGURES 5.8 and 5.9. Legend appears on following page





FIGURES 5.8 and 5.9. Medium- and high-power views of the lesion shown in Figure 5.7. The microscopic appearance of BOOP is stereotypic. In **Figure 5.9** a granulation tissue plug is seen in the lumen of a respiratory bronchiole.

FIGURE 5.10. Appearance of a granulation tissue plug in cross section. In BOOP the granulation tissue plugs tend to be separated from the underlying lung tissue, as here, whereas in fibroblast foci (see Chapter 6), the granulation tissue is closely applied to the underlying lung tissue. Note also the chronic interstitial inflammation.

lesion present. If extensive old dense fibrosis is present, then BOOP has been superimposed on some pre-existing fibrotic process.

Small foci of BOOP are common in many types of interstitial lung disease (ILD) such as nonspecific interstitial pneumonia (NSIP) (Chapter 7) and HP (Chapter 12), and in these settings the presence of BOOP is ignored when making a diagnosis. However, if large amounts of BOOP are present along with another defined ILD, then both components should be diagnosed; for example, the combination of BOOP and NSIP is common in patients with collagen vascular disease (see Chapter 21). BOOP superimposed on usual interstitial pneumonia (UIP) frequently represents an acute exacerbation of UIP (see Chapters 4 and 6).

PATHOLOGIC VARIANTS OF BOOP

Nodular BOOP

Most cases of BOOP have irregular margins when viewed grossly (Fig. 5.3) and microscopically, but occasionally BOOP is distinctly nodular on imaging, grossly, and microscopically (Figs. 5.4 and 5.7). Nodular BOOP can present as a solitary nodule on imaging.

Biopsies at the Edge of BOOP Lesions

Biopsies that sample the edge of a lesion of BOOP can be very confusing pathologically because BOOP is always associated with a chronic interstitial inflammatory reaction (Figs. 5.6, 5.9, and 5.10), and at the edge of BOOP lesions, the interstitial process sometimes spreads further than the granulation tissue plugs. This can produce an appearance mimicking cellular NSIP (Fig. 5.11 and see Chapter 7). However, reference to imaging will usually sort this out since NSIP and BOOP are radiologically distinct.

Acute Fibrinous and Organizing Pneumonia Pattern

It is not unusual to find small amounts of fibrin mixed in with the granulation tissue in BOOP, but occasionally the granulation tissue plugs are composed predominantly of fibrin (Figs. 5.12 to 5.14). This lesion has been called "acute fibrinous and organizing pneumonia (AFOP)"[7] but it is simply a reaction pattern that may be seen in BOOP,

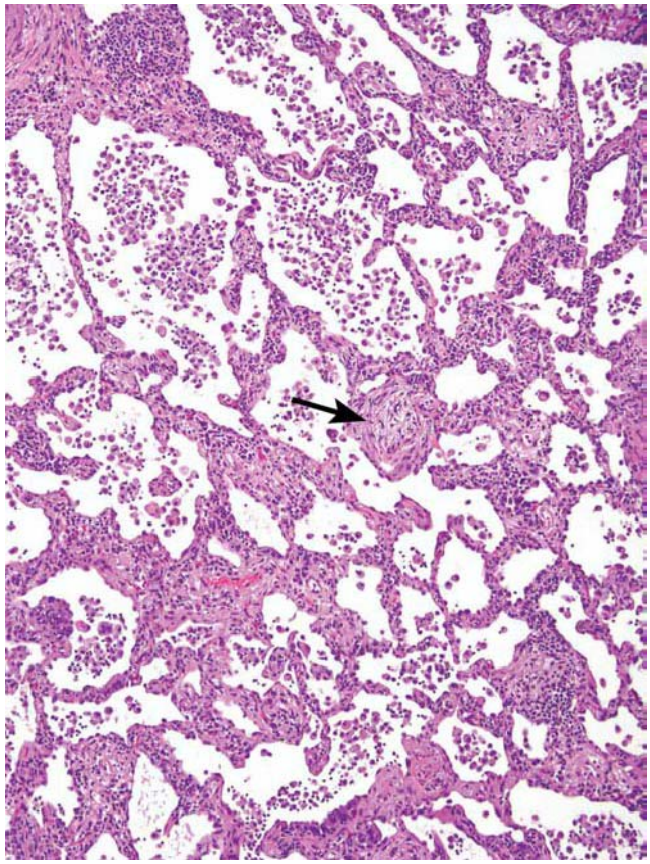


FIGURE 5.11. Edge of a lesion of BOOP mimicking NSIP (see Chapter 7). When a biopsy samples the edge of a BOOP lesion, the interstitial inflammatory infiltrate may predominate, and granulation tissue plugs (*arrow*) may be few or absent, as here. If the morphology is equivocal, the nature of the lesion can almost always be sorted out by examining the CT scan.

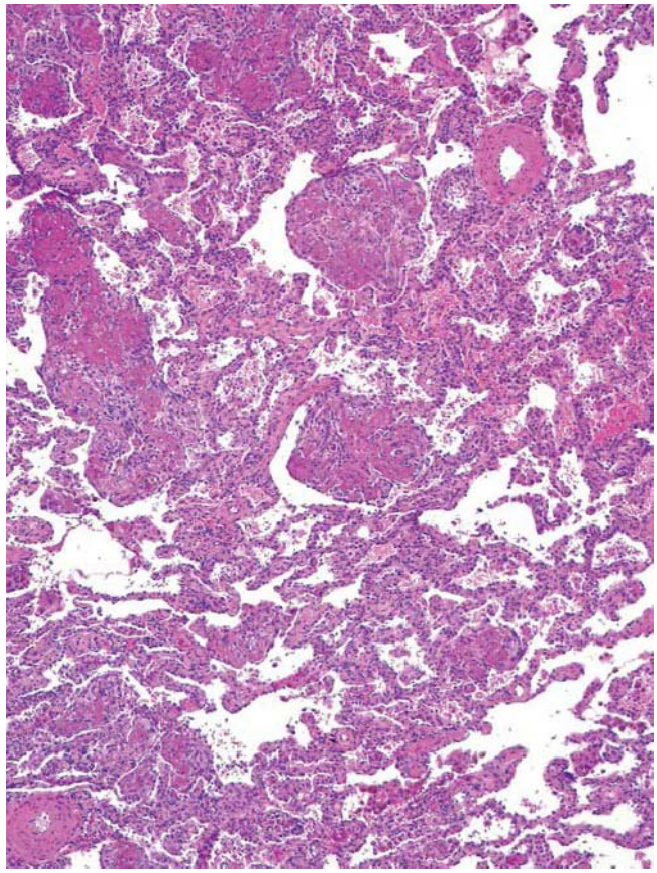
diffuse alveolar damage (DAD), and eosinophilic pneumonias. We advise against using AFOP as a diagnosis because it is not a specific entity and clinicians will not know what is implied; rather we simply diagnose the underlying lesion (BOOP, DAD, eosinophilic pneumonia) and ignore the fibrin.

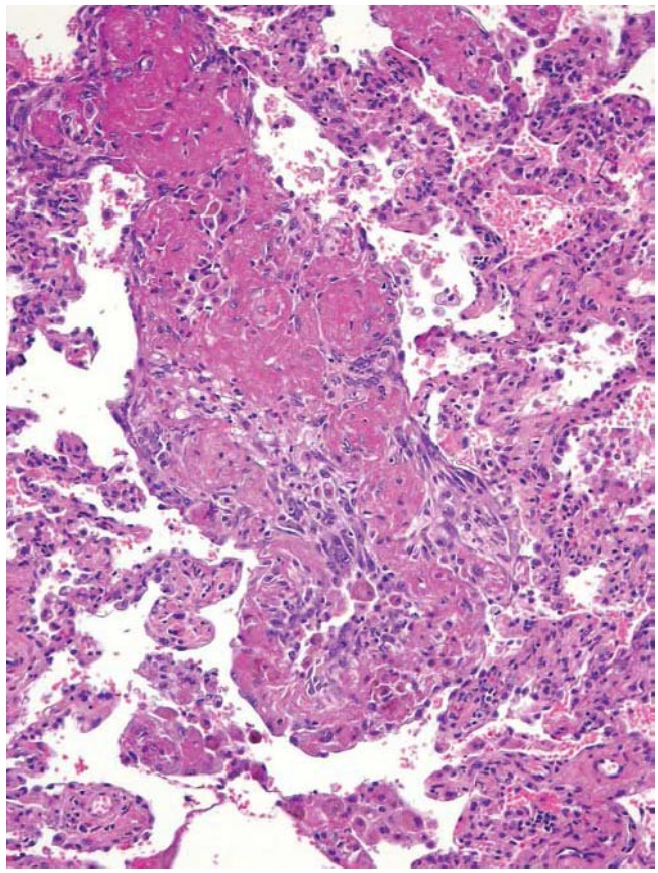
Other Patterns

On rare occasions BOOP can organize into dense fibrous tissue or can mimic fibroblast foci. Details and illustrations are discussed in the section Differential Diagnosis.

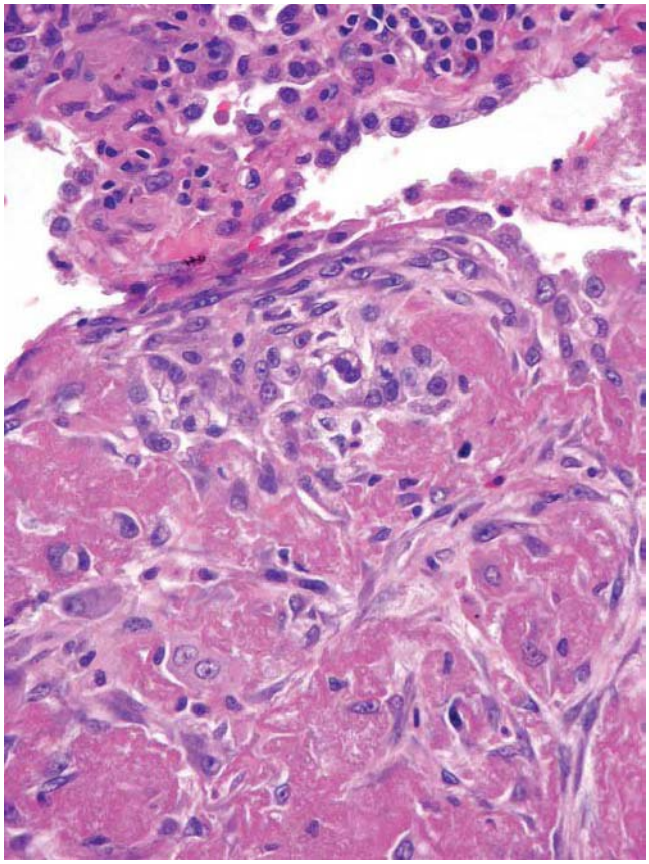
SECONDARY BOOP

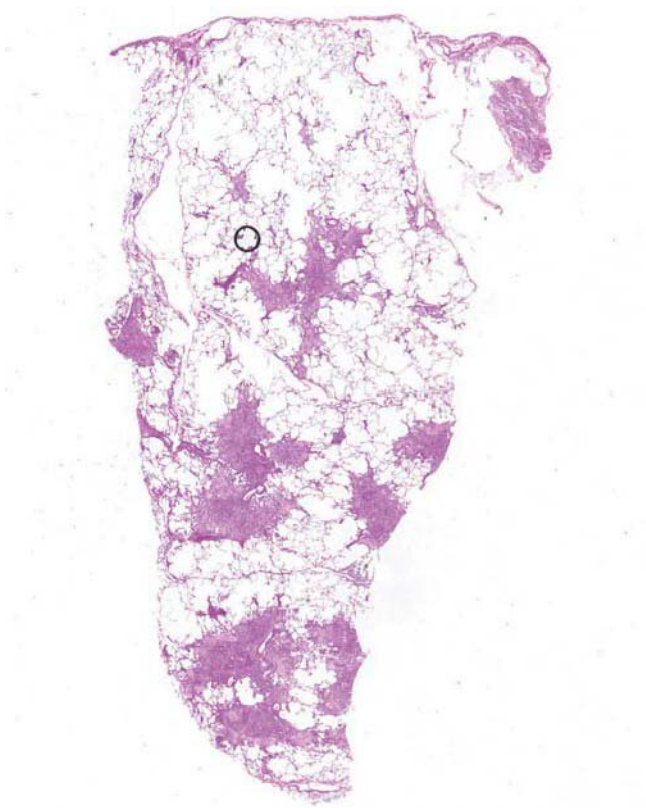
A pathologic picture of BOOP can be seen as part of many other processes in the lung, sometimes in conjunction with another lesion (Table 5.2), but sometimes producing a picture of pure BOOP; for example, post-mycoplasma infection (Figs. 5.15 to 5.17) or as a drug reaction (Figs. 5.18 and 5.19).

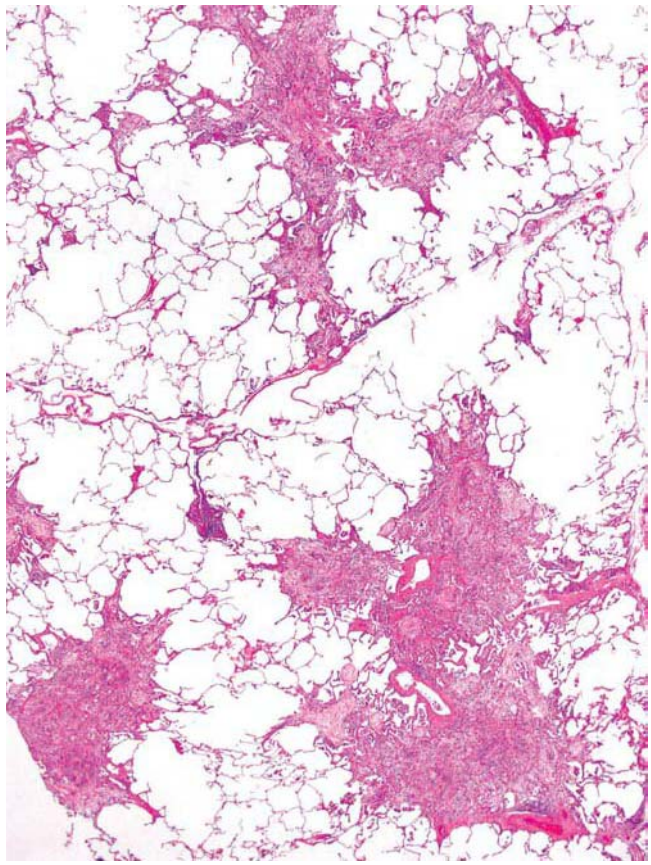




FIGURES 5.12 to 5.14. Legend appears on following page







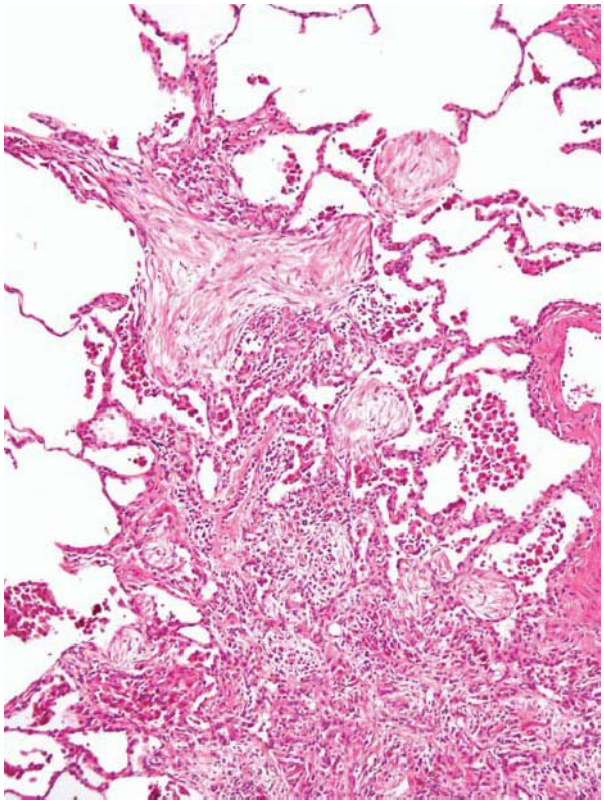
FIGURES 5.12 to 5.14. AFOP pattern. In AFOP fibrin replaces much of the granulation tissue of BOOP, although some granulation tissue still remains, as is clear from **Figure 5.14**. AFOP pattern may be seen in BOOP, DAD (Chapter 4), and chronic eosinophilic pneumonia (Chapter 15). AFOP is not a specific entity and should not be diagnosed.

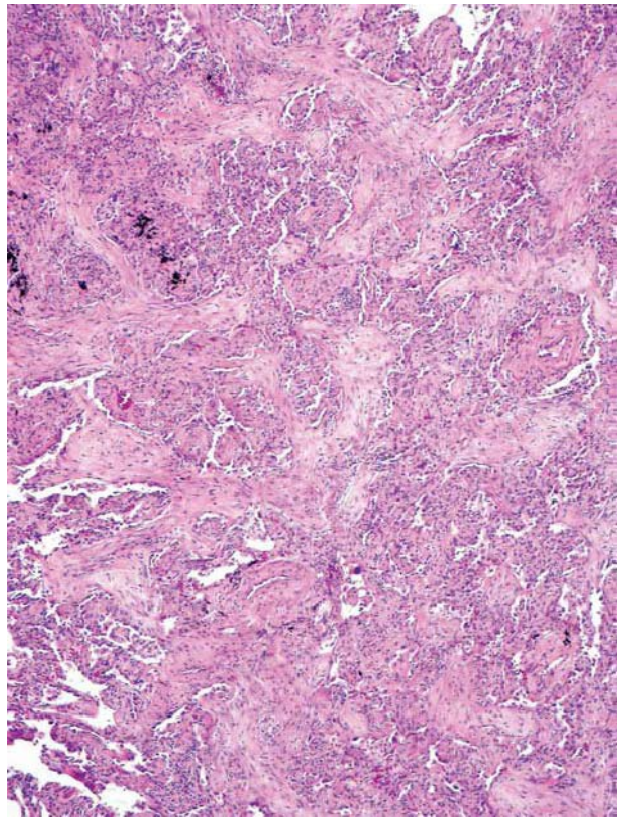
Table 5.2

Causes of secondary BOOP

Organizing bacterial pneumonia
Pneumocystis infection
Aspiration (look for giant cells/granulomas and foreign material)
Drug reactions (Chapter 18)
Infections
Reactions to inhaled toxins, especially noxious gases
Chronic eosinophilic pneumonia (look for eosinophils) (Chapter 15)
As a minor part of HP (Chapter 12)
As a minor part of NSIP (Chapter 6)
Collagen vascular disease
Distal to airway obstruction (especially by slow-growing tumors)
Inflammatory bowel disease
Acute or chronic hemorrhage
Around other inflammatory or mass lesions (tumors, abscesses, infarcts)

FIGURES 5.15 to 5.17. Legend appears on following page

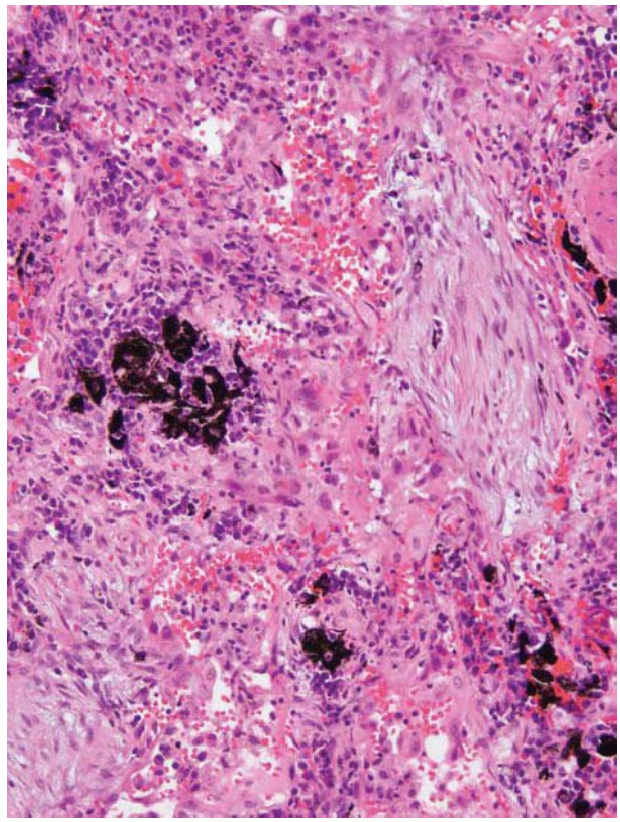




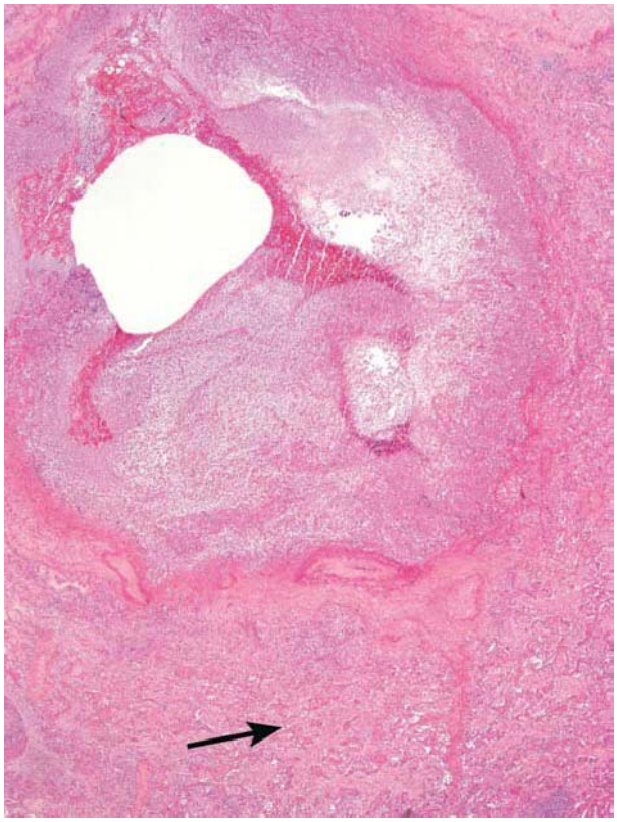
FIGURES 5.15 to 5.17. BOOP post-mycoplasma infection. The low-power view (**Fig. 5.15**) shows that the process is localized to the region of the bronchovascular bundles and reflects damage to the respiratory bronchioles during the acute phase of the infection (see Chapter 20). However, the morphology is simply that of BOOP and only the history indicates etiology.

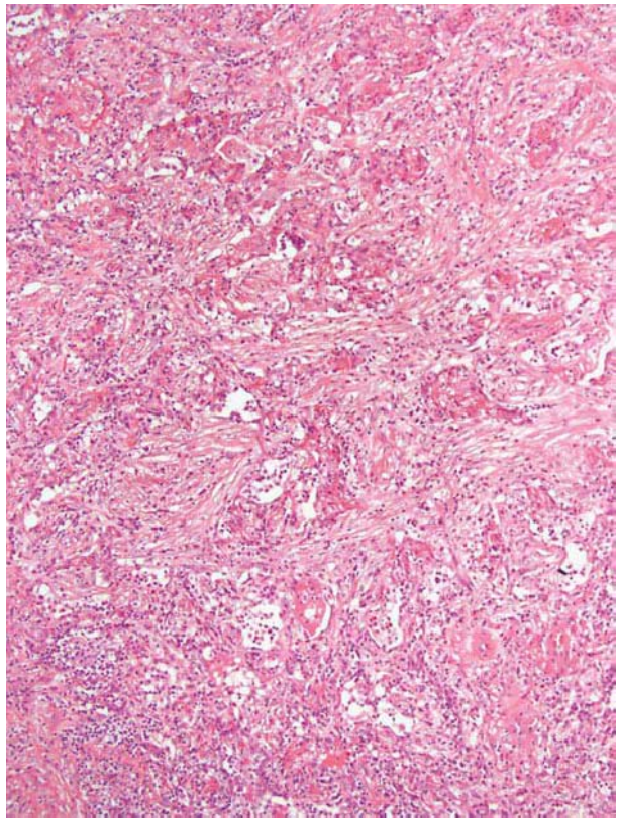
The proper pathologic diagnosis in this situation depends on the clinical situation, imaging, and pathologic findings. For example, with an abscess (Figs. 5.20 and 5.21) or tumor (Figs. 5.22 and 5.23) that has surrounding or distal BOOP, the BOOP can be ignored and only the lesion of interest should be diagnosed. As noted above, small foci of BOOP are common in HP but need not be diagnosed since the presence or absence of BOOP does not change prognosis or therapy. BOOP is extremely common in eosinophilic pneumonias and may be the predominant microscopic pattern (Figs. 5.24 and 5.25 and see Chapter 15), but the correct diagnosis is eosinophilic pneumonia because it tells the clinician to look for the sensitizing agent. BOOP is a common drug reaction pattern (Figs. 5.18 and 5.19 and see Chapter 18), and in this situation, a diagnosis of "BOOP, consistent with reaction [to drug]" is actually useful to the clinician because it implies both reversibility and suggests treatment with steroids. Similarly, a diagnosis of "BOOP secondary to previous mycoplasma infection" (Figs. 5.15 to 5.17) conveys the same information.

In addition to being a response to a previous infection, BOOP can be a reaction to an active infection. Pneumocystis is a particular problem in this regard, because the organism often produces no clues to its presence on hematoxylin

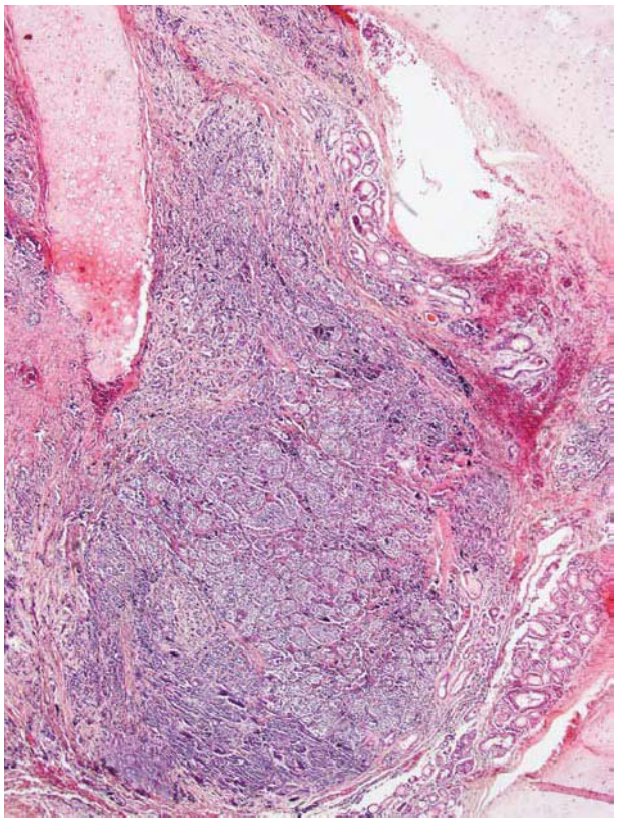


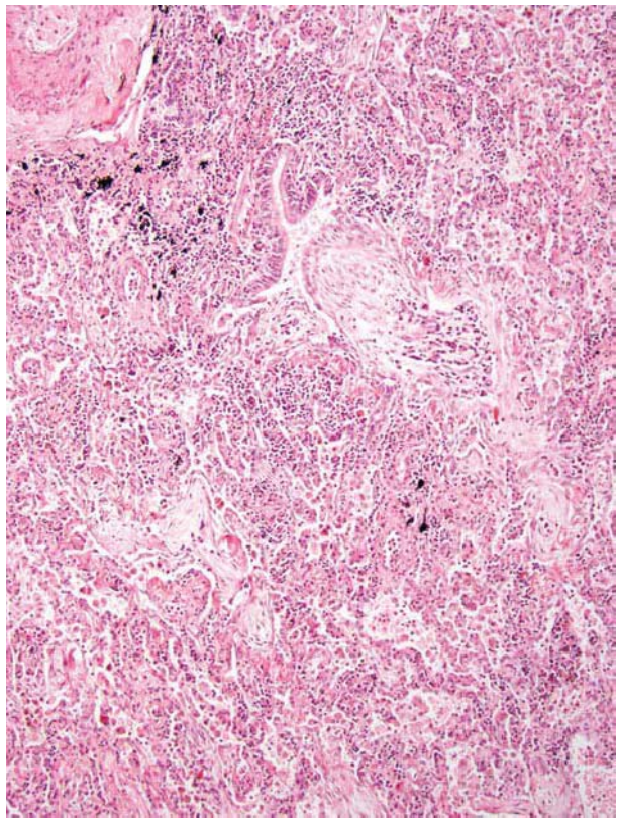
FIGURES 5.18 and 5.19. Two examples of BOOP as drug reaction: **Figure 5.18** is from a patient given cyclophosphamide for glomerulonephritis, and **Figure 5.19** is from a crack cocaine smoker (note the extensive dense black crack pigment).



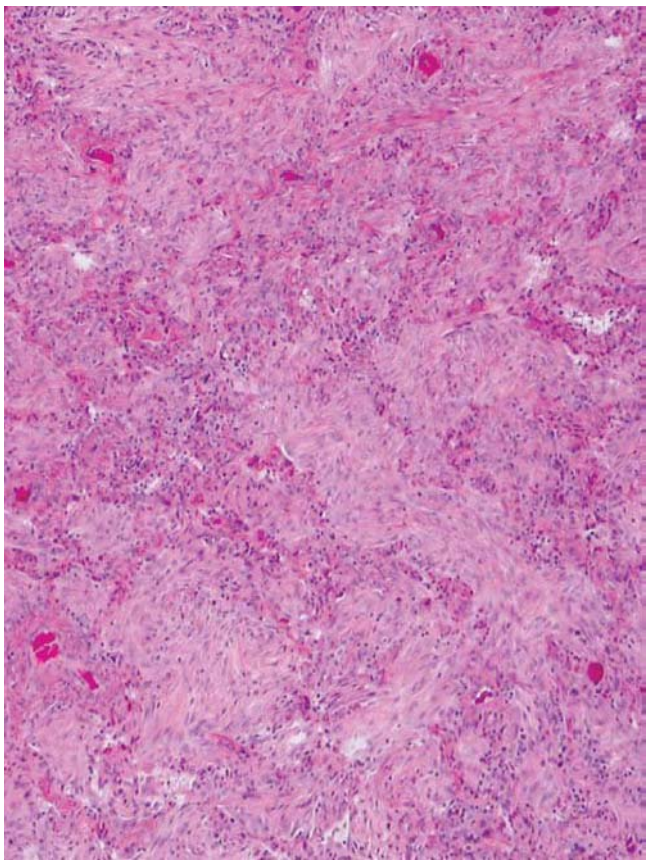


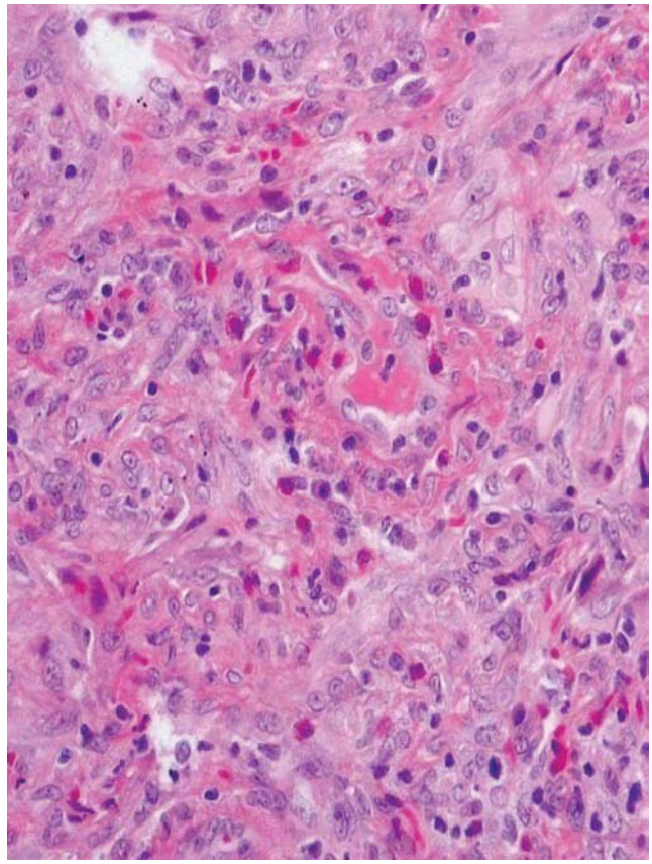
FIGURES 5.20 and 5.21. BOOP around an abscess. The lower-power view (**Fig. 5.20**) shows an abscess above. The region marked by the *arrow* is shown in **Figure 5.21** and is BOOP. In this setting the proper diagnosis is lung abscess and the BOOP can be ignored.





FIGURES 5.22 and 5.23. BOOP around a carcinoid tumor. The tumor completely obstructs the bronchus of origin (**Fig. 5.22**) and there is BOOP (**Fig. 5.23**) distal to the tumor.





FIGURES 5.24 and 5.25. Chronic eosinophilic pneumonia disguised as BOOP. The medium-power view (**Fig. 5.24**) looks like BOOP, but the high-power view (**Fig. 5.25**) shows numerous eosinophils. BOOP is a very common pattern in chronic eosinophilic pneumonia (see Figs. 15.14 and 15.15 for additional examples).

and eosin stain (Fig. 5.26). Therefore we routinely do silver stains for pneumocystis in all cases of BOOP (Fig. 5.27) unless there is another known cause for the process

BOOP is a very common reaction to aspiration.[8] Clues to the correct diagnosis are the presence of individual giant cells or foreign body granulomas, acute bronchiolitis, or occasionally necrotizing granulomas, along with the BOOP, and foreign material—most commonly vegetable particles (Figs. 5.28 and 5.29) or birefringent material.

BOOP can be a reaction to acute or chronic hemorrhage. With chronic hemorrhage hemosiderin may be found in the granulation tissue tufts (Fig. 5.30), and this is a useful clue that BOOP is a secondary process. Some cases will also show interstitial fibrosis and ferrugination of vessel elastic as a response to iron deposition (see Chapter 24). Care should be taken in such cases to look for capillaritis since this would indicate that the patient has vasculitis.

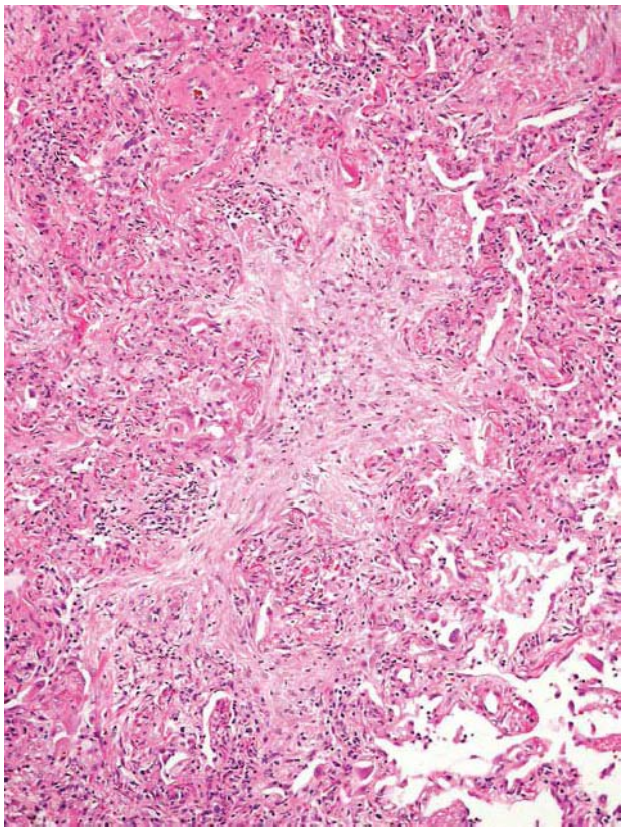
DIAGNOSTIC MODALITIES

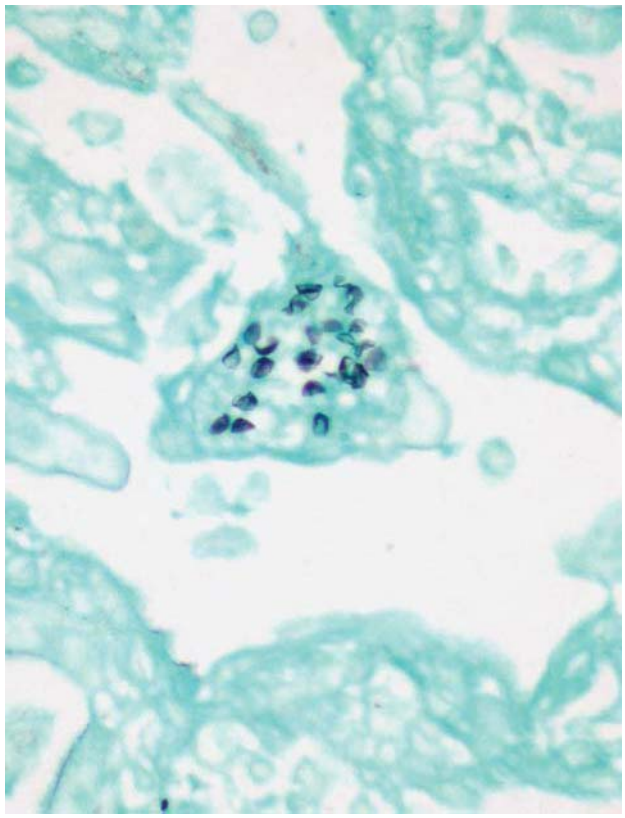
A BOOP pattern is fairly common in transbronchial biopsies (see Figs. 3.6 and 3.7) and even in core needle biopsies (see Fig. 3.1). A diagnosis of BOOP in a transbronchial biopsy may be morphologically accurate, but whether that morphology is relevant will depend on clinical and imaging findings, and a comment to that effect should be included when diagnosing BOOP in a transbronchial biopsy. A large video-assisted thoracoscopic surgery (VATS) biopsy is always more accurate in ensuring that some other lesion is not present. BOOP in a core needle biopsy (see Fig. 3.1) is almost always misleading since there is no way of knowing whether one is dealing with nodular BOOP (relatively uncommon) or BOOP around some other lesion such as a tumor (the usual scenario).

DIFFERENTIAL DIAGNOSIS

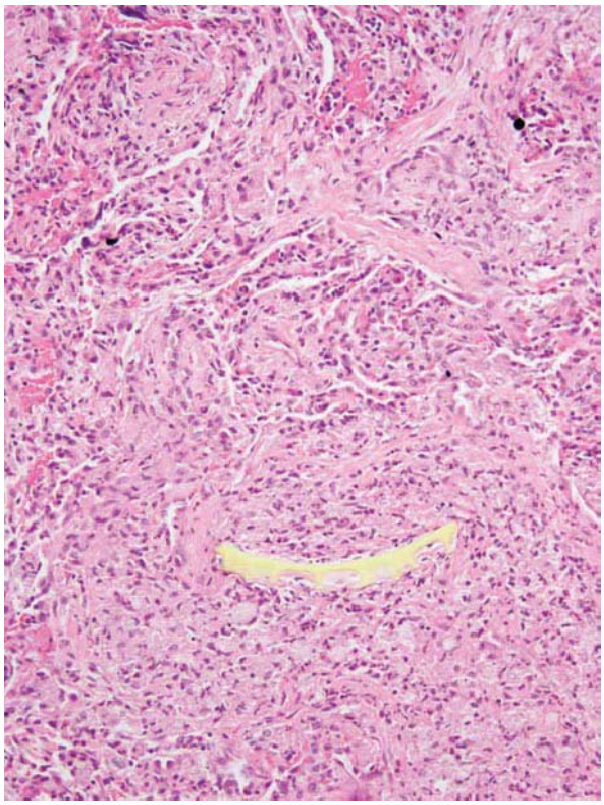
The morphology of BOOP is distinctive, and the differential diagnosis tends to reflect the presence of other morphologic features; for example, if an abscess with surrounding BOOP is present, the diagnosis is "abscess" rather than BOOP (Figs. 5.20 and 5.21).

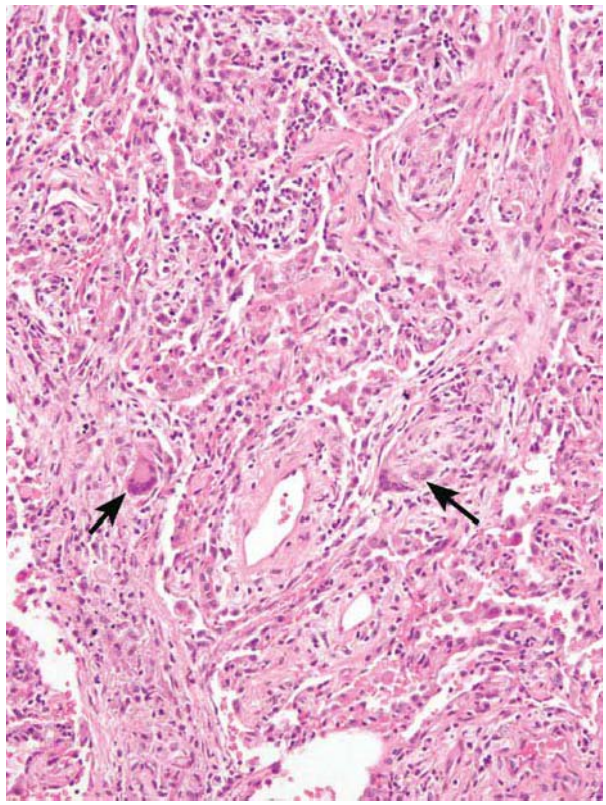
One important differential is the separation of BOOP from fibroblast foci since both are composed of granulation tissue. Details for this separation are listed in Table 5.3. Fibroblast foci are typically seen in UIP (Chapter 6) but can be found in any process characterized by actively developing dense fibrosis, whereas BOOP typically is not





FIGURES 5.26 and 5.27. BOOP caused by pneumocystis infection. The H&E view (**Fig. 5.26**) is indistinguishable from idiopathic BOOP, but the Grocott stain (**Fig. 5.27**) shows pneumocystis organisms. Because pneumocystis can hide in BOOP without any clue to its presence on H&E, we advise staining all cases of BOOP for pneumocystis unless there is another good reason for BOOP to be present.





FIGURES 5.28 and 5.29. BOOP caused by aspiration. BOOP is a common response to aspiration. Clues to the correct diagnosis are the finding of food particles (in this case a *fragment of a yellow vegetable wall* in **Fig. 5.28**) and/or giant cells/granulomas (*arrows* in **Fig. 5.29**).

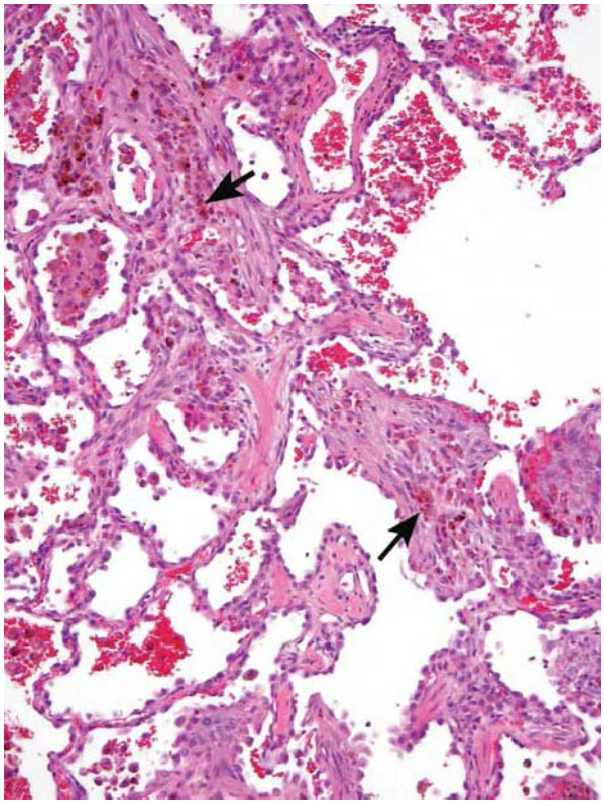


FIGURE 5.30. BOOP as a reaction to pulmonary hemorrhage. The presence of hemosiderin in the granulation tissue plugs (*arrows*) is a clue to the correct diagnosis.

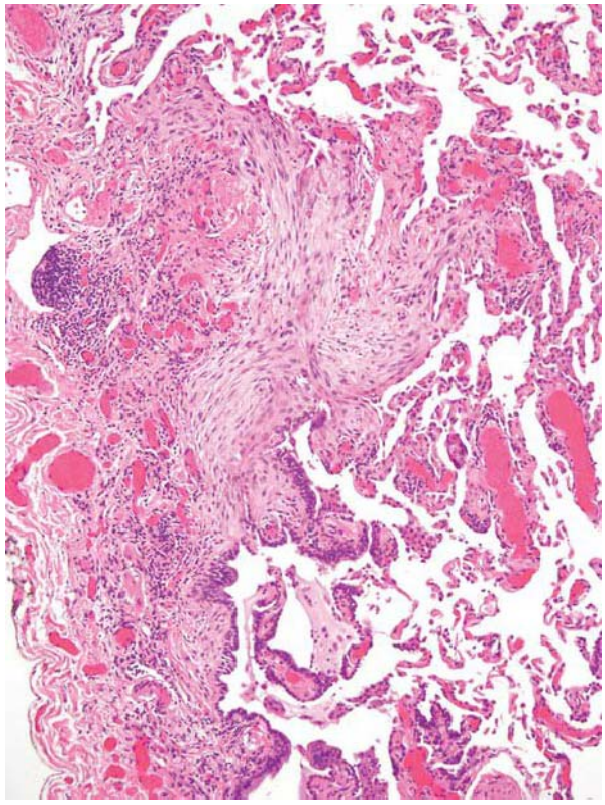
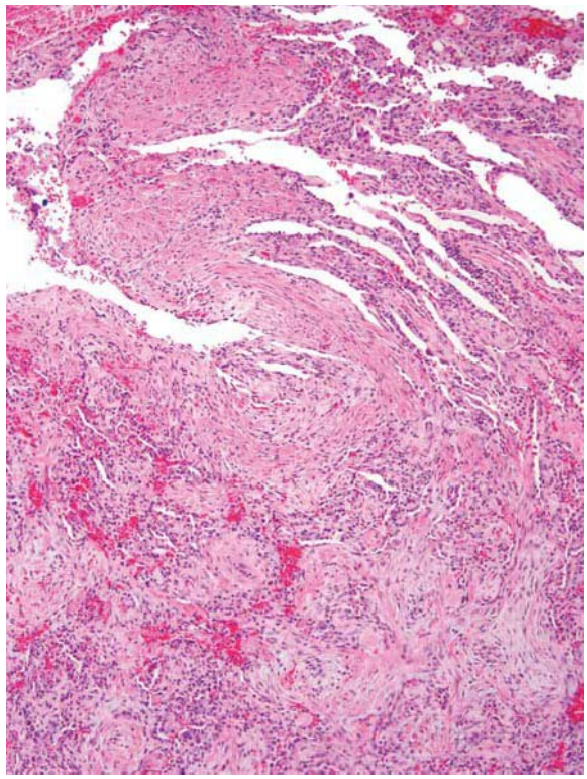


FIGURE 5.31. Unusual pattern of BOOP occasionally encountered in the periphery of the lung where granulation tissue plugs are applied directly to underlying tissue, mimicking fibroblast foci (see Chapter 6). This case had ordinary BOOP elsewhere and was probably secondary to aspiration.

associated with a fibrosing lung disease. Useful features to bear in mind are that fibroblast foci typically show granulation tissue with various degrees of organization from very loose to nearly completely collagenized and are always tightly applied to the underlying lung tissue (see Figs. 6.32 to 6.35), whereas in BOOP all the granulation is loose and is of the same age and most often is separated from the underlying lung tissue.

In rare cases these rules are violated. Occasionally BOOP in the very periphery of the lung shows granulation tissue tightly and directly applied to underlying somewhat fibrotic tissue (Fig. 5.31). This situation can be confusing, but if there is BOOP elsewhere and no evidence of an underlying fibrosing interstitial pneumonia, then the process is probably all BOOP.

The granulation tissue plugs of BOOP are ordinarily quite loose and disappear with therapy. However, on rare occasions BOOP organizes into dense fibrous bands (Figs. 5.32 to 5.35), and with the subsidence of the interstitial inflammatory reaction these fibrous bands can resemble fibrotic NSIP (see Chapter 7 and Figs. 5.34 and 5.35). The finding of areas that cover the spectrum from loose-to-dense fibrous tissue (such as Fig. 5.32) is helpful in arriving at the correct diagnosis.



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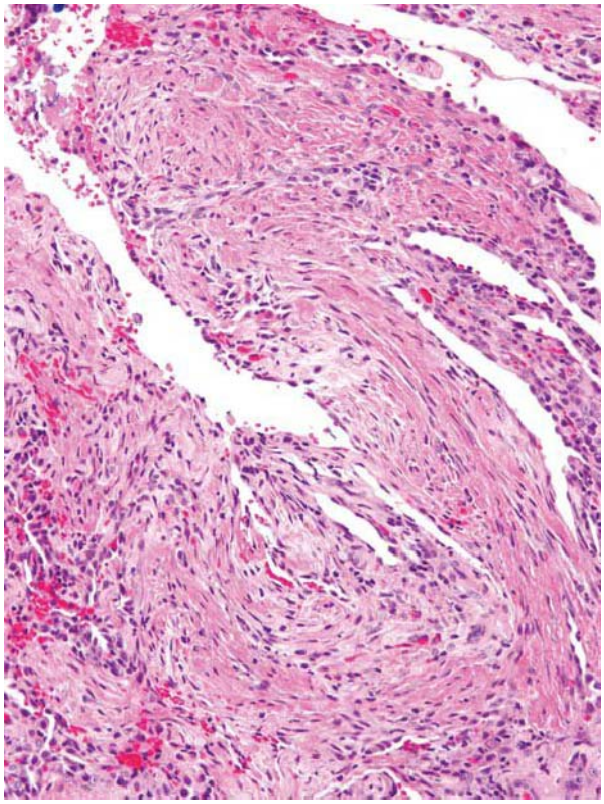
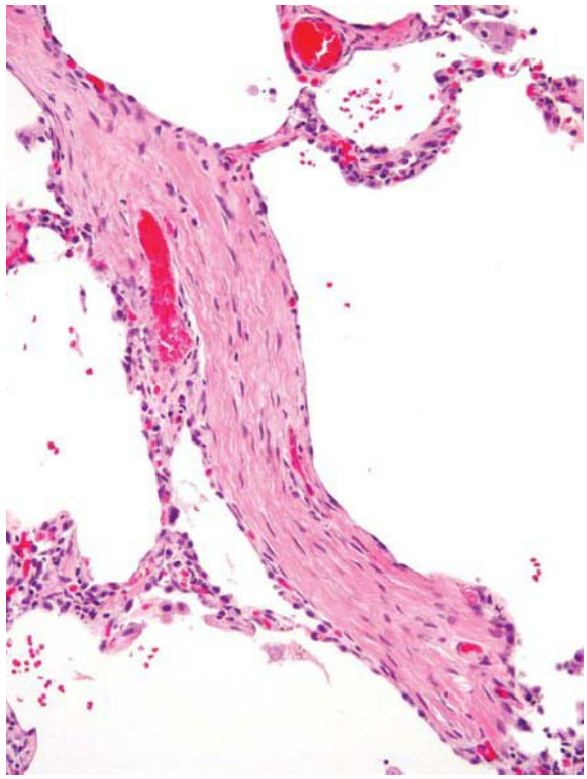


FIGURES 5.32 and 5.33. Unusual pattern of BOOP. On rare occasions BOOP can organize into dense fibrous tissue as seen in this example.



FIGURES 5.34 and 5.35. Same case as Figures 5.32 and 5.33. In this area only fine bands of organized fibrous tissue remain. If this was the only pattern seen, it would fit best for fibrotic NSIP, and some cases of fibrotic NSIP may represent organized BOOP.

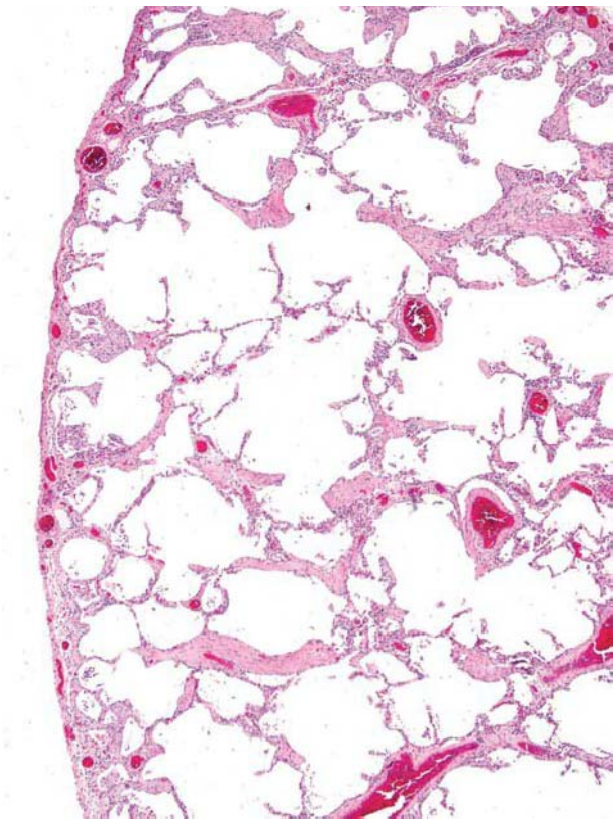


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Table 5.3

Separation of BOOP from fibroblast foci

BOOP
Granulation tissue clearly in airspaces or lumens of respiratory bronchioles
Granulation tissue largely separate from underlying lung
Granulation tissue fibroblasts randomly oriented vis-à-vis underlying lung
No dense fibrosis in surrounding lung
BOOP foci usually not covered by epithelium
BOOP foci usually much more numerous than fibroblast foci
BOOP rarely shows signs of organization (all the granulation tissue is the same age)
FIBROBLAST FOCI
A background fibrosing lung disease always present (usually UIP)
Granulation tissue always tightly attached to underlying lung
Granulation tissue typically applied to fibrotic lung
Granulation tissue fibroblasts oriented parallel to the underlying lung
Granulation tissue frequently re-epithelialized
Granulation tissue typically shows various degrees of organization (some granulation tissue is loose but some is partly collagenized)

PROGNOSIS

The prognosis in idiopathic BOOP overall is reasonably good, with 70% to 90% long-term survival in different series.[3,4,9,10] Relapses of idiopathic BOOP are common when steroids are tapered (50% of cases in some series), but the process generally responds to reinstitution of steroids. The prognosis of secondary BOOP depends on the underlying condition, but as noted above, the absence of dense fibrosis means that any lesion that has a pure BOOP pattern is potentially completely reversible.

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CHAPTER

6

Usual Interstitial Pneumonia

NOMENCLATURE ISSUES

The term "UIP" was coined by Liebow and dates back to the 1970s, whereas the British used the term "cryptogenic fibrosing alveolitis" for the same process. In the 2002 ATS/ERS classification of the idiopathic interstitial pneumonias, UIP is viewed as the pathologic diagnosis for a disease that—when clinical, radiologic, and pathologic findings are combined—is called "idiopathic pulmonary fibrosis" (IPF).[1]

The original Liebow term UIP was intended to replace some of the entities labeled "pulmonary fibrosis" with a more specific disease, but there is still clinical inconsistency in the use of "pulmonary fibrosis" and IPF because sometimes these labels are meant to convey UIP and at other times other fibrosing lung diseases. As UIP is widely recognized by clinicians, radiologists, and pathologists as a reasonably specific name, we shall use UIP in this book.

UIP, along with fibrotic NSIP and chronic HP are examples of "fibrosing interstitial pneumonias," meaning that that they are characterized by prominent old dense fibrosis. Fibrosing interstitial pneumonia is neither a term found in textbooks nor in formal classification, nor are we suggesting that it should be liberally applied, but occasionally a biopsy of a patient with ILD shows a fibrosing process that does not fit into conventional classifications, and in that setting a diagnosis of fibrosing interstitial pneumonia with a listing of possible differential diagnoses may be appropriate.

ETIOLOGIES

Table 6.1 lists the etiologies of UIP. Most cases that look like UIP on imaging or biopsy are either idiopathic or related to an underlying collagen vascular disease. Some cases of chronic HP are morphologically indistinguishable from UIP, although there are frequent differences between UIP and chronic hypersensitivity pneumonitis (HP) on imaging (Figs. 6.1 and 6.2). Asbestosis occasionally looks quite like UIP with the addition of asbestos bodies, but most cases of asbestosis are pathologically distinct[2] (see Chapter 22) and asbestosis is frequently accompanied by marked visceral pleural fibrosis, something that is usually not a feature of idiopathic UIP.

The term familial (or genetic) UIP is used in several ways: first, to describe UIP in two or more closely related individuals who have clinically, radiologically, and pathologically typical UIP; second, in patients with a pathologic picture of UIP and telomerase mutations[3]; third, as (an incorrect) descriptor for various fibrosing interstitial pneumonias in close relatives that, pathologically, may not resemble UIP[4]; and fourth, to describe an ILD, typically in children, who have mutations in surfactant processing genes. Microscopically, these latter cases are not similar to UIP. From the point of view of diagnosis, cases that pathologically look like UIP should be simply called UIP; if they do not fit any typical form of ILD, a diagnosis of fibrosing interstitial pneumonia is appropriate.

EPIDEMIOLOGY

Idiopathic UIP is a disease of the middle-aged and elderly and is rare among those below 50 years; the finding of a UIP picture on a biopsy from someone less than 50 years

Table 6.1

Etiologies of a radiologic and morphologic picture of UIP

Idiopathic UIP
- Equivalent to clinical IPF

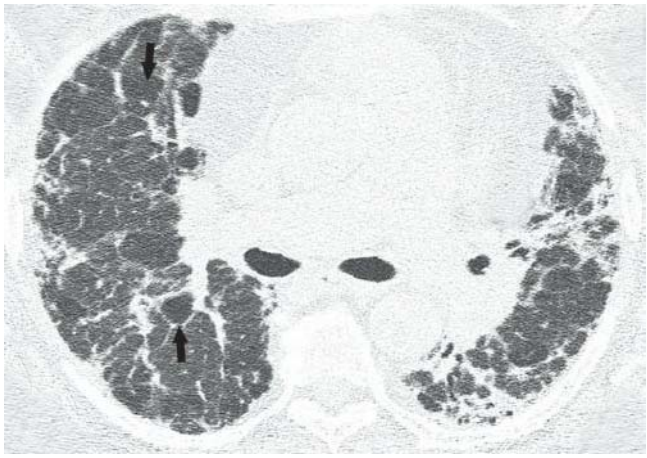
Collagen vascular disease
- Especially common in rheumatoid arthritis and scleroderma but can be seen in any form of collagen vascular disease

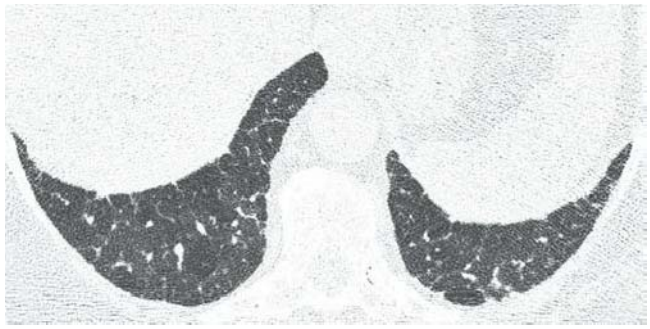
Drug reactions
- For example, amiodarone, nitrofurantoin, chemotherapeutic agents (see Chapter 18)

Familial /genetic UIP
- UIP in two or more family members
- Surfactant C processing deficiency [does not look like ordinary UIP]
- Telomerase mutations[3]

Some cases of chronic HP

Some pneumoconioses such as asbestosis (but usually not great microscopic mimics)





FIGURES 6.1 and 6.2. Chronic HP. **Figure 6.1:** HRCT at the level of the upper lobes demonstrates dense subpleural reticulation that is suggestive of UIP. Findings that favor the diagnosis of chronic HP in this image include diffuse inhomogeneity of the lung parenchyma and lobular areas of decreased attenuation and vascularity (*arrows*). **Figure 6.2:** HRCT at the level of the lung bases in the same case as Figure 6.1 shows minimal fibrosis. The predominant middle and upper lung zone distribution of the fibrosis with relative sparing of the lung bases is another feature that favors chronic HP over UIP. The patient was a 65-year-old woman with chronic HP owing to mold exposure.

should raise a question of an underlying collagen vascular disease, and we advise noting that point in a diagnosis comment, as the prognosis for UIP in some forms of collagen vascular disease is much better than that of idiopathic UIP.

Approximately 70% of cases of UIP occur in current or former cigarette smokers. Epidemiologic studies describe increased UIP cases in agricultural workers, but we suspect that these are actually cases of chronic HP. There are also epidemiologic associations of UIP and occupational metal exposures but with no details about the exact exposures or the morphology.

CLINICAL FEATURES

Most cases of UIP present with shortness of breath, sometimes progressive over several years, a restrictive pattern of pulmonary function tests and a decreased diffusing capacity. Clubbing is very common in UIP, probably more so than in any other form of ILD.

Some patients with a morphologic and clinical picture of UIP have an underlying collagen vascular disease with corresponding signs and symptoms as well as matching serology. However, isolated abnormal serologic tests (e.g., isolated positive rheumatoid factor) can be seen in cases that appear to be idiopathic UIP.

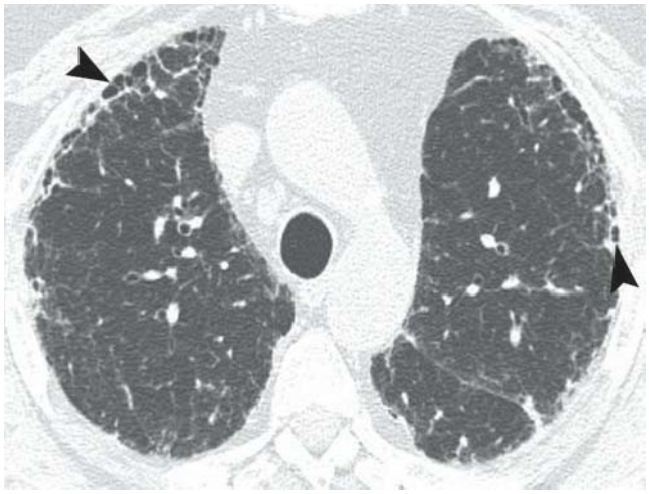
A small number of patients with UIP present for the first time as an acute exacerbation; that is, with the rapid development of hypoxemic respiratory failure and diffuse infiltrates on imaging mimicking ARDS/AIP (see below and also Chapter 4). In such patients imaging studies may reveal underlying fibrosis, but sometimes the underlying disease is demonstrable only on biopsy.

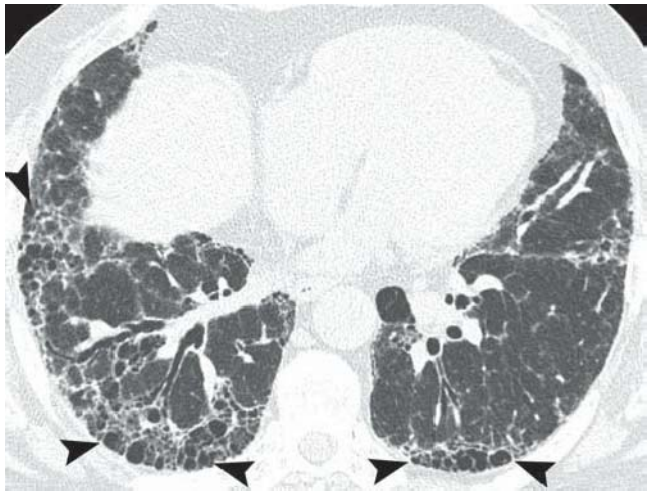
IMAGING

The characteristic manifestations of UIP on HRCT are a reticular pattern and honeycombing in a predominantly basal and peripheral distribution[5] (Figs. 6.3 and 6.4). The reticular pattern is commonly associated with traction bronchiectasis and bronchiolectasis. Although ground glass opacities (GGO) are commonly seen they are less extensive than the reticular pattern (Figs. 6.5 and 6.6).[6]

A UIP pattern on HRCT is highly accurate for the presence of a UIP pattern on surgical lung biopsy, with a positive predictive value of 90% to 100%.[7] Therefore in the appropriate clinical setting, the presence of a characteristic pattern of UIP on HRCT precludes the need for biopsy. A confident diagnosis of UIP on HRCT requires the presence of all the four following features: reticular pattern; honeycombing; subpleural and basal predominance; and absence of features considered atypical or inconsistent with a UIP pattern.[7]

It must be emphasized that although HRCT has a high specificity and positive predictive value in the diagnosis of UIP, the characteristic features that allow a confident diagnosis are present only in 50% to 75% of patients.[7] In the remaining 25% to 50% of cases, the HRCT findings are nondiagnostic, atypical, or suggestive of an alternate diagnosis. Features considered inconsistent with the diagnosis of UIP on HRCT include upper lobe predominance, peribronchovascular predominance, extensive GGOs, profuse micronodules, multiple discrete cysts away from honeycombing, diffuse mosaic attenuation/air-trapping, and consolidation.[6] The presence of any of these findings should suggest an alternate diagnosis.





FIGURES 6.3 and 6.4. UIP. HRCT at the level of the upper lobes (**Fig. 6.3**) shows mild peripheral reticulation and minimal honeycombing (*arrowheads*). HRCT at the level of the lung bases (**Fig. 6.4**) demonstrates extensive reticulation and honeycombing (*arrowheads*). The patient was a 58-year-old man with IPF.

PATHOLOGIC FEATURES

Gross Appearances

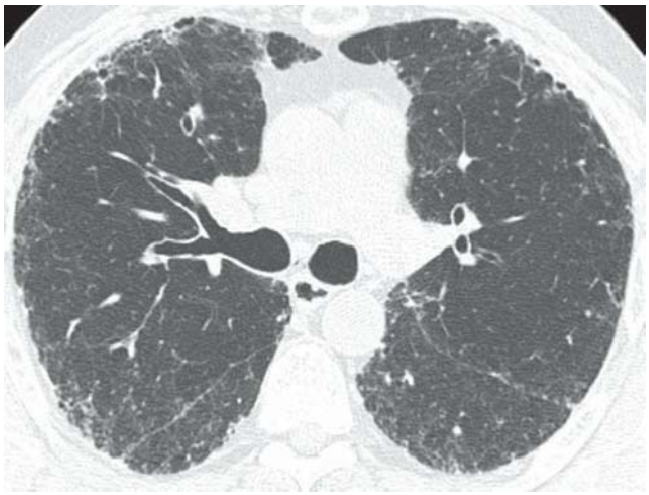
UIP is more severe in the lower zones and in the periphery of the lung (Figs. 6.7 to 6.9), but even at presentation the disease frequently involves the upper zones as well and may show increasing upper zone and central involvement over time. However, fibrosing disease that is predominantly upper zonal is unusual for UIP and suggests the entities shown in Table 6.2.

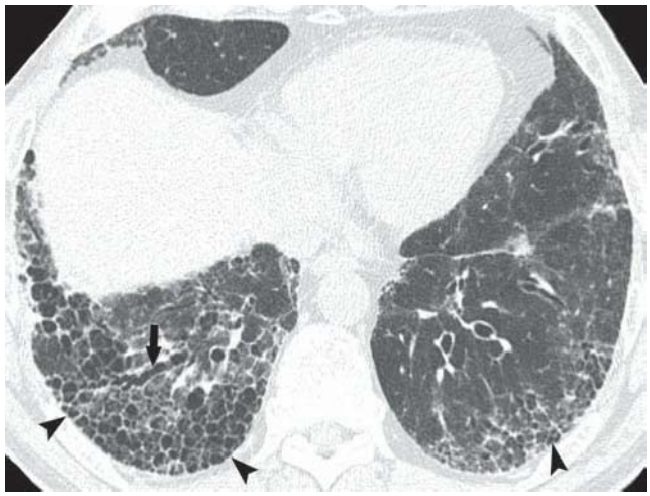
Honeycombing

Cases of UIP almost always show *honeycombing* (Figs. 6.9 to 6.16, 6.28 and 6.29) at a gross or microscopic level. Honeycombing is defined as abnormal enlarged airspaces with thick fibrous walls, and for convenience may be broken down into macroscopic honeycombing (visible on imaging and with the naked eye) and microscopic honeycombing, although in reality there is a continuous spectrum of airspace sizes. Macroscopic honeycombing can be visualized by HRCT and plays an important role in the radiologic diagnosis of UIP (see Section Imaging).

There is a mistaken belief that honeycombing is synonymous with UIP, but this is not correct: honeycombing is the end stage of a wide variety of fibrosing lung diseases (Table 6.3). However, most cases of UIP do show honeycombing at a gross or microscopic level or on imaging.

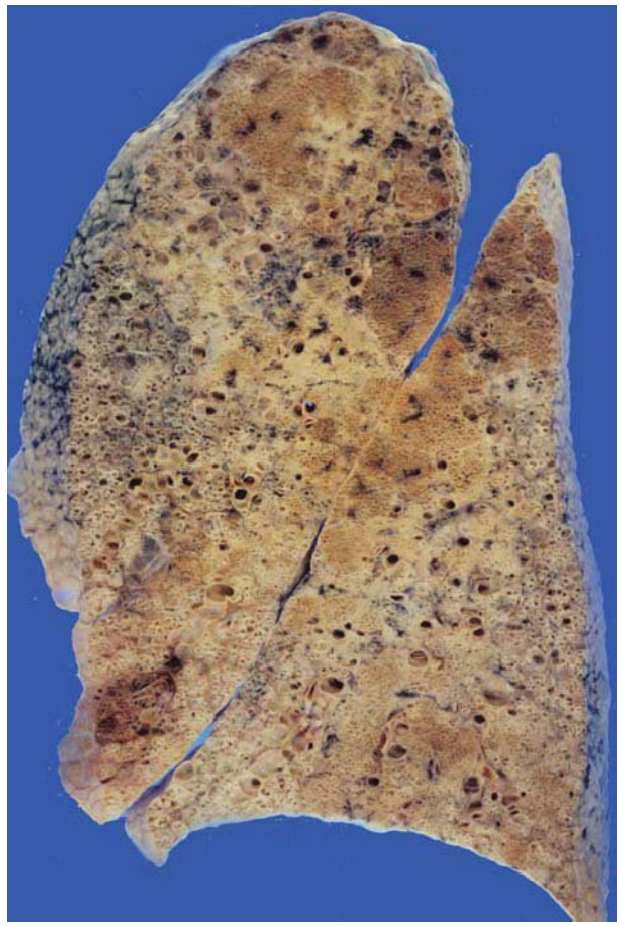
Microscopically, honeycombed spaces may have no lining at all but are frequently lined by metaplastic





FIGURES 6.5 and 6.6. UIP. HRCT at the level of the upper lobes (**Fig. 6.5**) shows mild peripheral reticulation and mild patchy GGOs. HRCT at the level of the lung bases (**Fig. 6.6**) demonstrates extensive reticulation, honeycombing (*arrowheads*), and patchy GGOs. Most of the GGOs are closely associated with areas of reticulation and probably represent fibrosis below the resolution of CT. The patient was a 62-year-old woman with clinical IPF.

6.7



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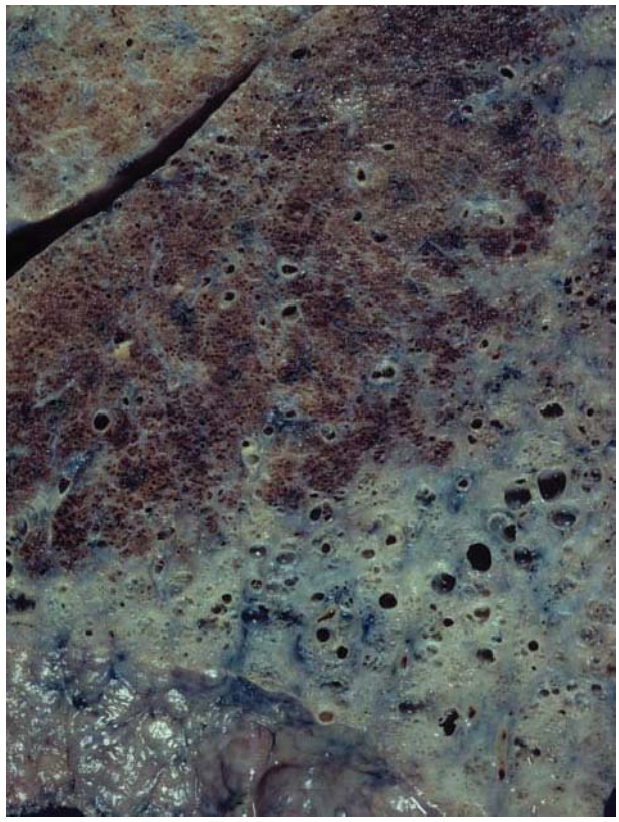


6.9

FIGURES 6.7 to 6.9. Gross images of UIP. The fibrotic process is worse in the periphery compared to the central portions of the lung and tends to be more severe in the lower zones. **Figure 6.9** illustrates an area of fibrosis and honeycombing in the lower portion of the image with irregular extension of fibrous tissue into the more normal lung in the upper portion of the image.

Table 6.2

Fibrosing lung disease that may have an upper zone predominance

Chronic HP (Chapter 12)
Sarcoid (Chapter 13)
Old TB and fungal infections
Ankylosing spondylitis
Pleuroparenchymal fibroelastosis (Chapter 23)
Rarely in UIP

respiratory epithelium (Figs. 6.14 and 6.15). Honeycombed spaces commonly contain inspissated mucus, inflammatory cells, and sometimes giant cells (Figs. 6.14 to 6.16). These do not indicate any infectious process or any specific disease but reflect local poor clearance. Interstitial inflammation can be prominent in honeycombed foci.

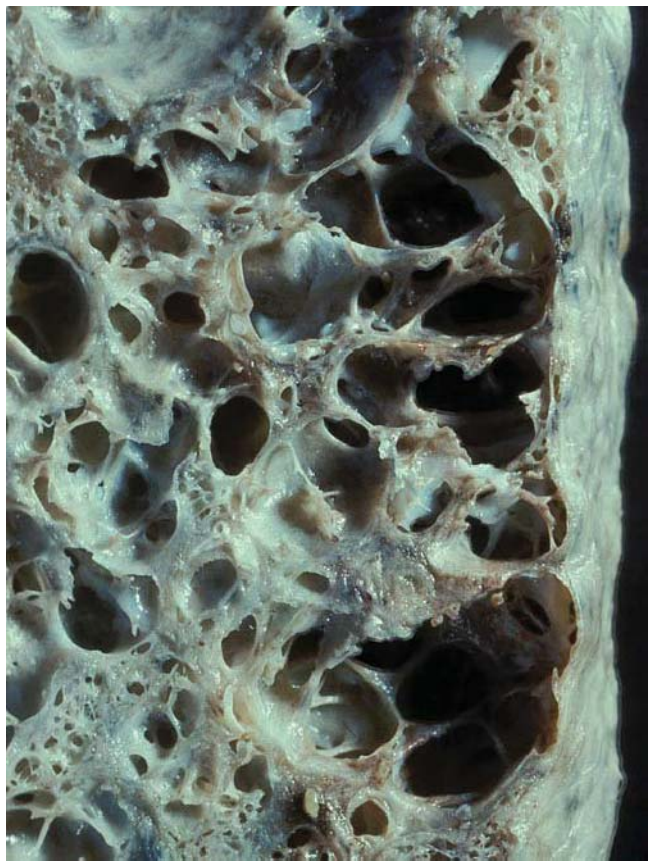
Unless one has a biopsy with just honeycombing and nothing else, honeycombing is not ordinarily part of a diagnosis; rather the underlying entity should be listed (i.e., "UIP" not "UIP with honeycombing"). A biopsy that shows only honeycombing is not specific (although many such cases turn out to be UIP) and a comment to that effect is appropriate.

Pleural Cobblestoning

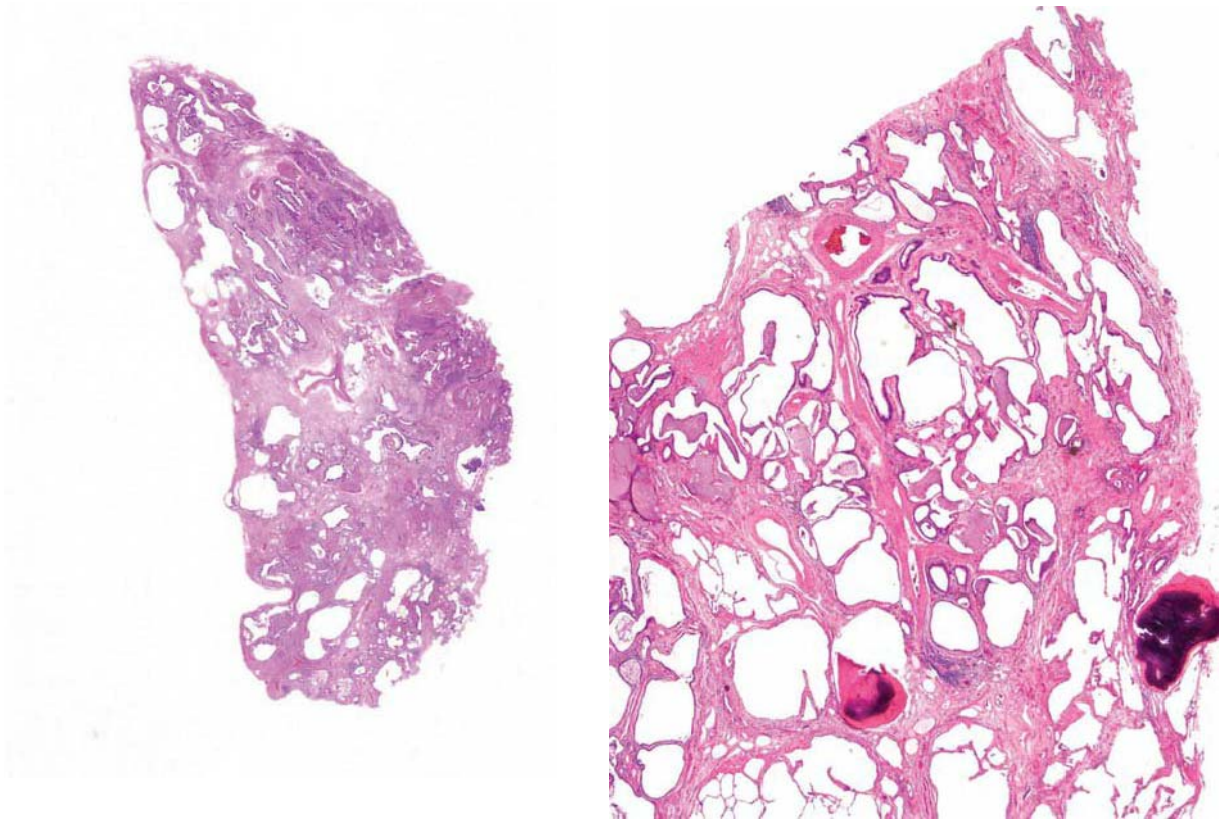
In resection specimens and autopsy lungs the pleura in UIP is usually *cobblestoned* (Figs. 6.10 and 6.11), meaning that it demonstrates irregular bumps surrounded by depressed lines. This effect is caused by underlying scarring causing retraction of the interlobular septa where they insert on the pleura. Like honeycombing it is not specific and can be seen with any process that produces subpleural fibrosis. The pleura may be slightly thickened in UIP, but marked pleural thickening suggests either an underlying collagen vascular disease (generally rheumatoid arthritis or lupus) or asbestosis.

Microscopic Features of UIP

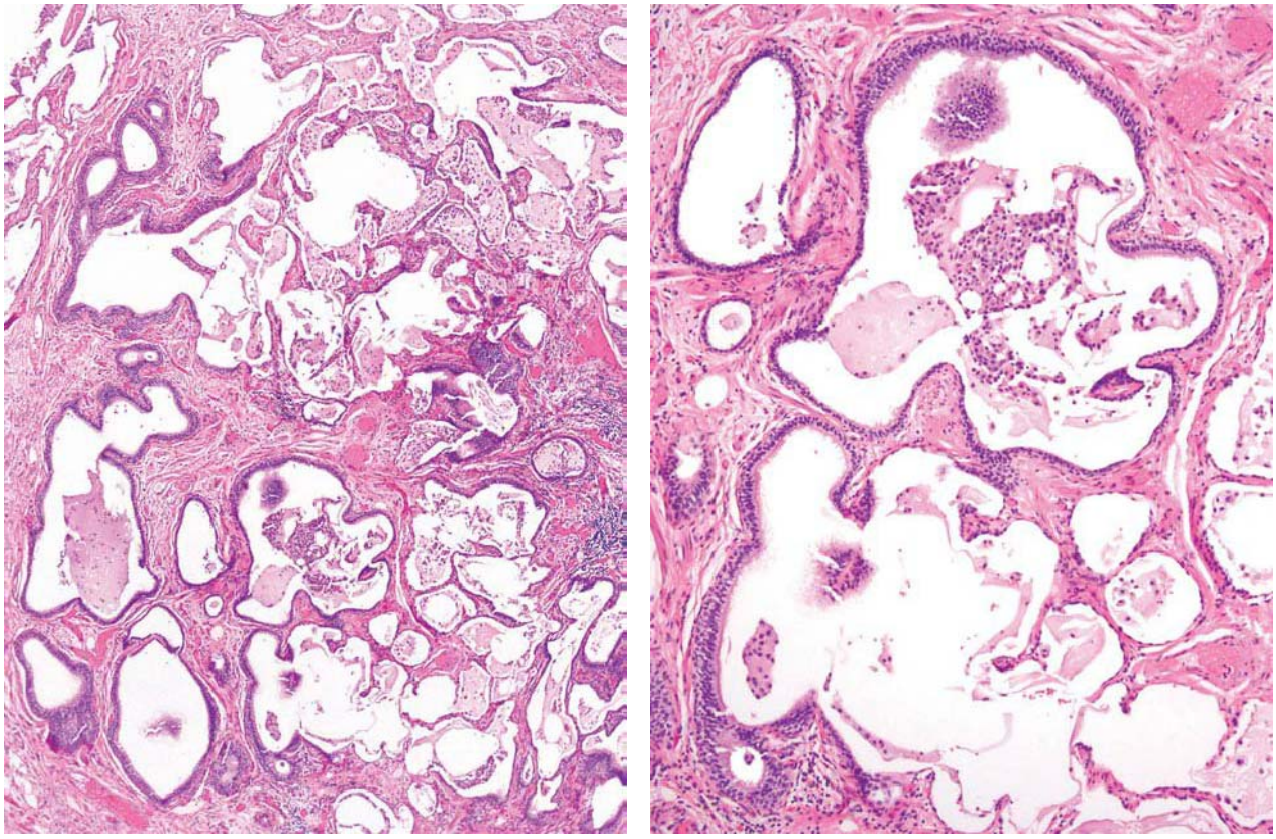
The microscopic features of UIP are summarized in Table 6.4. The most characteristic feature of UIP is *patchy interstitial fibrosis* mixed with normal parenchyma. The fibrosis and the patchiness are visible at scanning magnification (Figs. 6.17 to 6.21), and UIP is a disease best diagnosed at very low power. The fibrosing process typically jumps from very abnormal to completely normal in the space of less than 1 high-power microscope field (Fig.6.22). In early disease (Figs. 6.23 to 6.25) the fibrosis



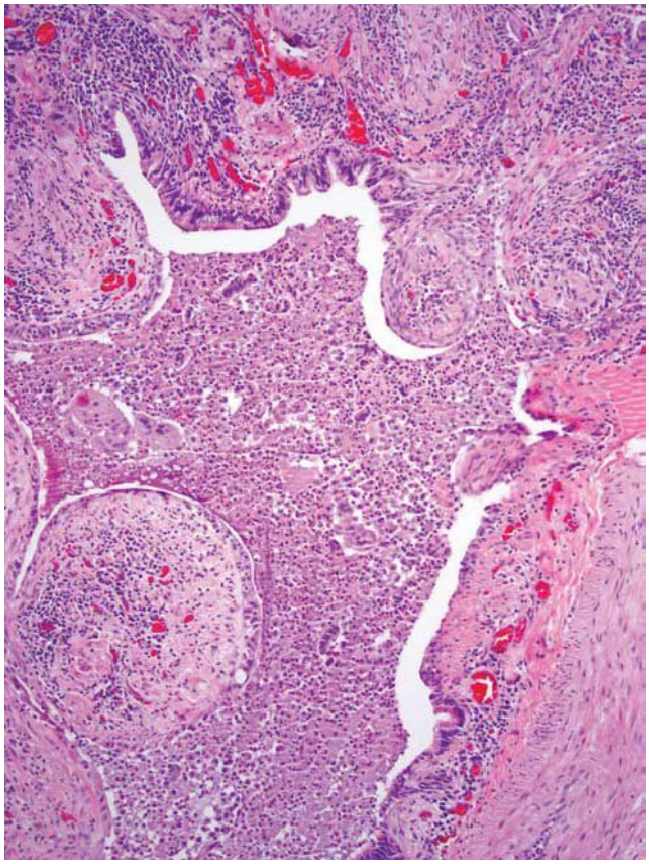
FIGURES 6.10 and 6.11. Gross views of macroscopic honeycombing. In **Figure 6.10** there is both honeycombing and extensive sheets of fibrous tissue. The pleura is also cobblestoned in both lungs, a finding that indicates the presence of underlying interstitial fibrosis.



FIGURES 6.12 and 6.13. Examples of microscopic honeycombing. All the images are from patients with UIP, but honeycombing is seen in many forms of interstitial lung disease (see Table 6.3). Many of the airspaces in honeycombed foci are lined by metaplastic bronchiolar epithelium. Although the airspaces of microscopic honeycombing typically have thick fibrous walls, sometimes the walls are relatively thin (**Fig. 6.13**). Note the metaplastic bone in Figure 6.13, a frequent but nonspecific occurrence in fibrotic lungs.



FIGURES 6.14 to 6.16. Legend appears on following page



FIGURES 6.14 to 6.16. Mucus and inflammatory cells in honeycombed airspaces. This is a common finding in areas of honeycombing and is presumed to reflect poor clearance; the presence of inflammatory cells in this setting does not indicate the presence of an infectious process.

Table 6.3

Conditions associated with honeycombing

UIP
DIP
NSIP (uncommon)
ARDS and AIP
Pulmonary radiation
Drugs
Sarcoidosis (upper zone)
Pneumoconioses (asbestosis, hard metal disease)
Langerhans cell histiocytosis (LCH)
Chronic HP (sometimes upper zone)
Healed infections, especially granulomatous infections
Localized nonspecific scars

may be present only or mostly immediately under the pleura, and early UIP sometimes shows a peripheral lobular predominance (Fig. 6.23), but as the disease progresses, more and more of the lobule is occupied by fibrous tissue.

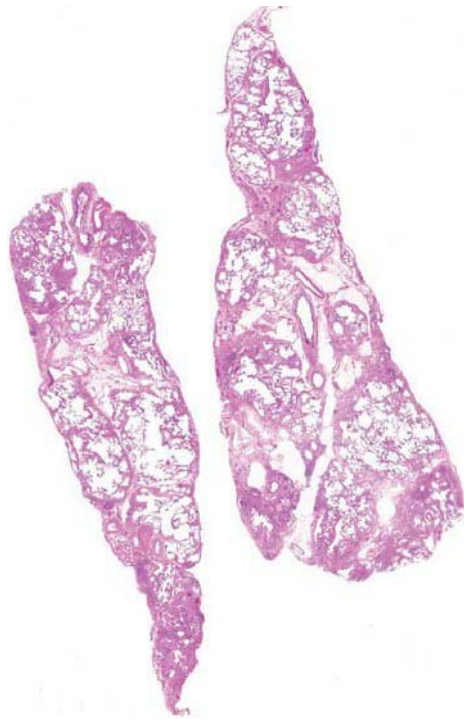
Table 6.4

Microscopic features of UIP

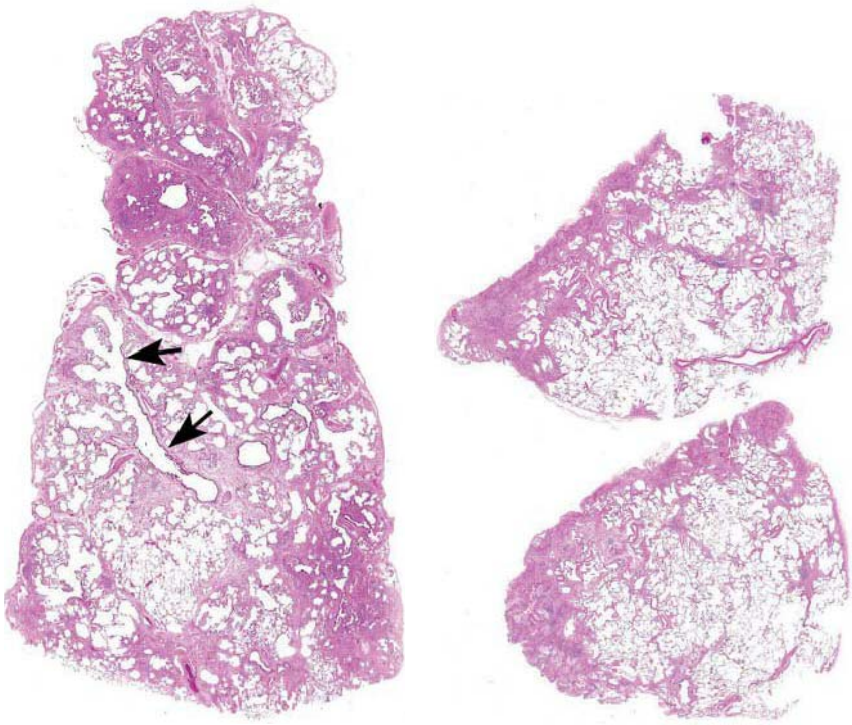
Patchy pattern of interstitial fibrosis mixed with normal parenchyma
Disease jumps back and forth abruptly between fibrotic and normal in <1 high-power field
Disease worse immediately under the pleura (early)
Honeycombed areas or solid sheets of fibrous tissue (architectural distortion)
Disease often worse in periphery of lobule with centrilobular sparing (early)
Scattered fibroblast foci
Interstitial inflammation minimal except in honeycombed foci
Airspace macrophages minimal except in honeycombed foci

However, fibrosing disease with a centrilobular predominance, meaning fibrosis predominantly around the bronchovascular bundle, is not UIP (Table 6.5)

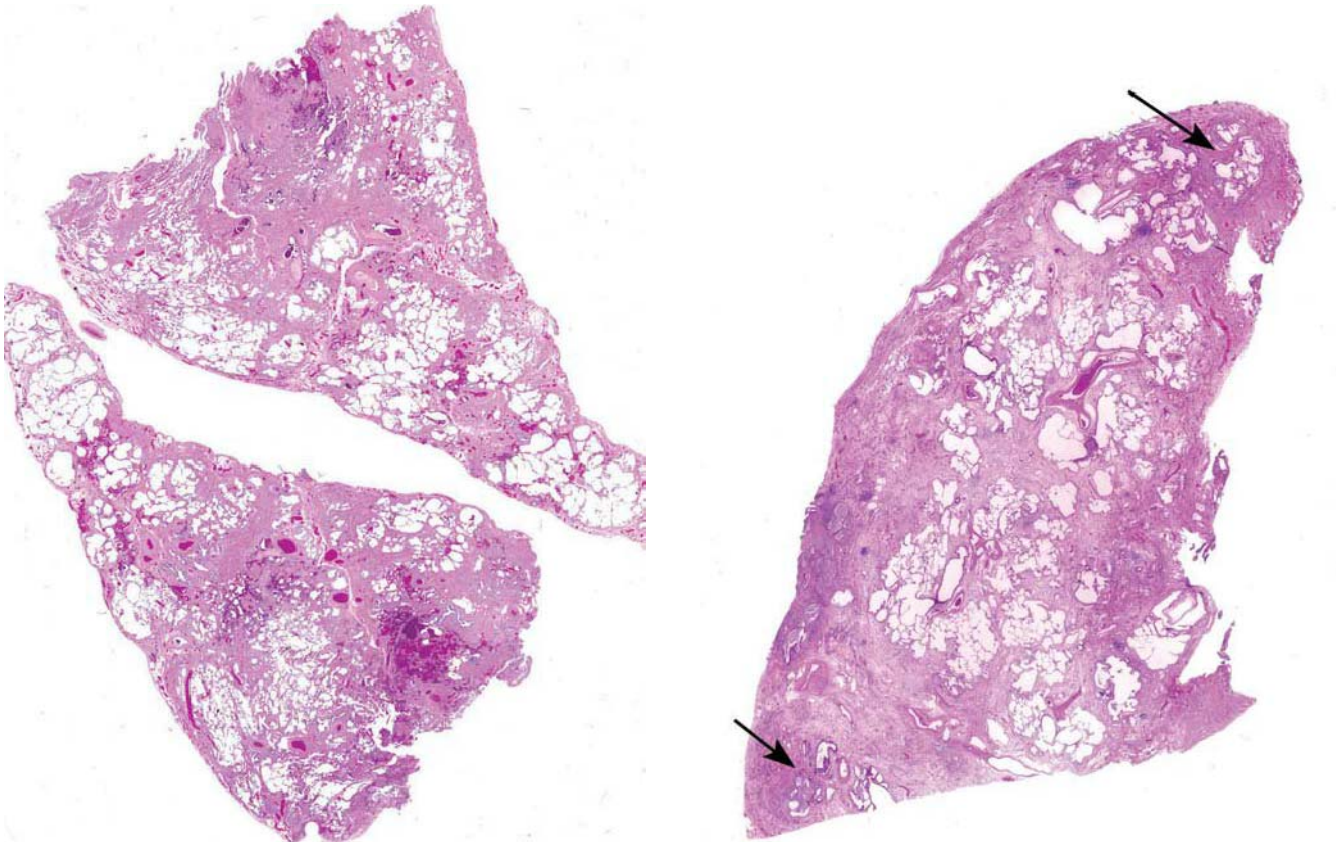
Two other constant features of UIP are *architectural distortion*, visible as areas of honeycombing or sheets of dense fibrous tissue (Figs. 6.26 to 6.29), sometimes with prominent muscular metaplasia of the fibrous tissue (Fig. 6.30), and *fibroblast foci*—tufts of granulation tissue tightly applied to underlying fibrous tissue, with the



FIGURES 6.17 to 6.19. Legend appears on following page



FIGURES 6.17 to 6.19. Whole mount views of relatively early UIP illustrating the typical pattern of patchy fibrosis and the tendency of the fibrosing process to involve the subpleural regions. Note the area of traction bronchiolectasis in **Figure 6.18** (*arrows*). Traction bronchiolectasis is often visible on HRCT and indicates the presence of underlying fibrosis.



FIGURES 6.20 and 6.21. Whole mount views of UIP, more severe than is shown in Figures 6.17 to 6.19. Even in relatively severe disease, there is still patchy fibrosis with fibrotic foci alternating with normal lung. **Figure 6.21** has areas of microscopic honeycombing (*arrows*).

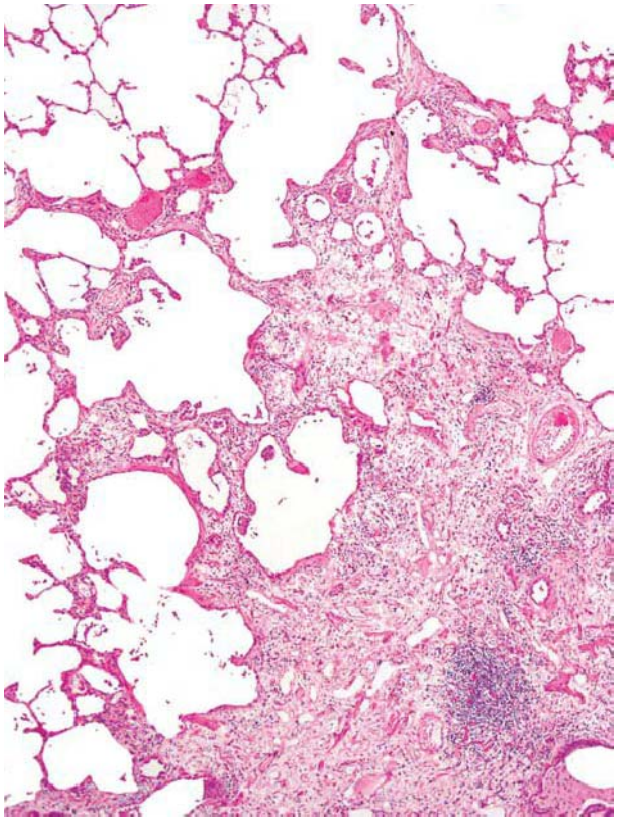
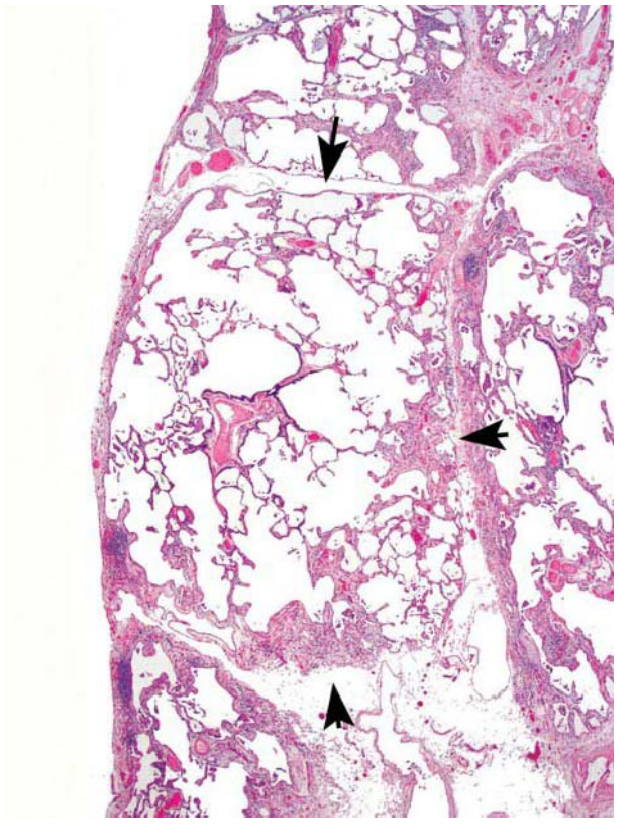
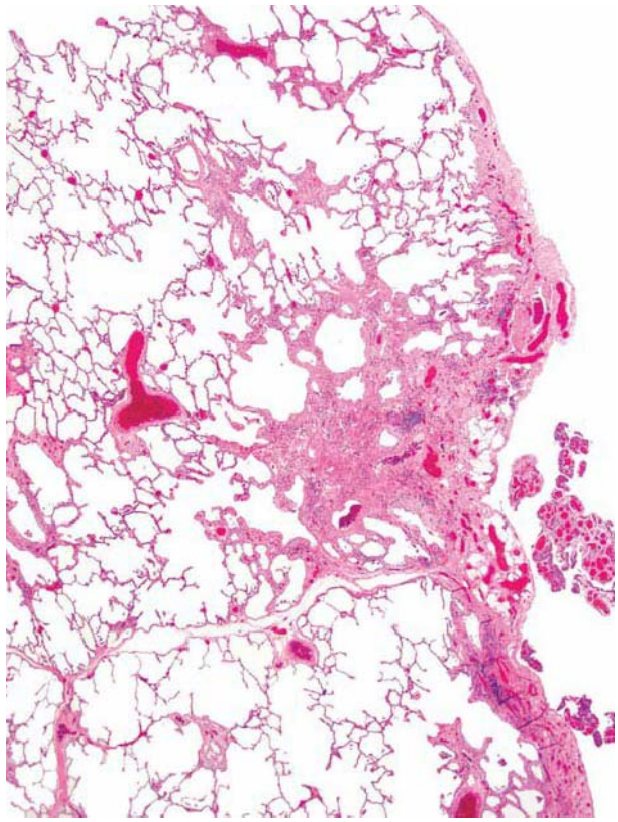
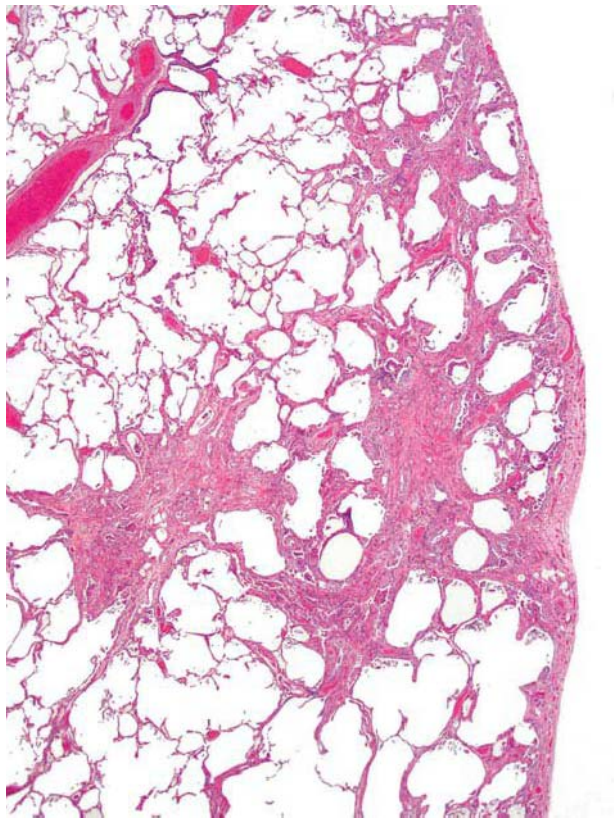


FIGURE 6.22. Characteristic pattern of patchy interstitial fibrosis that jumps back and forth between very abnormal and perfectly normal alveoli in the space of 1 high-power field. This kind of patchy fibrosis is sometimes referred to as morphologic heterogeneity and is very typical of UIP.



FIGURES 6.23 to 6.25. Legend appears on next column





FIGURES 6.23 to 6.25. Examples of early or minimal involvement in UIP. In **Figure 6.23,** the fibrosing process involves the periphery of a lobule with central sparing (*arrows* mark the interlobular septa). This is a characteristic pattern of UIP but is seen only occasionally. In **Figures 6.24** and **6.25**, the process is predominantly subpleural with minimal extension deeper into the lung.

Table 6.5

Fibrosing interstitial diseases with a centrilobular predominance

Not UIP
Chronic HP (Chapter 12)
Idiopathic bronchiolocentric interstitial fibrosis (Chapter 12)
Airway centered interstitial fibrosis (Chapter 23)
Peribronchiolar fibrosis (Chapter 23)

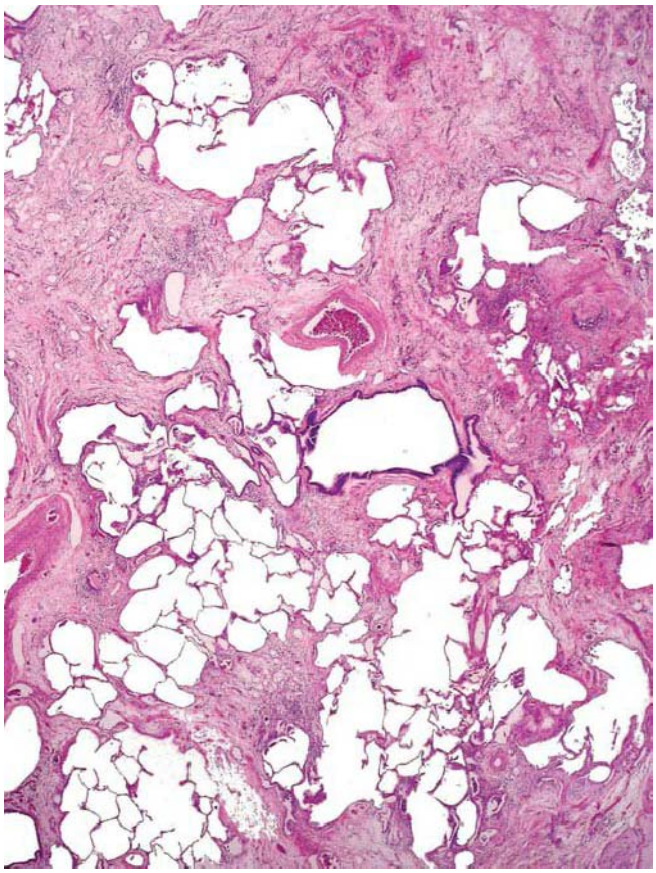
fibroblasts in the granulation tissue arranged parallel to the underlying lung (Fig. 6.31 to 6.35). Fibroblast foci can comprise young edematous granulation tissue (Fig. 6.32) or increasingly dense and collagenized granulation tissue (Figs. 6.33 to 6.35) and are covered by cuboidal to flattened epithelial cells (Figs. 6.32 to 6.34). Fibroblast foci are believed to be the sites of injury in UIP and repeated (unknown) insults leading to fibroblast foci that turn into dense fibrosis is the process by which UIP is thought to progress.

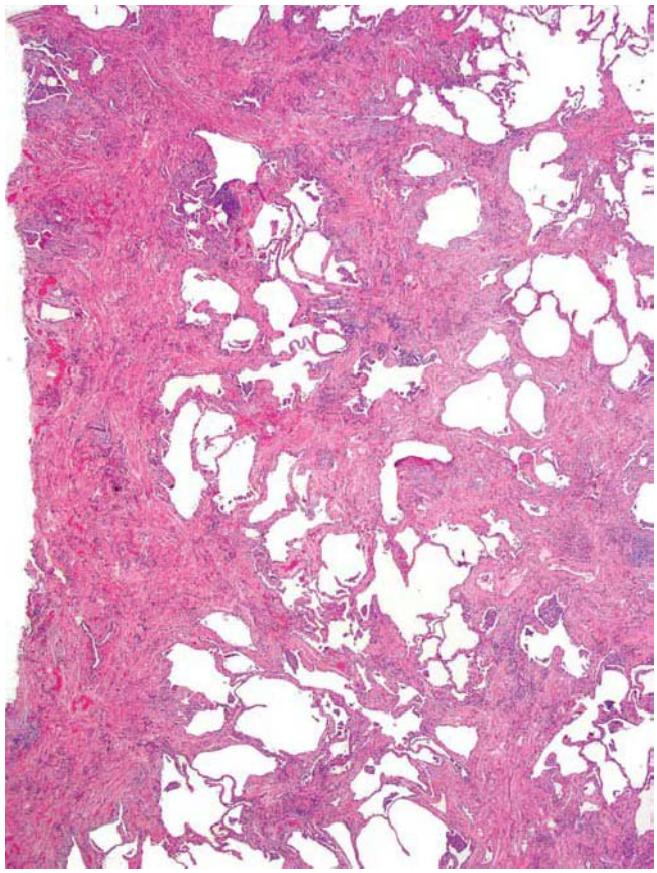
A myth has grown that fibroblast foci are specific to UIP. This is not true: fibroblast foci can be seen in any type of fibrosing process in the lung including around nonspecific scars (Figs. 6.40 and 6.41). The separation of fibroblast foci from the granulation tissue plugs of BOOP is discussed in Chapter 5 (Table 5.3).

Interstitial inflammation in UIP comprises lymphocytes and plasma cells and is generally sparse, except in honeycombed foci. If there are prominent lymphoid nodules (Fig. 6.36) or prominent interstitial inflammation (Fig. 6.37) in a biopsy that otherwise is typical of UIP, one should consider UIP associated with a collagen vascular disease.[8] Chronic HP that mimics UIP (Chapter 12) also may show a fairly marked chronic interstitial inflammatory response.

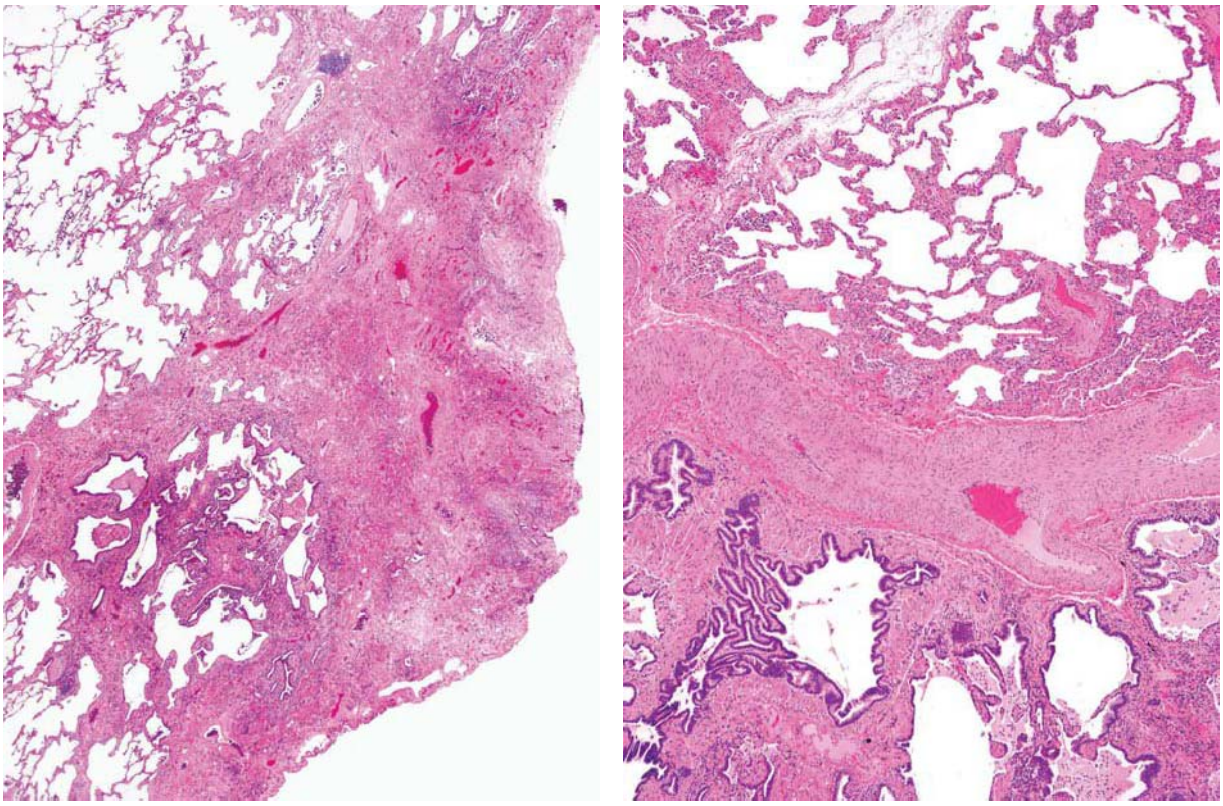
UIP in Patients with Collagen Vascular Disease

A UIP picture may be seen with any type of collagen vascular disease but is particularly common with systemic sclerosis and rheumatoid arthritis and is relatively rare with lupus.[8] UIP in patients with collagen vascular disease





FIGURES 6.26 and 6.27. More advanced fibrosis in UIP. Even with fairly advanced disease, the characteristic pattern of marked fibrosis alternating with completely normal lung is still present. Note the paucicellular nature of the fibrosis; this is typical of idiopathic UIP.



FIGURES 6.28 and 6.29. Microscopic honeycombing and sheets of fibrous tissue (i.e., architectural distortion) in UIP.

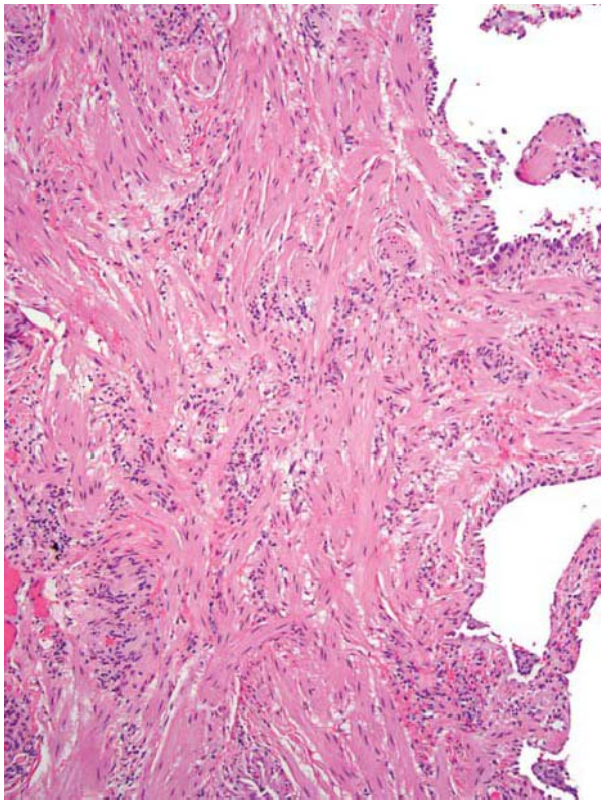


FIGURE 6.30. Smooth muscle metaplasia in UIP. Smooth muscle may replace the fibrous tissue in UIP. This is a common finding that has no diagnostic significance. In the past muscle metaplasia has sometimes been referred to as "muscular cirrhosis," but this term is archaic and has no diagnostic value.

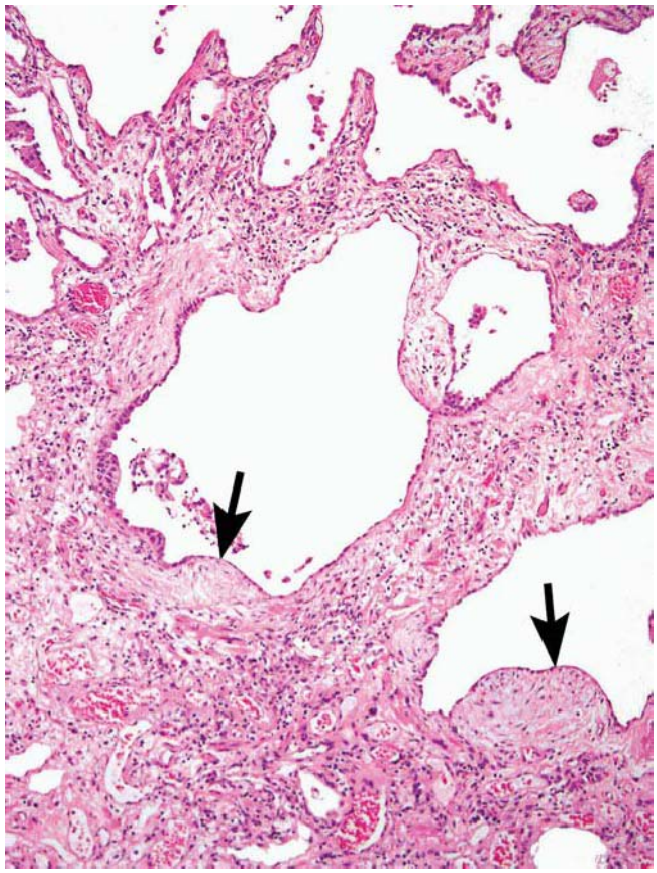
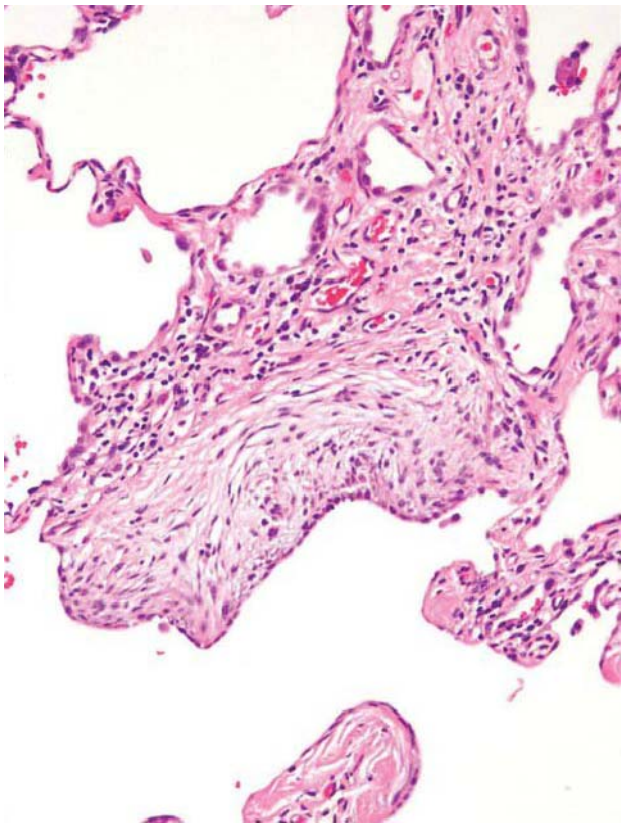


FIGURE 6.31. Fibroblast foci in UIP. The figure shows two fibroblast foci (*arrows*) tightly applied to areas of underlying fibrosis.



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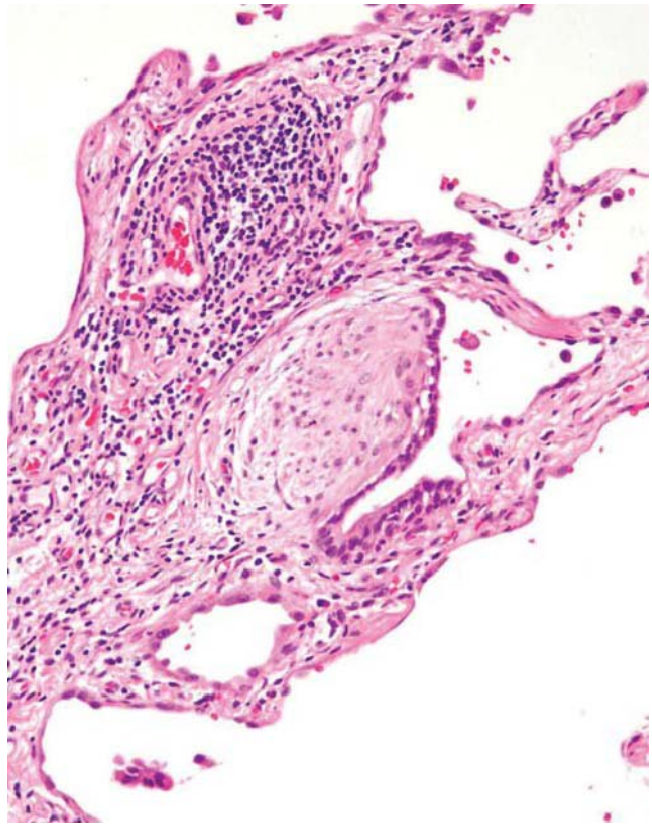

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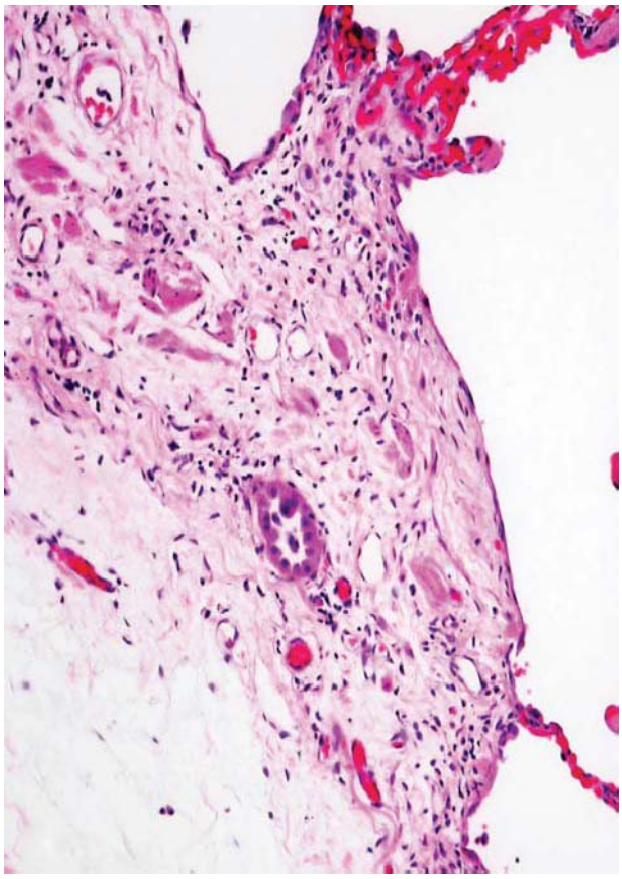

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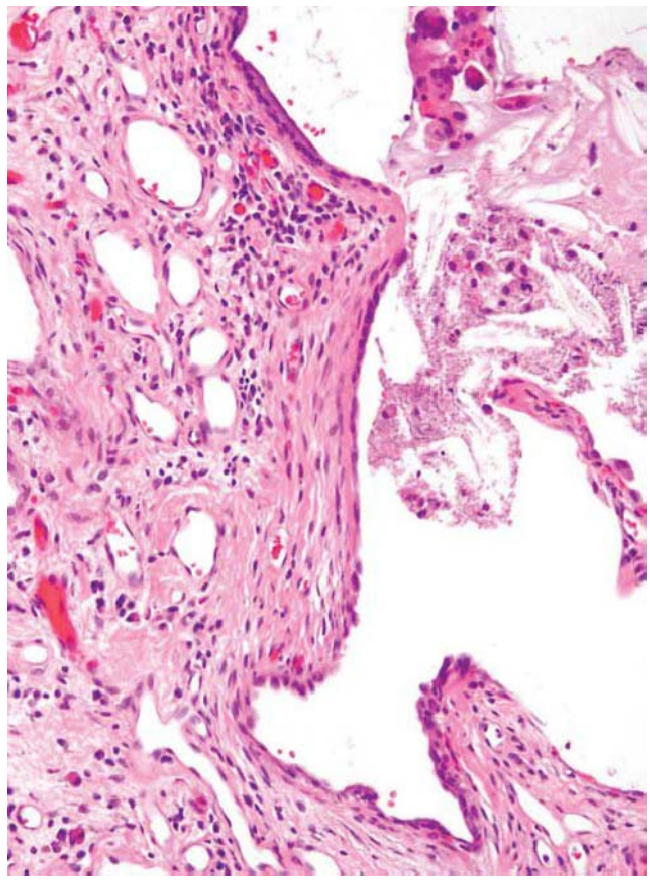
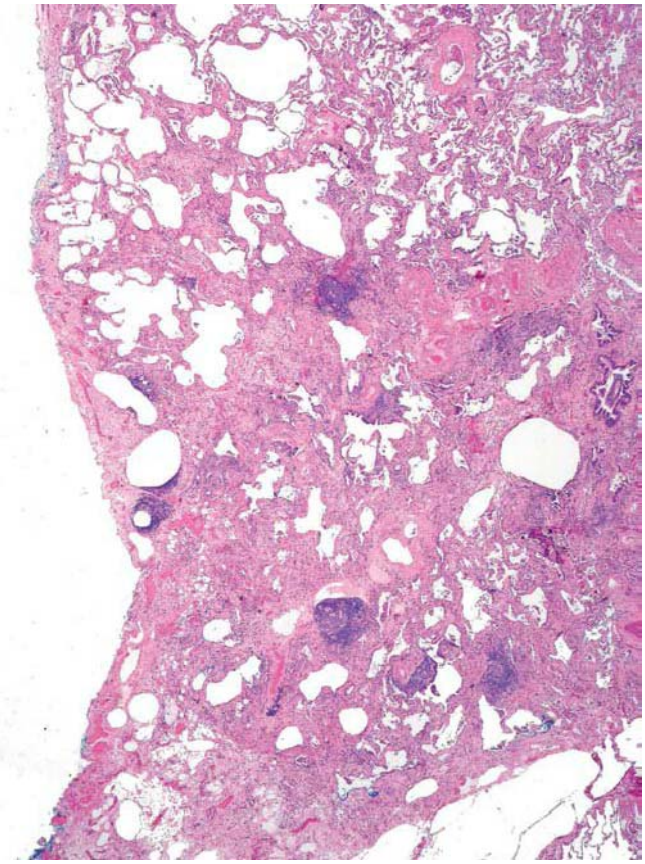
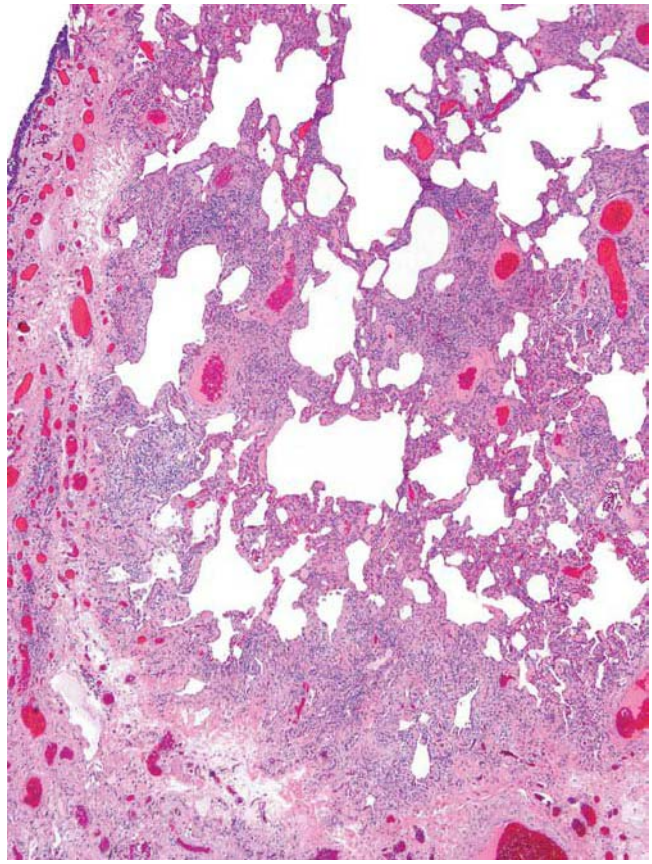


6.34

FIGURES 6.32 to 6.35. illustrate the progression of fibroblast foci from early cellular forms (*upper left panel,* Fig. 6.32) to (clockwise) progressively more fibrotic forms that eventually become part of the dense fibrosis of UIP. In **Figure 6.35** (*lower left*) the fibroblast focus is almost completely collagenized.





FIGURES 6.36 and 6.37. Markers of underlying collagen vascular disease in UIP. In **Figure 6.36** there are numerous lymphoid nodules, whereas in **Figure 6.37** there is a fairly marked chronic inflammatory interstitial infiltrate, something that is not generally present in idiopathic UIP.

is, pathologically, very similar to idiopathic UIP except for increased interstitial cellularity and, particularly, lymphoid nodules (Figs. 6.36 and 6.37). When features suggestive of a collagen vascular disease are present, this should be noted in the diagnosis line, as the prognosis may be better than idiopathic UIP (see section Prognosis).

Although UIP and NSIP (see Chapter 7) are different diseases, NSIP-like areas can sometimes be found in patients with UIP[9] (Figs. 6.38 and 6.39). Because the presence of a UIP pattern determines prognosis even when areas with an NSIP pattern are present,[10] NSIP-like areas should not be mentioned in the diagnosis in UIP cases.

DIAGNOSTIC MODALITIES

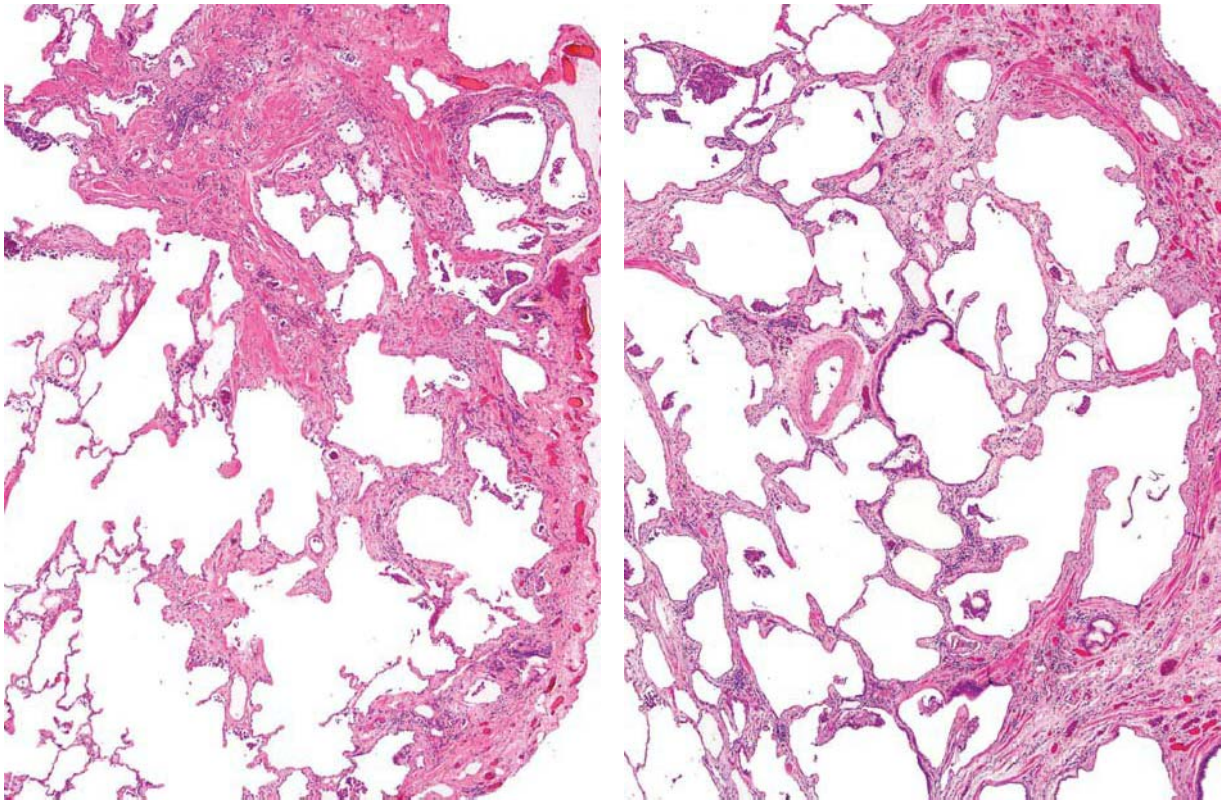
UIP is a diagnosis made primarily on low-power architecture and as such cannot be diagnosed on transbronchial biopsy. Even if definite fibrosis is present in a transbronchial biopsy, this finding is of no diagnostic utility (see Chapter 3) and we advise not mentioning fibrosis in the diagnosis line in transbronchial biopsies least that be misinterpreted as indicating that UIP or another fibrosing interstitial pneumonia is present.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of UIP is shown in Table 6.6. Any kind of localized scar can mimic UIP (Figs. 6.40 and 6.41). If in doubt, consultation with the radiologist is very helpful in showing that a particular process is localized rather than diffuse. Most of the other processes listed in Table 6.6 may mimic UIP in a given field but do not show a typical UIP picture at low power or on imaging; however, drug reactions (Fig. 6.42) and radiation reactions can be diffuse mimics of UIP and history is crucial for separating out these etiologies. Microscopically chronic HP can also be very similar, to UIP; in most such cases giant cells or granulomas, features that are not part of UIP, will allow the separation, but a small percentage of chronic HP cases are morphologically identical to UIP. This separation is not crucial, as the prognosis is similarly poor for both (see Chapter 12).

COMPLICATIONS AND CAUSES OF DEATH IN UIP

Table 6.7 lists the complications and causes of death in UIP. There is a markedly increased risk of lung cancer



FIGURES 6.38 and 6.39. Fibrotic NSIP-like area in UIP. Most of the biopsy in this case looked like typical UIP (**Fig. 6.38**), but areas mimicking fibrotic NSIP pattern were also present (**Fig. 6.39**). In the presence of a typical UIP pattern the fibrotic NSIP pattern should be ignored because the presence of a UIP pattern determines prognosis.

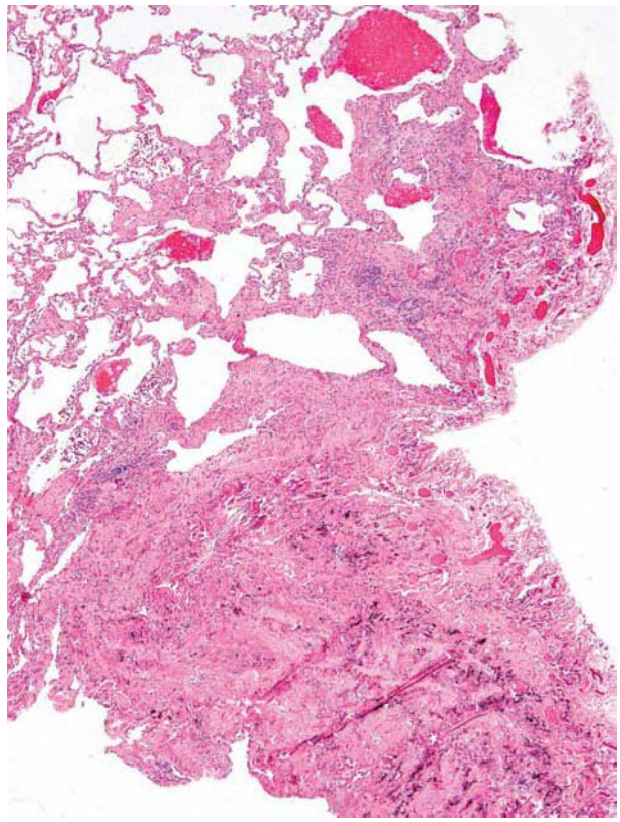
(Fig. 6.43), even in nonsmokers, but the overall prognosis of UIP is so poor that the presence of lung cancer seems to have little effect on survival.[11]

Pulmonary hypertension is seen in 30% to 40% of UIP patients awaiting transplantation, although the incidence may be lower if all UIP patients are considered,[12] and

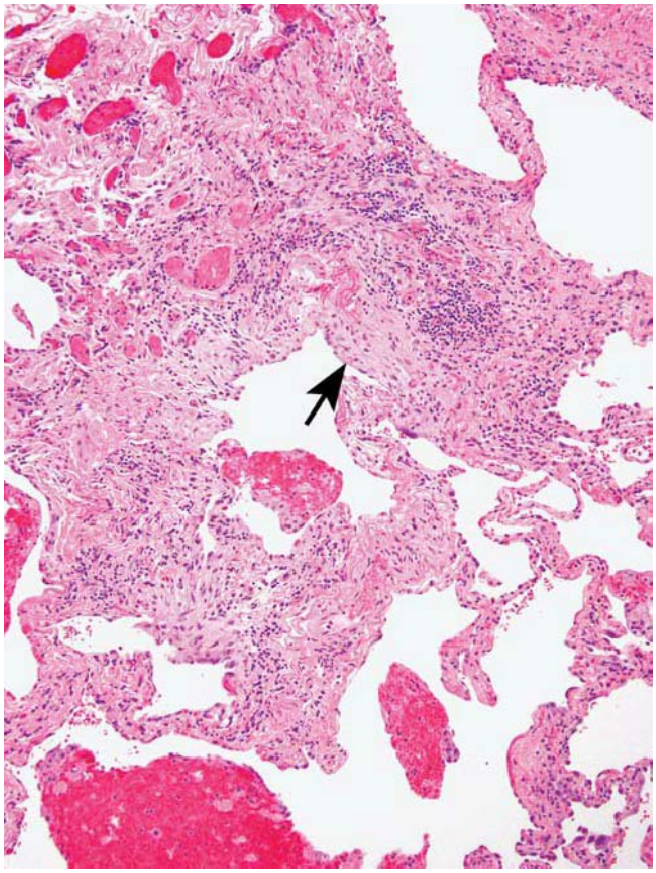
Table 6.6

Morphologic differential diagnosis of UIP

Fibrotic forms of hypersensitivity pneumonitis (look for giant cells/granulomas)
Burnt-out sarcoid
Burnt-out LCH
Burnt-out TB or fungal infection
Chronic aspiration with scarring (look for foreign body giant cells/lipid droplets)
Chronic eosinophilic pneumonia that has progressed to fibrosis
Organized and honeycombed ARDS
Old radiation injury
Old drug injury
Old local scars
Fibrotic foci around bronchiectasis



FIGURES 6.40 and 6.41. Legend appears on following page



FIGURES 6.40 and 6.41. Localized scar mimicking UIP. The patient had a wedge resection of a lung cancer and then developed a mass lesion at the site of the previous resection. The resulting scar shows patchy fibrosis (**Fig. 6.40**) and even a fibroblast focus (*arrow,* **Fig. 6.41**) . Fibroblast foci are not specific to UIP and can be seen in any kind of fibrosing process. This case illustrates the importance of clinical and radiologic correlation in diagnosing interstitial lung disease.

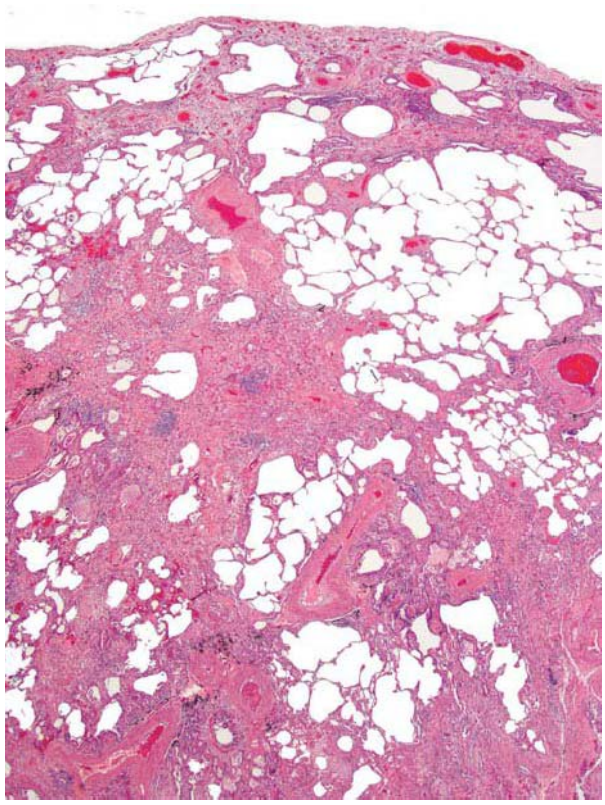


FIGURE 6.42. Drug reaction mimicking UIP. This patient was an elderly woman who received multiple chemotherapeutic drugs for ovarian cancer.

Table 6.7

Complications and causes of death in UIP

Carcinoma of lung (~10-fold increased risk)
Pulmonary hypertension/cor pulmonale
Respiratory failure secondary to progressive fibrosis
Pulmonary infections
Acute exacerbation = acute lung injury superimposed on UIP
  Incidence probably ~10% of UIP cases/year
  Cause of death in ~50% of cases

probably leads to a shortened life expectancy. Microscopically thick-walled pulmonary artery branches are commonly seen in UIP and in virtually all forms of interstitial lung disease; however, most of the time these changes are nonspecific and it is difficult to reliably predict the presence of pulmonary hypertension from the morphologic findings.

An *acute exacerbation* is the development of diffuse parenchymal opacities on imaging (see Fig. 4.21), usually accompanied by hypoxemia and marked shortness of breath, in a patient with UIP.[13,14] Acute exacerbations are also seen with other types of fibrosing ILD, but with much lower frequencies (Table 6.8). By definition the process is not caused by heart failure or infection. UIP lungs are probably very susceptible to infection, and the literature suggests that the incidence of infections and acute exacerbations are about equal.[13] Some acute exacerbations probably represent (undiagnosed) viral infections.[14]

The incidence of acute exacerbations in UIP is probably about 10% of cases per year, and acute exacerbations are an important cause of death; in some autopsy series 50% of UIP deaths have shown morphologic evidence of an acute exacerbation.[15]

Morphologically acute exacerbations look like diffuse alveolar damage (DAD), which may be in the acute or organizing phase, or bronchiolitis obliterans organizing pneumonia (BOOP), plus an underlying pattern of UIP.[16,17] (see Figs.4.21 to 4.25). When the acute injury pattern is spatially separated from the old fibrosis of UIP (Figs. 4.24 and 4.25), the diagnosis is readily made; however, in some instances the acute injury obscures the underlying disease (Figs. 4.22 and 4.23). A helpful hint is that neither DAD

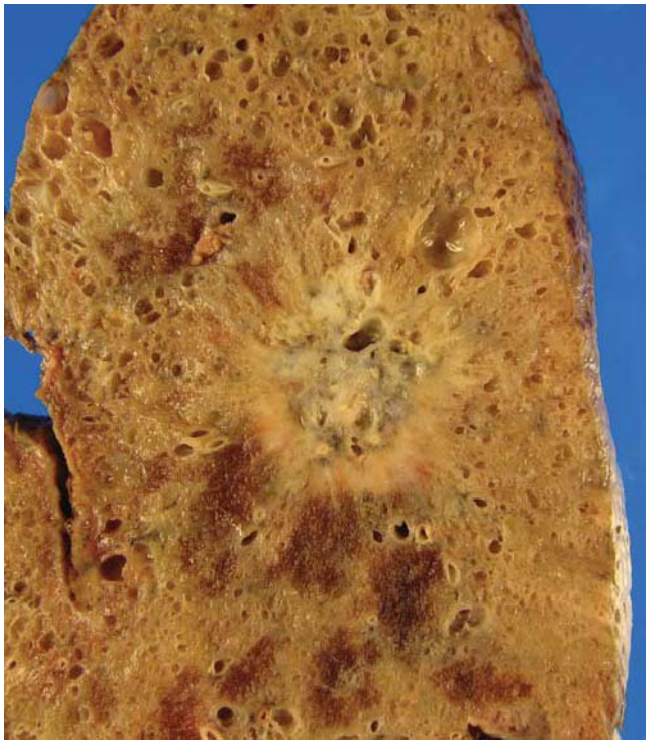


FIGURE 6.43. Lung carcinoma arising in UIP. Note the extensive honeycombing.

Table 6.8

Types of fibrosing ILD that are associated with acute exacerbations

UIP
Idiopathic
Associated with collagen vascular disease
Fibrotic NSIP
Idiopathic
Associated with collagen vascular disease
Chronic hypersensitivity pneumonitis with UIP-like pattern
DIP
Asbestosis

nor BOOP should show evidence of old fibrosis; if old fibrosis is present then the acute injury must be superimposed on some pre-existing condition. Sometimes the old fibrosis is more apparent on imaging studies than on biopsy (Fig. 4.21).

CHOICE OF BIOPSY

As discussed in Chapter 3, UIP cannot be diagnosed on transbronchial or core biopsy. A surgical lung biopsy or a resection specimen is required.

PROGNOSIS

The prognosis of idiopathic UIP is poor, with about a 3-year median survival.[7] The prognosis of UIP in collagen vascular disease is controversial and perhaps confounded by studies that fail to separate UIP from fibrotic NSIP. At this time UIP in rheumatoid arthritis appears to have the same poor prognosis as idiopathic UIP,[18] but UIP in other forms of collagen vascular disease may respond to steroids and/or cyclophosphamide and may have a much better prognosis.

The prognosis of acute exacerbations is, overall, very poor. Most patients do not leave the hospital, but some do respond to high dose steroids.[13,14] Patients with acute exacerbations and a pattern of BOOP on biopsy seem to do better than those with DAD.[17]

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CHAPTER

7

Nonspecific Interstitial Pneumonia

NOMENCLATURE ISSUES

Quite like bronchiolitis obliterans organizing pneumonia (BOOP), nonspecific interstitial pneumonia (NSIP) is both an idiopathic disease and a reaction pattern seen in other conditions—most notably, collagen vascular diseases, hypersensitivity pneumonitis (HP), and drug reactions. There are no universally agreed rules for names to be used in diagnosis, but when the underlying process is clearly not idiopathic NSIP, a different name or a qualifying name may be appropriate; for example, a patient with an NSIP pattern on imaging and biopsy, a history of bird exposures, and anti-avian protein antibodies in serum should be diagnosed with HP, rather than NSIP. A patient with rheumatoid arthritis and NSIP should be diagnosed for "NSIP associated with rheumatoid arthritis" or "NSIP with features of a collagen vascular disease," (assuming such features are present; see below).

CLINICAL FEATURES

The clinical features of NSIP depend somewhat on associated conditions, but regardless of etiology, NSIP is usually associated with signs and symptoms of an interstitial lung disease (ILD) (Chapter 1).[1] The age range is wide, extending even to children. Symptoms may be present for months to years and can include systemic symptoms such as fever.

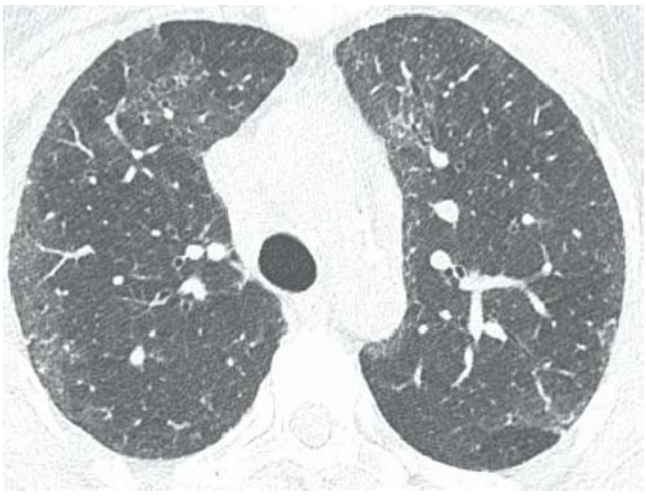


FIGURE 7.1. NSIP. HRCT at the level of the upper lobes shows bilateral GGOs.

NSIP is the most common pathologic pattern of ILD in patients with collagen vascular disease,[1] and in such patients extrapulmonary features of the underlying disease such as arthritis and arthralgias are usually evident, but NSIP can also be the first manifestation of a collagen vascular disease.

IMAGING

At initial presentation, NSIP is characterized on high resolution computed tomography (HRCT) by extensive bilateral ground-glass opacities (GGOs) frequently associated with mild reticulation but no honeycombing[2] (Figs. 7.1 and 7.2). The parenchymal abnormalities usually involve predominately the lower lung zones and are frequently associated with lower lobe volume loss.[3] A purely ground-glass pattern is seen in cellular NSIP. Reticulation superimposed on GGOs usually indicates fibrosis and may be seen in mixed cellular and fibrotic NSIP and in fibrotic NSIP. The distribution of the reticulation in the axial plane is variable: It may involve mainly the peripheral regions, have a random distribution, or spare the subpleural parenchyma.[3]

With progression of disease, there is a decrease in the extent of ground-glass attenuation and an increase in

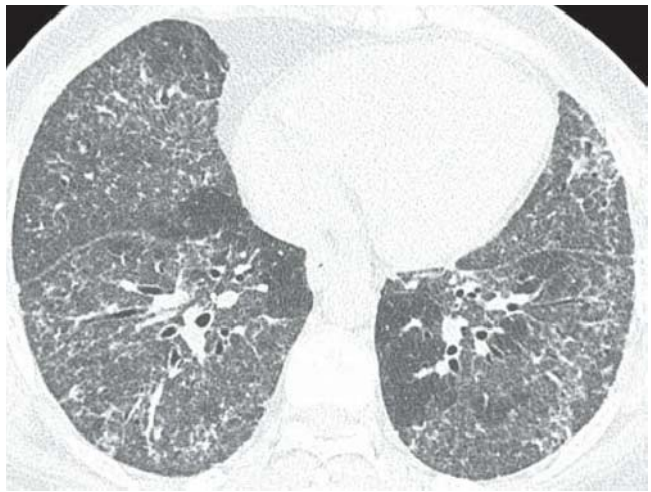


FIGURE 7.2. HRCT at the level of the lower lung zones demonstrates extensive bilateral GGOs with superimposed mild fine reticulation. Although the upper lobe changes are consistent with cellular NSIP, the reticulation in the lower lobes suggests the presence of some fibrosis. The patient was a 42-year-old woman with NSIP.

reticulation and traction bronchiectasis, and in some cases the development of honeycombing (Figs. 7.3 and 7.4).[2] Reticulation may become the predominant pattern. Findings that favor NSIP over usual interstitial pneumonia (UIP) in these patients include presence of extensive traction bronchiectasis with minimal or no honeycombing. Another helpful feature is that in approximately 40% of patients with NSIP and fibrosis, the reticulation spares the immediate subpleural lung in the dorsal portions of the lower lobes, a region that typically has honeycombing in UIP (Fig. 7.4).[2]

The HRCT manifestations of NSIP at presentation, when there is a predominance of GGOs, minimal reticulation and no honeycombing, are easily distinguishable from those of UIP but are otherwise relatively nonspecific and may mimic a variety of other chronic interstitial diseases, particularly HP and desquamative interstitial pneumonia (DIP).[4] When the reticulation becomes extensive the manifestations of NSIP may mimic those of UIP.[2] Although in certain clinical settings, such as patients with scleroderma, the HRCT findings may be characteristic enough to strongly suggest NSIP, a definitive diagnosis of NSIP requires surgical lung biopsy.

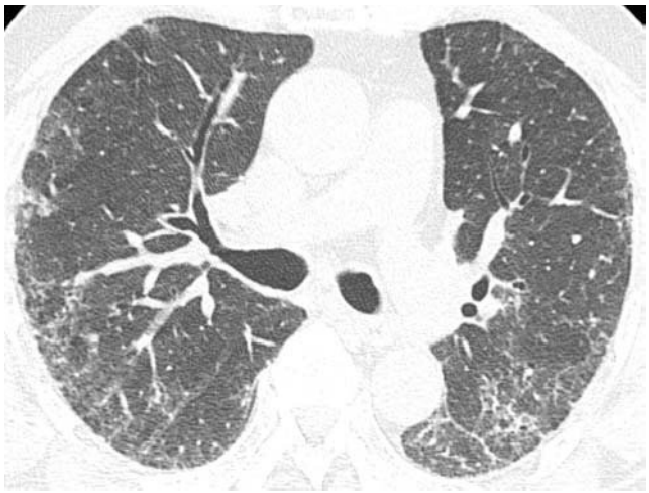


FIGURE 7.3. NSIP. HRCT at the level of the upper lobes shows bilateral GGOs and peripheral reticulation.

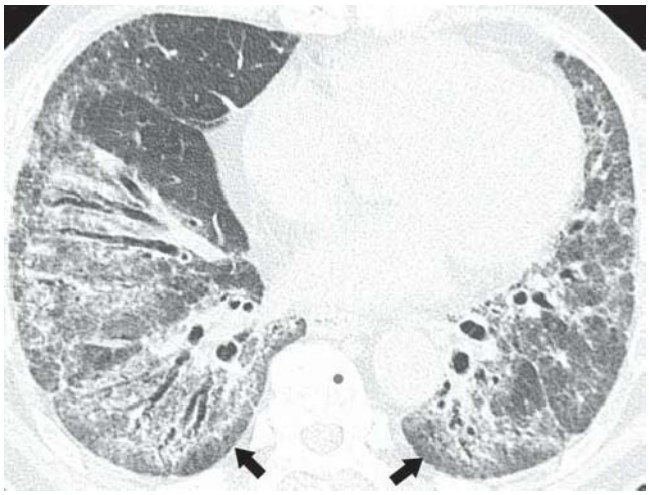


FIGURE 7.4. HRCT at the level of the lung bases demonstrates extensive bilateral GGOs with superimposed reticulation and traction bronchiectasis. Note the lack of reticulation in some of the subpleural lung of the dorsal regions (subpleural sparing; *arrows*). The patient was a 64-year-old man with fibrotic NSIP.

PATHOLOGIC FEATURES

Gross Appearances

NSIP typically is deceptively normal on gross examination, even when there is extensive microscopic fibrosis (Fig. 7.5). Honeycombing is uncommon and the presence of extensive honeycombing should raise a question of UIP.

Microscopic Features of NSIP

There is a certain amount of variability in the patterns that different experienced pulmonary pathologists put into the category of NSIP, but the original and prototypical description is that of extremely homogeneous *chronic interstitial inflammation* and/or *interstitial fibrosis that follows the original alveolar walls* and produces no or minimal architectural distortion (Fig. 7.6 to 7.8). In most cases there is neither honeycombing nor sheets of fibrosis. Because of

FIGURE 7.5. Gross photograph of a case of fibrotic NSIP at autopsy. Note the absence of honeycombing or obvious architectural distortion.

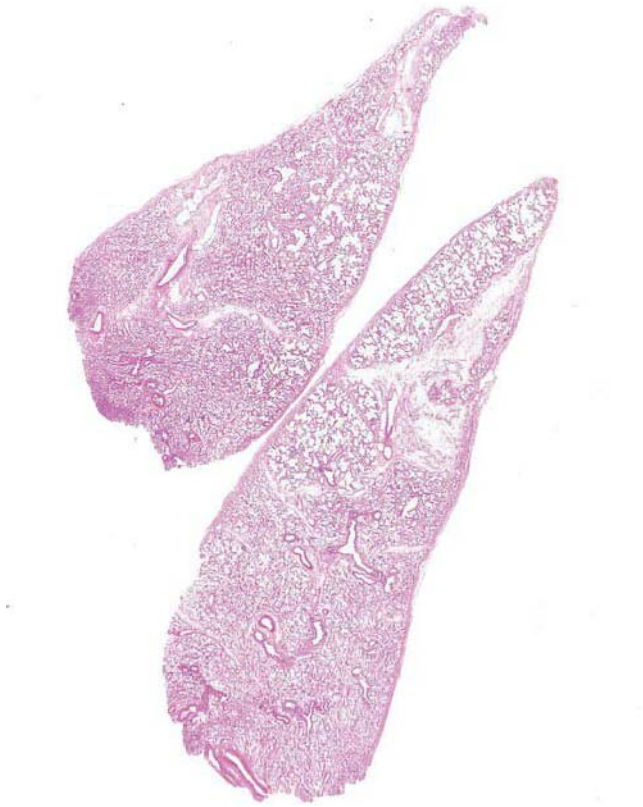
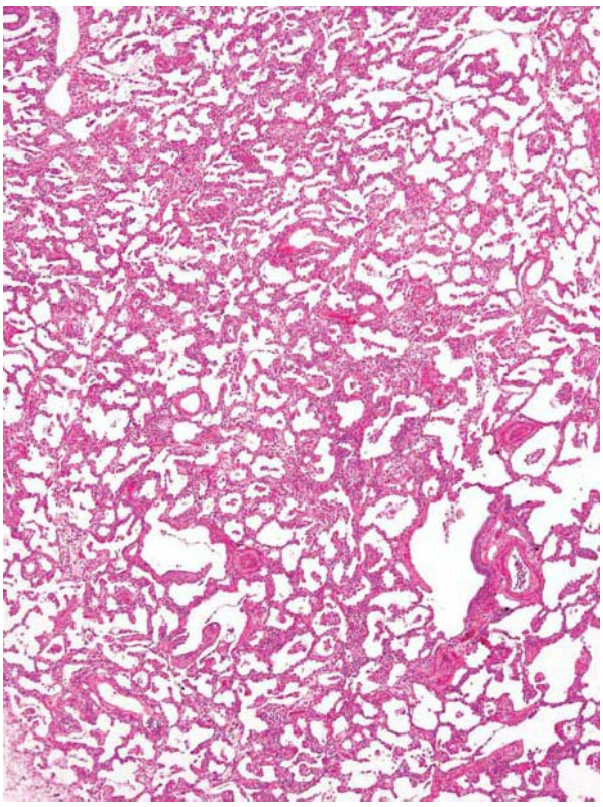


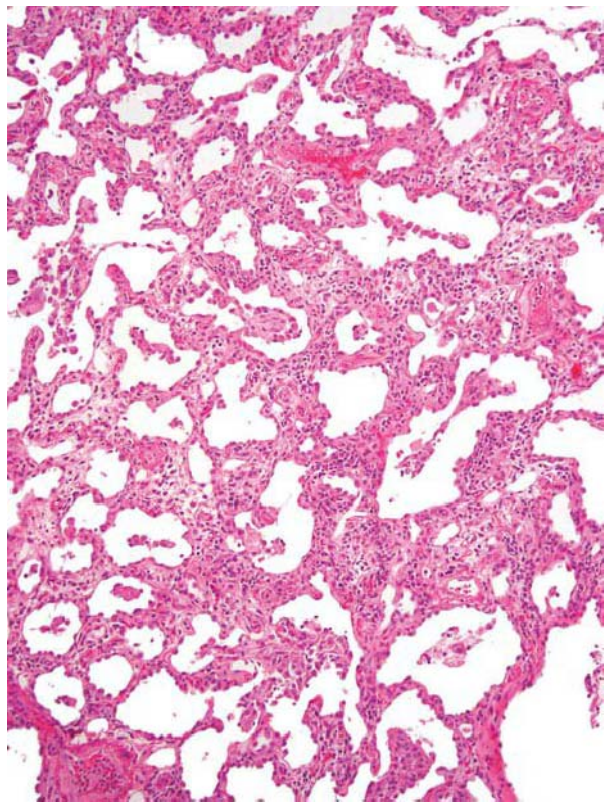
FIGURE 7.6. Scanning power view of a case of mixed cellular and fibrotic NSIP. Although this low-power view does not allow a specific diagnosis, it shows that there is no honeycombing and no architectural distortion.

the homogeneity of the process, the scanning power view is that of a lung that is only subtly abnormal (Fig. 7.6).

The term nonspecific interstitial pneumonia is also often applied to processes where the interstitial inflammation or fibrosis is not completely homogeneous, rather the lung is abnormal, and then the interstitial process becomes less severe, only to reappear again a short distance away (Fig. 7.9). Although this description may sound like UIP at first glance, the important point is that there is still no architectural distortion; rather the abnormality fades in and out of the parenchyma (Fig. 7.9), whereas in UIP there are sharp transitions between markedly abnormal fibrotic parenchyma and normal or relatively normal parenchyma (see Figs. 6.20 to 6.27).

In the original description of NSIP by Katzenstein and Fiorelli,[5] cases were divided into purely cellular (Figs. 7.10 and 7.11), purely fibrotic (Figs. 7.9, 7.12, and 7.13), and mixed cellular and fibrotic forms. There has been a tendency over the ensuing years to try to use only cellular or fibrotic as descriptors, but our experience is that some cases show both features (Figs. 7.6 to 7.8). *The presence or absence of fibrosis should always be noted when diagnosing NSIP* because purely cellular forms can completely disappear with treatment, leaving normal parenchyma, whereas the more fibrosis that is present, the less the reversibility and the worse the prognosis. Biopsies are not always representative of the amount of fibrosis and correlation with imaging studies can be helpful (Table 7.1).





FIGURES 7.7 and 7.8. Progressively higher-power views of the same case. The fibrotic and inflammatory process follows the original alveolar walls; this is the characteristic finding in NSIP.

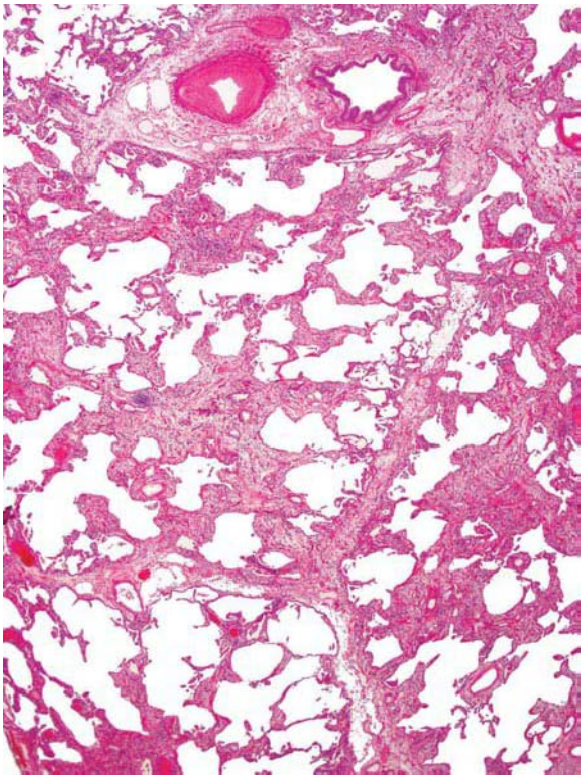
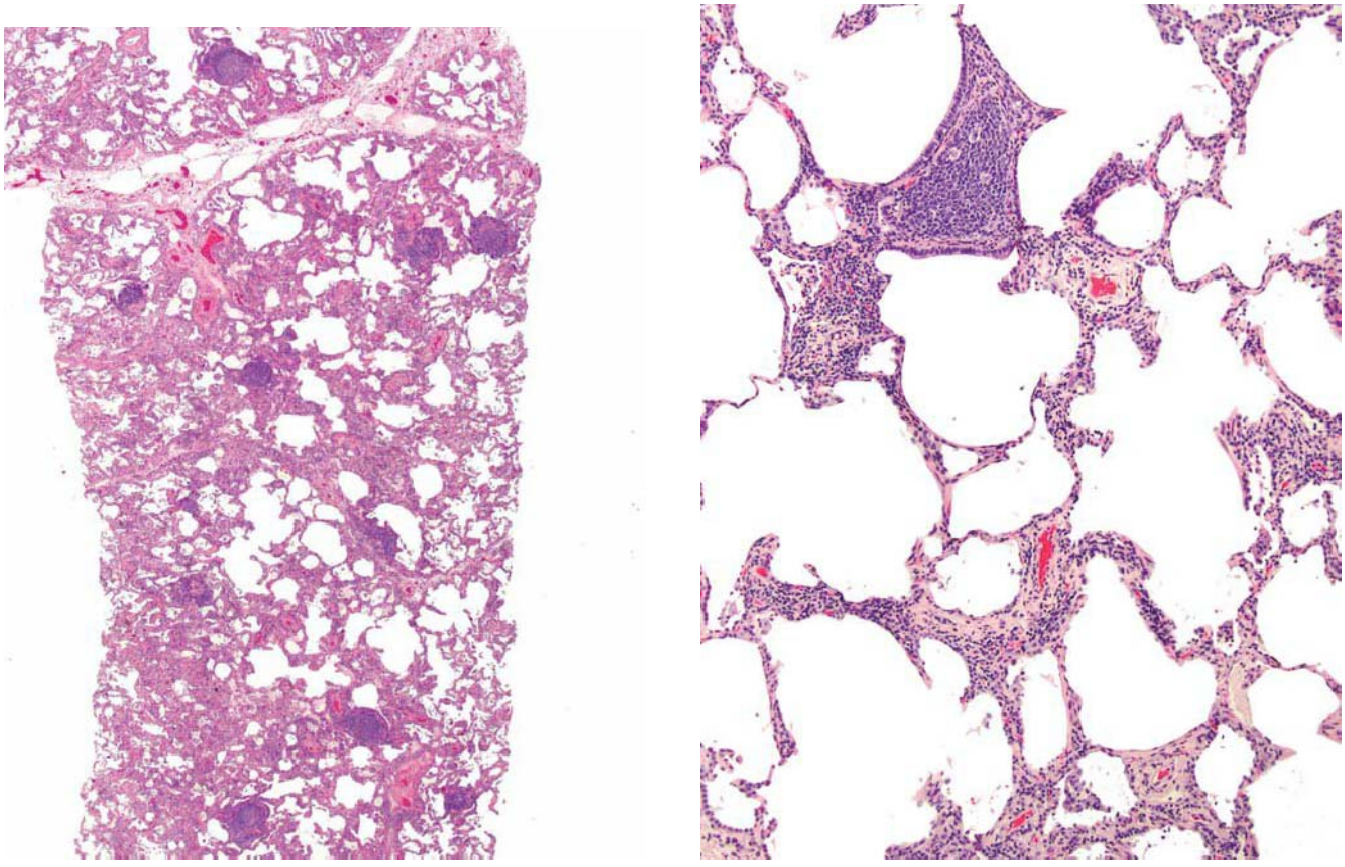


FIGURE 7.9. Fibrotic NSIP with area-to-area variation in the amount of interstitial fibrous tissue.

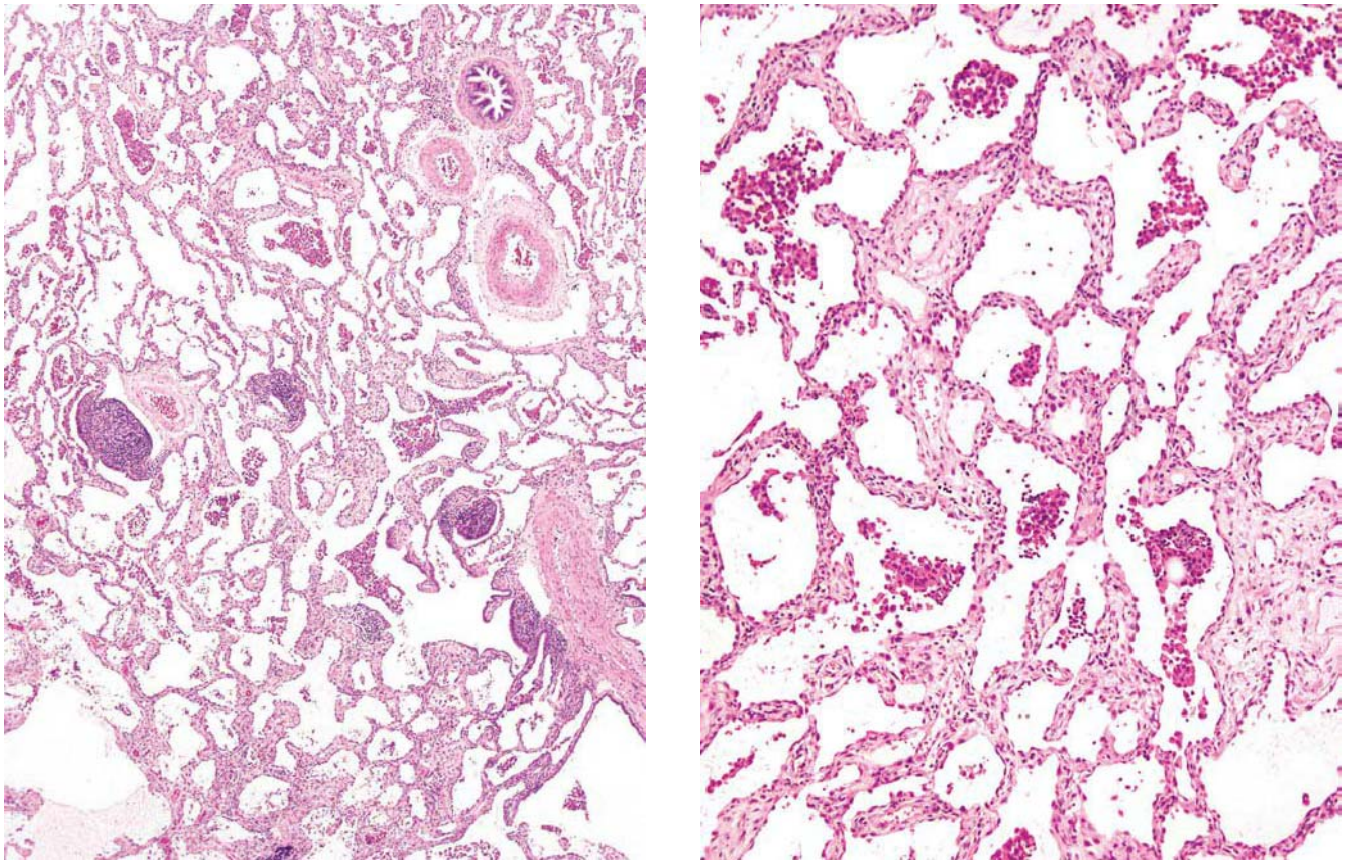
As noted honeycombing is unusual in NSIP, but in our experience it is found in cases of fibrotic NSIP where there is marked expansion of the alveolar walls, such that they tend to become confluent (Figs. 7.14 and 7.15). Sometimes only sheets of fibrosis without honeycombing are seen in such cases (Figs. 7.16 and 7.17). These processes are exceptions to the rule that NSIP does not produce architectural distortion. Fibroblast foci are occasionally seen in NSIP (Figs. 7.18 and 7.19), but large numbers of fibroblast foci raise a question of whether the biopsy is a bad sample of UIP.

Tiny widely spaced foci of BOOP are fairly common in NSIP of any cause (Figs. 7.20 and 7.21). However, extensive areas of BOOP on a background of NSIP suggest either an underlying collagen vascular disease (and this combination may be apparent on imaging as well) or a bad sample of a case that is actually BOOP and not NSIP but with the biopsy taken from the edge of the BOOP lesion (see Fig. 5.11). Interstitial inflammation is always part of BOOP, and the edge of a BOOP lesion may have mostly interstitial inflammation and little granulation tissue. Imaging studies are often very helpful in sorting out these possibilities.

As is true of UIP, the presence of lymphoid nodules (Figs. 7.10 to 7.12) suggests an underlying collagen vascular disease. Increased alveolar macrophages may be present (Fig. 7.13), but large numbers of macrophages filling airspaces should raise a question of DIP (see Chapter 8).



FIGURES 7.10 and 7.11. Cellular NSIP. The numerous lymphoid nodules are a hint that the patient has an underlying collagen vascular disease, and this should be noted in the diagnosis line.



FIGURES 7.12 and 7.13. Fibrotic NSIP in a patient with rheumatoid arthritis. The lymphoid nodules suggest an underlying collagen vascular disease. Note the airspace collections of alveolar macrophages; these are sometimes prominent in NSIP.

The original description of NSIP included cases with interstitial giant cells or granulomas, but the consensus from more recent studies is that giant cells and granulomas are not part of NSIP, and when present suggest that the correct diagnosis is HP (Figs. 7.22 and 7.23) or sometimes a drug reaction; for example, caused by methotrexate or anti-TNF agents.

Table 7.1

Pathologic features of NSIP

Cellular NSIP: chronic interstitial inflammation following the original alveolar walls
Fibrotic NSIP: old dense interstitial fibrosis following the original alveolar walls
Mixed cellular and fibrotic NSIP: combinations of the above
Tends to be morphologically homogeneous
Small areas of BOOP may be present
Generally no or only occasional fibroblast foci present
Lymphoid nodules may be present and suggest underlying collagen vascular disease
Usually absence of architectural distortion/ honeycombing

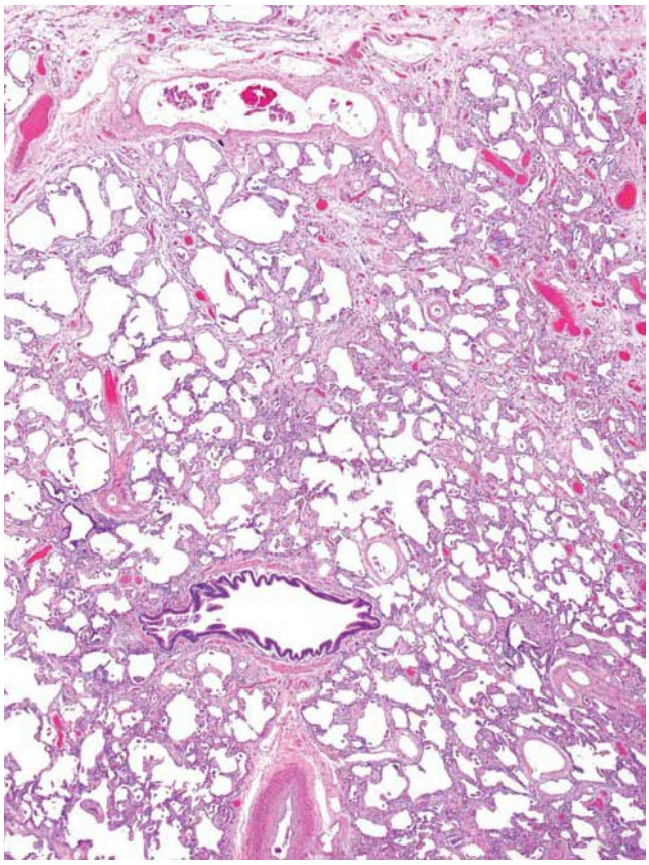
DIAGNOSTIC MODALITIES

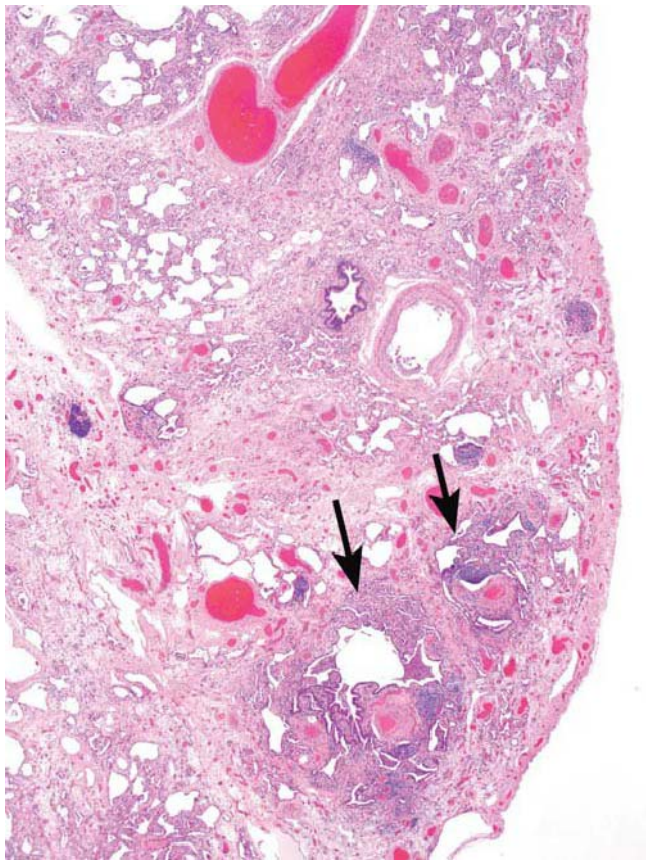
NSIP is a diagnosis that requires evaluation of low-power architecture over a large area. Only video-assisted thoracoscopic surgery (VATS) or open biopsies are suitable for this purpose. NSIP cannot be diagnosed on transbronchial biopsy and in fact such biopsies are often extremely misleading because many conditions can produce a local area of chronic interstitial inflammation (Figs. 7.27 and 7.28; and see Figs. 3.2 and 3.8).

DIFFERENTIAL DIAGNOSIS/ASSOCIATIONS

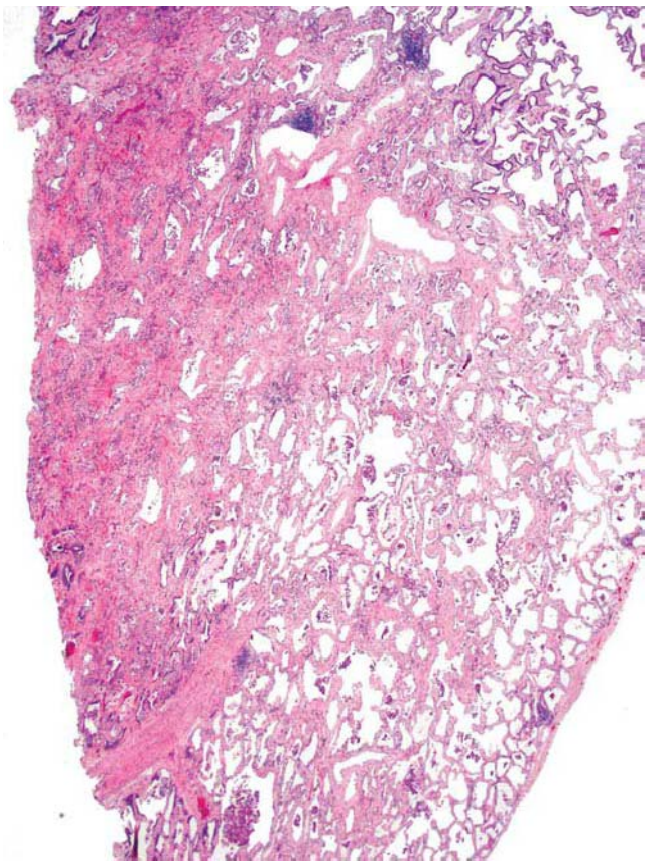
NSIP morphology is a fairly frequent finding in lung biopsies from patients with interstitial lung disease and has a wide differential diagnosis. Cases of idiopathic NSIP are actually relatively uncommon. HP (Figs. 7.22 and 7.23), drug reactions (Figs 7.24 to 7.26 and see Chapter 18), and collagen vascular diseases (Figs. 7.10 to 7.12) are the most frequent causes of an NSIP pattern, and *we recommend including these entities as important differential diagnoses in a comment when a diagnosis of NSIP is made.*

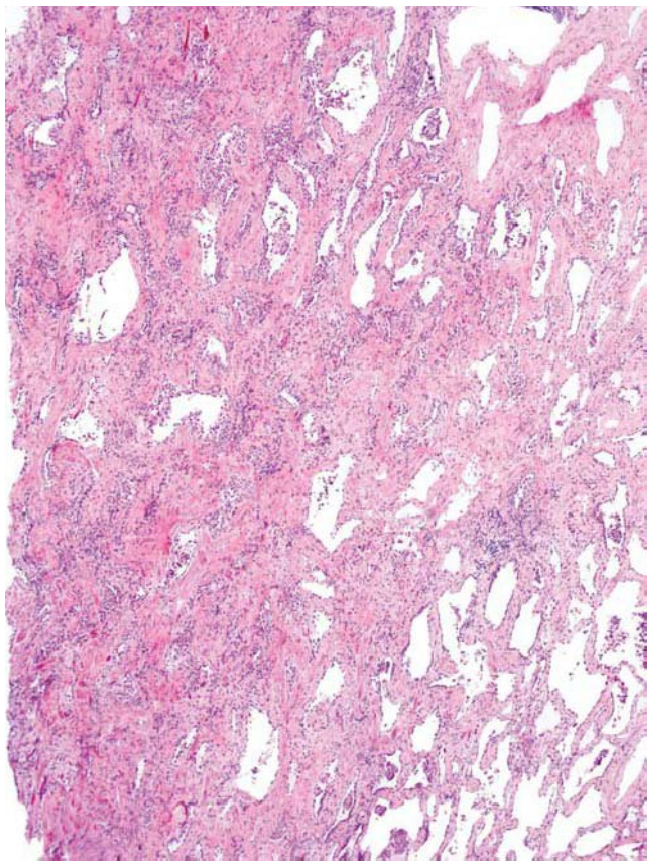
DIP (Chapter 8) can progress to fibrosis and when that happens the characteristic airspace alveolar macrophages may persist; however, in some cases they disappear,



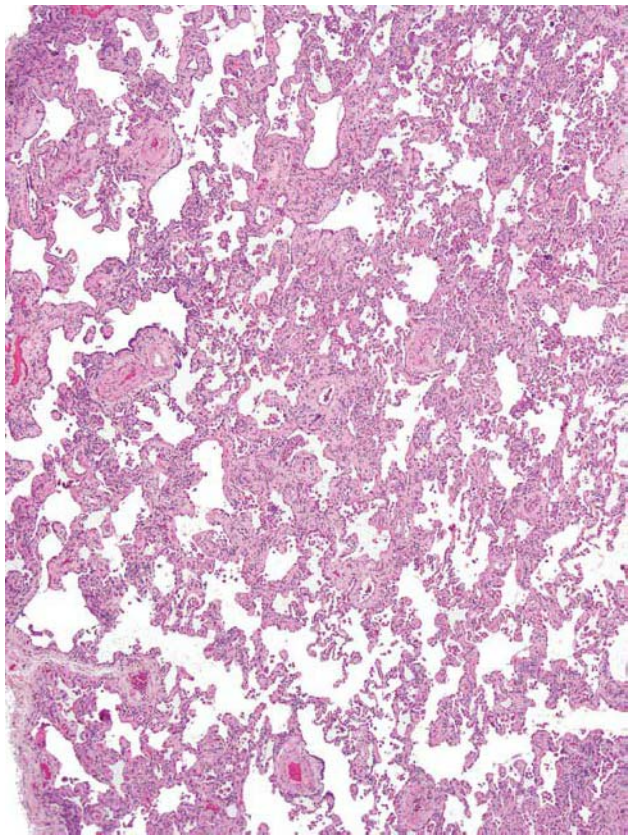


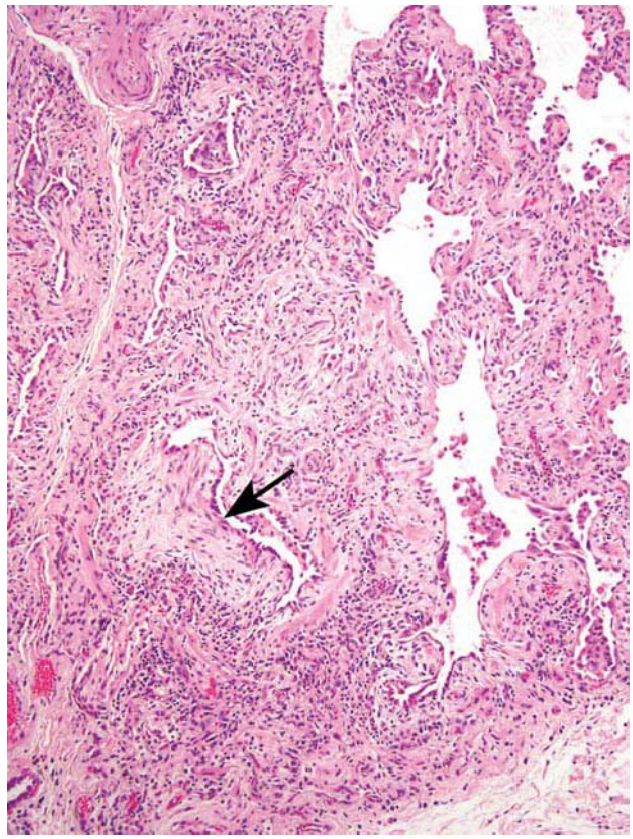
FIGURES 7.14 and 7.15. Fibrotic NSIP with an area of honeycombing (*arrows*). Honeycombing is relatively uncommon in NSIP but does occasionally occur.



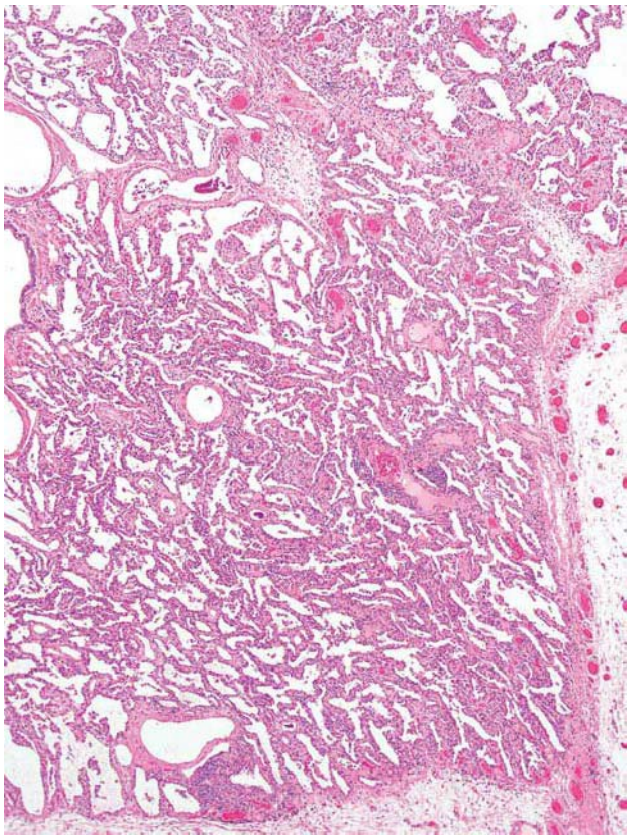


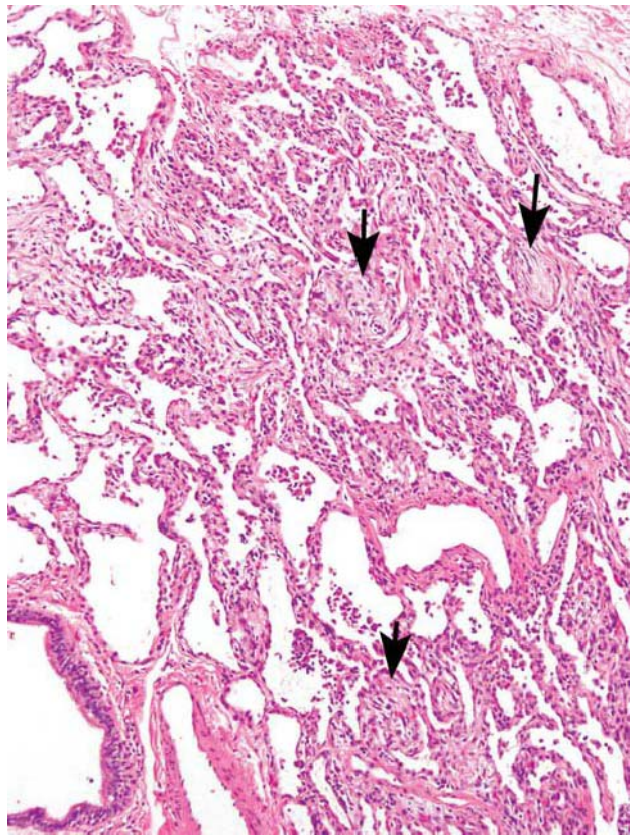
FIGURES 7.16 and 7.17. Fibrotic NSIP with an area of confluence. Confluent foci are formed by progressive expansion of alveolar walls (**Fig. 7.17**) and represent architectural distortion, a relatively uncommon finding in NSIP.



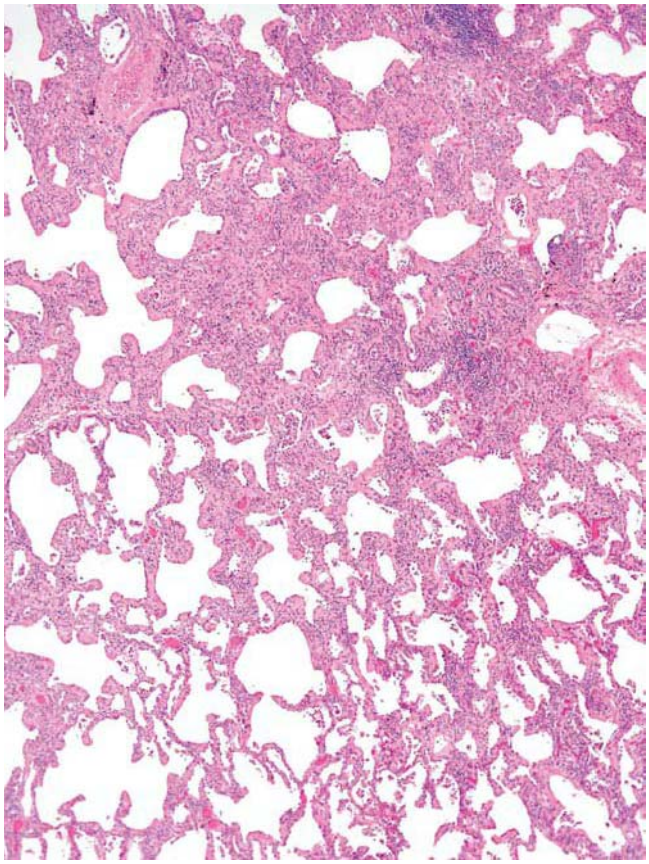


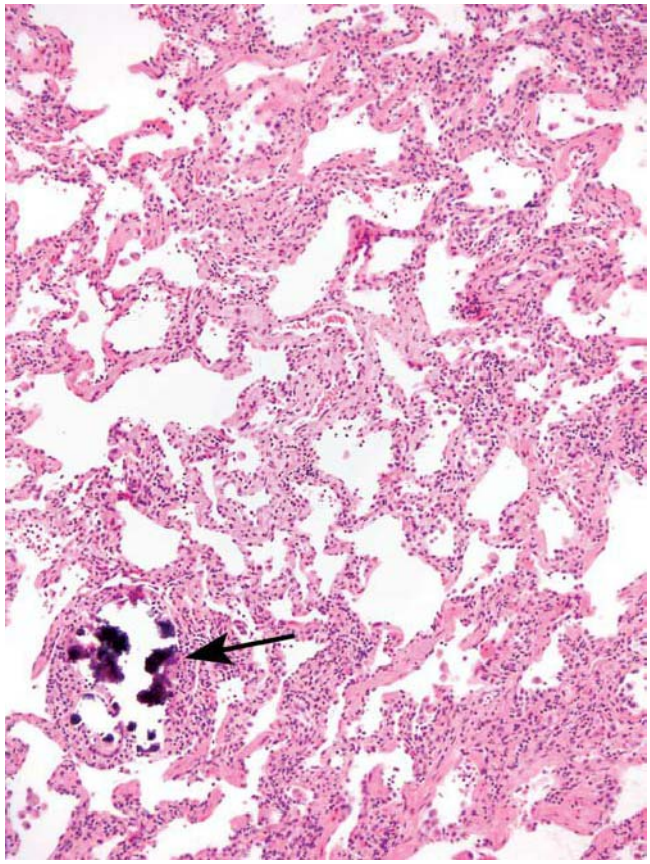
FIGURES 7.18 and 7.19. Mixed cellular and fibrotic NSIP with a fibroblast focus (*arrow*). Occasional fibroblast foci can be seen in NSIP, but the presence of numerous fibroblast foci raises a question of a bad sample of UIP.





FIGURES 7.20 and 7.21. Cellular NSIP with an area of BOOP visible in **Figure 7.21** (*arrows*). Occasional small foci of BOOP are not uncommon in NSIP, but if there are numerous foci of BOOP on a background that is clearly NSIP, the possibility of an underlying collagen vascular disease should be raised.





FIGURES 7.22 and 7.23. Chronic (fibrotic) hypersensitivity pneumonitis mimicking fibrotic NSIP. Most of the biopsy is indistinguishable from idiopathic NSIP, but the Schaumann body (*arrow*) in **Figure 7.23** marks the site of an old granuloma and indicates the correct diagnosis.

leaving a picture morphologically indistinguishable from fibrotic NSIP (see Figs. 8.18 and 8.19).

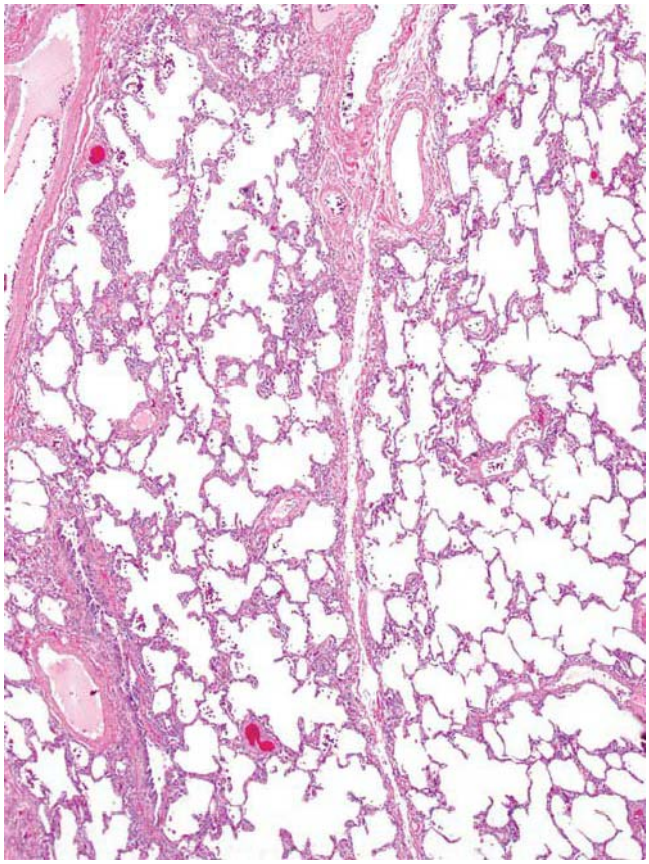
Chronic pulmonary hemorrhage can lead to interstitial fibrosis and produce a picture that very much mimics fibrotic NSIP. Clues to the diagnosis are the presence of interstitial hemosiderin or hemosiderin-laden macrophages (see Figs. 24.3 and 24.4) and iron encrustation of the elastic layers of small vessels (see Fig. 24.4). An identical phenomenon occurs in pulmonary veno-occlusive disease because of chronic alveolar hemorrhage (see Figs. 24.6 and 24.7); such patients have clinical evidence of pulmonary hypertension and thrombosed small intrapulmonary veins (see Fig. 24.8). In veno-occlusive disease the fibrosing process is limited to the subpleural regions, but with diffuse hemorrhage from capillaritis the fibrosis may be quite widespread.

Other types of fibrosing processes can produce linear fibrosis that somewhat mimics NSIP: these include burnt-out chronic eosinophilic pneumonia (see Fig. 15.18), old Langerhans cell histiocytosis (LCH) (see Fig. 10.23), and burnt-out sarcoid (see Fig. 13.28). In sarcoid and LCH the fibrosis is usually much more patchy than in fibrotic NSIP and typical granulomas or stellate nodules may be present. Imaging studies often make the diagnosis clear.

Smoker's respiratory bronchiolitis (RB) or RBILD (see Chapter 8) may produce a pattern of fibrosis following alveolar walls that mimics fibrotic NSIP (see Figs. 8.8 and 8.9). Clues to the diagnosis are that the fibrosing process is sharply localized to an area under the pleura rather than being diffuse, is often wedge-shaped with a respiratory bronchiole at the apex of the wedge, and pigmented smoker's macrophages (see Chapter 8) are present in the airspaces. Sometimes the fibrosis of RB/RBILD is quite hyalinized, as opposed to the fibrosis of NSIP.

Cellular NSIP needs to be separated from lymphocytic interstitial pneumonia (LIP). In LIP the interstitial chronic inflammatory infiltrate is much more marked than in cellular NSIP, so that the alveolar walls are considerably widened and sometimes become confluent (see Figs. 19.10 to 19.16). By definition, cellular NSIP with an intense enough inflammatory infiltrate to produce confluence would be labeled LIP; however, fibrotic NSIP may become confluent (Figs 7.16 and 7.17). LIP may also be associated with cysts (see Fig. 19.19). Small interstitial granulomas or individual giant cells are common in LIP. Most important, the intensity of the lymphoid infiltrate in LIP makes one think of a lymphoma.

NSIP-like morphology can also be seen as a local reaction pattern in completely unrelated conditions



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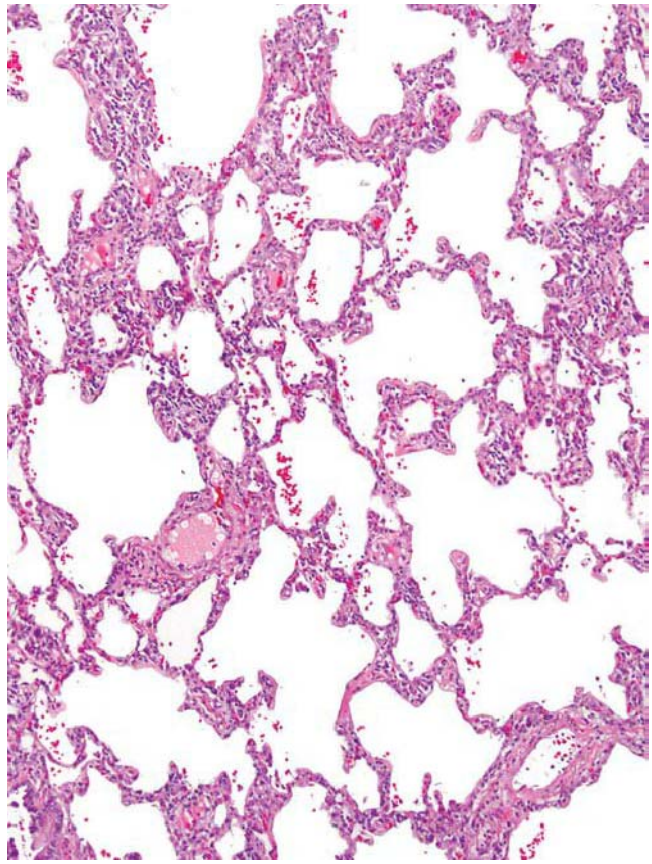

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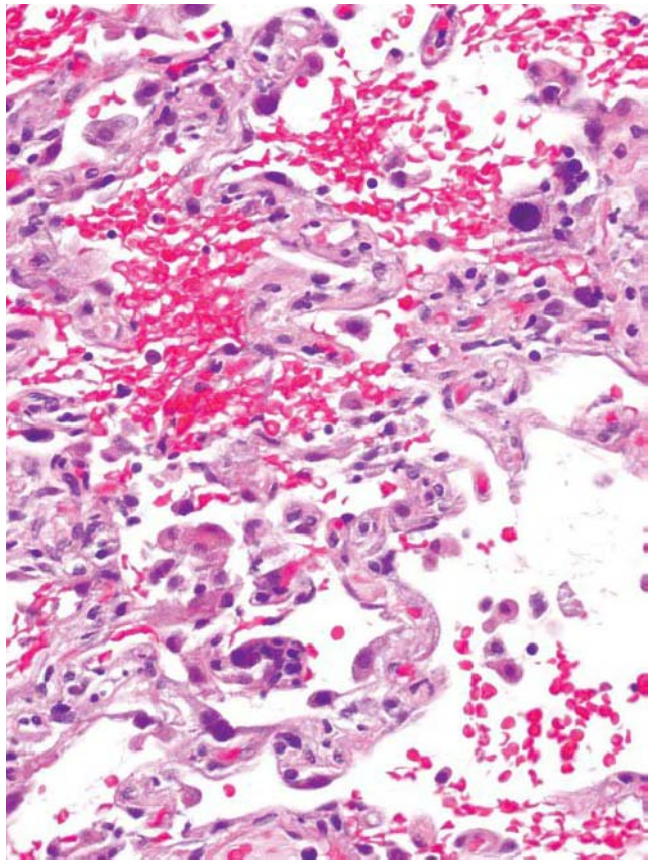
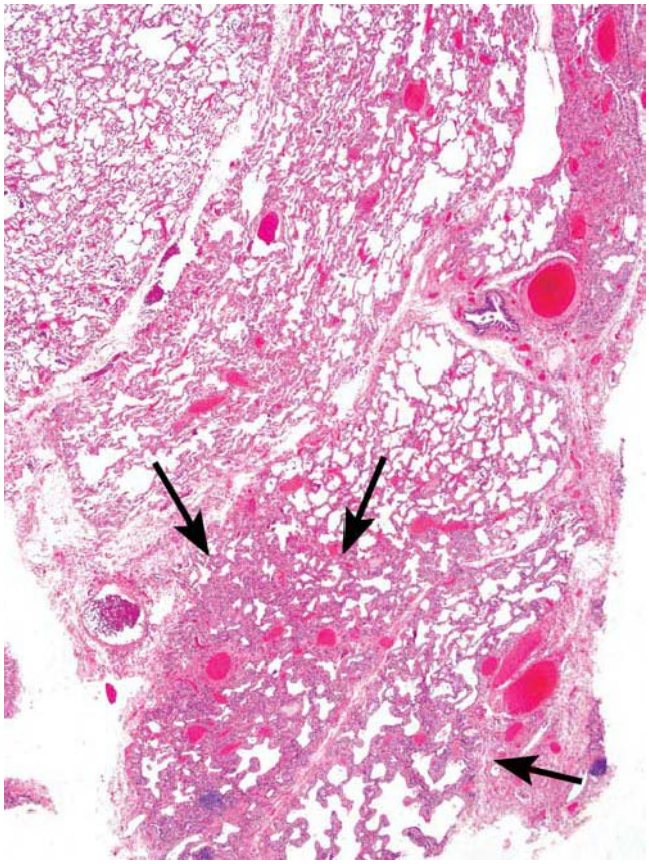
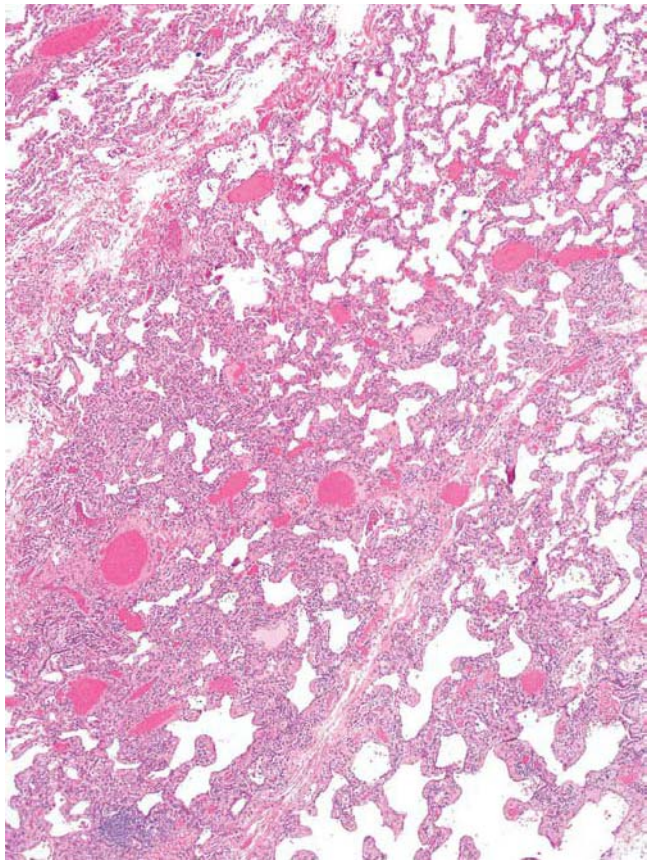


7.26

FIGURES 7.24 to 7.26. Busulfan toxicity appearing as cellular NSIP. Note the enlarged hyperchromatic nuclei typical of busulfan in **Figure 7.26.** NSIP is a common drug reaction pattern.





FIGURES 7.27 and 7.28. A local reaction mimicking NSIP. Images are from a case of spontaneous pneumothorax, and the photographed region is immediately under the inflamed pleura. The area bounded by *arrows* in **Figure 7.27** mimics cellular NSIP (higher-power magnification of this area shown in **Fig. 7.28**), but the rest of the parenchyma is normal. True NSIP is always a diffuse process. This is a localized reaction of no consequence.

(Figs. 7.27 and 7.28); it should be remembered that true NSIP is both pathologically and radiologically a diffuse process (Table 7.2).

SEPARATION OF UIP AND NSIP

The differential diagnosis that appears to cause the most difficulty is the separation of UIP and some cases of fibrotic NSIP.[6] Part of the problem arises from the fact that fibrotic NSIP-like areas can be present in otherwise perfectly ordinary UIP (see Figs. 6.38 and 6.39), and occasionally such areas occupy most of the biopsy, or if two biopsies are performed, one looks like fibrotic NSIP and the other like UIP. However, follow-up data have shown that the presence of a UIP pattern is what determines prognosis,[7,8] so that if unequivocal UIP is present, UIP should be diagnosed and the NSIP component ignored.

Features that suggest one disease or the other are shown in Table 7.3. Architectural distortion (sheets of-fibrosis and honeycombing) and patchiness of the process are the most important findings and strongly favor UIP. In most cases the distinction is easily made at scanning

Table 7.2

Differential diagnosis and associations of an NSIP pattern

Idiopathic NSIP (exclusionary diagnosis)
Some cases of HP (look for giant cells/ granulomas)
Drug reactions
Collagen vascular disease (all types)
Long-standing and largely burnt-out DIP
Old fibrotic chronic eosinophilic pneumonia
Old fibrotic DAD/ARDS
Some areas of burnt-out LCH
Edge of BOOP lesions
Chronic pulmonary hemorrhage (look for hemosiderin or iron encrusted vessel elastica)
Pulmonary veno-occlusive disease (look for hemosiderin or iron encrusted vessel elastica)
LIP
Smoker's RB/RBILD
Focally in UIP (diagnosis remains UIP)

Table 7.3

Separation of fibrotic NSIP and UIP

Fibrotic NSIP	UIP
Lack of architectural distortion	Architectural distortion always present
Honeycombing uncommon	Honeycombing seen in most biopsies
Fibrosis evenly spread throughout lobule	Fibrosis most severe under pleura
Fibrosing process very homogeneous	Fibrosing process patchy, alternates with normal or near-normal lung
Fibroblast foci sparse to nonexistent	Fibroblast foci common
	Focal NSIP-like areas may be present but do not change the diagnosis

magnification (see Figs. 6.17 to 6.21). A trick that can be helpful is to ask what happens if one mentally removes the inflammation and/or fibrosis: In NSIP, one generally ends up with normal lung parenchyma, whereas in UIP no amount of mental contortion can restore the distorted parenchyma to its normal state.

One study[9] based on biopsies and subsequent explanted lungs has suggested that NSIP can progress to UIP. This is the only morphologic study to have made such a claim and at present most pathologists regard the two conditions as completely separate entities.

TREATMENT AND PROGNOSIS

Regardless of etiology, the prognosis of NSIP depends very much on the presence or absence of fibrosis. NSIP with a purely cellular pattern typically responds to steroids and can completely resolve, whereas with fibrosis the prognosis is considerably worse, albeit not as poor as the prognosis of idiopathic UIP.[10] For this reason, it is important to always mention the presence or absence of fibrosis when making a diagnosis of NSIP.

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CHAPTER

8

Respiratory Bronchiolitis with Interstitial Lung Disease and Desquamative Interstitial Pneumonia

NOMENCLATURE AND DIAGNOSTIC ISSUES

Respiratory bronchiolitis with interstitial lung disease (RBILD) and desquamative interstitial pneumonia (DIP) are usually included in the idiopathic interstitial pneumonias[1]; but in fact RBILD, DIP, and Langerhans cell histiocytosis (LCH) (eosinophilic granuloma of lung [Chapter 10]) are all diseases that occur almost exclusively in cigarette smokers, and not surprisingly, they sometimes show overlapping features.[2]

RBILD presents some peculiar conceptual issues because the morphology of RBILD, a disease with clinical features of an ILD (see below), is identical to that of respiratory bronchiolitis (RB), a process found incidentally in virtually every cigarette smoker (as can be readily identified by examining any lobe resected for lung cancer in a smoker) and one that is associated with mild abnormalities of airflow or with no detectable functional abnormality. It was originally believed that the presence of interstitial fibrosis associated with RB automatically turned it into RBILD but more recent studies have shown that this is not true because fibrosis can be seen in both conditions.[3] Pathologic separation of RB and RBILD depends on the clinical and imaging context and cannot be determined from the biopsy alone.

An additional rule is that a diagnosis of RBILD requires clinical and radiologic evidence of an ILD with no other cause for an ILD evident in the biopsy; if there is another ILD present, it is considered the cause of the clinical interstitial process and smoking-related changes in the respiratory bronchioles are ignored.[3]

The consensus at present is that RBILD and DIP are related processes, with RBILD the earlier and more localized lesion that evolves, with continued smoking, into the more widespread DIP.[4] As one might expect under this scenario, there are cases that are morphologically intermediate between the two.[2]

A further complication is that DIP-like areas can also be found around the lesions of LCH, around tumors, and occasionally in other conditions if the patient is a cigarette smoker.[2] DIP by definition is a diffuse disease that is not accompanied by other types of ILD, and focal collections of smoker's macrophages in airspaces are not sufficient for a diagnosis of DIP.

Etiologies

Etiologies of RBILD and DIP are shown in Table 8.1. All of the published cases of RBILD have occurred in cigarette smokers, whereas a minority of DIP cases have occurred in nonsmokers (of tobacco) and have other putative associations.

Clinical Features

Patients with RBILD typically present with shortness of breath (SOB), whereas most cigarette smokers with RB are asymptomatic; however, some smokers are short of breath because they have chronic obstructive lung disease (COPD), so SOB does not reliably separate RB and RBILD. Physiologically patients with RB may have airflow obstruction or no abnormality, but RBILD is characterized by a pure restrictive abnormality, a combination of a restrictive and obstructive abnormality, or a markedly decreased diffusing capacity.[3] Patients with DIP are always

Table 8.1

Etiologies of RBILD and DIP

Cigarette smoking history 100% of patients with RBILD
Cigarette smoking history 60%–90% of patients with DIP
Other putative causes of DIP
Fumes
Dusts
Drugs
Marijuana smoke
Collagen vascular diseases

short of breath and always have a restrictive abnormality and/or a decreased diffusing capacity. Clubbing is seen in some patients with DIP.

Imaging

The high-resolution computed tomography (HRCT) manifestations of RBILD comprise centrilobular ground-glass nodules and/or patchy or confluent ground-glass opacities (GGOs)[5] (Fig. 8.1). These abnormalities tend to involve mainly the upper lobes but may be diffuse. A small percentage of patients have mild reticulation mainly in the lower lung zones.[5] Centrilobular emphysema (CLE) is commonly seen.

The main HRCT feature of DIP is extensive bilateral ground-glass opacification, and is present in all cases[5] (Fig. 8.2). It may be diffuse but tends to involve mainly the lower lobes. A reticular pattern may be seen but is usually mild and confined to the lower lung zones. Honeycombing is uncommon, but well-defined cysts may occur within the areas of ground-glass attenuation.[5] The CT findings of RBILD and DIP are indistinguishable from those of several other ILDs, particularly hypersensitivity pneumonitis (HP) and nonspecific interstitial pneumonia (NSIP).

Pathologic Features

Smoker's RB and RBILD show two features. First, there is accumulation of smoker's macrophages; that is, macrophages with a light golden or light brown color (Figs. 8.3 to 8.6) in the lumens of respiratory bronchioles and/or in the more distal alveolar ducts or alveoli. The pigment in smoker's macrophages reflects aluminum silicates derived from the smoke and ferruginated in macrophages; it appears smooth or finely granular on H&E stains (Fig. 8.6), and may give a blush of blue color on iron stains (Fig. 8.7).

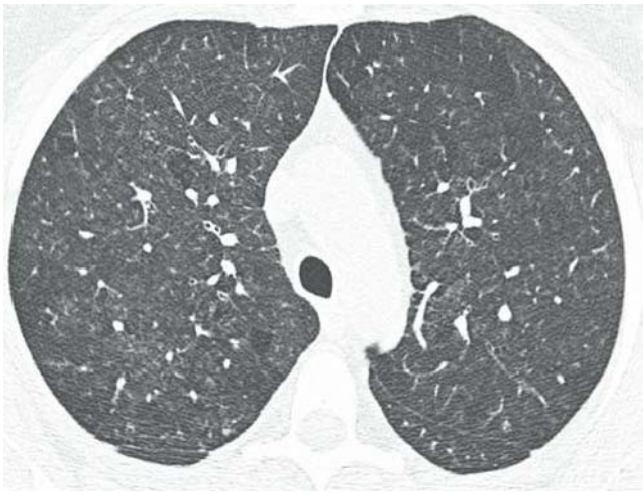


FIGURE 8.1. RBILD. HRCT at the level of the upper lobes shows bilateral GGOs and poorly defined centrilobular nodules. The patient was a 44-year-old woman.

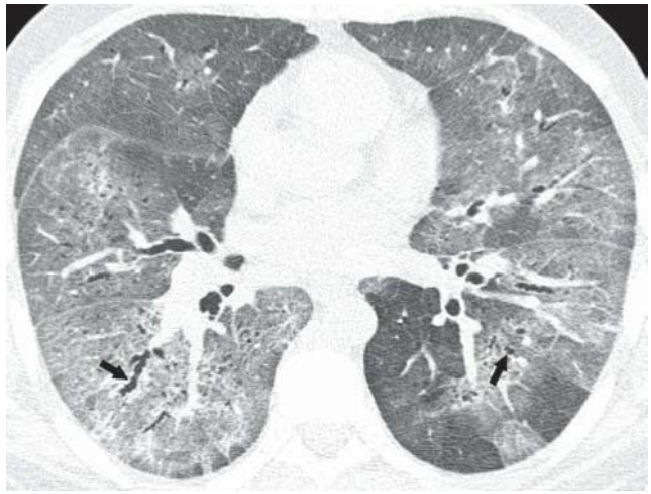


FIGURE 8.2. DIP. HRCT at the level of the lower lung zones demonstrates extensive bilateral GGOs and small focal areas of reticulation. Also noted is mild dilatation and a beaded appearance of some of the lower lobe bronchi (traction bronchiectasis) (*arrows*) consistent with fibrosis. The patient was a 59-year-old man with DIP secondary to marijuana smoke.

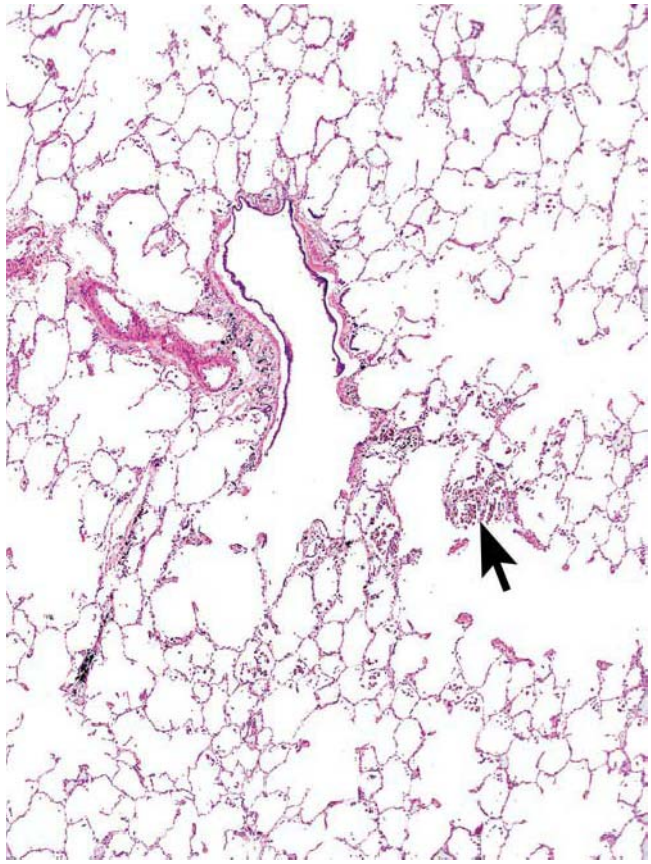


FIGURE 8.3. Low-power view of smoker's RB/RBILD. Note minimal fibrosis of the walls of the bronchiole in this example, and collections of pigmented macrophages in alveolar ducts and alveoli (*arrow*). The process in this figure and Figures 8.4 to 8.9 represents RBILD if there is clinical evidence of an ILD and no other cause for an ILD in the biopsy; otherwise it is simply RB.

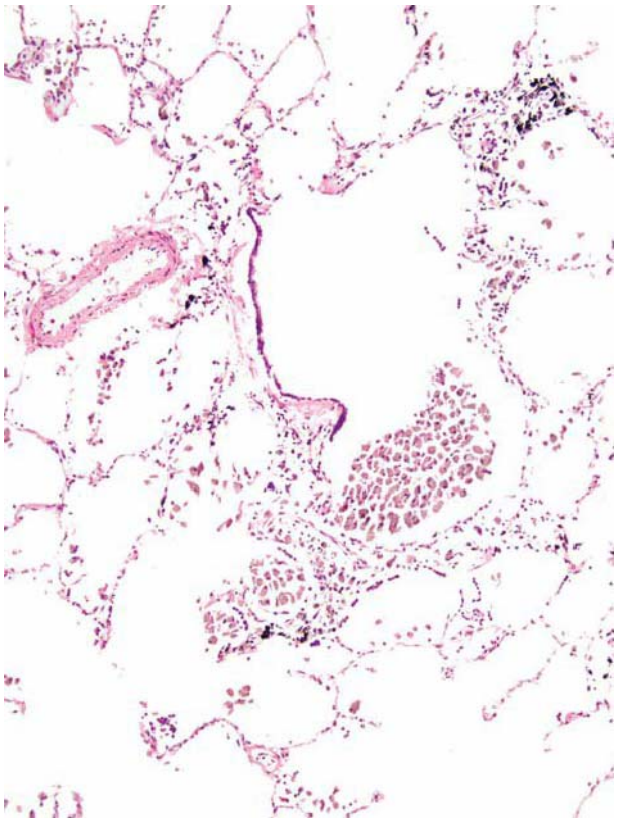


FIGURE 8.4. Higher-power view of RB/RBILD showing collections of golden-brown smoker's macrophages in the bronchiolar lumen. In this example there is no fibrosis of the bronchiolar walls.

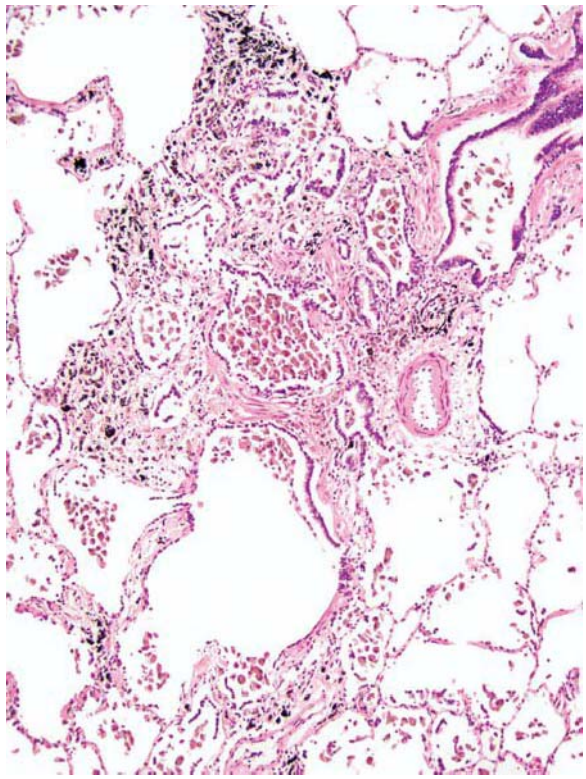


FIGURE 8.5. An example of RB/RBILD in which there is considerable fibrosis of the walls of the respiratory bronchiole. Despite the fibrosis, this is not RBILD unless there is clinical evidence of an ILD and no other cause for such a disease.

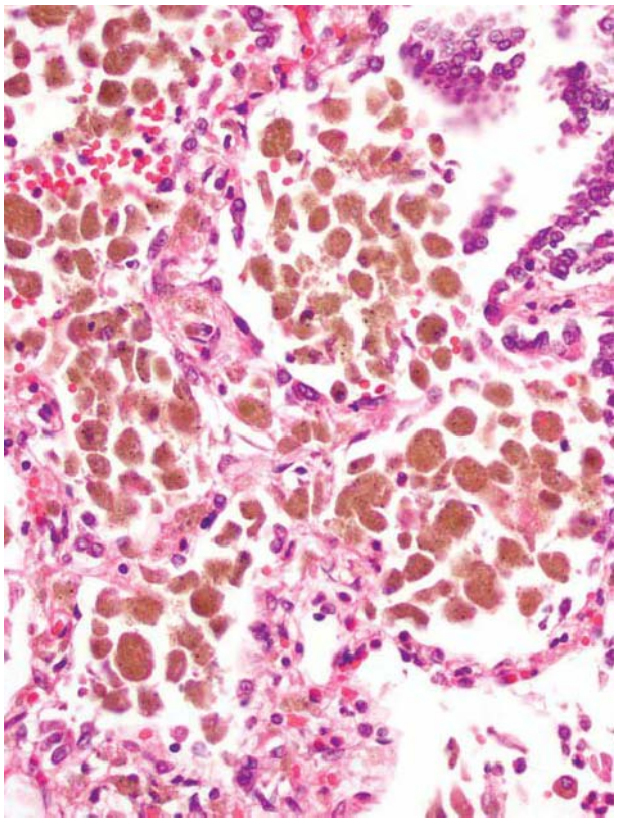


FIGURE 8.6. High-power view of smoker's macrophages showing typical golden-brown, faintly granular, pigmentation.

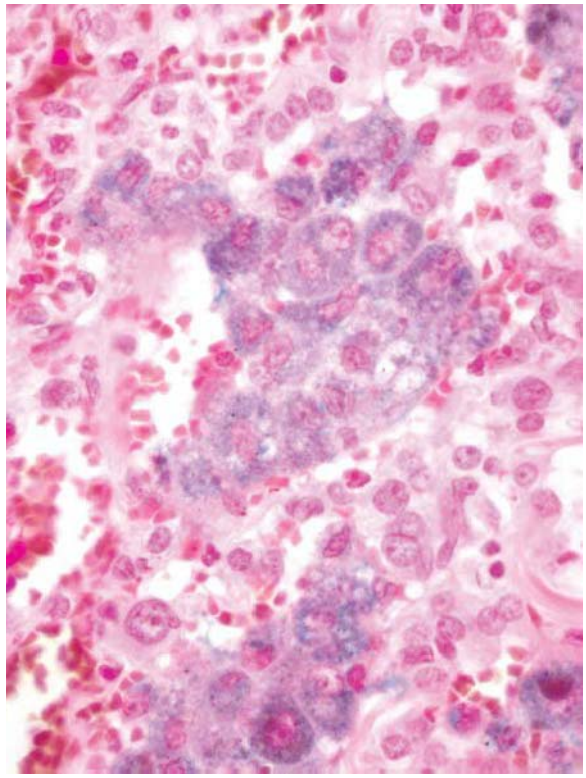


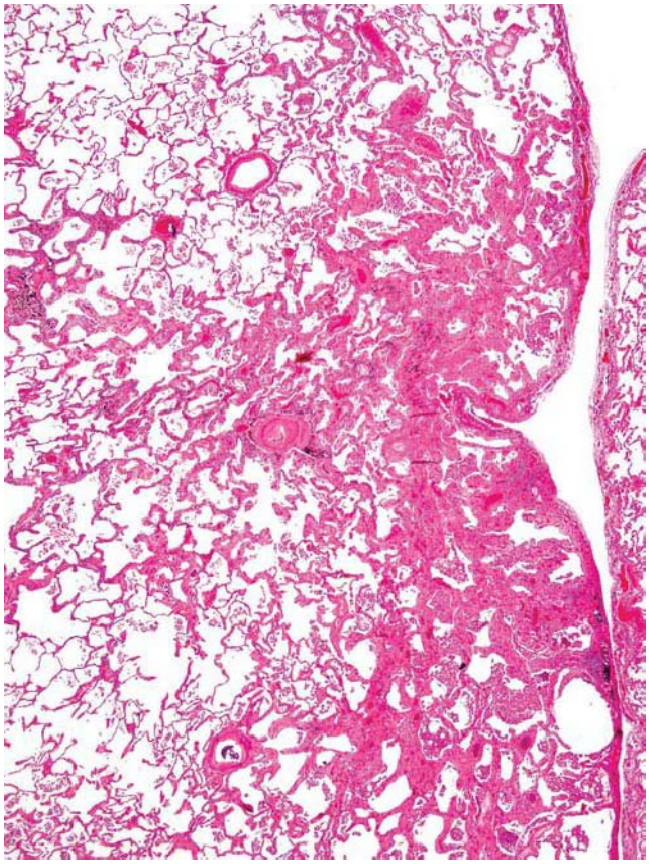
FIGURE 8.7. Iron stain of smoker's macrophages showing a faint blush of blue color. This is the most typical staining reaction. Hemosiderin, which is also golden brown, is distinctly coarser and stains intensely with Perl's iron stain.

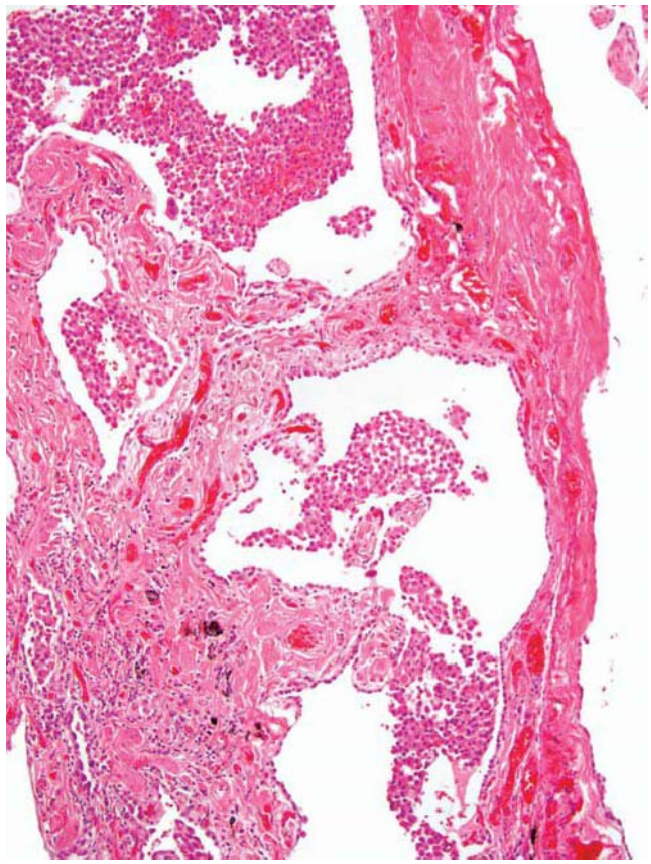
Smoker's pigment needs to be separated from hemosiderin, which is typically coarsely granular (See Figs. 24.3 and 24.4) and tends to stain intensely on iron stains.

Second, RB and RBILD are characterized by a variable degree of fibrosis in the walls of the respiratory bronchioles, sometimes with extension from the bronchioles toward the pleura (Figs. 8.3 to 8.9). There is tremendous variability in the amount and distribution of fibrosis. It may be almost nonexistent (Figs. 8.3 and 8.4), just confined to the walls of affected respiratory bronchioles (Figs. 8.5 and 8.6), or may be quite dramatic (Figs. 8.8 and 8.9) with involvement of all alveolar walls *in a local area,* typically just under the pleura. This type of fibrosis can mimic fibrotic NSIP, or DIP if there are numerous airspace macrophages (Fig. 8.9), but with the important difference that it is spatially restricted, most often forming a wedge-shaped area of fibrosis extending from the affected bronchiole to the pleura. Often the fibrosis is distinctly hyalinized,[7,8] something that is not a feature of fibrotic NSIP. In our experience fibroblast foci are rare in RB/RBILD, and patchy fibrosis with fibroblast foci immediately under the pleura should raise a question of early usual interstitial pneumonia (UIP). Criteria for the diagnosis of RB and RBILD are summarized in Table 8.2.

In contrast to the distinctly localized abnormalities of RB/RBILD, in DIP (Table 8.3) there is widespread filling of alveolar spaces by smoker's macrophages, and there is always accompanying chronic interstitial inflammation and/or interstitial fibrosis (Figs. 8.10 to 8.17). The interstitial fibrosis of DIP is, structurally, similar to that of fibrotic NSIP because there is usually no architectural distortion; however, long-standing DIP cases may develop honeycombing.[9,10] In some cases of DIP the alveolar macrophages persist, but in others they disappear over time, leaving a picture that is essentially indistinguishable from fibrotic NSIP (Figs. 8.18 and 8.19).

Small numbers of eosinophils are also commonly found in DIP, either in the airspaces or in the interstitium (Fig. 8.13), but large numbers of eosinophils should raise a question of chronic eosinophilic pneumonia (CEP; Chapter 15). Imaging will almost always sort out these two possibilities because DIP typically shows diffuse GGOs with or without reticulation, whereas CEP





FIGURES 8.8 and 8.9. Low- and high-power views of RB/RBILD with marked fibrosis. The process is quite localized under the pleura and has somewhat of a wedge shape. The high-power view mimics DIP, but the sharp circumscription of the lesion puts it in the RB/RBILD category. Note the hyaline appearance of the fibrosis at the left-hand edge of the image; this is a common finding in RB/RBILD of this type.

Table 8.2

Criteria for the diagnosis of RB and RBILD

Smoker's RB	RBILD
Smoker's macrophages in lumens of respiratory bronchioles/surrounding tissues	Smoker's macrophages in lumens of respiratory bronchioles/surrounding tissue
Variable interstitial fibrosis in the walls of respiratory bronchioles/surrounding tissues	Variable interstitial fibrosis in the walls of respiratory bronchioles/ surrounding tissues
Fibrosis often forms a wedge shape extending from bronchiole to pleura	Fibrosis often forms a wedge shape extending from bronchiole to pleura
Fibrosis often hyalinized	Fibrosis often hyalinized
Pulmonary function normal or airflow obstruction present	Restrictive or mixed restrictive-obstructive pulmonary function or markedly decreased diffusing capacity
Imaging shows centrilobular ground glass nodules and/or patchy GGOs	Imaging shows centrilobular ground glass nodules and/or patchy GGOs, and, occasionally, reticulation

shows consolidation that is usually peripheral and may be migratory. Other common features in DIP include lymphoid nodules (Figs. 8.10 and 8.11) and scattered giant cells (Fig. 8.14).

The alveolar macrophages in DIP have a variable appearance. In most cases there are relatively few pigmented smoker's macrophages and larger numbers of nonpigmented macrophages, but occasionally the alveolar are completely filled by smoker's macrophages (Fig. 8.15).

Occasional cases fall somewhere between RB/RBILD and DIP because the abnormalities are more widespread than typical RB/RBILD but less widespread than DIP. We suggest that such cases be diagnosed as DIP because the inflammatory/fibrotic process is extending, and presumably will end up as DIP, given sufficient time.

Table 8.3

Pathologic features of DIP

Homogeneous process over large areas
Airspaces filled by variably pigmented smoker's macrophages
Lymphoid nodules common
Small numbers of eosinophils common
Interstitial inflammation/fibrosis always present, usually follows original alveolar walls without architectural distortion
Individual fields indistinguishable from individual fields of RB/RBILD
Long-standing cases may look like fibrotic NSIP or may develop honeycombing

DIP has been reported to recur in transplanted lungs[11] (Fig. 8.20). It is not clear if this phenomenon is seen only in patients who continue to smoke.

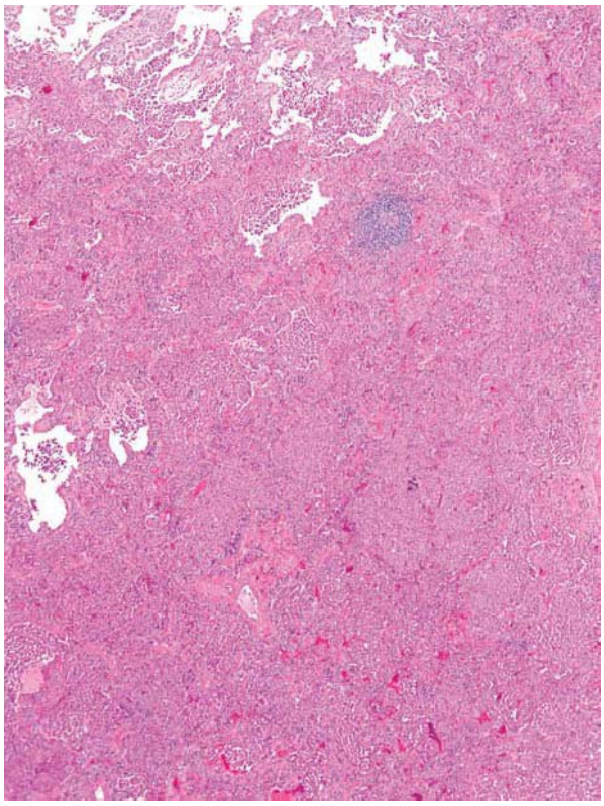
Diagnostic Modalities

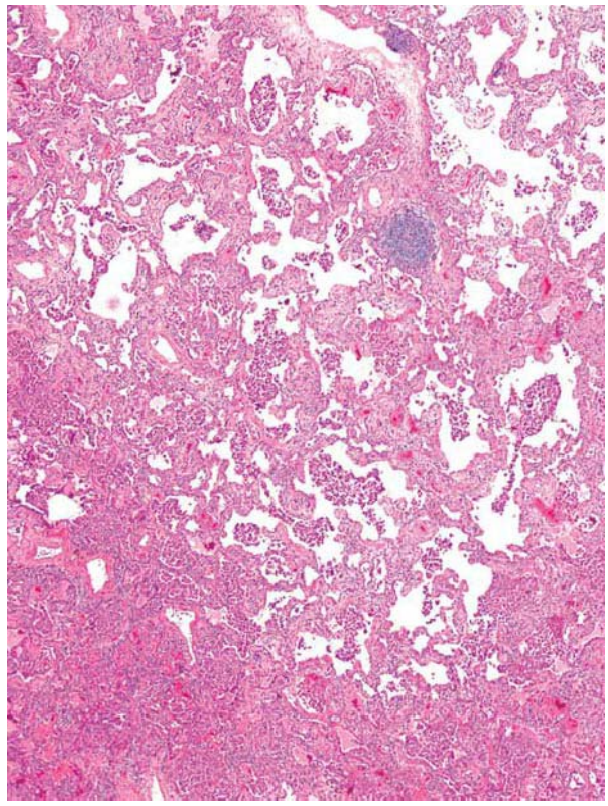
Both RBILD and DIP require evaluation of low-power architecture over a large area. As such transbronchial biopsy cannot be used and video assisted thoracoscopic surgery (VATS) biopsy is required.

Differential Diagnosis

RB/RBILD is distinctive and there is a very limited differential diagnosis. One never sees the metaplastic bronchiolar epithelium of peribronchiolar metaplasia (see Figs. 23.16 to 23.18) in RB/RBILD, or the narrowed or obliterated lumen of constrictive bronchiolitis (bronchiolitis obliterans, see Figs. 20.23 to 20.27); nor is there marked inflammation in the walls of the respiratory bronchioles such as is present with infectious bronchiolitis (see Figs. 20.7 to 20.9). RB/RBILD is commonly associated with centrilobular emphysema (CLE), and centrilobular emphysematous spaces may themselves have smoker's macrophages as well as fibrosis in the walls of the spaces, but the airspaces are markedly dilated (see Figs. 9.11 and 9.12).

The differential diagnosis of DIP is shown in Table 8.4. Smoker's macrophages can be seen focally around any lesion in cigarette smokers, for example, in LCH, or around tumors, and in that setting the macrophages should be ignored. Alveolar macrophages can accumulate around any kind of inflammatory mass lesion (Figs. 8.21 and 8.22), but DIP is always a diffuse disease and does not contain masses. Smoker's macrophages may also be seen in airspaces in otherwise unremarkable lungs





FIGURES 8.10 and 8.11. Two low-power views of the same case of DIP. In Figure 8.10, the process appears almost solid, whereas in Figure 8.11, collections of airspace macrophages separated from the underlying lung are visible.

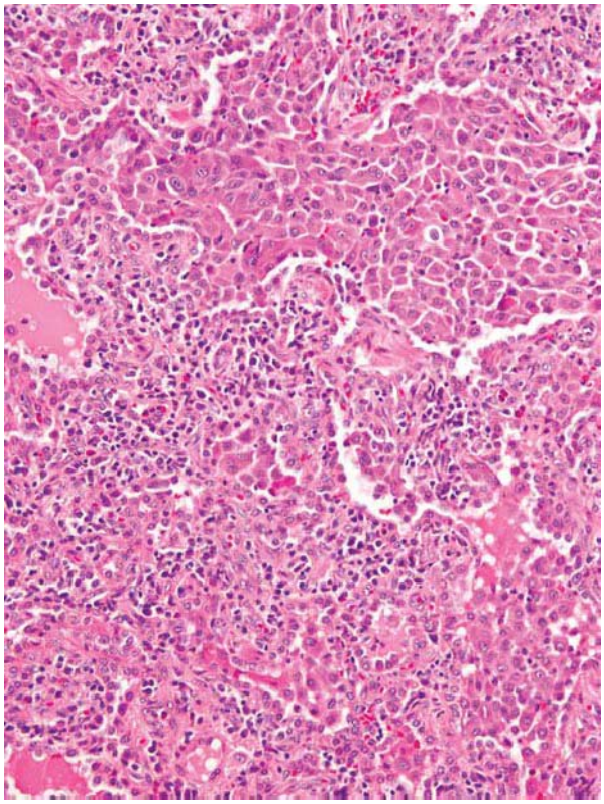


FIGURE 8.12. Higher-power view of the case shown in Figures 8.10 and 8.11. At this magnification the interstitial inflammatory infiltrate is clearly visible. DIP always has an interstitial inflammatory infiltrate and/or interstitial fibrosis.

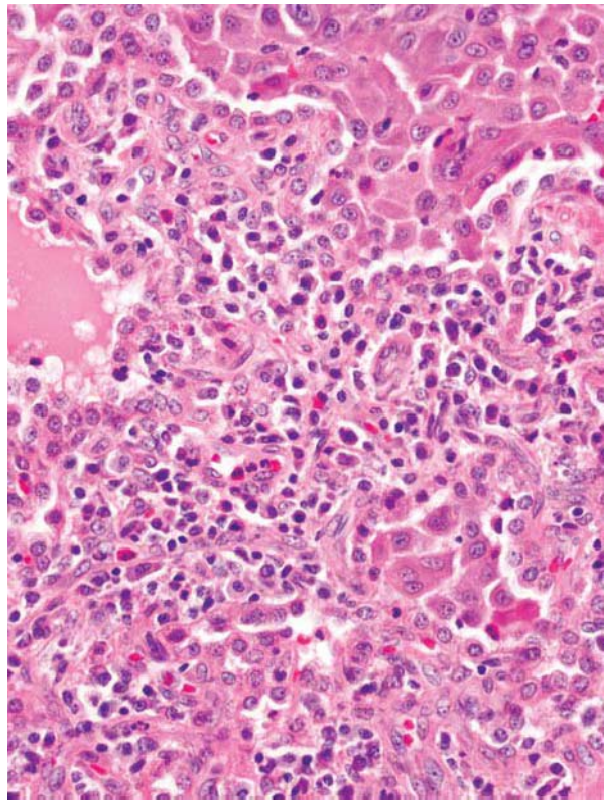


FIGURE 8.13. High-power view of the case shown in Figures 8.10 to 8.12. Scattered eosinophils are present in the interstitial inflammatory infiltrate. Small numbers of eosinophils in the interstitium or airspaces are common in DIP.

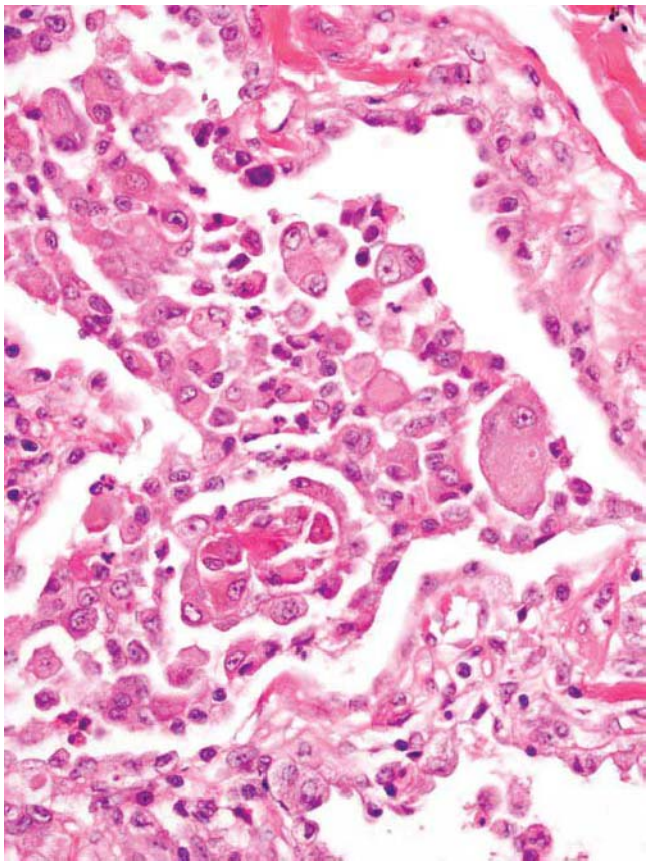


FIGURE 8.14. An example of DIP in which there is an airspace giant cell.

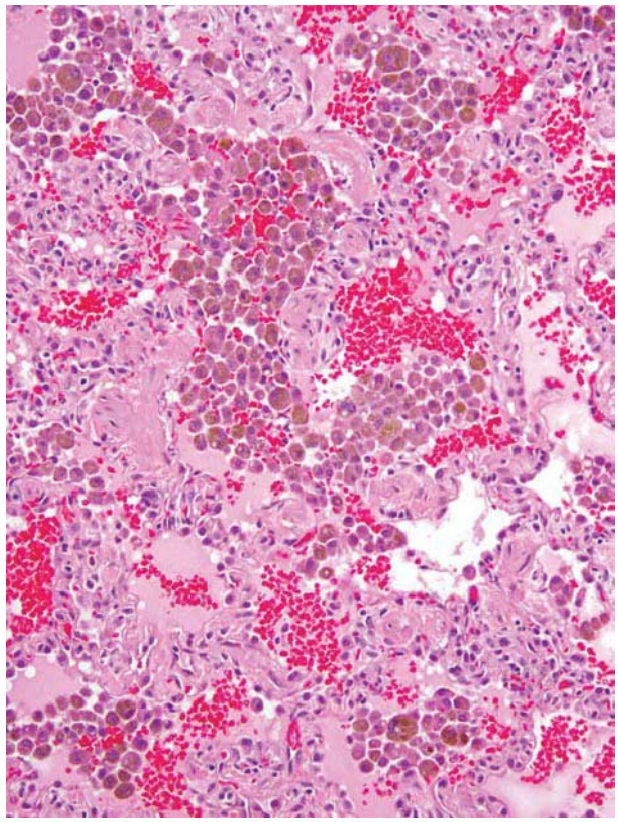
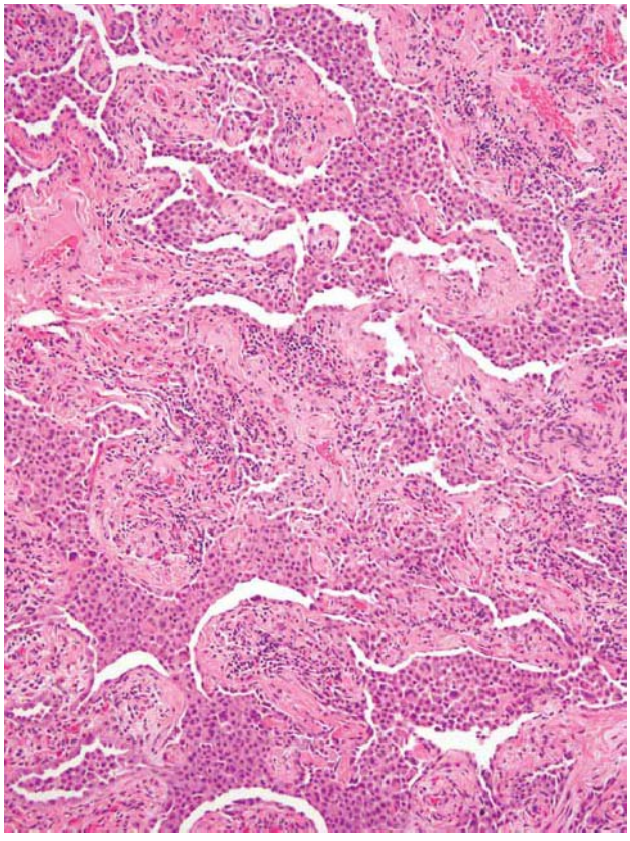
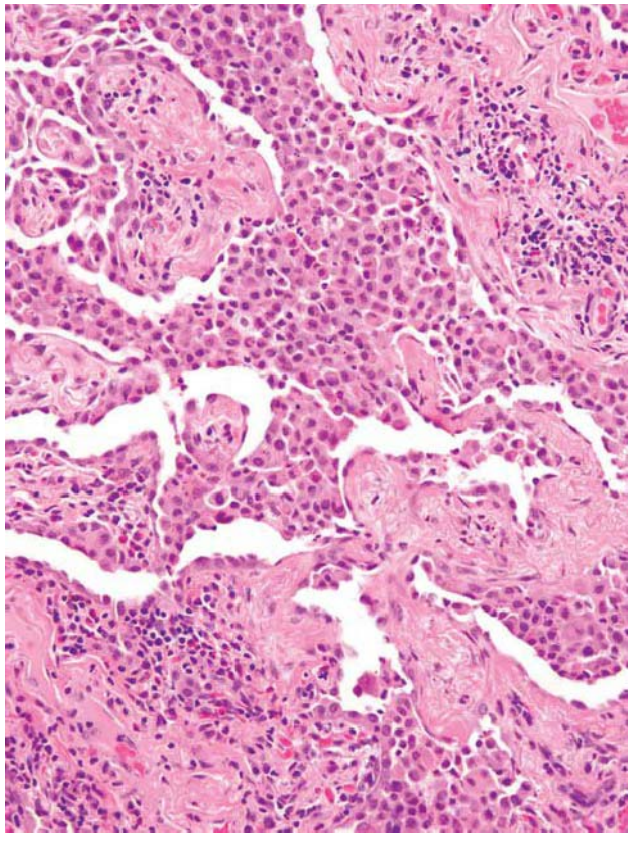
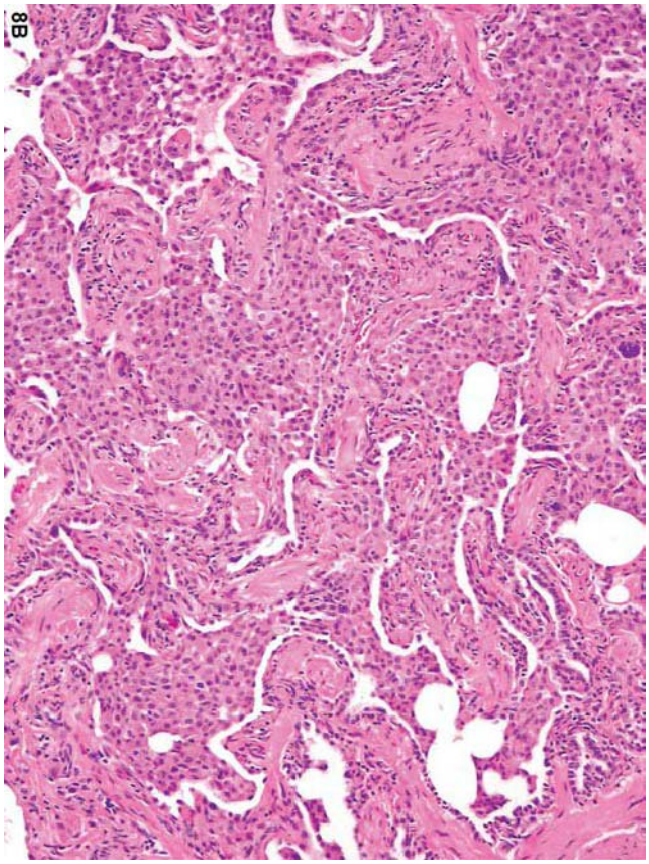


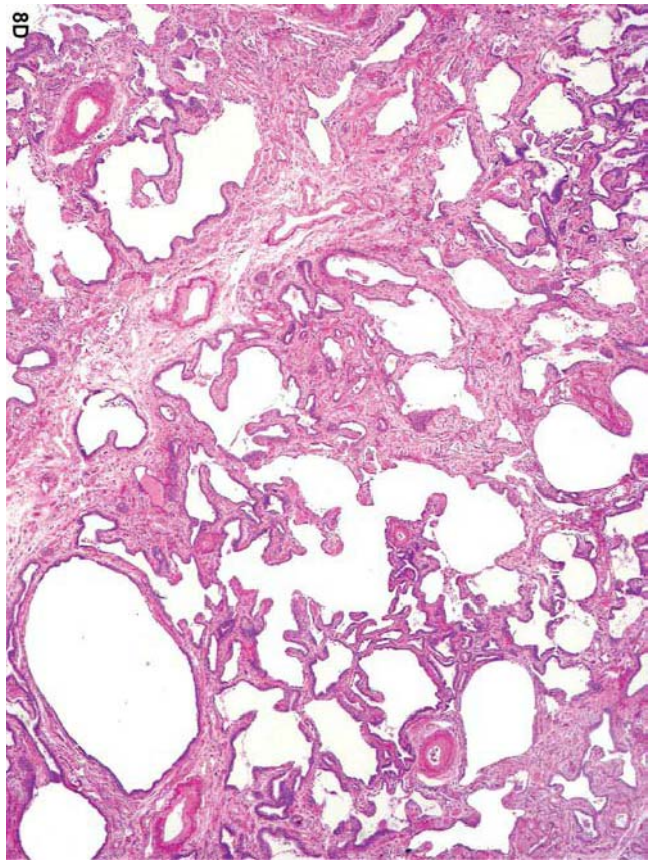
FIGURE 8.15. An example of DIP in which all of the alveolar macrophages are heavily pigmented smoker's macrophages. This occurs in a minority of cases; most cases show only scattered or sometimes no pigmented macrophages.





FIGURES 8.16 and 8.17. Low- and high-power views of DIP in a heavy marijuana smoker. There is distinct interstitial fibrosis.





FIGURES 8.18 and 8.19. Transformation of DIP into a picture of fibrotic NSIP. This patient had a biopsy showing DIP three years before undergoing lung transplantation. These images are from the explanted lung. In Figure 8.18, the appearance is still that of DIP, but most of the explanted lung looked like fibrotic NSIP (Fig. 8.19). (Reproduced by permission from Tazelaar HD, Wright JL, Churg A. Desquamative interstitial pneumonia. *Histopathology*. 2011;58:509–516.)

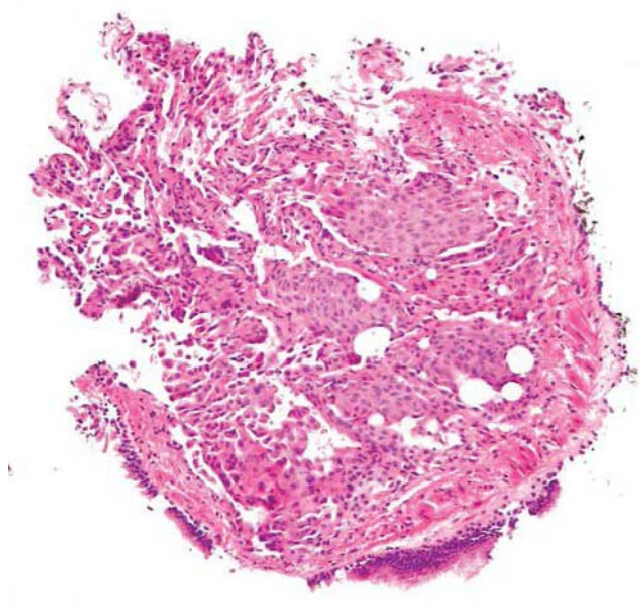


FIGURE 8.20. Recurrence of DIP in a transplanted lung. Ordinarily transbronchial biopsies are not suitable for the diagnosis of DIP, but they are sometimes useful for assessing recurrent disease in lung transplants.

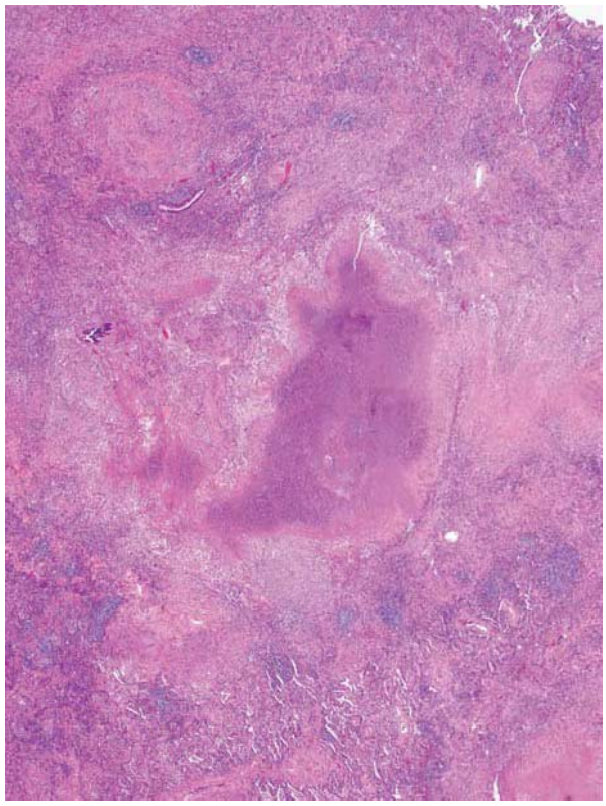
(Fig. 8.23), but airspace macrophages by themselves do not qualify for a diagnosis of DIP because DIP is always a diffuse disease with interstitial inflammation/fibrosis as well as airspace macrophages.

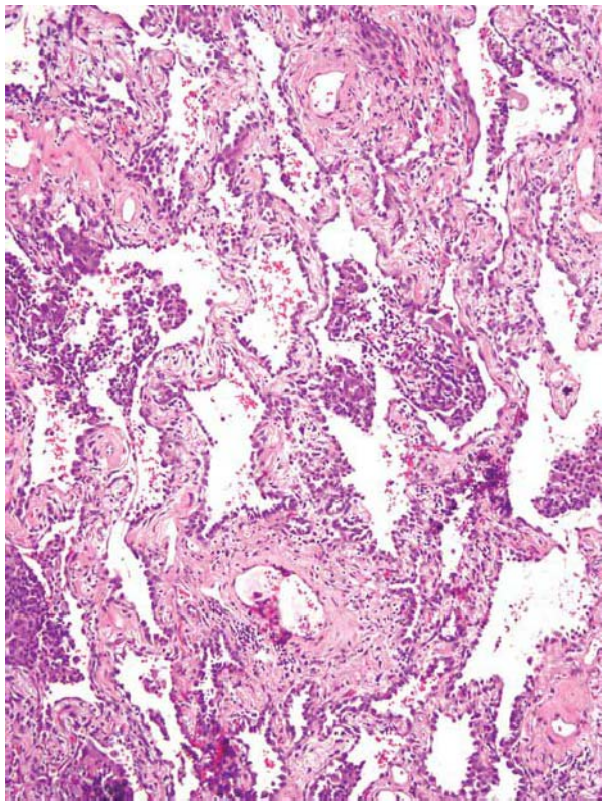
Any cause of airway obstruction, for example a tumor, will lead to collections of macrophages behind the obstructing lesion ("golden pneumonia" visible as a golden color on gross examination). In contrast to DIP, obstructing lesions typically are segmental or subsegmental and

Table 8.4

Differential diagnosis of DIP

Smoker's macrophage collections around lesions of LCH and sometimes around tumors and other lesions
Drug reactions, especially to amiodarone, statins
Obstructive pneumonias with collections of foamy macrophages
Rhodococcus and *Mycobacterium avium* infections in immunocompromised hosts
Chronic eosinophilic pneumonia (CEP)





FIGURES 8.21 and 8.22. Mimics of DIP. Localized reaction around a tuberculous granuloma (Fig. 8.21) mimicking DIP (Fig. 8.22). DIP is always diffuse and should not be associated with mass lesions.

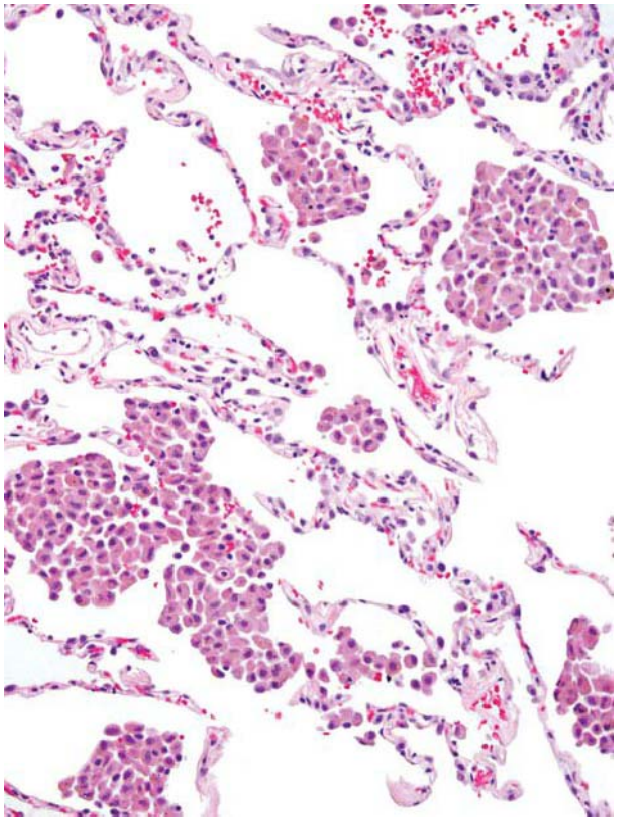


FIGURE 8.23. Mimics of DIP. In this example, there are collections of smoker's macrophages in the airspaces, but no interstitial inflammatory infiltrate or interstitial fibrosis, features that are required for the diagnosis of DIP.

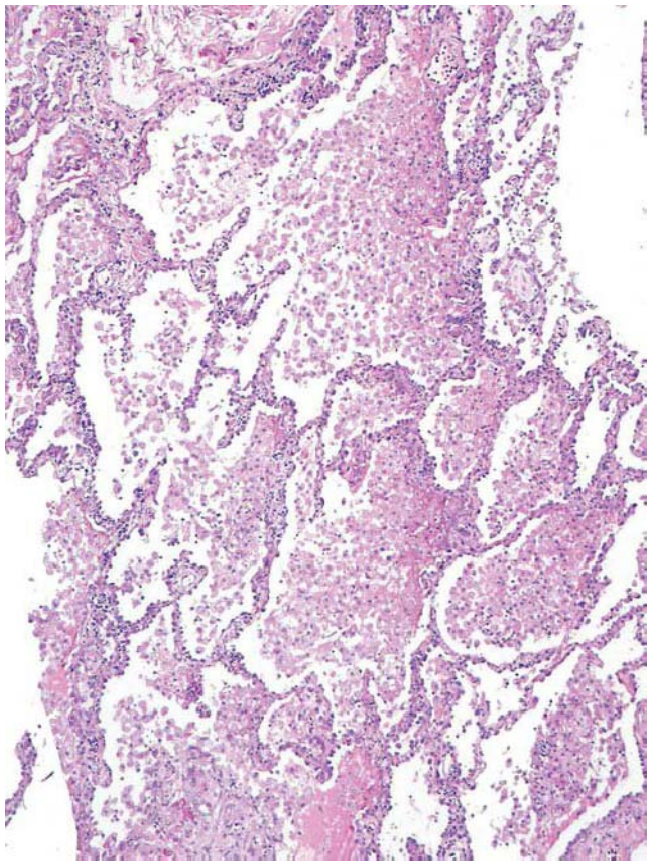
not diffusely present through the lung. The macrophages that accumulate behind obstructions are typically finely foamy, and do not have smoker's pigment, and in general obstructing lesions do not lead to interstitial inflammation/fibrosis, something that is always present in DIP.

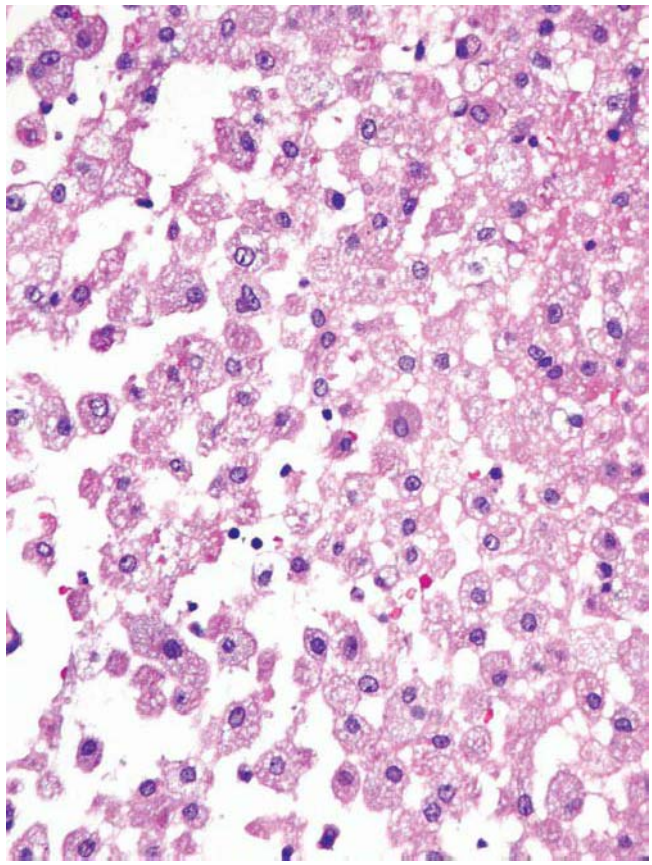
Widespread filling of alveoli by coarsely foamy macrophages without pigment can also be seen in patients treated with amiodarone (Figs. 8.24 and 8.25) or statins, and sometimes in patients inhaling lipids. In immunocompromised hosts slightly foamy macrophages containing large numbers of *Mycobacterium avium-intracellulare* or rhodococcus organisms can fill alveolar spaces, but again these macrophages are distinctly different from the macrophages of DIP, and there is generally no interstitial reaction.

CEP (see Figs. 15.11 and 15.12) may have not only large numbers of macrophages in the airspaces and an interstitial inflammatory reaction, but it also has large numbers of eosinophils in the airspaces, much greater numbers than are found in DIP.

Prognosis

The prognosis of RBILD is good, with all except one case in the literature responding to smoking cessation/steroids.[3] The prognosis for DIP is, overall, remarkably good (especially considering how much such cases resemble fibrotic NSIP), with long-term survivals of about 70% to 95% in various series, but some patients develop honeycombing and end-stage fibrosis.[9,10]





FIGURES 8.24 and 8.25. Amiodarone toxicity mimicking DIP. The airspaces are filled by macrophages, but they are coarsely foamy, the typical pattern seen with amiodarone. Obstructive pneumonia behind mass lesions can produce a similar pattern, but with generally more finely foamy macrophages.

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CHAPTER

9

Combined Fibrosis with Emphysema

CLINICAL FEATURES

The clinical disease known as "combined fibrosis with emphysema" (CFE) is typically seen in heavy smokers who have underlying chronic obstructive pulmonary disease (COPD) as well as an interstitial lung disease (ILD) that may be idiopathic or associated with a collagen vascular disease, particularly rheumatoid arthritis or systemic sclerosis.[1,2] In the recent times, CFE has attracted considerable clinical attention because it presents a confusing pulmonary function picture with apparently normal lung volumes and a markedly decreased diffusing capacity in the face of signs, symptoms, and imaging of an ILD.[1] Pulmonary hypertension is common in CFE patients.[1–3]

IMAGING

The high resolution computed tomography (HRCT) findings of CFE comprise upper lobe emphysema and predominantly lower lobe ILD (Figs. 9.1 and 9.2). In the majority of patients the ILD manifests as reticulation and honeycombing involving mainly the subpleural regions and lung bases, a pattern characteristic of usual interstitial pneumonia (UIP).[4] There may be some ground-glass opacities (GGOs), but these are seldom extensive. Less commonly the ILD manifests as diffuse GGOs with or without associated reticulation and traction bronchiectasis, a pattern that is suggestive of nonspecific interstitial pneumonia (NSIP) or desquamative interstitial pneumonia (DIP).[5]

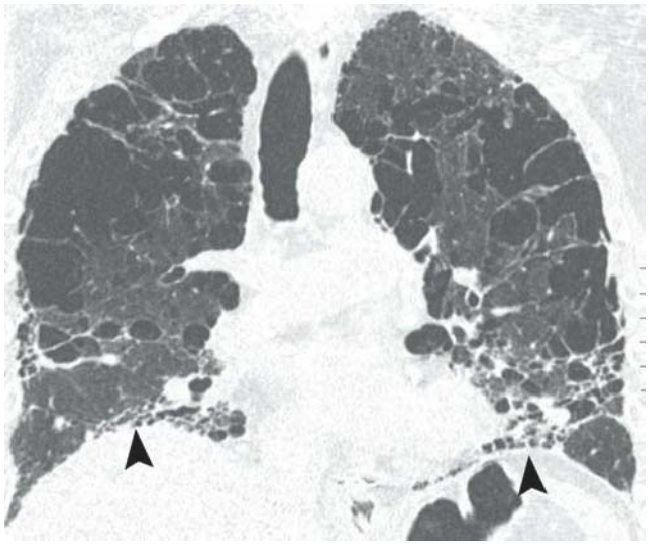

FIGURE 9.1. Combined emphysema and UIP. Coronal reformation of a volumetric HRCT demonstrates extensive upper lobe bullous emphysema and basal interstitial lung disease (*arrowheads*).

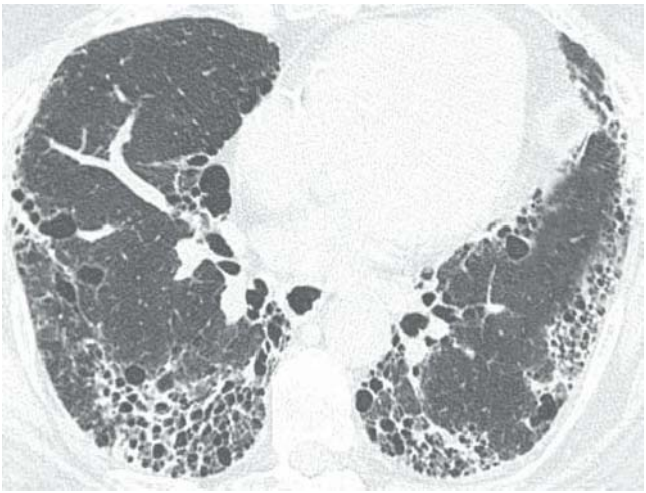

FIGURE 9.2. HRCT at the level of the lung bases in the same patient shows subpleural reticulation and honeycombing characteristic of UIP. The patient was a 67-year-old man who had a 100-pack-year smoking history.

PATHOLOGIC FEATURES

Combined Fibrosis with Emphysema

The scanty pathology literature and nomenclature in this area is very confusing because it encompasses two completely different clinical, radiologic, and pathologic situations. One is a diffuse fibrosing ILD in a patient who also has chronic obstructive pulmonary disease (COPD)—typically upper zone emphysema and lower zone fibrosis.

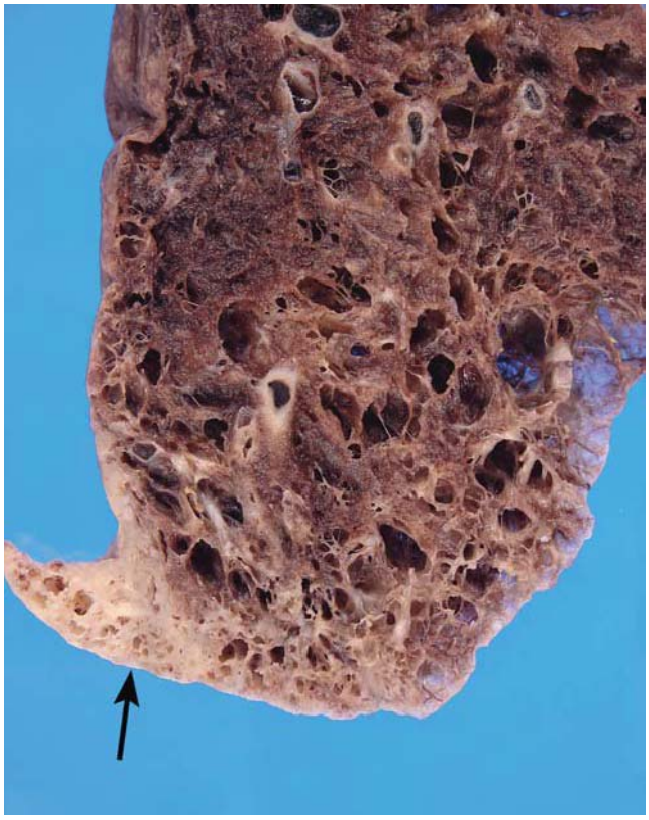

FIGURE 9.3. CFE. This patient has underlying UIP, which is largely hidden by the emphysema. However, the inferior portion of the lobe shows obvious fibrosis (*arrow*).

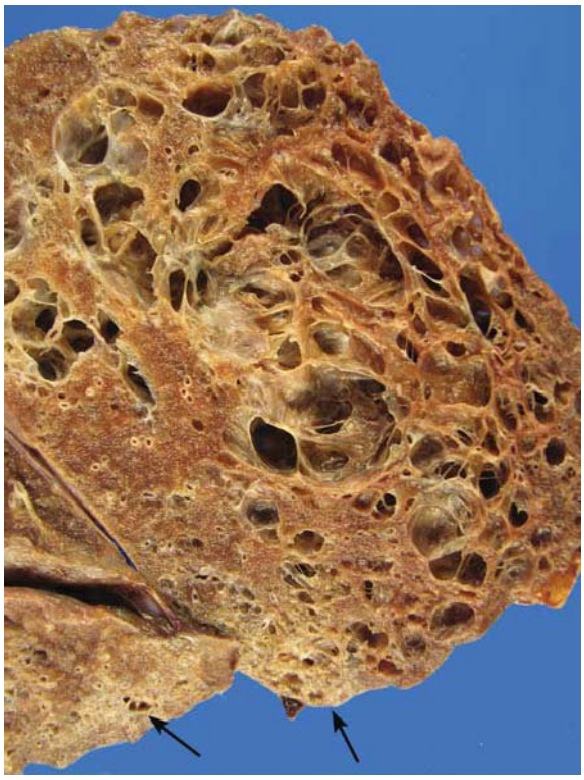

FIGURE 9.4. Combined fibrosis and emphysema where the fibrotic component is chronic HP. As in Figure 9.3, the emphysema hides the diffuse fibrosis, but fibrosis is grossly visible away from the emphysematous areas (*arrows*).

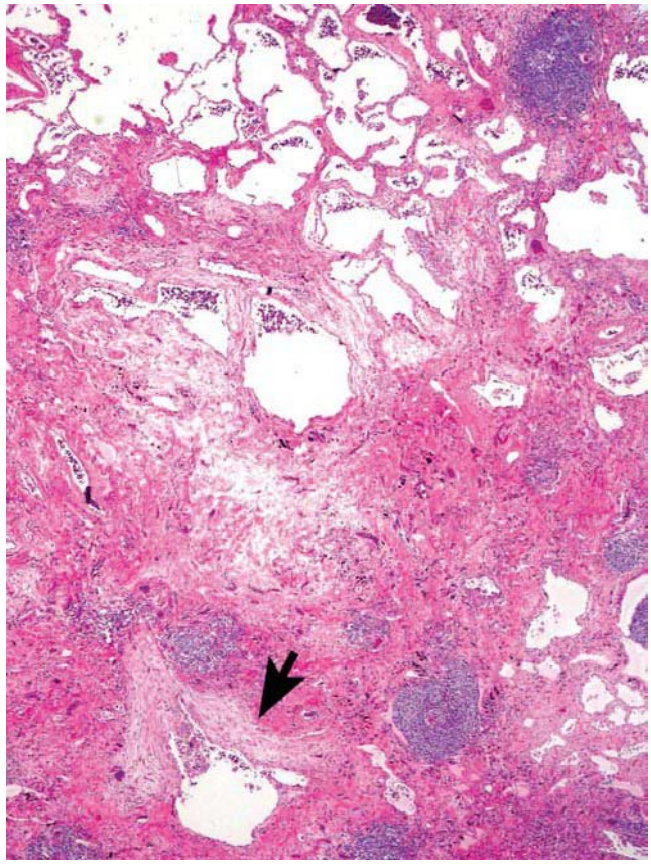

FIGURE 9.5. The fibrotic area of the case shown in Fig 9.4 looks like UIP (some cases of chronic HP look like UIP, see Chapter 12). A fibroblast focus is present at the arrow.

This is the setting to which the clinical term combined fibrosis with emphysema (CFE) has been applied. Most of the cases of CFE that have been described in the literature have been called UIP with emphysema or NSIP with emphysema, based largely on imaging, and very few have had biopsy confirmation of these diagnoses.[1,2] Some patients by description probably have underlying DIP[1,2] or respiratory bronchiolitis with interstitial lung disease (RBILD).[2]

The pathologic findings in CFE can also be confusing. On gross examination of lobectomy or large wedge resections, the emphysema can hide the presence of interstitial fibrosis (Figs. 9.3 and 9.4); however, in such specimens there is usually enough tissue available to find areas typical of the fibrotic lung disease, either grossly (Figs. 9.3 and 9.4) or microscopically (Fig. 9.5). However, in surgical lung biopsies there may only be an admixture, producing an unusual pattern of enlarged airspaces with fibrous walls (Figs. 9.6 and 9.7), which occasionally may mimic honeycombing (Fig. 9.8). But unlike honeycombing, there is no metaplastic bronchiolar epithelium in the enlarged spaces and usually no inspissated secretions (Fig. 9.8). Fibroblast foci may also be present in the enlarged airspaces (Figs. 9.5, 9.9, and 9.10), something that is never a feature of emphysema.

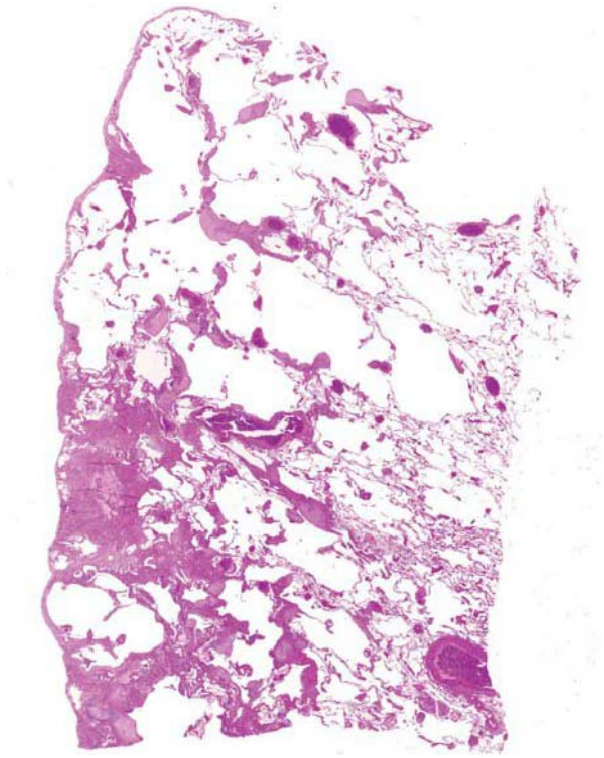

FIGURE 9.6. Low-power view of combined fibrosis (UIP) with emphysema (same case as Fig. 9.3). Because of the emphysema, the fibrosing process has much larger airspaces than are typical of UIP and the process does not look like UIP.

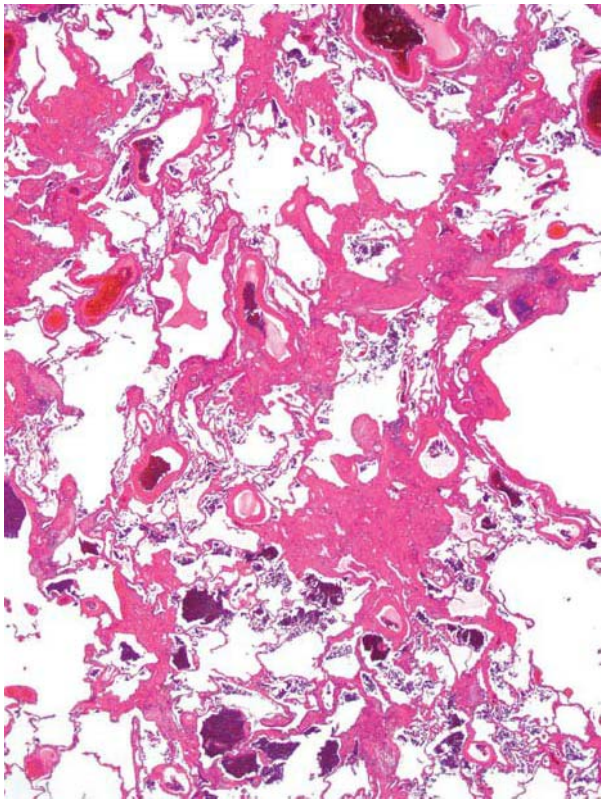

FIGURE 9.7. Another area of the same case. The process is clearly a fibrosing interstitial pneumonia but because of the emphysema the fibrosis is more irregular than is typical of UIP. When presented with this type of odd morphology, review of the CT imaging can be very helpful in pointing to the correct diagnosis.

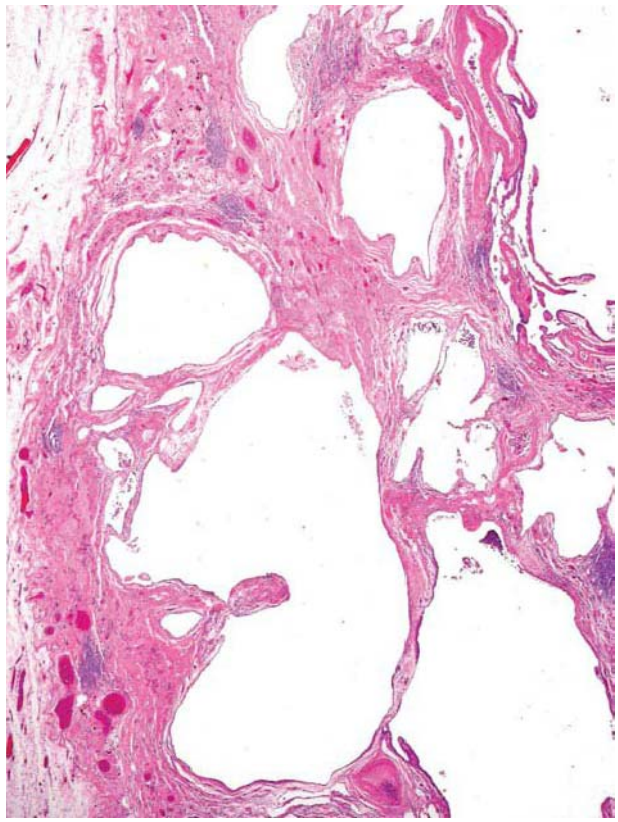

FIGURE 9.8. Same case as Figure 9.4. This area shows fibrosis surrounding emphysematous spaces and mimicking honeycombing. However, the metaplastic bronchiolar epithelium usually seen in honeycombed spaces is absent and there are no inspissated secretions.

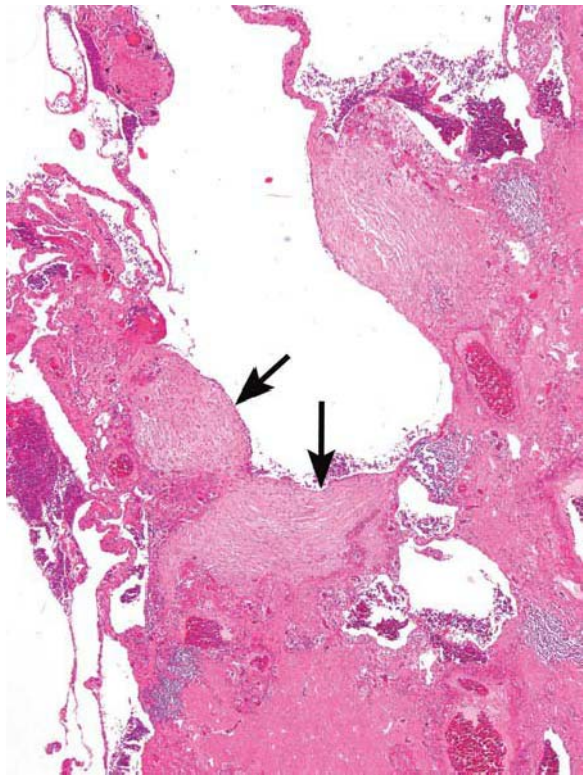

FIGURE 9.9. Another area of the same case shows fibroblast foci (*arrows*) around greatly enlarged airspaces.

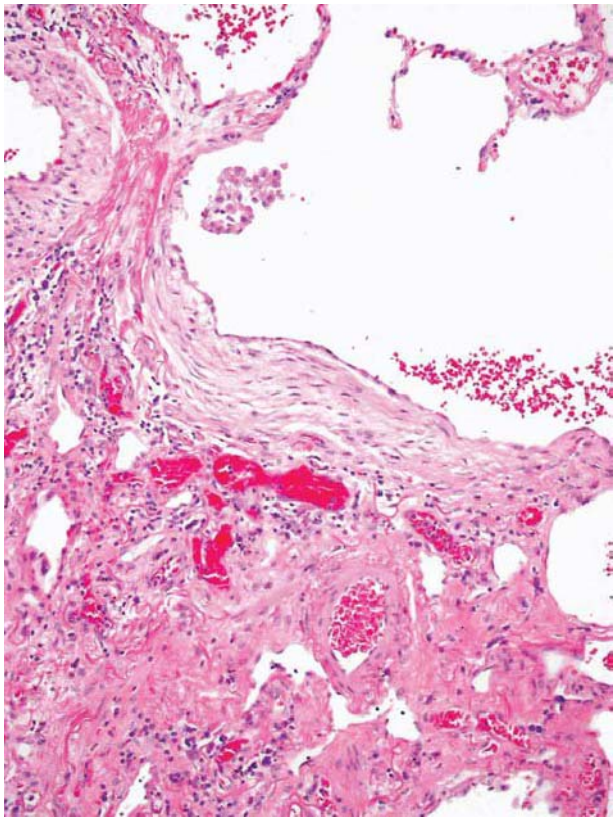

FIGURE 9.10. A fibroblast focus surrounding an emphysematous space in the same case.

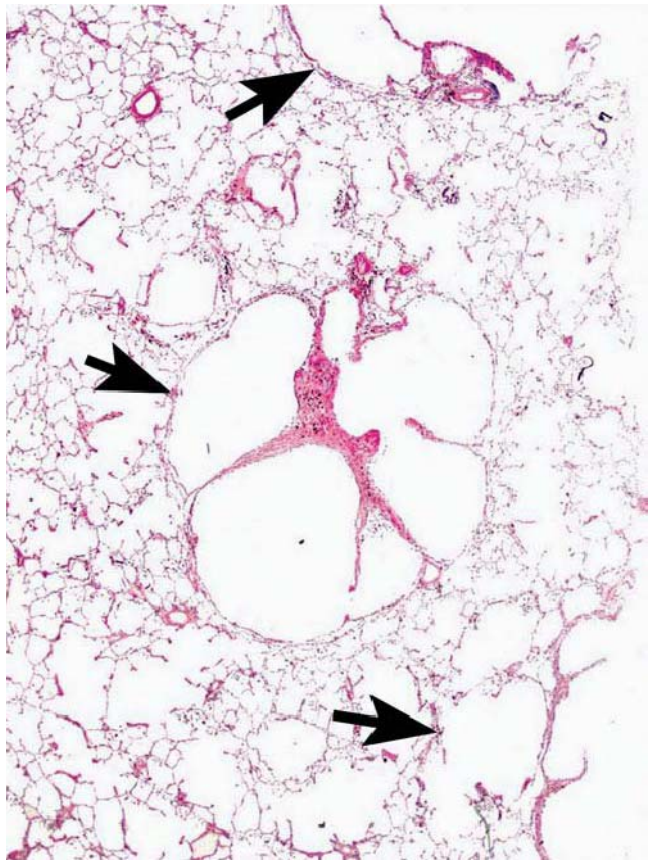

FIGURE 9.11. CLE with fibrosis. Three separate foci of CLE (*arrows*) show varying degrees of fibrosis. This is a common finding in CLE; the proper diagnosis is "CLE" and not "CLE with fibrosis," as the latter term can be mistaken for CFE, whereas fibrosis of this type in emphysema has no known functional consequences.

Localized Fibrosis with Emphysema

The other setting in which there is a combination of-fibrosis and emphysema is one in which the patient does not have a diffuse ILD, but has ordinary emphysema with fibrosis in the enlarged airspaces (Figs. 9.11 and 9.12) or has emphysema associated with smoker's RB/RBILD that has some degree of local fibrosis (Figs. 9.13 to 9.15, and see Chapter 8 on the distinction between smoker's RB and RBILD). These combinations exist in the pathology literature under various names including centrilobular emphysema (CLE) with fibrosis, RB, RBILD, RBILD with fibrosis, airspace enlargement with fibrosis (AEF); and clinically occult interstitial fibrosis in smokers.[6–9]

Fibrosis associated with centrilobular (Figs. 9.11 and 9.12) or paraseptal emphysema is actually quite common, and smoker's RB/RBILD sometimes also shows local areas of interstitial fibrosis (see Chapter 8 and Figs. 9.13 to 9.15), but neither of these findings changes the underlying diagnosis of emphysema or RB/RBILD; rather, the diagnosis of CFE as it is used clinically requires the presence of a *diffuse* (as opposed to localized) ILD. When it is not clear whether the process in a biopsy is diffuse or purely localized, review of the CT scans is extremely helpful: true CFE should show evidence of a diffuse fibrosing process, whereas purely localized disease will not.

In most clinical/pathologic settings we advise against diagnosing "CLE with fibrosis" because the diagnosis will be confusing to clinicians (i.e., clinicians know what CLE is, but if one writes "CLE with fibrosis" the implication is that the patient has a diffuse fibrosing lung disease or CFE). In fact, the presence of fibrosis in CLE or some-degree of fibrosis associated with smoker's RB/RBILD does not change patient management or prognosis.

DIAGNOSTIC MODALITIES

CFE may be diagnosable on imaging alone, but if tissue is required, then a video-assisted thoracoscopic surgery (VATS) biopsy must be performed. Transbronchial biopsy produces no useful information in this setting.

PROGNOSIS

The prognosis of CFE is unclear; it is worse than emphysema alone, but variably reported as equal to or better than, or worse than that of UIP alone.[10–13] The presence of significant pulmonary hypertension is a major determinant of mortality with one year survival of approximately 60%.[13,14]

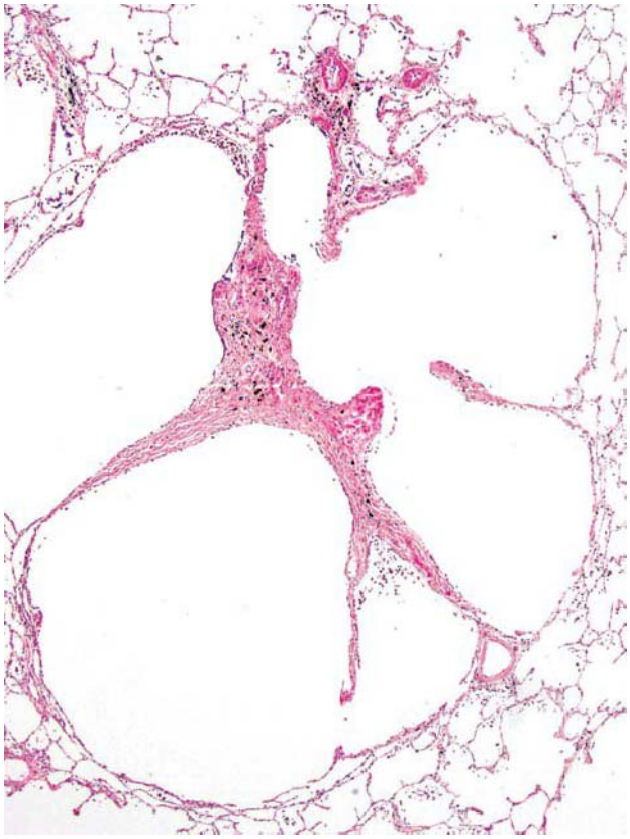

FIGURE 9.12. A higher-power view of the central lesion in Figure 9.5.

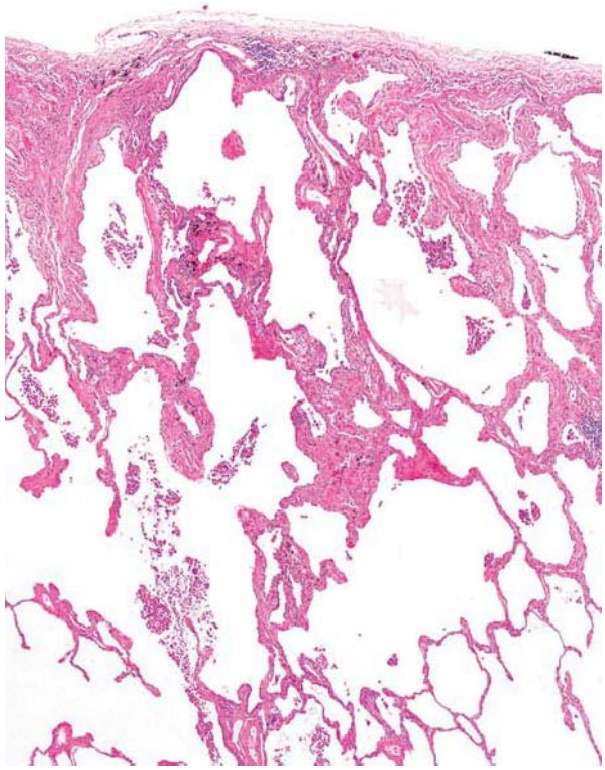

FIGURE 9.14. Higher-power view of the fibrotic area in Figure 9.12. If all one had was this field alone it would be impossible to determine whether the fibrosing process is localized or diffuse, but reference to CT imaging usually resolves the problem.

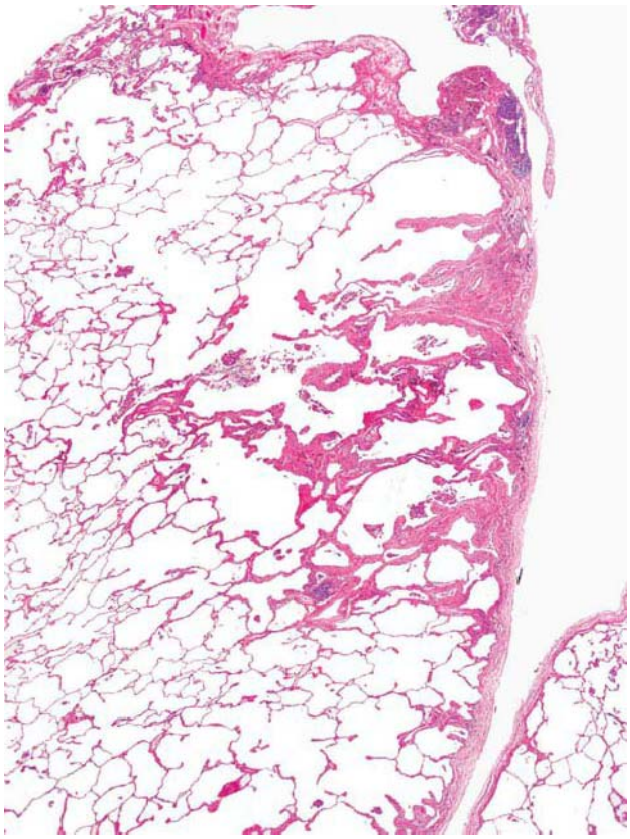

FIGURE 9.13. Low-power view of smoker's RB/RBILD with fibrosis. Note the distinct circumscription of the fibrosing process, a finding characteristic of RB/RBILD, as opposed to the diffuse fibrosis typical of CFE.

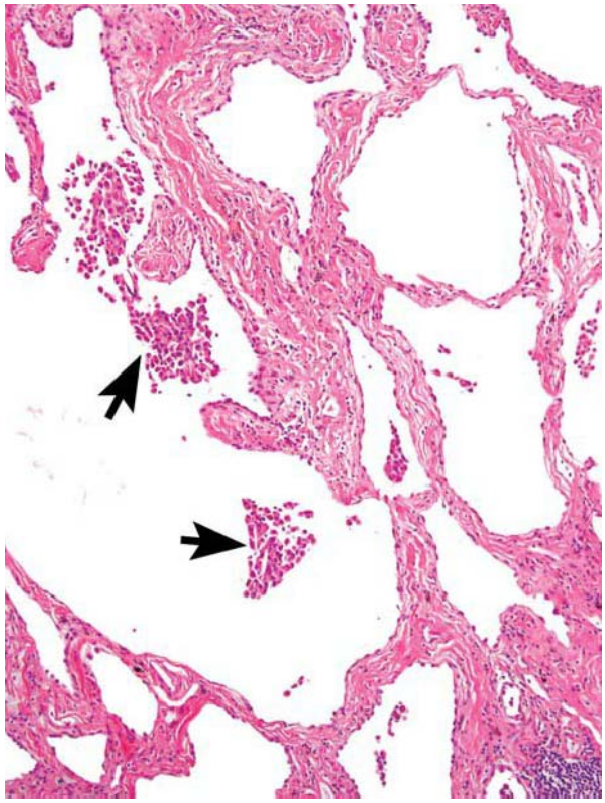

FIGURE 9.15. High-power view of Figure 9.14. The presence of aggregates of smoker's macrophages *(arrows)* suggests that this is RB/RBILD with fibrosis. See Chapter 8 for the distinction between RB and RBILD.

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CHAPTER

10

Langerhans Cell Histiocytosis (Eosinophilic Granuloma of Lung)

NOMENCLATURE ISSUES

Langerhans cell histiocytosis (LCH) is a proliferation of Langerhans cells, which are a form of dendritic cell, in response to cigarette smoke. The older term "eosinophilic granuloma of lung" is also applied sometimes to these lesions, and we believe it is a perfectly acceptable name, although somewhat misleading because there are no granulomas in eosinophilic granuloma and eosinophils may be scarce. The even older name, "histiocytosis X" is best avoided, as it includes a number of quite disparate entities: LCH (with the term sometimes used for disseminated disease), Letterer–Siwe disease, and Hand–Schiller-Christian disease, the latter two clonal, disseminated and sometimes aggressive conditions usually seen in infants and children.[1,2] The typical lung-isolated LCH of adult smokers is not clonal.[1,2]

ETIOLOGY

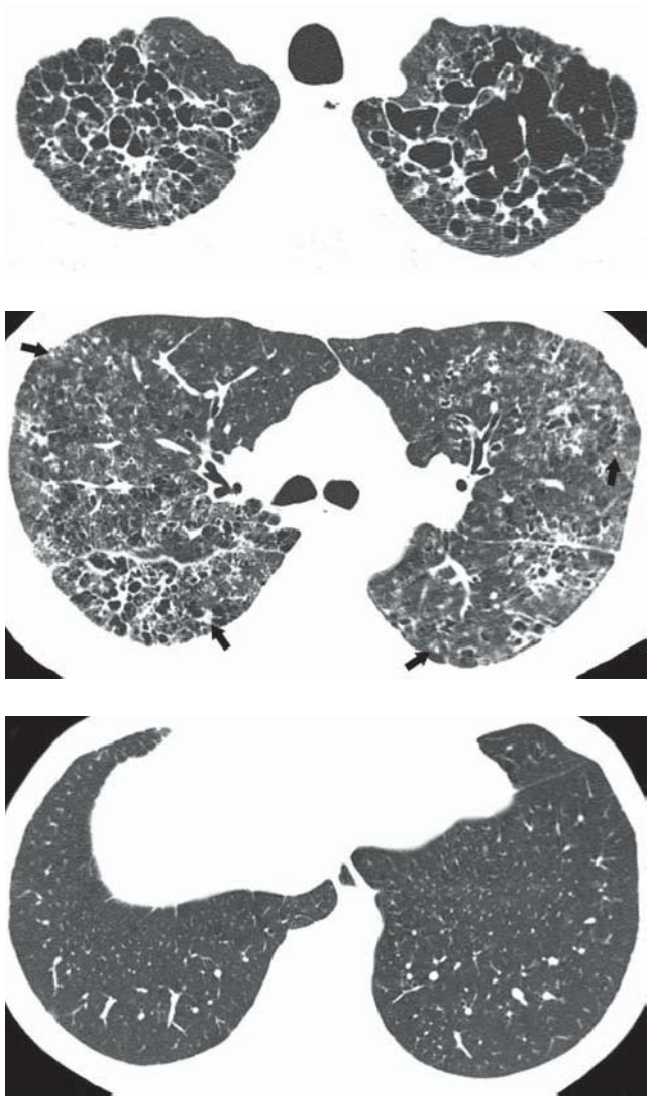
LCH in adults is almost always seen in current or ex-smokers. In humans and experimental animal models cigarette smoke functions as a dendritic cell attractant,[3] and LCH appears to represent an exaggerated or aberrant response to cigarette smoke.

CLINICAL FEATURES

LCH patients are typically young adults, most of whom are short of breath, but approximately 20% are asymptomatic,[4,5] and the lesions are picked up on routine chest radiographs. Another 15% present with spontaneous pneumothorax that may be recurrent.[6] Systemic complaints, particularly fever and weight loss, are seen in 15% to 20%. Pulmonary function tests may demonstrate a restrictive or an obstructive defect (the latter reflecting the fact that LCH lesions obliterate small airways) or sometimes just an isolated reduction in diffusing capacity.

IMAGING

The characteristic high resolution computed tomography (HRCT) manifestations of LCH comprise nodules and cysts in the upper and middle lung zones with relative sparing of the lung bases (Figs. 10.1 to 10.3). The nodules



FIGURES 10.1 to 10.3. LCH. **Figure 10.1:** HRCT at the level of the lung apices demonstrates multiple thin- and thick-walled cysts of various sizes and shapes and a few small nodules. **Figure 10.2:** HRCT at the level of the main bronchi shows multiple cysts and small nodules of various sizes and shapes (*arrows*). Also noted are ground-glass opacities presumably due to respiratory bronchiolitis. **Figure 10.3:** HRCT at the level of the lung bases shows normal parenchyma.

predominate in the early stages and the cysts in the later stages.[7] The nodules can have smooth or irregular margins, usually measure less than 10 mm in diameter, and have a centrilobular distribution. The cysts may have thin or thick walls. In the early stages the cysts usually measure less than 1 cm in diameter and are round or ovoid. In the later stages the cysts become confluent, larger than 2 cm in diameter and often have bizarre configurations.[8] HRCT shows no consistent central or peripheral predominance of lesions but in nearly all cases, the lung bases are relatively spared.

In the majority of patients the manifestations of LCH are characteristic enough to allow a confident diagnosis on HRCT.[9] Normally centrilobular emphysema (CLE) can be readily distinguished by the lack of visible walls and the presence of small vessels within the focal areas of lung destruction. The cysts in lymphangiomyomatosis (LAM) are typically diffuse throughout the lungs without any zonal predominance and are seldom associated with nodules.

PATHOLOGIC FEATURES

As a mnemonic tool, LCH lesions can be divided into the early or cellular phase and the late or scarred phase, but it is common to find mixtures of the two in a biopsy (Table 10.1).

The early phase consists of nodules that grossly are rounded to stellate (Fig. 10.4) and microscopically appear quite cellular at low power (Figs. 10.5 to 10.7). The lesions are centered on respiratory bronchioles and frequently obliterate the bronchiolar lumens. At high power they comprise a mixture of Langerhans cells (which resemble macrophages but have grooved nuclei), eosinophils, and often some numbers of smoker's macrophages (Figs. 10.8 to 10.10). The number of eosinophils is extremely variable and some cases have almost none (compare Figs. 10.8 and 10.9); an apparent absence of eosinophils does not invalidate the diagnosis of LCH, as it is the Langerhans cell that is really the diagnostic feature.

Occasionally Langerhans cells proliferate in the interstitium rather than forming distinct nodules (Figs.10.11 to 10.15) and mimic an interstitial pneumonia, although, as opposed to true interstitial pneumonias, such LCH lesions are always quite localized. Areas of bronchiolitis obliterans organizing pneumonia (BOOP) may also be present with the lesions of early LCH (Fig. 10.16). Vascular obliteration is sometimes seen in early lesions (Fig. 10.17).

Early phase LCH nodules frequently become cystic (Fig. 10.18) for reasons that are unclear, and if the cysts are immediately subpleural, they can rupture into the pleural space producing a pneumothorax. The cysts often have strange shapes and recent imaging data suggest that the peculiar shapes arise from fusion of cysts.[9]

Late lesions of LCH comprise fibrous scars that may be rounded, stellate, or more or less linear and grossly can produce a form of honeycombing (Fig. 10.19); unlike the honeycombing of usual interstitial pneumonia (UIP), old LCH tends to have cystic spaces but no sheets of fibrous tissue or the metaplastic bronchiolar epithelium, mucus collections, and inflammatory cells found in true honeycombing (see Figs. 6.14 to 6.16). Rather the lesions of old LCH comprise paucicellular fibrous scars that sometimes can be seen to be centered around respiratory bronchioles or are at least centrilobular in distribution (Figs. 10.20 to 10.24).

Table 10.1

Pathologic findings in LCH

Early lesions
Cellular rounded to stellate nodules centered on respiratory bronchioles
Occasionally areas with an interstitial pattern
Cellular lesions contain a variable mixture of eosinophils, Langerhans cells, chronic inflammatory cells, and smoker's macrophages
Cysts may be present
Aggregates of S-100 or CD1a positive cells
Eosinophils may be scarce
Late lesions
Irregular paucicellular scars that may be nodular or stellate or sometimes linear
Scars centered on respiratory bronchioles
No subpleural predominance
Fibrous walled cysts associated with scars may be present
Usually few or no S-100/CD1a positive cells
Respiratory bronchioles and/or accompanying pulmonary artery branches may be obliterated

FIGURE 10.4. Gross photograph of early LCH showing discrete nodules that, grossly, cannot be distinguished from a neoplasm. (Case Courtesy Dr. J. Flint.)

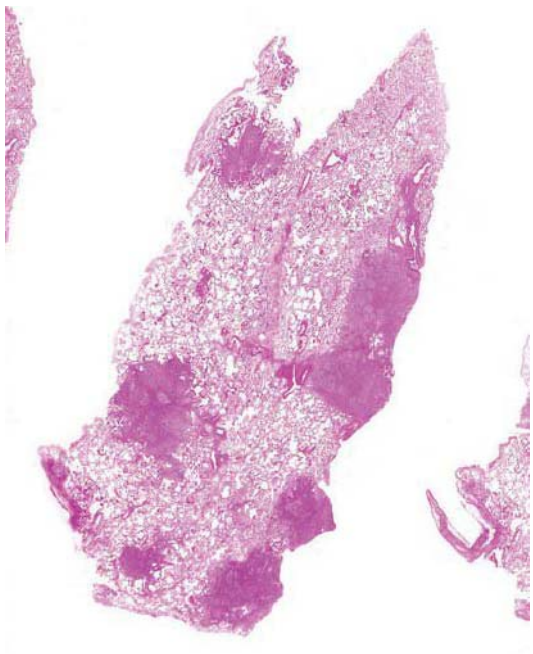


FIGURE 10.5. Whole mount view of early LCH showing cellular (stellate to irregular) nodules.

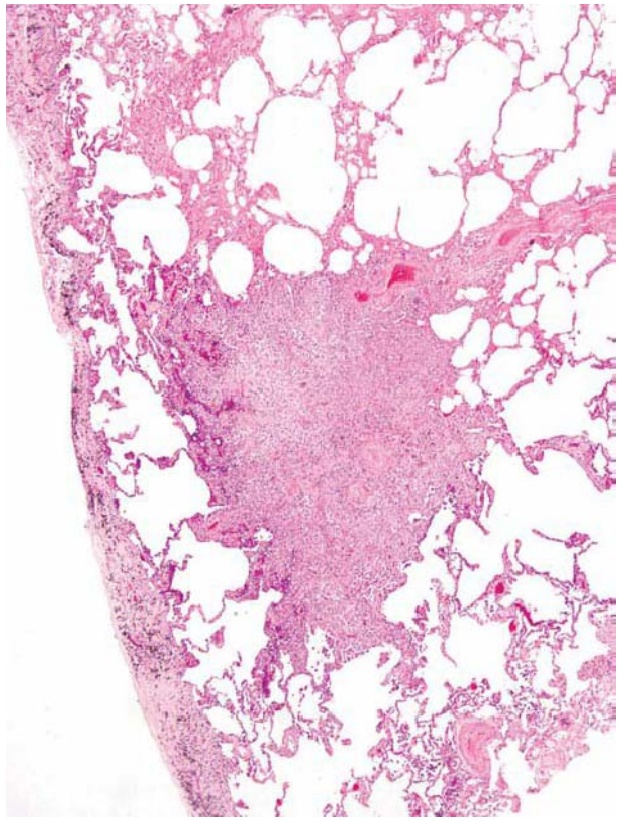


FIGURE 10.6. Low-power view of a nodule of early LCH. Note the stellate shape that is very common in LCH nodules.

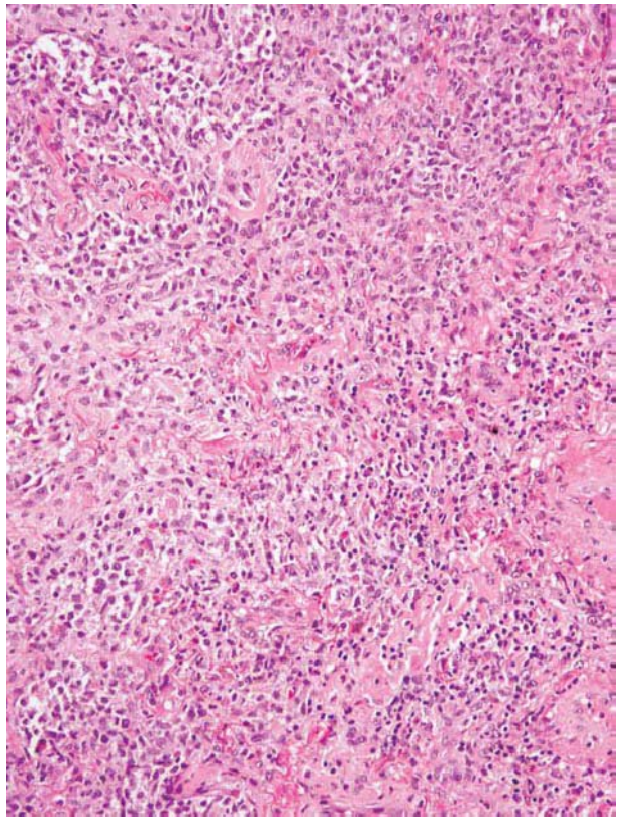


FIGURE 10.7. Higher-power view of the same nodule. Early LCH nodules are densely cellular.

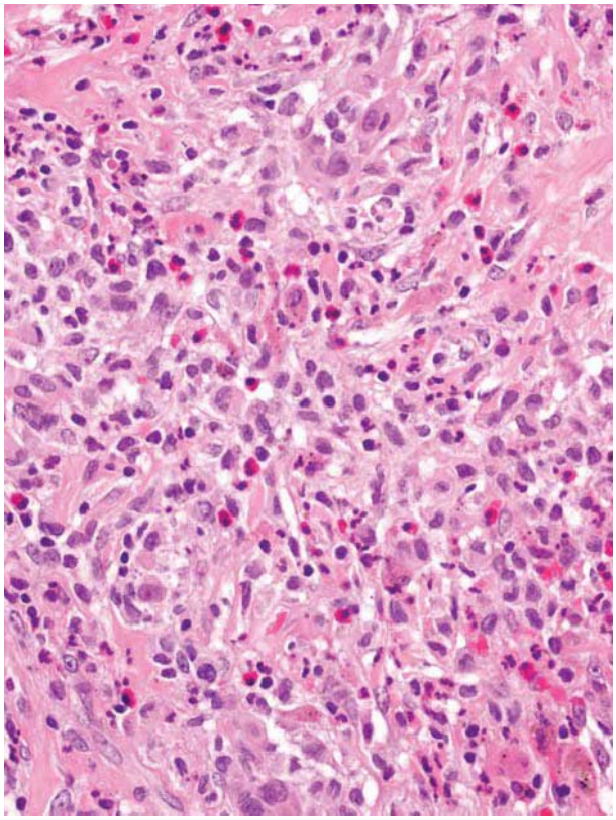


FIGURE 10.8. Early LCH nodule comprising Langerhans cells and fairly numerous eosinophils.

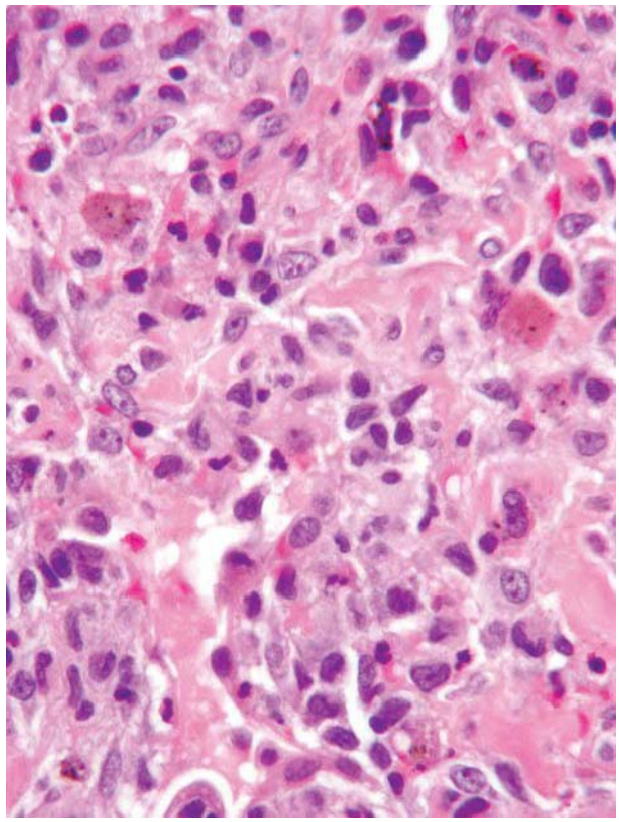


FIGURE 10.10. High-power view showing the bland and sometimes convoluted nuclei of Langerhans cells.

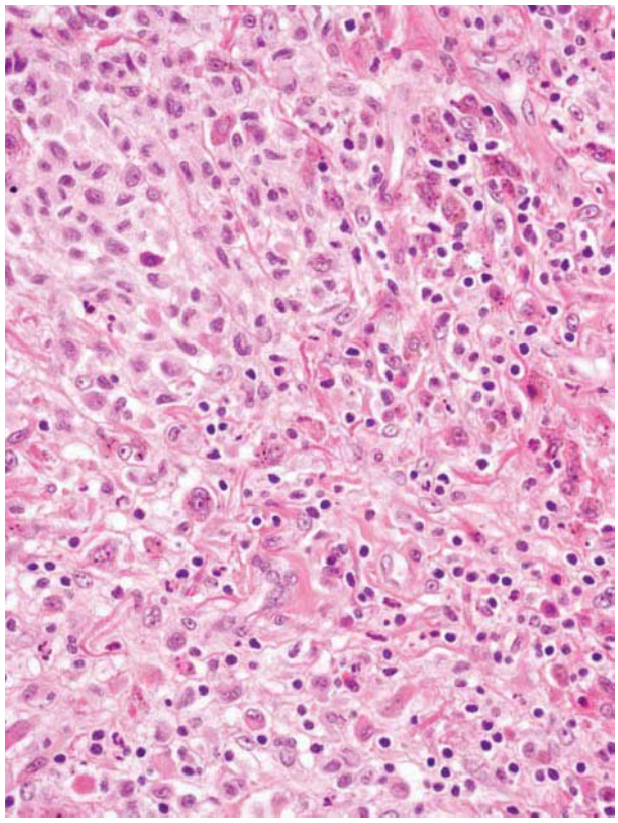
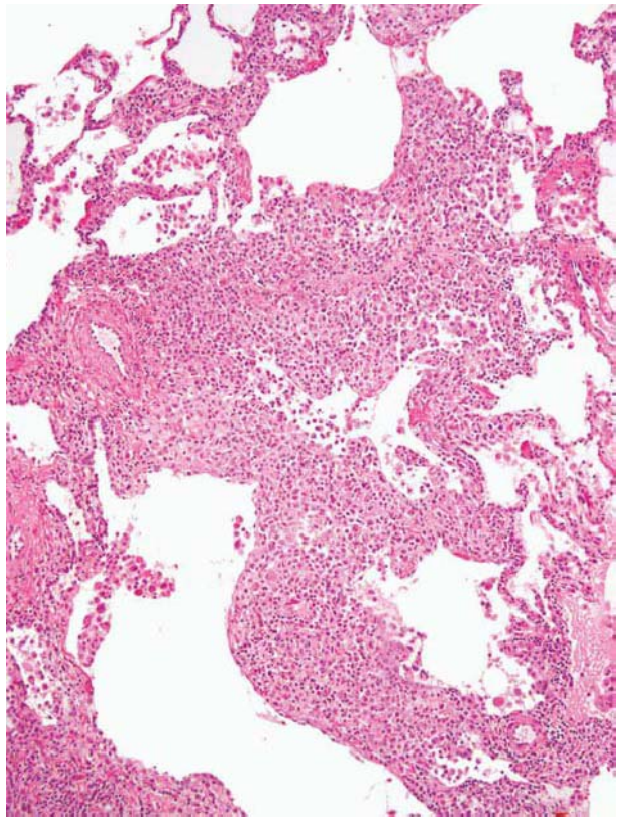
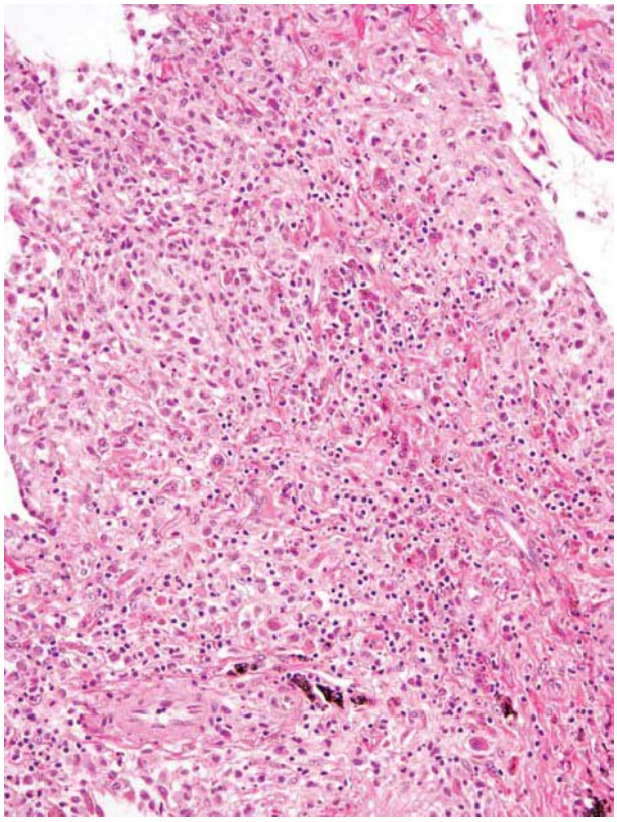


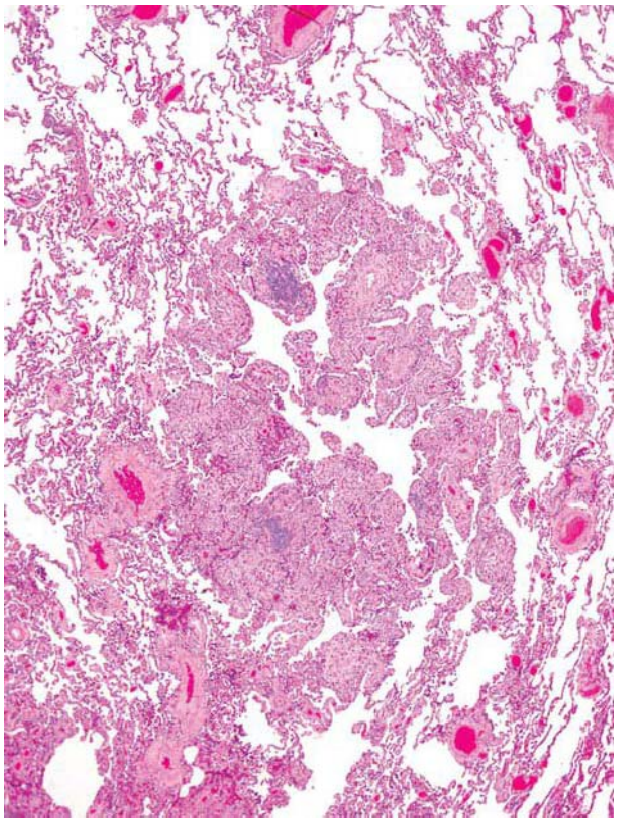
FIGURE 10.9. Early LCH nodule comprising sheets of Langerhans cells with only rare eosinophils. Eosinophils can be completely absent in LCH. Note the numerous smoker's macrophages, a common finding in and around LCH nodules.



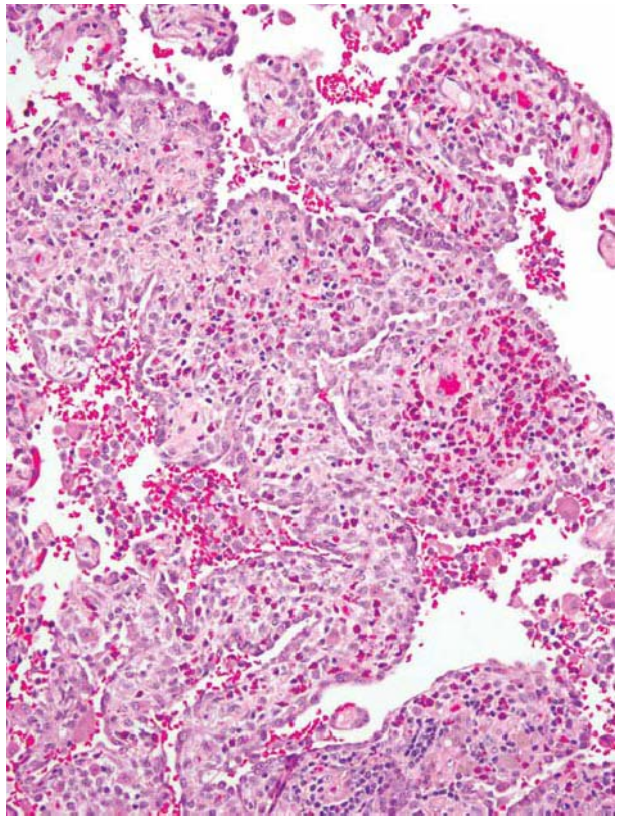
FIGURES 10.11 and 10.12. Legend appears on following page

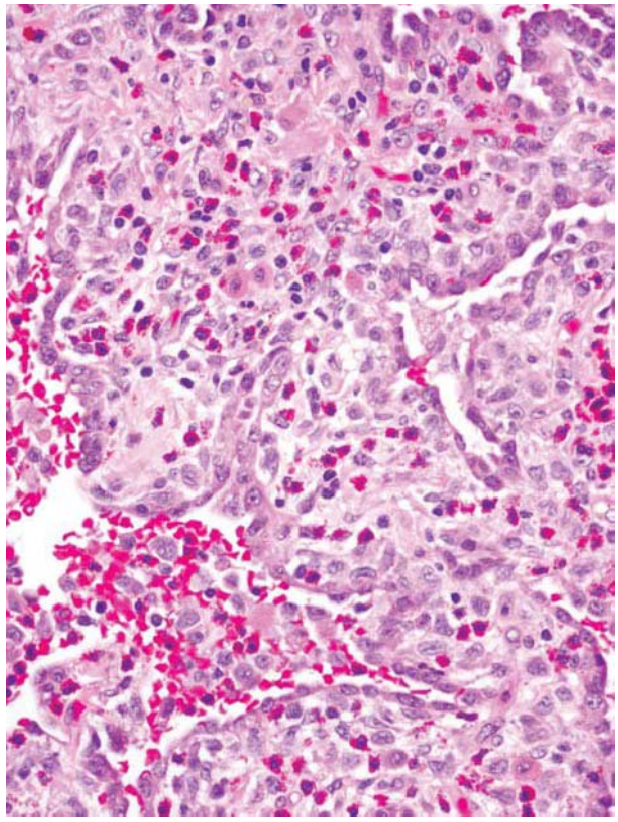


FIGURES 10.11 and 10.12. Low- and high-power views of early LCH with an interstitial pattern. Early LCH lesions are not always nodules, but even when apparently interstitial, the process is circumscribed.



FIGURES 10.13 to 10.15. Legend appears on next column





FIGURES 10.13 to 10.15. Another example of LCH with an interstitial pattern of growth.

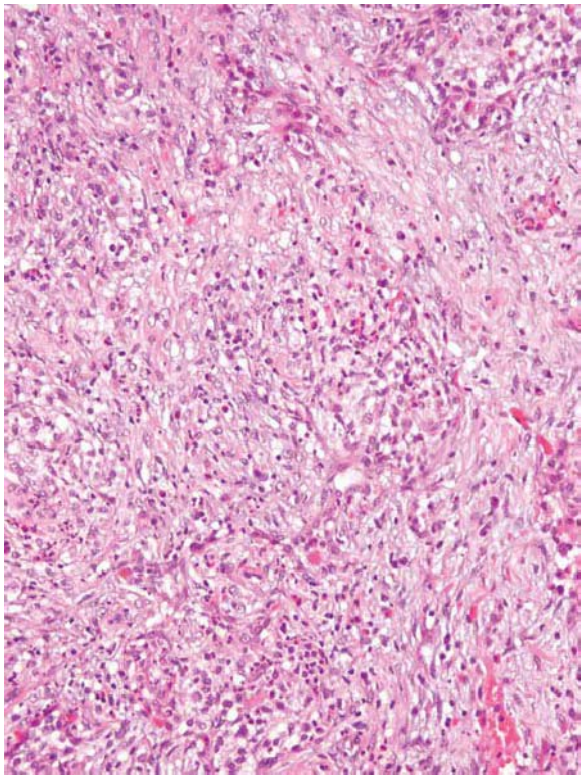


FIGURE 10.16. Areas of BOOP within an early LCH nodule.

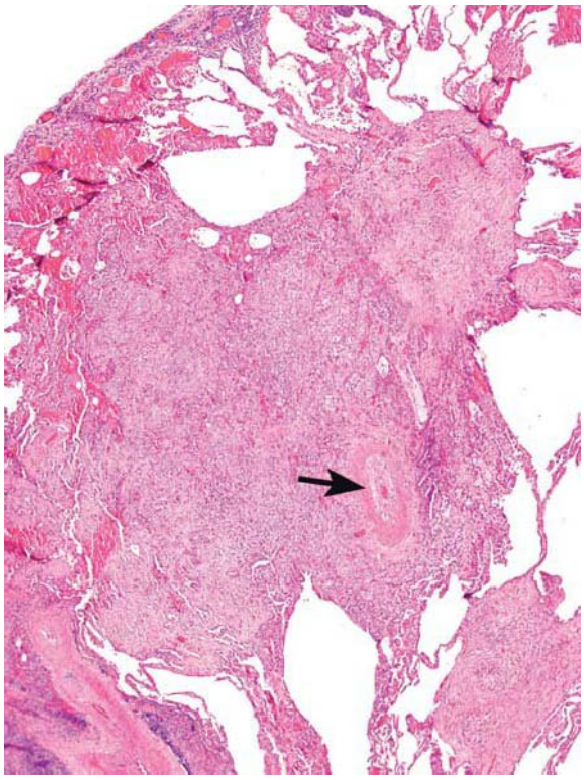


FIGURE 10.17. Obliterated vessel (*arrow*) in an early LCH nodule. Because LCH nodules typically form around respiratory bronchioles, they tend to engulf and obliterate pulmonary artery branches, eventually leading to pulmonary hypertension.

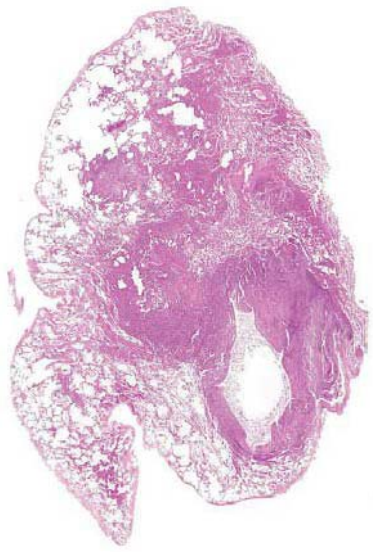


FIGURE 10.18. Early LCH nodule with a cyst. Rupture of cysts into the pleural space accounts for the high incidence of pneumothorax in LCH.

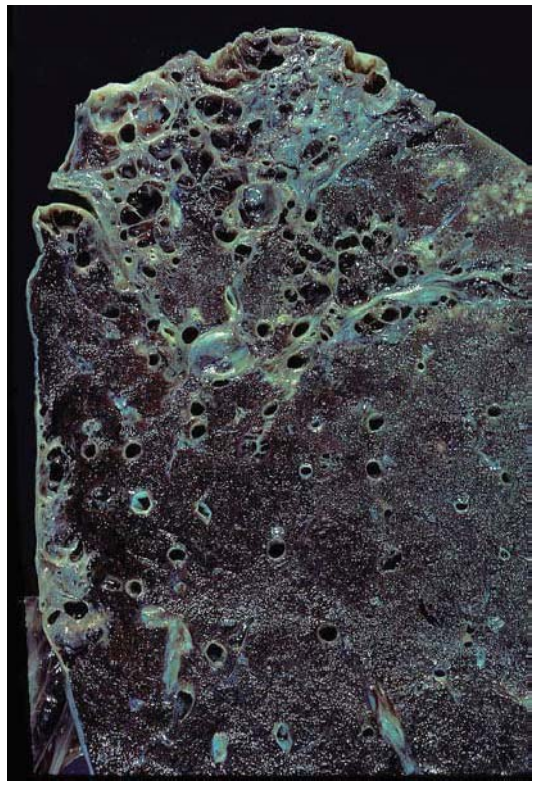
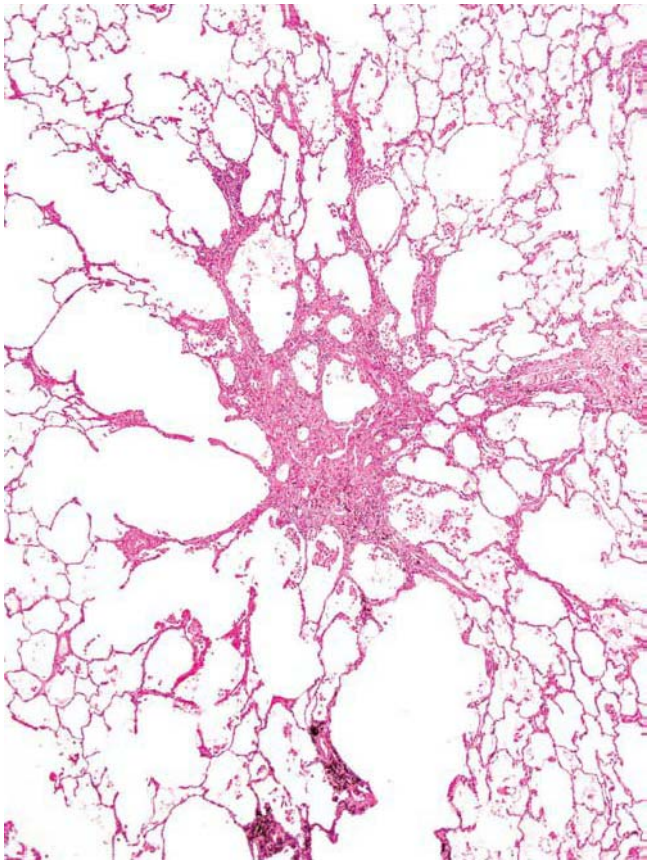
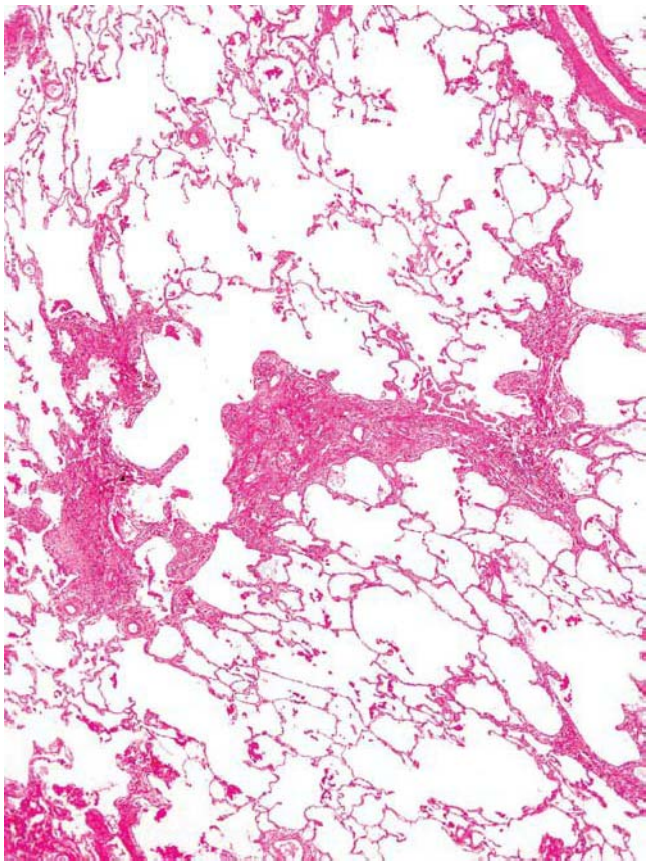


FIGURE 10.19. Gross view of late stage fibrotic LCH in the apex of the lung. LCH typically involves the upper lung zones and spares the lung bases.

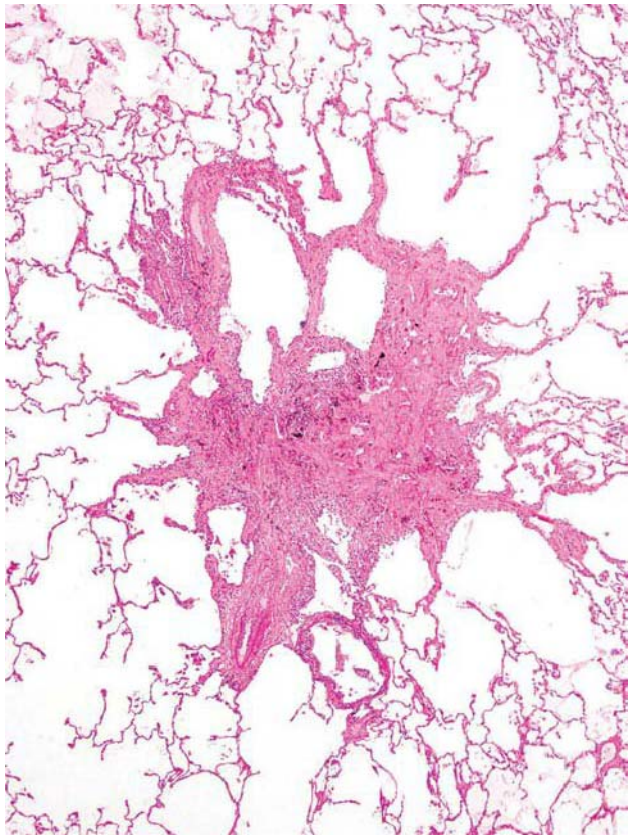
Old scarred LCH never shows the subpleural distribution of UIP or the homogeneous scarring of fibrotic nonspecific interstitial pneumonia (NSIP).

Depending on the age of the lesion, small numbers of Langerhans cells and/or eosinophils may be present

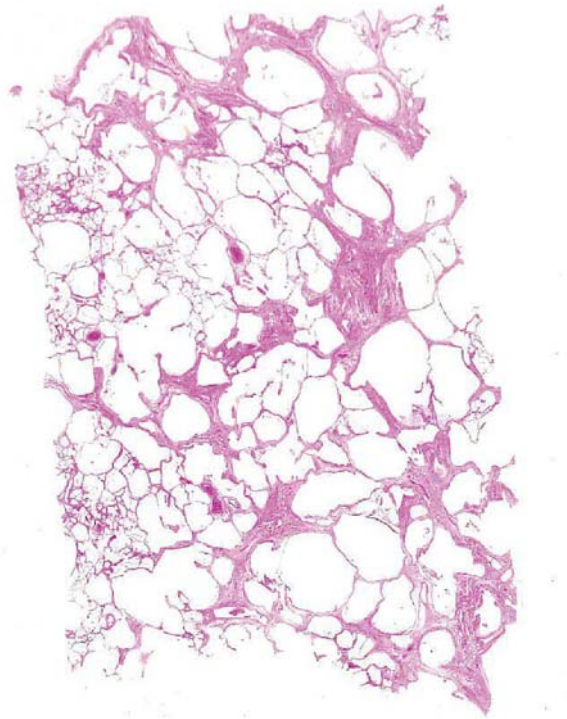




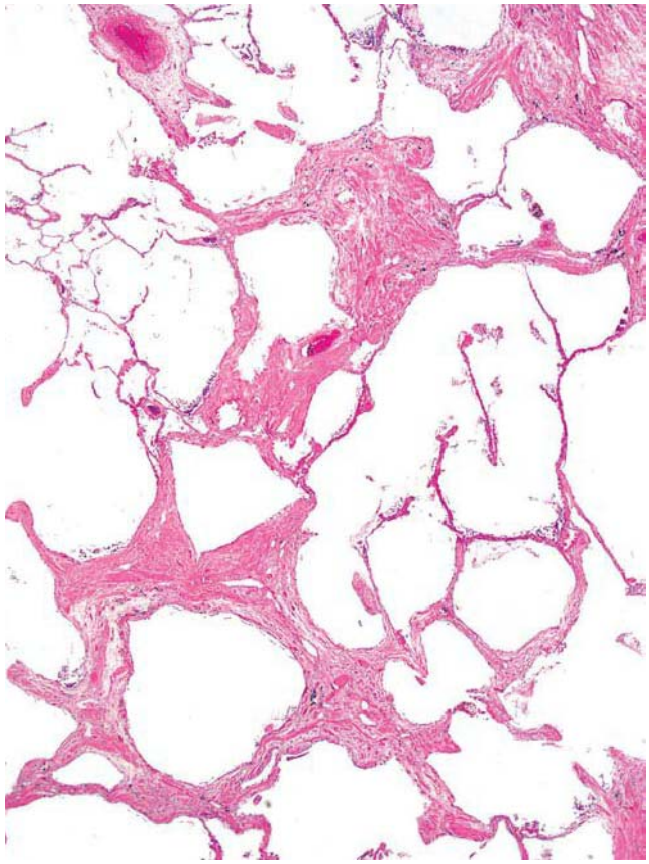
FIGURES 10.20 to 10.22. Legend appears on next column



FIGURES 10.20 to 10.22. Examples of different patterns of localized scarring in late stage LCH. Irregular or stellate centrilobular scars should suggest a diagnosis of old burnt out LCH; however, they can also be seen in old sarcoid.



FIGURES 10.23 and 10.24. Legend appears on following page



FIGURES 10.23 and 10.24. Diffuse scarring in late stage LCH. Although not specific, diffuse scarring of this type with bizarre shapes and a centrilobular distribution should suggest a diagnosis of old burnt out LCH.

(Figs. 10.25 and 10.26), but the older the lesion, the fewer such cells are found, and very old lesions are almost completely acellular. LCH scars can obliterate respiratory bronchioles and also the accompanying small pulmonary artery branches; if enough arterial branches are destroyed pulmonary hypertension develops.

Because LCH is a disease of smokers, LCH biopsies may also have focal desquamative interstitial pneumonia (DIP)-like areas and smoker's respiratory bronchiolitis (RB), but the convention is that these lesions are ignored, unless there is true widespread DIP (see Chapter 9) and not just collections of smoker's macrophages in alveoli.

IMMUNOHISTOCHEMISTRY

Langerhans cells are strongly S-100 and CD1a positive (Figs. 10.27 and 10.28), and this is a useful test when the identity of a cellular lesion is uncertain. However, care needs to be taken in interpreting these stains as any kind of inflammatory process in the lung will have a few Langerhans cells.[10] A positive diagnosis requires sheets or nodules of positive staining cells (Figs. 10.27 and 10.28) and not just scattered individual staining cells.[10]

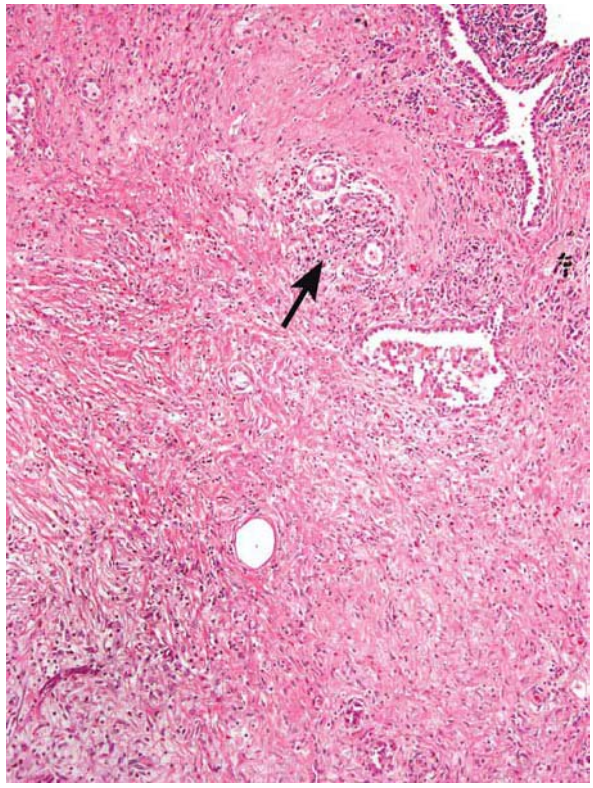


FIGURE 10.25. A largely scarred nodule of LCH in which there is a tiny focus of residual eosinophils and Langerhans cells (arrow).

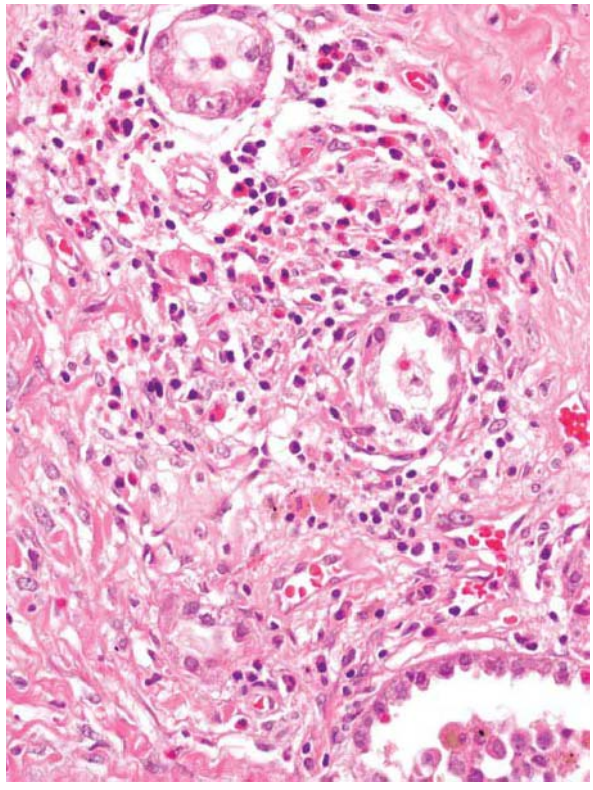
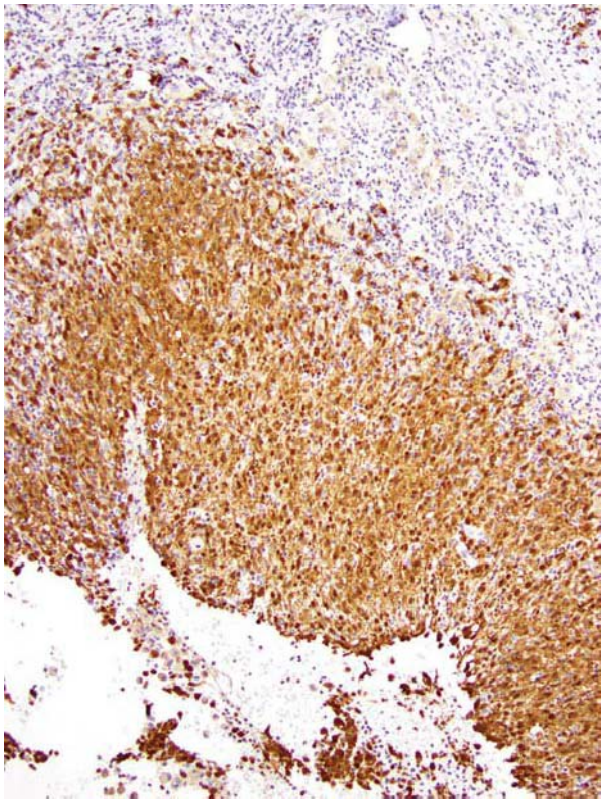
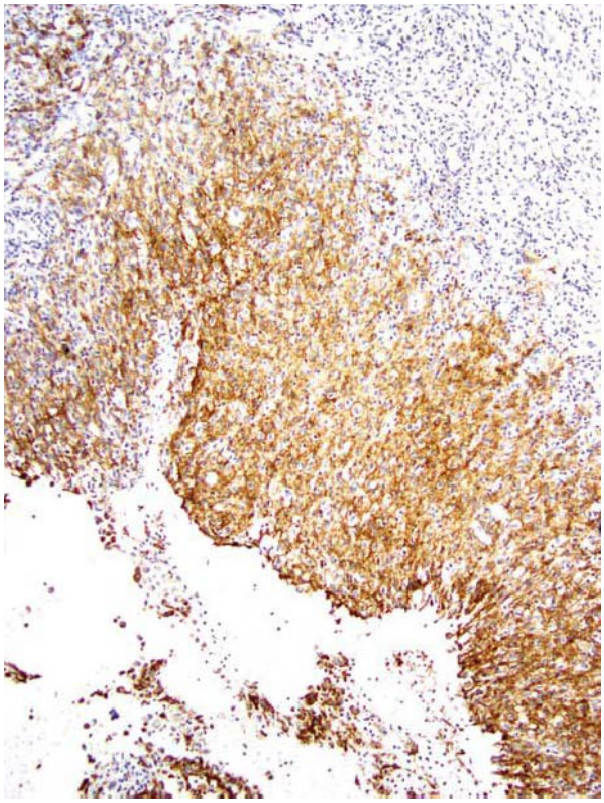


FIGURE 10.26. High power view of the region at the arrow in Figure 10.25. Foci such as this in otherwise scarred nodules allow a definitive diagnosis of LCH.





FIGURES 10.27 and 10.28. Staining for S100 (10.27) and CD1a (10.28) in a nodule of early LCH. No other lesion produces this pattern of sheets of S100/CD1a positive cells. However, Langerhans cells disappear as the lesions age, so that negative staining in old fibrotic lesions does not rule out LCH.

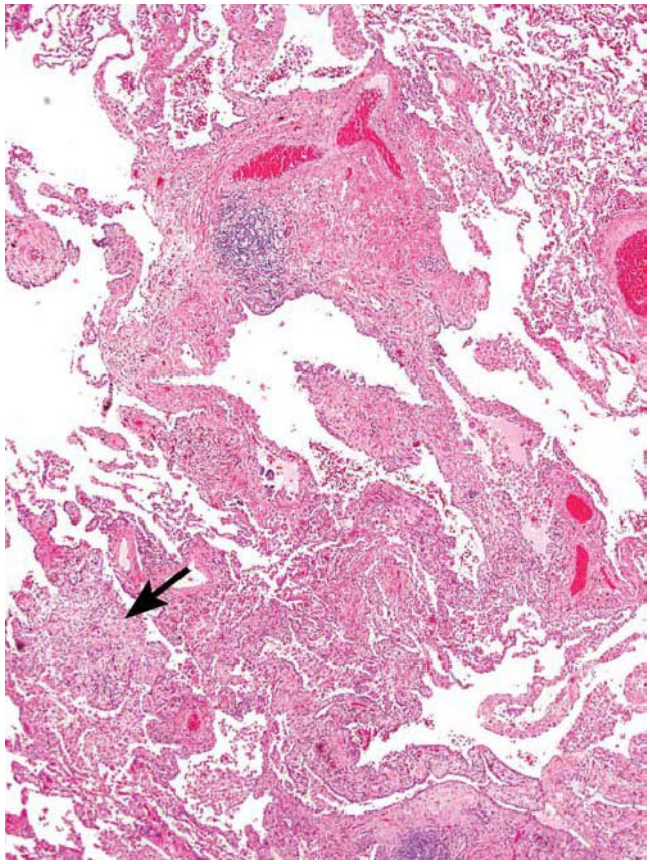


FIGURE 10.29. Low power view of an LCH lesion that has largely scarred; however, a more cellular area is present at the arrow.

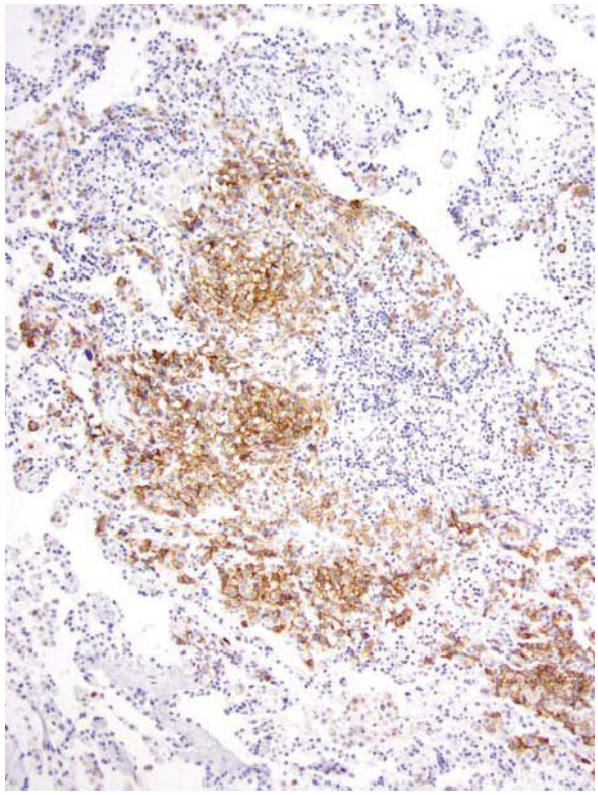
S-100 and CD1a staining is less useful in older lesions because the Langerhans cells disappear.[10] However, occasionally small aggregates of staining cells are still present and this is helpful in determining the etiology of a diffusely scarring process (Figs.10.29 to 10.31).

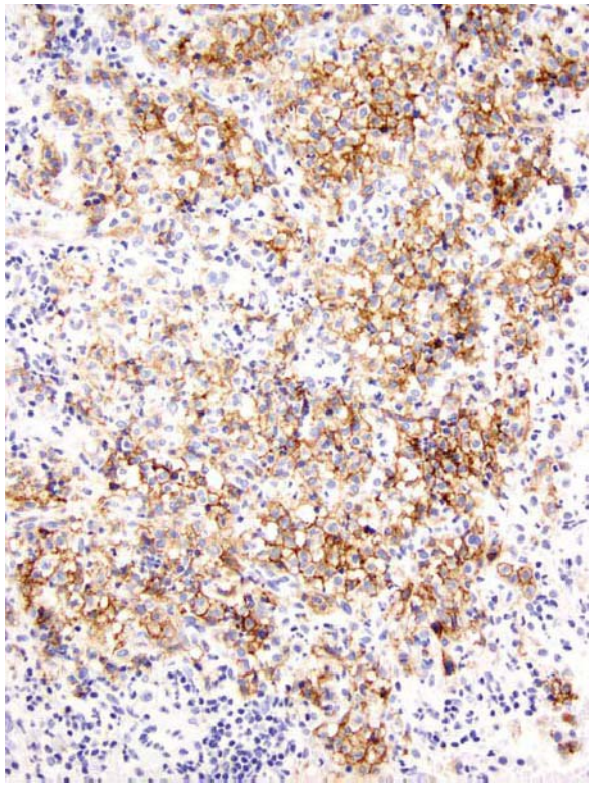
DIAGNOSTIC MODALITIES

In many instances, HRCT is diagnostic in LCH and no biopsy is required. Transbronchial biopsy is sometimes diagnostic (Figs.3.4 and 3.5); however as the lesions of LCH are scattered, the yield on transbronchial biopsies is fairly low.[11] If the lesions are large enough they can, occasionally, even be picked up on core biopsy.[12] However, VATS biopsy is the usual procedure of choice.

DIFFERENTIAL DIAGNOSIS

Table 10.2 shows the differential diagnosis of LCH. At first glance this appears quite broad but in practice is generally straightforward. At low power, cellular early lesions of LCH mimic neoplasms, but at high power, the only neoplasm that might be confused with LCH is classical Hodgkin disease involving the lung, since Hodgkin disease





FIGURES 10.30 and 10.31. CD1a stain of the same lesion as Fig 10.29. Note the absence of staining in the scarred area but intense and concentrated staining in the cellular area. Staining for S-100 or CD1a sometimes is useful for picking out residual diagnostic cellular foci when the morphologic pattern is not specific in late stage LCH, but only staining cellular aggregates of the type shown here are diagnostic.

Table 10.2

Differential diagnosis of LCH

Reactive eosinophilic pleuritis
- Common in cases of pneumothorax
- Also seen with drugs, tumors
- Cells are S-100/CD1a negative

Chronic eosinophilic pneumonia
- Eosinophils, no Langerhans cells, not nodules

Metastatic tumor (cellular nodules)

Hodgkin disease involving the lung

UIP or NSIP (vs. forms of LCH with extensive scarring)

Old burnt-out sarcoid

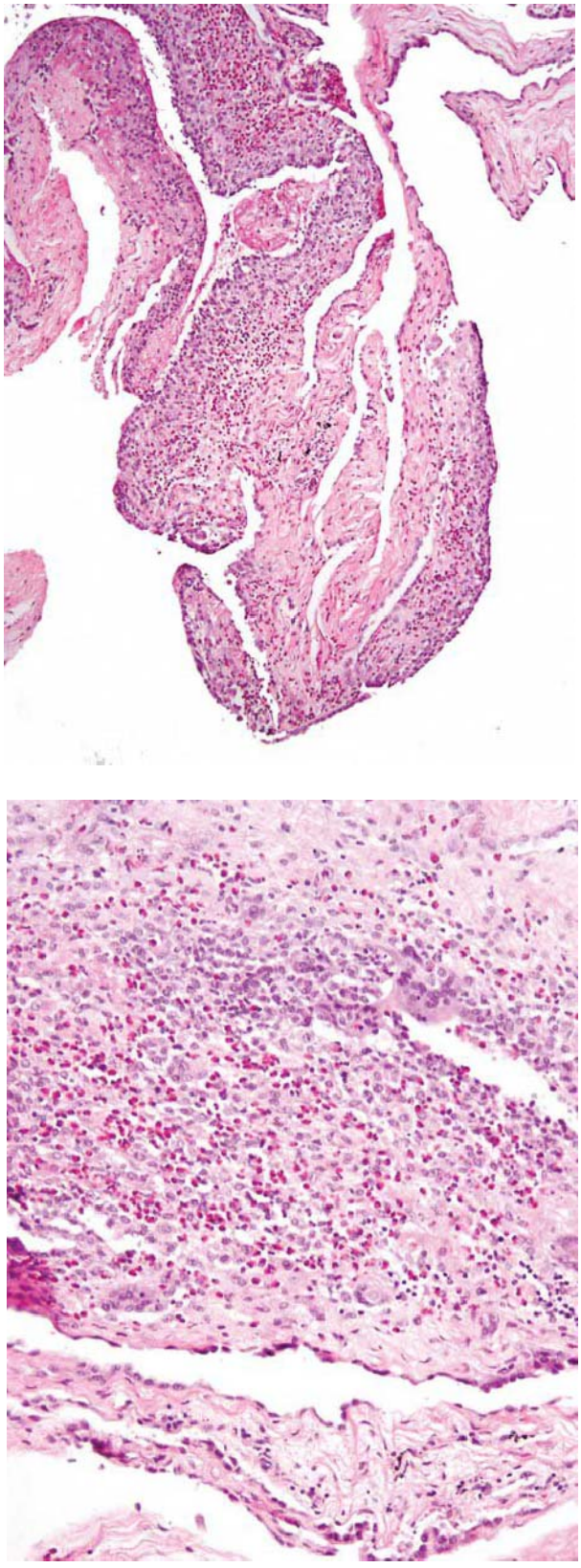
Erdheim–Chester disease

is typically centered around airways and usually has some number of eosinophils. However, Hodgkin disease does not have Langerhans cells or smoker's macrophages and Reed–Sternberg cells are not present in LCH.

Reactive eosinophilic pleuritis is a non-neoplastic process in which there are large numbers of eosinophils in the pleura, usually as a reaction to an inflammatory process, a tumor, a drug, or a pneumothorax[13] (Figs. 10.32 and 10.33). The latter situation can raise a question of underlying LCH, but usually it is clear in bullectomy specimens that LCH is not present. The infiltrating cells in chronic eosinophilic pleuritis are macrophages or mesothelial cells, neither of which are S-100 or CD1a positive. If in doubt, imaging will show an absence of parenchymal nodules/cysts in reactive eosinophilic pleuritis.

Chronic eosinophilic pneumonia (Chapter 15) can be localized and thus somewhat mimic LCH. However, microscopically, eosinophilic pneumonias typically have large numbers of eosinophils, often admixed with BOOP, and Langerhans cells are sparse or absent. Imaging again will readily sort this out because chronic eosinophilic pneumonia appears as consolidative lesions that are typically peripheral and are often migratory.

Erdheim–Chester disease (Chapter 23) is characterized by radiologic sclerosis of the long bones, chronic bone pain, and infiltration of a variety of extra-osseous sites by foamy CD68 and Factor 13a positive macrophages. In the lung, these macrophages are found primarily in the pleura, the interlobular septa, and around the bronchovascular bundles. The macrophages are accompanied by variable degrees of fibrosis (see Figs. 23.10 to 23.15). Collections of Erdheim–Chester cells around bronchovascular bundles (Fig. 23.13) can somewhat mimic LCH, but Langerhans cells are never foamy, and Erdheim–Chester disease does not have eosinophils and usually does not have smoker's macrophages. The immunochemical findings are



FIGURES 10.32 and 10.33. Low and high power views of reactive eosinophilic pleurits. The high power view mimics LCH. Both LCH and reactive eosinophilic pleuritis are associated with pneumothorax, but LCH will have nodules in the lung on imaging, whereas reactive eosinophilic pleuritis will not. The proliferating cells in reactive eosinophilic pleuritis are histiocytes or mesothelial cells and are negative with S100/CD1a.

obviously quite different. HRCT findings in the chest in Erdheim–Chester disease are also distinct from Langerhans, with marked septal thickening (Fig. 23.10 and see Chapter 23).

In terms of fibrotic mimics, UIP and NSIP do not show stellate scars, and true honeycombing with metaplastic bronchiolar epithelium, such as is seen in UIP (see Chapter 6), is not found in LCH. Sarcoid most commonly scars as nodules, but occasionally sarcoid can scar in a more or less linear fashion with bronchovascular predominance. When the lesions are not completely scarred and granulomas are still present, separation from LCH is easy, but completely burnt-out sarcoid with linear scars is not easily distinguished (see Fig. 13.27).

PROGNOSIS

Some cases of LCH appear to remit spontaneously or with smoking cessation,[4,5] but a recent study of 49 patients could not find any beneficial effect of smoking cessation on pulmonary function decline.[14] In the past LCH was believed to have an excellent prognosis, but more recent data make it clear that the long-term prognosis is guarded.[4,14] Vassallo et al.[4] reported a 15-year survival of approximately 50% patients. Some patients develop significant airflow obstruction.[5,14] Patients may die of respiratory failure secondary to extensive scarring, but pulmonary hypertension is also very common in long-term LCH survivors,[4,14] presumably because the centrilobular lesions pick off pulmonary artery branches when they scar.

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CHAPTER

11

Introduction to Granulomatous Forms of Interstitial Lung Disease

The various types of interstitial lung disease (ILD) that are always or sometimes characterized by granulomas are summarized in Table 11.1. This grouping is useful for the pathologist as a mnemonic because it limits the differential diagnosis, but it is only a mnemonic, as most of these entities have no relationship to each other.

This approach has more limitations than is commonly appreciated. Apart from hot tub lung, none of the diseases listed in Table 11.1 always has granulomas (even sarcoid may lack granulomas when it is burnt out), so that an absence of granulomas is not necessarily evidence against the diagnosis in question. Furthermore, pathologists tend to separate granulomas into non-necrotizing (i.e., sarcoidal) and necrotizing, with the implication that the latter are infectious, but this separation is less clear in actual practice as many of the entities in Table 11.1 can sometimes contain necrotizing granulomas.

Table 11.1

Interstitial lung disease characterized by granulomas

Disease	Are granulomas always present/ever necrotizing?
Hypersensitivity pneumonitis (Chapter 12)	No/no
Hot tub lung (Chapter 12)	Yes/sometimes
Sarcoid (Chapter 13)	No/sometimes
Drug reactions (Chapter 18)	No/rare
Common variable immunodeficiency (Chapter 14)	No/no
Aspiration (Chapters 5 and 20) including aspiration-related bronchiolitis	No/sometimes
Lymphocytic interstitial pneumonia (Chapter 19)	No/no

CHAPTER

12

Hypersensitivity Pneumonitis

NOMENCLATURE AND DEFINITION ISSUES

Hypersensitivity pneumonitis (HP) is also referred to as extrinsic allergic alveolitis (EAA), but the latter term seems to be falling out of favor, and we shall use the term hypersensitivity pneumonitis in this book.

HP is a lung-limited hypersensitivity reaction to an inhaled antigen, but the definitions of HP and particularly of the various subtypes of HP are somewhat confusing. Table 12.1 lists a generally accepted set of defining features that include known exposure to an offending agent. However in a substantial proportion of cases (approximately 25% to 30%) no antigen can be identified, and some of the other tests listed (bronchoalveolar lavage [BAL], serum precipitating antibodies, inhalation challenge) are often not carried out or are not available, so that the fundamental definition of HP frequently reduces to that of an interstitial lung disease (ILD) with characteristic findings on imaging and biopsy.

Traditionally HP is divided in acute, subacute, and chronic (meaning fibrotic) forms (Table 12.3) and we shall follow that convention here. There is considerable clinical debate about whether cases can really be separated in this fashion[1,2] and some authors view "chronic" HP as any case of HP where signs and symptoms have persisted for a long period (generally 6 months or a year), whether or not there is evidence of fibrosis.[3] We prefer not to use this type of categorization because it produces overlapping patterns on imaging and pathology, and, more important, obliterates clear prognostic differences between traditional subacute and chronic (fibrotic) HP, but the reader needs to be aware of the different ways in which this set of terms is used when reviewing the literature.

Table 12.1

Defining features of HP

Known exposure to offending antigen[a]
Compatible clinical, radiologic, physiologic findings (ILD)
BAL with lymphocytosis (often more than 40%)
Positive inhalation challenge/serum precipitating antibodies
Consistent pathologic findings

[a]In a significant proportion of cases, antigen cannot be identified.

ETIOLOGIES

HP is usually caused by inhaled organic antigens, but a small number of cases related to exposure to inorganic chemicals have also been described (Table 12.2). Exposures may be occupational or environmental (Table 12.2). At first glance Table 12.2 implies that there are huge numbers of HP cases, but many of the causes listed are confined to very specific industries that employ small numbers of workers at particular locations and are unlikely to be encountered by most physicians. Recent publications[4,5] suggest that the most common etiologies seen in general practice in North America are farming, household birds, hot tub lung, and household molds, sometimes in colonized humidifiers. In other parts of the world this breakdown is different; for example, in Mexico and Spain many individuals raise pigeons and avian protein-induced HP (often called "pigeon breeder's lung") is relatively more common.[6] In Japan, household mold contamination by *Trichosporon cutaneum* or *Cryptococcus albidus* produces the so-called summer type HP.

For reference purposes Table 12.2 follows the common convention of labeling HP of specific etiologies with different names, but this can produce confusion, and it is preferable to specifically use the term hypersensitivity pneumonitis when actually diagnosing HP of any cause; for example, "HP caused by bird exposure" rather than "bird fancier's lung"; "HP caused by maple bark stripping" rather than "maple bark stripper's disease."

CLINICAL FEATURES

The clinical features of HP are summarized in Table 12.3. The acute form is caused by exposure to high levels of the offending antigen and appears as a flu-like illness with the abrupt onset of fever, chills, and shortness of breath (SOB) a few hours after exposure. If the exposure does not continue the process resolves spontaneously, typically within about 48 hours.

Subacute HP is the most commonly encountered form and is believed to reflect continuing fairly low level exposure to the antigen in question. It usually presents with the insidious onset of SOB over weeks to months, occasionally accompanied by fever. Patients typically have Velcro rales at the lung bases and a mild restrictive functional abnormality with a decreased diffusing capacity; however, minor

Table 12.2

Etiologies and names of HP caused by specific types of exposures[a]

Name	Etiologic agents
Bird fancier's lung/pigeon[b] breeder's lung	Avian proteins in droppings, feathers, feather-filled pillows and duvets
Farmer's lung[b]	Moldy hay and grains
Hot tub lung[b]	Atypical mycobacteria colonizing hot tubs and saunas
Humidifier lung[b]	Humidifiers and forced air heating and cooling systems colonized by various organisms, most commonly *Aureobasidium pullulans* and thermophilic *Actinomycetes* species
Household mold-induced HP[b]	Moldy walls, floors, ceilings
Bagassosis	Moldy sugar cane
Chemical worker's lung	Isocyanates, trimellitic anhydride
Coffee worker's lung	Coffee bean dust
Fuel chip HP	Moldy wood fuel chips
Malt worker's lung	Moldy whiskey maltings
Maple bark stripper's disease	Moldy maple bark
Metalworker's/machine operator's HP	Contaminated metalworking fluids
Mollusk shell HP	Oyster and sea-snail shells
Mushroom worker's lung	Mushroom compost
Pituitary snufftaker's disease	Bovine and porcine pituitary snuff
Suberosis	Moldy cork dust
Swimming pool HP	Swimming pools contaminated with endotoxin, candida sp, thermophyllic actinomycetes, etc
Wood pulp and woodworker's lung	Pine or redwood extracts/moldy wood
Summer type HP (Japan)	Homes contaminated by *Trichosporon cutaneum* or *Cryptococcus albidus*

[a]For a detailed listing of specific antigens, see Myers.[7]
[b]Common causes of HP in North America.

degrees of airflow obstruction may also be found because the process pathologically involves the bronchioles.

The exact sequence of events behind chronic HP is unclear; some authors suggest it reflects frequent exposure to high levels of antigen, whereas others believe it is caused by persisting low level exposures. Most cases present in a fashion similar to subacute HP, but the pulmonary functional changes are often more marked, patients may be clubbed, and, by definition, there is evidence of fibrosis on biopsy or on imaging.

IMAGING

CT is seldom performed in acute HP because the clinical manifestations are characteristic and the symptoms usually resolve rapidly. The few reported cases demonstrated extensive bilateral ground-glass opacities (GGOs) with or without dependent areas of consolidation and centrilobular nodules (Fig. 12.1).

The majority of patients who undergo high resolution computed tomography (HRCT) have subacute HP. The typical finding consists of a heterogeneous appearance of the lung parenchyma (mosaic attenuation) with patchy or confluent GGOs and scattered lobular areas of decreased attenuation and vascularity[8] (Fig. 12.2). Another common finding is the presence of small centrilobular nodular opacities of ground-glass attenuation. Expiratory HRCT shows air trapping. The abnormalities can be diffuse but tend to have lower zone predominance. In the proper clinical context the HRCT findings are often characteristic enough to strongly suggest the diagnosis.[8]

The fibrosis in chronic HP is manifested by reticulation, traction bronchiectasis, and, commonly, honeycombing (Figs. 12.3 and 12.4). The distribution of the

Table 12.3

Clinical separation of HP subtypes

Acute form
Dyspnea, chills, fevers, SOB 4 to 6 h after exposure; resolves by 48 h
Subacute form
Insidious onset of shortness of breath over weeks to months
Often inspiratory rales
Generally mild restrictive pulmonary function/ decreased diffusing capacity
Sometimes mild airflow obstruction
Marked lymphocytosis in BAL
Chronic form
Insidious onset of SOB
Restrictive pulmonary function/decreased diffusing capacity
Clubbing sometimes present
Features of fibrotic interstitial lung disease on imaging or biopsy

fibrosis is variable. It may have a random cephalocaudal distribution or predominate in the upper, mid- or lower-lung zones, but often spares the extreme lung bases.[9] It may have a random distribution in the transverse plane or show peribronchial or subpleural predominance. The majority of patients have associated findings of subacute HP that are helpful in the differential diagnosis of other fibrotic lung diseases (Figs. 12.3 and 12.4). It should be noted however that confident distinction of chronic HP from idiopathic pulmonary fibrosis (IPF) and fibrotic nonspecific interstitial pneumonia (NSIP) on HRCT can be made only in approximately 50% of cases.[9]

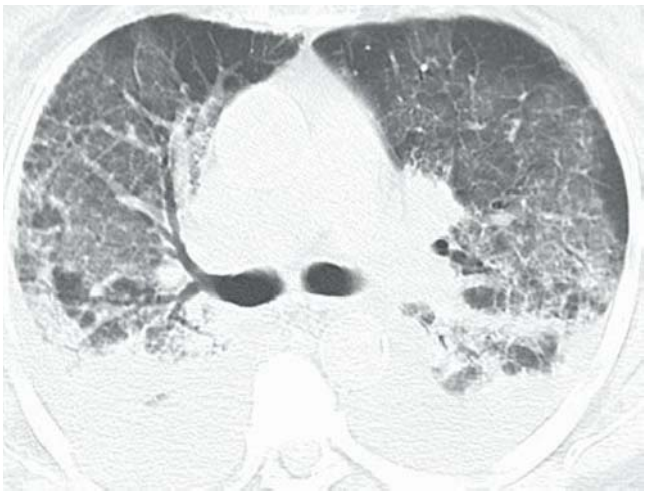


FIGURE 12.1. Acute HP. CT image at the level of the upper lobes shows extensive bilateral GGOs and dependent areas of consolidation. The appearance is consistent with DAD. The patient was a 69-year-old woman with acute HP owing to avian antigens (chicken).

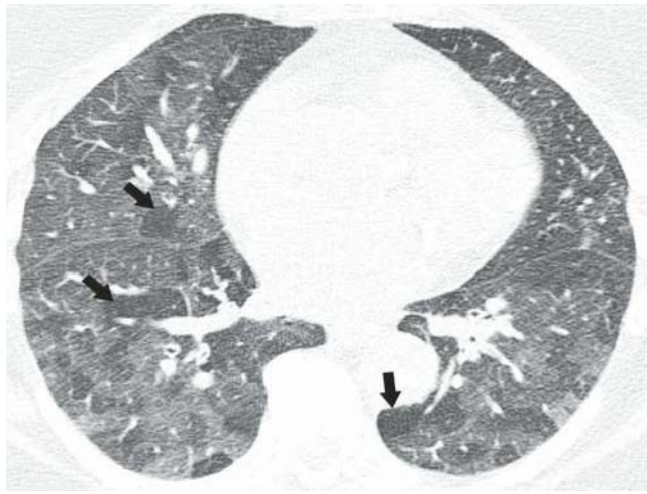


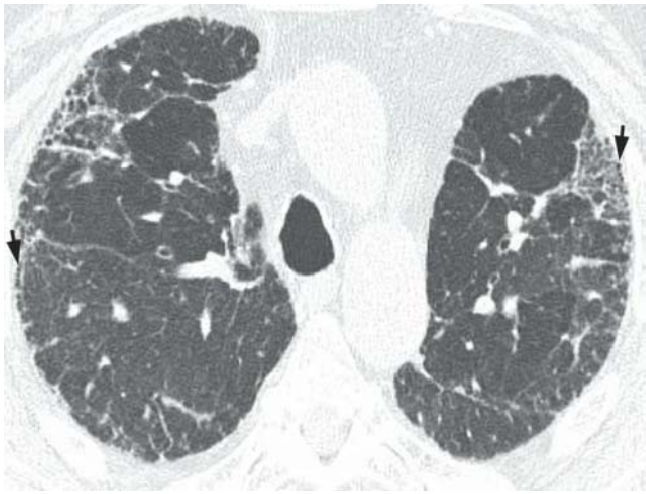
FIGURE 12.2. Subacute HP. HRCT demonstrates extensive bilateral GGOs and lobular areas of decreased attenuation and vascularity (*arrows*). The patient was an 86-year-old man with subacute HP caused by exposure to household mold.

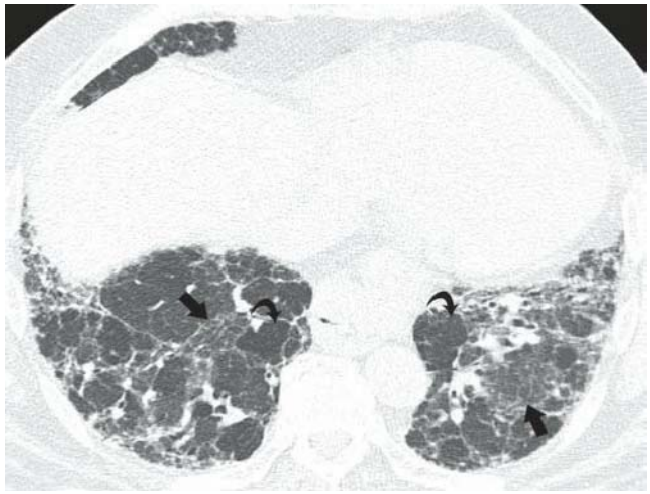
PATHOLOGIC FEATURES

The pathologic features of HP are summarized in Tables 12.4 to 12.6. Acute HP is rarely biopsied and its pathologic features are poorly defined. Diffuse alveolar damage (DAD), acute bronchiolitis, a cellular NSIP-like picture, and areas that look like subacute HP have all been described but only in case reports and one small series.[10] The few convincing cases that we have seen have had DAD as well as granulomas (Figs. 12.5 and 12.6).

Subacute HP (Table 12.5) is the form most commonly encountered in biopsies and usually shows a mild chronic interstitial inflammatory infiltrate that is most marked around the bronchovascular bundles in the centers of the lobules and fades off as one gets away from the bronchovascular bundles (Figs. 12.7 to 12.12). Sometimes there is chronic inflammation in the walls of the bronchioles as well (Fig. 12.13), a process occasionally referred to as "bronchiolitis." A minority of cases of subacute HP do not show bronchiolocentricity but have a much more even distribution of interstitial inflammation and produce a cellular NSIP pattern (Figs. 12.14 to 12.16).

Noncaseating granulomas or individual giant cells or Schaumann bodies are found in the interstitium, and occasionally in the alveoli, in approximately two-thirds of cases of subacute HP, but the number of granulomas/giant cells is extremely variable from case to case. The giant cells, granulomas, and Schaumann bodies (Figs. 12.17 to 12.20) are usually located in areas of interstitial inflammation, including the walls of involved bronchioles (Fig. 12.13); the combination of giant cells or granulomas in the midst of a chronic inflammatory infiltrate in a bronchiolar wall is very suggestive of HP but is not entirely specific as granulomas with inflammation can also be seen in bronchiolar walls





FIGURES 12.3 and 12.4. Chronic HP. **Figure 12.3**: HRCT at the level of the upper lobes shows peripheral reticulation and minimal honeycombing (*small arrows*). **Figure 12.4**: HRCT at the level of the lung bases demonstrates mild patchy reticulation and marked inhomogeneity of the lung parenchyma with areas of normal attenuation, patchy GGOs (*straight arrows*) and lobular areas of decreased attenuation and vascularity (*curved arrows*). The patient was a 68-year-old man with chronic HP owing to avian antigens (Bird-fancier's lung).

Table 12.4

Pathologic features of acute HP

Very poorly defined in the literature because most patients with acute HP are not biopsied
Reported reactions include
- DAD
- Acute bronchiolitis
- Cellular NSIP-like picture
- Subacute HP pattern

Granulomas may be present

Table 12.5

Pathologic features of subacute HP

Interstitial pneumonia with lymphocytes and plasma cells most often in a centrilobular (peribronchovascular) distribution
Chronic inflammation may involve walls of bronchioles ("bronchiolitis")
Some cases show a more homogeneous cellular NSIP type pattern
Interstitial, non-necrotizing granulomas or single giant cells or Schaumann bodies, often around bronchioles, in about two-thirds of cases

after aspiration (See Figs. 20.21 and 20.22). Sarcoid granulomas (Chapter 13) are also commonly found in bronchiolar walls but often show concentric lamellar fibrosis (See Figs. 13.5 and 13.14) and lack the chronic inflammatory infiltrate.

Table 12.6

Pathologic features of chronic HP

Old dense fibrosis always present
Patterns of fibrosis:
- Fibrotic NSIP
- UIP-like
- Centrilobular (peribronchovascular)
- Combinations of centrilobular and UIP-like
- So-called idiopathic bronchiolocentric interstitial fibrosis pattern

Interstitial, non-necrotizing granulomas, giant cells, or Schaumann bodies in about two-thirds of cases
Areas of subacute HP may be present

Granulomas in HP are frequently referred to as "poorly formed" in the literature but this is not always true: sometimes the granulomas are vague (Fig. 12.12), but more often they are quite distinct (Figs. 12.16 to 12.19). What is never seen in HP, however, is the concentric lamellar fibrosis typically present in sarcoid granulomas (See Fig. 13.5). The granulomas of HP frequently contain Schaumann bodies (Figs. 12.16, 12.19, and 12.20). These structures are not disease specific and may be seen in persisting granulomas of any cause but are uncommon in infectious granulomas and are considerably less frequent in sarcoid than in HP. Schaumann bodies are also useful diagnostically because in some cases of HP all the granulomas have disappeared but Schaumann bodies remain (Fig. 12.20). Giant cells and granulomas in HP may contain cholesterol clefts (Fig 12.23, 12.24, 12.31).

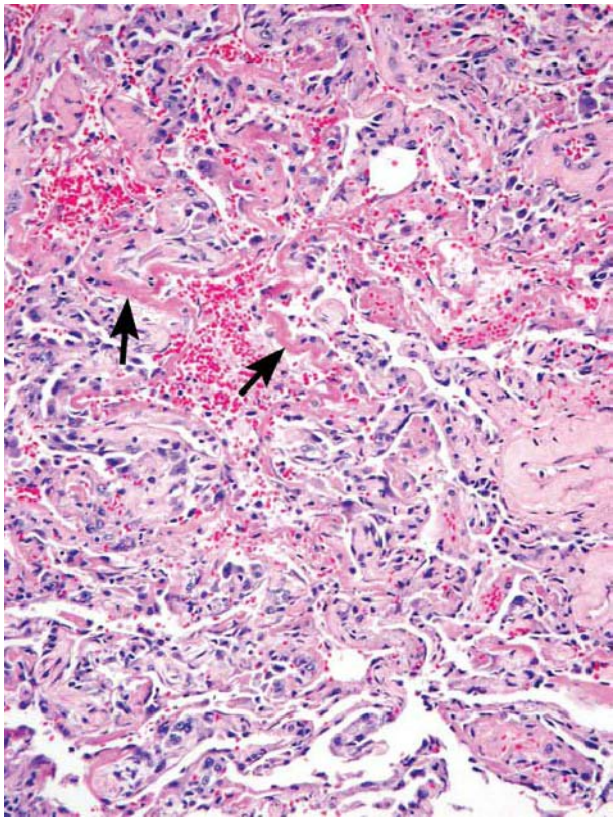


FIGURE 12.5. Acute HP. Low-power view from the same bird exposure case as Figure 12.1 showing hyaline membranes (*arrows*).

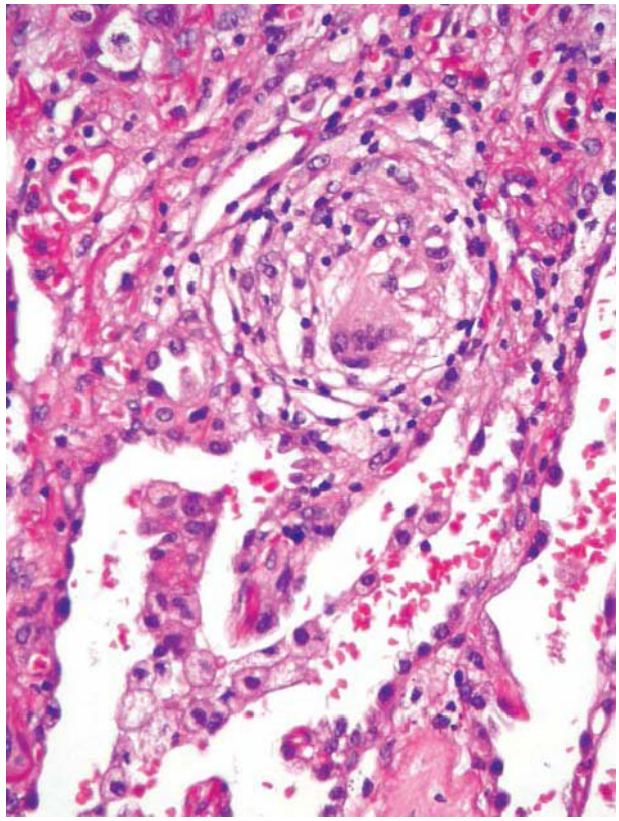
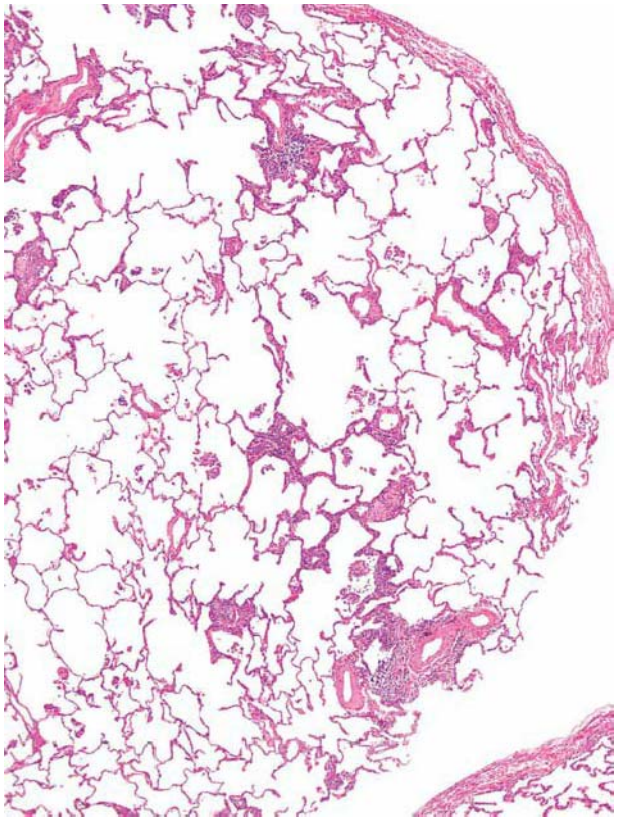
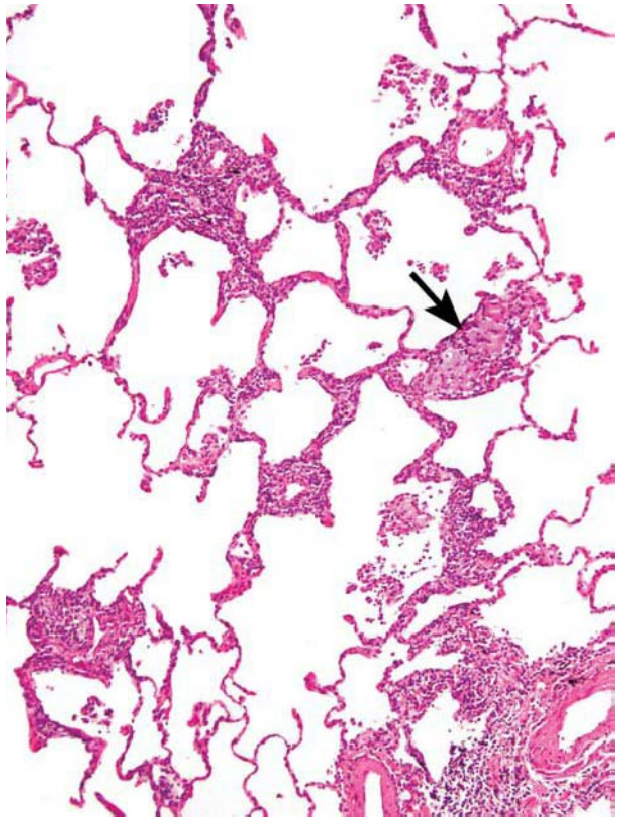


FIGURE 12.6. Acute HP. Another area of the same case showing a loose granuloma.





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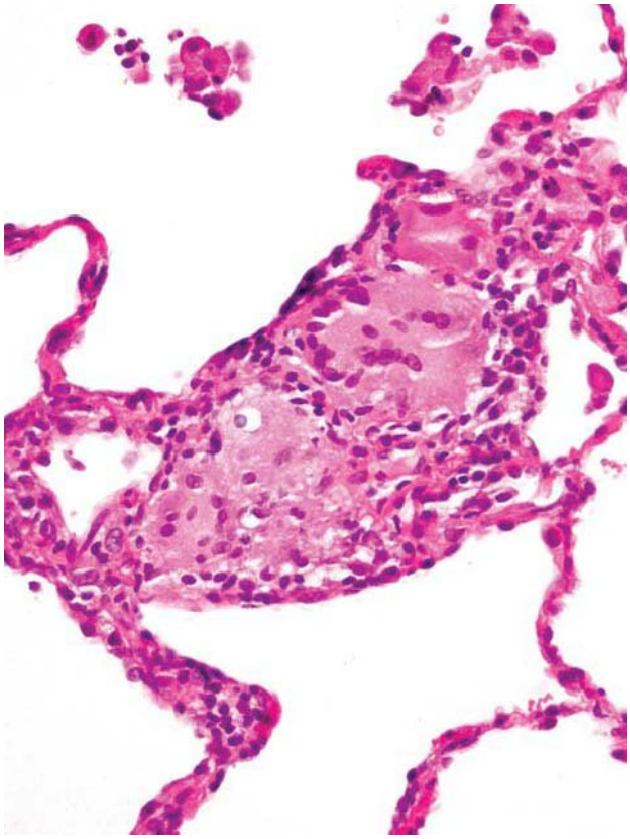
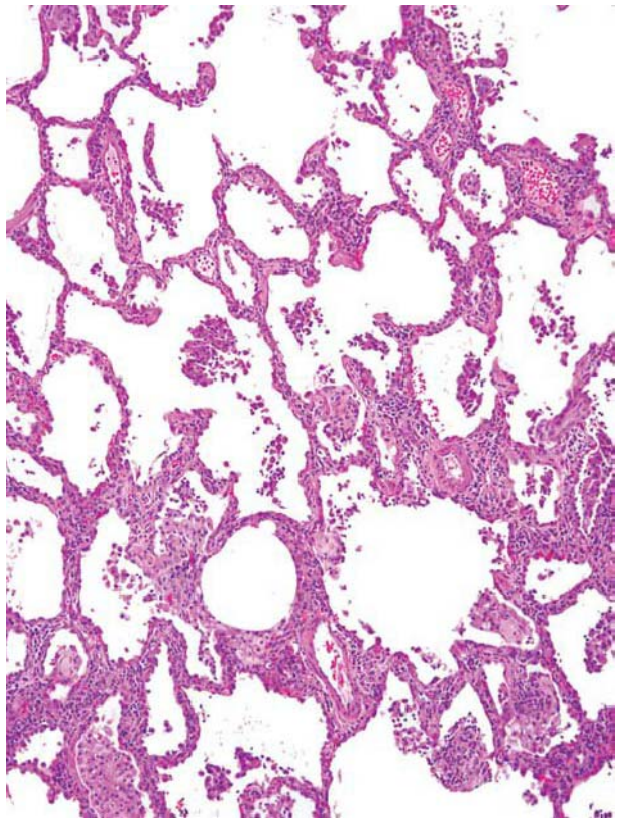
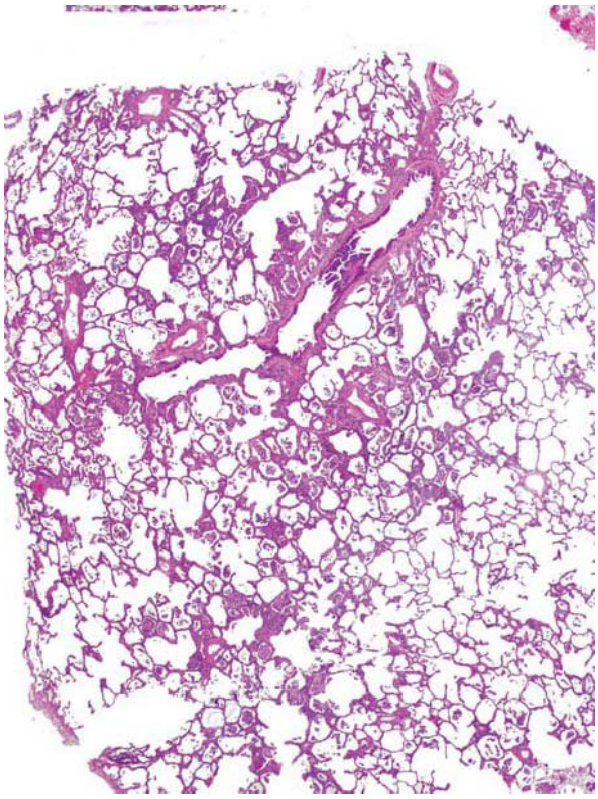




FIGURES 12.7 to 12.9. Subacute HP. Note the distinct centrilobular (peribronchovascular) localization of the infiltrate, a characteristic finding in most cases of subacute HP. A granuloma is present at the *arrow* in **Figure 12.8** and is shown at higher power in **Figure 12.9**. Patient was exposed to birds and had positive serology for avian proteins.



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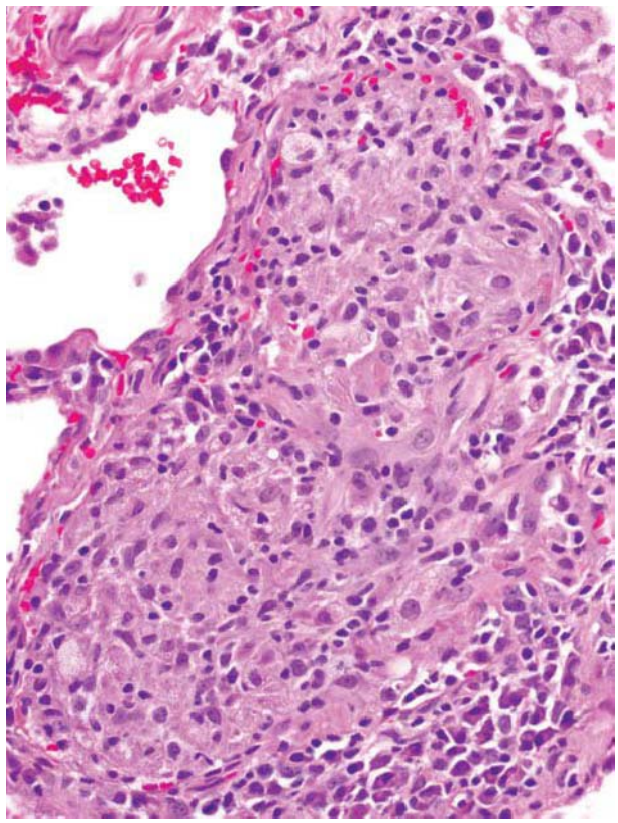


FIGURES 12.10 to 12.12. Subacute HP. The interstitial infiltrate is again centrilobular but more extensive than the example shown in Figures 12.7 to 12.9. **Figure 12.12** shows a somewhat indistinctly defined granuloma. Patient was exposed to birds.

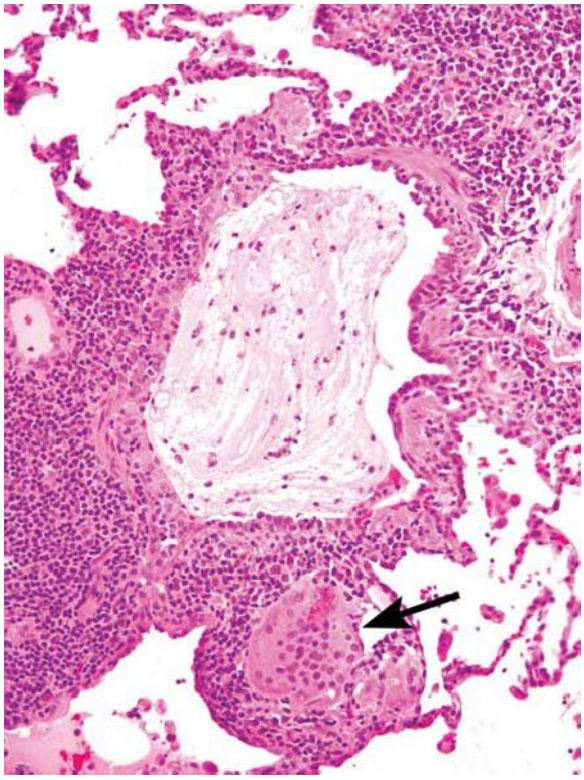
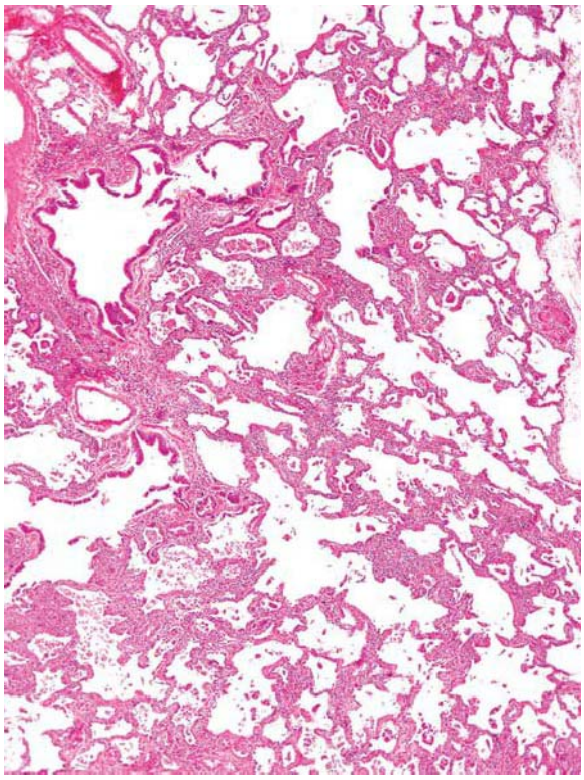
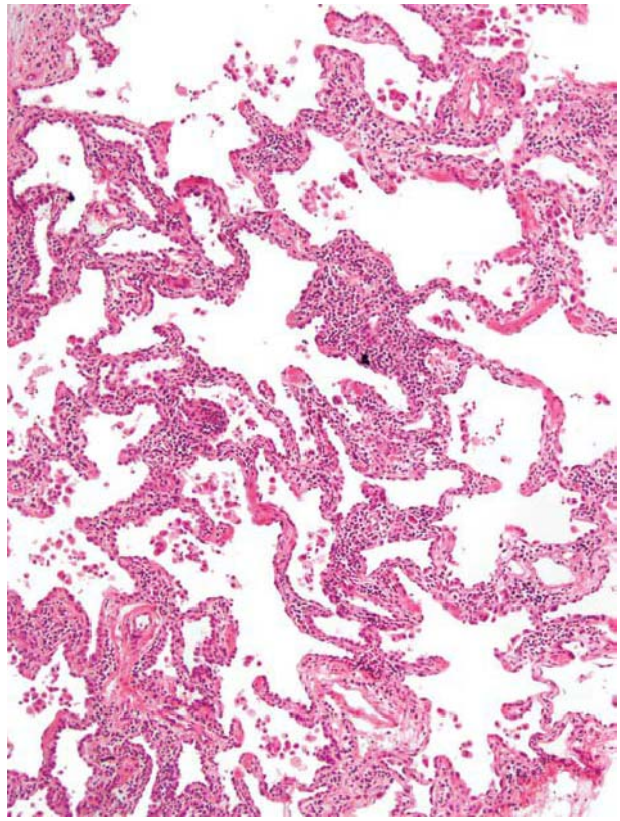
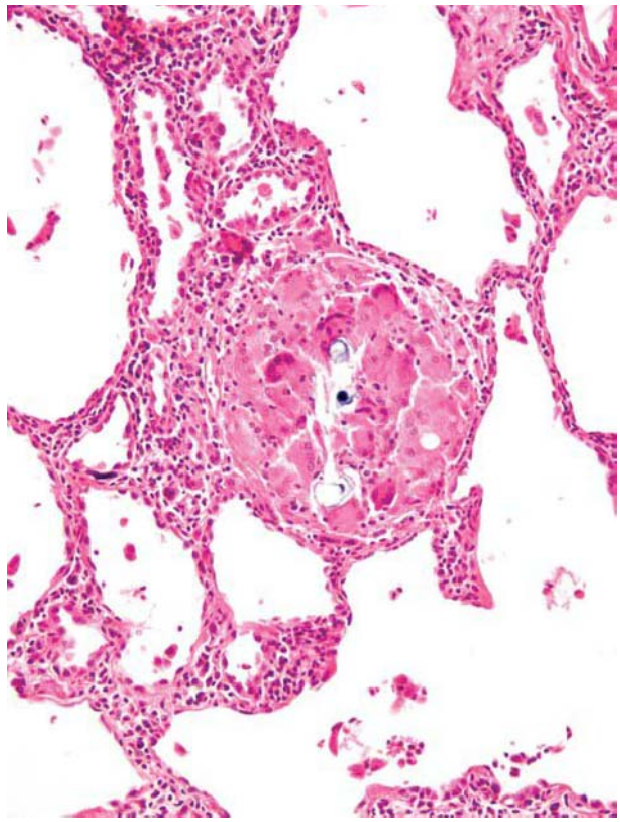


FIGURE 12.13. So-called bronchiolitis in subacute HP. Note the giant cells in the peribronchiolar inflammatory infiltrate (*arrow*). This is a common finding in HP but is not entirely specific because it can be seen occasionally with aspiration.

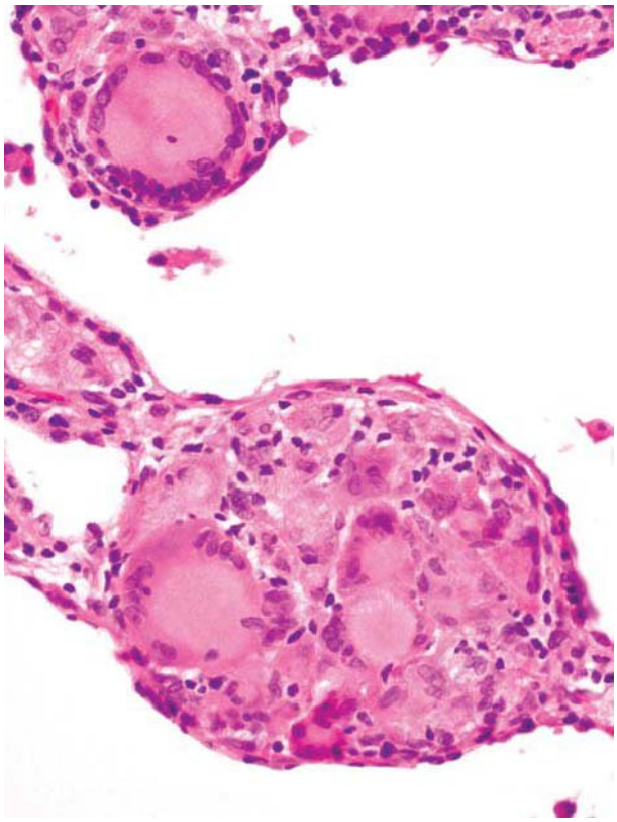


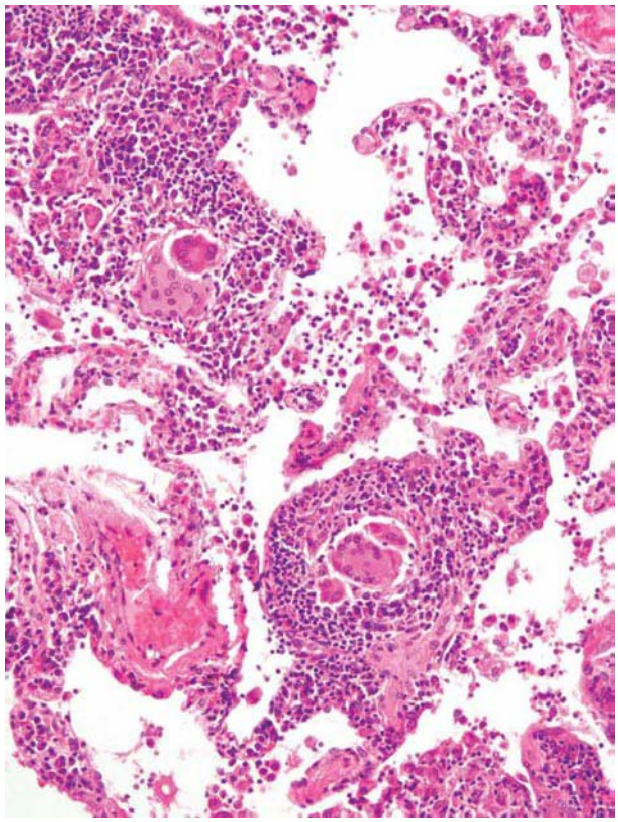
FIGURES 12.14 to 12.16. Legend appears on next column



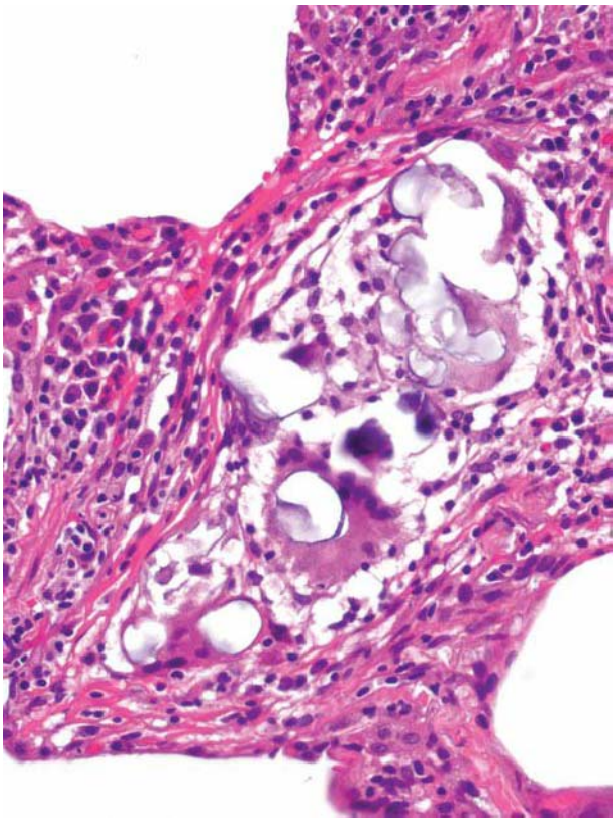


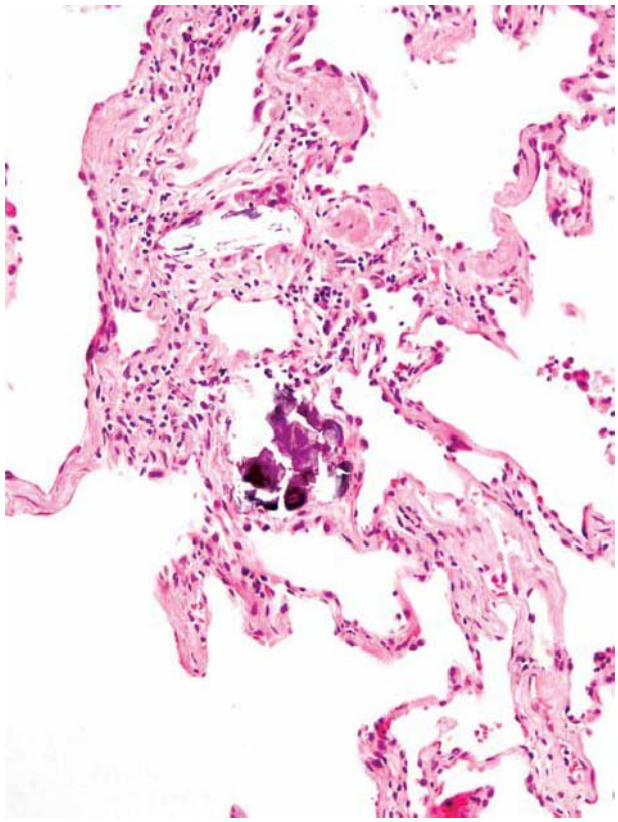
FIGURES 12.14 to 12.16. Subacute HP mimicking cellular NSIP. Note the absence of peribronchovascular accentuation. On biopsy, only the presence of granulomas (Fig. 12.16) indicates the correct diagnosis. Patient worked on a farm.





FIGURES 12.17 and 12.18. Examples of granulomas and individual giant cells in subacute HP. Although granulomas in HP are often described as poorly formed, in many instances they are quite distinct, but they always lack the peripheral concentric fibrosis often seen in sarcoid (compare Fig. 13.5).





FIGURES 12.19 and 12.20. Granulomas with Schaumann bodies. Schaumann bodies are common in the granulomas of HP but can sometimes be seen in sarcoid granulomas. In **Figure 12.20** (chronic HP) all the giant cells have disappeared leaving only the calcified concentrations.

Table 12.7

Differential diagnosis of subacute HP

Subacute HP	Sarcoid	LIP
Interstitial inflammation always present, usually mild and the predominant feature	Interstitial inflammation very uncommon; granulomas are the predominant feature	Interstitial inflammation always present and marked, often producing widening of alveolar walls to the point of confluence
Interstitial inflammation most often centrilobular (peribronchovascular)		Inflammation can be centrilobular but more often diffuse
Granulomas/giant cells in about two-thirds of cases	Granulomas in all except completely burnt-out disease	Granulomas may be present but usually inconspicuous
Granulomas not necrotizing (except hot tub lung)	Granulomas occasionally necrotizing	Granulomas not necrotizing
Granulomas usually centrilobular, often in walls of bronchioles	Granulomas follow bronchovascular bundles, interlobular septa, pleura	Granulomas random
No cysts	No cysts	Cysts sometimes present

Chronic HP (Table 12.7) has a more variable-appearance. The essential feature is old fibrosis that is grossly often centrilobular (Fig. 12.21) or a mixture of centrilobular and subpleural. Honeycombing may be present. The fibrosis of chronic HP can be upper, mid, or lower zonal.

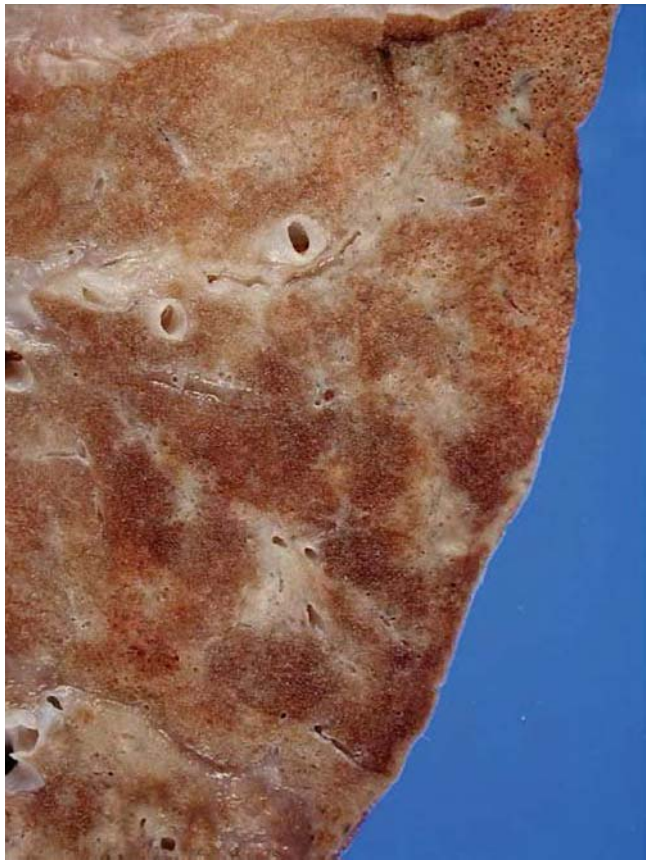
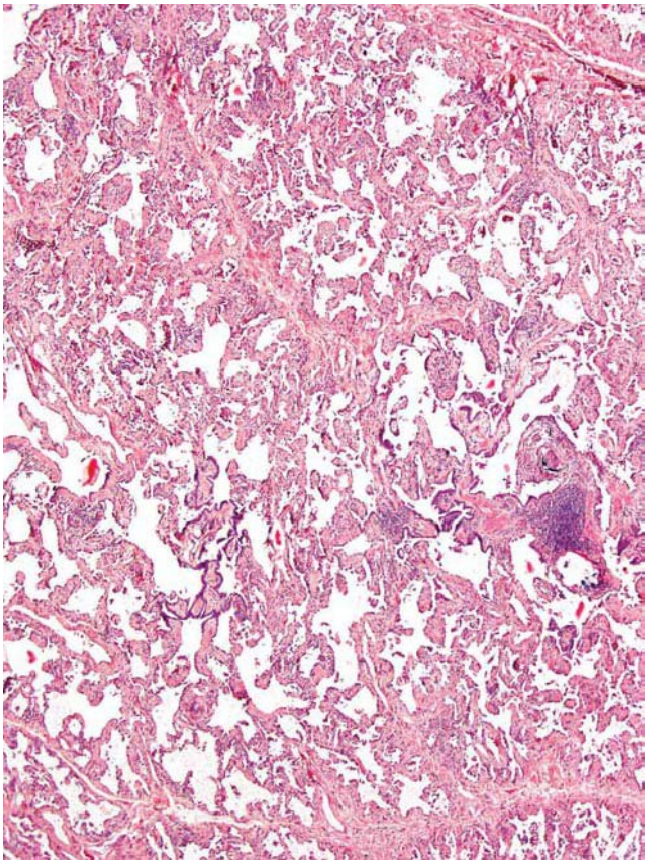


FIGURE 12.21. Gross view of chronic HP. In this example, the fibrosis is distinctly centrilobular. (Case courtesy Dr. J. English.)

Microscopically the fibrosing process in chronic HP can be divided into a fibrotic NSIP-like form (Figs. 12.22 to 12.24), a usual interstitial pneumonia (UIP)-like form (Figs. 12.25 to 12.28), and a centrilobular fibrosis form (Figs. 12.29 to 12.32). Combinations of the latter two are common. As in subacute HP, granulomas, giant cells, or Schaumann bodies are seen in approximately two-thirds of cases. Typical areas of subacute HP may also be evident (Figs. 12.27 and 12.28) but are not required for the diagnosis of chronic HP.

Unless giant cells, granulomas, or Schaumann bodies are present, the fibrotic NSIP-like form (Figs. 12.22 and 12.23) is indistinguishable from fibrotic NSIP of other etiologies (see Chapter 7). Similarly, a small percentage of chronic HP cases cannot be morphologically separated from UIP but this is relatively uncommon (probably no more than approximately 5% of cases)[5] and most cases of chronic HP that resemble UIP have a UIP picture with giant cells, granulomas, Schaumann bodies, or areas of subacute HP (Figs. 12.25 to 12.28), or distinct centrilobular fibrosis (Figs. 12.29 to 12.32). Fibroblast foci are common in the UIP-like areas of chronic HP (Fig. 12.32).

Centrilobular (peribronchiolar) fibrosis is sometimes the only morphologic abnormality in chronic HP, and these lesions frequently have associated fibroblast foci. More often, however, the centrilobular fibrosis is mixed with subpleural fibrosis that resembles UIP (Figs. 12.29 and 12.30). A useful point of distinction is that UIP does not normally involve the centrilobular regions until fibrosis is fairly advanced and the process has overrun most of the lobule, whereas in chronic HP there is often discontinuous centrilobular and peripheral lobular or subpleural involvement (Figs. 12.29 and 12.30).



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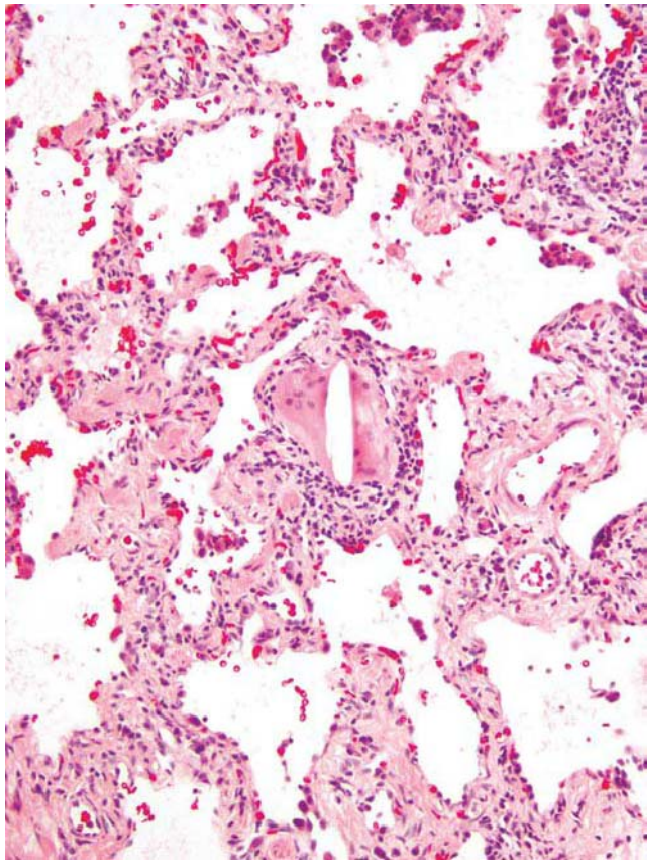

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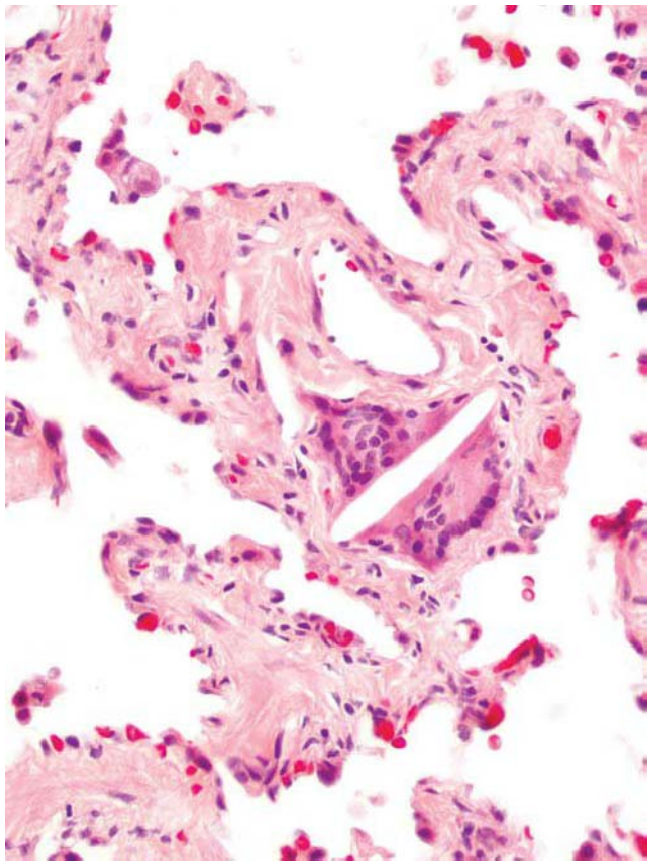
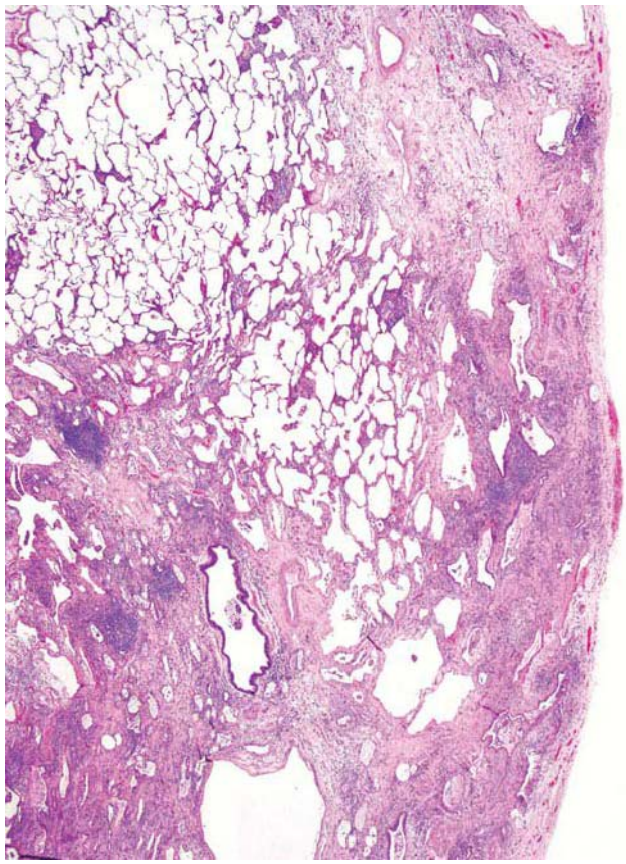


12.24

FIGURES 12.22 to 12.24. Chronic HP in a patient with bird exposure. In this example, the disease mimics fibrotic NSIP; however, there are interstitial giant cells as well (**Figs. 12.23** and **12.24**), clues to the correct diagnosis.



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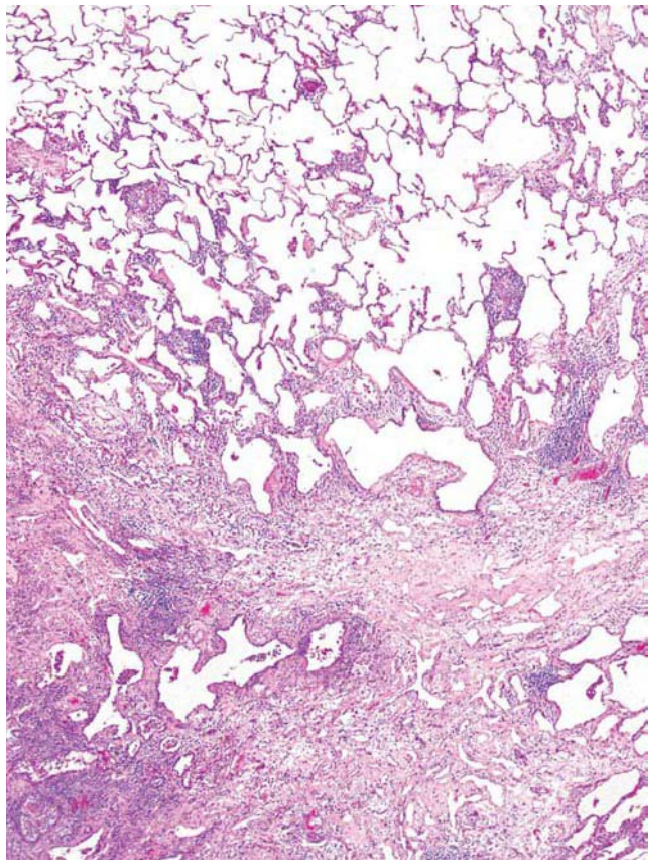

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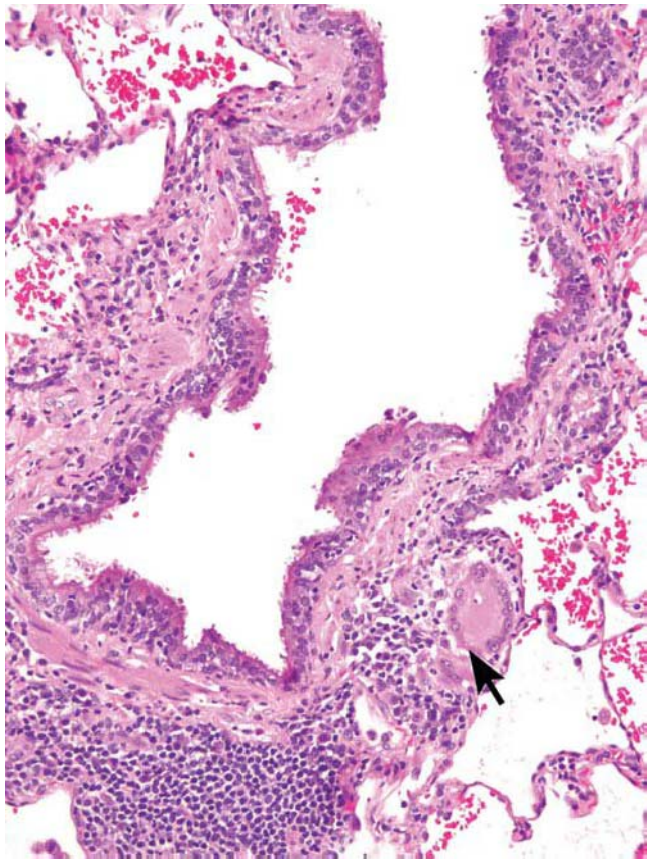

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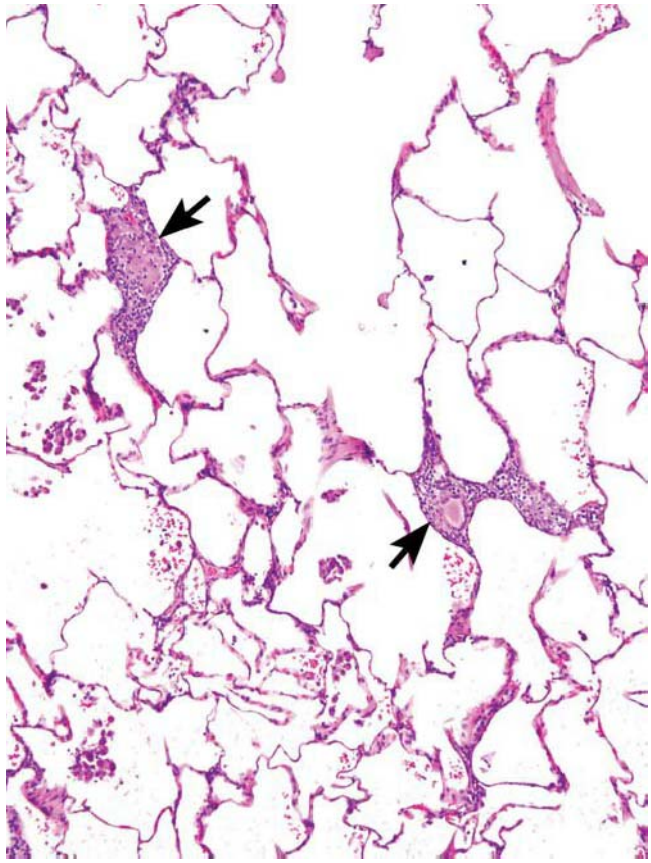

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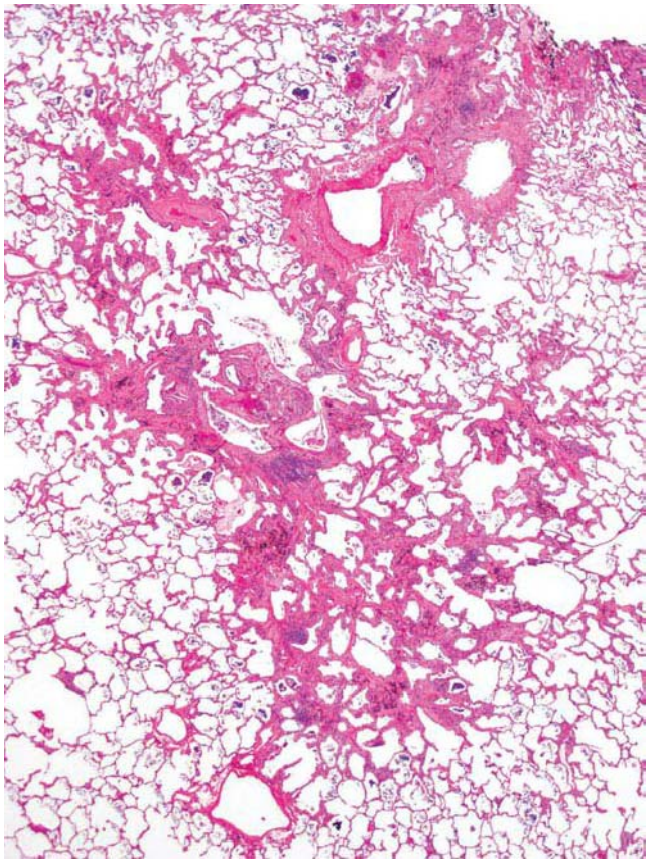
FIGURES 12.25 to 12.28. Chronic HP in a patient exposed to household mold. This example resembles UIP with patchy subpleural fibrosis (**Figs. 12.25** and **12.26**). However, there are also areas typical of subacute HP in the form of peribronchiolar (**Fig. 12.27**, *arrow*) and interstitial (**Fig. 12.28**, *arrows*) giant cells and granulomas. Although this case shows patterns clearly identifiable as HP, some cases of chronic HP are indistinguishable from UIP.



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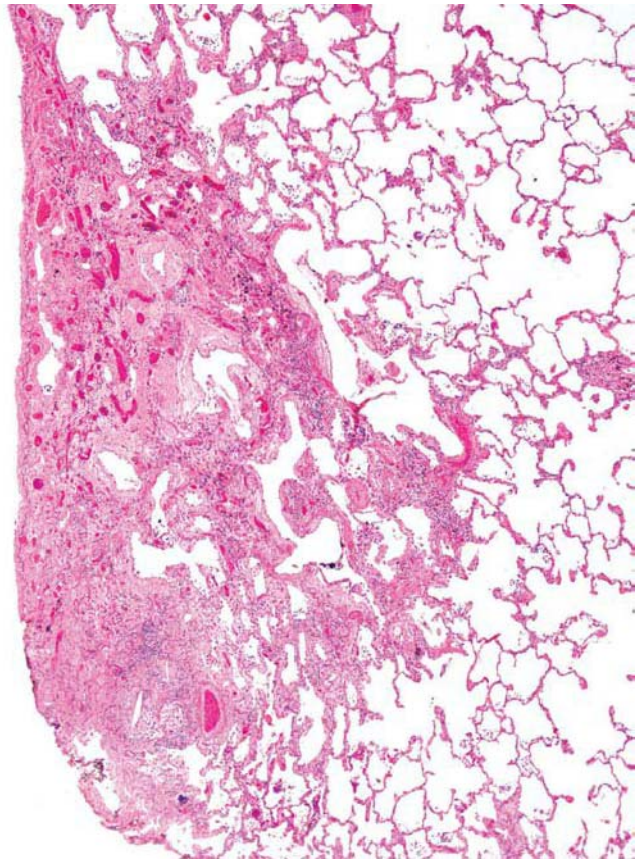

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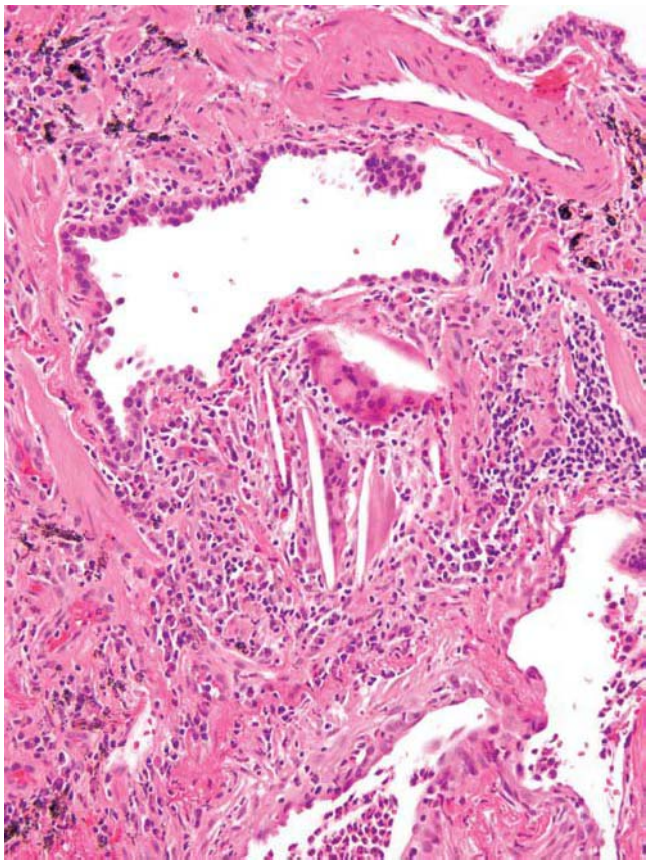

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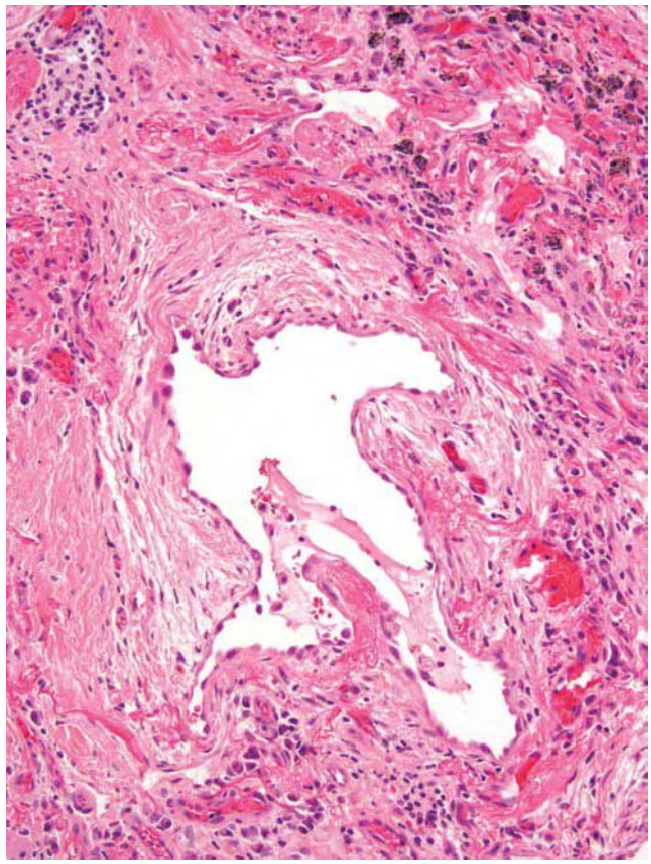


12.32

FIGURES 12.29 to 12.32. Chronic HP in a patient exposed to metal working fluid. **Figure 12.29** shows localized centrilobular fibrosis, one of the patterns seen in chronic HP. Subpleural fibrosis somewhat resembling UIP is also present (**Fig. 12.30**). At high-power giant cells with cholesterol clefts are present (**Fig. 12.31**) as well as fibroblast foci (Fig. 12.32).

In most cases of chronic HP with centrilobular involvement, the fibrotic tissue has overlying reactive alveolar lining cells or, more commonly, just nonreactive type 1 and 2 cells. Yousem[11] described an entity he labeled "idiopathic bronchiolocentric interstitial fibrosis," a fibrosing interstitial pneumonia in which there is fine fibrosis that radiates out from the bronchovascular bundle, following alveolar walls (Fig. 12.33). Characteristically this fibrosis is covered in whole or in part by metaplastic bronchiolar epithelium (Fig. 12.34). Yousem's cases did not have HRCT or serologic evidence of HP, but we believe such cases are variants of chronic HP.

EMPHYSEMA IN HP

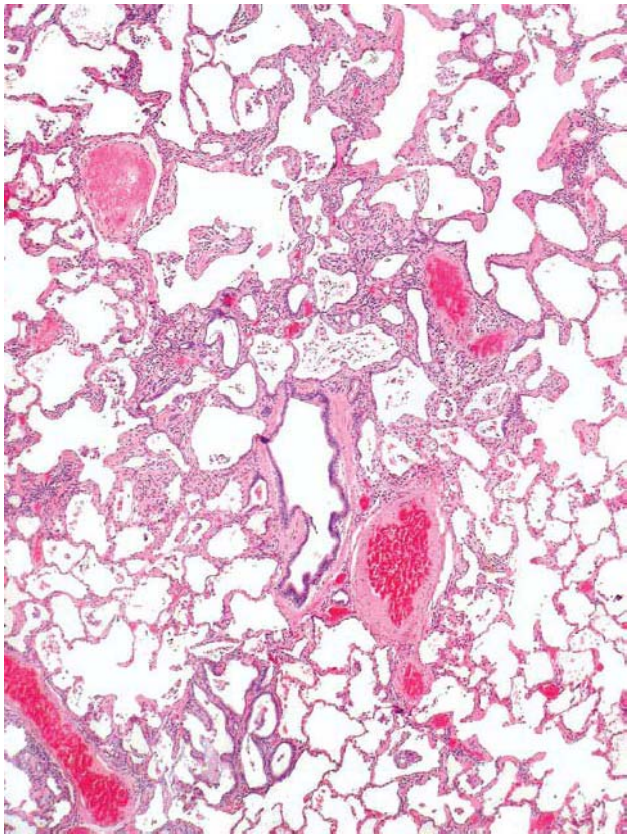
There appears to be an increased incidence of emphysema in farming-associated HP[2]; this occurs in both smokers and nonsmokers and is associated with airflow obstruction. We are not aware of any pathologic studies with specific descriptions of the combined emphysema/HP morphology.

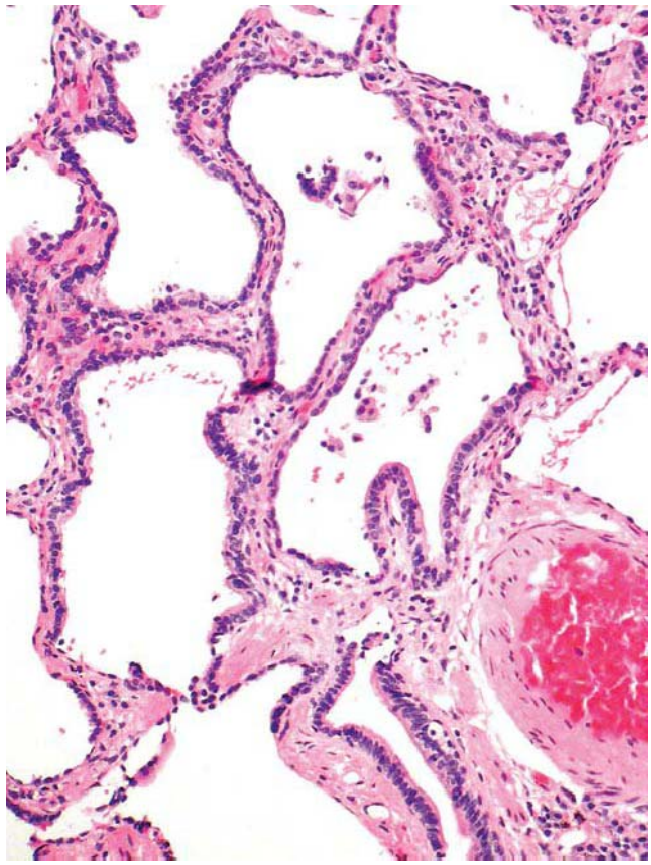
ACUTE EXACERBATIONS OF HP

UIP-like forms of HP have been reported to develop acute exacerbations.[12] Similar to acute exacerbations of UIP, these consist of a morphologic picture of DAD or bronchiolitis obliterans organizing pneumonia (BOOP) superimposed on an underlying fibrotic interstitial pneumonia. Biopsies of putative acute HP should be carefully examined to make sure that there is no old underlying fibrosis.

HOT TUB LUNG

Hot tub lung is caused by atypical mycobacteria and, in rare cases, other organisms, that colonize hot tubs, jacuzzis, saunas, and occasionally showers. Some believe that hot tub lung is actually an infectious process requiring anti-microbial therapy, but most view it as a peculiar form of HP[13]; the fact that patients respond to cleaning of the contaminated environment and/or steroids supports the idea that this is actually a variant of HP.





FIGURES 12.33 and 12.34. Chronic HP with a pattern of so-called bronchiolocentric interstitial fibrosis. Note the extensive bronchiolar epithelial metaplasia, a characteristic finding in this variant of chronic HP. Patient worked on a farm and had positive serology for avian proteins. (Reproduced by permission from Fenton ME, Cockcroft DW, Wright JL, et al. Hypersensitivity pneumonitis as a cause of airway centered interstitial fibrosis. *Ann Allergy Asthma Immunol.* 2007;9:465–466.)

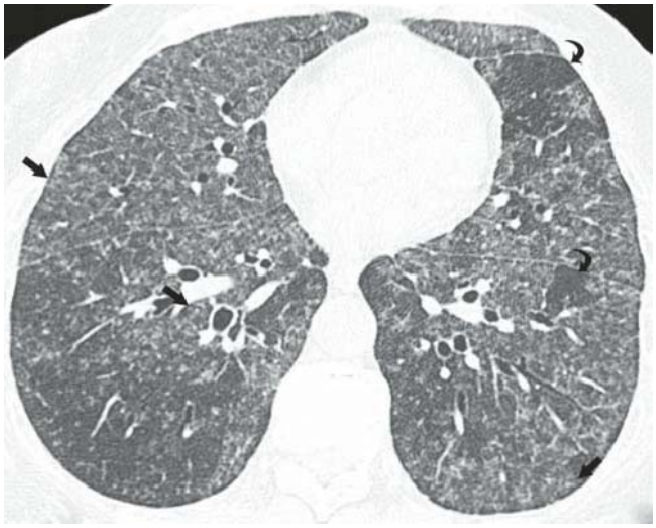


FIGURE 12.35. Hot tub lung. HRCT demonstrates extensive bilateral GGOs, poorly defined centrilobular nodules (*straight arrows*), and localized areas of decreased attenuation and vascularity (*curved arrows*). The patient was a 68-year-old woman.

HRCT of patients with hot tub lung typically shows bilateral GGOs and centrilobular nodular opacities, often with air trapping, and is indistinguishable from HP of other causes (Fig. 12.35).

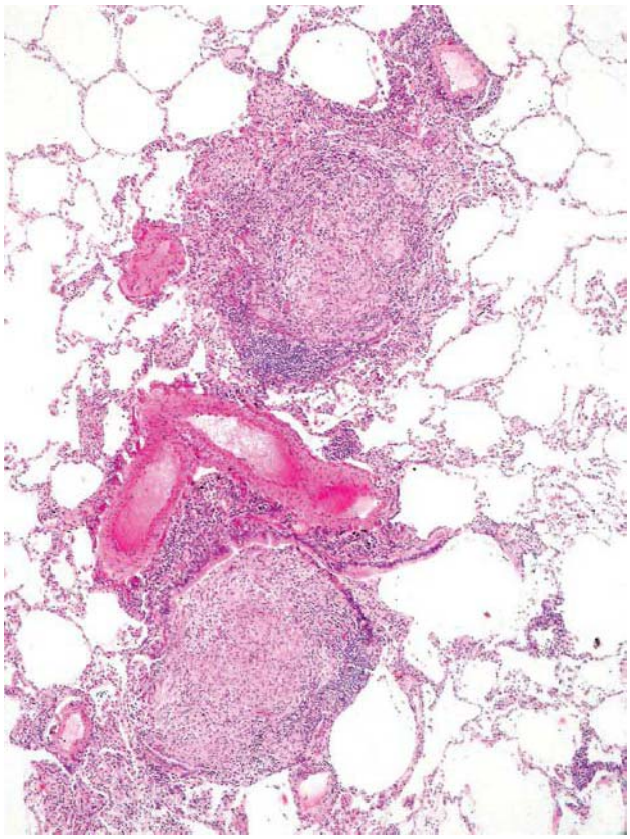


FIGURE 12.36. Hot tub lung. Hot tub lung typically has large granulomas and minimal interstitial infiltrates, as here. Note the granuloma in a bronchiolar lumen, a characteristic finding in hot tub lung.

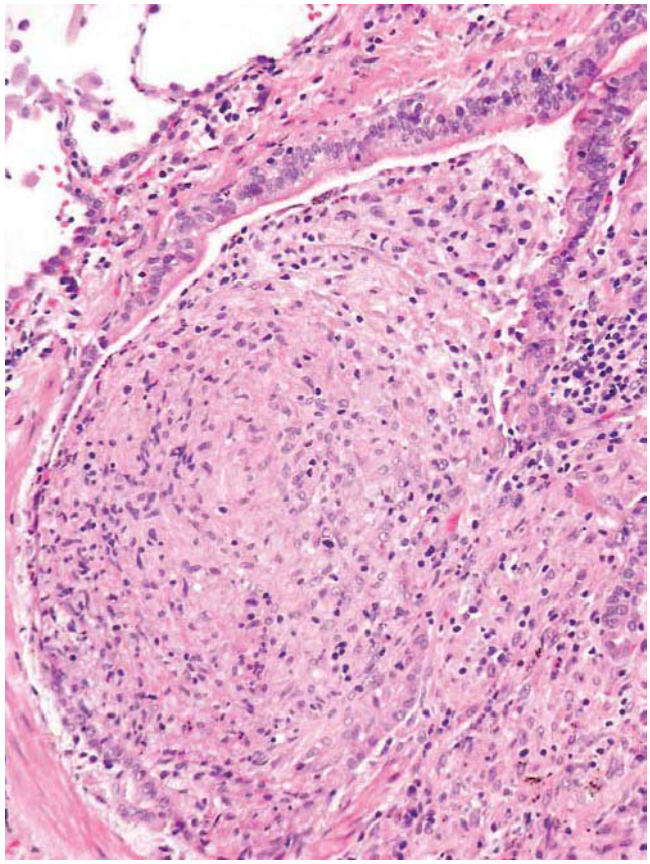
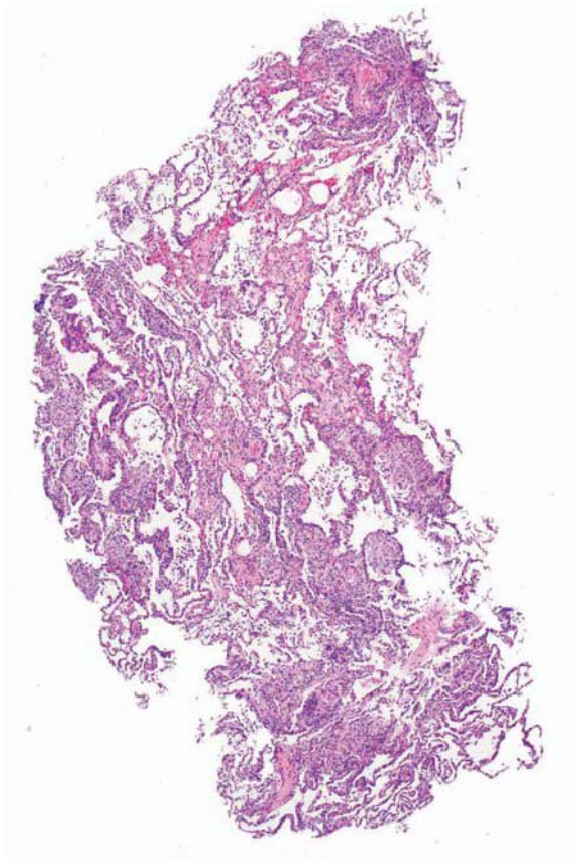


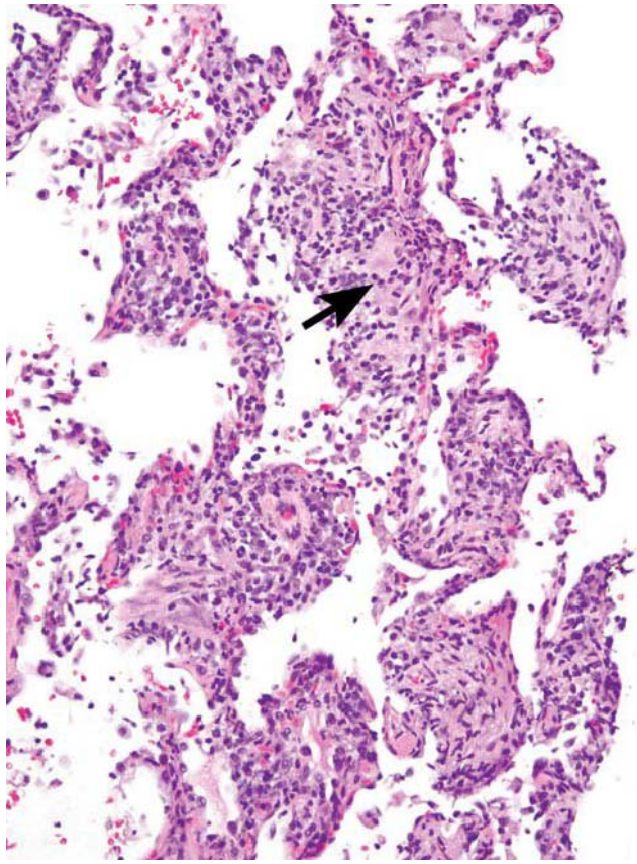
FIGURE 12.37. Hot tub lung. Another example of a large granuloma in a bronchiolar lumen.

The pathologic findings in hot tub lung resemble those of ordinary subacute HP, but the granulomas are large and numerous and the interstitial inflammatory infiltrate relatively minor (Fig. 12.36).[13] Areas of BOOP (Chapter 5) are sometimes present. Approximately 10% of cases have granulomas with necrosis, something that is never seen in ordinary HP. Another unusual feature is the presence of granulomas within the lumens of respiratory bronchioles (Figs. 12.36 and 12.37). Granulomas in the lumens of respiratory bronchioles are sometimes seen in aspiration, but they are never as large as in hot tub lung and are extremely rare to nonexistent in other conditions. In hot tub lung, mycobacteria can usually be demonstrated by staining or culture.

DIAGNOSTIC MODALITIES

Occasionally transbronchial biopsy will show a combination of chronic interstitial inflammation and interstitial giant cells, granulomas, or Schaumann bodies in a patient with clinical and imaging features of HP (Figs. 12.38 and 12.39). In this situation such a biopsy is diagnostic. However, if all that is present is chronic interstitial inflammation, we advise signing out such biopsies as nondiagnostic because chronic interstitial inflammation





FIGURES 12.38 and 12.39. Subacute HP diagnosed on transbronchial biopsy. Note the giant cell (*arrow*) in **Figure 12.39**. HP can occasionally be diagnosed on transbronchial biopsy but interstitial giant cells or granulomas are required. Interstitial inflammation by itself is completely nonspecific in transbronchial biopsies. Patient was exposed to birds and clinically and radiologically was thought to have HP.

alone in transbronchial biopsies is both common and nonspecific.

If the diagnosis cannot be made on transbronchial biopsy, video-assisted thoracoscopic surgery (VATS) biopsy is the procedure of choice. The diagnosis of chronic HP always requires evaluation of low-power architecture and hence a VATS biopsy is required.

Some clinicians use bronchoalveolar lavage instead of transbronchial biopsy; with supporting clinical and imaging features, a very high proportion of lymphocytes in lavage—at least 25% but usually more than 40%—supports a diagnosis of HP.[2]

DIFFERENTIAL DIAGNOSIS

Differential Diagnosis of Acute HP

Organic toxic dust syndrome (OTDS) is caused by massive exposures to moldy hay or grains containing large amounts of endotoxin, fungi, or *Actinomycetes*; it is also seen in workers exposed to textiles contaminated with *Fusarium* species. Clinically it is characterized by an acute, febrile, self-limited process that is very similar to acute HP. However, patients with OTDS are not sensitized and do not have serum antibodies against the offending organisms. The pathologic features are poorly defined, but acute bronchiolitis with numerous visible fungal organisms has been reported.[14]

Differential Diagnosis of Subacute HP

The important differential diagnoses for subacute HP are sarcoid (Chapter 13) and LIP (Chapter 19) and the important separating features are shown in Table 12.7.

Differential Diagnosis of Chronic HP

The major differential diagnoses of chronic HP are UIP and fibrotic NSIP, and the important separating features are shown in Table 12.8. However, some cases of chronic HP cannot be morphologically separated from fibrotic NSIP and some cannot be morphologically separated from UIP.

PROGNOSIS

The prognosis of HP depends on the type of disease (acute, subacute, or chronic) and possibly on the inciting antigen. Most authors believe that acute and subacute

TABLE 12.8

Differential diagnosis of chronic HP

Chronic HP	UIP	Fibrotic NSIP
Fibrosis can be patchy and mimic UIP, or diffuse and mimic NSIP, or centrilobular	Fibrosis patchy with subpleural predominance	Fibrosis follows alveolar walls
Combinations of patchy subpleural fibrosis and centrilobular fibrosis common	Centrilobular fibrosis only in relatively advanced disease	
Giant cells, granulomas, or Schaumann bodies in about two-thirds of cases	No giant cells, granulomas, or Schaumann bodies	No giant cells, granulomas, or Schaumann bodies
Areas of subacute HP may be present		

disease resolve completely. It is commonly stated that avoidance of the antigen is crucial for resolution, but cases in which no antigen can be identified seem to do as well as those with a known antigen.[5,15] For chronic HP the prognosis is poor: in our experience chronic HP that resembles UIP or fibrotic NSIP has a median survival of about 3 years, whereas purely centrilobular fibrosis does much better.[5]

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CHAPTER

13

Sarcoid

EPIDEMIOLOGY

In North America the reported incidence of sarcoid is approximately 100 per 1,000,000 in Whites and approximately three times this number in Blacks. In Europe sarcoid is more common in northern countries, particularly in Scandinavia. The reported numbers may be underestimates because a proportion of sarcoid patients are asymptomatic and many cases remit spontaneously. Most cases present under age 40, particularly in the 20 to 29 age range.[1]

CLINICAL FEATURES

Probably one-third of sarcoid patients who come to medical attention are asymptomatic, and the disease is picked up as an incidental finding on chest imaging. Another one-third have fever, malaise, and weight loss, and an equal proportion have shortness of breath (SOB), cough, and sometimes chest pain. Pulmonary function varies by radiologic stage (see next section Imaging). Low-stage disease patients may have normal pulmonary function, but airflow obstruction (because sarcoid granulomas can narrow the large and small airways[2] [Figs. 13.14 and 13.16]) and restriction are also seen. High-stage (i.e., diffuse fibrotic) disease shows a restrictive pattern with decreased diffusing capacity; pulmonary hypertension may also be present.[3]

Sarcoid is a systemic disease that can affect any organ. Extrapulmonary manifestations are beyond the scope of this book, but the reader is referred to volume 29 (2008) of *Clinics in Chest Medicine* for detailed reviews of sarcoid in various organ systems.

IMAGING

The most common and characteristic radiologic manifestation of sarcoidosis is symmetric bilateral hilar and right paratracheal lymph node enlargement (Fig. 13.1). Based on the findings on the radiograph, pulmonary sarcoidosis is classified into five stages.[4]

Stage 0: No demonstrable radiographic abnormality
Stage I: Hilar and mediastinal lymph node enlargement without radiographic parenchymal abnormality

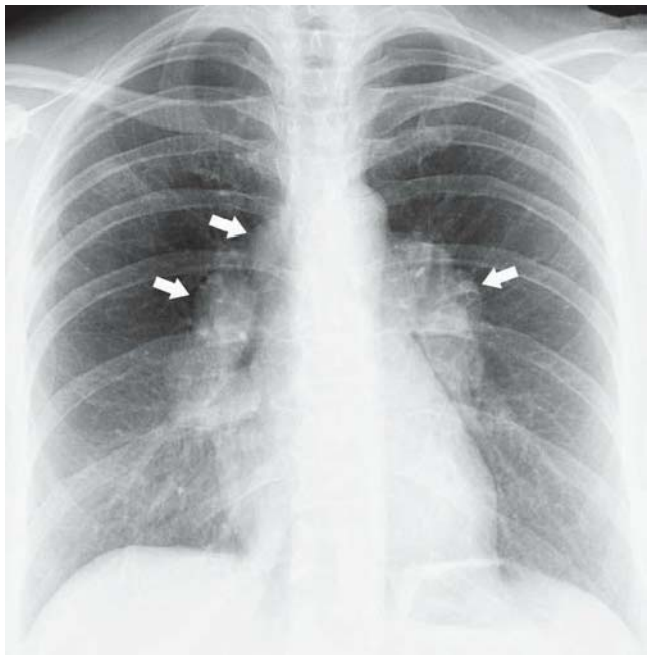


FIGURE 13.1. Sarcoidosis. Chest radiograph shows symmetric bilateral hilar and right paratracheal lymph node enlargement (*arrows*). The lungs are normal. The patient was a 37-year-old woman.

Stage II: Hilar and mediastinal lymph node enlargement plus parenchymal abnormality
Stage III: Parenchymal abnormality alone
Stage IV: Advanced fibrosis.

These so-called stages do not indicate degrees of disease chronicity but simply radiographic patterns, the main utility of which is predicting outcome. Spontaneous remissions occur in 55% to 90% of patients with Stage I disease, in 40% to 70% of those with Stage II, in 10% to 20% with Stage III disease, and in 0% with Stage IV sarcoidosis.[1]

Pulmonary parenchymal disease is evident on the chest radiograph at initial evaluation in approximately 60% of patients. The parenchymal abnormalities are typically bilateral and symmetrical, involve mainly the upper lobes, and usually comprise a small nodular or reticulonodular pattern. In the majority of patients with

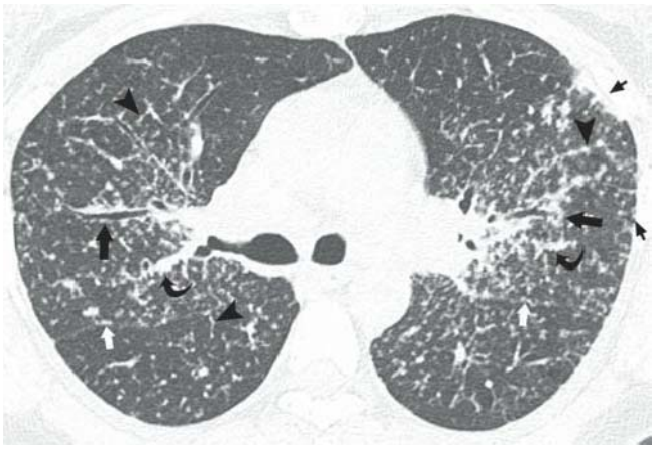


FIGURE 13.2. Sarcoidosis. HRCT demonstrates nodules and nodular thickening along the bronchi (*straight black arrows*), vessels (*curved arrows*), interlobular septa (*arrowheads*), interlobar fissures (*straight white arrows*), and along the costal pleura (small arrows).

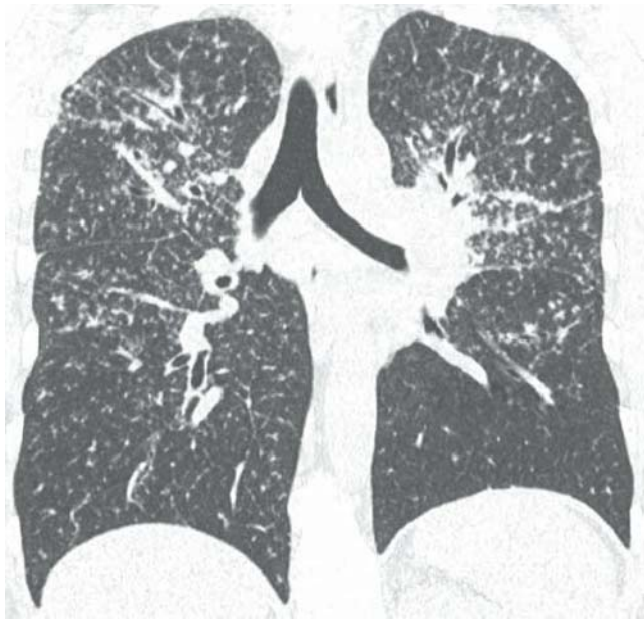


FIGURE 13.3. Coronal reformation of the same case shows upper lobe predominance. The patient was a 38-year-old woman.

sarcoidosis the chest radiograph is the only imaging modality performed. HRCT may be helpful when the radiographic manifestations are nonspecific or atypical, when there are suspected complications, or in selected patients to distinguish active inflammation from irreversible fibrosis.

The HRCT manifestations of pulmonary sarcoidosis closely reflect the histologic findings and typically consist of small nodules in a perilymphatic distribution, that is, mainly adjacent to the bronchi, pulmonary arteries and veins, and along the interlobular septa, interlobar fissures, and costal subpleural regions, and result in nodular thickening of these structures (Figs. 13.2 and 13.3).[5] The nodules and the nodular thickening reflect confluence of microscopic granulomas. The nodules may have smooth or irregular margins, are typically well-defined and most commonly measure 2 to 5 mm in diameter. Confluence of granulomas may also result in large nodules or masses measuring 1 to 4 cm in diameter, seen in 15% to 25% of patients.[5] Fibrosis results in irregular linear opacities (reticulation), irregular septal thickening, traction bronchiectasis, and, occasionally, honeycombing. The fibrosis, similar to the nodules, involves mainly the peribronchovascular regions of the upper lobes and typically results in cephalad displacement of the hila, and compensatory overinflation of the lower lobes.

PATHOLOGIC FEATURES

Features of Sarcoid Granulomas

Sarcoid granulomas are always well-defined and fairly well circumscribed interstitial collections of giant cells, epithelioid histiocytes, and chronic inflammatory cells (Fig. 13.4) (Table 13.1). Sarcoid granulomas are often surrounded by fine concentric layers of hyaline collagen (Fig. 13.5), and this feature is helpful in diagnosis as it is

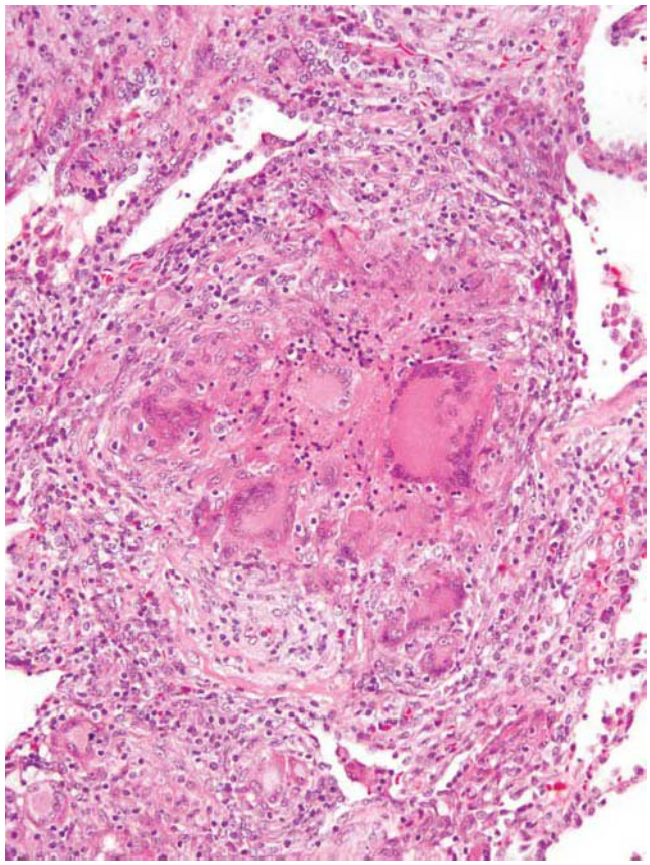


FIGURE 13.4. Sarcoid granuloma. In this example there are a moderate number of admixed lymphocytes.

Table 13.1

General pathologic features of sarcoid

Generally non-necrotizing well-defined interstitial granulomas
Small amounts of necrosis occasionally present
Often concentric hyaline fibrosis around the granulomas
Granulomas may contain asteroid bodies, Schaumann bodies or birefringent crystals of calcium oxalate or phosphate. These findings are not specific to sarcoid
Granulomas follow lymphatic routes
Along bronchovascular bundles
Along interlobular septa
Along pleura
Usually no interstitial infiltrate
BOOP usually not a feature of sarcoid

never seen in HP and is rare in infectious granulomas. In our experience this pattern is seen in sarcoid that is progressing to scar formation (see below).

Although medical school textbooks teach that sarcoid granulomas are non-necrotizing, this is not always true. Small amounts of necrosis are occasionally seen in ordinary sarcoid (Fig. 13.6), and by definition are present in necrotizing sarcoid (see below). Whether special stains for organisms are required in every case of sarcoid is controversial (see below), but they should always be carried out if any necrosis is present.

Another common fallacy is that asteroid bodies (Fig. 13.7) and Schaumann bodies are specific features of sarcoid. Asteroid bodies may be seen in giant cells or granulomas of any cause, as may Schaumann bodies, although they are much less common in infectious granulomas, probably because infectious granulomas tend not to persist for long periods. Schaumann bodies are much more frequent in HP than in sarcoid. Sometimes the granulomas of sarcoid disappear, leaving only Schaumann bodies as "tombstones," but this same phenomenon is seen in HP (see Figs. 12.19 and 12.20).

Granulomas of any cause, including sarcoid granulomas, may contain birefringent crystals of calcium oxalate or calcium phosphate (Figs. 13.8 and 13.9). These are endogenous products of macrophage metabolism and do not represent inhaled material.[6]

Distribution of Sarcoid Granulomas

Sarcoid granulomas characteristically show a lymphatic (lymphangitic) distribution; that is, they are present

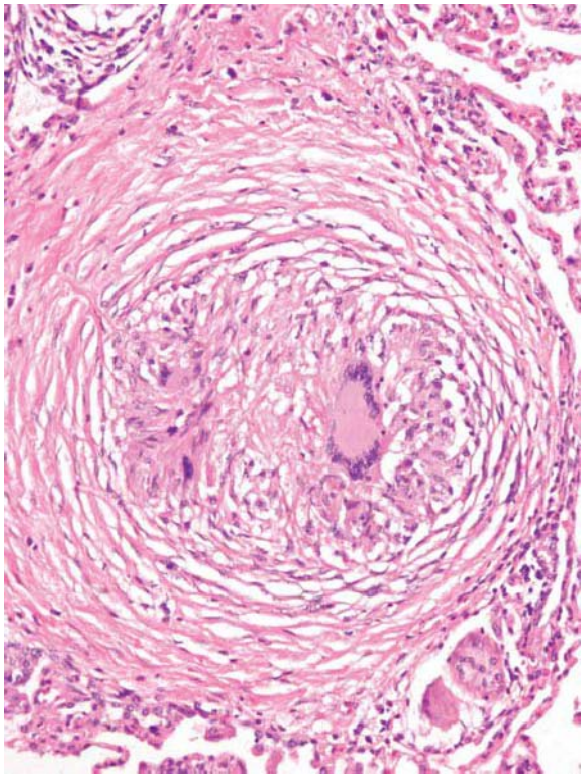


FIGURE 13.5. Sarcoid granuloma with prominent concentric lamellar fibrosis. This pattern is typical of sarcoid granulomas and rare in granulomas of other causes. Concentric lamellar fibrosis tends to be seen in sarcoid that is progressing to scarring.

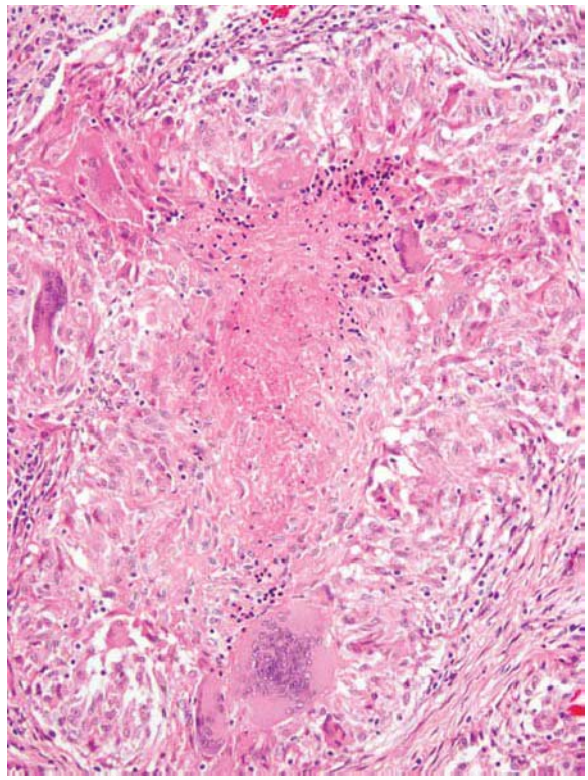


FIGURE 13.6. Necrosis in a sarcoid granuloma. Small amounts of central necrosis are not uncommon in sarcoid granulomas, but stains to rule out infection are required in this situation.

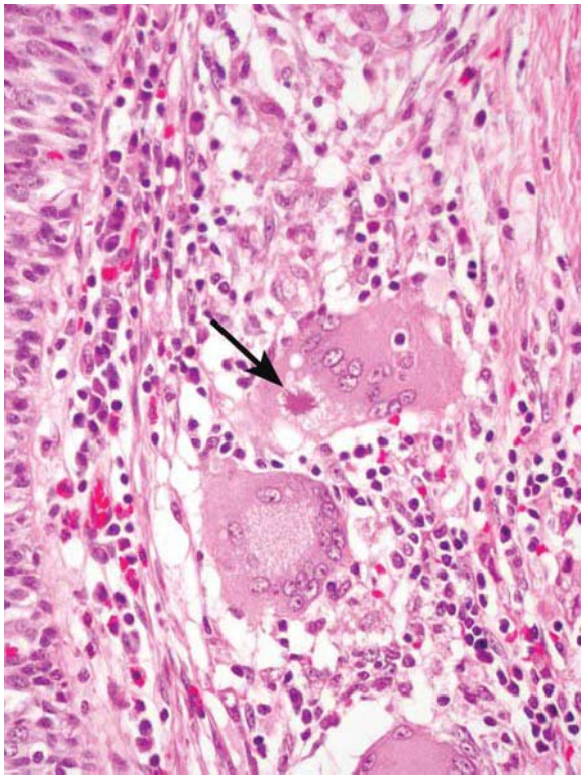


FIGURE 13.7. An asteroid body (*arrow*) in a sarcoid granuloma. Asteroid bodies may be seen in granulomas or giant cells of any etiology (although they are rare in HP) and have no diagnostic specificity.

around the bronchovascular bundles in the centers of the lobules, along interlobular septa, and in the pleura (Figs. 13.10 to 13.15). This distribution is extremely helpful in diagnosis: Infectious granulomas tend to be randomly scattered in the parenchyma, and although the granulomas of HP are often centrilobular, they are not present along interlobular septa or in the pleura.

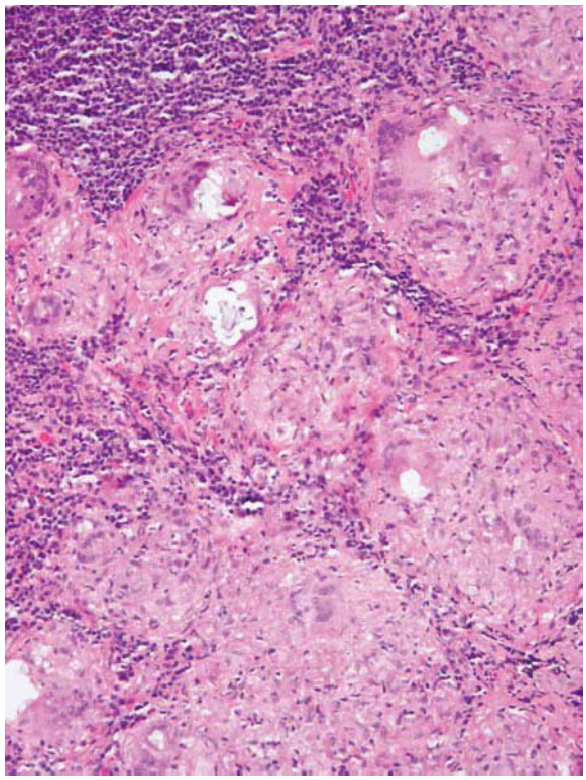
Sarcoid granulomas may be present in such numbers that they cause narrowing of the lumen of small airways (Fig. 13.14), and may also be present in the mucosa of large airways (Fig. 13.16). Granulomatous narrowing of small airways and endobronchial granulomas are never seen in HP.

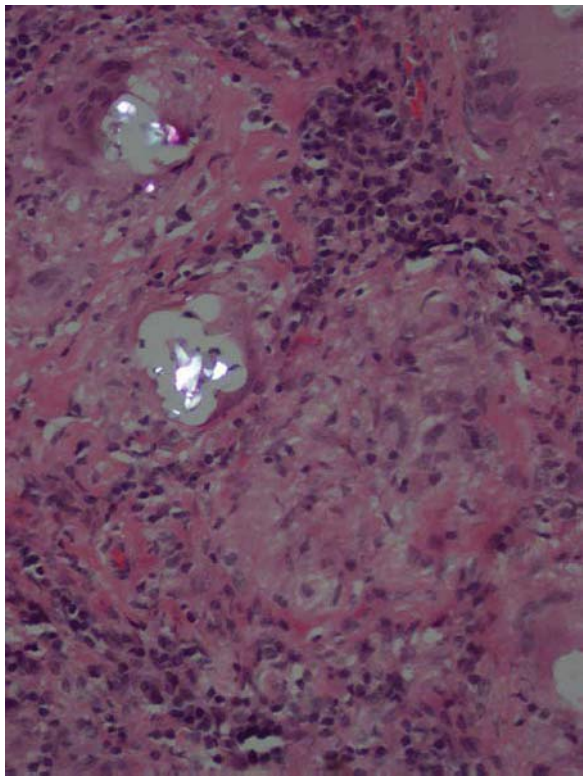
Sarcoid as a rule does not have an interstitial inflammatory infiltrate away from the granulomas, so that the intervening parenchyma is typically normal (Figs. 13.12 and 13.13) and the granulomas are the dominant feature, as opposed to HP, where there is always an interstitial inflammatory process and granulomas can be sparse or nonexistent (see Chapter 12).

Sarcoid granulomas may aggregate over time to form nodular collections (Figs. 13.19 and 13.20). Although this phenomenon was thought to be rare before the days of CT imaging, in fact it is now recognized as quite common.

Vascular Involvement ("Vasculitis")

Sarcoid granulomas may involve vessels (Figs. 13.17 and 13.18). This finding is extremely common (visible in





FIGURES 13.8 and 13.9. Crystalline inclusions (calcium oxalate or calcium carbonate) in sarcoid granulomas in a hilar lymph node under plain and polarized light. Similar crystals may be found in parenchymal granulomas. These crystals are numerous in some cases of sarcoid, but their presence has no diagnostic significance, and similar crystals can be seen in any granulomatous disease.

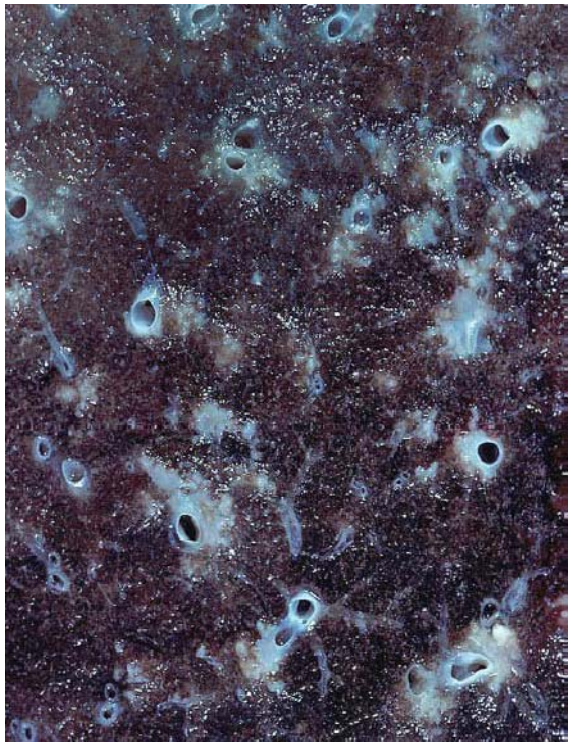


FIGURE 13.10. Gross view of active sarcoid showing granulomas distributed around the bronchovascular bundles.

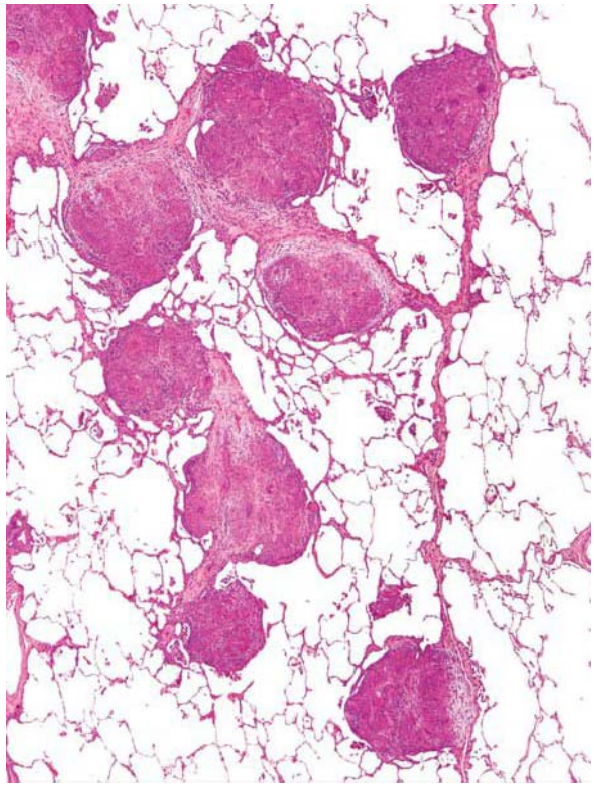


FIGURE 13.12. Granulomas distributed along two interlobular septa and a small vessel. In this figure granulomas are numerous, but in many cases of sarcoid, they are much fewer in number. Note the absence of interstitial inflammation, as opposed to HP, where there is prominent interstitial inflammation and far fewer and more inconspicuous granulomas.

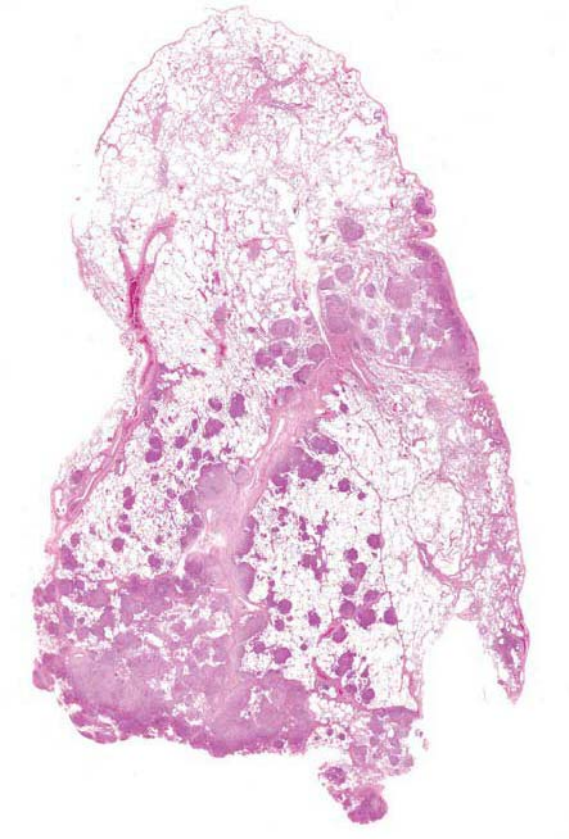


FIGURE 13.11. Low-power view of a case of active sarcoid. There are individual granulomas as well as granulomas coalescing to form nodules. Many of the individual granulomas are distributed along a very fibrotic interlobular septum.

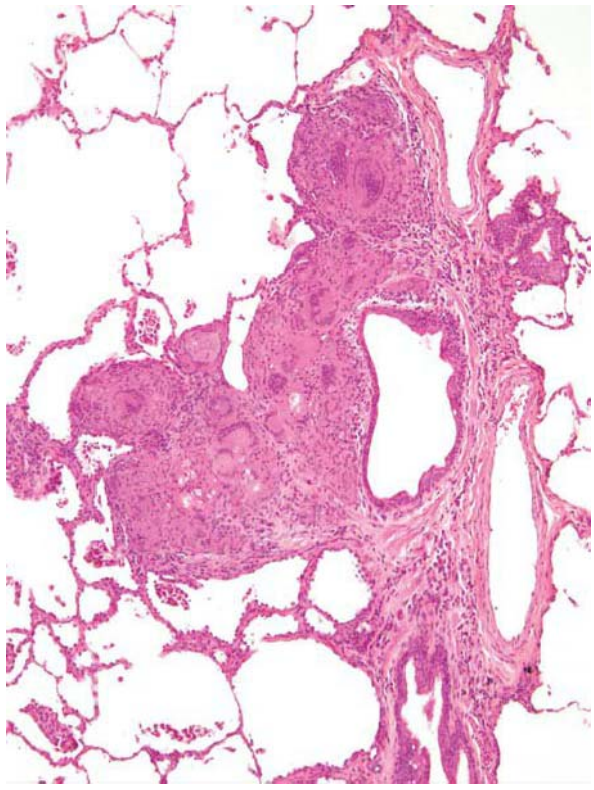


FIGURE 13.13. Multiple granulomas around a bronchovascular bundle in sarcoid. The parenchyma away from the granulomas is normal.

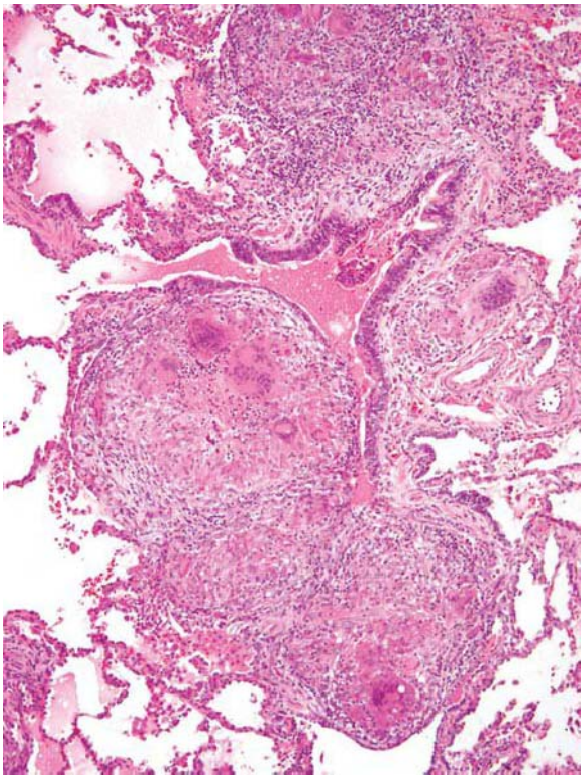


FIGURE 13.14. Granulomas surrounding and compressing a bronchiole. This process can lead to airflow obstruction.

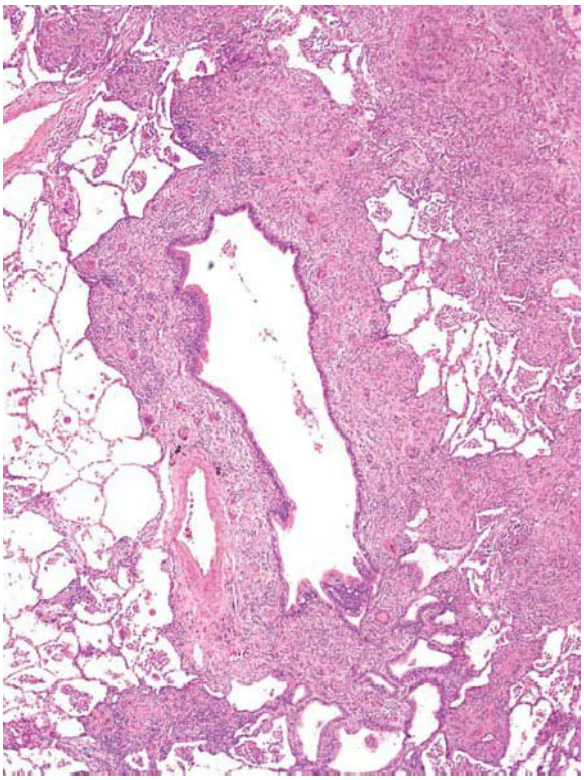


FIGURE 13.15. Granulomas completely surrounding a small airway. Because sarcoid granulomas tend to show a peribronchovascular distribution, the diagnostic yield is high on transbronchial biopsies.

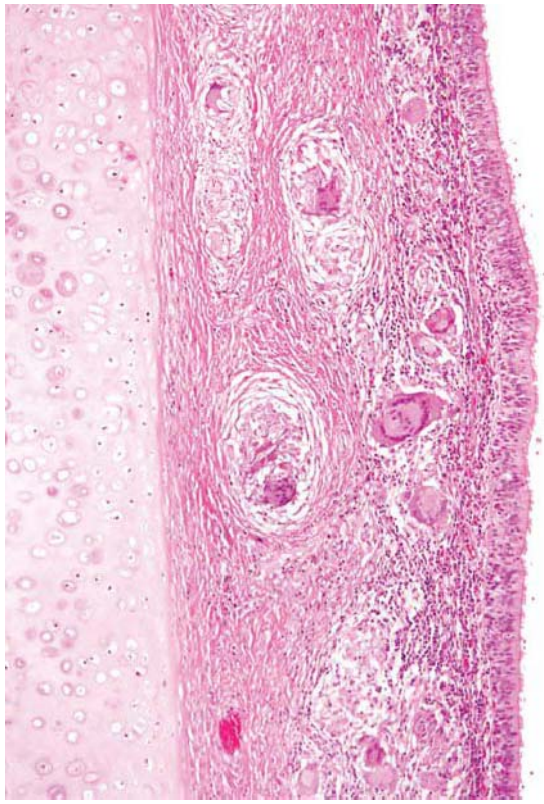
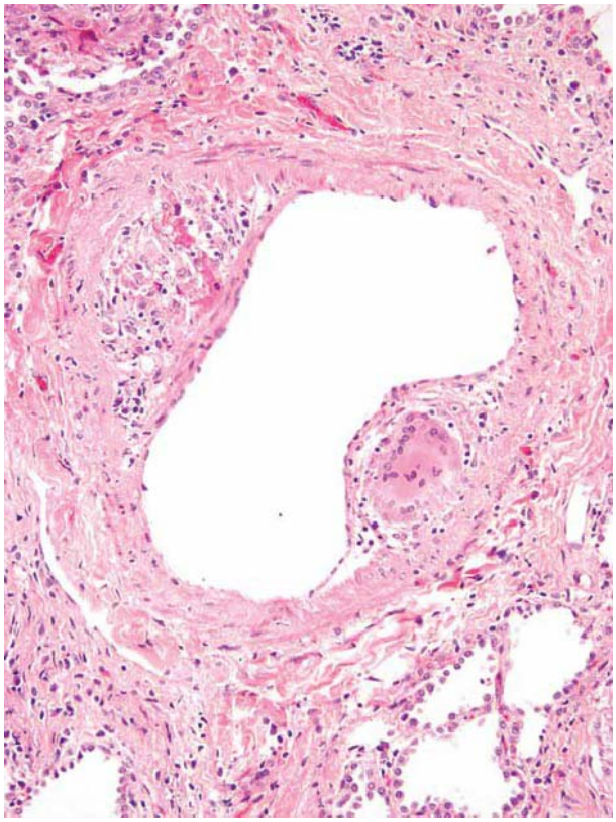


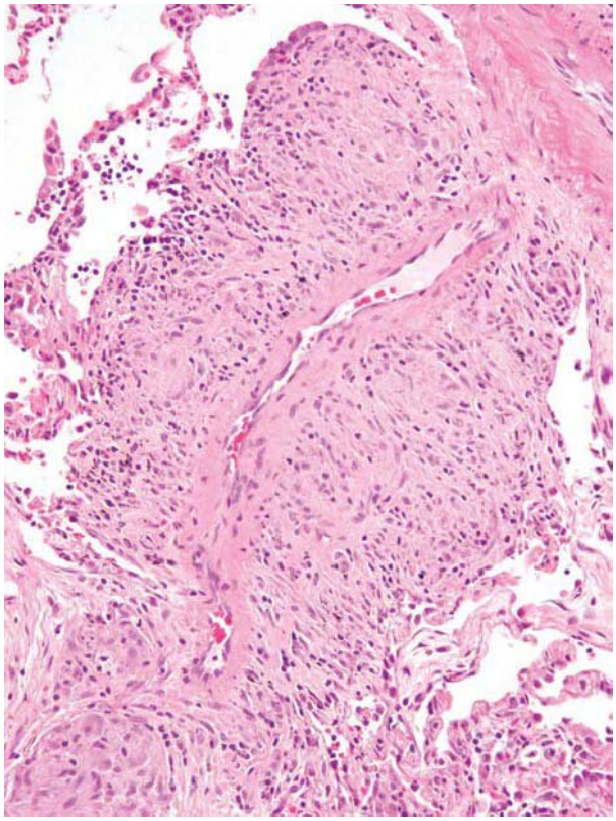
FIGURE 13.16. Endobronchial granulomas in sarcoid. Endobronchial granulomas produce small nodules visible on bronchoscopy and biopsy of such lesions is often diagnostic of sarcoid.

probably 70% of large biopsies) and some authors have referred to it as "vasculitis." As noted above, some patients with sarcoid develop pulmonary hypertension, but it is unclear whether this process reflects granulomatous involvement of vessels or fibrotic obliteration of vessels. Some patients with sarcoid and pulmonary hypertension respond to steroids,[3] suggesting that in a least a portion of cases granulomatous vasculitis has functional consequences.

Scarring in Sarcoid

Sarcoid may resolve spontaneously or with treatment, or it may scar. The most common pattern of scarring is progressive hyalinization of nodules containing aggregated granulomas (Figs. 13.19 to 13.23). Because sarcoid granulomas tend to be present along the bronchovascular bundles, nodules are frequently centrilobular in distribution (Fig. 13.22). Occasionally nodules of aggregated granulomas also contain a marked chronic inflammatory infiltrate (Fig. 13.24); this is more common with very large nodules (nodular sarcoid). Unless they are very large (see section on nodular sarcoid below), the presence of nodules does not change the pathologic diagnosis, and they do not need to be explicitly acknowledged in the diagnosis.





FIGURES 13.17 and 13.18. Granulomatous vasculitis in sarcoid in an artery (**Fig. 13.17**) and a vein (**Fig. 13.18**). Granulomatous vasculitis is visible in most cases of sarcoid if a surgical lung biopsy is available for review and is invariably present in nodular and necrotizing sarcoid. The granulomas may be on the intimal or adventitial side of the vessel.

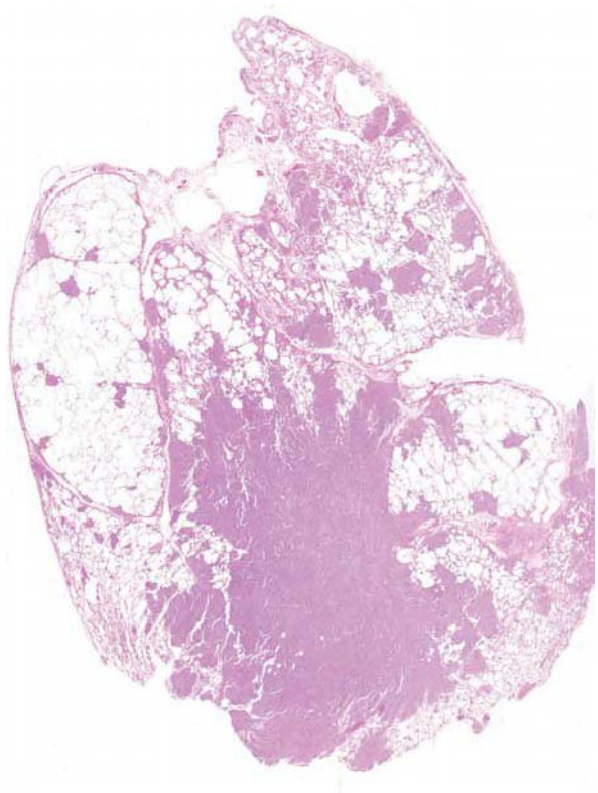


FIGURE 13.19. Nodular sarcoid. Nodules formed by aggregated granulomas are common in sarcoid; if the nodules are larger than 1 cm the disease is classified as "nodular sarcoid." In this example the large nodule is cellular and individual granulomas are still present.

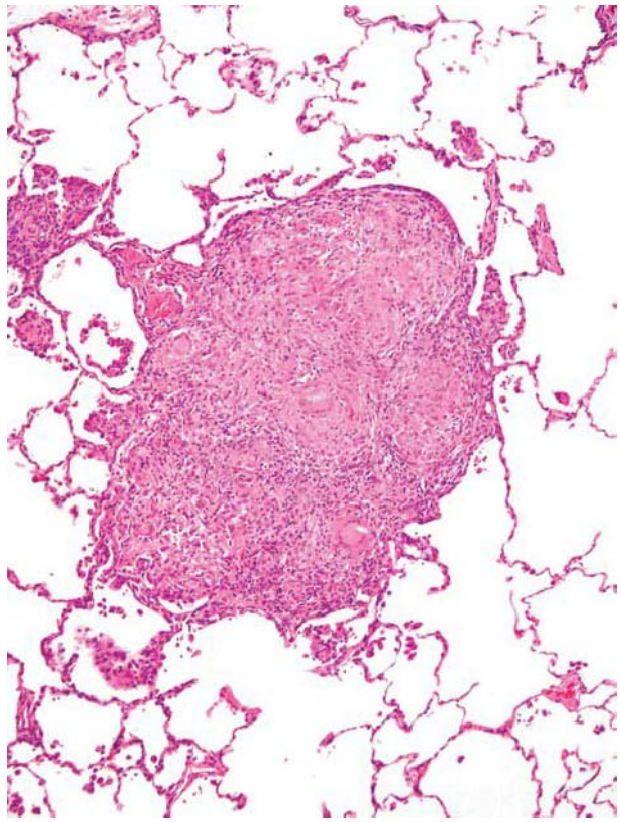


FIGURE 13.20. A cellular nodule formed by aggregation of sarcoid granulomas.

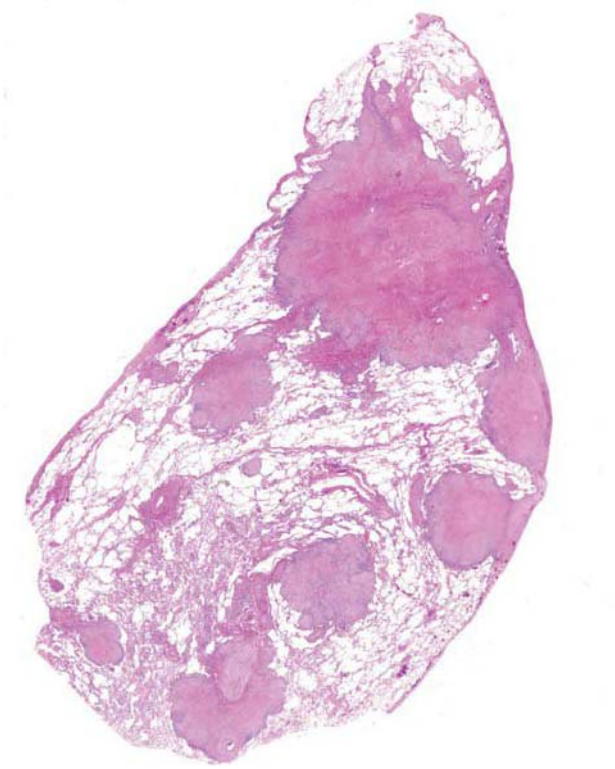


FIGURE 13.21. Nodular sarcoid with multiple hyalinized nodules.

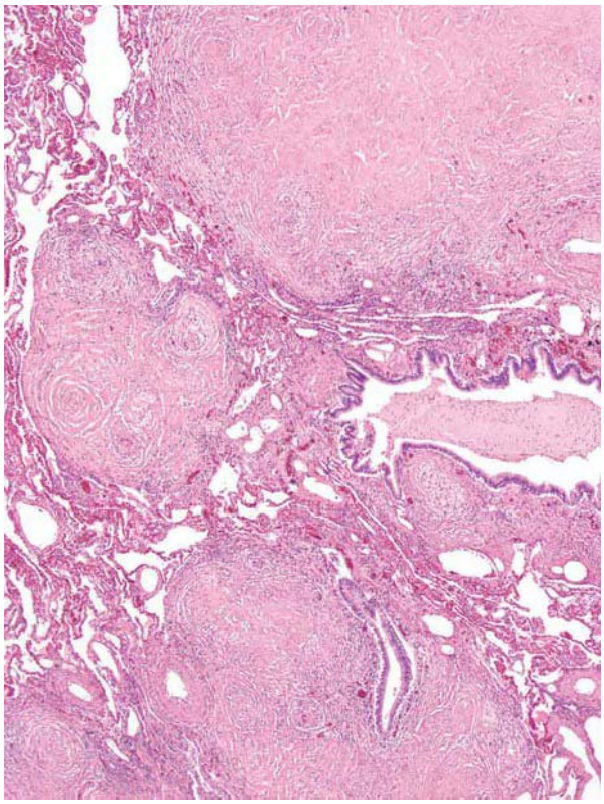


FIGURE 13.22. Nodular sarcoid. In this case the nodules are largely hyalinized and only a few individual granulomas remain. Formation of hyalinized nodules is one form of scarring in sarcoid.

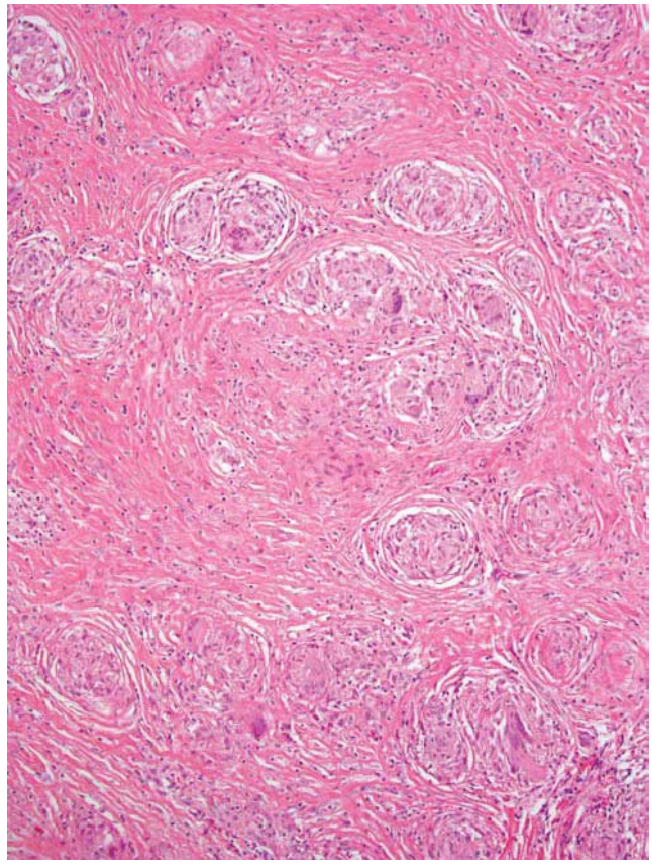


FIGURE 13.23. Higher-power view of a nodule in sarcoid showing a mixture of granulomas and dense hyalinized collagen.

A less common pattern of scarring is the formation of linear or stellate scars (Figs. 13.25 to 13.27), often centered on or incorporating the bronchovascular bundles (Fig. 13.27). When the granulomas have completely vanished, this type of scarring may not be distinguishable from old scarred Langerhans cell histiocytosis (LCH) (see Figs. 10.20 and 10.21). Occasionally scarred sarcoid produces a pattern mimicking fibrotic NSIP (Fig. 13.28 and see Chapter 7).

Sarcoid that progresses to stage 4 typically shows severe upper zonal scarring (Fig. 13.29). This distribution is a helpful guide to diagnosis in a completely scarred biopsy, but LCH, some cases of chronic HP, and old TB or fungal infections can also produce upper zone scarring.

Nodular and Necrotizing Sarcoid

Nodular sarcoid is a term that dates from the pre-CT era when nodules in sarcoid were considered to be unusual (Table 13.2). In its original meaning nodular sarcoid referred to sarcoid in which nodules were visible on plain chest radiograph, but today nodular sarcoid simply means sarcoid with nodules ≥ of 1 cm or more in diameter visible on imaging. The major clinical significance of nodular (and necrotizing) sarcoid was that the nodules carried a primary differential diagnosis of malignancy. This is

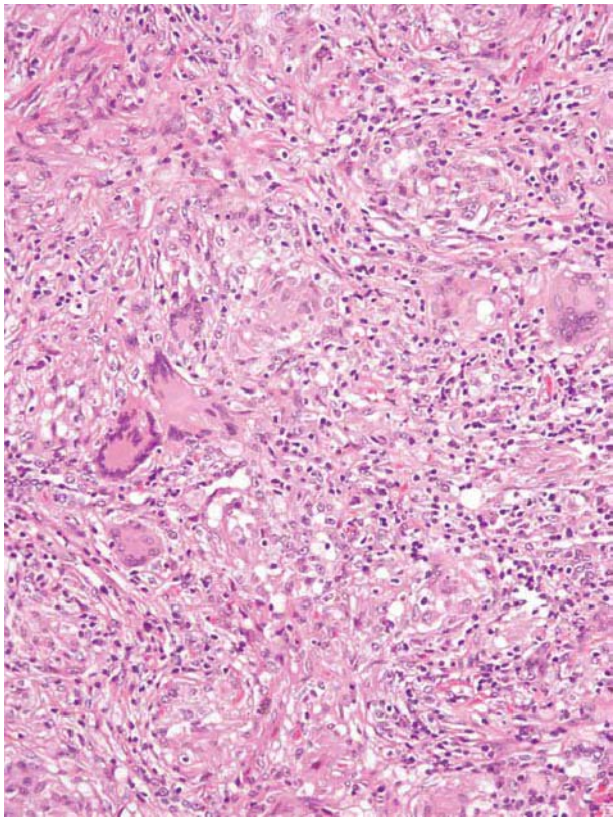


FIGURE 13.24. A sarcoid nodule in which there is considerable chronic inflammation but no fibrosis.

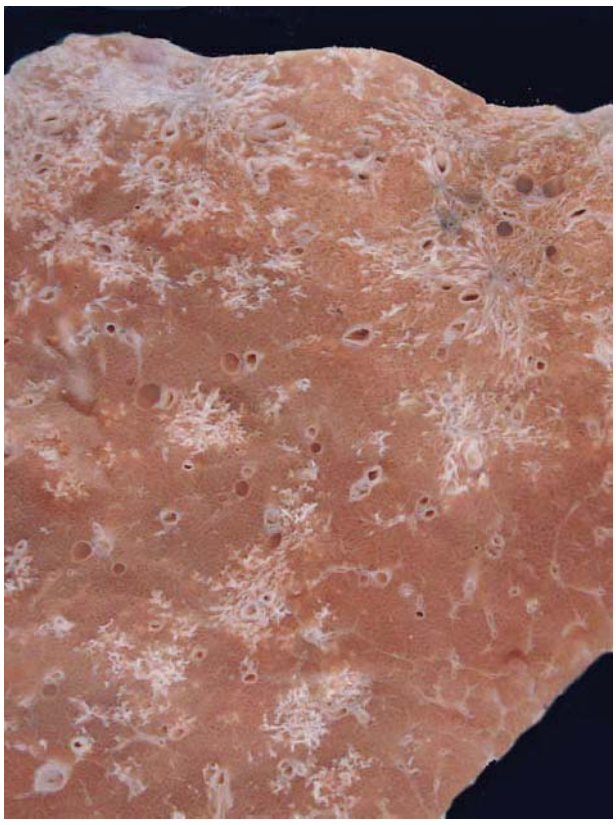


FIGURE 13.25. Fine peribronchovascular scarring in sarcoid.

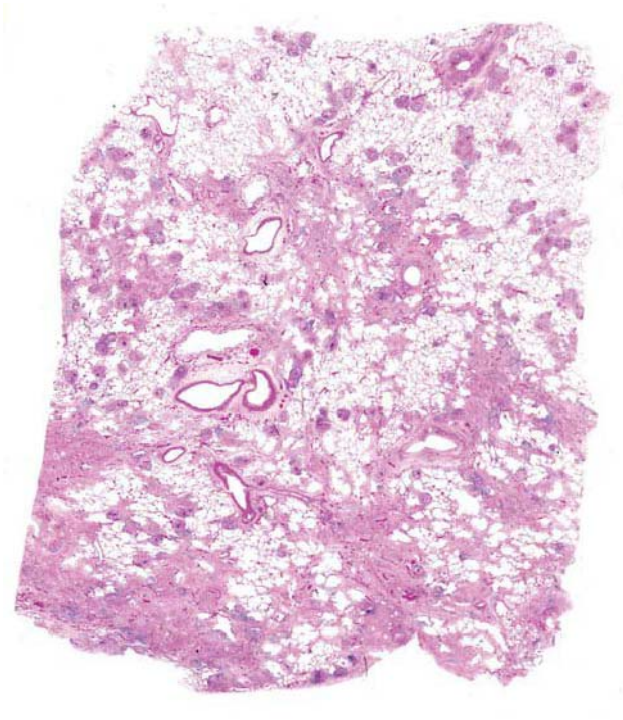


FIGURE 13.26. Sarcoid showing irregular, more or less linear scars mixed with individual granulomas.

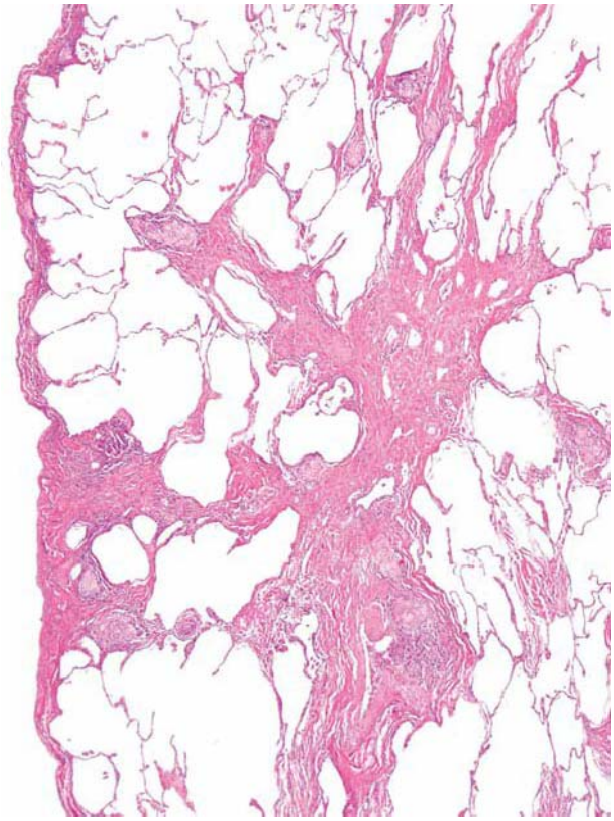


FIGURE 13.27. Sarcoid with peribronchovascular scars and a few small granulomas. Peribronchovascular scarring in sarcoid is less common than the formation of nodules and may also be seen in chronic HP and LCH (which lacks granulomas).

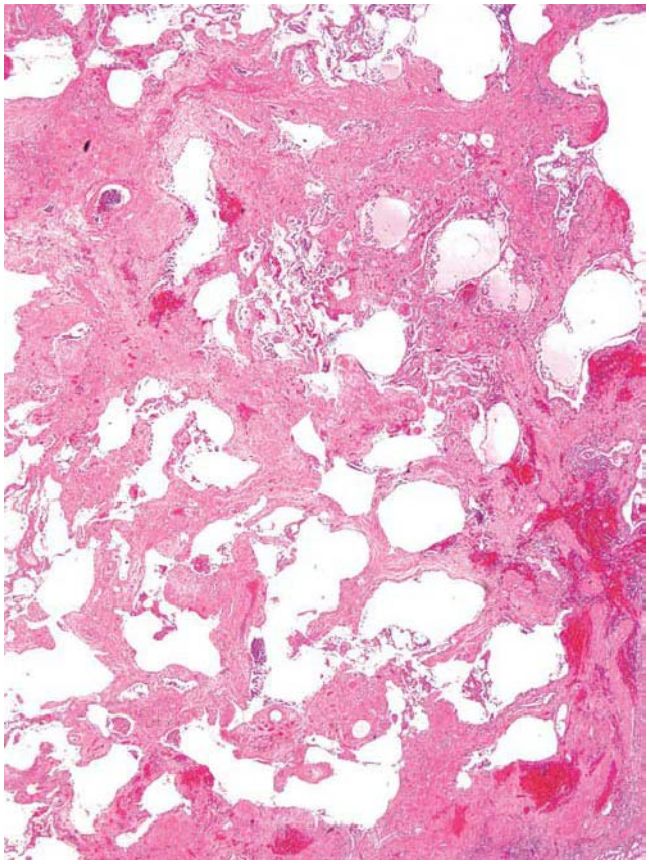


FIGURE 13.28. Diffuse scarring in sarcoid mimicking fibrotic NSIP.

occasionally still true, but because nodular and necrotizing sarcoid often have typical findings of sarcoid on HRCT, the distinction from ordinary sarcoid is not as sharp as it once was.

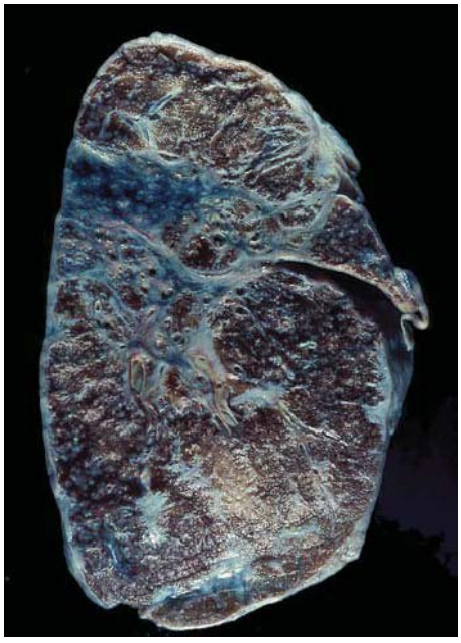


FIGURE 13.29. Gross view of end-stage (stage 4) scarring in sarcoid showing the typical mid to upper zonal distribution.

In nodular sarcoid the lesions comprise aggregated granulomas that undergo hyaline scarring in a fashion identical to that seen in the small nodules common in ordinary sarcoid (Figs. 13.19, 13.21 to 13.23); the only distinction is the size of the nodules. Necrotizing sarcoid is similar, except that small or large areas of necrosis are present in the aggregated granulomas (Figs. 13.30 and 13.31), but this finding mandates careful examination of stains for acid fast bacilli and fungi, as infectious processes can be microscopically identical. Nodular and necrotizing sarcoid always have smaller nodules or individual granulomas away from the large nodules.

Table 13.2

Features of nodular and necrotizing sarcoid

Large nodules formed by aggregated granulomas
Central hyalinization in nodular sarcoid
Necrosis in nodules in necrotizing sarcoid
Small nodules and/or individual granulomas present away from the large nodules
Granulomatous vascular involvement always present

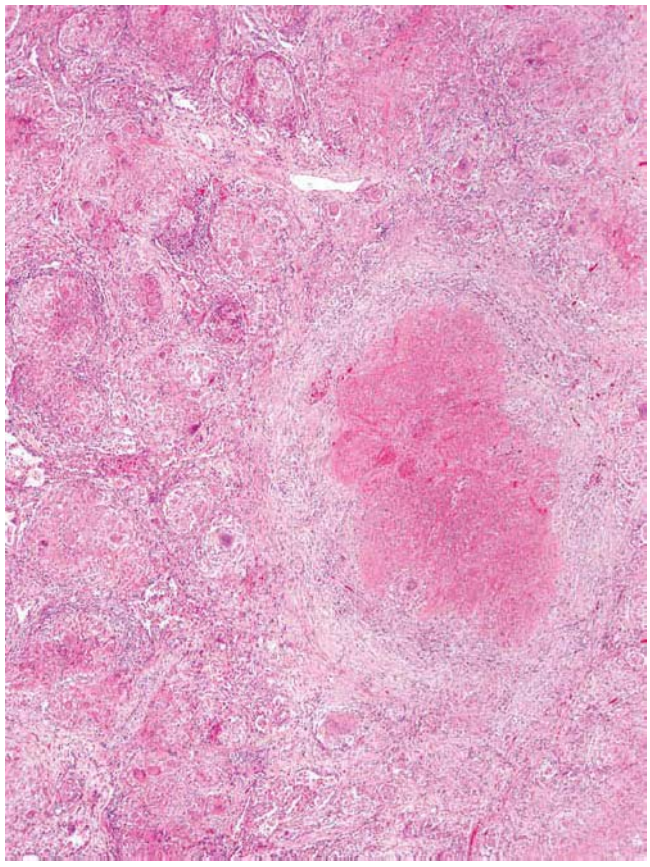


FIGURE 13.30. Necrotizing sarcoid. In this example an area of necrosis has appeared in the midst of aggregated granulomas.

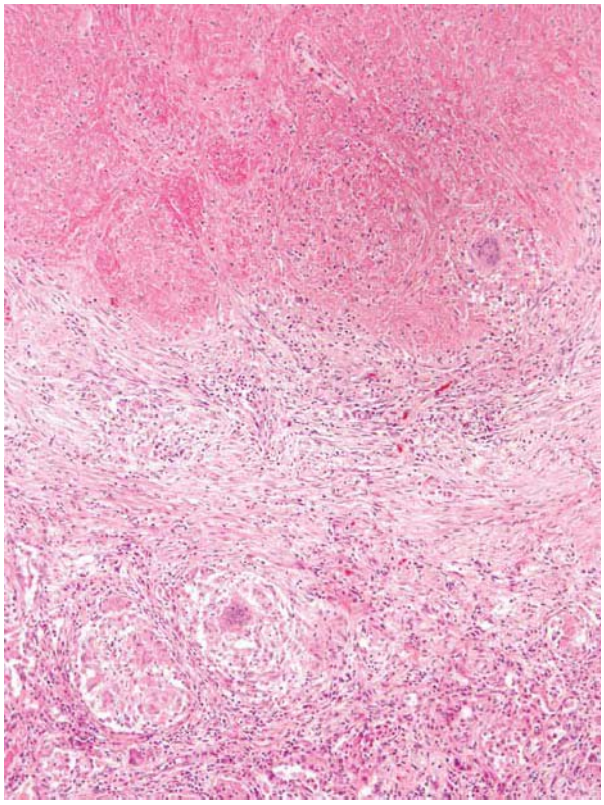


FIGURE 13.31. Necrotizing sarcoid. Higher-power view of the same case as Figure 13.30. Stains for acid fast organisms and fungi are mandatory in this setting because TB and fungal infections can produce an identical morphologic picture.

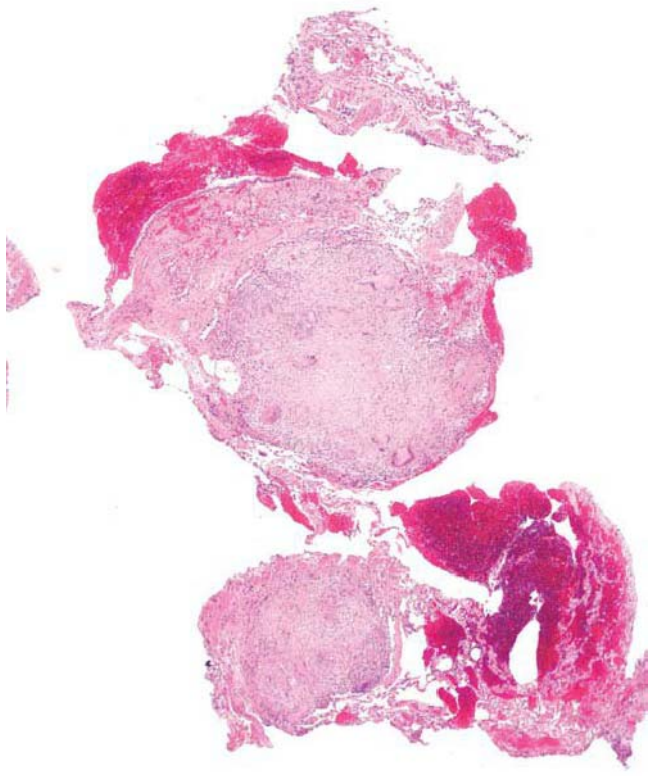


FIGURE 13.32. Transbronchial biopsy in sarcoid showing multiple granulomas.

Both nodular and necrotizing sarcoid are invariably associated with granulomatous vascular involvement, but granulomas in vessel walls are equally common with TB and fungal infections, so that this finding is not a useful diagnostic tool.

Special Stains in Sarcoid

Whether special stains for organisms always need to be performed in cases that clinically and morphologically are clearly sarcoid is controversial. Although it is very rare to find organisms in this setting, we believe that the stains should be performed nonetheless because atypical mycobacteria do not always produce necrotizing granulomas, and even the granulomas of ordinary TB can be nonnecrotizing for a short period.

DIAGNOSTIC MODALITIES

Transbronchial biopsies (Fig. 13.32) are commonly performed for the diagnosis of sarcoid and have a high yield, in large part because the peribronchovascular distribution of sarcoid granulomas (Figs. 13.14 to 13.16) means that the biopsy forceps sample the optimum region of the lung. If no granulomas are seen in the original cuts and the clinical impression is sarcoid, additional slides should be prepared because the yield improves with up to seven deeper levels.[7] Endobronchial biopsies also have a high yield in sarcoid, particularly if the endoscopist observes nodularity in the bronchial mucosa.

Sarcoid can involve any organ, and hilar and mediastinal nodes typically are filled with granulomas and occasionally contain hyalinized nodules derived from aggregated granulomas (Figs. 13.33 and 13.34). Sometimes histiocytes in lymph node sinuses mimic granulomas, but real granulomas in sarcoid do not show a sinus distribution and usually are packed together (Fig. 13.33).

Mediastinoscopic and endobronchial ultrasound (EBUS) biopsies (Figs. 13.35 and 13.36) of hilar or mediastinal lymph nodes produce a high yield,[8] and extrathoracic sites such as skin are also sometimes suitable for a biopsy diagnosis. Slit lamp examination may show characteristic features of ocular sarcoid and obviate the need for biopsy.

DIFFERENTIAL DIAGNOSIS

The major differential diagnoses of sarcoid are HP and infections. The distinction of sarcoid from HP has been referred to in the text above and in Chapter 12

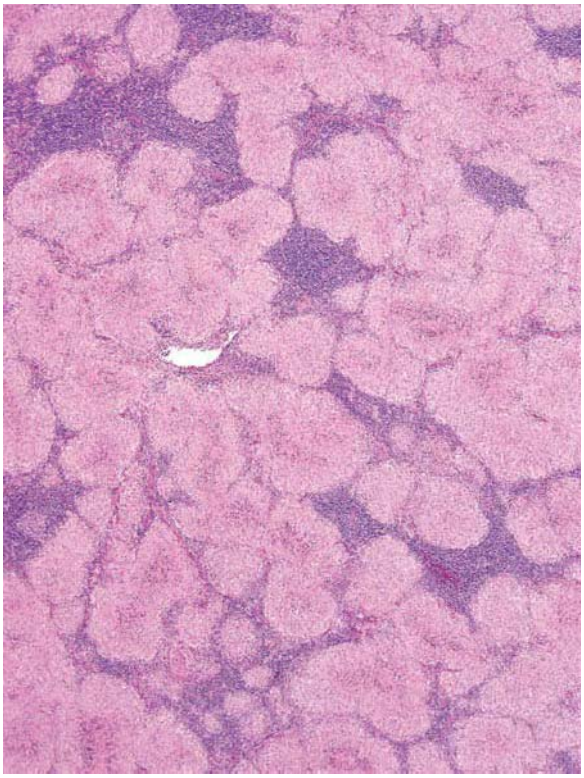


FIGURE 13.33. Sarcoid granulomas in a mediastinal lymph node. Some of these granulomas have small amounts of central necrosis. Sarcoid granulomas in hilar and mediastinal lymph nodes have distinct circumscribed structures and are not located in nodal sinuses, as opposed to sinus histiocytes.

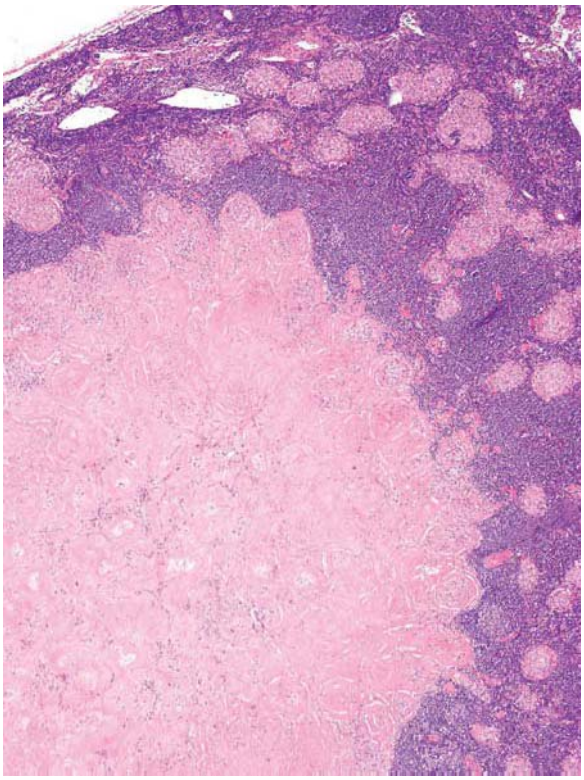
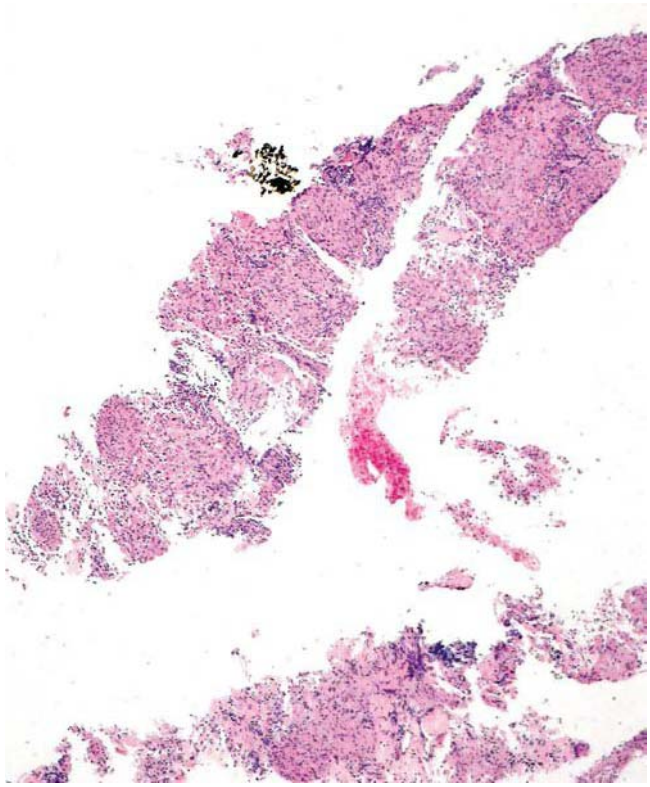
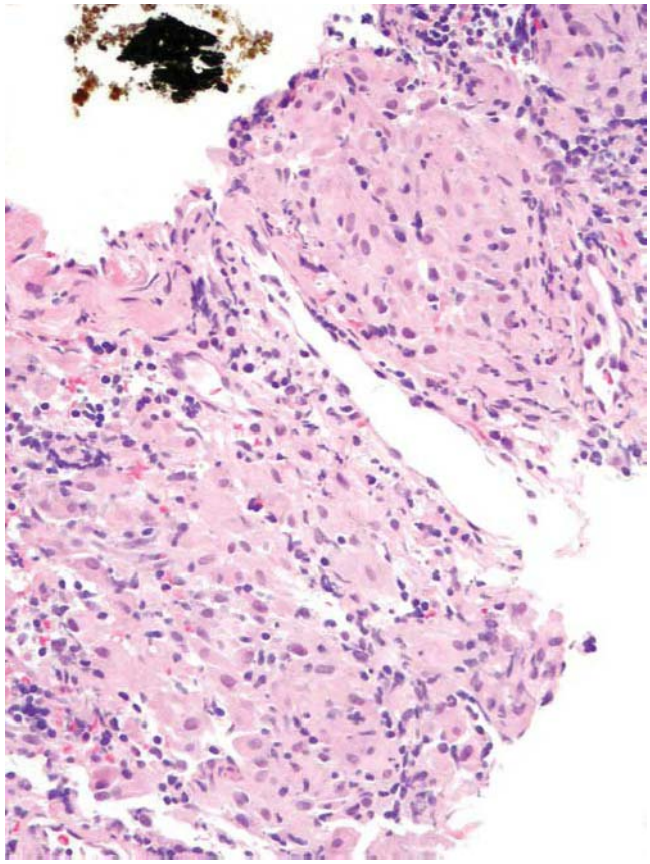


FIGURE 13.34. Individual granulomas and a large hyalinized nodule in a mediastinal lymph node. Nodal granulomas in sarcoid can coalesce to form nodules in the same fashion as parenchymal granulomas.





FIGURES 13.35 and 13.36. Sarcoid granulomas in an EBUS core of a mediastinal lymph node.

Table 13.3

Comparison of sarcoid and infectious granulomas

Sarcoid	TB and fungal infections	Atypical mycobacterial infections
Granulomas usually but not always non-necrotizing	Granulomas usually but not always necrotizing	Granulomas may be non-necrotizing or necrotizing
Granulomas follow lymphatic routes	Granulomas random in parenchyma	Granulomas random or in walls of *ectatic* bronchioles or bronchi
Aggregated granulomas scar to hyalinized nodules	Aggregated granulomas usually show necrosis	Aggregated granulomas usually show necrosis
Granulomas often surrounded by concentric bands of hyalinized collagen	Concentric hyalinization rare	Concentric hyalinization rare
Schaumann bodies occasionally present	Schaumann bodies rare	Schaumann bodies rare
No organisms demonstrable	Organisms often demonstrable	Organisms often demonstrable

(see particularly Table 12.7). Table 13.3 shows the features of sarcoid compared to fungal and mycobacterial infections. Particular note should be made of non-necrotizing granulomas that look like sarcoid granulomas in the walls of *ectactic* bronchioles or bronchi, because this pattern is seen very characteristic of atypical mycobacterial infections and not of sarcoid.

Chronic berylliosis is morphologically identical to sarcoid and in the lung and forms individual non-necrotizing granulomas as well as aggregated granulomas (Fig. 13.37). In practice berylliosis is rare and patients with berylliosis almost invariably give a history of beryllium exposure. In questionable cases beryllium lymphocyte blast transformation testing can be used,[9] and it is also possible to demonstrate beryllium by energy dispersive x-ray spectroscopy in histologic sections[10] or by various chemical analysis of lung tissue.[11]

Some drugs can produce a granulomatous reaction in the lung (see Chapter 18). With methotrexate the granulomas are scattered and the process can mimic HP, but anti-TNF agents and interferon therapy can cause the formation of multiple pulmonary granulomas in a pattern that mimics sarcoid[12,13] (see Figs. 18.12 and 18.13) and is sometimes even referred in the clinical literature as "sarcoidosis."[14] However, at least for anti-TNF agents the granulomas disappear if the drug is stopped,[14] indicating that this is really a drug reaction.

Sarcoid type granulomas are a common finding in lungs that harbor tumors and the hilar and mediastinal lymph nodes from such cases also may contain

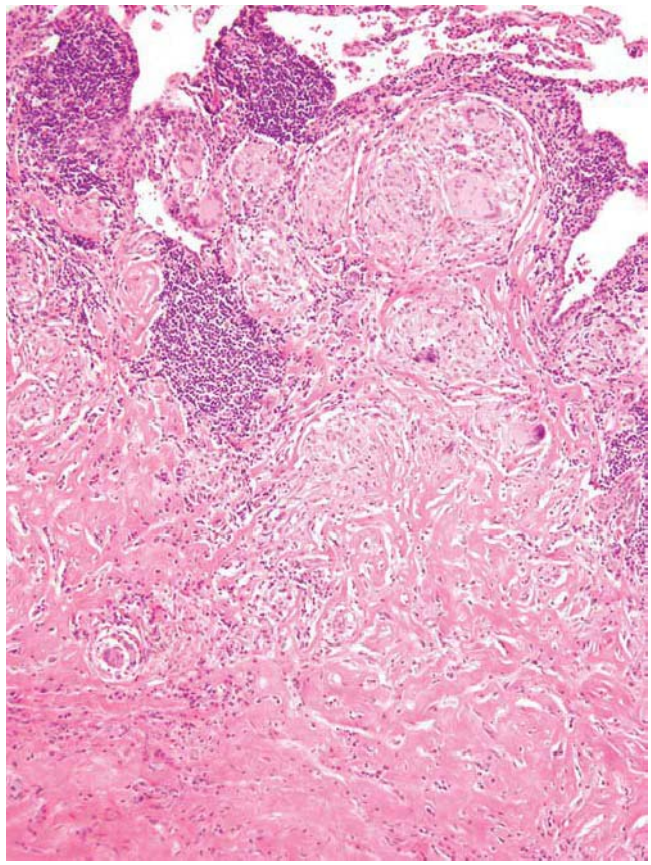


FIGURE 13.37. Chronic berylliosis. Image shows the edge of a nodular lesion comprising granulomas and hyalinized collagen. Morphologically chronic berylliosis is indistinguishable from sarcoid.

granulomas. In most such cases the number of granulomas is much fewer than in sarcoid and there are no radiologic findings to suggest sarcoid.

PROGNOSIS

As noted above, the prognosis of sarcoid depends to a large extent on the radiologic stage. The higher the stage, the lower the chance of remission (remission is seen in up to 90% of stage 1 cases and no stage 4 cases), but even with high stage the disease can be quite slowly progressive; a recent study of stage 4 sarcoid patients reported a 10-year survival of 84% from the time of diagnosis.[15] Overall remission is seen in approximately 70% of cases and only 1% to 5% of cases are fatal, and this number may be exaggerated because such cases tend to get referred to academic centers and enumerated. Neurosarcoid and cardiac sarcoid carry a worse prognosis. Nodular and necrotizing sarcoid appear to behave as low-stage disease with a good prognosis.[16] Sarcoid can recur in transplanted lungs, but usually does not cause clinically significant disease.[17]

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CHAPTER

14

Granulomatous Interstitial Lung Disease in Common Variable Immunodeficiency

CLINICAL FEATURES

Common variable immunodeficiency (CVI) is a primary immunodeficiency syndrome caused by failure of terminal B cell differentiation and abnormal T-cell function and is characterized by low levels of circulating immunoglobulins.

Patients with CVI have an increased risk of both bacterial and opportunistic lung infections. However, recent reports have indicated that they may also develop a noninfectious granulomatous and/or interstitial lung disease (ILD), referred to as "granulomatous–lymphocytic ILD (GLILD)."[1,2]

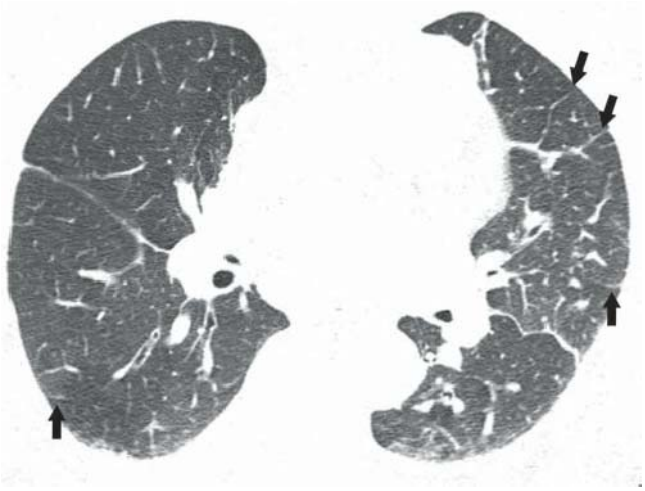
IMAGING

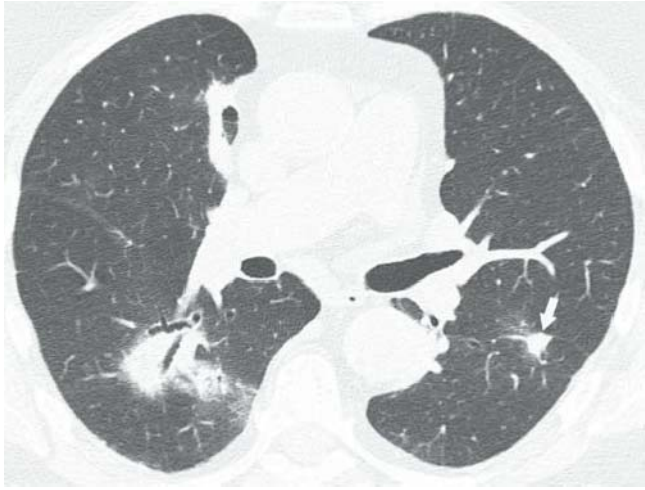
The majority of patients with CVI have pulmonary abnormalities evident on HRCT, the most frequent ones being bronchiectasis (usually mild) and air trapping.[3] The most common high resolution computed tomography (HRCT) manifestations of GLILD comprise multiple randomly distributed small nodules, smooth interlobular septal thickening, multifocal areas of consolidation, hilar and mediastinal lymph node enlargement, and splenomegaly[4] (Figs. 14.1 and 14.2). The abnormalities tend to involve mainly the lower lobes and to wax and wane over time. The areas of consolidation may represent acute infection, bronchiolitis obliterans organizing pneumonia (BOOP), or more severe GLILD.[4]

PATHOLOGIC FEATURES

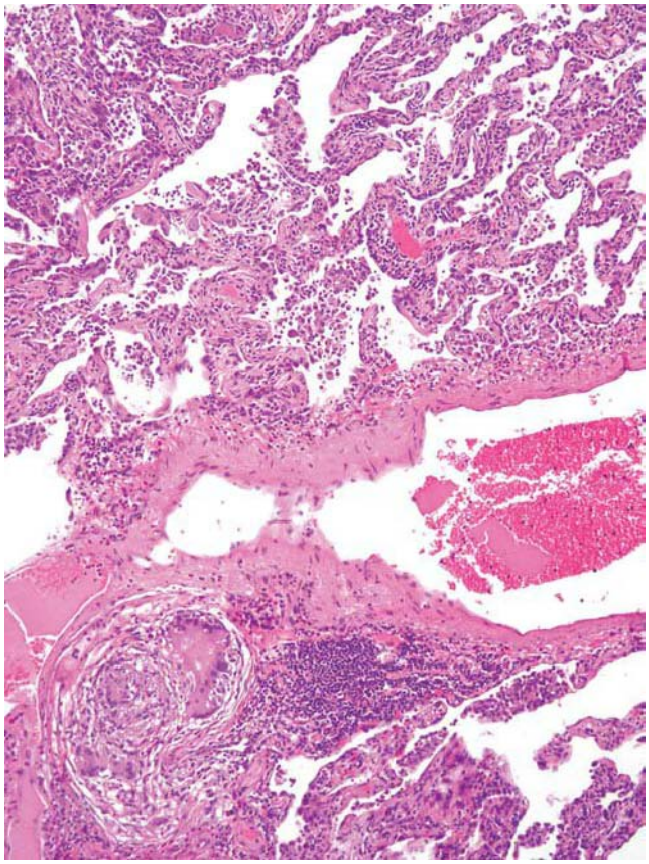
GLILD in CVI is characterized by a variable combination of noncaseating interstitial granulomas (Figs. 14.3 and 14.4), follicular bronchiolitis (see Chapter 19), lymphoid hyperplasia, and lymphocytic interstitial pneumonia (LIP) (Chapter 20). The granulomas may be associated with the lymphoid infiltrates or may be separated from them. There is also an increased risk of mucosa-associated lymphoid tissue (MALT) lymphomas.[5]

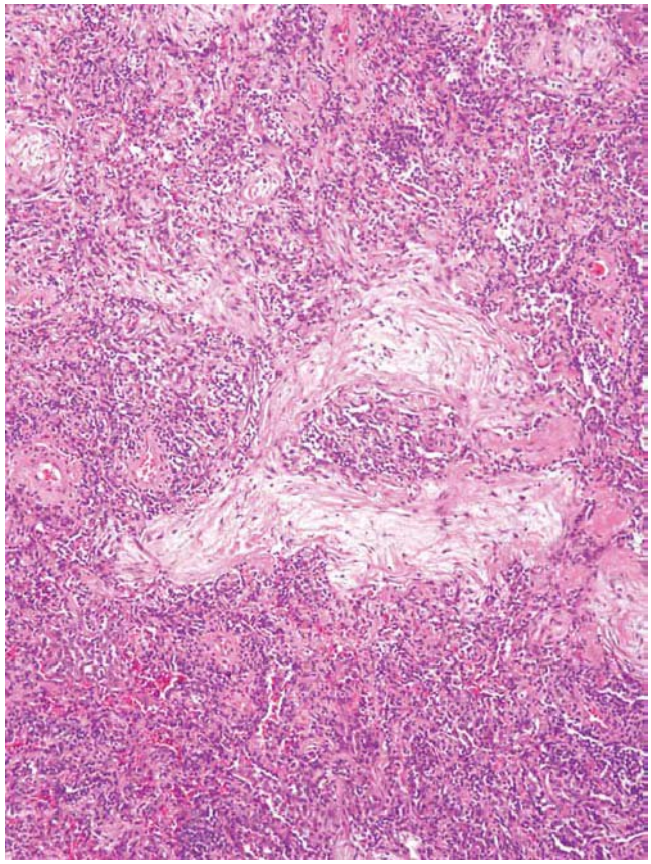
It has been suggested that the granulomas reflect aberrant T cell responses in which antigens are not removed and that the lymphoid proliferations are driven by human herpes virus-8 (HHV-8); HHV-8 can be demonstrated by immunohistochemistry or polymerase chain reaction (PCR) in some cases of CVI. Granulomas are also commonly found in extrapulmonary sites in patients with CVI.





FIGURES 14.1 and 14.2. Granulomatous–lymphocytic ILD. **Figure 14.1** shows HRCT at the level of the lower lobe bronchi demonstrates mild smooth interlobular septal thickening (*black arrows*) mainly in the lingula. **Figure 14.2** shows HRCT performed 4 months after Figure 14.1 at the level of the left upper lobe bronchus shows focal consolidation and GGOs in the right middle and lower lobes and a nodule in the left lower lobe (*white arrow*).





FIGURES 14.3 and 14.4. Biopsy of the case shown in Figures 14.1 and 14.2. **Figure 14.3** shows a granuloma and mild chronic interstitial inflammation, whereas **Figure 14.4** shows an area of BOOP.

Because they are susceptible to bacterial infections, patients with CVI also have an increased incidence of bronchiectasis.[5] BOOP has also been described, but its etiology is unclear.

DIAGNOSTIC MODALITIES

In a patient known to have CVI, GLILD might be diagnosable on transbronchial biopsy; however, the diagnosis requires a combination of findings that are unlikely to all be present in a transbronchial biopsy. Video-Assisted Thoracoscopic Surgery (VATS) biopsy is ordinarily the diagnostic procedure of choice.

DIFFERENTIAL DIAGNOSIS

CVI is difficult to diagnose without an appropriate history as many of the pathologic patterns are common to other forms of ILD, including BOOP (Chapter 5), nonspecific interstitial pneumonia (NSIP) (Chapter 7), hypersensitivity pneumonitis (HP) (Chapter 12), follicular bronchiolitis (Chapter 19), lymphoid hyperplasia (Chapter 20), and lymphocytic interstitial pneumonia (LIP) (Chapter 20). The combination of granulomas and interstitial inflammatory infiltrates can be seen in HP and LIP, and granulomas plus BOOP are often seen as a manifestation of aspiration (Chapters 5 and 19).

PROGNOSIS

Little is known about the prognosis of GLILD. In one study of 69 patients,[5] survival was considerably shorter in patients with this pattern of lung involvement than in those without.

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CHAPTER

15

Eosinophilic Pneumonias

NOMENCLATURE ISSUES

Eosinophilic pneumonias are conventionally separated into simple eosinophilic pneumonia (Loeffler syndrome), acute eosinophilic pneumonia (AEP)—a process that clinically resembles acute respiratory distress syndrome (ARDS), and chronic eosinophilic pneumonia (CEP) that has a longer time course and does not result in respiratory failure. However, these distinctions are sometimes not sharp and cases can be found that seem to sit (at least morphologically) on the borderline between acute and CEP.[1,2] As treatment is the same (high dose steroids) the distinction is usually not crucial.

CAUSES OF EOSINOPHILIC PNEUMONIAS

The causes of eosinophilic pneumonias are listed in Table 15.1. AEP is relatively rare and there are few described causes, most notably drugs and cigarette smoke, typically in those who start smoking or take it up after a hiatus. More than 120 drugs have been reported to produce eosinophilic pneumonias.[1,3] Eosinophilic pneumonia may be the only manifestation of Churg–Strauss syndrome (CSS)[4] or allergic bronchopulmonary aspergillosis (ABPA),[5] but usually these diseases show several other features.

CLINICAL FEATURES

Simple Eosinophilic Pneumonia (Loeffler Syndrome)

Simple eosinophilic pneumonia is characterized by fleeting migratory pulmonary infiltrates on imaging in the absence of pulmonary symptoms or with minimal symptoms. Patients typically have a peripheral blood eosinophilia. Most cases of Loeffler syndrome are believed to be caused by pulmonary passage of intestinal parasites, most commonly *Ascaris*,[1] but some cases do not have an identifiable cause.

Acute Eosinophilic Pneumonia

AEP (Table 15.2) is characterized by an abrupt onset, typically with symptoms for less than 7 days, fever, bilateral opacities on imaging, severe hypoxemia with the

Table 15.1

Causes of eosinophilic pneumonias

- Idiopathic
- Drug reactions (including illicit drugs)
- Inhaled organic antigens
- Churg-Strauss syndrome (CSS)
- Fungal hypersensitivity (allergic bronchopulmonary aspergillosis/mycosis)
- Infections
  - Loeffler syndrome (fleeting airspace infiltrates, often caused by *Ascaris* or other intestinal parasites)
  - Parasitic infections
  - Fungal infections, especially Coccidioides
  - Pneumocystis
  - Tuberculosis
  - HIV
  - Viral infections, especially respiratory syncytial virus
- Unusual response to recent onset of cigarette smoking (AEP and occasionally CEP)
- Malignancies
- Collagen vascular disease (particularly rheumatoid arthritis)
- Inflammatory bowel disease
- Hypereosinophilic syndrome

Table 15.2

Features of AEP

- Abrupt onset
- Hypoxemic respiratory failure
- Fever
- Diffuse GGOs and/or consolidation on HRCT
- Smooth interlobular septal thickening on HRCT
- >25% eosinophils on bronchoalveolar lavage
- Pathologic DAD (acute or organizing phase) with eosinophils
- Responds dramatically to steroids

development of respiratory failure, and more than 25% eosinophils on bronchoalveolar lavage, or eosinophils on lung biopsy.[1,2,6] Some patients give a history of a specific inhalation event or drug use immediately preceding the onset of symptoms. Serum IgE may be elevated, but most patients do not have a blood eosinophilia, at least at presentation, although blood eosinophil counts can increase during the course of the disease. AEP is thus, clinically, very similar to ARDS, and often it is only the presence of eosinophils on lavage or biopsy that indicates the correct diagnosis.

Chronic Eosinophilic Pneumonia

Most cases of CEP (Table 15.3) have an insidious onset and a long time course of symptoms, often many months before diagnosis. In addition to cough and shortness of breath (SOB), systemic symptoms (fever, weight loss, night sweats) are common. A history of asthma is present in 25% to 50% of patients and some have other forms of atopy.[1] Some patients have elevated serum IgE levels. Blood eosinophilia is seen in 90% of cases and eosinophils are frequently the majority of white cells. Pulmonary function testing can show an obstructive or restrictive defect. Recurrences of CEP are common, often with the infiltrates in new areas of the lung.

Table 15.3

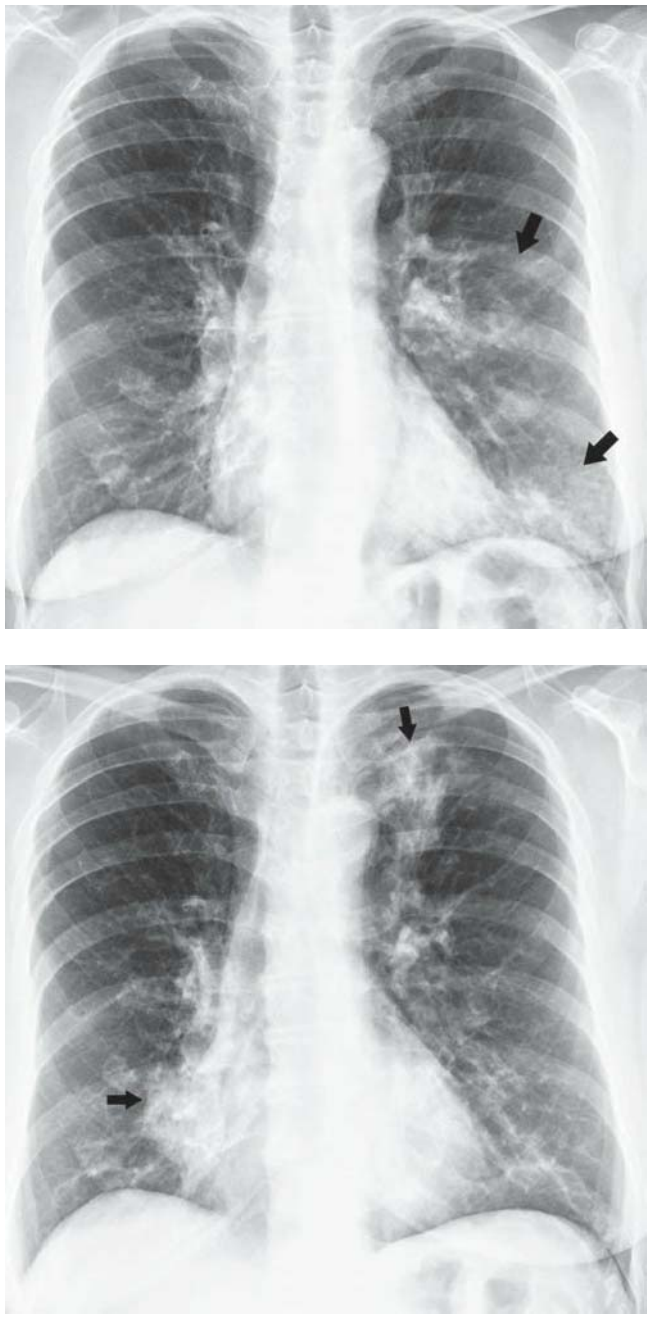
Features of CEP

- Often long history before diagnosis
- Systemic symptoms (fever, night sweats, weight loss) common
- History of asthma or atopy in many cases
- Blood eosinophilia in 90% of cases
- Peripheral consolidation, often migratory, on imaging
- Pathologic patterns:
  - Classic form (sheets of eosinophils and macrophages)
  - May have eosinophil necrosis with giant cells or granulomatous response
  - Noncaseating granulomas seen in a small percentage of cases
  - BOOP (bronchiolitis obliterans organizing pneumonia)
  - Cellular nonspecific interstitial pneumonia (NSIP)-like pattern with eosinophils
  - Organizing and fibrinous pneumonia pattern with eosinophils
  - Irregular scarring with eosinophils
  - Minor degrees of vascular infiltration by eosinophils

Note: eosinophils may be relatively few in all but the classic form, especially if the patient has been treated with steroids before biopsy

IMAGING

Simple pulmonary eosinophilia (Loeffler syndrome) is characterized by transient and migratory areas of consolidation that typically clear spontaneously within 1 month (Figs. 15.1 and 15.2).[7] The areas of consolidation may be single or multiple and tend to be patchy with ill-defined margins. The main radiologic differential diagnosis



FIGURES 15.1 and 15.2. Simple pulmonary eosinophilia. **Figure 15.1:** Chest radiograph shows ill-defined areas of consolidation (*arrows*) in the left lower lobe. **Figure 15.2:** Chest radiograph 6 days later demonstrates new areas of consolidation (*arrows*) in the left upper and right middle lobes and almost complete resolution of the left lower lobe consolidation. The patient was a 54-year-old woman.

includes pulmonary hemorrhage, bronchiolitis obliterans organizing pneumonia (BOOP), and recurrent aspiration.

The radiographic and high resolution computed tomography (HRCT) manifestations of AEP usually comprise extensive bilateral ground-glass opacities (GGOs), patchy areas of consolidation, interlobular septal thickening, thickening of bronchovascular bundles, and bilateral pleural effusions without cardiomegaly [8] (Fig. 15.3). The radiologic differential diagnosis includes hydrostatic pulmonary edema, ARDS, and atypical bacterial or viral pneumonia.

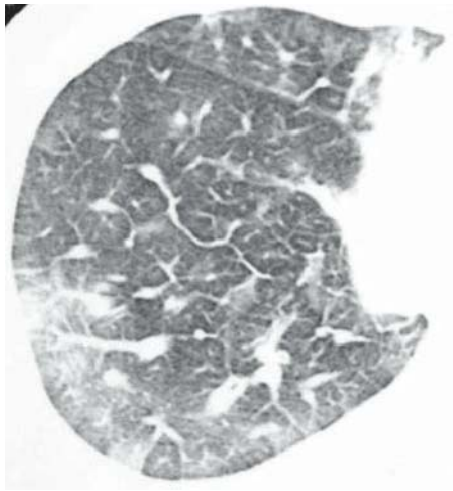


FIGURE 15.3. AEP. View of the right lower lobe from an HRCT shows diffuse GGOs, extensive thickening of the interlobular septa, and small foci of consolidation. Similar findings were present throughout both lungs. (Courtesy of Dr. Kiminori Fujimoto, Kurume, Japan.)

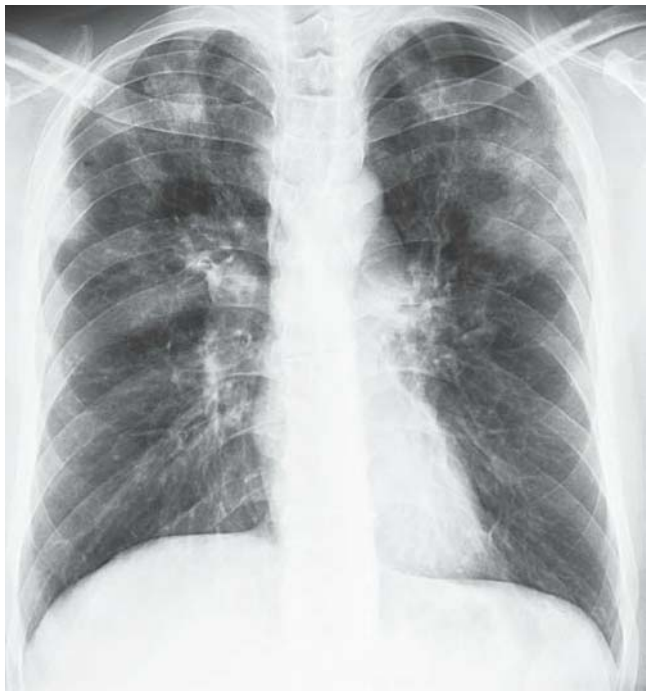


FIGURE 15.4. CEP. Chest radiograph shows bilateral patchy areas of consolidation mainly in the peripheral regions of the upper lobes. The patient was a 32-year-old man.

The classic description of the radiograph of CEP is that of peripheral airspace consolidation ("photographic negative shadow of pulmonary edema") involving mainly the upper lobes (Fig. 15.4).[7] It should be noted, however, that this finding is present in less than 50% of cases. In the remaining patients the peripheral distribution is not apparent on the radiograph but usually present on HRCT, which demonstrates a peripheral predominance of consolidation and GGOs in more than 90% of cases (Fig. 15.5). The main radiologic differential diagnosis is with BOOP and CSS.

In rare cases CEP may result in pulmonary fibrosis (Fig. 15.6).

PATHOLOGIC FEATURES

Simple eosinophilic pneumonia: Few cases are biopsied, but the morphologic picture is that of CEP (see below).

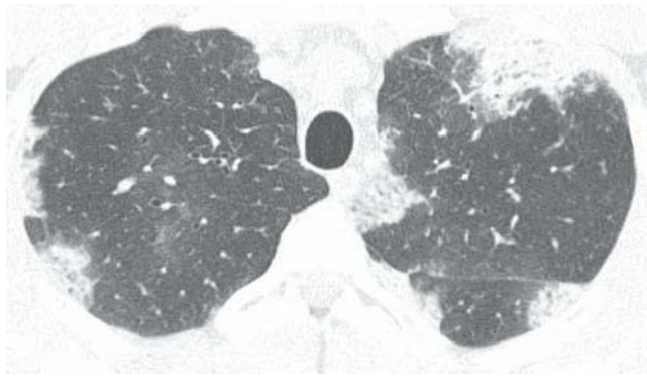


FIGURE 15.5. CEP. HRCT demonstrates peripheral consolidation and GGOs in the apical regions of the upper lobes. The patient was a 31-year-old woman.

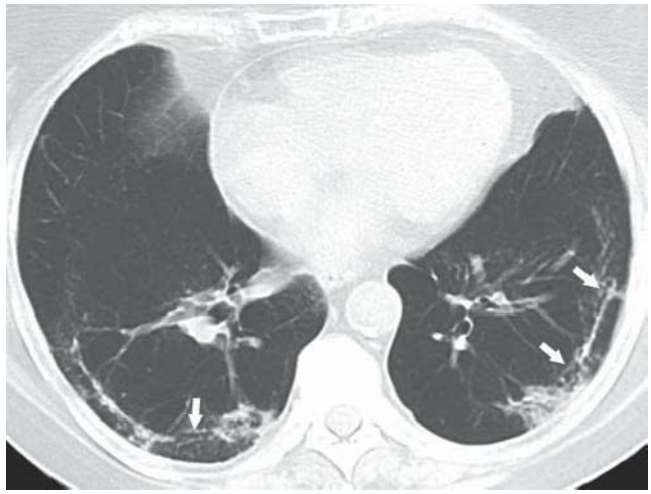
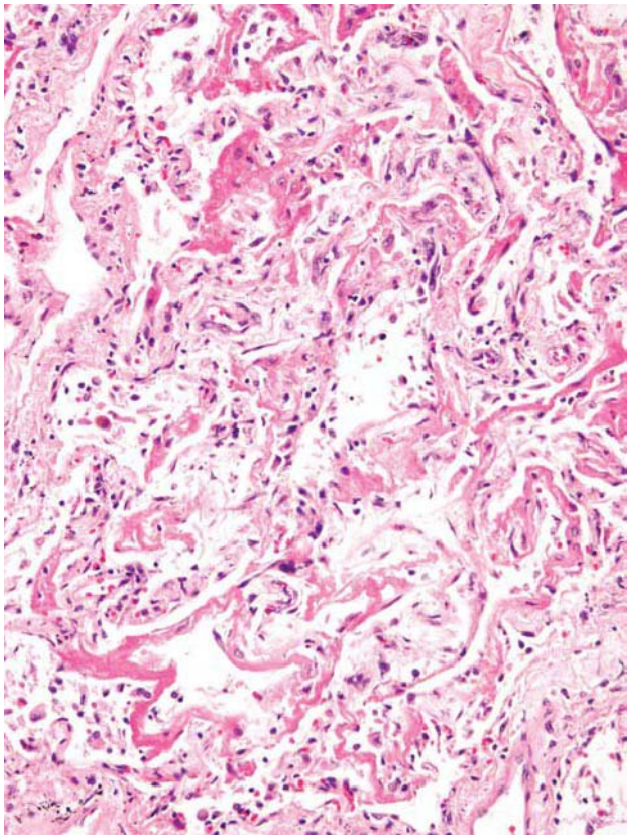
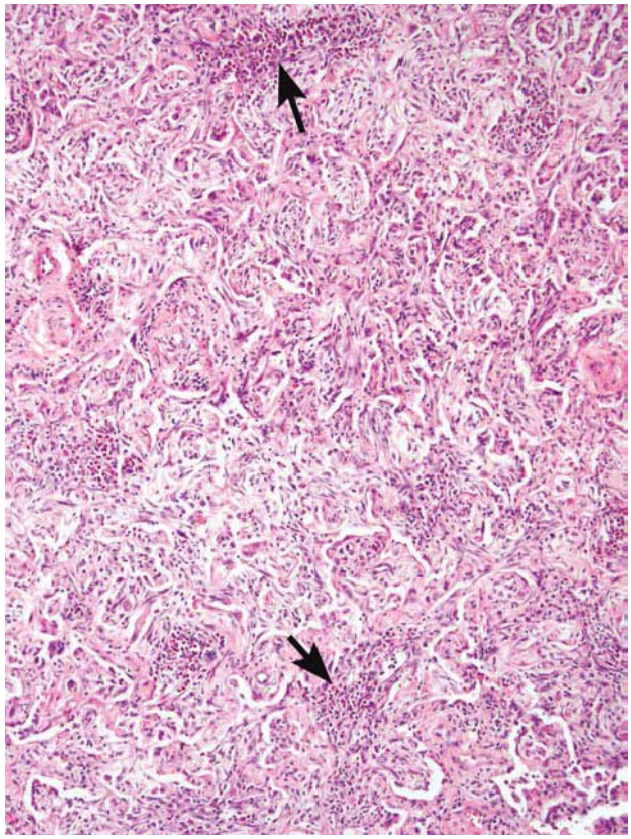
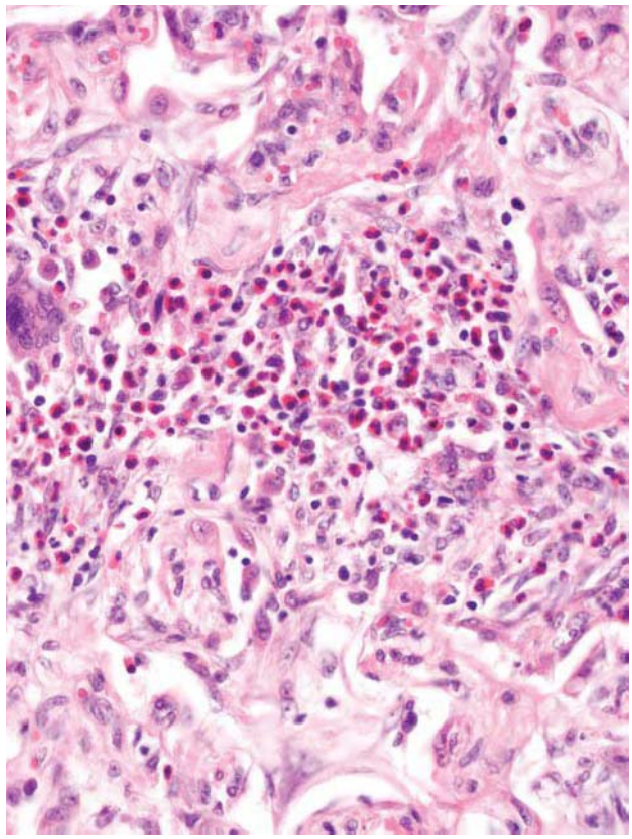


FIGURE 15.6. Fibrotic CEP. Conventional CT image at the level of the lower lung zones shows focal areas of peripheral reticulation and traction bronchiectasis (*arrows*) consistent with fibrosis. Also noted are peripheral band-like opacities and focal GGOs. Surgical biopsy (Figs. 15.24 and 15.25) demonstrated interstitial fibrosis with eosinophils.







FIGURES 15.7 to 15.9. AEP. **Figures 15.7** and **15.8** show what at first appears to be ordinary acute and organizing diffuse alveolar damage. However, there are collections of eosinophils present in **Figures 15.8** (*arrows*) and **15.9**, indicating that this is actually AEP. Patient had received chemotherapeutic agents and developed acute respiratory failure.

Acute Eosinophilic Pneumonia

Morphologically AEP looks like diffuse alveolar damage (DAD) but with added eosinophils[2] (Figs. 15.7 to 15.9) (Table 15.2). In ordinary DAD/ARDS/acute interstitial pneumonia (AIP), eosinophils are extremely rare to nonexistent, so the finding of even a few is noteworthy and should suggest a diagnosis of AEP. The DAD can be in the acute phase with hyaline membranes or demonstrate any morphologic pattern of organization typically seen in DAD (Figs. 15.7 and 15.8 and see Chapter 4). Eosinophils are usually fairly sparse but occasionally are quite numerous and the picture resembles more that of CEP with a few hyaline membranes.

Chronic Eosinophilic Pneumonia

CEP shows a considerable variety of morphologic patterns (Table 15.3). The classic form comprises sheets of eosinophils filling alveolar spaces (Figs. 15.10 and 15.11); that is, it looks like a bacterial pneumonia with eosinophils substituted for neutrophils. In our experience this form is seen as the only pattern in a minority of cases. More frequently there are large numbers of alveolar macrophages mixed with variable numbers of eosinophils (Figs. 15.12 and 15.13).

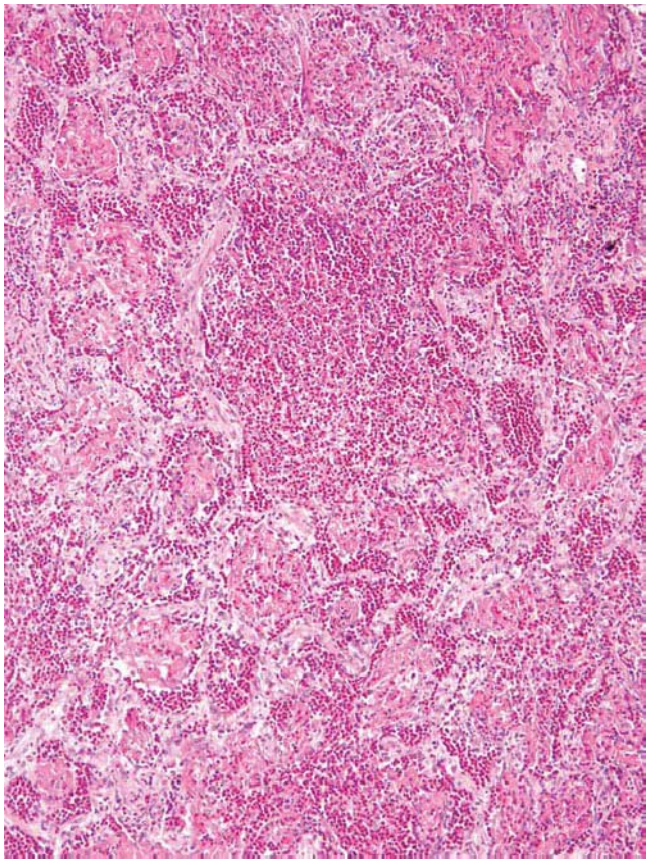
Areas of bronchiolitis obliterans organizing pneumonia (BOOP) are extremely common in CEP (Figs. 15.14 and 15.15; Figs. 5.24 and 5.25; and Figs. 18.18 and 18.19) and some cases look like BOOP at low power (Fig. 18.18). Idiopathic BOOP can have occasional eosinophils, but once eosinophils are readily found (several per high-power field in multiple fields, or sheets of eosinophils) in what appears to be BOOP, a diagnosis of CEP is more likely.

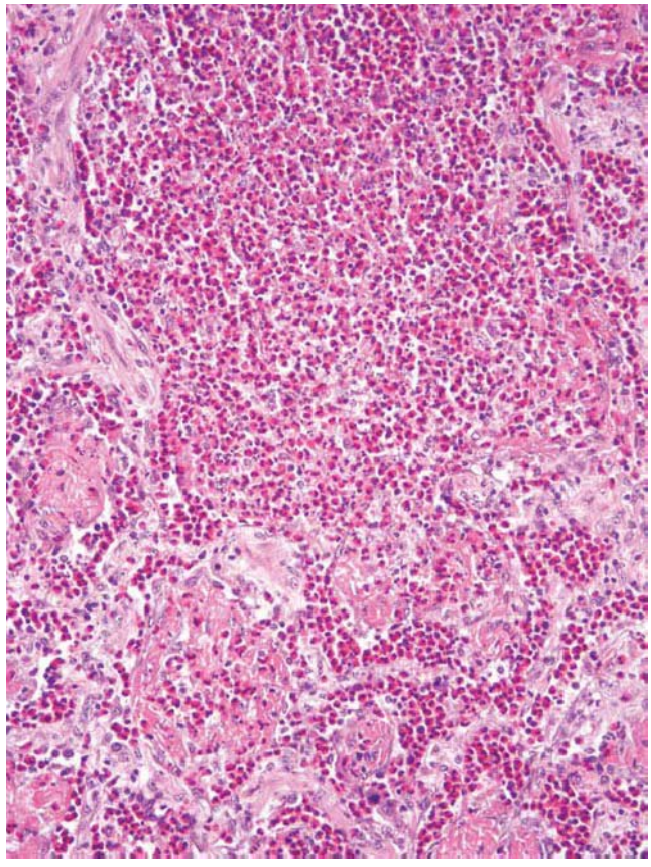
Some cases of CEP demonstrate a fibrinous and organizing pneumonia[9] picture comprising large amounts of alveolar fibrin mixed to a greater or lesser degree with BOOP-like granulation tissue (Figs. 15.16 and 15.17 and see Chapter 5 for a description of the fibrinous and organizing pneumonia pattern), whereas others mimic cellular nonspecific interstitial pneumonia (NSIP) (Figs. 15.18). The presence of eosinophils indicates the correct diagnosis.

Noncaseating granulomas are found in 10% to 20% of CEP cases (Fig. 15.19). Necrosis of eosinophils (Fig. 15.20) with a giant cell or epithelioid histiocyte response producing a granulomatous pattern (Figs. 15.21 and 15.22) is seen in approximately 15% of cases.[10] This pattern is not, per se, indicative of underlying Churg-Strauss syndrome (CSS).[4]

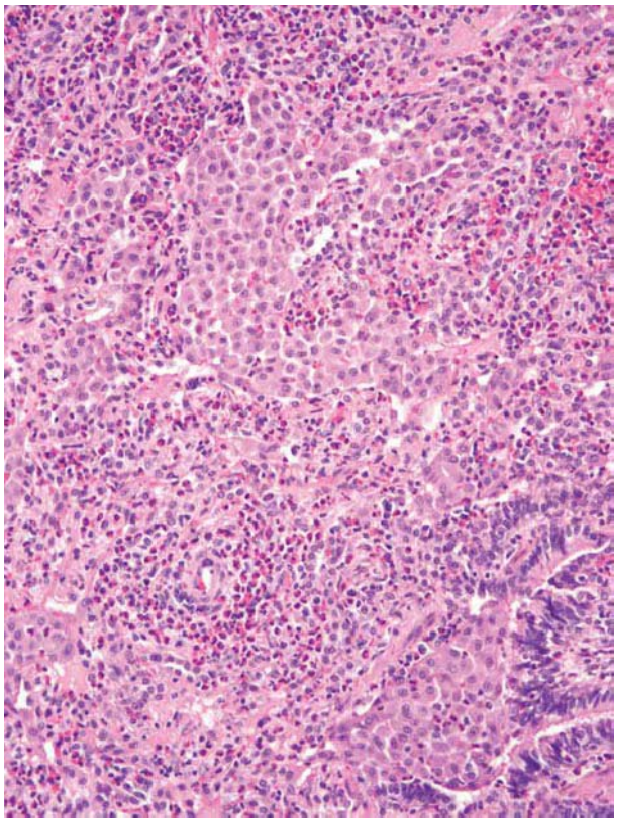
Minor degrees of infiltration of vessels by eosinophils and chronic inflammatory cells (Fig. 15.23) are a frequent finding in CEP and also are not indicative of CSS or underlying vasculitis.

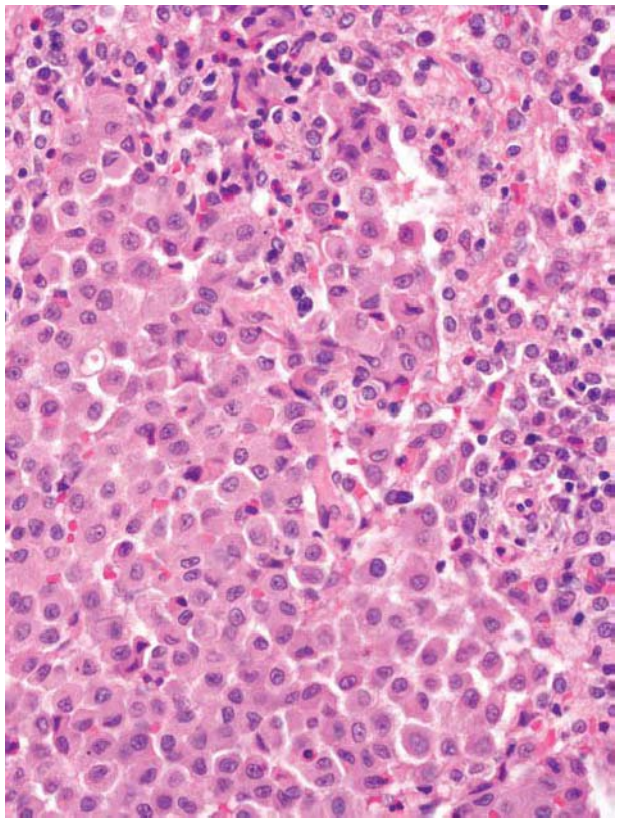
CEP tends to wax and wane and to appear in different areas of the lung over time; however, if the disease keeps



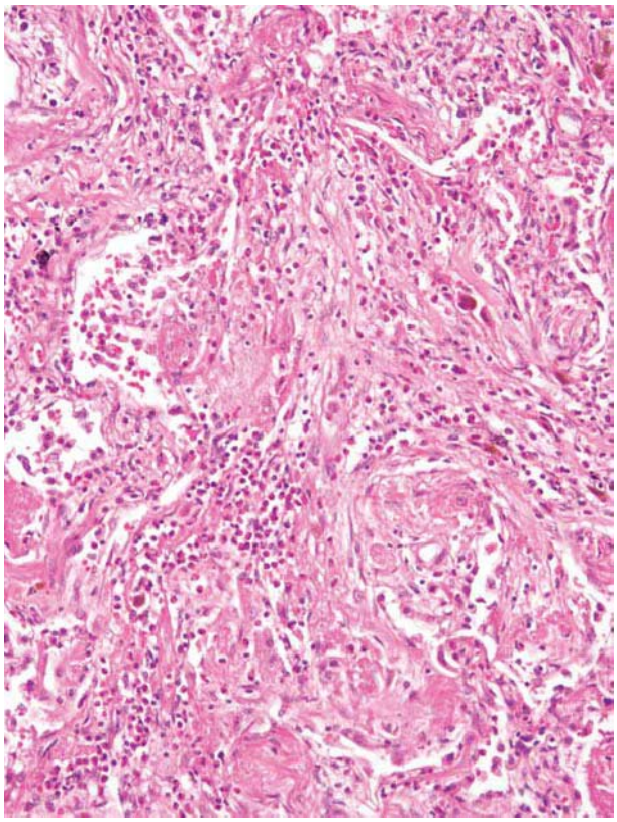


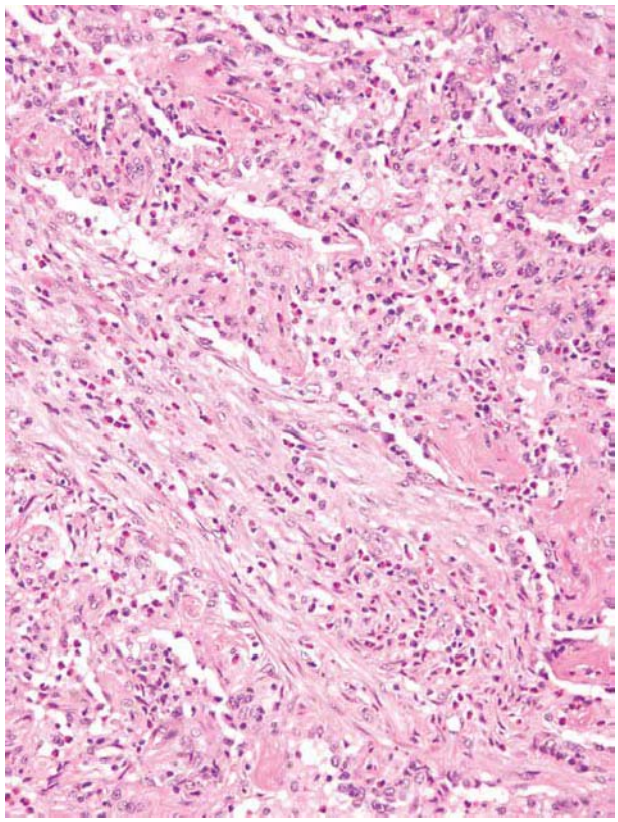
FIGURES 15.10 and 15.11. Classic pattern of CEP showing sheets of eosinophils filling airspaces. Patient cultivated mushrooms and mushroom exposure was believed clinically to be the source of his disease.



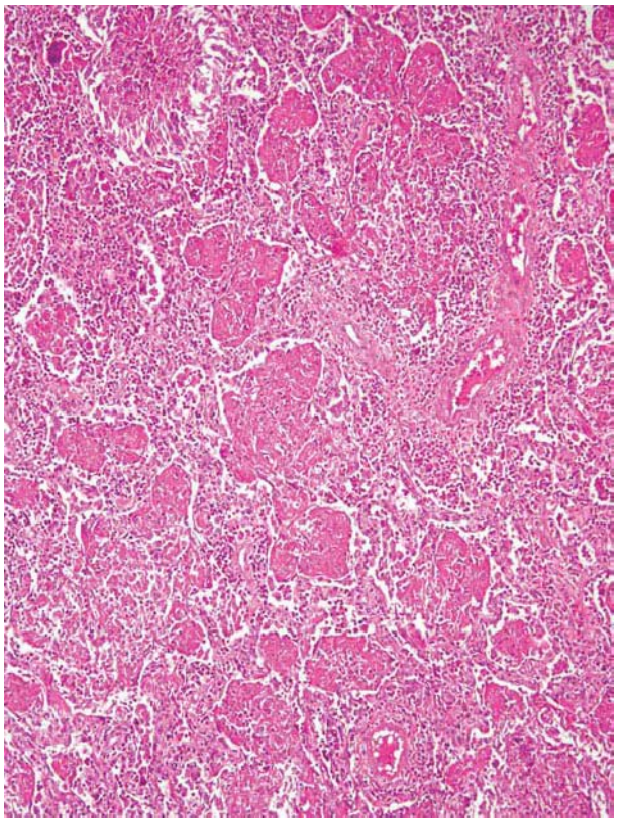


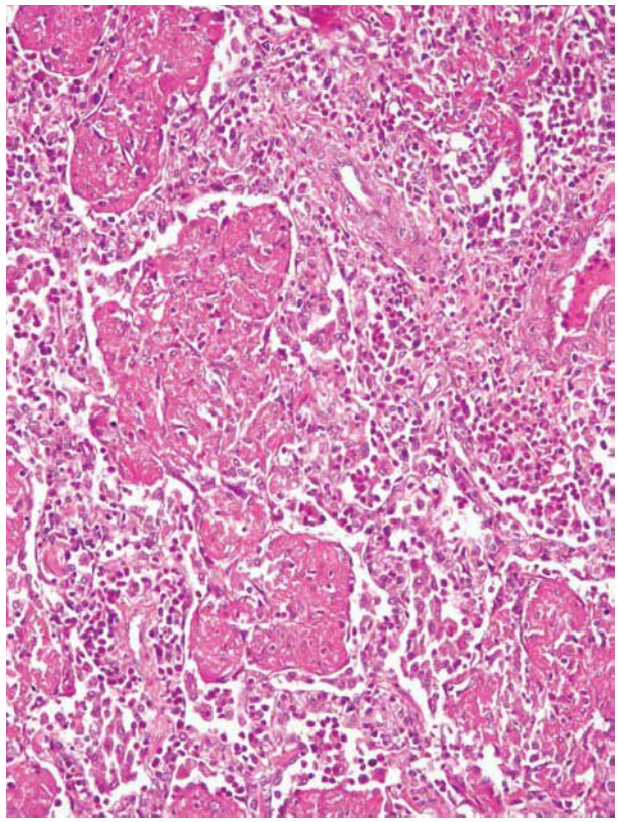
FIGURES 15.12 and 15.13. Pattern of CEP in which there are numerous airspace macrophages. Taken out of context, **Figure 15.13** could be mistaken for desquamative interstitial pneumonia (DIP) because DIP typically has a few eosinophils; however, CEP and DIP are completely different on imaging, and DIP never has the number of eosinophils seen in Figure 15.12. Patient developed SOB and consolidation after taking erythromycin.





FIGURES 15.14 and 15.15. Areas of BOOP in CEP. This is a very common finding and some cases of CEP microscopically look mostly like BOOP. **Figure 15.14** has admixed fibrin ("fibrinous and organizing pneumonia" pattern).





FIGURES 15.16 and 15.17. Marked airspace fibrin deposition in CEP ("fibrinous and organizing pneumonia" pattern). Cases like this should be simply reported as CEP.

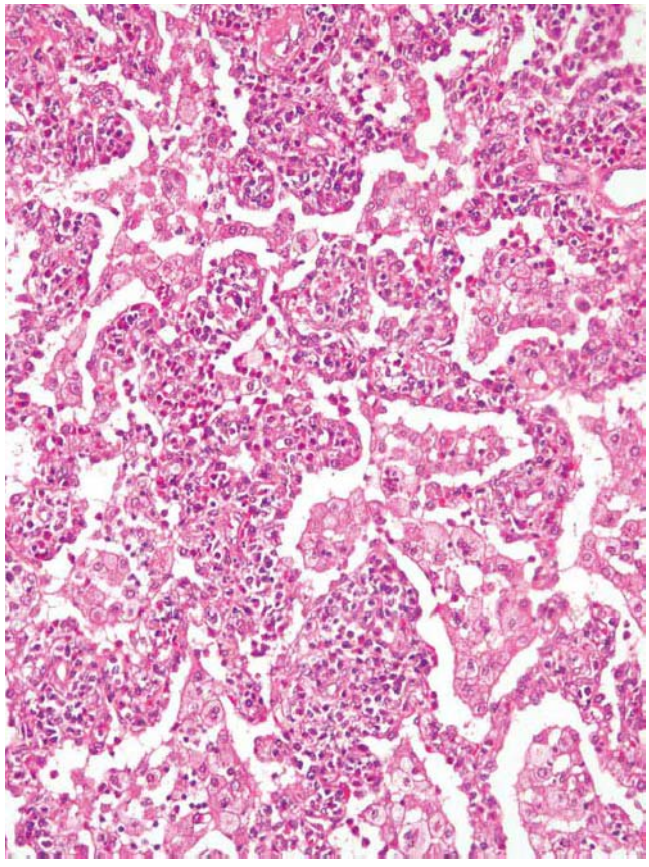


FIGURE 15.18. CEP mimicking cellular NSIP.

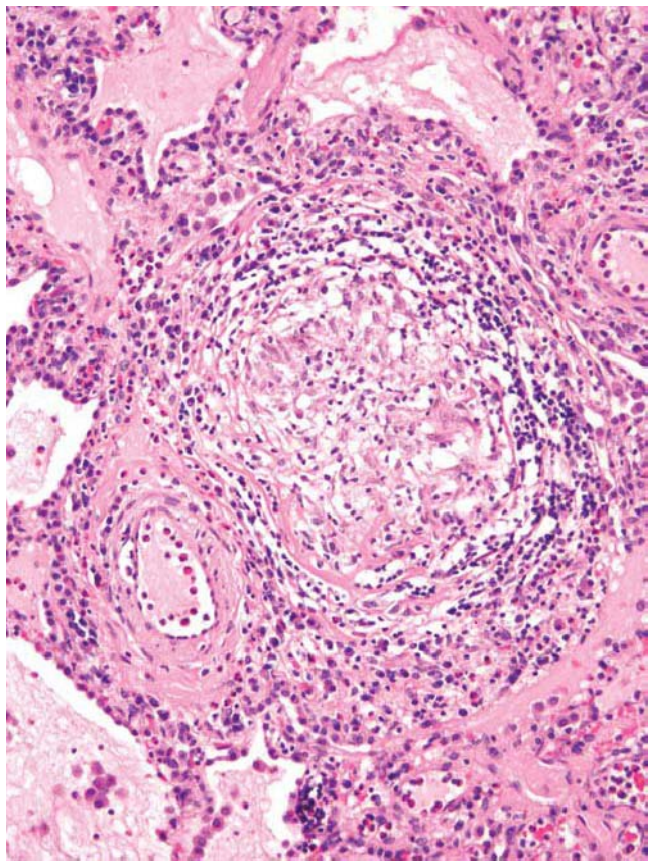


FIGURE 15.19. A noncaseating granuloma in the same case as Figures 15.12 and 15.13.

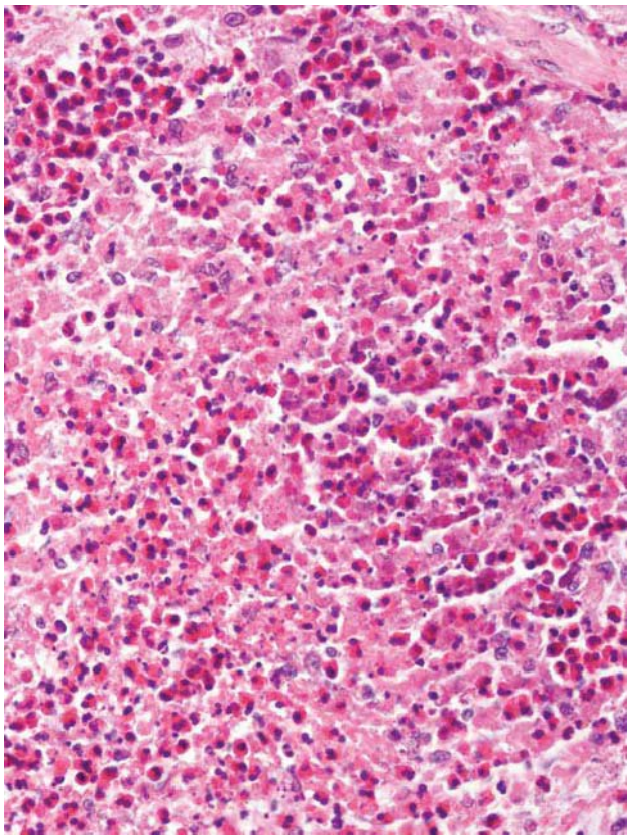
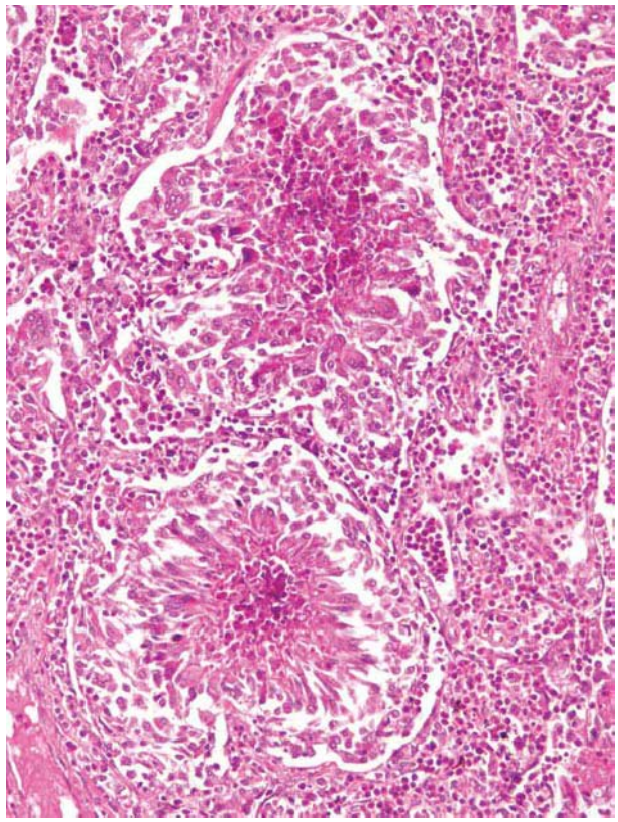
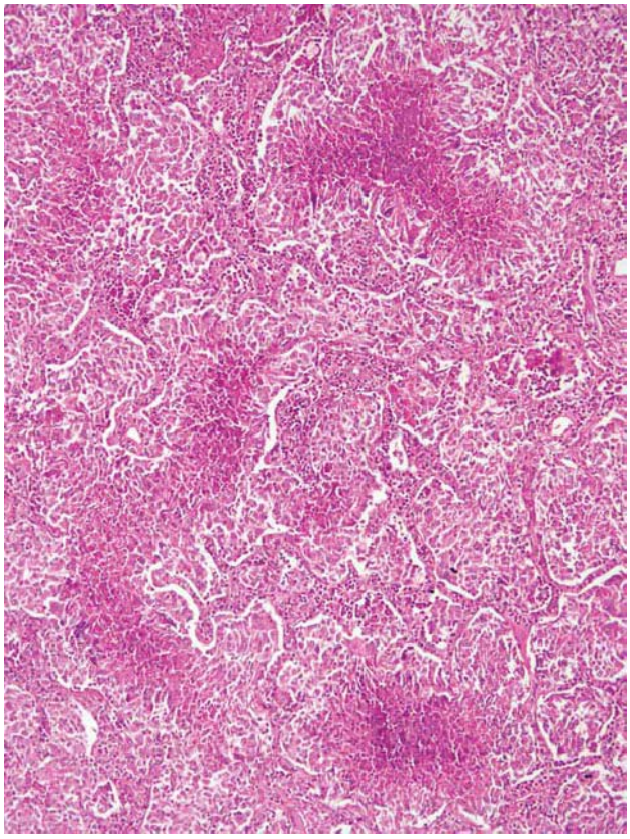


FIGURE 15.20. Early eosinophil necrosis in CEP.



FIGURES 15.21 and 15.22. Areas of eosinophil necrosis with a granulomatous response. This is a common finding in CEP and does not change the diagnosis to CSS.



FIGURES 15.21 and 15.22. Legend appears on next column

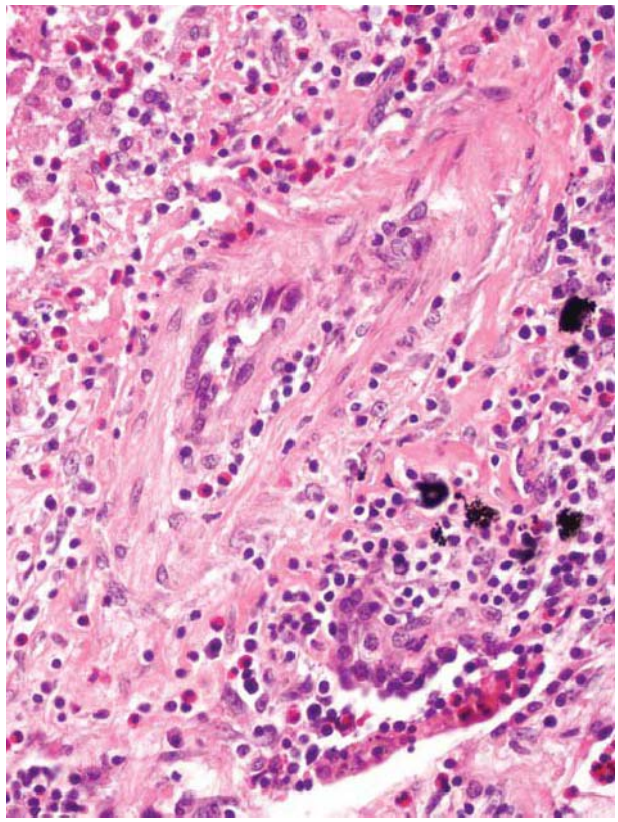
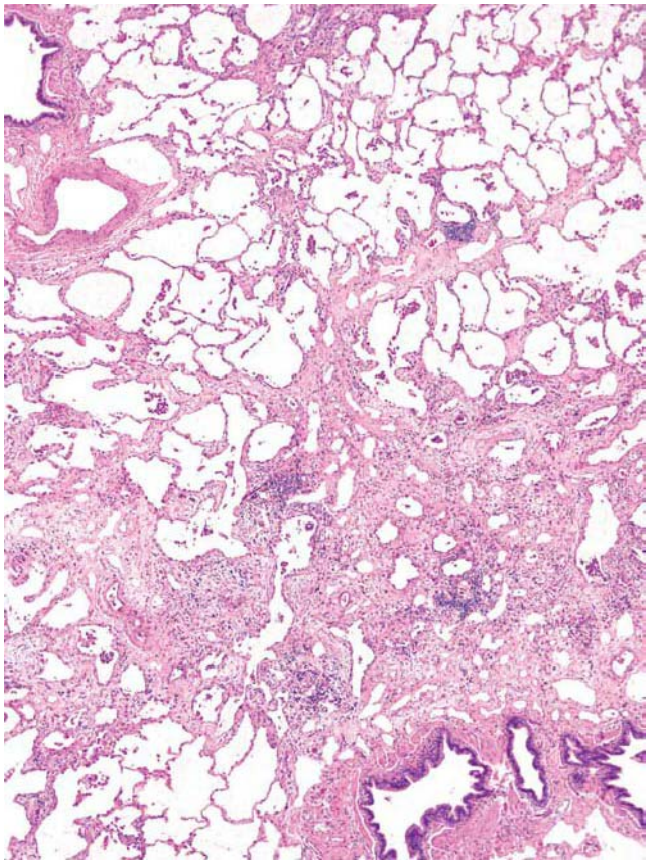
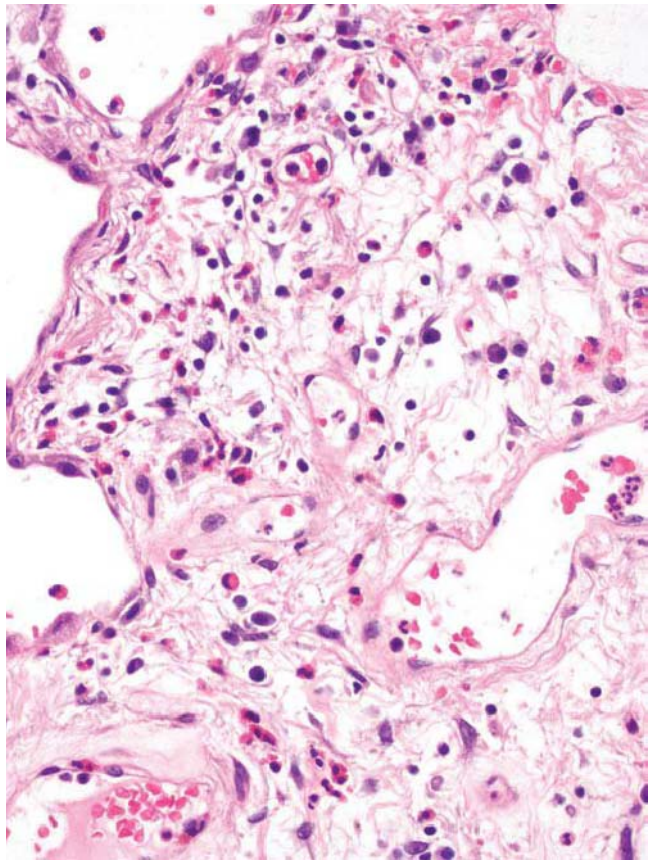


FIGURE 15.23. Vascular infiltration in CEP. Minor degrees of vascular infiltration such as this are common and do not indicate a diagnosis of vasculitis.





FIGURES 15.24 and 15.25. Fibrotic form of CEP. At low power the process somewhat resembles the patchy fibrosis of UIP and fibroblast foci are also present (not shown), but at high power (**Fig. 15.25**), there are numerous eosinophils. Same case as Figure 15.6.

recurring in the same area it can lead to fibrosis. There is very little in the literature on the patterns of fibrosis in CEP; in our experience such cases can look more or less like fibrotic NSIP or have a patchy pattern of fibrosis somewhat mimicking UIP but mixed with eosinophils (Figs. 15.24 and 15.25). Fibroblast foci may be present.

Effects of Treatment on Morphologic Appearances

Eosinophils are exquisitely sensitive to steroids and undergo apoptosis in a dramatic and rapid fashion. If a biopsy is performed even 1 or 2 days after starting treatment with high dose steroids, eosinophils can be very sparse. In this situation a history of migratory peripheral consolidation on imaging or a high lavage or serum eosinophil count are important clues to the correct diagnosis.

DIAGNOSTIC MODALITIES

Given an appropriate clinical and imaging setting, CEP can sometimes be diagnosed without need for a biopsy. Transbronchial biopsy is sometimes diagnostic (see Figs. 18.17 to 18.19), but in most cases video-assisted thoracoscopic surgery (VATS) biopsy is used. As is true of AIP/ARDS, AEP is more difficult to diagnose on transbronchial biopsy because the diagnostic features (eosinophils) may be focal; however, given a patient with a clinical and imaging picture of ARDS, a transbronchial biopsy showing DAD and eosinophils would allow a definitive diagnosis.

DIFFERENTIAL DIAGNOSIS

Major differential diagnoses are listed in Table 15.4. The morphologic distinction between DAD representing AEP and DAD representing AIP/ARDS depends entirely on the

Table 15.4

Morphologic differential diagnosis of eosinophilic pneumonias

AEP	Diffuse alveolar damage (AIP/ARDS)
CEP	BOOP
	Langerhans cell histiocytosis (LCH)
	Hodgkin disease
	Reactive eosinophilic pleuritis
	DIP
	CSS
	Allergic bronchopulmonary aspergillosis

finding of eosinophils in the former. The underlying patterns of DAD are not distinguishable.

The most important differential diagnosis of CEP is BOOP, and occasionally a VATS biopsy in a patient with peripheral consolidation on imaging shows BOOP with a small increase in eosinophils but not enough to be overtly diagnosable as CEP. In that setting we recommend making a comment to the effect that CEP should be considered; this alerts the clinician to look for blood eosinophilia and also for a potential offending agent.

LCH (Chapter 10) may have numerous eosinophils but the cellular nodules primarily comprise S-100/CD1a positive Langerhans cells; there are often smoker's macrophages mixed in, and the nodules center on small airways (see Figs. 10.6 to 10.10).

Hodgkin disease in the lung has a lymphocytic background with a few eosinophils but Reed–Sternberg cells are also present; the lesions are typically nodular and center around the bronchovascular bundles.

Reactive eosinophilic pleuritis (see Figs. 10.32 and 10.33) may also have large numbers of eosinophils, but they are confined to the pleural space and there is no underlying lung disease, or only apical blebs.

DIP (Chapter 8) usually has small numbers of eosinophils mixed with the alveolar macrophages or in the interstitium (see Figs. 8.12 and 8.13), and a given field of DIP and CEP may be indistinguishable (compare Figs. 8.13, 15.12, and 15.13); however, in most cases of CEP there are areas with considerably greater numbers of eosinophils and in doubtful cases imaging will solve the problem.

The separation of CEP, CSS, and ABPA is sometimes morphologically problematic, as all three conditions can produce a picture of CEP (Table 15.5). Some cases of CSS are difficult to separate from CEP because asthma is present in 100% of CSS patients and many CEP patients, and both conditions are associated with blood eosinophilia (Table 15.5). Many, but not all, CSS patients have evidence of systemic vasculitis and a positive ANCA,[4] findings that do not occur in CEP.

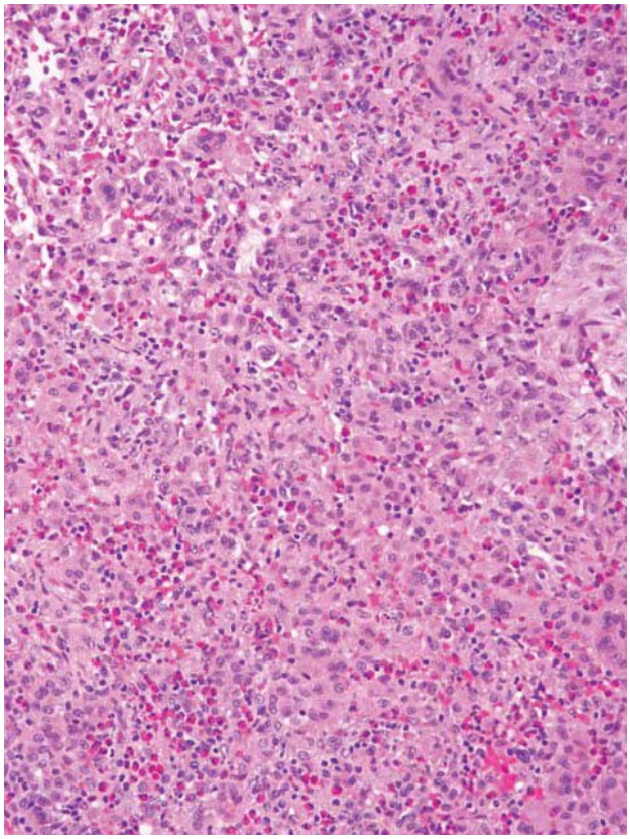
Morphologically CSS in the lung can be identical to CEP (Fig. 15.26), or it can have a picture of CEP with true vasculitis. Necrosis of eosinophils with or without a granulomatous response is seen in both CSS and ordinary CEP and is not useful as a diagnostic separator. As noted above, minor degrees of vascular infiltration by eosinophils and lymphocytes is common in CEP (Fig. 15.23) and does not constitute vasculitis. Features that suggest a true vasculitis are necrosis of vessel walls, marked infiltration of vessel walls by eosinophils in the midst of CEP-like area, or infiltration of vessel walls by eosinophils away from areas of CEP (Fig. 15.27).

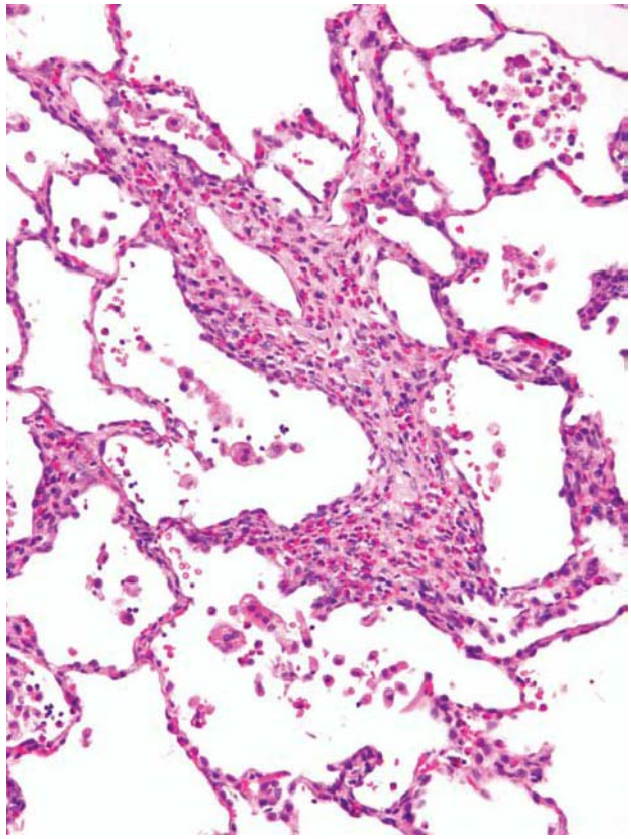
Table 15.5

Separation of CEP, CSS, and ABPA

Feature	CEP	CSS	ABPA
Asthma	25%–50% of cases	100% of cases	Almost all cases[a]
Blood eosinophilia	>90% of cases	100% of cases	Yes
Elevated IgE	Yes	Yes	Very high
Serum precipitins against *Aspergillus*	No	No	Yes
Cutaneous reaction to injected *Aspergillus* antigen	No	No	Yes
ANCA	Negative	p-ANCA 50% of cases	Negative
Imaging	Consolidation, typically peripheral	Often consolidation, may be peripheral	Central mucoid impaction and bronchiectasis
Pathologic picture of eosinphilic pneumonia,	Yes	Often	Usually a minor component[b]
True vasculitis	No[c]	Sometimes	No
Bronchiectasis	No	No	Yes
Mucoid impaction	No	No	Yes[b]
Bronchocentric granulomatosis	No	No	Yes[b]
Cellular bronchiolitis with eosinophils	No	No	Yes[b]

[a]ABPA is also seen in patients with cystic fibrosis who are not asthmatic.
[b]Any of these features may or may not be present in a given case of ABPA.
[c]CEP may show minor degrees of vascular infiltration within the lesions.





FIGURES 15.26 and 15.27. CSS. Parts of the biopsy show a morphologic picture that is indistinguishable from ordinary CEP (**Fig. 15.26**); however, there is also marked infiltration of vessel walls by eosinophils away from areas of eosinophilic pneumonia (**Fig. 15.27**), indicating that the correct diagnosis is CSS.

ABPA is a hypersensitivity reaction to ambient fungi, and the sensitizing agent is almost always aspergillus.[5] Most cases of ABPA occur in asthmatics, but some occur in patients with cystic fibrosis who are not asthmatic (Table 15.5). Pathologically, eosinophilic pneumonia, which is morphologically indistinguishable from ordinary CEP, is one of the changes that can be seen in ABPA, but it is usually a minor component and is absent in many cases. Central bronchiectasis with or without mucoid impaction is more common than eosinophilic pneumonia, and there may also be bronchocentric granulomatosis or bronchiolitis, typically associated with eosinophils.

PROGNOSIS

Simple eosinophilic pneumonia is, more or less by definition, a self-limited process. AEP responds dramatically and rapidly to steroids and the usual definition of AEP includes a statement that the disease does not relapse after steroids are discontinued.[1,6] As most other forms of ARDS/AIP are resistant to steroids, correct identification of AEP on biopsy is crucial to treatment. CEP also responds rapidly to steroids, but a significant proportion of patients have a relapse after steroids are tapered, although most again resolve when steroids are reinstituted.[1]

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CHAPTER

16

Pulmonary Alveolar Proteinosis

CLINICAL FEATURES

The clinical features of pulmonary alveolar proteinosis (PAP) are nonspecific and include cough, shortness of breath (SOB), malaise, and sometimes chest pain or weight loss, usually developing in an indolent fashion. Chest examination is frequently unremarkable, although crackles, clubbing, and cyanosis have occasionally been reported. Most studies have not shown an association with smoking, but some patients have a history of dust exposure.[1,2]

ETIOLOGY AND SUBCLASSIFICATION

All forms of PAP represent a failure of clearance of surfactant. Surfactant is secreted by type II cells and normally degraded by alveolar macrophages. Alveolar macrophages require granulocyte–macrophage-colony stimulating factor (GM-CSF) to degrade surfactant and for several other functions. PAP is subclassified by whether the macrophage defect is primary or secondary (Table 16.1).[7,8] As many as 90% of PAP cases are primary (also called acquired or autoimmune) and are associated with circulating anti-GM–CSF antibodies[1,7,8]; a small percentage is caused by mutations in genes for GM-CSF receptors or surfactant proteins, and the remainder, classified as secondary, has a variety of associations.

Table 16.1

Etiologic classification of pulmonary alveolar proteinosis

- Primary (also called acquired or autoimmune): caused by anti-GM-CSF antibodies
- Hereditary (mutations in GM-CSF receptors, surfactants A and B, ABCA3 genes)
- Secondary
  - Associated with hematologic malignancies, especially leukemias and myelodysplastic syndromes
  - Caused by inhalation of very high levels of very finely divided dust
    - Silica (called silicoproteinosis or acute silicosis)[3]
    - Aluminum[4]
    - Indium[5]
    - Titanium dioxide[6]
- Drug reactions (see Chapter 18 and pneumotox.com)
- Occasionally seen in fibrosing interstitial pneumonias as a local phenomenon

IMAGING

The chest radiograph usually shows patchy bilateral areas of consolidation. The characteristic high-resolution computed tomography (HRCT) manifestation comprises bilateral hazy areas of increased density (ground-glass opacities, GGOs) with a superimposed fine linear pattern owing to interlobular septal thickening, a combination known as crazy-paving pattern[9] (Fig. 16.1). Although this pattern is relatively nonspecific, in patients with chronic symptoms it should raise the possibility of PAP.

PATHOLOGIC FEATURES

Grossly, PAP appears as yellow homogeneous soft material that fills airspaces; the process can be quite patchy (Fig. 16.2). The characteristic microscopic feature of PAP is filling of alveolar spaces by coarsely granular eosinophilic material that frequently contains rounded or elongated dense bodies (possibly representing dead

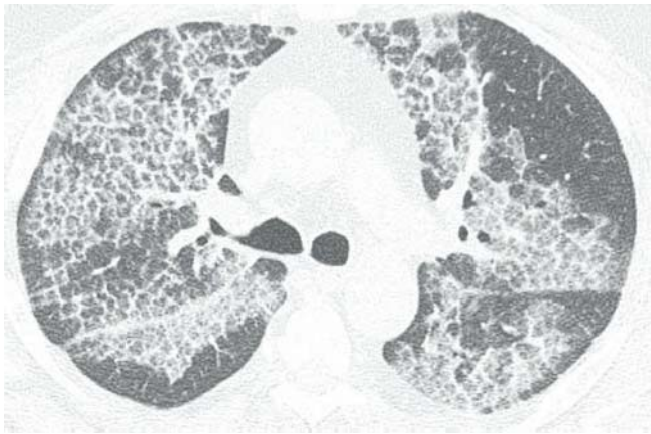


FIGURE 16.1. HRCT scan showing GGOs and interlobular septal thickening ("crazy paving"), typical of PAP.

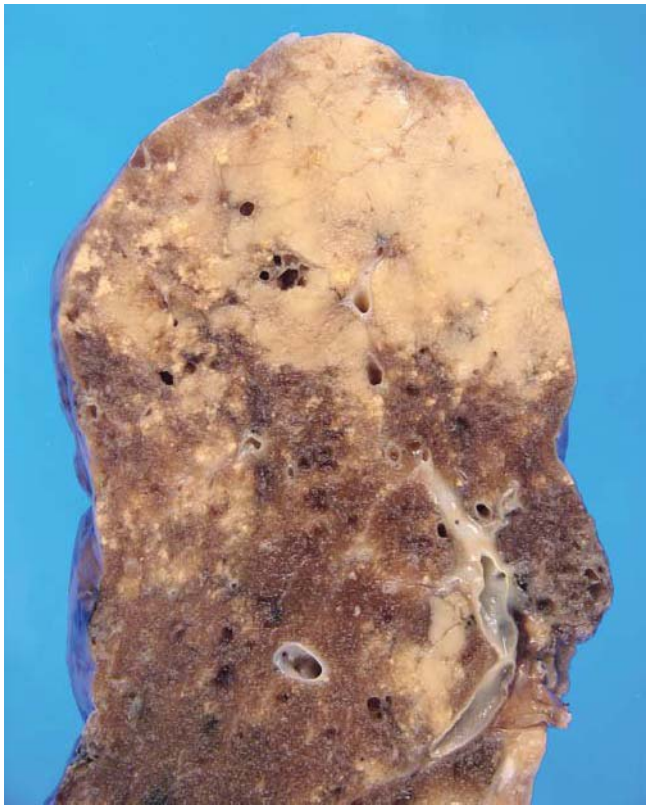


FIGURE 16.2. Gross appearance of PAP characterized by soft yellow material completely filling the airspaces in a localized area. (Case Courtesy Dr. Julia Flint.)

macrophages) (Figs. 16.3 to 16.5). Cholesterol clefts and small numbers of foamy macrophages may also be present in the granular material. Proteinosis material is strongly digested periodic acid–Schiff (dPAS) positive (Fig. 16.6) and this is useful for distinguishing it from edema fluid, which is dPAS negative (Fig. 16.13).

Mild degrees of interstitial inflammation and/or very mild interstitial fibrosis that just thicken alveolar walls are occasionally present, more often—in our experience—in secondary forms of PAP than in primary forms (Figs. 16.7 and 16.8).

Silicoproteinosis typically has a mild chronic interstitial infiltrate and polarization may reveal fine pale orange birefringent particles of silica (Fig. 16.9), but in some cases the silica particles are too small to be seen by light microscopy. Other dusts that have been reported to cause proteinosis are too finely divided to be visible by light microscopy, although they can be detected by electron microscopy (Fig. 16.10).

DIFFERENTIAL DIAGNOSIS

Edema fills airspaces with eosinophilic material that is smooth or very finely granular rather than coarsely granular, may show chatter artifact from cutting, and is dPAS negative (Figs. 16.11 to 16.13).

Pneumocystis is characterized by filling of airspaces by foamy rather than granular material (Fig. 16.14), and organisms are visible on silver stains.

Marked interstitial fibrosis or chronic inflammation or distortion of the underlying lung architecture by fibrosis suggests another underlying process such as fibrosis secondary to a chemotherapeutic agent or a fibrosing interstitial pneumonia in which the proteinosis may be a local finding.

DIAGNOSTIC MODALITIES

Transbronchial biopsy can be used to diagnose PAP (Figs. 16.15 and 16.16), but areas with PAP can be patchy and may be missed on transbronchial biopsy. Microscopic examination of bronchoalveolar lavage fluid can also be used: the finding of granular dPAS positive material that looks like proteinosis material as seen in histologic sections confirms the diagnosis (Figs. 16.17 and 16.18).

TREATMENT AND PROGNOSIS

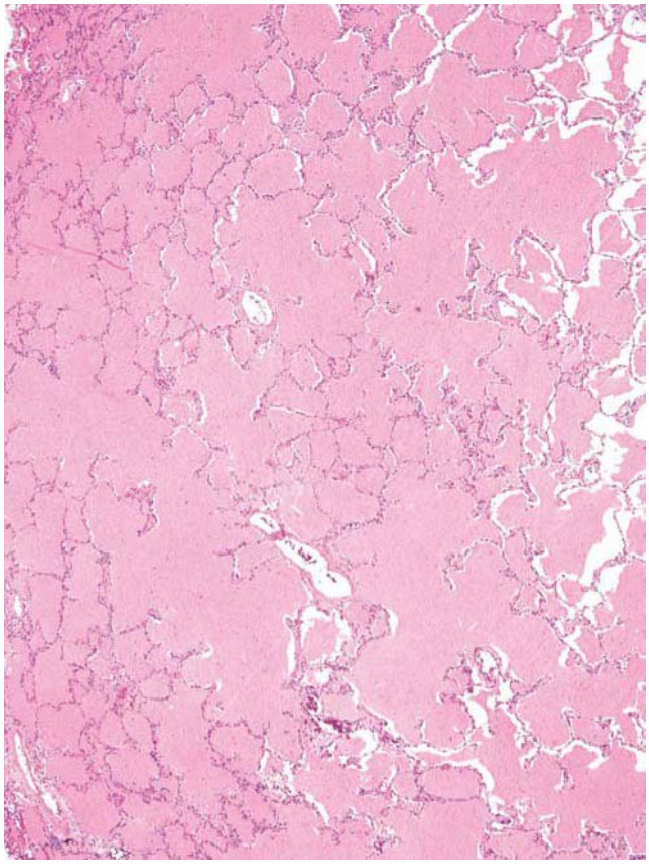
Primary (autoimmune) PAP is usually treated by large volume (whole lung) bronchoalveolar lavage. This is effective in most cases, but recurrence rates up to 70% have been reported and lavage may need to be repeated. Treatment with GM–CSF has also been employed but is expensive. More recently rituximab has been reported to be effective in a handful of cases.[1] The prognosis of primary PAP is good with 5-year survivals of 85% to 94%,[10,11] but these figures may be biased by inclusion of older cases; in newer material the survival rate is typically 100%.[1]

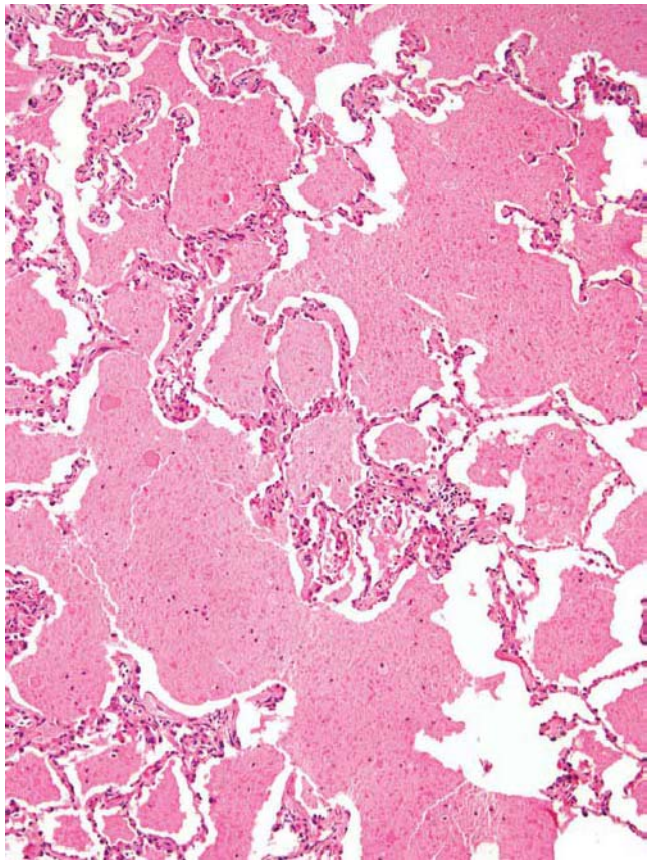
The prognosis of hereditary PAP depends on the exact mutation; some are lethal. The prognosis of secondary PAP depends on the underlying cause of the process, particularly in patients with underlying malignancies; recent data suggest the prognosis in such patients is poor.[2] The prognosis of silicoproteinosis is also poor, even with lavage.[3]

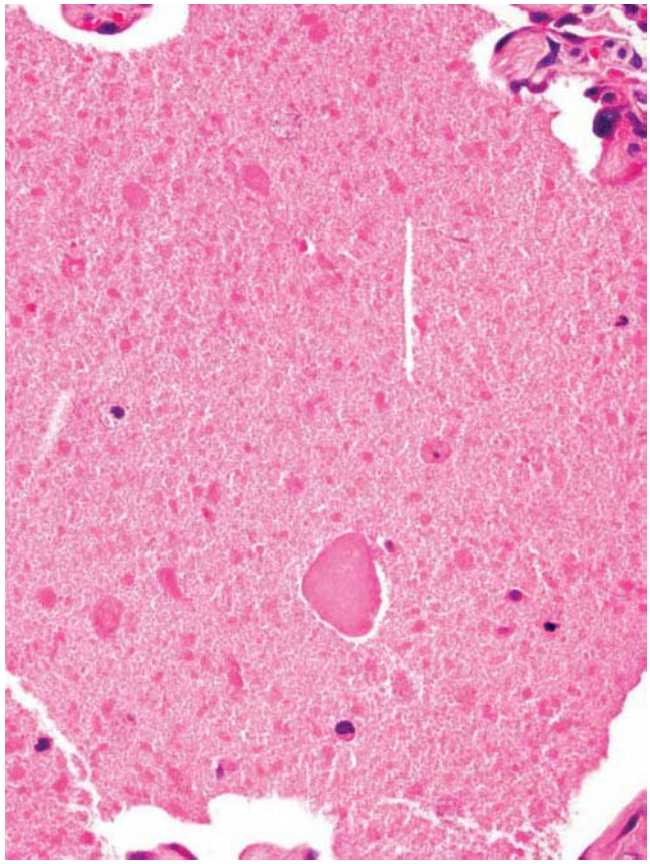
Proteinosis as an incidental local finding in a fibrosing interstitial pneumonia probably has no prognostic significance.

COMPLICATIONS

Infection with opportunistic organisms such as *Nocardia*, *Aspergillus*, *Mycobacterium tuberculosis*, atypical mycobacteria, and pneumocystis may occur,[1] either because the lack of GM–CSF leads to defects in macrophage killing of organisms, or because the PAP material serves as a culture medium.







FIGURES 16.3 to 16.5. PAP showing filling of airspaces by coarsely granular eosinophilic material. Note the absence of interstitial inflammation and interstitial fibrosis: this is the typical finding in most cases of PAP. At high power (**Fig. 16.5**) the proteinosis material is distinctly granular and contains more densely eosinophilic structures that may represent the remains of alveolar macrophages.

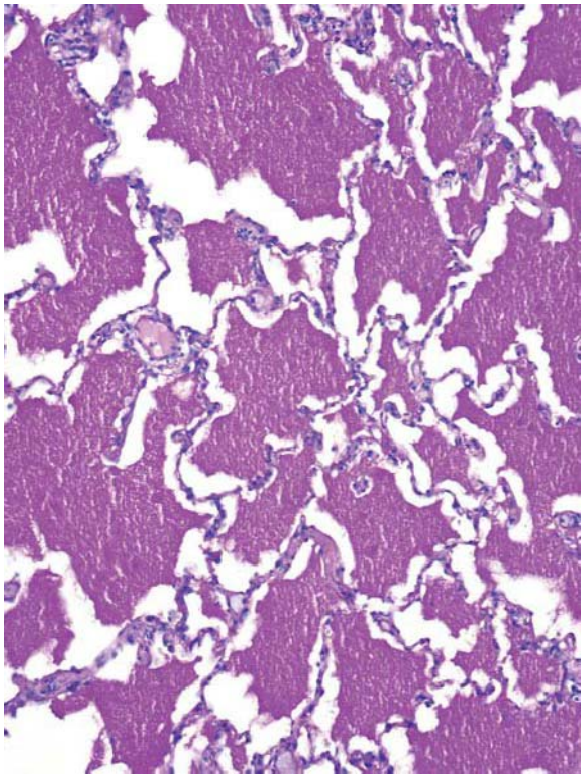
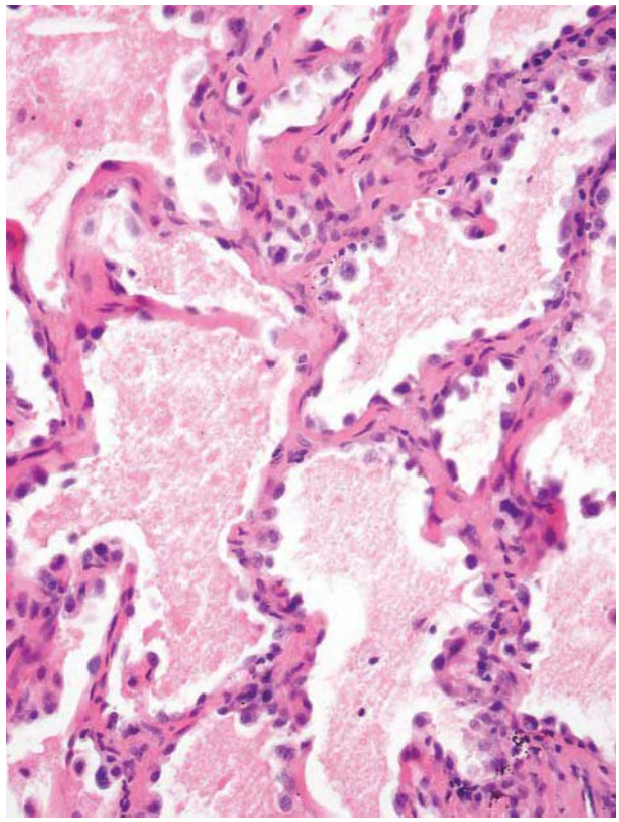
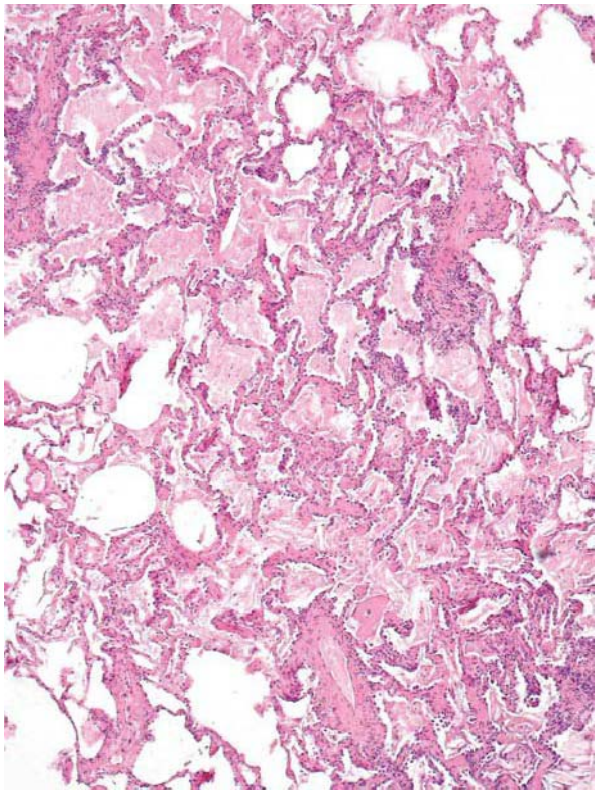


FIGURE 16.6. Digested PAS stain shows intense staining of the proteinosis material. Digested PAS stain is useful for separating PAP from pulmonary edema, which is PAS negative (compare Fig. 16.13).



FIGURES 16.7 and 16.8. Alveolar proteinosis in a patient treated with Busulfan for a hematologic malignancy. In this example there is fine interstitial fibrosis that may be part of the PAP but may also reflect Busulfan toxicity.



FIGURES 16.7 and 16.8. Legend appears on next column

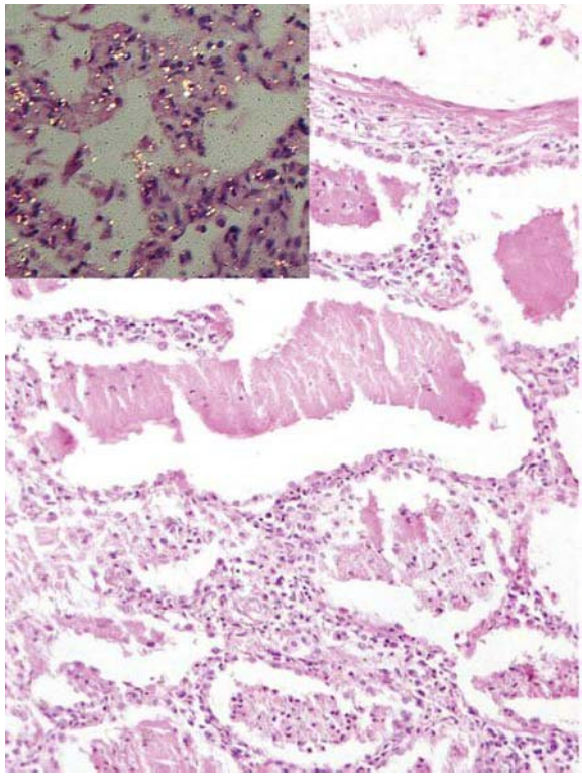


FIGURE 16.9. Silicoproteinosis (also called acute silicosis). In silicoproteinosis there is an interstitial chronic inflammatory infiltrate. Inset shows birefringent silica particles.

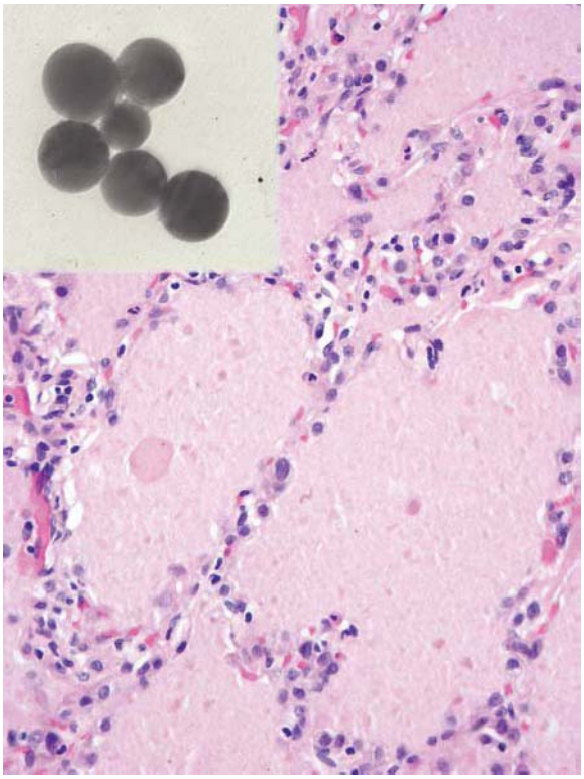
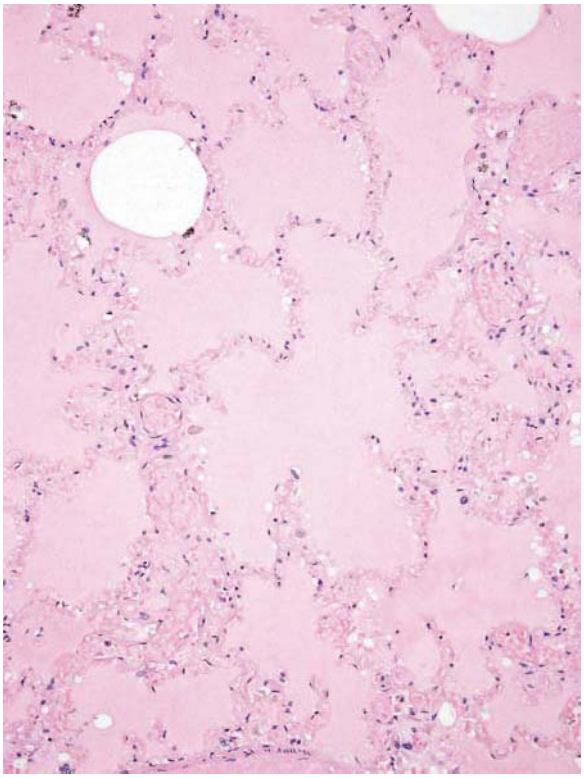
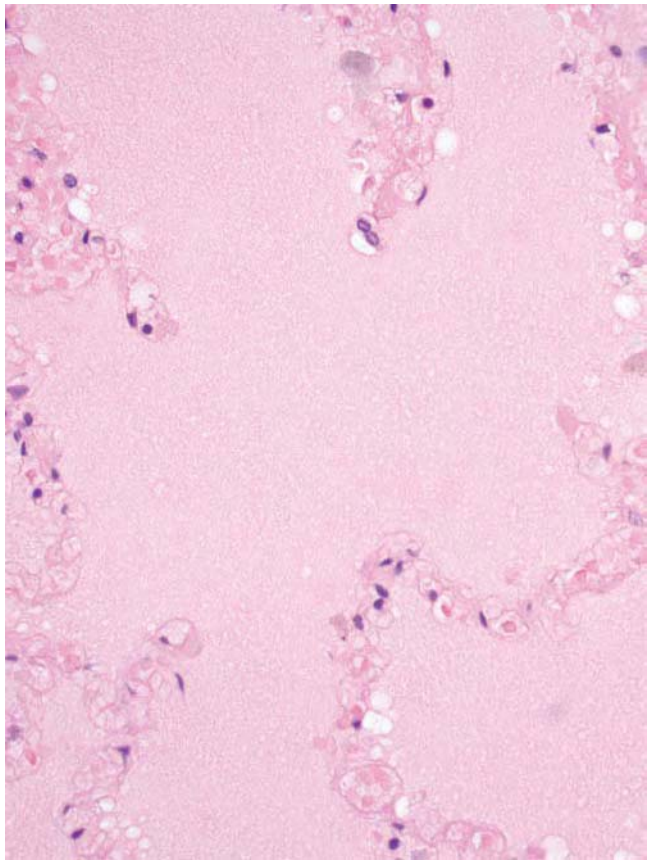
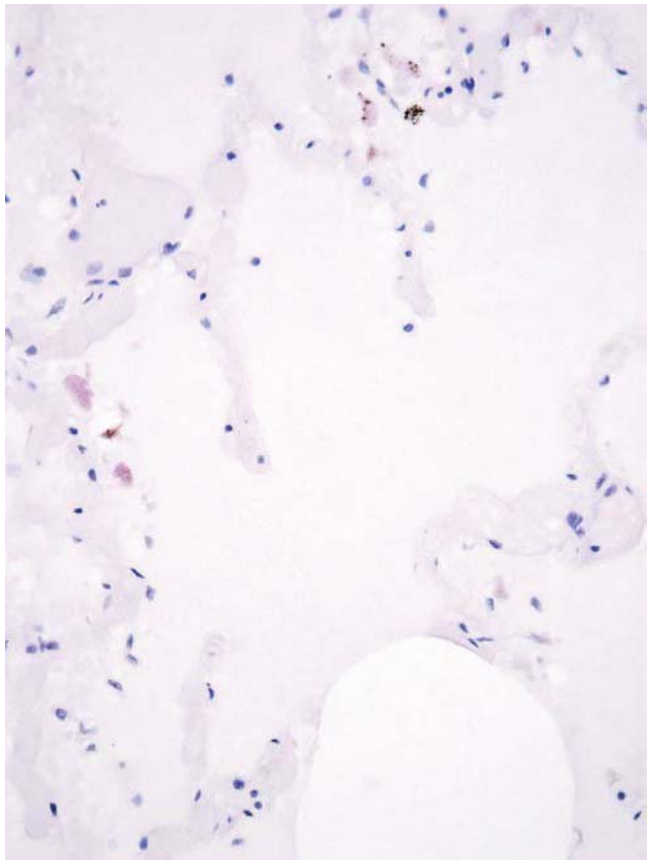


FIGURE 16.10. PAP in a man who ground aluminum metal. PAP is seen in some patients exposed to very high levels of very finely divided dust. **Inset:** Electron micrograph showing submicron aluminum spheres recovered from a digest of the biopsy. (Reproduced by permission from Miller RR, Churg AM, Hutcheon M, et al. Pulmonary alveolar proteinosis and aluminum dust exposure. *Am Rev Respir Dis.* 1984;130:312–315.)



FIGURES 16.11 to 16.13. Legend appears on next column





FIGURES 16.11 to 16.13. Pulmonary edema. In contrast to proteinosis material, edema fluid appears smooth or very finely granular and does not stain with digested PAS (**Fig. 16.13**).

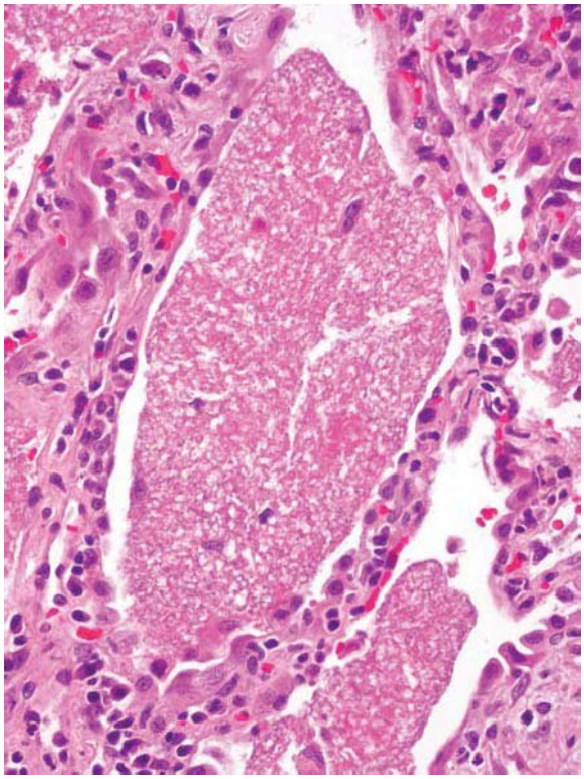
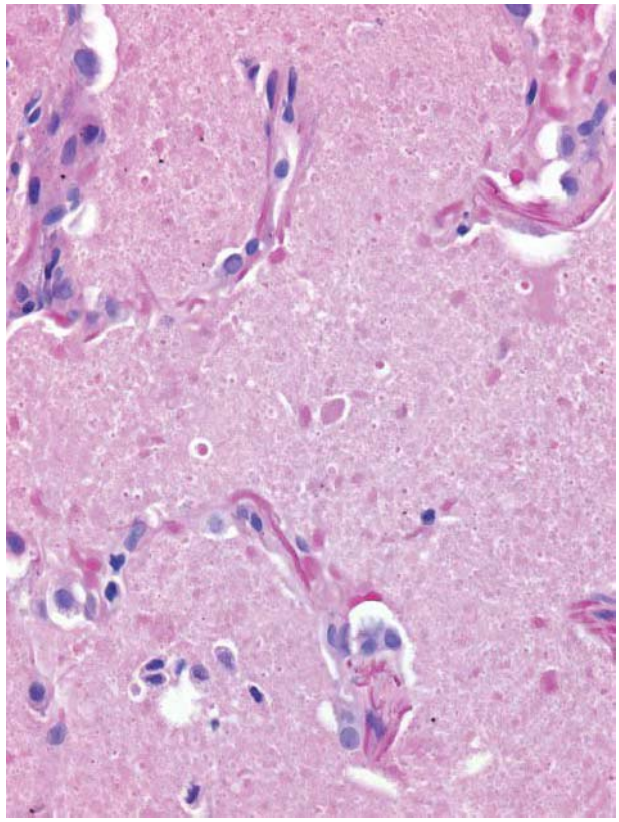
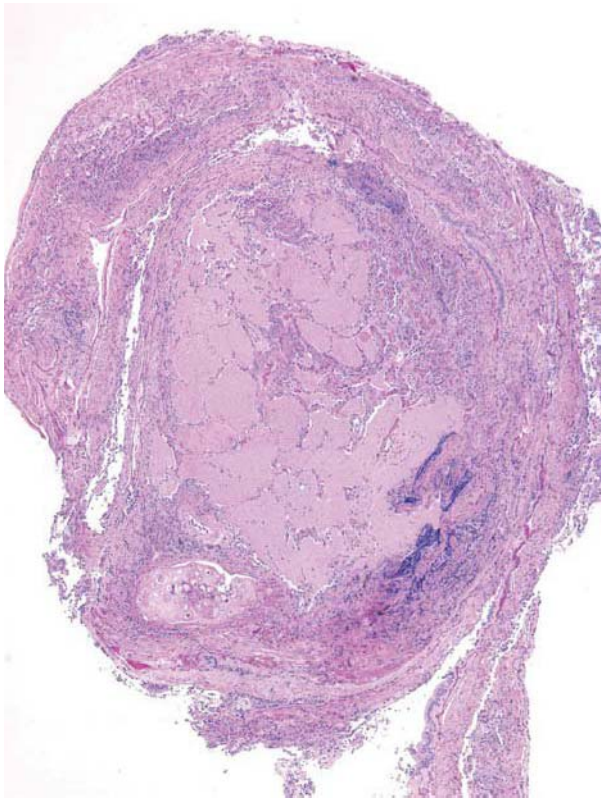


FIGURE 16.14. Pneumocystis pneumonia. In contrast to proteinosis fluid, pneumocystis produces foamy eosinophilic material in which fine dots are often visible.



FIGURES 16.15 and 16.16. PAP in a transbronchial biopsy. PAP is readily diagnosed in transbronchial biopsies if the biopsy samples the lesion, but PAP can be patchy (compare Fig. 16.2) and often is missed by transbronchial biopsy.



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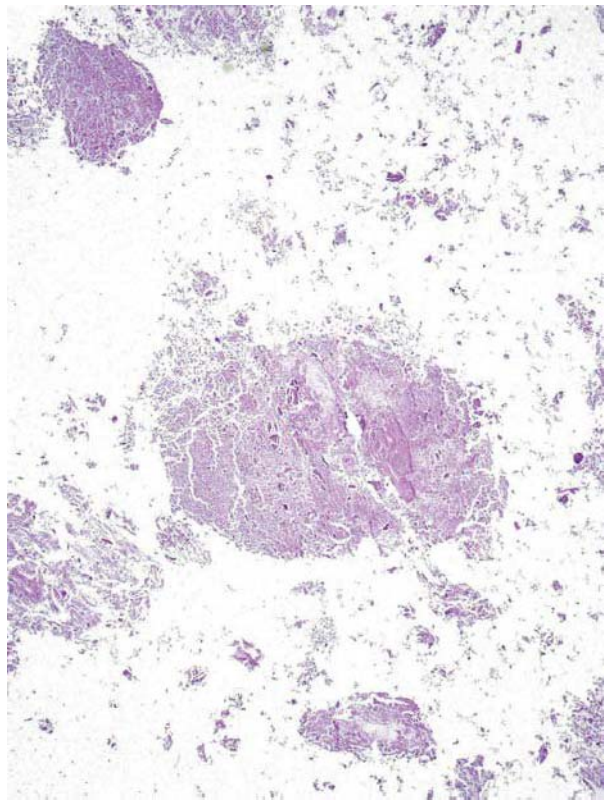
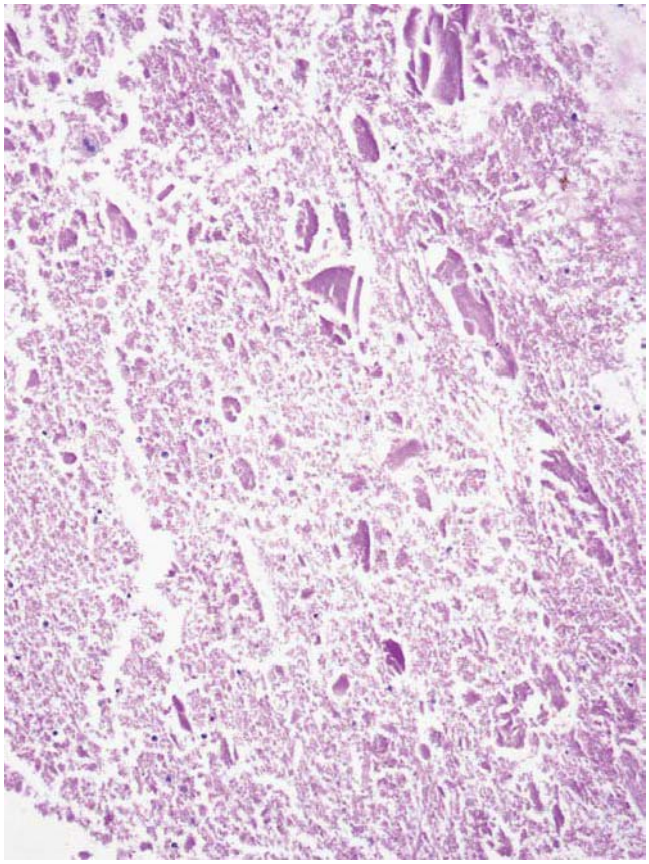


FIGURES 16.17 and 16.18. Legend appears on following page



FIGURES 16.17 and 16.18. Low- and high-power views of proteinosis material in lavage fluid stained with digested PAS. The material is essentially identical to what is seen in the alveolar spaces in histologic sections.

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CHAPTER

17

Lymphangioleiomyomatosis

PATHOGENESIS

Lymphangioleiomyomatosis is a proliferation of abnormal smooth muscle–like cells ("LAM cells") that tend to form abortive muscle/lymphatic channels (lymphangiomyomas) in many organs and cysts in the lung. The fundamental defect in LAM is a mutation in the Tuberous Sclerosis Complex 1 or Complex 2 genes (*TSC1, TSC2*), which control cell growth, motility, and invasiveness. Because of the mutated genes, the *Akt*/Mammalian Target of Rapamycin (*mTOR*) pathway is constituitively switched on, causing proliferation of LAM cells (reviewed in McCormack,[1] Taillé et al.,[2] Meraj et al.[3]). Interference with mTOR signaling by treatment with rapamycin (Sirolimus) has been shown to slow down or halt the loss of pulmonary function in LAM patients.[2,4]

LAM is almost exclusively a disease of women and estrogen also appears to signal through the *Akt* pathway, thus potentially driving LAM cell proliferation; however, the exact signaling pathways involved are unclear and estrogen antagonism with progesterone does not slow disease progression.[1]

Although LAM cells are not clonal, they behave somewhat in the fashion of a neoplasm and circulate in the lymph and blood to many parts of the body where they proliferate and produce lymphangiomyomas.[1,3]

CLINICAL FEATURES

LAM is seen in about one-third of women with tuberous sclerosis, but also in women who have no evidence of tuberous sclerosis ("sporadic LAM"), where the incidence has been estimated at 3 to 5 per million persons per year.[3] The traditional teaching has been that LAM is a disease of premenopausal women, but in a series of 230 patients accumulated by the NHLBI LAM Registry,[5] 40% were postmenopausal at presentation. A small number of LAM cases have been reported in males with tuberous sclerosis.[3]

Patients with LAM often present with shortness of breath (SOB), but pneumothorax (reflecting rupture of subpleural cysts) as a presenting complaint is seen in about one-third of cases.[5] Extrapulmonary manifestations including renal angiomyolipomas and lymphangiomyomas in various organs are extremely common. Some patients present with a renal angiomyolipoma and are then found to have cysts on chest imaging.[6] Lymphangiomyomas that obstruct the thoracic duct can cause chylous pleural effusions, and chylous effusions can also be found in the peritoneum and pericardial space. Serious hemoptysis is occasionally seen and is believed to reflect growth of LAM cells into small pulmonary vessels. LAM patients often show elevations in pulmonary artery pressure on exercise, presumably for the same reason.[3] LAM cells also grow into small airways, and pulmonary function tests may show an obstructive or mixed obstructive-restrictive pattern.

Recently serum vascular endothelial growth factor-D (VEGF-D) has been shown to be elevated in some, but not all, patients with LAM,[7] and has been proposed as a useful way of separating patients with LAM from those with other cystic lung diseases.

IMAGING

The characteristic HRCT finding of LAM consists of bilateral thin-walled cysts scattered uniformly throughout the lungs and surrounded by normal parenchyma (Fig. 17.1). The cysts tend to measure less than 5 mm in diameter in patients with mild disease but may become larger than

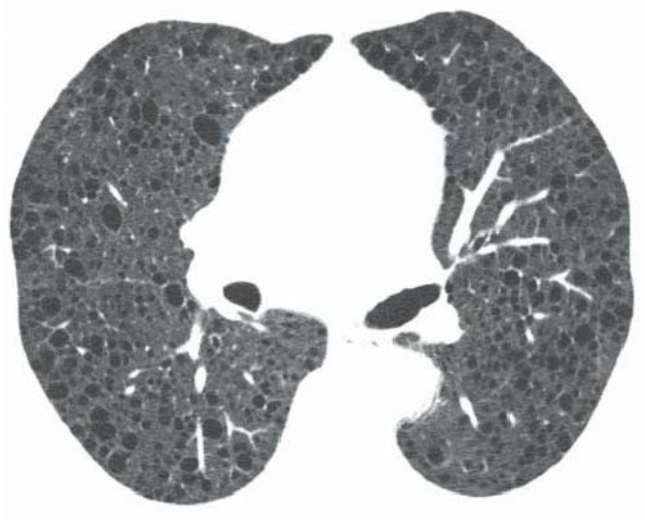


FIGURE 17.1. Lymphangioleiomyomatosis. HRCT demonstrates numerous bilateral thin-walled cysts ranging from approximately 3 to 15 mm in diameter. The parenchyma between the cysts is normal. The patient was a 53-year-old woman.

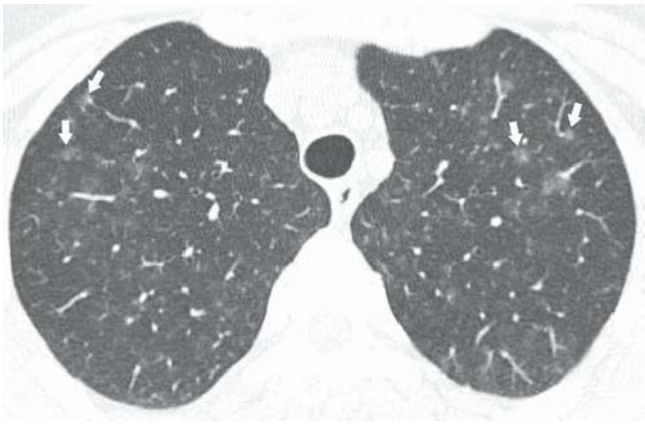


FIGURE 17.2. MMPH. HRCT shows multiple bilateral ground-glass nodules (*arrows*). The patient was a 43-year-old woman with tuberous sclerosis.

1 cm with severe involvement.[8] Spontaneous pneumothorax occurs in more than 50% of patients and is the primary event that leads to diagnosis in approximately 35% of cases.[5] Although in the proper clinical setting the HRCT findings may be characteristic enough to strongly suggest the diagnosis, there can be considerable overlap with other cystic lung diseases particularly Langerhans cell histiocytosis (LCH), lymphocytic interstitial pneumonia (LIP), and Birt–Hogg–Dubé syndrome.

The pulmonary manifestations of tuberous sclerosis include LAM and multifocal micronodular pneumocyte hyperplasia (MMPH). Up to one-third of women with tuberous sclerosis have lung cysts characteristic of LAM.[9] MMPH manifests as 1 to 8 mm diameter ground-glass nodules distributed throughout the two lungs, although they may have an upper lobe predominance (Fig. 17.2).[10] MMPH may be seen in isolation or in the presence of LAM.

PATHOLOGIC FEATURES

Gross Appearances

Cysts with walls that are (visually) thicker than those of emphysema but thinner and softer than those of honeycombing, are the characteristic finding in LAM (Fig. 17.3).

Microscopic Findings

The defining feature of LAM in the lung is the presence of cystic spaces with walls comprising the peculiar muscle-like LAM cells (Fig. 17.4). LAM cells typically have a slightly clearer or slightly vacuolated cytoplasm compared to ordinary smooth muscle cells (Fig. 17.4). The number/volume of LAM cells is extraordinarily variable. Textbooks typically illustrate cases in which the LAM cells produce bulky thickening of the entire wall of a cyst with many such cysts existing in the lung (Figs. 17.5 and 17.6), but in some cases there are only small nodular thickenings in the cyst walls (Figs. 17.7 and 17.8), and still other

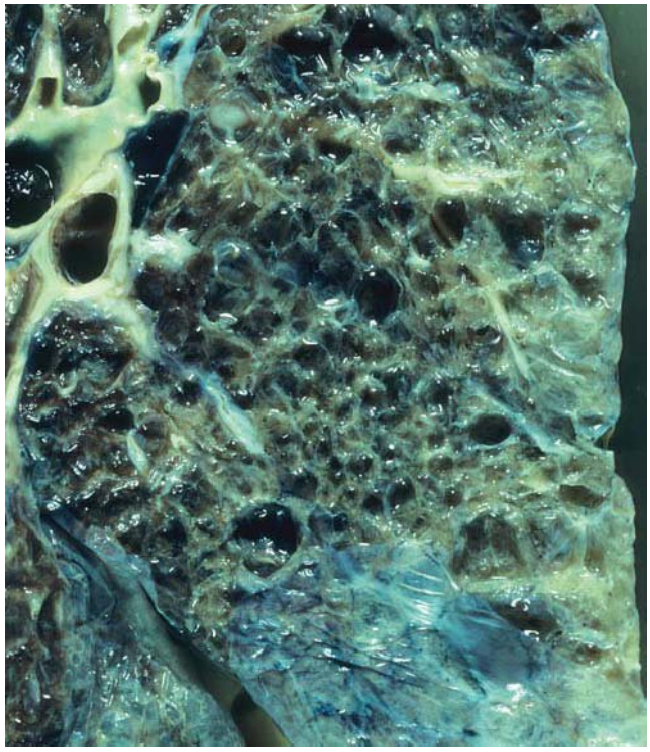


FIGURE 17.3. Gross appearance of LAM as slightly thick-walled cysts that somewhat mimic honeycombing. However, as opposed to honeycombing, the cyst walls are soft on palpation and have no fibrosis in their walls on microscopic examination.

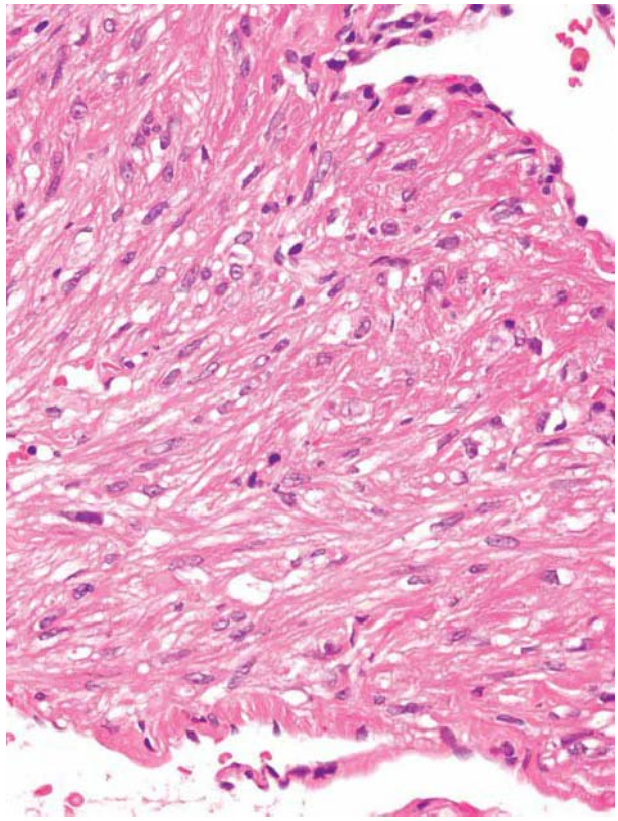
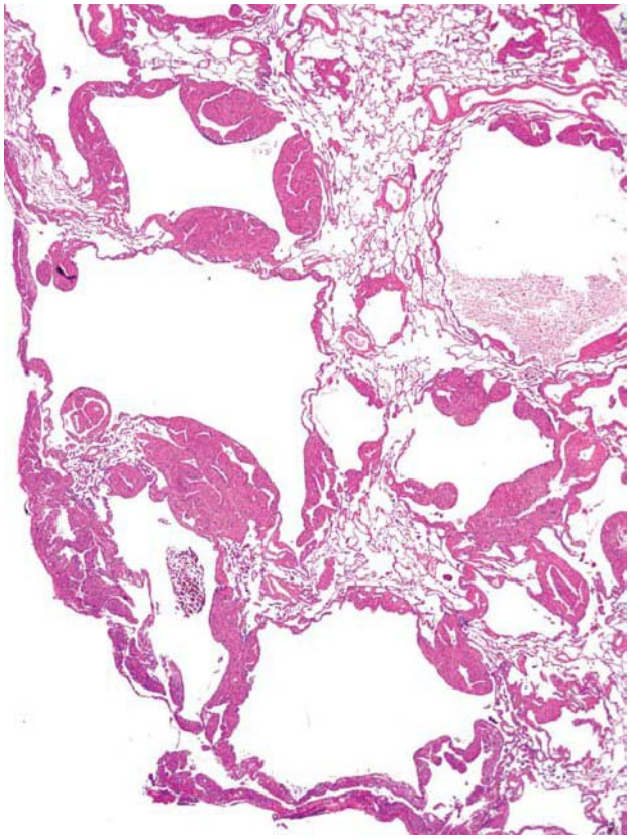
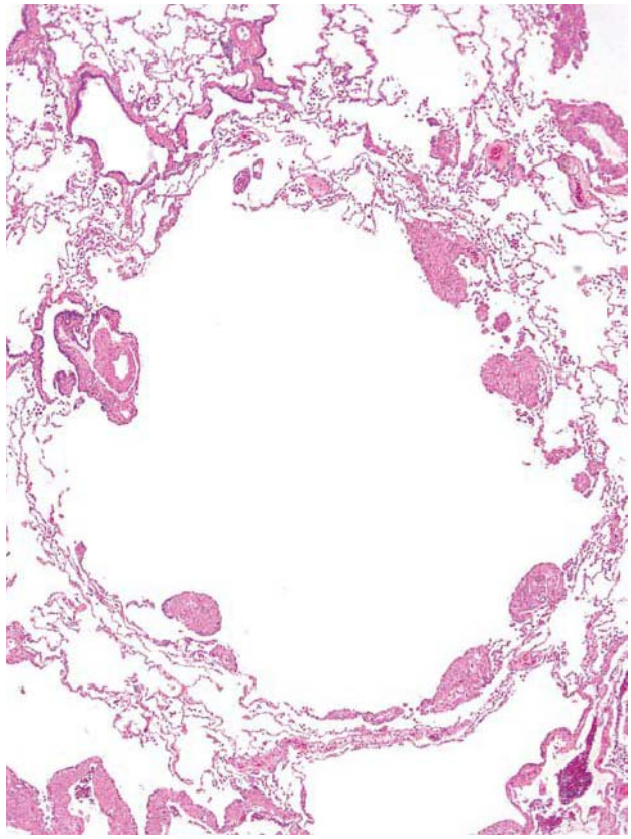
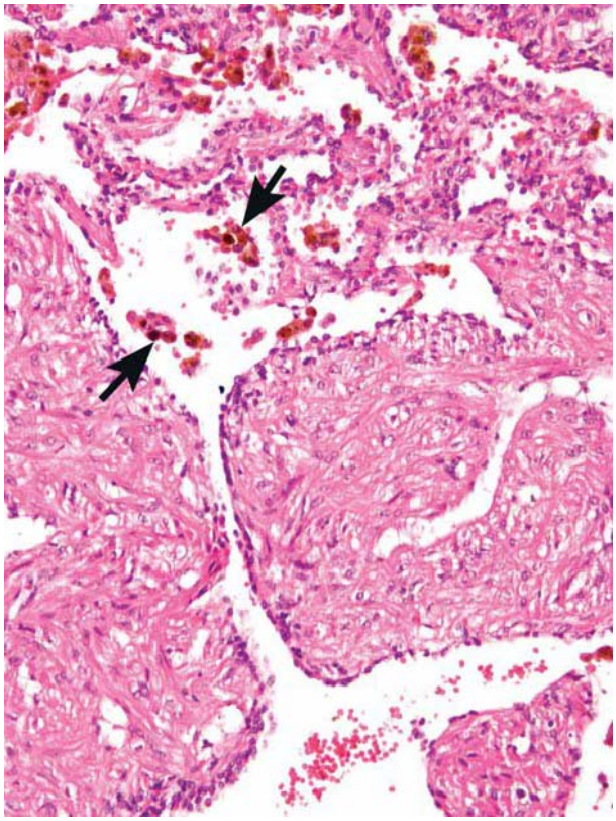
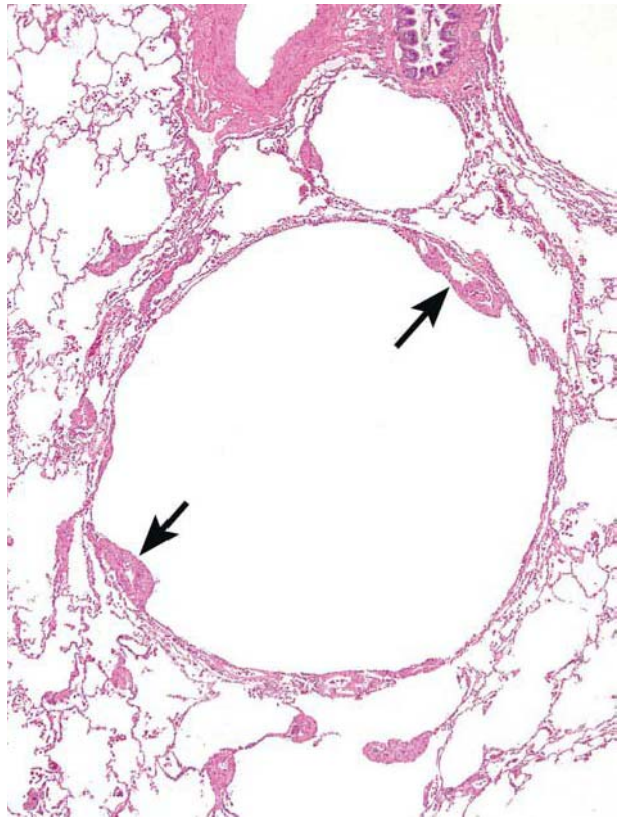


FIGURE 17.4. High-power appearance of LAM cells. Note the typical slightly cleared or vacuolated cytoplasm.









FIGURES 17.5 and 17.6. An example of LAM in which there are fairly bulky masses of LAM cells in the cyst walls. Hemosiderin secondary to chronic hemorrhage, a common finding in LAM, is visible in the high-power view (*arrows*).

FIGURES 17.7 and 17.8. An example of LAM in which the LAM cells form small nodular excrescences in the cyst walls. In **Figure 17.8** the area occupied by LAM cells (*arrows*) is fairly small and the cyst might be mistaken for an emphysematous space at first glance.

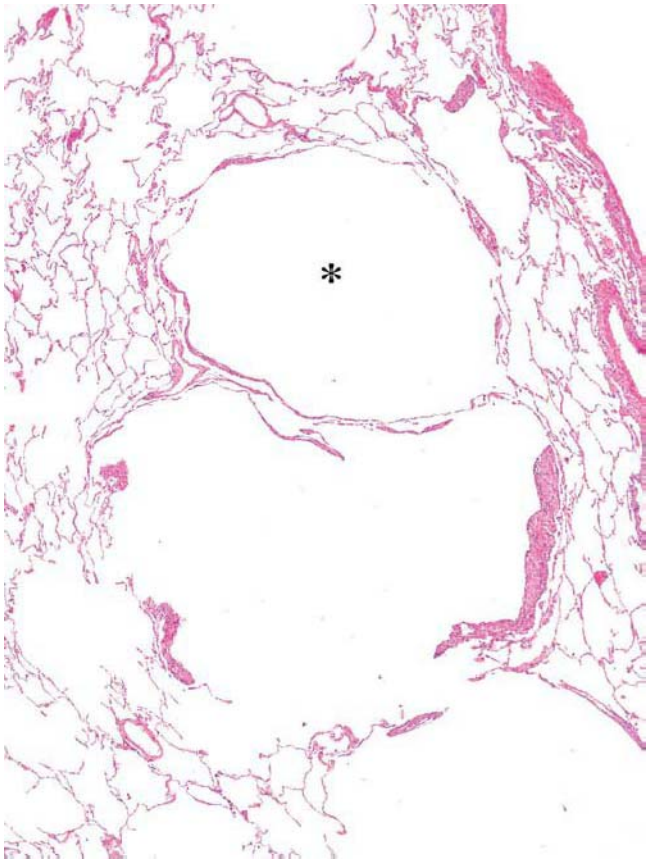
cases mimic emphysema (Fig. 17.9); only close inspection of one or more cysts reveals the characteristic LAM cells. (Fig. 17.10). LAM cells can grow into small airways and small blood vessels and hemosiderin, thought to reflect blood vessel invasion, is present in some cases (Fig. 17.6).

Immunohistochemical Staining

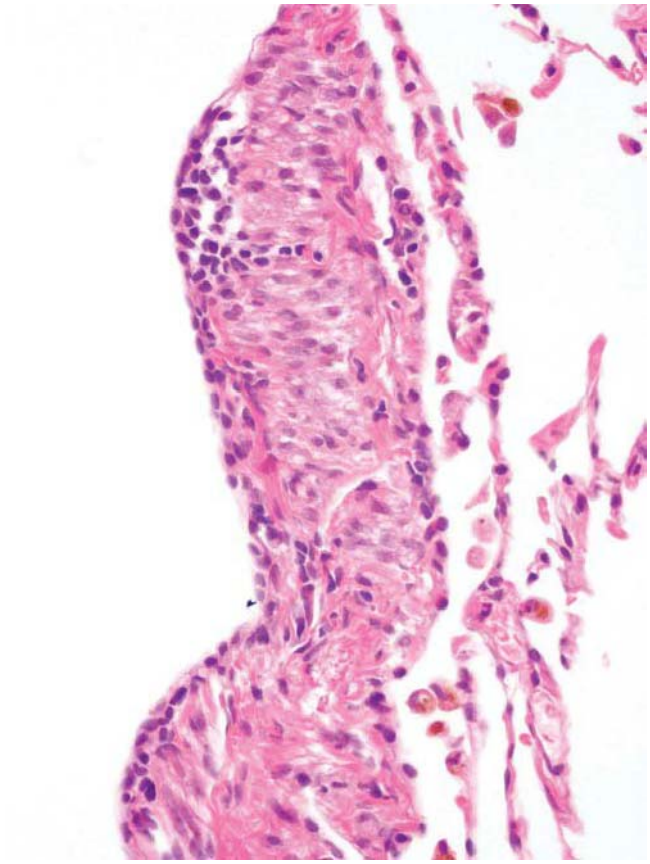
LAM cells express muscle markers such as desmin, but in addition are HMB-45 positive. Although articles on LAM frequently illustrate HMB-45 staining of almost every LAM cell in a given lesion, in our experience it is more common to find focal staining (Fig. 17.11). LAM cells in many cases are also positive for estrogen receptor (ER) and progesterone receptor (PR) that typically show more diffuse staining than HMB-45 (Figs. 17.13 and 17.14). Recently it has been reported that cytoplasmic staining for β-catenin is present in LAM cells,[12] and we find that this stain is also more diffusely positive than HMB-45 (Fig. 17.12).

Lymphangiomyomas

Lymphangiomyomas comprise LAM cells forming abortive lymphatic channels (Figs. 17.15 and 17.16). They are extremely rare in the lung but can affect any lymph node or lymphatic structure in the thorax. Angiomyolipomas are usually found in the kidneys but rare angiomyolipoma-like lesions have been reported in the lung.[11]



FIGURES 17.9 and 17.10. Legend appears on next column



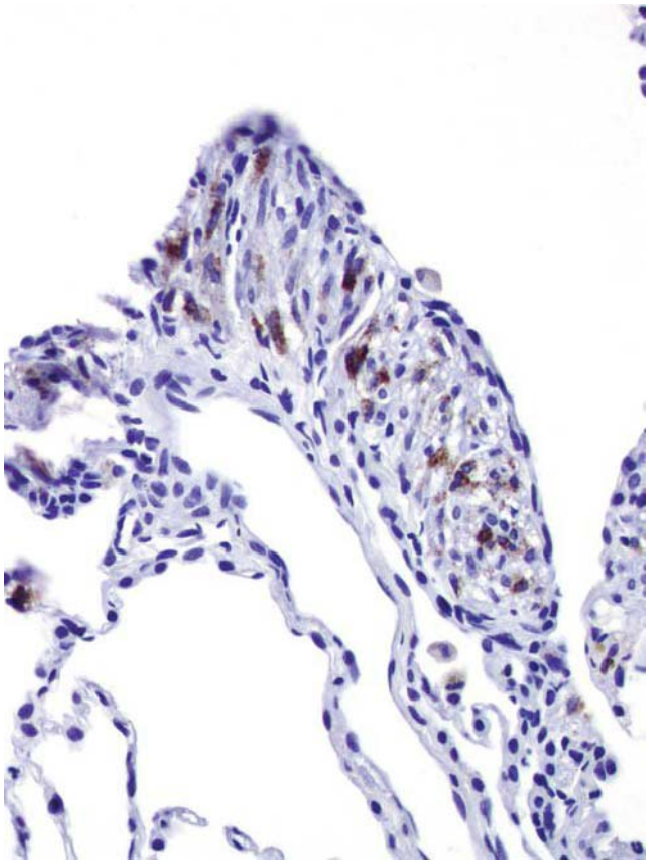
FIGURES 17.9 and 17.10. Portions of three LAM cysts in a patient with minimal proliferation of LAM cells. The middle cyst has an area of thickening of the wall by LAM cells (shown at higher power in **Fig. 17.10**), but the adjacent cyst (marked with an *asterisk* in Fig. 17.9) has almost none. Such cysts are difficult to separate from emphysematous spaces or Birt-Hogg-Dubé cysts (compare Fig. 17.24).

Multifocal Micronodular Pneumocyte Hyperplasia

MMPH is seen in some cases of LAM in patients with tuberous sclerosis but can also occur without LAM in these patients. It consists of multiple small nodules comprising bland-appearing hyperplastic type 2 cells growing along the alveolar walls with underlying dense interstitial fibrosis confined to the nodules (Figs. 17.17 to 17.19).

DIFFERENTIAL DIAGNOSIS

The major morphologic differential diagnoses of LAM are shown in Table 17.1. Centrilobular emphysema (CLE) forms cystic spaces with either a much attenuated wall or occasionally a fibrotic wall (Figs. 17.20 and 17.21). LAM with minimal muscle in the cyst wall can mimic emphysema (Fig. 17.9), but emphysematous spaces never have muscle



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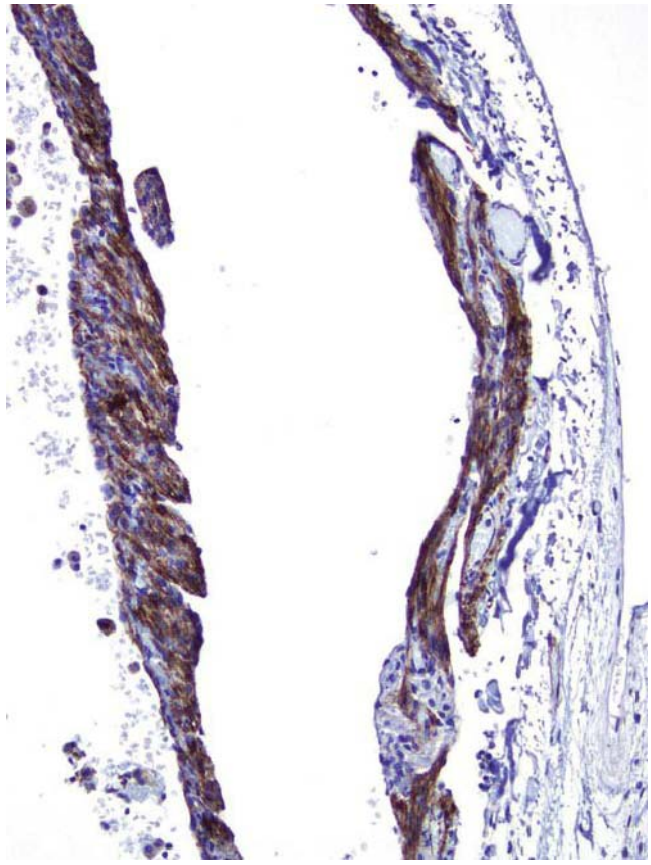

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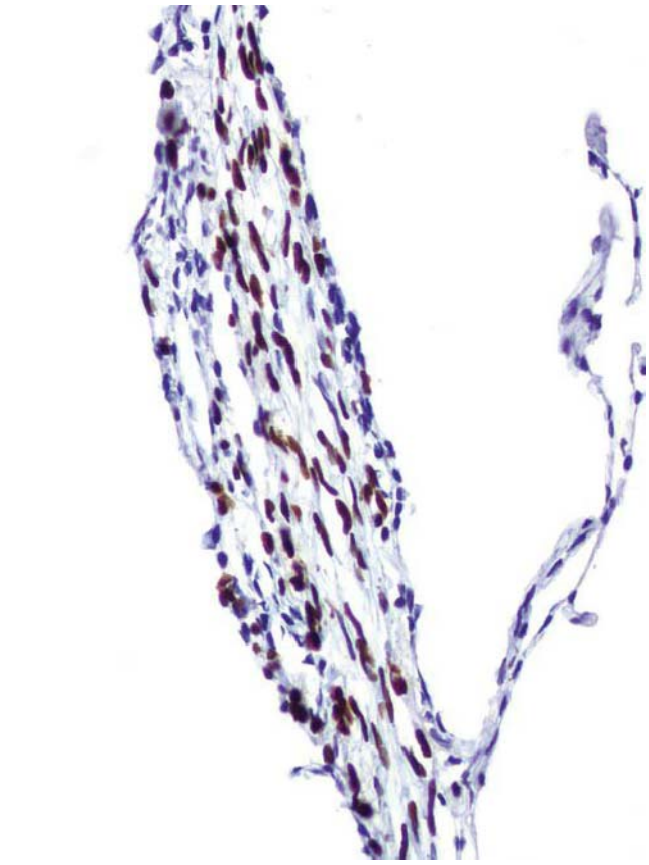

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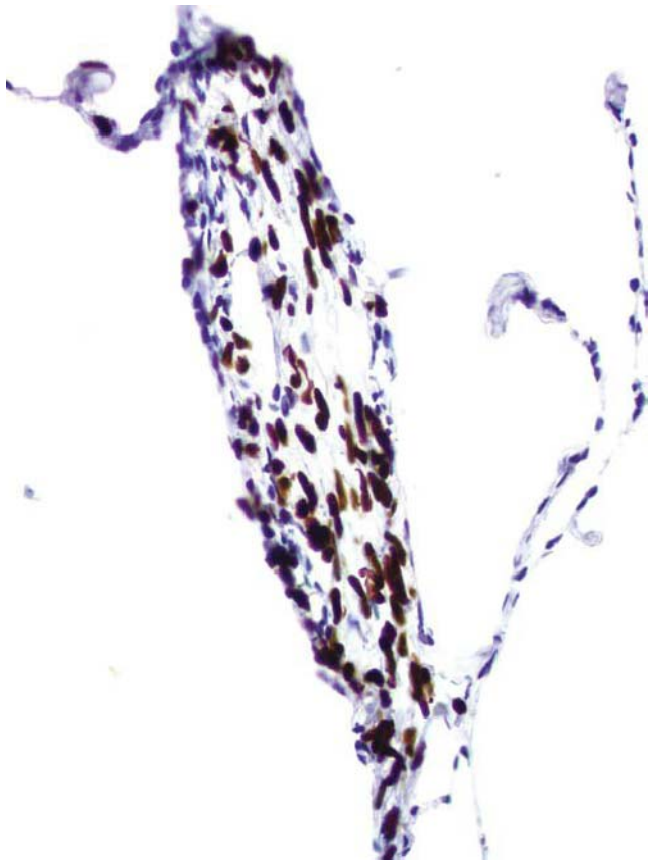
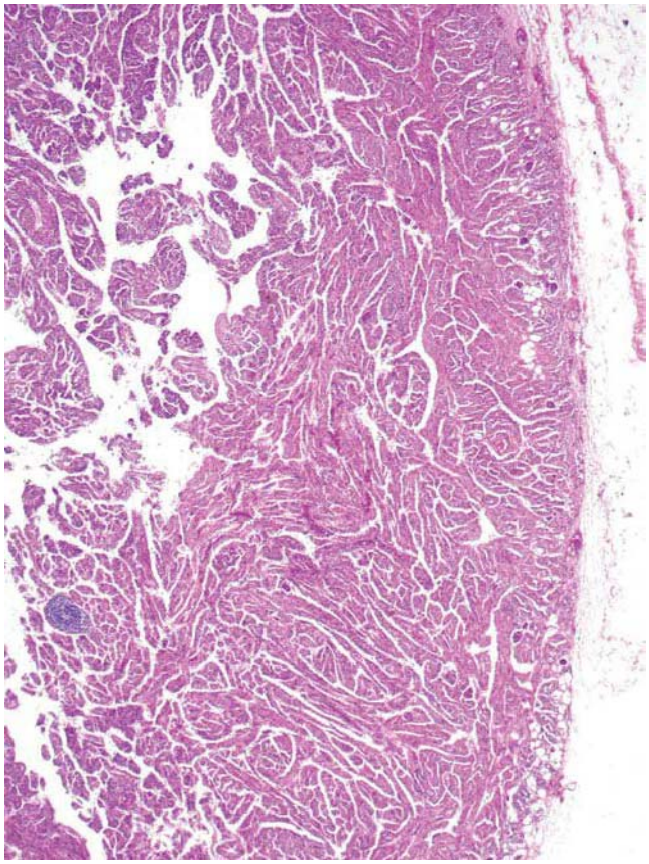
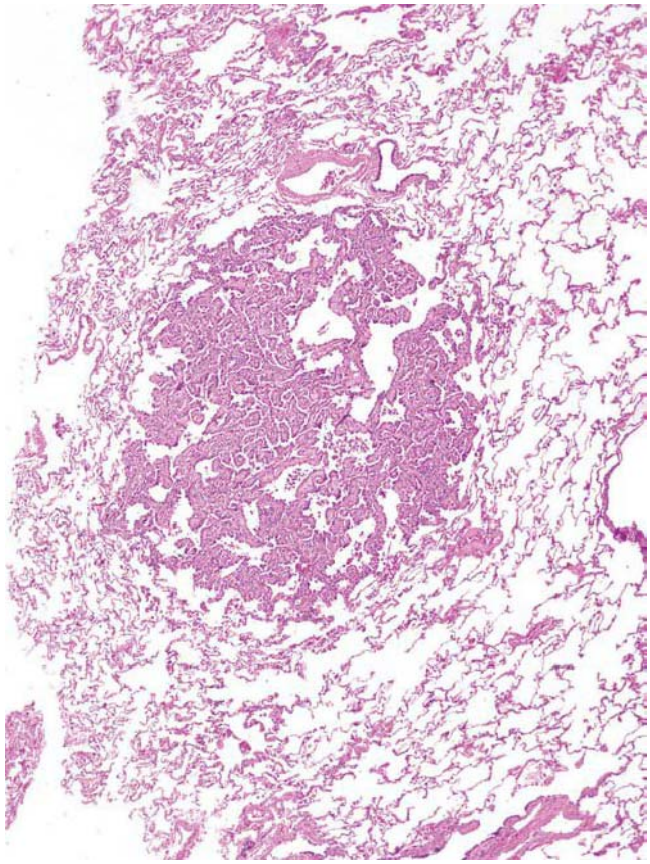
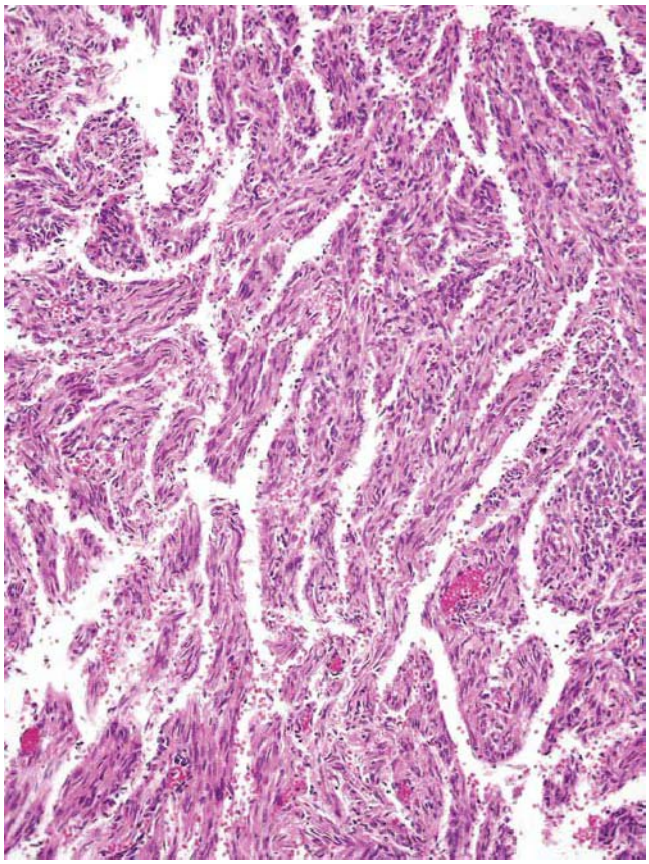


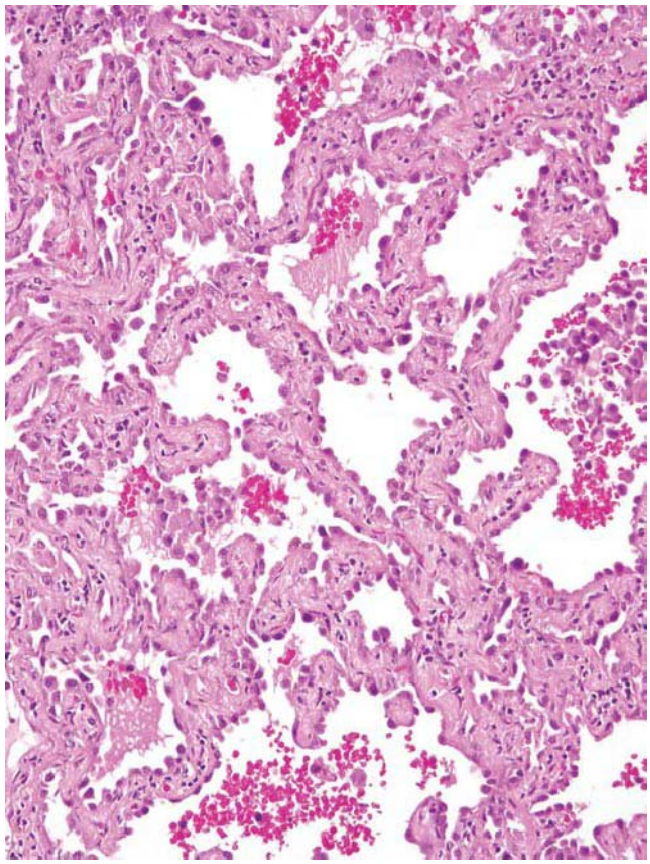
17.14

FIGURES 17.11 to 17.14. Immunohistochemical staining of LAM cells. In our experience HMB-45 staining (**Fig. 17.11**) is typically very patchy, whereas β-catenin staining (**Fig. 17.12**) is strong and diffuse. ER (**Fig. 17.13**) and PR (**Fig. 17.14**) staining is not always present but usually stains all or most of the LAM cells when positive.



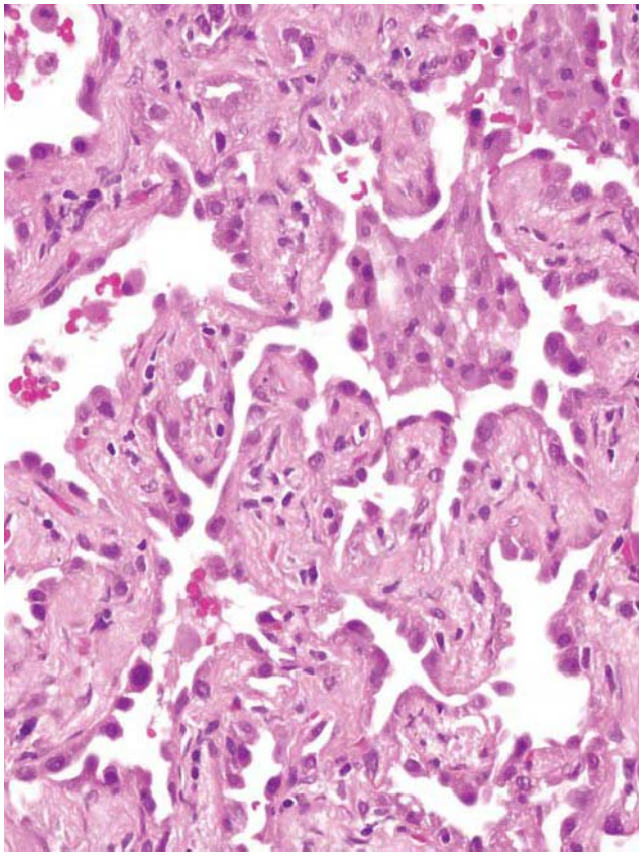






FIGURES 17.15 and 17.16. Low- and medium-power views of a mediastinal lymphangiomyoma in a patient with LAM.

FIGURES 17.17 to 17.19. Legend appears on following page



FIGURES 17.17 to 17.19. MMPH in a patient with LAM. The lesion comprises proliferating type II cells overlying a densely fibrotic interstitium.

in their walls. The respiratory bronchiole leading into the emphysematous space has a partially muscularized wall that might be confused with LAM. However, respiratory bronchioles leading into emphysematous spaces are not cystic, and they usually have a very obvious ciliated epithelium— a feature not seen in LAM. The smooth muscle in the walls of respiratory bronchioles is HMB-45 and β-catenin negative.

Benign metastasizing leiomyoma is really a very low-grade leiomyosarcoma that has metastasized to the lung; virtually all cases originate in the uterus. Benign metastasizing leiomyoma forms interstitial nodules without cysts, although they often incorporate small spaces lined by metaplastic alveolar epithelium (Figs. 17.22 and 17.23). The cells of benign metastasizing leiomyoma are ER receptor positive, but negative for HMB-45 and β-catenin.

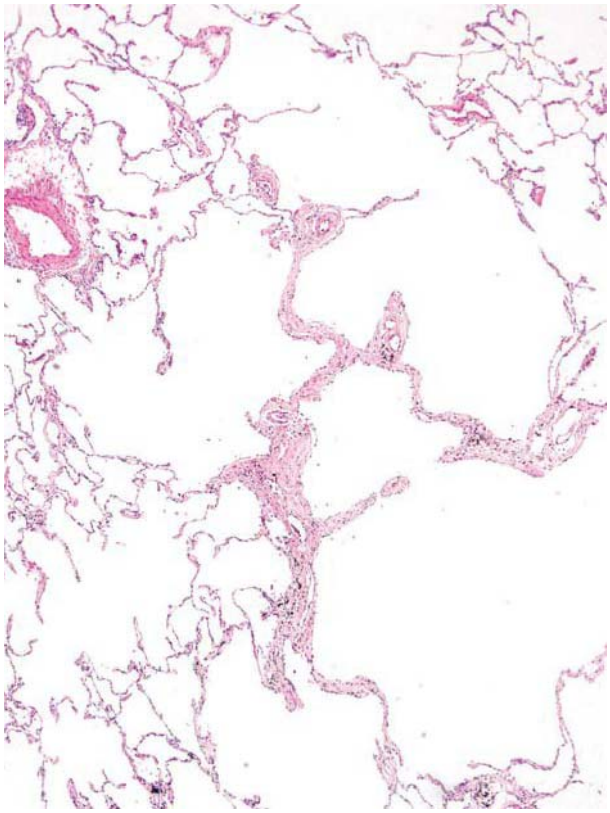
Langerhans cell histiocytosis (LCH) is described in detail Chapter 10. It can form cystic spaces, but the walls of these spaces are either cellular proliferations of Langerhans cells, eosinophils, and smoker's macrophages (see Fig. 10.18), or, if the lesions are old, they comprise dense fibrous tissue (see Fig. 10.22). Langerhans cells are S-100 and CD1a positive (see Figs. 10.27 and 10.28) and negative for HMB-45 and β-catenin.

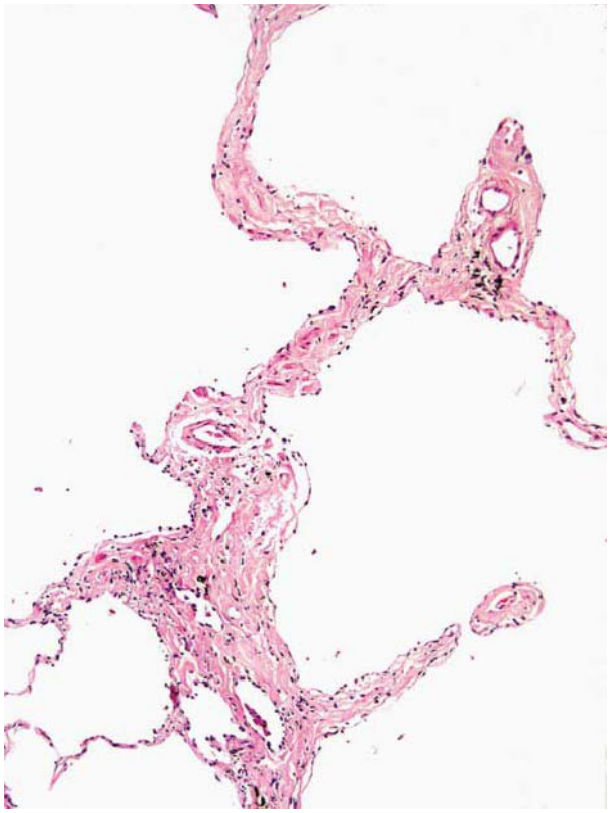
Birt–Hogg–Dubé syndrome is an autosomal dominant condition characterized by cutaneous fibrofolliculomas, renal cell carcinomas, lung cysts in 80% of cases, and, sometimes, pneumothoraces.[13,14] On computed tomography the cysts tend to be variable in size and larger than those seen in LAM and typically involve mainly the lower lung zones, whereas those of LAM usually have a random distribution throughout the lungs.[15] Birt–Hogg–Dubé syndrome is caused by a mutation in the gene encoding folliculin, a protein of unknown function. The lung cysts usually appear to be formed from keratin-positive thinly stretched alveolar walls, and there is neither aberrant smooth muscle nor fibrous tissue lining the cysts[14,16] (Fig. 17.24); however, some authors have suggested that the cysts tend to abut interlobular septa.[14]

TABLE 17.1

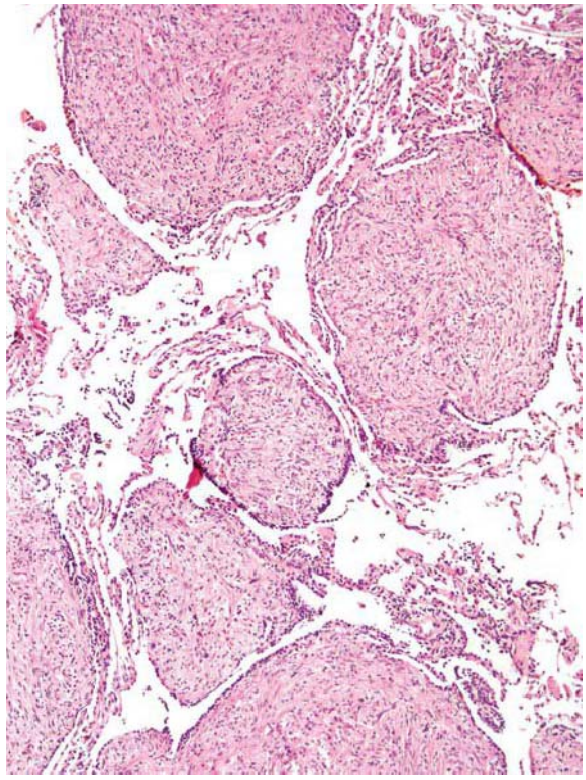
Morphologic differential diagnosis of LAM

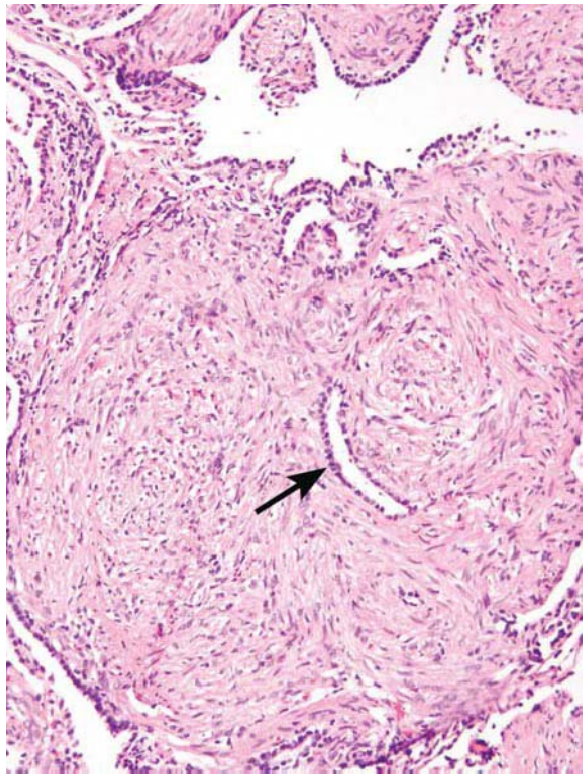
Centrilobular emphysema	Benign metastasizing leiomyoma	LCH	Birt–Hogg–Dubé syndrome
Cystic spaces have thin walls or occasionally fibrotic walls, but no muscle	Muscle forms interstitial nodules without cysts. Nodules can incorporate small airspaces with metaplastic alveolar lining cells.	In early disease cysts have a cellular wall comprising Langerhans cells, eosinophils, and smoker's macrophages	Cyst walls consist of attenuated alveolar parenchyma, no muscle or fibrous tissue (but cysts sometimes abut interlobular septa)
Muscular wall of respiratory bronchioles leading into emphysematous space has an epithelial lining. Muscle of respiratory bronchiole is HMB-45 and β-catenin negative	Muscle cells are ER +, negative for HMB-45, and β-catenin	Langerhans cells are S-100 and CD1a +, negative for HMB-45 and β-catenin Old Langerhans cell histiocytosis has cysts with fibrotic walls	Patients have cutaneous fibrofolliculomas and renal cell carcinomas.





FIGURES 17.20 and 17.21. CLE. The cystic spaces in CLE usually have attenuated walls, but sometimes, as in this example, there is fibrosis of walls of the spaces as well. Emphysematous spaces do not have muscle in the walls.





FIGURES 17.22 and 17.23. Benign metastasizing leiomyoma. The nodules of muscle in benign metastasizing leiomyoma are actually interstitial and sometimes contain small cyst-like spaces that are really metaplastic residual alveolar epithelium (**Fig. 17.23**, *arrow*). However, cystic spaces of the size seen in LAM are never present, and the muscle is HMB-45 negative but ER positive.

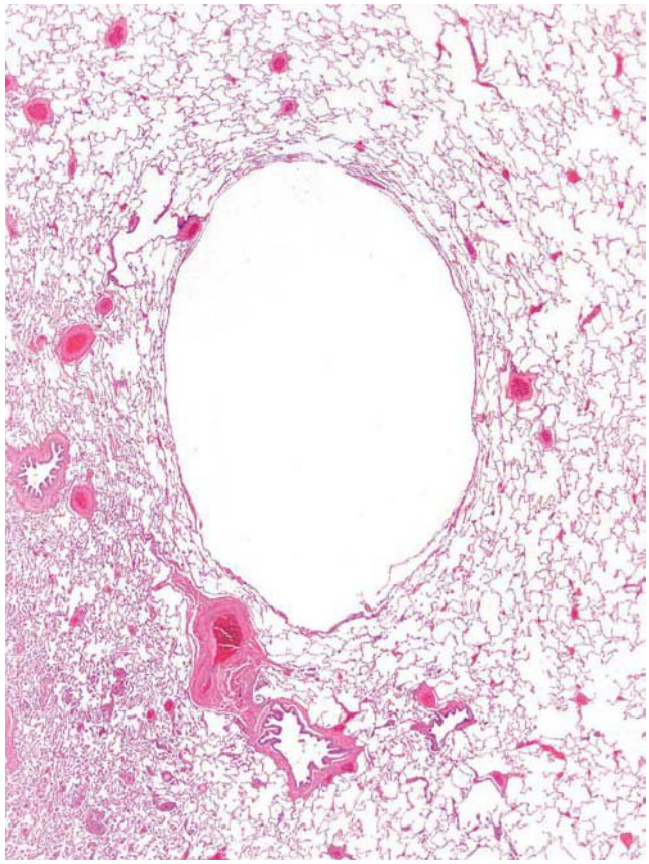


FIGURE 17.24. Birt-Hogg-Dubé syndrome. Cyst wall comprises attenuated lung parenchyma with no muscle in the wall.

DIAGNOSTIC MODALITIES

LAM can be diagnosed in some cases on transbronchial biopsy; generally cysts are not seen but the LAM cells with characteristic staining patterns can be identified. LAM cell aggregates can sometimes be found in cytologic preparations of chylous effusions or ascites.[3] VATS biopsies are commonly used in cases that are not clinically/radiologically evident.

PROGNOSIS

LAM is slowly progressive and the rate of progression is proportion to the relative amount of LAM cells seen in the biopsy. A pathologic grading scheme that predicts prognosis based on amount of LAM cells has been proposed by Matsui et al.[17] but is not widely used. Untreated, overall mortality is 10% to 20% at 10 years.[1] Transplantation is often performed for severe disease, but LAM can recur in transplanted lungs. As noted above, agents such as sirolimus that interfere with the abnormal signaling pathways in LAM cells have been reported to be effective.[2–4]

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CHAPTER

18

Drug Reactions Producing Interstitial Lung Disease

GENERAL APPROACH TO DRUG REACTIONS IN THE LUNG AND PLEURA

The diagnosis of drug reactions in the lung and pleura is a difficult area, partly because of the plethora of drugs that produce adverse reactions and partly because most drug reaction patterns are not specific, so that the diagnosis of drug reactions tends to be exclusionary, and the pathologist often ends up in the position of calling something a "possible" drug reaction. A further source of confusion is the tendency of drug reactions that appear as interstitial lung disease (ILD) to produce unusual patterns or combinations of findings, but this phenomenon is sometimes helpful in making one think about drug toxicity.

Some general principles for approaching cases that might represent drug reactions are listed in Table 18.1. Knowledge of the temporal sequence between the onset of drug use and the appearance of intrathoracic disease is crucial. Although most drug reactions start in reasonable time proximity after the onset of drug use, some drugs usually do not produce adverse reactions until a certain dose has been reached (amiodarone is a good example[1]), and some drugs, for example, Asacol[2] (and see Case Study 3) can cause a reaction after years of use with no previous ill effects. Other drugs, especially chemotherapeutic agents such as BCNU, may cause interstitial fibrosis long after drug administration has ceased.[3]

TABLE 18.1

General approach to drug reactions

Proper temporal sequence of drug administration and response required
Most drug reactions start fairly close in time to the onset of drug use, but occasionally drug reactions are seen after long-term use of the drug in question or long after the drug has been stopped
Known correlation between drug and pathologic reaction pattern helps establish diagnosis
See www.pneumotox.com for a listing of drugs and published reaction patterns
Disappearance of disease after discontinuing drug is best proof of etiology
Drug reactions are usually exclusionary diagnoses and *very few* pathologic reaction patterns are pathognomonic of a drug reaction

One of the most helpful diagnostic aids is information about whether the drug in question is known to cause the imaging/pathologic reaction pattern at hand. The literature on drug reactions is huge, but a concise summary can be found at www.pneumotox.com. This site is sponsored by Groupe d'Etudes de la Pathologie Pulmonaire Iatrogène and provides a compilation of pulmonary drug reactions in the literature classified by drug name and also by reaction pattern. One note of caution for pathologists: The pneumotox database is quite good but is compiled by clinicians who transcribe into the database whatever reaction pattern is described in the original article, and those articles are often not written by pathologists, so that sometimes a particular reaction pattern as described in pneumotox.com does not fit any easily recognizable pathologic diagnosis. A further complication is that some adverse drug reaction reports predate current classifications of ILD; in particular, many lesions were labeled usual interstitial pneumonia (UIP) in the past that now would be regarded as something else.

Probably the best proof of a drug reaction is disappearance of the abnormal imaging/pathology after the drug is discontinued (and, even better, reappearance of the lesions with rechallenge, something that is rarely done), but this means that many diagnoses of *definite* drug reactions are really made post hoc by the clinician following up the patient. Most often at the time of biopsy, all the pathologist can say is "possible" or "probable" drug reaction (see Case Studies).

CLINICAL FEATURES

There is an extremely broad range of clinical findings in patients with drug reactions. These vary from acute events (anaphylaxis, bronchospasm, pulmonary edema)

to processes that take weeks to months to develop (probably the majority of drug reactions) to lesions that are only seen after years, typically fibrotic reactions. Most clinical findings are nonspecific and include shortness of breath, cough, and frequently systemic complaints, including fever, fatigue, and weight loss. Blood eosinophilia is fairly common and helpful in suggesting a drug reaction.

IMAGING

The radiologic manifestations of drug reactions are protean and nonspecific. HRCT allows better assessment of the pattern and distribution of findings than the chest radiograph and may demonstrate abnormalities in patients with normal radiographs. The HRCT patterns of drug reaction, however, are similar to those seen in other interstitial and airspace diseases[4] (Fig. 18.1). Furthermore, particularly in patients receiving chemotherapy, pulmonary parenchymal opacities may result from a number of other complications, including infection, pulmonary edema, and progression of the underlying disease. Allowing for these limitations, the possibility of drug reaction should be suspected in all patients receiving medications that are known to cause the HRCT pattern being seen. Furthermore, drug reaction or collagen vascular disease should be suspected when the HRCT shows findings consistent with two different reaction patterns, most commonly NSIP and BOOP.

In a few cases the HRCT findings may be suggestive of a particular drug reaction. The best example is amiodarone, which contains approximately 37% iodine by weight and therefore has high attenuation on CT. As a consequence, pulmonary abnormalities resulting from amiodarone toxicity, particularly when chronic, frequently have high attenuation (80 to 175 Hounsfield units [HU]) on CT[5] (Figs. 18.2 and 18.3). Because amiodarone normally accumulates in the reticuloendothelial system, the liver also has high attenuation in patients who take amiodarone. It should be noted that high attenuation of the liver is usually a normal finding in patients who take amiodarone and that the lack of high attenuation of the lung abnormalities does not exclude amiodarone toxicity.

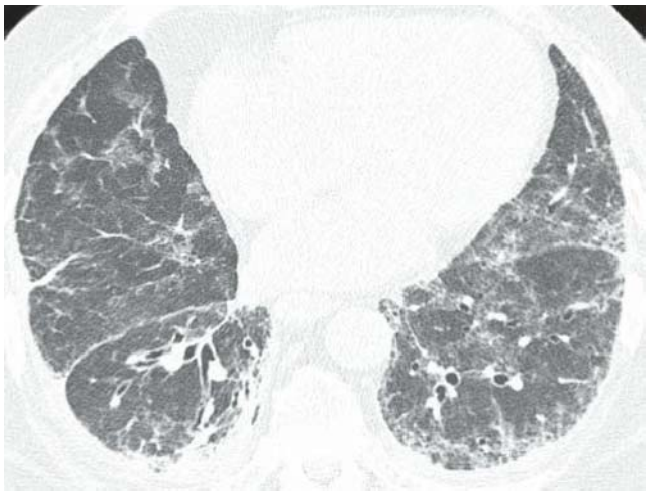
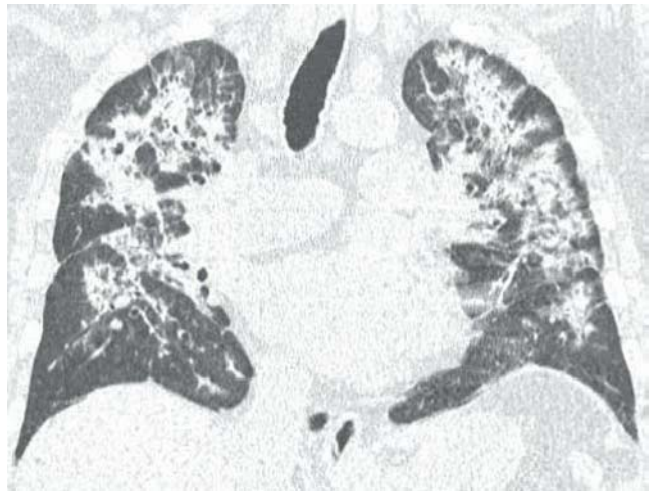
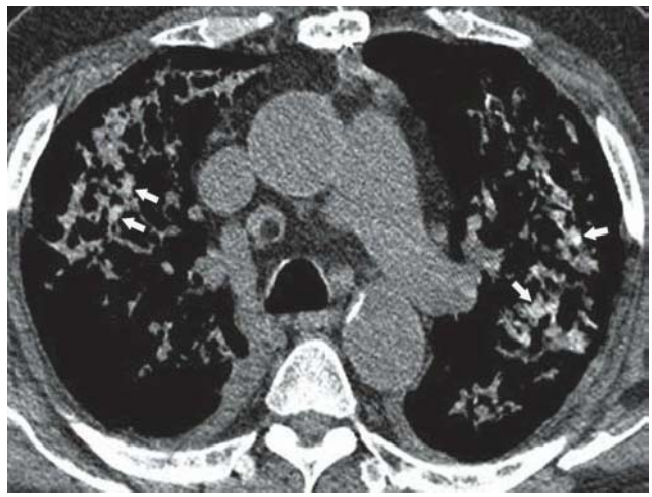


FIGURE 18.1. Nonspecific interstitial pneumonia resulting from drug reaction. HRCT shows extensive bilateral ground-glass opacities and mild peripheral reticulation and traction bronchiectasis. The patient had an NSIP reaction to methotrexate used in the treatment of psoriasis.





FIGURES 18.2 and 18.3. Amiodarone toxicity. **Figure 18.2:** Coronal reformation of a volumetric HRCT shows bilateral peribronchial areas of consolidation mainly in the middle and upper lung zones. **Figure 18.3**: Cross-sectional CT image photographed at soft tissue windows demonstrates regions of high attenuation (*arrows*) within the airspace consolidation, consistent with amiodarone deposition. The patient had a BOOP-like reaction to amiodarone.

PATHOLOGIC PATTERNS OF DRUG REACTIONS IN THE LUNG AND PLEURA

Drug reactions can affect any structure in the lung and also the pleura (Table 18.2). However, statistically, the majority of drug reactions affect the parenchyma and produce patterns that mimic ILD on imaging and biopsy[6,7] (Table 18.3).

TABLE 18.2

Drug reactions in relation to underlying anatomy

- Parenchyma—many patterns mimic ILD
  - Interstitial inflammation
  - Interstitial fibrosis
  - Granulomas, occasionally necrotizing
  - Bronchiolitis obliterans organizing pneumonia (BOOP)
  - Diffuse alveolar damage (DAD/AIP/ARDS)
  - Mimicking nonspecific interstitial pneumonia (NSIP)
  - Mimicking hypersensitivity pneumonitis (HP)
  - Mimicking usual interstitial pneumonia (UIP)
  - Mimicking sarcoid
  - Lymphoid hyperplasia and lymphocytic interstitial pneumonia (LIP)
  - Pulmonary alveolar proteinosis (PAP)
  - Eosinophilic pneumonias (acute and chronic)
- Parenchyma—nodular lesions, occasionally necrotizing
- Airways (bronchiolitis, constrictive bronchiolitis (bronchiolitis obliterans, bronchiectasis, asthma)
- Vascular (vasculitis, hemorrhage, veno-occlusive disease, pulmonary hypertensive changes)
- Pleura (pleural fibrosis, eosinophilic pleuritis)

A major problem in interpreting potential drug reactions is that some drugs can cause many different reaction patterns, sometimes even in the same biopsy (Table 18.3, Figs. 18.5 and 18.6). For example, methotrexate can produce non-necrotizing granulomas, hypersensitivity pneumonitis (HP)-like reactions, nonspecific interstitial pneumonia (NSIP)-like interstitial pneumonias, bronchiolitis obliterans interstitial pneumonia (BOOP, organizing pneumonia), ARDS (diffuse alveolar damage, DAD), and UIP-like fibrosis (Figs. 18.4 to 18.7). Conversely, the number of pathologic reaction patterns is limited, and a given reaction pattern can be seen with many drugs (Table 18.3). A further complication is that some combinations of drug/agents seem to produce toxicity or increase toxicity beyond that seen with either agent used singly: combinations of chemotherapeutic drugs and radiation are a good example.[6]

Sometimes it is not possible to separate a drug reaction from the underlying disease. For example, penicillamine, a drug used in the past as a treatment for rheumatoid arthritis, appears to produce DAD, BOOP, constrictive bronchiolitis, and follicular bronchiolitis; however, all of these lesions are seen in patients with rheumatoid arthritis who have not been treated with penicillamine, and it is still unclear whether penicillamine itself is really producing adverse effects. Many drugs produce immunosuppression, and such patients are at risk of infections that may mimic drug reactions (see Case Study 5).

Drugs that produce ILD-like patterns are listed in Table 18.3.[8,9] Note that the reaction pattern headers in Table 18.3 emphasize the word "-like" because drug reactions frequently are not perfect mimics of the notional ILD. Often drug reaction patterns are subtly different from the classic lesion or there is a combination of reaction patterns that will not normally occur together, or the reaction

TABLE 18.3

ILD-like drug reactions by pathologic pattern

Alveolar hemorrhage

- Abciximab
- Amiodarone
- Amphotericin B
- Clopidogrel
- Cocaine
- Cyclophosphamide
- Haloperidol
- Heparin
- Hydralazine
- Mitomycin
- Nitrofurantoin
- Penicillamine[a]
- Propylthiouracil
- Sirolimus
- Statins
- Streptokinase
- Sulfonamides
- Tirofiban
- Urokinase

BOOP

- Acebutolol
- Amiodarone
- Bleomycin
- Busulfan
- Carbamazepine
- Cephalexin
- Chlorambucil
- Chloroquine
- Chlorozotocin
- Cocaine
- Cromolyn sodium
- Cytosine arabinoside
- Cyclophosphamide
- Fludarabine

TABLE 18.3

ILD-like drug reactions by pathologic pattern (*Continued*)

Gold salts[a]
Herceptin (transtuzumab)
Hexamethonium
Hydroxyurea
Interferon-α
Mecamylamine
Mesalamine
Methotrexate
Minocycline
Mitomycin
Nilutamide
Nitrofurantoin
Penicillamine[a]
Phenytoin
Sirolimus
Sotalol
Statins
Sulfasalazine
Tocainide
Topotecan

Constrictive bronchiolitis

Aurothiopropanosulfonite
Busulfan
CCNU
Penicillamine[a]
Tiopronin

DAD

Amiodarone
Amitriptyline
Azathioprine
BCNU
Bleomycin
Busulfan
Carbamazepine
CCNU
Cocaine
Colchicine
Cyclophosphamide
Cytosine arabinoside
Deferoxamine
Docetaxcel
Fludarabine
Gemcitabine
Gold salts
Hexamethonium
Interferon-α
Interferon-α
Melphalan
Methotrexate
Mitomycin
Nitrofurantoin
Penicillamine[a]
Procarbazine
Pyrimethamine
Statins
Sirolimus
Streptokinase
Sulfathiazole
Teniposide
Urokinase
Vinblastine
Zinostatin

DIP-like

Amiodarone
Cyclophosphamide
Hydroxyurea
Nitrofurantoin
Sulfasalazine
Tocainide

Edema

Cytosine arabinoside
Cocaine
Haloperidol
Hydrochlorothiazide
Lidocaine
Methotrexate
Mitomycin
Opiates
Opiate antagonists
Penicillin
Propranolol
Salicylates

Eosinophilic pneumonia

Acebutolol
Acetominophen
Aminoglutethimide
Aminosalicylic acid
Amiodarone
Ampicillin
Bleomycin
Bicalutamide
Captopril
Carbamazepine
Chlorpropamide
Clarithyromcyin
Cocaine
Cromolyn sodium
Dapsone
Diflunisal
Ethambutol
Fludarabine
Imipramine
Indomethacin
Infliximab
Interferon-α
Meloxicam
Mephenesin
Mesalazine
Minocycline
Montelukast
Nabumetone
Naproxen
Nitrofurantoin
Nabumetone
Oxaliplatin
Phenylbutazone
Piroxicam

(*continued*)

TABLE 18.3

ILD-like drug reactions by pathologic pattern (*Continued*)

Eosinophilic pneumonia

Procarbazine
Prontosil
Pyrimethamine
Ranitidine
Sotalol
Sulfonamides
Tenidap
Tetracycline
Trazodone
Venlafaxine

Follicular bronchiolitis

Pencillamine[a]

Granulomas

Acebutolol
Cromolyn sodium
Etanercept
Fluoxetine
Infliximab
Interferon-α
Leflunomide
Methotrexate
Sirolimus
Venlafaxine

HP-like

Docetaxcel
Fluoextine
Hydroxyurea
Methotrexate

HP-like

Nitrofurantoin
Paclitaxel
Procarbazine
Statins
Sulfasalazine

LIP-like

Amiodarone
Carabamazepine
Phenytoin

PAP

Busulfan
Fentanyl patch
smoke
Imatinib
Leflunomide
Sirolimus

Sarcoid-like

Etanercept
Infliximab

UIP-like/NSIP-like

Amiodarone
BCNU
Busulfan
Chlorambucil
Cocaine
Cyclophosphamide
Docetaxcel
Fludarabine
Fluoxetine
Gemcitabine
Gold salts[a]
Hydroxyurea
Imatinib
Interferon-α
L-tryptophan
Leflunomide
Melphalan
Methotrexate
Methyl CCNU
Nilutamide
Nitrofurantoin
Pravastatin
Phenytoin
Pindolol
Procarbazine
Quinidine
sulfate
Sirolimus
Statins
Sulfasalazine
Ticlopidine
Tocainide
Topotecan
Tryptophan
Uracil mustard

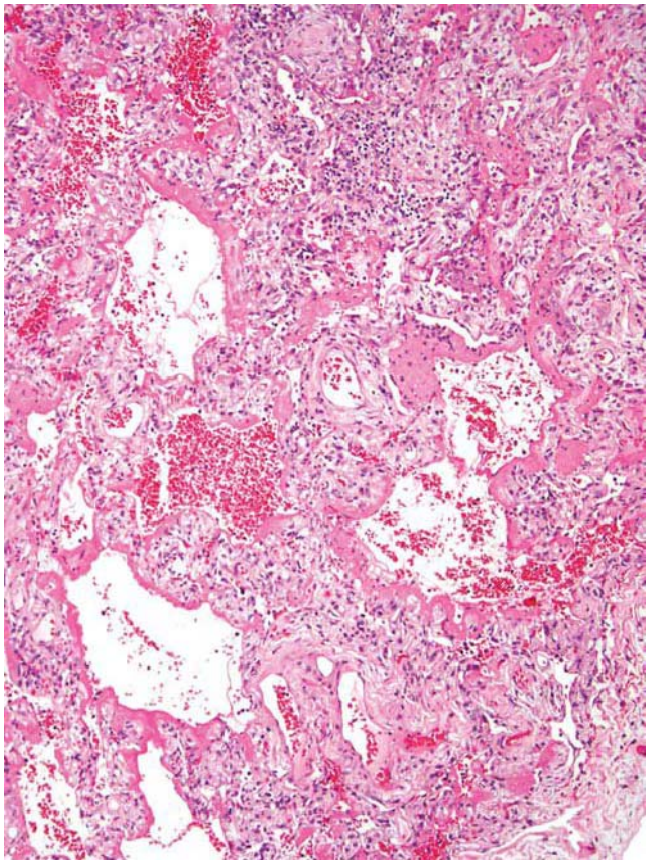
Tissue infiltration by coarsely foamy macrophages

Amiodarone
Statins

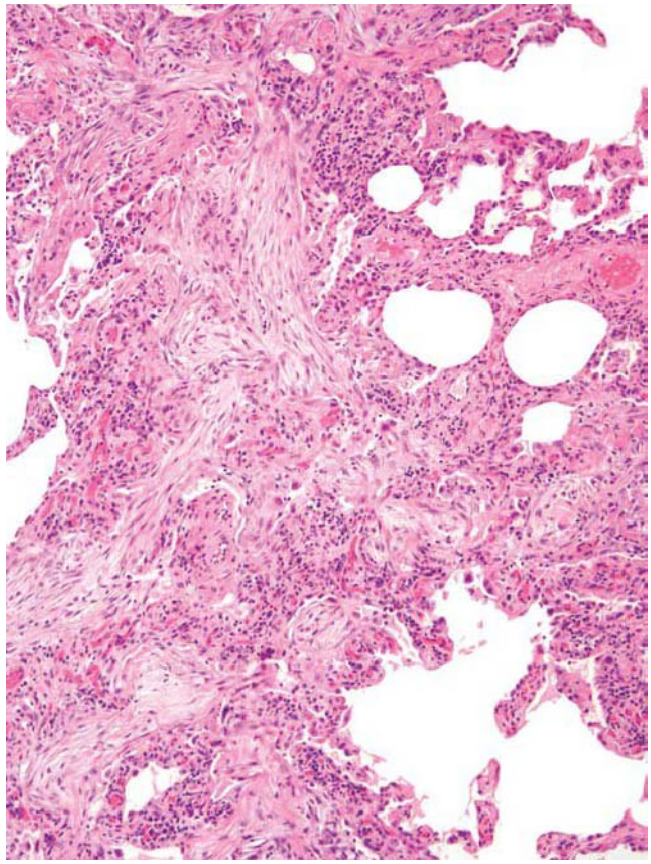
[a]It is unclear whether gold salts and penicillamine actually produce pulmonary toxicity, or whether the putative reaction patterns to these drugs are really caused by the underlying rheumatoid arthritis.
Modified from Myers JL, El-Zammar O. Pathology of drug-induced lung disease. In: Katzenstein A-LA. *Surgical Pathology of Non-Neoplastic Lung Disease*. 4th ed. 85–126 Saunders Elsevier, 2006; Myers J. Other diffuse lung diseases. In: Churg A, Myers J, Tazelaar H, et al. eds. *Thurlbeck's Pathology of the Lung*. 3rd ed. New York, NY: Thieme Medical Publishers; 2005:601–676; and Pneumotox.Com.

pattern varies from area to area within the biopsy. One useful rule of thumb is that when one encounters a strange pattern of ILD, a pattern that does not fit classic descriptions of a specific disease, a drug reaction or an underlying collagen vascular disease should be considered. Table 18.3 should also be viewed with caution because such tabulations are out of date the minute they are compiled, and pneumotox.com or the literature should be consulted if a drug/reaction pattern is not listed in Table 18.3.

Amiodarone, and to a much lesser extent, statins, bear special mention because they will produce coarsely foamy alveolar macrophages in anyone who has accumulated a sufficient dose.[1,10] By themselves, foamy macrophages are not a cause of a clinical drug reaction unless they are



18.4



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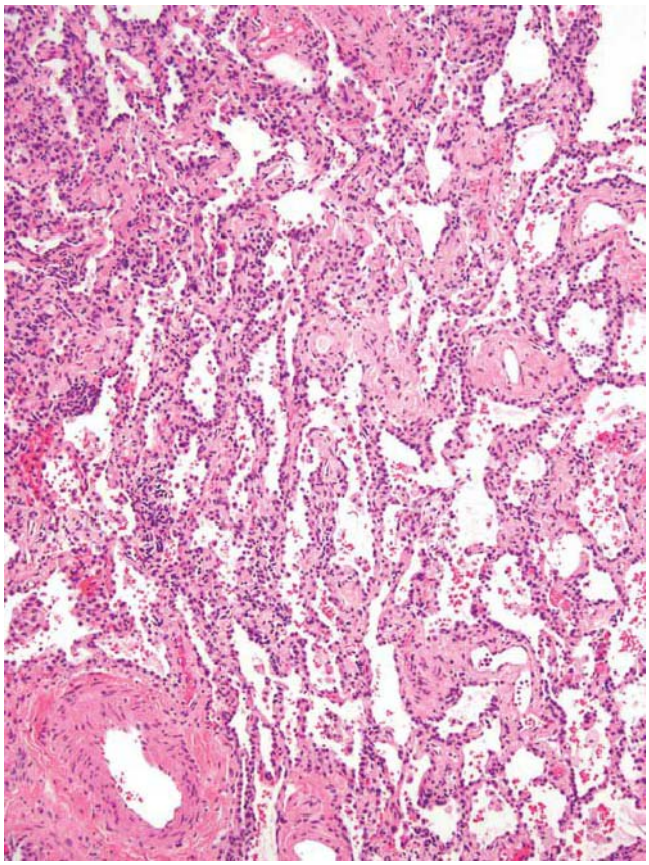

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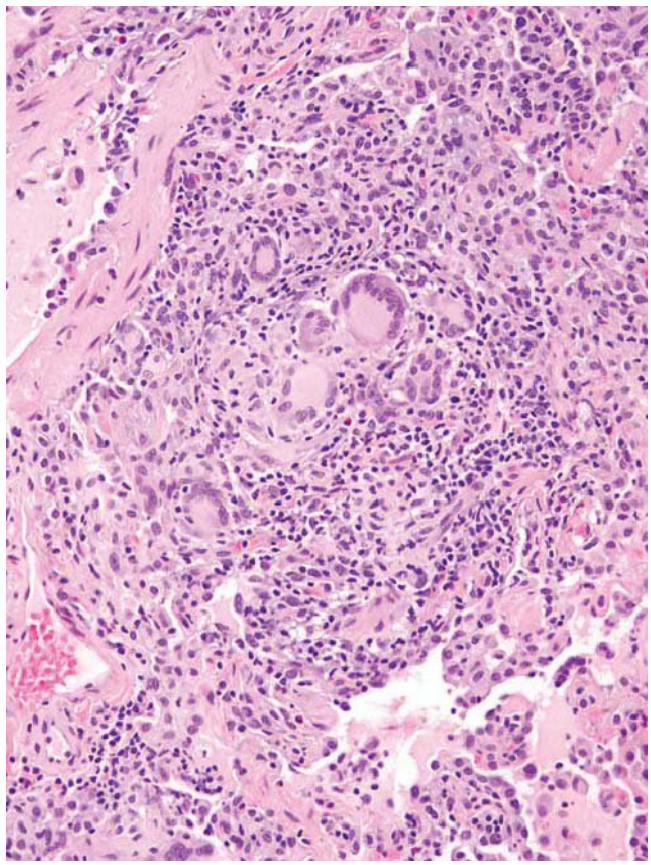
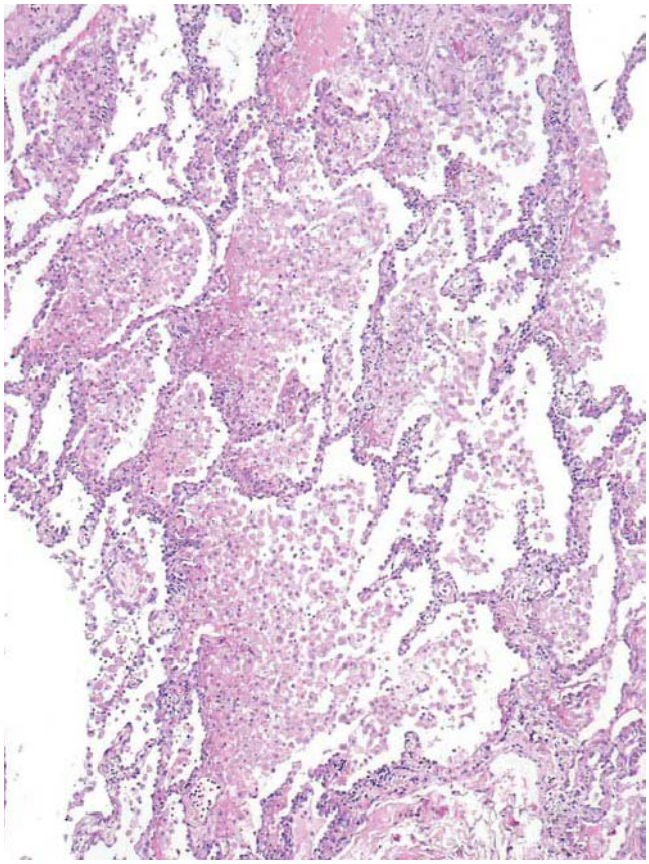
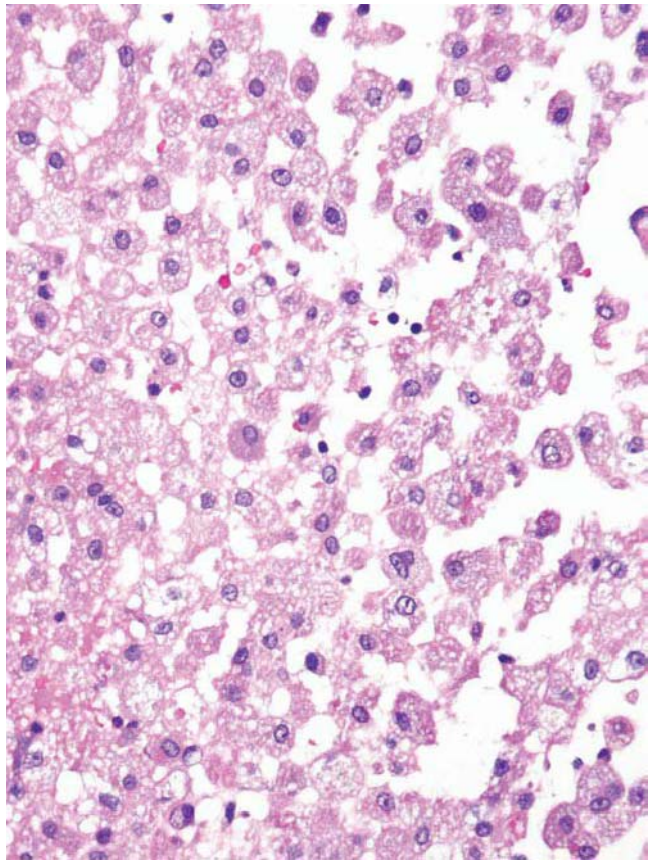


18.7

FIGURES 18.4 to 18.7. Examples of different reaction patterns caused by the same agent, methotrexate. **Figure 18.4:** DAD; **Figure 18.5:** BOOP; **Figure 18.6:** Fibrotic NSIP; **Figure 18.7:** Granulomas. Note that Figures 18.5 and 18.6 are from the same case.





FIGURES 18.8 and 18.9. Marked macrophage reaction to amiodarone. Amiodarone induces small numbers of coarsely foamy macrophages in everyone who takes the drug, and these are useful for identifying exposure to amiodarone but by themselves do not indicate a pathologic reaction. However, the extensive filling of airspaces by such macrophages in this example (corresponding to radiologic GGOs) is indicative of drug toxicity. This is only one of the numerous patterns of toxicity seen with amiodarone.

present in enormous numbers and produce a DIP-like pattern (Figs. 18.8 and 18.9).

Cytotoxic drugs are another problem because many can produce very atypical appearing nuclei (see Fig. 7.26) that in some cases mimic viral inclusions and in others make one worry about a neoplasm. However, cytotoxic drugs do not produce the pattern of lepidic growth seen in bronchoalveolar carcinoma (adenocarcinoma in situ).

EXAMPLES OF SPECIFIC CASES ILLUSTRATING THE APPROACH TO DRUG REACTIONS

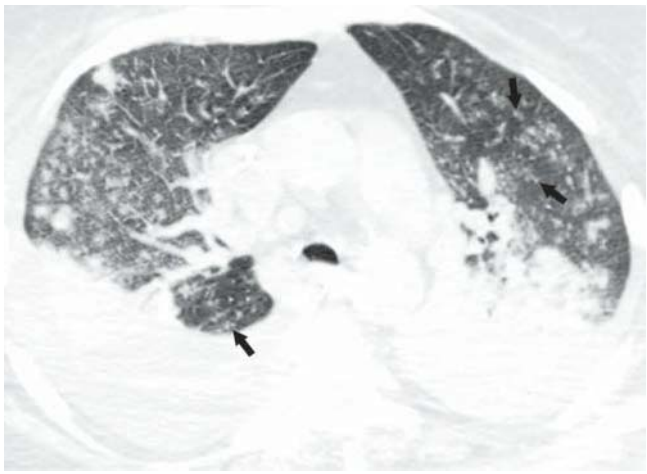
Case studies 1 to 6 provide examples of how to apply the principles set out in Table 18.1 to specific cases.

Case Study 1: Granulomatous Lung Disease Caused By an Anti-TNF Agent

A 48-year-old woman with a long history of rheumatoid arthritis, treated with methotrexate, developed increasingly severe joint disease. Humira (anti-TNF agent) was started in September of 2008. By October 2008, she had diffuse opacities on imaging (Fig. 18.10), and was in respiratory failure. A biopsy was performed and showed a granulomatous interstitial pneumonia (Figs. 18.12 and 18.13). Special stains and cultures of the biopsy for organisms were negative. Humira was discontinued. Her symptoms rapidly disappeared, and there was considerable clearing of her radiologic abnormalities by January 2009 (Fig. 18.11).

Analysis of case study 1

- The temporal sequence is correct: disease appeared shortly after starting Humira.
- The pathologic reaction pattern is correct: anti-TNF agents are known to produce granulomatous interstitial pneumonias.[11,12] Note that the pattern of disease does not correspond exactly to any ordinary ILD. Strange ILD-like patterns are a common finding with drug reactions and sometimes an important clue to the diagnosis.
- The process was not infectious by special stains and cultures.
- The temporal sequence suggests that Humira rather than methotrexate is the offending agent.



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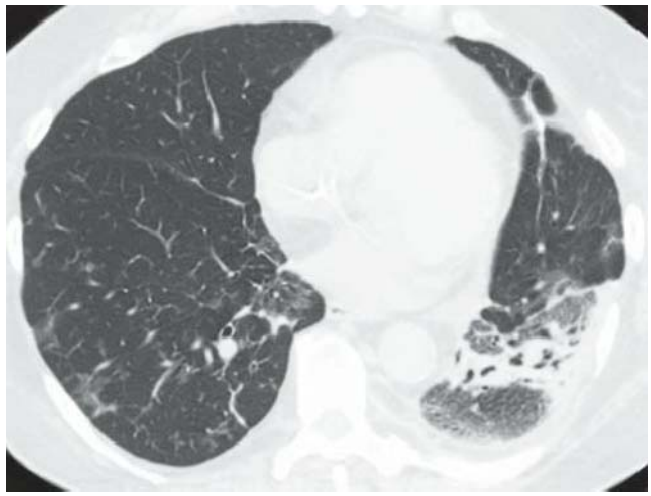

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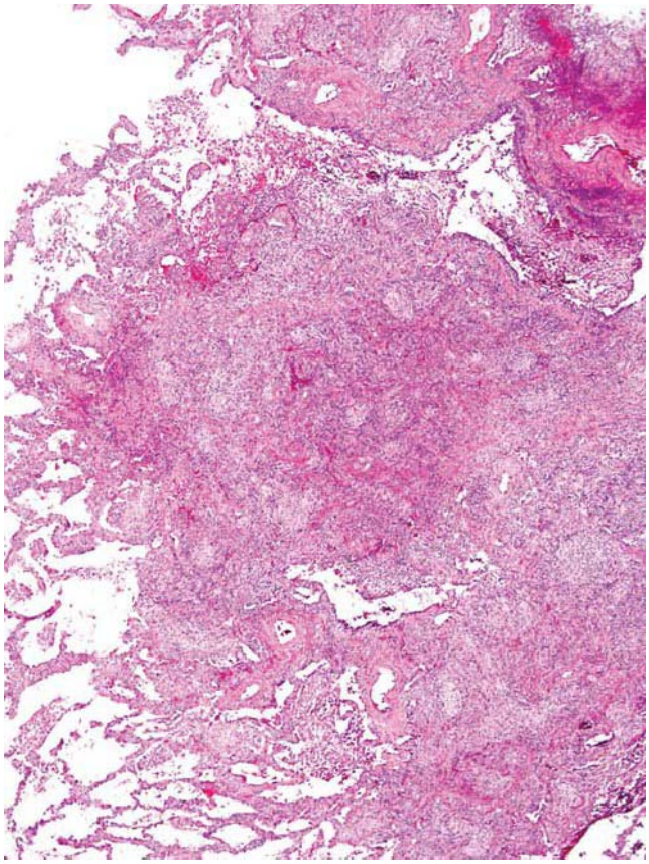

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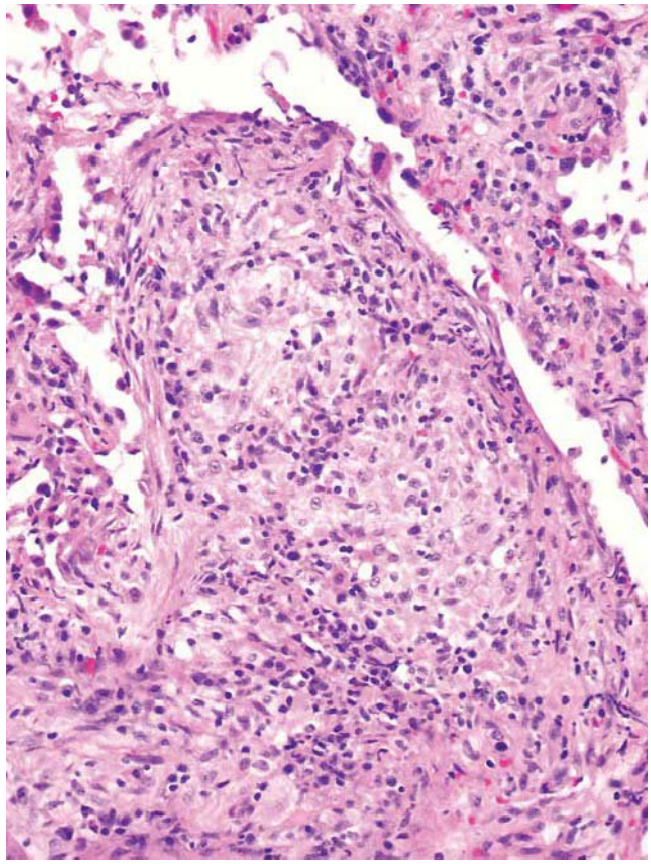


18.13

FIGURES 18.10 to 18.13. Case study 1: Humira toxicity. **Figure 18.10:** CT image shows extensive bilateral consolidation, patchy GGOs, and several small nodules (*arrows*). The patient also had bilateral pleural effusions. **Figure 18.11:** CT performed 3 months after Figure 18.10 shows marked improvement. The findings now comprise patchy bilateral GGOs, left lower lobe consolidation and volume loss and residual left pleural effusion and thickening. **Figure 18.12:** Low-power view of the biopsy shows masses of aggregated, somewhat ill-defined, granulomas, seen better at higher power in **Figure 18.13.** A granulomatous response somewhat mimicking sarcoid is well described with anti-TNF agents.

- Conclusion at the time of biopsy: granulomatous interstitial pneumonia consistent with reaction to Humira (i.e., probable drug reaction).
- Conclusion after drug discontinued and patient improved: definite drug reaction to Humira.

Case Study 2: Pulmonary Alveolar Proteinosis Caused By Smoking Fentanyl Patches

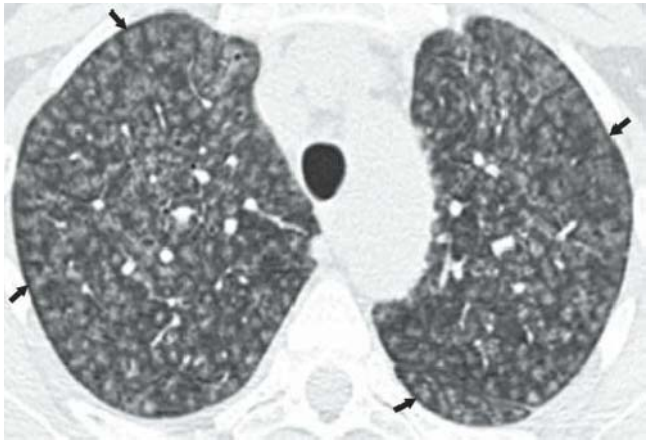
A 50-year-old woman presented with a 1-month history of cough and shortness of breath (SOB). She was afebrile. She had smoked about half a pack of cigarettes per day for 35 years. She had been prescribed Fentanyl patches for chronic pain related to old burn scars, but she smoked the patches instead of applying them to the skin. An initial chest radiograph showed diffuse parenchymal opacities and a CT scan demonstrated innumerable ground-glass centrilobular nodules (Fig. 18.14). A biopsy was performed and showed pulmonary alveolar proteinosis (PAP) but with some degree of interstitial fibrosis and interstitial eosinophils (Figs. 18.15 and 18.16). Post biopsy she discontinued smoking the Fentanyl patches and her symptoms and radiologic abnormalities rapidly cleared.

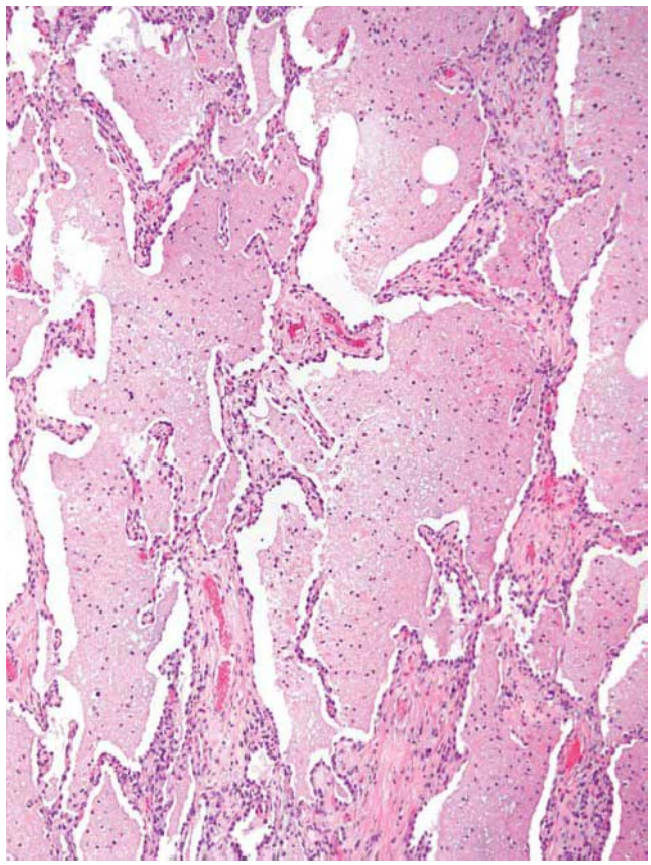
Analysis of case study 2

- The temporal sequence supports a reaction to Fentanyl patch smoke.
- The imaging studies are typical of an inhalation injury.
- PAP is occasionally seen as a drug reaction, but there is nothing in the literature on Fentanyl patch smoke.
- Conclusion post biopsy: pulmonary alveolar proteinosis consistent with reaction to Fentanyl patch smoke (probable drug reaction).
- Conclusion after drug discontinued and disease disappeared: definite reaction to Fentanyl patch smoke.

Case Study 3: Eosinophilic Pneumonia as a Late Complication of Asacol (Mesalamine) Use

A 45-year-old woman had used Asacol (Mesalamine) for ulcerative colitis since 1998 with a good response. In November 2005 she developed cough, and night sweats and was found to have an elevated sedimentation rate. In January 2006, iritis and abnormal chest imaging with migratory peripheral consolidation (Fig. 18.17) were seen, and she was found to have a peripheral eosinophilia.





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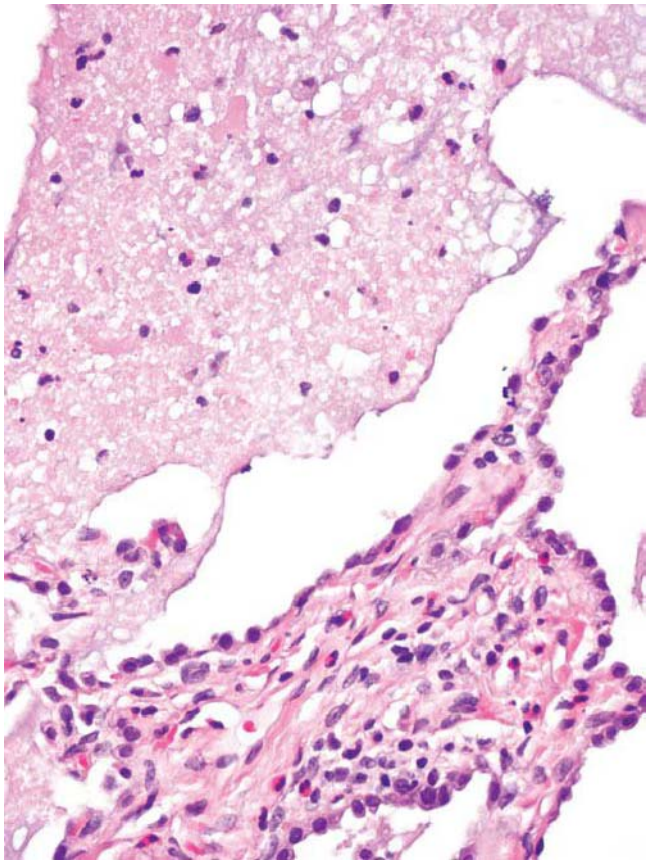


FIGURES 18.14 to 18.16. Case study 2: PAP caused by smoking Fentanyl patches. **Figure 18.14:** HRCT demonstrates bilateral centrilobular ground-glass nodules (*arrows*) and mild patchy GGOs. The centrilobular distribution is consistent with an inhalational injury. **Figures 18.15** and **18.16** show alveolar filling by proteinosis material and a modest degree of interstitial fibrosis, and eosinophils. Fibrosis is uncommon in PAP and eosinophils are very rare; The combination of findings suggests a drug reaction.

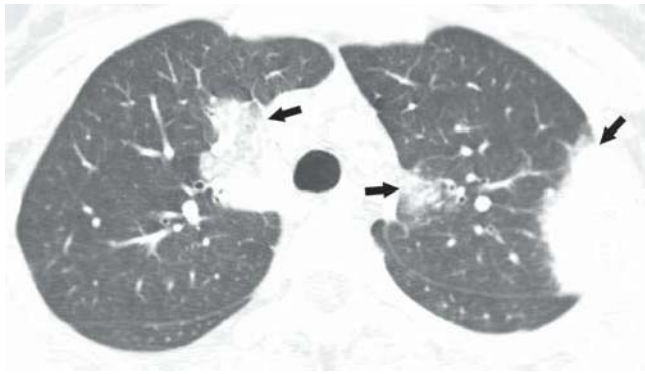
A transbronchial biopsy (Figs. 18.18 and 18.19) showed an eosinophilic pneumonia, in this instance appearing largely as BOOP, a common pathologic pattern in chronic eosinophilic pneumonia (see Chapter 15).

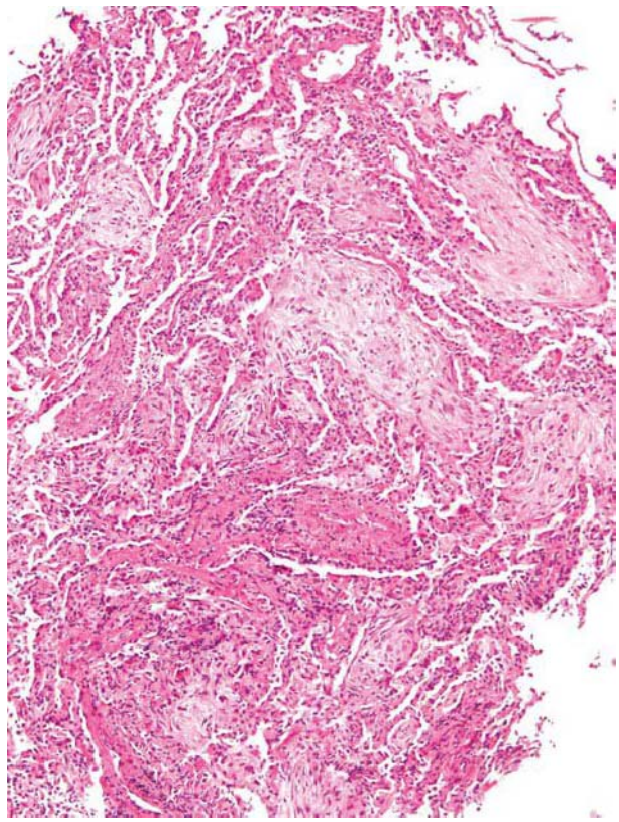
Analysis of case study 3

- The peripheral eosinophilia, imaging, and biopsy are characteristic of eosinophilic pneumonia and eosinophilic pneumonias are a common form of drug reaction.
- The development of eosinophilic pneumonias after Asacol use is well established in the literature.[2]
- The temporal sequence is somewhat unusual because of the 7-year hiatus between beginning drug use and the appearance of an adverse reaction; however, cases of this type with long temporal gaps as a reaction to Asacol have been published.[2]
- There is no other obvious cause for an eosinophilic pneumonia.
- Conclusion at the time of biopsy: eosinophilic pneumonia consistent with reaction to Asacol (probable drug reaction).
- Comment: No follow-up information was available, but disappearance of her pulmonary disease would put this case into the category of definite drug reaction.

Case Study 4: Constrictive Bronchiolitis Possibly Caused By Leflunomide in a Patient With Rheumatoid Arthritis

A 40-year-old woman presented with progressive SOB. She had a 10-year history of rheumatoid arthritis, treated with steroids. Because of increasingly severe disease, Leflunomide (Arava) was started a few months before she became short of breath. Pulmonary function testing showed





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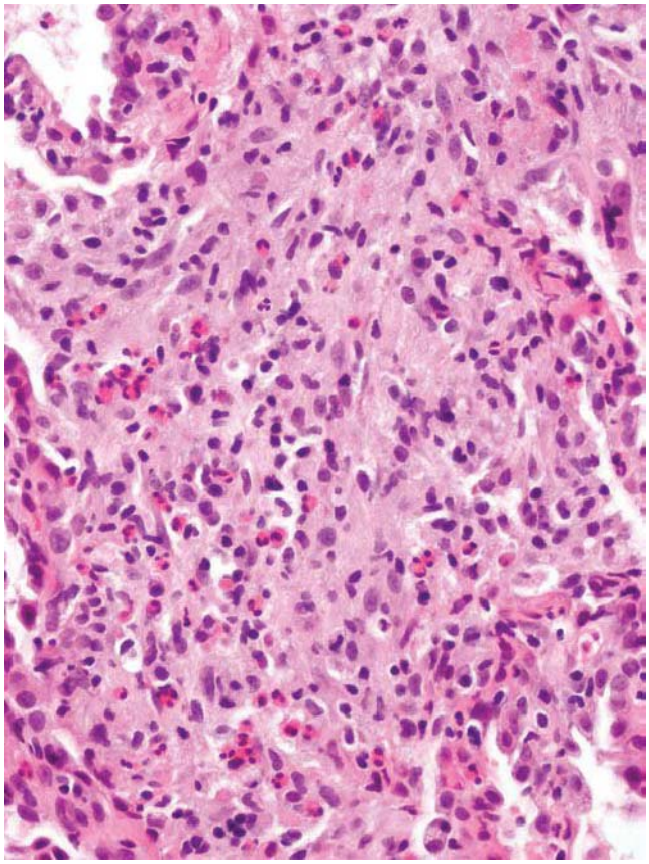

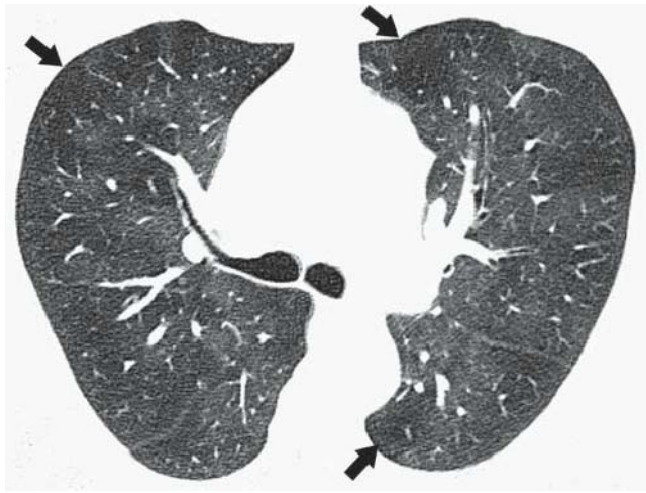

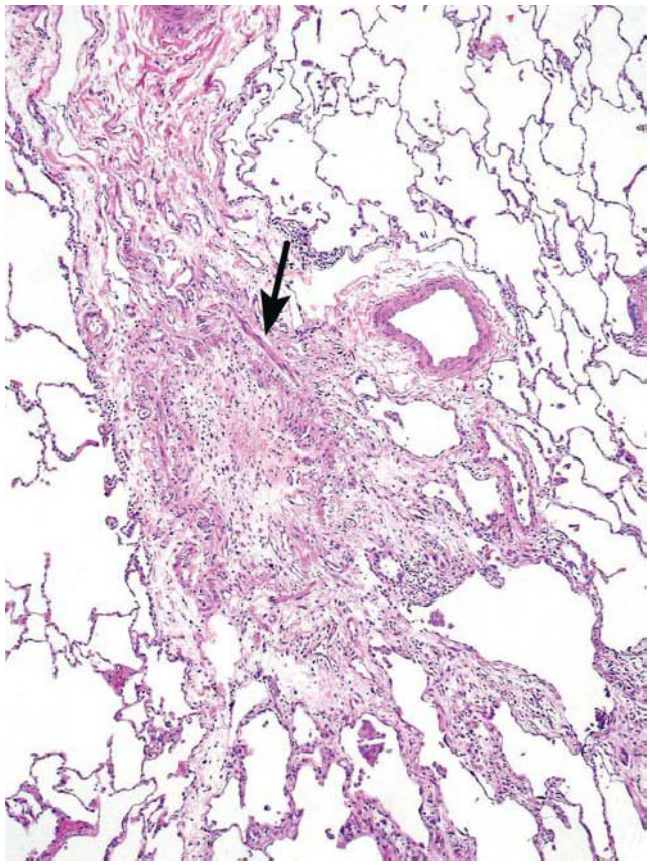

FIGURES 18.17 to 18.19. Case study 3: Eosinophilic pneumonia induced by Asacol. **Figure 18.17:** CT image shows bilateral peripheral areas of consolidation (*arrows*) in both lung apices. The pattern and distribution are characteristic of eosinophilic pneumonia. **Figures 18.18 and 18.19:** Transbronchial biopsy shows a pattern of BOOP, but the high-power view demonstrates numerous eosinophils. Chronic eosinophilic pneumonia (CEP) frequently mimics BOOP. Eosinophilic pneumonias are a very common drug reaction pattern.

airflow obstruction not responsive to bronchodilators. Imaging demonstrated extensive air trapping (Fig. 18.20). Lung biopsy showed constrictive bronchiolitis (bronchiolitis obliterans) (Figs. 18.21 to 18.23).

Analysis of case study 4

- The temporal sequence is correct for a drug reaction.
- Leflunomide is known to cause eosinophilic pneumonias, NSIP-like reactions, granulomas, and pulmonary alveolar proteinosis (www.pneumotox.com), but has not been reported to cause constrictive bronchiolitis.
- Rheumatoid arthritis itself is an established cause of constrictive bronchiolitis.[13]
- Conclusion: possible drug reaction. Sign out the biopsy as "surgical lung biopsy showing constrictive bronchiolitis. This might be a reaction to Leflunomide but might also be caused by underlying rheumatoid arthritis."
- Comment: If follow-up showed that discontinuing Leflunomide stabilized her pulmonary function, then this would be evidence for a definite drug reaction.

Case Study 5: Boop as a Possible Reaction to Cyclophosphamide

A 71-year-old woman was treated with steroids and cyclophosphamide for glomerulonephritis. A few weeks after

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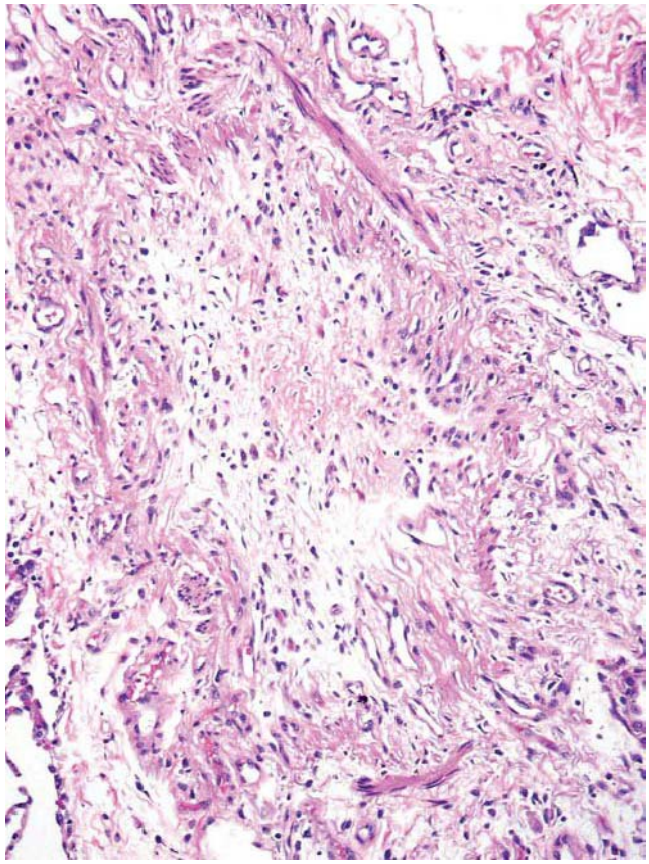
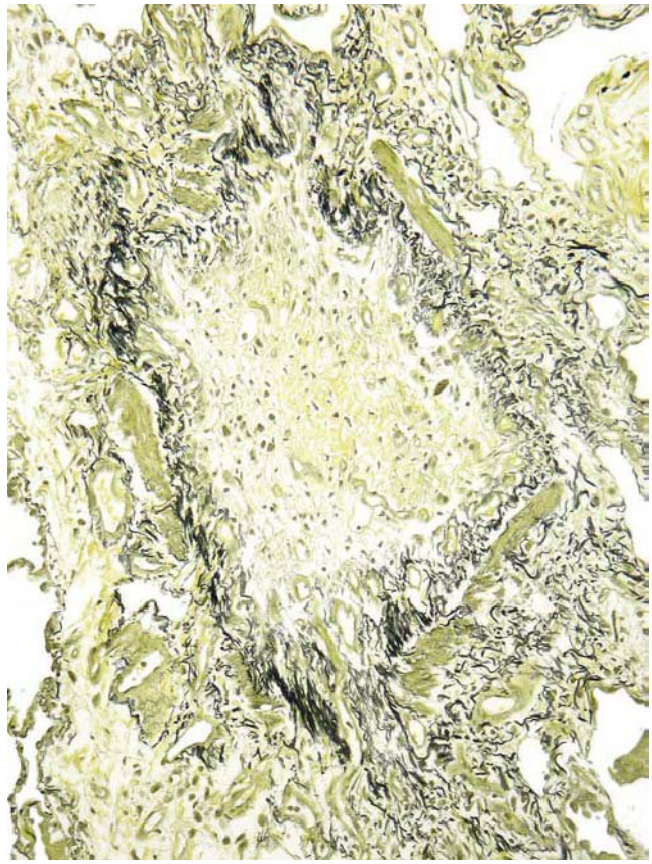




FIGURES 18.20 to 18.23. Case study 4: Constrictive bronchiolitis possibly induced by Leflunomide in a patient with rheumatoid arthritis. **Figure 18.20:** HRCT demonstrates bilateral areas of decreased attenuation and vascularity (*arrows*). Redistribution of blood flow to relatively normal lung results in areas of increased attenuation and vascularity. The findings are characteristic of constrictive bronchiolitis (bronchiolitis obliterans). **Figure 18.21:** Low-power view of the biopsy shows what at first appears to be a scar (*arrow*) next to a pulmonary artery branch. At higher power (**Fig. 18.22**) there is remnant muscle in the scar, and elastic stain (**Fig. 18.23**) confirms that this is a completely fibrosed bronchiole. In this case it was impossible to determine whether the disease was caused by the drug or the underlying rheumatoid arthritis.

treatment was begun, she developed SOB. HCRT showed peripheral consolidation. A VATS biopsy was performed and showed BOOP (Fig. 18.24). Special stains and cultures of the biopsy were negative

Analysis of case study 5

- The temporal sequence is correct for a drug reaction.
- The negative stains and cultures of the biopsy suggest that this is not BOOP on the basis of an *overt* infection.
- BOOP is well described in the literature as a reaction to cyclophosphamide,[14] but BOOP is a very common and fairly nonspecific finding in lung biopsies from immunocompromised patients.
- Biopsy should be signed out as "surgical lung biopsy showing BOOP. BOOP can be caused by cyclophosphamide but is a common finding in immunocompromised patients. Infection needs to be ruled out."
- As it stands, this is a possible drug reaction. If the clinical and imaging picture improved after discontinuing cyclophosphamide, then this would be a probable to definite drug reaction.

Case Study 6: Mixed Pattern of ILD Caused By Chemotherapeutic and Anti-Estrogen Agents

A 75-year-old woman presented with shortness of breath. She had been treated for the preceding 2 years with paclitaxel (Taxol), carboplatin, docetaxel (Taxotere), and topotecan for stage IV ovarian cancer. Imaging (Fig. 18.25) showed mild peripheral reticulation (indicative of underlying fibrosis) and some ground-glass opacities. VATS biopsy showed a fibrosing interstitial pneumonia, BOOP (not illustrated), and fibrotic damage to small airways (Figs. 18.26 and 18.27).

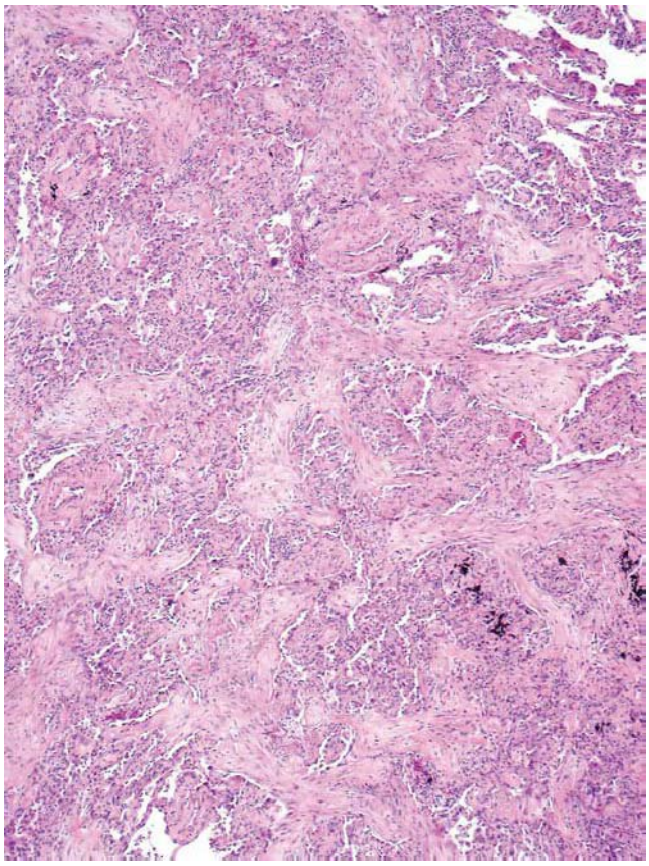


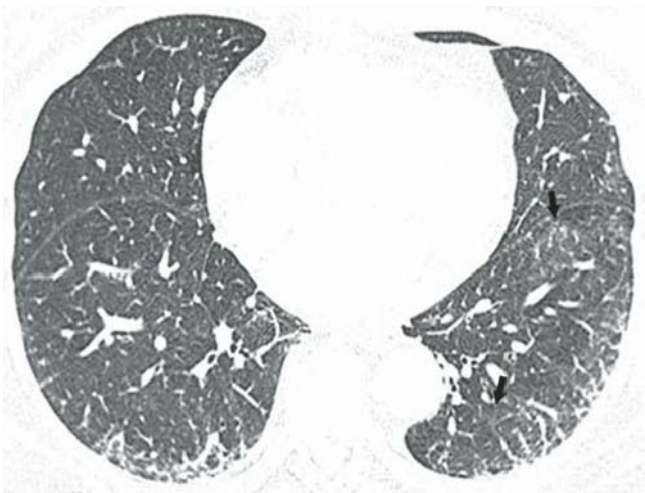
FIGURE 18.24. Case study 5: BOOP possibly induced by cyclophosphamide. The biopsy shows a typical pattern of BOOP. Cyclophosphamide is known to produce BOOP. However, BOOP is a very common finding in lung biopsies, particularly in immunocompromised patients, and the biopsy at best can be labeled a "possible" drug reaction.

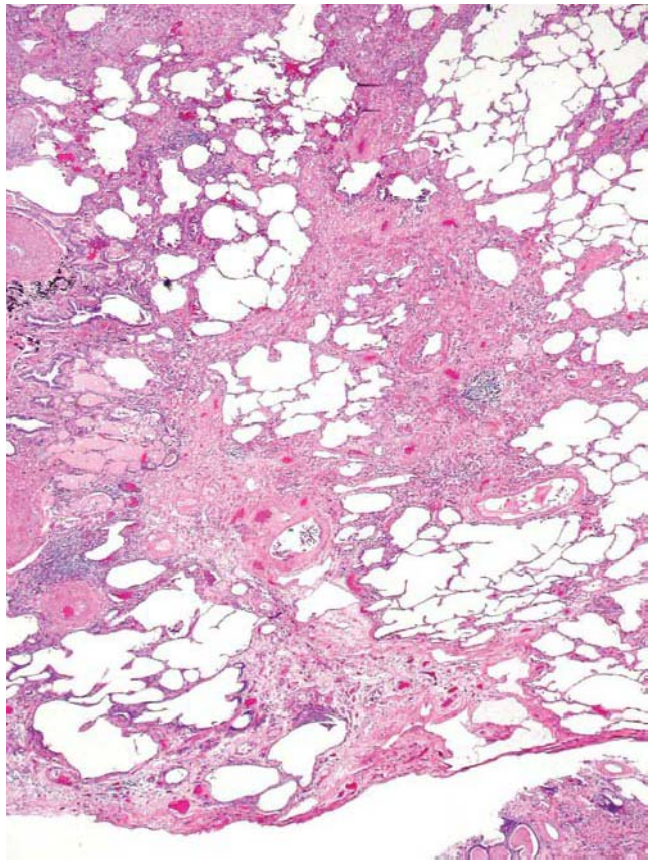
Analysis of case study 6

- Temporal sequence fits for a drug reaction.
- Many chemotherapeutic agents produce fibrotic reactions in the lung and these may develop after several years.[3] BOOP is also a common reaction to chemotherapeutic agents. Most fibrosing interstitial pneumonias do not produce bronchiolar fibrosis.
- An argument could be made that the patient actually has UIP (common in this age group) but the pattern is not quite correct for UIP and the BOOP and bronchiolar damage do not go along with UIP.
- The combination of a set of ILD-like reactions that do not normally occur together suggests a drug reaction.
- Conclusion: probable drug reaction caused by chemotherapeutic agents.

DIAGNOSTIC MODALITIES

Transbronchial biopsies are occasionally useful in documenting drug reactions when a very specific pattern such as eosinophilic pneumonia (Figs. 18.18 and 18.19) or non-necrotizing granulomas is found. Because many drug reactions produce relatively nonspecific patterns and often produce more than one pattern, VATS biopsy is usually required to obtain an adequately large sample. The choice and limitations of each type of biopsy depend very much on the drug and the specific lesion identified.





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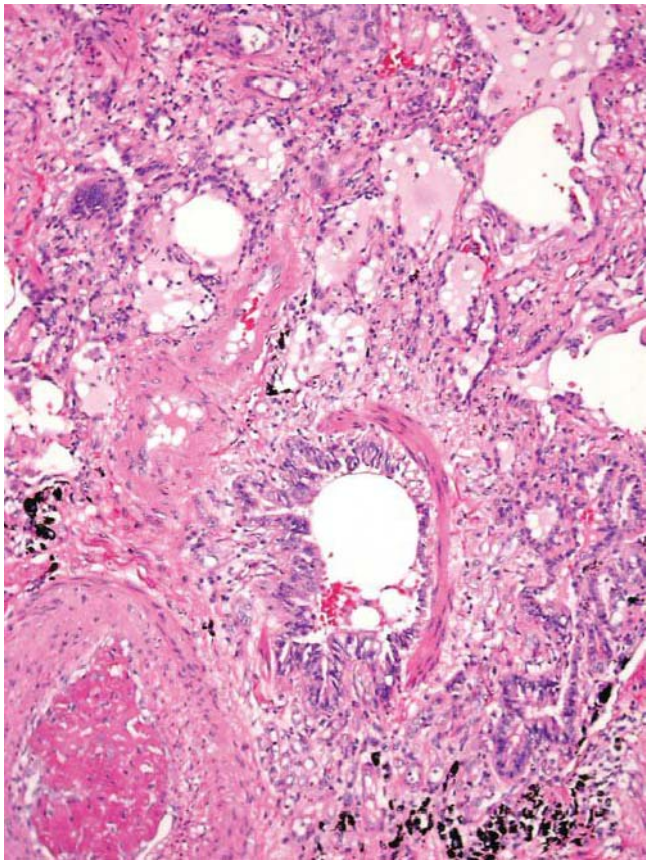

FIGURES 18.25 to 18.27. Case study 6: Unusual pattern of interstitial fibrosis probably caused by chemotherapeutic agents for ovarian cancer. **Figure 18.25:** HRCT demonstrates mild peripheral reticulation mainly in the dorsal lung regions and small patchy areas of ground-glass attenuation (*arrows*). The findings are consistent with interstitial fibrosis but are otherwise nonspecific. **Figure 18.26:** Low-power view of the biopsy shows a pattern of patchy fibrosis that somewhat mimics UIP but has more centrilobular disease and less subpleural disease than is typical of UIP At high power (**Fig. 18.27**), there is also fibrosis extending into the wall of a bronchiole. In other areas of the biopsy BOOP was present (not shown). Drug reactions can sometimes produce peculiar combinations of ILD patterns, and this is a useful clue to the diagnosis.

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CHAPTER

19

Lymphoid and Hematopoietic Processes Producing a Pattern of Interstitial Lung Disease

NOMENCLATURE ISSUES

Lymphoid proliferations in the lung go by various names (Table 19.1), some of which (follicular bronchiolitis, lymphocytic interstitial pneumonia [LIP]) are generally viewed as interstitial lung disease (ILD), while others are circumscribed processes that are nodular or produce localized consolidation. Nomenclature in this area is confused by numerous terms in the literature (Table 19.1), often not very clearly defined and by the fact that distinctions among the various entities in Table 19.1, particularly the benign diffuse proliferations, are sometimes arbitrary. As this book concerns diffuse lung disease, the emphasis in this chapter is on diffuse processes, but localized lymphoid lesions are described and illustrated in the section on differential diagnosis.

Table 19.1

Lymphoid and hematopoietic lesions in the lung

- Localized
  - Intrapulmonary lymph nodes
  - Nodular lymphoid hyperplasia (called in the past, pseudolymphoma)
  - Malignant lymphoma (primary or secondary)
- Diffuse
  - Follicular bronchiolitis and bronchitis (synonyms: pulmonary lymphoid hyperplasia, hyperplasia of BALT, hyperplasia of MALT)
  - Lymphoid hyperplasia
  - Lymphocytic interstitial pneumonia (LIP) (sometimes called diffuse lymphoid hyperplasia)
  - IgG4 sclerosing disease
  - Malignant lymphoma (primary or secondary)
  - Pulmonary involvement by leukemias

CLINICAL FEATURES

Follicular Bronchitis and Bronchiolitis

The clinical findings in follicular bronchitis and bronchiolitis are very heterogeneous. Most patients present with shortness of breath (SOB) and/or cough, but they may also have fever and weight loss. In some instances these lesions are the sequelae of pneumonia or other infections. Follicular bronchitis and bronchiolitis are also seen distal to or around bronchiectatic/bronchioloectatic airway segments, and the clinical features of bronchiectasis, particularly recurrent purulent infections, may predominate. Table 19.2 lists known

Table 19.2

Associations of follicular bronchitis and bronchiolitis

- Collagen vascular diseases, especially rheumatoid arthritis and Sjögren syndrome
- Post infectious, including pneumonias and infectious bronchiolitis
- Immunodeficiency syndromes, including HIV infection and IgA deficiency
- Distal to or around bronchiectasis and bronchiolectasis
- Dust inhalation
- Drug reactions (see Chapter 18)
- Associated with systemic eosinophilia
- Secondary to airway obstruction of any cause

From Ryu JH. Classification and approach to bronchiolar diseases. *Curr Opin Pulm Med.* 2006;12:145–151; Nicholson AG. Lymphocytic interstitial pneumonia and other lymphoproliferative disorders in the lung. *Semin Respir Crit Care Med.* 2001;22:409–422; Aerni MR, Vassallo R, Myers JL, et al. Follicular bronchiolitis in surgical lung biopsies: clinical implications in 12 patients. *Respir Med.* 2008;102:307–312; Romero S, Barroso E, Gil J, et al. Follicular bronchiolitis: clinical and pathologic findings in six patients. *Lung.* 2003;181:309–319.

associations. Pulmonary function tests can show an obstructive or restrictive pattern.[1–5]

Lymphoid Hyperplasia

Lymphoid hyperplasia as defined here (see Pathologic Features) frequently occurs as a postinflammatory and particularly postinfectious process, around mass lesions such as tumors, and in patients with bronchiectasis. It is also very common in patients with underlying collagen vascular disease, often in association with nonspecific interstitial pneumonia (NSIP) or usual interstitial pneumonia (UIP), but sometimes in otherwise morphologically normal lung. When it is not associated with follicular bronchiolitis, it probably produces no clinical symptoms and is purely a pathologic finding.

Lymphocytic Interstitial Pneumonia

LIP usually presents with cough and SOB but systemic symptoms (fever, weight loss) as well as features of an underlying disease, may be present. In adults, Sjögren syndrome is the single strongest association with LIP, accounting for about 25% of cases, but in children the most common association is with HIV infection. Other associations are listed in Table 19.3. Some cases are idiopathic and have been included in descriptions/classifications of the idiopathic interstitial pneumonias.[7] Dysproteinemias, usually hypergammaglobulinemias but sometimes hypogammaglobulinemias, are present in 80% of cases.[8] The presence of a monoclonal gammopathy suggests that the process is really a lymphoma and not LIP. Pulmonary function tests show a restrictive pattern and a decreased diffusing capacity, typical of diffuse ILD.

Table 19.3

Etiologies/associations of lymphocytic interstitial pneumonia

Collagen vascular diseases, especially Sjögren syndrome
Autoimmune diseases (primary biliary cirrhosis, myasthenia gravis, Hashimoto thyroiditis, celiac disease, pernicious anemia)
Common variable immunodeficiency
Infection with HIV (almost always in children), Epstein Barr virus, HHV8
Chronic viral hepatitis
Crohn disease
Bone marrow transplantation and graft vs. host disease
Drugs (see Chapter 18)
Idiopathic LIP

From Nicholson AG. Lymphocytic interstitial pneumonia and other lymphoproliferative disorders in the lung. *Semin Respir Crit Care Med.* 2001;22:409–422; Swigris JJ, Berry GJ, Raffin TA, et al. Lymphoid interstitial pneumonia: a narrative review. *Chest.* 2002;122:2150–2164; Travis WD, Colby TV, Koss MN, et al. *Non-Neoplastic Disorders of the Lower Respiratory Tract*. Washington, DC, WA: American Registry of Pathology; 2002:266–276.

IMAGING

The high resolution computed tomography (HRCT) findings of follicular bronchiolitis include bilateral centrilobular and peribronchial nodules and patchy ground-glass opacities (GGOs).[9] Most nodules measure less than 3 mm in diameter, although nodules up to 12 mm in diameter may be seen. The centrilobular nodules may be associated with branching linear opacities resulting in a tree-in-bud pattern (Fig. 19.1). The findings are nonspecific and resemble those seen in various other acute and chronic conditions.

The HRCT manifestations of LIP include bilateral GGOs, poorly defined centrilobular and subpleural nodules, mild interlobular septal thickening, and, in up to 70% of patients, cysts (Fig. 19.2).[10] The cysts are usually few in number and have thin walls. The abnormalities may be diffuse but tend to involve mainly the lower lobes. Although the findings are nonspecific, the presence

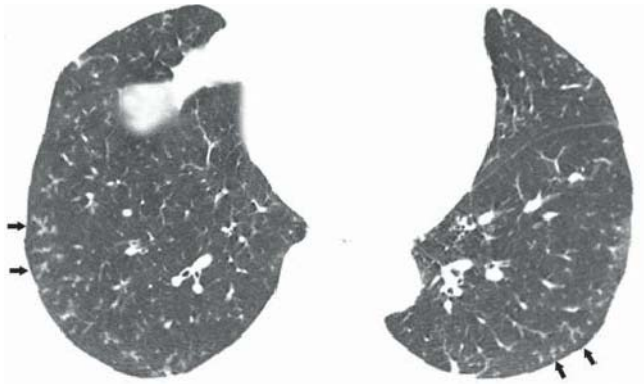


FIGURE 19.1. Follicular bronchiolitis. HRCT shows bilateral centrilobular nodular and branching opacities (*arrows*) in the peripheral lung regions. The patient was a 58-year-old man.

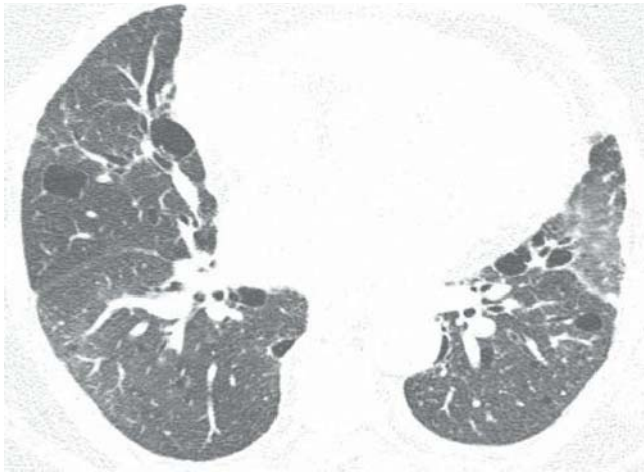


FIGURE 19.2. LIP. HRCT at the level the lower lung zones demonstrates patchy bilateral GGOs and several thin-walled cysts. The patient was a 63-year-old woman with Sjögren syndrome.

of bilateral GGOs with associated cysts in a predominantly lower lobe distribution in a patient with Sjögren syndrome is highly suggestive of LIP.

PATHOLOGIC FEATURES

Distribution of Lymphoid Tissue in the Normal Lung

In the normal lung, lymphoid tissue, called bronchial-associated lymphoid tissue (BALT) or mucosal-associated lymphoid tissue (MALT), is inconspicuous and appears as occasional small lymphoid nodules, usually without germinal centers, next to small airways (Fig. 19.3).

Pathologic Features of Benign Lymphoid Proliferations

Follicular Bronchitis and Bronchiolitis

Follicular bronchiolitis represents a hyperplasia of the normal BALT and is characterized by the formation of numerous lymphoid nodules adjacent to or within the walls of membranous or respiratory bronchioles[6] (Fig. 19.4). When the same process occurs around bronchi it is termed follicular bronchitis. The lymphoid nodules may or may not contain reactive germinal centers and there can be one nodule or many around any particular airway (Fig. 19.4). The nodules sometimes appear to compress the airway and compromise the airway lumen (Fig. 19.4). Follicular bronchitis/bronchiolitis may also be seen around bronchiectatic and bronchiolctatic airways (Fig. 19.5). Typically the germinal centers contain B cells that stain for CD20 and the surrounding lymphocytes are T cells that stain for CD3 (Figs. 19.6 and 19.7).

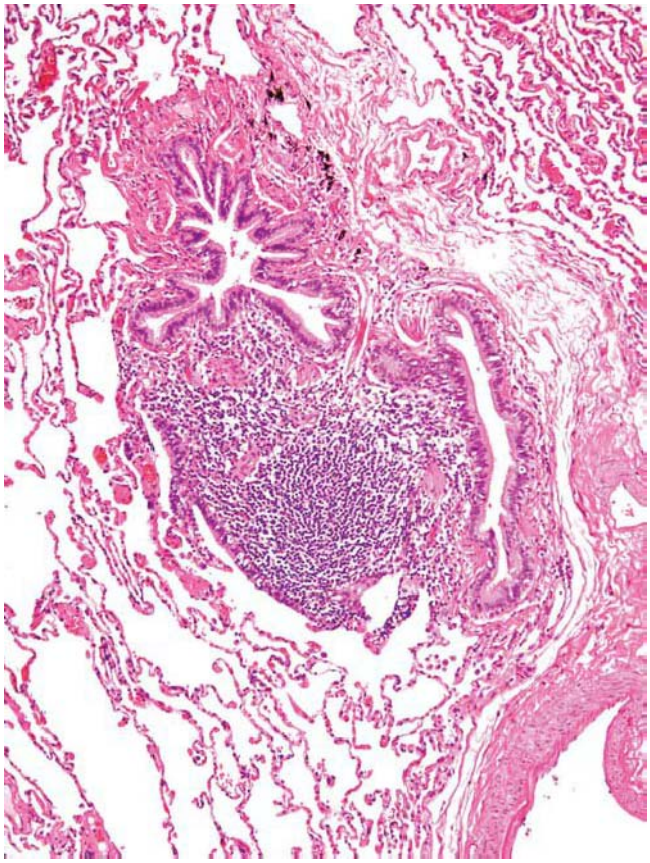


FIGURE 19.3. Normal BALT. Lymphoid aggregates such as this are seen in normal lung but should be infrequent and scattered; numerous lymphoid aggregates of this type mandate a diagnosis of follicular bronchiolitis (see Fig. 19.4).

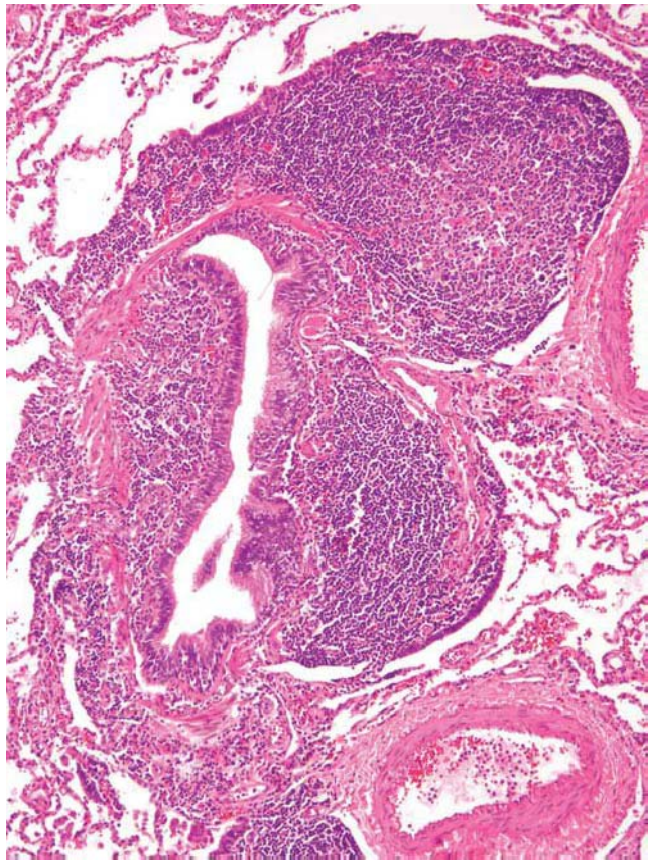


FIGURE 19.4. Follicular bronchiolitis (same case as Fig. 19.1). Lymphoid aggregates surround and compress a bronchiole. Note the suggestion of a lymphoid follicle, a common finding in follicular bronchiolitis. There were many such aggregrates in the biopsy.

Lymphoid Hyperplasia

We use the term lymphoid hyperplasia to refer to the formation of multiple discrete lymphoid aggregates, with or without follicles, in alveolar walls, interlobular septa, and the pleura. As opposed to LIP, the aggregates are *discontinuous* spatially separated lesions (Figs. 19.8 and 19.9). Such cases sometimes have follicular bronchiolitis as well, and some authors view lymphoid hyperplasia as defined here as a variant of follicular bronchiolitis.[11] Lymphoid

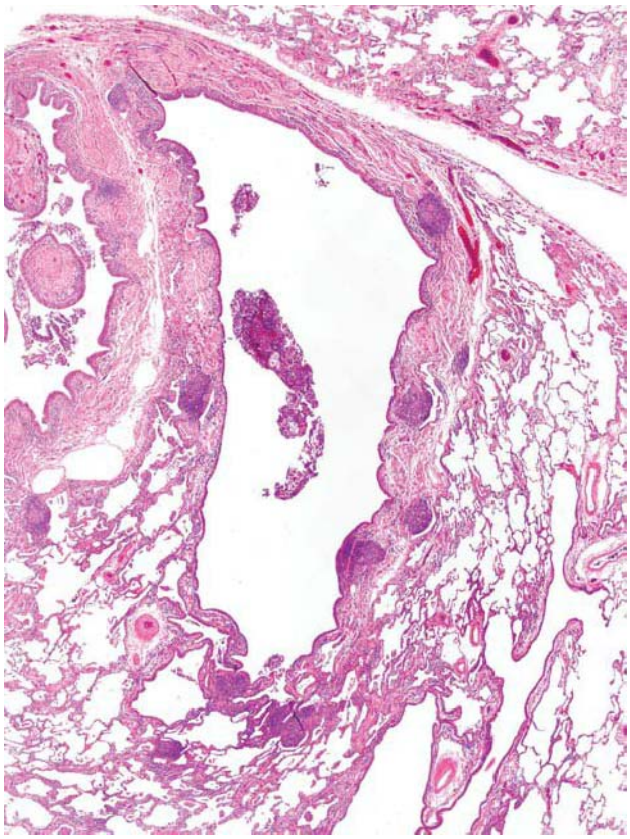


FIGURE 19.5. Follicular bronchitis. Numerous lymphoid follicles are present around a bronchiectactic bronchus.

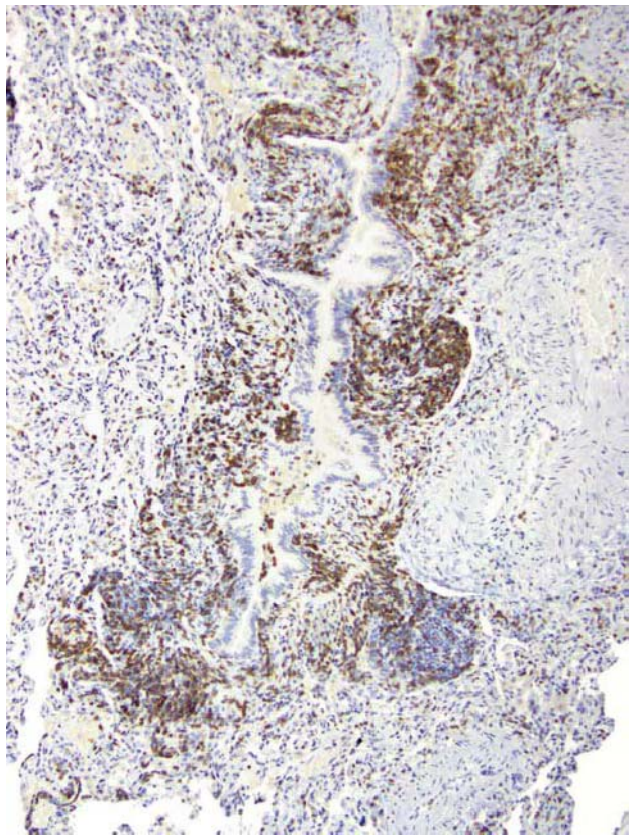


FIGURE 19.7. CD3 stain of the same bronchiole as Figure 19.6 shows a mild diffuse T cell infiltrate.

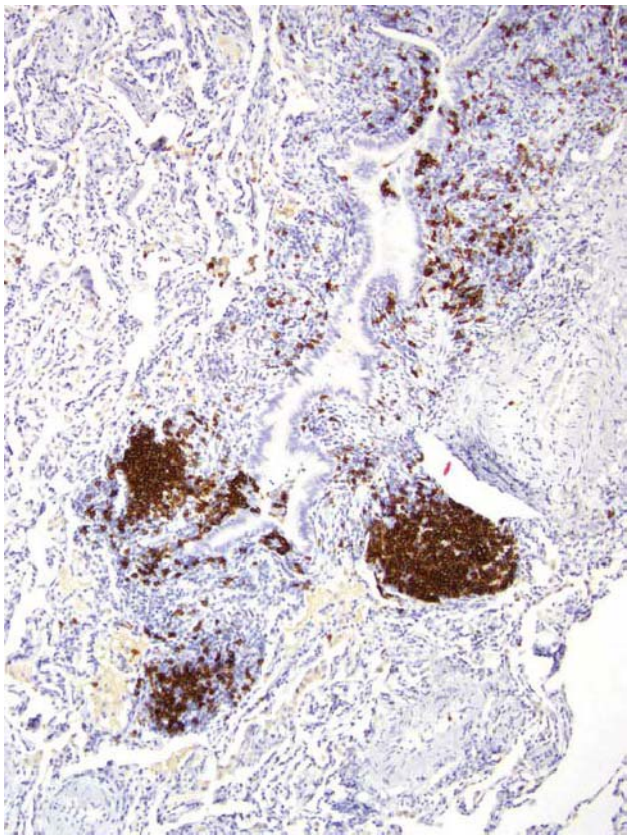


FIGURE 19.6. Follicular bronchiolitis. CD20 stain of a longitudinally cut bronchiole shows B cell aggregation in follicles

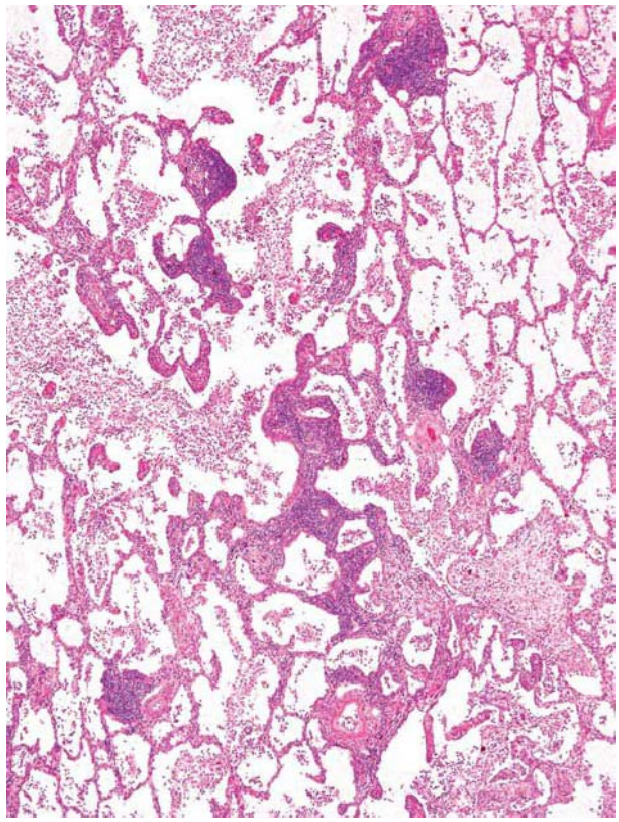


FIGURE 19.8. Lymphoid hyperplasia next to a bronchogenic carcinoma. The lymphoid reaction was localized to the region of lung containing the tumor.

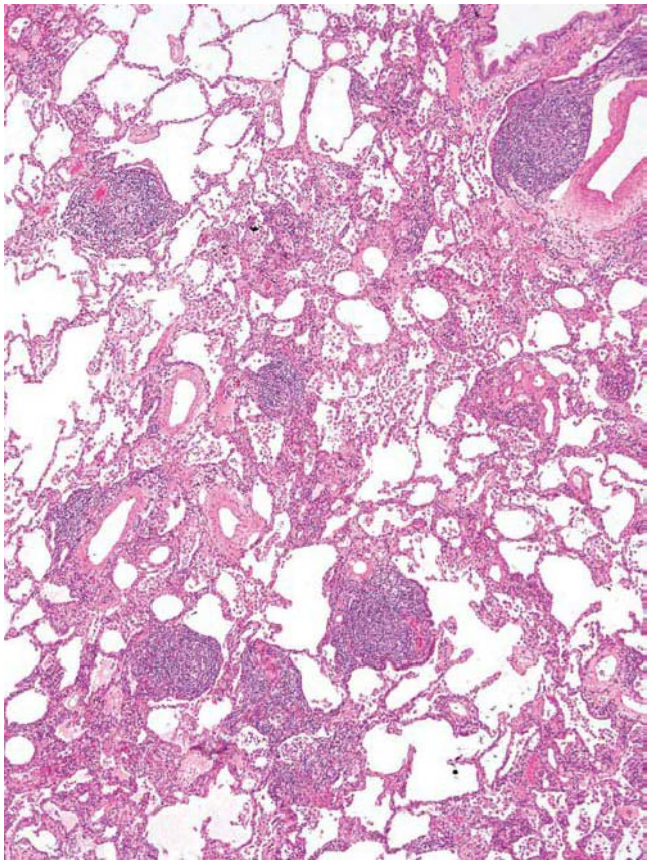
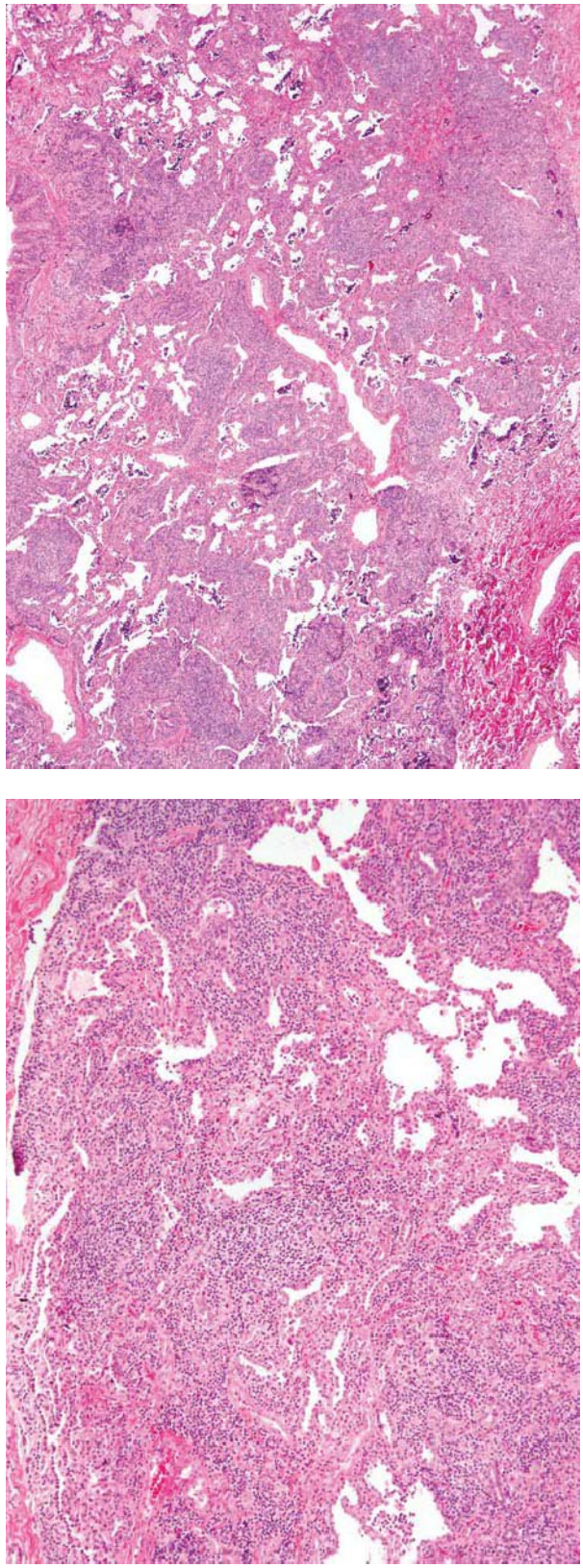


FIGURE 19.9. Lymphoid hyperplasia in a patient taking amiodarone. Some authors will classify this as follicular bronchiolitis, but the lymphoid aggregates do not only associate with bronchioles.

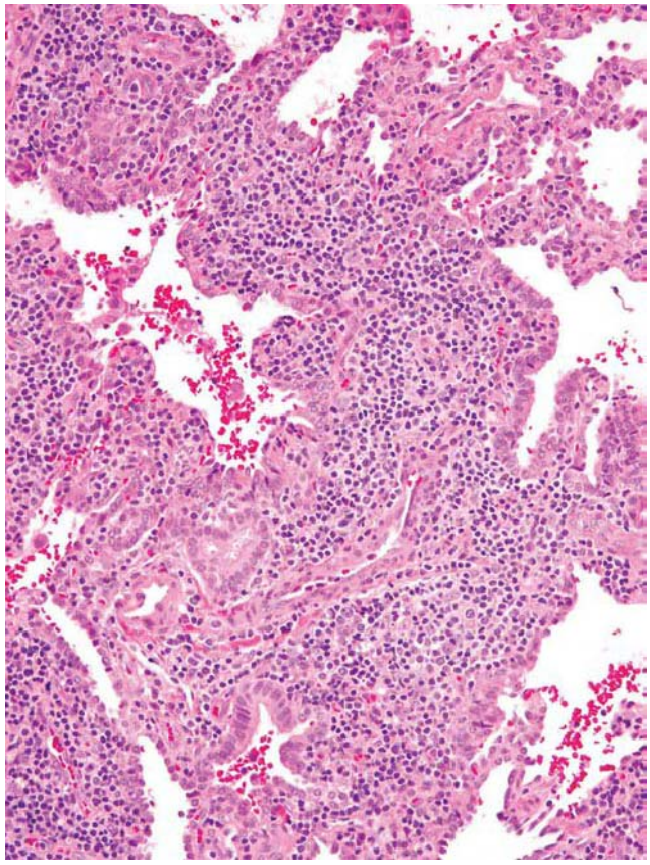
hyperplasia can be present over large areas of lung, particularly in collagen vascular disease patients or where the process represents a drug reaction (Fig. 19.9) but can occur in a more localized fashion as well (Fig. 19.8).

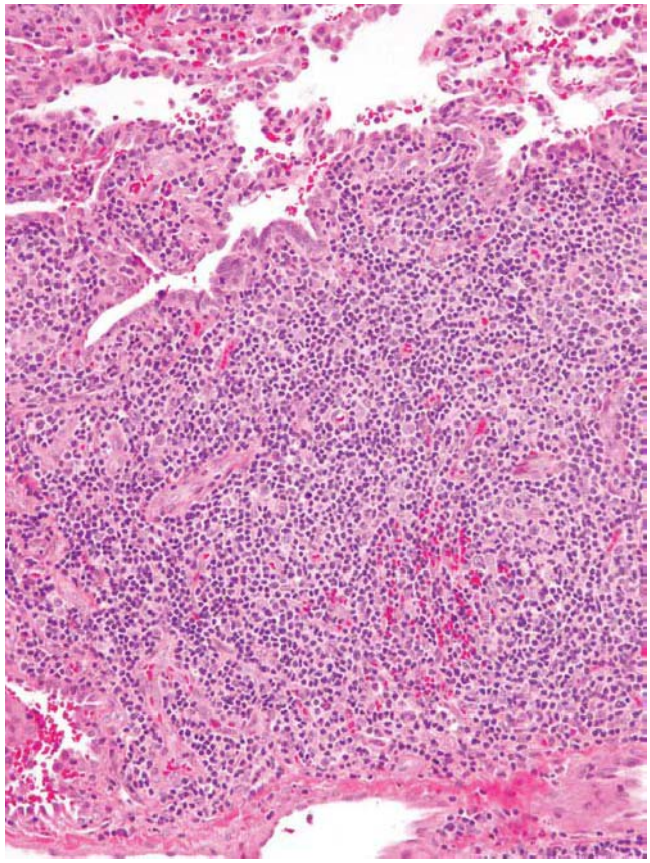
Lymphocytic interstitial pneumonia

In LIP the lymphoid proliferation is dense and interstitial and involves alveolar walls in a *continuous* fashion over large areas of the lung. Germinal centers may or may not be present, but the defining feature is the marked expansion of alveolar walls by small lymphocytes and plasma cells (Figs. 19.10 to 19.16) sometimes to the point that the airspaces are obliterated and the alveolar walls become contiguous. B cells are found in germinal centers, when these are present, with the remaining lymphocytes usually T cells (Figs. 19.17 and 19.18). Small noncaseating granulomas or individual giant cells are common (Fig. 19.14). Cysts may be seen on imaging but are rarely biopsied; in our experience such cysts have a mixture of fibrous tissue and chronic inflammatory cells in their walls (Figs. 19.19 to 19.22). In advanced cases interstitial fibrosis and honeycombing may be found (Figs. 19.23 and 19.24). By definition in LIP the process is polyclonal.



FIGURES 19.10 and 19.11. Lower- and medium-power views of a case of LIP in a patient with IgA deficiency. Note the diffuse lymphoid infiltrate which in this example does not form lymphoid follicles, and the marked widening of the alveolar walls, in some areas to the point of confluence.





FIGURES 19.12 and 19.13. Higher-power views of the case shown in Figures 19.10 and 19.11. Note the relatively homogeneous lymphoplasmacytic infiltrate and the marked widening of the alveolar walls.

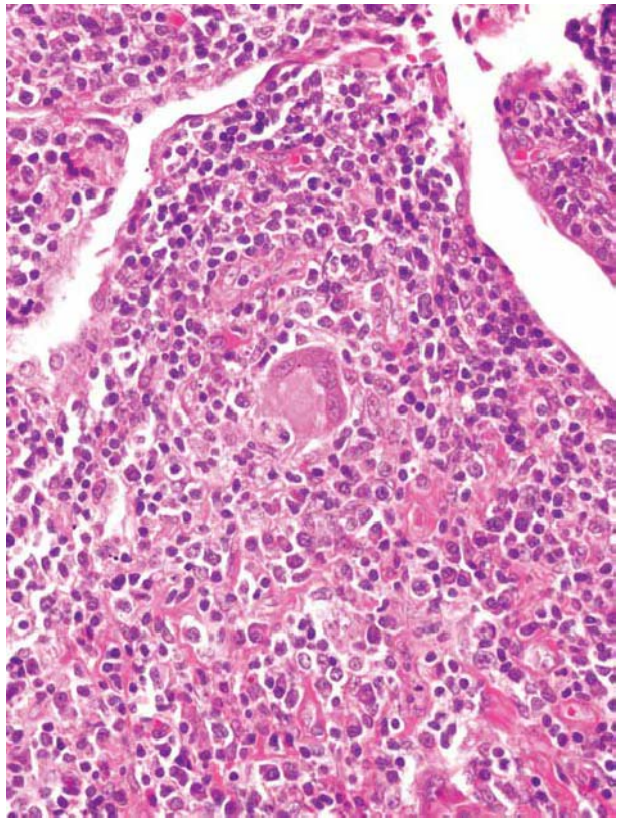
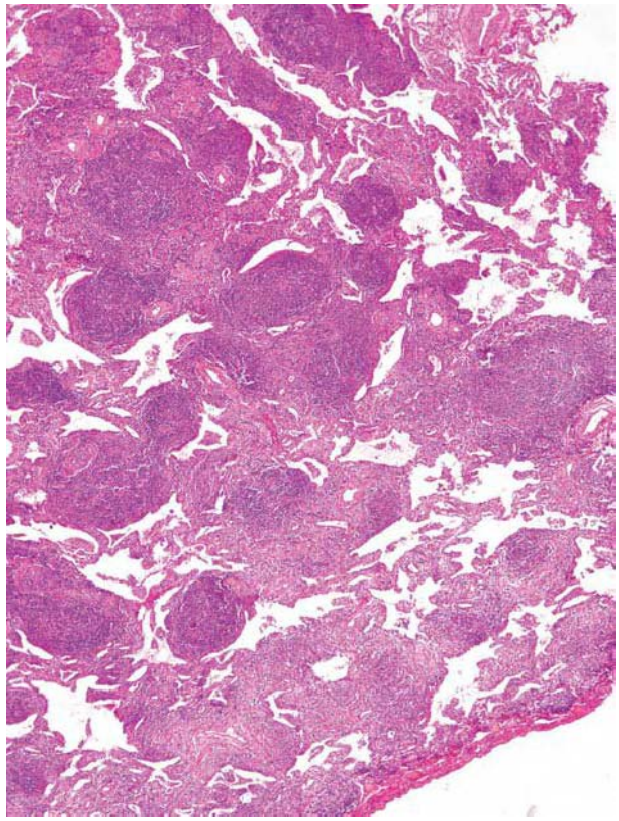
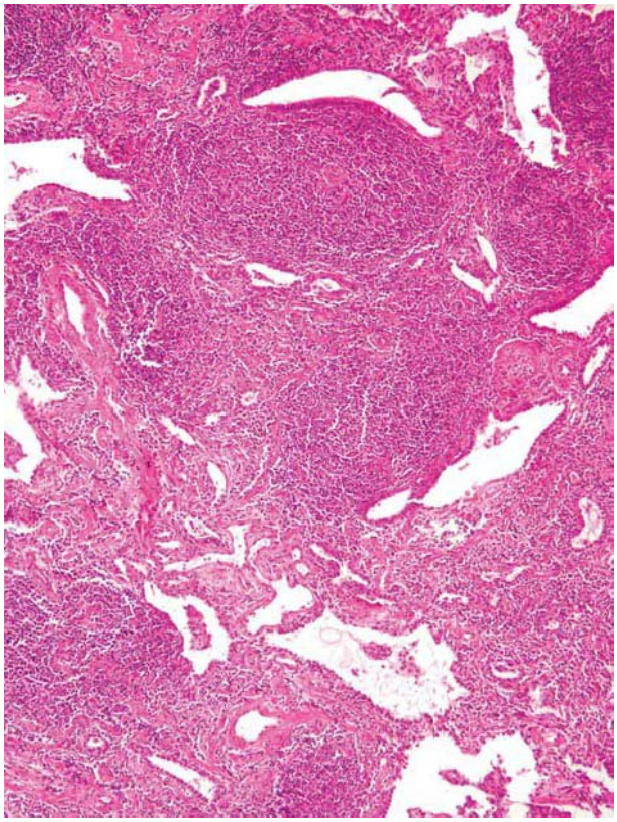


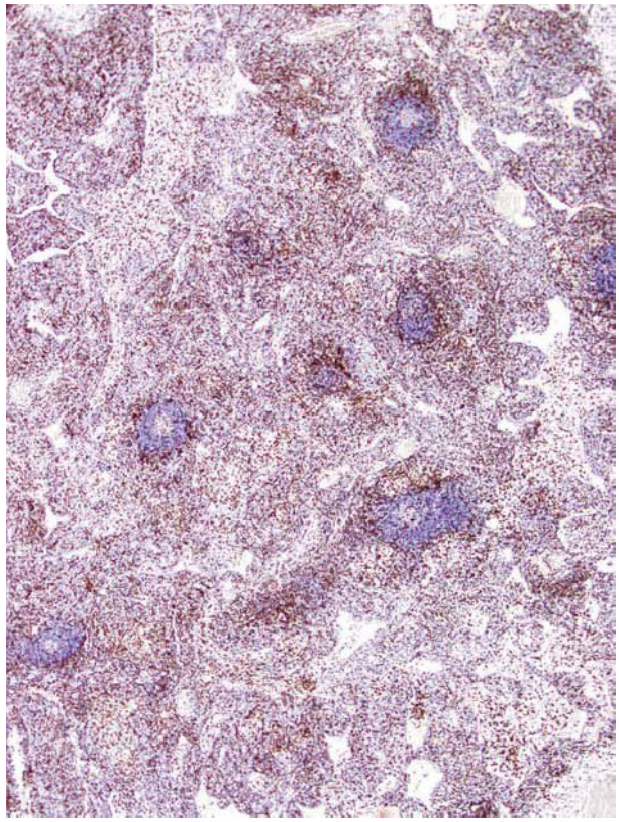
FIGURE 19.14. A giant cell in the midst of lymphocytes and plasma cells in a case of LIP. Interstitial giant cells and small loose granulomas are a common finding in LIP.



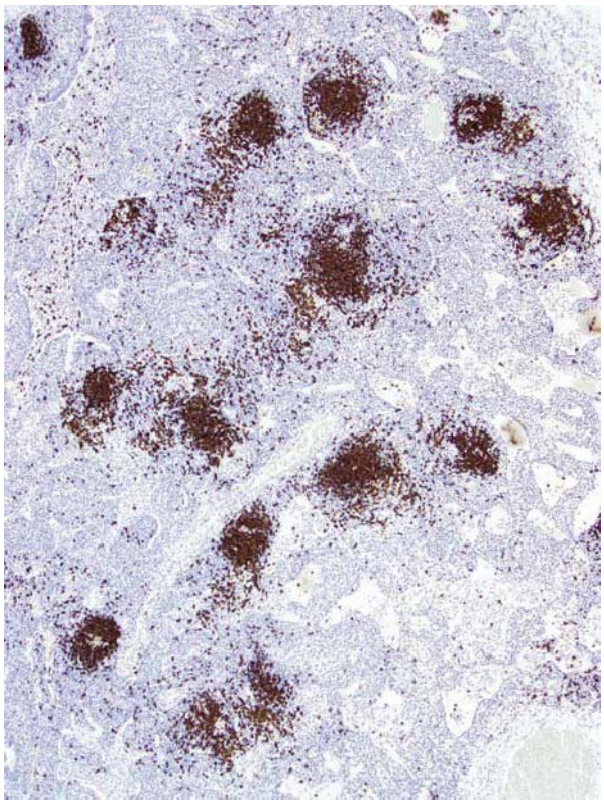
FIGURES 19.15 and 19.16. Legend appears on following page



FIGURES 19.15 and 19.16. Low- and medium-power views of a case of LIP in which there is a suggestion of lymphoid follicle formation.



FIGURES 19.17 and 19.18. CD20 (**Fig. 19.17**) and CD3 (**Fig. 19.18**) stains of a case of LIP showing follicle-like aggregates of B cells and a diffuse T cell infiltrate. Not all cases of LIP show formation of follicles and in some cases the B cell infiltrate is more diffuse and raises a question of a lymphoma.



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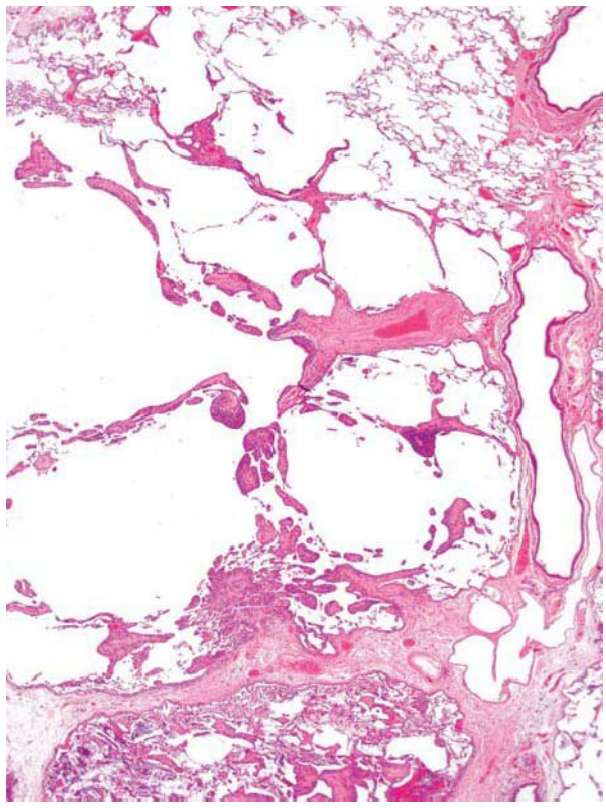
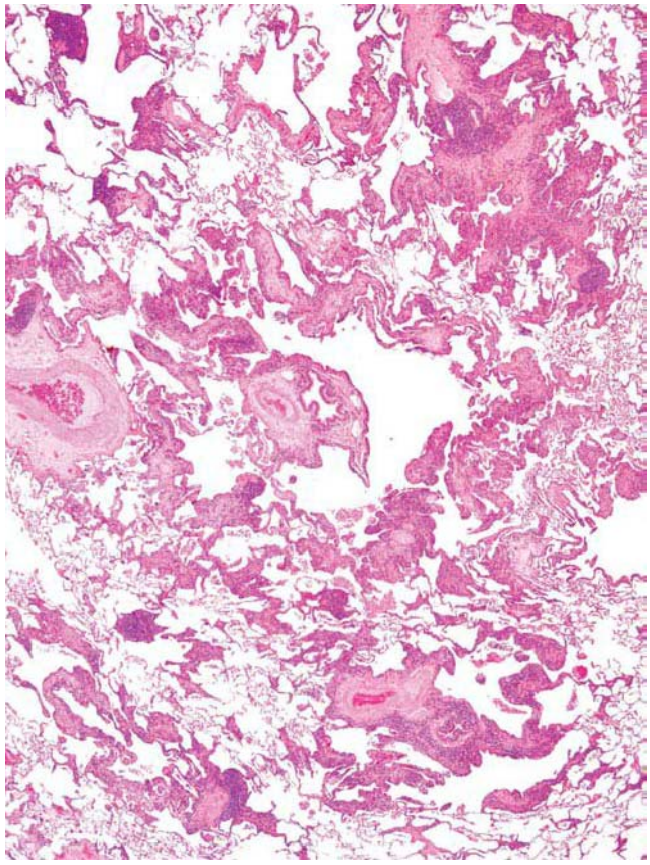
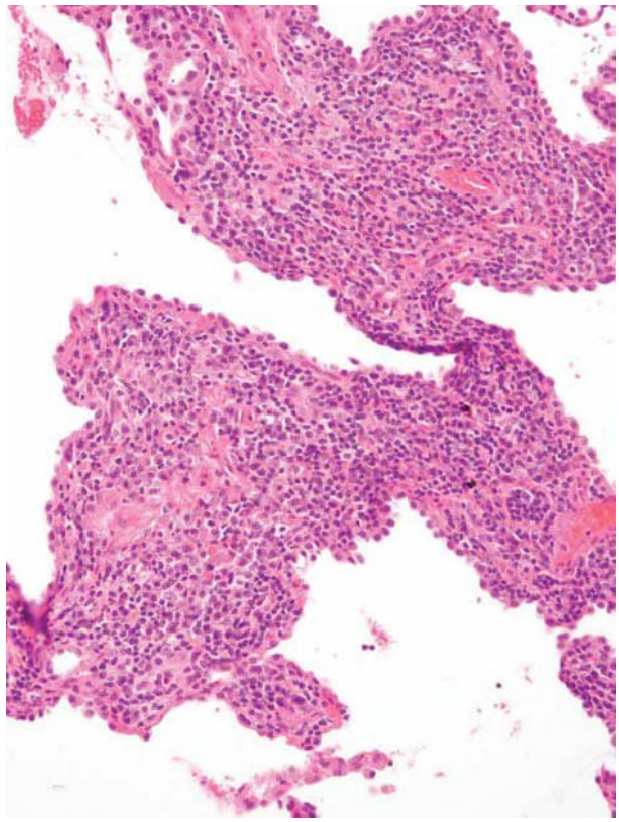
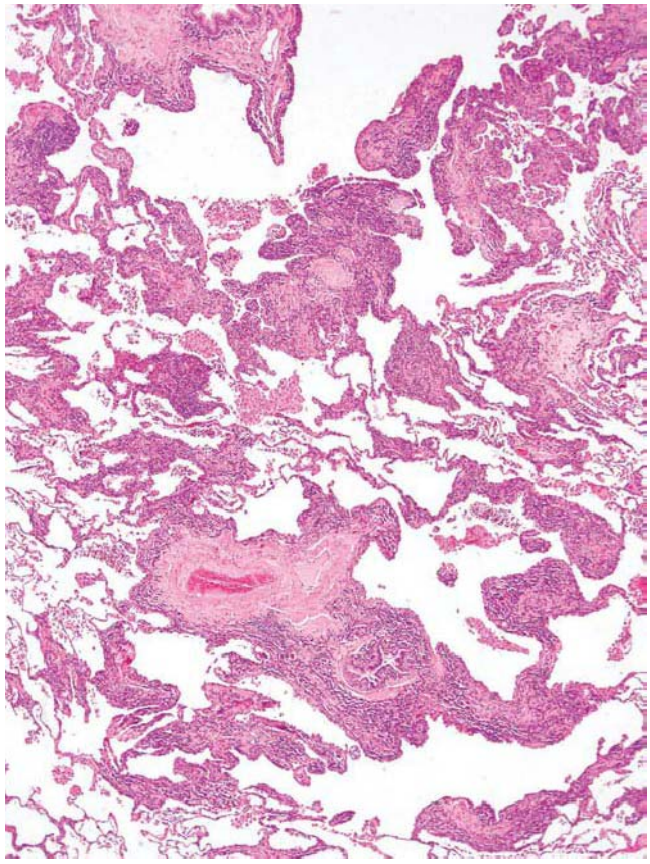


FIGURES 19.19 to 19.22. Legend appears on following page





FIGURES 19.19 to 19.22. An example of apparently early LIP in which cysts (**Fig. 19.19**) have been biopsied. The lymphoid infiltrate (**Figs. 19.20 to 19.22**) is locally typical of LIP but occurs in circumscribed areas. Radiologically this case was very similar to Figure 19.2. Patient had Sjögren syndrome.



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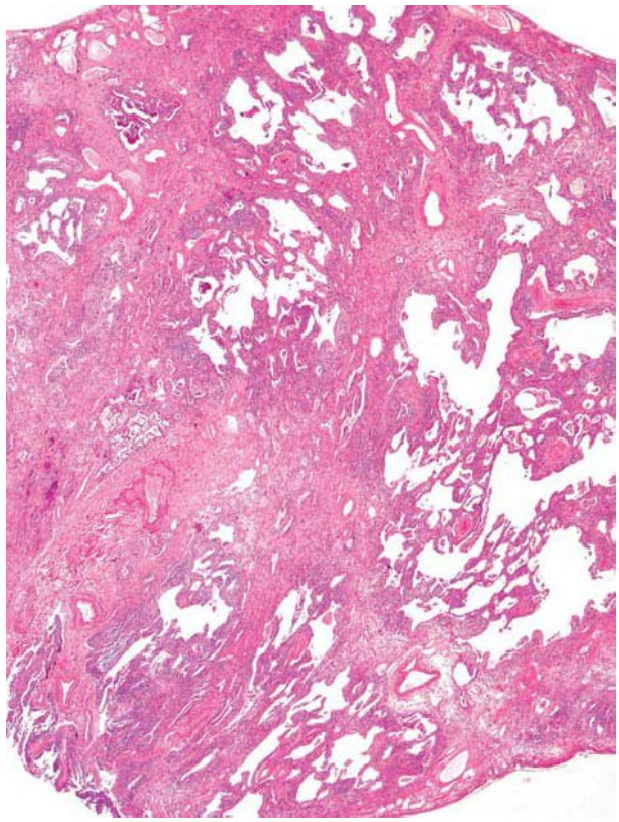
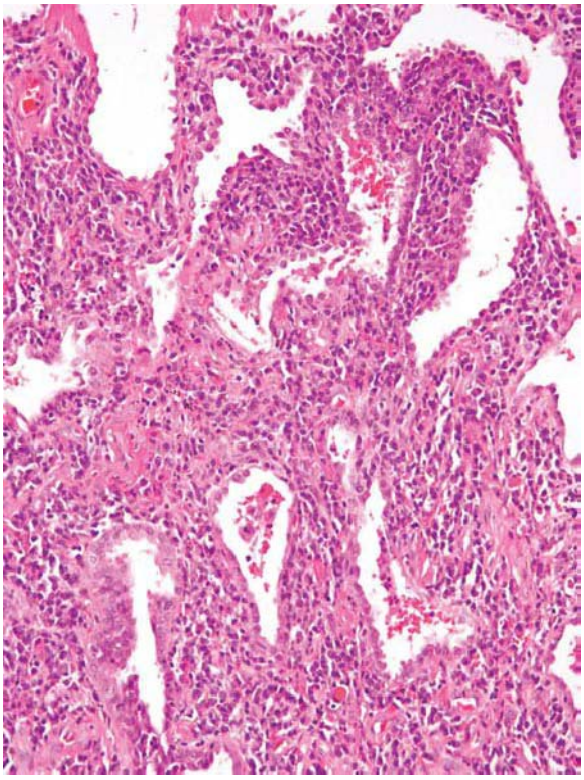


FIGURES 19.23 and 19.24. Legend appears on following page



FIGURES 19.23 and 19.24. LIP with fibrosis. Some cases of LIP progress to fibrosis and sometimes honeycombing. In this example LIP type areas **(Fig. 19.24)** are still present and allow the diagnosis.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of LIP is listed in Table 19.4. The most important differential diagnosis of all intrapulmonary lymphoid proliferations is malignant lymphoma, and in the lung this is most commonly a low-grade marginal zone B cell lymphoma (MALT lymphoma). MALT lymphomas are usually mass lesions and thus the usual distinction is from nodular lymphoid hyperplasia (see below), but they can also be diffuse and morphologically "interstitial" and at low power closely mimic LIP (see Figs. 24.18 and 24.19). In fact many of the original cases of LIP described by Liebow and Carrington[12] would now be classified as MALT lymphomas. Other types of lymphomas primary or secondary in the lung can also spread in alveolar walls (see Fig. 24.17).

Distinction of benign from malignant is complicated by the fact that MALT lymphomas frequently contain reactive germinal centers and sometimes small noncaseating granulomas as well, and there may be an admixture of B and T cells by immunohistochemistry. Features that suggest MALT lymphoma are sheets of monomorphous slightly atypical B cells that sometimes have clear cytoplasm (see Figs. 24.18 to 24.21), monoclonal gammopathy, clonality demonstrated by flow cytometry or by immunohistochemical staining of the proliferating cells for only kappa or lambda (see Figs. 24.22 and 24.23; demonstrable in the majority of MALT lymphomas but not all cases), infiltration of the airway epithelium by lymphocytes (lymphoepithelial lesions; see Fig. 24.19), and plaque-like infiltration of the pleura. MALT lymphomas are usually Bcl-2 positive. Molecular studies to show a gene rearrangement or a clonal process may be necessary to confirm the diagnosis.

Occasionally lymphomas involving the lung mimic follicular bronchiolitis because lymphomas tend to follow lymphatic pathways; however, in most instances lymphomas with this pattern produce a more homogeneous and intense lymphoid infiltrate (see Figs. 24.16 and 24.17) than is seen in follicular bronchiolitis and do not form germinal centers. Typically such cases are secondary rather than primary lymphomas, but primary MALT lymphomas can also spread in the lung in this fashion.

Leukemias involving the lung typically infiltrate the interstitium, as does intravascular lymphoma (see Fig. 24.24) and produce what at first glance appears to be an interstitial pneumonia. However, careful inspection shows that the infiltrating cells are not mature lymphocytes and plasma cells but rather morphologically atypical cells.

Pneumocystis pneumonia and cytomegalovirus (CMV) pneumonia sometimes produce a chronic interstitial inflammatory process that can mimic LIP but generally with a less intense interstitial infiltrate that is more similar to cellular NSIP. Usually with pneumocystis foamy alveolar exudates containing obvious organisms on silver stains are present, whereas with CMV viral inclusions are found.

LIP can mimic NSIP (Chapter 7), but in general in NSIP, the interstitial infiltrate is much less intense than in LIP, the alveolar walls are not widened to the same extent, and where NSIP is severe enough to produce confluence of alveolar walls the area of confluence is fibrotic rather than cellular (see Figs. 7.16 and 7.17). The combination of a lymphoid infiltrate and small noncaseating granulomas or giant cells in LIP can also mimic hypersensitivity pneumonitis (HP) (Chapter 12), but in HP the interstitial inflammatory infiltrate is again much less intense than in LIP and is present in the interstitium around the bronchovascular bundles, with minimal or no interstitial inflammatory infiltrate away from the bronchovascular bundles.

IgG4 sclerosing disease usually is associated with fibrotic reactions, but in the lung it sometimes takes the form of interstitial lymphoplasmacytic interstitial infiltrates with or without associated interstitial fibrosis and can resemble NSIP (Chapter 7) or LIP. In some examples the process is quite diffuse and in others fairly localized (Figs. 19.25 and 19.26). The infiltrating cells can invade vessels and mimic lymphoma[13,14] (Fig. 19.27). Staining for IgG4 shows a high number of positive cells, typically greater than 20/hpf (Fig. 19.28). Many of these patients have extrapulmonary manifestations of IgG4 disease, particularly autoimmune pancreatitis.

Nodular Lymphoid Hyperplasia

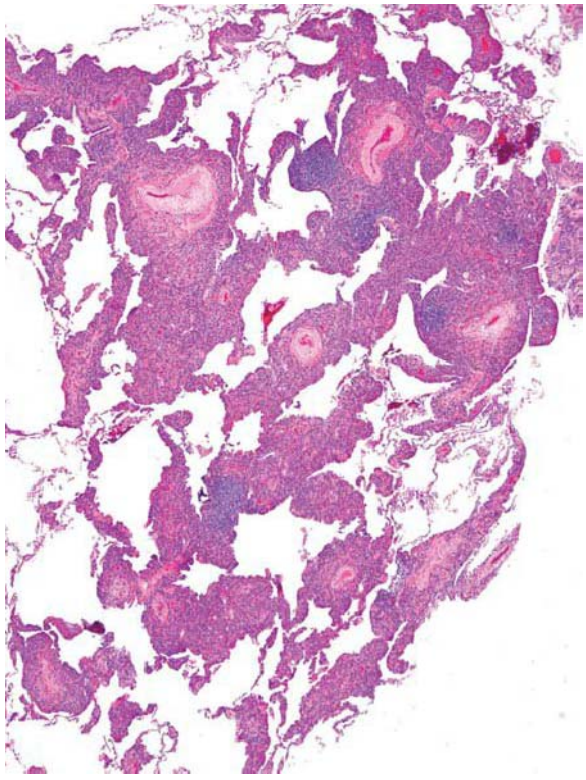
Nodular lymphoid hyperplasia consists of nodular or mass-like or occasionally more diffuse but still circumscribed lesions comprising contiguous lymphoid tissue with numerous germinal centers and, usually, some degree of localized interstitial fibrosis (Figs. 19.29 and 19.30). Small

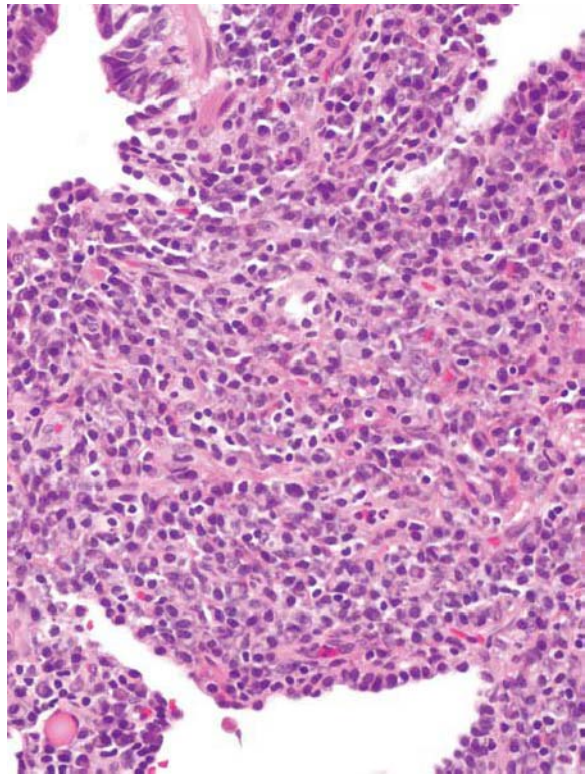
TABLE 19.4

Differential diagnosis of LIP

LIP	NSIP	HP	IgG4 disease	Lymphoma
Marked lymphoid infiltrate widens alveolar walls and may obliterate alveolar spaces	Lymphoid infiltrate usually only a few cells thick (alveolar spaces only obliterated by fibrous tissue not lymphoid cells)	Lymphoid infiltrate is peribronchovascular	Lymphoid infiltrate resembles NSIP but large numbers of IgG4+ plasma cells present (>20/hpf)[a]	Often marked lymphoid infiltrate with widening of alveolar walls and obliteration of alveolar spaces. Lymphoid cells may be monomorphous
Lymphoid infiltrate continuous over large areas	Lymphoid infiltrate continuous over large areas	Alveolar walls often normal away from bronchovascular bundles		Lymphoid infiltrate often continuous over large areas
No vascular infiltration	No vascular infiltration	No vascular infiltration	Vascular infiltration often present	Vascular infiltration often present
Small ill-defined granulomas or giant cells may be present	No granulomas	Granulomas present in areas of lymphoid infiltrate	No granulomas	Small ill-defined granulomas or giant cells may be present
Not clonal	Not clonal	Not clonal	Not clonal	Clonal (often demonstrable by staining for kappa and lambda in MALT lymphoma

[a]Intrathoracic IgG4 disease may also manifest as hilar lymphadenopathy, pleural nodules, fibrosing pleuritis, sclerosing mediastinitis, peribronchiolar inflammation, BOOP-like lesions, plasma cell granulomas, eosinophilic infiltrates, phlebitis, arteritis, pulmonary hyalinizing granulomas, and inflammatory pseudotumors (see Yi ES et al.[14] and Song et al.[15]).





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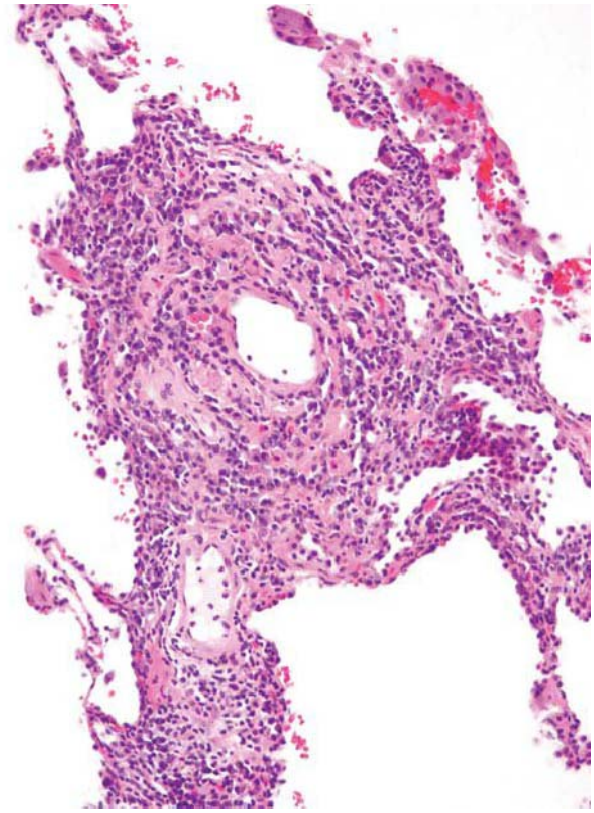
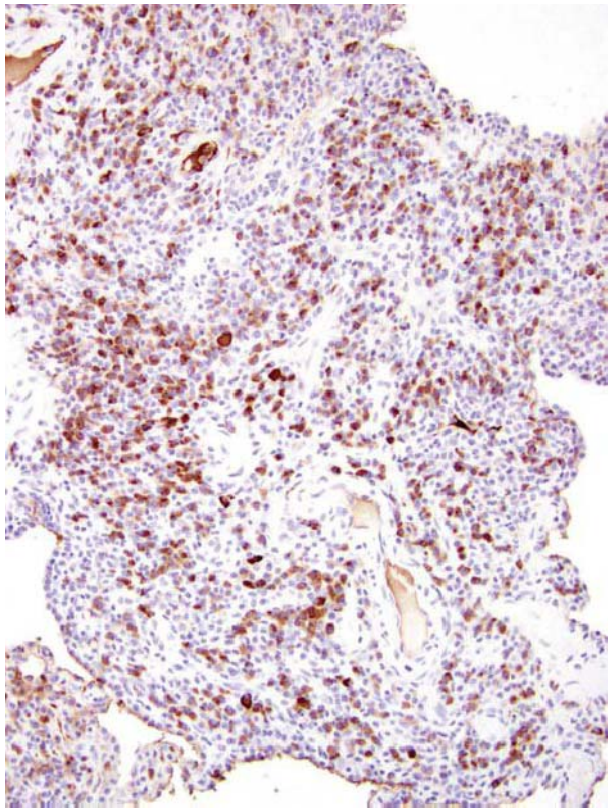
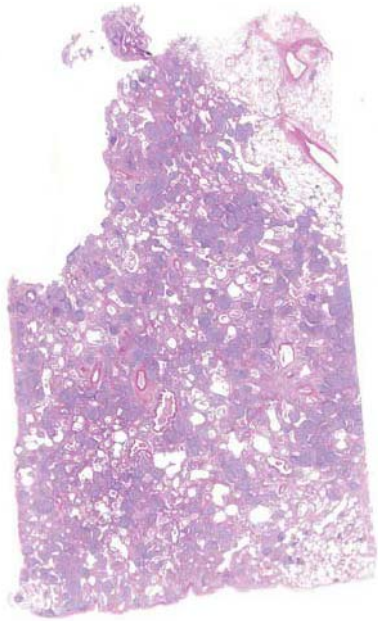
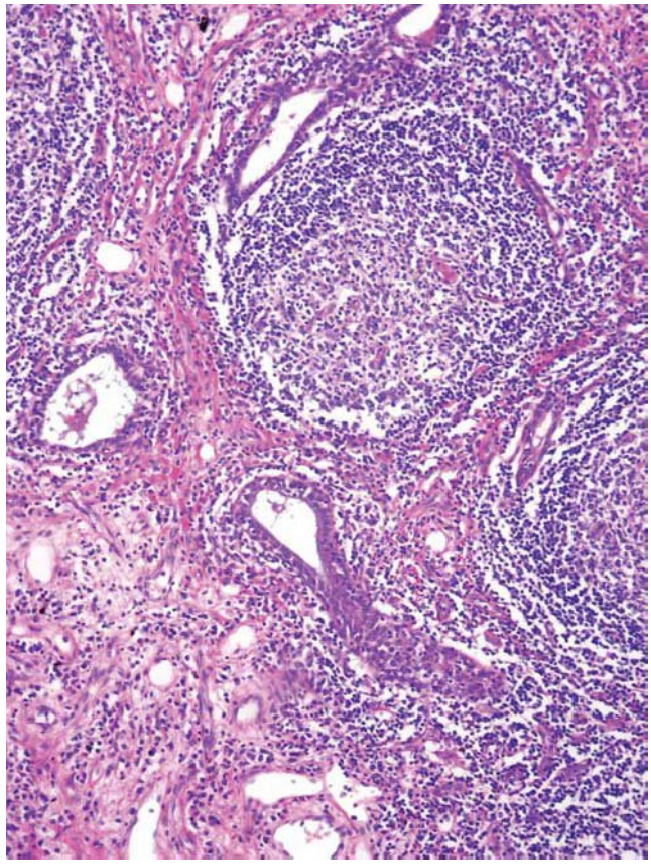




FIGURES 19.25 to 19.28. IgG4 disease. Patient had multiple nodular lesions on imaging and a low-power appearance mimicking LIP on biopsy **(Fig. 19.25)**, but the individual areas of interstitial infiltration were localized. At high power **(Fig. 19.26)**, there is a marked plasmacellular infiltrate, and the plasma cells and lymphocytes infiltrate vessels **(Fig. 19.27)**. IgG4 stain **(Fig. 19.28)** demonstrates very large numbers of staining cells.





FIGURES 19.29 and 19.30. Nodular lymphoid hyperplasia. Patient had several discrete nodules on HRCT. The edge of one such nodule is shown in **Figure 19.29** and a high-power view in **Figure 19.30**. Note that the process stops abruptly and is surrounded by normal lung, the typical finding in nodular lymphoid hyperplasia.

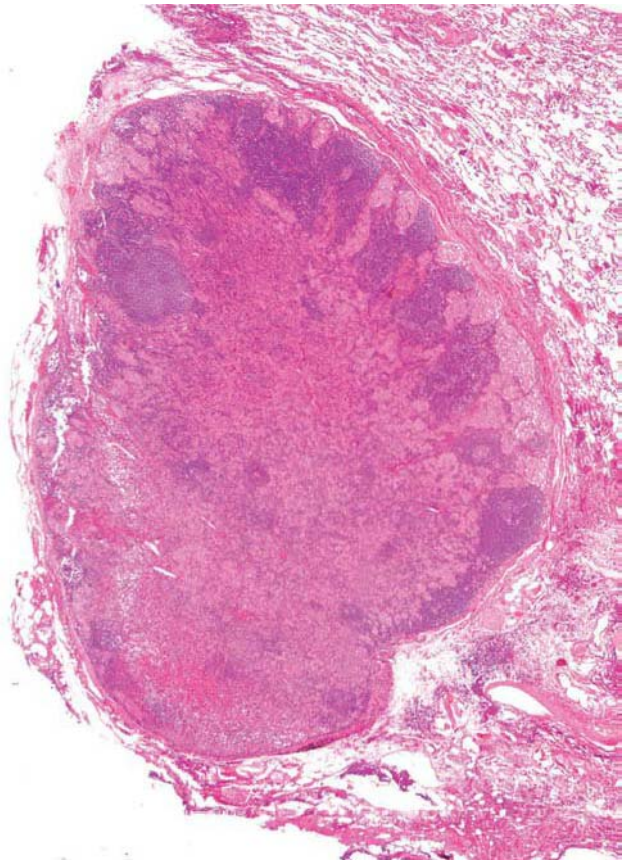


FIGURE 19.31. An intrapulmonary lymph node. This example has a capsule and prominent nodal sinuses.

noncaseating granulomas may be present. Most cases have only one lesion but occasionally several are present. Microscopically nodular lymphoid hyperplasia and LIP can be identical in a given field and the distinction is based on the diffuseness or circumscription of the process on biopsy or imaging. Most cases of nodular lymphoid hyperplasia appear to be reactions to previous inflammatory processes, but the disease is also associated with Sjögren syndrome.[15]

Intrapulmonary Lymph Nodes

Intrapulmonary lymph nodes are subpleural single or multiple nodular lymphoid lesions. As opposed to nodular lymphoid hyperplasia they usually have the sharp circumscription and microscopic structure of a lymph node including a capsule and subcapsular sinus (Fig. 19.31), but sometimes the capsule is missing and the distinction from nodular lymphoid hyperplasia becomes arbitrary. Intrapulmonary lymph nodes accumulate atmospheric carbon pigment in the same fashion as hilar and mediastinal lymph nodes. Occupational dust exposure appears to predispose to the formation of intrapulmonary lymph nodes and such nodes may contain large quantities of the inhaled dust.

DIAGNOSTIC MODALITIES

As a rule diagnosis of most of lymphoid lesions requires a large biopsy because low-power architecture is important and areas diagnostic of lymphomas, particularly MALT lymphomas, may be scattered. If transbronchial biopsies are used they need to be backed up by appropriate immunohistochemical and molecular testing to rule out a low-grade lymphoma.

PROGNOSIS

The prognosis of follicular bronchiolitis when it is the only lesion appears to be good, with stabilization or improvement on steroid therapy[4,5]; however, if it is present in a patient with a collagen vascular disease who has NSIP or UIP, then the latter determine prognosis. Lymphoid hyperplasia by itself probably produces no adverse effects but again is often seen in collagen vascular disease patients who have UIP or NSIP. The prognosis of LIP is highly variable. Overall survival is said to be to 50% to 70% at 5 years. Some patients improve with steroid therapy, whereas other progress to end stage fibrosis. The proportion of patients with LIP that develop lymphomas is controversial but probably small (of the order of 5%).[15] There are claims that LIP complicating AIDS improves survival but also reports that it makes survival worse.[8]

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CHAPTER

20

Bronchiolitis

CLINICAL FEATURES AND NOMENCLATURE ISSUES

Bronchiolar disorders are a complicated problem in that there are numerous, frequently overlapping, pathologic patterns with no universally agreed on names for many of them, considerably fewer patterns on imaging, and various clinical and pulmonary functional associations that often do not correspond to any specific morphologic entity.[1] Furthermore, bronchiolar abnormalities may be isolated to the bronchioles but may also be part of more proximal airway disease, as in asthma or bronchiectasis (including cystic fibrosis), or of diffuse distal disease involving large portions of the lobule such as Langerhans cell histiocytosis (LCH) (Chapter 10) and hypersensitivity pneumonitis (HP) (Chapter 12). Table 20.1 shows a general listing of etiologic/clinical associations of bronchiolitis and Tables 20.2 to 20.4 break down bronchiolitis by pathologic pattern.

The clinical features of bronchiolitis are extremely varied and often reflect another underlying systemic disease, for example, cystic fibrosis, collagen vascular disease, or inflammatory bowel disease. Although some forms of morphologic bronchiolitis, especially acute infectious bronchiolitis, constrictive bronchiolitis (bronchiolitis obliterans),[2,3] and diffuse panbronchiolitis,[4] usually produce signs and symptoms such as shortness of breath (SOB), others such as smoker's respiratory bronchiolitis (RB), usually do not, and the significance of bronchiolitis found in biopsies can be determined only by consultation with the radiologist and clinician.

Acute infectious bronchiolitis in infants is usually caused by adenovirus, respiratory syncytial virus, varicella, influenza, parainfluenza, or measles virus and is associated with pneumonia-like symptoms, wheezing, and often hypercapnea.[5] In infants acute infectious bronchiolitis may lead to postinfectious constrictive bronchiolitis (generally called bronchiolitis obliterans in the clinical literature). If one lung is affected more than the other, unilateral hyperlucent lung (Swyer–James–McLeod syndrome) may develop. Postinfectious constrictive bronchiolitis occurs in adults also but is much less frequent and is typically associated with mycoplasma infection. Constrictive bronchiolitis is usually associated with progressive SOB, nonproductive cough and sometimes wheezing, and an obstructive pulmonary functional pattern that is not improved with bronchodilators.[1–3]

In lung transplant recipients the clinical diagnosis of bronchiolitis obliterans syndrome (BOS, so named because pathologic constrictive bronchiolitis is histologically patchy and often cannot be demonstrated on transbronchial biopsy) requires a reduced FEV_1 for more than 3 weeks and the exclusion of acute rejection, infection, anastomotic complications, or other disease affecting pulmonary function.[6] BOS develops in a small percentage of bone marrow patients also where is it believed to represent a form of graft-versus-host disease.[7]

Table 20.1

Etiologic/clinical associations of bronchiolitis

Idiopathic
Infectious
Smoking-related
Asthma
Distal to bronchiectasis
Collagen vascular disease-related
Primary biliary cirrhosis
Inhalation of mineral dusts
Inhalation of toxic gases and fumes
Inhalation of hard metal (tungsten carbide, see Chapter 22)
Drug-related (see Chapter 18)
Aspiration
Inflammatory bowel disease
Lung transplant rejection
Bone marrow transplantation (graft vs. host disease)
Bronchiolitis obliterans (pathologic constrictive bronchiolitis)
Diffuse panbronchiolitis
Granulomatosis with polyangiitis (Wegener granulomatosis)

Table 20.2

Etiologies of acute bronchiolitis (with or without epithelial ulceration/necrosis, with or without chronic inflammation)

- Infection (may have epithelial necrosis/ulceration)
- Aspiration (may have granulomas and foreign material)
- Distal to bronchiectasis
- Inflammatory bowel disease (may have granulomas in Crohn disease)
- Inhaled fumes and gases (nitrogen dioxide, sulfur dioxide, chlorine, ammonia, phosgene)
- Diffuse panbronchiolitis
- Granulomatosis with polyangiitis (Wegener granulomatosis)

Diffuse panbronchiolitis is largely seen in Japan or persons of Japanese heritage and to a lesser extent in other areas of East Asia; it is rare in Western populations.

Table 20.3

Etiologies of chronic bronchiolitis (with or without airway wall fibrosis but without acute inflammation)

- Infection
- Cigarette smoke-induced "small airways disease" ("small airway remodeling")
- Smoker's respiratory bronchiolitis (Chapter 8)
- Aspiration (may have granulomas and foreign material)
- Distal to bronchiectasis
- Inflammatory bowel disease
- Inhalation of mineral dusts (may have inhaled dust, asbestos bodies)
- Hard metal disease (Chapter 22)
- Collagen vascular disease (follicular bronchiolitis) (Chapter 19)
- Inhaled fumes and gases (nitrogen dioxide, sulfur dioxide, chlorine, ammonia, phosgene)
- Drugs
- Asthma
- Hypersensitivity pneumonitis (HP) (may have granulomas) (Chapter 12)
- Lung transplant rejection
- Bone marrow transplantation (graft vs. host disease)
- Diffuse panbronchiolitis
- Lymphoma
- Granulomatosis with polyangiitis (Wegener granulomatosis)
- Idiopathic

Table 20.4

Etiologies of constrictive bronchiolitis (bronchiolitis obliterans)

- Asthma (rare)
- Postinfectious (viral [adenovirus, RSV, influenza, parainfluenza, measles, varicella], mycoplasma)[3,15]
- Inhaled gases and fumes (nitrogen dioxide, sulfur dioxide, chlorine, ammonia, phosgene, fly ash, nylon flock, polyamide-amine dyes, thionyl chloride, and possibly diacetyl)[13]
- Drugs (Chapter 18)
- Ingested toxins: *Sauropus androgynus*
- Collagen vascular disease, especially rheumatoid arthritis
- Inflammatory bowel disease
- Diffuse idiopathic pulmonary neuroendocrine hyperplasia (DIPNECH)
- Lung transplantation and bone marrow transplantation
- Distal to bronchiectasis (e.g., in cystic fibrosis)
- Idiopathic

Patients present with SOB, productive cough, and airflow obstruction on pulmonary function testing. Most (>80%) also have signs and symptoms of chronic sinusitis. Cold agglutinins are persistently elevated in the face of negative mycoplasma antibody titers, and rheumatoid factor may be positive.[4]

IMAGING

The high resolution computed tomography (HRCT) manifestations of bronchiolitis can be classified into three main types: tree-in-bud pattern, ill-defined centrilobular nodules, and areas of decreased attenuation and vascularity resulting in a mosaic attenuation pattern.[8] The tree-in-bud pattern consists of well-defined centrilobular nodules attached to branching linear or tubular opacities. Centrilobular opacities can be recognized on HRCT by their distribution a few millimeters away from the periphery of the secondary lobule, that is, from the interlobular septa, pleura, and large pulmonary vessels.

The tree-in-bud pattern usually reflects the presence of bronchiolar wall thickening and accumulation of intraluminal material (secretions, granulation tissue, etc.) and is a characteristic feature of infectious bronchiolitis (Fig. 20.1).[8] In infectious bronchiolitis the abnormalities usually have a patchy unilateral or asymmetric bilateral distribution. Similar findings may be seen in endobronchial spread of tuberculosis, atypical mycobacterial infection, and bronchiolar mucus impaction associated with bronchiectasis or allergic bronchopulmonary aspergillosis.

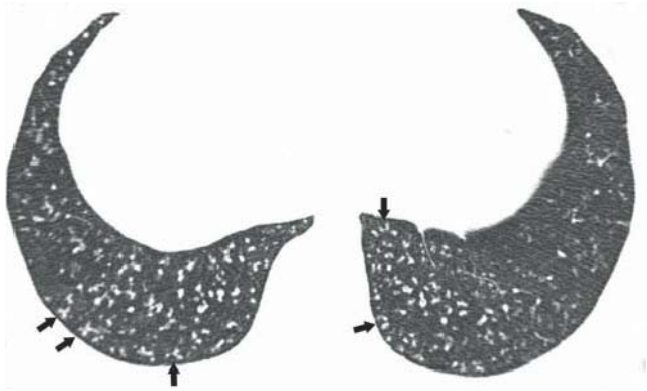


FIGURE 20.1. Infectious bronchiolitis. HRCT demonstrates well-defined small bilateral nodules (*arrows*) that are clustered a few millimeters away from the pleura and the interlobular septa characterizing a centrilobular distribution. Many of the nodules are attached to branching tubular opacities resulting in a pattern that resembles a tree-in-bud. The patient was a 20-year-old woman with infectious bronchiolitis.

In aspiration bronchiolitis the tree-in-bud pattern may be diffuse or involve mainly the dependent lung regions. Diffuse panbronchiolitis is characterized by the presence of extensive bilateral tree-in-bud pattern, bronchiolectasis, bronchiectasis, and, commonly, areas of decreased attenuation and vascularity resulting in a mosaic pattern of attenuation (Fig. 20.2).[9]

Ill-defined centrilobular ground-glass nodules are seen most commonly in patients with respiratory bronchiolitis (typically in the upper lobes in smokers) and in subacute HP (usually diffuse or with a lower lobe predominance) (Fig. 20.3). Centrilobular ground-glass nodules can also occur in a large number of other less common

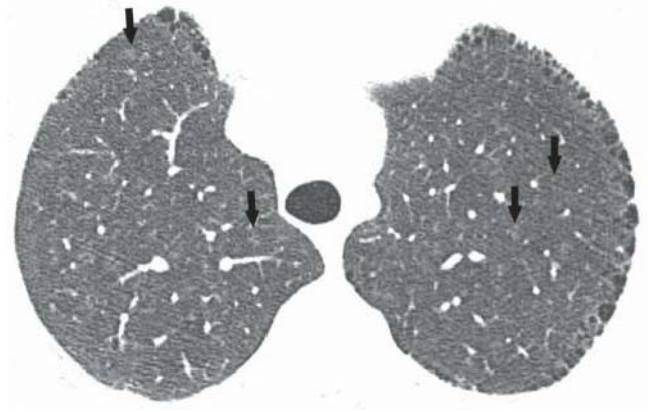


FIGURE 20.3. Respiratory bronchiolitis. HRCT shows bilateral poorly defined centrilobular ground-glass nodules (*arrows*) and mild emphysema. The patient was a 45-year-old smoker.

conditions including follicular bronchiolitis and mineral dust exposure.[8]

Areas of decreased attenuation and vascularity resulting in a heterogeneous appearance (mosaic attenuation) on inspiratory HRCT and associated with air trapping on HRCT scans obtained at end expiration are a characteristic manifestation of constrictive bronchiolitis (Fig. 20.4).[8] Ancillary findings include bronchiectasis and bronchial wall thickening. A mosaic attenuation pattern is a nonspecific finding seen on HRCT in a number of conditions. However, mosaic attenuation as the predominant or only abnormality and associated with decreased vascularity usually is the result of constrictive bronchiolitis, asthma, HP or chronic pulmonary thromboembolism.[8]

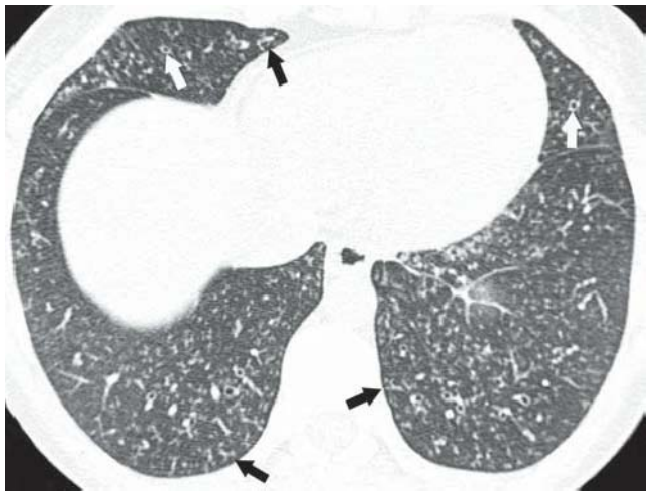


FIGURE 20.2. Diffuse panbronchiolitis. HRCT shows numerous bilateral well-defined centrilobular nodules and branching tubular structures resulting in a tree-in-bud pattern (*black arrows*). Also noted is mild bronchiectasis (*white arrows*). The patient was a 34-year-old woman with diffuse panbronchiolitis.

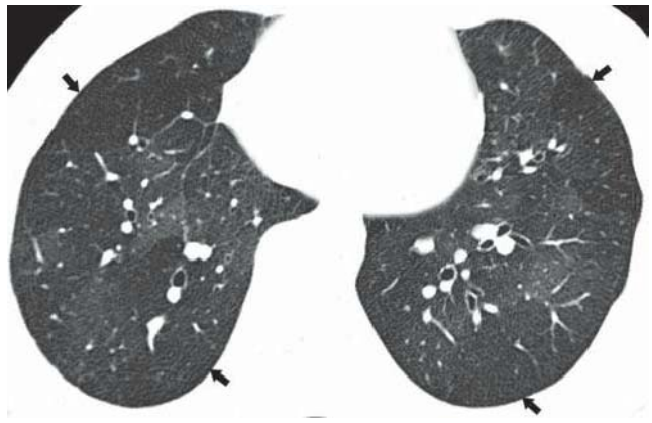


FIGURE 20.4. Constrictive bronchiolitis. HRCT demonstrates a heterogeneous appearance of the lungs (mosaic attenuation) caused by the presence of extensive bilateral areas of decreased attenuation and vascularity (*arrows*). The patient was a 23-year-old woman with constrictive bronchiolitis and severe airflow obstruction secondary to chronic graft-versus-host disease.

NORMAL ANATOMY

Bronchioles are conducting airways that lack cartilage in their walls. They are divided into the more proximal membranous bronchioles that have a completely muscularized wall (Figs. 20.5 and 20.6) and the more distal respiratory bronchioles with a partially muscularized and partially alveolated wall (Fig. 20.5). Both types of bronchiole normally have a predominantly ciliated epithelium with interspersed Clara cells, identified by apical snouts. Small numbers of mucus secreting cells are found in the normal membranous bronchioles but are rare in normal respiratory bronchioles. Most forms of bronchiolitis affect predominantly membranous bronchioles.

PATHOLOGIC FEATURES

Acute Bronchiolitis

Bronchiolitis with acute inflammation is most commonly infectious but can be seen in various other conditions (Table 20.2). In immunocompetent patients infections caused by viruses and mycoplasma frequently show a combination of neutrophils in the in the lumen and lymphocytes in the wall (Figs. 20.7 to 20.10), something that is less common in most of the other conditions listed in Table 20.2. Diffuse panbronchiolitis (Figs. 20.11 and 20.12; see below) can demonstrate the same combination but with interstitial foamy macrophages as well. The airway epithelium in viral and mycoplasma infections is often hyperplastic, disordered, and sometimes cytologically atypical (Figs. 20.8 to 20.10), useful clues to the underlying etiology. In severe cases the epithelium may be ulcerated or even obliterated by inflammation.

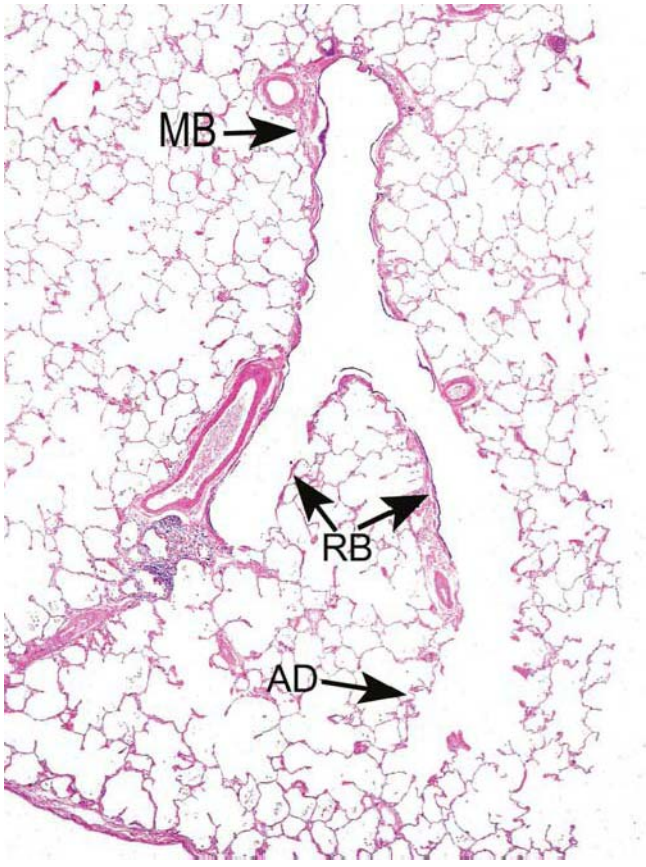


FIGURE 20.5. Normal distal conducting airways in longitudinal section. Membranous bronchioles (*MB*) have a continuous muscular wall. Respiratory bronchioles (*RB*) have a partially muscular and partially alveolated wall, whereas alveolar ducts (*AD*) have a completely alveolated wall.

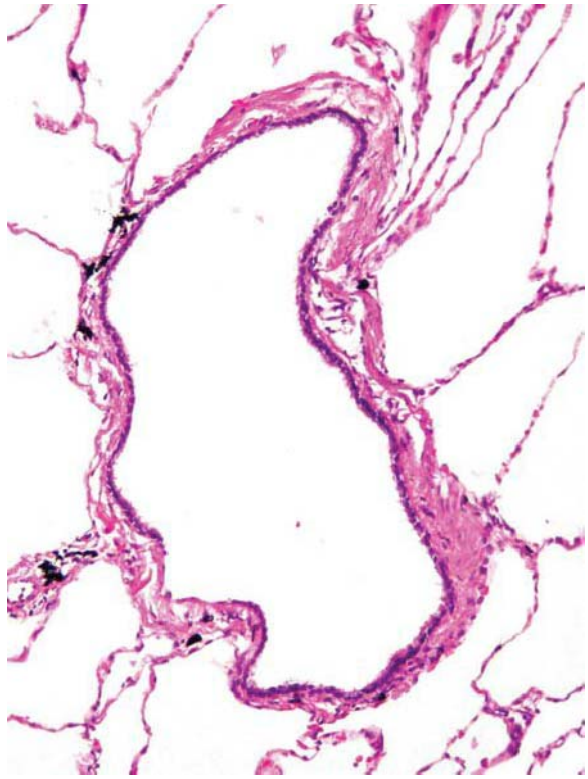


FIGURE 20.6. Higher-power view of a normal membranous bronchiole in cross section. There is at most a small space between the muscular layer and the epithelium.

In the immunocompromised patient acute bronchiolitis is often more severe with destruction of the airway wall, extensive acute inflammation, and large amounts of karyorrhexis (Figs. 20.13 and 20.14) producing a low-power view of necrotizing airway-centered nodules. This picture can be caused by viruses (usually adenovirus, herpes, or cytomegalovirus [CMV]), fungi, and toxoplasma.

Inflammatory bowel disease can produce a picture of an acute or chronic bronchiolitis; in most cases lung involvement occurs in patients already known to have Crohn disease or ulcerative colitis, but occasionally the initial presentation is in the lung.

Granulomatosis with polyangiitis (Wegener granulomatosis), although a vasculitis, often involves the trachea and large airways and occasionally the bronchioles as well,

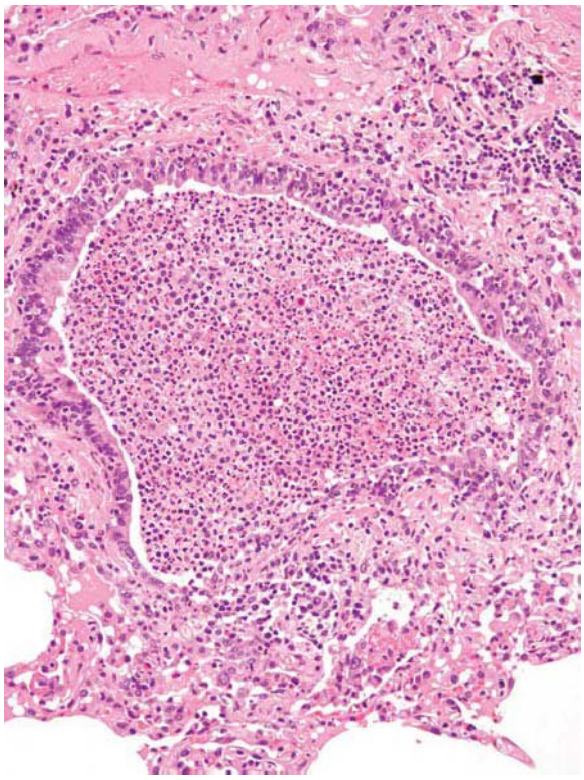


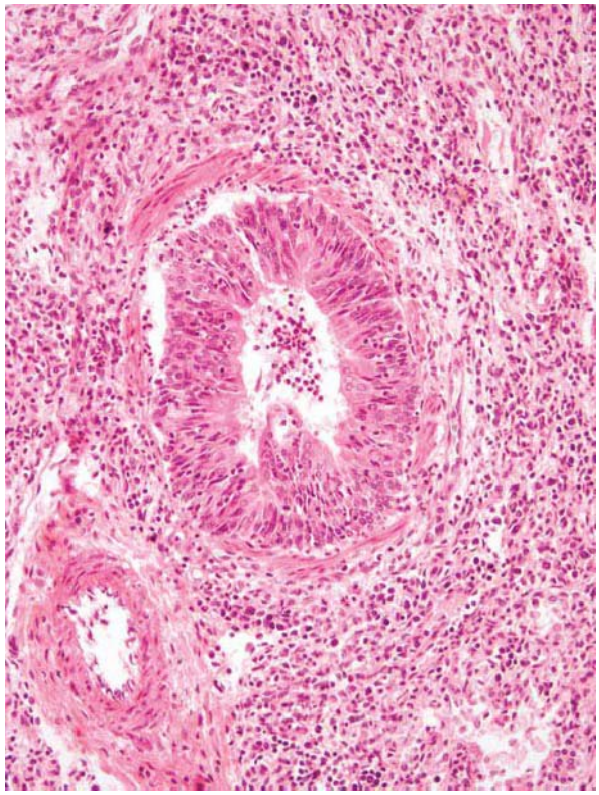
FIGURE 20.7. Acute bronchiolitis caused by mycoplasma. The lumen is filled with neutrophils, whereas the surrounding tissue contains chronic inflammatory cells. The epithelium is inflamed but otherwise normal.

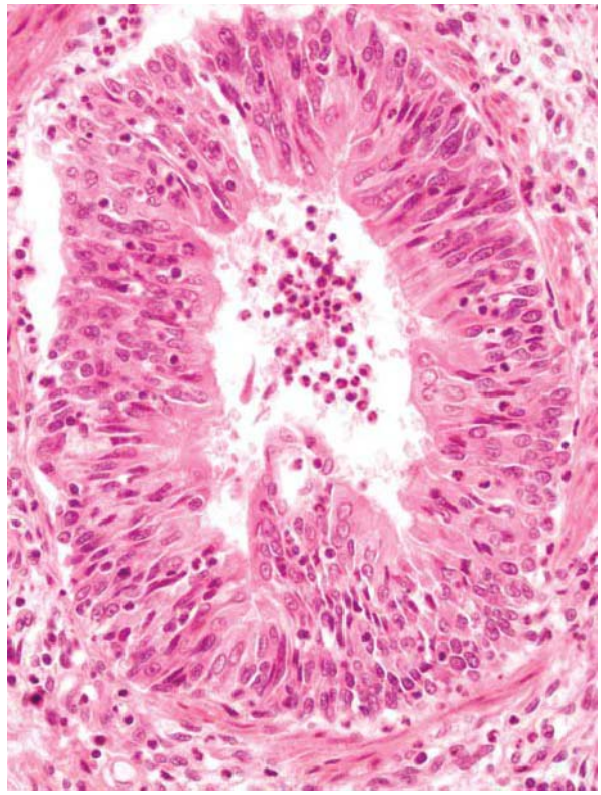
and can produce ulceration with acute and chronic inflammation. Unless vasculitis is also present, the morphologic features of the bronchiolitis are not specific.

Diffuse panbronchiolitis has distinctive clinical features (see above) and also reasonably distinctive pathologic findings including some combination of acute and chronic inflammation involving membranous and respiratory bronchioles and sometimes also small bronchi, and, by definition, foamy macrophages present in the bronchiolar walls, walls of alveolar ducts, and sometimes alveoli (Figs. 20.11 and 20.12). However, the diagnosis of diffuse panbronchiolitis requires these findings in conjunction with typical clinical features because, in rare cases, interstitial foamy macrophages can be found in the walls of alveolar ducts (and even more uncommonly in the walls of membranous bronchioles) in constrictive and follicular bronchiolitis, cystic fibrosis, aspiration, HP, granulomatosis with polyangiitis (Wegener granulomatosis), collagen vascular diseases, and lymphomas.[10]

Chronic Bronchiolitis

Bronchiolitis characterized by chronic inflammation in the wall without a significant neutrophil component is much less specific and has a wide range of etiologies (Table 20.4). There are three fundamental patterns: disorganized infiltration of the bronchiolar wall by lymphocytes and plasma





FIGURES 20.8 and 20.9. Acute bronchiolitis caused by influenza. The same pattern of luminal neutrophils and surrounding chronic inflammatory cells as seen in Figure 20.7 is present, but the epithelium is markedly hyperplastic.

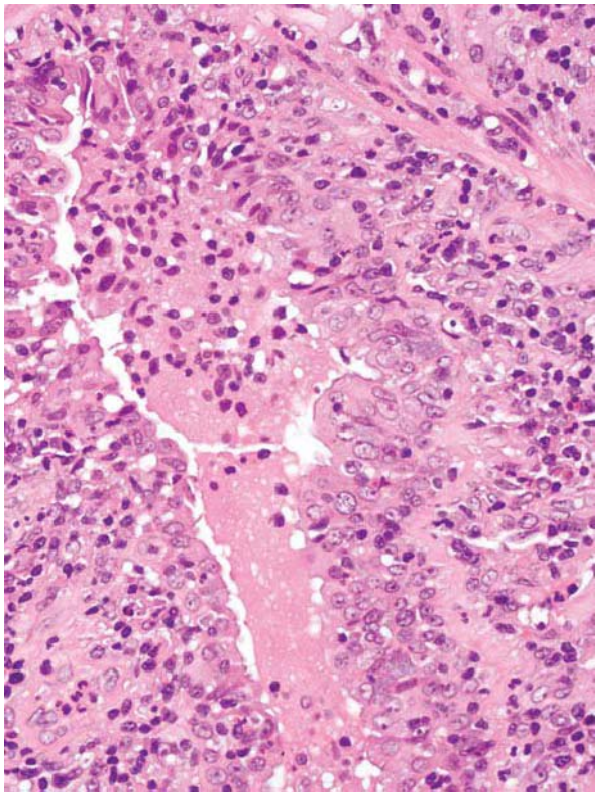


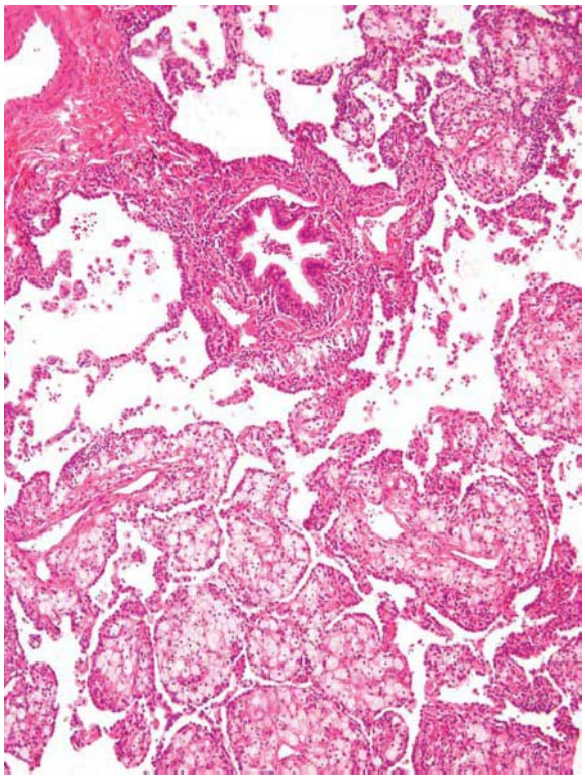
FIGURE 20.10. Acute bronchiolitis caused by mycoplasma. In this example the airway epithelium is disorganized and cytologically atypical.

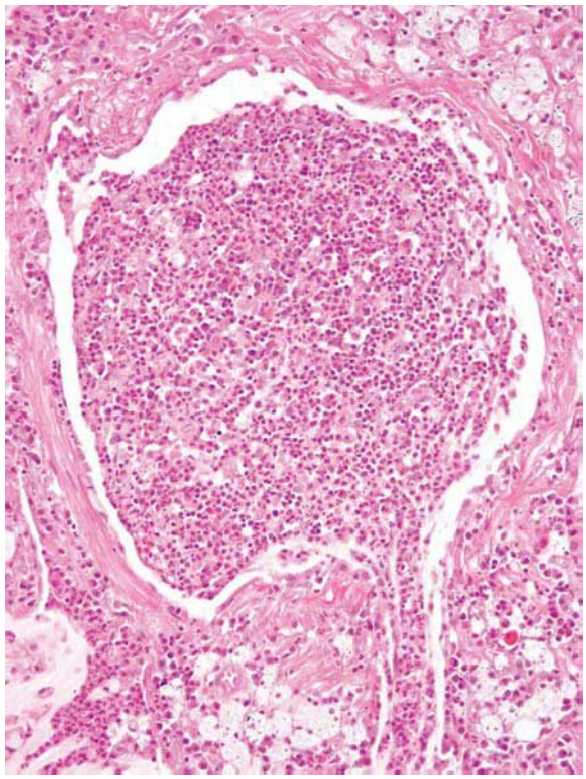
cells; follicular bronchiolitis (Chapter 19) in which one or more discrete lymphoid nodules, frequently with germinal centers, expand the bronchiolar wall and narrow the lumen (see Fig. 19.4); and fibrosis of the airway wall with or without chronic inflammation. The latter pattern overlaps into constrictive bronchiolitis.

Chronic bronchiolitis may be found in many of the same conditions that cause acute bronchiolitis, including infectious bronchiolitis (Figs. 20.15 to 20.17), but statistically the most common morphologic cause of chronic bronchiolitis is cigarette smoking, which produces both smoker's respiratory bronchioles (RB) (Chapter 8) and small airways disease (small airway remodeling) in the membranous bronchioles.

Smoker's RB (Chapter 8) is characterized by accumulation of pale golden or pale brown macrophages in the bronchiolar lumen (see Figs. 8.3 to 8.7) and a variable amount of fibrosis in the bronchiolar wall, sometimes with interstitial extension of the fibrosis into the distal parenchyma.

In cigarette smoke-induced small airways disease (Fig. 20.18), the bronchiolar wall is thickened by fibrous tissue and the lumen narrowed, and there is an associated chronic inflammatory infiltrate, sometimes with lymphoid follicles. Small numbers of neutrophils may be present. There is often extensive mucus metaplasia of the airway epithelium and mucus plugs may obstruct the airway lumen. By convention the process is not referred





FIGURES 20.11 and 20.12. Diffuse panbronchiolitis. In **Figure 20.11** there are a few neutrophils in the lumen and surrounding chronic inflammation, similar to the findings in many forms of acute infectious bronchiolitis (Figs. 20.7 to 20.10). However, the presence of foamy macrophages in the interstitium is strongly suggestive of diffuse panbronchiolitis **FIGURE 20.12.** An example of diffuse panbronchiolitis with a marked luminal neutrophil infiltrate and foamy macrophages in the bronchiolar wall.

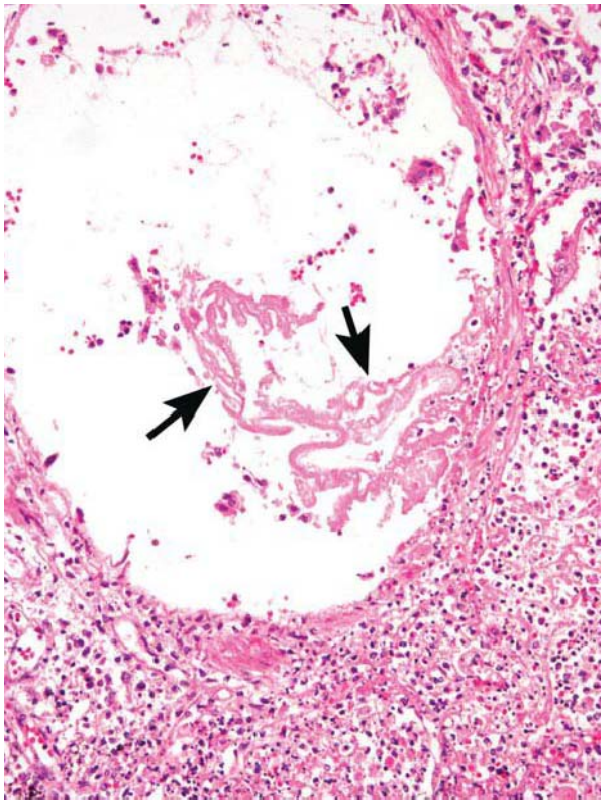


FIGURE 20.13. Herpes bronchiolitis in an immunocompromised patient. The airway epithelium (*arrows*) is completely necrotic. The surrounding tissue contains numerous karyorrhexic fragments.

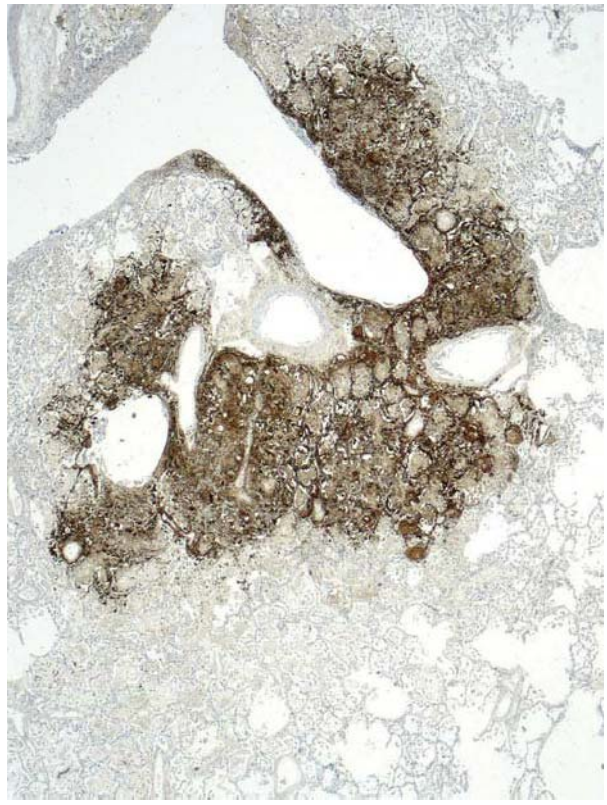
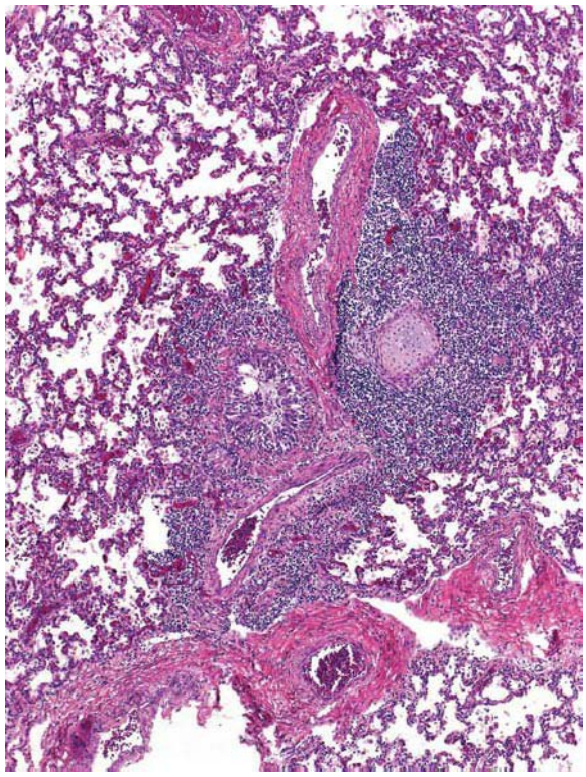
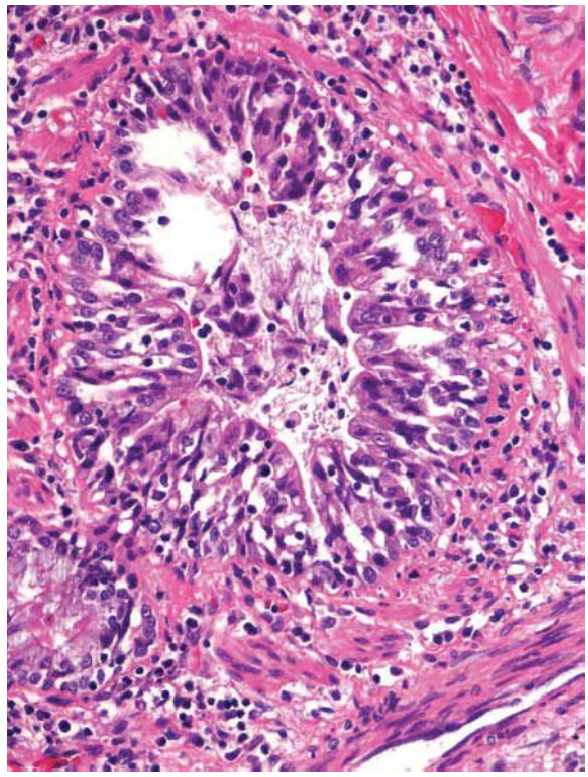
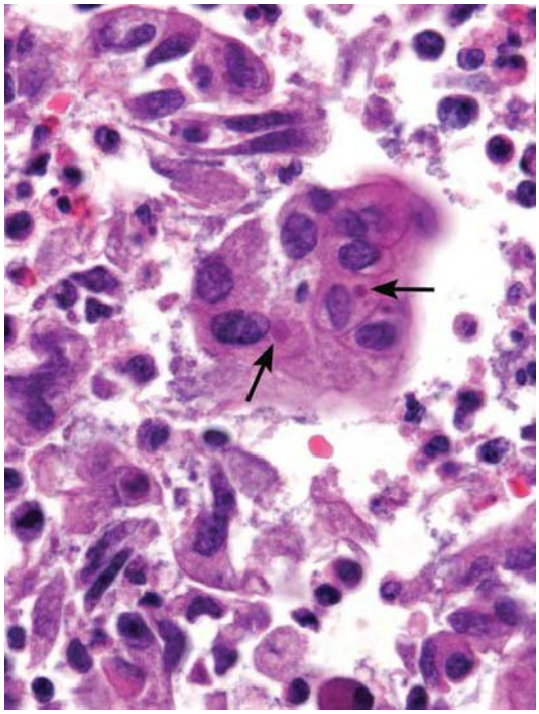


FIGURE 20.14. Herpes bronchiolitis. Immunostain for herpes shows extensive viral infection in the tissue surrounding the airway.





FIGURES 20.15 to 20.17. Legend appears on following page



FIGURES 20.15 to 20.17. Chronic bronchiolitis, in this case caused by RSV infection in a child. (Case Courtesy Dr. Michael Graham.) **Figure 20.15:** Low-power view shows an intense chronic inflammatory infiltrate surrounding the airways. **Figure 20.16:** Marked chronic inflammatory infiltration of the airway wall and epithelium with epithelial hyperplasia. **Figure 20.17:** Eosinophilic RSV inclusions (*arrows*).

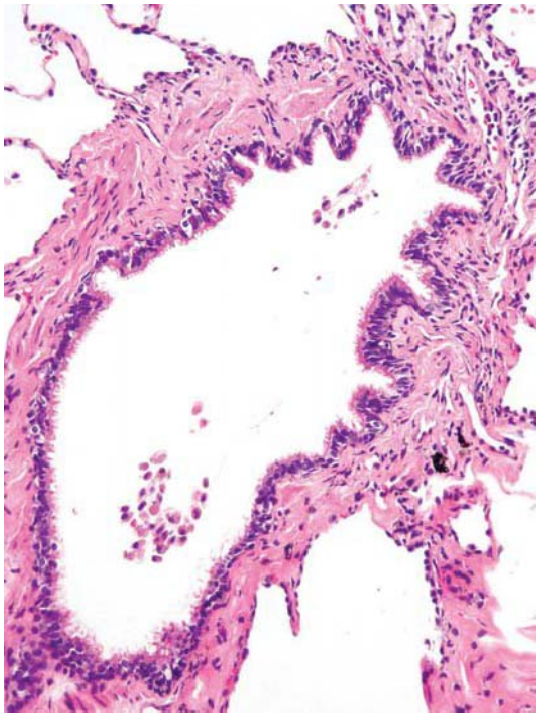


FIGURE 20.18. Cigarette smoke-induced chronic bronchiolitis. This process is referred to as "small airways disease" or "small airway remodeling." The bronchiolar wall is thickened by fibrous tissue and some degree of chronic inflammation.

to, diagnostically, as "bronchiolitis" but rather as cigarette smoke-induced small airways disease or small airway remodeling; however, functionally and morphologically it is really a variant of constrictive bronchiolitis.

Bronchiolitis caused by inhalation of mineral dusts (asbestos, iron oxide, aluminum oxide, talc, mice, silicates, and so on[11] is morphologically similar to cigarette smoke-induced small airways disease, but statistically there is more fibrosis of the airway wall and less chronic inflammation (Fig. 20.19); however, individual membranous bronchioles with changes caused by cigarette smoke and mineral dusts are often not distinguishable unless the mineral dust is pigmented or birefringent. With mineral dust exposure the fibrosis sometimes extends into the respiratory bronchioles, often with considerable accompanying pigmented dust (Figs. 20.19 and 20.20), and this is much less common with cigarette smoking.

Hard metal disease is a pneumoconiosis caused by exposure to tungsten carbide. The bronchiolar walls are chronically inflamed and markedly thickened and distorted by fibrous tissue, and the bronchiolar lumens contain macrophages and giant cells (see Figs. 22.24 and 22.25).

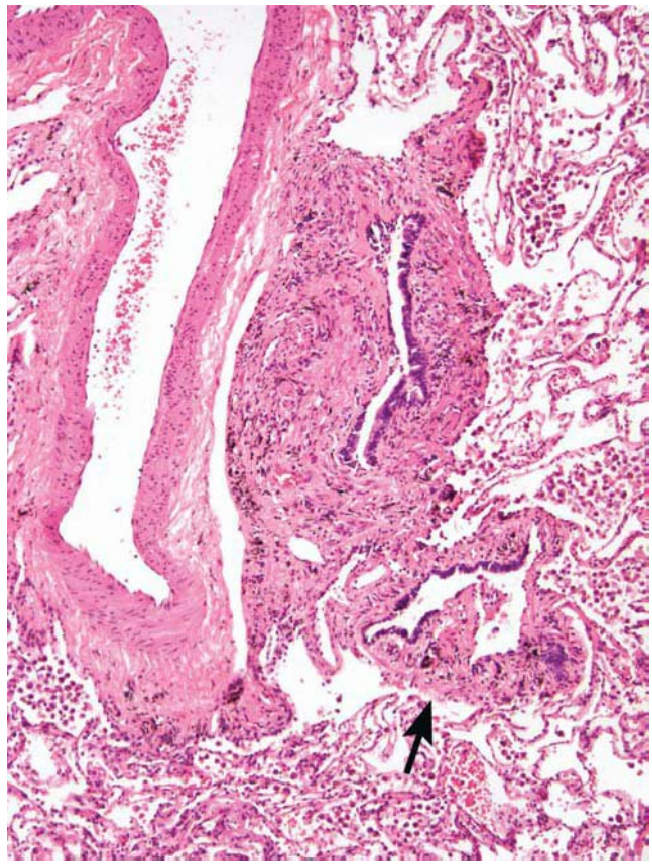


FIGURE 20.19. Chronic bronchiolitis caused by exposure to asbestos. The changes in the membranous bronchiole are similar to those caused by cigarette smoke, but the process also markedly thickens the wall of the adjacent respiratory bronchiole (*arrow*), something not usually seen with cigarette smoke exposure.

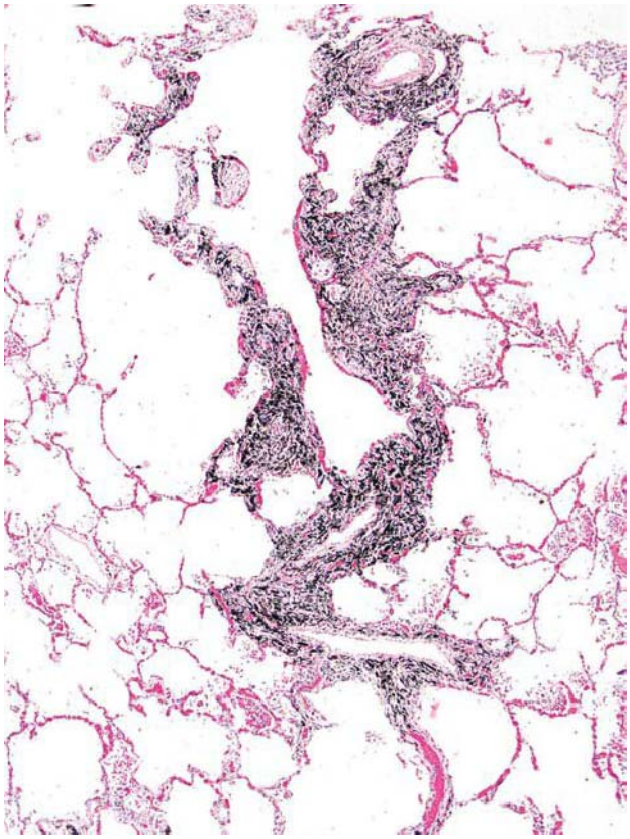
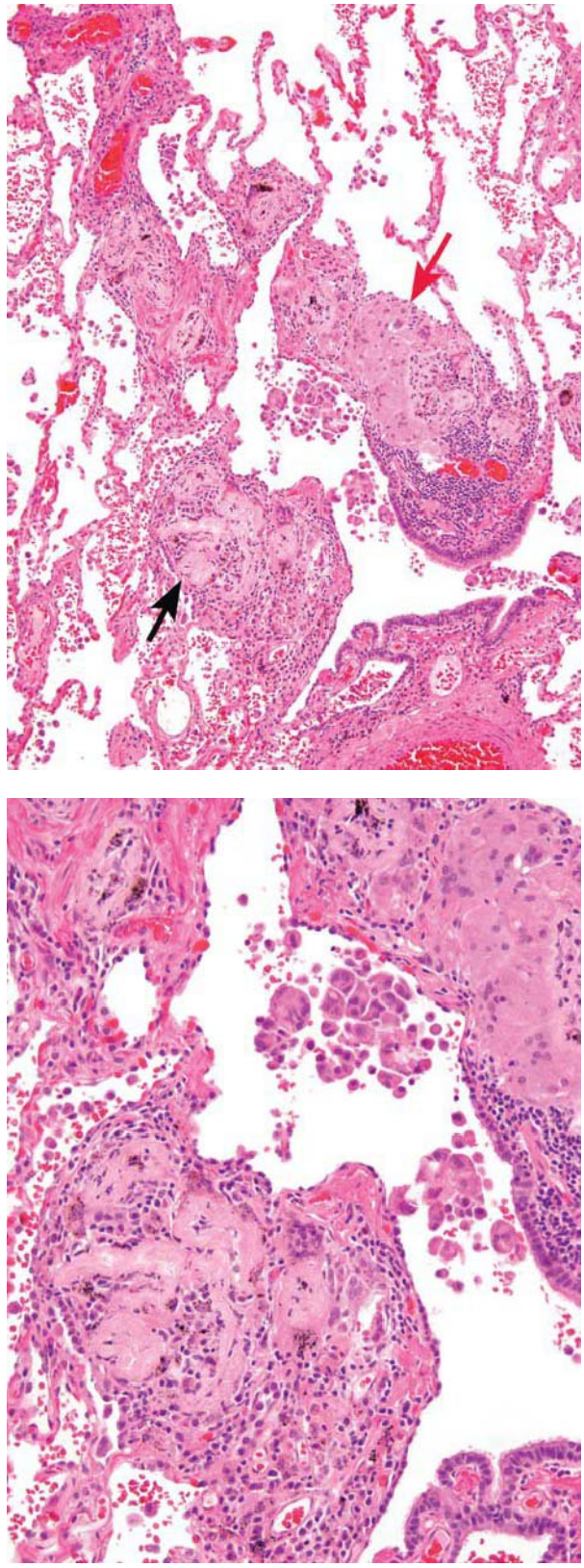


FIGURE 20.20. Chronic bronchiolitis caused by mineral dust exposure. Marked fibrosis and pigmentation of a respiratory bronchiole in patient with heavy exposure to silica plus another pigmented dust of uncertain nature.

"Bronchiolitis" characterized by chronic inflammatory cells in bronchiolar walls may also be seen in HP (see Fig. 12.13). By convention the term bronchiolitis is not used when diagnosing HP, but patients with HP may have some degree of airflow obstruction, indicating that the bronchiolitis is functionally important.

Asthma is another condition in which a bronchiolitis is often present but is not named as such pathologically. The findings in asthma are very variable and can include goblet cell metaplasia of the epithelium, luminal mucus plugs, a markedly thickened basement membrane (uniformly present in the large airways, sometimes present in bronchioles), increased smooth muscle, and eosinophils and chronic inflammatory cells, and, in rare cases, fibrosis of the airway wall.

Acute or chronic bronchiolitis with granulomas or foreign body giant cells (Figs. 20.21 and 20.22) should raise a question of aspiration; if aspirated food particles are not evident on routine stains, digested periodic acid-Schiff stain (PAS) stain can be helpful because the walls of vegetable particles are strongly PAS positive. Polarization may also be useful to demonstrate foreign material. The combination of bronchiolitis obliterans organizing



FIGURES 20.21 and 20.22. Chronic bronchiolitis caused by aspiration. **Figure 20.21:** The bronchiolar wall contains chronic inflammatory cells, a foreign body granuloma (*red arrow*) and a partially degraded aspirated vegetable particle (*black arrow*), seen better in the high-power view (**Fig. 20.22**).

pneumonia (BOOP) (Chapter 5) with giant cells or granulomas with or without acute inflammation is also strongly suggestive of aspiration (see Figs. 5.28 and 5.29).

In addition to aspiration, granulomas associated with bronchioles can be found in sarcoid (see Fig. 13.13), Crohn disease, and tuberculosis and fungal infections (usually necrotizing), and in the latter situation a diagnosis of tuberculous or fungal bronchiolitis is appropriate.

Lymphomas often show a lymphangitic distribution in the lung and hence can produce a morphologic picture resembling chronic bronchiolitis (see Fig. 24.17).

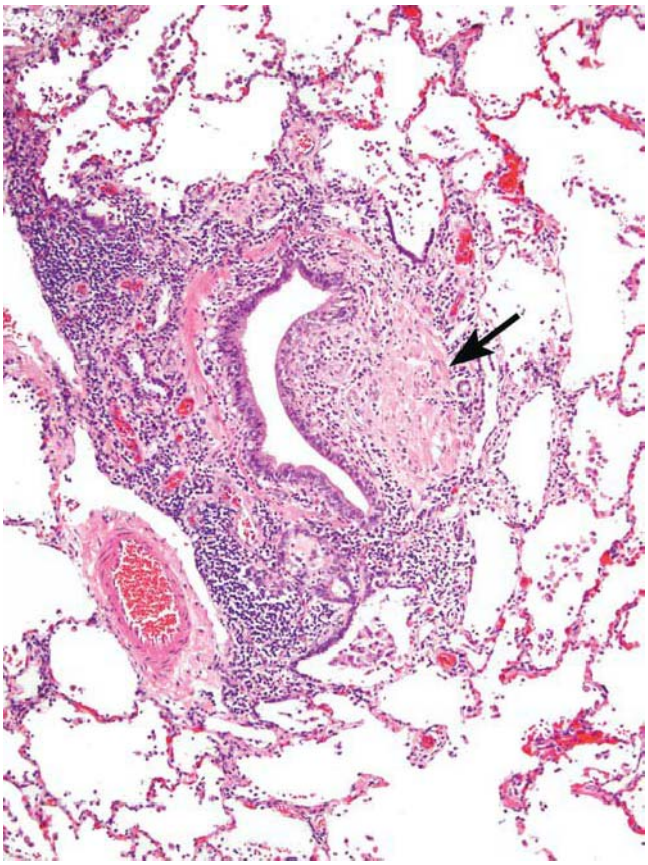
Constrictive Bronchiolitis

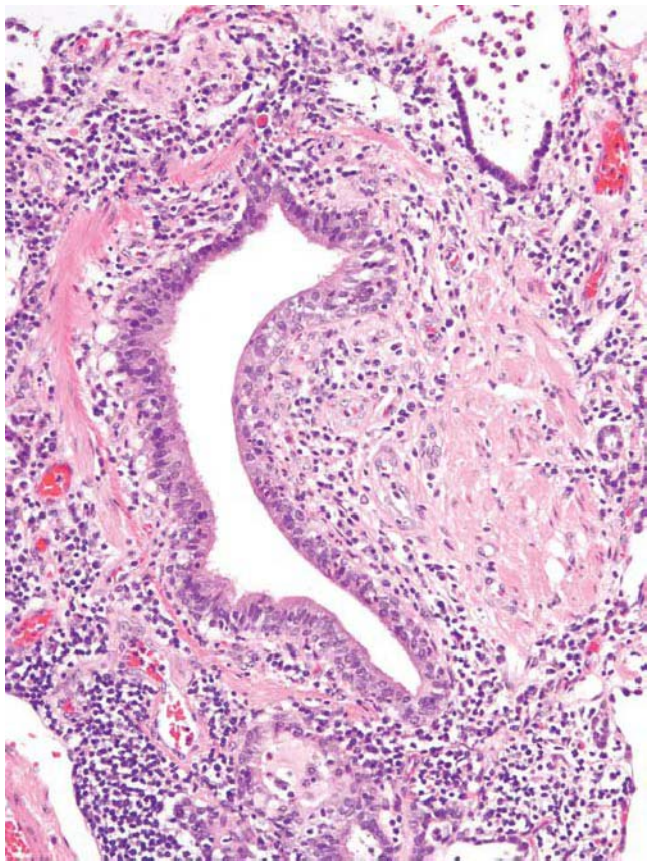
Historically the term "bronchiolitis obliterans" was used by pathologists both for bronchiolitis with intraluminal granulation tissue polyps and for fibrous narrowing/obliteration of the bronchiolar lumen. Luminal granulation tissue polyps are now regarded as part of BOOP (cryptogenic organizing pneumonia, organizing pneumonia pattern; see Chapter 5), and constrictive bronchiolitis is the name applied to processes in which the bronchiolar lumen is narrowed or obliterated by scar tissue. The distinction is important because BOOP is generally a treatable disease with a good prognosis, whereas constrictive bronchiolitis may lead to respiratory failure.

The newer term "constrictive bronchiolitis" has been extensively adopted by pathologists, but clinicians generally use the older name broncholitis obliterans or obliterative bronchiolitis for the clinical syndrome[3] and may not understand "constrictive bronchiolitis," so it is advisable to use both names in the diagnosis. However, in lung transplant rejection biopsies, the pathologic term bronchiolitis obliterans is still used.[12]

In the normal bronchiolar wall there is almost no space between the epithelium and the muscular layer (Fig. 20.6). In constrictive bronchiolitis, fibrous tissue, which may be accompanied early on by acute or chronic inflammatory cells and epithelial ulceration, is deposited between the epithelium and the muscle, so that the lumen is narrowed or completely obliterated (Figs. 20.23 to 20.33).

Constrictive bronchiolitis may be very patchy and is easy to overlook. In the normal lung there should be a bronchiole next to a pulmonary artery branch, and airway lumen and vessel should be of approximately the same diameter. A scarred bronchiole with an internal diameter much smaller than the artery represents constrictive





FIGURES 20.23 and 20.24. Early constrictive bronchiolitis in a patient with cystic fibrosis. There is a chronic inflammatory infiltrate in the bronchiolar wall along with a nodular scar (*arrow*) internal to the muscle layer. The process narrows the lumen.

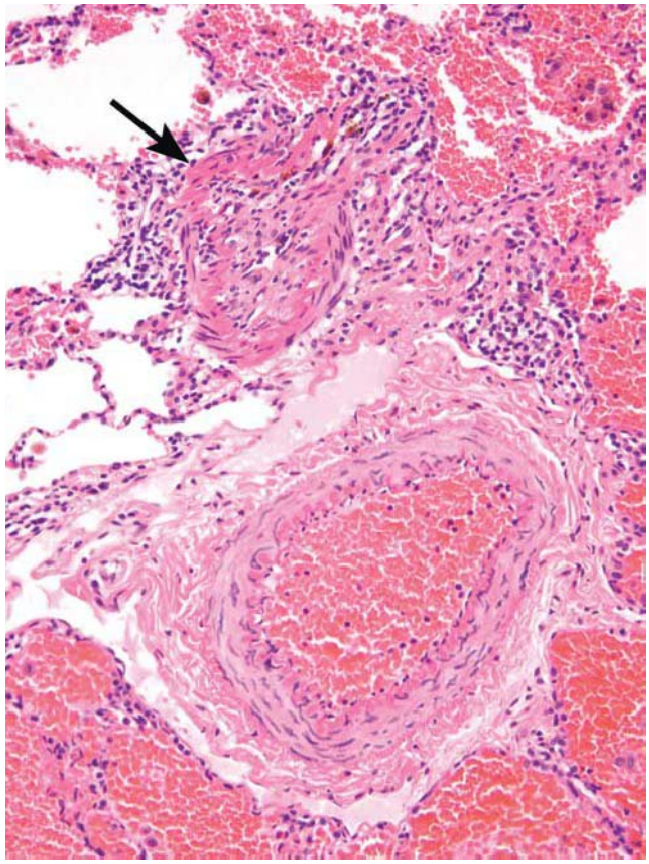
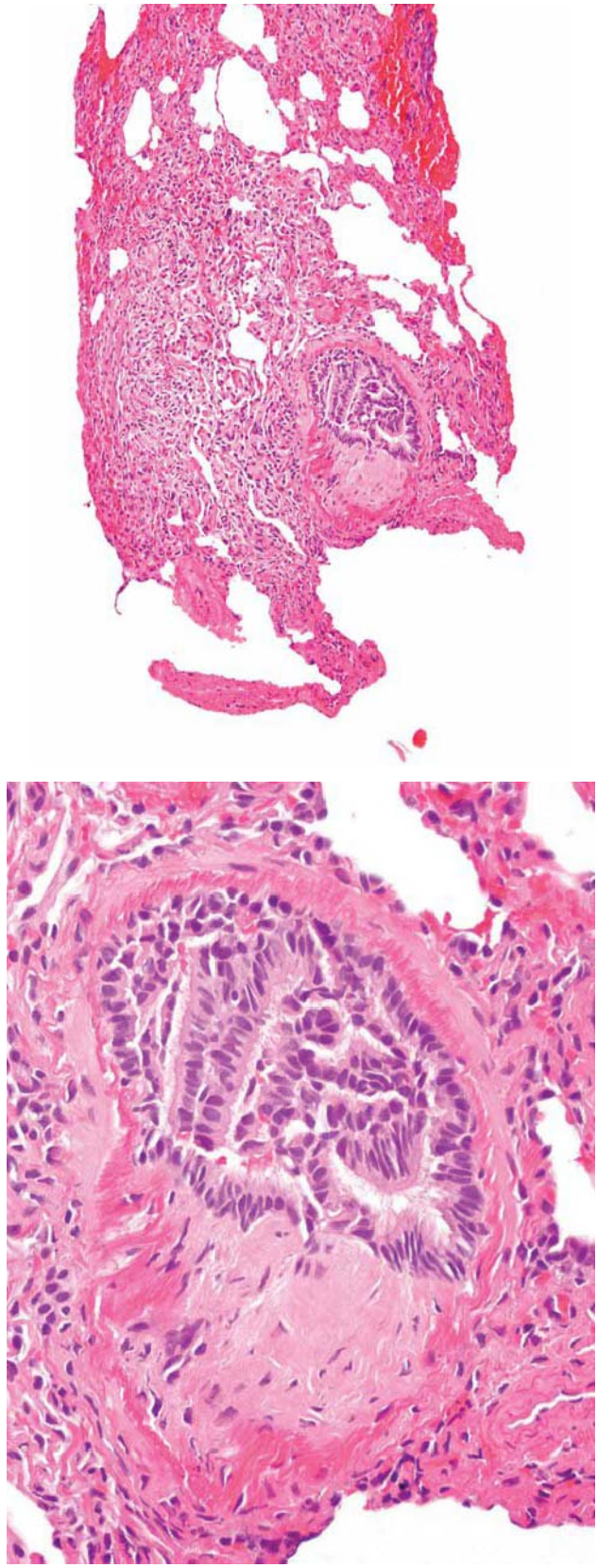


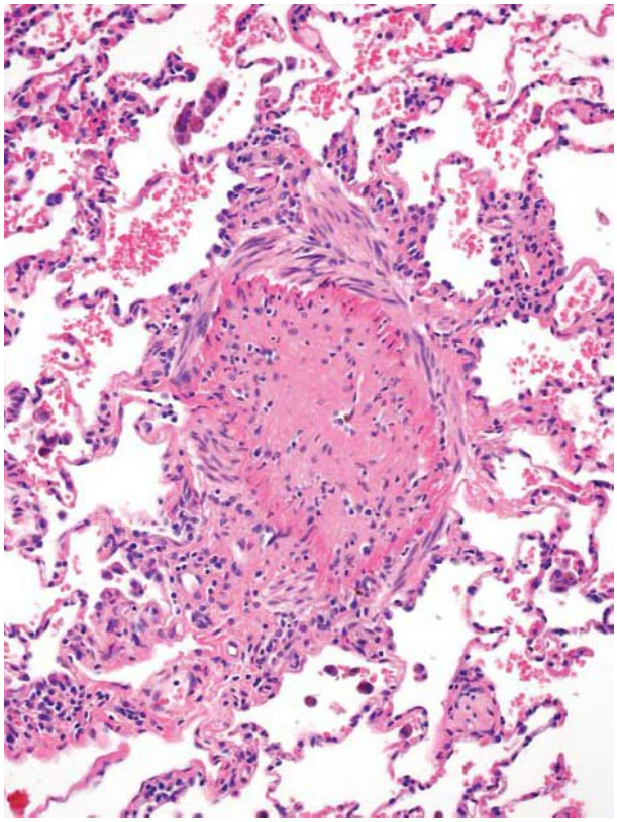
FIGURE 20.25. Constrictive bronchiolitis of unknown cause. The bronchiole (*arrow*) is much smaller than the accompanying pulmonary artery, and the lumen is almost completely obstructed by organizing granulation tissue.

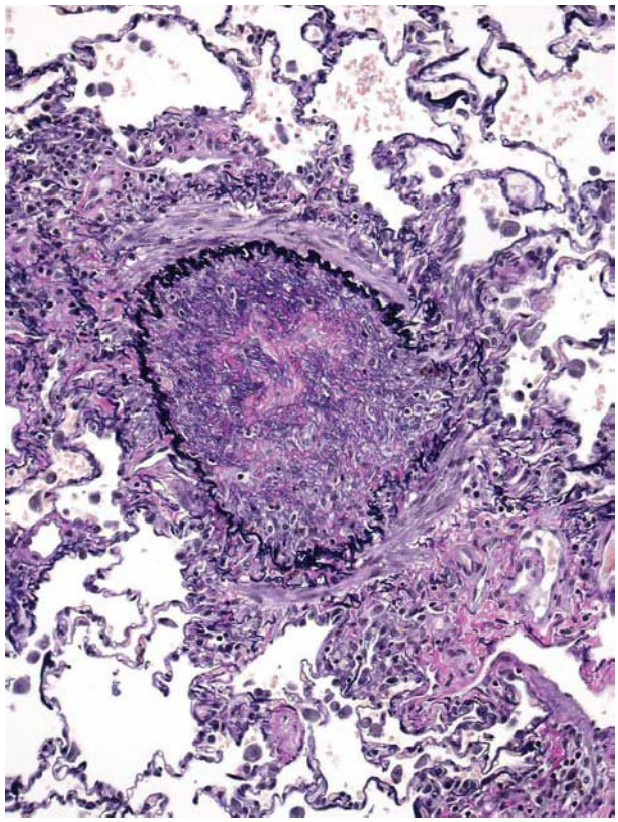
bronchiolitis (Fig. 20.25). The presence of a what at first glance appears to be a scar next to a pulmonary artery branch (see Figs. 18.21 to 18.23) should always raise a suspicion of constrictive bronchiolitis. Elastic stains are extremely helpful in finding old constrictive bronchiolitis because the normal bronchiole has an elastic layer and elastic stains outline the obliterated lumen in completely scarred constrictive bronchiolitis (see Figs. 20.27 to 20.29 and see Fig. 18.23); however, if the inflammatory process that has caused the bronchiolitis is severe enough, most of the elastica of the bronchiole may be lost with only a few fragments left to indicate the correct diagnosis (Figs. 20.32 and 20.33).

When constrictive bronchiolitis affects the respiratory bronchioles it can produce a picture somewhat mimicking BOOP (Figs. 20.30 and 20.31). The granulation tissue plugs of BOOP can be found in the lumens of respiratory bronchioles (see Fig. 5.9). However, in constrictive bronchiolitis the granulation tissue is much denser than one seen in BOOP, it is frequently collagenized, and is located in the wall of the airway. Typically the granulation tissue in constrictive bronchiolitis becomes re-epithelialized (Fig. 20.31).

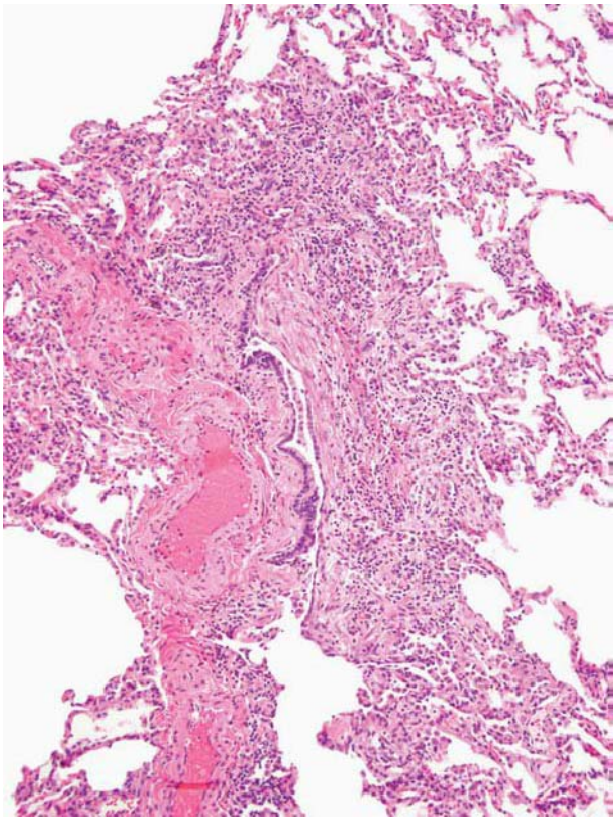


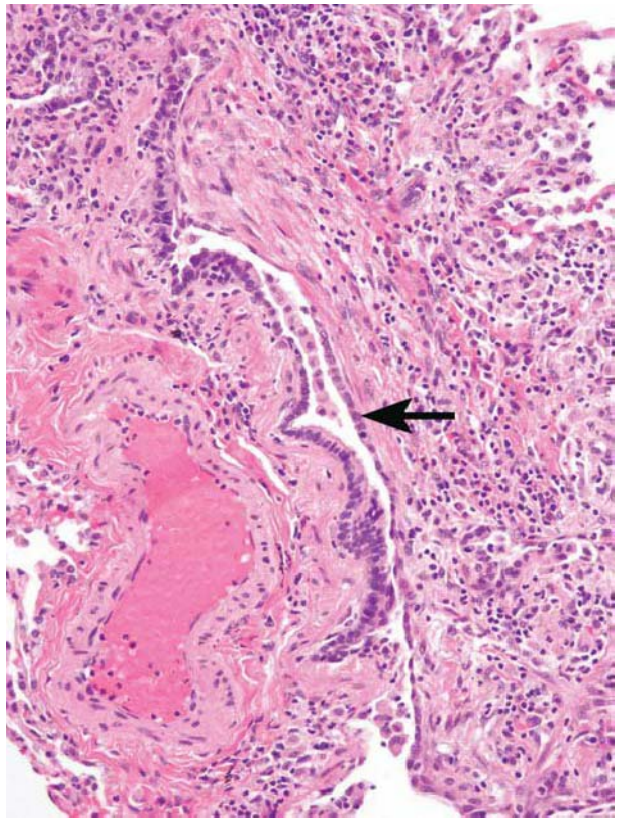
FIGURES 20.26 and 20.27. Constrictive bronchilolitis in a transbronchial biopsy from a lung transplant patient. A dense scar internal to the bronchiolar elastica narrows the lumen. The bronchiolar elastica is bright red (hematoxylin and aqueous eosin stain).



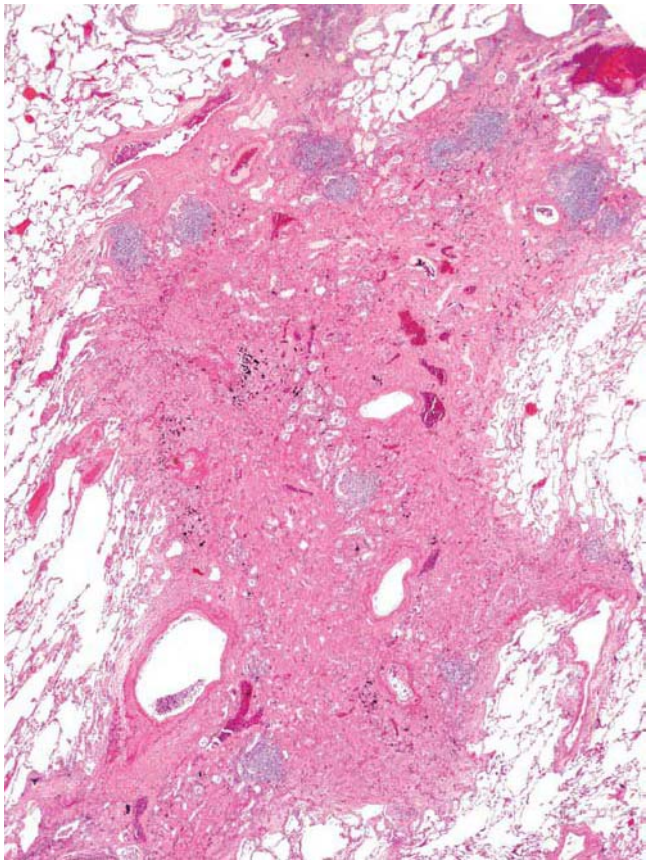


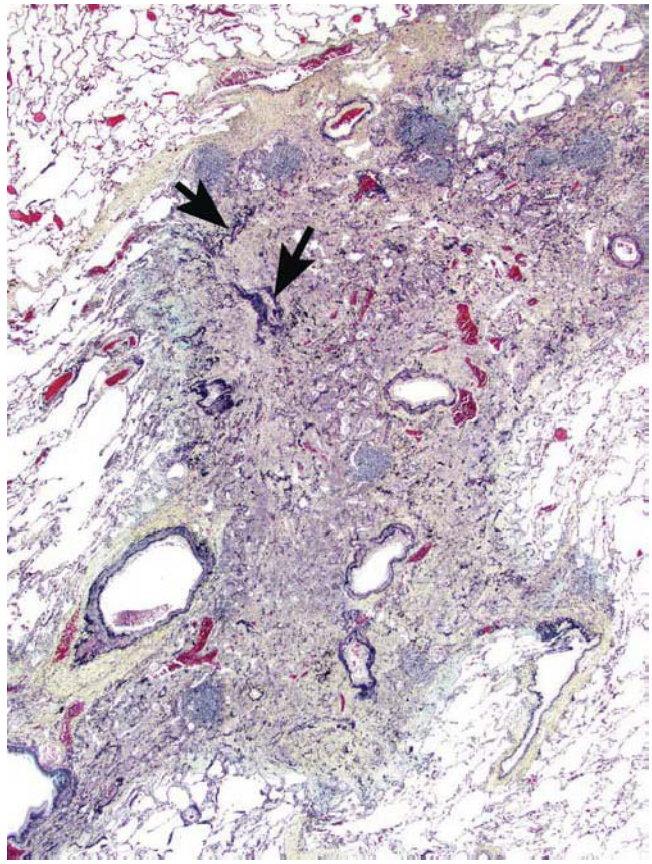
FIGURES 20.28 and 20.29. Constrictive bronchiolitis of unknown cause (same case as Fig. 20.25). **Figure 20.28:** On H&E, the obliterated bronchiole appears as a scar with surrounding muscle. **Figure 20.29:** Elastic stain confirms that the apparent scar is really an obliterated bronchiole.





FIGURES 20.30 and 20.31. Constrictive bronchiolitis, probably postinfectious, involving a respiratory bronchiole. This picture can be confused with BOOP, but the granulation tissue is denser than is typical of BOOP and shows considerable collagenization, and is also re-epithelialized (*arrow*), a finding that is unusual in BOOP.





FIGURES 20.32 and 20.33. Severe constrictive bronchiolitis in a patient with cystic fibrosis. The inflammatory process has completely destroyed the bronchiole, and only a few fragments of elastic tissue (*arrows*) are seen in the elastic stain (Fig. 20.29). Location of scar next to a pulmonary artery branch is an important clue to the diagnosis.

Most etiologies of constrictive bronchiolitis (Table 20.4) are morphologically indistinguishable, but one exception is diffuse idiopathic pulmonary neuroendocrine cell hyperplasia (DIPNECH) where minute carcinoid tumors arise in bronchiolar lumens and evoke a fibrotic reaction that obliterates the lumen.

DIAGNOSTIC MODALITIES

Accurate assessment of bronchiolitis generally requires one or preferably more whole bronchioles, and as a rule transbronchial biopsy does not provide adequate sampling. However, lung transplant rejection is one exception in which there are agreed upon rules for grading the inflammatory response even in partially sampled bronchioles in transbronchial biopsies.[13] Another exception is diffuse panbronchiolitis where a transbronchial biopsy may sample an inflamed bronchiole and show the characteristic foamy macrophages.

PROGNOSIS

For many types of bronchiolitis pathologic features do not provide a good guide to prognosis, and an underlying systemic disease, if present, may be the major determinant of outcome. However, cigarette smoke-induced small airways disease is now recognized as a major contributor to airflow obstruction in most patients with chronic obstructive pulmonary disease (COPD).[14] Acute adenovirus bronchiolitis in infants is associated with a mortality rate up to 20%.[5] The prognosis of constrictive bronchiolitis depends on the clinical setting. Postinfectious constrictive bronchiolitis in infants is associated with low mortality but considerable morbidity including recurrent respiratory infections.[5] In adults constrictive bronchiolitis often causes progressive fixed (i.e., unresponsive to bronchodilators) airflow obstruction and may lead to respiratory failure, but some patients appear to stabilize, albeit with residual functional impairment.[1,3] Constrictive bronchiolitis develops in approximately 50% of lung transplant recipients by 5 years and is the major cause of graft failure and mortality in long-term lung transplant survivors.[15]

Untreated, diffuse panbronchiolitis is slowly progressive with a 10-year survival of approximately 30% and may be complicated by colonization of the airways with infectious organisms, especially *Pseudomonas*, and by the development of bronchiectasis.[4] Treatment with macrolides appears to dramatically improve survival.[16,17]

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CHAPTER

21

Interstitial Lung Disease in Patients with Collagen Vascular Diseases

NOMENCLATURE ISSUES

Patients with collagen vascular diseases (CVDs) frequently develop intersitial lung disease (ILD) as well as diseases involving the pleura, the vasculature, and several other lesions (Table 21.1). In the past there was a tendency to simply lump such conditions together into "rheumatoid lung" or "lupus lung", and so on, but this approach provides no useful information to clinicians because the prognosis, and to a certain extent the treatment, varies by pathologic pattern. For example, a diagnosis of "rheumatoid lung" can be applied to usual interstitial pneumonia (UIP) or to cellular nonspecific interstitial pneumonia (NSIP) developing in a patient with underlying rheumatoid arthritis, or even to rheumatoid nodules, but the former probably behaves just as badly as idiopathic UIP (see Prognosis), whereas cellular NSIP appears to have a very good prognosis, and rheumatoid nodules generally do not require any treatment once their nature is established.

The older literature on ILD in CVD should be interpreted cautiously because until about 10 years ago NSIP was not always separated from UIP[1] and thus reports of prognostic differences by histologic pattern were not always accurate. In the past, the term "cellular interstitial pneumonia" was sometimes used for what would now be called NSIP.

One of the confusing features of ILD in patients with collagen vascular is that, although the pathologic patterns are often identical to those in idiopathic ILD, more than one pattern or unusual combinations or unusual patterns can be found in a given biopsy and are in fact a clue to the presence of a CVD (but see comments about drug reactions). Nonetheless, we believe that when dealing with ILD in patients with CVD, the pathologist should attempt to put the biopsy in question into as close a fit as possible to the corresponding idiopathic ILD(s) so that the clinician has some guidance to treatment and prognosis. Thus a patient with rheumatoid arthritis and a UIP pattern should be diagnosed as "UIP in a patient with rheumatoid arthritis"; or, if morphologic features suggestive of CVD are present (see below), a diagnosis of "UIP with features of CVD" would be appropriate. A patient with a mixture of cellular NSIP and bronchiolitis obliterans organizing pneumonia (BOOP), a combination that is not unusual in CVDs, should be diagnosed as such: "Surgical lung biopsy showing a mixture of cellular NSIP and BOOP in a patient with underlying (disease)."

Clinical Features

Pleuropulmonary manifestations vary considerably by type of CVD, with the lowest rate of involvement in patients with lupus and the highest in those with rheumatoid arthritis, mixed connective tissue disease, and systemic sclerosis.[2] ILD-type patterns in particular are common in CVD, and it has been estimated that 15% of ILD patients actually have an underlying CVD.[3] ILD is particularly frequent in rheumatoid arthritis and systemic sclerosis (in the latter

Table 21.1

Intrathoracic lesions in patients with CVD

Chronic pleural effusion/pleural fibrosis
DAD/ARDS
UIP
NSIP
BOOP
Lymphocytic interstitial pneumonia (LIP)
Chronic bronchiolitis
Follicular bronchiolitis/lymphoid hyperplasia
Constrictive bronchiolitis
Xerotrachea (Sjögren syndrome)
Eosinophilic pneumonia
Apical fibrosis
Rheumatoid nodules
Diffuse alveolar hemorrhage with/without capillaritis
Vasculitis
Vasculopathy (in systemic sclerosis)
Vascular thrombosis (typically in patients with lupus and anti-phospholipid antibodies)
Aspiration pneumonia (usually in polymyositis/dermatomyositis or systemic sclerosis)
Lymphoma (most commonly in Sjögren syndrome)

up to 75% of patients).[4,5] CVD-related ILD have been estimated to account for 25% of all ILD deaths in the U.S.[2]

The extrapulmonary clinical features of CVD vary with the disease and are beyond the scope of this book. When ILD is present, the clinical pulmonary features are no different from idiopathic ILD with the same histologic pattern, although patients with systemic sclerosis are also prone to develop pulmonary hypertension secondary to vasculopathy.[4] In addition to ILD, recurrent exudative pleural effusions, sometimes leading to visceral pleural fibrosis, as well as acute respiratory distress syndrome (ARDS) (sometimes labeled "acute lupus pneumonitis" in patients with lupus), diffuse pulmonary hemorrhage, vasculitis, vasculopathy (in systemic sclerosis), and pulmonary hypertension may be found in patients with underlying CVD. In most instances the pulmonary disease develops after the CVD but sometimes pulmonary disease is the initial manifestation and only the presence of follicular bronchiolitis or lymphoid hyperplasia by itself or superimposed on another ILD points to the underlying disease.

Imaging

Pulmonary abnormalities seen in patients in CVD may be related to the underlying CVD or may result from complications of treatment, such as drug toxicity and opportunistic infection. The radiologic manifestations of ILD in patients with CVD are similar to those found in idiopathic interstitial pneumonias.[6] The only difference is that patients with CVD are more likely to have more than one pattern, the most common combination being NSIP and organizing pneumonia (OP, BOOP).[7]

The most common patterns of ILD seen in CVD are NSIP, UIP, and OP (BOOP). NSIP is characterized on high resolution computed tomography (HRCT) by bilateral symmetric ground glass opacities (GGOs), irregular linear (reticular) opacities, and traction bronchiectasis involving mainly the lower lobes (Figs. 21.1 and 21.2). UIP typically manifests with reticulation and honeycombing involving predominantly the subpleural regions and lung bases (Fig. 21.3). The characteristic HRCT of OP (BOOP) comprise patchy bilateral consolidation, which in 60% to 80% of cases has a subpleural and/or peribronchial distribution (Fig. 21.4).

Certain extraparenchymal findings when present can be helpful in suggesting the possibility of CVD on imaging. These include an enlarged pulmonary artery out of proportion to the extent of ILD, pleural effusion or pleural thickening, dilated esophagus (systemic sclerosis), shoulder and acromioclavicular joint abnormalities (rheumatoid arthritis), and soft tissue calcifications (polymyositis/dermatomyositis or scleroderma).[6]

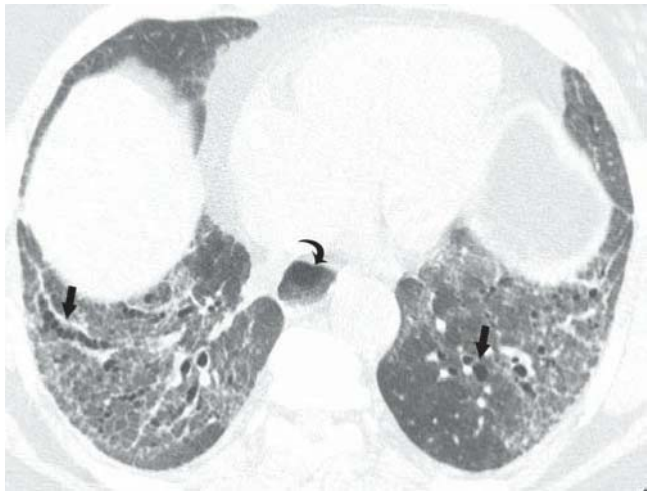


FIGURE 21.2. Same case as Figure 21.1. HRCT at the level of the lung bases demonstrates extensive bilateral GGOs with superimposed reticulation and traction bronchiectasis (*straight arrows*). The esophagus (*curved arrow*) is dilated and contains air and debris, a common finding in patients with scleroderma. The patient was a 61-year-old woman with NSIP associated with scleroderma.

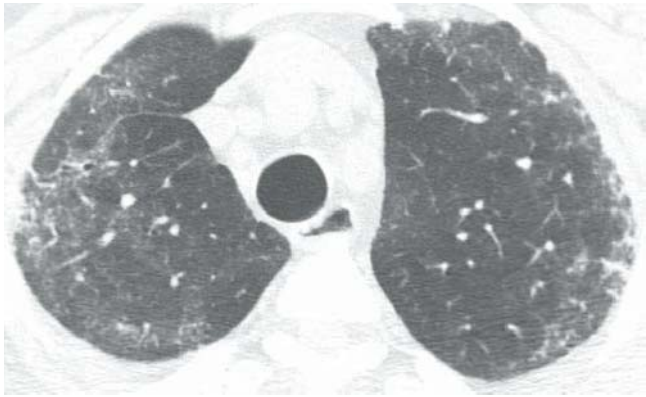


FIGURE 21.1. NSIP in scleroderma. HRCT at the level of the upper lobes shows bilateral GGOs and mild peripheral reticulation.

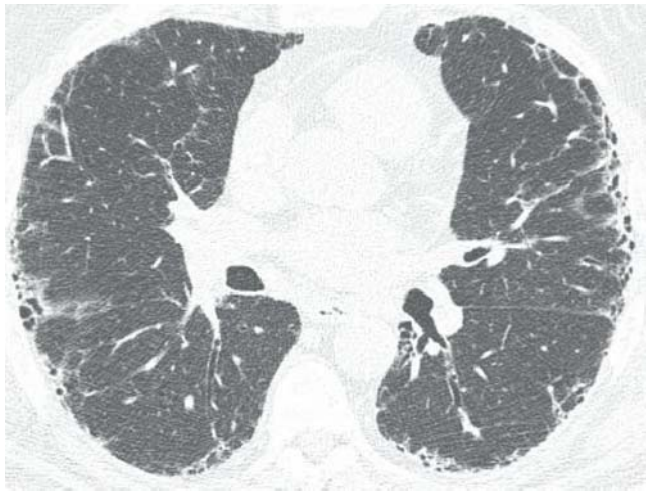


FIGURE 21.3. UIP in rheumatoid arthritis. HRCT demonstrates peripheral reticulation and honeycombing. The patient was a 64-year-old man with UIP associated with rheumatoid arthritis.

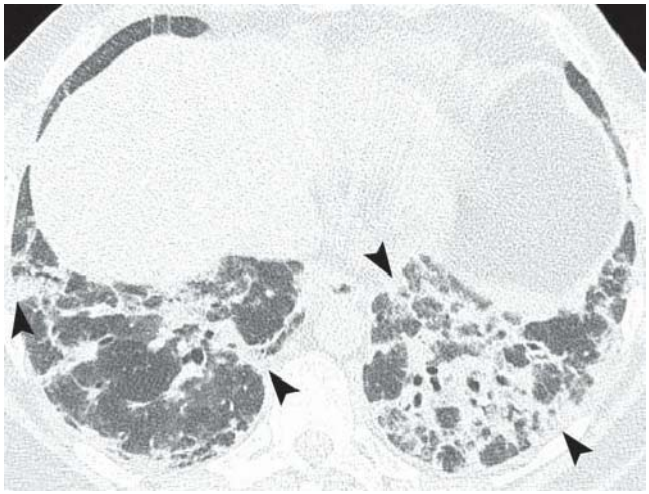
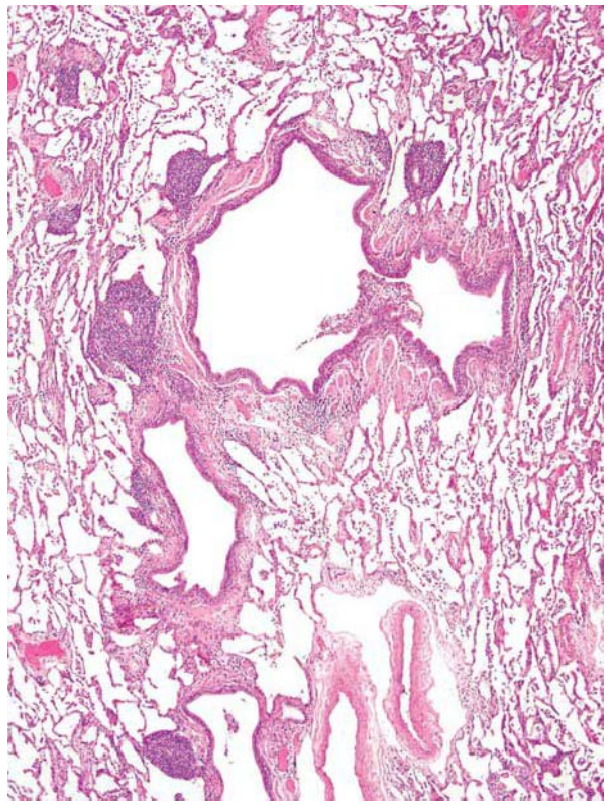


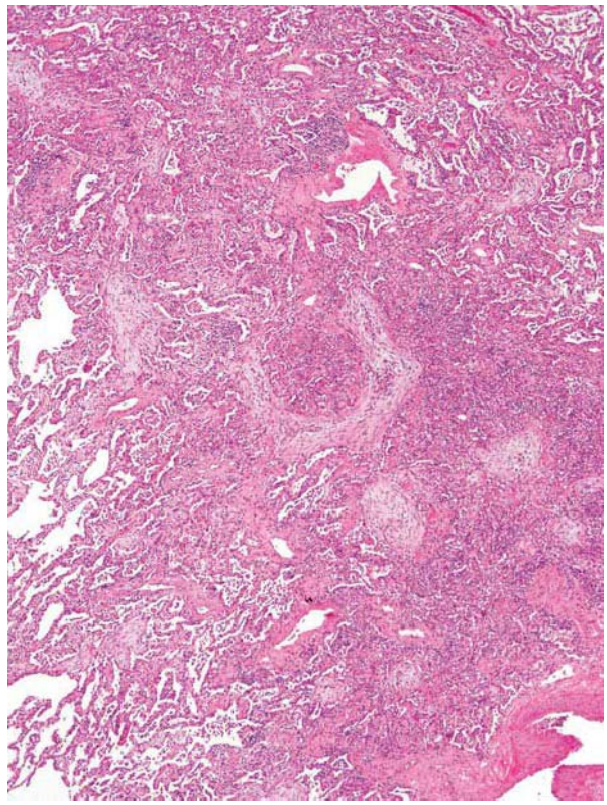
FIGURE 21.4. Organizing pneumonia in polymyositis. HRCT shows bilateral areas of consolidation in a predominantly peripheral (*arrowheads*) and peribronchial distribution. The patient was a 44-year-old man with polymyositis.

Pathologic Features of Collagen Vascular Disease—Associated Interstitial Lung Disease

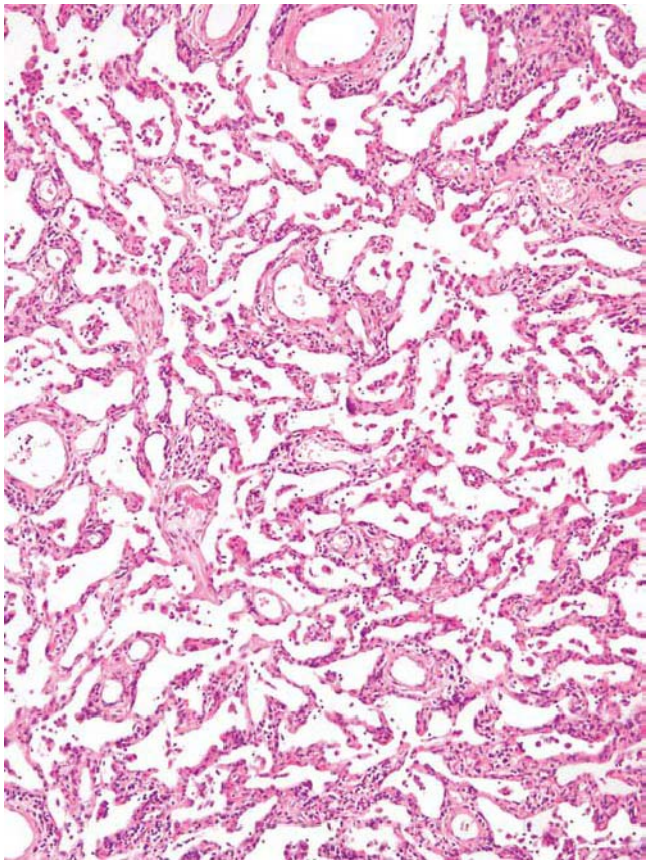
For the most part the pathologic features of ILD in CVD are identical to those seen in patients without CVD, although there is variation in disease frequency from CVD to CVD; for example, UIP is relatively common in patients with rheumatoid arthritis[8,9] and uncommon in patients with lupus, whereas fibrotic NSIP is the most common ILD in systemic sclerosis[8,10] and polymyositis/dermatomyositis.[11] If one takes all forms of ILD, an NSIP pattern is the most frequent.[9] However, these statistical differences are not diagnostically useful in an individual case. As noted above, mixtures of patterns that do not usually occur together raise the possibility of CVD (Figs. 21.5 to 21.7). Very rarely, lupus erythematosus (LE) cells similar to those seen in peripheral blood can be found in tissue in biopsies from patients with lupus[12] and electron microscopy may also show lupus fingerprint type immune complex deposits.[13]

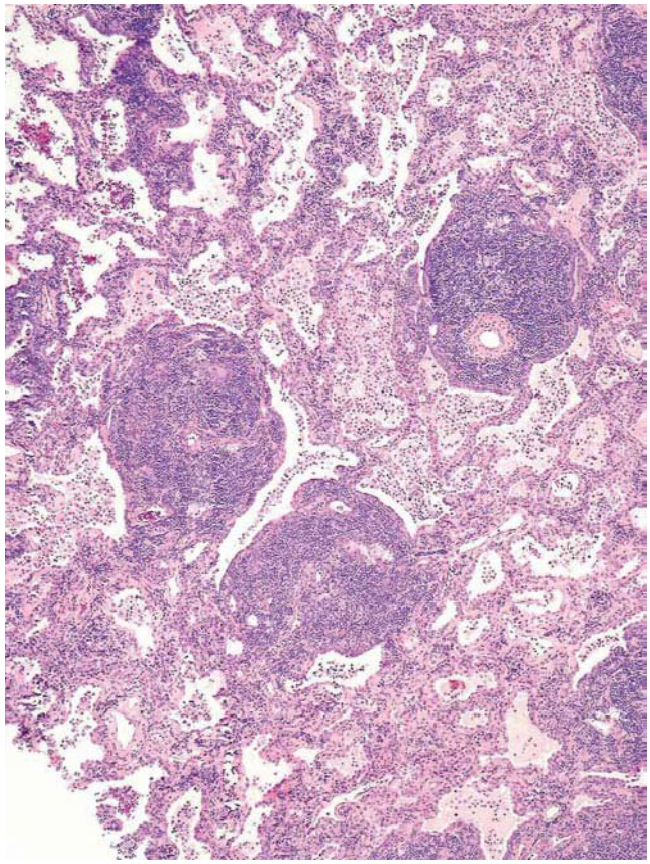
The finding of follicular bronchiolitis, lymphoid hyperplasia, or lymphocytic interstitial pneumonia (LIP) (see Chapter 19 for definitions) should always raise a question of underlying CVD. Sometimes follicular bronchiolitis/lymphoid hyperplasia are the only lesions in a biopsy but more frequently are superimposed on a UIP or NSIP picture[14] (Figs. 21.6 and 21.8; and see Fig. 6.36; Figs. 7.10 to 7.12) and in this circumstance the possibility that the patient has CVD should be indicated in the diagnosis line (e.g., "UIP with features of CVD" or "UIP with lymphoid hyperplasia suggestive of underlying CVD."). Idiopathic UIP is generally quite paucicellular and the presence of a UIP pattern with increased interstitial lymphocytes and plasma cells (see Fig. 6.37) is also suggestive of underlying CVD[14] (with a differential diagnosis of chronic hypersensitivity pneumonitis). LIP is strongly associated with Sjögren syndrome but occasionally is seen in other CVD as well as in patients with dysgammaglobulinemias (see Chapter 19).





FIGURES 21.5. to 21.7. Legend appears on following page





FIGURES 21.5. to 21.7. Mixture of pathologic patterns in the same biopsy from a patient with rheumatoid arthritis. **Figure 21.5** shows follicular bronchiolitis associated with bronchiolectasis. **Figure 21.6** shows BOOP. Other areas (**Fig. 21.7**) demonstrate a cellular NSIP pattern. Combinations of ILD patterns are common in patients with CVD.

FIGURE 21.8. Mixture of ILD patterns in a patient with rheumatoid arthritis. Follicular bronchiolitis is superimposed on an underlying pattern that is either a somewhat unusual (because of the sharp variations from fibrotic to cellular) NSIP or a somewhat unusual LIP (parts of the interstitium have a fairly intense lymphoid infiltrate while other parts show fibrosis with little cellularity). Patterns that do not quite match those seen in "ordinary" ILD are frequent in patients with CVD.

Pathologic Confounders/Differential Diagnosis

Patients with CVD may be immunosuppressed because they have been treated with steroids and/or other immunosuppressive agents, and biopsy may demonstrate an infectious agent with or without pathologic features of CVD. Patients with systemic sclerosis and dermatomyositis are at risk of aspiration pneumonias because of esophageal dysfunction (see Chapters 5 and 20 for a discussion of pathologic patterns of aspiration).

Drug reactions represent a more complex problem. First, drug reactions can produce strange combinations of ILD-like patterns—the same phenomenon that is seen in untreated CVD. Methotrexate, which is now commonly employed in patients with CVD, can cause a whole range of pathologic reactions including NSIP-like and hypersensitivity-like ILD with granulomas as well as eosinophilic pneumonias (see Figs. 18.4 to 18.7). Anti-tumor necrosis factor (TNF) agents such as etanercept and infliximab often cause a picture of multiple sarcoid-like granulomas (see Figs. 18.12 and 18.13), and this is a reasonably specific finding but needs to be separated from the effects of methotrexate, as these agents are often used together, and from infections.

Second, drugs can produce pathologic patterns identical to those in untreated CVD. Thus penicillamine, which has been used in the past to treat rheumatoid arthritis, is believed to cause constrictive bronchiolitis, bronchiolitis obliterans organizing pneumonia (BOOP), follicular bronchiolitis, diffuse alveolar damage (DAD), and eosinophilic pneumonias,[15,16] all processes found in rheumatoid arthritis absent drug therapy, and there is controversy about whether these lesions are really penicillamine reactions or underlying disease.[17] Figures 18.21 to 18.23 illustrate the same problem in a patient with rheumatoid arthritis treated with leflunomide who developed constrictive bronchiolitis.

The general principles set forth in Chapter 18 for evaluating potential drug reactions should be followed in such cases; in particular, the development of new disease shortly after starting drug therapy and unusual new systemic findings such as fever or rash after starting drug therapy,[18] support a drug reactions, but in most instances

morphology cannot sort out the problem and such cases should be signed out to indicate that the drug or the underlying disease could cause the picture in question.

Diagnostic Modalities

As a rule transbronchial biopsy is not suitable for the diagnosis of ILD-like manifestations of CVD and video assisted thoracoscopic surgery (VATS) biopsy is required. Core needle biopsy may be suitable for diagnosing rheumatoid nodules.

Prognosis

The prognosis of ILD-type lesions in patients with CVD is difficult to evaluate, in part because the literature often is based on radiologic rather than pathologic diagnoses,[19] and in part because it is unclear whether there are differences among different CVD with the same pathologic pattern. Patients with BOOP or cellular NSIP appear to do relatively well.[10] Overall, patients with systemic sclerosis and ILD tend to fare worse than patients with other CVD,[10] but that conclusion appears to reflect the greater prevalence of fibrotic ILD in systemic sclerosis[10,19] and the frequent development of pulmonary hypertension.[20]

The prognosis of UIP in the setting of CVD is controversial, with some reports claiming a considerably better outcome than is seen in idiopathic UIP[21,22]; and others finding no difference, at least for patients with rheumatoid arthritis and a UIP pattern.[9,23] In systemic sclerosis, pulmonary involvement is the leading cause of death[24] and some reports suggest that there is no difference between fibrotic NSIP and UIP patterns[10] but these figures are based on small case numbers.

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CHAPTER

22

Pneumoconioses Producing a Pattern of Interstitial Lung Disease

NOMENCLATURE ISSUES

Pneumoconioses are lung diseases caused by the inhalation of dusts. Although generally viewed as a distinctive set of entities, many pneumoconioses are very similar in terms of pulmonary function, imaging, and pathologic changes to intersititial lung disease (ILD), and occasionally the distinction between pneumoconiosis and non-dust–related ILD can be difficult.

Pneumoconioses are usually separated into those characterized by macular/nodular lesions around the bronchovascular bundles in the centers of the lobules (see definitions under Pathologic Features) and those that appear as diffuse interstitial disease, but this distinction is somewhat artificial because most dust-related diseases start in or around the bronchioles, and many of the dusts that usually produce bronchiolocentric macular/nodular lesions can occasionally cause diffuse interstitial inflammation/fibrosis, for example, coal dust and silica. Conversely some of the diseases that typically cause diffuse interstitial fibrosis start as peribronchovascular lesions, for example, asbestosis.

Pneumoconioses characterized by nodular lesions on imaging and nodular or macular lesions on pathologic examination are subclassified into "simple" pneumoconioses, meaning the lesions measure up to 1 cm on imaging or pathology, or "complicated" pneumoconioses (also called "progressive massive fibrosis" or PMF), meaning the nodules or mass-like lesions are larger than 1 cm[1] (Tables 22.1 and 22.2). This terminology applies only to nodular/macular lesions and is not used for diseases that appear as interstitial fibrosis.

Table 22.1

Types of macular/nodular pneumoconioses

Size of lesion	Terminology
Up to 1 cm	Simple pneumoconiosis
Greater than 1 cm	Complicated pneumoconiosis, also called PMF

CLINICAL FEATURES

The clinical features of the pneumoconioses vary enormously. Many dusts that produce macules on pathologic examination and nodules on imaging have no or minimal functional effects (typically some degree of airflow obstruction if anything) and are usually picked up on imaging. Examples are siderosis (welder's pneumoconiosis) caused by exposure to iron dust or fumes and stannosis caused by exposure to tin dust or fumes. However, simple coal worker's pneumoconiosis (CWP) is associated with shortness of breath (SOB) and significant airflow obstruction in some patients.[2] Simple silicosis may produce no functional abnormality and no symptoms, or may cause airflow obstruction, or, if the nodules are present in great profusion, some degree of restriction.

When the same dusts produce large lesions of PMF, patients are often short of breath and pulmonary function tests can show an obstructive or restrictive or combined abnormality. Pulmonary hypertension may also be present if the mass lesions have destroyed many small arterial branches.

In contrast, dusts that produce diffuse interstitial inflammation/fibrosis, for example, asbestos (asbestosis), result in a restrictive pulmonary function profile and decreased diffusing capacity when the disease is advanced, and this is accompanied by SOB. However, mild forms of asbestosis may produce minimal functional changes and may not be symptomatic.

IMAGING

The chest radiograph has been for many years a key component in the detection and characterization of pneumoconiosis. The presence, pattern, and severity of abnormalities are assessed objectively by comparing the findings with those of the International Labor Organization (ILO) classification of pneumoconiosis standard radiographs and following the ILO guidelines.[3] The radiograph however has limited sensitivity and specificity. Several studies have shown that high resolution computed

Table 22.2

Summary of disease patterns by agent

Agent/disease	Simple pneumoconiosis[a]	Complicated pneumoconiosis[a]	Diffuse interstitial inflammation/fibrosis	Mineral dust-induced bronchiolitis	PAP[b]
Coal dust (CWP)[c]	Yes	Yes	Uncommon	Yes	No
Silica/silicosis and mixed dust fibrosis	Yes	Yes	Uncommon	Yes	Yes
Silicates (e.g., talc/talcosis)	Yes	Yes	Yes	Yes	No
Asbestos/asbestosis	No[d]	No	Yes	Yes	No
Hard metal/hard metal disease	No[d]	No	Yes[e]	Yes	No

[a]Simple pneumoconiosis = dust macules or nodules measuring up to 1 cm. Complicated pneumoconiosis = nodules or masses larger than 1 cm.
[b]PAP = pulmonary alveolar proteinosis.
[c]CWP = coal worker's pneumoconiosis.
[d]Early asbestosis and hard metal disease appear as centrilobular fibrotic lesions involving the walls of bronchioles but by convention are not referred to as simple pneumoconiosis.
[e]Diffuse lesions of hard metal disease may mimic DIP or be similar to UIP.

tomography (HRCT) is superior to the radiograph in detecting the presence of pneumoconiosis and in characterizing the parenchymal abnormalities.[4]

The parenchymal manifestations of pneumoconiosis on imaging mainly comprise (a) small nodular opacities relating to the presence of peribronchiolar dust accumulation with or without associated fibrosis; (b) aggregation of small nodular opacities into large nodules (>1 cm) or masses; or (c) findings of ILD comprising mainly irregular linear opacities (reticulation) on the radiograph and ground-glass opacities (GGOs), reticulation, and, in advanced stage fibrosis, honeycombing, on HRCT.

Pneumoconioses presenting with small nodular opacities, usually with an upper lobe predominance (radiograph and HRCT), and predominantly centrilobular distribution (HRCT) include CWP (Fig. 22.1), silicosis, and siderosis.[5] The nodules may be poorly defined (ground-glass) or well-defined. Aggregation of small nodules into large nodules and masses (progressive massive fibrosis) is seen most commonly in silicosis (Fig. 22.2) and CWP but may also occur in other conditions, including mixed dust pneumoconiosis, berylliosis, and talcosis either inhaled or injected.[5] Findings of diffuse ILD are seen most commonly in asbestosis (Figs. 22.3 and 22.4), hard metal pneumoconiosis (Fig. 22.5), berylliosis, and acute silicosis (silicoproteinosis) but may occasionally occur in many other pneumoconiosis including CWP and silicosis.[5]

The diagnosis of pneumoconiosis is usually based on a history of exposure and consistent radiologic findings. It

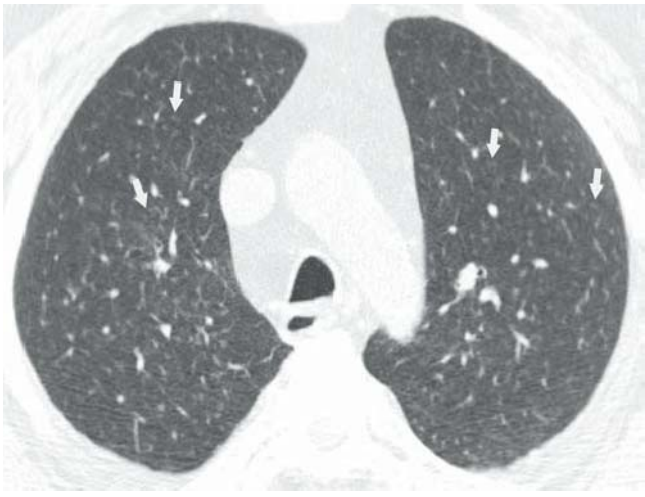


FIGURE 22.1. CWP. HRCT image at the level of the upper lobes shows bilateral poorly defined (ground-glass) nodules (*arrows*). The patient was a 64-year-old man with CWP.

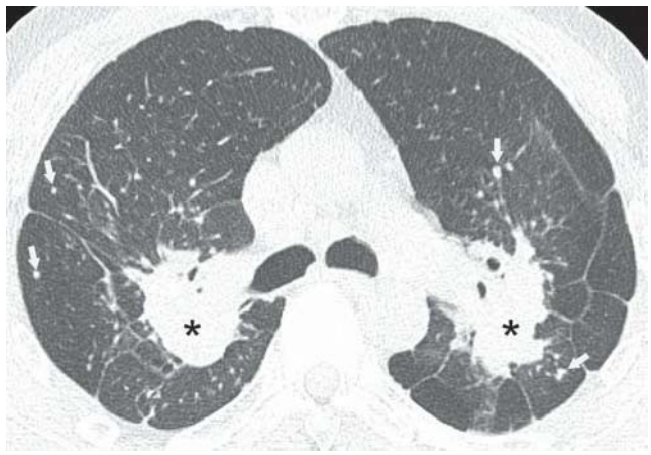


FIGURE 22.2. Progressive massive fibrosis in silicosis. HRCT image at the level of the main bronchi demonstrates bilateral perihilar conglomerate masses (asterisks). Also noted are architectural distortion owing to the fibrosis and a few well-defined silicotic nodules (*arrows*). The patient was a 65-year-old man with longstanding silicosis.

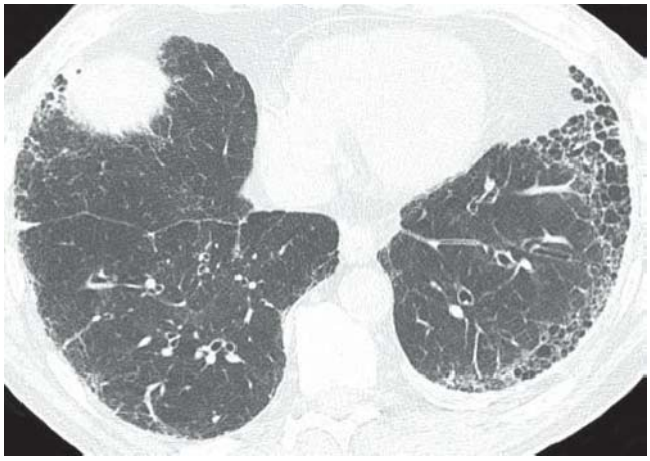


FIGURE 22.3. Asbestosis. HRCT image at the level of the lung bases shows subpleural reticulation in the right lower and middle lobes and honeycombing in the left lower lobe and lingula.

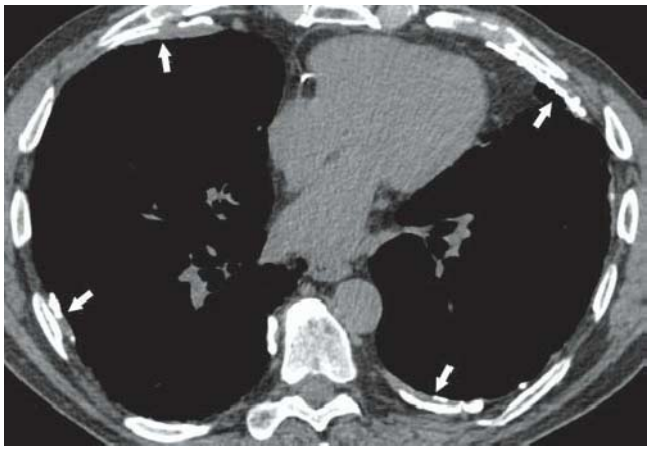


FIGURE 22.4. Asbestosis. HRCT photographed at soft tissue windows shows bilateral calcified pleural plaques (*arrows*). Same case as Figure 22.3. The patient was a 72-year-old man with asbestosis.

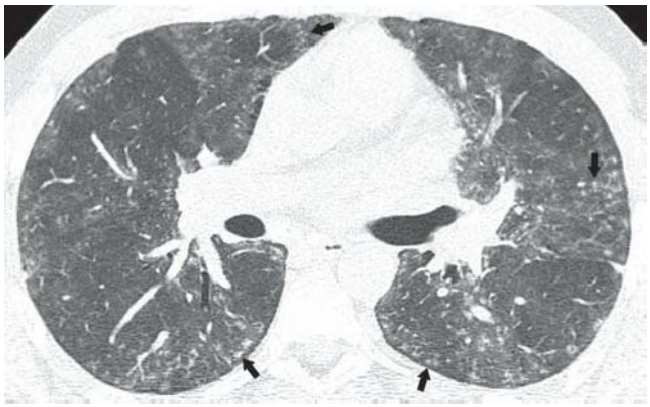


FIGURE 22.5. Hard metal pneumoconiosis HRCT image demonstrates extensive bilateral GGOs and several centrilobular nodules (*arrows*). The patient was a 34-year-old man with a 15-year history of exposure to tungsten carbide dust as a machinist sharpening tungsten carbide blades and hard metal disease on surgical lung biopsy.

is important to emphasize, however, that the radiographic and HRCT findings of pneumoconiosis are nonspecific. For example, early CWP and siderosis may be indistinguishable from respiratory bronchiolitis or hypersensitivity pneumonitis (HP) on HRCT. Furthermore, although the presence of bilateral pleural plaques is highly suggestive of asbestos exposure, interstitial fibrosis in patients with asbestos exposure may be from other causes or represent idiopathic pulmonary fibrosis rather than asbestosis.[6]

PATHOLOGIC FEATURES

Dust Deposition and Disease Patterns

Most dusts encountered in the workplace or the environment are preferentially deposited in the membranous and respiratory bronchioles. As a consequence most dust diseases start in or around the bronchioles. Even diffuse fibrosing disease tends to spread from bronchiole to bronchiole and then into the surrounding parenchyma, and when this occurs the typical pattern resembles either fibrotic nonspecific interstitial pneumonia (NSIP) (Chapter 6) or usual interstitial pneumonia (UIP) (Chapter 7). However, the mimicry is usually not exact, because dust macules, or nodules, or pigmented or birefringent dust may be mixed with the more diffuse fibrosis (see below).

Macules and Nodules

Macules are defined as nonpalpable, nonfibrotic, collections of dust, usually pigmented, located around the respiratory bronchioles and accompanying pulmonary artery branches. Despite the definition, in practice many types of macules show some degree of fibrosis. Macules are found with fairly inert dusts such as iron (Fig. 22.6) or tin, silicate minerals such as talc and mica, mixed dust fibrosis (i.e., combinations of silica with another dust) and with coal dust exposure (CWP). In CWP the macular fibrosis can be locally quite marked with severe distortion of the respiratory bronchiole (Fig. 22.7), and the abnormal bronchiole is frequently surrounded by enlarged airspaces termed "focal emphysema," (Fig. 22.7), a process that is morphologically very similar to centrilobular emphysema (CLE) found in smokers.

Nodules are rounded or stellate solid lesions that typically start next to respiratory bronchioles. Silicotic nodules have a more or less rounded contour and contain dense whorled collagen (Figs. 22.8 and 22.9) and, if the patient is currently or recently exposed to silica, dust-laden macrophages around the periphery (Fig. 22.10). Although the difference between nodules and macules is usually evident on microscopic examination, both appear as nodules on imaging.

Most macular and nodular lesions are distinctive and do not cause confusion with ILD, but lesions such as those shown in Figure 22.10 can raise a question of Langerhans

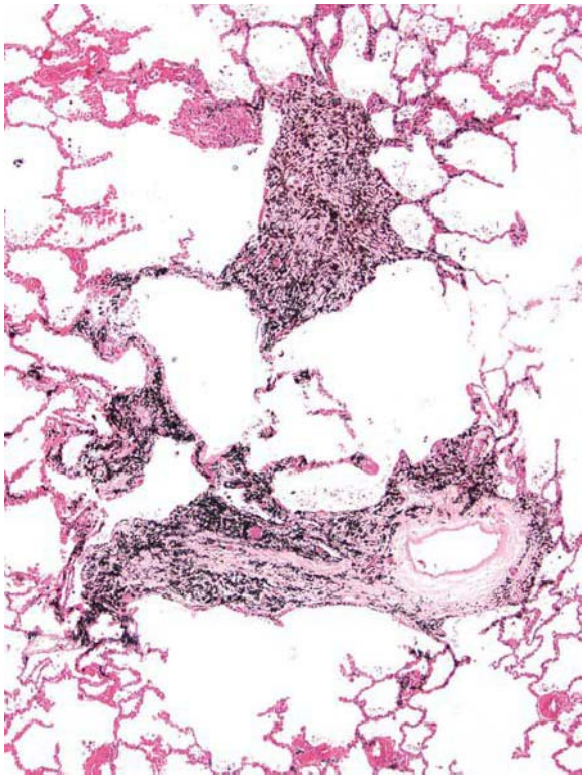


FIGURE 22.6. A dust macule. Dust macules are composed of dust, free and in macrophages, around the bronchovascular bundles. Like many dust macules, this one shows some degree of fibrosis. Patient was a hematite (iron ore) miner.

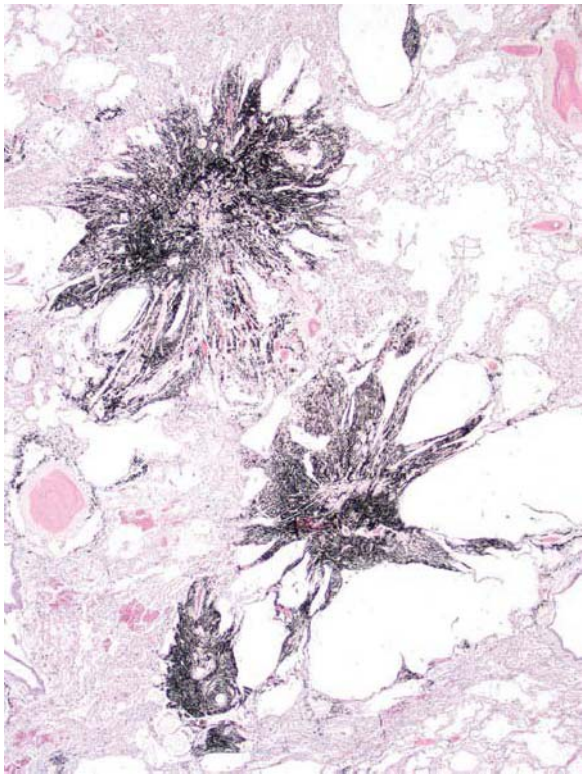
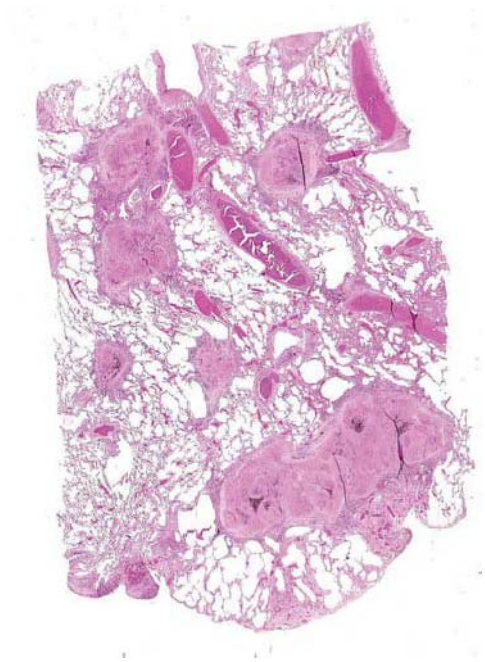
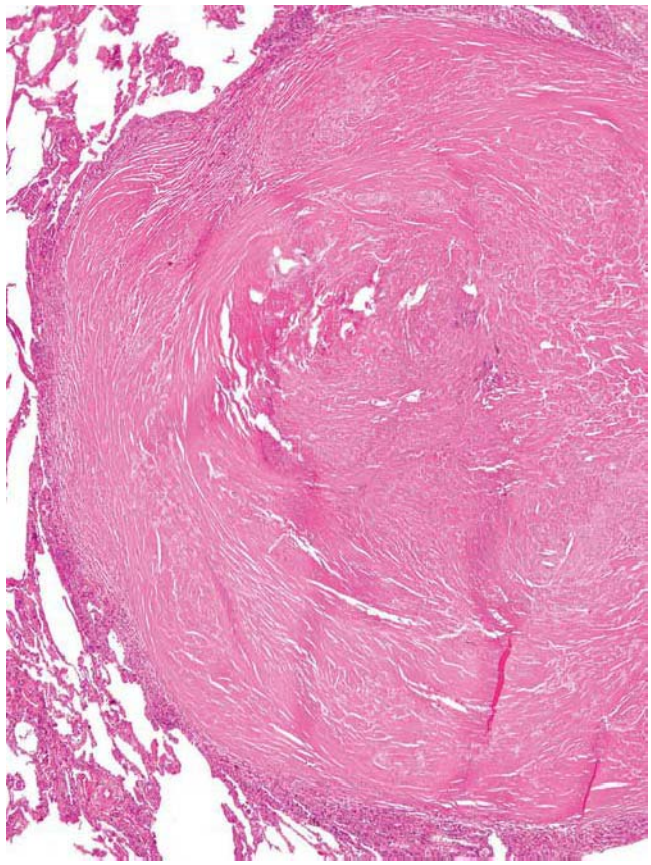


FIGURE 22.7. Simple coal worker's pneumoconiosis. The figure illustrates two coal dust macules with associated focal emphysema. The fibrotic portions of the macules are derived from greatly distorted and scarred respiratory bronchioles.





FIGURES 22.8 and 22.9. Simple silicosis. The lesions comprise discrete nodules composed of dense whorled collagen. In patients whose silica exposure is fairly remote, the nodules have little or no surrounding macrophage infiltrate, as here.

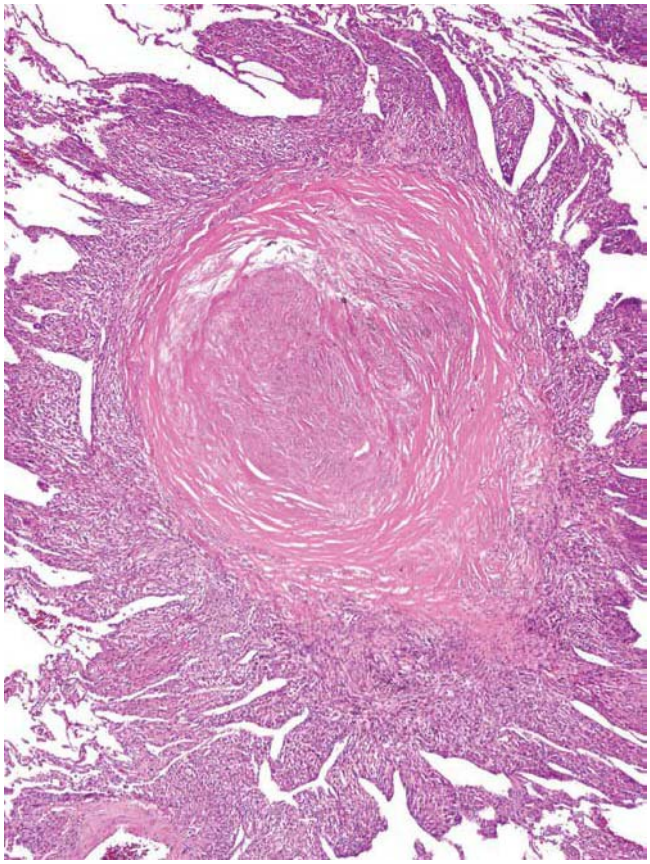


FIGURE 22.10. Simple silicosis. This example is from a patient with current or recent dust exposure, and the silicotic nodule is surrounded by a macrophage and chronic inflammatory infiltrate. Nodules of this appearance can raise differential diagnoses of LCH (which should not have whorled collagenous centers) and sarcoidosis (which should have definite granulomas).

cell histiocytosis (LCH) (Chapter 10) because of the appearance of a stellate cellular nodule. However, LCH produces irregular scars and never nodular scars, and old LCH scars do not contain whorled collagen (see Figs. 10.20 to 10.22).

Complicated Pneumoconioses (Progressive Massive Fibrosis)

PMF is seen with many dusts (Table 22.2) including coal, silica, silicates, and mixed dust fibrosis. PMF comprises masses of heavily collagenized tissue with large amounts of dust. PMF almost always develops on a background of simple pneumoconiosis. In silicosis and silicate pneumoconioses, PMF forms by conglomeration of simple silicotic/silicate nodules/macules, but in CWP PMF appears to form as a reaction to large amounts of coal dust without agglomeration of macules. PMF lesions can be very large and can occasionally occupy an entire lobe.

Mineral Dust-Induced Bronchiolitis

Mineral dust-induced bronchiolitis, also called mineral dust small airways disease, consists of fibrosis of the walls of membranous and respiratory bronchioles (see Figs. 20.19 and 20.20), often accompanied by pigmented dust or asbestos bodies. Mineral dust-induced bronchiolitis can be seen with exposure to silica, iron oxide, aluminum oxide, and asbestos.[7,8] Cigarette smoke can produce similar abnormalities, particularly in the membranous bronchioles (see Fig. 20.18), but extension of process down the respiratory bronchioles is more characteristic of dust exposures (see Fig. 20.20).

Granulomatous Reactions

Berylliosis produces non-caseating granulomas that are morphologically indistinguishable from those seen in sarcoid (see Fig. 13.37). As is true of sarcoid granulomas, granulomas in berylliosis can aggregate to form nodules that become hyalinized (Fig. 13.37). Granulomas may also be seen in organs other than the lung.

Granulomatous responses to silicate minerals such as talc and mica do not produce the well-defined granulomas of sarcoid or berylliosis. These reactions are described and illustrated below.

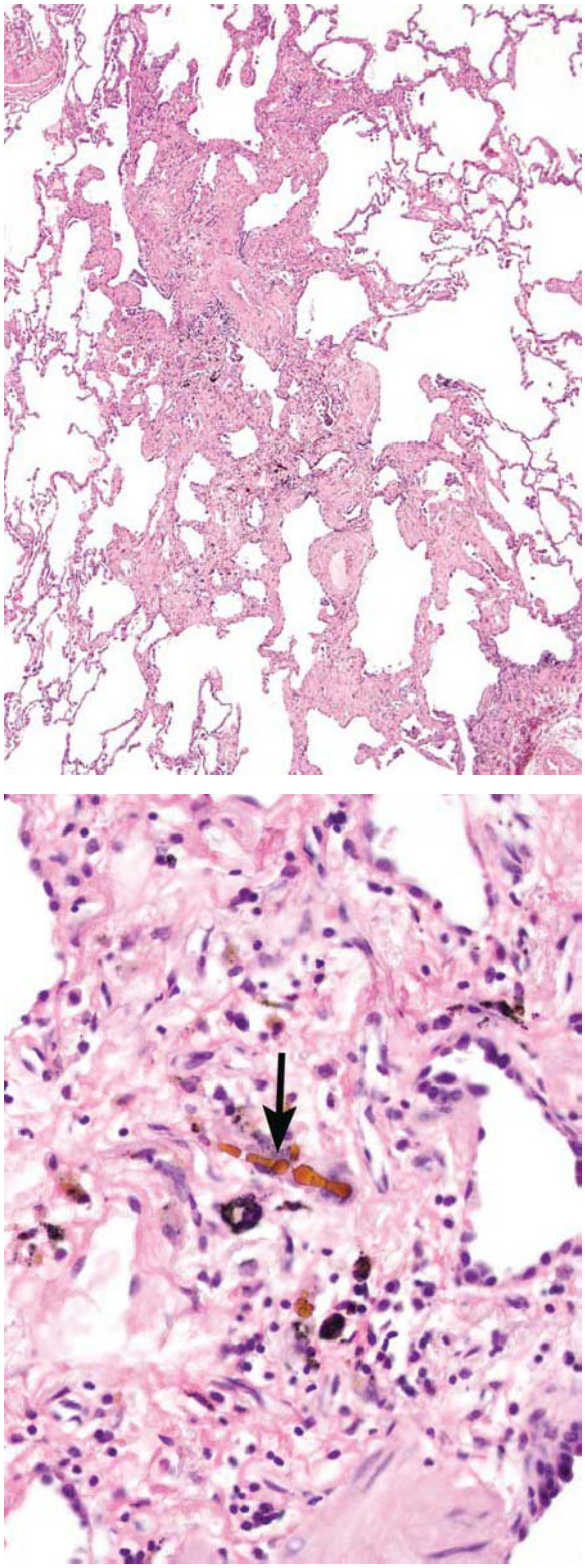
Diffuse Interstitial Inflammation and Fibrosis

Diffuse interstitial fibrosis is the area in which separation of pneumoconioses from non-dust–induced ILD can be problematic, and, except for asbestosis, the problem is compounded by scanty pathologic descriptions, most of which predate current ILD classifications. Features that are helpful in deciding that diffuse interstitial inflammation/fibrosis is caused by dust exposure are (1) the presence of large amounts of visible/pigmented and/or birefringent dust in the affected parenchyma; (2) the presence of ferruginous bodies formed on the dust in question; and (3) the presence of macular or nodular lesions mixed with the areas of inflammation/fibrosis. History is also crucial because some dusts that cause fibrosis, notably hard metal, are not visible by light microscopy, and others (asbestos/asbestos bodies) are easily overlooked unless there is a reason to search for them.

Asbestosis

Asbestosis is defined as diffuse interstitial fibrosis caused by asbestos exposure. Disease is always predominantly lower zonal. Advanced asbestosis is grossly very similar to UIP, but asbestosis cases often have asbestos-induced visceral pleural fibrosis and frequently also plaques on the parietal pleura or diaphragm (Fig. 22.4)—useful clues to the diagnosis.

The early microscopic lesions of asbestosis are not diffuse but instead comprise small foci of interstitial fibrosis in the alveolar interstitium around membranous and respiratory bronchioles[9] (Figs. 22.11 and 22.12). The type of peribronchiolar scarring shown in Figure 22.12 raises

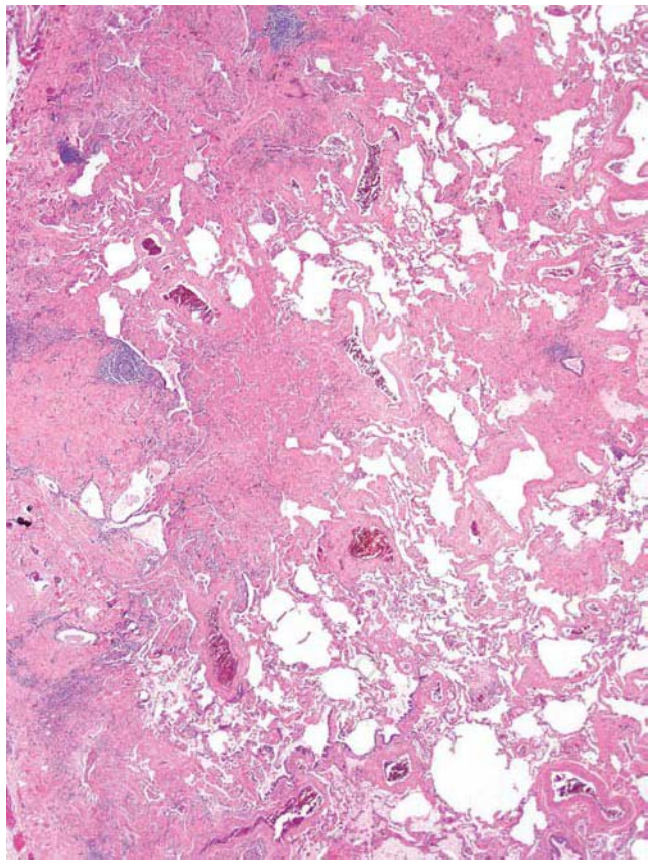


FIGURES 22.11 and 22.12. Early asbestosis. **Figure 22.11.** The lesions of early asbestosis consist of interstitial fibrosis around membranous and respiratory bronchioles. The morphologic differential diagnosis includes burnt-out LCH, burnt-out sarcoid, and chronic hypersensitivity pneumonitis (HP). **Figure 22.12.** An asbestos body (*arrow*) is present in the fibrous tissue. The presence of asbestos bodies in adequate numbers (2 or more/cm^2, see text) supports a diagnosis of asbestosis. This lesion would be graded as 2 under the current diagnostic criteria (see text).

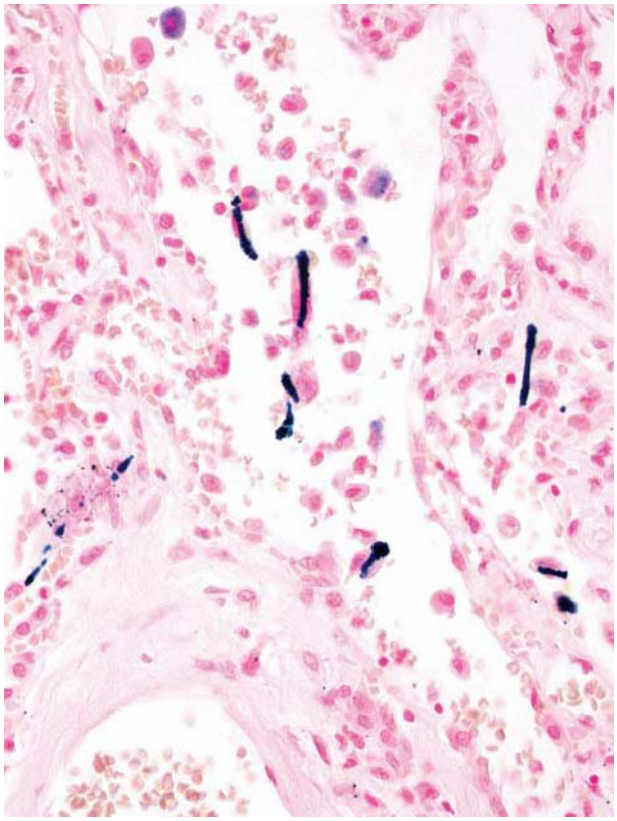
a differential diagnosis of old burnt-out LCH (compare Figs. 10.20 to 10.22), burnt-out sarcoid (Fig. 13.27), or chronic HP (Fig. 12.29). Early asbestosis will have asbestos bodies present (Figs. 22.11 and 22.12) and history is again important in arriving at the correct diagnosis.

As asbestosis progresses, fibrosis spreads interstitially to link bronchioles and then more diffusely in the parenchyma. Sometimes the disease in advanced asbestosis resembles fibrotic NSIP but more commonly it mimics UIP (Fig. 22.13). The interstitial process in asbestosis is generally more paucicellular than in idiopathic ILD, and fibroblast foci are less common than in UIP,[9] but some cases of asbestosis are morphologically indistinguishable from UIP, apart from the presence of asbestos bodies (Fig. 22.14). A grading scheme for asbestosis[9] is shown in Table 22.3.

By definition the diagnosis of asbestosis requires the finding of two or more asbestos bodies/cm^2 of lung parenchyma in addition to a proper pathologic pattern.[9] Counting of asbestos bodies should be carried out on iron-stained 5 μ thick sections (Fig. 22.14). Some individuals appear to form asbestos bodies poorly and in such cases electron microscopic analysis to determine total asbestos fiber burden may be helpful; however, cases of this type are quite rare, and in most instances iron stains provide an excellent way of separating asbestosis from idiopathic ILD.[10]



FIGURES 22.13 and 22.14. Legend appears on following page



FIGURES 22.13 and 22.14. Advanced asbestosis. This example mimics UIP at low power, but the presence of two or more asbestos bodies/cm^2 (Fig. 22.14, iron stain) allows a diagnosis of asbestosis. This example would be graded as 4 under the current diagnostic criteria (see text).

Table 22.3

Grading of asbestosis

Grade 0: No interstitial fibrosis or fibrosis confined to bronchiolar walls
Grade 1: Fibrosis confined to the walls of respiratory bronchioles and the first tier of adjacent alveoli
Grade 2: Extension of fibrosis to involve alveolar ducts and/or two or more tiers of alveoli adjacent to the respiratory bronchiole, with sparing of at least some alveoli between adjacent bronchioles
Grade 3: Fibrotic thickening of the walls of all alveoli between two or more adjacent bronchioles
Grade 4: Honeycomb change

Roggli VL, Gibbs AR, Attanoos R, et al. Pathology of asbestosis—an update of the diagnostic criteria: Report of the Asbestosis Committee of the College of American Pathologists and Pulmonary Pathology Society. *Arch Pathol Lab Med.* 2010;134:462–480.

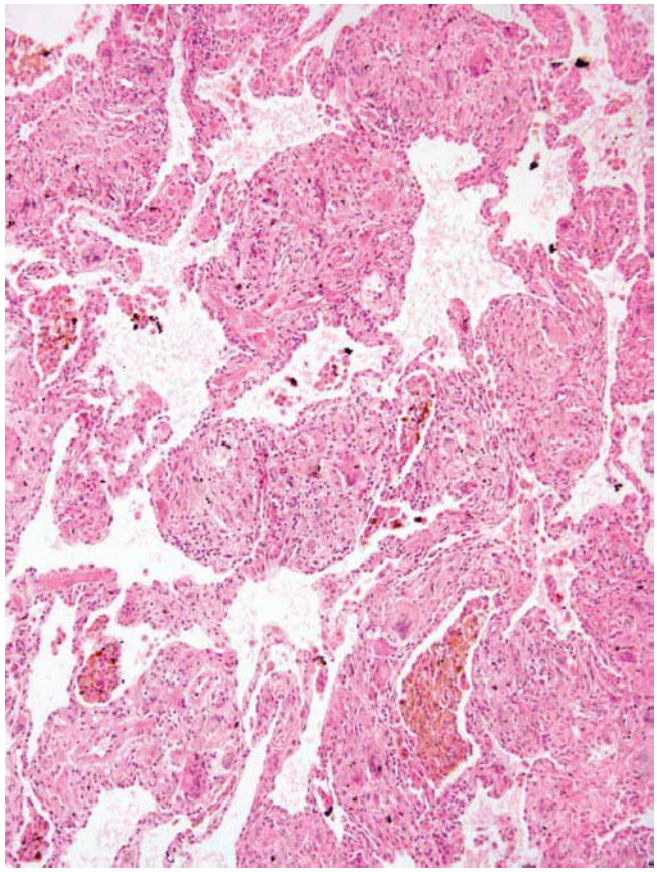
Diffuse Interstitial Fibrosis with Coal and Silica Exposure

The literature suggests that diffuse interstitial fibrosis is seen in up to 18% of autopsied coal miners,[11] but in our experience the frequency is much lower. Two patterns of diffuse fibrosis are seen: (1) fibrosis that links macular or nodular lesions of simple CWP, and (2) fibrosis that is more diffuse and resembles fibrotic NSIP or UIP.[11,12] Green et al.[2] have proposed that cases in which there is extensive coal dust mixed with the fibrosis should be regarded as caused by coal exposure, whereas those without much dust should be viewed as idiopathic ILD. The presence or absence of simple CWP on imaging or biopsy may also be a useful guide to etiology.

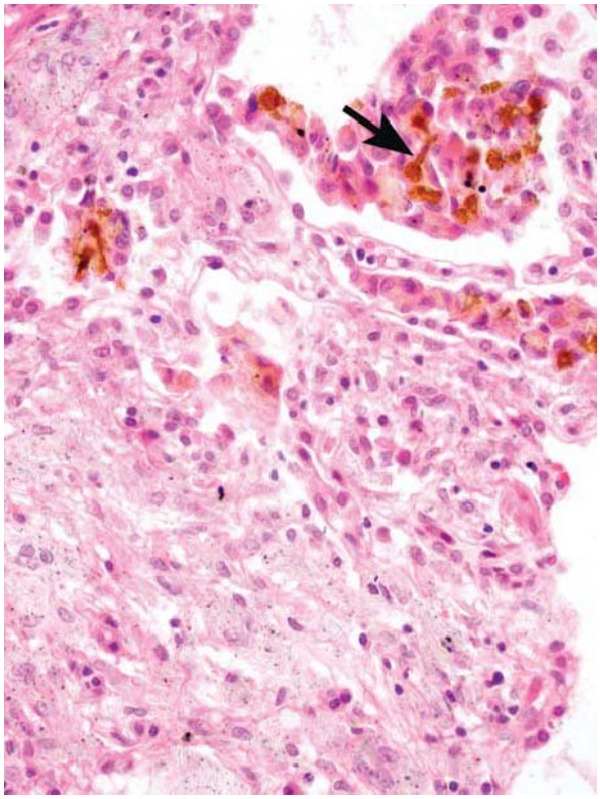
Diffuse ILD resembling fibrotic NSIP or UIP also occurs in patients with silicosis.[13] We suggest that cases with a mixture of silicotic nodules and diffuse fibrosis should be viewed as caused by dust, whereas in patients with silica exposure but no nodules the diffuse disease is probably not related to silica exposure.

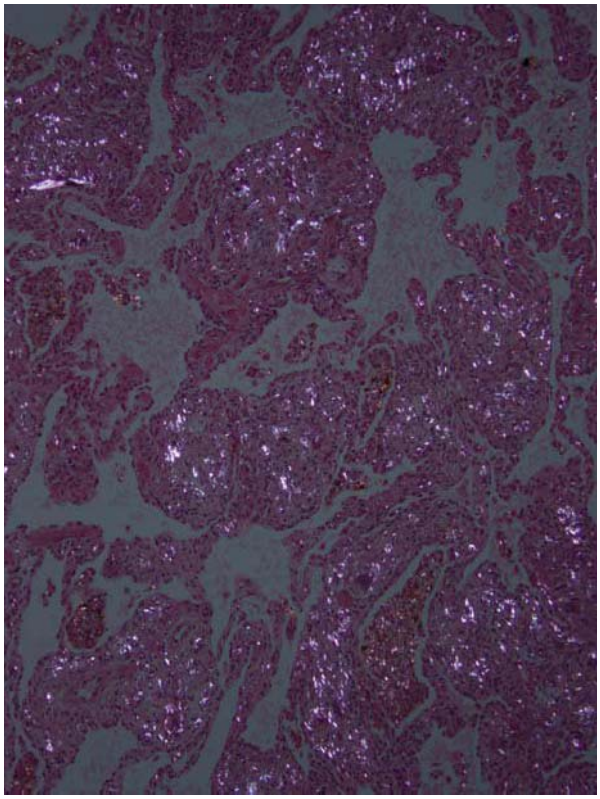
Diffuse Interstitial Fibrosis with Silicate Exposure

Exposure to silicate minerals (talc, mica, kaolinite, slate, sepiolite, montmorillonite, vermiculite, and wollastonite) causes various pathologic patterns. Most commonly these are macules, but with greater exposure diffuse interstitial dust collections that are vaguely granulomatous and variably fibrotic may be seen[14–17] (Figs. 22.15 to 22.17). Silicate minerals can also form ferruginous bodies (Fig. 22.16).



FIGURES 22.15 to 22.17. Legend appears on following page





FIGURES 22.15 to 22.17. Talcosis. This is an example of a sheet silicate (talc) pneumoconiosis mimicking a diffuse interstitial lung disease. The presence of large amounts of talc, visible as pale staining crystals on H&E (**Fig. 22.16**) and brightly birefringent material on polarization (**Fig. 22.17**) indicates that this is a pneumoconiosis. Ferruginous bodies (Fig. 22.16, *arrow*) also are helpful in diagnosing a pneumoconiosis.

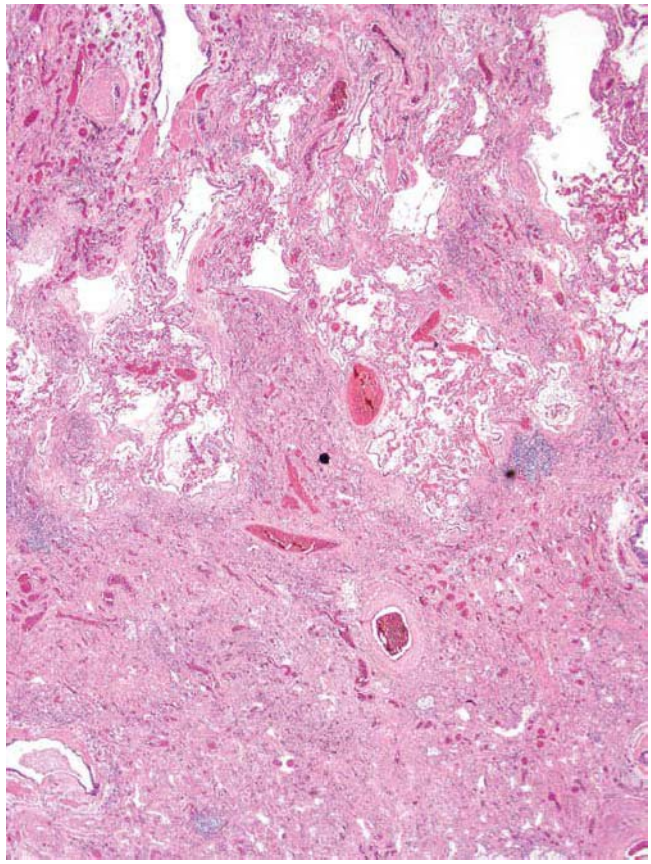
With heavy exposure many silicate minerals can produce diffuse fibrosis with or without honeycombing, again in patterns that more or less resemble fibrotic NSIP or UIP but mixed with copious dust (Figs. 22.18 and 22.19).[14–17] Many, but not all, silicates are brightly birefringent, so polarization is sometimes very helpful in elucidating the cause of fibrosis (Figs. 22.17 and 22.19).

Intravenous Drug Abuse

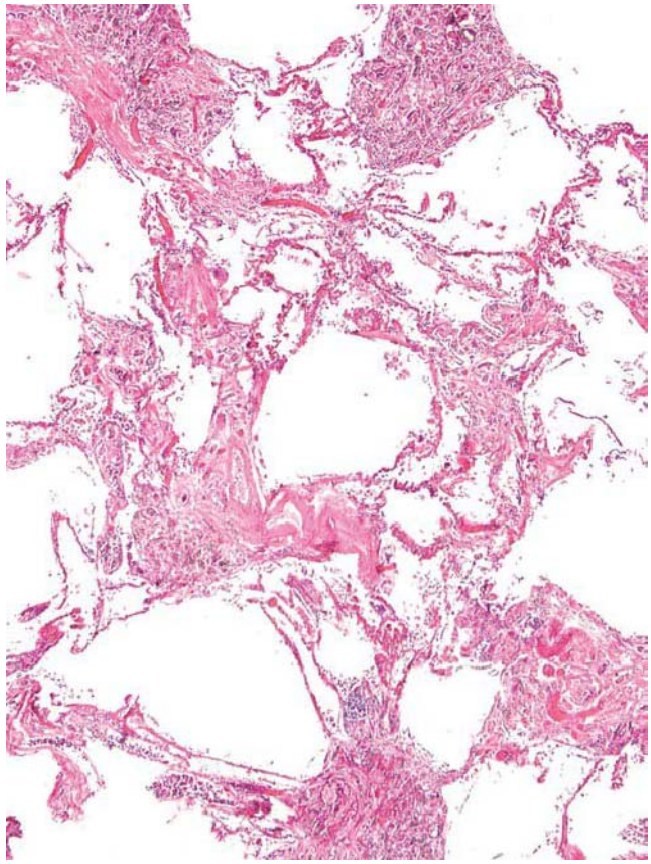
In intravenous drug abuse, the drug filler, which is typically insoluble particles of talc or microcrystalline cellulose, is deposited in the lung and can cause interstitial granulomas, diffuse interstitial fibrosis (Figs. 22.20 to 22.22), PMF, and lesions that resemble macules. IV drug abuse can usually be separated from inhalation particulate exposure because in the former the particles are all interstitial and generally also intravascular, whereas in inhalation injuries dust is usually present in the alveoli as well as the interstitium and is not present in vessels. Talc and microcrystalline cellulose are brightly birefringent (Fig. 22.23), useful clues to the diagnosis.

Pulmonary Alveolar Proteinosis

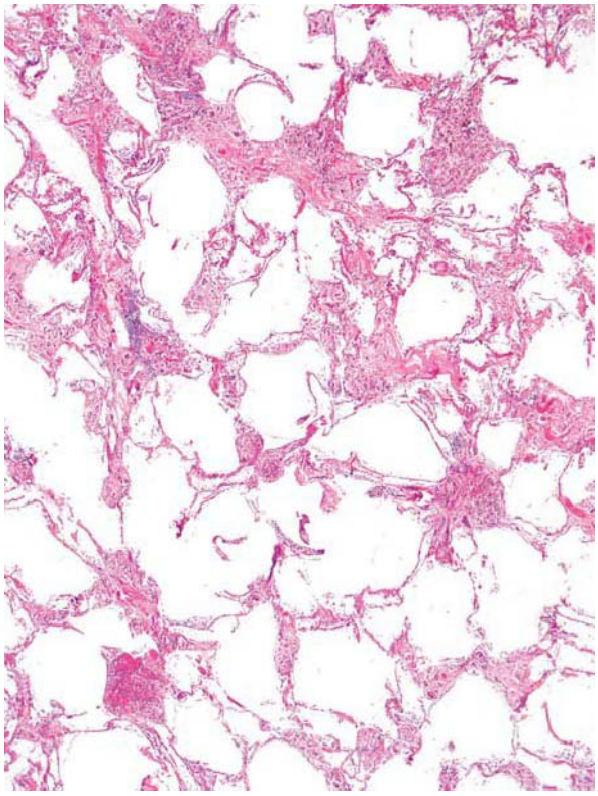
PAP can be caused by exposure to very large amounts of finely divided dust (see Chapter 16), including silica (quartz), titanium dioxide, aluminum, and indium.



FIGURES 22.18 and 22.19. Legend appears on following page



FIGURES 22.18 and 22.19. Talcosis. In this example of very advanced disease there is extensive fibrosis in a pattern that somewhat mimics UIP. Polarization (**Fig. 22.19**) shows numerous brightly birefringent particles, indicating that this is a pneumoconiosis.



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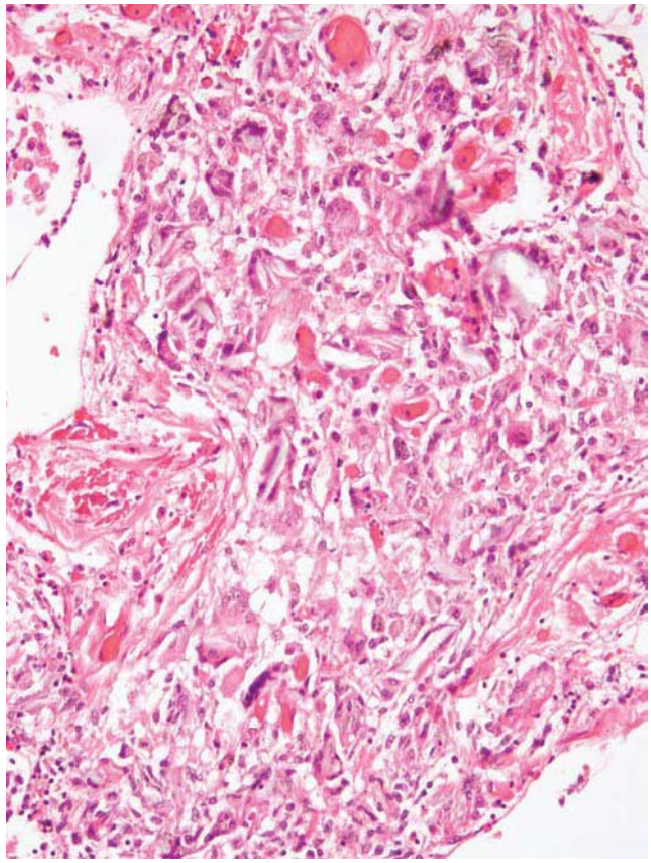

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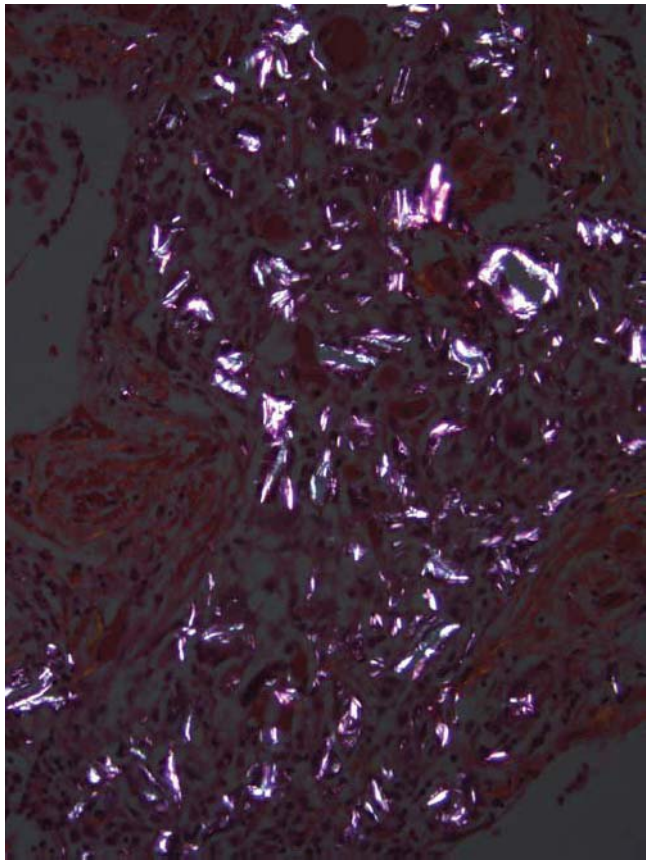
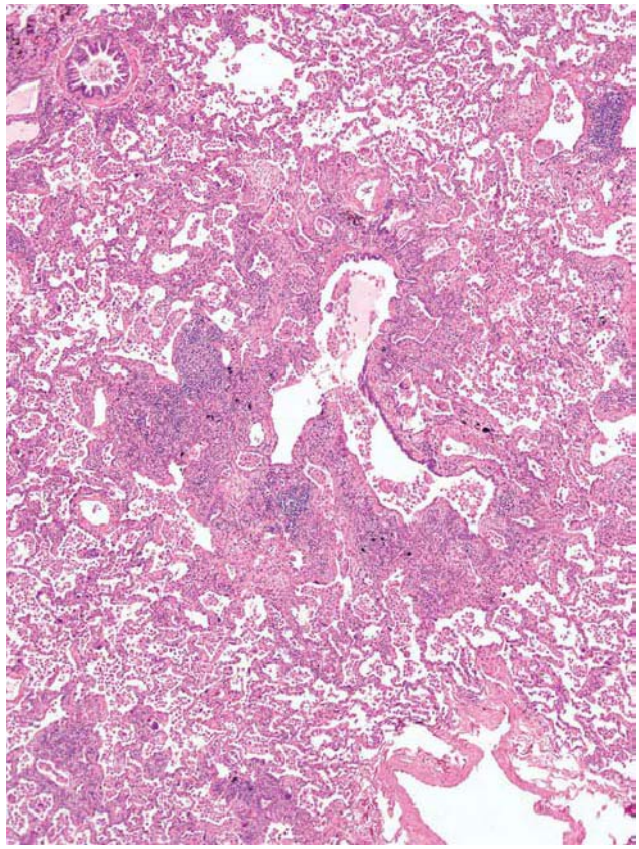




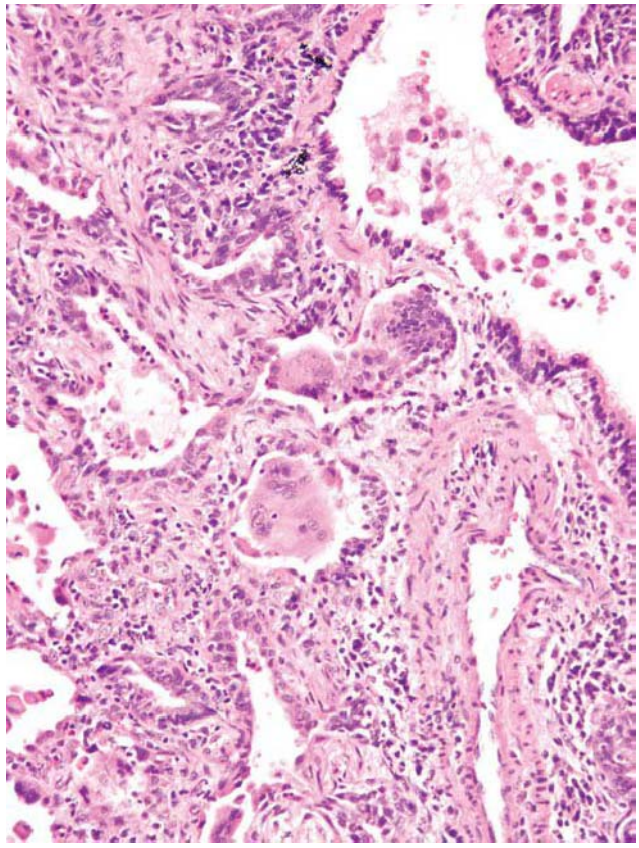
FIGURES 22.20 to 22.23. Interstitial fibrosis caused by IV drug abuse. At lower power (**Figs. 22.20** and **22.21**) the process resembles fibrotic NSIP, but high-power images show numerous plates of crystalline material (**Fig. 22.22**) that is brightly birefringent on polarized light (**Fig. 22.23**).

Silicoproteinosis, also called acute silicosis, is morphologically very similar to primary (autoimmune) alveolar proteinosis (see Chapter 16), but in our experience shows a mild interstitial inflammatory reaction (see Fig. 16.9). Numerous poorly birefringent silica particles are usually visible on polarization (see Fig. 16.9), but occasionally the dust may be too small to resolve with the light microscope.

Hard Metal Disease

Hard metal disease or hard metal pneumoconiosis (called in the past "giant cell interstitial pneumonia" or GIP) is caused by exposure to hard metal (tungsten carbide), either during manufacture of hard metal cutting tools or during welding of hard metal tools. Hard metal disease is actually a hypersensitivity reaction to cobalt, which is added to the hard metal in manufacturing, and exposure to cooling baths that extract cobalt from hard metal blades, for example in sawmills, can also cause hard metal disease.

Hard metal disease is pathologically distinctive. It consists of marked fibrosis and inflammation of the walls of respiratory bronchioles with a luminal infiltrate of macrophages and large, often bizarre, giant cells



FIGURES 22.24 and 22.25. Hard metal disease. **Figure 22.24** shows a typical picture of a markedly fibrotic and inflamed respiratory bronchiole. The process is associated with numerous giant cells (Fig. 22.24).

(Figs. 22.24 and 22.25).[18] As the disease progresses fibrosis may spread between bronchioles and more diffusely in the interstitium, producing a pattern that resembles desquamative interstitial pneumonia (DIP) (Figs. 22.26 and 22.27, and see Chapter 8). Cigarette smoke-related DIP may have small numbers of giant cells, but not the numbers or the sometimes bizarre forms (Fig. 22.27) seen in hard metal disease.

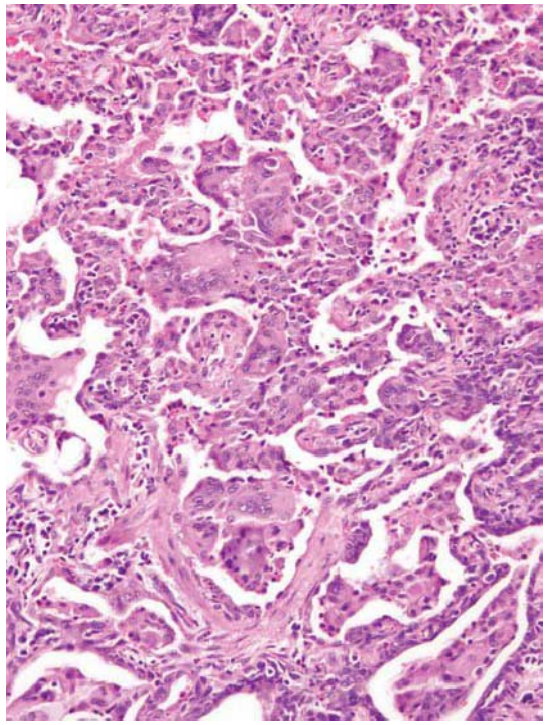
Hard metal disease can progress to severe diffuse fibrosis and honeycombing (Fig. 22.28) that is difficult to separate from non-dust–related ILD, unless one has a history of exposure, or there are typical bronchiolar lesions.

Silicon Carbide

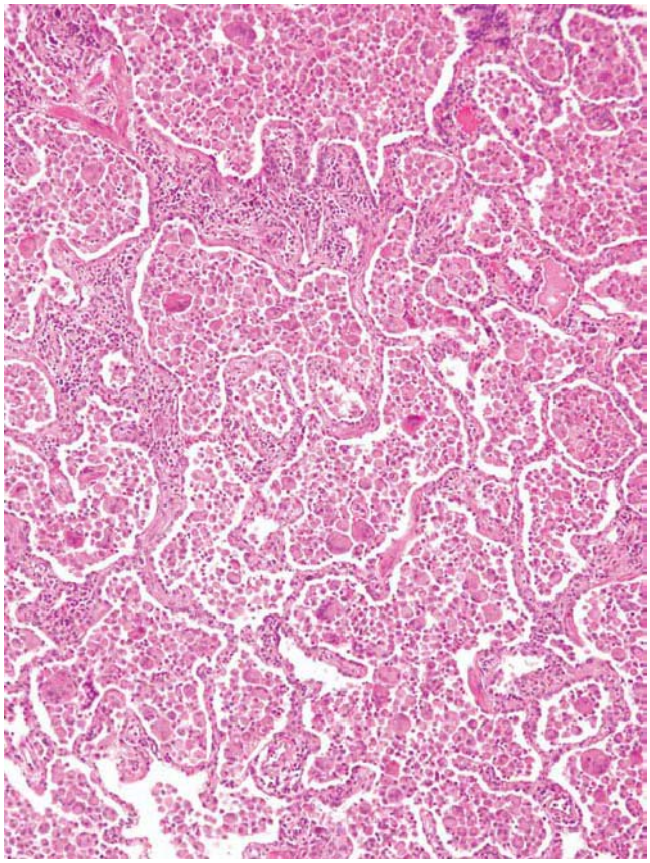
Silicon carbide (carborundum) has been reported to produce a mixture of nodules with more diffuse fibrosis and a prominent alveolar macrophage response.[19] The silicon carbide is fibrous and forms ferruginous bodies with black cores.[19]

Iron and Aluminum

When inhaled in extremely large amounts, iron and aluminum metal can produce a form of diffuse interstitial fibrosis somewhat resembling fibrotic NSIP but with very large amounts of visible dust (Figs. 22.29 and 22.30).



FIGURES 22.26 and 22.27. Hard metal disease mimicking DIP. At low power the process is very similar to cigarette smoke-induced DIP except for the large number of giant cells; the latter occur in DIP but in much fewer numbers. **Figure 22.27** is a high-power view from a different case in which there are numerous giant cells.



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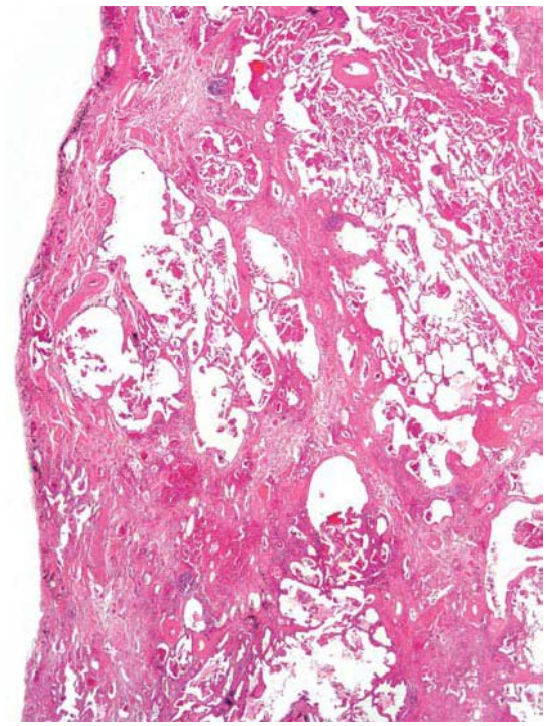
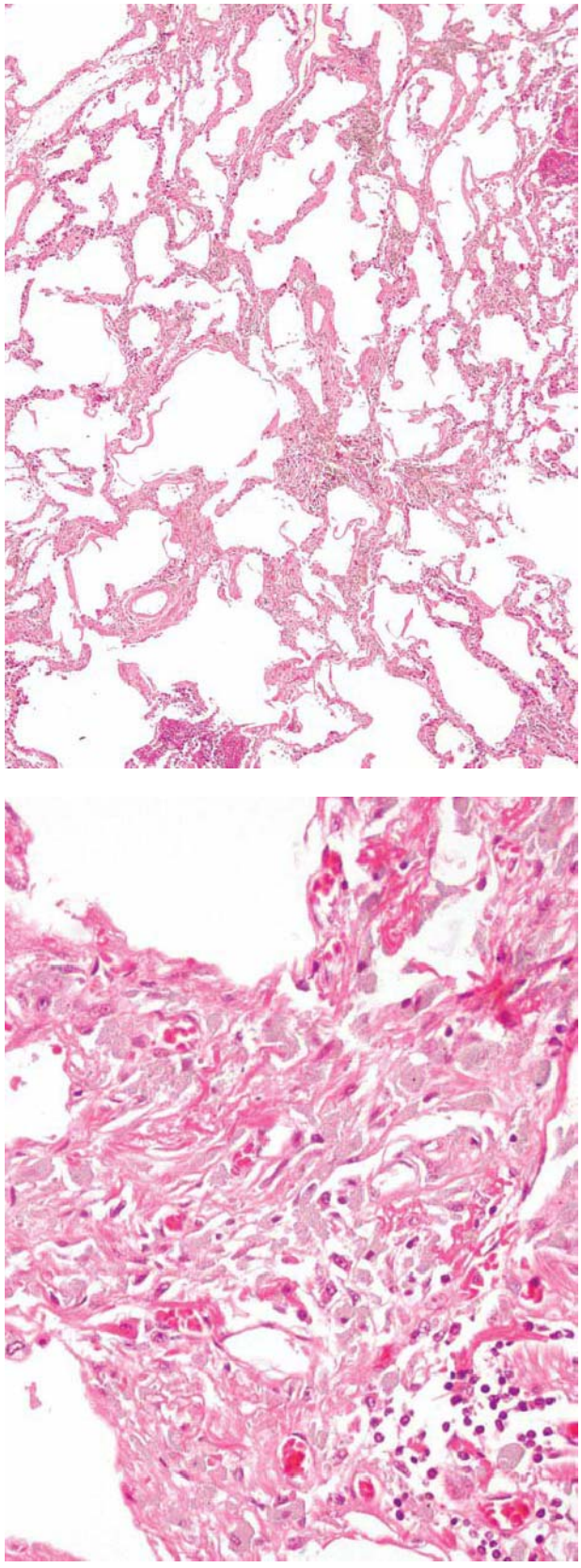


FIGURE 22.28. Advanced fibrosis in hard metal disease. This appearance is not specific and might be seen in idiopathic UIP. If there are no characteristic airway lesions such as Figure 22.24 in the biopsy, only exposure history will indicate the correct diagnosis.



FIGURES 22.29 and 22.30. Interstitial fibrosis induced by very high exposure to aluminum dust. At low power the process mimics fibrotic NSIP. At high power (**Fig. 22.30**) macrophages loaded with silvery yellow aluminum particles are visible.

DIAGNOSTIC MODALITIES

Many pneumoconioses are diagnosed on imaging without need for a biopsy. Transbronchial biopsy is occasionally useful if it picks up a nodular or macular lesion, for example, in silicosis, but the diagnosis of conditions such as asbestosis that appear as diffuse fibrosis requires a surgical lung biopsy.

PROGNOSIS

Many pneumoconioses characterized by macular/nodular lesions have little functional significance and do not affect life expectancy, although there is increasing recognition that they can cause airflow obstruction.[11,22] Large PMF lesions of any cause can produce functional deficits and increased mortality. Of note, diffuse fibrosis in coal workers has a very slow course,[11] much slower than is seen with UIP. Exposure to silica increases the risk of mycobacterial infections[23] and the presence of silicosis may increase the risk of lung cancer, although this issue is disputed.[20]

Asbestosis can progress to severe end-stage fibrosis, but the risk of progression is proportion to the severity of the initial radiologic changes and mild cases may stabilize. The presence of asbestosis greatly increases the risk of lung cancer, especially in cigarette smokers.[21]

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CHAPTER

23

Miscellaneous Forms of Interstitial Lung Disease

PULMONARY DISEASE CAUSED BY THERAPEUTIC RADIATION

Lung toxicity is seen with external radiation to the mediastinum, lung, esophagus, and chest wall (e.g., for breast carcinoma) and occasionally in patients treated with radioactive iodine for thyroid carcinoma metastatic to the lung.[1] Radiation injury depends on the volume of radiated lung tissue (the greater the volume radiated, the greater the risk of toxicity) and dose of radiation (fractionated doses are less dangerous than single large doses).[1] Prior radio- or chemotherapy, particularly with bleomycin, as well as cigarette smoking may sensitize the lung to subsequent radiation.[2] In most cases, radiation injury is confined to the area radiated, but occasionally toxicity is seen in a large area outside the radiation port,[3] including the contralateral lung.

Clinical Features

Acute radiation injury (acute radiation pneumonitis) typically appears within a few weeks to a few months after radiation and can manifest as a febrile illness with accompanying shortness of breath (SOB) or in severe cases as acute respiratory distress syndrome (ARDS). Radiation-induced fibrosis (chronic radiation pneumonitis) typically appears 1 year or more after completing radiation and resembles a fibrosing interstitial pneumonia. Sporadic radiation pneumonitis is less common; it can appear at any time and mimics BOOP.[3]

Imaging

Radiation pneumonitis is characterized on high resolution computed tomography (HRCT) by ground-glass opacities (GGOs) or consolidation involving the irradiated portions of lung and conforming to the shape of the radiation ports (Fig. 23.1).[4] Radiation fibrosis manifests as streaky opacities, dense consolidation, volume loss, and traction bronchiectasis within the irradiated lung regions. There is a sharply defined edge between normal and irradiated lung, allowing distinction of radiation pneumonitis or fibrosis from other lung diseases on CT.

Pathologic Features

Acute radiation injury microscopically looks like diffuse alveolar damage (DAD) (Fig. 23.2 and see Chapter 4) in the acute or organizing phase. However, bizarre radiation fibroblasts may be present (Fig. 23.3), and there may also be marked vascular sclerosis—features not seen in ordinary DAD. Sporadic radiation pneumonitis is not often biopsied, but morphologically looks like bronchiolitis obliterans organizing pneumonia (BOOP) (Fig. 23.4) and occurs outside as well as inside the radiation field.[3,5,6]

Chronic radiation injury appears as a fibrosing interstitial pneumonia. An important clue to the diagnosis is that the process in most cases is sharply localized to the radiation ports (Fig. 23.5). Some cases resemble fibrotic nonspecific interstitial pneumonia (NSIP), whereas others are more like usual interstitial pneumonia (UIP) (Fig. 23.6). As opposed to typical cases of NSIP or UIP, marked elastosis mixed with the fibrosis may be present and the elastofibrotic reaction can obliterate large areas of lung parenchyma (Figs. 23.7 and 23.8). Radiation fibroblasts and vascular obliteration may also be seen (Fig. 23.9).

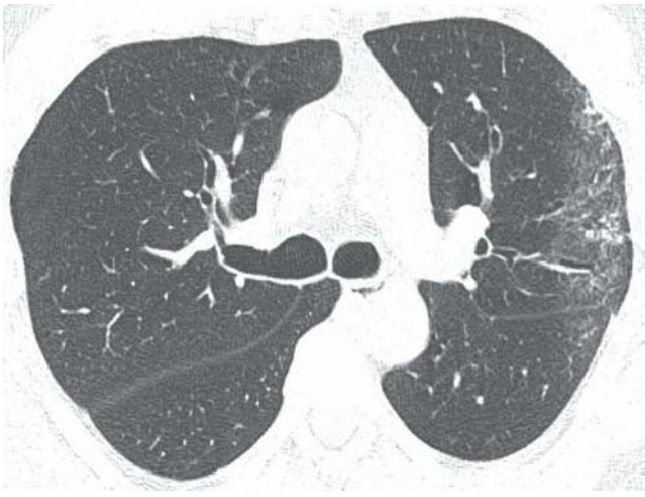


FIGURE 23.1. Radiation pneumonitis. HRCT image shows GGOs and small focal areas of consolidation in the periphery of the left lung. Note the sharp demarcation between the irradiated and the normal lung. The patient had radiation therapy to the left chest wall.

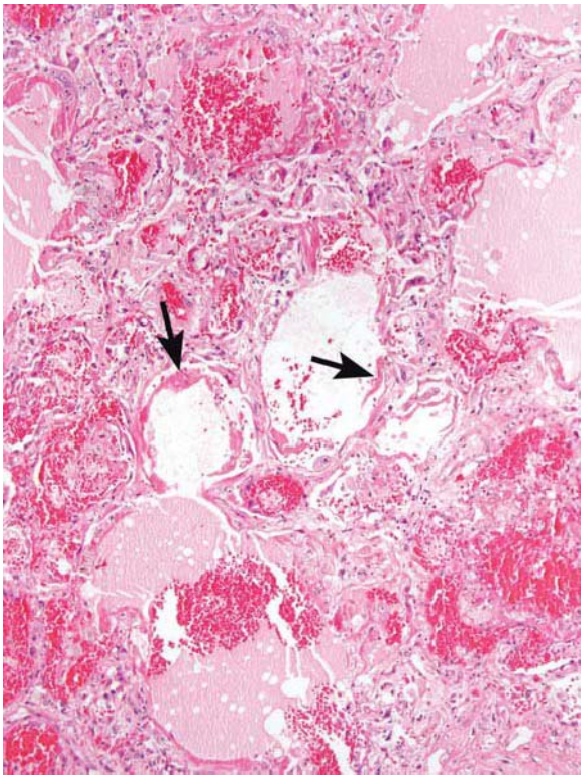


FIGURE 23.2. Acute radiation pneumonitis manifest as DAD in a patient receiving therapeutic radiation for Hodgkin disease approximately 1 month before death. *Arrows* point to hyaline membranes.

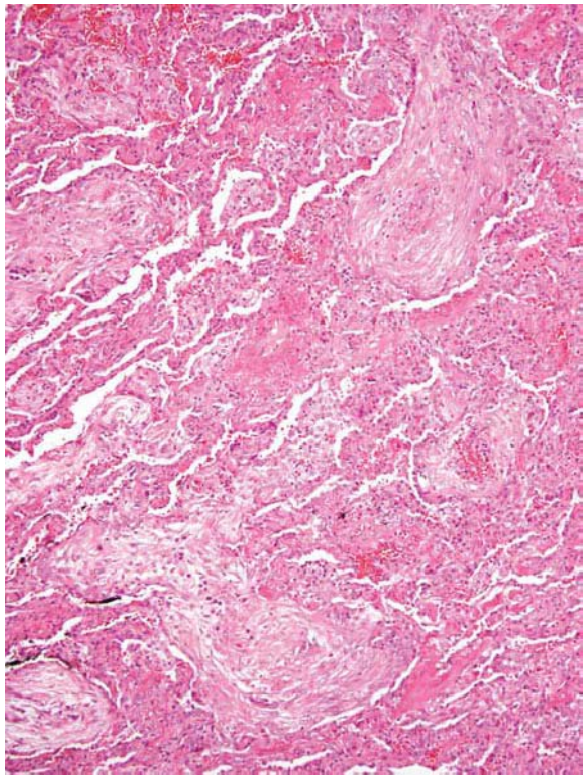


FIGURE 23.4. Sporadic radiation pneumonitis appearing as BOOP. BOOP developed 6 months after the patient completed radiation therapy for carcinoma of the breast and was present both within and outside the radiation port.

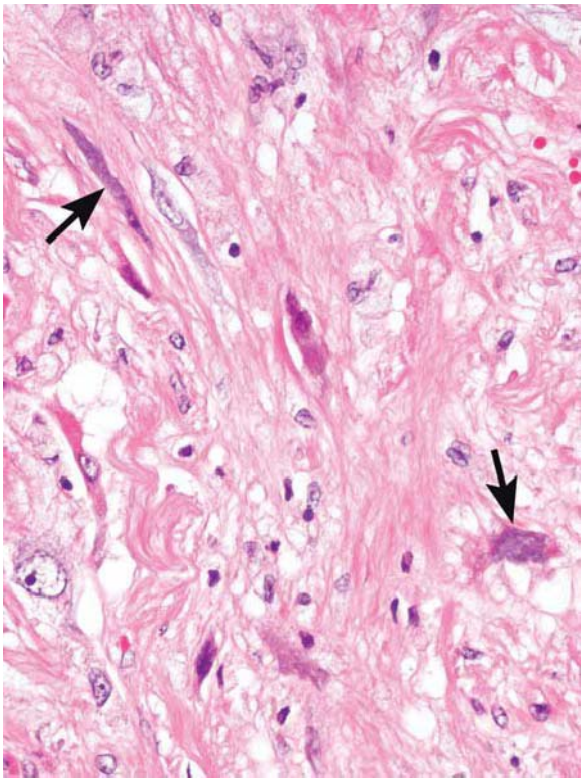


FIGURE 23.3. Another area of the lung shown in Figure 23.2. Note the bizarre radiation fibroblasts (*arrows*).

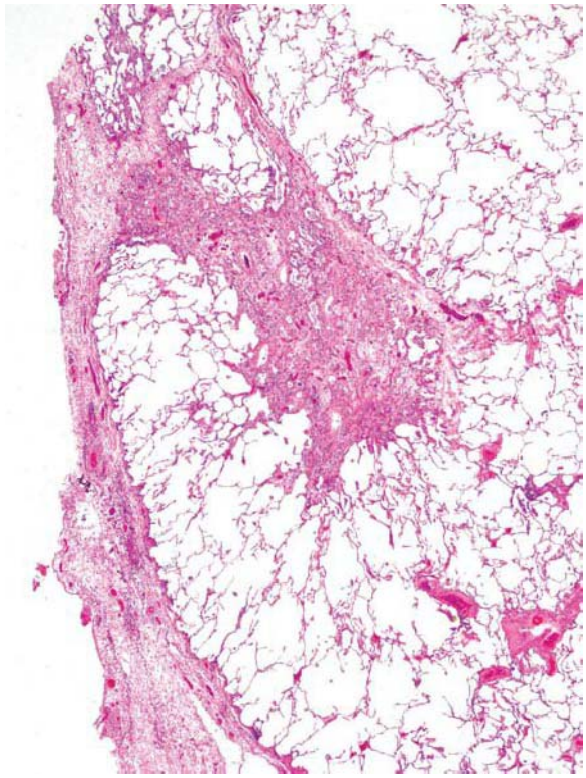


FIGURE 23.5. Chronic radiation pneumonitis. Sharply demarcated area of fibrosis at the edge of a radiation port.

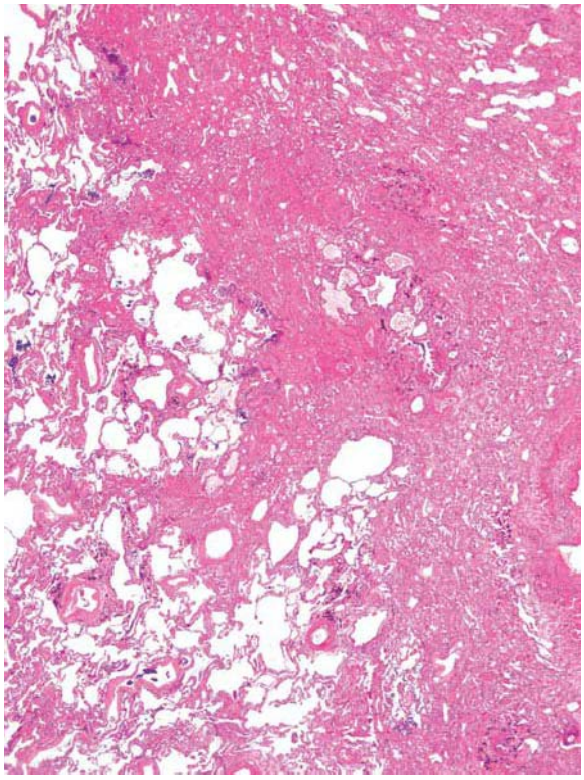


FIGURE 23.6. Chronic radiation pneumonitis. Dense radiation-induced fibrosis mimicking UIP.

Radiation to the chest can also induce malignant mesotheliomas of the pleura, typically appearing fairly long (10 years or more) after the completion of therapy.[7]

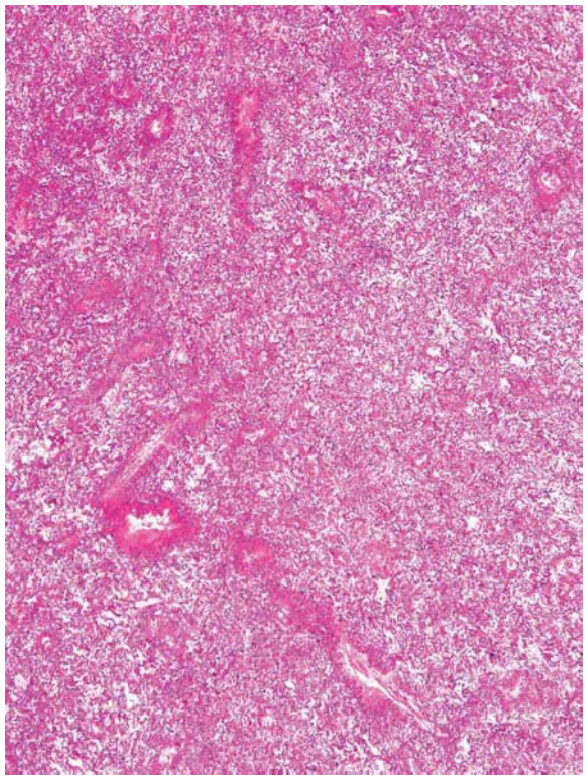
Prognosis

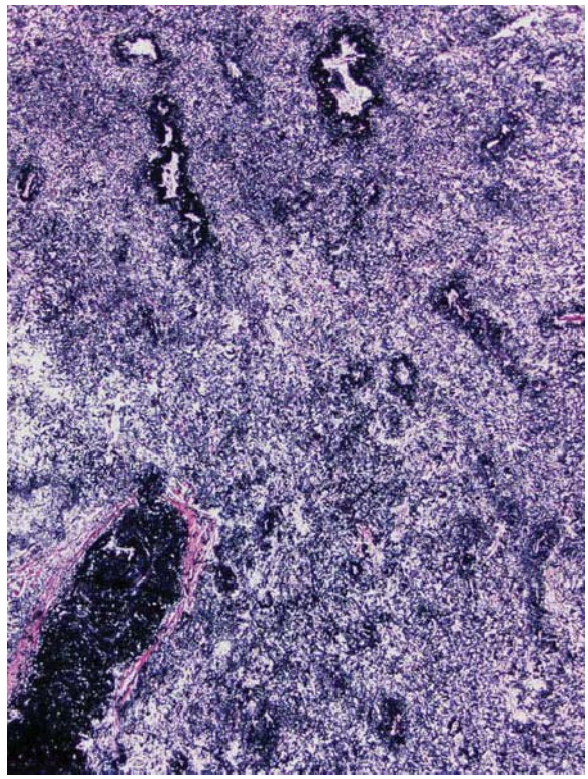
Acute radiation injury subsides in most patients[8]; however, some patients develop fatal disease.[9] Purely localized fibrosis has a good prognosis. A wide variety of therapeutic approaches, including steroids, antioxidants, and antifibrotic agents, have been tried for widespread radiation-induced fibrosis, but at this point there is no consensus on treatment or outcome.[2]

ERDHEIM–CHESTER DISEASE

Clinical Features

Erdheim–Chester disease is a form of histiocytosis that primarily affects the long bones causing bone pain and radiologic osteosclerosis, but any organ can be involved. Nonpulmonary manifestations include exophthalmos, diabetes insipidus, xanthelasma, and retroperitoneal fibrosis.[10] Erdheim–Chester histiocytes can infiltrate the myocardium, pericardium, and central nervous system leading to significant functional impairment. Pulmonary involvement is seen in approximately 50% of cases.[11]





FIGURES 23.7 and 23.8. Chronic radiation pneumonitis. Higher-power H&E and elastic stain views of another area from the same case as Figure 23.6. Note the extensive elastotic reaction. Although not specific, this type of fibroelastosis is very common in radiation-induced fibrosis.

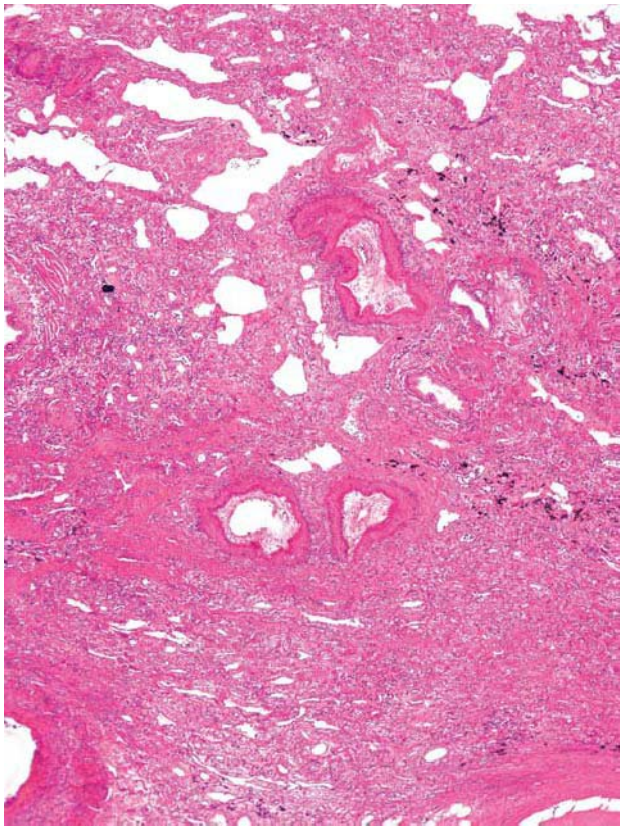


FIGURE 23.9. Nearly completely sclerosed vessels within an area of radiation-induced fibrosis. Vascular obliteration is common as a radiation reaction.

Imaging

Pulmonary involvement in Erdheim–Chester disease is usually manifested on CT by extensive bilateral smooth thickening of the interlobular septa and interlobar fissures (Fig. 23.10).[11] Other common findings include poorly defined centrilobular nodules and GGOs. The pulmonary abnormalities are frequently associated with other signs of intrathoracic involvement, most commonly soft tissue infiltration around the aorta, and pleural and pericardial thickening and/or effusion.

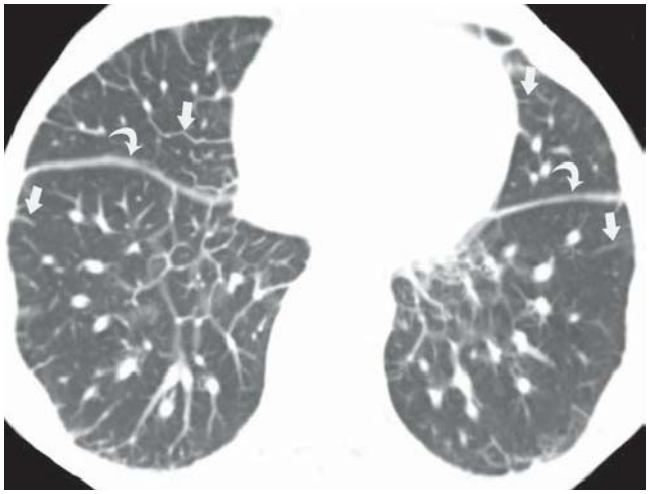


FIGURE 23.10. Erdheim–Chester disease. CT scan in a patient with pulmonary involvement in Erdheim–Chester disease shows bilateral smooth thickening of the interlobular septa (*straight arrows*) and interlobar fissures (*curved arrows*).

Pathologic Features

In the lung, Erdheim–Chester disease appears as histiocytes that follow lymphatic routes along the bronchovascular bundles and interlobular septa and are accompanied by a variable degree of fibrosis (Figs. 23.11 to 23.14). The histiocytes have clear or foamy to eosinophilic cytoplasm (Fig. 23.14), and are CD68 (Fig. 23.15) and Factor 13a positive. In some cases they are also S-100 positive but they are invariably CD1a negative.

Differential Diagnosis

Erdheim–Chester disease is sometimes compared with Langerhans cell histiocytosis (LCH) (see Chapter 10), but the morphologic overlaps are actually minimal. Langerhans cells typically have grooved nuclei and never have foamy cytoplasm or very copious cytoplasm. Langerhans cells are always S-100 and CD1a positive (Figs. 10.27 and 10.28).

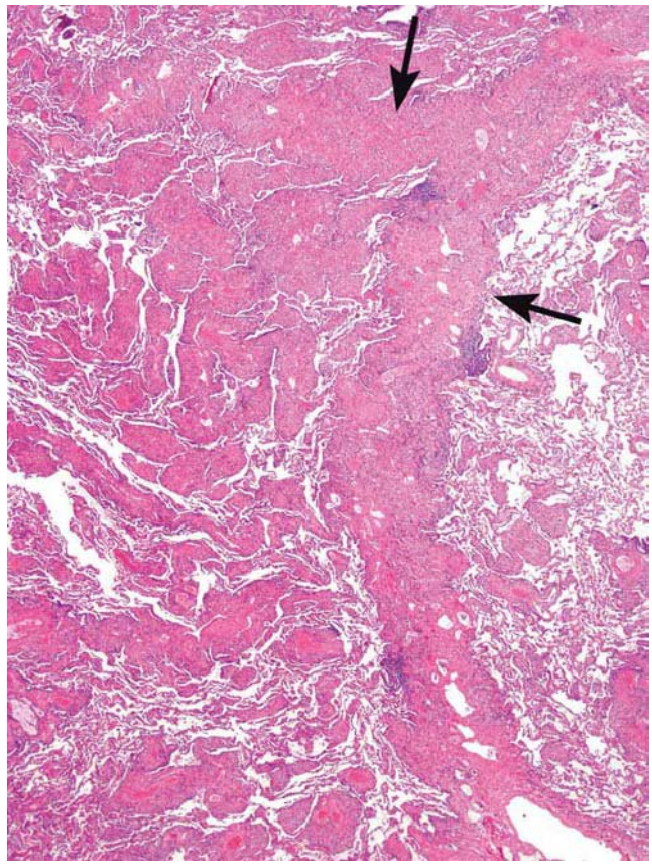


FIGURE 23.11. Low view of Erdheim–Chester disease. There is a fibrosing reaction that follows the interlobular septa (*arrows*). This process corresponds to the thickened interlobular septa seen in Figure 23.10.

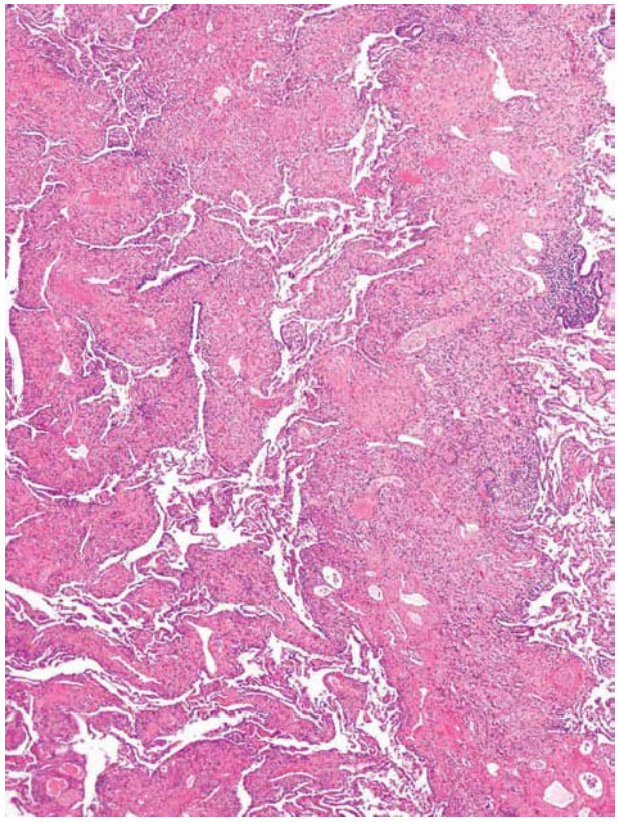


FIGURE 23.12. Medium-power view of Figure 23.11. Fibrosis extends irregularly into the lung parenchyma.

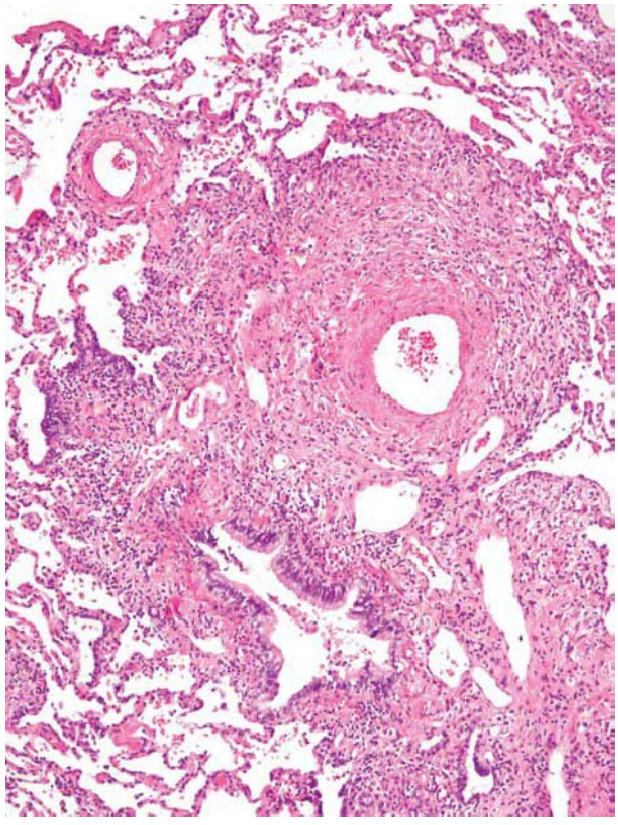


FIGURE 23.13. Higher-power view of an affected bronchovascular bundle. At this magnification, histiocyte infiltration is just visible.

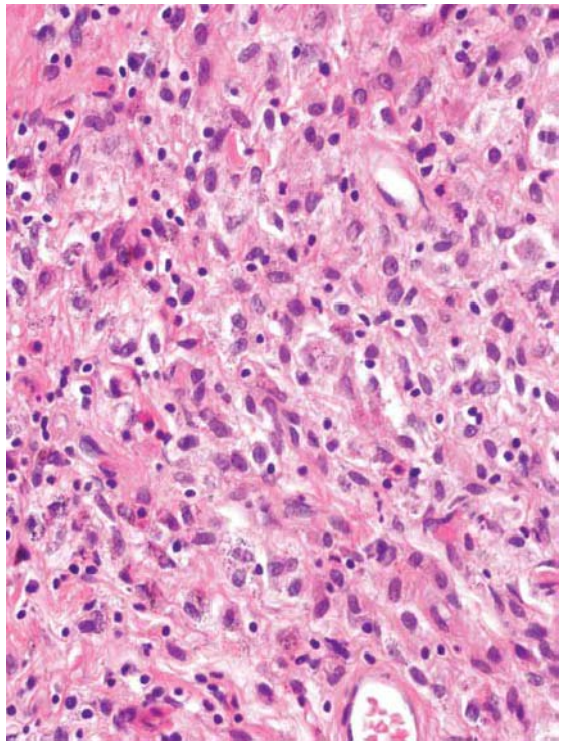


FIGURE 23.14. High-power view showing a combination of pale-staining histiocytes and fibrous tissue. In some cases the histiocytes of Erdheim–Chester disease are eosinophilic rather than pale or foamy.

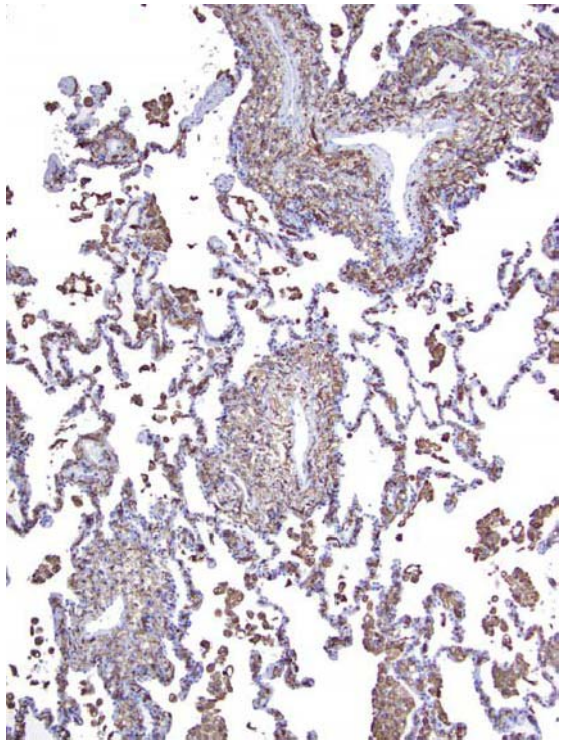


FIGURE 23.15. CD68 stain showing that the histiocytes are diffusely positive in Erdheim–Chester disease. They are also usually Factor 13a positive. These findings are in contradistinction to LCH where the Langerhans cells are CD1a positive. S-100 staining can be seen in either condition but is invariably positive in LCH and only occasionally positive in Erdheim–Chester disease.

Although the lesions of LCH affect the bronchovascular bundles, they do not involve the interlobular septa, and the lesions along the bronchovascular bundles are either cellular nodules (see Fig. 10.6) or dense scars (see Figs. 10.20 to 10.22). When LCH scars, the scars are irregular and center on the bronchovascular bundles but do not follow the interlobular septa (see Figs. 10.20 to 10.22).

Prognosis

The prognosis of Erdheim–Chester disease is quite variable, but the overall mortality in the literature is 60%. Some patients are asymptomatic and are detected because of bony abnormalities found on imaging. Central nervous system and cardiac involvement is associated with a poor outcome.[10] The importance of pulmonary involvement is unclear: some authors[10] claim that it is usually of little consequence, whereas others[12] state that pulmonary involvement is usually fatal.

PERIBRONCHIOLAR METAPLASIA/ PERIBRONCHIOLAR FIBROSIS

Clinical Features

Peribronchiolar metaplasia/peribronchiolar fibrosis, sometimes called lambertosis, is usually an incidental finding on pathologic examination, and the associated clinical features, if any, are unclear. The only study specifically addressing the subject[13] reported 15 patients with clinical interstitial lung disease (ILD) and peribronchiolar metaplasia as the predominant finding on biopsy. Apart from a marked male predominance there was a wide variety of clinical, functional (some obstructive, some restrictive, some mixed, some normal), and radiologic findings. This spectrum is so broad that it raises questions of whether peribronchiolar metaplasia/fibrosis was really the cause of the ILD, or whether these cases might represent bad samples of other diseases.

Imaging

The chest CT may be normal or show areas of decreased attenuation and vascularity resulting in a mosaic pattern of attenuation on inspiratory images and air trapping on expiratory images.[13]

Pathologic Features

Peribronchiolar metaplasia/fibrosis consists of the development of bronchiolar epithelium, usually ciliated, along with variable degrees of underlying interstitial fibrosis in the alveolar walls immediately surrounding membranous and, particularly, respiratory bronchioles (Figs. 23.16 to 23.18). In some cases small bronchiolar lumen-like structures are formed (Fig. 23.17), and occasionally there is extension of bronchiolar smooth muscle for a distance away from the bronchiole.

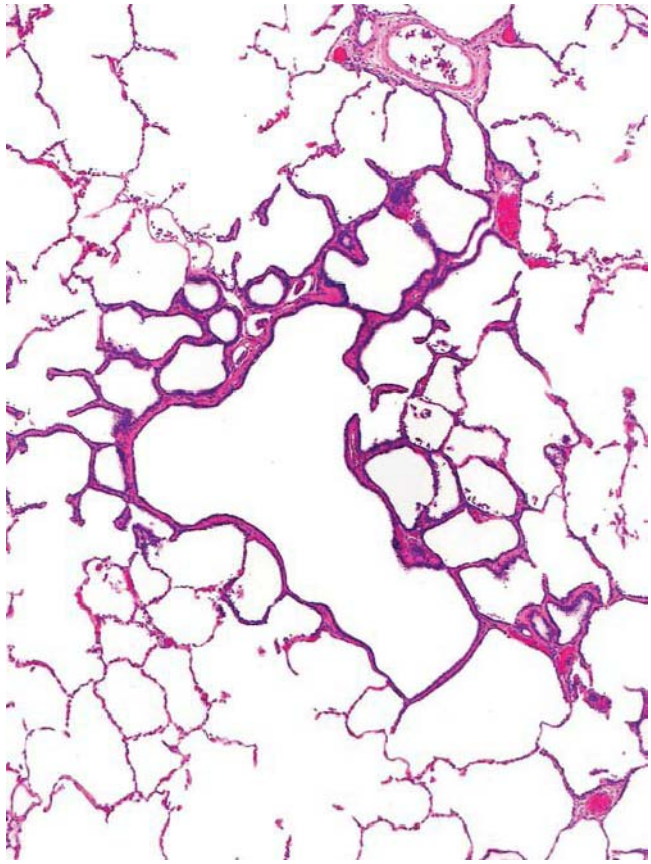


FIGURE 23.16. Peribronchiolar metaplasia. In this example, peribronchiolar metaplasia has developed in otherwise normal lung. The image shows the characteristic fine interstitial fibrosis surrounding a respiratory bronchiole.

Peribronchiolar metaplasia/fibrosis is most commonly seen in other forms of fibrosing interstitial pneumonias (approximately 50% of cases of UIP, desquamative interstitial pneumonia [DIP], and NSIP [Fig. 23.17] in the series of Fukuoka et al.[13]), but sometimes is found in otherwise normal lung tissue (Fig. 23.16).

Differential Diagnosis

Considerably exaggerated forms of peribronchiolar fibrosis/metaplasia are found in the entity labeled "idiopathic bronchiolocentric interstitial fibrosis,"[14] a lesion that is probably a variant of chronic hypersensitivity pneumonitis (HP) (see Figs. 12.33 and 12.34), and in "airway-centered interstitial fibrosis,"[15] which is described elsewhere in this chapter. In both these conditions the fibrosing process often has overlying bronchiolar metaplasia, but the fibrosis is much more diffuse than in simple peribronchiolar metaplasia/fibrosis, frequently affecting every bronchiole and sometimes linking bronchioles, or extending all the way to the pleura.

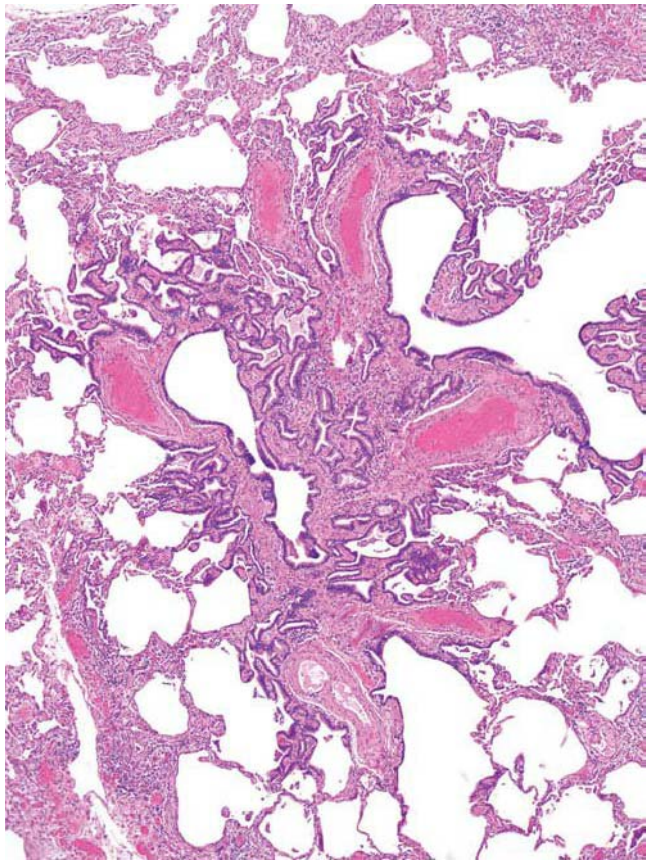


FIGURE 23.17. Peribronchiolar metaplasia in a lung with underlying fibrotic NSIP. There is fibrosis surrounding the bronchiole and forming small channels lined by metaplastic bronchiolar epithelium.

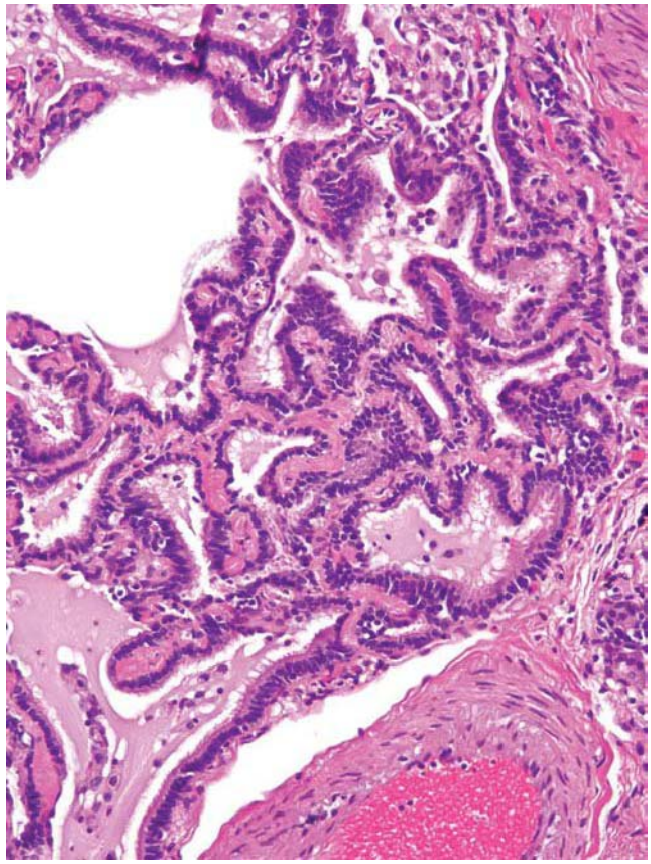


FIGURE 23.18. High-power view of another case showing peribronchiolar metaplasia with metaplastic bronchiolar epithelium covering the fibrotic alveolar walls.

Prognosis

In most cases, peribronchiolar metaplasia/fibrosis is an incidental finding that does not produce any clear-cut abnormality; in particular, despite the occasional appearance of narrow bronchiolar-like structures (Fig. 23.17), it does not produce the fixed airflow obstruction seen in constrictive bronchiolitis (see Chapter 20). None of the cases described by Fukuoka et al.[13] had progressive disease.

AIRWAY-CENTERED INTERSTITIAL FIBROSIS

Clinical Features

Churg et al.[15] described 12 patients with progressive SOB and a widespread pattern somewhat resembling marked peribronchiolar metaplasia/fibrosis on biopsy. These patients came from Mexico City, and they had a variety of exposures that suggested HP, but none had supporting serologic evidence and only four had an increase in lavage lymphocytes. Most had a restrictive pulmonary impairment.

The CT findings have been described in a small number of patients. The main abnormalities comprise peribronchovascular interstitial thickening, traction bronchiectasis, thickened airway walls, and surrounding fibrosis (Fig. 23.19).[15] Fibrosis may result in central peribronchial conglomerate masses.

Pathologic Features

Pathologically airway-centered interstitial fibrosis shows a variable pattern of fibrosis that encompasses membranous and respiratory bronchioles and spreads in the interstitum, often linking bronchioles or extending from the bronchioles to the pleura. The fibrosis may be fairly fine with associated overlying bronchiolar metaplasia (Fig. 23.20) and resemble an exaggerated form of peribronchiolar metaplasia or idiopathic bronchiolocentric fibrosis,[14] or can form larger more diffuse blocks (Fig. 23.21).

Prognosis

In the series of Churg et al.,[15] four patients died, one progressed, and five others remained stable or improved with steroid therapy.

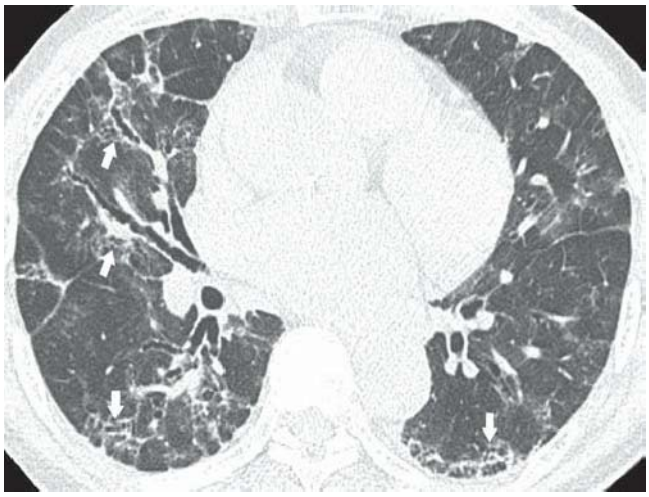


FIGURE 23.19. Airway-centered interstitial fibrosis. HRCT image shows extensive peribronchovascular fibrosis with associated traction bronchiectasis (*arrows*). These findings are easier to see on the right side on the illustrated image because several airways are cut along their long axes. At other levels, similar findings could be seen on the left. Also noted are thickened airway walls, patchy GGOs, and small foci of peripheral reticulation.

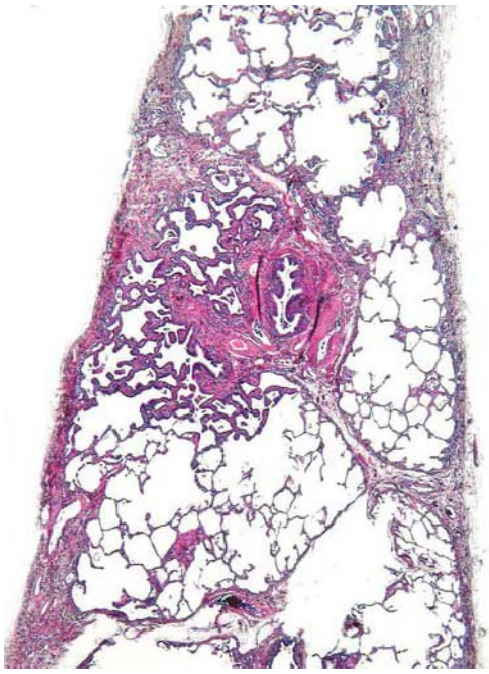


FIGURE 23.20. In this example of airway-centered interstitial fibrosis there is fine fibrosis slightly widening the alveolar walls and extending from the bronchiole to the pleura. This pattern is similar to that seen in idiopathic bronchiolo-centric interstitial fibrosis (Chapter 12). (Reproduced with permission from Churg A, Myers J, Suarez T, et al. Airway-centered interstitial fibrosis: a distinct form of aggressive diffuse lung disease. *Am J Surg Pathol*. 2004;28:62–68.)

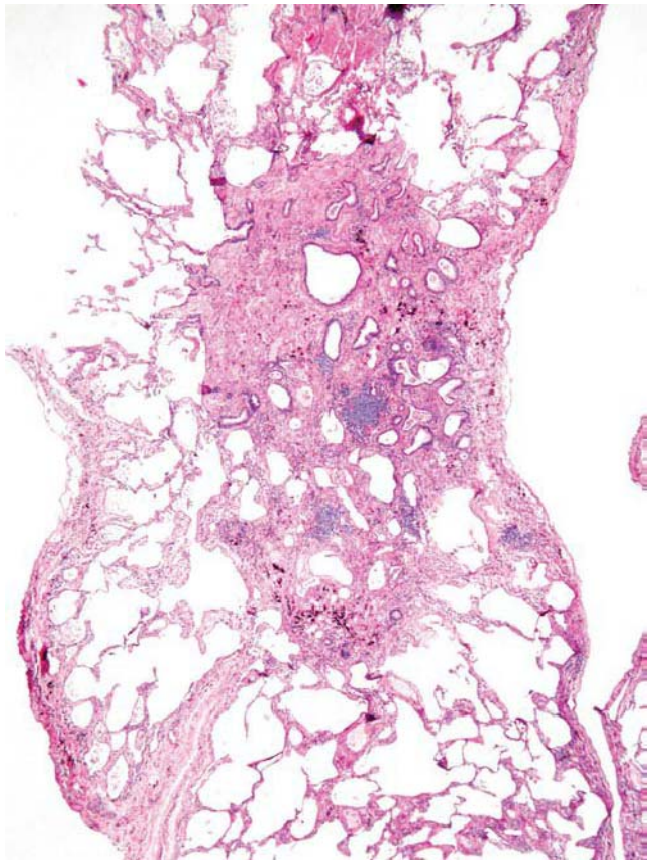


FIGURE 23.21. An example of airway centered interstitial fibrosis in which the fibrosis forms more of a mass-like lesion around the respiratory bronchiole. Again note extension to the pleura. (Reproduced with permission from Churg A, Myers J, Suarez T, et al. Airway-centered interstitial fibrosis: a distinct form of aggressive diffuse lung disease. *Am J Surg Pathol*. 2004;28:62–68.)

PLEUROPARENCHYMAL FIBROELASTOSIS

Clinical Features

Pleuroparenchymal fibroelastasosis is a poorly defined entity associated with upper zone fibrosis of the pleura and underlying parenchyma; some of the patients also have a fibrosing interstitial pneumonia in the lower zones (reviewed in Reddy et al.[16]). There are relatively few cases reported and no clear etiologic agents, although Reddy et al.[16] have suggested that the fibroelastosis may be related to recurrent pulmonary infections, particularly aspergillus infections. Some patients also have serologic evidence of a collagen vascular disease. von der Thüsen et al.[17] reported a small series of patients who developed fibroelastosis after bone marrow transplantation. Some cases have been described in family members.[16,18]

Imaging

The radiologic findings consist of marked apical pleural thickening associated with upper lobe subpleural reticulation, traction bronchiectasis, and volume loss with superior retraction of the hila.[18] Lower lobe fibrosis is either absent or less extensive than the upper lobe involvement.

Pathologic Features

Pleuroparenchymal fibroelastosis shows fibrosis and marked widening of the pleura in the upper lung zones with underlying intra-alveolar fibrosis and prominent deposition of elastic tissue (Figs. 23.22 to 23.24). Vessels and airways are obliterated as well. Often the fibroelastotic process is sharply demarcated from relatively normal parenchyma (Fig. 23.22). Some authors describe fibroblast foci at the end of the elastotic zone.[18] Occasionally fibroelastosis extends into the lower zones, but in other cases the lower zones show a fibrosing interstitial pneumonia that variably resembles UIP or fibrotic NSIP.[16]

Prognosis

Most reported patients have developed progressive fibrotic disease.

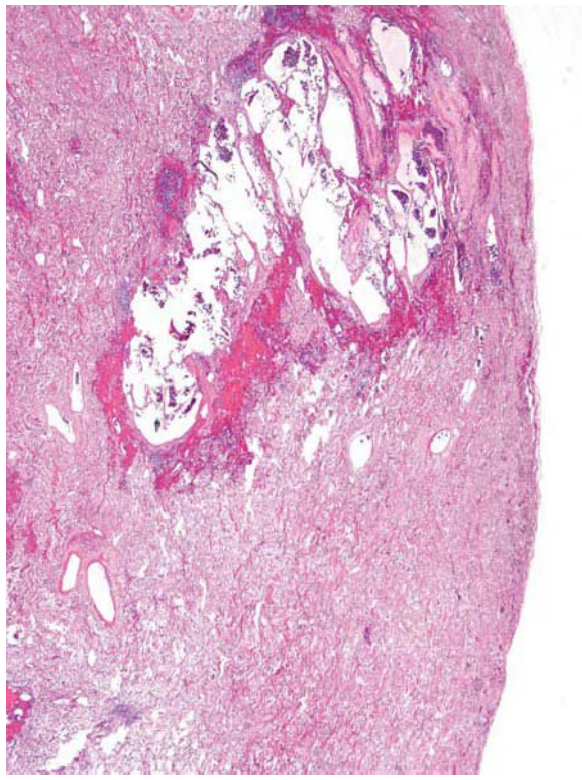


FIGURE 23.23. Higher-power view of another case.

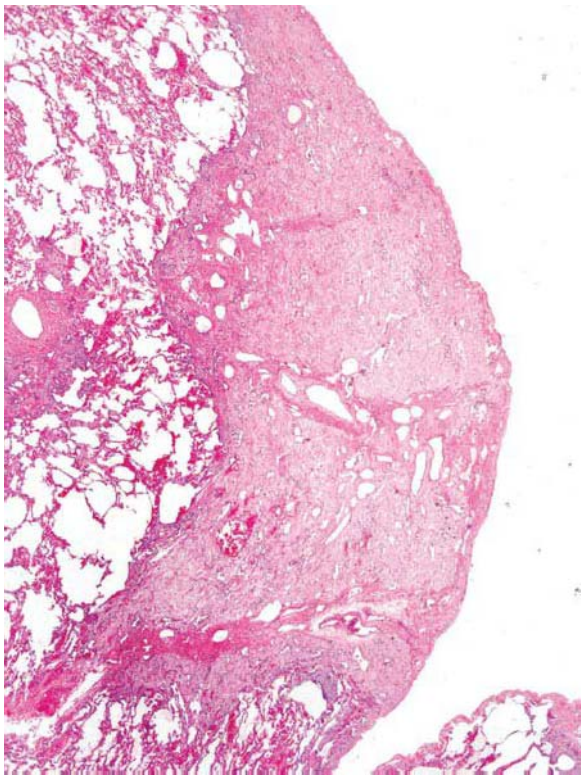


FIGURE 23.22. Pleuroparenchymal fibroelastosis. Low-power view shows a sharply demarcated mass of fibroelastic tissue under the pleura and extending into the parenchyma.

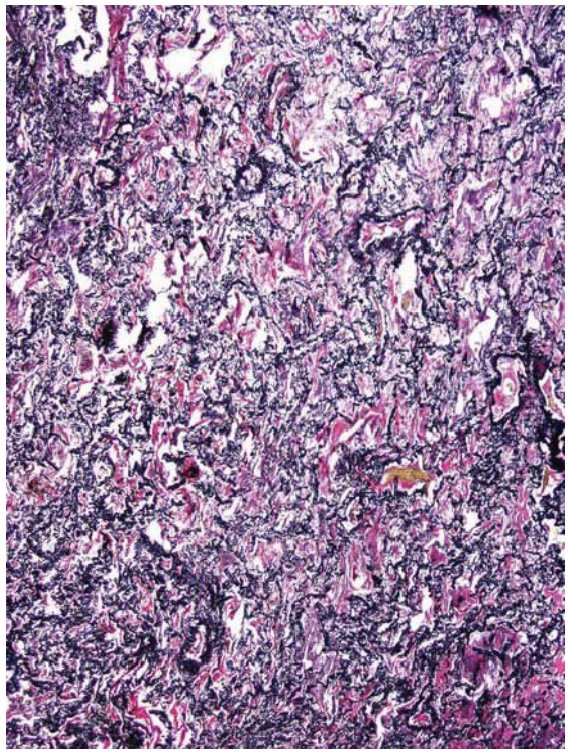


FIGURE 23.24. Elastic stain of the same case as Figure 23.23. Note the extensive elastin deposition, a pattern that is not seen in most forms of interstitial fibrosis. However, similar elastin deposition is common in radiation-induced fibrosis.

DIFFUSE SEPTAL AMYLOIDOSIS

Clinical Features

Amyloid can be deposited in the lung as part of generalized amyloidosis, which may be idiopathic or associated with myeloma; and in secondary amyloidosis, for example with chronic infection, in familial Mediterranean fever, in patients with collagen vascular disease, as part of senile amyloidosis, accompanying monoclonal gammopathies, and in chronic dialysis patients.[19]

In patients with nodular amyloidosis, one or more nodules are found on imaging, sometimes incidentally, and sometimes because of nonspecific pulmonary complaints such as cough, SOB, or chest pain. Such patients may have associated lymphocytic interstitial pneumonia (LIP), marginal zone lymphomas, or plasmacytomas. In tracheobronchial amyloidosis, there may be sufficient airway narrowing to cause dyspnea, wheezing, stridor, and even spontaneous pneumothorax. Heavy vascular deposition of amyloid can lead to pulmonary hypertension.[19,20] Some patients with diffuse septal amyloidosis have cough and SOB as well as a restrictive impairment, but most do not.[19,21] Amyloid deposits in the lung can be associated with pulmonary hemorrhage.[22]

Imaging

The most common HRCT manifestations of diffuse septal amyloidosis consist of small nodules, patchy GGOs, interlobular septal thickening, and irregular lines (reticular pattern) in a predominantly basilar and peripheral distribution.[23]

Pathologic Features

In diffuse septal amyloidosis there are fine deposits of amorphous eosinophilic amyloid that slightly widen the alveolar walls, producing what at first glance can be mistaken for fine interstitial fibrosis (Figs. 23.25 to 23.27). Typically there is no inflammatory infiltrate and the diagnosis is made on Congo Red stains (Fig. 23.27). In some patients disease that is diffuse on biopsy may nonetheless be radiologically localized.[21,24]

In pulmonary light chain deposition disease, diffuse septal deposits of amorphous material identical to amyloid on H&E stains can be found[25]; however, the material does not stain with Congo Red. On electron microscopy the material is fibrillar or crystalline.[25]

Small amounts of interstitial amyloid can be seen in the interstitium as well as in the vessels in senile amyloidosis

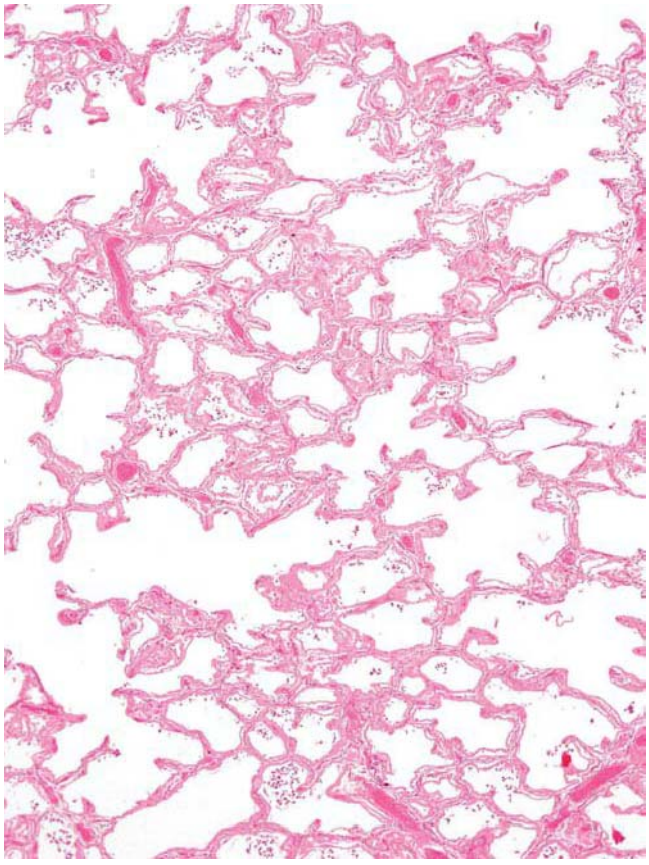


FIGURE 23.25. Diffuse pulmonary amyloidosis. Low-power view shows slightly widened alveolar walls mimicking fibrotic NSIP.

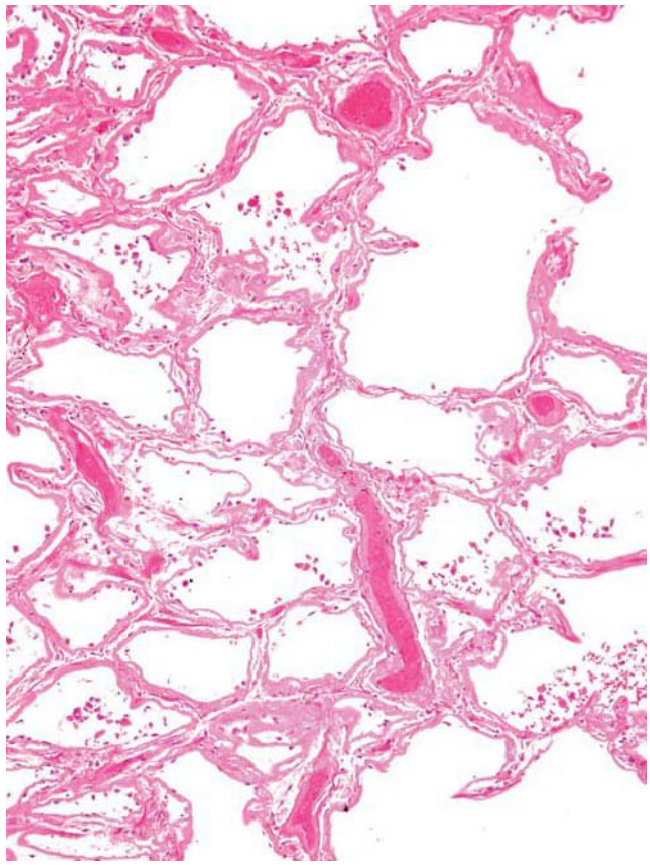


FIGURE 23.26. At higher power, deposition of amyloid is evident along the alveolar walls.

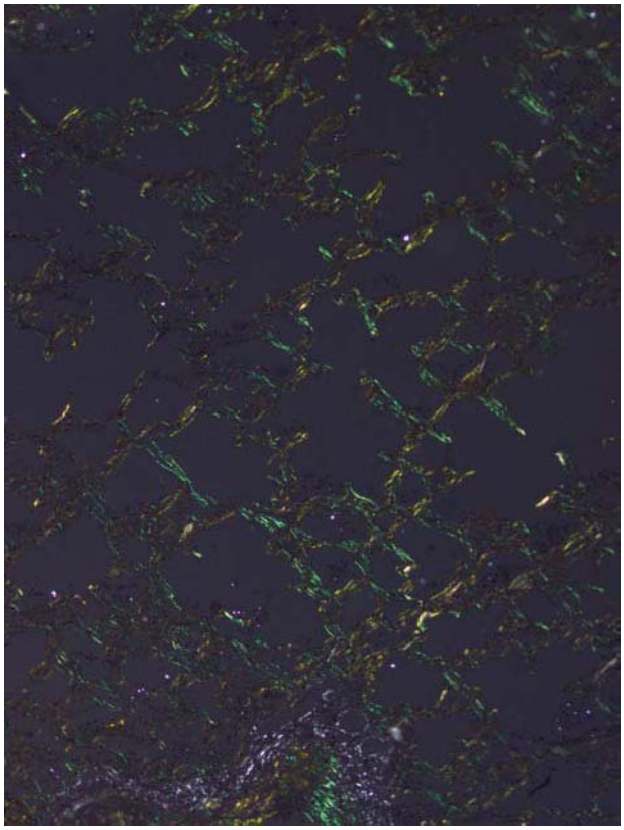


FIGURE 23.27. The same case viewed under polarized light after staining with Congo Red. Note the diagnostic apple-green birefringence.

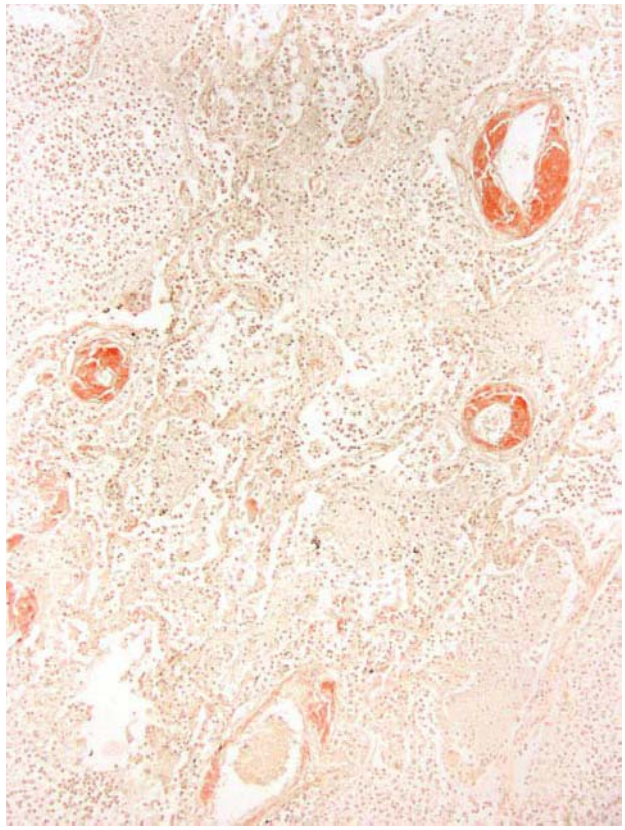


FIGURE 23.28. Senile amyloidosis. Most of the amyloid is in the vessels with little in the interstitium. This is a common finding at autopsy in the elderly and may be associated with cardiac amyloid; however, the pulmonary amyloid appears to be innocuous (stained with Congo Red).

(Fig. 23.28), but these interstitial deposits do not appear to produce clinically detectable abnormalities.[21]

Prognosis

Most patients with diffuse septal amyloidosis do not develop clinically significant respiratory disease; rather, the amount of septal amyloid correlates with the amount of cardiac amyloid, and these patients often have marked cardiac impairment.[21] However, some patients' die of respiratory failure.[19,21]

EHLERS–DANLOS SYNDROME

Clinical Features

Vascular Ehlers–Danlos syndrome, also known as type IV Ehlers–Danlos syndrome, is an autosomal dominant condition caused by a mutation in the gene for the α chain of type III collagen. The mutation leads to collagen with low tensile strength and a tendency toward vascular rupture and organ laceration.

Imaging

The most common and life-threatening intrathoracic manifestations evident on CT are aortic aneurysm and dissection and pulmonary artery aneurysm.[26] Pulmonary manifestations are seldom evident on CT and consist mainly of bulla formation and pneumothorax.[27]

Pathologic Features

In the lung repeated hemorrhages lead to hemosiderin deposition, BOOP, and parenchymal fibrous nodules that probably represent organization of hemorrhage/BOOP, along with evidence of vascular disruption on elastic stains[28] (Figs. 23.29 and 23.30). The fibrous nodules frequently ossify.

LYSOSOMAL STORAGE DISORDERS CAUSING INTERSTITIAL LUNG DISEASE

Gaucher disease is an autosomal recessive disorder characterized by lysosomal storage of glucoyl ceramide, a product of cell breakdown, owing to a deficiency of glucocerebrosidase. Most patients have functional evidence of airflow obstruction, but some are restricted.[29] Microscopically Gaucher cells with so-called wrinkled tissue paper cytoplasm infiltrate the lung in either a lymphangitic or a diffuse alveolar wall pattern (Figs. 23.31 and 23.32), but can also accumulate in the alveoli and in the capillaries.[30]

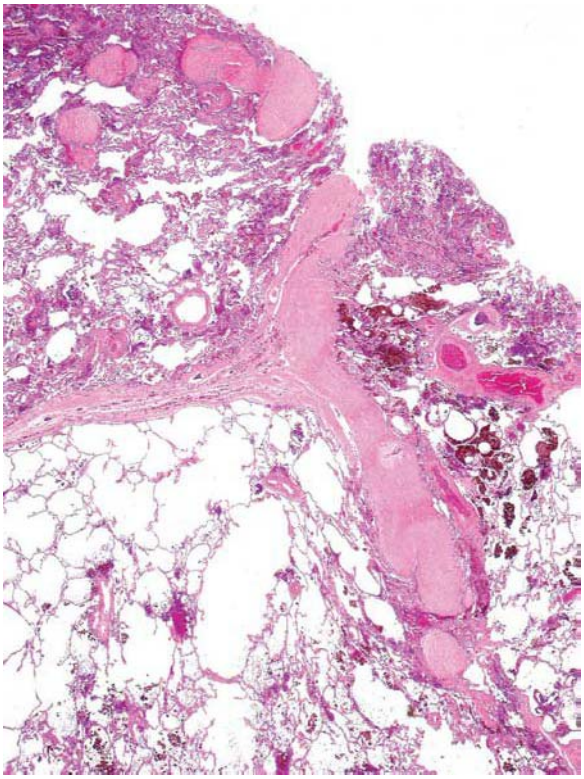


FIGURE 23.29. Vascular Ehlers–Danlos syndrome. Low-power view showing the characteristic irregular masses of fibrous tissue; these are often associated with interlobular septa (as here) or with vessels and are thought to represent a peculiar form of organization of small hemorrhages/foci of BOOP.

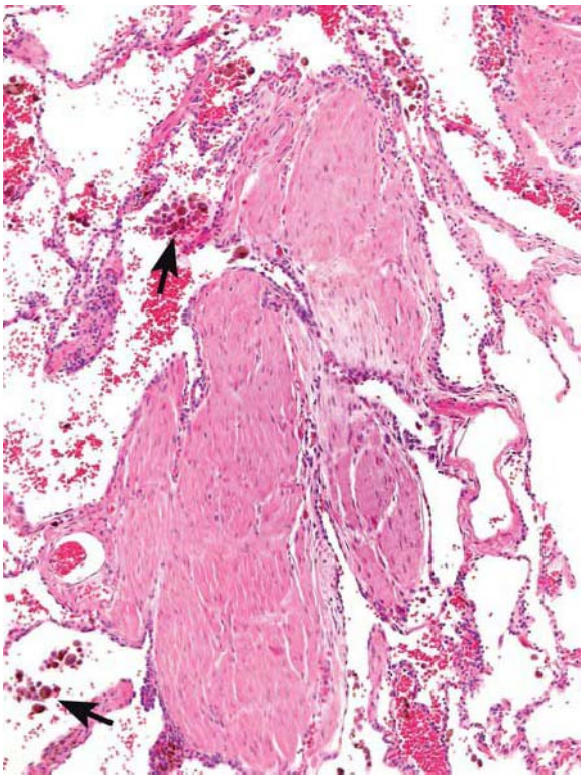
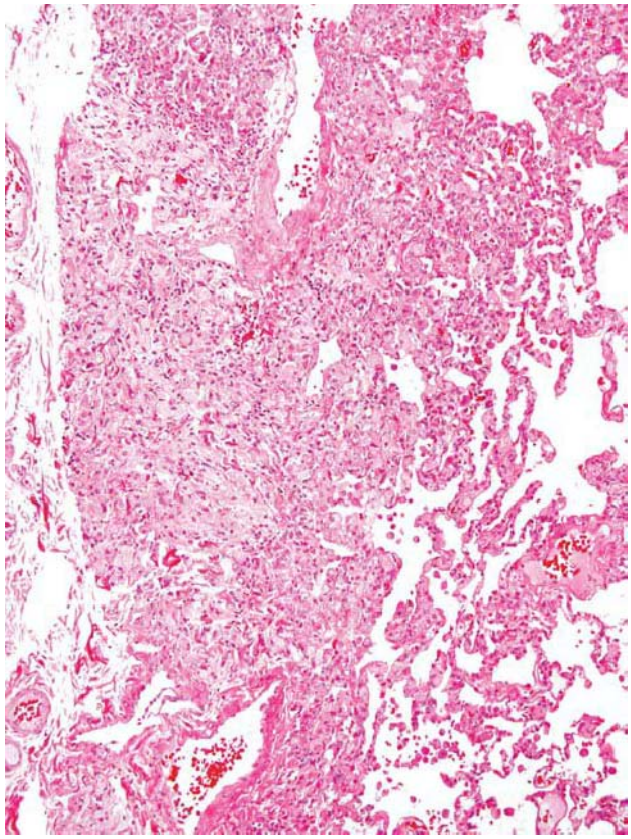


FIGURE 23.30. At higher power, hemosiderin-laden macrophages can just be discerned (*arrows*).



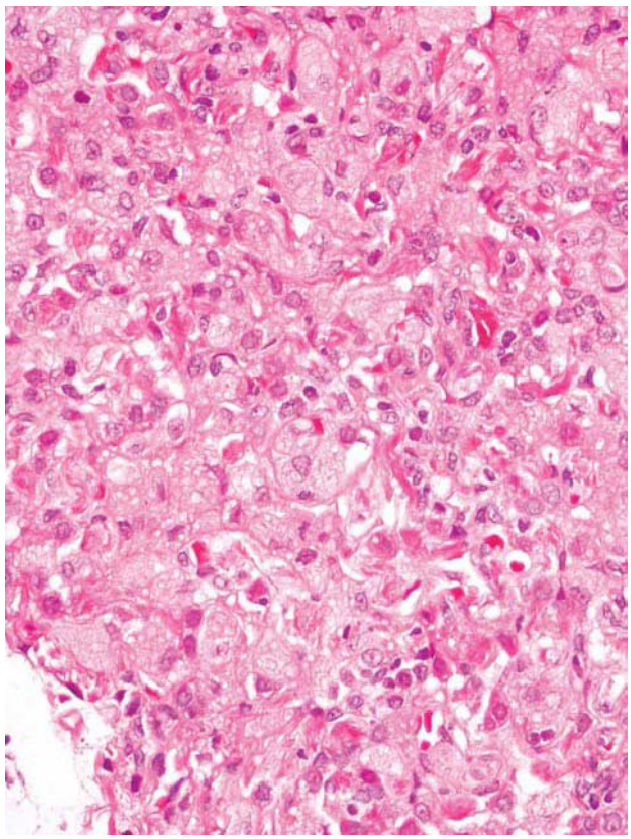


FIGURE 23.31 and 23.32. Gaucher disease. Lower-power view shows expansion of the alveolar walls by an infiltrate of pale-staining histiocytes with a wrinkled appearance (Gaucher cells). These are seen better in the high-power view.

Niemann–Pick disease is an autosomal recessive disorder caused by a lack of sphingomyelinase, leading to accumulation of sphingomyelin. Pulmonary accumulation of abnormal foamy histiocytes (Pick cells) is common and the patterns are similar to those seen in Gaucher disease.[31]

Hermansky–Pudlak syndrome is an autosomal recessive condition characterized by the accumulation of ceroid-filled histiocytes, oculo-cutaneous albinism, platelet defects, and ILD variably described as similar to UIP or to fibrotic NSIP.[32]

DIFFUSE PARENCHYMAL CALCIFICATION AND OSSIFICATION

Clinical Features

Metastatic calcification can be seen not only in the lungs in patients with abnormal calcium or phosphorus metabolism—most commonly associated with renal failure and chronic dialysis, but also in sarcoid, systemic sclerosis, following liver transplantation, hyperparathyroidism, and hypervitaminosis A and D, and in patients with tumors involving bone. In most patients with diffuse calcium deposition in the lung, calcium deposition is seen in other organs as well. In general, patients with diffuse calcification do not have pulmonary symptoms.

Diffuse pulmonary ossification is referred to as dendriform, racemose, or branching ossification. It is most commonly seen in patients with an underlying fibrosing interstitial pneumonia. Localized or nodular ossification is usually found in patients with elevated pulmonary venous pressure, typically secondary to mitral stenosis. Neither dendriform nor nodular ossification is symptomatic.

Imaging

The HRCT manifestations of metastatic calcification usually consist of fluffy poorly defined nodular opacities measuring 3 to 10 mm in diameter in a predominantly upper lobe distribution.[33] Foci of calcification within the nodular opacities are evident on CT in only approximately 50% of cases but can be confirmed on scintigraphy using bone-imaging agents when there is high clinical suspicion and the calcification is not apparent on CT.

Fine linear or small nodular foci of calcification representing dendriform pulmonary ossification are seen on HRCT in up to 7% of patients with idiopathic pulmonary fibrosis (Fig. 23.33).[34] They tend to be evident in the areas with most severe fibrosis, typically in the subpleural regions of the lower lobes.

Pathologic Features

Metastatic calcification appears most often as lines of hematoxyphilic material that follow the alveolar walls (Fig. 23.34) and vessel walls. The material stains with von Kossa and other calcium stains (Fig. 23.35). Sometimes the calcium deposits expand the alveolar walls and are associated with a giant cell reaction. In other instances, the calcium appears to evoke intra-alveolar fibrosis.

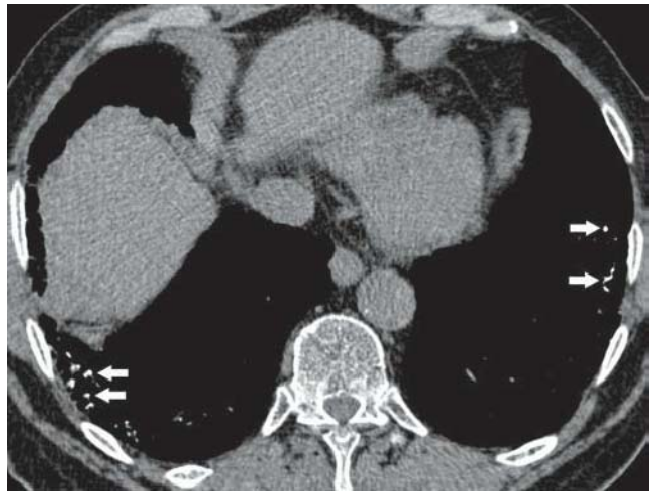


FIGURE 23.33. Pulmonary ossification. HRCT shows bilateral small nodular and linear foci of calcification (*arrows*) in the peripheral regions of the lower lobes. The patient had interstitial pulmonary ossification associated with idiopathic pulmonary fibrosis.

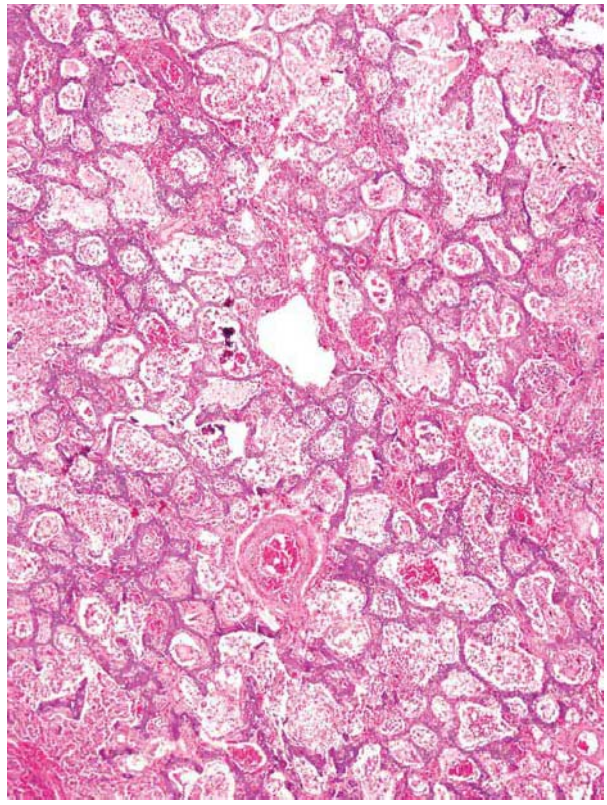


FIGURE 23.34. Diffuse pulmonary calcification. On H&E hematoxyphilic material outlines the alveolar walls.

Dendriform ossification appears as branching mature bone in the airspaces or in foci of interstitial fibrosis (Fig. 23.36).[35] In nodular ossification, the bone forms

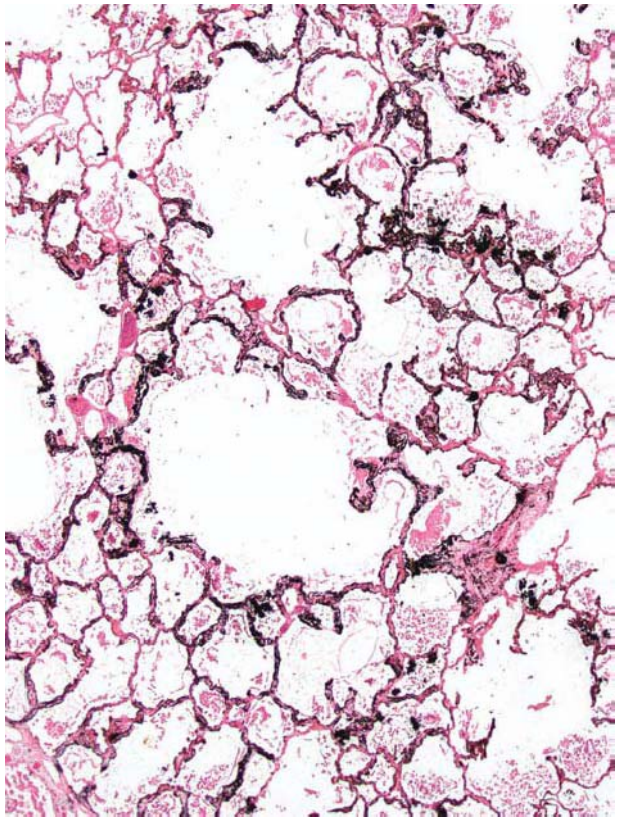


FIGURE 23.35. Calcium stain of another case highlights the widespread calcium deposition.

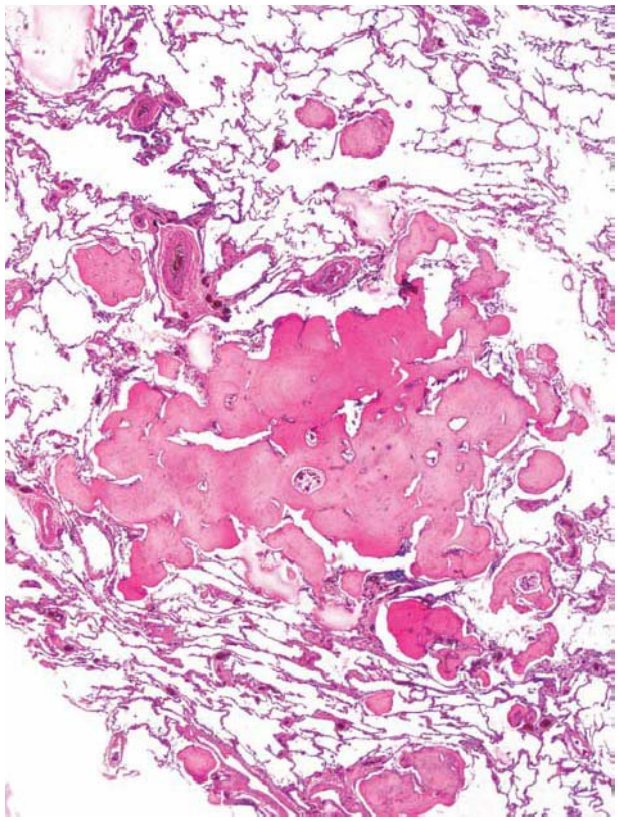


FIGURE 23.36. Dendriform ossification showing the typical pattern of irregular, somewhat branched, masses of osteoid filling airspaces.

spherical nodules in the airspaces. Ossification may also be seen in the bronchial cartilages as an aging change.

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CHAPTER

24

Mimics of Interstitial Lung Disease

ILD-LIKE DISEASE SECONDARY TO PULMONARY HEMORRHAGE

Clinical Features

Pulmonary hemorrhage can produce reactions that mimic interstitial lung disease (ILD). Significant pulmonary hemorrhage is seen in various clinical settings, of which the most common are mechanical causes such as tumors or cavities that typically produce localized hemorrhage. Diffuse alveolar hemorrhage (i.e., hemorrhage that is widespread in both lungs and does not have a mechanical etiology) has a strong association with underlying vasculitis, but there are numerous other causes including diffuse alveolar damage (DAD), drug reactions, collagen vascular diseases, coagulation disorders, left-sided cardiac disease, pulmonary venous hypertension, idiopathic pulmonary hemosiderosis, and anti-phospholipid antibody syndrome.

Patients with diffuse hemorrhage commonly present with hemoptysis, but hemoptysis is absent in up to one-third of cases.[1] Alveolar hemorrhage can be associated with nonspecific symptoms such as fever, chest pain, cough, and dyspnea. Findings that suggest hemorrhage in the absence of hemoptysis are a falling hematocrit and low serum hemoglobin, and increasing return of red cells on serial lavage or a high percentage of hemosiderin-laden macrophages in lavage, in the presence of compatible high resolution computed tomography (HRCT) findings.[1]

Bronchiolitis obliterans organizing pneumonia (BOOP) can be seen as a reaction to alveolar hemorrhage but has no specific clinical features. In patients who develop widespread interstitial fibrosis from chronic hemorrhage associated with vasculitis, the process can present as an ILD clinically, functionally, and radiologically,[2] and some of these patients never have overt hemoptysis. They do, however, have glomerulonephritis.[2] Patients with idiopathic pulmonary hemosiderosis can also develop diffuse fibrosis.

Patients with pulmonary veno-occlusive disease always have pulmonary hypertension but usually not hemoptysis. Patients with chronic hemorrhage secondary to cardiac disease may or may not have pulmonary hypertension and sometimes have small hemoptyses, but the cardiac disease usually overshadows the pulmonary disease.

Imaging

The HRCT findings in diffuse pulmonary hemorrhage resemble those of ILD. The CT manifestations of acute pulmonary hemorrhage consist of ground-glass opacities (GGOs) and, less commonly, areas of consolidation (Fig. 24.1).[3] The GGOs may be focal, have a patchy distribution, or be diffuse. CT scans performed 2 to 3 days after the acute episode show a decrease in the GGOs and consolidation and presence of interlobular septal thickening and small poorly defined centrilobular nodules.[4] These findings are presumably secondary to lymphatic resorption of the blood and gradually resolve over the next 1 to 2 weeks. In patients with recurrent pulmonary hemorrhage, GGOs may be seen superimposed on a background of reticular and small nodular opacities (Fig. 24.2). CT may demonstrate the underlying cause, such as bronchiectasis and carcinoma, in patients with focal pulmonary hemorrhage.

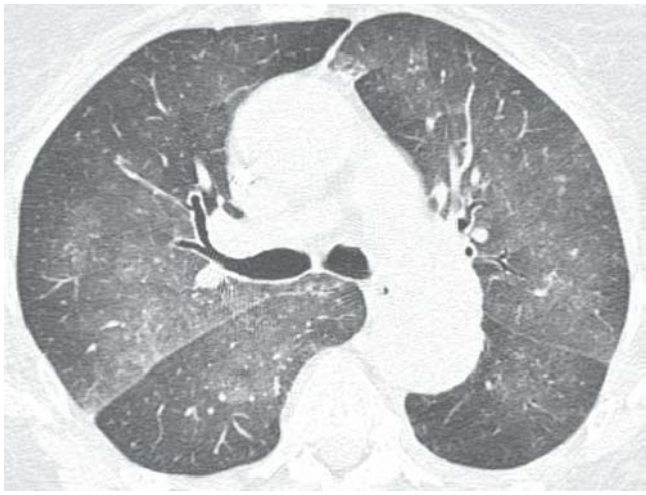


FIGURE 24.1. Diffuse pulmonary hemorrhage. HRCT image shows extensive bilateral ground-glass opacities in a patient with Goodpasture syndrome and diffuse pulmonary hemorrhage.

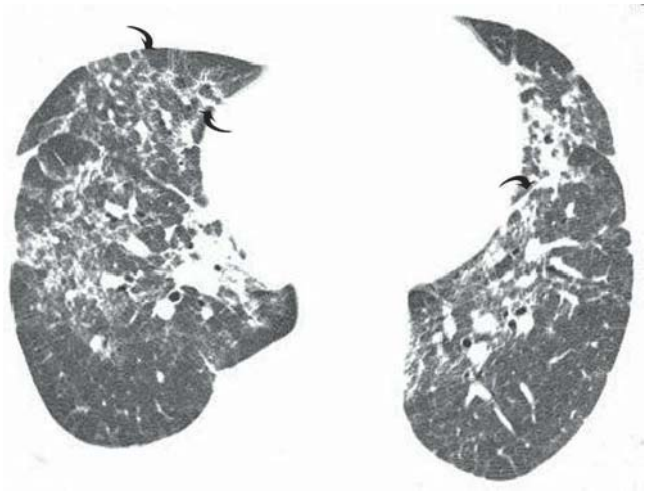


FIGURE 24.2. Recurrent pulmonary hemorrhage. HRCT image demonstrates thickening of the interlobular septa (*arrows*), small nodules, and patchy bilateral ground-glass opacities. The patient was a 45-year-old woman with Wegener granulomatosis and recurrent pulmonary hemorrhage.

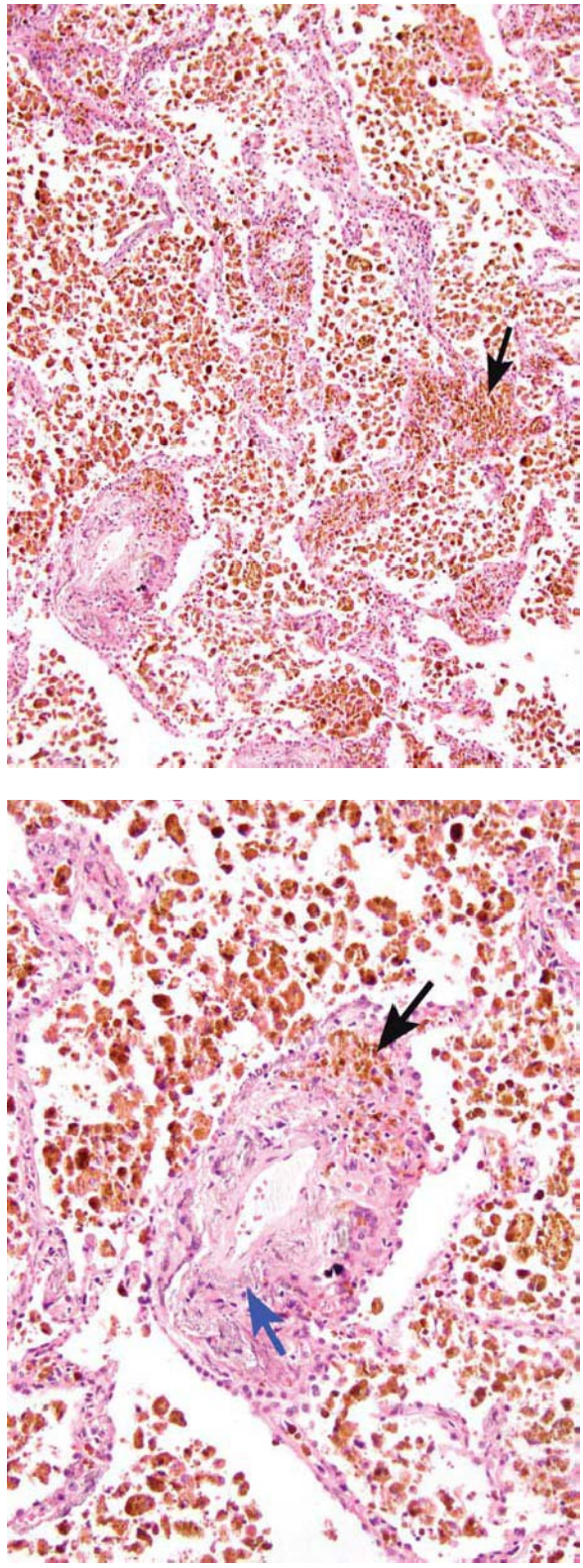
Pathologic Patterns of Hemorrhage and Ild-Like Reactions to Hemorrhage

Acute alveolar hemorrhage (i.e., just red cells in alveolar spaces) may be found in any of the conditions described above, but by far the most common cause of acute hemorrhage in a lung biopsy is the surgical procedure itself. Thus, in the absence of hemoptysis or clinical evidence of hemorrhage, caution should be exercised in labeling pure acute hemorrhage as a pathologic reaction.

The presence of hemosiderin-laden macrophages indicates that the hemorrhage is real but provides no indication of chronicity, as hemosiderin-laden macrophages form in a few days and can persist for months or years. Free hemosiderin may also be present. Hemosiderin-laden macrophages need to be distinguished from smoker's macrophages (Chapter 8). Both stain with iron, but in smoker's macrophages the brown/golden pigment is finely granular and dispersed throughout the cytoplasm, producing a blush on iron stain (see Fig. 8.7), whereas hemosiderin typically appears as coarse iron-positive particles (Figs. 24.3 and 24.4).[5]

Hemorrhage can produce three reaction patterns that mimic ILD (Table 24.1). DAD secondary to hemorrhage is morphologically no different from DAD of other causes (Chapter 4) and is difficult to accurately diagnose without a good clinical/radiologic story, as DAD itself sometimes causes hemorrhage. However, if DAD is secondary to hemorrhage, it may be localized to the areas with hemorrhage.

BOOP is a frequent reaction to hemorrhage. Because BOOP is a common reaction pattern after many types of insults (see Chapter 5), it is often difficult to be sure that hemorrhage is the cause of BOOP in a given case; however a clue that BOOP is caused by hemorrhage and not a bystander is the finding of free hemosiderin or



FIGURES 24.3 and 24.4. Low- and high-power views of chronic alveolar hemorrhage in a patient with microscopic polyangiitis leading to interstitial fibrosis. The fibrosis resembles fibrotic NSIP. Note the interstitial hemosiderin (*black arrows*), an indication that the fibrosis is secondary to hemorrhage. The vessel in Figure 24.4 also demonstrates pale gray ferruginated elastica (*blue arrow*) another characteristic finding in chronic hemorrhage.

Table 24.1

Pathologic reactions to hemorrhage

DAD
BOOP (organizing pneumonia)
- Clue: hemosiderin embedded in the granulation tissue

More or less diffuse interstitial fibrosis
- Usually NSIP-like
- Seen with microscopic polyangiitis, veno-occlusive disease, idiopathic hemosiderosis, occasionally Goodpasture syndrome or Wegener granulomatosis, and in mild forms with heart failure or mitral valvular disease
- Clue: hemosiderin embedded in the fibrous tissue
- Clue: iron/calcium encrustation of vessel elastic fibers

hemosiderin-laden macrophages within the granulation tissue plugs (Fig. 24.5).

Low-grade persisting hemorrhage that goes on for months or years can lead to interstitial fibrosis (Figs. 24.3 and 24.4) (Table 24.1). This process is seen in some forms of vasculitis, particularly microscopic polyangiitis, and occasionally Goodpasture syndrome or Wegener granulomatosis.[1] Locally marked interstitial fibrosis secondary to hemorrhage can also be found in veno-occlusive disease (Figs. 24.6 to 24.8) and idiopathic hemosiderosis; generally much milder forms are found in patients with heart failure or mitral valvular diseases.

There are several clues to the diagnosis of hemorrhage-related fibrosis. Most such cases will have hemosiderin—free or in macrophages—in the fibrotic interstitium (Figs. 24.3 and 24.4), and often in the alveolar spaces as well (Figs. 24.3 and 24.4). Cases of fibrosis secondary to hemorrhage usually will also show iron/calcium encrustation of vessel elastic fibers (Figs. 24.4 and 24.7), a process that has been termed "endogenous pneumoconiosis" because the encrusted elastic can resemble asbestos bodies.

In processes such as vasculitis that produce fairly widespread hemorrhage, the pattern of fibrosis resembles fibrotic nonspecific interstitial pneumonia (NSIP) (Chapter 7) and is present over large areas of lung (Fig. 24.3). In contrast, in veno-occlusive disease and fibrosis secondary to cardiac disease, the fibrosis is usually localized to the subpleural region. The local pattern again most often resembles fibrotic NSIP (Fig. 24.6) but sometimes resembles usual interstitial pneumonia (UIP). In veno-occlusive disease, evidence of venous thrombosis is always present and is best detected in veins in the interlobular septa (Fig. 24.8); with time, these veins become arterialized (develop a double elastic lamina), thus mimicking pulmonary artery

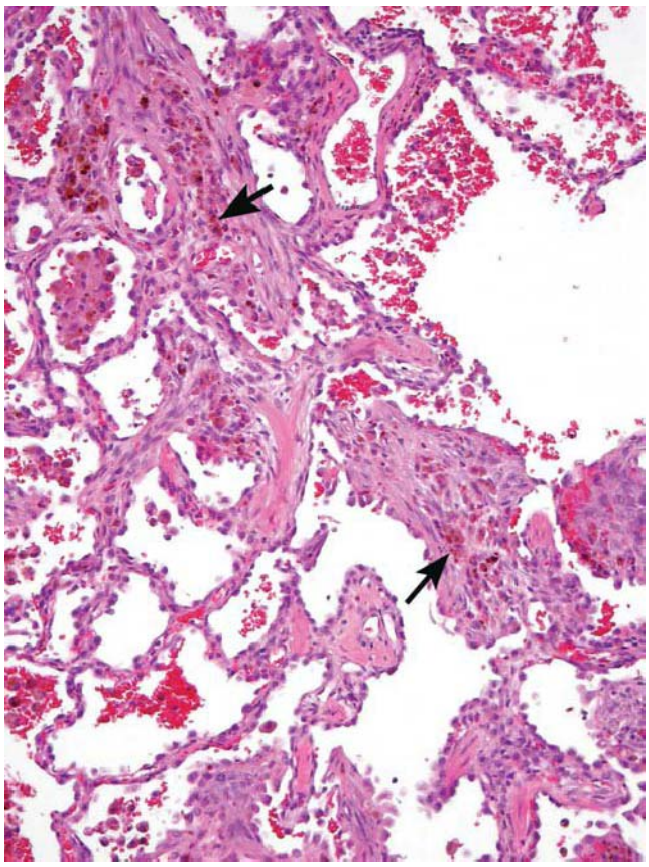
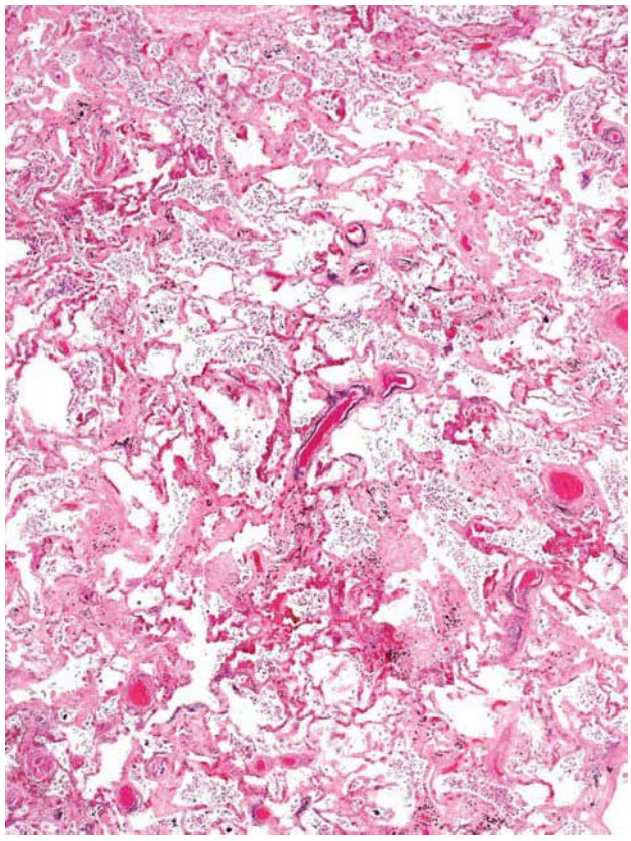
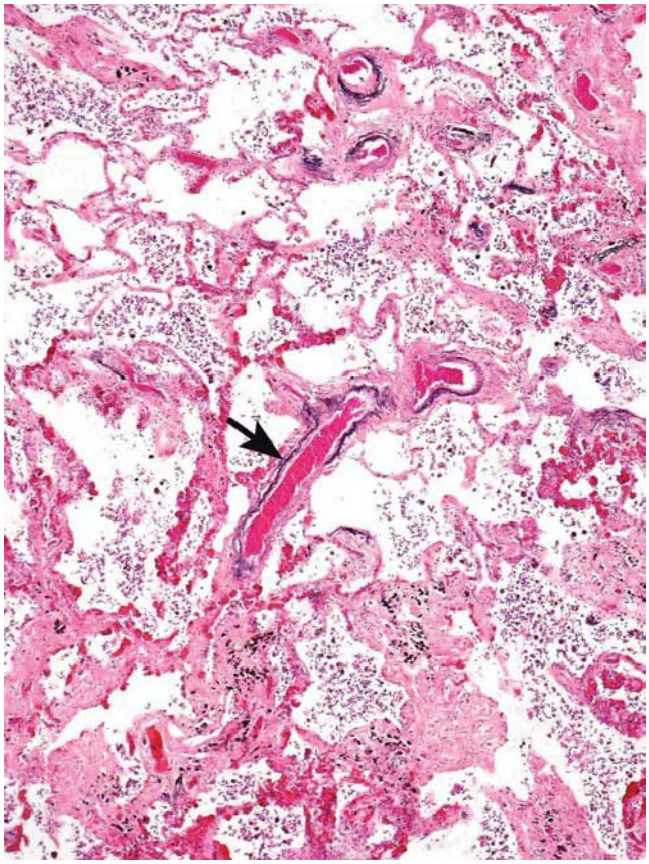
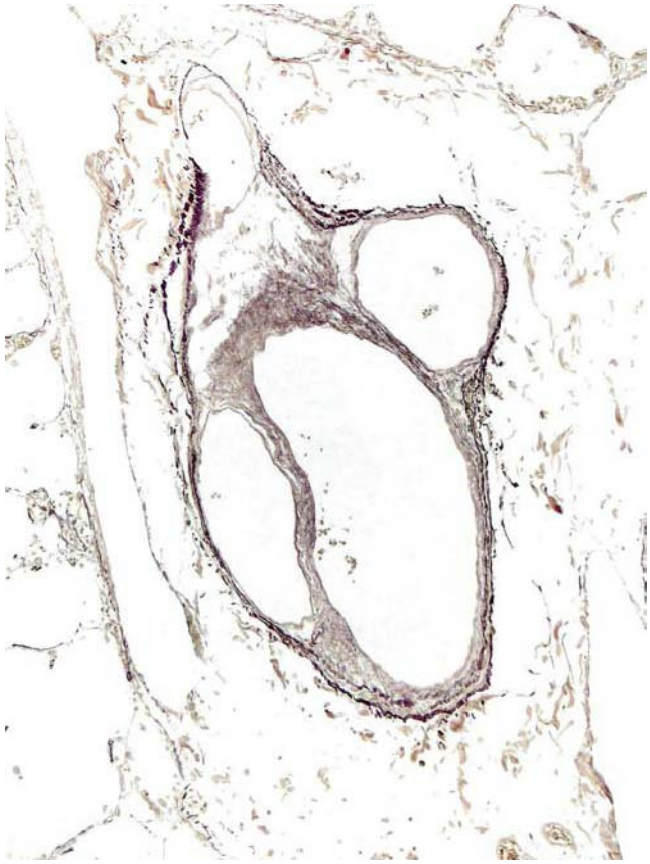


FIGURE 24.5. BOOP secondary to alveolar hemorrhage. The presence of hemosiderin in the granulation tissue (*arrows*) is an indication that the BOOP is probably a reaction to hemorrhage.



FIGURES 24.6 to 24.8. Legend appears on following page





FIGURES 24.6 to 24.8. Fibrosis secondary to hemorrhage in pulmonary veno-occlusive disease. On low-power view (**Fig. 24.6**), the process resembles fibrotic NSIP, but this image is taken from a subpleural region; away from the subpleural area there is no fibrosis. The higher-power view (**Fig. 24.7**) shows a vessel with ferruginated elastica (*arrow*), a marker of chronic hemorrhage. Elastic stain (**Fig. 24.8**) demonstrates a recanalized thrombus in a vein in an interlobular septum, a diagnositc finding in veno-occlusive disease.

branches. Similar venous changes, minus thromboses, can be found in the veins in patients with heart failure or mitral valvular diseases.

NEOPLASMS PRODUCING ILD-LIKE PATTERNS: KAPOSI SARCOMA, LYMPHOMAS, LEUKEMIAS, AND LYMPHANGITIC CARCINOMA

Clinical Features

Kaposi sarcoma (KS) presents in various forms including classic (elderly men, usually of Eastern European or Mediterranean origin); endemic (non-HIV-related) seen in parts of Africa; associated with immunosuppressive states such as organ transplantation; and epidemic, associated with HIV infection.[6] The classic appearance is violaceous skin papules, but disease can involve any organ. Pulmonary involvement is usually seen in patients who have disease in other sites and is nonspecific with shortness of breath (SOB), cough, fevers, night sweats, and chest pain, sometimes but not always accompanied by hemoptysis.[7,8] Tumor can often be seen on bronchoscopy as red or purple macular or papular lesions at airway bifurcations.[8]

Patients with pulmonary involvement by lymphoma can present with asymptomatic tumor masses found on imaging, or with nonspecific pulmonary complaints, and sometimes have a restrictive pattern of pulmonary function if tumor has spread widely in the interstitium.

Lymphangitic carcinoma presents with the insidious onset of SOB and often cough caused by submucosal endobronchial lymphatic tumor. Pulmonary function tests show a restrictive impairment with decreased diffusing capacity. Endobronchial involvement may be visible as plaque-like lesions on endoscopsy. If tumor gains access to the small pulmonary artery branches, cor pulmonale may develop. The prognosis for widespread lymphangitic carcinoma is poor, with typically 3 to 6 month survivals. Statistically lung, breast, stomach, pancreas, ovary, and prostate are the most frequent sites of origin.[9]

Imaging

The characteristic HRCT manifestations of KS consist of bilateral irregularly shaped or poorly defined nodules in a peribronchovascular distribution (Fig. 24.9).[10]

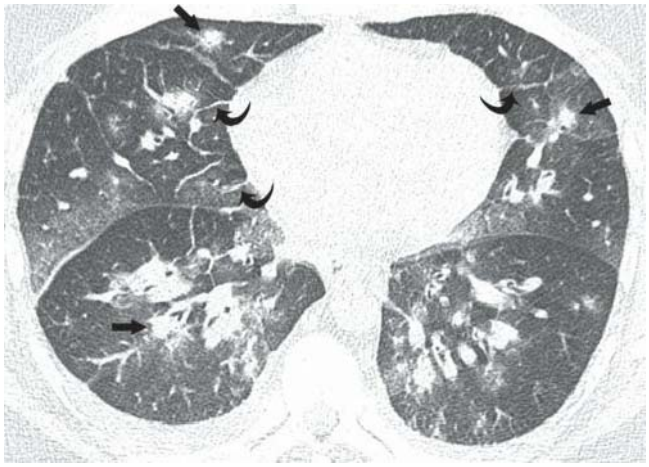


FIGURE 24.9. Kaposi sarcoma. HRCT image demonstrates poorly defined nodules (*straight arrows*), thickening of the interlobular septa (*curved arrows*), peribronchovascular interstitial thickening, and patchy ground-glass opacities. The patient was a 31-year-old man with AIDS and Kaposi sarcoma.

The nodules are frequently surrounded by a halo of ground-glass attenuation. Other common findings include GGOs, interlobular septal thickening, peribronchovascular thickening, hilar and mediastinal lymphadenopathy, and unilateral or bilateral pleural effusions.

The CT manifestations of pulmonary lymphoma include multiple small or single or multiple large nodules, mass-like areas of consolidation, thickening of the bronchovascular sheaths and interlobular septa, and GGOs[11] (Fig. 24.15).

The HRCT manifestations of pulmonary leukemic cell infiltration consist mainly of bilateral thickening of the peribronchovascular sheaths and interlobular septa, a pattern that resembles that of interstitial pulmonary edema.[12] Less common findings include 3- to 10-mm diameter nodules in a predominantly peribronchovascular distribution, GGOs, and areas of consolidation. In the majority of patients with leukemia the parenchymal abnormalities seen on CT are the result of pulmonary edema, infection, or hemorrhage, rather than leukemic infiltration.

The HRCT manifestations of lymphangitic carcinoma typically consist of thickening of the interlobular septa and bronchovascular bundles with preservation of normal lung architecture (Fig. 24.25).[13] The thickened interlobular septa are seen in the periphery of the lung as lines extending to the pleural surface and centrally as polygonal arcades. Associated findings may include discrete nodules representing metastases, pleural effusion, and hilar, or mediastinal lymph node enlargement.

Pathologic Features

Kaposi sarcoma

KS can form nodules that are obviously neoplastic, but the tumor also commonly grows in a lymphangitic pattern along the bronchovascular bundles and interlobular septa, producing a pattern that looks grossly like very fine hemorrhage outlining the bronchial and pulmonary artery walls and interlobular septa (Figs. 24.10 and 24.11), with hemorrhagic discoloration of the bronchial mucosa.

Microscopically KS can be subtle. At low-power view the lymphangitic pattern of tumor often looks like hemorrhage in the walls of thickened airways and pulmonary arteries (Fig. 24.12), but at high power, this picture resolves itself into closely packed spindled cells (Fig. 24.13) that may contain red cells in abortive lumina or red cells extravasated between the tumor cells. Intracellular hyaline globules are sometimes also found. In some cases, small lakes of hemorrhage form in the midst of the spindled cells. KS cells are positive for CD31, variably positive for D2-40, and positive for human herpes virus 8 (HHV8) (Fig. 24.14).

Lymphomas and Leukemias

Lymphomas, either primary or secondary, can involve the lung in three patterns: (1) as lymphoid cells in spreading in a lymphangitic pattern around the bronchovascular bundles and in the interlobular septa (Figs. 24.16 and 24.17); (2) as lymphoid cells spreading diffusely through

FIGURE 24.10. Kaposi sarcoma at autopsy. Tumor spreads in a lymphangitic fashion and outlines the interlobular septa (*arrows*) and bronchovascular bundles (case courtesy Dr. Joanne Wright).

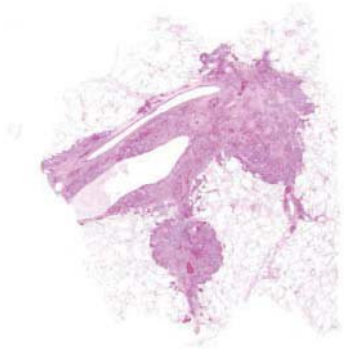


FIGURE 24.11. Kaposi sarcoma: Tumor spreads in a lymphangitic fashion around around a bronchovascular bundle.

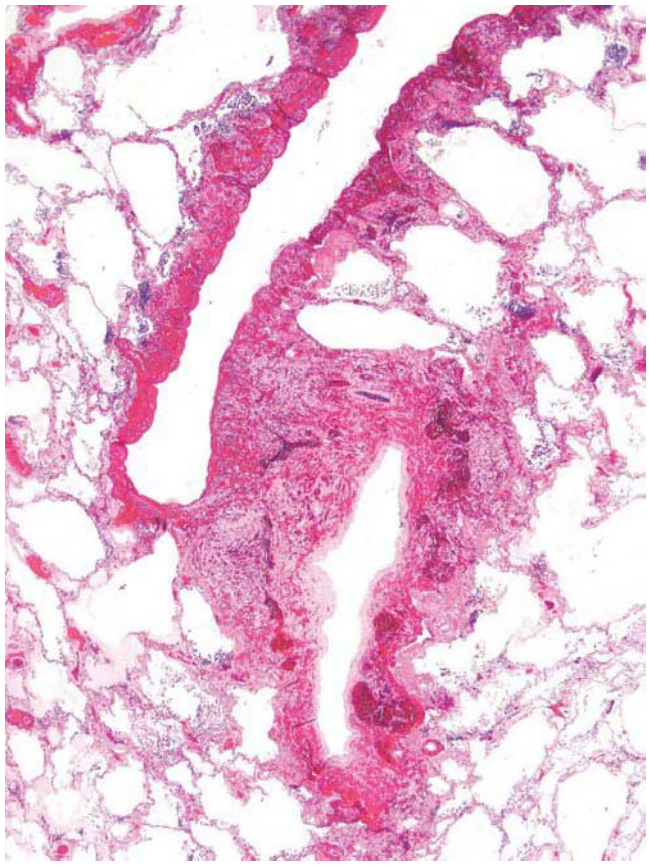


FIGURE 24.12. Kaposi sarcoma. In this example the lymphangitic tumor appears at low-power view as hemorrhage in the walls of the airway and vessel.

the whole interstitium (Figs. 24.18 and 24.19); and (3) as tumor masses.

High-grade lymphomas are cytologically obvious and frequently infiltrate vessels, but low-grade lymphomas with a lymphangitic distribution (Fig. 24.17) can mimic follicular bronchiolitis/lymphoid hyperplasia (Chapter 19). For diffuse low-grade lymphomas spreading through the interstitium (Fig. 24.18), the major differential diagnoses are lymphocytic interstitial pneumonia (LIP, see Chapter 19), cellular nonspecific interstitial pneumonia (NSIP, see Chapter 7), and hypersensitivity pneumonitis (HP, see Chapter 11).

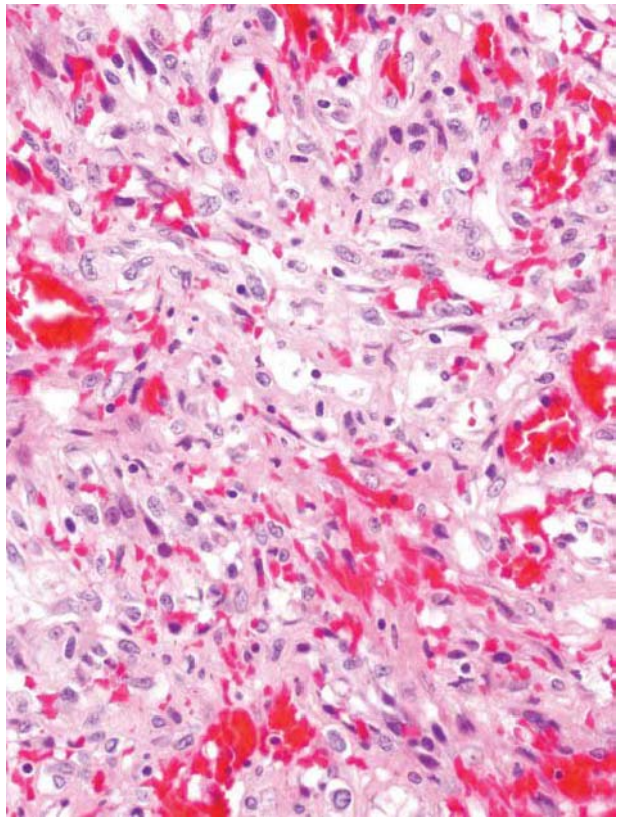


FIGURE 24.13. High-power view of Kaposi sarcoma showing spindle cells and extravasated red cells.

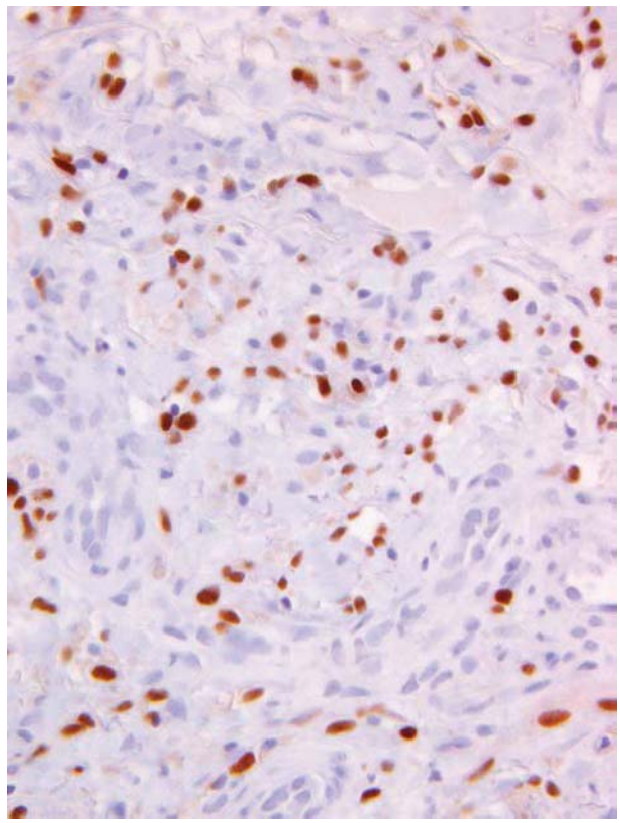


FIGURE 24.14. HHV8 staining in Kaposi sarcoma.

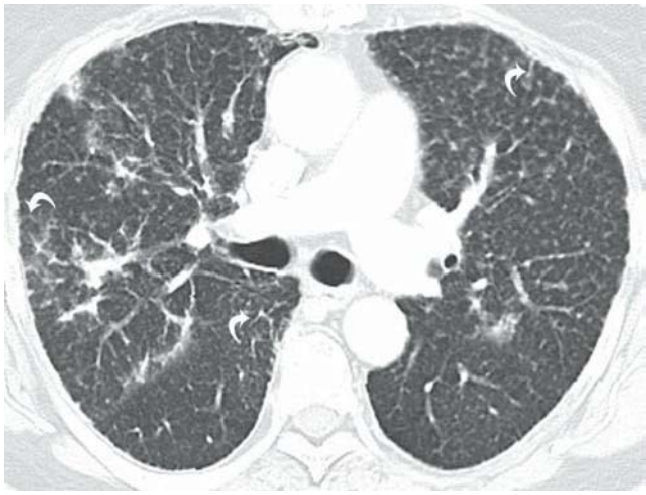


FIGURE 24.15. Pulmonary lymphoma. CT image shows numerous bilateral small nodules, bilateral thickening of the interlobular septa (*arrows*), patchy ground-glass opacities, and small foci of consolidation. The patient was a 64-year-old woman with pulmonary T-cell lymphoma following heart transplant.

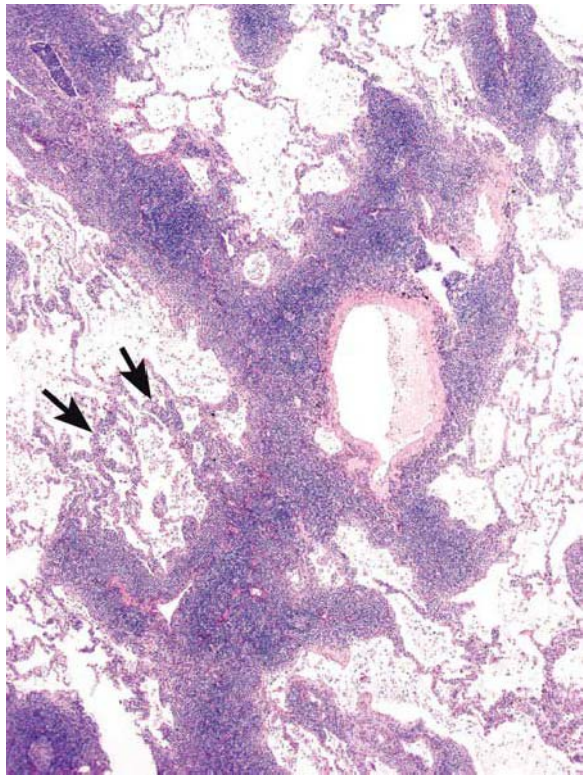


FIGURE 24.17. Lymphoma spreading in a lymphangitic fashion along the bronchovascular bundles and interlobular septa. There is also early spread into the interstitium (*arrows*).

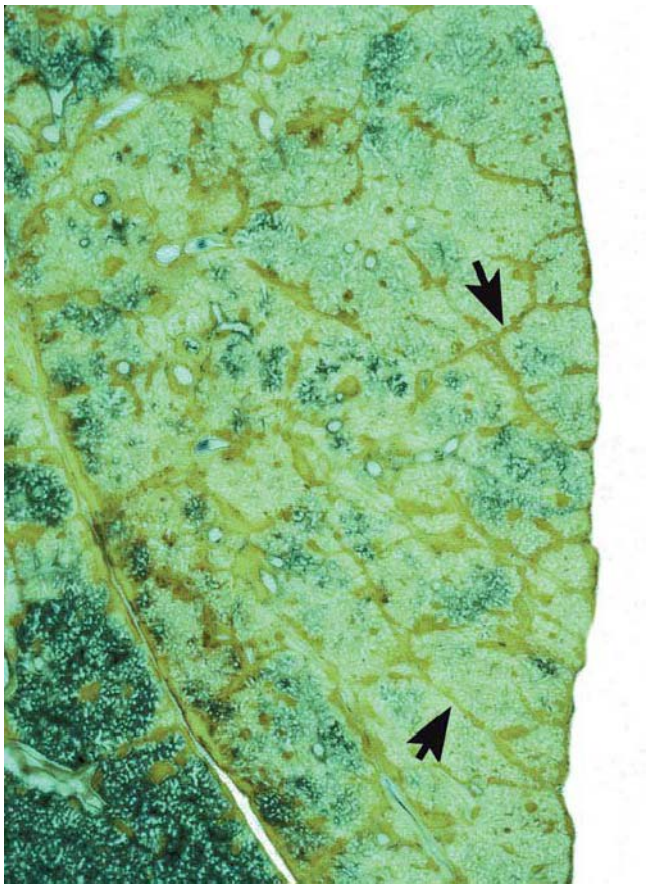


FIGURE 24.16. Gough (1-mm-thick whole lung) section showing lymphoma along the interlobular septa (*arrows*) and bronchovascular bundles; i.e., in a lymphangitic distribution.

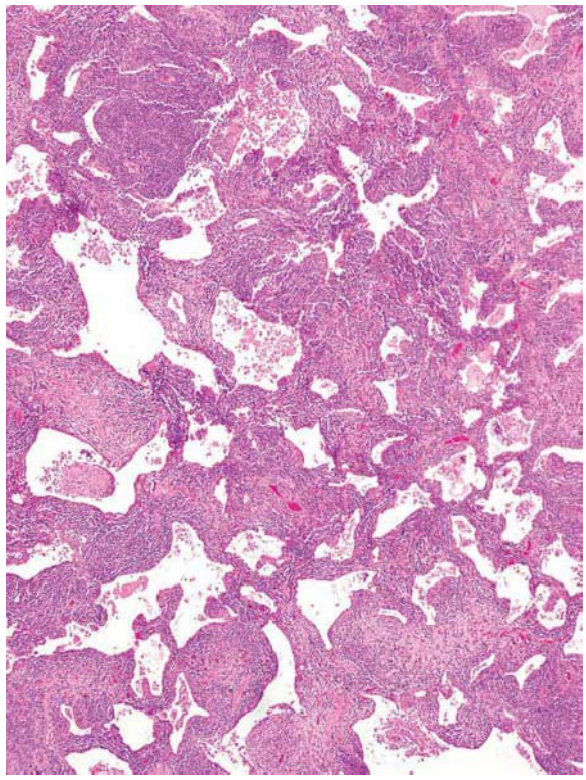


FIGURE 24.18. Low-power view of a MALT lymphoma spreading in the interstitium and widening the alveolar walls. The process mimics LIP (see Chapter 19).

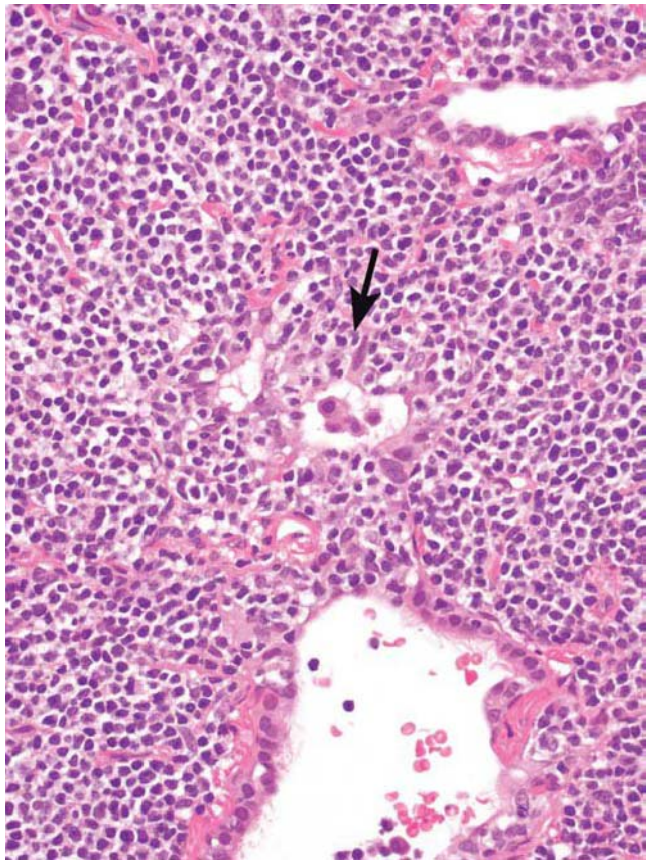
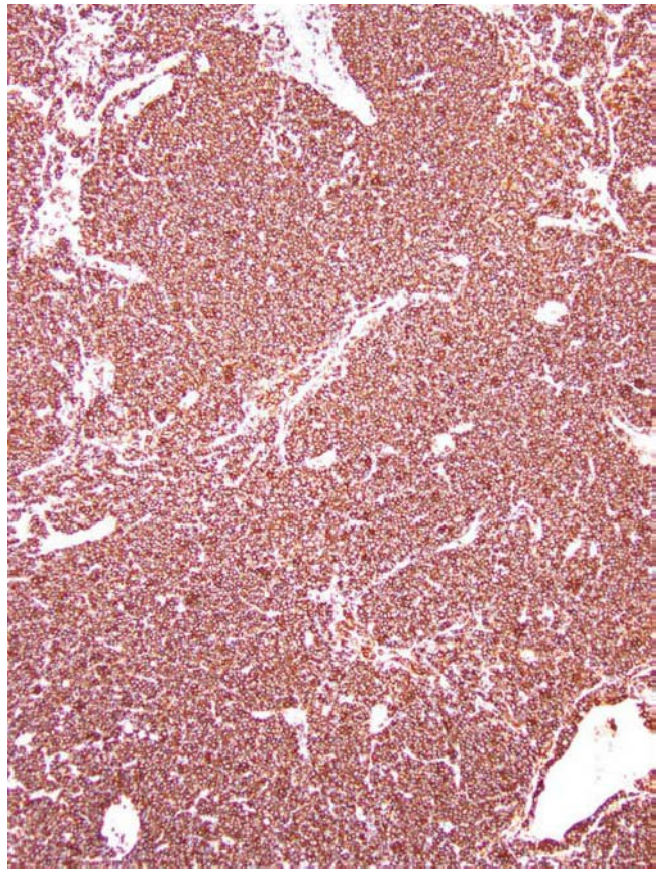


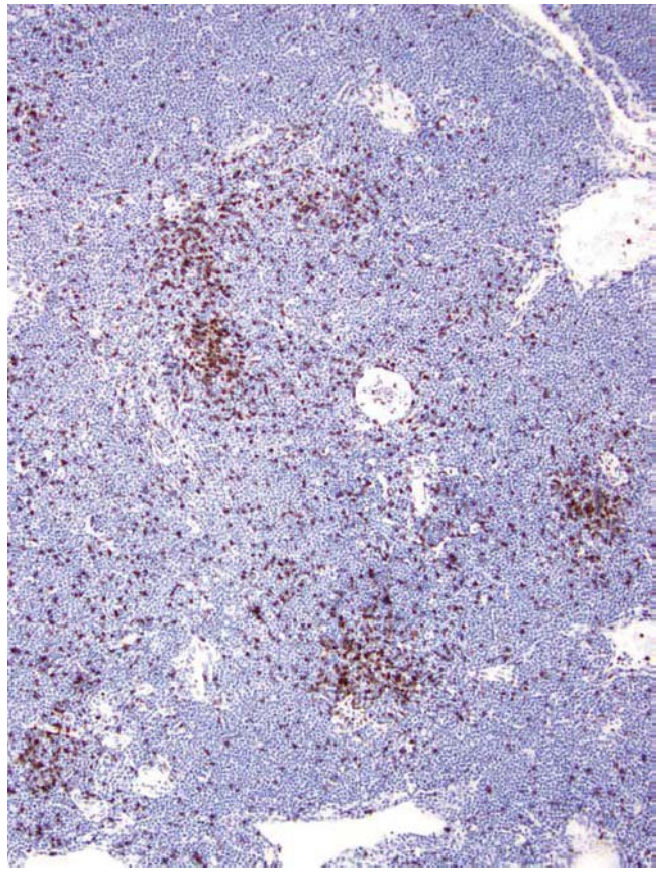
FIGURE 24.19. Another MALT lymphoma showing the monotony of the infiltrating cells and a lymphoepithelial lesion (*arrow*).

The features of these entities are compared in Chapter 19 (see Table 19.4). Most low-grade lymphomas that spread around the bronchovascular bundles or in the interstitium are cytologically monotonous (Fig. 24.19). However, residual germinal centers around bronchovascular bundles can produce a spurious appearance of a polymorphous population, and Hodgkin disease with a lymphangitic pattern can also appear polymorphous.

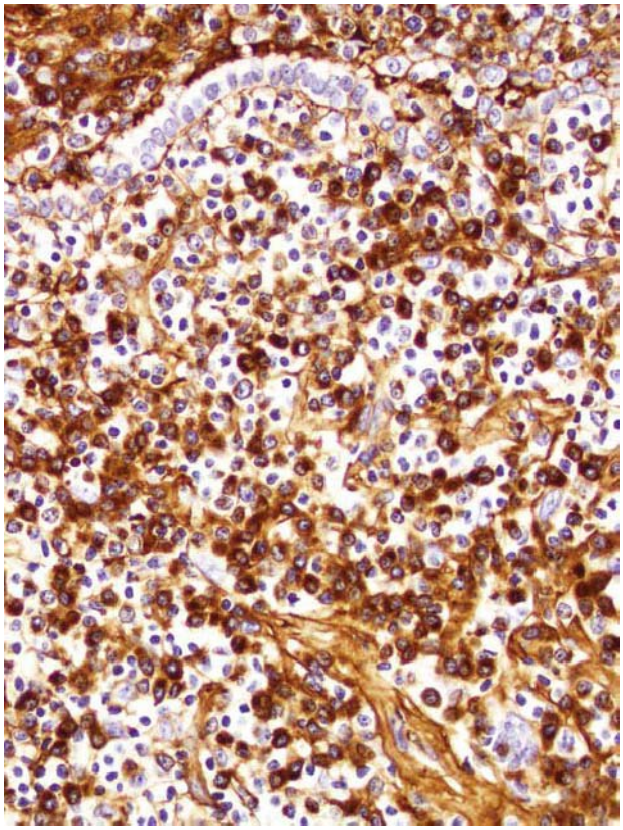
Lymphomas of all types typically produce a marked expansion of the interstitium and the combination of interstitial expansion and a monotonous cell population (Figs. 24.18 and 24.19) are the most important clues to the diagnosis; immunohistochemical (Figs 24.20 to 24.23) and/or molecular testing should be used to confirm the diagnosis. The interstitial expansion caused by lymphomas is generally much greater than one sees in cellular NSIP or HP, but LIP can also greatly expand the interstitium to the point of loss of alveolar spaces (see Figs. 19.10 to 19.16). In lymphomas the interstitial infiltrates may coalesce to give rise to true tumor masses. Some types of lymphomas, especially marginal zone lymphomas, tend to infiltrate bronchiolar epithelium, forming lymphoepithelial lesions (Fig. 24.19). Small noncaseating granulomas can be found not only in lymphomas but also in LIP and HP.

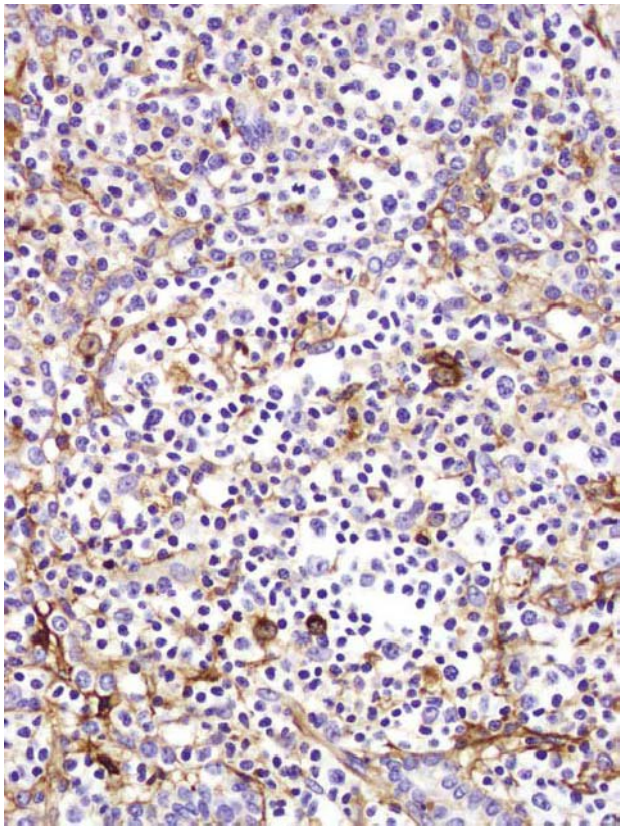
Leukemias can also spread in the interstitium to produce a pattern of lymphangitic or diffuse interstitial infiltration.





FIGURES 24.20 to 24.23. Legend appears on following page





FIGURES 24.20 to 24.23. Immunostaining of a MALT lymphoma reveals that it is composed almost entirely of B cells (Fig 24.21 CD20 and Fig 24.22 CD3). This example is kappa clonal (Figs. 24.22 kappa and 24.23 lambda). Compare the staining pattern of LIP as shown in Chapter 19, Figures 19.17 and 19.18.

These processes are almost always very diffuse and thus mimic cellular NSIP or LIP; however, except for chronic lymphocytic leukemia, the infiltrating cells are usually cytologically atypical. Intravascular lymphoma can be more subtle, with atypical cells in vessels in the interstitium but without marked interstitial cellularity or widening (Fig. 24.24).

Lymphangitic carcinoma is often grossly visible as fine white lines that outline the interlobular septa (Fig. 24.26) and create visually prominent bronchovascular bundles (Fig. 24.26). The process can be widespread as in Figures 24.26 and 24.27, or quite localized, particularly around primary lung cancers. Microscopically, lymphangitic carcinoma appears as individual or small groups of tumor cells that initially fill the lymphatics; that is, they are present in the visceral pleura, interlobular septa, and around the bronchovascular bundles (Figs. 24.28 and 24.29). Some tumors evoke a fibrotic reaction, particularly in the interlobular septa (Fig. 24.29). With time tumor tends to escape from lymphatics and can be found in the airspaces and/or in the vessels.

ARTIFACTUAL COLLAPSE OF THE LUNG PARENCHYMA PRODUCING A FALSE IMPRESSION OF INTERSTITIAL LUNG DISEASE

Collapse of lung biopsy specimens is one of the commonest causes of processes that, at first glance, look like ILD but are really collapse artifacts. In general if there is clear

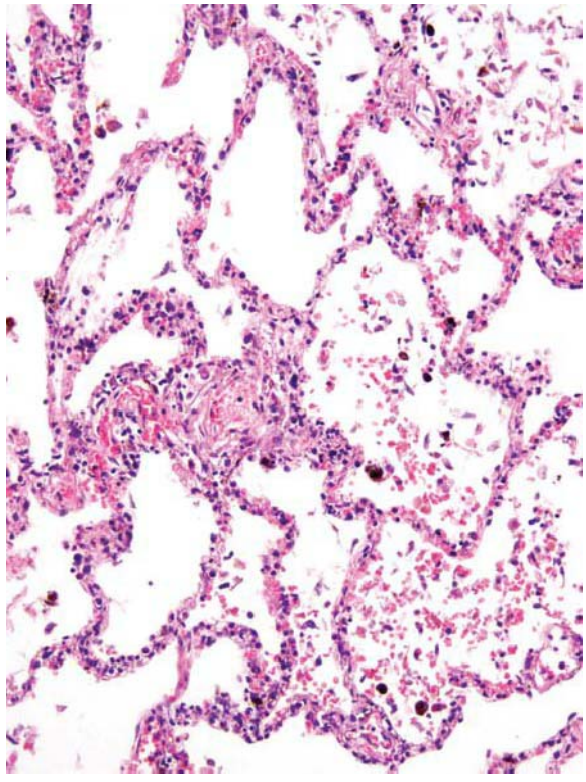


FIGURE 24.24. Intravascular lymphoma mimicking cellular NSIP.

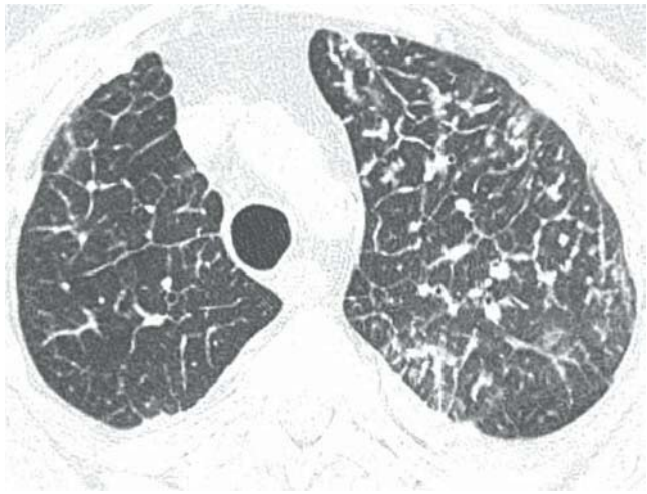


FIGURE 24.25. Lymphangitic carcinoma. HRCT shows extensive bilateral interlobular septal thickening and small pleural effusions in a patient with lymphangitic carcinoma secondary to metastatic carcinoma of the stomach.

old dense fibrosis this separation is not a problem, but the collapse can mimic mild interstitial fibrosis or cellular NSIP (Figs. 24.30 to 24.33 and see Chapter 7 for examples of NSIP)

There are no hard and fast rules about how to separate collapse from mild ILD, but layers of alveolar walls

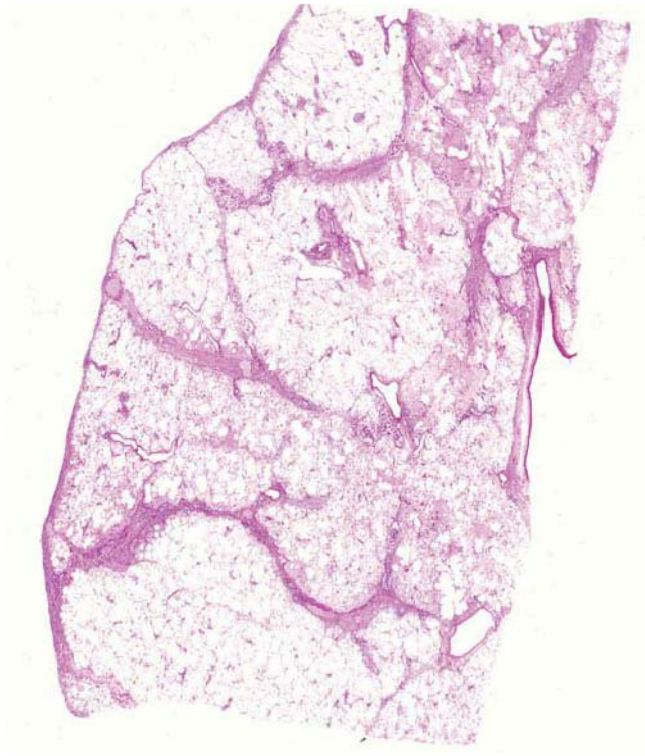


FIGURE 24.27. Lymphangitic carcinoma. Low-power view of the same case as Figure 24.26. Note the prominent, partially fibrotic, interlobular septa.

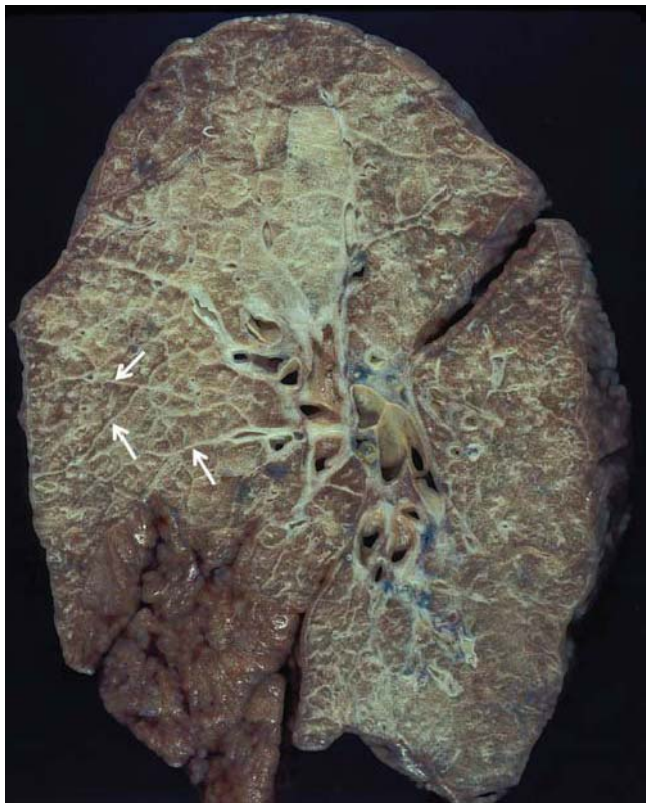
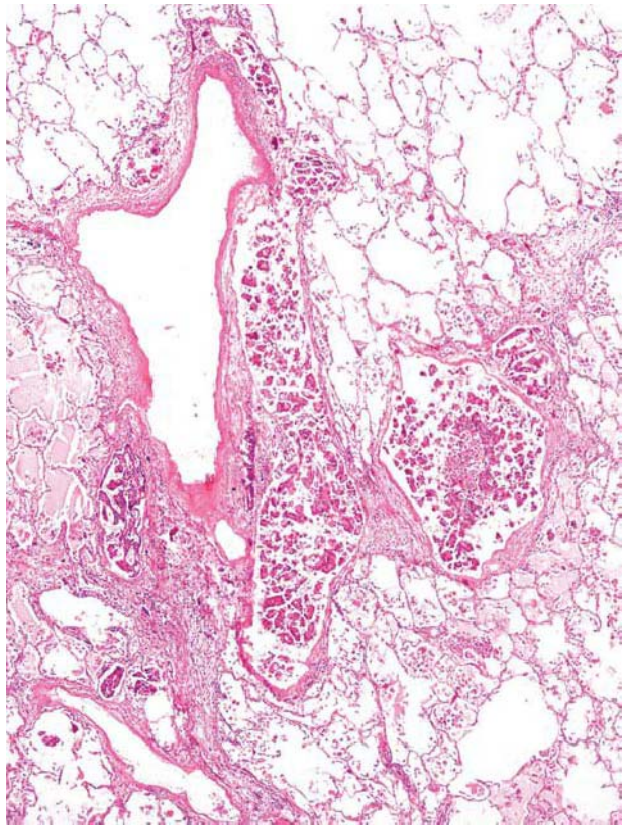
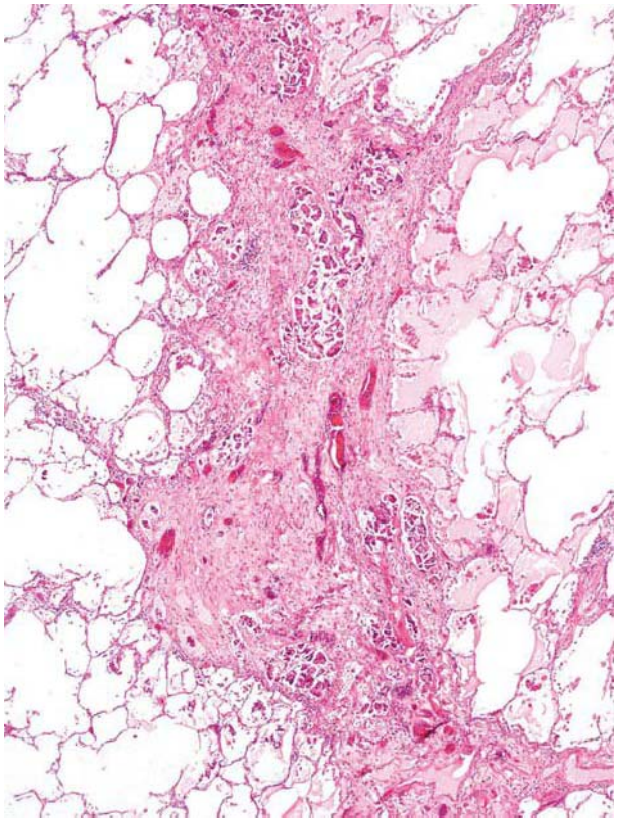


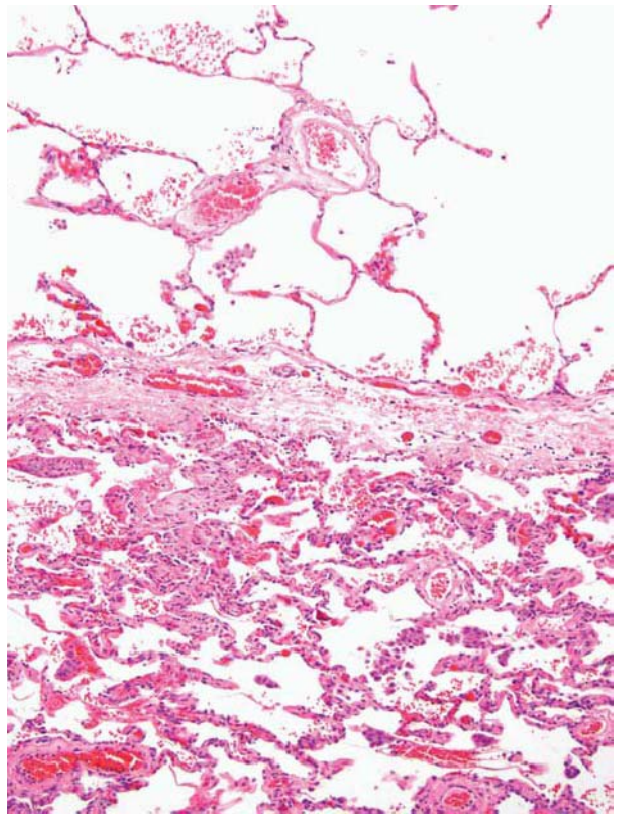
FIGURE 24.26. Gross photograph of lymphangitic tumor. The tumor appears as raised thickened interlobular septa (*arrows*) and bronchovascular bundles.



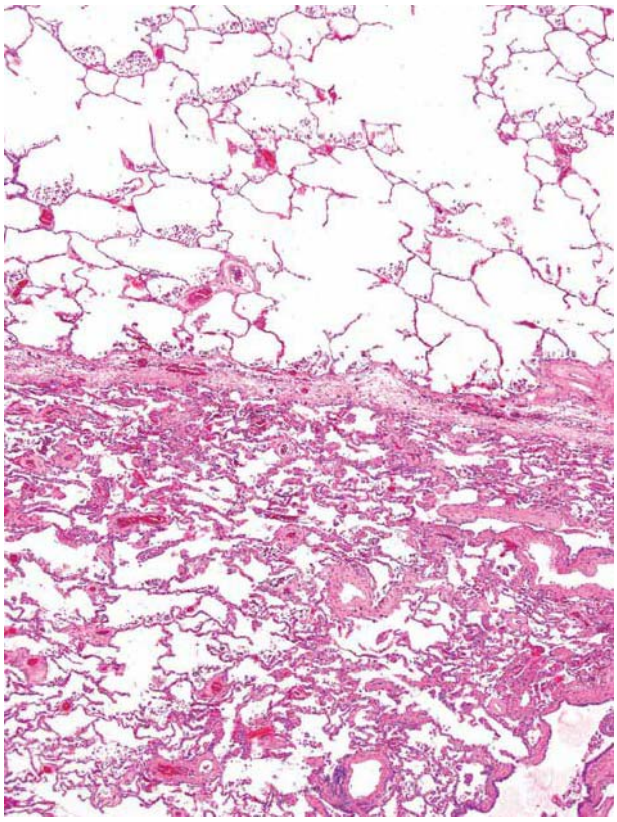
FIGURES 24.28 and 24.29. Legend appears on following page



FIGURES 24.28 and 24.29. Lymphangitic carcinoma. Higher-power views of the case shown in Figures 24.26 and 24.27. In Figure 24.28 tumor is present in lymphatics around a bronchovascular bundle; in Figure 24.29 tumor is present in lymphatics in an interlobular septum and has evoked a fibrotic reaction in the septum.



FIGURES 24.30 and 24.31. Collapse artifact mimicking ILD. Low- and high-power views of a lung in which the lobule at the top of the field has been inflated but the lobule at the bottom has not. The parenchyma in the upper portion is clearly normal whereas the parenchyma in the lower portion is partially collapsed and mimics fine fibrotic NSIP.



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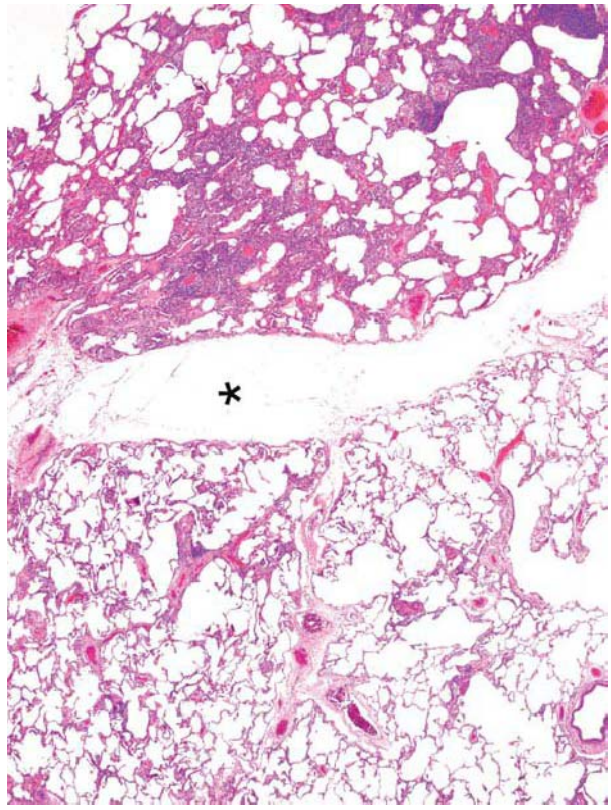

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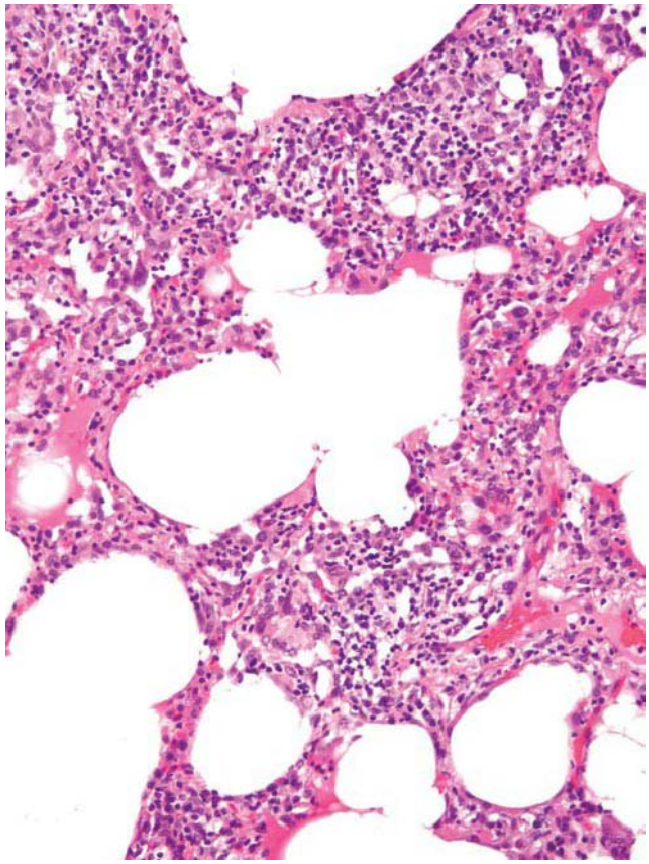

FIGURES 24.32 and 24.33. Collapse artifact mimicking ILD. Another example of a case in which one lobule has been inflated and the other not. The parenchyma in the inflated lobule is normal whereas that in the collapsed lobule appears to have interstitial inflammation. The rounded bubble shaped airspaces are a hint that the parenchyma is collapsed. The interlobular septum (*) is artifactually widened as a result of inflating the biopsy.

stacked one on top of another represent collapse. Elastic stains can be helpful in showing the stacking. Gradual transitions from obviously normal to increasingly "fibrotic" should be examined with care, because this is a common pattern of collapse, and often one can trace individual alveolar walls into the "fibrotic" area. A very common finding is that in collapsed areas the parenchyma has airspaces with rounded "bubble" configurations (Figs. 24.32 and 24.33).

Collapse cannot be avoided in transbronchial biopsies but inflation of surgical lung biopsies, wedge resections, and resected lobes/lungs is the best way to avoid collapse artifacts (see Chapter 3).

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Index

Note: Page numbers followed by *f* indicate figures; those followed by *t* indicate tables.