A large and diverse group of pathologic conditions manifests clinically and radiologically as diffuse parenchymal lung disease. In practice, this group of disorders has been categorized on the basis of clinical dysfunction (“restrictive lung disease”) or radiologic appearance (“interstitial lung disease [ILD]”), neither of which accurately reflects the pathologic processes involved [1]. Diffuse ILDs encompass mainly inflammatory processes that involve the structural elements of this organ. Some ILDs are caused by infections, but most are the result of immunologic, environmental, or toxic mechanisms. These diseases are discussed together because they have in common the tendency to produce bilateral abnormalities on chest imaging studies and are mainly nonneoplastic conditions [2]. Currently, less morbid sampling techniques have increased dramatically the probability that pulmonologists and their general pathology colleagues will be faced with establishing a specific and clinically relevant diagnosis using surgical lung biopsy material. Most of the concepts presented in this article have been established using this type of specimen.

In the early years of surgical lung biopsy, a small number of diffuse inflammatory conditions came to light that exclusively involved the lungs and did not seem to be caused by infection, toxin, sarcoidosis, pneumoconiosis, or neoplasm. Liebow is credited with recognizing these conditions and devising a classification system for them. These disorders came to be known as the idiopathic interstitial pneumonias [3]. The original classification proposed by Liebow is presented for historical purposes in Box 1. Much has changed in medical science over the years, and none of the entities proposed in Liebow’s original classification is viewed today exactly as he described them more than 30 years ago. A recent international consensus conference updated the classification of idiopathic interstitial pneumonias (Box 2) [4]. In this article, these “idiopathic” disorders are discussed in the context of their dominant pathologic findings rather than presented as a separate group of entities (as has been traditional in past). A comparison of the pathologic manifestations of the idiopathic ILDs is presented in Table 1.

Interpretation of lung biopsies in a patient with ILD is best accomplished using a multidisciplinary approach that results in a composite clinico-radiologic-pathologic diagnosis. Unfortunately, this is not always realistic in many clinical practice settings. For diffuse lung diseases, a pathologist must have some essential information regarding the clinical and radiologic findings to arrive at a clinically meaningful diagnosis. In many instances, more extensive clinical and radiologic consultation may be necessary. The pulmonologist who is conversant with the pathology of ILD is a powerful ally in this process.

Pattern analysis approach to surgical lung biopsies

The concept of “losing the forest for the trees” becomes evident in the evaluation of lung wedge biopsies. The age-old training method of requiring
that the microscope slide be evaluated first by the naked eye may seem overly methodical, but it does force the interpreter to see the “big picture” before getting lost in the fine details. For nonneoplastic lung diseases, the scanning low power objective (2× or 4×) is useful, if not essential, because different diseases give rise to different architectural patterns, which may immediately raise a narrow differential diagnosis. For diffuse lung diseases, several helpful patterns emerge.

**Pattern 1: acute lung injury**

The prototype of this pattern is diffuse alveolar damage (DAD) with hyaline membranes, classically encountered in the clinical setting of adult respiratory distress syndrome (ARDS) (Fig. 1).

**Pattern 2: fibrosis**

Lung diseases that lead to the accrual of collagen in the lung, with permanent structural remodeling, are represented by this pattern (Fig. 2). Idiopathic pulmonary fibrosis (IPF) (pathologic usual interstitial pneumonia [UIP]) is the prototype and is often the diagnosis of greatest clinical concern in older adult patients because of the dismal prognosis of this condition.

**Pattern 3: cellular interstitial infiltrates**

Lymphocytes, plasma cells, and macrophages are present in the alveolar walls in Pattern 3 (Fig. 3). Hypersensitivity pneumonitis (extrinsic allergic alveolitis) is the prototype of this pattern.

**Pattern 4: airspace filling**

This pattern is characterized by the presence of cells or other material filling the alveolar spaces (Fig. 4). Organizing pneumonia is the prototype of this pattern. The airspace filling pattern also includes infectious bronchopneumonias (neutrophils in the alveoli), classic Pneumocystis infection in the immunocompromised host (foamy casts in alveoli), pulmonary alveolar proteinosis (PAP) (proteinaceous material in alveoli), diffuse pulmonary hemorrhage (blood, siderophages, and patchy organizing pneumonia in alveoli), and DIP, in which lightly pigmented “smokers”-type macrophages are the dominant intra-alveolar element.

**Pattern 5: nodules**

The presence of discrete nodules (Fig. 5) in the lung parenchyma raises a differential diagnosis that includes nodular infections, benign and malignant neoplasms, sarcoidosis, Langerhans’ cell histiocytosis, and various bronchiolocentric diseases. The prototype is Wegener’s granulomatosis (large nodular pattern), but small (miliary) patterns of disease also are included.

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**Box 1. Liebow classification of interstitial pneumonia (1975)**

- Usual interstitial pneumonia (UIP)
- Bronchiolitis obliterans with usual interstitial pneumonia (BIP)
- Desquamative interstitial pneumonia (DIP)
- Lymphoid interstitial pneumonia (LIP)
- Giant cell interstitial pneumonia (GIP)


**Box 2. International Consensus Committee classification of idiopathic interstitial pneumonia (2002)**

- Acute interstitial pneumonia
- DIP/respiratory bronchiolitis–associated interstitial disease (RB-ILD)
- Cryptogenic organizing pneumonia (COP)
- Nonspecific interstitial pneumonia/fibrosis (NSIP/F)*
- LIP

*Provisional.

Pattern 6: near normal lung

The surgical lung biopsy that has barely discernible abnormalities is often the result of diseases that affect the airways and blood vessels of the lung. The changes may be subtle at low magnification. The prototype is small airways disease, in which pruning, dilatation, and generalized scarring of the small airways occur and this may be difficult to appreciate at scanning magnification. Vascular diseases (eg, pulmonary hypertension), cystic diseases (eg, lymphangiomyomatosis [LAM]), and conditions with patchy scarring also can produce subtle disease that results in what seems to be “normal” lung from scanning magnification (Fig. 6).

Once the dominant pattern is determined, additional microscopic findings help narrow the diagnostic possibilities. A list of these findings with their

Fig. 1. Pattern 1: acute lung injury. DAD with hyaline membranes, classically encountered in the clinical setting of ARDS, is the prototype of the acute lung injury pattern.

Fig. 2. Pattern 2: fibrosis. Lung diseases that lead to the accrual of collagen in the lung, with permanent structural remodeling, are represented by this pattern. IPF (pathologic UIP) often is the diagnosis of greatest clinical concern in older adult patients because of the dismal prognosis of this condition.
respective differential diagnosis is presented in Table 2. Overlap between patterns occurs and may be a useful clue in the differential diagnosis. For example, when nearly all of the six patterns are present in the same biopsy specimen, rheumatoid arthritis is often the correct diagnosis. Acute lung injury also proceeds through several distinctive histopathologic patterns during the repair phase after injury. If a lung biopsy is performed in the subacute phase of DAD, airspace organization may dominate the picture and potentially cause confusion with organizing pneumonia.

**Acute lung injury pattern (days to weeks in evolution, rapid onset of symptoms)**

The pattern of acute lung injury is characterized by variable interstitial and alveolar edema, fibrin in airspaces, and reactive type-II cell hyperplasia (Fig. 7). Hyaline membranes, neutrophils, necrosis, eosino-
<table>
<thead>
<tr>
<th>Acute lung injury</th>
<th>Fibrosis</th>
<th>Cellular interstitial pneumonia</th>
<th>Alveolar filling</th>
<th>Nodular</th>
<th>Minimal change</th>
</tr>
</thead>
<tbody>
<tr>
<td>With hyaline membranes</td>
<td>With variable fibrosis (normal to HC)</td>
<td>With lymphs and plasma cells C-NSIP, CVD</td>
<td>With macrophages Smoking-related</td>
<td>With lymphoid Follicular bronch</td>
<td>With SAD Constrictive bronchiolitis</td>
</tr>
<tr>
<td>Infection</td>
<td>CVD</td>
<td>UIP/IPF</td>
<td>HSP, drug</td>
<td>Local fibrosis</td>
<td>Wegener’s Lymphoma</td>
</tr>
<tr>
<td>Drug</td>
<td>Asbestosis</td>
<td>Infection</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>RA</td>
<td>Chronic HSP</td>
<td>Lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With eosinophils</td>
<td>With honeycombing only</td>
<td>With neutrophils</td>
<td></td>
<td>With necrosis</td>
<td>With vascular pathology</td>
</tr>
<tr>
<td>AEP</td>
<td>Diffuse</td>
<td>Infection</td>
<td>DPH</td>
<td>Infections</td>
<td>Tumor</td>
</tr>
<tr>
<td>Drug</td>
<td>Late UIP</td>
<td>CVD</td>
<td>Wegener’s</td>
<td>PHT</td>
<td></td>
</tr>
<tr>
<td>DAD in smoker</td>
<td>Focal</td>
<td>Hemorrhage</td>
<td></td>
<td>VOD</td>
<td></td>
</tr>
<tr>
<td>With necrosis</td>
<td>With diffuse fibrosis</td>
<td>With granulomas</td>
<td>With OP</td>
<td>With atypical cells</td>
<td>With cysts</td>
</tr>
<tr>
<td>Infections</td>
<td>CVD</td>
<td>Infection, HSP, sarcoid/berylliosis, aspiration</td>
<td>Infection, drug CVD</td>
<td>Infections, Ca</td>
<td>PLCH</td>
</tr>
<tr>
<td>Viral</td>
<td>Drug</td>
<td>With eosinophilic material</td>
<td>With sarcomas</td>
<td>Lymphomas</td>
<td>LAM</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Sarcoi (with granulomas)</td>
<td>Infection. CVD, Drug, DPH CHF, PAP</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fungal</td>
<td>PLCH (with stellate scars) Pneumococcosis F-NSIP</td>
<td>With focal OP</td>
<td>With hemorrhage</td>
<td>With OP</td>
<td></td>
</tr>
<tr>
<td>With siderophages</td>
<td>With pleuritis</td>
<td>With pleuritis</td>
<td></td>
<td>Infections, CVD</td>
<td></td>
</tr>
<tr>
<td>DPH</td>
<td>CVD</td>
<td></td>
<td>CVD</td>
<td>Drug, Wegener’s</td>
<td>Infarct</td>
</tr>
<tr>
<td>CVD</td>
<td></td>
<td></td>
<td>DPH</td>
<td></td>
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</tbody>
</table>

Abbreviations: AEP, acute eosinophilic pneumonia; bronch, bronchiolitis; CHF, congestive heart failure; C-NSIP, cellular NSIP; CVD, collagen vascular disease; DPH, diffuse pulmonary hemorrhage; Drug, drug toxicity; F-NSIP, fibrotic NSIP; HC, honeycomb; HSP, hypersensitivity pneumonitis; OP, organizing pneumonia; PHT, pulmonary hypertension; PLCH, pulmonary Langerhans cell histiocytosis; RA, rheumatoid arthritis; SAD, small airways disease; VOD, veno-occlusive disease.
philms, and siderophages are the qualifying elements to be searched for once this pattern is identified. When hyaline membranes are present (Fig. 8), the term “diffuse alveolar damage” is appropriate (see later discussion). The differential diagnosis in the setting of DAD always includes infection at the top of the list, but several other causes must be considered once infection has been reasonably excluded (Box 3).

**Adult respiratory distress syndrome and diffuse alveolar damage**

The clinical prototype of acute lung disease is ARDS. ARDS is a relatively common condition in the United States, where it is estimated to occur at a rate of 150,000 cases per year. The pathologic manifestation of ARDS is DAD. Although DAD is the prototypic manifestation of ARDS, pathologic DAD does not necessarily correspond to the clinical entity of ARDS. In current practice in the United States, most cases of DAD arise as a consequence of lung infection or immunologically mediated acute pulmonary injury.

**Box 3. Causes of diffuse alveolar damage**

- **Infections**
  - *Pneumocystis jiroveci*
  - Viruses (eg, influenza, cytomegalovirus, varicella, and adenovirus)
  - Fungi (eg, blastomycosis, aspergillosis)
  - *Legionella* sp.

- **Toxins**
  - Inhaled toxins (eg, O₂ NO₂, household ammonia and bleach, mercury vapor)
  - Ingested toxins (eg, paraquat)

- **Drugs**
  - Cytotoxic (eg, azathioprine, carmustine [BCNU], bleomycin, busulfan, lomustine [CCNU], cyclophosphamide, melphalan, methotrexate, mitomycin, procarbazine, teniposide, vinblastin, and zinostatin)
  - Noncytotoxic (eg, amiodarone, amitriptyline, colchicine, gold salts, hexamethonium, nitrofurantoin, penicillamine, streptokinase, sulphathiozole)
  - Illicit (heroin)

- **Shock**
- **Trauma**
- **Sepsis**
- **Cardiogenesis**
- **Radiation**
- **Miscellaneous**
- **Acute pancreatitis**

lung injury related to drug toxicity or connective tissue disease. In the immunocompromised patient, infection dominates this picture.

Infections

A complete discussion of pulmonary infections that produce acute lung injury is beyond the scope of this article. Bacteria, fungi, and viruses can produce acute lung injury and are the diagnosis of exclusion in this setting. Viruses are the most common of these infections to cause diffuse acute lung injury. The more common viruses that cause pneumonia and their susceptible hosts are presented in Table 3.

Drugs and radiation reactions

Medications taken orally or by injection may produce various lesions within the lung, including DAD, pulmonary edema, asthma, eosinophilic pneumonia, and even advanced fibrosis [5,6]. For many drugs, acute and chronic forms of toxicity have been reported. This discussion emphasizes a few reactions that classically manifest as acute lung disease and highlight those that may produce chronic disease.

Nitrofurantoin

Nitrofurantoin is an antimicrobial agent used in the treatment of urinary tract infections. This agent is responsible for more cases of pulmonary toxicity than any other drug, with acute and chronic reactions reported [7,8]. Acute reactions are accompanied by fever, dyspnea, and peripheral eosinophilia, which typically appear within 2 weeks of initiating therapy. The histopathologic findings are similar to those of acute eosinophilic pneumonia. Chronic reactions occur in a few patients taking the drug, and clinical manifestations appear after 1 to 6 months of treatment. The chronic cases are more often subjected to biopsy and show interstitial inflammation and fibrosis accompanied by vascular sclerosis.

Cytotoxic chemotherapeutic drugs

The most common group of drugs that produces acute lung injury includes the antineoplastic agents. From a clinical standpoint, some drugs (eg, 5-fluorouracil, vinblastine, cytarabine, adriamycin, thiopeta, azathioprine) almost never produce pulmonary disease. With increasing numbers of newer antineoplastic agents being used, pulmonary toxicity undoubtedly will increase. Excellent on-line resources that provide comprehensive and up-to-date lists of these agents are available [9].

Analgesics

Heroin [10], methadone, propoxyphene, and even aspirin can produce acute lung reactions [11,12]. Toxicity typically results from overdose and is characterized by pulmonary edema, sometimes complicated by aspiration of gastric contents. When pill binding agents, such as talc or microcrystalline cellulose, are injected with a drug intravenously, a foreign body giant cell reaction may be seen in lung tissue in a characteristic perivascular distribution.

Radiation pneumonitis

Radiation therapy was a common cause of acute lung injury before improved technology and modifications in dosing were instituted [13]. Radiation injury can be exacerbated by infection [14] and chemotherapeutic drugs [15]. Initial clinical signs and symptoms often are absent or mild. In the acute phase, chest radiographs and high-resolution CT (HRCT) reveal ground-glass opacities or airspace consolidation with some loss of lung volume.

Acute eosinophilic lung disease

Acute lung injury that occurs in the presence of significant numbers of tissue eosinophils is referred to as “acute eosinophilic lung disease.” Peripheral blood and bronchoalveolar lavage eosinophils are commonly elevated in these conditions. Eosinophilia may not be persistent throughout the disease, and eosinophilic vasculitis is not a prerequisite for the diagnosis in lung tissue. Several forms have been
described over the years, the mildest of which has been referred to as Loeffler syndrome or simple eosinophilic pneumonia. Ascaris infestation was documented eventually in the initial series by Loeffler, which led to the hypothesis that simple eosinophilic pneumonia was a manifestation of hypersensitivity to Ascaris antigens.

The second form occurs commonly in patients with asthma, presumably as an allergic manifestation to an unknown antigen. The clinical course is more chronic and typically evolves slowly over many months. Patients with the “chronic” form of eosinophilic pneumonia may have a typical clinical syndrome and radiographic appearance [16].

Finally, a dramatic new manifestation of idiopathic eosinophilic lung disease has been described that is characterized by rapid onset of breathlessness in an otherwise healthy young adult without asthma [17]. This form may mimic DAD clinically and pathologically, even with the presence of hyaline membranes. The importance of recognizing this entity lies in its excellent prognosis and characteristic rapid response to corticosteroid therapy.

Some other well-recognized associations have been described with eosinophilic pneumonia. The best example is that produced by sensitivity to nitrofurantoin and other drugs. Eosinophilic pneumonia, in the presence of asthma, may be a manifestation of hypersensitivity to aspergillus and other fungal organisms (eg, allergic bronchopulmonary fungal disease).

The histopathologic features of eosinophilic pneumonia include intra-alveolar eosinophils, fibrin, and plump eosinophilic macrophages, surrounded by striking reactive type II cell hyperplasia (Fig. 9).

Acute fibrinous pleuritis may occur. Eosinophilic microabscesses and eosinophilic vasculitis may be present but are not necessary for the diagnosis (Fig. 10).

**Acute pulmonary manifestations of the collagen vascular diseases**

The most common acute manifestation of the collagen vascular diseases is DAD, but diffuse pulmonary hemorrhage also occurs. The more common collagen vascular diseases that produce acute manifestations are presented herein.

Fig. 9. Eosinophilic pneumonia. The histopathologic features of eosinophilic pneumonia are characterized by intra-alveolar eosinophils, fibrin, and plump eosinophilic macrophages, surrounded by striking reactive type II cell hyperplasia. (A) Low magnification with parenchymal consolidation. (B) Prominent fibrin in airspaces with eosinophils and reactive type II cells.

Fig. 10. Eosinophilic pneumonia. Eosinophilic microabscesses and eosinophilic vasculitis may be present but are not necessary for the diagnosis.
Rheumatoid arthritis

Nearly one-half of all patients with rheumatoid arthritis (RA) develop one or more forms of rheumatoid lung disease [18], and patients with more severe joint involvement are more likely to develop pleuropulmonary manifestations. Lung disease typically follows the development of joint disease, but occasionally, the lung or pleura may herald the disease. DAD is a well-recognized complication of RA [19].

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) also commonly involves the lungs and pleura [18]. Painful pleuritis with or without effusion is the most common abnormality [20], but acute lupus pneumonitis is a potentially disastrous complication, with a mortality rate of 50% [21]. Acute lupus pneumonitis is characterized morphologically by DAD. Diffuse pulmonary hemorrhage also may occur, usually accompanied by vasculitis and capillaritis (Fig. 11). Immune complexes may be identified on capillary basement membranes in this setting [22].

Dermatomyositis-polymyositis

DAD is not common in dermatomyositis-polymyositis, but the clinical presentation may be particularly dramatic. Tazelaar et al [23] presented 14 patients with dermatomyositis-polymyositis who developed lung disease. Three patients developed DAD, all of whom died, most frequently in the acute episode. The authors also reviewed 27 additional cases of dermatomyositis-polymyositis lung disease reported in the literature and found similar results. DAD may be the first clinical manifestation of dermatomyositis-polymyositis and may precede the clinical and serologic diagnosis of the disease by many months.

Acute fibrinous and organizing pneumonia

A new entity with some similarities to DAD recently has been described, and it is termed “acute fibrinous and organizing pneumonia” [24]. Acute fibrinous and organizing pneumonia can be patchy and typically lacks hyaline membranes but is rich in fibrinous alveolar exudates (Fig. 12) without evi-

Fig. 11. Acute lupus pneumonitis is a serious complication of SLE. The pattern is acute lung injury (A) with or without hyaline membranes. Diffuse pulmonary hemorrhage also may occur, usually accompanied by vasculitis (B) and capillaritis.

Fig. 12. Acute fibrinous and organizing pneumonia. This condition typically lacks hyaline membranes but is rich in fibrinous alveolar exudates.
dence of infection. Like DAD, acute fibrinous and organizing pneumonia can be idiopathic or associated with several underlying or associated conditions, such as collagen vascular disease, drug reaction, and occupational exposures. Survival is similar to DAD in general, but the requirement for mechanical ventilation was associated with a worse prognosis.

**Acute diffuse alveolar hemorrhage**

Diffuse alveolar hemorrhage (DAH) is characterized by a triad of (1) hemoptysis, (2) anemia, and (3) bilateral ground-glass opacities (or consolidation) that rapidly wax and wane. Hemorrhage and hemosiderin-laden macrophages in alveolar spaces are essential to the pathologic diagnosis [25–27]. In practice, artifactual hemorrhage can occur commonly in lung biopsy specimens. Hemosiderin-laden macrophages (with coarsely granular, golden-brown refractile pigment) always should be present in the alveolar spaces before one invokes the diagnosis of DAH (Fig. 13). The differential diagnosis of DAH is presented in Box 4.

**Antiglomerular basement membrane disease (Goodpasture’s syndrome)**

When diffuse pulmonary hemorrhage occurs with renal disease in the presence of circulating antibodies against glomerular basement membranes, the condition is referred to as antiglomerular basement membrane disease [28–31]. Lung biopsy is less desirable than kidney as a diagnostic specimen in antiglomerular basement membrane disease, but because renal disease is commonly occult at the time of presentation, the lung is often the first tissue sample examined by the pathologist. Unfortunately, the lung findings are relatively nonspecific and consist of fresh alveolar hemorrhage, hemosiderin deposition in macrophages (siderophages), and variable interstitial inflammation with delicate interstitial fibrosis (Fig. 14). The presence of capillaritis in the alveolar wall is also helpful in distinguishing antiglomerular basement membrane disease from idiopathic pulmonary hemosiderosis (IPH) and chronic passive lung congestion. The results of immunofluorescent studies on lung tissue are not as reliable as they are on kidney tissue [30], and for cost-effective practice, we generally recommend serologic confirmation (radioimmunoassay or ELISA), even when appropriately preserved lung tissue is available.

**Diffuse alveolar hemorrhage associated with the systemic collagen vascular diseases**

DAH may occur as a consequence of several immune-mediated vasculitides, including those that

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**Box 4. Causes of diffuse alveolar hemorrhage**

- Goodpasture’s syndrome (antiglomerular basement membrane antibody disease)
- Vasculitides (especially Wegener’s granulomatosis)
- Mitral stenosis
- IgA nephropathy
- Behçet’s syndrome
- Certain systemic collagen vascular diseases (especially SLE)
- HIV infection
- Antiphospholipid syndrome
- Pulmonary veno-occlusive disease
- Idiopathic pulmonary hemosiderosis
- Drug reactions, including toxic reactions and anticoagulants
- Acute lung allograft rejection
- Unclassified forms

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**Fig. 13. DAH. Fresh blood in the lung is not sufficient evidence for a diagnosis of DAH. Hemosiderin-laden macrophages with coarsely granular, golden-brown refractile pigment always should be present.**
occur in the setting of collagen vascular disease. Potential causes of DAH in this setting include microscopic polyangiitis, SLE, Wegener’s granulomatosis, cryoglobulinemia, RA, crescentic glomerulonephritis, and scleroderma [25,27,29,30]. The common histopathologic feature is acute capillaritis, with or without larger vessel vasculitis (Fig. 15).

Idiopathic pulmonary hemosiderosis

In the absence of renal disease or demonstrable immunologic disease, DAH has been termed IPH. IPH occurs most commonly in children younger than 10 years and young adults in the second and third decades of life. Anemia is accompanied by bilateral areas of consolidation on the chest radiograph. The sexes are equally affected in the younger age group, but men predominate in the older age group. The histopathology is similar to that of antiglomerular basement membrane disease, namely, alveolar hemorrhage and hemosiderin-laden macrophages, but in IPH there is less interstitial inflammation and more fibrosis (Fig. 16). By definition,

Fig. 14. Antiglomerular basement membrane disease. The lung findings consist of fresh alveolar hemorrhage, hemosiderin deposition in macrophages (siderophages), and variable interstitial inflammation with delicate interstitial fibrosis (A). At higher magnification, hemosiderin-laden macrophages are present (B).

Fig. 15. DAH in the collagen vascular diseases. The common histopathologic feature of DAH in the setting of connective tissue disease is acute capillaritis (A) with or without larger vessel vasculitis (B).
tissue immunoglobulin studies and electron microscopy are nondiagnostic.

Idiopathic diffuse alveolar damage: acute interstitial pneumonia

The term “acute interstitial pneumonia” was first introduced in 1986 to describe a syndrome of rapidly evolving acute respiratory failure that occurred in immunocompetent individuals [32]. The patients described included three men and five women (two of whom were pregnant) who developed sudden unexplained respiratory failure. Six reported a viral-like prodrome. None of the patients was reported to have underlying collagen vascular disease. By definition, acute interstitial pneumonia is of unknown cause and is a diagnosis of exclusion. The usual causes of ARDS must be absent (ie, shock, sepsis, trauma, aspiration, or drug toxicity).

Surgical lung biopsies show DAD in varying stages (Fig. 17). The changes observed in biopsy specimens depend on the stage at which the biopsy is taken and tend to be relatively diffuse throughout the specimen. Like other forms of DAD, the early stages show an exudative phase with edema and hyaline membranes. Bronchioles may show squamous metaplasia that extend peripherally to involve adjacent alveolar walls. Organizing arterial thrombi were seen in five of the seven patients who died in the Katzenstein series [32]. In the last stages, fibrosis distorts the lung architecture.

Collagen vascular disease or allergic disorders may be responsible for many cases of acute interstitial pneumonia, although they may not be clinically apparent at the time of presentation. acute interstitial pneumonia has been formally added to the classification of the idiopathic interstitial pneumonias by a recent international consensus committee [4].

Pattern 2: interstitial lung disease dominated by fibrosis (typically months to years in evolution)

A large number of systemic diseases, inhalational exposures, toxins and drugs, and even genetic disorders are well known to cause scarring in the lungs with permanent structural remodeling. A list of these diseases is presented in Box 5. UIP is the most notorious of these diseases and is the diagnosis of exclusion for patients over the age of 50 because of the dismal prognosis of this idiopathic condition. In younger patients, the systemic connective tissue diseases figure prominently as causes of chronic lung disease with fibrosis.

Pulmonary fibrosis in the systemic connective tissue diseases

The collagen vascular diseases as a group involve the respiratory system frequently. Each of these diseases may involve the lung and pleura in several different ways. Although the lung morphologic abnormalities are not specific for any one of these diseases, some features are more commonly manifested than others in each of them (Table 4). A few of the more prominent collagen vascular diseases known to produce fibrosis are presented herein.

Rheumatoid arthritis

The most common thoracic complication of RA is pleural disease (effusion or pleuritis), which is seen in as much as 50% of patients in autopsy studies. According to a study by Walker and Wright [33], approximately one-third of the patients with pleural effusions also have pulmonary manifestations of RA in the form of nodules or interstitial disease. Nodules may be seen in the lung parenchyma and occasionally in the walls of airways in persons with RA, which represents lymphoid hyperplasia with germinal centers in most instances (Fig. 18). The interstitial pneumonia of RA may be cellular with little fibrosis (cellular NSIP-like, see later discussion), fibrotic with honeycomb cystic remodeling (UIP-like, see later discussion), and occasionally may have a macrophage-rich DIP pattern (discussed in Pattern 4) [19].
Systemic lupus erythematosus

Similar to RA, SLE also commonly involves the respiratory system [18]. Painful pleuritis with or without effusion is the most common abnormality [20]. Noninfectious organizing pneumonia also has been reported, and advanced fibrosis with honeycomb remodeling occurs (Fig. 19) [34].

Progressive systemic sclerosis

The most notable feature of “scleroderma lung” is the presence of extensive alveolar wall fibrosis without much inflammation (Fig. 20) [35]. Some degree of diffuse lung fibrosis occurs in nearly every patient with pulmonary involvement [18]. Patients with longstanding progressive systemic sclerosis–related lung fibrosis are at high risk of developing bronchoalveolar carcinoma. Vascular sclerosis, usually without true vasculitis, is typical; if sufficiently severe, it produces pulmonary hypertension [36]. Pleural disease is less common in progressive systemic sclerosis than in RA or SLE.

Mixed connective tissue disease

Mixed connective tissue disease is relatively common in producing interstitial pulmonary disease or pleural effusions [18]. In many cases, the abnormalities respond well to corticosteroid therapy, but severe and progressive pulmonary disease with
fibrosis does occur. A pattern of fibrosis that resembles the pattern seen in UIP (see later discussion) occurs, and pulmonary hypertension may occur, accompanied by plexiform lesions similar to those seen in persons with primary pulmonary hypertension [37].

Dermatomyositis/Polymyositis

Several forms of ILD have been reported in dermatomyositis/polymyositis, and the histologic findings seen on biopsy seem to be better predictors of prognosis than clinical or radiologic features [23]. A subacute presentation with a noninfectious organizing pneumonia pattern has been associated with the best prognosis, whereas the worst prognosis has been associated with advanced lung fibrosis [23].

Sjögren’s syndrome

The common pulmonary lesions of Sjögren’s syndrome generally evolve over weeks to months and are analogous to the disease manifestations in the salivary glands. The range of disease patterns in Sjögren’s syndrome is broad, especially when Sjögren’s syndrome is accompanied by other connective tissue disease. A hallmark of pure Sjögren's syndrome in the lung is marked lymphoreticular infiltrates in the submucosal glands of the tracheobronchial tree (Fig. 21) [18]. Patients with Sjögren’s syndrome also are at risk for LIP and occasionally develop lymphoproliferative disorders that involve the pulmonary interstitium, ranging from relatively low-grade extranodal marginal zone lymphoma (MALToma) to a high-grade lymphoma. Advanced lung fibrosis also occurs as pleuropulmonary manifestation in Sjögren’s syndrome (Fig. 22) [38,39].

Certain chronic drug reactions

Many drugs are reported to produce lung fibrosis, among them bleomycin, carmustine, penicillamine, nitrofurantoin, mexiletine, amiodarone, aza-thioprine, methotrexate, melphalan, and mitomycin C. Unfortunately, the list of agents is growing rapidly, and the reader is referred to on-line resources such as www.pneumotox.com [188] for continuously updated information on reported drug reactions. Bleomycin is presented in this article because it causes subacute and chronic toxicity and has been used widely as an experimental model of pulmonary fibrosis.

Bleomycin

Bleomycin is an antineoplastic agent that becomes concentrated in skin, lungs, and lymphatic fluid. Pulmonary lesions may be dose-related [40,41], and prior radiotherapy seems to predispose to toxicity [42]. The initial site of injury in experimental models seems to be the venous endothelial cell [43], but type I cell injury allows fibrin and other serum proteins to leak into the alveolus. Type II cell hyperplasia occurs as a regenerative phenomenon that results in atypical enlarged forms, and intra-alveolar fibroplasia occurs (often in a subpleural distribution), eventually resulting in alveolar septal widening (Fig. 23).

Hermansky-Pudlak syndrome

The Hermansky-Pudlak syndromes are a group of autosomal-recessive inherited genetic disorders that share oculocutaneous albinism, platelet storage pool deficiency, and variable tissue lipofuscinosis [44–46]. The most common form of Hermansky-

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**Box 5. Diseases with fibrosis and honeycombing**

| Idiopathic pulmonary fibrosis (idiopathic UIP) |
| DIP |
| Lymphocytic interstitial pneumonia |
| Systemic collagen vascular disease |
| Chronic drug reactions |
| Pneumoconioses (eg, asbestosis, berylliosis, silicosis, hard metal pneumoconiosis) |
| Sarcoidosis |
| Pulmonary Langerhans’ cell histiocytosis (PLCH; histiocytosis X) |
| Chronic granulomatous infections |
| Chronic aspiration |
| Chronic hypersensitivity pneumonitis |
| Organized chronic eosinophilic pneumonia |
| Organized and organizing DAD |
| Chronic interstitial pulmonary edema/passive congestion |
| Radiation (chronic) |
| Healed infectious pneumonias and other inflammatory processes |

Pudlak syndrome arises from a 16-base pair duplication in the *HPS1* gene at exon 15 on the long arm of chromosome 10 (10q23) [47]. This form is referred to as *HPS1* and is associated with progressive, lethal pulmonary fibrosis. *HPS1* affects between 400 and 500 individuals in northwest Puerto Rico [48,49]. Pulmonary fibrosis typically begins in the fourth decade and results in death from respiratory failure within 1 to 6 years of onset [50]. No effective therapy has been identified for patients with Hermansky-Pudlak syndrome with lung fibrosis, but newer antifibrotic therapies are being explored [51]. HRCT findings include peribronchovascular thickening, ground-glass opacification, and septal thickening.

Table 4
Lung manifestations of the collagen vascular diseases

<table>
<thead>
<tr>
<th>Lung manifestations</th>
<th>RA</th>
<th>J-RA</th>
<th>SLE</th>
<th>PSS</th>
<th>DM-PM</th>
<th>MCTD</th>
<th>Sjögren’s syndrome</th>
<th>Ankylosing spondylitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural inflammation, fibrosis, effusions</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Airway disease: inflammation, obstruction,</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lymphoid hyperplasia, follicular bronchiolitis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interstitial disease</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Acute (DAD), with or without hemorrhage</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Subacute/organizing (OP pattern)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute cellular</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Chronic cellular</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophilic infiltrates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Granulomatous interstitial pneumonia</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular diseases; hypertension/vasculitis</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Parenchymal nodules</td>
<td>X</td>
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<td></td>
<td></td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Apical fibrobulous disease</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphoid proliferation (reactive, neoplastic)</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>X</td>
</tr>
</tbody>
</table>

*Abbreviations:* DM/PM, dermatomyositis/polymyositis; J-RA, juvenile rheumatoid arthritis; MCTD, mixed connective tissue disease; OP, organizing pneumonia; PSS, progressive systemic sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.


Pulmonary fibrosis typically begins in the fourth decade and results in death from respiratory failure within 1 to 6 years of onset [50]. No effective therapy has been identified for patients with Hermansky-Pudlak syndrome with lung fibrosis, but newer antifibrotic therapies are being explored [51]. HRCT findings include peribronchovascular thickening, ground-glass opacification, and septal thickening.

**Fig. 18.** RA. Nodules of hyperplastic lymphoid tissue with germinal centers may be seen in the lung parenchyma in persons with RA and occasionally in the walls of airways (follicular bronchiolitis) (A). When advanced fibrosis and remodeling occurs in RA (B), the distribution may suggest UIP of idiopathic pulmonary fibrosis, but typically with more chronic inflammation and more diffuse alveolar wall fibrosis throughout the lobule.
A granulomatous colitis also may occur in patients with Hermansky-Pudlak syndrome. Histopathologically, the findings in Hermansky-Pudlak syndrome are distinctive. At scanning magnification, broad irregular zones of fibrosis are seen, some of which are pleural based, whereas others are centered on the airways (Fig. 24). Alveolar septal thickening is present and associated with prominent, clear, vacuolated type II pneumocytes (Fig. 25). Constrictive bronchiolitis occurs, and microscopic honeycombing is present without a consistent distribution. Ultrastructurally, numerous giant lamellar bodies can be found in the vacuolated macrophages and type II cells. The phospholipid material in the vacuoles is weakly positive, with antibodies directed against surfactant apoprotein by immunohistochemistry.

Idiopathic: nonspecific interstitial pneumonia

In the 30 years after the original Liebow classification of the idiopathic interstitial pneumonias, a "new" category of interstitial pneumonia emerged and was informally referred to as "unclassified or
unclassifiable” interstitial pneumonia by some or simple “cellular interstitial pneumonia” by others. In an effort to group these “unclassifiable” patterns of interstitial pneumonia, Katzenstein and Fiorelli [53] published in 1994 a review of 64 patients whose biopsies showed diffuse interstitial inflammation or fibrosis that did not fit Liebow’s classification scheme. The pathologic findings for this group of patients were referred to as “nonspecific interstitial pneumonia/fibrosis” or simply NSIP. NSIP was not a specific disease entity but likely represented several unrelated diseases and conditions.

Katzenstein and Fiorelli subdivided their cases into three groups: group I had diffuse interstitial inflammation alone (Fig. 26), group II had interstitial inflammation and early interstitial fibrosis occurring together (Fig. 27), and group III had denser, diffuse interstitial fibrosis without significant active inflammation (Fig. 28). These uniform injury patterns were judged to be separable from the “temporally heterogeneous” injury seen in UIP (transitions from uninvolved “new” lung to “old” injury with fibrosis and honeycombing). Group I NSIP (cellular NSIP) is discussed under Pattern 3 later in this article.

![Fig. 23. Bleomycin toxicity. Advanced lung fibrosis may occur after bleomycin therapy, which is one of the main reasons that bleomycin is used in experimental models of IPF.](image1)

![Fig. 24. Hermansky-Pudlak syndrome. The histopathologic findings in Hermansky-Pudlak syndrome are distinctive. At scanning magnification, broad, irregular zones of fibrosis are seen—some pleural based and others centered on the airways. A focus of metaplastic bone is present in the upper left portion of this image (a nonspecific sign of chronicity in fibrotic lung disease).](image2)

![Fig. 25. Hermansky-Pudlak syndrome. Alveolar septal thickening is present and is associated with prominent clear vacuolated type II pneumocytes in Hermansky-Pudlak syndrome.](image3)

![Fig. 26. NSIP: group I. Katzenstein and Fiorelli subdivided their cases into three groups. Group I had diffuse interstitial inflammation alone (without fibrosis). In this photograph, there is only mild interstitial thickening by small lymphocytes and a few plasma cells.](image4)
Several significant systemic disease associations were identified in their population. Connective tissue disease was identified in 16% of patients, including RA, SLE, polymyositis/dermatomyositis, scleroderma, and Sjögren’s syndrome. Pulmonary disease preceded the development of systemic collagen vascular disease in some of their cases—a phenomenon well documented for some collagen vascular diseases, such as dermatomyositis/polymyositis. Other autoimmune diseases that occurred in their series included Hashimoto’s thyroiditis, glomerulonephritis, and primary biliary cirrhosis. Beyond these systemic associations, another subset of patients was found to have a history of chemical, organic antigen, or drug exposures, which suggested the possibility of a hypersensitivity phenomenon. Two additional patients were status post-ARDS, and two patients had suffered pneumonia months before their biopsies were performed.

Perhaps the most important finding in the Katzenstein and Fiorelli study was that their population of patients had morbidity and mortality rates significantly different from that of UIP, in which reported mortality figures were more in the range of 90%, with median survival in the range of 3 years. Only 5 of 48 patients with clinical follow-up died of progressive lung disease (11%), whereas 39 patients either recovered or were alive with stable lung disease. For the patients with follow-up, no deaths were reported in group I patients, whereas 3 patients from group II and 2 patients from group III died. Unfortunately, a significant number of patients were lost to follow-up, and mean lengths of follow-up varied. Since 1994, there have been several additional reported series of patients with NSIP [54–61] with variable reported survival rates (Table 5). Deaths occurred in patients with NSIP who had fibrosis (groups II and III), analogous to results reported by Katzenstein and Fiorelli. Nagai et al [58] restricted the scope of NSIP to patients with idiopathic disease, primarily by excluding patients with known collagen vascular diseases and environmental exposures. Two of 31 patients in their study (6.5%) died of progressive lung disease, both of whom had group III disease. By contrast, the highest mortality rate was reported in the series by Travis et al [61], in which 9 of 22 patients (41%) died with group II and III disease. These deaths occurred after 5 years, somewhat
different from the course of most patients with UIP. Travis et al also reported 5- and 10-year survival rates of 90% and 35%, respectively, in their patients with NSIP, compared with 5- and 10-year survival rates of 43% and 15%, respectively, for patients with UIP.

Idiopathic: usual interstitial pneumonia (cryptogenic fibrosing alveolitis)

UIP is a chronic diffuse lung disease of unknown origin, characterized by a progressive tendency to produce fibrosis. UIP has had many names over the years, including chronic Hamman-Rich syndrome, fibrosing alveolitis, cryptogenic fibrosing alveolitis, idiopathic pulmonary fibrosis, widespread pulmonary fibrosis, and idiopathic interstitial fibrosis of the lung. For Liebow, UIP was the most common, or “usual,” form of diffuse lung fibrosis. According to Liebow, UIP was idiopathic in approximately half of the patients originally studied. In the other half, the disease was “heterogeneous in terms of structure and causation” [3]. Currently, UIP has been restricted to a subset of the broad and heterogeneous group of diseases initially encompassed by this term [114].

UIP is a disease of older individuals, typically older than 50 years [62]. Men are slightly more commonly affected than women. Characteristic clinical findings include distinctive end-inspiratory crackles (“Velcro crackles”) at the lung bases and the eventual development of lung fibrosis with cor pulmonale. Clubbing occurs commonly with the disease. Many patients die of respiratory failure. The average duration of symptoms in one series was

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of patients</th>
<th>Sex</th>
<th>Progression (%)</th>
<th>Deaths (NSIP) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Katzenstein and Fiorelli</td>
<td>64</td>
<td>26 M, 38 F</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>Nagai et al 1998 [58]</td>
<td>31</td>
<td>15 M, 16 F</td>
<td>16</td>
<td>6</td>
</tr>
<tr>
<td>Cottin et al 1998 [55]</td>
<td>12</td>
<td>6 M, 6 F</td>
<td>33</td>
<td>0</td>
</tr>
<tr>
<td>Park et al 1995 [59]</td>
<td>7</td>
<td>1 M, 6 F</td>
<td>29</td>
<td>29</td>
</tr>
<tr>
<td>Kim et al 1998 [57]</td>
<td>23</td>
<td>1 M, 22 F</td>
<td>Not given</td>
<td>Not given</td>
</tr>
<tr>
<td>Travis et al 2000 [61]</td>
<td>29</td>
<td>10 M, 9 F</td>
<td>41 (at least)</td>
<td>41</td>
</tr>
<tr>
<td>Daniil et al 1999 [56]</td>
<td>15</td>
<td>7 M, 8 F</td>
<td>33</td>
<td>13</td>
</tr>
<tr>
<td>Bjoraker et al 1998 [54]</td>
<td>14</td>
<td>8 M, 6 F</td>
<td>Not given</td>
<td>25 (5 yr); 35 (10 yr)</td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male.

Fig. 29. Cryptogenic fibrosing alveolitis. (A) At scanning magnification, the lung lobules are accentuated by the presence of peripheral fibrosis. There is tractional emphysema centrally in lobules, which further adds to the distinctive low magnification appearance of UIP in the setting of cryptogenic fibrosing alveolitis. The disease begins at the periphery of the pulmonary lobe and has a consistent tendency to leave lung fibrosis and honeycomb cystic lung remodeling in its wake. (B) An entire lobe is illustrated. Note the presence of subpleural fibrosis immediately adjacent to thin and delicate alveolar septa. Fibroblast foci can be seen at the lower left as paler zones of tissue.
3 years [3], and the mean survival after diagnosis has been reported as 4.2 years in a population-based study [63]. Different from other chronic inflammatory lung diseases, immunosuppressive therapy improves neither survival nor quality of life for patients with UIP [62].

HRCT has added a new dimension to the diagnosis of UIP. The abnormalities are most prominent at the periphery of the lungs and in the lung bases, regardless of the stage [64]. Irregular linear opacities result in a reticular pattern [64]. Advanced lung remodeling with cyst formation (honeycombing) is seen in approximately 90% of patients at presentation [65]. Ground-glass opacities can be seen in approximately 80% of cases of UIP but are seldom extensive.

The gross examination of the lung often reveals a characteristic nodular external surface (Fig. 29). Histopathologically, UIP is best envisioned as a smoldering alveolitis of unknown cause accompanied by microscopic foci of injury, repair, and lung remodeling with dense fibrosis. The disease begins at the periphery of the pulmonary lobule and has a consistent tendency to leave lung fibrosis and honeycomb cystic lung remodeling in its wake as it progresses from the periphery to the center of the lobule (Fig. 30). This transition from dense fibrosis, with or without honeycombing, to near normal lung through an intermediate stage of alveolar organization and inflammation is the histologic hallmark of so-called “temporal heterogeneity.” Thick irregular bundles of smooth muscle typically are present within areas of fibrosis (Fig. 31), presumably arising as a consequence of progressive parenchymal collapse with incorporation of native airway and vascular smooth muscle into fibrosis. Less well-recognized additional features of UIP are distortion and narrowing of bronchioles, together with peribronchiolar fibrosis and inflammation. This observation likely accounts for the functional evidence of small airway obstruction that may be found in UIP [66]. Widespread bronchial dilation (traction bronchiectasis) may be present at postmortem examination in advanced disease and is evident on HRCT late in the course of IPF.

Fig. 30. Cryptogenic fibrosing alveolitis. The renowned fibroblast focus (A) is not unique to cryptogenic fibrosing alveolitis but is distinctive and occurs at the interface between dense peripheral fibrosis and more normal lung centrally in the lobule. Another consistent finding, seen even in early examples of cryptogenic fibrosing alveolitis, is microscopic honeycombing (B). This focus was presumably an intact lobule once but was replaced by cysts partially filled with mucus. No alveoli remain.

Fig. 31. Cryptogenic fibrosing alveolitis. Smooth muscle is typically present within areas of fibrosis.
Acute exacerbation of idiopathic pulmonary fibrosis

Episodes of clinical deterioration are expected in patients with UIP. Although “respiratory failure” is the cause of death in approximately one half of affected individuals, for a small subset, death is sudden after acute respiratory failure. This manifestation of the disease has been termed “acute exacerbation of IPF” when no infectious cause is identified. The typical history is that of a patient being followed for IPF who suddenly develops acute respiratory distress that often is accompanied by fever, elevation of the sedimentation rate, marked increase in dyspnea, and new infiltrates that often have an “alveolar” character radiologically. For many years this manifestation was believed to be infectious pneumonia (possibly viral) superimposed on a fibrotic lung with marginal reserve. Because cases are sufficiently common, organisms are rarely identified, and a small percentage of patients respond to pulse systemic corticosteroid therapy, many investigators consider such exacerbation to be a form of fulminant progression of the disease process itself. Overall, acute exacerbation has a poor prognosis, and death within 1 week is not unusual. Pathologically, acute lung injury that resembles DAD or organizing pneumonia is superimposed on a background of peripherally accentuated lobular fibrosis with honeycombing. This latter finding can be highlighted in tissue sections using the Masson trichrome stain for collagen (Fig. 32). That acute exacerbation is a real phenomenon in IPF is underscored by the results of a recent large randomized trial of human recombinant interferon gamma 1b in IPF. In this study of patients with early clinical disease (FVC ≥50% of predicted), 44 of 330 enrolled subjects died unexpectedly within the 48-week trial period. Eighty percent of deaths in the experimental and control groups were respiratory in origin and without a defined cause [67].

Pattern 3: interstitial lung diseases dominated by interstitial mononuclear cells (chronic inflammation)

The most classic manifestation of ILD is embodied in this pattern, in which mononuclear inflammatory cells (eg, lymphocytes, plasma cells, and histiocytes) distend the interstitium of the alveolar walls. The pattern is common and has several associated conditions (Box 6).

Hypersensitivity pneumonitis

Lung disease can result from inhalation of various organic antigens. In most of these exposures, the disease is immunologically mediated, presumably through a type III hypersensitivity reaction, although the immunologic mechanisms have not been well documented in all conditions [68]. The prototypic example is so-called “farmer’s lung,” which is caused by hypersensitivity to thermophilic actinomycetes (Micromonospora vulgaris and Thermophyl- liae polyspora) that grow in moldy hay.

The radiologic appearance depends on the stage of the disease. In the acute stage, airspace consolidation is the dominant feature. In the subacute stage, there is a fine nodular pattern or ground-glass opacification. The chronic stage is dominated by fibrosis, with

Fig. 32. In acute exacerbation of cryptogenic fibrosing alveolitis, acute lung injury that resembles DAD or organizing pneumonia is superimposed on a background of peripherally accentuated lobular fibrosis with honeycombing (A). This latter finding can be highlighted in tissue sections using the Masson trichrome stain for collagen (B).
irregular linear opacities resulting in a reticular pattern. The HRCT reveals bilateral 3- to 5-mm poorly defined centrilobular nodular opacities or symmetric bilateral ground-glass opacities, which are often associated with lobular areas of air trapping [69]. The chronic phase is characterized by irregular linear opacities (reticular pattern) that represent fibrosis, which are usually most severe in the mid-lung zones [70].

The classic histologic features of hypersensitivity pneumonia are presented in Table 6. Because biopsy is typically performed in the subacute phase, the picture is usually one of a chronic inflammatory interstitial infiltrate, with lymphocytes and variable numbers of plasma cells. Lung structure is preserved, and alveoli usually can be distinguished. A few scattered, poorly formed granulomas are seen in the interstitium (Fig. 33). The epithelioid cells in the “granulomas” are loosely aggregated and mixed with lymphocytes. Characteristically, scattered giant cells of the foreign body type are seen around terminal airways and may contain cleft-like spaces or small particles that are doubly refractile (Fig. 34). Terminal airways display chronic inflammation of their walls (bronchiolitis), often with destruction, distortion, and even occlusion. Pale or lightly eosinophilic vacuolated macrophages are typically found in alveolar spaces and are a common sign of bronchiolar obstruction. Similar macrophages also are seen within alveolar walls.

In the largest series reported, the inciting allergen was not identified in 37% of patients who had unequivocal evidence of hypersensitivity pneumonitis on biopsy [71], even with careful retrospective search [72]. As the condition becomes more chronic, there is progressive distortion of the lung architecture by fibrosis and microscopic honeycombing, occasionally attended by extensive pleural fibrosis. At this stage, the lesions are difficult to distinguish from

---

### Table 6
Summary of morphologic features in pulmonary biopsies of 60 farmer’s lung patients

<table>
<thead>
<tr>
<th>Morphologic criteria</th>
<th>Present</th>
<th>%</th>
<th>±</th>
<th>1+</th>
<th>2+</th>
<th>3+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interstitial infiltrate</td>
<td>60</td>
<td>100</td>
<td>0</td>
<td>14</td>
<td>19</td>
<td>27</td>
</tr>
<tr>
<td>Unresolved pneumonia</td>
<td>39</td>
<td>65</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Pleural fibrosis</td>
<td>29</td>
<td>48</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Fibrosis, interstitial</td>
<td>39</td>
<td>65</td>
<td>10</td>
<td>24</td>
<td>5</td>
<td>—</td>
</tr>
<tr>
<td>Bronchiolitis obliterans</td>
<td>30</td>
<td>50</td>
<td>3</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Foam cells</td>
<td>39</td>
<td>65</td>
<td>6</td>
<td>24</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Edema</td>
<td>31</td>
<td>52</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Granulomas</td>
<td>42</td>
<td>70</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>With giant cells**</td>
<td>30</td>
<td>50</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Without giant cells</td>
<td>35</td>
<td>58</td>
<td>—</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>Solitary giant cells</td>
<td>32</td>
<td>53</td>
<td>—</td>
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<td>—</td>
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<tr>
<td>Foreign bodies</td>
<td>36</td>
<td>60</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Birefringent**</td>
<td>28</td>
<td>47</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Non-birefringent</td>
<td>24</td>
<td>40</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

* Degree of involvement rated on an arbitrary but documented scale for each criterion.

** The discrepancy in the total numbers is caused by the fact that in some cases granulomas with and without giant cells may be found. This discrepancy also applies with the foreign bodies.

other chronic lung diseases with fibrosis, because the lymphocytic infiltrate diminishes and only rare giant cells may be evident. The differential diagnosis of hypersensitivity pneumonitis is presented in Table 7.

**Bioaerosol-associated atypical mycobacterial infection**

The nontuberculous mycobacteria species, such as *Mycobacterium kansasii*, *Mycobacterium avium intracellulare* complex, and *Mycobacterium xenopi*, often are referred to as the atypical mycobacteria [73]. Being inherently less pathogenic than *Myobacterium tuberculosis*, these organisms often flourish in the setting of compromised immunity or enhanced opportunity for colonization and low-grade infection. Acute pneumonia can be produced by these organisms in patients with compromised immunity. Chronic airway disease–associated nontuberculous mycobacteria pose a difficult clinical management problem and are well known to pulmonologists. A distinctive and recently highlighted manifestation of nontuberculous mycobacteria may mimic hypersensitivity pneumonitis. Nontuberculous mycobacterial infection occurs in the normal host as a result of bioaerosol exposure (so-called “hot tub lung”) [74]. The characteristic histopathologic findings are chronic cellular bronchiolitis accompanied by nonnecrotizing or minimally necrotizing granulomas in the terminal airways and adjacent alveolar spaces (Fig. 35).

**Idiopathic: nonspecific interstitial pneumonia-cellular**

A pure “cellular” (chronflammatory) form of NSIP (group I) was identified in Katzenstein and Fiorelli’s original report. In the absence of fibrosis, the prognosis of NSIP seems to be good. The distinction of cellular NSIP from hypersensitivity pneumonitis, LIP (see later discussion), some manifestations of drug, and a pulmonary manifestation of collagen vascular disease may be difficult on histopathologic grounds alone.
Methotrexate seems to manifest pulmonary toxicity through a hypersensitivity reaction [75]. There does not seem to be a dose relationship to toxicity, although intravenous administration has been shown to be associated with more toxic effects. Symptoms typically begin with a cough that occurs within the first 3 months after administration and is accompanied by fever, malaise, and progressive breathlessness. Peripheral eosinophilia occurs in a significant number of patients who develop toxicity. A chronic interstitial infiltrate is observed in lung tissue, with lymphocytes, plasma cells, and a few eosinophils (Fig. 36). Poorly formed granulomas without necrosis may be seen, and scattered multinucleated giant cells are common (Fig. 37). Symptoms gradually abate after the drug is withdrawn [76], but systemic corticosteroids also have been used successfully.

Amiodarone

Amiodarone is an effective agent used in the setting of refractory cardiac arrhythmias. It is estimated that pulmonary toxicity occurs in 5% to 10% of patients who take this medication, and older patients seem to be at greater risk. Toxicity is heralded by slowly progressive dyspnea and dry cough that usually occurs within months of initiating therapy. In some patients, the onset of disease may

---

**Table 7**

<table>
<thead>
<tr>
<th>Histologic features</th>
<th>Hypersensitivity pneumonitis</th>
<th>Sarcoidosis</th>
<th>Lymphocytic interstitial pneumonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomas</td>
<td>Two thirds of open biopsies</td>
<td>100%</td>
<td>5%–10% of cases</td>
</tr>
<tr>
<td>Frequency</td>
<td>Poorly formed</td>
<td>Well formed</td>
<td>Well formed or poorly formed</td>
</tr>
<tr>
<td>Morphology</td>
<td>Poorly formed</td>
<td>Lymphangitic, poorly formed, perivascular</td>
<td></td>
</tr>
<tr>
<td>Distribution</td>
<td>Mostly random, some peribronchiolar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intrapulmonary fibrosis</td>
<td>Two thirds of open biopsies</td>
<td>Rare</td>
<td>Unusual</td>
</tr>
<tr>
<td>Lymphocyte infiltrates</td>
<td>Mild-moderate, peribronchiolar</td>
<td>Absent or minimal</td>
<td>Extensive, diffuse</td>
</tr>
<tr>
<td>Dense fibrosis</td>
<td>In advanced cases</td>
<td>In advanced cases</td>
<td>Unusual</td>
</tr>
<tr>
<td>BAL lymphocytosis</td>
<td>CD8 &gt; CD4</td>
<td>CD4 &gt; CD8</td>
<td>Usually B cells</td>
</tr>
</tbody>
</table>

Abbreviation: BAL, bronchoalveolar lavage.


**Drug reactions**

**Methotrexate**

Methotrexate seems to manifest pulmonary toxicity through a hypersensitivity reaction [75]. There does not seem to be a dose relationship to toxicity, although intravenous administration has been shown to be associated with more toxic effects. Symptoms typically begin with a cough that occurs within the first 3 months after administration and is accompanied by fever, malaise, and progressive breathlessness. Peripheral eosinophilia occurs in a significant number of patients who develop toxicity. A chronic interstitial infiltrate is observed in lung tissue, with lymphocytes, plasma cells, and a few eosinophils (Fig. 36). Poorly formed granulomas without necrosis may be seen, and scattered multinucleated giant cells are common (Fig. 37). Symptoms gradually abate after the drug is withdrawn [76], but systemic corticosteroids also have been used successfully.
mimic infectious pneumonia [77–80]. Diffuse infiltrates may be present on HRCT scans, but basilar and peripherally accentuated high attenuation opacities and nonspecific infiltrates are described [81,82]. Amiodarone toxicity produces a cellular interstitial pneumonia associated with prominent intra-alveolar macrophages whose cytoplasm shows fine vacuolation [77,83–85]. This vacuolation is also present in adjacent reactive type 2 pneumocytes. Characteristic lamellar cytoplasmic inclusions are present ultrastructurally [86]. Unfortunately, these cytoplasmic changes are an expected manifestation of the drug, so their presence is not sufficient to warrant a diagnosis of amiodarone toxicity [83]. Pleural inflammation and pleural effusion have been reported [87]. Some patients with amiodarone toxicity develop an organizing pneumonia pattern or even DAD [83,88,89]. Most patients who develop pulmonary toxicity related to amiodarone recover once the drug is discontinued [77,78,83–85].

**Idiopathic: lymphoid interstitial pneumonia**

LIP is a clinical pathologic entity that fits descriptively within the chronic interstitial pneumonias. By consensus, LIP has been included in the current classification of the idiopathic interstitial pneumonias, despite decades of controversy about what diseases are encompassed by this term. In 1969, Liebow and Carrington [3] briefly presented a group of patients and used the term LIP to describe their biopsy findings. The defining criteria were morphologic, and included “an exquisitely interstitial infiltrate” that was described as generally polymorphous and consisted of lymphocytes, plasma cells, and large mononuclear cells (Fig. 38). Several associated clinical conditions have been described, including connective tissue diseases, bone marrow transplantation, acquired and congenital immunodeficiency syndromes, and diffuse lymphoid hyperplasia of the intestine. This disease is considered idiopathic only when a cause or association cannot be identified.

The idiopathic form of LIP occurs most commonly between the ages of 50 and 70, but children may be affected. Women are more commonly affected than men. Cough, dyspnea, and progressive shortness of breath occur and often are accompanied by weight loss, fever, and adenopathy. Dysproteine-
mnia with abnormalities in gamma globulin production is reported, and pulmonary function studies show restriction, with abnormal gas exchange. The predominant HRCT finding is ground-glass opacification [90], although thickening of the bronchovascular bundles and thin-walled cysts may be seen [90].

LIP is best thought of as a histopathologic pattern rather than a diagnosis because LIP, as proposed initially, has morphologic features that are difficult to separate accurately from other lymphoplasmacellular interstitial infiltrates, including low-grade lymphomas of extranodal marginal zone type (maltoma). The LIP pattern requires clinical and laboratory correlation for accurate assessment, similar to organizing pneumonia, NSIP, and DIP. The histopathologic hallmarks of the LIP pattern include diffuse interstitial infiltration by lymphocytes, plasmacytoid lymphocytes, plasma cells, and histiocytes (Fig. 39). Giant cells and small granulomas may be present [91]. Honeycombing with interstitial fibrosis can occur. Immunophenotyping shows lack of clonality in the lymphoid infiltrate.

When LIP accompanies HIV infection, a wide age range occurs, and it is commonly found in children [92–95]. These HIV-infected patients have the same nonspecific respiratory symptoms, but weight loss is more common. Other features of HIV and AIDS, such as lymphadenopathy and hepatosplenomegaly, are also more common. Mean survival is worse than that of LIP alone, with adults living an average of 14 months and children an average of 32 months [96]. The morphology of LIP with or without HIV is similar.

Pattern 4: interstitial lung diseases dominated by airspace filling

A significant number of ILDs are attended or dominated by the presence of material filling the alveolar spaces. Depending on the composition of this airspace filling process, a narrow differential diagnosis typically emerges. The prototype for the airspace filling pattern is organizing pneumonia, in which immature fibroblasts (myofibroblasts) form polypoid growths within the terminal airways and alveoli. Organizing pneumonia is a common and nonspecific reaction to lung injury. Other material also can occur in the airspaces, such as neutrophils in the case of bacterial pneumonia, proteinaceous material in alveolar proteinosis, and even bone in so-called “racemose” or dendritic calcification.

Neutrophils

When neutrophils fill the alveolar spaces, the disease is usually acute clinically, and bacterial pneumonia leads the differential diagnosis (Fig. 40). Rarely, immunologically mediated pulmonary hemorrhage can be associated with brisk episodes of neutrophilic capillaritis; these cells can shed into the alveolar spaces and mimic bronchopneumonia.

Organizing pneumonia

When fibroblasts fill the alveolar spaces, the appropriate pathologic term is “organizing pneumo-

Fig. 39. LIP. The histopathologic hallmarks of the LIP pattern include “an exquisitely interstitial infiltrate” that must be proven to be polymorphous (not clonal) and consists of lymphocytes, plasma cells, and large mononuclear cells.

Fig. 40. Pattern 4 alveolar filling: neutrophils. When neutrophils fill the alveolar spaces, the disease is usually acute clinically and bacterial pneumonia leads the differential diagnosis. Neutrophils are accompanied by necrosis (upper right).
nia,” although many clinicians believe that this is an automatic indictment of infection. Unfortunately, the lung has a limited capacity for repair after any injury, and organizing pneumonia often is a part of this process, regardless of the exact mechanism of injury. The more generic term “airspace organization” is preferable, but longstanding habits are hard to change. Some of the more common causes of the organizing pneumonia pattern are presented in Box 7.

One particular form of diffuse lung disease is characterized by airspace organization and is idiopathic. This clinicopathologic condition was previously referred to as “idiopathic bronchiolitis obliterans organizing pneumonia” (idiopathic BOOP). The name of this disorder recently was changed to COP.

**Idiopathic: cryptogenic organizing pneumonia**

In 1983, Davison et al [97] described a group of patients with COP, and 2 years later Epler et al [98] described similar cases as idiopathic BOOP. The process described in these series is believed to be the same [1] as those cases described by Liebow and Carrington in 1969 as “idiopathic bronchiolitis obliterans interstitial pneumonia” [3]. Currently, a reasonable consensus has emerged regarding what is being called COP [97–100]. King and Mortensen [101] recently compiled the findings from 4 major case series reported from North America, adding 18 of their own cases (112 cases in all). Based on these compiled data, the following description of COP emerges.

The evolution of clinical symptoms is subacute (4 months on average and 3 months in most) and follows a flu-like illness in 40% of cases. The average age at presentation is 58 years (range, 21–80 years) and there is no sex predominance. Dyspnea and cough are present in half the patients. Fever is common, and leukocytosis occurs in approximately one fourth. The erythrocyte sedimentation rate is typically elevated [102]. Clubbing is rare. Restrictive lung disease is present in approximately half of the patients with COP, and the diffusing capacity is reduced in most. Airflow obstruction is mild and typically affects patients who are smokers.

Chest radiographs show patchy, bilateral (sometimes unilateral) nonsegmental airspace consolidation [103], which may be migratory and similar to those of eosinophilic pneumonia. Reticulation may be seen in 10% to 40% of patients but rarely is predominant [103,104]. The most characteristic HRCT features of COP are patchy unilateral or bilateral areas of consolidation, which have a predominantly peribronchial or subpleural distribution (or both) in approximately 60% of cases. In 30% to 50% of cases, small, ill-defined nodules (3–10 mm in diameter) are seen [105–108], and a reticular pattern is seen in 10% to 30% of cases.

The major histopathologic feature of COP is alveolar space organization (so-called “Masson bodies”), but it also extends to involve alveolar ducts and respiratory bronchioles, in which the process has a characteristic polypoid and fibromyxoid appearance (Fig. 41). The parenchymal involvement tends to be patchy. All of the organization seems to be recent. Unfortunately, the term BOOP has become one of the most commonly misused descriptions in lung pathology, much to the dismay of clinicians. Pathologists use the term to describe nonspecific organization that occurs in alveolar ducts and alveolar spaces of lung biopsies. Clinicians hear the term BOOP or BOOP pattern and often interpret this as a clinical diagnosis of idiopathic BOOP. Because of this misuse, there is a growing consensus [101,109] regarding use of the term COP to describe the clinicopathologic entity for the following reasons: (1) Although COP is primarily an organizing pneumonia, in up to 30% or more of cases, granulation tissue is not present in membranous bronchioles and at times may not even be seen.

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**Box 7. Causes of the organizing pneumonia pattern**

- Organizing infections
- Organizing DAD
- Drug and toxic reactions
- Collagen vascular diseases
- Hypersensitivity pneumonitis
- Chronic eosinophil pneumonia
- Airway diseases (eg, bronchitis and emphysema, bronchiectasis, cystic fibrosis, aspiration pneumonia, chronic bronchiolitis) complicated by infection
- Airway obstruction
- Peripheral reaction around abscesses, infarcts, Wegener’s granulomatosis, and others
- Idiopathic (likely immunologic) lung disease (COP)

in respiratory bronchioles [97]. (2) The term “bronchiolitis obliterans” has been used in so many different ways that it has become a highly ambiguous term. (3) Bronchiolitis generally produces obstruction to airflow, and COP is primarily characterized by a restrictive defect.

The expected prognosis of COP is relatively good. In 63% of affected patients, the condition resolves, mainly as a response to systemic corticosteroids. Twelve percent die, typically in approximately 3 months. The disease persists in the remaining subset or relapses if steroids are tapered too quickly. Patients with COP who fare poorly frequently have comorbid disorders, such as connective tissue disease or thyroiditis, or have been taking nitrofurantoin [110]. A recent study showed that the presence of reticular opacities in a patient with COP portended a worse prognosis [111].

Macrophages

Macrophages are an integral part of the lung’s defense system. These cells are migratory and generally do not accumulate in the lung to a significant degree in the absence of obstruction of the airways or other pathology. In smokers, dusty brown macrophages tend to accumulate around the terminal airways and peribronchiolar alveolar spaces and in association with interstitial fibrosis. The cigarette smoking–related airway disease known as respiratory bronchiolitis–associated ILD is discussed later in this article with the smoking-related ILDs. Beyond smoking, some infectious diseases are characterized by a prominent alveolar macrophage reaction, such as the malacoplakia-like reaction to Rhodococcus equi infection in the immunocompromised host or the mucoid pneumonia reaction to cryptococcal pneumonia. Conditions associated with a DIP-like reaction are presented in Box 8.

Eosinophilic pneumonia

Acute eosinophilic pneumonia was discussed earlier with the acute ILDs, but the acute and chronic forms of eosinophilic pneumonia often are accompanied by a striking macrophage reaction in the airspaces. Different from the macrophages in a patient with smoking-related macrophage accumulation, the macrophages of eosinophilic pneumonia tend to have a brightly eosinophilic appearance and are plump with dense cytoplasm. Multinucleated forms may occur, and the macrophages may aggregate in sufficient density to suggest granulomas in the alveolar spaces. When this occurs, a careful search for eosinophils in the alveolar spaces and reactive

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**Box 8. Conditions associated with a desquamative interstitial pneumonia–like reaction**

- Idiopathic DIP
- RB-ILD
- Pulmonary histiocytosis X (PLCH)
- Drug reactions (especially associated with amiodarone)
- Chronic alveolar hemorrhage
- Eosinophilic pneumonia (especially after corticosteroid therapy)
- Certain pneumoconioses (especially talcosis, hard metal disease, and asbestosis)
- Obstructive pneumonias (with foamy alveolar macrophages)
- Exogenous lipid pneumonia and lipid storage diseases
- Infection in immunosuppressed patients (histiocytic pneumonia)

type II cell hyperplasia is often helpful in distinguishing eosinophilic lung disease from other conditions characterized by a histiocytic reaction.

**Idiopathic: desquamative interstitial pneumonia**

In 1965, Liebow et al [112] described 18 cases of diffuse lung diseases that differed in many respects from UIP. The striking histologic feature was the presence of numerous cells filling the airspaces. Liebow et al. believed that the cells were chiefly desquamated alveolar epithelial lining cells and coined the term “desquamative interstitial pneumonia.” It is currently known that these cells are predominately macrophages, however [113]. DIP and the cigarette smoking–related disease known as RB-ILD are believed to be similar, if not identical, diseases, possibly representing different expressions of disease severity [115]. RB-ILD is discussed later in this article in the section on smoking-related diffuse lung disease.

The patients described by Liebow et al [112] were, on average, slightly younger than patients with UIP, and their symptoms were usually milder. Clubbing was uncommon, but in later series some patients with clubbing were identified [4]. Most patients have a subacute lung disease of weeks to months of evolution. The predominant finding on the radiograph and HRCT in patients with DIP consists of ground-glass opacities, particularly at the bases and at the costophrenic angles [115]. Some patients have mild reticular changes superimposed on ground-glass opacities.

In lung biopsy, the scanning magnification appearance of DIP is striking (Fig. 42). The alveolar spaces are filled with lightly pigmented (brown) macrophages, and multinucleated cells are commonly present. Additional important features include the relative preservation of lung architecture, with only mild thickening of alveolar walls and absence of severe fibrosis or honeycombing [116–118]. Interstitial mononuclear inflammation is seen, sometimes with scattered lymphoid follicles. The histologic appearance of DIP is not specific. It is commonly present in other diffuse and localized lung diseases, including UIP, asbestosis [119], and other dust-related diseases [120]. DIP-like reactions occur after nitrofurantoin therapy [121,122] and in alveolar spaces adjacent to the nodules of PLCH (see later section on smoking-related diseases).

Cases have been reported in which classic DIP “progressed to fibrosing alveolitis” [117,123]. It seems clear that DIP represents a nonspecific reaction and more commonly occurs in smokers. It is critical to distinguish between DIP and UIP, especially because these diseases are regarded as different from one another. Research has shown conclusively that the clinical features are different, the prognosis is much better in DIP, and DIP may respond to corticosteroid administration [124], whereas UIP does not [62].

**Proteinaceous material**

When eosinophilic material fills the alveolar spaces, the differential diagnosis includes pulmonary edema and alveolar proteinosis.

**Pulmonary alveolar proteinosis**

PAP (alveolar lipoproteinosis) is a rare diffuse lung disease characterized by the intra-alveolar

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**Fig. 42. DIP.** The scanning magnification appearance of DIP is striking (A). The alveolar spaces are filled with lightly pigmented (brown) macrophages, and multinucleated cells are commonly present (B).
accumulation of lipid-rich eosinophilic material [125]. PAP likely occurs as a result of overproduction of surfactant by type II cells, impaired clearance of surfactant by alveolar macrophages, or a combination of these mechanisms. The disease can occur as an idiopathic form but also occurs in the settings of occupational disease (especially dust-related), drug-induced injury, hematologic diseases, and in many settings of immunodeficiency [125–128]. PAP is commonly associated with exposure to inhaled crystalline material and silica, although other substances have been implicated [126]. The idiopathic form is the most common presentation, with a male predominance and an age range of 30 to 50 years. The usual presenting symptom is insidious dyspnea, sometimes with cough [129], although the clinical symptoms are often less dramatic than the radiologic abnormalities.

Chest radiographs show extensive bilateral airspace consolidation that involves mainly the perihilar regions. CT demonstrates what seems to be smooth thickening of lobular septa that is not seen on the chest radiograph. The thickening of lobular septae within areas of ground-glass attenuation is characteristic of alveolar proteinosis on CT and is referred to as “crazy paving” [130]. The areas of ground-glass attenuation and consolidation are often sharply demarcated from the surrounding normal lung without an apparent anatomic correlation [130–132].

Histopathologically, the scanning magnification appearance is distinctive, if not diagnostic. Pink granular material fills the airspaces, often with a rim of retraction that separates the alveolar wall slightly from the exudate (Fig. 43). Embedded clumps of dense globular granules and cholesterol clefts are seen (Fig. 44). The periodic-acid Schiff stain reveals a diastase-resistant positive reaction in the proteinaceous material of PAP. Dramatic inflammatory changes should suggest comorbid infection.

The idiopathic form of PAP has an excellent prognosis. Many patients are only mildly symptomatic. In patients with severe dyspnea and hypoxemia, treatment can be accomplished with one or more sessions of whole lung lavage, which usually induces remission and excellent long-term survival [133].

Pattern 5: interstitial lung diseases dominated by nodules

Some ILDs are dominated by or significantly associated with nodules. For most of the diffuse ILDs, the nodules are small and appreciated best under the microscope. In some instances, nodules may be sufficiently large and diffuse in distribution that they are identified on HRCT. In others cases, a few large nodules may be present in two or more lobes or bilaterally (eg, Wegener granulomatosis). For neoplasms that diffusely involve the lung, the nodular pattern is overwhelmingly represented (eg, lymphangetic carcinomatosis). The differential diagnosis of the nodular pattern is presented in Box 9.

Nodular granulomas

When granulomas are present in a lung biopsy, the differential diagnosis always includes infection, sarcoidosis and berylliosis, aspiration pneumonia, and some lymphoproliferative diseases. Hypersensitivity pneumonitis is classically grouped with “gran-
ulomatous lung disease,” but this condition rarely produces well-formed granulomas. Hypersensitivity pneumonia is discussed under Pattern 3 because the pattern is more one of cellular chronic interstitial pneumonia, with granulomas being subtle.

Granulomatous infection

Most nodular granulomatous reactions in the lung are of infectious origin until proven otherwise, especially in the presence of necrosis. The infectious diseases that characteristically produce well-formed granulomas are typically caused by mycobacteria, fungi, and, rarely, bacteria. Sometimes Pneumocystis infection produces a nodular pattern. A list of the diffuse lung diseases associated with granulomas is presented in Box 10.

Sarcoidosis

Sarcoidosis is a systemic granulomatous disease of uncertain origin. The disease commonly affects the lungs [134,135]. The origin, pathogenesis, and epidemiology of sarcoidosis suggest that it is a disorder of immune regulation [136–138]. The observation that sarcoid granulomas recur after lung transplantation [139–141] seems to underscore further the notion that this is an acquired systemic abnormality of immunity. It also emphasizes the fact that even profound immunosuppression (such as that used in transplantation) may be ineffective in halting disease progression for the subset whose condition persists and progresses to lung fibrosis.

Sarcoidosis occurs most frequently in young adults but has been described in all ages. There is a decreased incidence of sarcoidosis in cigarette smokers. Many patients with intrathoracic sarcoidosis are symptom free. Systemic manifestations may be identified (in decreasing frequency) in lymph nodes, eyes, liver, skin, spleen, salivary glands, bone, heart, and kidneys. Breathlessness is the most common pulmonary symptom.

The chest radiographic appearance is often characteristic, with a combination of symmetrical bilateral hilar and paratracheal lymph node enlargement, together with a varied pattern of parenchymal involvement, including linear, nodular, and ground-glass opacities [142]. In approximately 25% of the patients the radiographic appearance is atypical, and in approximately 10% it is normal [143]. Staging of the disease is based on pattern of involvement on plain chest radiographs only [135,142].

The histopathologic hallmark of sarcoidosis is the presence of well-formed granulomas without necrosis (Fig. 45). Granulomas are classically distributed along lymphatic channels of the bronchovascular bundles, interlobular septa, and pleura (Fig. 46). The area between granulomas is frequently sclerotic, and adjacent small granulomas tend to coalesce into larger nodules. Because of involvement of the bronchovascular bundles and the characteristic histology, sarcoidosis is one of the few diffuse lung diseases that can be diagnosed with a high degree of success by transbronchial biopsy (Fig. 47) [144]. Although necrosis is not a feature of the disease, sometimes...
foci of granular eosinophilic material may be seen at the center of the granulomas. The “dirty” necrosis so typical of mycobacterial and fungal disease granulomas is not seen. Distinctive inclusions may be present within giant cells in the granulomas, such as asteroid and Schaumann’s bodies (Fig. 48), but these can be seen in other granulomatous diseases. There is a generally held belief that a mild interstitial inflammatory infiltrate accompanies granulomas in sarcoidosis [145–147]. If this “interstitial pneumonia” of sarcoidosis exists, it is subtle in the best example and consists of a few lymphocytes, mononuclear cells, and macrophages.

The prognosis for patients with sarcoidosis is excellent. The disease typically resolves or improves, with only 5% to 10% of patients developing significant pulmonary fibrosis. Most patients recover completely with minimal residual disease.

**Berylliosis**

Occupational exposure to beryllium was first recognized as a health hazard in fluorescent lamp factory workers. The use of beryllium in this industry was discontinued, but because of beryllium’s remarkable structural characteristics, it continues to be used in metallic, alloy, and oxide forms in numerous industries. Berylliosis may occur as acute and chronic forms. The acute disease is usually seen in refinery workers.
workers and produces DAD. Chronic berylliosis is a multiorgan disease, but the lung is most severely affected. The radiologic findings are similar to sarcoidosis except that hilar and mediastinal adenopathy is seen in only 30% to 40% of cases compared with 80% to 90% in sarcoidosis [148,149]. Berylliosis is characterized by nonnecrotizing lung parenchymal granulomas indistinguishable from those of sarcoidosis [150].

Nodular lymphohistiocytic lesions (lymphoid cells, lymphoid follicles, variable histiocytes)

Follicular bronchiolitis

When lymphoid germinal centers (secondary lymphoid follicles) are present in the lung biopsy (Fig. 49), the differential diagnosis always includes a lung manifestation of RA, Sjögren’s syndrome, or other systemic connective tissue disease, immunoglobulin deficiency, diffuse lymphoid hyperplasia, and malignant lymphoma. When in doubt, immunohistochemical studies and molecular techniques may be useful in excluding a neoplastic process.

Diffuse panbronchiolitis

Diffuse panbronchiolitis can produce a dramatic diffuse nodular pattern in lung biopsies. This condition is a distinctive form of chronic bronchiolitis seen almost exclusively in people of East Asian descent (ie, Japan, Korea, China). Diffuse panbronchiolitis may occur rarely in individuals in the United States [151–153] and in patients of non-Asian descent.

Fig. 49. Follicular bronchiolitis. Lymphoid germinal centers (secondary lymphoid follicles) are present around a severely compromised bronchiole in this case of follicular bronchiolitis.

Fig. 50. Diffuse panbronchiolitis. A characteristic low-magnification appearance is that of nodular bronchiolocentric lesions.

Severe chronic inflammation is centered on respiratory bronchioles early in the disease, followed by involvement of distal membranous bronchioles and peribroncholar alveolar spaces as the disease progresses. A characteristic low magnification appearance is that of nodular bronchiolocentric lesions (Fig. 50). The characteristic and nearly diagnostic feature of diffuse panbronchiolitis is the accumulation of many pale vacuolated macrophages in the walls and lumens of respiratory bronchioles and in adjacent airspaces (Fig. 51). Japanese investigators suspect that the condition occurs in the United States and has been underrecognized. This view was substantiated.
by a study of 81 US patients previously diagnosed with cellular chronic bronchiolitis [151]. On review, 7 of these patients were reclassified as having diffuse panbronchiolitis (8.6%).

**Nodules of neoplastic cells**

Isolated nodules of neoplastic cells occur commonly as primary and metastatic cancer in the lung. When nodules of neoplastic cells are seen in the radiologic context of ILD, lymphangitic carcinomatosis leads the differential diagnosis. LAM also can produce diffuse ILD, typically with small nodules and cysts. LAM is discussed later in this article under Pattern 6. PLCH also can produce small nodules and cysts diffusely in the lung (typically in the upper lung zones), and this entity is discussed with the smoking-related interstitial diseases.

**Lymphangitic carcinomatosis**

Pulmonary lymphangitic carcinomatosis (lymphangitis carcinomatosa) is a form of metastatic carcinoma that involves the lung, primarily within lymphatics. The disease produces a miliary nodular pattern at scanning magnification. Lymphangitic carcinoma is typically adenocarcinoma. The most common sites of origin are breast, lung, and stomach, although primary disease in pancreas, ovary, kidney, and uterine cervix also can give rise to this manifestation of metastatic spread. Patients often present with insidious onset of dyspnea that is frequently accompanied by an irritating cough. The radiographic abnormalities include linear opacities, Kerley B lines, subpleural edema, and hilar and mediastinal lymph node enlargement [154]. The HRCT findings are highly characteristic and accurately reflect the microscopic distribution in this disease, with uneven thickening of the bronchovascular bundles and lobular septa, which gives them a beaded appearance [155,156].

Histopathologically, malignant tumor cells are typically present in small aggregates within lymphatic channels of the bronchovascular sheath and pleura (Fig. 52). Variable amounts of tumor may be present throughout the lung in the interstitium of the alveolar walls, in the airspaces, and in small muscular pulmonary arteries. This latter finding (microangiopathic obliterator endarteritis) may be the origin of the edema, inflammation, and interstitial fibrosis that frequently accompany the disease and likely accounts for the clinical and radiologic impression of nonneoplastic diffuse lung disease [154,157].

**Pattern 6: interstitial lung disease with subtle findings in surgical biopsies (chronic evolution)**

A limited differential diagnosis is invoked by the relative absence of abnormalities in a surgical lung biopsy (Box 11). Three main categories of disease emerge in this setting: (1) diseases of the small

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**Box 11. Causes of a normal biopsy in clinically apparent interstitial lung disease**

- Subtle interstitial inflammatory infiltrate or early diffuse alveolar damage
- Small airway disease
- Pulmonary edema
- Pulmonary emboli (including fat emboli)
- LAM with inconspicuous lesions
- Pulmonary vascular disease
- Sampling error (e.g., histiocytosis X lesions may not be included)

airways (eg, constrictive bronchiolitis), (2) vasculo-pathic conditions (eg, pulmonary hypertension), and (3) two diseases that may be dominated by cysts; the rare disease known as LAM; and PLCH in the inactive or healed phase of the disease. All of these may be dramatic in biopsy specimens, but when confronted with the “nearly normal” lung biopsy in a patient with significant clinical disease, these three groups of diseases dominate the differential diagnosis.

Small airways disease and constrictive bronchiolitis

Obliteration of the small membranous bronchioles can occur as a result of infection, toxic inhalational exposure, drugs, systemic connective tissue diseases, and as an idiopathic form. Outside of the setting of lung transplantation, in which so-called “bronchiolitis obliterans” (having histopathology similar to constrictive bronchiolitis) occurs as a chronic manifestation of organ rejection, the diagnosis presents a challenge for pulmonologists and pathologists alike. In this section we present a few recognized forms of non–transplant-associated constrictive bronchiolitis.

Irritants and infections

Many irritant gases can produce severe bronchiolitis. This inflammatory injury may be followed by the accumulation of loose granulation tissue and finally by complete stenosis and occlusion of the airways. The best known of these agents are nitrogen dioxide [158], sulfur dioxide [159], and ammonia [160]. Viral infection also can cause permanent bronchiolar injury, particularly adenovirus infection [161]. Mycoplasma pneumonia is also cited as a potential cause [162]. The course of events is similar to that for the toxic gases. Variable degrees of bronchiectasis or bronchiolocoection may occur secondarily up- and downstream from the area of occlusion. Lung biopsy is performed rarely and then usually because the patient is young and unusual airflow obstruction is present. Occasionally, mixed obstruction and restriction may occur, presumably on the basis of diffuse peribronchiolar scarring. This airway-associated scarring may produce CT findings of “interstitial” disease. The airway lesions are subtle but can be recognized by variable reduction in bronchiolar luminal diameter compared with the adjacent pulmonary artery branch. (Normally these should be roughly equal in diameter when viewed as cross-sections.) The diagnosis depends on careful clinical correlation and sometimes the addition of a comparison between inspiratory and expiratory HRCT scans, which typically shows prominent mosaic air trapping.

Rheumatoid bronchiolitis

Patients with RA may develop constrictive bronchiolitis as a consequence of their disease. In some patients, small rheumatoid nodules can be seen in the walls of airways, which results in their partial or total occlusion (Fig. 53). From a practical point of view, the lesions are focal within the airways, often in small bronchi, and may not be visualized easily in the biopsy specimen. Because of the widespread recognition of rheumatoid bronchiolitis, biopsy is rarely performed in these patients. Morphologically, scattered occlusion of small bronchi and bronchioles is observed and is associated with the presence of loose connective tissue in their lumens.

Neuroendocrine cell hyperplasia with occlusive bronchiolar fibrosis

In 1992, Aguayo et al [163] reported six patients with moderate chronic airflow obstruction, all of whom never smoked. Diffuse neuroendocrine cell hyperplasia of the bronchioles associated with partial or total occlusion of airway lumens by fibrous tissue was present in all six patients (Fig. 54). Three of the patients also had peripheral carcinoid tumors and three had progressive dyspnea.

In a study of 25 peripheral carcinoid tumors that occurred in smokers and nonsmokers, Miller and Müller [164] identified 19 patients (76%) with neuroendocrine cell hyperplasia of the airways, which occurred mostly in bronchioles. Eight patients (32%)

Fig. 53. Rheumatoid bronchiolitis. In this example of rheumatoid bronchiolitis, complex bronchiolar metaplasia involves a membranous bronchiole, accompanied by follicular bronchiolitis. Small rheumatoid nodules (similar to those that occur around the joints) also can be seen occasionally in the walls of airways, which results in partial or total occlusion.
were found to have occlusive bronchiolar fibrosis. Four of the 8 had mild chronic airflow obstruction, and 2 of these 4 patients were nonsmokers.

An increase in neuroendocrine cells was present in more than 20% of bronchioles examined in lung adjacent to the tumor and in tissue blocks taken well away from tumor. Less than half of these airways were partially or totally occluded. The mildest lesion consisted of linear zones of neuroendocrine cell hyperplasia with focal subepithelial fibrosis. The most severely involved bronchioles showed total luminal occlusion by fibrous tissue, with few visible neuroendocrine cells.

In both of these studies, most of the patients with airway neuroendocrine hyperplasia were women. Presumably, fibrosis in this setting of neuroendocrine hyperplasia is related to one or more peptides secreted by neuroendocrine cells; possibly these cells are more effective in stimulating airway fibrosis in women.

Cryptogenic constrictive bronchiolitis

Unexplained chronic airflow obstruction that occurs in nonsmokers may be a result of selective (and likely multifocal) obliteration of the membranous bronchioles (constrictive bronchiolitis). In a study of 2094 patients with a forced expiratory volume in the first second (FEV₁) of less than 60% of predicted [165], 10 patients (9 women) were identified. They ranged in age from 27 to 60 years. Five were found to have RA and presumably rheumatoid bronchiolitis. The other 5 had airflow obstruction of unknown cause, believed to be caused by “bronchiolitis.” Other studies also identified a cryptogenic form of bronchiolar disease that produces airflow obstruction [166,167]. When biopsies have been performed, constrictive bronchiolitis seems to be the common pathologic manifestation (Fig. 55). It is fair to conclude that a rare but fairly distinct clinical syndrome exists that consists of mild airflow obstruction and usually affects middle-aged women, who manifest nonspecific respiratory symptoms.
such as cough and dyspnea. It is possible that these cryptogenic cases of constrictive bronchiolitis are manifestations of undeclared systemic connective tissue disease, the sequelae of prior undetected community-acquired infections (eg, viral, mycoplasmal, chlamydial), or exposure to toxin.

**Interstitial lung disease dominated by airway-associated scarring**

A form of small airway-associated ILD has been described in recent years under the names “idiopathic bronchiocentric interstitial pneumonia” [168] and “airway-centered interstitial fibrosis” [169]. Affected patients have more of a restrictive than obstructive functional deficit, and the process is characterized histopathologically by the presence of significant small airway–associated scarring, similar to that seen in forms of chronic hypersensitivity pneumonia, certain chronic inhalational injuries (including subclinical chronic aspiration pneumonia), and even some examples of late-stage inactive PLCH (which typically lacks characteristic Langerhans’ cells). This morphologic group may pose diagnostic challenges because of the absence of interstitial inflammatory changes, despite the radiologic and functional impression of ILD.

**Vasculopathic disease**

Diseases that involve the small arteries and veins of the lung can be subtle when viewed from low magnification under the microscope (Fig. 56). At higher magnification, scattered plexiform vascular lesions (Fig. 57) are present in this example of primary pulmonary hypertension.

**Lymphangioleiomyomatosis**

Pulmonary LAM is a rare disease characterized by an abnormal proliferation of smooth muscle cells in
the pulmonary interstitium and associated with the formation of cysts [170–173]. The disease is centered on lymphatic channels, blood vessels, and airways. LAM is a disease of women, typically in their childbearing years. The disease does occur in older women and rarely in men [174]. There is a strong association between the inherited genetic disorder known as tuberous sclerosis complex and the occurrence of LAM. Most patients with LAM do not have tuberous sclerosis complex, but approximately one fourth of patients with tuberous sclerosis complex have LAM, as diagnosed by chest HRCT [175]. The most common presenting symptoms are spontaneous pneumothorax and exertional dyspnea. Others symptoms include chyloptosis, hemoptysis, and chest pain. The characteristic findings on CT are numerous cysts separated by normal-appearing lung parenchyma. The cysts range from 2 to 10 mm in diameter and are seen much better with HRCT [171,176].

The appearance of the abnormal smooth muscle in LAM is sufficiently characteristic so that once recognized it is rarely forgotten. Cystic spaces are present at low magnification (Fig. 58). The walls of these spaces have variable amounts of bundled spindled cells (Fig. 59). The nuclei of these spindled cells (Fig. 60) are larger than those of normal smooth muscle bundles seen around alveolar ducts or in the walls of airways or vessels. Immunohistochemical staining is positive in these cells using antibodies directed against the melanoma markers, HMB45 and Mart-1 (Fig. 61). These findings may be useful in the evaluation of transbronchial biopsy, in which only a few spindled cells may be present. Actin, desmin, estrogen receptors, and progesterone receptors also can be demonstrated in the spindled cells of LAM [177]. Other lung parenchymal abnormalities may be present, including peculiar nodules of hyperplastic pneumocytes (Fig. 62), that lack immunoreactivity for HMB45 or Mart-1 but show immunoreactivity for cytokeratins and surfactant apoproteins [178]. These epithelial lesions have been referred to as “micronodular pneumocyte hyperplasia.”

The expected survival is more than 10 years. All of the patients who died in one large series did...
so within 5 years of disease onset [179], which suggests that the rate of progression can vary widely among patients.

**Interstitial lung disease related to cigarette smoking**

DIP was discussed earlier in this article as an idiopathic interstitial pneumonia. In this section we present two additional well-recognized smoking-related diseases, the first of which is related to DIP and likely represents an earlier stage, or alternate manifestation, along a spectrum of macrophage accumulation in the lung in the context of cigarette smoking. Conceptually, respiratory bronchiolitis, RB-ILD, DIP, and PLCH can be viewed as interrelated components in the setting of cigarette smoking (Fig. 63).

**Respiratory bronchiolitis-associated interstitial lung disease**

Respiratory bronchiolitis is a common finding in the lungs of cigarette smokers, and some investigators consider this lesion to be a precursor of centriacinar emphysema. Respiratory bronchiolitis affects the terminal airways and is characterized by delicate fibrous bands that radiate from the peribronchiolar connective tissue into the surrounding lung (Fig. 64). Dusty appearing, tan-brown pigmented alveolar macrophages are present in the adjacent airspaces, and a mild amount of interstitial chronic inflammation is present. Bronchiolar metaplasia (extension of terminal airway epithelium to alveolar ducts) is usually present to some degree. In the bronchioles, submucosal fibrosis may be present, but constrictive changes are not a characteristic finding. When respiratory bronchiolitis becomes extensive and patients have signs and symptoms of ILD, use of the term RB-ILD has been suggested [180,181]. The exact relationship between RB-ILD and DIP is unclear, and in smokers, these two conditions are probably part of a continuous spectrum of disease. Symptoms of RB-ILD include dyspnea, excess sputum production, and cough [182]. Rarely, patients may be asymptomatic. Men are slightly more present two additional well-recognized smoking-related diseases, the first of which is related to DIP and likely represents an earlier stage, or alternate manifestation, along a spectrum of macrophage accumulation in the lung in the context of cigarette smoking. Conceptually, respiratory bronchiolitis, RB-ILD, DIP, and PLCH can be viewed as interrelated components in the setting of cigarette smoking (Fig. 63).

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commonly affected than women, and the mean age of onset is approximately 36 years (range 22–53 years). The average pack year smoking history is 32 (range 7–75).

Most patients with respiratory bronchiolitis alone have normal radiologic studies. The most common findings in RB-ILD include thickening of the bronchial walls, ground-glass opacities, and poorly defined centrilobular nodular opacities [183]. Because most patients with RB-ILD are heavy smokers, centrilobular emphysema is common.

On histopathologic examination, lightly pigmented macrophages are present in the airspaces around the terminal airways with variable bronchiolar metaplasia (Fig. 65). Iron stains may reveal delicate positive staining within these cells. The relatively patchy nature of the disease is important in differentiating RB-ILD from DIP (Fig. 66). A spectrum of pathologic severity emerges, with isolated lesions of respiratory bronchiolitis on one end and diffuse macrophage accumulation in DIP on the other. RB-ILD exists somewhere in between. The diagnosis of RB-ILD should be reserved for situations in which respiratory bronchiolitis is prominent, with associated clinical and pathologic ILD [184]. No other cause for ILD should be apparent. The prognosis is excellent, and there does not seem to be evidence for progression to end-stage fibrosis in the absence of other lung disease.

Pulmonary Langerhans’ cell histiocytosis

PLCH (formerly known as pulmonary eosinophilic granuloma or pulmonary histiocytosis X) is currently recognized as a lung disease strongly associated with cigarette smoking. Proliferation of Langerhans’ cells is associated with the formation of stellate airway-centered lung scars and cystic change in affected individuals. The incidence of the disease is unknown but it is generally considered to be a rare complication of cigarette smoking [185].
PLCH affects smokers between the ages of 20 and 40. The most common presenting symptom is cough with dyspnea, but some patients may be asymptomatic despite chest radiographic abnormalities. Chest pain, fever, weight loss, and hemoptysis have been reported to occur. HRCT scan shows nearly pathognomonic changes, including predominately upper and middle lung zone nodules and cysts [185,186].

The classic lesion of PLCH is illustrated in Fig. 67. Characteristically, the nodules have a stellate shape and are always centered on the bronchioles.

Pigmented alveolar macrophages and variable numbers of eosinophils surround and permeate the lesions. Immunohistochemistry using antibodies directed against S100 protein/CD1a highlight numerous positive Langerhans’ cells at the periphery of the cellular lesions (Fig. 68). The Langerhans’ cell has a slightly pale, basophilic nucleus with characteristic sharp nuclear folds that resemble crumpled tissue paper (Fig. 69). One or two small nucleoli are usually present. Late lesions (so-called “inactive” or resolved PLCH) consist only of fibrotic centrilobular scars [187] with a stellate configuration (Fig. 70). Microcysts and honeycombing may be present.
Up to 20% of transbronchial biopsies in patients with Langerhans’ cell histiocytosis may have diagnostic changes. The presence of more than 5% Langerhans’ cells in bronchoalveolar lavage is considered diagnostic of Langerhans’ cell histiocytosis in the appropriate clinical setting. Unfortunately, cigarette smokers without Langerhans’ cell histiocytosis also may have increased numbers of Langerhans’ cells in the bronchoalveolar lavage.

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