19
Interstitial Pneumonias

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The idiopathic interstitial pneumonias are part of the wide spectrum of diffuse parenchymal lung diseases (Fig. 19.1).[1] While recognition of diffuse interstitial pulmonary fibrosis can be traced back to studies by Hamman and Rich[2] in the 1930s and 1940s, they were first classified as a set of histopathologic patterns in the 1960s by Liebow and Carrington[3] into usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia (BIP), giant cell interstitial pneumonia (GIP) and lymphoid interstitial pneumonia (LIP). At about the same time, Scadding[4] in the United Kingdom proposed the term *fibrosing alveolitis,* suggesting (incorrectly) that DIP and UIP were early and late phases of a single disorder.[5] There has subsequently been much discussion and controversy over what patterns should be included in such a classification system, in terms of both histology and what these patterns represent regarding clinical disease. As a result, some patterns have now been categorized according to their recognized causes; for example, GIP has been reclassified as a pneumoconiosis, the cause being exposure to cobalt during the production of hard metals or during diamond polishing (see Chapter 26).[6,7] Other patterns such as LIP were reclassified as preneoplastic disorders in the context of lymphoproliferative disease during the 1980s and 1990s (see Chapter 32), but with greater understanding of the pathogenesis of pulmonary lymphomas through proteomics and genomics, cases are again treated more as interstitial pneumonias.

In addition to this greater understanding of pathogenesis in relation to the five initial histopathologic patterns, new histopathologic patterns have been described, such as respiratory bronchiolitis-associated interstitial lung disease (RBILD)[8,9] and nonspecific interstitial pneumonia (NSIP),[10] as well as new clinicopathologic entities such as acute interstitial pneumonia (AIP),[11] leading to proposed revisions (Table 19.1).[12]

However, the usage of both new and old terminology was not without problems. First, terms were being used in different ways by clinicians and pathologists, some as purely histopathologic patterns, some as clinical diseases, and some as both. For example, in the 1980s and 1990s, idiopathic pulmonary fibrosis (IPF) and cryptogenic fibrosing alveolitis (CFA) described the same well-defined clinical entity, but had different histopathologic equivalents; IPF was said to show only a pattern of UIP,[13] while CFA encompassed a wider range of patterns, including UIP and DIP.[14] Second, some terms were not histogenetically accurate; for example, DIP is neither desquamative nor predominantly interstitial. Third, more recently described patterns such as NSIP were poorly characterized in terms of their clinical correlates. Yet, despite these shortcomings, evidence accumulated from around the world that recognition of these histopathologic patterns provides significant prognostic data (Fig. 19.2).[14–20] The 1990s also saw a meteoric rise in the importance of the high-resolution computed tomography (HRCT) for diagnosing any diffuse parenchymal lung disease, especially interstitial pneumonias,[21–23] and all these factors, therefore, led to the creation of an American Thoracic Society/European Respiratory Society–sponsored committee comprising clinicians, radiologists, and pathologists, who then developed and proposed a consensus classification system for idiopathic interstitial pneumonias (Table 19.2) and an algorithm for its usage (Fig. 19.3).[24] This classification, based on seven histopathologic patterns, has become the cornerstone for interpreting surgical lung biopsies in this setting, although it is not without its critics and is already undergoing refinement in relation to smoking-related disease and new patterns of disease described since 2002.

When and What to Biopsy

The diagnostic accuracy of HRCT in identifying patients with a UIP pattern in IPF/CFA is now such that patients seldom come to biopsy.[13,24] Indeed in the United Kingdom,

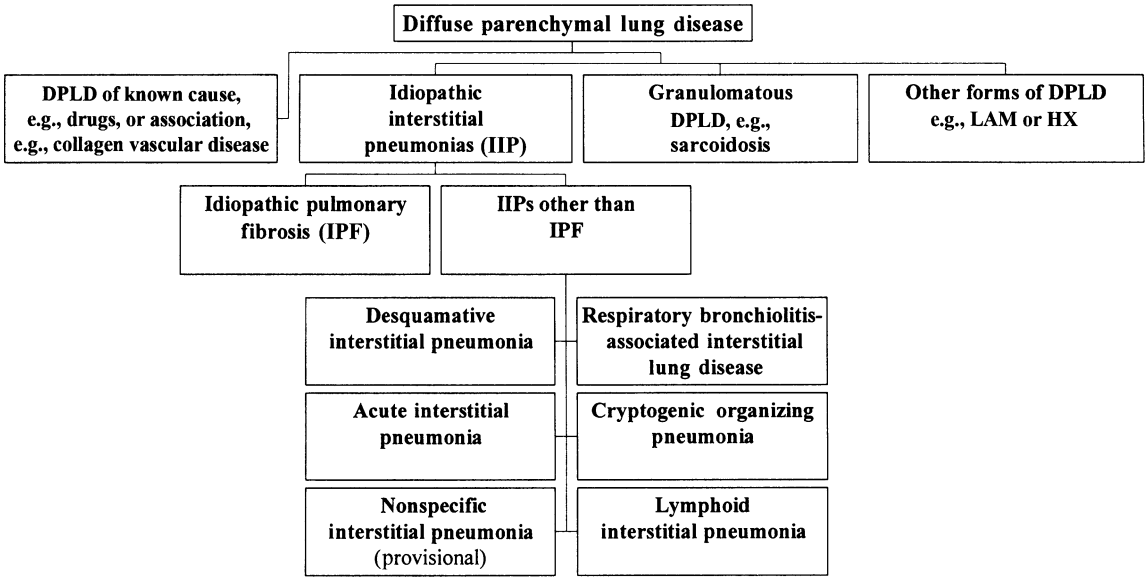

FIGURE 19.1. Spectrum of diffuse parenchymal lung disease (DPLDs). HX, histiocytosis X; LAM, lymphangioleiomyomatosis. (Adapted from American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias,[24] with permission. Copyright © 2002, American Thoracic Society.)

TABLE 19.1. Proposed classifications of interstitial pneumonias

Liebow and Carrington[3] (1969)	Katzenstein and Myers[12] (1998)	American Thoracic Society/European Respiratory Society Consensus[24] (2002)
Usual interstitial pneumonia	Usual interstitial pneumonia	Usual interstitial pneumonia
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia/respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia Respiratory bronchiolitis
Bronchiolitis obliterans interstitial pneumonia		Organizing pneumonia
	Acute interstitial pneumonia	Diffuse alveolar damage
	Nonspecific interstitial pneumonia	Nonspecific interstitial pneumonia
Lymphoid interstitial pneumonia		Lymphoid interstitial pneumonia
Giant cell pneumonia		

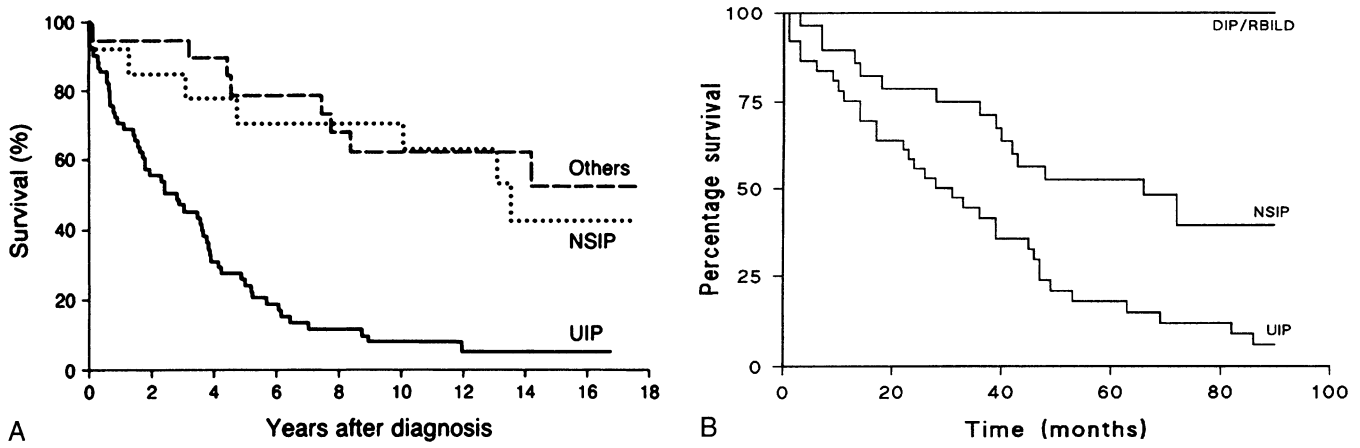

FIGURE 19.2. Survival graphs from the United States **(A)** and from the United Kingdom **(B)**, show variations in prognosis associated with histologic patterns of interstitial pneumonia. NSIP, nonspecific interstitial pneumonia; UIP, usual interstitial pneumonia. (A and B reprinted with permission from, respectively, Bjoraker et al.,[15] with permission; and Nicholson et al.,[14] with permission. Copyright © 2000, American Thoracic Society.)

TABLE 19.2. Histologic patterns of interstitial pneumonias and clinicopathologic counterparts in an idiopathic setting

Histopathologic pattern	Clinicopathologic diagnosis
Usual interstitial pneumonia (UIP)	Cryptogenic fibrosing alveolitis (CFA)/idiopathic pulmonary fibrosis (IPF)
Nonspecific interstitial pneumonia (NSIP)	Nonspecific interstitial pneumonia*
Organizing pneumonia (OP)	Cryptogenic organizing pneumonia
Diffuse alveolar damage (DAD)	Acute interstitial pneumonia
Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia
Respiratory bronchiolitis (RB)	Respiratory bronchiolitis-associated Interstitial lung disease (RBILD)
Lymphoid interstitial pneumonia (LIP)	Lymphoid interstitial pneumonia

*Provisional term for clinicopathologic diagnosis.
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only 40% of patients with IPF/CFA undergo any form of biopsy: 28% have a transbronchial biopsy and 12% a surgical lung biopsy.[25] Indeed it is often the atypical cases (Fig. 19.3), in relation to either presenting signs and HRCT data, or unusual longitudinal behavior, that generally lead to sampling of tissue.[26]

When tissue is sampled, a surgical biopsy is nearly always required to determine the pattern of interstitial pneumonia, and is now usually obtained at video-assisted thoracoscopy. Typically, the physician, radiologist, and surgeon discuss the case prior to operation, to determine the area(s) where disease activity is thought to be best

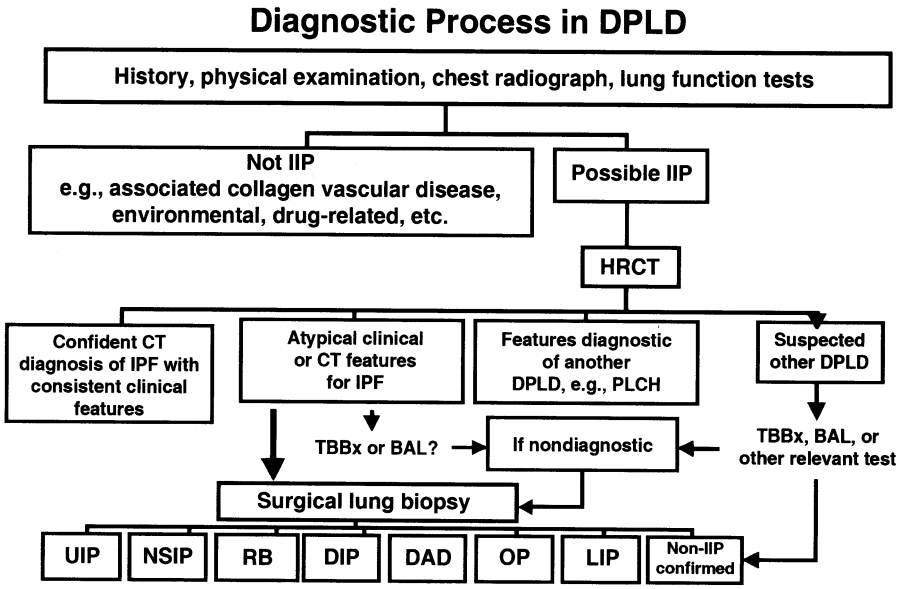

FIGURE 19.3. The diagnostic process in diffuse parenchymal lung diseases (DPLDs) begins with a clinical evaluation that includes a history, physical examination, chest radiograph, and lung function tests. On the basis of the information, patients may be divided into two groups: those who do not have idiopathic interstitial pneumonia (IIP) and those who could have IIP. Patients in the latter category are further evaluated with high-resolution computed tomography (HRCT). This generally results in four categories of patients: (1) those with distinctive features that enable a confident diagnosis of idiopathic pulmonary fibrosis (IPF)/usual interstitial pneumonia (UIP), (2) those with atypical clinical or HRCT features of IPF, (3) those with features diagnostic of another DPLD, and (4) those with suspected other forms of DPLD. Although some patients go directly to surgical lung biopsy, others undergo only transbronchial biopsy or bronchoalveolar lavage (BAL). If these findings are nondiagnostic, a surgical lung biopsy may then be necessary to separate the various IIPs from non-IIP DPLD. DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; LIP, lymphoid interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; PLCH, pulmonary Langerhans' cell histiocytosis; RB, respiratory bronchiolitis; TBB, transbronchial biopsy. (From American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias,[24] with permission. Copyright © 2002, American Thoracic Society.)

represented, so that the biopsy is most likely to provide diagnostic tissue.[13,24] Studies suggest that taking biopsies from multiple sites also reduces sampling error and provides more valuable prognostic data.[19] It is also especially important to avoid areas of end-stage lung (fortunately the days of receiving solely the tip of the right middle lobe or lingula are largely over) (see Chapter 1). Historically, such cases have always been reported as being "consistent with IPF/CFA," and it is true that most cases of end-stage lung are the result of UIP. However, studies looking at the ability to differentiate end-stage UIP from other end-stage disorders such NSIP have shown poor interobserver reproducibility,[14] and it is preferable to classify these changes as no more than end-stage lung or honeycomb lung rather than assign a histopathologic pattern.[12,14,27] As stated above, such areas can be avoided by preoperative discussion in order to select the ideal site for biopsy[13,24]; otherwise HRCT data are usually of more value than the biopsy.[28]

Opinion is divided as to whether biopsies should be inflated with formalin upon receipt in the laboratory, in that this process improves morphology and fixation, but runs the risk of both washing out diagnostic features such as accumulation of macrophages and distorting the architecture if undertaken in too zealous a fashion. My approach is to undertake very gentle injection of formalin only. Sampling of fresh frozen tissue and for electron microscopy is also recommended in case other rare forms of diffuse parenchymal lung disease are unexpectedly found on microscopy and further investigations are required, although this tissue is not processed in the majority of cases.

Transbronchial biopsy may establish an alternative diagnosis, but will not provide tissue for the diagnosis of UIP or NSIP. However, it may be of value in confirming organizing pneumonia (OP) and, in the last few years, has provided sufficient data in classic cases of RBILD to provide a diagnosis without recourse to surgical lung biopsy, an example of how advances in translational research between pathogenesis and investigative modalities such as HRCT have influenced management (see Chapter 1).

Usual Interstitial Pneumonia and Idiopathic Pulmonary Fibrosis

Usual interstitial pneumonia is the most common histopathologic pattern seen in cases of idiopathic interstitial pneumonia, and in most cases it correlates clinically with IPF, also known as CFA (see below).[24]

Histopathologic Features

Usual interstitial pneumonia is characterized primarily by progressive chronic fibrosis of the parenchyma that is more marked at the periphery of the lungs and in the lower lobes, both macroscopically (Fig. 19.4) and microscopically. At an acinar level, the changes are characteristically subpleural or paraseptal in distribution, typically being sharply demarcated from areas of normal or nearly normal alveolar lung (Fig. 19.5). This low power distribution is one of the cardinal features of UIP. The other cardinal feature is localized areas of fibroblastic proliferation termed fibroblastic foci that abut the areas of established fibrosis. The fibroblastic foci comprise an abundance of plump spindle cells and little intervening collagen, compared to the poorly cellular hyalinized collagen seen in

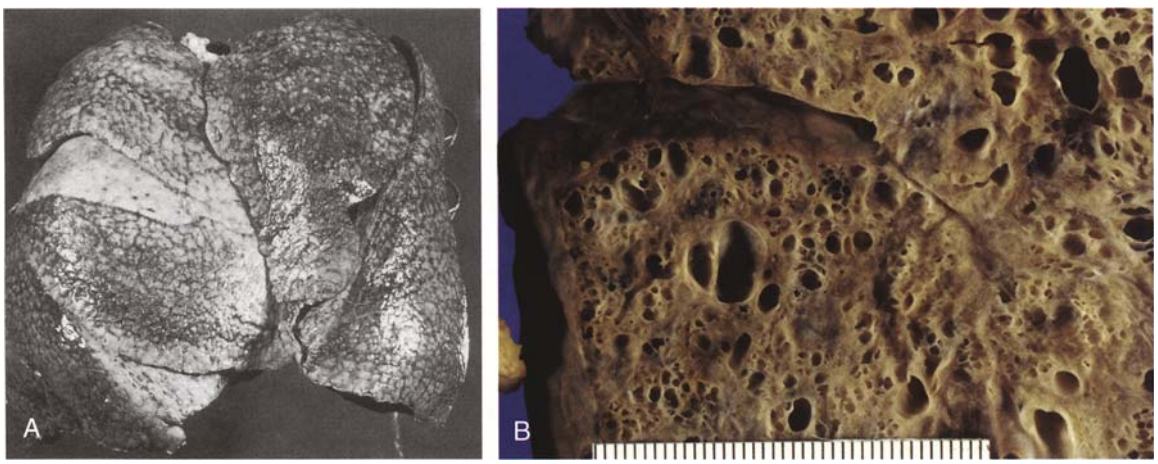

FIGURE 19.4. **A.** Right and left lungs from a patient dying of idiopathic pulmonary fibrosis. Note the nodular pleural surface that is similar to the surface of cirrhotic liver. **B.** The cut surface of a lung in idiopathic pulmonary fibrosis shows extensive peripheral honeycombing.

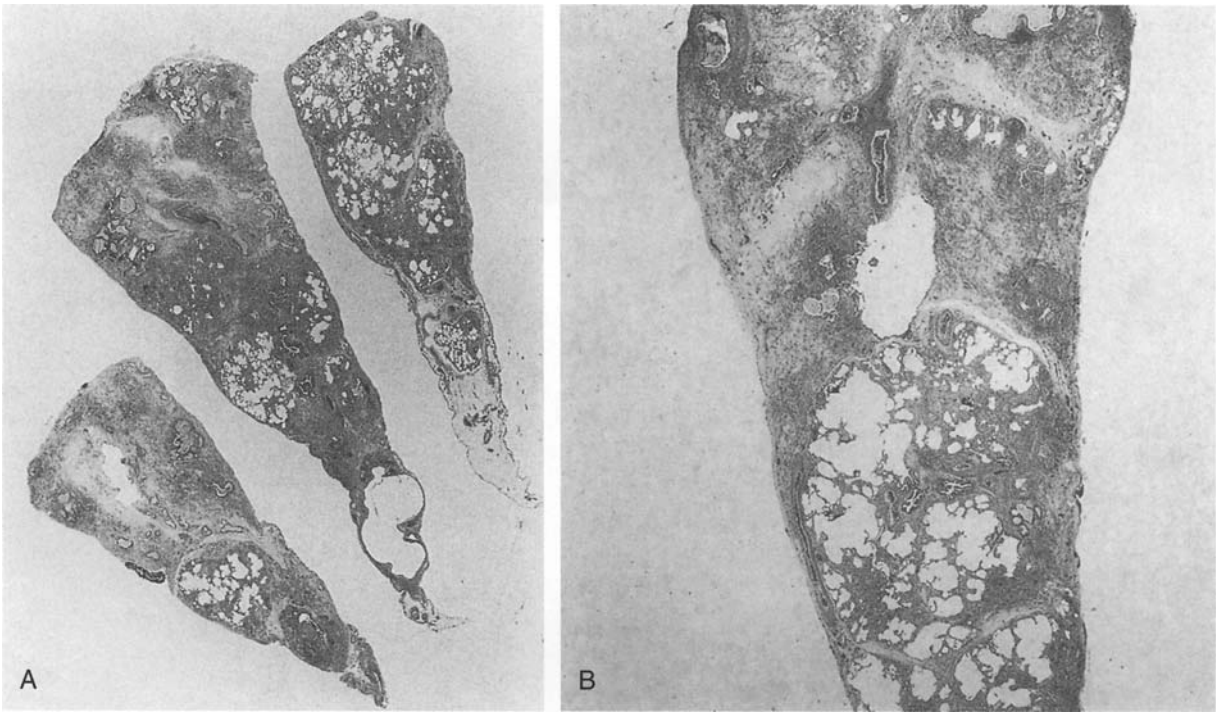

FIGURE 19.5. **A,B.** A case of usual interstitial pneumonia shows patchy, heterogeneous inflammation and fibrosis with a subpleural distribution, alternating with areas of normal alveolar lung. Focal honeycombing is present (**B,** top left).

areas of established fibrosis (Fig. 19.6). This variation in the age of fibrosis is termed by some as "temporal heterogeneity," and the patchy distribution as "spatial heterogeneity." These fibroblastic foci are thought to represent the sites of repeated and continued lung damage,[29–31] not least because the extent of these foci is associated with mortality and an increased rate of disease progression.[32,33] However, although there have been significant advances in understanding the pathogenesis of IPF/CFA, the exact cause remains unknown.[34]

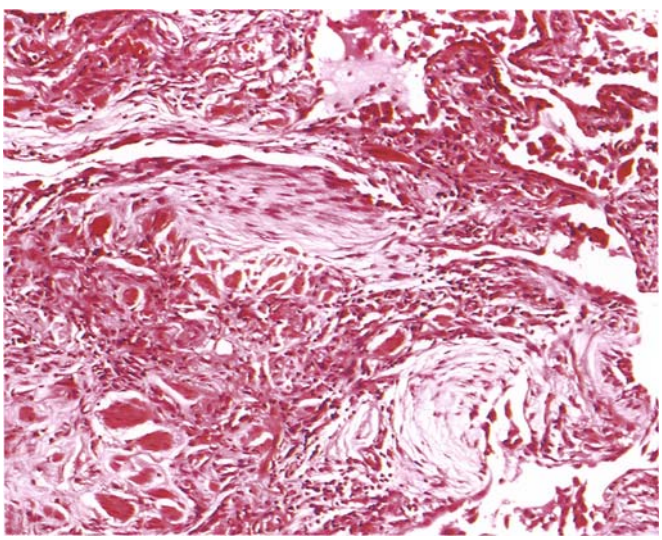

FIGURE 19.6. A high-power view from a case of usual interstitial pneumonia shows several fibroblastic foci in continuity with areas of established fibrosis.

In association with the fibrosis, there is a chronic inflammatory cell infiltrate of usually mild and no more than moderate intensity, mainly comprising small lymphocytes with occasional plasma cells. Aggregates of B lymphocytes may also be present, although these are not usually prominent in idiopathic disease. Small aggregates of inflammation and vascularity may be seen immediately beneath the fibroblastic foci (Fig. 19.6). As the disease becomes more advanced, alveolar architecture is increasingly lost with the eventual formation of cysts separated by bands of fibrosis, so-called end-stage lung or honeycombing. These dilated air spaces show varying degrees of bronchiolization and, less commonly, goblet cell hyperplasia. Features such as smooth muscle hypertrophy, type 2 cell hyperplasia, endarteritis obliterans, osseous metaplasia, and squamous metaplasia are also found in UIP, but these are likely to be secondary phenomena and are not specific to this pattern (Fig. 19.7). Occasionally, eosinophilic pneumonia-like areas may be seen in UIP. These patients are described as slightly younger at presentation, although prognosis appears similar to cases without such

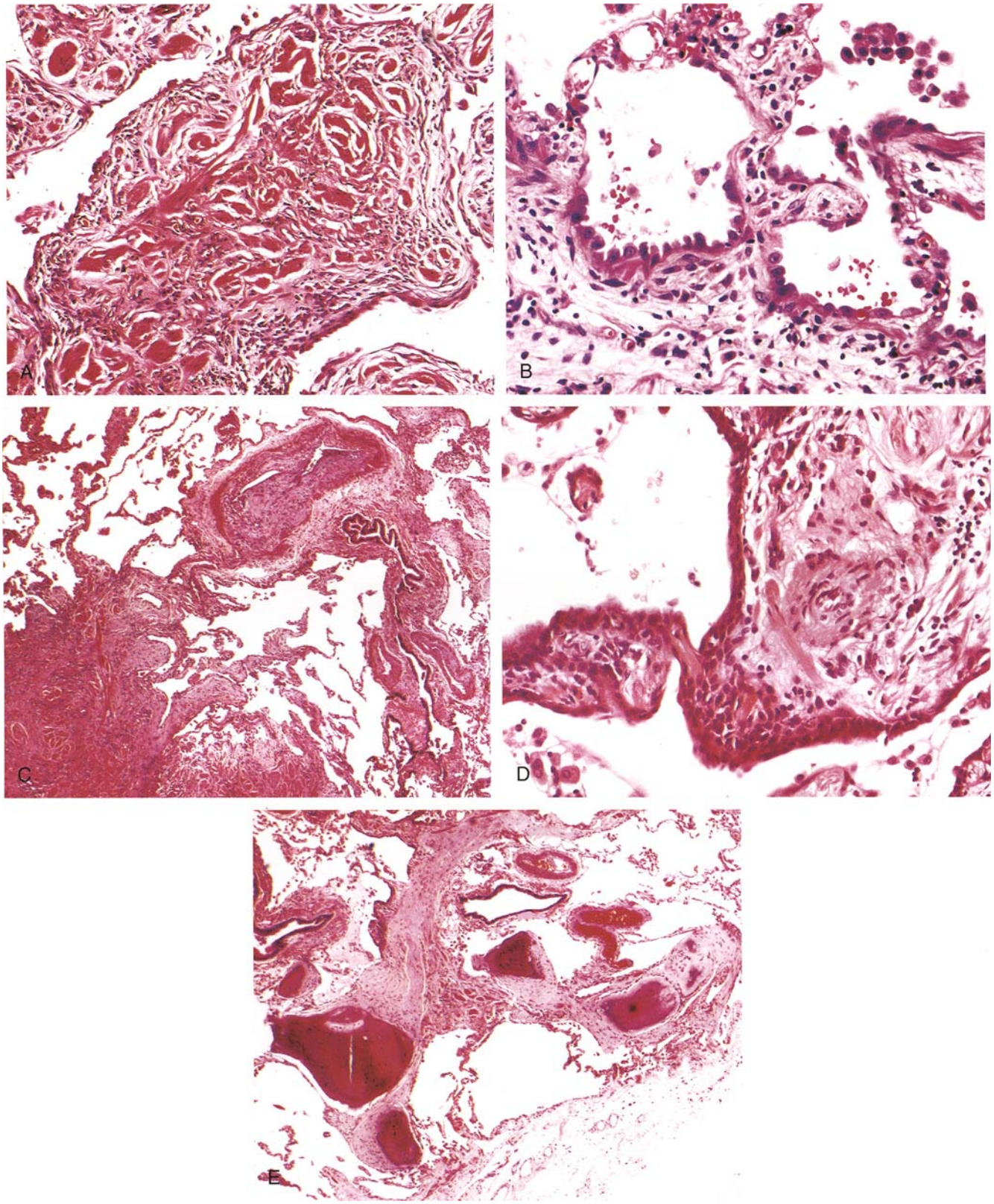

FIGURE 19.7. Examples of the more commonly seen secondary changes in usual interstitial pneumonia: **A.** Smooth muscle hypertrophy. **B.** Type 2 cell hyperplasia. **C.** Endarteritis. **D.** Squamous metaplasia. **E.** Osseous metaplasia.

TABLE 19.3. Histologic features of usual interstitial pneumonia

Major features	Minor (or secondary) changes	Pertinent negative features
Established fibrosis	Alveolar macrophage accumulation	Lack of inorganic dusts (e.g.,asbestos)
Patchy parenchymal involvement with subpleural/paraseptal predominance	Follicular hyperplasia	Lack of granulomas
Fibroblastic foci	Smooth muscle hypertrophy/hyperplasia	Lack of Langerhans' cells
Typically mild interstitial chronic inflammation	Endarteritis	
Honeycomb change when advanced	Alveolar neutrophil accumulation	
	Bronchiolar, bony, fatty, and squamous metaplasia	
	Mild pleuritis and pleural fibrosis	
	Cholesterol clefts	
	Subpleural blebs	
	Prominent eosinophil accumulation	
	Focal alveolar fibrin	

Source: Adapted from American Thoracic Society.[13] Copyright © 2000, American Thoracic Society.

areas. How these cases relate to levels of eosinophils in bronchoalveolar lavage (BAL) is also unknown.[35] The histopathologic features of UIP are summarized in Table 19.3.

Clinicopathologic Correlation

Idiopathic pulmonary fibrosis (IPF)/CFA is the clinical correlate for a histopathologic pattern of UIP in the vast majority of patients. However, a minority of patients have other disorders, such as chronic hypersensitivity pneumonia (see Chapter 17) and drug toxicity (see Chapter 22). A pattern of UIP is also described in association with collagen vascular diseases (see Chapter 20), asbestosis (see Chapter 27), and Hermansky-Pudlak syndrome (see Chapter 16). Because these latter disorders are discussed in other chapters, only IPF/CFA is discussed here.

Idiopathic Pulmonary Fibrosis

Clinical Presentation

Patients with IPF/CFA have chronically progressive disease with a mean survival from the onset of dyspnea of 2 to 3 years (Fig. 19.2).[5,14–20,36–41] Most patients present over the age of 50 years and the disease is twice as common in males. Early studies have suggested smoking as a risk factor, although more recent data argue against this.[42] There is no geographic or ethnic predilection. Rarely, the disease may be familial.[43] Symptoms include dyspnea, dry cough, and loss of weight. Inspiratory bilateral basal crackles are heard, and there is often clubbing of the fingers. Lung function tests show restrictive abnormalities. In terms of imaging, chest x-rays typically show small lung fields and irregular reticulonodular or nodular shadows at the periphery and bases of the lungs. In advanced disease, honeycomb shadows and features of pulmonary hypertension may also be seen. However, the chest x-ray has been largely superseded by HRCT since the early 1990s, and the features are virtually pathognomonic in classic cases of IPF, these being bilateral coarse irregular reticular changes that predominate in a subpleural and peripheral distribution (Fig. 19.8). Traction bronchiectasias and honeycomb change are also frequently seen. A ground-glass pattern may also be present.[24] Serologic investigations may show a raised erythrocyte sedimentation rate, and there may also be antinuclear antibodies or rheumatoid factor present in about one third of patients, although the titers are usually low compared to those patients with pulmonary fibrosis associated with connective tissue disorders abnormalities. Bronchoalveolar lavage is a further investigative tool that has had impact on research and to a lesser degree management of these patients, via assessing the differential cell count within fluid injected into and then aspirated from the peripheral lung.[44,45] In a typical patient with IPF, there is an increase in the overall cell count with excess neutrophils and, to a lesser extent, eosinophils (Fig. 19.9). The presence of increased neutrophils and eosinophils has been associated with a worse prognosis in patients classified as CFA,[46] and more recent studies looking specifically at UIP support the earlier data,[47] although neutrophils may merely reflect severity whereas eosinophils may reflect future disease progression.[48] A lymphocytosis is comparatively rare and warrants investigation of other causes of pulmonary fibrosis, particularly chronic hypersensitivity pneumonia.[44,47]

Treatment and Prognosis

There is no standard or optimal treatment for IPF, but the consensus view is that first-line treatment should consist of low-dose prednisolone together with immunosuppression using drugs such as azathioprine or cyclophosphamide.[13] There are also several potential drugs

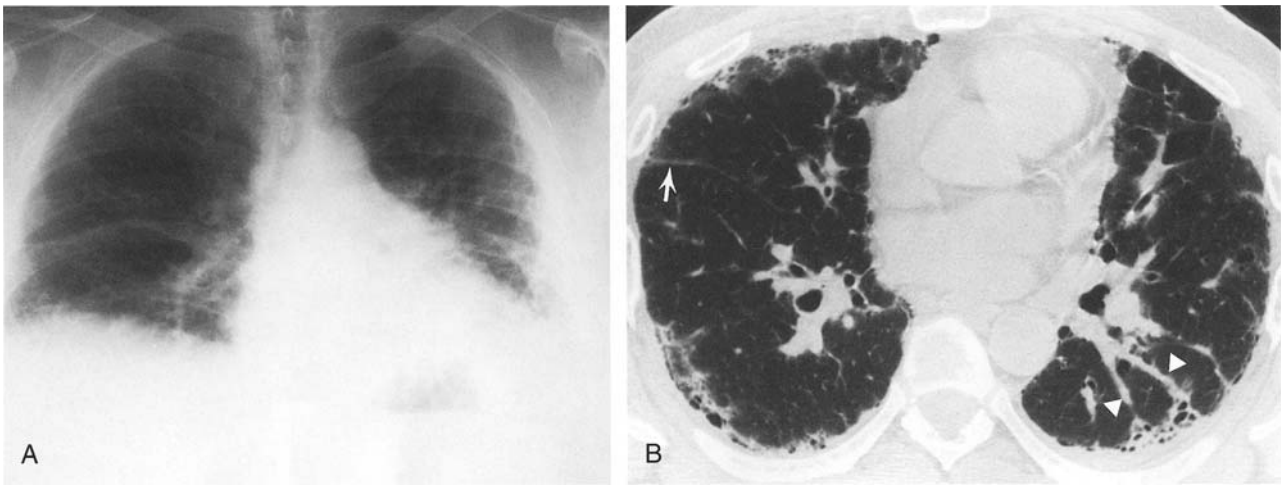

FIGURE 19.8. **A.** A chest radiograph of idiopathic pulmonary fibrosis shows markedly reduced lung volumes and coarse fibrosis concentrated peripherally and at lung bases. **B.** A high-resolution CT of idiopathic pulmonary fibrosis shows patchy peripheral subpleural honeycombing Note thickening of major fissure (arrow) and thickening and nodularity of vessel interfaces in left lung base (arrowheads). (Courtesy of Dr. D. Godwin, University Hospital, Seattle, WA.)

that are undergoing clinical evaluation at present that target various cytokines related to the development of fibrosis. Of these recent trials, data suggest that interferon-γ[49–51] and *N*-acetylcysteine[52,53] may provide additional benefit to the patient, but these drugs are yet to be fully evaluated.[54,55] Transplantation, often of a single lung, is an alternative treatment option, although this is clearly dependent on constraints of organ availability.

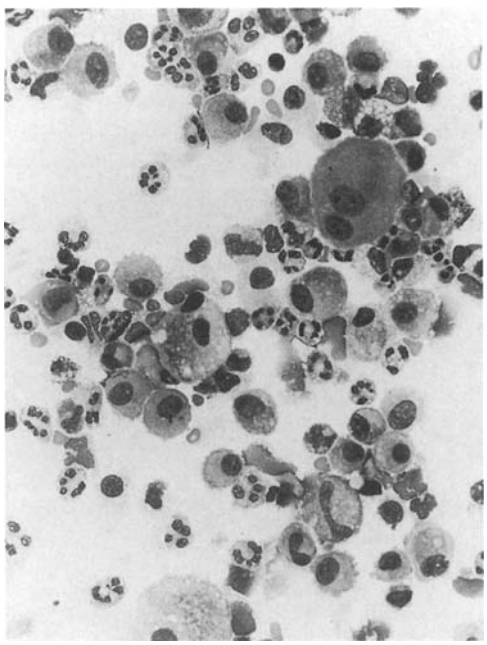

FIGURE 19.9. Increased neutrophils (~20%) form the cellular component of bronchoalveolar lavage fluid from a patient with idiopathic pulmonary fibrosis.

Prognosis is poor, with more recent studies showing 50% survival of less than 3 years.[5,14–20,36–41] Death is usually due to respiratory failure, either chronically progressive or due to an acute exacerbation (see Diffuse Alveolar Damage and Acute Interstitial Pneumonia, below), cardiac failure, or lung cancer. Idiopathic pulmonary fibrosis was found to have a 14-fold increased risk of carcinoma of the lung in patients matched for age and smoking (see Chapter 34).[56] The tumors may be of any histopathologic type, more commonly non–small-cell carcinomas. These carcinomas may be resectable during life, but operative mortality is higher.[57] Various clinical and pathologic features are related to prognosis, although some (for example, cellular versus fibrotic phases) may reflect other histopathologic patterns that were historically included in cohorts of patients with cryptogenic fibrosing alveolitis. Clinical parameters associated with a longer survival include younger age (<50 years), female sex, shorter symptomatic period (≤1 year) with less dyspnea and relatively preserved lung function, the presence of ground-glass and reticular opacities on HRCT, an increased proportion of lymphocytes on BAL fluid, a beneficial response or stable disease 3 to 6 months after corticosteroid therapy, and current cigarette smoking.[13,42] Lung function data in the form of a composite physiologic index and longitudinal behavior also helpful regarding the prognosis.[58,59] In addition, the extent of fibroblastic foci is associated with disease progression and mortality,[32,33] a finding that dovetails with the increasingly held view that IPF is related to epithelial damage and dysregulation of repair.

Pathogenesis

The histopathologic features of IPF suggest that the disease results from repeated episodes of focal damage to the alveolar epithelium. However, the injurious agent or agents are not known, with viruses,[60–63] occupational agents,[64] gastric reflux,[65] and drugs[66,67] all being putative candidates. However, no single agent appears to play a causative role.[34] There are also features in common with pulmonary fibrosis seen in association with connective tissue disorders, with serologic investigations not infrequently showing hyperglobulinemia and the presence of autoantibodies such as rheumatoid factor.[25,36] Other studies have shown antibodies directed against the alveolar epithelium.[68] Therefore, IPF/CFA may represent a form of autoimmune disease with the alveolar epithelium as the target tissue. Genetic susceptibility may also play a role, with functional polymorphisms for various cytokines associated with increased incidence of IPF[69,70] and familial cases being associated with mutations related to the surfactant protein-C gene.[71]

Considerable research effort is now concentrated on the alveolar epithelial cells as the site of initial injury. The hyperplastic pneumocytes express numerous profibrotic cytokines, including transforming growth factor-β (TGF-β), as well as other cytokines that may inhibit cell migration and therefore repair of damaged alveoli. This lack of reepithelialization in part may also be due to increased pneumocyte apoptosis and cell death, perhaps promoted by cytokines the epithelial cells and myofibroblasts secrete, such as TGF-β. The loss of epithelium, with apposition of basement membranes and subsequent collapse likely contributes to the remodeling process, and this dysregulation of repair may also drive sustained fibroblastic proliferation in the underlying stroma.[55] As stated earlier, the extent of these fibroblastic foci correlates with the rate of disease progression and mortality.[32,33] The fibroblasts show an altered typically myofibroblastic phenotype that reflects activation with regard to production of extracellular matrix proteins. Persistence of this activated phenotype likely contributes to development of chronic fibrosis and remodeling, along with a reduced capacity for degradation of extracellular matrix proteins, through imbalances between matrix metalloproteinases and their tissue inhibitors. A detailed review of the various cytokines has recently been published by Thannickal et al. (Fig. 19.10).[55]

However, although emphasis has shifted away from IPF's being a disease driven by inflammation, inflammatory cells still likely play significant roles in modulating disease.[33] Lymphocytes are the predominant interstitial inflammatory cell in IPF, largely comprising T lymphocytes, particularly of the suppressor/cytotoxic (T8) variety.[72,73] The alveolar epithelial cells show aberrant expression of human leukocyte antigen (HLA)-DR, suggesting that the epithelium may be recognized as autoantigenic by the cytotoxic T8 cells.[68,74] However T-helper lymphocytes are also found, and a shift from type I (generally antifibrotic) to type II (generally profibrotic) cytokine profiles may also contribute to fibrosis.[55,75] Other inflammatory cells such as macrophages, mast cells, eosinophils, and neutrophils, also likely contribute to overall disease activity.

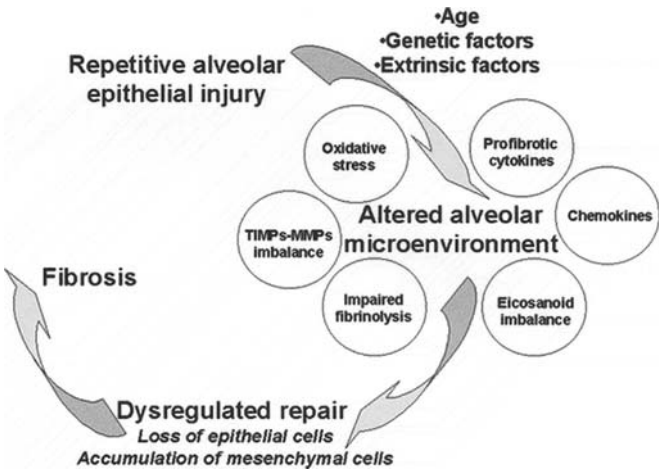

FIGURE 19.10. Progressive pulmonary fibrosis results from dynamic alterations in the alveolar microenvironment that eventually promote loss of alveolar epithelial cells and accumulation of activated fibroblasts/myofibroblasts. Such alterations include the presence or activation of profibrotic cytokines, growth factors, and chemokines; eicosanoid imbalance with increased production of profibrotic leukotrienes and deficiency in prostaglandin E_2; impaired fibrinolysis; overproduction of tissue inhibitors of matrix metalloproteinases (TIMPs) and matrix metalloproteinases. (From Thannickal et al.,[55] with permission. Copyright © 2004, Annual Reviews; www.annualreviews.org.)

Angiogenesis also likely plays a role, with new vessel formation being well characterized in normal tissue repair. However, there are conflicting data with regard to various proangiogenic factors in UIP/IPF; for example, there is increased IL-8 in the tissue of patients with IPF,[76] but while vascular endothelial growth factor (VEGF) is expressed in fibroblastic foci in UIP,[77] its levels are reduced in BAL fluid.[78] It has also been shown that the granulation tissue of OP is of greater vascularity than that within fibroblastic foci of UIP/IPF,[79] and also expresses VEGF to a greater degree.[77] Conversely, foci of increased vascularity can be seen at the bases of fibroblastic foci if correctly oriented, while others describe decreasing vascularity as fibrosis increases within the interstitium.[80] Therefore, exactly how and if remodeling of architecture relates to angiogenesis currently remains uncertain.[81]

Differential Diagnosis

The most problematic area is the distinction of UIP from fibrotic NSIP, with diagnostic confidence often low in this situation in interobserver studies.[82] Key distinguishing features are a relatively diffuse pattern of interstitial fibrosis and an absence or scarcity of fibroblastic foci in NSIP. Indeed, some cases of IPF show a pattern of fibrotic NSIP,[14,19] in part explaining this potential overlap. In these difficult cases, consideration of the clinical and imaging features may be of great help in deciding whether the patient truly has IPF or whether the histology represents some other clinicopathologic entity. There are also occasions when multiple biopsies show UIP at one site and fibrotic NSIP at another, so-called discordant UIP. In this instance, the prognosis is driven by the pattern of UIP.[19,83] Discordance between radiologic and histopathologic diagnoses of UIP and fibrotic NSIP also indicate that the presence of UIP is the adverse prognostic factor in either modality.[84]

Organizing pneumonia may progress to interstitial fibrosis, and when foci of intraalveolar organization are closely applied to the interstitium, presumably as they become incorporated, they can look identical to the fibroblastic foci of UIP. However, the presence of more typical areas of organizing pneumonia elsewhere in the biopsy, plus clinical and radiologic correlation, usually allows distinction from IPF/CFA.

Sometimes there are abundant macrophages, resulting in a DIP-like pattern, but if there is an underlying pattern of patchy subpleural fibrosis with fibroblastic foci, then the biopsy should be classified as UIP. Interstitial fibrosis, when present in DIP, is usually mild and diffuse. There may also rarely be a superimposed pattern of diffuse alveolar damage (DAD) superimposed on background UIP in patients with an acute exacerbation (see Diffuse Alveolar Damage and Acute Interstitial Pneumonia, below), although DAD itself is easily distinguished by the characteristic hyaline membranes or diffuse intraalveolar organization (see Chapter 4).

The absence of asbestos bodies excludes asbestosis and, although Langerhans cells may not always be present in burned-out Langerhans cells granulomatosis, the stellate and more bronchocentric distribution of fibrosis and especially HRCT data usually exclude IPF/CFA. Drug reactions should also be excluded especially in the presence of focal eosinophilic-pneumonia–like areas.[35] Chronic hypersensitivity pneumonia may show small granulomas, be more bronchocentric in its distribution of fibrosis, and have a greater extent of chronic inflammation than UIP in IPF/CFA, but this is not always the case and again emphasizes the need for clinical and imaging correlation in order to avoid misdiagnosis.

Nonspecific Interstitial Pneumonia

The term *nonspecific interstitial pneumonia* (NSIP) was first used in relation to a pattern of inflammation seen in association with HIV infection,[85] but it was the seminal paper in 1994 by Katzenstein and Fiorelli[10] that first used NSIP in the context of interstitial pneumonias. Nonspecific interstitial pneumonia has subsequently evolved into a recognized pattern of idiopathic interstitial pneumonia[14–19] with defined characteristics on histology[24] and HRCT,[86–88] although its clinical correlate(s) remain less well defined and the term *nonspecific interstitial pneumonia* is regarded as provisional in the consensus classification system (Table 19.1).[24]

Histopathologic Features

Histologically, NSIP has a temporally uniform pattern, characterized by expansion of the interstitium, a variable extent of chronic inflammation and fibrosis. The inflammatory cell infiltrate comprises mainly small lymphocytes with some plasma cells and macrophages, while the fibrosis can be collagenous or fibroblastic in nature, or even both. However, the overall *age* of the fibrosis, when present, appears relatively constant within the affected areas. Although initially subdivided into grades 1 to 3, dependent on the degrees of fibrosis and inflammation,[10] later studies showed that the survival for the mixed (grade 2) and fibrotic (grade 3) patterns were similar,[14,18] while those with no fibrosis (grade 1) had a much better prognosis. Therefore, the consensus classification recommended usage of only two subtypes: cellular NSIP (Fig. 19.11) and fibrotic NSIP (Fig. 19.12).[24] The other main feature in the diagnosis of fibrotic NSIP is a lack or scarcity of fibroblastic foci, primarily distinguishing it from UIP. There is also relative preservation of architecture in NSIP compared to UIP. The minor features of cellular NSIP are listed in Table 19.4 and of fibrotic NSIP in Table 19.5. For fibrotic NSIP, these are not dissimilar to those seen in UIP, although they are of lesser intensity.

Clinicopathologic Correlation

Clinical Presentation

Because of continued uncertainty over what NSIP clinically represents, its incidence and prevalence remain to be defined, with variations in published series likely reflecting bias within individual cohorts. In time, subsets of NSIP in relation to pathogenesis (as discussed below in this section) may evolve, but current data reflect populations of NSIP based on histology alone. With this in mind, patients generally present at around 50 years of age, being slightly younger than those with IPF/CFA and UIP. Those with cellular NSIP are younger still, averaging

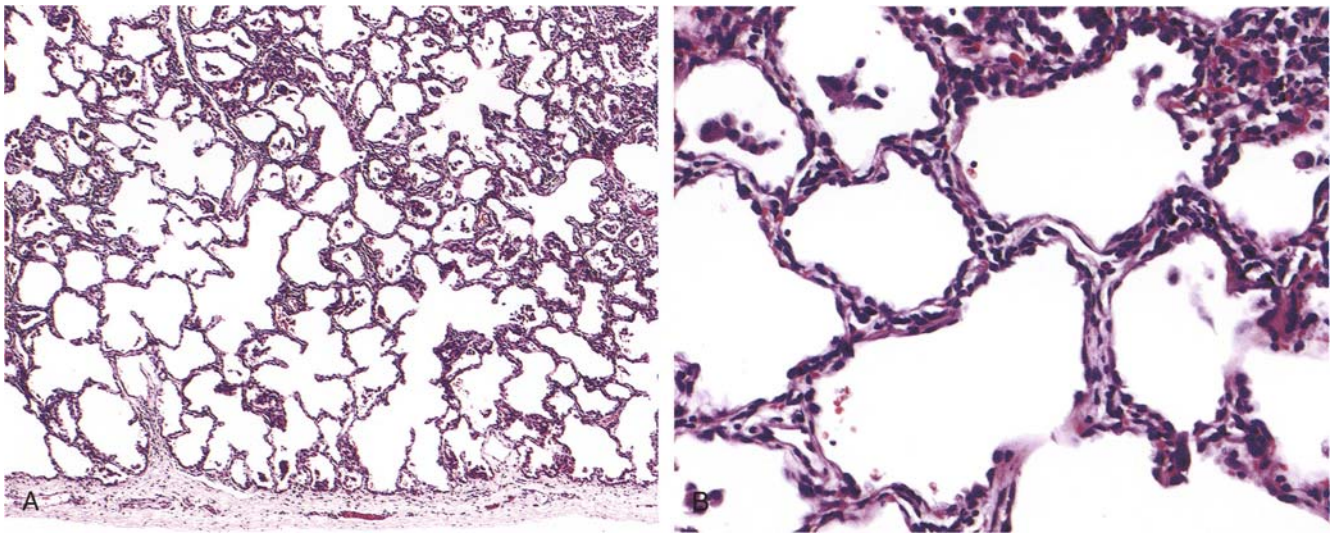

FIGURE 19.11. **A.** A case of cellular nonspecific interstitial pneumonia shows a mild diffuse interstitial infiltrate of chronic inflammatory cells with no interstitial fibrosis. **B.** At high power, mild type 2 cell hyperplasia is also seen.

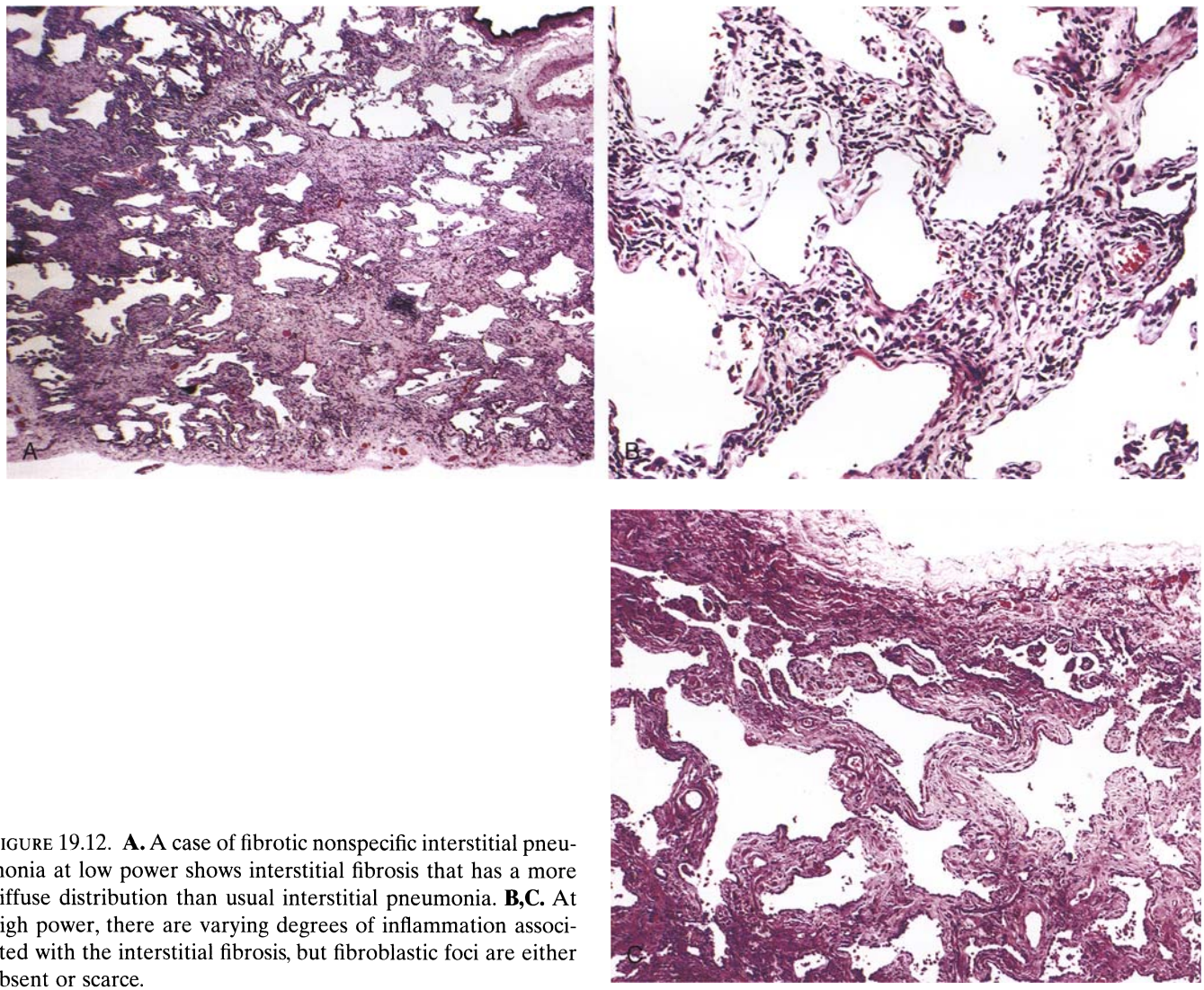

FIGURE 19.12. **A.** A case of fibrotic nonspecific interstitial pneumonia at low power shows interstitial fibrosis that has a more diffuse distribution than usual interstitial pneumonia. **B,C.** At high power, there are varying degrees of inflammation associated with the interstitial fibrosis, but fibroblastic foci are either absent or scarce.

TABLE 19.4. Histologic features of cellular nonspecific interstitial pneumonia

Major features	Minor (or secondary) changes	Pertinent negative features
Mild to moderate interstitial chronic inflammation	Mild alveolar macrophage accumulation	
Diffuse involvement of affected parenchyma	Follicular hyperplasia	Dense interstitial fibrosis
Preservation of alveolar architecture	Organizing pneumonia	Lack of inorganic dusts (e.g., asbestos)
	Peribronchiolar fibrosis	Lack of granulomas
	Mild chronic pleuritis	Lack or paucity of eosinophils
	Type 2 pneumocyte hyperplasia	Lack of organisms (e.g., viral inclusions)
	Focal alveolar fibrin	

Source: Adapted from American Thoracic Society.[13] Copyright © 2000, American Thoracic Society.

39 years.[18,24] Many of the patients are smokers or ex-smokers. Symptoms and signs are similar to those seen in IPF/CFA, with patients presenting with dyspnea, cough, and fever, and having crackles on auscultation and frequently clubbing of the fingers. Lung function studies generally show a restrictive defect.[16,89] High-resolution computed tomography shows ground-glass opacities and reticular changes, which may be diffuse but mainly involve the lower lobes (Fig. 19.13). Honeycombing is less prevalent than in UIP.[86–88] Some BAL studies have shown increased numbers of lymphocytes,[89] while others have shown no difference from UIP,[47] again likely reflecting the source of the studied cohorts.

Treatment and Prognosis

Nonspecific interstitial pneumonia appears to be responsive to corticosteroid therapy, especially cellular NSIP, but is often treated in addition with immunosuppressive therapy, either azathioprine or cyclophosphamide. In one series, survival for fibrotic NSIP is significantly better than that seen in UIP (90% versus 43%) but the difference is considerably less in one study that followed the patients to 10 years (35% versus 15%).[18] Five-year survival for cellular NSIP approaches 100%.[14,18]

Pathogenesis

A noticeable feature of the consensus classification was that, although the histopathologic and radiologic features of NSIP were well characterized, there was uncertainty as to its clinical correlate. The term *nonspecific interstitial pneumonia* was therefore left as provisional (Table 19.2), and subsequent studies have focused on addressing this issue. Currently, it seems likely that there is more than one etiology and if one returns to the original paper by Katzenstein and Fiorelli,[10] it is interesting to note that they were particular in stating that there were several clinical associations with this histopathologic pattern (collagen vascular diseases, exposure to environmental allergens, history of acute lung injury), many of which reflect more recent conclusions as to the causes of this pattern (Fig. 19.14).

Nonspecific Interstitial Pneumonia in Idiopathic Pulmonary Fibrosis/Cryptogenic Fibrosing Alveolitis

There is now good evidence that fibrotic NSIP can occur in a setting of IPF/CFA,[14,19] as both patterns can be seen in the same patient and even in the same lobe.[19] However, whether these cases of NSIP represent early or inactive

TABLE 19.5. Histologic features of fibrotic nonspecific interstitial pneumonia

Major features	Minor (or secondary) changes	Pertinent negative features
Mild to moderate interstitial chronic inflammation	Alveolar macrophage accumulation	Lack of inorganic dusts (e.g., asbestos)
Diffuse involvement of affected parenchyma	Follicular hyperplasia	Lack of granulomas
Mild to moderate loss of alveolar architecture	Organizing pneumonia	Lack or paucity of eosinophils
Variable degree of interstitial fibrosis	Bronchiolar, bony, fatty and squamous metaplasia*	Lack of organisms (e.g., viral inclusions)
Lack or rarity of fibroblastic foci	Smooth muscle hypertrophy/hyperplasia*	
	Endarteritis	Lack of Langerhans' cells
	Mild chronic pleuritis and pleural fibrosis	Lack or paucity of honeycomb change
	Type 2 pneumocyte hyperplasia	
	Focal alveolar fibrin	

*Features less intense than in UIP.

Source: Adapted from American Thoracic Society.[13] Copyright © 2000, American Thoracic Society.

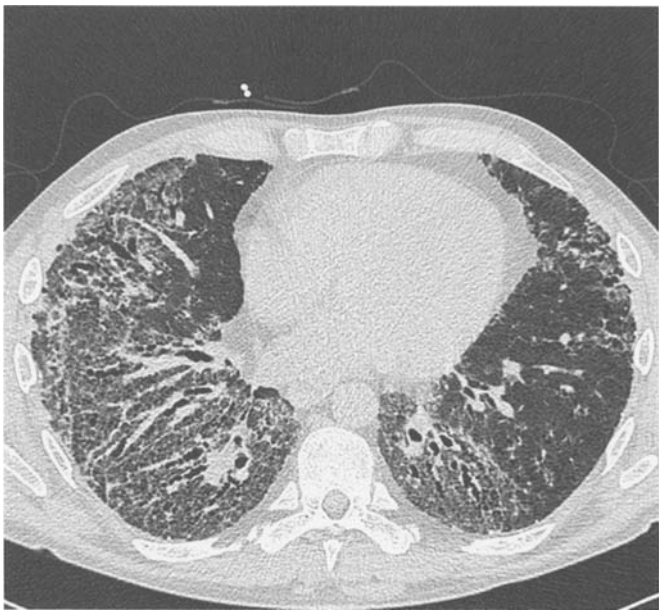

FIGURE 19.13. An HRCT of fibrotic nonspecific interstitial pneumonia shows coarse reticular shadowing and traction bronchiectasis, but no honeycombing.

phases of IPF remains unclear.[19,90] The prevalence of such cases in individual cohorts of patients with a histopathologic pattern of NSIP may be part of the cause of variations in prognosis for this pattern seen between different institutions, and the fact that some series of fibrotic NSIP describe a mortality at 10 years closer to that of UIP than a comparison at 5 years.[18]

Nonspecific Interstitial Pneumonia in Hypersensitivity Pneumonia

Some cases of fibrotic NSIP are likely due to chronic hypersensitivity, in which the granulomas are absent and there is a relative or absolute lack of bronchocentricity to the inflammation and fibrosis that points toward an airway-centered disease. Occasional fibroblastic foci may further confuse the picture. However, although bronchocentricity may be absent on biopsy, it may be more easily apparent on HRCT with the advantage therein of assessing the whole lung. A similar lack of bronchocentricity and granulomas may cause less chronic cases to be preferentially classified as cellular NSIP. In both instances, undertaking biopsies from different sites obviates what is often a sampling error, and good clinical correlation will often identify other salient features, on clinical questioning, bronchoalveolar lavage, or via serologic investigations.

Nonspecific Interstitial Pneumonia in Relation to Smoking

It is well established that histopathologic patterns of DIP and RB are mainly caused by injury due to cigarette smoking (see Respiratory Bronchiolitis and Respiratory Bronchiolitis-Associated Interstitial Lung Disease, below, and Desquamative Interstitial Pneumonia, below), but there may be a further cohort of patients who show a pattern of fibrotic NSIP due to a similar injury, often in association with microscopic evidence of emphysema.[91] In these putative cases, there is typically very little chronic inflammation, and the fibrosis appears distinctly hyaline. However, there is little conclusive data as yet to confirm this hypothesis.

Nonspecific Interstitial Pneumonia in Relation to Acute Lung Injury

In Katzenstein and Fiorelli's[10] original paper, a few long-term survivors of diffuse alveolar damage were noted to have a pattern of NSIP in areas of residual lung fibrosis. These should be easily identified by obtaining a clinical history of a previous episode of acute respiratory failure. In addition to this, there is also a cohort of patients with organizing pneumonia who progress to fibrosis, and they

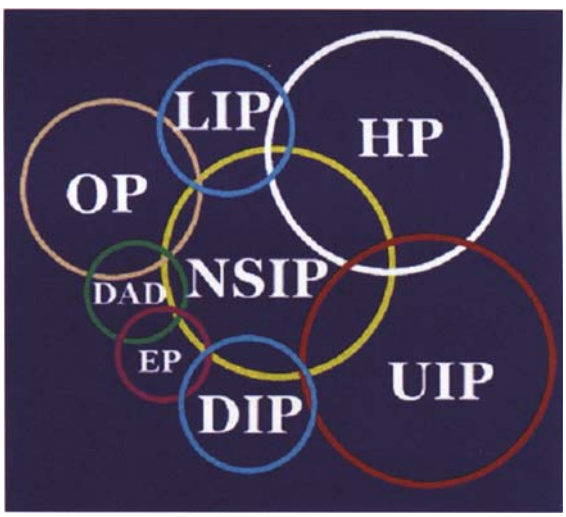

FIGURE 19.14. Nonspecific interstitial pneumonia (NSIP): overlap with interstitial diseases. NSIP has some degree of overlap with a variety of interstitial diseases. UIP, usual interstitial pneumonia; HP, hypersensitivity pneumonia; OP, organizing pneumonia; DIP, desquamative interstitial pneumonia; EP, eosinophilic pneumonia; LIP, lymphocytic interstitial pneumonia; DAD, diffuse alveolar damage. (From Travis WD, ed., Armed Forces Institute of Pathology. Non-neoplastic disorders of the lower respiratory tract. In: Atlas of nontumor pathology. Washington, DC: American Registry of Pathology, 2002, with permission.)

may also show a pattern of fibrotic NSIP. This is discussed in more detail in Chapter 4.

Nonspecific Interstitial Pneumonia in the Context of Collagen Vascular Disease

Collagen vascular diseases (CVDs) are a heterogeneous group of diseases that includes rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis (PM/DM), systemic lupus erythematosus (SLE), Sjögren's syndrome, and mixed connective tissue disorders (MCTDs). Series published after recognition of NSIP show this pattern to be prevalent in systemic sclerosis,[92] polmyositis,[93,94] Sjögren's syndrome,[95] and rheumatoid arthritis,[94] although there are subtle variations in the prevalence of other patterns or overlapping features when viewed collectively. These are discussed in greater detail in Chapter 20.

Idiopathic Nonspecific Interstitial Pneumonia

When a pathologist first makes a histopathologic diagnosis of NSIP, it should be regarded as a "holding pattern" from which the clinician can then return to the patient to look for the clinical associations described above, rather than as a final "wastebasket" diagnosis.[90] As such, many cases will be given a clinicopathologic diagnosis that relates to the above discussion (Fig. 19.14), but there remain a minority of cases that are truly idiopathic. Some of these may be patients presenting with pulmonary manifestations of a CVD, as it is known that these can precede other systemic manifestations. Others may represent as yet undiscovered gene mutations or environmental insults.

Differential Diagnosis

Many of the differential diagnoses of a histopathologic pattern of NSIP are reflected in the above discussion on pathogenesis. However, clinical correlation notwithstanding, it is the opinion of the pathologist that there is a lack or absence of fibroblastic foci and patchy subpleural distribution (as in UIP), bronchocentric inflammation, fibrosis and granulomas (as in hypersensitivity pneumonia), intraalveolar organization (as in OP), alveolar macrophage accumulation (as in DIP), hyaline membranes (as in DAD), and density of interstitial chronic inflammation (as in LIP) that leads to the eventual histopathologic classification as NSIP. Another approach when viewing such biopsies is that, in the context of interstitial fibrosis and inflammation, none of the above histopathologic features predominates, and this relative lack of cardinal diagnostic features for other patterns leads to classification as NSIP.

Respiratory Bronchiolitis and Respiratory Bronchiolitis-Associated Interstitial Lung Disease

Respiratory bronchiolitis is a common incidental histopathologic finding in heavy smokers,[96] and is seen in most resections for lung cancer in the parenchyma removed at anatomic resection. However, these changes were not known to cause symptoms in terms of diffuse parenchymal lung disease until Myers et al.[8] described six patients in 1987, all heavy smokers, who had clinical, radiologic, and physiologic evidence of chronic interstitial lung disease but only respiratory bronchiolitis on surgical lung biopsy. The term *respiratory bronchiolitis–associated interstitial lung disease* (RBILD) was later coined in a further series that clarified the histopathologic differences among the incidental changes of smoking, RBILD, and DIP.[9]

Histopathologic Features

Respiratory bronchiolitis is characterized by an accumulation of alveolar macrophages within respiratory bronchioles spilling into neighboring alveoli. Their accumulation may be associated with peribronchiolar alveolar septal thickening by fibroblasts and collagen deposition, characteristically radiating from the bronchiole (Fig. 19.15). There is usually an accompanying chronic inflammatory cell infiltrate in the walls of the bronchioles and the surrounding alveolar interstitium. The alveolar parenchyma at the periphery of acini is either mildly affected or normal. No honeycomb changes have been described, although there may be varying amounts of centrilobular emphysema (Table 19.6).[8,9,24,97,98]

Clinicopathologic Correlation

Clinical Presentation

The most important consideration when assessing a patient whose biopsy shows RB is to determine whether the patient truly has RB-ILD or if the biopsy features are a sampling error in a smoker with a different disease process. Almost all patients with RBILD are cigarette smokers, and they are aged between 22 and 53 years with an equal sex distribution. The commonest presenting features are a gradual onset of shortness of breath and a prominent cough.[99] Other symptoms include chest pain, weight loss, and rarely fever and hemoptysis. Clubbing is extremely rare.[8,9,97–100] A normal chest radiograph is found in approximately 20% of patients with RBILD. High-resolution CT scans show varying degrees of patchy ground-glass opacity and centrilobular nodules

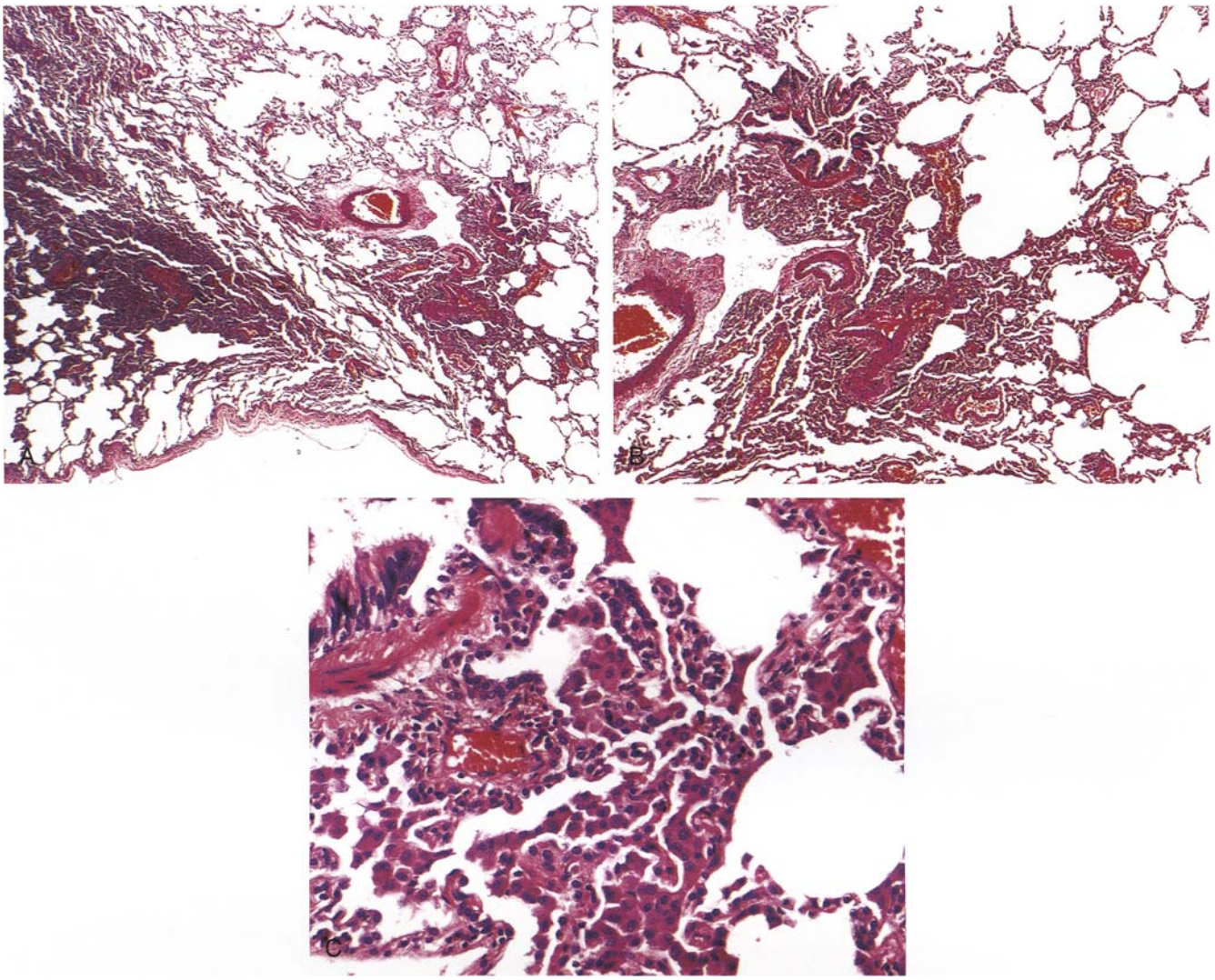

FIGURE 19.15. **A–C.** A case of respiratory bronchiolitis-associated interstitial lung disease (RBILD) shows a milder and more centrilobular distribution of the macrophages when compared to desquamative interstitial pneumonia in Figure 19.17.

(Fig. 19.16),[97] and, as expected, several series have noted considerable overlap in the HRCT appearances of RBILD and DIP, supporting the idea that they represent different degrees of reaction to cigarette smoke. Indeed, similar but less extensive findings are also seen in asymptomatic smokers.[8,9,97,99,101] Lung function tests show both restrictive and obstructive abnormalities, despite the centriacinar nature of RBILD, although most frequently there is a mixed, predominantly restrictive ventilatory defect, usually associated with a mild to moderate reduction in the carbon monoxide diffusing capacity (DL_{CO}).[8,9,97] Airflow obstruction is usually mild. Bronchoalveolar lavage studies show an increase in pigmented alveolar macrophages with serial data suggesting that, on average, BAL macrophage percentages in ex-smokers fall to lifelong nonsmoking levels in 3 years.[102]

TABLE 19.6. Histologic features of respiratory bronchiolitis

Major features	Minor (or secondary) changes	Pertinent negative features
Bronchocentric accumulation of macrophages	Coexistent centrilobular emphysema	Lack of diffuse involvement of pulmonary acini
Mild bronchiolar fibrosis and chronic inflammation		No honeycomb change
Light brown cytoplasmic pigmentation within macrophages		No evidence of other airway damaging agents

Source: Adapted from American Thoracic Society.[13] Copyright © 2000, American Thoracic Society.

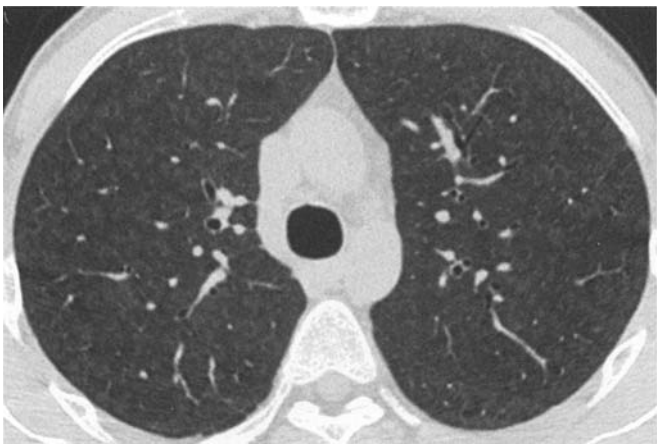

FIGURE 19.16. An HRCT of respiratory bronchiolitis shows randomly distributed, poorly defined, low attenuation centrilobular nodules.

Treatment and Prognosis

Cessation of smoking has led to the improvement of symptoms in some patients, and there have also been reported responses to corticosteroid therapy. Five-year survival approaches 100% for these patients, although there are some reports of deterioration of symptoms.[97,100]

Pathogenesis

Epidemiologic evidence in published series shows that smoking plays a prime role in the development of RB in nearly all patients who are either current or ex-smokers.[8,9,97,98] Rare patients have given history of other inhalational exposures.[97] The level of cytoplasmic pigmentation of macrophages and the presence of peribronchial fibrosis correlated with the pack-year smoking history in one study.[98] Although there are no studies that address why only certain patients become symptomatic, there are interesting follow-up HRCT studies on smokers with presumed RB who develop evidence of emphysema at these sites over time, providing data in relation to the pathogenetic role of macrophages in the development of emphysema.[103]

Differential Diagnosis

Respiratory bronchiolitis (RB) is easily distinguishable from UIP, NSIP, OP, LIP, and DAD, as a significant accumulation of macrophages is not seen and other diagnostic histopathologic features (marked established fibrosis, fibroblastic foci, intraalveolar organization, dense lymphoid interstitial infiltrate, and hyaline membranes) are absent. If any of these features are present, even in one of multiple biopsies, it should raise the possibility of the respiratory bronchiolitis being incidental to a second pathology. Indeed, in terms of diagnosis, confirmation through a clinicopathologic review that RB is the cause of symptoms and not an incidental finding is as important as its identification. Distinction from DIP is discussed below in the context of smoking-related interstitial lung disease.

Desquamative Interstitial Pneumonia

Desquamative interstitial pneumonia (DIP) is mainly an alveolar filling defect, first described by Liebow in 1965, in which alveoli are expanded by macrophages,[3,104] although these were initially thought to be desquamated pneumocytes, hence the name. Historically, some groups viewed DIP as an early cellular phase of cryptogenic fibrosing alveolitis,[5,37] although this is now known not to be the case from data on prognosis[14,15,18] and studies on disease progression using HRCT.[105,106] Most cases are more closely associated with RBILD and a history of smoking. An alternative term, *alveolar macrophage pneumonia,* has been proposed, given that it is neither desquamative nor predominantly interstitial, but the consensus view is to continue with the term DIP.[24]

Histopathologic Features

The major feature is the presence of large numbers of macrophages within alveoli, with a diffuse distribution throughout pulmonary acini. These macrophages characteristically have abundant eosinophilic cytoplasm, which may have a glassy appearance and often contain a finely granular light brown pigment that stains variably for fine granular hemosiderin. The alveolar architecture is generally well maintained, although there is usually a mild chronic inflammatory cell infiltrate within the interstitium. Lymphoid follicles are also not infrequently present. Moderate numbers of eosinophils may also be seen, both within the interstitium and admixed with the alveolar macrophages (Fig. 19.17). Interstitial fibrosis is rarely more than mild in intensity and it lacks the fibroblastic foci characteristic of UIP.[107] Although there may be loss of architecture and cystic air-space formation, the changes appears closer to emphysema than the honeycomb change seen in UIP, with the remodeling of architecture and bronchiolization of honeycomb change being exceptional (Table 19.7).

Clinicopathologic Correlation

Clinical Presentation

Patients usually present in the fourth or fifth decade, complaining of a gradual increase in shortness of breath in association with a dry cough. Fever, fatigue, and loss of

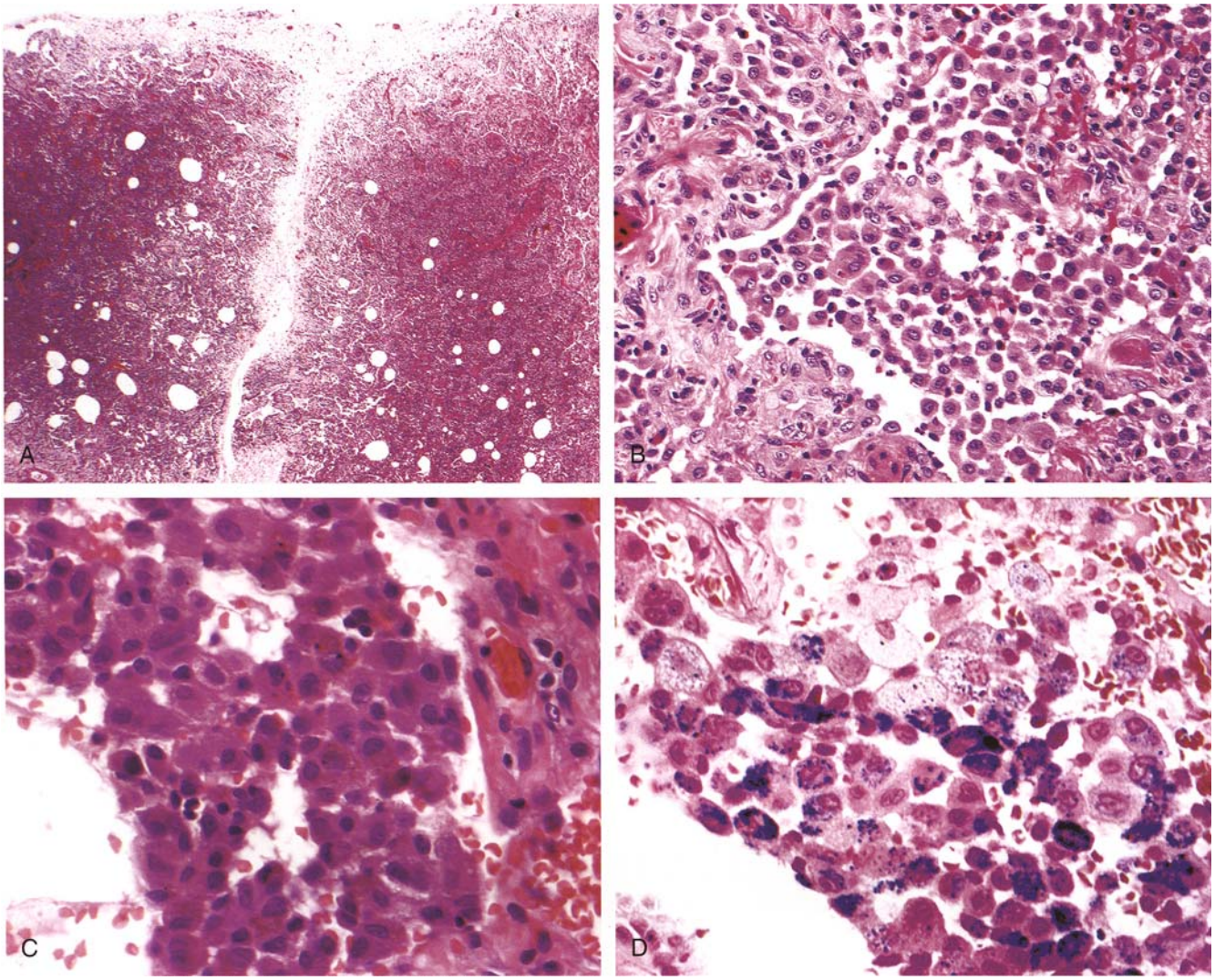

FIGURE 19.17. **A.** A case of desquamative interstitial pneumonia shows uniform distribution of alveolar macrophage accumulation. **B,C.** The macrophages have abundant glassy eosinophilic cytoplasm, sometimes with light brown pigmentation that shows variable staining for hemosiderin **(D).** At high power, the macrophages responsible for desquamative interstitial pneumonia and RBILD appear identical (cf. Figure 19.15C).

TABLE 19.7. Histologic features of desquamative interstitial pneumonia

Major features	Minor (or secondary) changes	Pertinent negative features
Uniform involvement of lung parenchyma	Mild to moderate interstitial fibrosis	No honeycomb change
Marked accumulation of macrophages	Mild interstitial chronic inflammation	Lack of fibroblastic foci typical of UIP
Light brown cytoplasmic pigmentation within macrophages	Mild follicular hyperplasia	No eosinophilic microabscesses
	Often a mildly increased numbers of eosinophils	Lack of inorganic dusts (e.g., asbestos)
	Concomitant centrilobular emphysema	Lack of granulomas

Source: Adapted from American Thoracic Society.[13] Copyright © 2000, American Thoracic Society; and Craig et al.[107]

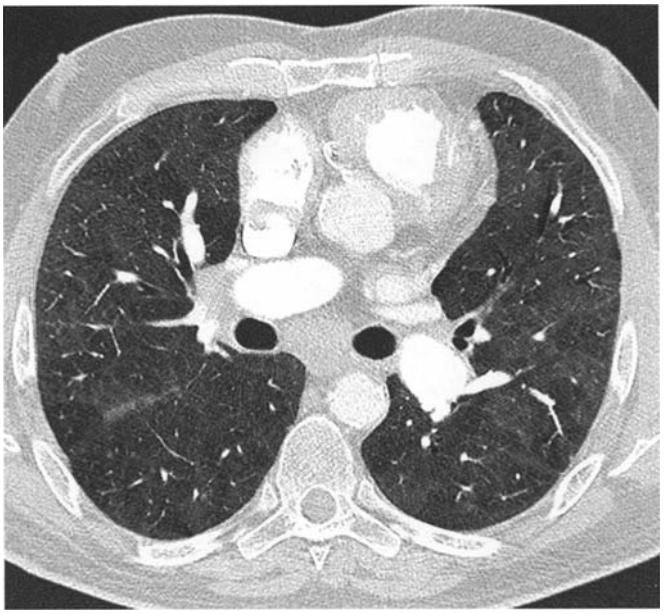

FIGURE 19.18. An HRCT of desquamative interstitial pneumonia shows widespread ground-glass opacification.

weight may occur, although clubbing is rare. Bilateral basal inspiratory crackles are frequently found on auscultation. The HRCT findings of DIP are documented in several studies,[105,106,108] with ground-glass opacities the most common feature (Fig. 19.18). Pulmonary function tests are consistently restrictive with the reduction in DL_{CO} a useful guide to the underlying severity of disease. Hypoxia only appears to supervene in advanced disease. There are few studies on BAL, but it is said to show an increase in cell numbers, particularly macrophages, and occasionally increased eosinophils.[109]

Treatment and Prognosis

Cessation of smoking plays a prime role in treatment, and may in itself lead to symptomatic improvement.[110,111] However, the disease is typically treated with corticosteroids with or without immunosuppressive agents, often with a good response to treatment. It is likely that in occasional cases, a poor response to corticosteroids or immunosuppressive agents is indicative of significant underlying fibrosis, especially in long-standing disease. Also, some patients do progress with a poor prognosis.[105]

Desquamative interstitial pneumonia has a better outcome than UIP and fibrotic NSIP,[14,29] with poor outcome only in a minority of cases.[105] In recent studies, 5-year survival approaches 100%.[14,18,107] In adults, there is no difference in prognosis between smokers and nonsmokers.[107] Prognosis is worse in children, especially those with familial disease, likely reflecting a different etiology such as an inborn error of metabolism.[112,113]

Pathogenesis

Epidemiologic studies suggest that DIP is a pathologic response to a variety of pulmonary insults rather than a specific disease. In adults, there is a history of smoking in about 90% of cases, and in these individuals DIP may be regarded as an excessive macrophage response to the smoke. However, although RBILD is almost exclusively a disease of smokers, there are several other agents that are rarely reported as causing a DIP-like reaction such as dust inhalation,[114–116] drug reactions,[117] and inborn errors of metabolism.[118] There is also a small group of patients, who are never smokers and have no evidence of any other causative association and are therefore regarded as having idiopathic disease.[107]

The Concept of Smoking-Related Interstitial Lung Disease

Smoking related-interstitial lung disease (SRILD) has been proposed as a term to encompass DIP, RBILD, and Langerhans' cell granulomatosis (LCG),[91,119–122] with RB- and DIP-like changes frequently seen in the lung adjacent to LCG.[123] Small stellate scars that are likely foci of burned-out Langerhans' cell granulomatosis may also be seen in biopsies from patients with RB and DIP. However, defining SRILD is not that straightforward, as interstitial changes are complicated by emphysema of varying degree, and there may be some cases that histopathologically are closer to NSIP (see Nonspecific Interstitial Pneumonia, above). These areas of research notwithstanding, it is reasonable to group cases with RB, DIP, or LCG as SRILD, *but only in the context of a history of smoking and appropriate radiology*, and it is often useful to ascribe this term when features overlap among the various patterns in surgical lung biopsies and there is a history of smoking. However, the individual terms should be maintained within this heading, as there remain important differences between the entities therein. For example, histopathologically there are differences in severity between the RB and DIP, with an increased extent of fibrosis, lymphoid hyperplasia, and eosinophil numbers in DIP.[107] Epidemiologically, nearly all cases of RB are related to inhalation of smoke, while about 10% of DIP may be due to other causes. Clinical presentation and courses also differ, with DIP being more aggressive than RBILD and with no evidence that progression from RBILD to DIP occurs.[119] The BAL profiles of the two diseases are also dissimilar.[47] On HRCT, the micronodular abnormalities of RBILD are not seen in DIP, and although HRCT follow-up data are rare, there is evidence that DIP may progress to a fine fibrosis akin to fibrotic NSIP,[107] while the only follow-up data on RB suggest it may progress to centrilobular emphysema.[103] Finally, the indications for corticosteroid treatment are often

marginal in RBILD, whereas treatment is usually more active in DIP. Therefore, DIP and RBILD should continue to be regarded as separate entities, and the term *smoking related-interstitial lung disease* should be used with caution outside of DIP, RBILD, and LCG in patients with a smoking history until the relevance of coexistent emphysema and interstitial fibrosis are better clarified.

Differential Diagnosis

In DIP, severe fibrosis and honeycombing are exceptional features, and UIP should be thoroughly excluded in these instances. Also, UIP will usually show fibroblastic foci and does not typically have an abundance of macrophages. In cases where there is doubt over the histopathologic pattern, correlation with clinical and imaging data helps in distinguishing IPF/CFA from DIP. With regard to other histopathologic patterns, DIP should be easily distinguishable from OP, LIP, and DAD, as a significant accumulation of macrophages is not seen and other diagnostic histopathologic features (intraalveolar organization, dense lymphoid interstitial infiltrate, and hyaline membranes) are absent. In relation to NSIP, there may occasionally be an overlap between these patterns, as the volume of macrophages is not consistently present throughout all lung fields. However, correlation with the clinical and imaging data in these situations usually leads to the correct clinicopathologic diagnosis. The overlap among DIP, NSIP, and smoking is discussed in the previous section. Occasionally eosinophils may be notably prominent in DIP, raising the differential diagnosis of eosinophilic pneumonia. However, clinical presentation and HRCT patterns differ, and eosinophilic microabscesses are not seen in DIP.

Diffuse Alveolar Damage and Acute Interstitial Pneumonia

Diffuse alveolar damage is the histopathologic pattern seen most commonly in the acute respiratory distress syndrome (ARDS), which is discussed in detail in Chapter 4. It may also be seen in the context of an acute exacerbation of patients with IPF/CFA and even more rarely, in an idiopathic setting.

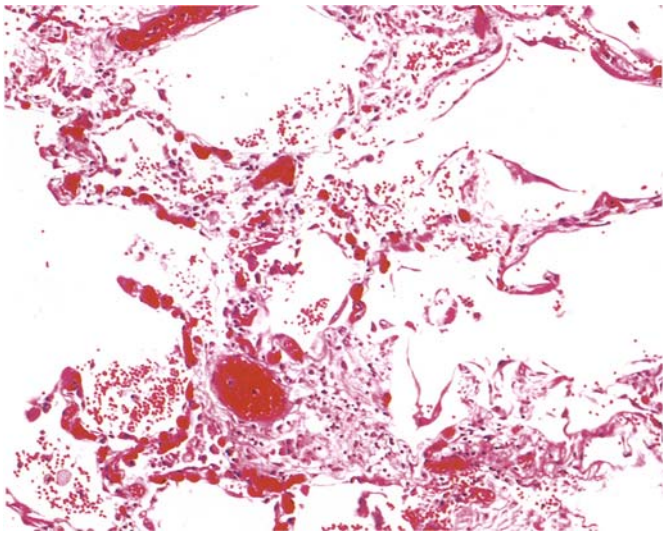

FIGURE 19.19. A case of acute interstitial pneumonia shows diffuse alveolar damage in the exudative phase. The interstitium is expanded by a few fibroblasts and a mixed inflammatory cell infiltrate, with hyaline membranes lining alveoli.

Histopathologic Features

Diffuse alveolar damage is characterized by marked expansion of the interstitium by a predominantly fibroblastic proliferation with an accompanying mixed inflammatory cell infiltrate of variable intensity. There is hyperplasia of type 2 pneumocytes that may show sufficient cytologic atypia to enter the differential diagnosis of malignancy in cytologic specimens. The bronchiolar epithelium may also show squamous metaplasia. In the exudative phase, hyaline membranes are nearly always present (Fig. 19.19), while organizing pneumonia by definition predominates in the organizing phase. Thrombi are not infrequent within small pulmonary arteries (Table 19.8).[11] In a patient with an acute exacerbation of IPF/

TABLE 19.8. Histologic features of diffuse alveolar damage/acute interstitial pneumonia

Major features	Minor features	Pertinent negative features
Diffuse distribution	A background of UIP in acute exacerbations	Lack of granulomas, abscess or necrosis
Uniform temporal appearance		No evidence of infection (viral inclusions, special stains, culture, etc.)
Diffuse alveolar septal thickening, either cellular or fibroblastic		No marked increase in eosinophils
Hyaline membranes (exudative phase)		
Organizing pneumonia (organizing phase)		

Source: American Thoracic Society.[13] Copyright © 2000, American Thoracic Society; and Rice et al.[124]

CFA, the features of DAD will be superimposed on a background of UIP and very rarely fibrotic NSIP.[124]

Clinicopathologic Correlation

Clinical Presentation

Acute Interstitial Pneumonia

Although far more commonly seen in the setting of ARDS, DAD may also rarely occur in an idiopathic setting, in which situation the disorder is termed acute interstitial pneumonia (AIP). As opposed to the other clinicopathologic disorders in the consensus classification, AIP has an acute presentation and rapid clinical progression,[11] considered in some cases to be synonymous with Hamman-Rich disease.[2] There is a wide age range, and patients have no underlying disease or predisposing factors for acute respiratory failure.[11,125] Clinical presentation begins with a flu-like episode, which is succeeded by rapidly progressive severe dyspnea usually leading to death from respiratory failure. High-resolution CT shows bilateral ground-glass opacities, bronchial dilatation, and dependent consolidation.

Acute Exacerbation of Idiopathic Pulmonary Fibrosis/ Cryptogenic Fibrosing Alveolitis

Although the clinical course of IPF/CFA is usually chronic and slowly progressive, some patients experience rapid deterioration during the course of their illness. This phenomenon has been termed acute exacerbation of IPF/CFA and until recently has been considered very rare, although series are increasingly being reported, most often in the radiology literature.[124,126–129] Criteria for acute exacerbation vary between publications, and there is likely a spectrum of severity of these changes within a subpopulation of patients with IPF/CFA.[126,127] For example, Kondoh et al.[126] define acute exacerbation as exacerbation of dyspnea within 1 month, new diffuse pulmonary opacities on chest radiography, a decrease in arterial oxygen tension (PaO_2) of more than 10 mm Hg under similar conditions, and absence of apparent infectious agents and heart failure. The age range mirrors approximately that for IPF/CFA. High-resolution CT shows features of DAD superimposed on those of UIP.

Treatment and Prognosis

Most patients with AIP die of their disease, with mortality reported as up to 70%.[11,125] However, a minority shows complete recovery or survival with residual fibrosis. Some may have repeated episodes of AIP and develop chronic progressive fibrosis.[130] Most patients with acute exacerbations of IPF/CFA also die of their disease (Fig. 19.20).[124]

FIGURE 19.20. A case of acute exacerbation of idiopathic pulmonary fibrosis at autopsy. The lung is densely congested and hemorrhagic in the central areas of diffuse alveolar damage, with classic honeycomb change at the periphery of the lung representing background idiopathic pulmonary fibrosis.

Some survive initially, only to succumb to further episodes. Quantification of HRCT features may provide prognostic information in both AIP[131] and acute exacerbations of IPF.[127]

Pathogenesis

The pathogenesis remains unknown for AIP in terms of the precipitating event, although the biologic progression of AIP likely reflects that seen in ARDS (see Chapter 4). The etiology of acute exacerbations is also unknown, but oxygen toxicity and triggering infection are unlikely causes.[124] Some cases of acute exacerbation have been precipitated by BAL[132] or surgical lung biopsy,[133] and others by surgical resection of lung cancers associated with IPF/CFA.[57]

Differential Diagnosis

In terms of differential diagnosis, UIP should be distinguishable through an absence of temporal heterogeneity and the presence of hyaline membranes, excluding the

acute exacerbations discussed above.[126,127] If patients survive the acute episode in AIP, which comprises histopathologically the exudative and organizing phases, the residual fibrosis can show a pattern of fibrotic NSIP[10] and the clinical presentation is then essential in making the diagnosis in such cases.[11,125] In similar fashion, the organizing phase of DAD may be indistinguishable from organizing pneumonia due to other chronic causes, although cryptogenic organizing pneumonia (COP) often has a more patchy and peribronchial distribution with less prominent interstitial changes.[134] Nevertheless, a review of the clinical and imaging data is again required for accurate clinicopathologic diagnosis.[135]

Organizing Pneumonia and Cryptogenic Organizing Pneumonia

Organizing pneumonia (OP) is a nonspecific pattern of repair seen in response to injury. Although not strictly an interstitial process, it often enters the differential diagnosis of the interstitial pneumonias. It may be classified as primary (or idiopathic when it is termed cryptogenic organizing pneumonia [COP])[136–138] or secondary (with a recognized cause/association). Organizing pneumonia and its clinical correlates are discussed in detail in Chapter 4 in relation to acute lung injury.

Lymphoid Interstitial Pneumonia

Although LIP was part of Liebow and Carrington's[3] original classification, it was subsequently reclassified as a lymphoproliferative disease due to the largely erroneous view that it was a preneoplastic condition. However, although it is discussed in detail in Chapter 32, as diagnostic difficulties more often reflect distinction from lymphoma than other patterns of interstitial pneumonia, it is currently included in the consensus classification, as it is now viewed as a reactive pulmonary lymphoid hyperplasia that predominantly involves the interstitium. In reality, idiopathic LIP is exceptionally rare, as most cases are associated with Epstein-Barr virus infection, immunosuppression, or a connective tissue disorder.[139–145]

Idiopathic Bronchiolocentric Interstitial Pneumonia or Airway-Centered Interstitial Fibrosis

Since the consensus classification, there have been two publications describing a pattern of small airway-centered interstitial fibrosis, which was initially termed *idiopathic bronchiolocentric interstitial pneumonia.*[146,147] In both papers, there is a female predominance (about 75%), the age range being 28 and 69, and averaging about 40 years. Clinically, patients presented with chronic cough, progressive dyspnea, and more rarely wheeze, recurrent pneumonia, and chest pain. Only a minority of patients were smokers or ex-smokers. Eight of 12 patients in one study had a history of possible inhalational exposures, including wood smoke, birds, cotton, pasture, chalk dust, agrochemical compounds, and cocaine use.[147] In the other study, two of 10 patients had a previous diagnosis of gastroesophageal reflux.[146]

Chest radiographs and pulmonary function tests show interstitial and restrictive lung disease, while the histopathologic appearance is that of a centrilobular inflammatory process with small airway fibrosis and inflammation that radiates into the interstitium of the distal acinus in a patchy fashion.[146] Chest radiographs have revealed predominantly diffuse reticular and reticulonodular infiltrates, often in the central lung fields, with thickening of the bronchial walls and decreased lung volumes. High-resolution CTs demonstrated peribronchovascular fibrosis and interstitial thickening.[147] Bronchoalveolar lavage showed a mild increase in lymphocytes in four patients.[147] No patients had serologic evidence of a collagen vascular disease. Pulmonary function tests showed moderate to severe physiologic abnormalities, in most instances indicating a restrictive lung disease with decreased peripheral flow rates.[146,147]

The histopathologic features are similar to those in chronic hypersensitivity pneumonia, with bronchiolocentric interstitial fibrosis and peribronchiolar metaplasia extending around and often linking fibrotic and sometimes heavily muscularized bronchioles (Fig. 19.21). However, granulomas are not seen.[146,147]

Prognostic data are limited, but in the earlier study, at a mean follow-up of 4 years, one third of patients died of disease and most of the others had persistent or progressive disease, suggesting a more aggressive course than hypersensitivity pneumonitis and nonspecific interstitial pneumonia, the two major differential diagnoses.[146] In the latter study, mortality was similar, although about one third responded to therapy with corticosteroids and bronchodilators.[147] However, one further cohort of patients with peribronchiolar metaplasia as the primary histopathology on surgical lung biopsy for investigation of interstitial lung disease had an excellent survival.[148]

Whether or not the patterns of bronchiolocentric interstitial pneumonia or indeed peribronchiolar metaplasia relate to specific entities, further investigation is warranted into this pattern of bronchiolocentric, yet mainly interstitial, injury to the lung and its overlap with small airways disease.

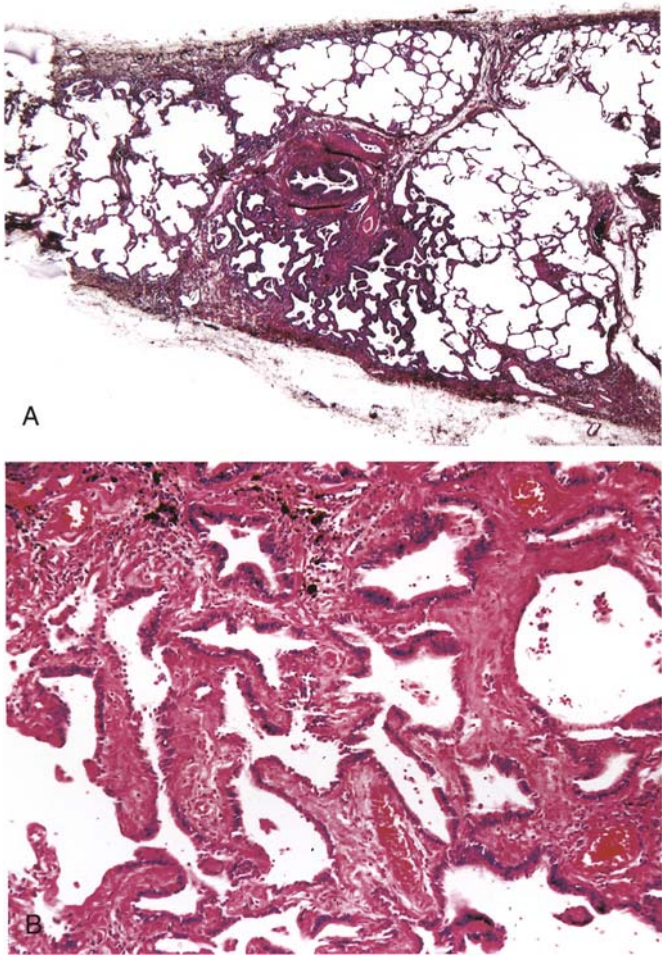

FIGURE 19.21. Airway centered interstitial fibrosis. **A.** Low-power view shows interstitial fibrosis spreading around a membranous bronchiole. The pleura is noted to be fibrotic. **B.** High-power view shows diffuse fairly paucicellular interstitial fibrosis, with overlying metaplastic bronchiolar epithelium. (From Churg et al.,[147] with permission.)

Interstitial Pneumonias in Children

Most authors have classified pediatric interstitial lung disease according to systems devised for diseases for adults,[149,150] although there are additional terms such as *chronic pneumonitis of infancy*[151] and *cellular pneumonitis in infants.*[152] There is a comparative lack of data on HRCT in children,[153] so tissue sampling is more frequently required[154] and, as in adults, this usually is a surgical lung biopsy for cases with a suspected interstitial pneumonia.[153,155] A set of guidelines is due to be published by the European Respiratory Society.[156]

In terms of the interstitial pneumonias, there are several series of CFA in children, but most predate recognition of NSIP. Indeed, when the adult histopathologic criteria are applied, UIP is exceptionally rare in children and most reported cases would be classified as other patterns.[157–159] Most are probably more appropriately classified as NSIP, although this pattern is even less well characterized in children than in adults, and there is increasing evidence that some such cases may represent mutations in relation to surfactant protein genes, particular type C.[160,161] Lymphoid interstitial pneumonia is also comparatively common in children[157,159] and, as in adults, is typically associated with either collagen vascular diseases or congenital[157] and acquired[162] immunodeficiency states.

Desquamative interstitial pneumonia is well described but rare in children.[163] The outcome is worse, especially in infancy[112] and familial disease.[113] Clearly, smoking is not the etiology in children, and some children have been shown to have surfactant B deficiency or Gaucher's disease.[118,159] Respiratory bronchiolitis–associated interstitial lung disease appears to be limited to adults.

Diffuse alveolar damage is not infrequently seen in infancy, being the histopathologic pattern seen in both adult and infantile respiratory distress syndromes. However, occasional cases of acute respiratory failure develop in older children with a histopathologic pattern of DAD, and a clinical diagnosis of AIP is appropriate if no underlying causes are identified.[11] Rare cases of OP have also been reported in children.

In addition to these patterns, chronic pneumonitis of infancy[151] and cellular interstitial pneumonitis in infants[152] are also described, although, while chronic pneumonitis of infancy has a distinct histopathologic pattern, cellular interstitial pneumonitis of infants appears similar to NSIP. Histologically, cases of chronic pneumonitis of infancy show extremely florid type 2 cell hyperplasia and diffuse expansion of the interstitium by fibroblastic tissue, with comparatively little interstitial chronic inflammation. Acellular intraalveolar material resembling that seen in alveolar proteinosis is a frequent finding.[151,157] Some cases may represent surfactant protein B deficiency (see Chapter 6).

Conclusion

This consensus classification provides an appropriate system based on current knowledge, which appears reproducible in terms of the pathologist's identifying patterns in isolation,[82] and workable in terms of the role of the pathologist in making the final clinicopathologic diagnosis. It also highlights the fact that the gold standard for diagnosis is no longer the biopsy in isolation but more the clinicopathologic conference in which clinical, imaging, and histopathologic data are jointly discussed. Optimally, the conference provides greater consistency in

diagnosis and also identifies purer cohorts for studies investigating causation. These patterns are also recognizable in the context of collagen vascular diseases (see Chapter 20) and pediatric disease (see Chapters 6 and 7), although clinical data differ and patterns should be interpreted accordingly. Finally, pathologists and physicians alike should be aware that all classifications are dynamic, and this system, in particular, will likely change as new patterns are encountered and discussed (such as idiopathic bronchiolocentric interstitial pneumonia) and new etiologic data come to light, already noted in the context of SRILD.

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