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REVIEW

Beyond a consensus classification for idiopathic interstitial pneumonias: progress and controversies

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Beyond a consensus classification for idiopathic interstitial pneumonias: progress and controversies

Histopathological classification schemes provide the underpinnings for separating idiopathic interstitial pneumonias into clinically meaningful groups. An interdisciplinary classification system based on a combination of evidence and expert opinion was published in 2002 and set the stage for controversy in several areas, including not only nomenclature but also the role of surgical lung biopsy and pathologists in diagnosis. We provide a brief overview of the clinical and histological features of the idiopathic interstitial pneumonias, and focus on selected topics of interest that have emerged in recent years.

Keywords: idiopathic interstitial pneumonia, non-specific interstitial pneumonia, pulmonary fibrosis, usual interstitial pneumonia

Abbreviations: AIP, acute interstitial pneumonia; ATS, American Thoracic Society; BOOP, bronchiolitis obliterans organizing pneumonia; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; HRCT, high-resolution computed tomography; IPF, idiopathic pulmonary fibrosis; LIP, lymphoid interstitial pneumonia; NSIP, non-specific interstitial pneumonia; RB, respiratory bronchiolitis; RBILD, respiratory bronchiolitis interstitial lung disease; UIP, usual interstitial pneumonia

Introduction

Idiopathic interstitial pneumonias are an important subset of the broader category of diffuse, non-neoplastic interstitial lung diseases.[1] The common feature is unexplained expansion and distortion of distal lung interstitium by variable combinations of inflammation and/or fibrosis. Fibrosis, when present, may take the form of increased numbers of fibroblasts and myofibroblasts and/or collagen deposition. These changes occur in the context of breathlessness or cough, typically associated with evidence of physiological dysfunction and diffuse radiological abnormalities.

Averill Liebow pioneered the notion that morphological classification of idiopathic interstitial pneumonias is useful in separating them into distinct clinical categories.[2] Since then a number of classification schemes have been proposed. In 2002 an international committee, supported by the American Thoracic Society (ATS) and the European Respiratory Society, proposed a classification scheme based on consensus opinion developed by a large interdisciplinary group of experts.[3] This statement has had a profound impact, influencing management of patients with suspected idiopathic interstitial pneumonias, driving study design for clinical trials and creating opportunities for research to challenge areas in which

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evidence was weak. The purpose of this review is to summarize briefly current knowledge of the clinical and histological features of the idiopathic interstitial pneumonias, focusing primarily on areas of controversy that have emerged in recent years.

Classification of idiopathic interstitial pneumonias

The consensus classification proposed seven categories of idiopathic interstitial pneumonia, ordering them by relative frequency and separating 'histological patterns' from 'clinical-radiological-pathological diagnosis' (see Table 1).[3] We prefer a simplified approach that uses a single unifying terminology and omits cryptogenic organizing pneumonia, also termed idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) and lymphoid interstitial pneumonia (LIP).[4] The rationale for omitting idiopathic BOOP from this schema is that this disease pathologically is predominantly an air space, rather than interstitial process, and clinically it usually mimics infectious pneumonias rather than a diffuse interstitial process. LIP is omitted because it represents a form of lymphoproliferative disorder more closely allied to follicular bronchiolitis on one hand and low-grade lymphoma on the other, and thus it differs from the inflammatory interstitial pneumonias. The simplified approach will serve as the framework for this review. We will return to the values and risks of separating histological patterns from clinical diagnoses toward the end of our discussion.

Usual interstitial pneumonia

Usual interstitial pneumonia (UIP) is the most common of the idiopathic interstitial pneumonias, accounting for about 60% of biopsied patients.[5–7] An ATS consensus statement published in 2000 linked UIP to idiopathic pulmonary fibrosis (IPF) by defining the latter as 'a specific form of chronic fibrosing interstitial pneumonia limited to the lung and associated with histological appearance of usual interstitial pneumonia (UIP) on surgical (thoracoscopic or open) lung biopsy'.[8] As this definition implies, UIP and IPF are interchangeable terms, the potential exceptions being those patients with underlying systemic illnesses or occupational exposures that may suggest an aetiology for their lung disease (e.g. asbestosis).

CLINICAL FEATURES

Patients with UIP usually present in the sixth or seventh decade of life with slowly progressive dyspnoea and non-productive cough. Men are affected more commonly than women by a ratio of nearly 2:1. Physical findings include bibasilar inspiratory crackles, a non-specific but characteristic finding in nearly all patients. Pulmonary function studies show restrictive abnormalities (i.e. reduced lung volumes with relative preservation of airflow) in most patients accompanied by a reduction in the diffusion capacity for carbon monoxide (DL_{CO}) with hypoxaemia at rest and/or with exercise. No single pharmacological agent or combination of drugs has shown consistent efficacy in patients

Table 1. Classification of idiopathic interstitial pneumonias

	International consensus classification	
Katzenstein	Histological patterns	Clinical-radiological-pathological diagnoses
Usual interstitial pneumonia (UIP)	Usual interstitial pneumonia (UIP)	Idiopathic pulmonary fibrosis (IPF)
Desquamative interstitial pneumonia (DIP)/respiratory bronchiolitis interstitial lung disease (RBILD)	Desquamative interstitial pneumonia (DIP)	Desquamative interstitial pneumonia (DIP)
	Respiratory bronchiolitis	Respiratory bronchiolitis interstitial lung disease (RBILD)
Acute interstitial pneumonia (AIP)	Diffuse alveolar damage (DAD)	Acute interstitial pneumonia (AIP)
Non-specific interstitial pneumonia (NSIP)	Non-specific interstitial pneumonia (NSIP)	Non-specific interstitial pneumonia (NSIP)
	Organizing pneumonia	Cryptogenic organizing pneumonia (COP)
	Lymphoid interstitial pneumonia (LIP)	Lymphoid interstitial pneumonia (LIP)

with UIP, although a large number of novel therapies are being investigated in clinical trials. Lung transplantation is used in some patients, but its application is limited due to older age and frequent comorbidities. In most patients UIP pursues a progressive course, with median survivals from the time of diagnosis of about 3 years.[5,9]

Occasional patients present with a more acute onset of respiratory symptoms that may mimic the clinical presentation of acute interstitial pneumonia (AIP).[10,11] This syndrome has been termed acute exacerbation of IPF (or accelerated UIP) and occurs in as many as 14% of untreated patients observed for 2 years.[12] A recent autopsy study suggests that acute exacerbation is a common cause of death in UIP patients.[13] Acute exacerbation is defined as the sudden onset of rapid clinical deterioration without an identifiable cause in patients with IPF. A diagnosis of acute exacerbation hinges on exclusion of other known and potentially treatable causes of clinical worsening, such as cardiac disease, pulmonary embolism, and infection. Most patients are known to have UIP at the time of acute worsening, but a few patients present with acute exacerbation without a previously established diagnosis of IPF. The prognosis is grim, with short-term mortality rates in excess of 50% in the majority of reported series.

The relative role of imaging studies and surgical lung biopsies in patients with UIP has changed over the last decade. High-resolution computed tomography (HRCT) has greatly improved diagnostic accuracy over conventional chest radiography and has therefore revolutionized the role of radiology in managing patients with diffuse interstitial lung diseases. HRCT in about half of patients shows a characteristic combination of peripheral (subpleural), irregular, linear ('reticular') opacities involving predominantly the lower lung zones with associated architectural distortion in the form of traction bronchiectasis and bibasilar honeycomb change.[14–17] Experienced radiologists can make a specific diagnosis of UIP with a high degree of accuracy in patients with this combination of findings, thus obviating the need for lung biopsy. Lung biopsy is increasingly limited to those patients with atypical radiological findings, meaning that there is a growing selection bias toward reserving surgical lung biopsy for patients with potentially 'discordant' or atypical radiological findings. It is this change that has created confusion around the relative roles of clinicians, radiologists and pathologists in biopsied patients. In this context, the bulk of the evidence indicates that a biopsy diagnosis of UIP remains the single most important predictor of outcome at the time of diagnosis and thus remains the 'gold standard' for diagnosis.[14,18]

PATHOLOGIC FEATURES

UIP is a specific morphological entity defined by a combination of (i) fibrosis distributed in a heterogeneous ('patchwork') fashion, (ii) fibroblast foci, and (iii) honeycomb change and/or scars.[1,4,19] The histological hallmark and chief diagnostic criterion in surgical lung biopsy specimens is a heterogeneous or variegated appearance resulting from irregular juxtaposition of fibrotic scarring, honeycomb change, interstitial inflammation and normal lung (Figure 1). This distinctive 'patchwork' appearance due to alternating areas of qualitatively different abnormalities is the key to low-magnification diagnosis.

Fibrosis predominates over inflammation in classical UIP and comprises mainly dense eosinophilic collagen deposition. Fibroblast foci are a characteristic but nonspecific finding, representing small interstitial foci of acute lung injury in which fibroblasts and myofibroblasts are arranged in a linear fashion within a pale staining matrix (Figure 2). Overlying epithelium consists of hyperplastic pneumocytes or columnar nonciliated bronchiolar cells. Fibroblast foci are not unique to UIP, but are a very important feature in establishing the diagnosis. The presence of these microscopic zones of acute lung injury set against a backdrop of chronic scarring further contributes to the variegated appearance (temporal heterogeneity) typical of UIP.

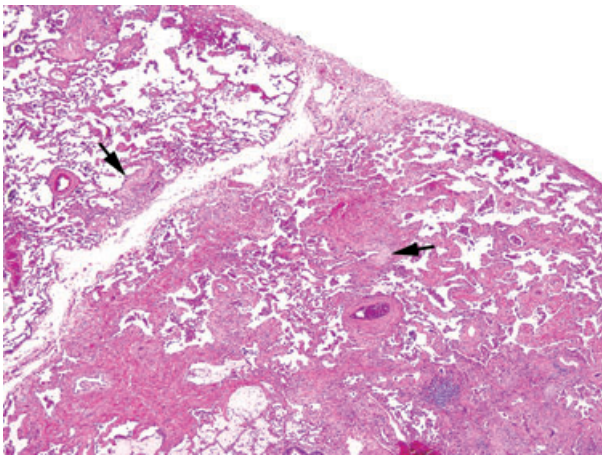

Figure 1. Low-magnification photomicrograph of usual interstitial pneumonia demonstrating characteristic 'patchwork' distribution of fibrosis (H&E). Areas of collagen fibrosis are distributed in a random fashion with only minimal inflammation. Scattered fibroblast foci are also present (arrows).

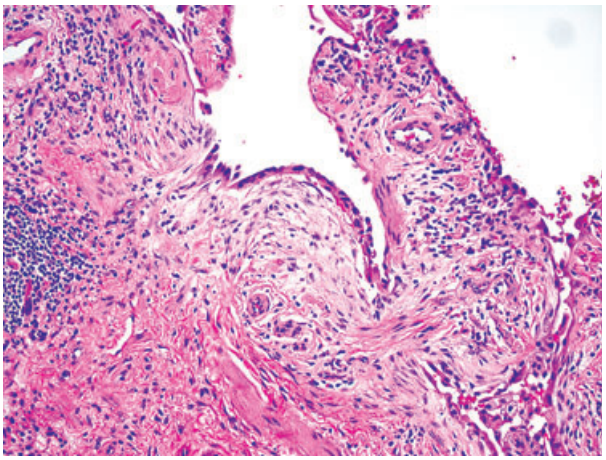

Figure 2. High-magnification photomicrograph showing a fibroblast focus in usual interstitial pneumonia (H&E). Fibroblasts and myofibroblasts are confined to a small interstitial area and are arranged in a somewhat linear fashion within a pale-staining matrix. Hyperplastic epithelial cells are present overlying the fibroblast focus.

Honeycomb change is present in most surgical lung biopsy specimens and is another important diagnostic feature. Honeycomb change is defined by cystically dilated air spaces frequently lined by columnar respiratory epithelium in scarred, fibrotic lung tissue (Figure 3). Fibrotic scars that obscure the underlying lung architecture without associated honeycomb change are another form of architectural distortion characteristic of UIP. Smooth muscle hyperplasia is commonly seen in areas of fibrosis and honeycomb change and can be striking in some cases.

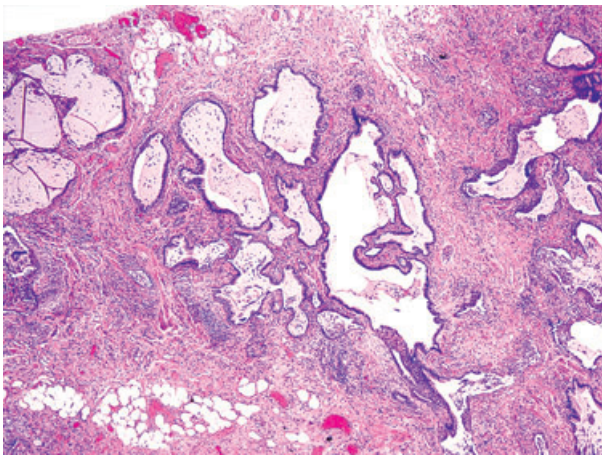

Figure 3. Low-magnification photomicrograph showing honeycomb change in usual interstitial pneumonia (H&E). Cystically dilated air spaces are lined by bronchiolar-type epithelium and are situated within scarred, fibrotic lung.

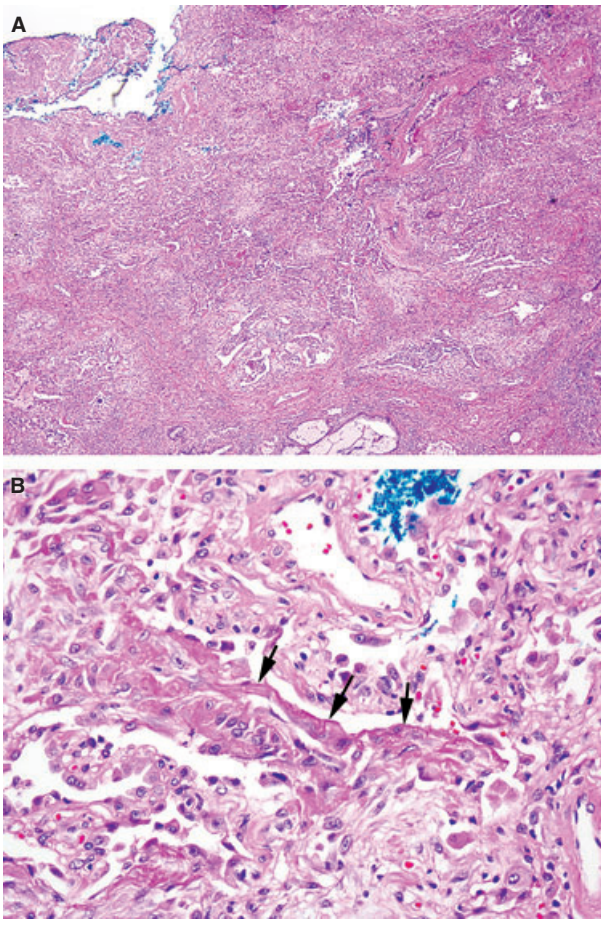

Figure 4. Surgical lung biopsy specimen showing a combination of usual interstitial pneumonia and diffuse alveolar damage in a patient with acute exacerbation of idiopathic pulmonary fibrosis. **A**, Low-magnification photomicrograph showing underlying fibrosis including a broad zone of scarring and honeycomb change in lower right portion (H&E). **B**, Higher-magnification photomicrograph from area in upper left of previous image showing expansion and distortion of interstitium by fibroblasts and myofibroblasts with associated hyaline membrane (arrows) (H&E).

Biopsy specimens from patients with acute exacerbation usually show a combination of UIP and superimposed diffuse alveolar damage (DAD) or, less often, organizing pneumonia (Figure 4).[10,11] The features of DAD may be patchy and typically include some combination of confluent alveolar septal thickening and distortion by fibroblasts and myofibroblasts with minimal associated inflammatory cells, marked hyperplasia and cytological atypia in type 2 pneumocytes, hyaline membranes, fibrin thrombi in small vessels, and squamous metaplasia of bronchiolar epithelium. In other patients the superimposed pattern of acute lung injury more closely resembles organizing pneumonia.

No single histological finding consistently predicts prognosis in individual patients with UIP. Patients with more extensive fibroblast foci have experienced shorter mean survivals in some studies, whereas other investigators have failed to demonstrate the same relationship to survival.[20]

Desquamative interstitial pneumonia/ respiratory bronchiolitis interstitial lung disease

Desquamative interstitial pneumonia (DIP) and respiratory bronchiolitis interstitial lung disease (RBILD) are two highly related, if not inseparable, forms of diffuse interstitial lung disease typically grouped with the idiopathic interstitial pneumonias. We have collapsed the two into a single category for reasons described later. DIP/RBILD is uncommon, accounting for only a small minority of surgical lung biopsy specimens from patients with idiopathic interstitial pneumonias.[5]

CLINICAL FEATURES

DIP/RBILD affects younger patients, with a mean age at diagnosis in the fourth or fifth decade of life.[1,4] Nearly all patients have strong histories of cigarette smoking, prompting many to consider DIP/RBILD a form of smoking-related interstitial lung disease.[23,47] Physiological testing usually shows mild reduction in lung volumes associated with a moderate decrease in diffusing capacity. Radiological abnormalities are common but relatively non-specific. HRCT shows patchy ground glass opacities, often with a lower lung zone distribution, without the traction bronchiectasis and honeycomb change typical of UIP.

DIP/RBILD is associated with a significantly better prognosis than UIP. Overall survival in published studies of DIP is nearly 90%, ranging from around 70–80% in older studies to 100% in more recently published series.[1,21] Higher survival rates in more recent studies may reflect a trend toward assigning cases with associated fibrosis to the category of non-specific interstitial pneumonia (NSIP) (see Controversies below). RBILD is associated with an equally good or better prognosis.[21–23] Retrospective case series suggest smoking cessation as an important therapeutic strategy, but the impact on outcome is controversial.[22]

PATHOLOGICAL FEATURES

DIP/RBILD is characterized by the presence of pigmented ('smokers') macrophages within the lumens of distal airways (i.e. respiratory bronchioles) and air spaces. The macrophages are distinctive in that they have abundant cytoplasm containing finely granular dusty brown pigment. In RBILD the changes are patchy at low magnification and limited to the airways without significant interstitial inflammation or fibrosis (Figure 5). The appearance is indistinguishable from isolated respiratory bronchiolitis (RB), a common, incidental finding in otherwise asymptomatic cigarette smokers without clinical evidence of restrictive lung

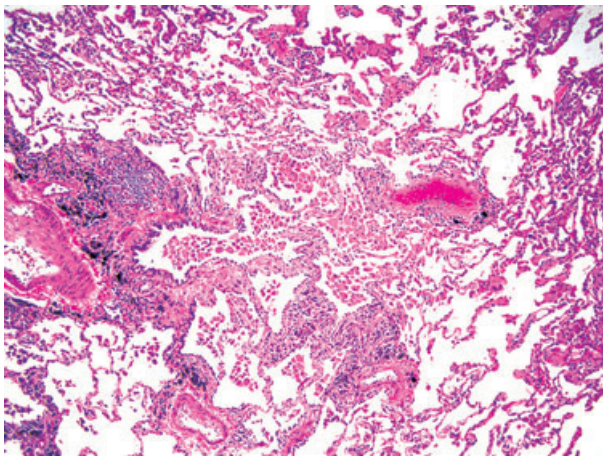

Figure 5. Photomicrograph showing respiratory bronchiolitis in a patient with respiratory bronchiolitis interstitial lung disease (H&E). Pigmented ('smoker's') histiocytes are present within the lumens of distal bronchioles and immediately adjacent air spaces without associated interstitial pneumonia.

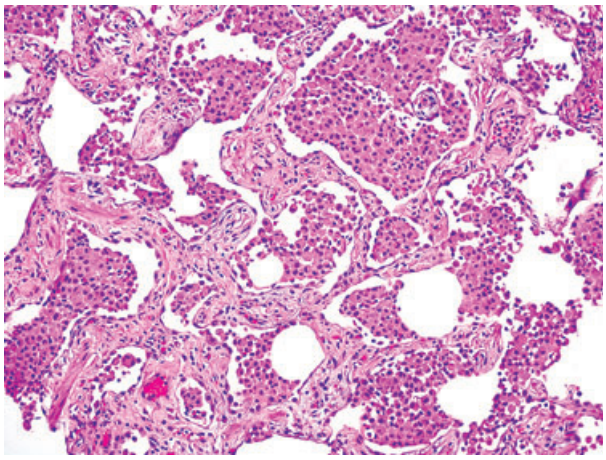

Figure 6. Photomicrograph showing desquamative interstitial pneumonia characterized by a combination of pigmented ('smoker's') intra-alveolar histiocytes and concomitant interstitial thickening due to mild, acellular fibrosis without significant associated inflammation (H&E). Occasional eosinophils accompany the predominantly histiocytic air space exudate.

disease. RBILD may include mild fibrotic thickening of alveolar septa immediately adjacent to the visceral pleura in some patients, a finding of no special or prognostic significance.[24]

DIP includes the airway-centred changes described in RBILD, but also shows areas in which the process is more diffuse. There may be accompanying mild interstitial thickening due to alveolar pneumocyte hyperplasia or mild collagen deposition (Figure 6), but interstitial inflammation is minimal or absent. DIP differs histologically from UIP in that the changes are more uniform at low magnification with a focally bronchiolocentric distribution and without significant fibrosis, honeycomb change or fibrotic scarring.

SIGNIFICANCE OF PATHOLOGICAL DIAGNOSES OF DIP OR RBILD

Neither DIP nor RBILD should be viewed as free-standing histopathological entities, since areas resembling both commonly occur as incidental findings in cigarette smokers with other lung diseases, including UIP.[19,25] There are no histological changes that reliably separate patients with DIP/RBILD from those with other lung diseases in whom RB and 'DIP-like reactions' represent incidental findings.[25] For that reason, DIP/RBILD should be diagnosed only when other forms of interstitial lung disease have been vigorously excluded by carefully examining all aspects of the microscopic slides and by correlating surgical lung biopsy specimen diagnosis with clinical and radiological features. Although incidental RB can be recognized on transbronchial biopsy, this technique cannot be used to diagnose DIP/RBILD.

Acute interstitial pneumonia

Most idiopathic interstitial pneumonias are chronic processes characterized by an insidious or subacute onset and a slowly progressive course. A small number of patients present with the acute onset of breathlessness followed by rapidly progressive respiratory failure. Some patients in this category may have acute exacerbation of IPF (see Usual interstitial pneumonia above), but most have AIP, also termed Hamman–Rich disease. This acute variant of idiopathic interstitial pneumonia is analogous to acute respiratory distress syndrome, differing from classical cases only in that it is not preceded by an identifiable catastrophic event such as trauma or shock. It is the least common of the idiopathic interstitial pneumonias. Little new information has emerged since publication of the international consensus classification, making AIP perhaps the least controversial of the idiopathic interstitial pneumonias.

CLINICAL FEATURES

Patients with AIP present with rapidly evolving shortness of breath and non-productive cough of 1–3 weeks' duration preceded by a flu-like illness characterized by sore throat, cough, fever, myalgias and malaise.[1,4,26] Men and women are affected equally, with a mean age at diagnosis of 55 years, similar to that described for UIP but with a much broader age range that includes children. Most patients are severely hypoxaemic at the time of diagnosis and require hospitalization and mechanical ventilation. HRCT demonstrates a combination of ground glass attenuation and consolidation in a bilateral and symmetrical distribution. AIP is associated with a poor prognosis with an acute fatality rate of about 70%.[26] The natural history in survivors is variable and includes patients who fully recover, others who suffer multiple relapses, and a small number who develop persistent chronic interstitial lung disease.[27] Some survivors with persistent fibrotic lung disease may represent patients with previously unrecognized UIP who present with accelerated disease.

PATHOLOGICAL FEATURES

Biopsy specimens from patients with AIP demonstrate DAD, usually in the late or organizing stage.[1,4,28,29] There are no histological features that reliably distinguish DAD in the setting of AIP from DAD of other known causes. Before a diagnosis of AIP can be made, therefore, all potential causes of DAD should be excluded. Special stains, cultures and serological studies are especially helpful in excluding infectious causes, and careful clinical history may provide clues to other aetiologies.

Extensive fibroblast and myofibroblast proliferation is the dominant finding in biopsy specimens of AIP (Figure 7). Alveolar septa are thickened and distorted by proliferating spindle cells within a pale-staining basophilic matrix. The uniformity of the findings contrasts sharply with the patchwork distribution of highly variegated abnormalities in UIP. Intraluminal, polypoid plugs of spindle cells indistinguishable from those seen in organizing pneumonia may be present and are sometimes a prominent feature. Fibroblast proliferation is accompanied by marked hyperplasia of cytologically atypical alveolar lining cells characterized by nuclear enlargement and prominent nucleoli. Remnants of hyaline membranes are present in some cases, but are often inconspicuous (Figure 8). Multiple fibrin

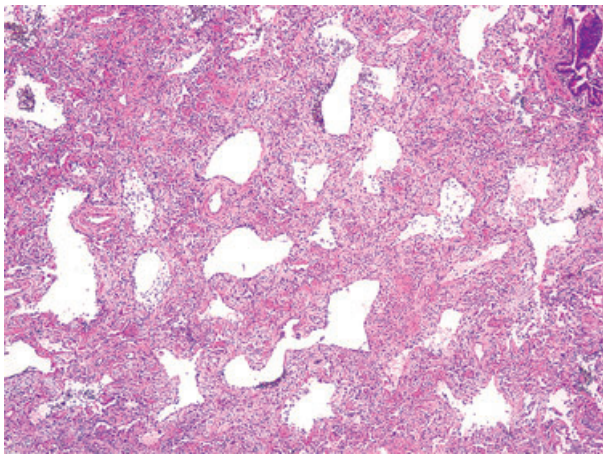

Figure 7. Low-magnification photomicrograph showing organizing diffuse alveolar damage in a patient with acute interstitial pneumonia (H&E). Collapse of distal alveolar spaces and dilation of alveolar ducts result in the appearance of dramatic but uniform interstitial thickening. Hyaline membranes are present within collapsed spaces.

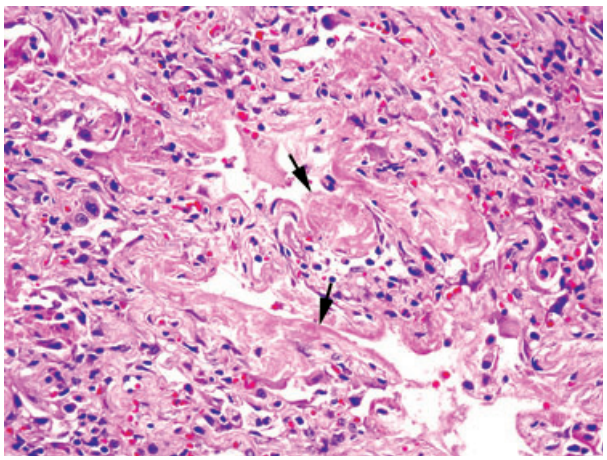

Figure 8. High-magnification photomicrograph showing hyaline membranes (arrows) in lung biopsy from patient with acute interstitial pneumonia (H&E).

thrombi in small muscular arteries and squamous metaplasia of bronchiolar epithelium are manifestations of acute lung injury that can be important clues to the diagnosis.

Non-specific interstitial pneumonia

NSIP was proposed in 1994 as a form of chronic interstitial pneumonia characterized by relatively uniform expansion of alveolar septa by inflammation and/or fibrosis without the geographical and temporal heterogeneity of UIP.[30] As the term implies, the histological findings in NSIP are not specific. Findings indistinguishable from NSIP can occur focally in other conditions, most importantly UIP. The findings are also non-specific from a clinical perspective given that identical changes can occur in surgical lung biopsy specimens from patients with a variety of underlying causes or associations, including hypersensitivity pneumonia and various systemic connective tissue diseases.[30–32] Recognizing idiopathic NSIP as a distinct entity is therefore a process of exclusion that, like DIP/RBILD and AIP, requires careful correlation with clinical and radiological information. Given the difficulty in identifying patients with idiopathic NSIP, the authors of the consensus classification suggested that NSIP be considered 'a *provisional diagnosis* until there is further clarity on the nature of the corresponding clinical condition'.[3] In our view, clarity has emerged and we advocate separating NSIP from UIP as an important form of idiopathic interstitial pneumonia with very marked differences in treatment response and natural history.[31,32]

CLINICAL FEATURES

NSIP is the second most common idiopathic interstitial pneumonia, accounting for as many as a third of patients undergoing surgical lung biopsy in retrospective series.[31] NSIP fails to show the gender predilection for men seen in UIP, and in some series is more common in women.[32] NSIP also differs from UIP in that it tends to affect younger patients, with an average age at diagnosis of around 50 years.[31,32] Shortness of breath and dry cough are the most common complaints, often developing in an insidious fashion indistinguishable from that described for UIP. Pulmonary function studies show restricted lung volumes and abnormalities of oxygenation, although the degree of abnormality tends to be less severe compared with patients with UIP. HRCT shows a non-specific combination of ground glass opacities, irregular lines, and traction bronchiectasis occasionally with subpleural sparing. The radiological findings, although frequently characteristic, cannot reliably distinguish between patients with NSIP and those with early or radiologically atypical UIP or certain other interstitial lung diseases.[14,33]

Multiple studies have now confirmed the survival advantage associated with a diagnosis of NSIP compared with UIP.[31,32] Median survival for all NSIP cases is >9 years, with the best prognosis occurring in patients with minimal fibrosis (cellular variant, see below). Most patients with cellular NSIP survive, but about half have persistent stable disease. Patients in whom fibrosis predominates in surgical lung biopsy

specimens do worse than those with more cellular lesions, although still better than UIP.[30,34–38] Mortality rates for patients with fibrotic NSIP vary widely, ranging from 11 to 68% in various studies (mean ± SD, 30.4 ± 18.9%).[6,30,32,34–36,39] Reported 5-year survival of such patients is about 76% compared with about 45% for UIP[37,38]. To some extent, variation in mortality rates reported for patients with fibrotic NSIP reflects differences in histological definitions and the difficulty in separating fibrotic NSIP from UIP (see below). Survivors typically have persistent lung disease. Corticosteroids have not been prospectively evaluated in a randomized fashion, but may be effective in a subset of patients, especially those with minimal associated fibrosis.[34]

PATHOLOGICAL FEATURES

A diagnosis of NSIP in surgical lung biopsy specimens requires the presence of a chronic interstitial pneumonia without findings to prompt diagnosis of a more specific pathological process. Unlike UIP, NSIP is in many respects a diagnosis of exclusion. Defined in this way, NSIP spans a spectrum of histological abnormalities ranging from a predominantly cellular process (i.e. cellular NSIP) to paucicellular lung fibrosis (i.e. fibrotic or fibrosing NSIP). The most cellular forms are characterized by an alveolar septal infiltrate of mononuclear cells that may be patchy or diffuse (Figure 9). Whether patchy or diffuse, the qualitative features of the interstitial abnormalities remain constant without the geographical and temporal heterogeneity associated with UIP (Figure 10). The inflammatory infiltrate consists of lymphocytes and variable numbers of admixed plasma cells. Neutrophils, eosinophils and histiocytes are relatively inconspicuous. Granulomas are rare in NSIP and, if present, should raise other considerations (see below).

The relative frequency of fibrosis in NSIP is variable. Patients with fibrotic NSIP outnumber patients with cellular NSIP by a ratio of nearly 4:1 in published studies, but this may reflect selection bias, in that most

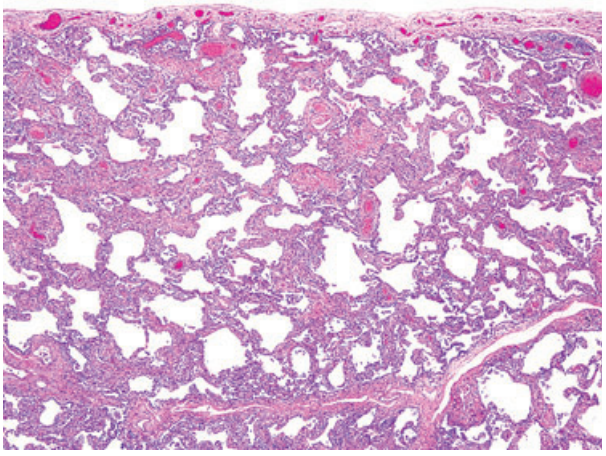

Figure 10. Low-magnification photomicrograph showing another example of cellular non-specific interstitial pneumonia/fibrosis, this time accompanied by mild fibrosis but without architectural distortion (H&E).

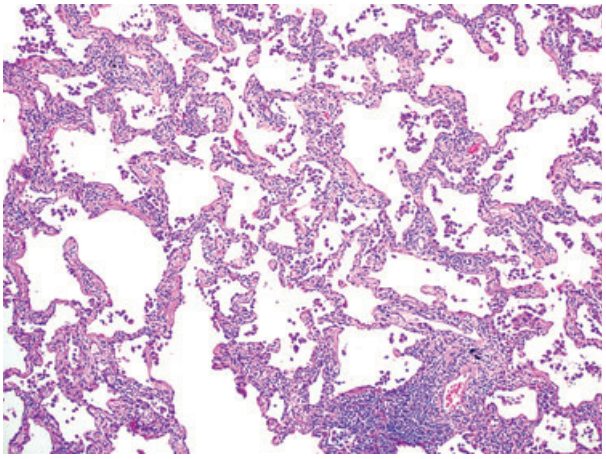

Figure 9. Photomicrograph showing cellular variant of non-specific interstitial pneumonia/fibrosis (H&E). There is a diffuse infiltrate of predominantly lymphocytes expanding peribronchiolar interstitium and alveolar septa in a uniform fashion. No significant fibrosis or architectural distortion are present.

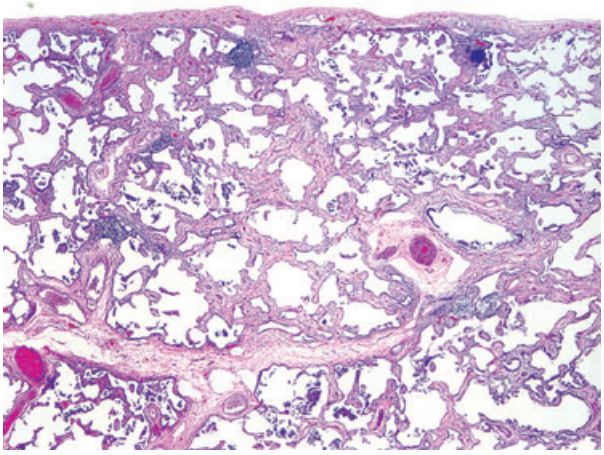

Figure 11. Low-magnification photomicrograph showing a fibrotic variant of non-specific interstitial pneumonia/fibrosis (H&E). Uniform collagen deposition expands all compartments of the interstitium, including interlobular septa, but without architectural distortion in the form of fibrotic scars or honeycomb change. Contrast with the patchwork distribution of qualitatively heterogeneous abnormalities in usual interstitial pneumonia illustrated in Figure 1.

reports are from tertiary referral centres where patients with fibrotic interstitial lung disease may be over-represented. In addition, there are no clearly articulated criteria for separating cellular from fibrotic NSIP. We limit the term fibrotic NSIP to those cases in which paucicellular fibrosis with minimal or mild inflammation is the predominant feature. Defined in this way, the extent of interstitial fibrosis is variable. Fibrosis takes the form of uniform collagen accumulation resulting in expansion of alveolar septa and peribronchiolar interstitium (Figure 11) without the patchwork distribution characteristic of UIP. Interlobular septa and visceral pleura may also be involved. Pathology reports should comment on the presence and extent of interstitial fibrosis, since it is associated with significantly increased risk for disease-specific mortality.[1,4,30–32] Associated smooth muscle hyperplasia tends to be less extensive than that seen in UIP. Fibroblast foci should be absent or, at most, rare and inconspicuous. Honeycomb change and broad zones of scarring should be absent, an important feature in distinguishing fibrotic NSIP from UIP. Patchy intraluminal fibrosis resembling organizing pneumonia is common, but should be a focal and relatively inconspicuous finding that is overshadowed by the interstitial changes.

Controversies in classification and diagnosis of idiopathic interstitial pneumonias

'PATTERN' VERSUS 'DIAGNOSIS' AND THE ROLE OF SURGICAL LUNG BIOPSY

The authors of the consensus classification advocated use of the term 'pattern' when reporting lung biopsy findings in order to distinguish the pathological diagnosis from a final 'clinico-radiological-pathological diagnosis'. Although this may emphasize the value of an iterative dynamic process that correlates histological findings with other relevant data, it seems to us unnecessary and potentially dangerous—unnecessary in that the same could be said of nearly all conditions in which pathological diagnoses play a key role in disease recognition. Many pathological diagnoses are not isolated events but, rather, essential components of an iterative process in which final interpretation is dynamic and framed by ongoing data collection. For example, a lung biopsy diagnosis of adenocarcinoma may be reinterpreted as metastatic adenocarcinoma after discovery of a previously occult primary malignancy outside the lung. This possibility should not drive an argument for substituting the term 'adenocarcinoma pattern', terminology that may interfere with the end-user's recognition that the diagnosis of malignancy is certain. Indeed, the danger in using the term 'pattern' is that others may not fully understand those circumstances in which the specificity of the histopathological findings is the primary driver of a final diagnosis.

UIP stands alone among the idiopathic interstitial pneumonias in being a specific histopathological entity. Several studies have demonstrated the primary role of a lung biopsy specimen diagnosis of UIP in establishing a clinical diagnosis of IPF.[14,15,18,40,41] This is especially important given that many patients are selected for lung biopsy because there is some level of doubt regarding the likelihood of IPF. It is precisely in this context that a biopsy diagnosis of UIP establishes the clinical diagnosis with certainty, and in this context the biopsy result remains the single most powerful predictor of disease-specific mortality at the time of diagnosis.[6,14] Other histological forms of idiopathic interstitial pneumonia are less specific, and perhaps for these a stronger argument can be made for using the term 'pattern'. In our view, however, this diminishes the role of the pathologist to that of technician rather than a diagnostician engaged in proactively integrating histological observations with clinical information. This proactive approach is common in other areas of medicine, for example orthopaedic oncology and hepatology, in which the pathologist and the pathology report are the driving force for integrating relevant clinical, laboratory and radiological information that facilitates accurate interpretation of microscopic findings.

The second argument for using the term 'pattern' in reporting diagnoses of UIP is that it occurs in patients for whom the term IPF is deemed inappropriate. The implication is that sorting patients with UIP into different clinical groups may impact therapeutic options and outcome. The preponderance of evidence suggests that patients with a biopsy specimen diagnosis of UIP have a form of fibrotic lung disease that is relatively insensitive to conventional immunosuppressive therapy and likely to be associated with a progressive course regardless of the underlying or associated condition. Although a number of studies have indicated a better prognosis for UIP associated with collagen vascular diseases, others have found no difference in survival when comparing patients with and without connective tissue disease.[9,42–44] The differences observed in some studies may be related to confounding factors such as younger age, greater prevalence of women, and lower smoking rates in patients with collagen vascular disease, factors that themselves are associated with a better prognosis.[44]

Furthermore, the survival advantage does not apply to patients with rheumatoid arthritis.[44] Similarly, asbestos can be viewed as a potential cause of UIP without any meaningful differences between asbestosis and IPF in terms of signs and symptoms, morphology, treatment response or natural history.[45,46] Even in patients with an exposure history suggesting chronic hypersensitivity pneumonias as an alternative, a biopsy specimen diagnosis of UIP predicts a natural history indistinguishable from IPF.[47] Returning to our previous analogy, adenocarcinoma of the lung occurs in smokers and non-smokers, and whereas smoking history may predict important differences in the molecular underpinnings of carcinogenesis, the clinical implications of a pathological diagnosis of adenocarcinoma remain the same.

DISTINGUISHING RBILD FROM DIP

RBILD and DIP may be separable at their extremes, but demonstrate a degree of histological overlap that blurs distinction in a substantial proportion of cases. The consensus classification recognized this overlap in stating that DIP 'is considered by many to represent the end of a spectrum of RB-ILD in view of its similar pathology and almost invariable association with cigarette smoke'.[3] In theory, RBILD comprises a lesion limited to the airways, whereas DIP is a more diffuse process. From its inception, however, DIP included patients with patchy airway-centred lesions described as mild or early disease.[2] This overlap was observed in four of 10 patients with respiratory bronchiolitis reported by Moon and associates, prompting the authors to conclude that 'the distinction between RBILD and DIP is histopathologically quite arbitrary, being dependent on the field of focus'.[48] For these reasons, we combine DIP and RBILD into a single category, separating them when possible and arbitrarily choosing between the two on occasion.

DISTINGUISHING DIP FROM NSIP

The consensus classification highlighted the relationship between DIP and the fibrotic variant of NSIP as an area of uncertainty.[3] A recent study has suggested that when the term DIP is reserved for biopsy specimens showing well-established diffuse interstitial pneumonia accompanied by fibrosis, it shows a weaker relationship to cigarette smoking and may have more in common with NSIP than with RBILD.[23] In our view, the term DIP remains appropriate for lung biopsy specimens showing a combination of pigmented alveolar macrophages typical of RBILD as well as areas in which lung parenchyma is more diffusely involved but without significant fibrosis. In those cases characterized by a combination of pigmented alveolar macrophages and a true interstitial pneumonia accompanied by fibrosis, we prefer the term NSIP. We acknowledge, however, that in some patients distinguishing between DIP and NSIP may be arbitrary. Fortunately, the distinction is unlikely to impact either patient management or prognosis.

DISTINGUISHING FIBROTIC NSIP FROM UIP

Separating fibrotic NSIP from UIP is perhaps the greatest challenge when it comes to making meaningful distinctions between the idiopathic interstitial pneumonias.[49] Separating fibrotic NSIP from UIP hinges on recognition of the patchwork distribution, fibroblast foci and honeycomb change typical of UIP.[19] In our view, recognition of any one of these features in a specimen for which a diagnosis of fibrotic NSIP is being contemplated is reason for caution. In this circumstance, correlation with other clinical data, especially the findings on HRCT, may be helpful.

The primary problem is that areas typical of NSIP can occur focally in other conditions, making sampling bias a potential barrier to accurate diagnosis. In a review of 20 explanted lungs with UIP, all but three showed isolated areas that were indistinguishable from NSIP ('NSIP-like areas').[19] Other studies have shown that the presence of UIP in even a single piece of tissue defined a survival curve typical of IPF in patients from whom surgical lung biopsy specimens taken from more than one site demonstrated both UIP and NSIP ('discordant UIP').[50,51] For these reasons, establishing a diagnosis of idiopathic NSIP requires the absence of clinical, radiological or pathological findings to suggest an alternative. For example, a biopsy diagnosis of fibrotic NSIP in a patient with bibasilar honeycomb change on HRCT is almost certainly a sampling error in a patient with UIP. Although the consensus classification would suggest that this issue be resolved by producing a pathology report with a diagnosis of fibrotic NSIP pattern, it is our practice instead to offer a descriptive diagnosis (e.g. chronic interstitial pneumonia with fibrosis most consistent with UIP) and a comment acknowledging that the biopsy falls short of being diagnostic but the imaging studies indicate UIP as the correct diagnosis. This approach avoids the risk of others engaged in a patient's care having to reconcile seemingly discordant information when comparing pathology reports with other clinical or radiological data.

RECOGNITION OF UNCLASSIFIABLE LESIONS IN PATIENTS SUSPECTED OF HAVING IDIOPATHIC INTERSTITIAL PNEUMONIAS

Occasionally, lung biopsy specimens show a fibrotic lesion in a clinical context strongly suggesting an idiopathic interstitial pneumonia but without sufficiently distinctive radiological or histological findings to allow confident diagnosis of a specific entity. Typically, these specimens show fibrosis, but with neither the combination of a patchwork distribution, fibroblast foci and honeycomb change diagnostic of UIP nor the uniform parenchymal involvement required for a diagnosis of NSIP. In other cases a portion of the specimen may show a lesion unusually cellular for UIP but with other areas in which the degree of honeycomb change precludes a diagnosis of NSIP. The consensus classification anticipated this category and proposed the term unclassifiable interstitial pneumonia for those patients in whom no clear diagnosis could be made. No additional information has emerged regarding either the frequency or significance of this group.

ROLE OF EXPERT INTERPRETATION OF LUNG BIOPSY SPECIMENS

The importance of subspecialty expertise in accurately and consistently recognizing the various forms of idiopathic interstitial pneumonia is controversial. The consensus classification suggested that the 'interobserver variability of pathological interpretation, particularly among general pathologists, needs to be defined'.[3] Since then, Nicholson and colleagues have examined the performance of 10 pathologists experienced in biopsy diagnosis of diffuse lung disease by circulating slides identified only with patient age, sex and biopsy site.[52] No additional clinical information was provided. With this limited information there were reasonably high rates of interobserver agreement when diagnoses of UIP, DIP and DAD (κ coefficients 0.58, 0.58 and 0.69, respectively) were made with confidence. There were low rates of agreement for NSIP (κ coefficient 0.31). This is not surprising given the importance of additional clinical and radiological data when interpreting slides for which NSIP is a consideration.

Flaherty and associates compared the diagnostic performance of community and academic physicians also using rates of interobserver agreement, rather than patient outcome, as a primary end-point.[40] Although this study is frequently cited as evidence that academic pathologists perform better, the academic participants comprised a group that has worked together extensively in this area, including publications in which they had previously analysed their rates of interobserver agreement. In addition, those patients in whom biopsy results were associated with the lowest rates of interobserver agreement between community and academic pathologists tended to be complex, with significant disagreement among all participants. For example, a patient ultimately assigned a diagnosis of 'CVD related IIP' (patient 376) was thought to have UIP by three of four academic pathologists and two of two community pathologists prior to knowledge of the clinical circumstances. Interestingly, half of both the academic and community radiologists and even one academic clinician assigned this patient a final diagnosis of UIP. After clinical information was shared with the pathologists, one academic and both community practitioners remained committed to a diagnosis of UIP, an interpretation that probably reflects disagreement regarding terminology rather than a substantive diagnostic error. Lettieri *et al.* also showed low rates of interobserver agreement between community-based pathologists and pathologists with subspecialty expertise in pulmonary diseases (κ 0.21; $P < 0.0001$) in a cohort of surgical lung biopsy specimens from patients referred to a tertiary care centre.[53] In this study the authors argued that expert opinion resulted in a change in management in 60% of patients, but left open the question of whether changes in management impacted patient outcome. In addition, there was no comparison of patient outcomes between those whose biopsy specimens were not reviewed by a subspecialist and those whose specimens were referred for expert review.

On the basis of the available data as well as our own anecdotal experience, no broad statement can be made regarding which patients' interests are best served by having their surgical lung biopsy specimens reviewed by recognized experts. It is our view that there are competent practitioners in both community and academic practices with variable degrees of interest and experience. Many patients with straightforward diagnoses, such as classical UIP, are well served by interested and experienced community practitioners, and there is little rationale for routine re-review in the absence of potentially discordant clinical or radiological findings.

ROLE OF TRANSBRONCHIAL BIOPSIES

The role of transbronchial biopsies in managing patients suspected of having idiopathic interstitial pneumonia remains controversial. The previously referenced consensus statement on idiopathic pulmonary fibrosis asserts that 'transbronchial biopsies are not helpful in making the diagnosis of UIP'.[8] The

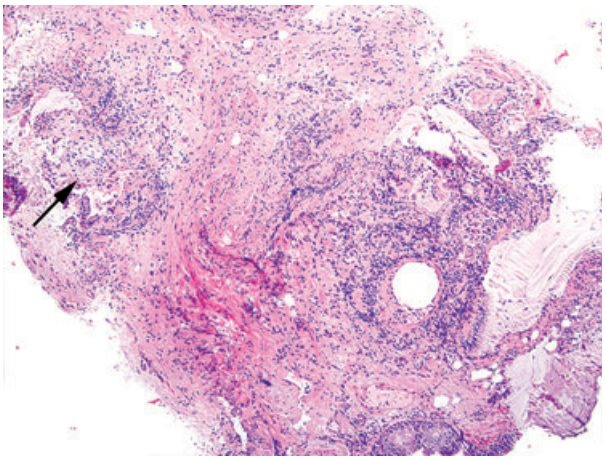

Figure 12. Photomicrograph of transbronchial biopsy from patient suspected of having usual interstitial pneumonia (H&E). There is architectural distortion in the form of scarring and honeycomb change with associated fibroblast foci (arrows).

subsequent consensus classification also describes transbronchial biopsies as 'not useful' in the diagnosis of idiopathic interstitial pneumonias, citing acute interstitial pneumonia as the exception.[3] This viewpoint is usually supported by referencing a paper published in 1981, a paper that antedates current diagnostic criteria and the advent of modern bronchoscopes, biopsy instruments and imaging techniques.[54] More recent studies have suggested that transbronchial biopsies may be more useful in managing immunocompetent patients with idiopathic interstitial pneumonias, especially UIP.[55,56] In a retrospective case study limited to patients with UIP, about a third of transbronchial biopsy specimens showed some combination of fibrosis distributed in a patchwork pattern, fibroblast foci, and honeycomb change considered diagnostic or at least suggestive of UIP (Figure 12). In an accompanying editorial, Churg and Schwarz recommended that transbronchial biopsies not be used to diagnose UIP until these preliminary observations were validated in a prospective and blinded fashion.[57] Although we agree that additional studies are necessary to understand more fully the diagnostic sensitivity and specificity of transbronchial lung biopsy in this setting, in our combined experience there is a small subset of patients in whom UIP can be diagnosed with confidence if carefully correlated with clinical and radiological findings.

Summary

Lung biopsy specimen diagnosis is a powerful and essential tool for accurately diagnosing patients with idiopathic interstitial pneumonia. Differentiating these entities is important because of significant differences in therapeutic options and prognosis. As HRCT gains widespread acceptance as a primary diagnostic modality for some of these entities, biopsies will be used mainly in patients with atypical and non-diagnostic HRCT results. The pathological diagnosis will be more important than ever in managing these patients.

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