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IDIOPATHIC INTERSTITIAL PNEUMONIA—*PART 1: OVERVIEW*
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Histopathology of the idiopathic interstitial pneumonias (IIP): A review

GABRIELA C. TABAJ,[1] CRISTINA F. FERNANDEZ,[2] EDUARDO SABBAGH[3] AND KEVIN O. LESLIE[4]

[1]*Pulmonary Medicine, Cetrangolo Hospital, Buenos Aires, Argentina,* [2]*Department of Pathology and* [3]*Department of Radiology, Instituto Nacional del Torax, Universidad de Chile, Santiago, Chile, and* [4]*Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, Scottsdale, Arizona, USA*

ABSTRACT

The 2013 American Thoracic Society/European Respiratory Society consensus classification update of the idiopathic interstitial pneumonias (IIP) included several important modifications to the organization and spectrum of the diseases that were proposed in an earlier multidisciplinary consensus document in 2002. The histopathology of the now 'major' and 'rare' IIP is presented here with exposition of the newly included entity of a distinctive upper lobe fibrotic lung disease referred to as idiopathic pleuroparenchymal fibroelastosis. The 'rare histological patterns' of acute fibrinous and organizing pneumonia and bronchiolocentric patterns of interstitial pneumonia are illustrated and discussed.

Key words: classification, idiopathic interstitial pneumonia, interstitial, lung disease, pathology.

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Summary:

Pleuroparenchymal fibroelastosis is a newly recognized ands accepted rare form of interstitial lung disease with distinct radiological and pathological appearance. Many cases are idiopathic, but a number are associated with underlying conditions. Familiarity with this entity will prevent confusion with other more recognized forms of fibrosing interstitial pneumonia.

Main teaching points:

- **Pleural thickening and pulmonary parenchymal fibrosis begin in the upper zones and progress inferiorly with time**
- **Pathology is distinctive with consolidative fibroelastosis showing demarcation from the uninvolved lung**
- **PPFE may be idiopathic or associated with other pulmonary diseases**

Correspondence: Kevin O. Leslie, Department of Laboratory Medicine and Pathology, Mayo Clinic Arizona, 13400 East Shea Boulevard, Scottsdale, AZ 95259, USA. Email: leslie.kevin@mayo.edu

The Authors:

Dr Tabaj is an attending physician in the division of pulmonary medicine at Cetrángolo Hospital in Buenos Aires, Argentina, where she is also the director of the residency programme. Dr Tabaj received her medical degree from Barceló University in Buenos Aires. Then she completed her residency in respiratory medicine at Cetrángolo Hospital, and subsequently a fellowship in interstitial lung diseases at British Hospital in Buenos Aires. She is a member of several medical organizations, including the American College of Chest Physicians and the Argentinian Association of Respiratory Medicine. Her clinical and research interests include interstitial lung diseases, idiopathic pulmonary fibrosis and idiopathic interstitial pneumonias. Dr Fernandez is a graduate of the School of Medicine at the Universidad Central de Venezuela and completed her pathology residency training in surgical pathology at Universidad de Chile. She is Chairman of Pathology Department at Instituto Nacional del Torax, and holds the academic appointment of assistant professor at Universidad de Chile. She is an active member of the Chilean Study Group of Interstitial Lung Diseases. Dr Sabbagh did his medical training in the University of Navarra, Spain, and completed residency training in general radiology at the University of Chile Medical Center. Following completion of a research fellowship in chest radiology at the University of Alabama in Birmingham with Dr Robert G. Fraser, he returned to Chile and serves as Chief of the Radiology Department at the National Chest Institute of Chile. His major achievements include teaching activities with residents and staff, as well as giving lectures and writing papers on the radiology of thoracic diseases. Dr Leslie received his medical degree from the Albert Einstein College of Medicine in 1978, trained in anatomic and clinical pathology at the University of Colorado, and completed a fellowship in surgical pathology at Stanford University Medical Center in 1983. He is a Consultant at the Department of Laboratory Medicine and Pathology and holds the academic rank of professor in the Mayo Clinic College of Medicine. In 2005 he co-authored and co-edited (with Dr Mark Wick) a textbook (now in its 2nd edition) entitled *Practical Pulmonary Pathology. A Diagnostic Approach*. This work was awarded 'Medical Textbook of the Year' by the Royal Society of Medicine.

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Abbreviations: AFOP, acute fibrinous and organizing pneumonia; AIP, acute interstitial pneumonia; ATS, American Thoracic Society; BIP, bronchiolitis obliterans with classical interstitial pneumonia/diffuse alveolar damage; BOOP, bronchiolitis obliterans organizing pneumonia; CFA, cryptogenic fibrosing alveolitis; COP, cryptogenic organizing pneumonia; CRP, clinical-radiological-pathological; DAD, diffuse alveolar damage; DIP, desquamative interstitial pneumonia; ERS, European Respiratory Society; HP, hypersensitivity pneumonitis; HRCT, high-resolution computed tomography; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; IPPFE, idiopathic pleuroparenchymal fibroelastosis; LIP, lymphoid interstitial pneumonia; MDD, multidisciplinary diagnosis; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; RB-ILD, respiratory bronchiolitis-associated interstitial lung disease; UIP, usual (classical) interstitial pneumonia.

INTRODUCTION

The idiopathic interstitial pneumonias (IIP) represent a subset of interstitial lung diseases of unknown origin that have been grouped together for many decades, beginning in 1969 in the original pathological classification by Liebow and Carrington.[1] Their classification recognized five main histopathological entities: usual (classical) interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with classical interstitial pneumonia/diffuse alveolar damage (BIP), lymphoid interstitial pneumonia (LIP) and giant cell interstitial pneumonia. Liebow revisited his IIP classification in a later publication.[2] In this monograph, Liebow acknowledged that although the IIP was morphology-based, clinical associations could be identified. Although not inclusive of every idiopathic interstitial lung disease (e.g. sarcoidosis), these subtypes of IIP became the gold standard for a generation of pathologists.

An important evolution of the classification of IIP occurred in 2002 with the publication of the first American Thoracic Society (ATS)/European Respiratory Society (ERS) international multidisciplinary consensus classification of the IIP.[3] A major change in approach was introduced in this document underscoring an earlier ATS/ERS consensus statement on idiopathic pulmonary fibrosis (IPF),[4] with the notion of a combined clinical-radiological-pathological (CRP) diagnosis in contrast to a strictly histopathological pattern of disease. Based on reasonable evidence, UIP, DIP and LIP were recognized as CRP entities corresponding to similar counterparts in the Liebow and Carrington classification. BIP was excluded, at least as Liebow and Carrington had conceived it. Instead, cryptogenic organizing pneumonia (COP) was added as a CRP entity providing a preferred terminology for what had been described initially as idiopathic bronchiolitis obliterans organizing pneumonia (BOOP) in 1983 by Davison *et al.*[5] and 1985 by Epler *et al.*[6] A new entity, respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), was added to the classification and proposed as a form of mild or early DIP. Both RB-ILD and DIP were considered to be smoking-related disease at ends of a histopathological spectrum. Another newly described entity, nonspecific interstitial pneumonia (NSIP) was included as a provisional subtype pending accrual of further data.

In the 2013 ATS/ERS revision/update of the IIP classification,[7] the main entities proposed in 2002 were preserved and not revisited in detail. Several important changes were introduced, however. Major IIP was set apart from rare and unclassifiable ones, a new entity of idiopathic pleuroparenchymal fibroelastosis (IPPFE) was formally acknowledged, and two rare *histological patterns* were introduced. The major IIP was grouped further into chronic fibrosing type (IPF and NSIP), smoking-related (RB-ILD and DIP), and acute/subacute types (COP and acute interstitial pneumonia (AIP)). A novel clinical disease behaviour classification was also proposed. In hopes that one day more objective measures might prove useful in the classification of ILD, the 2013 update presented a slate of emerging biomarkers and their evolving utility. In the pages that follow, we will present the key distinguishing features of the main IIP, as originally presented in the 2002 ATS/ERS consensus classification and elaborate on the additions proposed in 2013. We have purposely changed the order of presentation within the major IIP category to reflect the natural history of the injury repair cycle (acute disease preceding chronic disease).

MAJOR IDIOPATHIC INTERSTITIAL PNEUMONIA

Acute/Subacute

Acute interstitial pneumonia

In 1944, Hamman and Rich described a rapidly progressive form of lung disease in a small group of patients who died within months of disease onset and who had lung fibrosis at autopsy.[8,9] This apparent fulminant evolution of lung fibrosis became known as the Hamman and Rich syndrome. Three of the four patients presented in their paper had lung sections available for contemporary review in 1990 and had what would be called today organizing diffuse alveolar damage (DAD).[10] Katzenstein and co-workers were first to apply the term 'acute interstitial pneumonia' to this pattern of unexplained organizing DAD.[11]

Today, AIP is the multidisciplinary diagnosis (MDD) derived from histopathology showing DAD of unknown aetiology. DAD is perhaps one of the most straightforward histopathology diagnoses for general pathologists who encounter lung biopsies in this context, as the hyaline membranes of DAD are distinctive and quickly recognized in the biopsy evaluation. Of the IIP, AIP is best discussed first as it represents an early expression of the lung's stereotypic response to injury, albeit an overwhelmingly dramatic form. This then presents a conceptual backdrop for our understanding of the IIP, where DAD histopathology exists at one end of the spectrum and UIP with advanced fibrosis at the other. The challenges with DAD are centred on the exclusion of the myriad potential causes for this dramatic acute injury reaction.[12] Importantly, the term 'acute interstitial pneumonia' (AIP) should be reserved for those cases

that have been rigorously evaluated to exclude the common potential aetiologies for a DAD pattern.

The histopathology of DAD can be quite variable and highly dependent on when a biopsy is performed relative to onset of acute injury.[10,12] In the initial phases, hyaline membranes appear within 2–4 days and become most prominent by the fourth day.[12,13] Following each injury episode, the process will then progress through an accumulation of inflammatory cells in the lung interstitium, and even within hyaline membranes, followed by a proliferation of immature fibroblasts that grow out of the interstitium and fill the alveolar spaces.[14] At this last stage of DAD, the lung biopsy has alveoli filled with an organizing pneumonia (OP) pattern, and some of these patients will be referred to pathologically as 'OP', especially if tiny remnants of hyaline membranes are overlooked. When an acute injury begins at day 0, the process will progress through to OP over a 10-day period, followed by resolution or persistence of fibrosis over the ensuing months. An important feature of DAD from any aetiology is the presence of fibrin thrombi in pulmonary artery branches. These are often noticed early in the histopathology evaluation and may mislead the reviewer into believing that the patient has thromboembolic disease rather than DAD with secondary intravascular thrombosis. The evaluation of the lung biopsy in this setting is made more complicated in cases where more than one episode of acute injury has occurred because the stereotypic sequence of events that transpire after a single severe injury to the lung interstitium becomes intertwined. The characteristic morphological features of DAD are presented in the context of the classical high-resolution computed tomography (HRCT) pattern and distribution in Figure 1.

The 2002 consensus classification emphasized that lung biopsies from patients with AIP should not have visible evidence of infection, granulomas, tissue necrosis, microabscesses, areas of prominent tissue eosinophils or neutrophils, or positive special stains for microorganisms (whether bacterial, mycobacterial, fungal or viral).[7] All cases of DAD warrant investigation for infection, and special stains (a minimum of acid fast and silver stains) should always be performed when a DAD pattern is identified.

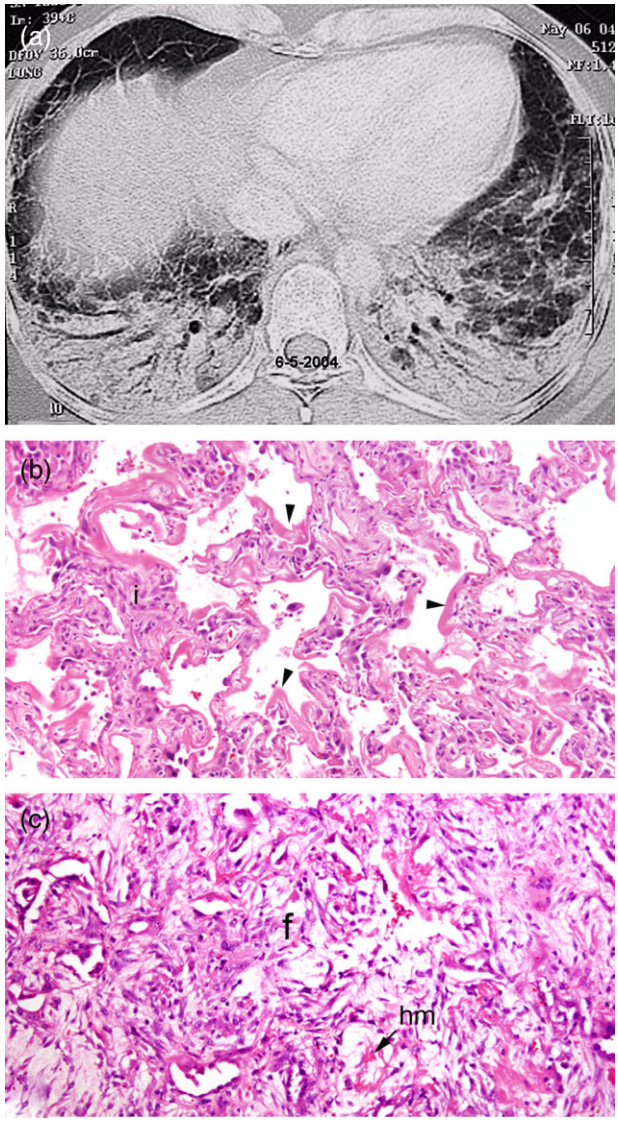

Figure 1 Acute interstitial pneumonia (diffuse alveolar damage pattern). (a) High-resolution computed tomography from a patient with acute interstitial pneumonia. The lower lobe distribution is predominantly posterior, with severe consolidation, retraction and traction bronchiectasis. (b) Early diffuse alveolar damage (DAD) is evident with prominent hyaline membranes readily visible (arrow heads) lining alveolar spaces without exudates. The alveolar wall interstitium (i) is slightly widened by matrix and mild cellular proliferation. HE stain, 100× original magnification. (c) In later disease (8–10 days after injury), the alveolar spaces are filled with immature fibroblasts (f), producing an organizing pneumonia appearance. Scattered remnants of hyaline membranes (hm) help confirm a diagnosis of 'organizing DAD'. HE stain, 100× original magnification.

Role of biopsy

Most patients with AIP do not undergo lung biopsy until rigorous exclusion of other potential aetiologies has been achieved using clinical and laboratory evaluation. For this reason, there may be an artificial increase in the occurrence of DAD in the organizing phase. Diagnosing this particular evolution to repair as unqualified 'OP' may confuse (or even mistakenly imply COP), so a careful search in this context for lingering hyaline membranes is essential, and likely prognostic, given the unfavourable outcome associated with this most dramatic form of lung injury. It is the exceptionally rare lung biopsy that shows a pure histopathological picture of early DAD.

Cryptogenic OP

The histopathology of COP is not new. Publications beginning in the early 19th century described a form of lung injury response characterized by the appearance of fibroblastic proliferation in the terminal airways and alveoli variably referred to as bronchiolitis fibrosa obliterans or simply bronchiolitis obliterans. Over many decades, this 'organizing

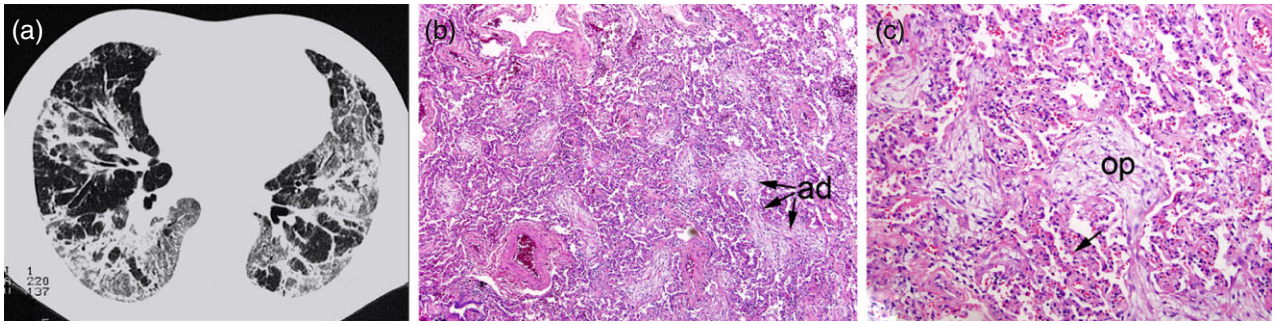

Figure 2 Cryptogenic organizing pneumonia (organizing pneumonia pattern). (a) High-resolution computed tomography from a patient with cryptogenic organizing pneumonia showing subsegmental basal distribution of partially confluent areas of consolidation. The lung architecture is preserved and there is no air trapping. (b) Organizing pneumonia pattern at scanning magnification shows alveolar filling by pale immature fibroblasts, sometimes interconnected through branching alveolar ducts (ad). The background lung architecture is preserved but slightly thickened by minimal chronic inflammation. HE stain, 100× original magnification. (c) Organizing pneumonia pattern at higher magnification. Here the alveolar polyps of immature fibroblasts (op) can be seen coursing between slightly thickened and inflamed alveolar walls (arrow). HE stain, 200× original magnification.

pneumonia' reaction was recognized as the lung's stereotypic reparative response to injury from a wide variety of insults. In 1985, Davison and co-workers and later Epler and co-workers described an idiopathic form of 'bronchiolitis obliterans' and coined the term 'idiopathic bronchiolitis obliterans organizing pneumonia'.[5,6,15] COP was proposed as the preferred term for the condition in the 2002 consensus classification.[3]

As the name of this IIP implies, patients with COP have an OP pattern of subacute lung injury that has a particular clinical and radiological context and importantly no identifiable aetiology. Most OP patterns encountered by pathologists in lung biopsies have an identifiable cause. The characteristic finding in patients with COP is a patchy OP pattern of subacute lung injury with airspace fibroblasts filling terminal airways, alveolar ducts and alveoli to variable extent. Scant chronic inflammation is typically present in the alveolar walls attesting to an ongoing 'interstitial injury'. Type II cells with reactive features may be present and alveolar macrophages are commonly a part of the process, frequently having a vacuolated or foamy-appearing cytoplasm. Fibrin tends not to be a dominant process in COP, but can be present very focally. Importantly, there should not be established fibrosis diffusely in the biopsy as this would imply a different process with a potentially different response to therapy and overall prognosis (such as acute exacerbation of a fibrotic lung disease). Additional specific features that should be absent include neutrophils, eosinophils, hyaline membranes, necrosis or granulomas. The characteristic HRCT findings and corresponding histopathology are presented in Figure 2.

Role of biopsy

Transbronchial biopsy can be effective for diagnosis but only if the clinical and radiology data are suggestive of this diagnosis. To safely accomplish (and encourage) this MDD, the pathologist should refrain from diagnosing 'COP' in any setting (transbronchial or surgical lung biopsy), but rather describe the presence of patchy alveolar organization as a manifestation of subacute injury to the lung and provide a robust differential diagnosis for clinical consideration. To invoke 'OP', or worse the pathological term 'BOOP', carries the risk of communicating an implication of COP. In practice, COP is the least likely diagnosis for a biopsy showing 'alveolar organization'.

Chronic fibrosing

Usual interstitial pneumonia/idiopathic pulmonary fibrosis

UIP was described first by Liebow and Carrington in their histopathological classification of chronic interstitial pneumonias, published in 1969.[1] Simultaneously, the term 'cryptogenic fibrosing alveolitis' (CFA) was in use in Europe for a likely identical histopathology, namely advanced diffuse pulmonary fibrosis of unknown causation.[16,17] The 2002 ATS/ERS consensus document favoured a *multidisciplinary diagnosis* terminology of IPF/CFA. CFA was removed from the 2013 ATS/ERS consensus for being a redundant term. Today, IPF is the MDD corresponding to a UIP histopathological pattern in the appropriate clinical and radiological context.

As detailed in an earlier ATS/ERS IPF consensus document in 2000,[4] UIP/IPF is a disease of unknown aetiology occurring in older individuals (typically over 60 years of age). The radiological manifestations identifiable on HRCT are always worse at the periphery of the lung bases, progressing cephalad over the course of the disease. Fibrosis in UIP/IPF histopathologically appears to begin at the periphery of the lung lobule, and this is where microscopic honeycomb remodelling is identified first in cases of low-burden disease. UIP has solid areas of well-established fibrosis that alternate with zones of normal lung producing a 'patchwork' appearance of scar at scanning magnification under the microscope. Closer inspection

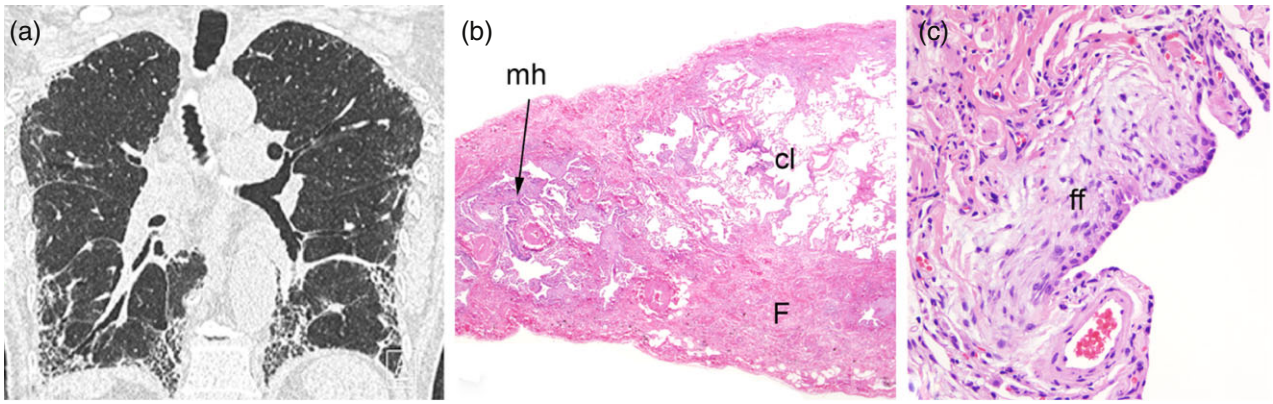

Figure 3 Idiopathic pulmonary fibrosis (usual interstitial pneumonia (UIP) pattern). (a) Coronal high-resolution computed tomography demonstrates characteristic basal, subpleural, irregular (geographical) distribution. Small irregular opacities, honeycomb microcysts and traction bronchiectasis complete the picture. (b) UIP in a surgical lung biopsy at scanning magnification reveals the characteristic dense, established fibrosis (F) surrounding regions of centrilobular spared lung (c). Microscopic honeycomb (mh) remodelling completes the picture at this magnification and may be seen before honeycomb cysts are visible on chest imaging. HE stain, 12.5× original magnification. (c) The fibroblast focus (ff) is found most commonly at the leading edge of dense scar where this abuts normal lung. HE stain, 200× original magnification.

reveals minute foci of immature fibroblastic proliferation at the edge of dense fibrosis where this interfaces with normal lung. These are referred to as *fibroblast* or *fibroblastic* foci. They are a required feature of the UIP histopathological pattern, but they are not specific for the disease. Another peculiarity of UIP is the presence of abundant smooth muscle in fibrosis. A composite image of UIP radiology and pathology is presented in Figure 3.

In general, the centrilobular regions in UIP lack fibrosis, that is, the bronchovascular bundles are not involved by the disease. Nevertheless, because patients with IPF are most often prior cigarette smokers, a certain level of chronic small airways remodelling is expected. When extensive airway-centred fibrosis is evident, typically coupled with evidence of airways remodelling (the so-called peribronchiolar metaplasia), an alternate (or comorbid) diagnosis should be considered. One of the diagnostic challenges in cases of suspected IPF is the distinction of airway-centred disease with peribronchiolar metaplasia from foci of microscopic honeycombing. A system for communicating confidence for a histopathological diagnosis of UIP was proposed in the second international consensus statement on IPF, whereby the degree of certainty (UIP, probable UIP, possible UIP, not UIP) was based on the presence or absence of specific morphological findings observable in the surgical lung biopsy.[18]

Role of lung biopsy

Today surgical lung biopsy should be restricted to patients without definite features of UIP on HRCT, or to those in whom there are other confounding clinical features, such as young age. The 2011 ATS/ERS consensus classification of IPF provided a 'degrees of certainty' paradigm for both the HRCT findings and the histopathology of UIP, based on the presence (or absence) of key features. In practice, this system is marginally beneficial in the best of circumstances (a knowledgeable clinician) and confusing in most others. For clinical trial enrolment, it provides a useful common lexicon, but in the case of pathology rarely is the final disposition (UIP, probable UIP, possible UIP, not UIP) based solely on the proposed 'elements' expected to be present in each 'certainty category'. The transbronchial biopsy is not recommended for diagnosis. Diseases diagnosed easily by transbronchial biopsy tend to be airway-centred or perilymphatic processes, quite different from UIP. A newly available technique known as *transbronchial cryobiopsy* may change this recommendation as the procedure produces larger tissue fragments with very little artefact. In a study of 40 patients published by Poletti and co-workers, 85% showed two or three criteria for a confident diagnosis of UIP.[19]

Nonspecific interstitial pneumonia

This histopathology pattern was described by Katzenstein and Fiorelli in 1994[20] in a series including 64 patients. The authors introduced the concept of *temporally and spatially homogeneous interstitial fibrosis* in direct contrast to the temporal and spatial *heterogeneity* expected in UIP. For the diagnosis, findings typical of other IIPs had to be absent, and in the beginning this point was highlighted by the notion that NSIP was defined by what it was not. The histopathological features of NSIP were divided initially into three groups, based on the extent of chronic inflammation and fibrosis present in the lung interstitium. Travis *et al.*[21] proposed improved utility for two groups, a cellular (chronic inflammatory) form and a fibrosing form (with or without associated chronic inflammation).[22] In a later report from the ATS project on NSIP,[21] the frequency of the fibrosing pattern was estimated at 84%, with the pure cellular pattern being much less frequent. A detailed

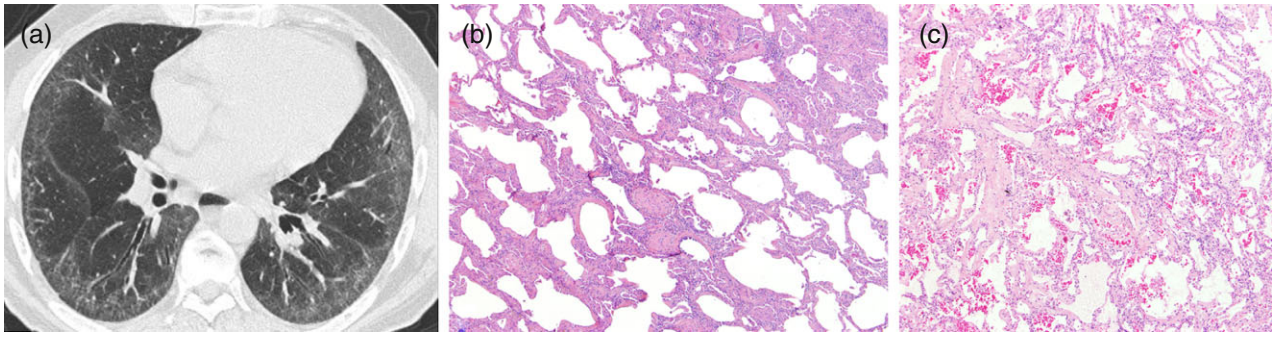

Figure 4 Nonspecific interstitial pneumonia (NSIP pattern). (a) High-resolution computed tomography demonstrates increased lung density in a subcortical and central distribution. The lung architecture is preserve. There is mild traction bronchiectasis. Slight subpleural sparing is evident. (b) The 'dusty cobwebs' of NSIP pattern are evident in this case of mixed cellular and fibrotic NSIP. Note the relative preservation of the background alveolar walls with only minimal fusion into thicker structures. HE stain, 40× original magnification. (c) An example of fibrotic NSIP with less overall interstitial fibrosis and less chronic interstitial inflammation. HE stain, 200× original magnification.

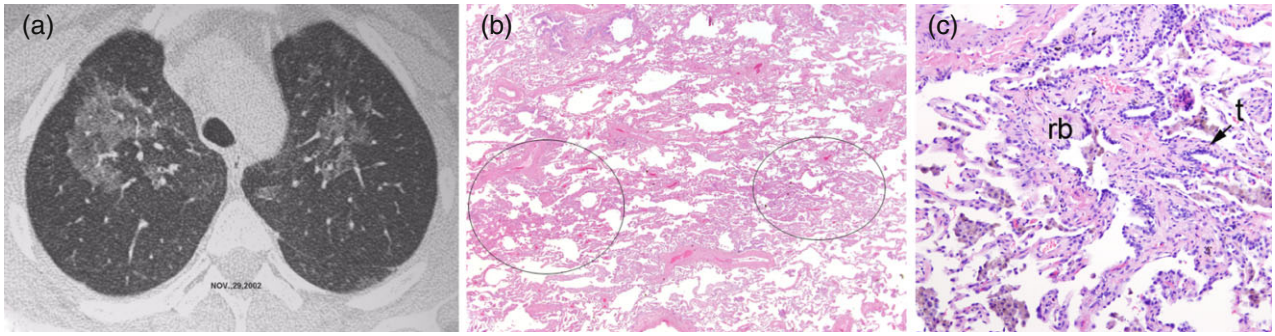

Figure 5 Respiratory bronchiolitis-associated interstitial lung disease (RB-ILD pattern). (a) On high-resolution computed tomography, upper lobe predominant, ill-defined, centrilobular opacities are characteristic. (b) RB-ILD at scanning magnification shows ill-defined nodularity (circles) within which a central respiratory bronchiole (with respiratory bronchiolitis) is surrounded by a zone of macrophage accumulation in alveolar spaces. The lack of uniform alveolar filling helps distinguish RB-ILD from desquamative interstitial pneumonia. HE stain, 100× original magnification. (c) At higher magnification, the central lesion of respiratory bronchiolitis is evident. Note the small amount of peribronchiolar collagen deposition extending short tendrils (t) into surrounding alveolar walls. There is minimal associated chronic inflammation. HE stain, 200× original magnification.

description of the histopathology is less informative than the images of the process in lung tissue (Fig. 4).

Intra-alveolar buds of granulation tissue (OP) should be minimal to avoid confusion with COP.[20,22] Moreover, unexpected findings that would argue against a diagnosis of NSIP were underscored, such as intra-alveolar accumulation of pigmented macrophages, granulomas, many fibroblastic foci and prominent honeycombing.

Role of lung biopsy

A clinical or radiological diagnosis of NSIP without a biopsy is highly inaccurate. The transbronchial lung biopsy is not strongly recommended; however, in selected cases NSIP can be inferred in the proper radiological context. The recent introduction of the cryobiopsy technique may make this the optimal technique for obtaining a reasonable amount of lung tissue for diagnosis.[23,24]

Smoking-related

Respiratory bronchiolitis-interstitial lung disease

RB-ILD and DIP continue to be considered together as ends of a spectrum of ILD affecting cigarette smokers mainly, with unknown frequency. The rationale for this proposed continuum is unsupported by existing data in our opinion, although both conditions have alveolar macrophage accumulation. Cigarette smokers commonly have a condition referred to as 'respiratory bronchiolitis' where mild inflammation, fibrosis and pigmented airspace macrophages occur around distal bronchioles (Fig. 5c). When smokers become symptomatic with upper lung zone ground glass opacities (Fig. 5a), lung biopsies may show a distinctive expansion of RB foci, accentuated by a zone of macrophage accumulation in centrilobular alveolar spaces (Fig. 5b). This combination of respiratory symptoms, radiological findings

and histopathology has come to be referred to as RB-ILD.[25]

The histopathology is characterized by mild chronic inflammation centred on the respiratory bronchioles and associated with minimal fibrosis. Increased numbers of lightly pigmented macrophages are present within immediate adjacent airspaces, but limited in extent, such that a patchy appearance is appreciated at scanning magnification.[25–27] Centriacinar emphysema is present frequently, but may be difficult to recognize in the biopsy sample. Lung biopsies from patients with RB-ILD lack intra-alveolar eosinophils, giant cells and lymphoid follicles within the lung interstitium, findings that should suggest DIP.

Role of biopsy

RB-ILD is often diagnosed without the necessity for a surgical lung biopsy. If findings suggesting RB-ILD are identified in surgical biopsies or resected specimens for tumour, the pathologist should highlight the presence of prominent RB, and suggest clinical and radiological correlation rather than attempt to diagnose RB-ILD on histopathology alone.

Desquamative interstitial pneumonia

Described first by Liebow *et al.* in 1965,[28] and later expanded in detail by Carrington *et al.*,[29] DIP is a chronic interstitial pneumonia distinguished by the presence of abundant alveolar cells, thought initially to be sloughed epithelium (desquamation). Later, the macrophage nature of the intra-alveolar cells was confirmed by electron microscopy, but the name remained. DIP was distinguished from UIP given its good response to corticosteroid administration and a better prognosis. In the 2013 update of the IIP, DIP was maintained in the classification with some reservations, recognizing that the actual incidence of DIP today seems to be extremely low. Furthermore, the authors seem to imply that if indeed DIP is the late phase of RB-ILD, this concept would justify maintaining it in the IIP classification.

At scanning magnification, the lung architecture is preserved, with peribronchiolar and sometimes interstitial lymphoid aggregates visible. The alveolar walls are mildly thickened by uniform fibrosis, obscured by the presence of large numbers of macrophages filling the alveolar spaces throughout most of the biopsy sections. This extent of macrophage accumulation distinguishes DIP from RB-ILD (Fig. 6). In smokers, the characteristic macrophage of DIP has abundant pale eosinophilic cytoplasm with finely granular light-brown pigment (so-called smokers-type macrophages). Iron stains are positive in these cells, but the pigment most often lacks the dense, golden, refractile pigment of the siderophages of pulmonary haemorrhage. In children with DIP, macrophages may lack such pigmentation. A few multinucleated giant cells and eosinophils are often admixed with the alveolar macrophages in DIP.[30]

Role of biopsy

A surgical lung biopsy is necessary for a diagnosis of DIP, given significant clinical and radiological overlap with NSIP. The transbronchial biopsy is not sufficient for a confident diagnosis in most cases.

RARE IDIOPATHIC INTERSTITIAL PNEUMONIA

Lymphoid interstitial pneumonia

LIP was described in Liebow's original classification on the basis of 13 patients who underwent lung biopsy and/or autopsy. Liebow recognized that LIP was a lymphoid infiltrate in lung parenchyma so dense as to suggest lymphoma, but that in the patients he studied the disease was more indolent than would be expected for lung involvement by lymphoma. With the advent of ancillary studies for the diagnosis of lymphoma, most cases with LIP histopathology were proven to be low-grade B-cell lymphomas involving lung. Nevertheless, in 2002, the international consensus felt that a form of LIP did

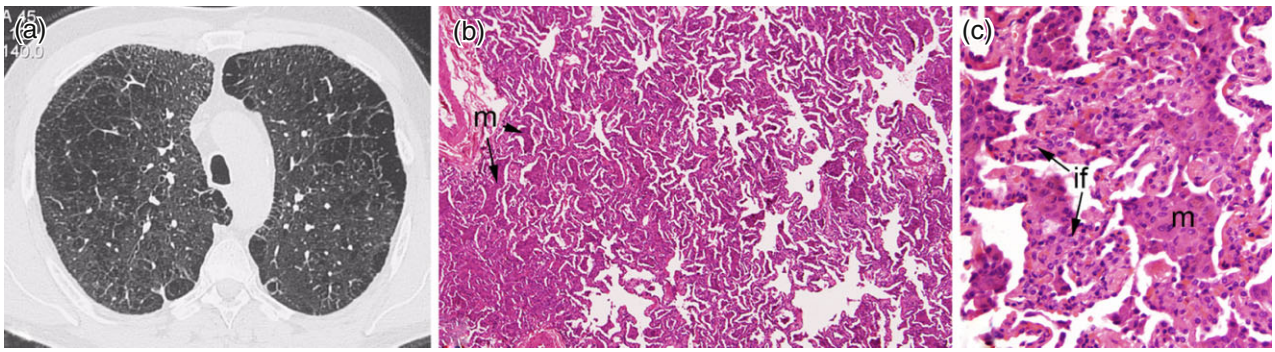

Figure 6 Desquamative interstitial pneumonia (DIP pattern). (a) High-resolution computed tomography shows centrilobular emphysema and thickening of bronchial walls, accompanied by an increase in lung density, of homogenous appearance and with a predominantly basal, central and cortical distribution. (b) The lung in DIP is distinctive at scanning magnification with alveolar spaces filled with aggregations of eosinophilic macrophages. A reticulated image is produced by retraction of the macrophage aggregates (m) away from adjacent alveolar walls. HE stain, 40× original magnification. (c) At higher magnification, the characteristic smokers-type lightly brown pigmented macrophages of adult DIP are evident in alveolar spaces (m). There is always a modicum of interstitial fibrosis in DIP (if). HE stain, 200× original magnification.

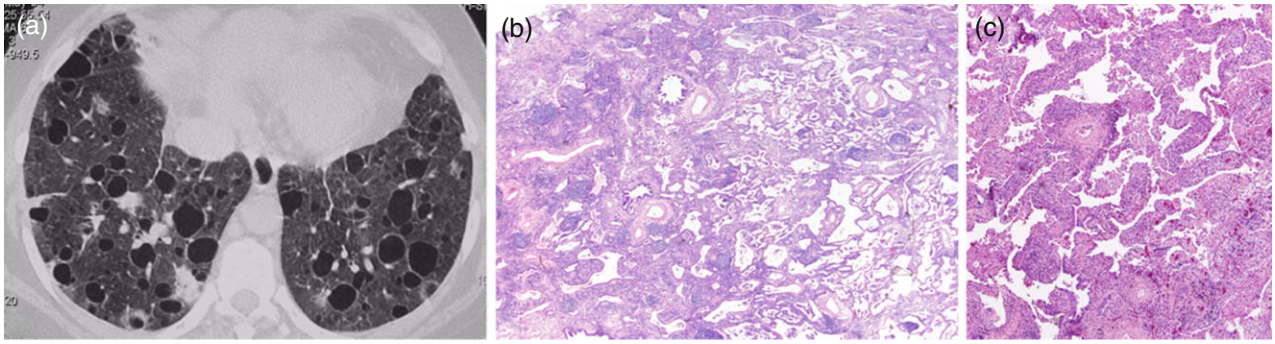

Figure 7 Lymphoid interstitial pneumonia (LIP pattern). (a) High-resolution computed tomography demonstrates the basal segmental distribution of nodular consolidation in LIP, in this case, with well-defined cysts. Consolidation and cysts can be highly variable in idiopathic LIP. (b) LIP at scanning magnification is always more cellular than nonspecific interstitial pneumonia (NSIP) (a clue to their distinction). Note the bluntly thickened interstitium and parenchymal distortion. Lymphoid aggregates and follicles are common. The diagnosis of exclusion in LIP is low-grade lymphoma, so ancillary laboratory testing is required before making this diagnosis. HE stain, 100× original magnification. (c) At higher magnification, the degree of interstitial expansion by lymphoid cells exceeds that expected for cellular NSIP, and LIP always has fibrosis with distortion of alveolar architecture, an uncommon finding in cellular NSIP. Multinucleated giant cells and small non-necrotizing granulomas may be seen raising concern for hypersensitivity pneumonitis. HE stain, 200× original magnification.

exist that was not lymphoma. Patients with non-neoplastic LIP may have underlying Sjogren syndrome or other connective tissue disease, and this should always be a point of exploration in the patient who presents with an LIP pattern on imaging (as cystic disease) or in biopsy as LIP.[31]

The most important histopathological clue to the diagnosis of LIP is the presence of diffuse, dense, interstitial lymphoplasmacellular infiltration of lung parenchyma with associated background distortion of lung architecture and the addition of small non-necrotizing granulomas and giant cells. The latter tend to be somewhat zonal in distribution such that giant cells and tiny granulomas are not expected throughout the process. Follicular lymphoid hyperplasia is often present, often with focal OP and sometimes with a focal DIP reaction with macrophages accumulating in air spaces, but these should be inconspicuous (Fig. 7).

In all cases where LIP is a diagnostic consideration histopathologically, rigorous studies are required to exclude the possibility of a definable lymphoproliferative disease. When lymphoma is present, the lung becomes relatively solidified by the process, whereas in the idiopathic form of LIP, the process is more interstitial. Key features that should be absent before entertaining a diagnosis of idiopathic LIP are the presence of necrotizing granulomas, extensive pleural or interlobular septal involvement by lymphoid cells, absence of visible Dutcher bodies, and overall lack of a perilymphatic distribution (distribution along lymphatic routes in the bronchovascular bundles, interlobular septa and pleura). By immunohistochemistry, the majority of lymphoid cells in idiopathic LIP should be small T lymphocytes with some included plasma cells. If CD20 positive lymphocytes by immunohistochemistry are dominant in a diffuse distribution, B-cell lymphoma becomes the diagnosis of exclusion.

Diseases that can be confused with LIP include those where a lung biopsy of an isolated lesion reveals a process rich in lymphocytes and plasma cells, diffuse lymphoid hyperplasia, nodular lymphoid hyperplasia, and lymphoma. NSIP in the cellular phase may be distinguishable based on the intensity of lymphoid infiltration in the alveolar walls in the biopsy. While hypersensitivity pneumonitis (HP) is technically in the differential diagnosis of an LIP pattern, the intensity of lymphoid infiltration is significantly less in HP and the infiltrates tend to be airway-centred.

Idiopathic pleuroparenchymal fibroelastosis

The first description of this newly included form of IIP is credited to Amitani and co-workers, who described a distinctive pattern of upper pulmonary lobe fibrosis in Japanese patients.[32] Later, Frankel *et al.*[33] coined the term 'idiopathic pleuroparenchymal fibroelastosis' for this entity. Approximately 69 cases have been reported in the literature.[34,35]

The upper lobe fibrosis that defines IPPFE is elastotic in nature, identical in appearance to the so-called apical cap fibroelastosis. Different from apical cap (an incidental finding in most biopsies), the fibroelastosis of IPPFE involves large areas of pleura and extends into the lung parenchyma. A sharp interface with surrounding parenchyma is typical (Fig. 8). Fibroblastic foci may be present at this interface, similar to those seen in UIP.[33]

Role of biopsy

A surgical lung biopsy is required for both of these rare entities. Many questions regarding IPPFE remain, underscored by the work of Reddy *et al.*,[36] who suggested infection (especially that related to *Aspergillus* sp.), immune dysfunction and genetic mechanisms as important predisposing factors based on a clinical-radiological-histopathological study of 12 patients.

RARE HISTOLOGICAL PATTERNS

Two rare histological interstitial pneumonia patterns (acute fibrinous and organizing pneumonia (AFOP) and bronchiolocentric interstitial pneumonia) were added to the consensus statement in 2013. These were not judged to be sufficiently robust from a clinical and radiological standpoint for inclusion as new entities given available evidence. The main concern was that these patterns might represent variants of existing IIP or exist only in association with other conditions, such as HP or connective tissue disease manifesting in the lung.

Acute fibrinous and organizing pneumonia

AFOP was first reported in 17 patients with acute respiratory failure and initially regarded to represent a possible new IIP.[37] The dominant histopathological pattern is intra-alveolar fibrin deposition and associated OP in the absence of classical hyaline membranes of DAD or intra-alveolar eosinophils of acute eosinophilic pneumonia (Fig. 9). AFOP may represent a histological pattern that can occur in the clinical spectrum of DAD and OP, or it may reflect a tissue sampling issue. AFOP may be idiopathic, or associated with collagen vascular disease, HP and drug reaction, among others.[38–40] Alveolar fibrin accompanied by organization is an exceptionally common lung response to acute injury and only becomes a 'rare disorder' when defined by nebulous and irreproducible defining criteria.

Idiopathic bronchiolocentric interstitial pneumonia

A distinctive form of pulmonary fibrosis can be seen in biopsies and autopsy lungs where the dominant finding is fibrosis confined to bronchovascular bundles, with variable amounts of advanced parenchymal remodelling (so-called peribronchiolar metaplasia) (Fig. 10). When giant cells and granulomas are seen associated with this 'airway-centred scarring', a diagnosis of chronic HP would be appropriate histopathologically, in the proper imaging and clinical context. Without visible granulomas or

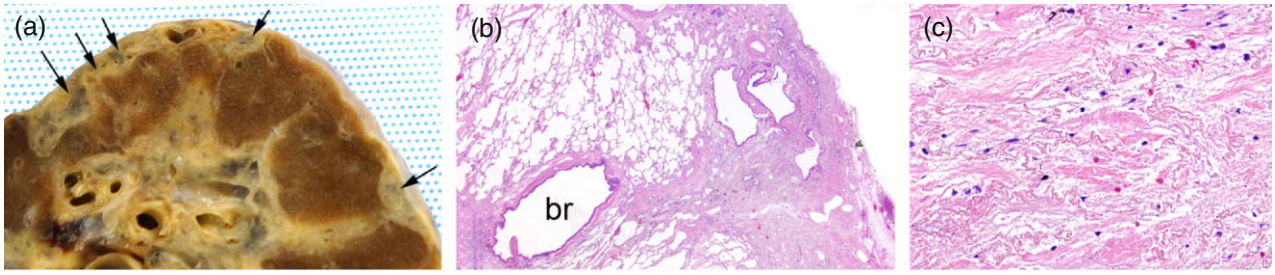

Figure 8 Idiopathic pleuroparenchymal fibroelastosis (IPPFE) (pleuroparenchymal fibroelastosis pattern). (a) The gross appearance of IPPFE is distinctive in this image image from explanted lung (courtesy of Dr John English, Vancouver General Hospital, Vancouver, BC). The distribution of subpleural thickening (arrows) is reminiscent of that seen in the lung bases in patients with idiopathic pulmonary fibrosis. (b) At scanning magnification, the gross appearance is nicely complemented with pale elastotic scar extending from a thickened subpleural rind into lung towards (and surrounding) subjacent bronchovascular bundles (br) in lung parenchyma. It is the sheer extent of disease that helps separate IPPFE from routinely identified 'apical cap'-type fibroelastosis. HE stain, 12.5× original magnification. (c) A high magnification view of the characteristic fine fibrillar elastosis of IPPFE is presented. This is identical in appearance to that seen in apical cap. HE stain, 200× original magnification.

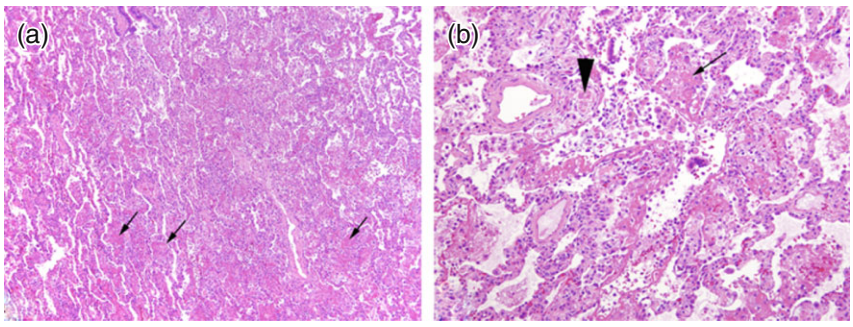

Figure 9 Acute fibrinous and organizing pneumonia pattern. (a) At scanning magnification, the lung is involved by localized or diffuse fibrinous injury with fibrin aggregates (arrows) in alveolar spaces. Organization is inconspicuous. HE stain, 100× original magnification. (b) At higher magnification, the fibrin aggregates (arrow) can be seen within alveolar spaces, accompanied by very focal organization (arrowhead). The interstitium is marginally widened by the inflammatory process. A key element that should be missing for this pattern is the eosinophil. With eosinophils, an argument could be made for eosinophilic pneumonia as a better pathological diagnosis. HE stain, 200× original magnification.

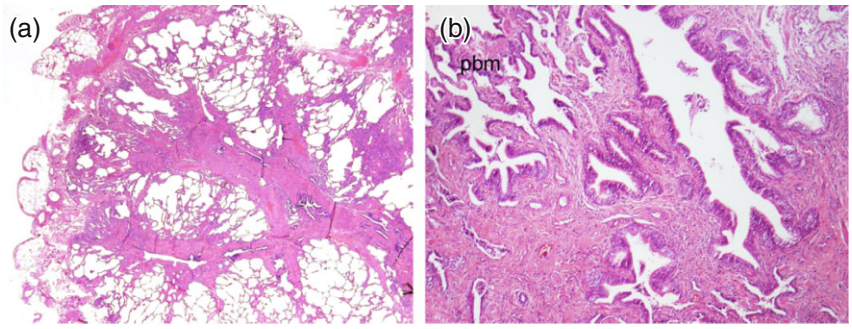

Figure 10 Bronchiolocentric patterns of fibrosis. The 2013 consensus classification update did not include representative images of this process, presumably given some variability in the described entities in the literature. For purposes of illustration, two examples of unexplained airway-centred fibrosis are illustrated. (a) A dramatic low magnification image of the process of airway-centred fibrosis, in this case with no definable aetiology by histopathology (no granulomas). Note the branching airways extending to pleura, accentuated by fibrosis expanding the bronchovascular sheaths. HE stain, 12.5× original magnification. (b) Another case of airway-centred fibrosis attended by peribronchiolar metaplasia (pbm). HE stain, 200× original magnification.

characteristic clinical features (including HRCT), the finding remains of unknown aetiology. In 2002, Yousem and Dacic[41] described 10 patients with a 'distinctive idiopathic bronchiolocentric interstitial pneumonia'. All 10 patients had airway-centred fibroinflammatory infiltrates with variable extension into surrounding lung. The authors noted histopathological similarities to HP. Churg and co-workers[42] presented 12 cases with 'a distinctive pattern of airway centered interstitial fibrosis centered on membranous and respiratory bronchioles' at scanning magnification. In both series, a distinction from the peripheral lobular distribution of fibrosis typical of UIP was emphasized. The 2013 consensus statement felt that these small series were insufficiently compelling from a clinical and radiological perspective to warrant inclusion as a formal IIP. We believe this entity exists as an idiopathic disease and is as valid as 'NSIP', a diffuse lung disease that was defined initially by all of the known conditions it was not.

UNCLASSIFIABLE IDIOPATHIC INTERSTITIAL PNEUMONIA

In 2002, the inclusion of an 'unclassifiable' category was debated and rejected, purportedly because it was not useful in clinical management. Now, the value of including such a category has been recognized, with emphasis on the multitude of reasons such a diagnosis might be necessary. If an ILD is difficult or impossible to classify, management should be based on the most probable diagnosis after MDD and consideration with the expected disease behaviour. A useful approach is presented in the consensus statement in 2013, including most likely diagnosis and best approach to management.[7]

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