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The role of histology in idiopathic pulmonary fibrosis: An update

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Review

Summary
The diagnosis of idiopathic pulmonary fibrosis (IPF) currently requires an integrated clinical–radiological–pathological approach in which the histology plays a different role from in the past. The first reason for this change is that non-invasive diagnostic procedures, particularly pulmonary function tests and high resolution computed tomography, have become increasingly competitive with biopsy in providing prognostic information. The other reason is a better appreciation of the limitations of histology: sampling error and interobserver variation. In this review we analyze the reasons for this change of perspective, provide an update on the practical role of histology in the diagnosis of IPF and discuss some of its complications.

Introduction

In the last few years the diagnosis of idiopathic pulmonary fibrosis (IPF) has gradually shifted from a situation in which biopsy was the single gold standard to a more complex paradigm in which the histology is part of a dynamic multidisciplinary approach integrating the clinical, radiological and pathological data.[1–4]

The reasons for this profound change are twofold. First, the non-invasive diagnostic procedures, particularly pulmonary function tests[5–9] and high resolution computed tomography (HRCT),[10,11] became increasingly competitive with biopsy in providing prognostic information. Nowadays they are a sufficient surrogate of biopsy in a significant proportion of patients, and when biopsy remains necessary they integrate with histological results. For example,

Abbreviations: AE, acute exacerbation; CVD, collagen vascular disease; DAD, diffuse alveolar damage; HP, hypersensitivity pneumonitis; HRCT, high resolution computed tomography; ILD, interstitial lung disease; IPF, idiopathic pulmonary fibrosis; LCH, Langerhans' cell histiocytosis; NSIP, non-specific interstitial pneumonia; OP, organizing pneumonia; UIP, usual interstitial pneumonia.

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when HRCT appearance is typical of usual interstitial pneumonia (UIP) a non-invasive (clinico-radiological) diagnosis of IPF is almost always accurate.[12] As a corollary, biopsy is required only when the HRCT scan and/or the clinical features are not typical of UIP, a situation occurring in <50% of patients with IPF. In this scenario the correct classification of the disease is based on histology, and the histological distinction between UIP and non-specific interstitial pneumonia (NSIP) provides important prognostic information.[13] In other words, when clinico-radiological data are inconclusive and biopsy is deemed necessary, histology generally remains the most important piece of the diagnostic puzzle. However, HRCT maintains a role in determining the most appropriate site of biopsy, and the prognosis is further refined when histological data are integrated with HRCT[14] and clinico-functional parameters.[15]

Together with the growing importance of non-invasive procedures, the other reason for the change in the role of histology in IPF is a better appreciation of its limitations. The first limit of histology is sampling errors — any disease in the lung is heterogeneous, and a biopsy in different areas may provide different results. For example, in IPF an optimal biopsy will demonstrate UIP, but a suboptimal biopsy may show only non-diagnostic honeycomb, areas of NSIP or a background of smoking-related changes. In particular, areas histologically indistinguishable from NSIP commonly occur in UIP[16]: they are generally focal, but sometimes they are extensive. If the wrong area is sampled a histological diagnosis of NSIP can be misleading because the prognosis will be dictated by the non-sampled UIP.[17,18]

The problems related to sampling can be reduced by obtaining an optimal biopsy (Table 1) and correlating the histology with the clinical and radiological data: if the histology does not explain the clinico-radiological scenario, the possibility that the relevant disease has not been sampled should be considered. It is important to note that the pathologist has to maintain an open mind because the histological interpretation can be modified by clinical and radiological data.

The second limit of histology in interstitial lung disease (ILD) is interobserver variation. Several recent studies evaluating this issue showed variable agreement not only among pathologists but also among clinicians and radiologists.[19–23] In particular, Flaherty et al.[23] reached the following conclusions: 1) interobserver agreement is better among experts than non-experts, but is not perfect even among experts; 2) agreement between experts and non-experts is variable, but in general is quite low — the field in which experts and non-experts most frequently disagree is the differential diagnosis of IPF, NSIP, collagen vascular disease (CVD) and chronic hypersensitivity pneumonitis (HP), with non-experts being more likely to assign a diagnosis of IPF; and 3) an iterative diagnostic approach improves the interobserver agreement.

It is likely that continued education and increased interaction between experts and non-experts could reduce interobserver variation[23]; however both interobserver variation and sampling errors are only partially avoidable because they are intrinsic to histology. Not surprisingly, pathologists have to deal with them not only in ILD but also in many other fields.[24–33] As emphasized by Wells, "… histopathologic appearances may be intermediate between two entities in a significant proportion of cases, and observer variation may be an appropriate and accurate reflection of this fact".[2]

In summary, in IPF (and in ILD in general) the growing importance of non-invasive procedures and the better perception of the limits of histology (particularly sampling errors and observer variation) have gradually transformed histology from the sole gold standard to a piece of the diagnostic puzzle, a much more complex and stimulating situation for the pathologist because it requires not only correct evaluation of the histology but also its correct interpretation in light of the clinical and radiological information. In the following pages we will examine the practical role of histology in IPF, focusing on the main scenarios in which the pathologist can be involved.

Histological diagnosis of UIP

The histological features of UIP are beautifully described in recent papers.[34–36] The diagnostic keys are: 1) a patchwork appearance resulting from alternating areas of scarred and normal lung; 2) architectural distortion; and 3) fibroblastic foci.

At low magnification (Fig. 1A), the disease is non-uniform because of an irregular juxtaposition of scarred and normal or nearly normal lung (spatial heterogeneity). The scarred areas frequently prevail in the subpleural/paraseptal regions (Fig. 1B), with an abrupt transition with normal lung (patchwork pattern).[16,34] The architecture is distorted, with honeycomb and thick scars obscuring the alveolar framework.

Honeycomb (Fig. 1C), which can be absent in early cases, consists of enlarged airspaces lined by bronchiolar epithelium and frequently filled by mucous and inflammatory cells, mostly neutrophils and macrophages. The background architecture is distorted, which is the key to differentiating honeycomb from the enlarged airspaces

Table 1 Characteristics of an optimal biopsy.

Surgical biopsy	Transbronchial biopsy
Accurate selection of the site of biopsy (based on computed tomography)	Accurate selection of the site of biopsy (based on computed tomography)
Artefacts as few as possible	Artefacts as few as possible
Multiple biopsies from at least two different areas; biopsies deep and large enough (>3 cm)	Biopsies adequate for dimension and number (at least 4—6 fragments, with alveolar parenchyma present in the majority)

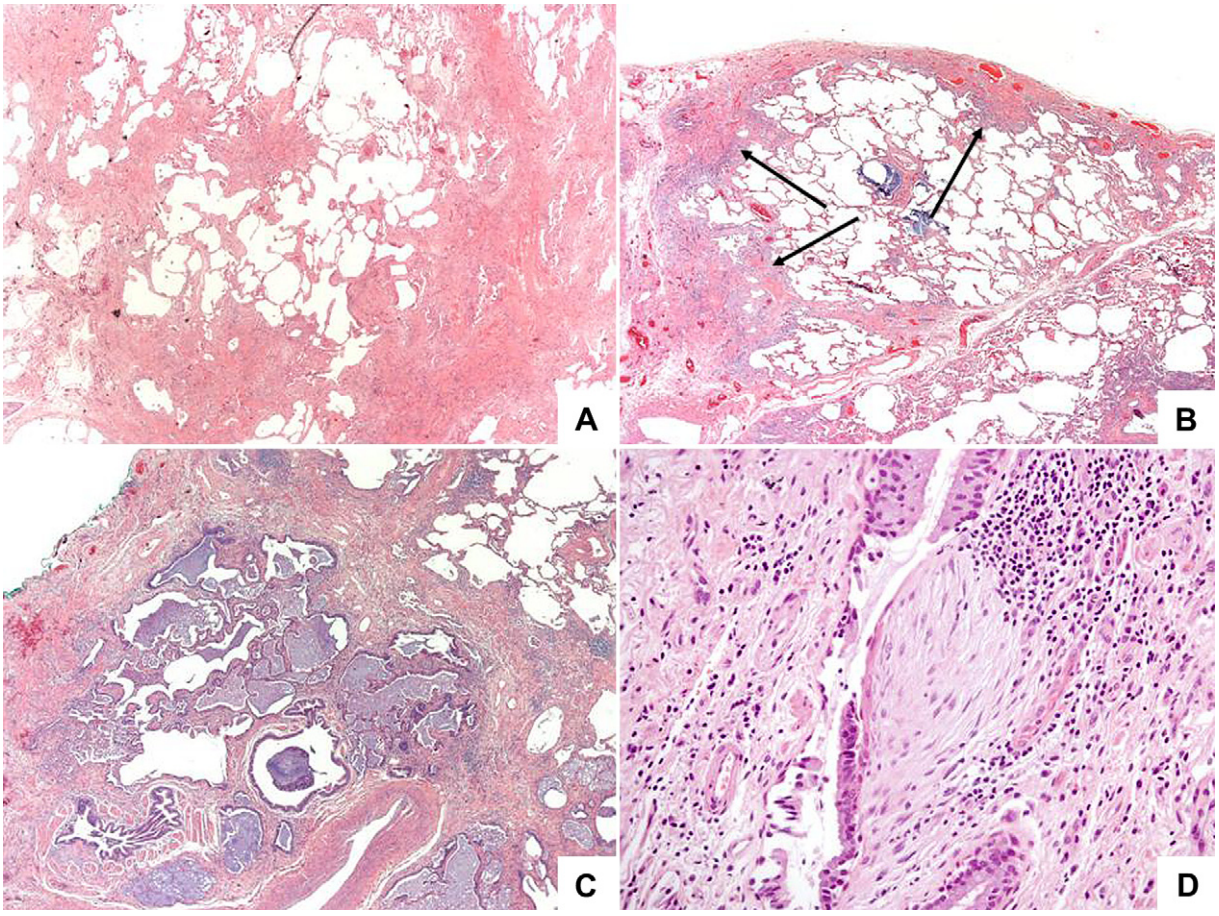

Figure 1 Histology of usual interstitial pneumonia. A) At low magnification the diagnostic key is the abrupt alternating of scarred and normal lung (patchwork pattern: scar-normal-scar-normal). In the scarred areas the alveolar architecture is obliterated (haematoxylin–eosin × 20). B) The fibrosis frequently prevails at the periphery of the lobule in the subpleural–paraseptal regions (arrows), with relative sparing of the centrolobule. This is a useful diagnostic clue, particularly in early cases like here (haematoxylin–eosin × 20). C) Honeycomb consists of enlarged airspaces lined by bronchiolar epithelium, frequently filled by mucus and surrounded by dense scars. Note the architectural distortion and the abrupt transition with residual normal lung seen in the right upper corner (haematoxylin–eosin × 20). D) A fibroblastic focus consisting of a dome-shaped proliferation of myofibroblasts immersed in a myxoid matrix. Fibroblastic foci can be covered by bronchiolar epithelium, as here, or by hyperplasic pneumocytes (haematoxylin–eosin × 100).

that can be seen in fibrosing NSIP (see below) and from peribronchiolar metaplasia, a frequent incidental finding in many conditions, including UIP.[37] Smooth-muscle hyperplasia is frequently seen in scarred lung and can be prominent in some cases.

Fibroblastic foci (Fig. 1D) are present in the background of scarring, frequently at the interface with normal lung, and consist of small, dome-shaped interstitial collections of myofibroblasts within myxoid stroma, covered by hyperplastic pneumocytes or bronchiolar cells. Generally they are easily seen, even at low magnification, because of their pale appearance, which contrasts with the pink colour of scars. Being the site of ongoing injury fibroblastic foci indicate active disease, whereas fibrotic scars and honeycomb indicate an injury occurring in the distant past (temporal heterogeneity). In patients with IPF extensive fibroblastic foci have been associated with a particularly poor prognosis in some studies, but not all.[38]

Inflammation is frequently present in UIP, including small areas simulating eosinophilic pneumonia[39] and occasional incidental granulomas. A cellular infiltrate including lymphoid follicles can be quite prominent in honeycomb, but outside these areas inflammation is generally minimal and overshadowed by fibrosis.

The role of special stains

Histochemical and immunohistochemical stains are invaluable in some specific settings, in particular Ziehl-Neelsen, Grocott, Gram and several immunohistochemical markers if an overinfection is a consideration; elastic stains to evaluate vessels in pulmonary hypertension; iron stains to search for asbestos bodies; and p63 or high-molecular-weight cytokeratins to differentiate adenocarcinoma from peribronchiolar metaplasia in difficult cases.[40] However, none of these markers has proved useful in the diagnosis of uncomplicated UIP. Trichrome stains fibrosis, but fibrosis is generally obvious in sections routinely stained with haematoxylin–eosin.

Much more promising are immunohistochemical markers, which may be useful in difficult cases to highlight subtle modifications that may be overlooked when stained with haematoxylin–eosin.[41] We think it is worth investigating if this level of sensitivity is practically relevant, i.e. if diagnosing IPF with immunomarkers has a superior prognostic impact to using haematoxylin–eosin. Until these studies are performed, in our opinion, the pathological diagnosis of UIP should be based on the careful evaluation of high-quality routinely stained slides. In our practice we use special stains when the artefacts are so heavy as to preclude a detailed evaluation of routine sections.

The role of transbronchial biopsy

Occasionally, transbronchial (but also transthoracic) biopsies performed in patients with IPF show histological features of UIP (Fig. 2). In the only article addressing this topic, the diagnostic sensitivity of transbronchial biopsies in UIP was about 30%.[42] However, this was a retrospective and unblinded study in which all the patients were known to have UIP, and further prospective studies in which a variety of fibrotic ILD are blindly evaluated are clearly needed before transbronchial biopsy can be recommended in the workup of patients with suspected IPF. In our opinion, as also emphasized in the editorial accompanying the paper of Berbescu et al.,[43] until such studies are performed the histological diagnosis of UIP requires a surgical biopsy.

We also think that the claimed role of transbronchial biopsy in suggesting an alternative diagnosis[44] is questionable in the subset of well-studied patients with idiopathic fibrosing ILD and an HRCT atypical for UIP, the setting in which a biopsy is required for the diagnosis. For example, occasional granulomas can be found in IPF as an incidental finding, and their presence is not *per se* diagnostic of HP or sarcoidosis if the clinico-radiological scenario does not support these possibilities. In practice, if the fibrosing ILD is considered idiopathic after an accurate clinical workup, very rarely will the results of a transbronchial biopsy be strong enough to be diagnostic and spare the patient a subsequent surgical biopsy.

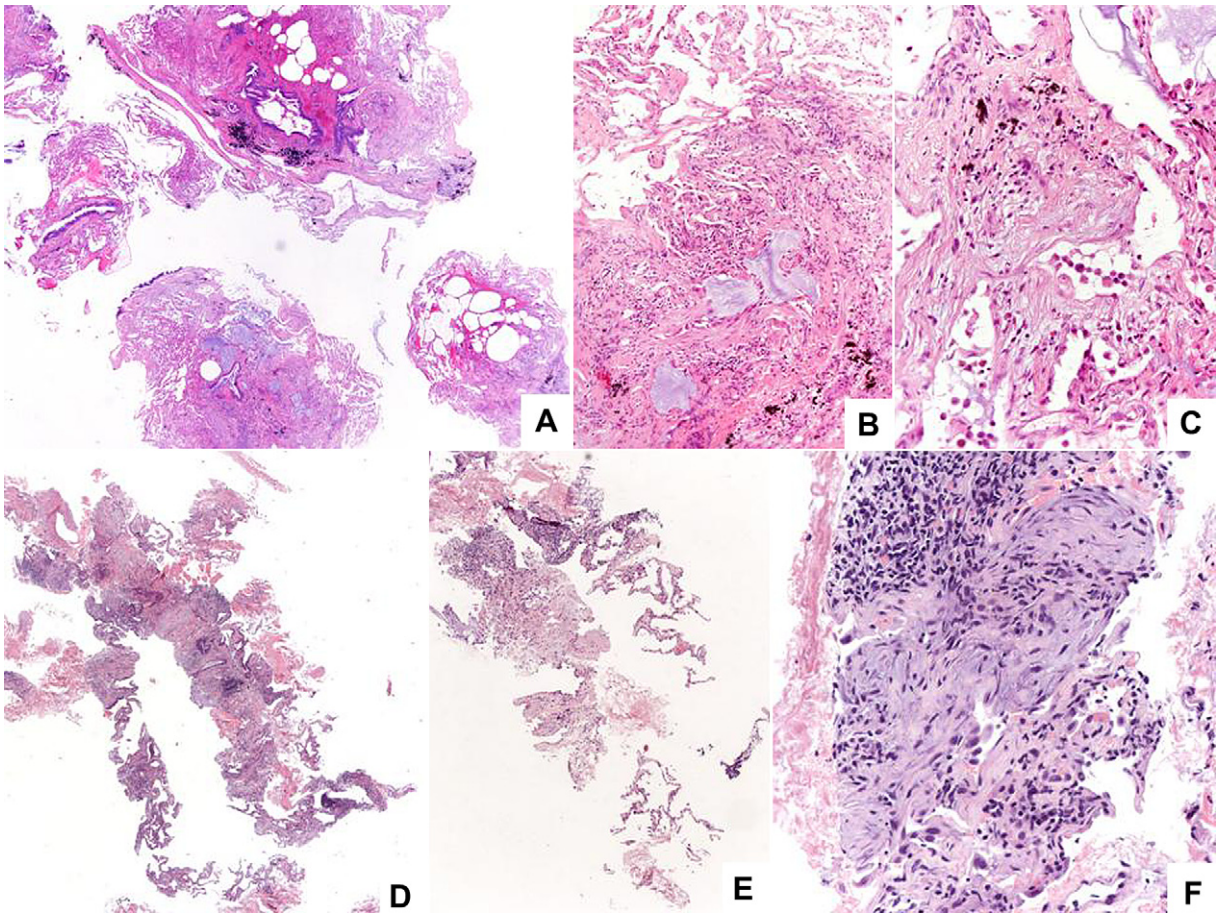

Figure 2 Histological features of usual interstitial pneumonia in small biopsies. A) A generous transbronchial biopsy in an elderly male with a clinico-radiological diagnosis of idiopathic pulmonary fibrosis (haematoxylin–eosin × 20). B) A small area of patchwork pattern, with a dense scar side-by-side with normal lung (haematoxylin–eosin × 100). C) A fibroblastic focus (haematoxylin–eosin × 200). D) A transthoracic biopsy in an elderly male with a clinico-radiological diagnosis of IPF, showing a scarred lung. The biopsy was performed for a peripheral nodule, which was not sampled (haematoxylin–eosin × 20). E) Abrupt transition between scarred and normal parenchyma (haematoxylin–eosin × 20). F) A fibroblastic focus (haematoxylin–eosin × 200). Although suggestive of usual interstitial pneumonia, the diagnostic specificity of these findings is not proved.

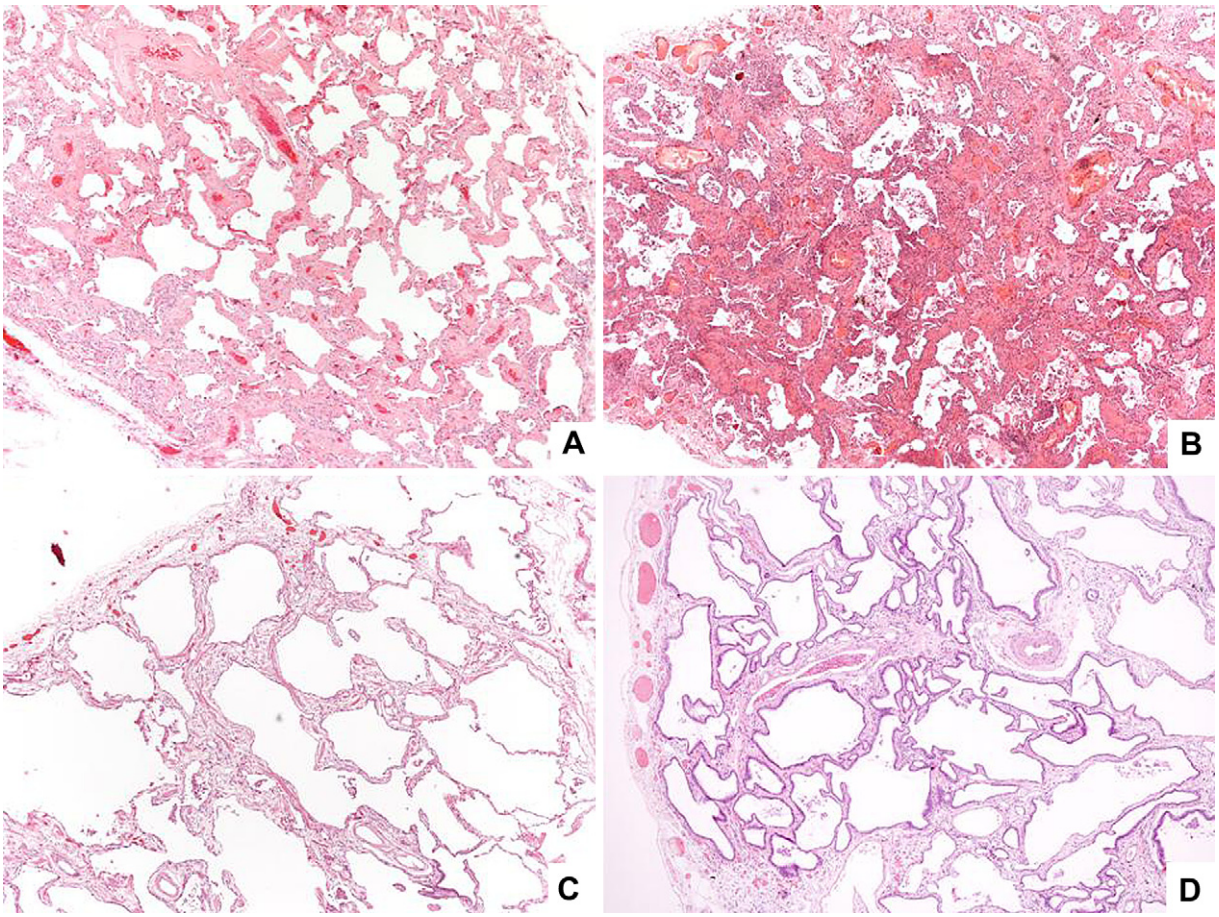

Figure 3 Histology of fibrosing non-specific interstitial pneumonia (NSIP). A) Uniform interstitial fibrosis with preservation of the alveolar architecture. At low magnification the absence of patchwork and architectural distortion are the keys to differentiating NSIP from usual interstitial pneumonia (compare with Fig. 1A). Note the absence of honeycomb and fibroblastic foci (the fibrosis is all of the same age) (haematoxylin–eosin × 20). B) Also in areas in which fibrosis is more marked, the alveolar framework is still recognizable (haematoxylin–eosin × 20). C) Sometimes in NSIP the fibrosis is looser, a feature rarely seen in usual interstitial pneumonia (haematoxylin–eosin × 40). D) Enlarged airspaces surrounded by interstitial fibrosis and lined with bronchiolar or alveolar epithelium. These enlarged airspaces are quite frequent in fibrosing NSIP and differ from honeycomb in the finer character of the fibrosis, which respects the alveolar architecture (compare with Fig. 1C) (haematoxylin–eosin × 40).

Differential diagnosis of UIP and fibrosing NSIP

A pattern of NSIP can be found at histology in several clinical settings, particularly CVD, HP and drug reactions, or it can be idiopathic. In two recent papers[13,45] 4% and 10% of patients initially considered idiopathic developed a CVD during the follow-up, and in another study[46] 88% of idiopathic cases met the definition of undifferentiated connective tissue disease. In practice, a histological diagnosis of NSIP should prompt the clinician to carefully exclude a secondary form. By contrast with IPF, which typically occurs in old smokers, idiopathic NSIP prevails in middle-aged patients who have never smoked.[13] Although it is not clear how much weight can be attached to this clinical difference in a single case,[47,48] in practice the pathologist has to be particularly careful before making a diagnosis of UIP in a relatively young patient who never smoked or a diagnosis of NSIP in an old smoker.

Table 2 Contrasting histological features of usual interstitial pneumonia (UIP) and fibrosing non-specific interstitial pneumonia (NSIP).

	UIP	Fibrotic NSIP
Character of the fibrosis	Non-uniform (spatial heterogeneity/patchwork)	Uniform
Architecture	Distorted	Preserved
Honeycomb	Frequently present	Absent or minimal
Fibroblastic foci	Present (temporal heterogeneity)	Absent or very few

Table 3 Histological features which, when present in usual interstitial pneumonia, suggest diseases different from idiopathic pulmonary fibrosis (IPF).

Histological feature	Consider
Cellular lymphoplasmacytic infiltrate and/or cellular bronchiolitis and/or lymphoid follicles	Collagen vascular disease, chronic hypersensitivity pneumonitis
Peribronchiolar fibrosis (sometimes bridging to the periphery of the lobule)	Chronic hypersensitivity pneumonitis, pneumoconiosis
Pleuritis	Collagen vascular disease
Granulomas	Depending on the morphology and localization of granulomas[64,65]: infection (particularly atypical mycobacterial infection secondary to traction bronchiectasis), chronic hypersensitivity pneumonitis, chronic sarcoidosis, IPF arising in a background of incidental sarcoidosis, incidental finding in IPF
Abundant coarse iron pigment	Asbestosis (do iron stains on several slides to search for asbestos bodies, which can be few), chronic haemorrhage (consider the possibility of ANCA-associated fibrosis[66])
Foamy macrophages with eosinophils	Drug reaction (focal areas resembling eosinophilic pneumonia are an unusual incidental finding in IPF[39])

Microscopically, NSIP is characterized by thickening of the interstitium by inflammatory cells (lymphocytes and plasma cells) in the cellular variant, or by fibrosis in the fibrosing variant.[13,49] Mixed forms occur, and are included in the fibrosing group.[13] Whereas the distinction between UIP and cellular NSIP is straightforward, in a minority of patients the differential diagnosis between UIP and fibrosing NSIP (although clinically relevant)[13,50] is difficult, with occasional cases in which a firm distinction is impossible. This generally results from poor sampling, although occasional cases are difficult to classify because they lie in the grey zone between the two entities. In these situations an open discussion between clinician, radiologist and pathologist can be particularly fruitful, but when the case remains

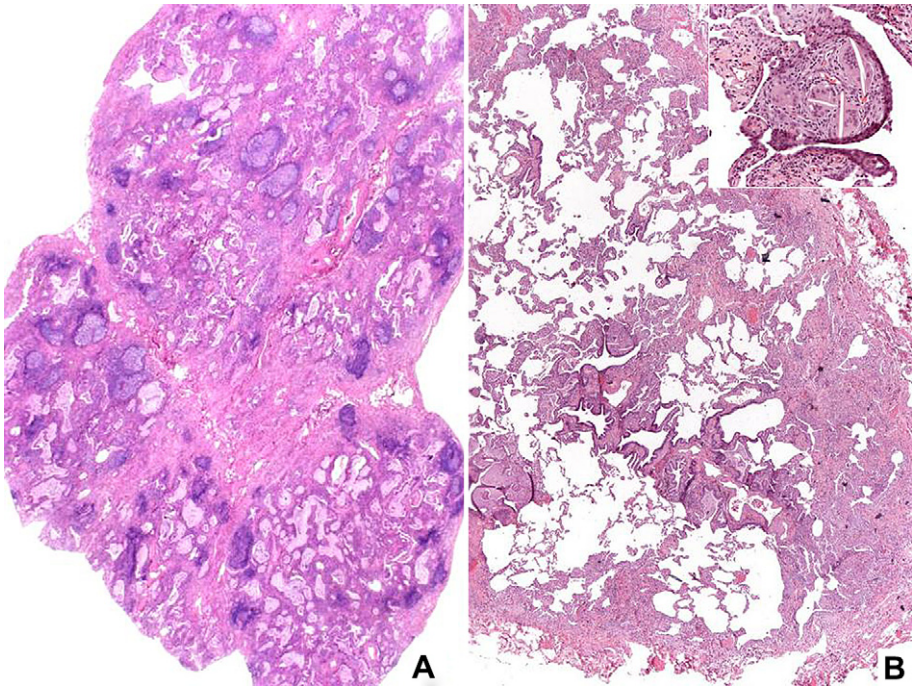

Figure 4 Examples of secondary usual interstitial pneumonia. A) Surgical lung biopsy in a middle-aged woman with rheumatoid arthritis (case courtesy of Prof. T.V. Colby, Scottsdale, USA). Note the numerous lymphoid follicles with germinal centres, which are the clue to suspecting an underlying collagen vascular disease (haematoxylin–eosin × 20). B) Surgical lung biopsy in an elderly farmer. The centrolobular involvement with fibrosis bridging to the periphery of the lobule, and the small peribronchiolar granuloma (insert), are characteristic of chronic hypersensitivity pneumonitis (haematoxylin–eosin × 20).

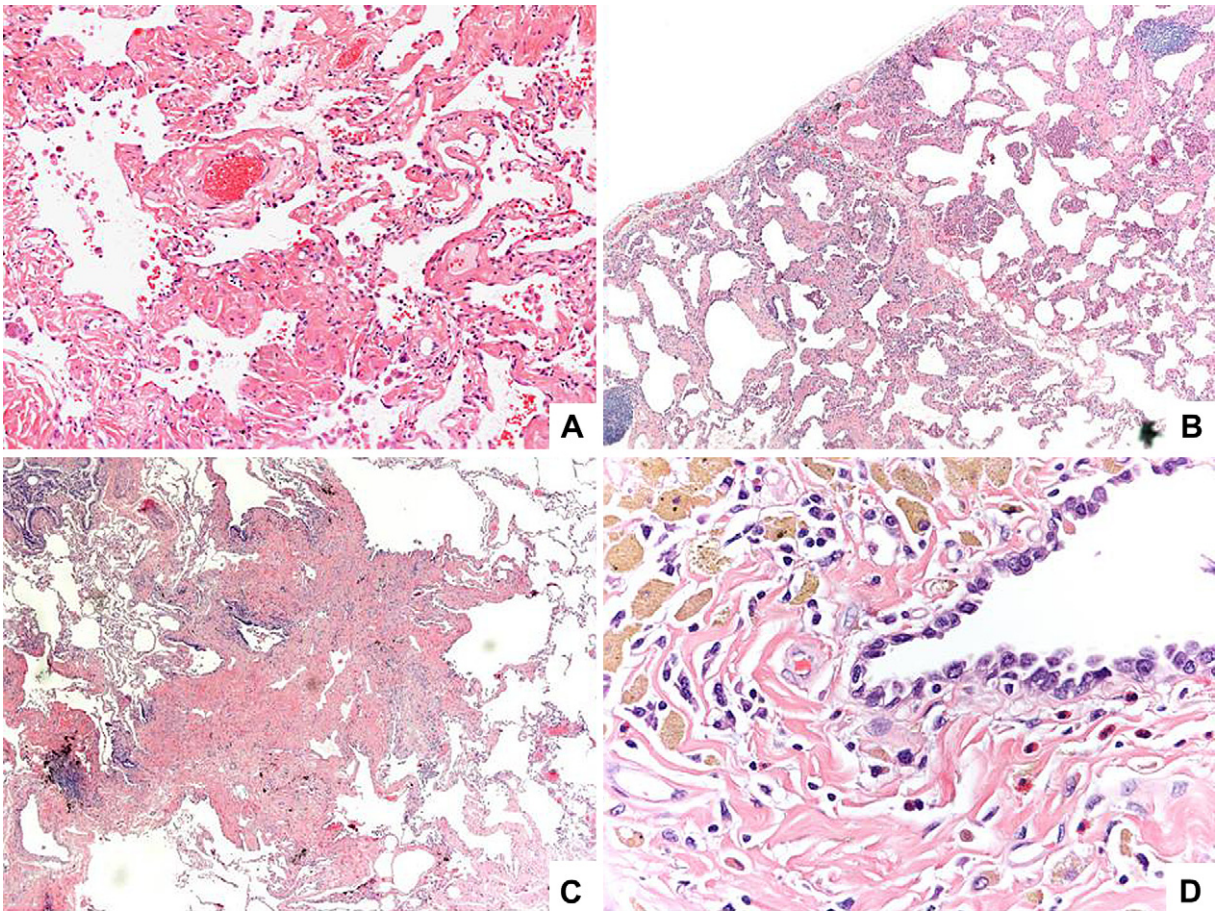

Figure 5 Histology of smoking-related fibrosis and chronic Langerhans' cell histiocytosis (LCH). A) Dense ropy collagen typical of smoking-related fibrosis (haematoxylin—eosin × 40). B) Smoking-related fibrosis frequently surrounds enlarged airspaces, both in subpleural and centrolobular regions. In the centre-right of the picture note the intra-alveolar accumulation of pigmented macrophages (respiratory bronchiolitis) (haematoxylin—eosin × 20). C) Stellate peribronchiolar scar typical of chronic LCH, causing traction emphysema. This kind of fibrosis, totally different from usual interstitial pneumonia, is diagnostic of chronic LCH even in the absence of residual Langerhans' cells (haematoxylin—eosin × 20). D) Pigmented macrophages entrapped within fibrosis. Although not entirely diagnostic, this feature is characteristic of LCH (haematoxylin—eosin × 200).

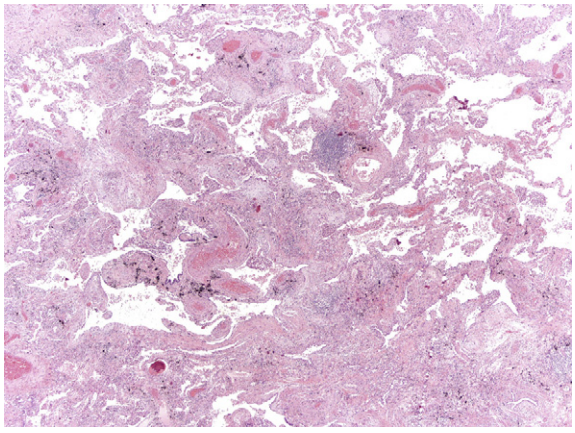

Figure 6 Surgical lung biopsy showing usual interstitial pneumonia with numerous fibroblastic foci and organizing pneumonia. A case like this lies somewhere on the spectrum between stable idiopathic pulmonary fibrosis and acute exacerbation. This biopsy was performed for a recent worsening of symptoms, but the patient did not satisfy the clinical criteria for acute exacerbation (haematoxylin—eosin × 40).

unsolved it may be advisable to refer the patient (or the slides) to a centre with expertise in ILD.[23] The histology of fibrosing NSIP is shown in Fig. 3, and the contrasting features with UIP are presented in Table 2.

Differential diagnosis of IPF and secondary UIP

In addition to IPF other diseases that may present with a UIP pattern include CVD,[51,52] chronic HP,[53—59] asbestosis,[60] drug reaction[61] and familial ILD.[62,63] In some cases these diseases are perfect histological mimics of IPF and the distinction is based exclusively on clinical grounds. In other cases there are histological features (sometimes subtle) that may suggest the possibility of one of these diseases (Table 3, Fig. 4). Importantly, none of these features is diagnostic *per se* and the final diagnosis should always rest on the careful correlation of the histology with the clinical data. Nonetheless, it is important for the pathologist to suggest (when it is possible) a secondary UIP rather than IPF because the distinction may have prognostic implications in some settings, although it is probably less

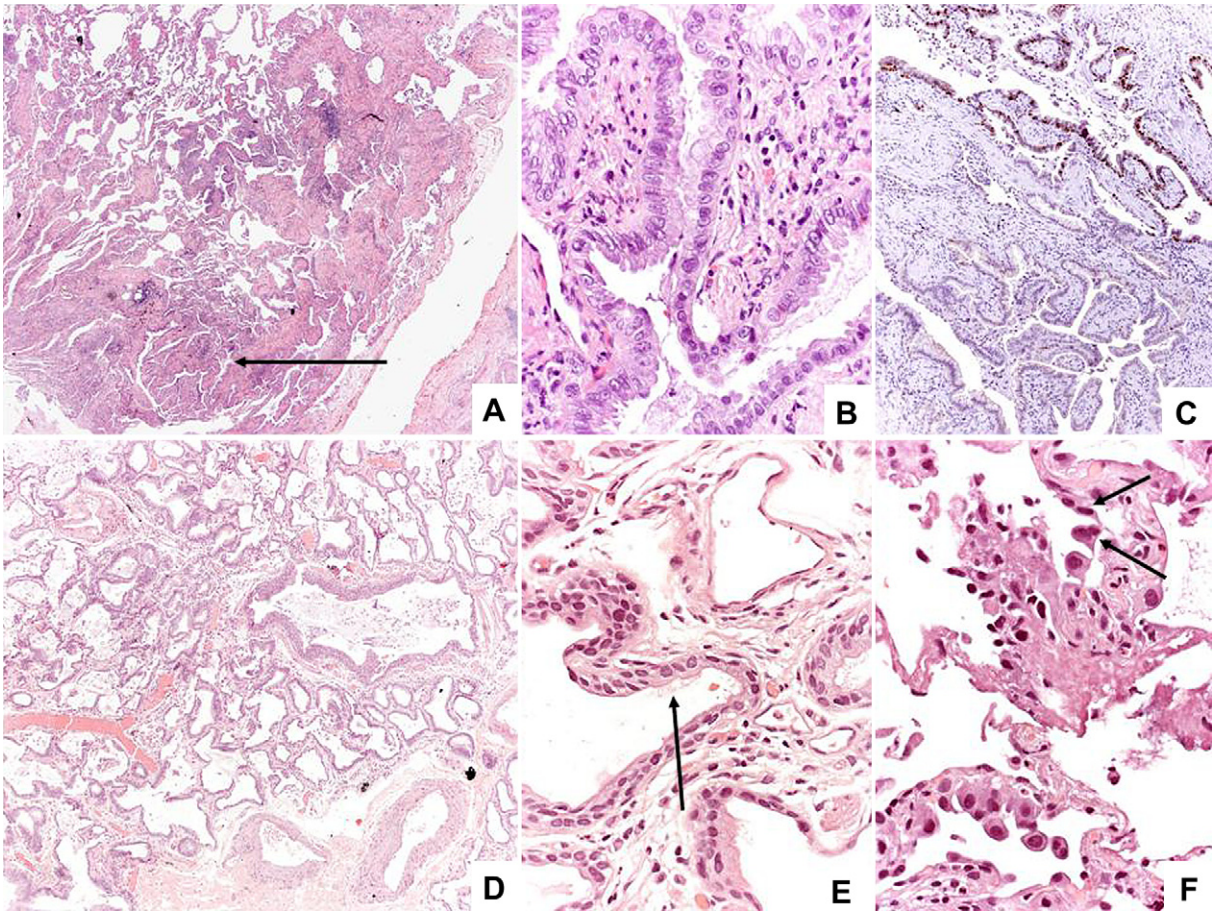

Figure 7 Adenocarcinoma arising in usual interstitial pneumonia and its main simulators. A) Surgical lung biopsy showing usual interstitial pneumonia partially obscuring a complex epithelial proliferation (arrow) (haematoxylin—eosin × 20). B) At higher magnification the epithelial proliferation is composed of columnar cells with crowded nuclei and uniform moderate atypia: their monomorphism and the lack of cilia are the keys to recognizing this bland proliferation as adenocarcinoma (haematoxylin—eosin × 400). C) An immunohistochemical stain for p63 demonstrating the lack of basal cells in adenocarcinoma; by contrast, p63-positive basal cells are present in the benign bronchiole seen in the upper part of the picture (peroxidase—antiperoxidase × 100). D) A surgical lung biopsy showing fibrosing non-specific interstitial pneumonia, with a marked peribronchiolar metaplasia, simulating an adenocarcinoma in its complexity (haematoxylin—eosin × 20). E) At higher magnification the proliferating cells are bland and focally show long cilia (arrow). Long cilia are not present in adenocarcinoma of the lung and are a helpful clue to benign disease (haematoxylin—eosin × 200). F) Transbronchial biopsy with diffuse alveolar damage secondary to methotrexate, showing markedly atypical pneumocytes. These worrisome but benign cells are flatter, less crowded and less uniform than adenocarcinoma: large bizarre cells are present side-by-side with small bland cells (arrows; compare with the monotony of adenocarcinoma shown in Fig. 7B). The acute background with fibrin is a further clue to their reactive nature (haematoxylin—eosin × 400). Case shown in A, B and C is courtesy of Prof. C. Capella, Varese, Italy; case shown in D and E is courtesy of Dr A. Dubini and Dr V. Poletti, Forli, Italy.

meaningful in others. The field is still controversial, but the presence of UIP at histology seems to predict a poor survival, similar to IPF in patients with rheumatoid arthritis and chronic HP, whereas the prognosis seems better than IPF when UIP is related to other CVD.[51,67]

Diagnosis of UIP against a background of smoking-related changes

Alongside the more frequent chronic bronchitis, emphysema, bronchogenic carcinoma and accumulation of finely pigmented macrophages (respiratory bronchiolitis),[68] cigarette smoking can cause fibrosis, sometimes significant, which is part of the morphological spectrum of smoking-related ILD (Fig. 5A and B).[69–72] In some cases the diagnosis of early UIP arising on a background of smoking-related fibrosis can be challenging. To complicate matters, in a recent paper in which the background parenchyma of specimens resected for lung cancer was carefully evaluated, foci of UIP were found in 3.5% of non-smokers, 15.4% of mild smokers, 23.6% of moderate smokers and 22.4% of heavy smokers.[72] The patients for the most part had no clinical evidence of ILD, and whether these foci of UIP corresponded to early/subclinical IPF or were just incidental findings is not known. Interestingly, acute respiratory failure following surgery developed only in patients with foci of UIP.[72]

Table 4 Contrasting features of well-differentiated adenocarcinoma, pneumocyte hyperplasia and peribronchiolar metaplasia in the setting of interstitial lung disease.

Feature	Adenocarcinoma	Pneumocyte hyperplasia	Peribronchiolar metaplasia
Clinical context	A mass is frequently (but not always) present	No mass	No mass
Characteristics of the cells (better appreciated if compared with nearby benign bronchiolar cells)	Uniform mild—moderate atypia, columnar and crowded, no cilia	Polymorphous (large atypical cells side-by-side with small bland cells), flattened/ cuboidal	Bland, with long cilia
Characteristics of the histological background	Fibrosis/inflammation	Acute lung injury (diffuse alveolar damage or organizing pneumonia)	Fibrosis/inflammation
Immunomarkers for basal cells (p63, cytokeratin 5/6, cytokeratin 34βE12)	Negative	Negative	Positive in the basal cells surrounding the proliferation

Another smoking-related ILD that can superficially mimic UIP is Langerhans' cell histiocytosis (LCH) in its chronic phase, when the lesion becomes fibrotic and the Langerhans' cells frequently disappear (Fig. 5C and D).[73,74]

Acute exacerbation of IPF and other fibrosing ILD

Some patients with IPF (but also with other fibrosing ILD, including idiopathic NSIP,[75–77] chronic HP[75,78,79] and ILD related to CVD[76,77,80,81]) experience episodes of acute deterioration of their illness with a high mortality rate. When idiopathic these episodes are called acute exacerbation (AE).[82–87] The frequency of AE in IPF is not known. A recent retrospective review on 147 patients with IPF[84] showed a 2-year incidence of AE of 9.6%; interestingly, the incidence increased to 18% if less strict diagnostic criteria were applied (see below). Several studies suggest that surgical lung biopsy[88] and bronchoscopy[84] may occasionally contribute to AE. AE can occur at any time during the course of IPF and occasionally is the presenting manifestation of the disease.[89] In any patient in whom acute interstitial pneumonia/idiopathic diffuse alveolar damage (DAD) is a consideration, the possibility of an underlying chronic ILD should be kept in mind, particularly in older smokers.

A recent paper[82] proposed the following diagnostic criteria for AE of IPF: 1) previous or concurrent diagnosis of IPF; 2) unexplained worsening or development of dyspnoea within 30 days; 3) HRCT with new bilateral alveolar infiltrates superimposed on a background reticular or honeycomb pattern; and 4) exclusion of alternative causes (including no evidence of pulmonary infection by endotracheal aspirate or bronchoalveolar lavage). The previously required documentation of abnormal gas exchange, which rendered very strict the inclusion criteria in the studies preceding this definition, was dropped.

Biopsy is not necessary for the diagnosis in most patients; when it is performed it generally shows DAD (or less frequently organizing pneumonia (OP) or numerous large fibroblastic foci)[75,90] superimposed on a chronic background of UIP. Because of the sampling problems outlined above, the biopsy may show just one of the two components (DAD or UIP), and documentation of the non-sampled component requires the correlation with the clinico-radiological data.

An important point is that the definition of AE is clinico-radiological, not histological. In a biopsy showing fibrotic ILD there is sometimes an extensive acute/subacute component (profusion of large fibroblastic foci or OP, Fig. 6). In these cases the biopsy is generally performed for worsening of symptoms, but the patient may or may not reach the clinical level of impairment required for the diagnosis of AE. As it is currently defined (and particularly as it was defined before the paper of Collard et al.)[82] AE represents the most severe end of a spectrum. Not surprisingly, patients with less extensive opacities at HRCT[91] and with OP rather than DAD at histology[75,76,90] have less severe disease and a better outcome.

Carcinoma in IPF

Patients with IPF or other fibrosing ILD are at increased risk of developing pulmonary carcinoma. Preliminary data suggest that squamous cell carcinoma[92] and unusual variants of adenocarcinoma, including the enteric type[93] (Chilosi M, personal communication) are more frequently seen in IPF than the general population. The diagnosis of malignancy in this setting is generally straightforward but occasionally very difficult, particularly on small biopsies, but sometimes also on surgical specimens.[94,95] Some pulmonary adenocarcinomas are so well differentiated they are difficult to appreciate as neoplastic, in particular if the tumour cells are few and masked by fibrosis; moreover, some reactive conditions, particularly pneumocyte hyperplasia and peribronchiolar metaplasia, can be so exuberant as to closely mimic a tumour. Some examples are shown in Fig. 7, and the criteria for differentiating adenocarcinoma from reactive conditions in ILD are summarized in Table 4.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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References

1. Travis WD, King TE, Bateman ED, et al. American Thoracic Society/European Respiratory Society international multidisciplinary consensus classification of the idiopathic interstitial pneumonias. *Am J Respir Crit Care Med* 2002;**165**:277—304.
2. Wells AU. Histopathologic diagnosis in diffuse lung disease. An ailing gold standard. *Am J Respir Crit Care Med* 2004;**170**: 828—9.
3. Flaherty KR, King TE, Raghu G, et al. Idiopathic interstitial pneumonia. What is the effect of a multidisciplinary approach to diagnosis? *Am J Respir Crit Care Med* 2004;**170**:904—10.
4. Quigley M, Hansell DM, Nicholson AG. Interstitial lung disease-the new synergy between radiology and pathology. *Histopathology* 2006;**49**:334—42.
5. Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia. The prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003;**168**:531—7.
6. Flaherty KR, Mumford JA, Murray S, et al. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;**168**: 543—8.
7. Collard HR, King TE, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;**168**:538—42.
8. Jegal Y, Kim DS, Shim TS, et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. *Am J Respir Crit Care Med* 2005;**171**:639—44.
9. Egan JJ, Martinez FJ, Wells AU, Williams T. Lung function estimates in idiopathic pulmonary fibrosis: the potential for a simple classification. *Thorax* 2005;**60**:270—3.
10. Shin KM, Lee KS, Chung MP, et al. Prognostic determinants among clinical, thin-section CT, and histopathologic findings for fibrotic idiopathic interstitial pneumonias: tertiary hospital study. *Radiology* 2008;**249**:328—37.
11. Wells AU, Hansell DM. Radiologic evaluation. In: Baughman RP, du Bois RM, Lynch JP, Wells AU, editors. *Diffuse lung disease. A practical approach*. London: Arnold; 2004.
12. Hunninghake GW, Zimmerman MB, Schwartz DA, et al. Utility of a lung biopsy for the diagnosis of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2001;**164**:193—6.
13. Travis WD, Hunninghake G, King TE, et al. Idiopathic nonspecific interstitial pneumonia. Report of an American Thoracic Society project. *Am J Respir Crit Care Med* 2008;**177**:1338—47.
14. Flaherty KR, Thwaite EL, Kazerooni EA, et al. Radiological versus histological diagnosis in UIP and NSIP: survival implications. *Thorax* 2003;**58**:143—8.
15. Flaherty KR, Andrei AC, Murray S, et al. Idiopathic pulmonary fibrosis. Prognostic value of changes in physiology and six-minute-walk test. *Am J Respir Crit Care Med* 2006;**174**:803—9.
16. Katzenstein ALA, Zisman DA, Litzky LA, Nguyen BT, Kotloff RM. Usual interstitial pneumonia. Histologic study of biopsy and explant specimens. *Am J Surg Pathol* 2002;**26**:1567—77.
17. Flaherty KR, Travis WD, Colby TV, et al. Histopathologic variability in usual and nonspecific interstitial pneumonias. *Am J Respir Crit Care Med* 2001;**164**:1722—7.
18. Monaghan H, Wells AU, Colby TV, du Bois RM, Hansell DM, Nicholson AG. Prognostic implications of histologic patterns in multiple surgical lung biopsies from patients with idiopathic interstitial pneumonia. *Chest* 2004;**125**:522—6.
19. Nicholson AG, Addis BJ, Bharucha H, et al. Inter-observer variation between pathologists in diffuse parenchymal lung disease. *Thorax* 2004;**59**:500—5.
20. Aziz ZA, Wells AU, Hansell DM, et al. HRCT diagnosis of diffuse parenchymal lung disease: inter-observer variation. *Thorax* 2004;**59**:506—11.
21. Lettieri CJ, Veerappan GR, Parker JM, et al. Discordance between general and pulmonary pathologists in the diagnosis of interstitial lung disease. *Respir Med* 2005;**99**:1425—30.
22. Thomeer M, Demedts M, Behr J, et al. Multidisciplinary interobserver agreement in the diagnosis of idiopathic pulmonary fibrosis. *Eur Respir J* 2008;**31**:585—91.
23. Flaherty KR, Andrei AC, King TE, et al. Idiopathic interstitial pneumonia. Do community and academic physicians agree on diagnosis? *Am J Respir Crit Care Med* 2007;**175**:1054—60.
24. Rosai J. Borderline epithelial lesions of the breast. *Am J Surg Pathol* 1991;**15**:209—21.
25. Frierson HF, Wolber RA, Berean KW, et al. Interobserver reproducibility of the Nottingham modification of the Bloom and Richardson histologic grading scheme for infiltrating ductal carcinoma. *Am J Clin Pathol* 1995;**103**:195—8.
26. Barnhill RL, Argenyi ZB, From L, et al. Atypical Spitz nevi/tumors: lack of consensus for diagnosis, discrimination from melanoma, and prediction of outcome. *Hum Pathol* 1999;**30**: 513—20.
27. Travis WD, Gal AA, Colby TV, Klimstra DS, Falk R, Koss MN. Reproducibility of neuroendocrine lung tumor classification. *Hum Pathol* 1998;**29**:272—9.
28. Fukunaga M, Katabuchi H, Nagasaka T, et al. Interobserver and intraobserver variability in the diagnosis of hydatiform mole. *Am J Surg Pathol* 2005;**29**:942—7.
29. Allsbrook WC, Mangold KT, Johnson MH, et al. Interobserver reproducibility of Gleason grading of prostatic adenocarcinoma: general pathologists. *Hum Pathol* 2001;**32**:81—8.
30. Kerkhof M, van Dekken H, Steyerberg EW, et al. Grading of dysplasia in Barrett's oesophagus: substantial interobserver variation between general and gastrointestinal pathologists. *Histopathology* 2007;**50**:920—7.
31. Elsheikh TM, Asa SL, Chan JKC, et al. Interobserver and intraobserver variation among experts in the diagnosis of thyroid follicular lesions with borderline nuclear features of papillary carcinoma. *Am J Clin Pathol* 2008;**130**:736—44.
32. Verghese ET, den Bakker MA, Campbell A, et al. Interobserver variation in the classification of thymic tumors: a multicentric study using the WHO classification. *Histopathology* 2008;**53**: 218—23.
33. Evans AJ, Henry PC, Van der Kwast TH, et al. Interobserver variability between expert urologic pathologists for extraprostatic extension and surgical margin status in radical prostatectomy specimens. *Am J Surg Pathol* 2008;**32**:1503—12.
34. Katzenstein ALA, Mukhopadhyay S, Myers JL. Diagnosis of usual interstitial pneumonia and distinction from other fibrosing interstitial lung diseases. *Hum Pathol* 2008;**39**:1275—94 [erratum in Hum Pathol 2008; 39:1562—81].
35. Myers JL, Katzenstein ALA. Beyond a consensus classification for idiopathic interstitial pneumonias: progress and controversies. *Histopathology* 2009;**54**:90—103.
36. Leslie KO. My approach to interstitial lung disease using clinical, radiological and histopathological patterns. *J Clin Pathol* 2009;**62**:387—401.
37. Fukuoka J, Franks TJ, Colby TV, et al. Peribronchiolar metaplasia: a common histologic lesion in diffuse lung disease and a rare cause of interstitial lung disease: clinicopathologic features of 15 cases. *Am J Surg Pathol* 2005;**29**: 948—54.
38. Hanak V, Ryu JH, de Carvalho E, et al. Profusion of fibroblastic foci in patients with idiopathic pulmonary fibrosis does not predict outcome. *Respir Med* 2008;**102**:852—6.

39. Yousem SA. Eosinophilic pneumonia-like areas in idiopathic usual interstitial pneumonia. *Mod Pathol* 2000;**13**:1280—4.
40. Sheikh HA, Fuhrer K, Cieply K, Yousem SA. p63 expression in assessment of bronchioloalveolar proliferations of the lung. *Mod Pathol* 2004;**17**:1134—40.
41. Chilosi M, Murer B, Poletti V. Diffuse parenchymal lung disease — histopathologic patterns. In: Costabel U, du Bois RM, Egan JJ, editors. *Diffuse parenchymal lung disease*. Basel: Karger; 2007.
42. Berbescu EA, Katzenstein ALA, Snow JL, Zisman DA. Transbronchial biopsy in usual interstitial pneumonia. *Chest* 2006; **129**:1126—31.
43. Churg A, Schwarz M. Transbronchial biopsy and usual interstitial pneumonia. A new paradigm? *Chest* 2006;**129**:1117—8.
44. King TE, Costabel U, Cordier JF, et al. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. *Am J Respir Crit Care Med* 2000;**161**:646—64.
45. Park IN, Jegal Y, Kim DS, et al. Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia. *Eur Respir J* 2009;**33**:68—76.
46. Kinder BW, Collard HR, Koth L, et al. Idiopathic nonspecific interstitial pneumonia. Lung manifestation of undifferentiated connective tissue disease? *Am J Respir Crit Care Med* 2007; **176**:691—7.
47. Romagnoli M, Gurioli C, Casoni G, Poletti V. Surgical lung biopsy in the diagnosis of idiopathic NSIP: do we always need it in the initial approach? *Am J Respir Crit Care Med* 2009; **179**:1071.
48. Travis WD, Colby TV, Galvin JR, Hunninghake G, King TE, Lynch DA. Surgical lung biopsy in the diagnosis of idiopathic NSIP: do we always need it in the initial approach? *Am J Respir Crit Care Med* 2009;**179**:1071. author reply 1071—2. (questa è la risposta alla lettera di Romagnoli et al).
49. Myers JL. Nonspecific interstitial pneumonia: pathologic features and clinical implications. *Semin Diagn Pathol* 2007; **24**:183—7.
50. du Bois R, King TE. Challenges in pulmonary fibrosis. The NSIP/UIP debate. *Thorax* 2007;**62**:1008—12.
51. Park JH, Kim DS, Park IN, et al. Prognosis of fibrotic interstitial pneumonia. Idiopathic versus collagen vascular disease-related subtypes. *Am J Respir Crit Care Med* 2007;**175**:705—11.
52. Song JW, Do KH, Kim MY, Jang SJ, Colby TV, Kim DS. Pathologic and radiologic differences between idiopathic and collagen vascular disease-related usual interstitial pneumonia. *Chest* 2009;**136**:23—30.
53. Coleman A, Colby TV. Histologic diagnosis of extrinsic allergic alveolitis. *Am J Surg Pathol* 1988;**27**:514—8.
54. Colby TV, Coleman A. The histologic diagnosis of extrinsic allergic alveolitis and its differential diagnosis. In: Fenoglio CM, Wolff M, Rilke F, editors. *Progress in surgical pathology*. New York: Field & Wood; 1989.
55. Ohtani Y, Saiki S, Kitaichi M, et al. Chronic bird fancier's lung: histopathological and clinical correlation: an application of the 2002 ATS/ERS consensus classification of the idiopathic interstitial pneumonias. *Thorax* 2005;**60**:665—71.
56. Churg A, Muller NL, Flint J, Wright JL. Chronic hypersensitivity pneumonitis. *Am J Surg Pathol* 2006;**30**:201—8.
57. Trahan S, Hanak V, Ryu JH, Myers JL. Role of surgical lung biopsy in separating chronic hypersensitivity pneumonia from usual interstitial pneumonia/idiopathic pulmonary fibrosis. Analysis of 31 biopsies from 15 patients. *Chest* 2008;**134**: 126—32.
58. Takemura T, Akashi T, Ohtani Y, Inase N, Yoshizawa Y. Pathology of hypersensitivity pneumonitis. *Curr Opin Pulm Med* 2008;**14**:440—54.
59. Akashi T, Takemura T, Ando N, et al. Histopathologic analysis of sixteen autopsy cases of chronic hypersensitivity pneumonitis and comparison with idiopathic pulmonary fibrosis/usual interstitial pneumonia. *Am J Clin Pathol* 2009; **131**:405—15.
60. Churg A. Nonneoplastic disease caused by asbestos. In: Churg A, Green FHY, editors. *Pathology of occupational lung disease*. Baltimore, MD: Williams & Wilkins; 1998.
61. Camus P. Drug-induced infiltrative lung diseases. In: Schwarz MI, King TE, editors. *Interstitial lung disease*. 4th ed. London: Decker; 2003.
62. Lee HL, Ryu JH, Wittmer MH, et al. Familial idiopathic pulmonary fibrosis. Clinical features and outcome. *Chest* 2005; **127**:2034—41.
63. Rosas IO, Ren P, Avila NA, et al. Early interstitial lung disease in familial pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; **176**:698—705.
64. Cheung OY, Muhm JR, Helmers RA, et al. Surgical pathology of granulomatous interstitial pneumonia. *Ann Diagn Pathol* 2003; **7**:127—38.
65. Cavazza A, Harari S, Caminati A, et al. The histology of pulmonary sarcoidosis: a review, with particular emphasis on unusual and underrecognized features. *Int J Surg Pathol* 2009; **17**:219—30.
66. Foulon G, Delaval P, Valeyre D, et al. ANCA-associated lung fibrosis: analysis of 17 patients. *Respir Med* 2008;**102**: 1392—8.
67. Perez-Padilla R, Salas J, Chapela R, et al. Mortality in Mexican patients with chronic pigeon breeder's lung compared with those of usual interstitial pneumonia. *Am Rev Respir Dis* 1993; **148**:49—53.
68. Fraig M, Shreesha U, Savici D, Katzenstein ALA. Respiratory bronchiolitis. A clinicopathologic study in current smokers, ex-smokers, and never-smokers. *Am J Surg Pathol* 2002;**26**:647—53.
69. Caminati A, Harari S. Smoking-related interstitial pneumonias and pulmonary Langerhans cell histiocytosis. *Proc Am Thorac Soc* 2006;**3**:299—306.
70. Ryu JH, Colby TV, Hartman TE, Vassallo R. Smoking-related interstitial lung diseases: a concise review. *Eur Respir J* 2001; **17**:122—32.
71. Yousem SA. Respiratory bronchiolitis-associated interstitial lung disease with fibrosis is a lesion distinct from fibrotic nonspecific interstitial pneumonia: a proposal. *Mod Pathol* 2006;**19**:1474—9.
72. Kawabata Y, Hoshi E, Murai K, et al. Smoking-related changes in the background lung of specimens resected for lung cancer: a semiquantitative study with correlation to postoperative course. *Histopathology* 2008;**53**:707—14.
73. Vassallo R, Ryu JH, Colby TV, Hartman T, Limper AH. Pulmonary Langerhans cell histiocytosis. *N Engl J Med* 2000;**342**: 1969—78.
74. Colby TV, Lombard C. Histiocytosis X in the lung. *Hum Pathol* 1983;**14**:847—56.
75. Churg A, Muller NL, Silva CIS, Wright JL. Acute exacerbation (acute lung injury of unknown cause) in UIP and other forms of fibrotic interstitial pneumonias. *Am J Surg Pathol* 2007;**31**: 277—84.
76. Silva CIS, Muller NL, Fujimoto K, et al. Acute exacerbation of chronic interstitial pneumonia. High-resolution computer tomography and pathologic findings. *J Thorac Imaging* 2007;**22**: 221—9.
77. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest* 2007;**132**:214—20.
78. Miyazaki Y, Tateishi T, Akasashi T, Ohtani Y, Inase N, Yoshizawa Y. Clinical predictors and histologic appearance of acute exacerbation in chronic hypersensitivity pneumonitis. *Chest* 2008;**134**:1265—70.
79. Olson AL, Huie TJ, Groshong SD, et al. Acute exacerbations of fibrotic hypersensitivity pneumonitis. A case series. *Chest* 2008;**134**:844—50.

80. Rice AJ, Wells AU, Bouros D, et al. Terminal diffuse alveolar damage in relation to interstitial pneumonias. An autopsy study. *Am J Clin Pathol* 2003;**119**:709—14.
81. Suda T, Kaida Y, Nakamura Y, et al. Acute exacerbation of interstitial pneumonia associated with collagen vascular diseases. *Respir Med* 2009;**103**:846—53.
82. Collard H, Moore BB, Flaherty KR, et al. Acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; **176**:636—43.
83. Hyzy R, Huang S, Myers JL, Flaherty KR, Martinez F. Acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2007;**132**: 1652—8.
84. Kim DS, Park JH, Park BK, Lee JS, Nicholson AG, Colby TV. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J* 2006;**27**:143—50.
85. Parambil JG, Myers JL, Ryu JH. Histopathologic features and outcome of patients with acute exacerbation of idiopathic pulmonary fibrosis undergoing surgical lung biopsy. *Chest* 2005; **128**:3310—5.
86. Ambrosini V, Cancellieri A, Chilosi M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. *Eur Respir J* 2003;**22**:821—6.
87. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;**142**:963—7.
88. Kondoh Y, Taniguchi H, Kitaichi M, et al. Acute exacerbation of interstitial pneumonia following surgical lung biopsy. *Respir Med* 2006;**100**:1753—9.
89. Sakamoto K, Taniguchi H, Kondoh Y, Ono K, Hasegawa Y, Kitaichi M. Acute exacerbation of idiopathic pulmonary fibrosis as the initial presentation of the disease. *Eur Respir Rev* 2009; **18**:129—32.
90. Dallari R, Foglia M, Paci M, Cavazza A. Acute exacerbation of idiopathic pulmonary fibrosis. *Eur Respir J* 2004;**23**:792.
91. Akira M, Kozuka T, Yamamoto S, Sakatani M. Computer tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008;**178**:372—8.
92. Aubry MCA, Myers JL, Douglas W, et al. Primary pulmonary carcinoma in patients with idiopathic pulmonary fibrosis. *Mayo Clin Proc* 2002;**77**:763—70.
93. Inamura K, Satoh Y, Okumura S, et al. Pulmonary adenocarcinoma with enteric differentiation. Histologic and immunohistochemical characteristics compared with metastatic colorectal cancers and usual pulmonary adenocarcinomas. *Am J Surg Pathol* 2005;**29**:660—5.
94. Lantuejoul S, Colby TV, Ferretti GR, Brichon PY, Brambilla C, Brambilla E. Adenocarcinoma of the lung mimicking inflammatory lung disease with honeycombing. *Eur Respir J* 2004;**24**:502—5.
95. Colby TV. Malignancy in the lung and pleura mimicking benign processes. *Semin Diagn Pathol* 1995;**12**:30—44.