

# Interstitial lung disease

William D Travis

## Abstract

Idiopathic interstitial pneumonias represent an important group of interstitial lung diseases, encompassing seven entities: (1) usual interstitial pneumonia (UIP)/idiopathic pulmonary fibrosis; (2) non-specific interstitial pneumonia (NSIP); (3) organizing pneumonia/cryptogenic organizing pneumonia (COP); (4) diffuse alveolar damage (DAD)/acute interstitial pneumonia (AIP); (5) respiratory bronchiolitis (RB)/respiratory bronchiolitis–interstitial lung disease (RB–ILD); (6) desquamative interstitial pneumonia (DIP); and (7) lymphocytic interstitial pneumonia (LIP). The term idiopathic means that the cause is not certain at the time of diagnosis, but each of these patterns of interstitial pneumonia can occur in the setting of known causes as well.

This review will highlight the pathological features and differential diagnosis of interstitial pneumonias, along with the high-resolution computed tomography (HRCT) scan and clinical features, emphasizing the importance of clinical, radiological and pathological correlation to establish the correct diagnosis. Familiarity with the histological patterns of lung injury in these disorders will aid pathologists in recognizing the correct diagnosis. It is also important for pathologists and clinicians to understand the settings in which HRCT can overrule pathological findings. In particular, if an HRCT scan shows classical features of UIP, despite surgical biopsy findings of NSIP, the clinical–radiological–pathological diagnosis would be UIP.

**Keywords** acute interstitial pneumonia; biopsy; cryptogenic organizing pneumonia; desquamative interstitial pneumonia; diffuse alveolar damage; high-resolution CT; idiopathic pulmonary fibrosis; lung; lymphocytic interstitial pneumonia; non-specific interstitial pneumonia; organizing pneumonia; respiratory bronchiolitis; usual interstitial pneumonia

Interstitial lung diseases are caused by interstitial inflammation and fibrosis and account for approximately 200 chronic lung diseases. The aetiology can be determined in only about 30% of the interstitial lung disorders; in the remaining 70% the cause is unknown.<sup>1,2</sup> The term ‘idiopathic’ is often applied to these disorders, meaning that the cause cannot be determined. The idiopathic interstitial pneumonias (IIPs) will be the focus of this review.

In recent years the technique of high-resolution computed tomography (HRCT) scanning has transformed the field. Now there are well defined cases where a diagnosis can be established with a high degree of certainty based on HRCT. For example, in

approximately 50% of patients with idiopathic pulmonary fibrosis (IPF), the HRCT shows pathognomonic features that obviate the need for biopsy. This technique has also helped to define a set of patients for whom surgical lung biopsies are needed because neither radiologists nor pulmonologists can make an accurate diagnosis. A multidisciplinary approach is needed to diagnose and manage patients with interstitial lung disease.

Pathological diagnosis of most of the histological patterns of the IIPs requires a surgical lung biopsy. The role of transbronchial biopsies in the diagnosis of the IIPs in most cases is to exclude sarcoidosis and certain infections. In some cases with typical clinical and radiological features of cryptogenic organizing pneumonia (COP)<sup>3,4</sup> or acute interstitial pneumonia (AIP), a bronchoscopic biopsy showing histological patterns of organizing pneumonia or diffuse alveolar damage (DAD), respectively, may allow the diagnosis.

In 2002 the American Thoracic Society (ATS) and European Respiratory Society (ERS) published a Classification of Idiopathic Interstitial Pneumonias that was based on consensus by an international multidisciplinary panel. It identified a set of seven entities, summarized in Table 1 with matching pathological and clinical terms.<sup>1</sup> A small percentage of patients with interstitial pneumonia remain unclassifiable after extensive clinical, radiological and/or pathological examination. This is not a distinctive clinicopathological subset of patients but rather a group consisting of problematic cases for whom some critical piece of information cannot be obtained, such as inadequate clinical information, poor quality chest HRCT or inadequate lung biopsy material.

## Histological and clinical classification of idiopathic interstitial pneumonias (modified from the ATS/ERS Classification of idiopathic interstitial pneumonias)<sup>1</sup>\*

Histological patterns	Clinical–radiological–pathological diagnoses
Usual interstitial pneumonia	Idiopathic pulmonary fibrosis/cryptogenic fibrosing alveolitis
Non-specific interstitial pneumonia	Non-specific interstitial pneumonia (provisional) <sup>‡</sup>
Organizing pneumonia	Cryptogenic organizing pneumonia (COP) <sup>†</sup>
Diffuse alveolar damage	Acute interstitial pneumonia
Respiratory bronchiolitis	Respiratory bronchiolitis–interstitial lung disease
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia
Lymphocytic interstitial pneumonia	Lymphocytic interstitial pneumonia

\* Unclassifiable interstitial pneumonia – some cases are unclassifiable for a variety of reasons (see text).

† COP is the preferred term, but it is synonymous with idiopathic bronchiolitis obliterans organizing pneumonia (BOOP).

‡ This group represents a heterogeneous group with poorly characterized clinical and radiological features that need further study.

Table 1

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## Usual interstitial pneumonia/idiopathic pulmonary fibrosis

### Pathological features

The term usual interstitial pneumonia (UIP) refers to a distinctive pathological pattern of pulmonary fibrosis (Table 2). Grossly, the lungs show diffuse bilateral fibrosis, predominantly in the lower lobe and subpleural regions, with frequent honeycomb changes. Histologically, the fibrosis consists of patchy dense scarring in a peripheral acinar and subpleural distribution (Figure 1). Honeycomb change consisting of cystic spaces within dense fibrotic scars with pseudostratified respiratory epithelium is common. The fibrotic lung shows severe destruction of the lung architecture, alternating with areas of relatively preserved lung (Figure 1a). Fibroblastic foci consisting of small foci of loose fibroblastic connective tissue are typically seen at the edges of the dense fibrotic scars (Figure 1b,c). Interstitial inflammation is mild to moderate. In up to 25% of surgical lung biopsies where multiple lobes have been sampled there may be histological heterogeneity; areas that show a more uniform histological pattern resemble non-specific interstitial pneumonia (NSIP). In explanted lung specimens where more tissue can be examined, this heterogeneity can be seen in up to 80% of cases.<sup>5</sup>

In acute exacerbation the typical finding is acute lung injury most often with features of DAD followed by OP, or prominent fibroblastic foci superimposed on a UIP pattern.<sup>6</sup> The mixture of histological patterns often makes it difficult for pathologists to recognize the UIP pattern.

The UIP pattern is so important that the pathology of interstitial lung disease (ILD) is often classified into UIP and non-UIP disorders. The UIP pattern can occur in a variety of settings including collagen vascular disease (Table 3). In the absence of any identifiable cause, the clinical term idiopathic pulmonary fibrosis (IPF) is appropriate. Since the term UIP is often used for clinical conditions with known causes, it is useful to use add 'pattern' to the term UIP when referring to histological findings on lung biopsy.

### Usual interstitial pneumonia pattern: Histological features<sup>1</sup>

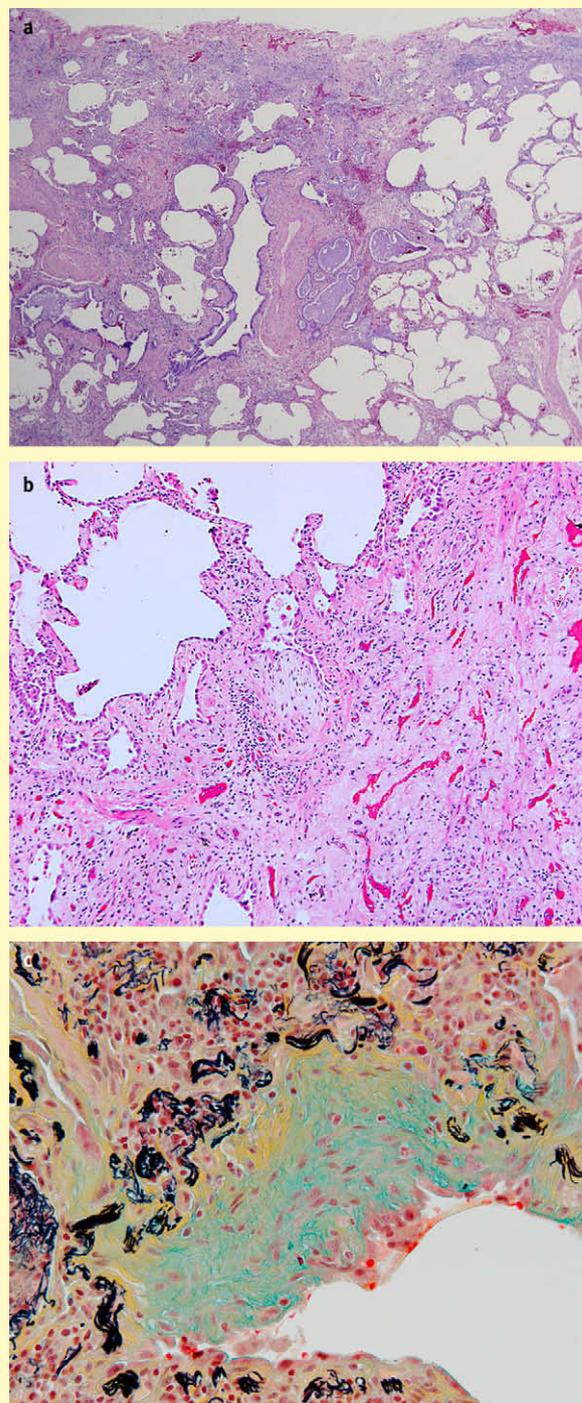
#### Major features

- Patchy lung involvement
- Frequent subpleural, paraseptal and/or peribronchiolar distribution
- Dense fibrosis causing remodelling of lung architecture with frequent 'honeycomb' fibrosis
- Fibroblast foci scattered at the edges of the dense scars
- Interstitial inflammation, mild to moderate

#### Pertinent negative findings

- Lack of active lesions of other interstitial diseases (i.e. sarcoidosis or Langerhans histiocytosis)
- Lack of marked interstitial chronic inflammation
- Granulomas—inconspicuous or absent
- Lack of substantial inorganic dust deposits, i.e. asbestos bodies (except for carbon black pigment)

Table 2



**a** Usual interstitial pneumonia pattern. Patchy fibrosis with remodelling of the lung architecture shows a striking subpleural distribution. Interstitial chronic inflammation is mild with a few lymphoid aggregates. Areas of 'normal' lung are present that lack active lesions of other interstitial lung disorders. **b** There is marked fibrosis consisting of dense collagenous scarring with remodelling of the lung architecture and a fibroblastic focus at the edge of the scar. **c** This Movat stain highlights the fibroblastic focus in green, the dense collagen in yellow and collapsed elastic fibres in black.

Figure 1

The differential diagnosis for the UIP pattern includes histological and aetiological considerations (Table 3). Clinical, radiological and pathological features need consideration. Marked interstitial chronic inflammation or bronchiolocentricity can be seen in hypersensitivity pneumonitis or collagen vascular disease.<sup>7,8</sup> Poorly formed granulomas raise the possibility of hypersensitivity pneumonitis<sup>7,8</sup> and pleuritis prompts consideration of collagen vascular disease. An HRCT showing more upper lobe distribution with centrilobular nodules and mosaic attenuation is suggestive of hypersensitivity pneumonitis.

#### Clinical features

IPF usually presents in patients over 50 years of age with gradual onset of dyspnoea on exertion and dry cough over 6 months to several years.<sup>2</sup> In pulmonary function tests patients demonstrate a restrictive pattern with a decreased diffusing capacity ( $DL_{CO}$ ) and abnormal gas exchange. Digital clubbing is common. The prognosis is poor with a 5-year survival of approximately 20%.<sup>2</sup>

Patients with IPF typically have a gradual progressive downhill course leading to death. However, some patients develop an acute exacerbation with a rapidly fatal course<sup>9</sup> Others develop fatal complications such as opportunistic infections due to their immunosuppressive therapy.<sup>2</sup>

There is no established effective therapy for IPF.<sup>10</sup> Steroids have minimal if any benefit. Cyclophosphamide and steroids appear to have no effect. A variety of novel antifibrotic agents have been studied, such as interferon- $\gamma$ 1b, perfinidone, sildenafil and N-acetyl cysteine, but they are not yet proven to be effective. Lung transplantation is the most effective form of treatment.

#### Radiological features

The HRCT manifestations of IPF consist of irregular lines (reticular pattern) with traction bronchiectasis and honeycombing primarily affecting the subpleural lung regions and lower lobes.<sup>2,11</sup> When classical HRCT findings of IPF are present, even

### Histological and aetiological differential diagnosis for usual interstitial pneumonia pattern<sup>1</sup>

#### Histological patterns

- Non-specific interstitial pneumonia, fibrosing pattern
- Desquamative interstitial pneumonia pattern
- Fibrotic phases of other interstitial disorders
  - Langerhans cell histiocytosis
  - Hypersensitivity pneumonitis pattern
  - Diffuse alveolar damage

#### Aetiological possibilities

- Collagen vascular disease
- Drug-induced pneumonitis
- Radiation pneumonitis
- Familial idiopathic pulmonary fibrosis
- Hermansky Pudlak syndrome
- Pneumoconiosis, i.e. asbestosis
- Idiopathic UIP (clinicopathological term: idiopathic pulmonary fibrosis)

Table 3

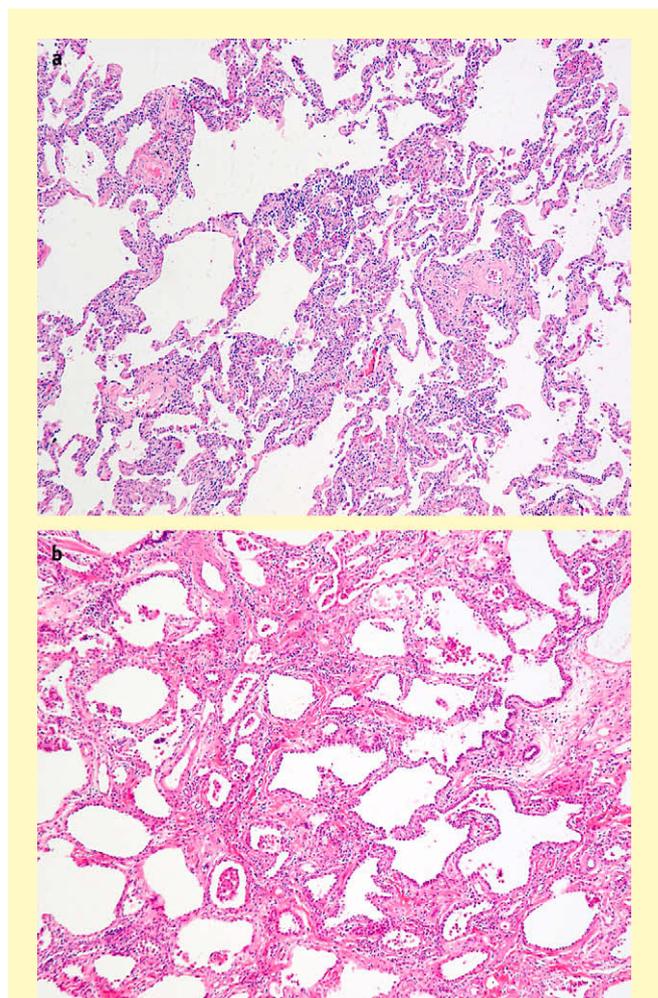
if the surgical lung biopsy shows an NSIP pattern, the clinical-radiological-pathological diagnosis is UIP/IPF.

### Non-specific interstitial pneumonia

NSIP is a form of interstitial pneumonia that is characterized by a uniform histological appearance.<sup>12,13</sup> Despite some debate, the distinction between NSIP and UIP has clinical relevance.<sup>12,13</sup> The importance of the NSIP concept rests on the favourable outcome of these patients relative to that of UIP patients.

#### Pathological features

The cellular pattern of NSIP is characterized by a mild to moderate interstitial chronic inflammatory infiltrate (Figure 2a) consisting of lymphocytes and a few plasma cells (Table 4). There is



Non-specific interstitial pneumonia (NSIP), cellular pattern. **a** The interstitium is infiltrated by a moderate chronic inflammatory infiltrate. Fibrosis is absent. The infiltrate consists of lymphocytes and plasma cells. **b** NSIP, fibrosing pattern. The alveolar walls show diffuse thickening by fibrosis and mild interstitial inflammation. No fibroblastic foci are present. The alveolar walls are thickened by dense collagen and a few lymphocytes and plasma cells.

Figure 2

## Proposed revised histological features of non-specific interstitial pneumonia (NSIP)<sup>1</sup>

### Key features

- Cellular pattern<sup>‡</sup>
  - Mild to moderate interstitial chronic inflammation
  - Type II pneumocyte hyperplasia in areas of inflammation
- Fibrosing pattern<sup>‡</sup>
  - Dense or loose interstitial fibrosis *with uniform appearance*
  - *Lung architecture is frequently preserved*
  - Interstitial chronic inflammation – mild or moderate

### Pertinent negative findings

- Cellular pattern
  - Dense interstitial fibrosis—absent
  - Organizing pneumonia is not the prominent feature (*< 20% of biopsy specimens*)
  - Lack of diffuse severe alveolar septal inflammation
- Fibrosing pattern
  - Temporal heterogeneity pattern fibroblastic foci with dense fibrosis are inconspicuous or absent—this is especially important in cases with patchy involvement and subpleural or paraseptal distribution
  - *Honeycombing inconspicuous or absent*
  - *(Enlarged fibrotic airspaces may be present)*
- Both patterns
  - Acute lung injury pattern, especially hyaline membranes: absent
  - Eosinophils—inconspicuous or absent
  - Granulomas—*absent*<sup>13</sup>
  - Lack of viral inclusions and organisms on special stains for organisms
  - *Dominant airway disease such as extensive peribronchiolar metaplasia*

Modifications from the 2002 ATS/ERS criteria for NSIP<sup>1</sup> are highlighted in italics. The key features are listed as a set of positive criteria, with all exclusions moved to a list of pertinent negative findings. It is emphasized that the dense or loose interstitial fibrosis should have a uniform appearance. The phrase 'lacking the temporal heterogeneity pattern and/or patchy features of UIP' is deleted as this is mentioned in the 'Pertinent negative findings' section. The phrase about lung architecture is modified to 'Lung architecture is frequently preserved' and the statement about elastic stains is deleted. In the fibrosing NSIP section, 'honeycombing inconspicuous or absent' is added. Under pertinent negatives for both patterns, 'dominant airway disease such as extensive peribronchiolar metaplasia' is added. We changed the criteria about granulomas being inconspicuous or absent, so for idiopathic NSIP, granulomas should be absent.

‡There is a spectrum from cellular to fibrosing patterns with some cases showing a combination of cellular and fibrosing features.

**Table 4**

usually uniform lung involvement. Focal organizing pneumonia can be present, but this is not a prominent feature. Lymphoid aggregates are often seen.

The fibrosing pattern of NSIP is characterized by uniform dense or loose interstitial fibrosis (Figure 2b) causing thickening of the alveolar walls (Table 4). Honeycombing should be absent and fibroblastic foci should be absent or inconspicuous. The architecture of

the lung is generally preserved. Lymphoid aggregates are common. Interstitial chronic inflammation is usually mild to moderate.

The differential diagnosis of NSIP can be viewed in terms of the important pertinent negatives (Table 4). These help to separate NSIP from OP, lymphocytic interstitial pneumonia, UIP, DAD, eosinophilic pneumonia and hypersensitivity pneumonitis. The most important distinction is between the fibrosing pattern of NSIP and the UIP pattern. The latter frequently shows a subpleural or paraseptal distribution which is seen less often in the fibrosing NSIP pattern. However, the lack of honeycombing and fibroblastic foci are key distinguishing features of the NSIP pattern.

### Clinical features

Patients with NSIP present with dyspnoea and cough of an average duration of 7–8 months.<sup>13</sup> The average age is 46–55 years.<sup>13</sup> Patients with the cellular pattern of idiopathic NSIP are younger than those with idiopathic UIP. Most series show a female predominance of up to 2:1 and a predominance of never smokers.<sup>13</sup> Up to 40% of patients may have positive antinuclear antibodies or rheumatoid factors. Pulmonary function is restrictive in 80% of patients. A recent international study demonstrated 5- and 10-year survival for NSIP of 82% and 73%, respectively.<sup>13</sup> NSIP patients are more likely to respond to treatment with steroids than patients with IPF.<sup>10</sup> Recent speculation has raised the consideration that some cases may be a manifestation of undifferentiated connective tissue disease.<sup>14</sup>

### Radiological features

The HRCT shows reticular opacities with a predominant lower lobe distribution associated with traction bronchiectasis and lobar volume loss.<sup>11,13,15</sup> Ground-glass opacities can be seen in about 50% of cases. The infiltrates are distributed diffusely or subpleurally. Although about one-third of cases show a peripheral distribution, in up to 20% there can be subpleural sparing. Honeycombing is not a characteristic finding.

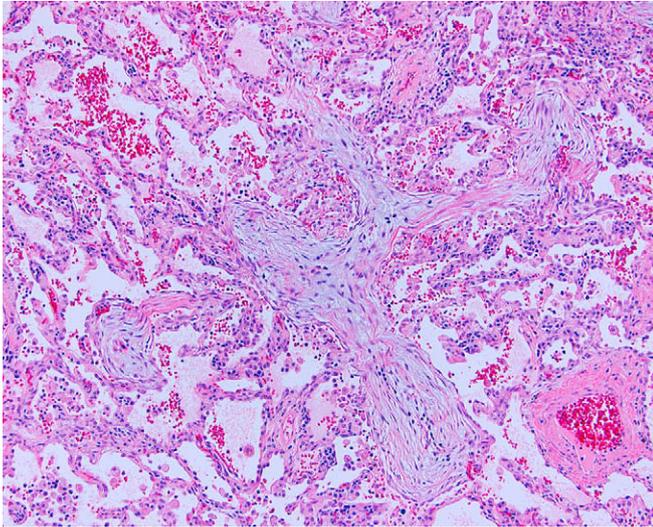
### Cryptogenic organizing pneumonia

COP is a clinicopathological entity described by Davison *et al* in 1983.<sup>16</sup> The same entity was reported in 1985 by Epler and colleagues but they used the name bronchiolitis obliterans organizing pneumonia (BOOP). The ATS/ERS Idiopathic Interstitial Pneumonia classification recommended use of the term COP rather than BOOP, which has been used in many different and confusing ways by clinicians and pathologists.

### Pathological features

The organizing pneumonia pattern is characterized by patchy lung involvement by polypoid plugs of loose organizing connective tissue (Figure 3) involving alveolar ducts and alveoli (Table 5).<sup>1,2</sup> Bronchioles may or may not be involved. All the connective tissue is of the same age and the lung architecture is preserved. The majority of changes centre on the small airways. Interstitial inflammation is chronic and mild. Type II cell hyperplasia may be mild or moderate. Alveolar macrophages may be increased and have foamy cytoplasm. A small amount of air-space fibrin may be focally present.

The organizing pneumonia pattern can occur in a wide variety of clinical and pathological settings (Table 6). The diagnosis of



**Figure 3** Organizing pneumonia pattern. There is patchy lung involvement by loose polypoid plugs of connective tissue within alveolar ducts and alveolar spaces. The architecture of the lung is preserved and the all the connective tissue is of the same age.

COP requires exclusion of these other considerations. The primary histological differential diagnoses include DAD, NSIP, desquamate interstitial pneumonia (DIP) and UIP. Histological findings that suggest a diagnosis other than COP include neutrophils, acute bronchiolitis, granulomas, necrosis, hyaline membranes and prominent eosinophils. DAD is distinguished from organizing pneumonia by the finding of hyaline membranes or more diffuse lung injury, with marked oedematous thickening, organization in alveolar walls and prominent pneumocyte hyperplasia.

#### Clinical features

COP patients typically present between 50 and 60 years with cough and/or dyspnoea 4–6 weeks following a flu-like illness.<sup>1,2,17</sup>

#### Histological features of organizing pneumonia pattern<sup>1</sup>

##### Key histological features

- Organizing pneumonia: intraluminal organizing fibrosis in distal airspaces (bronchioles, alveolar ducts and alveoli)
- Patchy distribution
- Preservation of lung architecture
- Uniform temporal appearance
- Mild interstitial chronic inflammation

##### Pertinent negatives

- Lack of interstitial fibrosis (except for incidental scars or apical fibrosis)
- Absence of granulomas
- Lack neutrophils or abscesses
- Absence of necrosis
- Lack of hyaline membranes or prominent airspace fibrin
- Lack of prominent infiltration of eosinophils
- Absence of vasculitis

**Table 5**

#### Clinical settings associated with organizing pneumonia pattern<sup>1</sup>

- As an idiopathic process that may be a localized nodule or infiltrative lung disease (COP)
- Organizing diffuse alveolar damage
- Organizing infections
- Organization distal to obstruction
- Organizing aspiration pneumonia
- Organizing drug reactions, fume and toxic exposures
- Collagen vascular disease
- Extrinsic allergic alveolitis/hypersensitivity pneumonitis
- Eosinophilic lung disease
- Inflammatory bowel disease
- As a secondary reaction in chronic bronchiolitis
- As a reparative reaction around other processes (including abscesses, Wegener granulomatosis, neoplasms and others)

**Table 6**

There is no sex predilection. There is usually mild to moderate restriction on pulmonary function tests.<sup>2</sup> Patients usually respond to oral corticosteroids and a few recover spontaneously. Relapse can occur within 1–3 months if corticosteroids are given for <6 months.<sup>2</sup>

In the appropriate clinical setting and with characteristic chest imaging studies, the diagnosis may be established by obtaining a transbronchial lung biopsy that shows consistent histopathological features. However, if the follow-up and response to therapy are not as expected for COP, alternative diagnoses should be considered.

#### Radiological features

The HRCT in COP demonstrates patchy areas of airspace consolidation that are often subpleural or peribronchial and show air bronchograms.<sup>18</sup> Small nodules situated along bronchovascular bundles or ground-glass attenuation can be seen in up to one-half of patients. Multiple large nodules may be seen in 15% of patients.<sup>19</sup>

#### Acute interstitial pneumonia

AIP differs from the other IIPs in that patients present with acute respiratory failure rather than chronic lung disease<sup>1</sup> The histological finding on lung biopsy is DAD, which can be associated with a variety of causes including infection, sepsis, collagen vascular disease, uraemia or drug toxicity (Table 7). In the absence of any identifiable cause, the clinical term AIP is appropriate.

#### Pathological features

DAD is the characteristic lung biopsy finding in patients with AIP (Table 8).<sup>20,21</sup> The early phase is characterized by hyaline membranes, oedema and mild interstitial acute inflammation. As the condition progresses to the organizing phase, the alveolar walls are thickened by loose organizing fibrosis, mostly within alveolar septa and type II pneumocyte hyperplasia (Figure 4).<sup>20</sup> Thromboemboli may be present in small to medium sized pulmonary

### Clinical conditions associated with diffuse alveolar damage pattern<sup>1</sup>

- Idiopathic (acute interstitial pneumonia)
- Infection (severe acute respiratory distress syndrome)
- Collagen vascular disease
- Drug toxicity
- Toxic inhalation
- Uraemia
- Sepsis
- Transfusion-related acute lung injury
- Shock
- Trauma

**Table 7**

arterioles.<sup>20,22</sup> If patients recover the lung may return to normal, but they may progress to a fibrosing phase, sometimes with honeycomb fibrosis.

The histological differential diagnosis includes other patterns of diffuse parenchymal lung disorders such as OP, eosinophilic pneumonia and UIP, as well as potential aetiological considerations such as infection. Infection is suggested by the presence of granulomas, viral inclusions or foci of necrosis or neutrophilic abscesses. Infectious agents should be excluded with special stains. Patients with AIP are frequently biopsied after the disease has progressed to the organizing phase of DAD, so hyaline membranes are often difficult to find.<sup>23</sup> Exclusion of many of the conditions that can be associated with the DAD pattern may require clinical correlation (see Table 7).

A rare subset of patients with acute lung injury will show a pattern described as acute fibrinous and organizing pneumonia (AFOP).<sup>24</sup> Biopsies show abundant alveolar fibrin and some OP, but features of classical DAD, such as hyaline membranes, and of eosinophilic pneumonia, such as prominent eosinophils, are absent.

### Histological features of diffuse alveolar damage<sup>1</sup>

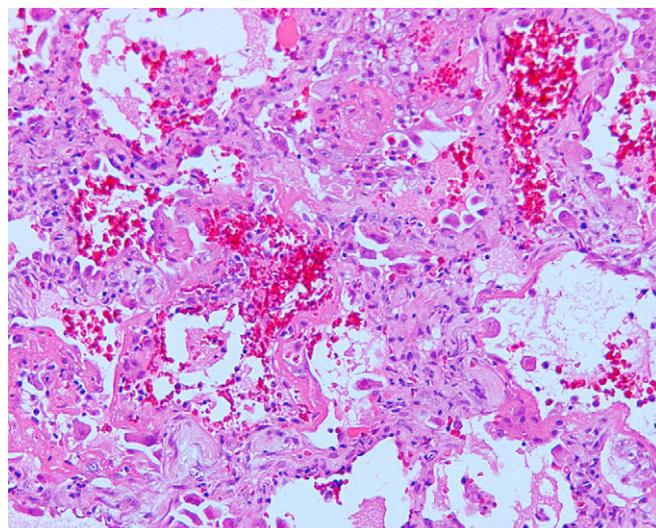
#### Key histological features

- Diffuse distribution
- Uniform temporal appearance
- Alveolar septal thickening due to organizing fibrosis, usually diffuse
- Airspace organization (may be patchy or diffuse)
- Hyaline membranes (may be focal or diffuse)

#### Pertinent negatives

- Lack of granulomas, necrosis or abscesses
- Lack of infectious agents (no viral inclusions and negative special stains for organisms)
- Lack of prominent eosinophils and neutrophils
- Negative cultures

**Table 8**



**Figure 4** Diffuse alveolar damage. The lung shows diffuse alveolar wall thickening by proliferating connective tissue, type II pneumocytes and hyaline membranes.

#### Clinical features

The mean age of patients with AIP is approximately 50 years and there is no sex predilection.<sup>20,25</sup> Patients typically present with acute respiratory failure, often following an illness of usually < 3 weeks in duration that resembles an upper respiratory tract infection. Virtually all patients require mechanical ventilation.<sup>20</sup> The mortality rate is approximately 50% with most deaths occurring 1–2 months after presentation.<sup>22,25</sup> If the patient survives, they may develop recurrences and chronic interstitial lung disease.

Patients with AFOP can have associated conditions such as collagen vascular disease or infection similar to DAD, and it can also be idiopathic. Patients may have a clinical picture that resembles AIP or one that is close to that of COP. When patients require mechanical ventilation mortality is high. AFOP seen on biopsy may represent inadequate sampling in some cases that are otherwise DAD.

#### Radiological features

The CT findings in AIP include ground-glass attenuation, bronchial dilatation, architectural distortion and consolidation.<sup>26–28</sup> When AIP progresses to the organizing phase it shows distortion of bronchovascular bundles, traction bronchiectasis and ultimately cystic changes.

#### Respiratory bronchiolitis-associated interstitial lung disease

Respiratory bronchiolitis is a common histological lesion seen in lung tissue from cigarette smokers. It can occur in non-smokers, but these patients usually have some type of inhalational exposure which may include passive smoke exposure. When this histological lesion is found in patients who have mild clinical findings of interstitial lung disease, the clinical term respiratory bronchiolitis–interstitial lung disease (RB-ILD) is appropriate.<sup>29–31</sup> RB-ILD and DIP are part of the spectrum of smoking-related ILD.

#### Pathological features

The histological lesion of respiratory bronchiolitis consists of a bronchiocentric accumulation of pigmented macrophages

(Figure 5) within bronchioles, alveolar ducts and peribronchiolar alveolar spaces (Table 9).<sup>32</sup> The faintly pigmented macrophages have cytoplasmic finely granular golden-brown particles. Bronchioles show a mild interstitial chronic inflammatory infiltrate and mild to moderate fibrotic thickening. Emphysema is often present.

There can be some degree of overlap between DIP and NSIP with heterogeneity but most cases can be classified into one of these categories.

#### Clinical features

RB-ILD patients usually have mild symptoms characterized by insidious onset of dyspnoea and cough.<sup>29-31</sup> A few patients may have significant dyspnoea and hypoxaemia. A high percentage of patients are current cigarette smokers aged 30-50 years, and they are usually heavy smokers averaging > 30 pack years. There is a 2:1 male predominance. Pulmonary function testing typically reveals a mild to moderate reduction in carbon monoxide transfer factor. In more established cases, features of both airway obstruction and restriction, or occasionally an isolated increase in residual volume, may be found. DL<sub>CO</sub> may be reduced in patients with severe symptoms. Optimal treatment includes cessation of smoking typically results in improvement.<sup>29-31</sup>

#### Radiological features

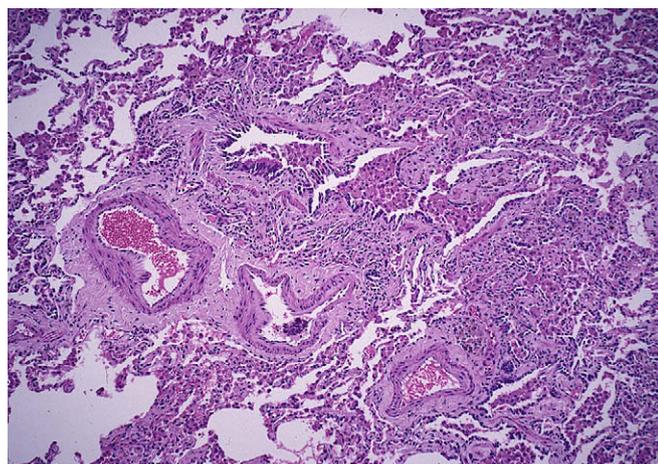
The CT characteristics of RB-ILD are centrilobular nodules, patchy ground-glass attenuation and thickening of the walls of the central and peripheral airways.<sup>28,33</sup> Upper lobe centrilobular emphysema is common.

#### Desquamative interstitial pneumonia

While DIP is part of the spectrum of cigarette smoking-related lung disease,<sup>29,30,34</sup> in most cases it represents a distinct clinical, radiological and histological category of IIP.<sup>1,2</sup>

#### Pathological features

The DIP pattern is characterized by diffuse and prominent intra-alveolar pigmented macrophage accumulation (Figure 6).



**Figure 5** Respiratory bronchiolitis. Faintly pigmented alveolar macrophages fill the lumen of this respiratory bronchiole and the surrounding airspaces. There is mild thickening of the wall of the respiratory bronchiole.

#### Histological features of respiratory bronchiolitis pattern<sup>1</sup>

##### Key histological features

- Bronchiolocentric alveolar macrophage accumulation
- Mild bronchiolar fibrosis and chronic inflammation
- Macrophages have dusty brown cytoplasm (may be positive for iron stains)

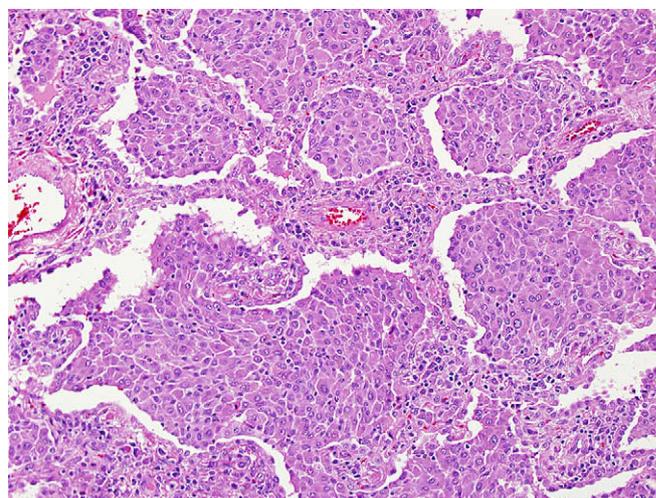
##### Pertinent negatives

- Lack of diffuse macrophage accumulation
- Lack of interstitial fibrosis and/or honeycomb fibrosis

**Table 9**

There is mild to moderate thickening of alveolar septa by fibrous thickening and a sparse chronic inflammatory infiltrate. Pneumocyte hyperplasia is common (Table 10). DIP differs from RB in that it diffusely affects the lung, lacking the bronchiolocentric distribution seen in RB. The macrophages contain dusty-brown pigment identical to that seen in RB. Emphysema is common.

The histological differential diagnosis of the DIP pattern includes eosinophilic pneumonia, hypersensitivity pneumonitis, NSIP, amiodarone toxicity and chronic haemorrhage. Patients with eosinophilic pneumonia treated with steroids may have prominent alveolar macrophages on biopsy. Biopsies from patients with hypersensitivity pneumonitis can also show prominent alveolar macrophage accumulation. When smokers develop prominent interstitial fibrosis that exceeds the severity accepted in DIP, they may best fit the diagnosis of fibrosing NSIP. Macrophages in amiodarone have foamy cytoplasm rather than the dusty pigmented morphology seen in DIP. Chronic haemorrhage is characterized by coarse haemosiderin in alveolar macrophages rather than the fine dusty pigment of DIP.



**Figure 6** Desquamative interstitial pneumonia pattern. The alveolar spaces are diffusely involved by marked alveolar macrophage accumulation and there is mild interstitial thickening. The alveolar walls are mildly thickened by fibrous connective tissue and a few chronic inflammatory cells.

## Histological features of desquamative interstitial pneumonia<sup>1</sup>

### Key features

- Uniform involvement of lung parenchyma
- Prominent accumulation of alveolar macrophages (may show fine granular positivity with iron stains)
- Mild to moderate fibrotic thickening of alveolar septa
- Mild interstitial chronic inflammation (lymphoid aggregates)

### Pertinent negative findings

- Dense and extensive fibrosis—inconspicuous or absent
- Smooth muscle proliferation—inconspicuous or absent
- Honeycomb fibrosis absent
- Fibroblastic foci and organizing pneumonia—inconspicuous or absent
- Eosinophils—inconspicuous, absent or only focal

**Table 10**

### Clinical features

DIP presents in patients aged 30–50 years and more often in men than in women.<sup>29,30,34</sup> Virtually all patients are cigarette smokers, although in one study up to 40% were never smokers.<sup>29</sup> Patients present with gradual onset of dyspnoea and dry cough, often associated with digital clubbing.<sup>29,34</sup> Pulmonary function usually shows a mild restrictive abnormality with moderate reduction of the DL<sub>CO</sub>.<sup>29,34</sup> Patients typically have a good prognosis with smoking cessation and corticosteroid treatment. The overall survival is about 70% after 10 years<sup>29,34</sup>; however, some studies have shown 100% survival.<sup>35,36</sup>

### Radiological features

The characteristic finding on CT is ground-glass opacification, usually affecting the lower zones or lung periphery.<sup>37</sup>

## Lymphocytic interstitial pneumonia

Lymphocytic interstitial pneumonia (LIP) is a form of interstitial pneumonia that is characterized by diffuse infiltration of the alveolar septa by a dense lymphocytic infiltrate.<sup>38,39</sup> Several terms have been used for this lesion including lymphoid interstitial pneumonia and plasma cell interstitial pneumonitis. Historically, confusion has occurred with LIP and lesions now recognized as low grade lymphomas, cellular NSIP and follicular bronchiolitis. It occurs in a wide variety of conditions but rarely it may be idiopathic (Table 11).<sup>1</sup>

### Pathological features

The histology of LIP consists of a diffuse, marked lymphoid infiltration of alveolar septa (Table 12). The lymphoid infiltrate consists mostly of lymphocytes with varying numbers of plasma cells. Lymphoid follicles are common (Figure 7). The lymphoid infiltrate is composed of both B cells and T cells. Mild to moderate degrees of interstitial fibrosis and small foci of organizing pneumonia may be present. Occasional non-necrotizing granulomas also may be present.

The differential diagnosis of LIP includes malignant lymphoma, follicular bronchiolitis, nodular lymphoid hyperplasia,

## Clinical conditions associated with the lymphocytic interstitial pneumonia pattern.<sup>1</sup>

- Collagen vascular disease—Sjögren syndrome, rheumatoid arthritis, systemic lupus erythematosus
- Other immunological disorders:
  - Autoimmune haemolytic anaemia
  - Pernicious anaemia
  - Myasthenia gravis
  - Hashimoto thyroiditis
  - Primary biliary cirrhosis
  - Celiac sprue
  - Dysproteinemia
- Immunodeficiency:
  - Acquired immunodeficiency syndrome, particularly in children
  - Common variable immunodeficiency
- Infections:
  - *Pneumocystis (carinii) jiroveci*
  - Legionella pneumonia
  - Chronic active hepatitis
- Drug-induced/toxic exposure:
  - Dilantin (phenytoin)
- Allogeneic bone marrow transplantation:
  - Familial
  - Idiopathic

**Table 11**

infection and cellular NSIP. Pure follicular bronchiolitis without extensive alveolar septal infiltration should not be classified as LIP. Low-grade lymphomas show more extensive lymphoid infiltration with tracking along lymphatic routes or formation of

## Histological features of lymphocytic interstitial pneumonia.<sup>1</sup>

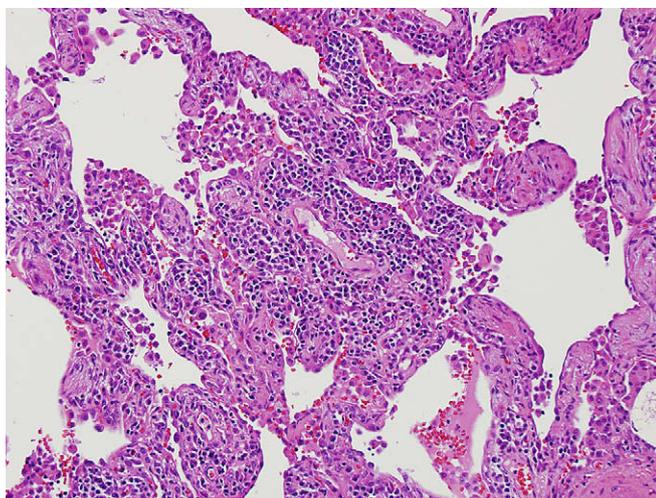
### Major features

- Diffuse interstitial infiltration of involved areas
- Predominantly alveolar septal distribution
- Infiltrates comprise mostly T-lymphocytes, plasma cells and macrophages
- Lymphoid hyperplasia (BALT hyperplasia) - frequent

### Pertinent negatives

- Lack of tracking along lymphatic routes (bronchovascular bundles, pleura and interlobular septae), characteristic of lymphomas
- Organizing pneumonia, inconspicuous or absent
- Lack of Dutcher bodies
- Lack of monoclonal light chain staining pattern of plasma cells (polyclonal pattern present)
- Lack of extensive pleural involvement or lymph node involvement
- Lack of necrotizing granulomas

**Table 12**



**Figure 7** Lymphocytic interstitial pneumonia pattern. There is diffuse thickening of alveolar walls by a moderately severe infiltrate of lymphocytes and plasma cells.

nodular masses. Clonality is demonstrated by light chain restriction using immunohistochemistry for kappa/lambda light chains or heavy chain gene rearrangements. An LIP-like reaction can be associated with certain infections, especially *Pneumocystis jirovecii*.<sup>40</sup> Special stains, including GMS and AFB, should be performed on cases with marked lymphoid infiltrates to exclude the presence of infectious organisms.

#### Clinical and radiological features

The presenting manifestations of LIP are often dominated by the underlying condition, such as collagen vascular disease. The presentation of idiopathic LIP is not well defined.<sup>1</sup> Women are affected more commonly than men and LIP presents most often in the fourth to sixth decades of life.<sup>1,38</sup> LIP is rare in human immunodeficiency virus (HIV)-infected adults, but in infected children under age 13 years it is frequent. Cases of resolution of LIP have been reported in HIV-infected adults receiving highly active antiretroviral therapy (HAART).<sup>30,34,41</sup>

Patients with LIP present with gradual onset of dyspnoea ranging in duration from 2 months to 12 years. Pulmonary function typically shows a low diffusing capacity and a restrictive ventilatory defect. Collagen vascular serology should be performed. If a monoclonal gammopathy or hypogammaglobulinaemia is found, it raises concern for lymphoma.

Cha *et al* reported the death of 7 of 15 patients with a median survival of 11.5 years.<sup>38</sup> Progression to end-stage lung disease occurred in three patients. Optimal therapy is administration of corticosteroids, which usually results in improvement or resolution of symptoms.<sup>38</sup> Other agents such as cyclophosphamide, azathioprine and cyclosporine A may be given with variable response.

HRCT scans typically show ground-glass opacities. Nodular lesions and cysts may be seen.<sup>38</sup> ◆

#### REFERENCES

- 1 Travis WD, King TE, Bateman ED, et al. ATS/ERS international multidisciplinary consensus classification of idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2002; **165**: 277–304.
- 2 Travis WD, Colby TV, Koss MN, Müller NL, Rosado-de-Christenson ML, King Jr. TE. Non-neoplastic disorders of the lower respiratory tract, Washington, DC: American Registry of Pathology, 2002.
- 3 Poletti V, Cazzato S, Minicuci N, Zompatori M, Burzi M, Schiattone ML. The diagnostic value of bronchoalveolar lavage and transbronchial lung biopsy in cryptogenic organizing pneumonia. *Eur Respir J* 1996; **9**: 2513–2516.
- 4 Bartter T, Irwin RS, Nash G, Balikian JP, Hollingsworth HH. Idiopathic bronchiolitis obliterans organizing pneumonia with peripheral infiltrates on chest roentgenogram. *Arch Intern Med* 1989; **149**: 273–279.
- 5 Katzenstein AL, Zisman DA, Litzky LA, Nguyen BT, Kotloff RM. Usual interstitial pneumonia: histologic study of biopsy and explant specimens. *Am J Surg Pathol* 2002; **26**: 1567–1577.
- 6 Churg A, Muller NL, Silva CI, 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**: 277–284.
- 7 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 Mar 13 Epub ahead of print.
- 8 Churg A, Muller NL, Flint J, Wright JL. Chronic hypersensitivity pneumonitis. *Am J Surg Pathol* 2006; **30**: 201–208.
- 9 Collard HR, Moore BB, Flaherty KR, et al. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2007; **176**: 636–643.
- 10 Martinez FJ. Idiopathic interstitial pneumonias: usual interstitial pneumonia versus nonspecific interstitial pneumonia. *Proc Am Thorac Soc* 2006; **3**: 81–95.
- 11 Silva CI, Muller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. *Radiology* 2008; **246**: 288–297.
- 12 Collard HR, King Jr. TE. Idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia should stay separate. *Eur Respir J* 2008; **31**: 1141–1142.
- 13 Travis WD, Hunninghake G, King Jr. TE, et al. Idiopathic nonspecific interstitial pneumonia report of an ATS Project. *Am J Respir Crit Care Med* 2008; **177**: 1338–1347.
- 14 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**: 691–697.
- 15 Silva CI, Muller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. *Radiology* 2008; **247**: 251–259.
- 16 Davison AG, Heard BE, McAllister WAC, Turner-Warwick ME. Cryptogenic organizing pneumonitis. *Q J Med* 1983; **207**: 382–394.
- 17 Cordier JF. Cryptogenic organising pneumonia. *Eur Respir J* 2006; **28**: 422–446.
- 18 Oikonomou A, Hansell DM. Organizing pneumonia: the many morphological faces. *Eur Radiol* 2002; **12**: 1486–1496.
- 19 Akira M, Yamamoto S, Sakatani M. Bronchiolitis obliterans organizing pneumonia manifesting as multiple large nodules or masses. *AJR Am J Roentgenol* 1998; **170**: 291–295.
- 20 Olson J, Colby TV, Elliott CG. Hamman-Rich syndrome revisited. *Mayo Clin Proc* 1990; **65**: 1538–1548.
- 21 Tomashefski JFJ. Pulmonary pathology of the adult respiratory distress syndrome. *Clin Chest Med* 1990; **11**: 593–619.

- 22** Katzenstein AL, Myers JL, Mazur MT. Acute interstitial pneumonia. A clinicopathologic, ultrastructural, and cell kinetic study. *Am J Surg Pathol* 1986; **10**: 256–267.
- 23** Katzenstein A-LA, Askin FB. Surgical pathology of non-neoplastic lung disease, Philadelphia: WB Saunders, 1997.
- 24** Beasley MB, Franks TJ, Galvin JR, Gochuico B, Travis WD. Acute fibrinous and organizing pneumonia. *Arch Pathol Lab Med* 2002; **126**: 1064–1070.
- 25** Vourekis JS. Acute interstitial pneumonia. *Clin Chest Med* 2004; **25**: 739–747 vii.
- 26** Johkoh T, Muller NL, Taniguchi H, et al. Acute interstitial pneumonia: thin-section CT findings in 36 patients. *Radiology* 1999; **211**: 859–863.
- 27** Johkoh T. Imaging of idiopathic interstitial pneumonias. *Clin Chest Med* 2008; **29**: 133–147 vi.
- 28** Lynch DA, Travis WD, Muller NL, et al. Idiopathic interstitial pneumonias: CT features. *Radiology* 2005; **236**: 10–21.
- 29** Craig PJ, Wells AU, Doffman S, et al. Desquamative interstitial pneumonia, respiratory bronchiolitis and their relationship to smoking. *Histopathology* 2004; **45**: 275–282.
- 30** Vassallo R, Jensen EA, Colby TV, et al. The overlap between respiratory bronchiolitis and desquamative interstitial pneumonia in pulmonary Langerhans cell histiocytosis: high-resolution CT, histologic, and functional correlations. *Chest* 2003; **124**: 1199–1205.
- 31** Wells AU, Nicholson AG, Hansell DM, du Bois RM. Respiratory bronchiolitis-associated interstitial lung disease. *Semin Respir Crit Care Med* 2003; **24**: 585–594.
- 32** Fraig M, Shreeshu U, Savici D, Katzenstein AL. Respiratory bronchiolitis: a clinicopathologic study in current smokers, ex-smokers, and never-smokers. *Am J Surg Pathol* 2002; **26**: 647–653.
- 33** Hansell DM, Nicholson AG. Smoking-related diffuse parenchymal lung disease: HRCT-pathologic correlation. *Semin Respir Crit Care Med* 2003; **24**: 377–392.
- 34** Ryu JH, Myers JL, Capizzi SA, Douglas WW, Vassallo R, Decker PA. Desquamative interstitial pneumonia and respiratory bronchiolitis-associated interstitial lung disease. *Chest* 2005; **127**: 178–184.
- 35** Nicholson AG, Colby TV, Dubois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. *Am J Respir Crit Care Med* 2000; **162**: 2213–2217.
- 36** Travis WD, Matsui K, Moss JE, Ferrans VJ. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns. Survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. *Am J Surg Pathol* 2000; **24**: 19–33.
- 37** Hartman TE, Primack SL, Swensen SJ, Hansell D, McGuinness G, Muller NL. Desquamative interstitial pneumonia: thin-section CT findings in 22 patients. *Radiology* 1993; **187**: 787–790.
- 38** Cha SI, Fessler MB, Cool CD, Schwarz MI, Brown KK. Lymphoid interstitial pneumonia: clinical features, associations, and prognosis. *Eur Respir J* 2006; **28**: 364–369.
- 39** Travis WD, Galvin JR. Non-neoplastic pulmonary lymphoid lesions. *Thorax* 2001; **56**: 964–971.
- 40** Murphy PM, Fox C, Travis WD, Koenig S, Fauci AS. Acquired immunodeficiency syndrome may present as severe restrictive lung disease. *Am J Med* 1989; **86**: 237–240.
- 41** Innes AL, Huang L, Nishimura SL. Resolution of lymphocytic interstitial pneumonitis in an HIV infected adult after treatment with HAART. *Sex Transm Infect* 2004; **80**: 417–418.

### Practice points

- Histological patterns of IIPs are not specific: they occur in association with known causes such as collagen vascular disease, as well as in an idiopathic setting
- UIP is the most important histological pattern for pathologists to recognize due to the adverse prognosis of the clinical entity idiopathic pulmonary fibrosis
- Correlation between clinical and HRCT findings is essential because even with classical UIP or NSIP patterns, CT findings may suggest alternative diagnoses such as chronic hypersensitivity pneumonitis
- Discussion of difficult cases at a multidisciplinary conference is a powerful tool in reaching an accurate diagnosis

### Research directions

- All research in this field should be performed in carefully characterized cases for whom diagnoses are based upon clinical–radiological–pathological correlation.
- A better definition of the term honeycombing needs to be clarified.
- The pathogeneses of UIP and NSIP need to be defined.
- The genetics of IIPs need to be defined.