

# Update on idiopathic interstitial pneumonias

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## Summary

**The idiopathic interstitial pneumonias (IIPs) comprise a major portion of diffuse infiltrative (interstitial) lung diseases. The classification of IIPs was initially conceived 4 decades ago and has undergone revisions over the intervening years with the most recent version published in 2013. Current classification distinguishes “major” forms of IIPs (idiopathic pulmonary fibrosis, idiopathic nonspecific interstitial pneumonia, respiratory-bronchiolitis-interstitial lung disease, desquamative interstitial pneumonia, cryptogenic organizing pneumonia, and acute interstitial pneumonia) from “rare” forms (idiopathic lymphoid interstitial pneumonia, idiopathic pleuroparenchymal fibroelastosis). In addition, the category of “unclassifiable” IIP is introduced in recognition of IIP cases that remain difficult to classify even with the current scheme. This review describes the historical background for IIPs, current perspectives, and summarizes the clinical-pathologic entities included in the current classification scheme.**

**KEY WORDS:** *idiopathic interstitial pneumonia, idiopathic pulmonary fibrosis, nonspecific interstitial pneumonia, interstitial lung disease, respiratory bronchiolitis, desquamative interstitial pneumonia, organizing pneumonia, acute interstitial pneumonia, lymphoid interstitial pneumonia, pleuroparenchymal fibroelastosis.*

## Introduction

Interstitial lung diseases (ILDs) comprise a heterogeneous spectrum of diffuse infiltrative lung diseases that give rise to respiratory symptoms, pulmonary infiltrates, and impaired gas exchange. Potential causes of ILD are numerous while for some patients no cause can be identified. A substantial portion of these latter patients have idiopathic interstitial pneumonias (IIPs), most commonly idiopathic pulmonary fibrosis (IPF) which histopathologically manifests usual interstitial pneumonia (UIP) pattern.

The concept of IIPs dates back to mid-1970s and has undergone several revisions in the intervening years (1-4). The most recent iteration of this concept was formulated by an international panel of experts and investigators and published in 2013 (4). This review will highlight the clinically relevant aspects of IIPs as currently classified.

## Historical perspective

Averill Liebow initially articulated the concept of IIPs in 1975 (Table 1) (1). The term was used to describe several histopathologic entities that share the feature of diffuse parenchymal infiltration with a tendency for fibrosis. This initial classification of IIPs included UIP, desquamative interstitial pneumonia (DIP), bronchiolitis obliterans with interstitial pneumonia, lymphoid interstitial pneumonia (LIP), and giant cell interstitial pneumonia. In the following years the cause of giant cell interstitial pneumonia was identified to be heavy metal exposure and thus not “idiopathic”. In addition, three forms of IIP became recognized, namely, respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) (5), nonspecific interstitial pneumonia (NSIP) (6), and acute interstitial pneumonia (AIP) (7). In 2002, a panel of experts representing the American Thoracic Society and the European Respiratory Society published the first consensus statement on IIPs (3) which was followed by an updated version earlier this year (Table 2) (4).

Terminology used in IIPs can be confusing for clinicians. It is important to keep in mind that some of the terms refer to histopathologic patterns while others connote specific disease entities. For example, UIP is

**These histopathologic patterns of interstitial pneumonias do not, in and of themselves, constitute a specific disease entity which requires integration of clinical and radiologic findings.**

Table 1 -Prior IIPs classifications.

Liebow, 1975	Katzenstein, 1998	ATS/ERS, 2002
Usual interstitial pneumonia	Usual interstitial pneumonia	Idiopathic pulmonary fibrosis (usual interstitial pneumonia)
Desquamative interstitial pneumonia	Desquamative interstitial pneumonia / Respiratory bronchiolitis interstitial lung disease	Desquamative interstitial pneumonia
Bronchiolitis obliterans with interstitial pneumonia	Nonspecific interstitial pneumonia	Respiratory bronchiolitis-interstitial lung disease
Lymphoid interstitial pneumonia	Acute interstitial pneumonia	Nonspecific interstitial pneumonia
Giant cell interstitial pneumonia		Acute interstitial pneumonia
		Lymphoid interstitial pneumonia
		Cryptogenic organizing pneumonia

Table 2 - ATS/ERS 2013 Classification of idiopathic interstitial pneumonias.

Major idiopathic interstitial pneumonias
Idiopathic pulmonary fibrosis
Idiopathic nonspecific interstitial pneumonia
Respiratory bronchiolitis-interstitial lung disease
Desquamative interstitial pneumonia
Cryptogenic organizing pneumonia
Acute interstitial pneumonia
Rare idiopathic interstitial pneumonias
Idiopathic lymphoid interstitial pneumonia
Idiopathic pleuroparenchymal fibroelastosis
Unclassifiable idiopathic interstitial pneumonias

a histopathologic pattern underlying the diagnosis IPF but can also be seen in other diseases such as drug-induced lung diseases, connective tissue diseases, asbestosis and chronic hypersensitivity pneumonitis. Thus, an underlying cause can be identified in some patients with UIP pattern. Similar concepts hold true for other histopathologic patterns of interstitial pneumonia such as NSIP and diffuse alveolar damage (underlying histopathologic pattern for AIP) as will be explained later in this review. These histopathologic patterns of interstitial pneumonias do not, in and of themselves, constitute a specific disease entity which requires integration of clinical and radiologic findings.

### 2013 update on IIPs

As already noted, an international panel of experts published an update on the classification of IIPs in 2013 (4). The current classification separates “major”

forms of IIPs from “rare” forms to which is added idiopathic pleuroparenchymal fibroelastosis (PPFE). In addition, it is recognized that some cases of IIP remain difficult to classify even with the current scheme and are designated as “unclassifiable” IIP. Although most investigators acknowledge the relationship between smoking with RB-ILD and DIP (“smoking-related ILDs”), these two entities are retained in the 2013 classification. In the remainder of this review key aspects of each IIP are highlighted.

### Idiopathic Pulmonary Fibrosis (IPF)

The concept of IPF remains as defined in the 2011 ATS/ERS consensus statement on diagnosis and management of IPF (8). IPF remains defined as a progressive ILD of unknown cause characterized by UIP pattern on lung biopsy or high-resolution computed tomography (HRCT). It is important to note that the demonstration of UIP pattern alone is not sufficient to make the diagnosis of IPF in the absence of appropriate clinical context. For example, histopathologic pattern of UIP can be encountered in patients with chronic hypersensitivity pneumonitis. In such patients atypical HRCT features (extensive ground-glass opacities or mosaic pattern due to air-trapping) can be a tipoff to the correct diagnosis (Figure 1). This example demonstrates the concept of clinico-radiologic-pathologic correlation required in diagnosing IIPs since histopathologic patterns in these disorders have varying degrees of specificity as to the underlying etiology.

UIP pattern can be diagnosed by HRCT in the presence of several key features (8). These imaging features include reticular opacities and honeycombing that have subpleural and

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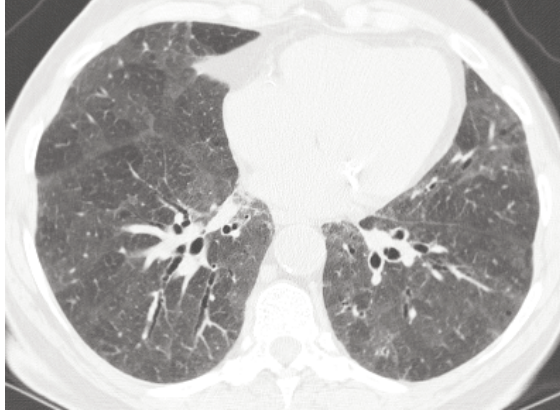


Figure 1 - High-resolution chest CT of a 75-year-old woman, nonsmoker, whose surgical lung biopsy showed a usual interstitial pneumonia (UIP) pattern. CT findings include patchy ground-glass opacities with a background of mosaic pattern and absence of subpleural honeycombing. Expiratory imaging confirmed patchy areas of air-trapping. Serologic testing revealed positivity to avian antigens, likely related to her bird feeders in the back yard. She improved with avoidance of additional exposure and prednisone treatment consistent with the diagnosis of chronic hypersensitivity pneumonitis.

basal predominance in the absence of features that are inconsistent with UIP pattern such as extensive ground-glass opacities, micronodules, or diffuse mosaic attenuation. If these characteristic imaging features are not present, a surgical lung biopsy may be needed to confirm the presence of UIP pattern.

The histologic pattern of UIP consists of several components including architectural distortion with dense fibrosis including honeycombing, fibroblast foci, temporal and geographic heterogeneity, and subpleural distribution (3, 8). Histopathologic pattern of UIP is difficult to diagnose by bronchoscopic biopsy which generally does not provide adequate amount of lung tissue to verify pattern diagnosis. However, recent studies suggest that bronchoscopic biopsy, particularly cryobiopsy, yields larger lung specimens with better preserved architecture which may avert the need for surgical lung biopsy in a substantial portion of patients with undiagnosed ILD (9-12)

Management options for patients with IPF remain limited. Pirfenidone has been approved for the treatment of IPF in Japan, Europe, and Canada, but not in the US (8, 13, 14). Pulmonary rehabilitation measures are underused in this population and deserve additional consideration by clinicians caring for these patients (15, 16). Multiple pharmacologic agents including tyrosine kinase inhibitors (17) are undergoing clinical trials and may allow expansion of pharmacotherapeutic options for this disease (18).

### Idiopathic nonspecific interstitial pneumonia

Nonspecific interstitial pneumonia is a histopathologic pattern characterized by varying degrees of chronic in-

terstitial inflammation and interstitial fibrosis (3, 6, 19). In contrast to UIP, overall lung architecture is generally preserved with absence of conspicuous temporal heterogeneity (including fibroblast foci) or honeycombing that characterize UIP pattern. Some investigators subdivide this histopathologic entity into cellular, mixed and fibrotic patterns depending on the predominant feature (6, 20).

NSIP was initially described by Katzenstein et al. (6) in 1994 and these authors noted a heterogeneous spectrum of causes and underlying diseases that can be associated with this histopathologic pattern. These associations included connective tissue diseases, hypersensitivity pneumonitis, drug-induced lung disease, infections, immunodeficiency disorders, resolving acute lung injury, and many others.

On HRCT, NSIP is characterized by bilateral ground-glass and reticular opacities that are predominantly peripheral and in the lower lungs. Traction bronchiectasis can be seen but subpleural honeycombing is generally absent. Although the presence of these features may allow the presumptive diagnosis of NSIP pattern in some clinical contexts, *e.g.*, patients with connective tissue diseases, confirmation by surgical lung biopsy may be needed in other situations to distinguish NSIP from other ILDs with similar HRCT features such as chronic hypersensitivity pneumonitis, RB-ILD, DIP, organizing pneumonia, and eosinophilic pneumonias. Also, it is not uncommon that cases with radiologic pattern of NSIP prove to be UIP on histologic examination of lung biopsy; microscopic honeycomb changes appreciated in the lung biopsy might not be apparent on CT scan, which presumably leads to the radiologic interpretation as NSIP pattern in such cases.

In the absence of an identifiable cause or associated disease, the presence of NSIP pattern confers a diagnosis of idiopathic NSIP which is associated with a better response to therapy (typically corticosteroids) and prognosis compared to IPF (19, 21). Thus, distinguishing NSIP from UIP has treatment and prognostic implications.

In recent years, several reports have emerged suggesting the presence of evolving CTD in a substantial portion of patients diagnosed with idiopathic NSIP (22, 23). Such patients can be identified by the presence of autoimmune serologic markers such as antinuclear autoantibodies or anti-cyclic citrullinated peptide autoantibodies. Terms such as “undifferentiated CTD”, “lung-dominant CTD”, and “autoimmune featured ILD” have been used to refer to such patients (22, 24, 25). Some of these patients will eventually manifest overt clinical features diagnostic of a specific CTD (23, 25).

Treatment of idiopathic NSIP usually involves corticosteroids and other immunosuppressive agents, particularly azathioprine and mycophenolate mofetil, which is moderately effective in stabilizing or improving the lung

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disease and associated respiratory impairment (19, 21, 26).

### Respiratory bronchiolitis-interstitial lung disease

Respiratory bronchiolitis (RB) is a very common histopathologic finding in current or prior smokers and is characterized by the presence of pigmented macrophages in the respiratory bronchioles and peribronchiolar alveolar spaces (3, 27, 28). Some patients with RB manifest evidence of ILD such as parenchymal opacities on HRCT or abnormalities on pulmonary function assessment. These latter subjects are said to have RB-associated ILD (RB-ILD) which can also be seen in some individuals exposed to solder fumes, diesel smoke and fiberglass dust (5, 29, 30).

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Clinical presentation of patients with RB-ILD may include respiratory symptoms such as cough and exertional shortness of breath while others are asymptomatic (5, 30-32). Most patients diagnosed with RB-ILD are between the ages of 30 and 60 years (30-32). Pulmonary function testing will typically reveal mild to

moderate physiologic impairment with restrictive or obstructive pattern (30, 32).

Main findings on HRCT include patchy ground-glass opacities, ill-defined centrilobular nodules, and bronchial wall thickening (33, 34). Honeycombing and traction bronchiectasis are not seen. HRCT findings are not specific for RB-ILD, often overlapping with NSIP, DIP, and hypersensitivity pneumonitis.

For a definitive diagnosis, surgical lung biopsy is generally needed since bronchoscopic biopsy has a relatively low yield in this disorder. However, in recent years, the trend has been to diagnose RB-ILD without confirmation by surgical lung biopsy when typical HRCT features (Figure 2) are seen in smokers or ex-smokers with a substantial smoking history. Some caution needs to be exercised in this regard since adenocarcinomas of the lung can also present with ground-glass opacities.

Main mode of treatment for RB-ILD is smoking cessation which usually leads to improvement or stability (5, 29-32, 35). The role of corticosteroid therapy remains limited to those with progressive disease or moderate to severe functional impairment. Prognosis is generally favorable for most patients especially for those who are able to quit smoking. However, there have been occasional reports of progressive RB-ILD resulting in death (32).

### Desquamative interstitial pneumonia

Desquamative interstitial pneumonia (DIP) has several features similar to RB-ILD including a strong associa-

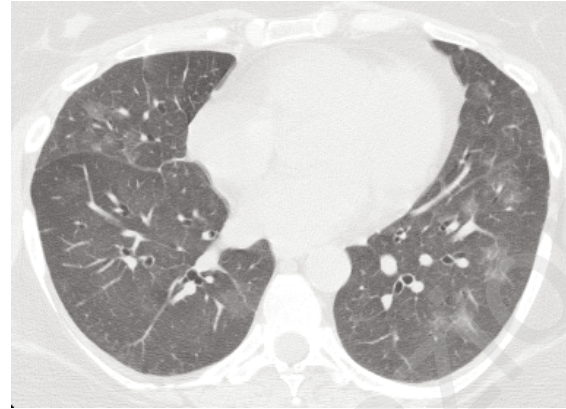


Figure 2 - High-resolution chest CT of a 51-year-old woman, active smoker, with respiratory bronchiolitis-associated interstitial lung disease (RB-ILD) demonstrating patchy ground-glass opacities bilaterally. Surgical lung biopsy revealed marked respiratory bronchiolitis.

tion with smoking (30, 35). As with RB-ILD, DIP is characterized histopathologically by the accumulation of pigmented macrophages which is more diffuse and evenly dispersed within alveolar spaces compared to the bronchiolocentric distribution seen in RB-ILD (3, 36). Alveolar septae are mild to moderately thickened by interstitial inflammation and fibrosis. Dense fibrosis including honeycombing is absent.

Most patients diagnosed with DIP are between the ages of 30 and 60 years and 60 to 90% of the patients have a smoking history (30, 35, 37). Less commonly DIP pattern can be seen in patients with drug-induced lung disease, connective tissue disease, and environmental exposures (36-38). Typical presentation includes dyspnea and cough of insidious onset. Various patterns of pulmonary function abnormalities may be encountered in patients with DIP (30, 31). On HRCT, the predominant finding is ground-glass opacities that are bilateral and more extensive than those seen in RB-ILD (33, 34). In some patients, reticular opacities, emphysema, and cysts may also be present.

Confirming the diagnosis of DIP usually requires a surgical lung biopsy. In the presence of typical clinical and radiologic features, bronchoscopic biopsy demonstrating predominantly pigmented macrophages may suffice for diagnosis.

As with RB-ILD, smoking cessation is fundamental for those patients with DIP when it is associated with smoking. Smoking cessation can lead to improvement while continued smoking portends a worse prognosis (30, 37). Corticosteroids are commonly used but response is not uniform and approximately one-fourth of

**In the presence of typical clinical and radiological features, bronchoscopic biopsy demonstrating predominantly pigmented macrophages may be diagnostic for DIP.**

treated patients may exhibit worsening of lung disease (30). The role of cytotoxic and other immunomodulating therapies remain unclear. Mortality associated with DIP is higher compared to RB-ILD (30, 31).

### **Cryptogenic organizing pneumonia**

Organizing pneumonia (OP) is a rather nonspecific histopathologic pattern of lung injury characterized by polypoid intraluminal plugs of granulation tissue within alveolar ducts and spaces along with adjacent bronchioles (3, 39). Lung parenchyma tends to be involved in a patchy fashion while underlying lung architecture is generally preserved. While some authors have argued for excluding OP from the

**If bronchoscopic biopsy is nondiagnostic, a surgical lung biopsy may be needed to distinguish COP from other disease with similar clinico-radiologic features.**

classification of IIPs based on this predominantly intraluminal rather than interstitial nature of this lesion (2), it is retained in the 2013 ATS/ERS classification of IIPs. OP pattern can be associated with a wide spectrum of causes and underlying diseases including infections, connective tissue diseases, radiation injury, aspiration, drug toxicity, and inhalational injuries. In approximately one-half of patients with OP pattern no cause or underlying disease can be identified for the lung injury. Such patients are diagnosed with cryptogenic organizing pneumonia (COP) (28, 40). As seen in NSIP, some patients with COP will eventually manifest evidence of an evolving connective tissue disease.

Most patients diagnosed with COP are in their 6<sup>th</sup> or 7<sup>th</sup> decade of life (28, 40, 41). Presenting manifestations usually include cough and dyspnea of subacute onset (few to several weeks) but systemic symptoms such as fever, malaise, anorexia, and weight loss are also commonly present. Occasionally, fulminant presentation similar to acute respiratory distress syndrome may be seen (42).

Chest radiography usually demonstrates bilateral patchy alveolar opacities that have ground-glass or consolidative character and peripheral distribution on HRCT (41, 43). CT appearance may be similar to that seen in chronic eosinophilic pneumonia. Pulmonary function testing usually demonstrates a restrictive pattern (39, 40).

The diagnosis of COP requires histopathologic demonstration of the OP pattern and exclusion of known causes or underlying diseases. Bronchoscopic lung biopsy may suffice if characteristic lesion is identified in the presence of compatible clinical and radiologic findings. If the latter features are inconsistent or the bronchoscopic biopsy is nondiagnostic, a surgical lung biopsy may be needed to distinguish COP from other lung disease with similar clinico-radiologic features including hypersensitivity pneumonitis, NSIP, chronic eosinophilic pneumonia, diffuse alveolar damage, adenocarcinoma, and lymphoma.

Spontaneous improvement of COP is unusual and

most patients require corticosteroid therapy, usually initiated with oral prednisone 30-60 mg per day (39, 40). Clinical improvement tends to be seen promptly, usually within several days. The duration of therapy varies depending on the initial response and whether relapse occurs but is typically in the range of 6 to 12 months (40). Although prognosis associated with COP is generally excellent, death from progressive lung disease may sometimes occur despite corticosteroid therapy. Cytotoxic agents such as azathioprine and cyclophosphamide have been employed for some patients with progressive COP despite corticosteroid therapy.

### **Acute interstitial pneumonia**

In contrast to other forms of IIPs, AIP is a rapidly progressive form of interstitial pneumonia. Clinically and radiologically, AIP presents with features similar to acute respiratory distress syndrome and corresponds to the Hamman-Rich syndrome originally described more than 60 years ago (44, 45). The histopathologic features of AIP are those of organizing diffuse alveolar damage which include the presence of hyaline membranes, diffuse septal edema, type II pneumocyte hyperplasia, and interstitial fibroblast proliferation (7, 46). Overall appearance is temporally homogeneous.

**The histopathologic features of AIP are those of organizing diffuse alveolar damage which include the presence of hyaline membranes, diffuse septal edema, type II pneumocyte hyperplasia, and interstitial fibroblast proliferation.**

AIP is encountered in patients of wide age range with a mean age of approximately 50 years (46-49). Clinical presentation is usually that of a rapidly progressive respiratory disorder over a course of days to weeks and commonly includes constitutional symptoms such as fever, chills, malaise, myalgias, and arthralgias. Hypoxemia is common at presentation.

Chest radiography reveals bilateral alveolar infiltrates that may be patchy initially but tends to become diffuse. HRCT findings include diffuse ground-glass opacities and consolidation with air bronchograms (43, 50, 51). Reticular opacities and traction bronchiectasis become apparent in the later phases of AIP.

There is no treatment that has been proven to be effective in the treatment of AIP although high-dose corticosteroid therapy is commonly employed (46, 49). Most patients require mechanical ventilation in setting of respiratory failure. Mortality rate associated with AIP is approximately 50% (46, 49).

### **Idiopathic lymphoid interstitial pneumonia**

In the 2013 ATS/ERS classification of IIPS, lymphoid interstitial pneumonia (also called lymphocytic interstitial pneumonia) has been relegated to the category of

“rare” IIPs. LIP is characterized histopathologically by diffuse infiltration of alveolar septae with T-lymphocytes, plasma cells, and histiocytes (3, 52, 53). Over the past decade it has been recognized that idiopathic LIP is exceedingly rare. Cases diagnosed as LIP in earlier reports likely included what would now be classified as NSIP or lymphoma

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(based on currently available immunohistochemical and molecular techniques). LIP pattern can be seen in a wide spectrum of clinical contexts including immunodeficiencies, connective tissue diseases (particularly Sjögren’s syndrome), drug-induced lung disease, viral infections, and other systemic diseases. Those with LIP in whom no known cause or association is identified have idiopathic LIP.

Imaging findings reported with LIP have been diverse and includes ground-glass opacities, ill-defined centrilobular nodules, thickening of the bronchovascular bundles, and interlobular septal thickening. In addition, parenchymal cysts have been reported in the majority of patients with LIP and have been thought to result from peribronchiolar lymphocytic infiltration with airway obstruction and distal dilatation. However, recent reports have questioned the association of cystic lung disease with LIP, particularly in patients with Sjögren syndrome in whom cystic disease has been associated with mucosa-associated lymphoid tissue (MALT) lymphoma and amyloidosis (54).

Most patients with idiopathic LIP are treated with corticosteroid therapy and clinical stability or improvement is generally expected (55-57). Prognosis is favorable but deaths from progressive lung disease and cor pulmonale or complications related to immunosuppressive therapy can occur (55-57).

### Idiopathic pleuroparenchymal fibroelastosis

A new entry into the classification of IIPs is idiopathic pleuroparenchymal fibroelastosis (PPFE), a rare but distinct clinicopathologic entity characterized histopathologically by fibrosis involving the pleura and subpleural lung parenchyma (intraalveolar fibrosis with septal elastosis), predominantly affecting the upper lobes. Familial cases and association with hematopoietic stem

**Role of genetic predisposition and autoimmunity has been suggested in the pathogenesis of pleuropulmonary fibroelastosis.**

cell transplantation have been reported but most cases are idiopathic (58-61). Role of genetic predisposition and autoimmunity has been suggested in the pathogenesis of this disorder (61).

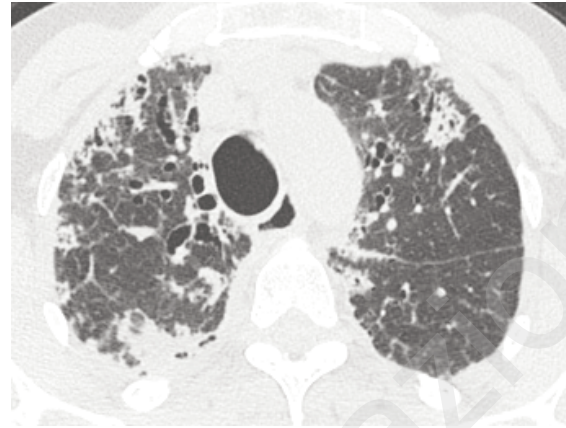


Figure 3 - High-resolution chest CT of the chest on a 60-year-old woman with idiopathic pleuroparenchymal fibroelastosis (confirmed by surgical lung biopsy) demonstrating pleural thickening, particularly in the right lung posteriorly, along with predominantly peripheral parenchymal fibrosis.

Patients with idiopathic PPFE are adults of wide age range presenting with shortness of breath and cough persistent over several months or years (58, 61). HRCT demonstrates pleural thickening and subpleural parenchymal fibrosis with upper lung predominance (Figure 3) (61, 62).

The majority of patients with idiopathic PPFE tend to progress despite treatment with corticosteroids and cytotoxic agents including azathioprine and cyclophosphamide (58, 60, 61). In a recent report by Reddy et al. 5 of 10 patients died with the interval from diagnosis ranging from 4 months to 2 years (61).

### Unclassifiable idiopathic interstitial pneumonia

Although the current classification accounts for most cases of IIPs encountered in clinical practice, it is acknowledged that there remain

cases that do not easily fit into the entities described above. This dilemma may occur when overlapping or unusual histopathologic features are encountered or major discrepancies exist between clinical, radiologic and histopathologic findings. Some authors have included patients with undetermined ILD who are unable or unwilling to undergo a

**Patients with undetermined ILD who are unable or unwilling to undergo a surgical lung biopsy as well as those with insufficient lung biopsy sample may result having unclassifiable idiopathic interstitial pneumonia.**

surgical lung biopsy as well as those with insufficient lung biopsy sample (63). Using the latter inclusive criteria, 10% of patients with ILD are “unclassifiable” (63). These patients with unclassifiable ILD have a heterogeneous clinical course and overall similar survival to non-IPF ILD patients (63).

## Conclusions

Our understanding of IIPs is improving and, accordingly, the classification of these disorders continues to evolve to reflect the gained knowledge. IPF, the most common form of IIP, remains a lethal disorder with limited management options.

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The importance of integrating clinical, radiologic and histopathologic (when available) cannot be overemphasized in optimizing the diagnosis and management

of patients with IIPs.

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