Novel patterns of interstitial lung disease

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Abstract

The 2002 ATS/ERS Idiopathic Interstitial Pneumonia Classification provided diagnostic criteria for seven well-known entities. Since then, new information has enriched our knowledge about these conditions and rare new entities have been proposed by different authors. Among these, pleuroparenchymal fibroelastosis has been recognized as a distinct clinicopathologic entity characterized by pleura and subpleural parenchymal fibrosis, predominantly composed of elastic fibres. Moreover, unusual histologic patterns, including acute fibrinous and organizing pneumonia and airway-centred interstitial fibrotic diseases, have also been described. The former is characterized by intra-alveolar fibrin deposition and associated organizing pneumonia in the absence classical hyaline membranes, while the latter includes a group of patterns remarkable for inflammation and fibrosis centred around the bronchioles. Whether these latter two patterns represent distinct entities or variants of existing idiopathic lung diseases requires further study. Since the practicing pathologists should to be aware these rare entities and patterns, this paper highlights the current knowledge about these conditions.

Keywords acute fibrinous and organizing pneumonia; airway-centred fibrosis; bronchiolocentric interstitial pneumonia; pleuroparenchymal fibroelastosis; pulmonary fibrosis; small airway disease

Introduction

Since to publication of the American Thoracic Society/European Respiratory Society (ATS/ERS) consensus classification of idiopathic interstitial pneumonias in 2002,[1] the body of literature and knowledge of these entities has greatly expanded. No classification system is ever perfect, nor is it able to provide an appropriate diagnostic category for every permutation of disease that may occur. In the past decade there have been several descriptions of pathologic entities that have been defined and/or have been repeatedly described in the literature. Chief among these are pleuroparenchymal fibroelastosis, acute fibrinous and organizing pneumonia and airway-centred interstitial fibrotic diseases. While there is still ongoing debate in regard to whether some of these truly represent distinct interstitial lung diseases or whether they represent infrequently encountered variants of existing lung disease, the aim of this article is to outline the current state of knowledge of these entities.

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Pleuroparenchymal fibroelastosis

The term pleuroparenchymal fibroelastosis (PPFE) was coined by the National Jewish Medical and Research Center of Denver in 2004 to describe a novel clinicopathologic entity characterized by upper lobe radiographic predominance and pathological findings that did not fit with any of the defined interstitial lung diseases.[2] The group reported a case series of five patients presenting with progressive chronic pulmonary symptoms suggestive of an idiopathic pneumonia. Chest radiographs showed apical pleural thickening, while high-resolution CT scans highlighted intense pleural thickening with evidence of fibrosis. The unique pathological features described were markedly thickened visceral pleura and prominent predominantly elastic subpleural fibrosis.

Since the initial description of this entity, sixteen additional cases with similar characteristics and lacking a potential unifying aetiology have been published.[3–5] Additionally, it is likely that some cases originally described as "idiopathic pulmonary upper lobe fibrosis" by Kobayashi et al., and Shiota et al., may also represent cases of IPPFE.[6,7] Albeit a limited number of cases, these reports have helped to delineate the overall clinico-radio-pathological features of PPFE. Onset of symptoms is usually gradual, with dyspnoea on exertion as predominant presentation. Non-productive cough is also usual. Approximately half of patients have experienced recurrent infections. PPFE occurs over a wide age range (24—85 years) with a mean age of 52 years. The disease is more common in women than men by a ratio of 2.5:1. The majority of patients are never-smokers. While most cases to date have no known cause, not all cases of PPFE are idiopathic. With respect to occupational and environmental exposures, no definitive common factor has been identified. However, a small percentage of patients have reported birds, mould, radiation and questionable asbestos exposure. Significant drug history was reported in few patients who underwent chemotherapy treatment for a variety of malignancies. A low frequency of family history of interstitial lung disease has been reported, including two twin sisters. In addition a minority has non-specific auto-antibodies. Additionally, a series of four cases wee described in 2011 in which PPFE was associated with bone marrow transplantation and recurrent pneumothoraces. All four of these patients additionally showed features of constrictive bronchiolitis, and it was postulated that in these cases PPFE may have been a manifestation of possible graft-versus-host disease or drug/radiation effect.[8] Regardless, a distinctive clinical finding of PPFE is the development of secondary spontaneous pneumothoraces and persistent post-operative bronchopleural fistulae, in about one third of cases. The clinical course of this affection is progressive. Forty-three percent of reported patients have died of disease, with the time interval between diagnosis and death ranging from 4 months to 7 years.

The most common chest X-ray abnormality in patients with PPFE is marked pleural thickening, predominantly apical and associated with superior hilar retraction. High-resolution CT scans reveal bilateral irregular pleuroparenchymal thickening, most marked in the upper and middle zones. There is a subpleural reticular pattern consistent with fibrosis (Figure 1). Reported associated features included traction bronchiectasis, lung volume loss, honeycombing, interstitial fibrosis remote from pleural and subpleural changes, small foci of consolidation, architectural distortion and interlobular septal thickening.

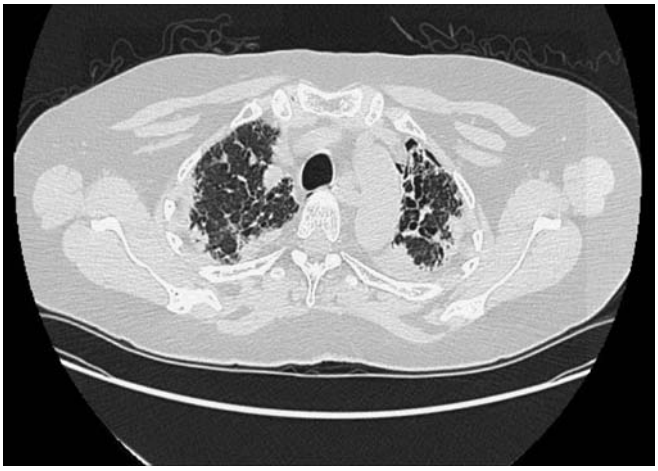

Figure 1 CT scan of pleuroparenchymal fibroelastosis. PPFE is predominantly an upper lobe disease and this CT demonstrates upper lobes show bilateral pleural thickening and irregular subpleural fibrosis.

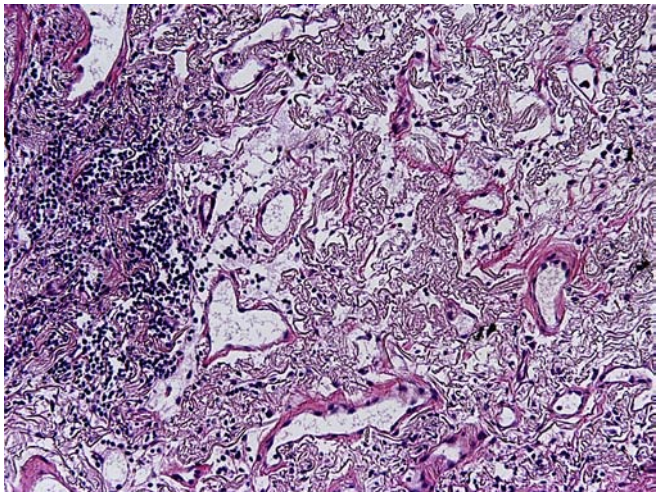

Figure 3 Pleuroparenchymal fibroelastosis (PPFE). PPFE is characterized by prominent deposition of elastic fibres as opposed to the dense collagenous fibrosis typical of most fibrosing lung diseases. H&E, 400×.

The classic histological features of PPFE include intense fibrosis with of the visceral pleura accompanied with prominent intra-alveolar subpleural fibrosis (Figure 2). The fibrosis consists predominately of homogeneous elastic fibres as opposed to dense collagen (Figure 3). The central lung parenchyma is generally spared. Thus, performing elastic fibres stains in cases with predominately pleural and subpleural fibrosis may aid in establishing the diagnosis (Figure 4). The transition between the fibroelastosis and the underlying normal lung parenchyma is characteristically sharp. Rare fibroblastic foci present are present at the leading edge of the fibrosis. Mild patchy lymphoplasmacytic infiltrates are noted. The key histologic features of PPFE are presented in Table 1.

The differential diagnosis of PPFE includes conditions with predominant pleural and subpleural fibrosis. Usual interstitial pneumonia (UIP) in particular may share features with PPFE. UIP, however, has a different radiographic presentation and disease distribution characterized by a lower lobe predominance and peripheral honeycomb changes. Histologically, UIP is characterized by subpleural fibrosis with remodelling of lung architecture with honeycomb changes juxtaposed to areas of relatively spared parenchyma. The fibrosis of UIP is temporally heterogeneous and consists of densely collagenous fibrosis and fibroblast foci comprised loose fibroblastic tissue. Elastic fibres may be encountered but are not the predominant finding. Pleuropulmonary rheumatic disease encompasses several histopathological patterns and should be suspected when pleural effusions with pleuritis are seen. Progressive pulmonary honeycomb fibrosis in a lymphatic distribution (pleura and septa) may develop in a small percentage of sarcoidosis. In such cases, the identification of granulomas prompts the correct diagnosis. Pulmonary apical plural cap is generally an incidental finding, and is characterized by zones of eosinophilic fibrosis traversed by a network of dense, wavy birefringent elastic fibres. The features of apical cap tend to be localized and do not extend into the lung parenchyma in comparison to PPFE. When considering differential diagnosis of PPFE, one should remember that its unique feature is a fibrosis pattern with predominant elastic fibres and an upper lobe predominance.

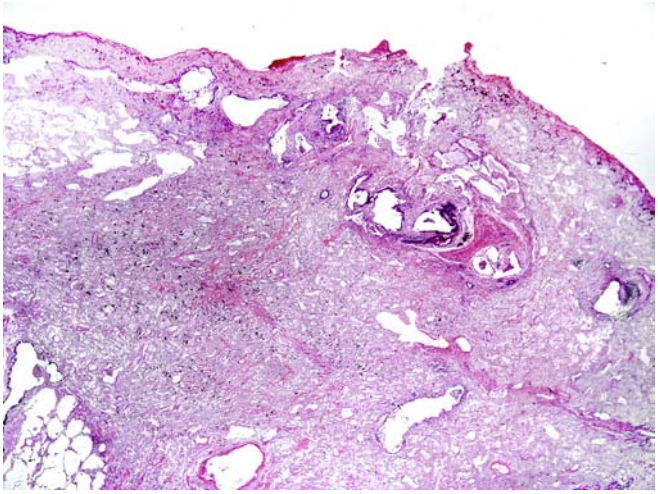

Figure 2 Pleuroparenchymal fibroelastosis (PPFE). PPFE is characterized by prominent pleural and irregular subpleural fibrosis juxtaposed to spared lung parenchyma. H&E, 200×.

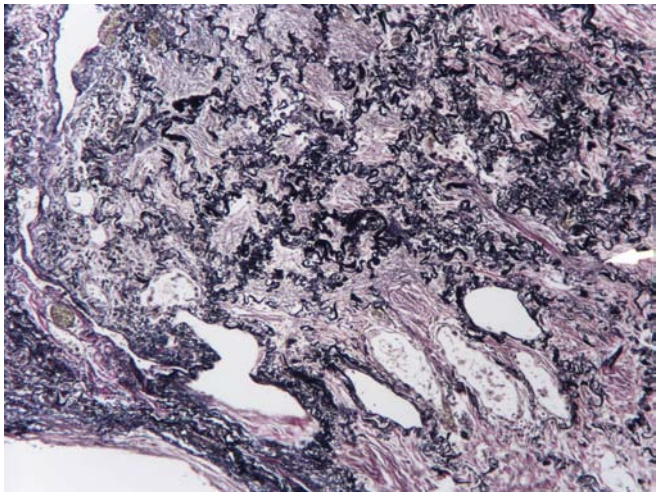

Figure 4 Pleuroparenchymal fibroelastosis (PPFE). An elastic stain highlights the abundant elastic tissue present. Elastic Van Geisen, 400×.

Histologic features of pleuroparenchymal fibroelastosis

Major features
Intense fibrosis of the visceral pleura
Prominent, homogeneous, subpleural fibroelastosis
Sparing of the parenchyma distant from the pleura
Mild, patchy lymphoplasmacytic infiltrates
Small numbers of fibroblastic foci present at the leading edge of the fibrosis
Minor features
Secondary spontaneous pneumothoraces
Persistent post-operative bronchopleural fistulae
Pertinent negatives
Lower lobe predominant disease
Temporal and spatial heterogeneous fibrosis Honeycomb changes
Granulomatous inflammation absent

Table 1

Acute fibrinous and organizing pneumonia

Acute fibrinous and organizing pneumonia (AFOP) is a pattern of acute lung injury that was first used to describe the histological findings of 17 cases retrieved from the consultation files of the Armed Forces Institute of Pathology (AFIP) which did not meet the criteria for classical patterns of acute lung injury, namely diffuse alveolar damage (DAD) or organizing pneumonia (OP).[9] The original series illustrated 10 men and 7 women with an average age of 62 years (age range 33–88 years). Patients presented with acute and subacute respiratory symptoms, including dyspnoea, cough and haemoptysis. Constitutional symptoms as fever, weakness and malaise were also noted. One third of the cases appeared to be idiopathic, while the rest had an array of possible underlying associations such as infection, collagen vascular disease, environmental or drug exposure. Most common radiographic pattern was that of diffuse bilateral basilar infiltrates. AFOP appears to have a bimodal pattern of progression and outcome. One half of the patients presented with a fulminate illness with rapid progression to death. This mortality rate overall was similar to that seen in DAD, therefore the AFOP pattern was felt to likely represent a rare or poorly described variant of latter. However, the other half of patients a subacute less fulminate course, that did not require mechanical ventilation and recovered. Defining histologic features discriminating between the two outcomes were not elucidated.

The dominant histological feature of AFOP is the presence of intra-alveolar fibrin in form of balls without formation of hyaline membranes (Figures 5 and 6). The fibrin is found in a patchy distribution but may also be relatively diffuse. Organizing pneumonia consisting of intraluminal loose connective tissue may be present with the fibroblastic tissue surrounding cores of intra-alveolar fibrin. Mild acute and chronic inflammation, type 2 pneumocyte hyperplasia and alveolar expansion with myxoid connective tissue are also seen. Marked acute inflammation typical of conventional acute pneumonia or abscess should not be present. The interstitial changes are predominately confined to areas adjacent to the intra-alveolar fibrin. The intervening lung shows minimal changes.[9] This histologic features of AFOP are summarized in Table 2.

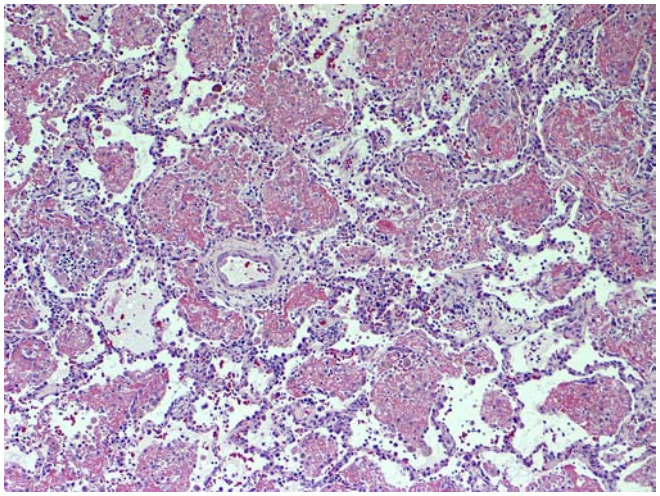

Figure 5 Acute fibrinous and organizing pneumonia (AFOP). AFOP is characterized by intra-alveolar organizing fibrin which may involve the lung in a patchy or relatively diffuse pattern. H&E, 200×.

Since the initial description of this entity, eighteen unequivocal cases with similar clinicopathological characteristics have been published. The majority of cases can be attributed to an underlying factor, such as collagen vascular disease, infection, drug toxicity and stem cell transplantation.[10–13] However, apparent idiopathic cases exist.[14] The bimodal pattern of progression and outcome can be appreciated in among these reports. Recently, Hariri et al., described the pattern of AFOP in association with acute hypersensitivity pneumonitis.[15] Therefore, like other acute lung injury patterns, particularly DAD, the potential underlying etiologies for AFOP are many and the aetiology is generally not apparent from the histology alone. Microorganism stains should be performed on all cases.

AFOP is a distinctive pattern that should be separated from the classical patterns of acute lung injury such as DAD, organizing pneumonia (OP) and eosinophilic pneumonia (EP). The histological findings of DAD vary depending on the time the lung biopsy was sample. During the exudative phase, hyaline membranes are the histological hallmarks. Thus, the lack of latter and

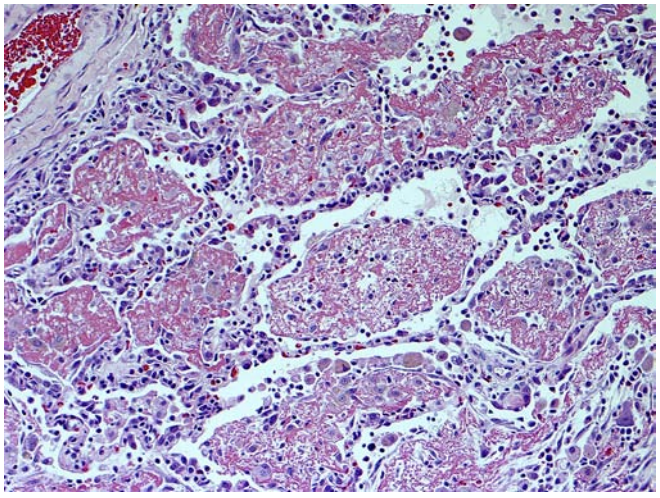

Figure 6 Acute fibrinous and organizing pneumonia (AFOP). At higher power, the fibrin is organized into balls as opposed to forming hyaline membranes. Eosinophils are inconspicuous or absent. H&E, 400×.

Histologic features of acute fibrinous and organizing pneumonia

Major features
Dominant finding of organizing intra-alveolar fibrin
Organizing pneumonia
Patchy distribution
Minor features
Associated interstitial changes
Acute and/or chronic inflammation
Type 2 pneumocyte hyperplasia
Alveolar septal expansion with myxoid connective tissue
Interstitial inflammation and expansion typically mild to moderate
Interstitial changes primarily confined to areas adjacent to intra-alveolar fibrin with the intervening lung showing only minimal changes
Pertinent negatives
Hyaline membranes NOT observed
Eosinophils inconspicuous or absent
Extensive bronchopneumonia and/or abscess formation absent
Granulomatous inflammation absent

Table 2

the patchy nature of the process exclude DAD. However, focal areas of intra-alveolar organizing fibrin can be seen in otherwise classic cases of DAD. Patchy accumulations of intra-alveolar organizing fibroblastic tissue centred on bronchioles are the dominant finding in OP, whereas in AFOP, organizing fibrin balls which may be surrounded by organizing loose connective tissue are the dominant finding is AFOP. EP is characterized by intra-alveolar accumulation of fibrin and macrophages admixed with eosinophils. Inconspicuous or absent intra-alveolar eosinophils and macrophages negates EP. However, partially treated EP lacks eosinophils and may be a diagnostic consideration if a biopsy is obtained after steroid administration. In this case, the distinction between EP and AFOP can usually be made clinically by the presence of peripheral blood eosinophilia of the former. Importantly, a diagnosis of AFOP should be only made in on large biopsy specimens with appropriate clinical information given that intra-alveolar organizing fibrin may occur as a non-specific finding either adjacent to or as a component of an unrelated entity.

Interstitial pneumonia with bronchiolocentric patterns

Since 2002, different groups have described series of patients with clinically significant interstitial lung disease with a unique histological pattern of inflammation and fibrosis centred around the bronchioles. Based on clinical, radiographic and pathological differences, each group claims that their series represents a distinct clinicopathological condition. However, they may represent a morphological continuum of the same bronchiolocentric process.

In 2002, Yousem and Dacic reported a series of eight women and two men with a mean age of 46.7 years presenting with a history of insidious onset respiratory complaints.[16] Chest radiographs showed bilateral predominately lower lobe interstitial infiltrates and high-resolution CT scans confirmed those findings. The patients' pulmonary function test demonstrated a restrictive lung disease. No patient had known causes of interstitial lung disease. At mean follow-up (48.2 months), 33% of patients were dead of disease and 56% alive with persistent or progressive disease. Histologically, the most striking finding was a centrilobular inflammatory process with small airway fibrosis and considerable chronic inflammation that radiates into the interstitium of the distal acinus in a patchy fashion. Granulomas were absent and bronchiolar metaplasia accompanied the fibroinflammatory process. The term used to describe these findings was idiopathic bronchiolocentric interstitial pneumonia.

Two years later, Churg et al., used the term airway-centred interstitial fibrosis to describe the histological findings of 12 patients with a 2:1 female predominance and mean age of 54 years[17] All patients presented with chronic cough and progressive dyspnoea and restrictive pulmonary function test. The majority of the patients had various environmental of occupational exposures. Despite bronchodilators and corticosteroids, four patients died and one patient presented progressive clinical course. The predominant X-ray pattern was diffuse reticulonodular infiltrates in the central lungs fields with thickening of the bronchial walls. Peribronchovascular fibrosis and interstitial thickening evident seen in CT scans. The key pathological finding was marked interstitial fibrosis centred around bronchioles with peribronchial fibrosis extending around and often linking other involved bronchioles (Figure 7). Marked smooth muscle hyperplasia, bronchiolar metaplasia and sparse interstitial inflammation were evident (Figure 8).[17]

Fukuoka et al., followed with a report of 15 patients with clinical evidence of interstitial lung disease. In this series there was a female predominance and mean age was 56.7 years.[18] About half of the patients had either an occupational exposure or evidence of a collagen vascular disease. The pulmonary function test results were variable, however a restrictive pattern predominated. Mosaic attenuation and lobular air trapping were the characteristic CT scan findings. All patients were alive with after a mean follow-up 2.4 years. Interestingly, the sole histological finding was thickened bronchioles and peribronchiolar

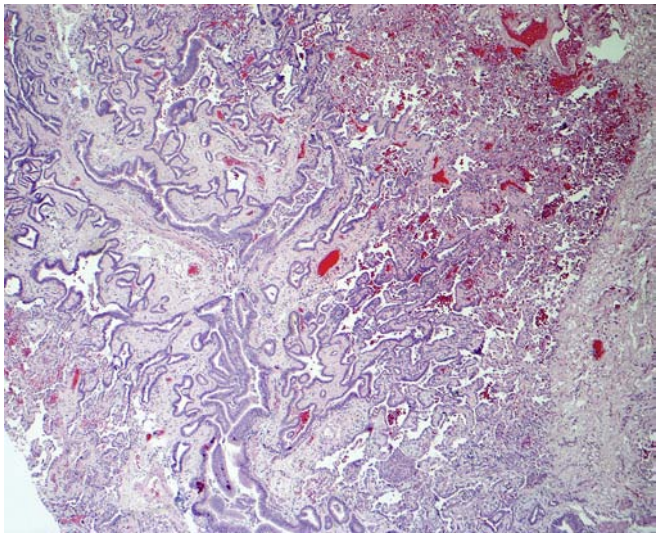

Figure 7 Airway-centered/bronchiolocentric interstitial fibrosis is characterized by prominent bronchiolocentric fibrosis with bronchiolar metaplasia which may link adjacent airways. H&E, 100×.

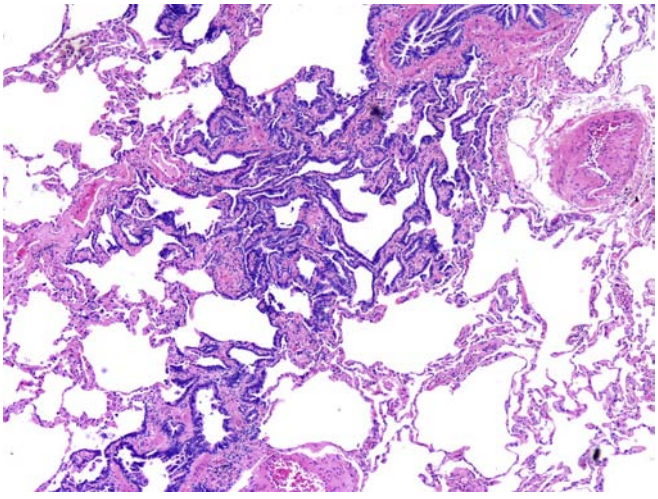

Figure 8 At higher power, the epithelium in the lesions of airway-centered/bronchiolocentric interstitial fibrosis shows characteristic features of respiratory epithelium. H&E, 100×.

alveolar walls lined by bronchiolar epithelium. The surrounding parenchyma was unremarkable and inflammation, pneumocyte hyperplasia and fibrosis were absent. Since peribronchiolar metaplasia was the only histological explanation for the symptoms, the authors coined the term peribronchiolar metaplasia-related interstitial lung disease.[18]

Chronic hypersensitivity pneumonitis was considered as the most important differential diagnosis in the three series. However, all cases lacked the histological features of poorly formed granulomas typical of hypersensitivity pneumonitis. In spite of the differing nomenclature, it is likely that these three series of cases represent the same or similar processes or possibly exemplify a spectrum. The differing clinical outcome in the Fukuoka series is unclear, but is potentially due to the inclusion of cases with less extensive disease and/or more patients with known underlying disorders in contrast to the other two series. At this time it is unclear whether these series of airway centred disease represent a distinct interstitial lung disease or a variant of other entities. The relationship of these cases to hypersensitivity pneumonitis warrants further study and the reason for the female predominance and generally poor prognosis remains unclear.

Conclusion

PPFE, AFOP and airway-centred fibrosis are among the most frequently reported patterns of interstitial lung disease not included in the 2002 ATS/ERS classification of idiopathic interstitial pneumonias. While PPFE appears to be a distinct clinicopathologic entity, AFOP appears to more likely represent a pattern of acute lung injury associated with a variety of potential etiologies rather than a distinct entity. Similarly, the relationship of airway centred fibrosis to other lung disease requires further study. Further refinement of all three entities is likely to occur as the body of literature expands. From a practical standpoint, knowledge of these three emerging diseases is important for practicing pathologists in order to understand the significance of the findings, discriminate them from other defined categories of ILD and to facilitate further studies of these problematic areas. ◆

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Practice points

- Pleuroparenchymal fibroelastosis (PPFE) is characterized by pleural and subpleural fibrosis with prominent elastic fibres
- PPFE is an upper lobe predominant disease, whereas usual interstitial pneumonia is a lower lobe predominant disease
- Patients with PPFE may experience air leak or persistent pneumothorax following surgery
- Acute fibrinous and organizing pneumonia (AFOP) is a histologic pattern of acute lung injury characterized by intra-alveolar organizing fibrin balls and lacking classic hyaline membranes or significant eosinophils
- The histologic pattern of AFOP may be associated with a variety of potential underlying etiologies, similar to other forms of acute lung injury such as diffuse alveolar damage
- Organizing fibrin may occur as a secondary finding in association with an unrelated entity so a definitive diagnosis of AFOP should be made preferentially on large/wedge biopsy specimens
- Airway-centered/bronchiolocentric interstitial fibrosis as described in three separate series is characterized by fairly extensive peribronchiolar metaplasia without giant cells or granulomas
- Airway-centered/bronchiolocentric interstitial fibrosis has shown a striking female predominance and a generally poor prognosis

Research directions

- Pleuroparenchymal fibroelastosis appears to represent a distinct interstitial lung disease however further evaluation of underlying etiologies and pathogenesis are needed
- Further investigation into the bimodal distribution of behaviour and outcome in AFOP is needed
- Further investigation into the relationship of AFOP to other forms of acute lung injury is needed
- Further investigation into the relationship of airway-centered/bronchiolocentric interstitial fibrosis to other lung diseases, particularly hypersensitivity pneumonitis is needed
- Investigation as to why airway-centered/bronchiolocentric interstitial fibrosis has a female predominance and a poor prognosis is needed
- Investigation into an optimal approach to treatment is needed for PPFE, AFOP and airway-centered/bronchiolocentric fibrosis