Pleuroparenchymal Fibroelastosis of the Lung

A Review

Shaun Kian Hong Cheng, MB ChB; Khoon Leong Chuah, MBBS, FRCPA

In 1992, the entity of idiopathic pulmonary upper lobe fibrosis was described by Amitani et al1 in Japan, and this disease shows a predilection for upper lobe involvement where pleural fibrosis and adjacent lung parenchymal fibroelastosis are present. Subsequently, in 2004 Frankel et al2 applied the term pleuroparenchymal fibroelastosis (PPFE) to describe a similar fibrosing process affecting the lung, which was then defined as a “unique idiopathic pleuroparenchymal lung disease that is characterized by upper lobe radiographic predominance and pathologic findings that do not fit with any currently defined interstitial pneumonias.” It is now accepted that pulmonary upper lobe fibrosis and PPFE represent the same entity,3,4 and the morphologic changes seen in PPFE may have been noted as early as the 1960s.5 The cause of PPFE is not clearly known, and PPFE has been described in association with drugs, chronic hypersensitivity pneumonia, collagen vascular disease, infections, and bone marrow transplantsations.5 Many cases have no known associations and are regarded as idiopathic, for which the term idiopathic PPFE (IPPFE) is applied.6 The latest update of international multidisciplinary classification of idiopathic interstitial pneumonia in 2013 includes idiopathic PPFE in the section of rare idiopathic interstitial pneumonia.6 However, although PPFE was initially thought to represent a specific entity and was originally believed to be rare, current literature suggests that PPFE may not be a specific entity and that it is likely to represent a form of chronic lung injury seen in association with a variety of clinicopathologic conditions.7 In this review, we present the clinical, radiologic, and pathologic findings associated with PPFE in light of current understanding of the disease. Recent studies implicated that PPFE may not be as uncommon as claimed. The various differential diagnoses and implications of diagnosing PPFE are discussed.


In the initial description of PPFE by Amitani et al1 in the Japanese literature, 13 patients were affected by an upper lobe localized pulmonary fibrosis, which was then followed by several descriptions of the disease in the Japanese-language literature. The first documented description in the English-language literature appeared in 2004 by Frankel et al,2 and it included 5 patients. Subsequently, von der Thüsen4 summarized the information gleaned from properly documented case series, which were mostly from the English literature. With that information as well as information from recent publications,5,7,8 there have been about 120 cases reported in the world literature. The age range of the patients is from 13 to 87 years. The mean age is 53.0 years. Two peaks are noted, the smaller one occurring around the third decade of life and the larger one occurring at the sixth decade. The male to female ratio is 37:45, indicating an almost total parity of sex (45% of the patients are male and the rest are female). In the younger peak, there is a slight female predominance, the predominance becoming more striking in the cohort of patients who have not undergone any form of tissue transplantation.3 This implies that there is predilection of PPFE for the male sex in this younger age peak in the cohort of patients who underwent tissue transplantation. There is no significant association between smoking and the occurrence of PPFE,9 although a smoking history may be elicited in up to 29% of patients. The most common presenting complaints are those of breathlessness, cough, weight loss, pneumothorax, and...
Figure 1. Low-power view showing dense pleural fibrosis associated with subjacent intra-alveolar fibrosis and accompanying septal elastosis, the latter being better seen on elastic Van Gieson stain. Note the lack of fibrosing process away from the subpleural region (hematoxylin-eosin, original magnification ×20).

Figure 2. Scanning-power view revealing the presence of marked alveolar septal elastosis in the subpleural region, with partial extension into the connective tissue septum. Note the dense pleural fibrosis and the lack of elastosis in the lung parenchyma away from the subpleural region (elastic Van Gieson stain, original magnification ×20).

Figure 3. Medium-power view in the subpleural fibroelastotic region revealing elastic fiber deposition in relation to the alveolar walls, with intervening collagen deposition (elastic Van Gieson stain, original magnification ×100).

Figure 4. Note the presence of obliterative bronchiolitis in a case of pleuroparenchymal fibroelastosis associated with bone marrow transplantation (hematoxylin-eosin, original magnification ×200).
often slender, and a restrictive ventilatory impairment. On auscultation, respiratory crackles are not common. Clubbed fingers are unusual for patients with PPFE. Bullae and large cysts in the upper fields can be identified.9 Bronchiectasis extending to adjacent lobes with multiple this is associated with subjacent fibrosis and elevated hilar changes in the middle and lower lobes.9 However, with disease progression,4 pleuroparenchymal thickening, with the thickness ranging from 4 to 15 mm, can be seen, and this is associated with subjacent fibrosis and elevated hilar shadows. In advanced stage, fibrotic opacities with traction bronchiectasis extending to adjacent lobes with multiple bullae and large cysts in the upper fields can be identified.9 In addition, interstitial lung disease patterns can be appreciated in the other parts of the lung, such as the lower lobes, and the patterns described include usual interstitial pneumonia (UIP) pattern, nonspecific interstitial pneumonia (NSIP) pattern, diffuse PPFE, and others.4,5

In 2012, Reddy et al4 proposed criteria on radiology for the diagnosis of PPFE. A definitive diagnosis of PPFE is made when a high-resolution computed tomography scan discloses the presence of upper lobe pleural thickening and subpleural fibrosis associated with less marked or absent lower lobe involvement. A consistent with PPFE diagnosis is rendered when there is upper lobe pleural thickening and subpleural fibrosis that are not concentrated on the upper lobe (ie, present elsewhere) or there is the presence of coexistent disease elsewhere.

### Radiologic Findings

On chest x-ray,9 the early changes described include bilateral irregular thickening of the apical portions of the lungs in an otherwise apparently normal lung x-ray. Bilateral hilar opacities may also present as the disease progresses. With time, reticular and nodular opacities may appear in the upper lung fields bilaterally, being associated with further accentuation of the hilar opacities. Lateral view of the chest x-ray may demonstrate narrowed anterior-posterior dimensions.

In the initial stages, high-resolution computed tomography scan of the lung may disclose subpleural nodular and reticular opacities in the apical region, with usually minimal changes in the middle and lower lobes.9 However, with disease progression, pleuroparenchymal thickening, with the thickness ranging from 4 to 15 mm, can be seen, and this is associated with subjacent fibrosis and elevated hilar shadows. In advanced stage, fibrotic opacities with traction bronchiectasis extending to adjacent lobes with multiple bullae and large cysts in the upper fields can be identified.9 In addition, interstitial lung disease patterns can be appreciated in the other parts of the lung, such as the lower lobes, and the patterns described include usual interstitial pneumonia (UIP) pattern, nonspecific interstitial pneumonia (NSIP) pattern, diffuse PPFE, and others.4,5

In 2012, Reddy et al4 proposed criteria on radiology for the diagnosis of PPFE. A definitive diagnosis of PPFE is made when a high-resolution computed tomography scan discloses the presence of upper lobe pleural thickening and subpleural fibrosis associated with less marked or absent lower lobe involvement. A consistent with PPFE diagnosis is rendered when there is upper lobe pleural thickening and subpleural fibrosis that are not concentrated on the upper lobe (ie, present elsewhere) or there is the presence of coexistent disease elsewhere.

### Pathologic Findings

It must be emphasized that a conclusive diagnosis of PPFE requires a multidisciplinary approach with input involving the clinician, radiologist, and pathologist.4,5 Nonetheless, in terms of histological diagnosis, Kusagaya et al10 using a series of studies defined the criteria for the diagnosis of PPFE. Subsequently, Reddy et al4 added additional criteria for the diagnosis of PPFE. A definite diagnosis of PPFE is made based on the constellation features of upper zone fibrosis of the visceral pleura (described as intense by Kusagaya et al10; Figures 1 and 2); prominent homogenous subpleural intra-alveolar fibrosis with alveolar septal elastosis (Figure 3); sparing of the parenchyma away from the pleura (Figure 1); scant, patchy lymphoplasmacytic infiltration; and small numbers, at the very most, of fibroblastic foci.

A diagnosis of consistent with PPFE3 is made when the above-described intra-alveolar fibrosis with alveolar septal elastosis is present and is without significant pleural fibrosis, or is not predominantly beneath the pleura or not in the upper lobe biopsy.

In addition to the above pathologies, other pathologies that can be associated with PPFE may be present. For instance, in the setting of bone marrow transplantation,3 obliterative bronchiolitis (Figure 4) as a manifestation of chronic graft-versus-host disease may be observed.

### Pathologic Differential Diagnoses

In terms of differential diagnoses of PPFE, interstitial lung disease with accompanying fibrosis may be confused with it, and the Table summarizes the main differential diagnoses. In view of the predominant pleural and subpleural fibrosis in PPFE, the main histologic differential diagnosis would be that of UIP pattern,3 whether it is in the idiopathic form (ie, idiopathic pulmonary fibrosis) or secondary to other known causes, such as chronic hypersensitivity pneumonia, drugs, etc.6 Generally, UIP pattern is associated with extensive remodeling of the lung parenchyma with the eventuality of end-stage fibrosis and honeycomb change, resulting in the effacement of the original parenchymal architecture (Figure 5). This feature is not characteristic of PPFE, because in PPFE there is a homogenous intra-alveolar fibrosis with generally preserved alveolar structure and even thickening of the alveolar structures through the process of elastic fiber deposition. In addition, the temporal heterogeneity of the fibrosing process, with the presence of fibroblastic foci adjacent to areas of established fibrosis and interspersed areas of lung parenchyma unaffected by the fibrosing process (Figure 5), is not consistent with PPFE. In contrast to UIP pattern, fibroblastic foci in PPFE should be sparse. In the idiopathic form of UIP or idiopathic pulmonary fibrosis, the disease characteristically involves the lower lobes of the lung in the initial stages, whereas classical PPFE typically affects the upper lobes. However, UIP pattern can be seen in chronic hypersensitivity pneumonia, and in such a setting these changes may be seen in the upper lobes.6 In such a situation, careful examination of the fibrosing pattern as described above, as well as correlation with the clinical and

---

**Figure 5.** Medium-power view of an example of usual interstitial pneumonia with honeycomb change. Note the proliferation of fibrous tissue and smooth muscles from the subpleural region and extending into the lung parenchyma, resulting in remodeling (hematoxylin-eosin, original magnification ×200).

**Figure 6.** Apical cap showing resemblance to pleuroparenchymal fibroelastosis (hematoxylin-eosin, original magnification ×40).
radiologic findings, would be pivotal in establishing the correct diagnosis. In problematic cases, performance elastic fiber stain, such as elastic Van Gieson stain, would be useful because the stain demonstrates a more sparse, fragmented, and disorganized elastic fiber distribution in the areas of fibrosis in UIP compared with more marked and established elastic fiber deposition in relation to the alveolar walls in PPFE, which is described as containing at least twice as much elastin compared with UIP. Recently, lesion with combined patterns of UIP and PPFE has been noted; in such an instance Oda et al proposed labeling the lesion as PPFE, and this entity with combined patterns is associated with a much more dismal outcome compared with either idiopathic pulmonary fibrosis or PPFE alone.

Although NSIP has been suggested as a differential diagnosis, NSIP shows a more diffuse lung parenchymal involvement not associated with pleural fibrosis (unless in the setting of collagen vascular disease–related NSIP changes). Moreover, an interstitial process (be it inflammation or fibrosis or both) is characteristic of NSIP, whereas in PPFE the process involves elastin deposition in relation to the alveolar walls, with intervening collagen deposition.

In view of both pleural and parenchymal fibrosis, asbestososis, advanced fibrosing sarcoidosis, and radiation/drug-induced lung disease are possible differential diagnoses. However, none of these differential diagnoses are associated with intra-alveolar fibrosis and septal elastosis as seen in PPFE. Furthermore, clinical correlation will point to the correct diagnosis. Nonetheless, a confident diagnosis of PPFE should only be made in the absence of a relevant occupational exposure history to asbestos as well as the lack of significant numbers of asbestos bodies and sarcoid-type granulomas on histology of a surgical lung excision biopsy sample.

The apical caps representing a localized area of subpleural fibrosis occurring predominantly at the apices of the upper lobes can mimic PPFE (Figure 6). Although PPFE affects younger, nonsmoking individuals and is associated with a poor clinical outcome generally, apical caps have a predilection for older individuals around age 65 years who are smokers, and the disease is often nonprogressive, without causing symptoms in the patients. In addition, apical caps typically occur as a localized mass lesion in the apical region of the upper lobes, whereas PPFE may show a more diffuse subpleural distribution affecting basal portions of the upper lobe as well as other lobes, despite a preference for the upper lobes of the lung. Besides, sclerotic pleural plaques with extensive alveolar collapse, which may be seen in association with apical caps, are not seen in PPFE.

In the event that there is progression to chronic fibrosis, the chronic fibrosis phase of organizing pneumonia may simulate PPFE by virtue of incorporation of the alveolar myofibroblastic proliferation into alveolar septa and irregular interstitial fibrosis. However, in this instance the fibrosis is patchy and haphazard in distribution, frequently around the peribronchiolar regions compared with the predominant subpleural and paraseptal contiguous areas of fibrosis of PPFE, which tends to be diffuse and homogenous in the intra-alveolar region associated with septal elastosis.

**RECENT UPDATES REGARDING PPFE**

Although PPFE is thought to be a rare disease, recent studies reveal that the entity may not be as rare as once thought. Recently, Nakatani et al, in a series of consecutive patients undergoing surgical lung biopsy for interstitial lung disease, reported about 6% of patients having features of PPFE after multidisciplinary panel discussion. In addition, coexistent interstitial lung disease apart from fibroelastosis was present in about 75% of PPFE, a figure higher than the figure of 43% quoted by Reddy et al. Similarly, Watanabe et al noted that 8 of 9 cases with histology-proven PPFE displayed lower lobe lesions on high-resolution computed tomography. Although these were not examined histologically, the coexistence of interstitial lung disease in other parts of the lung may be more frequent than once presumed.

Significantly, Rosenbaum et al attribute PPFE as being an underrecognized or underreported entity rather than being rare. In their series, they encountered 5 cases of PPFE within a span of less than 2 years in a single institution. In addition, they noted the presence of diffuse parenchymal fibroelastosis involving both upper and lower lobes of the lung in all of their cases, suggesting that this disease may be more diffuse than once thought. As such, they opined that PPFE may represent a pattern of chronic lung injury rather than a specific entity and that this form of chronic injury can coexist with a variety of clinicoradiologic conditions, a hypothesis similar to that raised by Hirota et al. Hence, they proposed a set of diagnostic criteria for a diagnosis of PPFE, the criteria comprising the presence of multilobar subpleural and/or centrilobular fibrous interstitial pneumonia characterized by more than 80% proliferation of elastic fibers in the nonatelectatic lung in association with absent to scant chronic inflammation and no or rare granulomas.

**CONCLUSIONS**

In summary, PPFE represents a distinct pattern of pulmonary fibrosis that may not be as rare as once perceived and may not only involve the upper lobe. Although the idiopathic form of PPFE is included in the latest classification scheme of idiopathic interstitial pneumonia, the changes may represent a form of chronic lung injury rather being a specific disease. Its pathogenesis remains unclear, although it is proposed that the starting point may involve an element of acute lung injury or interstitial inflammation. In fact, areas of diffuse alveolar damage in patients with restrictive allograft syndrome after lung transplantation with ensuing PPFE appear to support this hypothesis. Nonetheless, whatever the pathogenesis may be, it remains clear that once PPFE pattern is identified, the disease is often rapidly progressive, with frequent complication of pneumothorax and poor prognosis. No effective therapy is available at this juncture, and hence the importance of diagnosing this entity in conjunction with clinical, radiologic, and pathologic findings.
References