

## Two Different Aspects of Pleuroparenchymal Fibroelastosis: A Disease of Pulmonary Fibrosis, and of the Chest Wall

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### Abstract

The essential histology of PPFE is subpleural fibroelastosis in the upper lobes, which is different from that of usual interstitial pneumonia (UIP). However, PPFE might share a pathologic process leading to end-stage fibrosis with UIP: it might have an antecedent inflammatory or acute lung injury process prior to the development of the thick subpleural bands of fibroelastosis, possibly corresponding to a honeycomb lung in UIP. Fibroblastic foci are found in the leading edge of fibroelastosis, and acute exacerbation occurs in patients with PPFE. The numbers of fibroblastic foci might be correlated with acute exacerbation or poor prognosis in patients with PPFE, as in those with UIP.

Flattened thoracic cage and increased ratio of reserve volume/total lung capacity (RV/TLC) are distinctive characteristics seen in patients with PPFE, but not seen in those with UIP. Flattened thoracic cage that occurs secondary to the fibrotic shrinkage of bilateral upper lobes further decreases the distensibility of thoracic cage, restricting the expansion of the lungs and enhancing the atelectatic shrinkage of upper lobes. Such pathophysiology is similar to that of kyphoscoliosis and ankylosing spondylitis. Therapeutic interventions including the use of steroids and antifibrotic agents for patients with PPFE have disappointing results to date. Chest wall mechanics need to be given more attention in the treatment of patients with PPFE.

Heterogeneous clinical background and clinical course of PPFE remind us that PPFE might need to be named "PPFE syndrome" rather than a single disease.

### Introduction

In 2004, Frankel et al. reported five cases with upper-lobe-dominant pulmonary fibrosis that progressed gradually to respiratory insufficiency [1]. As the histology comprised subpleural elastosis, intraalveolar collagenous fibrosis with septal elastosis and collagenous thickening of the visceral pleura, they named this unique disorder pleuroparenchymal fibroelastosis (PPFE). In 2013, PPFE of unknown etiology (idiopathic PPFE, IPPFE) appeared as one of the forms of idiopathic interstitial pneumonias (IIPs) in the international classification of these diseases [2]. Since then, there have been increasing numbers of papers on PPFE. Although IPPFE is categorized as a rare form of IIP [2], it might not be as rare as reported previously [3]. IPPFE, as a form of chronic fibrosing interstitial pneumonia, has a similar clinical course to that of idiopathic pulmonary fibrosis (IPF), and could be confused with IPF in clinical practice.

PPFE is a unique form of pulmonary fibrosis. Upper-lobe-predominant fibrosis, a histology of elastofibrosis in the subpleural areas, a flattened thoracic cage [4] with a thin body build, and restrictive ventilatory impairment associated with increased residual volume/total lung capacity (RV/TLC) [5,6], are observed in subjects with PPFE, but not in those with IPF.

This review article describes the histopathology and pathophysiology of PPFE and will mainly focus on the flattened thoracic cage, because this deformity is closely related to the characteristic pathophysiology of PPFE and is not seen in other chronic fibrosing interstitial pneumonias such as IPF.

### PPFE as a form of Chronic Fibrosing Interstitial Pneumonia with Unique Pathology

The histopathological features of PPFE are quite different from those of usual interstitial pneumonia (UIP). The simplest but most important difference that discriminates PPFE from UIP is the anatomical distribution of the lesions: upper lobe predominance in PPFE and lower lobe predominance in UIP. The essential histological findings of PPFE are subpleural elastosis with collapsed alveoli and intraalveolar collagenous fibrosis, but without architectural distortion. The essential histological findings of UIP are 1) patchy fibrosis with temporal variegation: a collagenous fibrosis that is inactive and a fibroblastic focus that is active ongoing fibrosis, and 2) architectural distortion expressed as interstitial scars and honeycomb changes.

Although subpleural elastofibrosis has histology inconsistent with that of UIP, PPFE might share a pathologic process with UIP that leads to end-stage fibrosis. In 2013, Ofek et al. demonstrated a temporal sequence of diffuse alveolar damage followed by the development of PPFE in their analysis of 493 patients who underwent lung transplantation [7]. We demonstrated that not only transplantation-associated PPFE but also other forms of PPFE had an antecedent inflammatory or acute lung injury process prior to the development of the thick subpleural bands of fibroelastosis and the end-stage fibrosis seen in PPFE, possibly corresponding to a honeycomb lung in cases of UIP. This was done using first and second biopsies, or on biopsy and autopsy specimens from four patients with PPFE as the final diagnosis [8].

Fibroblastic foci representing sites of acute lung injury [9] are usually seen in cases of UIP. Quantitative scoring of such foci has been reported to be a prognostic factor for UIP [10,11]. However, it should be noted that such foci are also seen in cases of PPFE. Acute exacerbation, a major cause of death in those with IPF, has also been reported to be a cause of death in those with PPFE [5,6,12].

What do these findings mean? The characteristic component of fibrosis in cases of PPFE is elastosis, compared with collagenous fibrosis in cases of UIP. However, not only elastosis but also collagenous fibrosis is observed in patients with PPFE. Fibroblastic foci are found especially at the leading edge of intraalveolar collagenous fibrosis with septal elastosis [5], although they are not found as frequently as in cases of UIP. The numbers of fibroblastic foci might be correlated with acute exacerbation or a poor prognosis in patients with PPFE, as in those with UIP. PPFE is a chronic fibrosing interstitial pneumonia, and the median survival of patients with this has been reported as 11 years [13] or 7.3 years [14], which seems to be better than for IPF/UIP.

As in cases of PPFE, not only collagenous fibrosis but also elastosis can be observed in cases of UIP. Elastosis is not exclusively found in those with PPFE. Increased deposition of elastic fibers is also present in cases of UIP [15,16]. However, the deposition of elastic fibers has been largely ignored in studies of pulmonary remodeling in cases of human interstitial lung diseases [16]. In certain clinical situations, the boundary between PPFE and IPF is ambiguous. We observed that six of 21 patients with histologically proven PPFE had equal involvement of the upper and lower lung fields, as seen by chest computed tomography [14].

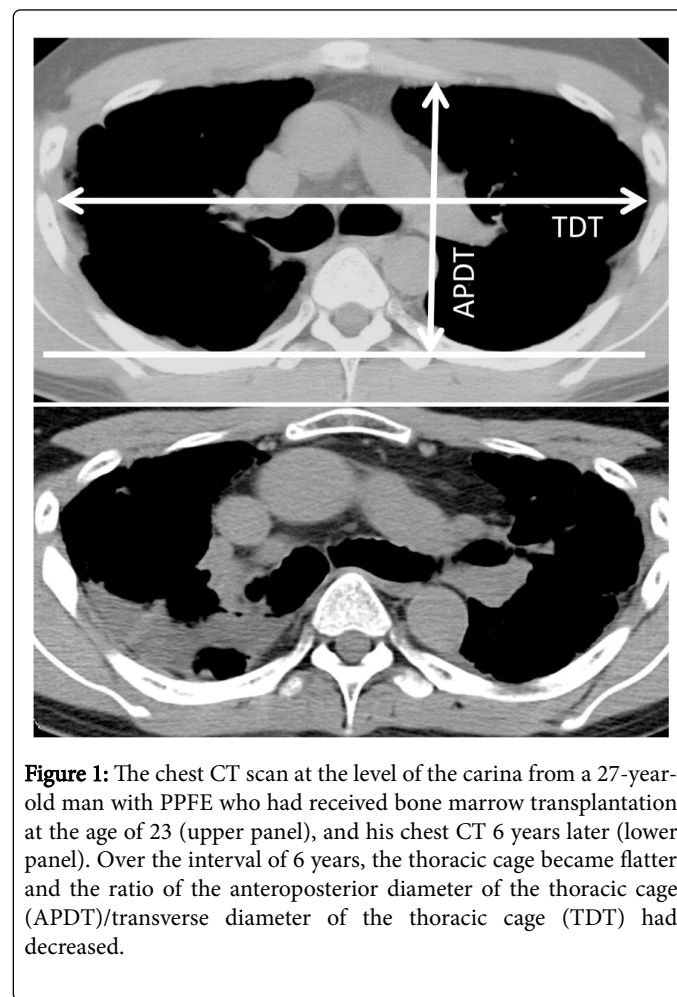
Elastic fiber staining could bring additional information for the histology of upper lung fields in patients with clinically diagnosed IPF and that of lower lung fields in patients with clinically diagnosed PPFE. There might be a continuous spectrum between idiopathic PPFE and IPF/UIP.

### Flattened Thoracic Cage and Distinctive Physiologic Characteristics

Not all, but many patients with PPFE have a flattened thoracic cage with reduced anterior-posterior diameter [4,12,13,17]. We observed that the thoracic cage in patients with PPFE became flatter as the upper lobe fibrosis progressed (Figure 1) [4]. As such anatomy is observed not only in patients with IPPFE, but also in those with transplantation-associated PPFE, it is likely that this deformity might not be congenital, but acquired. Therefore, a flattened thoracic cage might be a deformity that arises secondary to fibrotic shrinkage of the upper lung lobes, although some investigators claim that a flattened thoracic cage is the initial event of the disease and that the upper lobe fibrosis is secondary to the deformity, especially in the pure form of upper lobe fibrosis without lower lobe lesions: namely Amitani disease [17].

We also showed that an increased RV/TLC ratio was inversely correlated with the forced vital capacity (FVC) [14]; thus, an increase in this ratio can appear in patients with advanced stages of PPFE. These findings suggest that the development of a flattened thoracic cage is closely associated with a decreased FVC and increased RV/TLC ratio in those with PPFE. Some mechanisms have been considered as explanations for the increased RV/TLC ratio: compensatory overinflation of the lower lung lobes caused by fibrotic collapse of the upper lobes; restricted mobility of well-preserved lower lobes in the

deformed thoracic cage, and; a diminished strength of the respiratory muscles could be responsible [14].



**Figure 1:** The chest CT scan at the level of the carina from a 27-year-old man with PPFE who had received bone marrow transplantation at the age of 23 (upper panel), and his chest CT 6 years later (lower panel). Over the interval of 6 years, the thoracic cage became flatter and the ratio of the anteroposterior diameter of the thoracic cage (APDT)/transverse diameter of the thoracic cage (TDT) had decreased.

Patients with kyphoscoliosis have severe restrictive impairment and respiratory failure, which are attributable to the deformity of their thoracic cage. The pathophysiology of PPFE is similar to that of kyphoscoliosis by sharing marked decreases in the TLC and FVC, but with a preserved RV [18]. However, the pulmonary parenchyma in patients with kyphoscoliosis is basically intact with the exception of atelectasis, probably resulting from compression by the deformed thoracic cage.

Ankylosing spondylitis is another example of a pathophysiological defect that is similar to that of PPFE. In affected patients, the main lesions of the disease are in the vertebrae, with unknown inflammatory processes making the spine less flexible, resulting in impaired expansion of the thoracic cage. It is possible that the resulting defective ventilation induces similar pathophysiological processes as listed above. However, unlike those with kyphoscoliosis, patients with ankylosing spondylitis have upper lobe fibrosis as well as atelectasis in the upper lobes of the lungs [19,20], which could be termed “secondary PPFE”.

Therapeutic interventions including the use of steroids and antifibrotic agents for patients with PPFE have disappointing results to date [6,13,21]. The American Thoracic Society and European Respiratory Society have stated officially that IPPFE is a rare subset of IIPs [2]. However, we should note that PPFE is not only a chronic

fibrosing interstitial pneumonia, but is also a disorder of the chest wall with deformity: the flattened thoracic cage that occurs secondary to fibrotic shrinkage of both upper lobes could further enhance upper lobe fibrosis caused by decreased distensibility of the thoracic cage and subsequent ventilatory impairment. Subpleural fibroelastosis is an essential feature of the histopathology in cases of PPFE, as stated above. However, PPFE has another peculiar characteristic: the collapsed alveoli are embedded in a mass of subpleural fibroelastosis. It is not surprising that both lungs confined in the narrowed thoracic cage fail to expand and remain atelectatic.

Pneumothorax is a complication in patients with PPFE as well as in those with IPF. However, it occurs more frequently in patients with PPFE than in those with IPF, sometimes repeatedly or bilaterally. Our study demonstrated that about 40% of patients experienced pneumothorax [14]. A ruptured bulla seems to be the major cause of pneumothorax in both UIP and PPFE, because bullae often develop in the course of both diseases. However, this does not fully explain the mechanism of the more frequent occurrence of pneumothorax in PPFE. The flattened thoracic cage might be involved in the pathogenesis of the pneumothorax: during inspiration, lungs are forced to expand in the narrowed thoracic space created by the flattened thoracic cage, which leads to the development of shear stresses in the lung parenchyma rubbing against the bony thorax that could tear vulnerable bullae.

Given the evidence of the pathophysiology of PPFE mentioned above, we might have another therapeutic option to an antifibrotic strategy. Chest wall mechanics need to be given more attention in the treatment of patients with PPFE. In patients with PPFE, respiratory failure progresses concurrently with the progression of the flattened thoracic cage. To avoid the vicious cycle between upper-lobe fibrosis and flattened thoracic cage, patients with PPFE could be registered as candidates for lung transplantation at an earlier stage of the disease. The development of the deformity of the thorax will restrict the volume of transplanted lung in recipients and make it difficult to select donors appropriate for the size of the recipient's thorax, in addition to the technical difficulty of lung transplantation in such patients.

## Heterogeneous Clinical Background and Clinical Course of PPFE

The disease progression in patients with PPFE is heterogeneous. Some cases are rapidly progressive [21], but others progress slowly within 10-20 years of the initial clinical presentation [14,17]. Various underlying conditions or comorbidities in patients with PPFE have been reported. These include 1) autoimmune features with or without collagen vascular disease [14,21,22]; 2) a hereditary disposition [1,6,12,17,22]; 3) environmental or occupational exposures, including to dust [14,22]; 4) treatment with chemotherapy agents such as cyclophosphamide [1,6,23]; 5) irradiation for the treatment of malignancies [1,14]; and 6) repeated infections. There have been reports of PPFE patients with disease complicated by chronic pulmonary disease caused by *Mycobacterium avium* intracellulare complex (MAC) [14,21] and by aspergillus infection [22-26]. Reddy et al. speculated that repeated inflammatory damage in a predisposed individual may lead to the pathology of PPFE [13,22].

Recently, there have been increasing numbers of transplantation-associated cases of PPFE: it can occur either in the lungs after hematopoietic stem cell transplantation [27,28], or in transplanted

lungs [7,29]. Age at onset has been also reported to range widely, from the second [6,23,27] to the ninth decades [14].

Such variations in the clinical features of PPFE remind us that PPFE might need to be named "PPFE syndrome" rather than a single disease. Therapeutic interventions should be investigated based on documented variations in its pathogenesis.

## References

1. Frankel SK, Cool CD, Lynch DA, Brown KK (2004) Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity. *Chest* 126: 2007-2013.
2. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, et al. (2013) An official American Thoracic Society/European Respiratory Society Statement: Update of the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias. *Amer J Respir Crit Care Med* 188: 733-748.
3. Nakatani T, Arai T, Kitaichi M, Akira M, Tachibana K, et al. (2015) Pleuroparenchymal fibroelastosis from a consecutive database: a rare disease entity? *Eur Respir J* 45: 1183-1186.
4. Harada T, Yoshida Y, Kitasato Y, Tsuruta N, Wakamatsu K, et al. (2014) The thoracic cage becomes flattened in the progression of pleuroparenchymal fibroelastosis. *Eur Respir Rev* 23: 263-266.
5. Kusagaya H, Nakamura Y, Kono M, Kaida Y, Kuroishi S, et al. (2012) Idiopathic pleuroparenchymal fibroelastosis: consideration of a clinicopathological entity in a series of Japanese patients. *BMC Pulm Med* 12:72.
6. Watanabe S, Waseda Y, Takato H, Matsunuma R, Johkoh T, et al. (2015) Pleuroparenchymal fibroelastosis: Distinct pulmonary physiological features in nine patients. *Respir Invest* 53: 149-155.
7. Ofek E, Sato M, Saito T, Wagnetz U, Roberts HC, et al. (2013) Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis. *Mod Pathol* 26: 350-356.
8. Hirota T, Yoshida Y, Kitasato Y, Yoshimi M, Koga T, et al. (2015) Histological evolution of pleuroparenchymal fibroelastosis. *Histopathology* 66: 545-554.
9. Myers JL, Katzenstein AL (1988) Epithelial necrosis and alveolar collapse in the pathogenesis of usual interstitial pneumonia. *Chest* 94: 1309-1311.
10. Enomoto N, Suda T, Kato M, Kaida Y, Nakamura Y, et al. (2006) Quantitative analysis of fibroblastic foci in usual interstitial pneumonia. *Chest* 130: 22-29.
11. Harada T, Watanabe K, Nabeshima K, Hamasaki M, Iwasaki H (2013) Prognostic significance of fibroblastic foci in usual interstitial pneumonia and non-specific interstitial pneumonia. *Respirology* 18: 278-283.
12. Oda T, Ogura T, Kitamura F, Hagiwara E, Baba T, et al. (2014) Distinct characteristics of pleuroparenchymal fibroelastosis with usual interstitial pneumonia compared with idiopathic pulmonary fibrosis. *Chest* 146: 1248-1255.
13. Watanabe K (2013) Pleuroparenchymal Fibroelastosis: Its Clinical Characteristics. *Curr Respir Med Rev* 9: 299-237.
14. Yoshida Y, Nagata N, Tsuruta N, Kitasato Y, Wakamatsu K, et al. (2015) Heterogeneous clinical features in patients with pulmonary fibrosis showing histology of pleuroparenchymal fibroelastosis. *Respir Investig*.
15. Negri EM, Montes GS, Saldiva PH, Capelozzi VL (2000) Architectural remodelling in acute and chronic interstitial lung disease: fibrosis or fibroelastosis? *Histopathology* 37: 393-401.
16. Rozin GF, Gomes MM, Parra ER, Kairalla RA, de Carvalho CR, et al. (2005) Collagen and elastic system in the remodelling process of major types of idiopathic interstitial pneumonias (IIP). *Histopathology* 46: 413-421.
17. Amitani R, Niimi A, Kuze F (1992) Idiopathic pulmonary upper lobe fibrosis. *Kokyu* 11: 693-699.
18. Kafer ER (1974) Respiratory function in paralytic scoliosis. *Am Rev Respir Dis* 110: 450-457.

19. Davies D (1972) Ankylosing spondylitis and lung fibrosis. *Q J Med* 41: 395-417.
20. Momeni M, Yaylor N, Tehrani M (2011) Carduiopulmonary manifestations of ankylosing spondylitis. *Internatl J Rheumatol*.
21. Watanabe K, Nagata N, Kitasato Y, Wakamatsu K, Nabeshima K, et al. (2012) Rapid decrease in forced vital capacity in patients with idiopathic pulmonary upper lobe fibrosis. *Respir Investig* 50: 88-97.
22. Reddy TL, Tominaga M, Hansell DM, von der Thusen J, Rassi D, et al. (2012) Pleuroparenchymal fibroelastosis: a spectrum of histopathological and imaging phenotypes. *Eur Respir J* 40: 377-385.
23. Beynat-Mouterde C, Beltramo G, Lezmi G, Pernet D, Camus C, et al. (2014) Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents. *Eur Respir J* 44: 523-527.
24. Shiota S, Shimizu K, Suzuki M, Nakaya Y, Sakamoto K, et al. (1999) [Seven cases of marked pulmonary fibrosis in the upper lobe]. *Nihon Kogyuki Gakkai Zasshi* 37: 87-96.
25. Fuke S, Betsuyaku T, Oizumi S, Nasuhara Y, Saito H, et al. (2003) Case of idiopathic pulmonary upper lobe fibrosis complicated by invasive pulmonary aspergillosis. *Nihon Kogyuki Gaskkai Zasshi* 41: 196-201.
26. Piciucchi S, Tomassetti S, Gasoni G, Sverzellati N, Carloni A, et al (2011) High resolution CT and histological findings in idiopathic pleuroparenchymal fibroelastosis: Features and differential diagnosis. *Respir Res* 12:111.
27. Von der Thusen JH, Hansell DM, Tominaga M, Veys PA, Ashworth MT, et al (2011) Pleuroparenchymal fibroelastosis in patients with pulmonary disease secondary to bone marrow transplantation. *Modern Pathol* 24: 1633-1639.
28. Takeuchi Y, Miyagawa-Hayashino A, Chen F, Kubo T, Handa T, et al (2015) Pleuroparenchymal fibroelastosis and nonspecific interstitial pneumonia: frequent pulmonary sequelae of haematopoietic stem cell transplantation. *Histopathology* 66: 536-544.
29. Hirota T, Fujita M, Matsumoto T, Higuchi T, Shiraiishi T, et al. (2013) Pleuroparenchymal fibroelastosis as a manifestation of chronic lung rejection? *Eur Respir J* 41: 243-245.