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INVITED COMMENTARY

Pleuroparenchymal Fibroelastosis (PPFE) — An Update

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Abstract

Purpose of Review This review highlights the clinical, radiological and histological features of pleuroparenchymal fibroelastosis (PPFE) as well as the typical disease course and management.

Recent Findings PPFE has been associated with a number of conditions including post-transplantation, respiratory infection and connective tissue disease. The clinical course of PPFE is varied although the overall prognosis is poor. Pneumothorax occurs frequently but can often be managed conservatively. Lung transplant outcomes comparable with those in idiopathic pulmonary fibrosis (IPF) have been reported although long-term outcome data is limited. The efficacy of nintedanib in slowing PPFE progression remains unclear.

Summary PPFE is a rare disease characterised by progressive breathlessness due to upper lobe pleural thickening and subpleural lung fibrosis. Although awareness of PPFE has increased over the last decade, the underlying pathogenesis remains unknown and the condition carries a poor prognosis with little in the way of established treatment options.

Keywords Pleuroparenchymal fibroelastosis · Interstitial lung disease · Pneumothorax · Pleural thickening

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare and previously under-recognised disease characterised by progressive pleural thickening and adjacent subpleural interstitial lung fibrosis seen predominantly in an upper lobe distribution. The disease may be idiopathic or secondary to a range of causes, including post-transplantation and recurrent respiratory infection.

The distinct clinical, radiological and pathological characteristics of PPFE differentiate it from other idiopathic interstitial pneumonias (IIPs). A number of these features were initially described by Amitani in Japanese literature, who referred to the condition as "idiopathic pulmonary upper lobe fibrosis" [1]. The term "pleuroparenchymal fibroelastosis" was first used by Frankel in 2004 when reporting a series of patients presenting with similar features to those previously described by Amitani [1, 2]. PPFE was eventually incorporated into the international multidisciplinary classification of rare idiopathic interstitial pneumonias in 2013 [3].

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Despite increased recognition of PPFE in recent years, the current evidence base consists largely of case reports and retrospective analysis of small cohorts of patients and there remains a lack of robust large randomised control trial data to better inform clinicians regarding key facets of the condition. While disease associations with a range of conditions have been identified, there remains a lack of understanding as to the exact pathogenesis of PPFE and there is currently no effective pharmacological treatment.

Epidemiology

The true incidence and prevalence of idiopathic PPFE (iPPFE) is uncertain with varying figures reported in the literature. A study of 375 patients diagnosed with IIPs observed radiological features indicative of PPFE in 7.7% of cases [4]. Additionally, a review of 205 consecutive single lung biopsy cases identified 12 instances (5.9%) of PPFE, with a reported frequency of 10.4% among all IIPs within the cohort [5]. In a retrospective review of 118 patients referred for lung transplantation over a 5-year period, 30 patients (25%) exhibited radiological evidence of PPFE [6]. Finally, an analysis of 445 cases of idiopathic pulmonary fibrosis (IPF) demonstrated radiological evidence of PPFE in 28 patients (6.3%) [7].

There is limited data regarding the incidence of the development of secondary pleuroparenchymal fibroelastosis (sPPFE) in patients following transplantation. Post-transplant radiological findings indicative of PPFE were observed in 2 cases (0.28%) from a cohort of 700 haematopoietic stem cell transplant (HCST) recipients and 4 cases (7.54%) among 53 lung transplant recipients [8]. In contrast, there were 13 (1.9%) cases of upper lobe fibrosis reported in a cohort of 686 lung transplant recipients [9]. In terms of other causes of sPPFE, 6.5% of patients with rheumatoid arthritis related ILD (RA-ILD) and 18.1% of patients with systemic sclerosis (SSc) were reported to have features of PPFE in separate studies [10•, 11•]. Finally, radiological PPFE was observed in 11.9% of cases from a cohort of 850 patients with mycobacterium avium complex.

Pathogenesis

The underlying mechanisms through which PPFE develops and subsequently progresses in both idiopathic and secondary forms remain unclear. Current theories include an initial inflammatory process triggered by lung injury with subsequent diffuse alveolar damage and collapse followed by the eventual formation of fibroelastosis [12–14]. Factors including alveolar epithelial denudation and the overexpression of TGF-alpha may also play a role [15, 16]. The specific involvement of the lung apices may be the result of poor lymphatic drainage or ischaemia [12, 13]. The existence of familial cases of PPFE and the discovery of genetic mutations in cases of PPFE including the telomere-related genes telomerase reverse transcriptase (TERT) and telomerase RNA component (TERC) suggest that genetic factors are also likely to contribute to disease development [17, 18].

A number of studies of sPPFE occurring in transplant recipients have noted that histological features in keeping with bronchiolitis obliterans often co-exist with typical features of PPFE suggesting that chronic graft versus host disease may be implicated in the development of PPFE in this context [12, 13, 19, 20]. Examination of pulmonary arteries has demonstrated increased adventitial thickness as well as increased medial layer elastosis in iPPFE when compared with IPF suggesting a different process of pulmonary artery remodelling between the two conditions [21].

Disease Associations

Cases of PPFE have been reported occurring secondary to or in association with various conditions (Table 1). Cases of PPFE occurring in transplant recipients (bone marrow, HSCT, lung) are well documented [8, 9, 20, 22–24]. Other associations include chronic or recurrent respiratory infection, drugs including alkylating agents, radiation and occupational dust inhalation [1, 2, 25–38]. A family history of ILD is reported relatively frequently and telomere-related gene mutations have been identified in association with PPFE [1, 2, 17, 18, 27, 39].

Radiological and histological features of other forms of ILD are often identified in association with PPFE, of which hypersensitivity pneumonitis and usual interstitial pneumonia (UIP) are the most frequently reported [27, 28, 39–41]. PPFE has been observed in various connective tissue diseases, including SSc, RA and Sjogren's syndrome (SS) [10•, 11•, 27, 42–44]. Cases of PPFE in other autoimmune conditions including inflammatory bowel disease and IGG4 disease have also been reported [45, 46]. Hypothyroidism was found in 54% of cases from a cohort of 13 patients with PPFE although the nature of any association is unclear [47].

Clinical Presentation

PPFE has been reported across a wide age range (13–85) was a bimodal distribution suggested featuring peaks in the third and sixth decades [12]. The reported median age at onset varies from 50 to 70 [27, 39, 48••, 49, 50]. The age of onset may be lower in cases of sPPFE when compared with iPPFE although other clinical characteristics are largely similar between both cohorts [48••]. There are conflicting reports regarding any gender predominance with no clearly established pattern in the literature. PPFE is reported more frequently in non-smokers while a history of recurrent respiratory infection or pneumothorax predating the initial presentation is frequently noted [27, 39, 48••, 50]. A wide range of conditions associated with sPPFE have been identified and a thorough medical history is required to assess for the presence of these factors (Table 1).

The most common symptom of PPFE is that of exertional dyspnoea, which is often insidious in onset and progressive. Cough is also frequently reported and typically non-productive, while chest pain and weight loss may also be noted. The duration of symptoms prior to eventual diagnosis varies with a mean duration of 2–3 years [27]. While symptoms generally progress, there is significant variability of the clinical course, although the overall prognosis in most cases remains poor [51••, 52].

Characteristic clinical signs include a low body mass index (BMI), flattening of the chest wall (platythorax) and deepening of the sternoclavicular notch. Chest auscultation may be unremarkable in cases where there is no lower lobe involvement; however, basal inspiratory crackles or squawks may be heard in the presence of lower lobe fibrosis or co-existent ILD [53]. Finger clubbing is an infrequent finding [39, 50].

Pneumothorax

Pneumothorax may be the initial presenting feature of PPFE and a history of previous pneumothorax is often noted at diagnosis [1, 27, 39, 54•]. Pneumothorax may

Table 1 Conditions associated with secondary PPFE

Associated condition	Evidence summary	References
Transplantation • Bone marrow transplant • HCST • Lung transplant	Reported PPFE incidence 0.28–4% in HCST recipients and 1.9–7.5% of lung transplant recipients. Cases documented across a range of initial transplant indications with varying onset time post-transplant observed (2–18 years)	[8, 9, 20, 22–24]
Chronic or recurrent respiratory infection • Aspergillus • Nontuberculous mycobacteria • Tuberculosis	Cases in the context of recurrent bronchial infection, aspergillus, tuberculosis and nontuberculous mycobacterial infection reported. Incidence of radiological PPFE found to be 11.9% in a cohort of 850 patients with MAC	[1, 25–28, 32, 38]
Radiation	Cases reported following radiation treatment	[1]
Drugs including alkylating agents • Chemotherapy agents including cyclophosphamide • Amiodarone	Reported associations with various chemotherapy drugs including cyclophosphamide as well as other drugs including amiodarone	[34–37]
Occupational dust inhalation • Asbestos • Silica • Aluminium • Hard metal	Cases secondary to asbestos, silica, aluminium and hard metal exposure reported	[1, 29–33]
Connective tissue disease • RA • SSc • SS	Association with a range of rheumatological conditions recognised. PPFE reported in 6.5% of patients with RA-ILD and 18.1% of SSc patients	[10•, 11•, 42–44]
Familial history and/or genetic mutations • TERC/TERT mutations	A number of cases with familial link reported. Gene mutations in telomere-regulating genes TERC and TERT identified in patients with PPFE	[1, 17, 18, 27, 39]
Interstitial lung disease • Hypersensitivity pneumonitis • UIP pattern fibrosis	A co-existing UIP pattern of fibrosis is also frequently reported. PPFE features reported in 53 cases (23%) from a cohort of 233 patients with hypersensitivity pneumonitis	[27, 28, 40, 41]
Others	Case reports of PPFE development in inflammatory bowel disease and IGG4 disease	[45, 46]

PPFE pleuroparenchymal fibroelastosis, *HCST* haematopoietic stem cell transplant, *MAC* mycobacterial avium complex, *RA* rheumatoid arthritis, *SSc* systemic sclerosis, *SS* Sjogren's syndrome, *RA-ILD* rheumatoid arthritis associated interstitial lung disease, *TERC* telomerase RNA component, *TERT* telomerase reverse transcriptase, *UIP* usual interstitial pneumonia, *IGG4* immunoglobulin G4 related disease

occur in up to 75% of patients throughout the disease course and identified risk factors include male gender, older age and a lower lobe UIP pattern [39, 54•]. Pneumomediastinum development has also been reported [39]. A retrospective multicentre study of 89 patients with iPPFE reported that 59.6% of patients developed a pneumothorax, with a total of 120 events over a 3.5-year period [54•]. The majority of these were both asymptomatic and small in size [54•]. Conservative management was successful in the most cases, while chest drain insertion was required in 19% of cases, of which over half were complicated by persistent air leak [54•].

Lung Function Tests

Lung function tests typically demonstrate a reduced forced vital capacity (FVC) and total lung capacity (TLC) with a restrictive spirometry pattern [39, 48••, 50]. Diffusion capacity for carbon monoxide (DLCO) may be preserved or reduced. A high residual volume to total lung capacity ratio (RV/TLC) is often seen and may be due to progressive flattening of the chest wall or compensatory hyperinflation of the middle and lower lobes in response to upper lobe volume loss [50, 55].

Lab Tests

At present, there are no established biomarkers that have been validated for use in PPFE. The measurement of levels of surfactant protein-D (Sp-D) and Krebs von den Lungen-6 (KL-6) in PPFE has yielded conflicting results, and their clinical significance remains unclear [4, 39, 49, 56, 57]. Elevated serum levels of latent transforming growth factor β binding protein 4 (LTBP-4), which plays a role in elastogenesis, have been noted in PPFE compared with control samples; however, further research is required to explore its potential role as a biomarker in PPFE [58]. In addition, elevated levels of urinary desmosines have been observed in PPFE in comparison with IPF [59]. Finally, positive autoantibodies have been noted in cases of PPFE, but their significance is not established [27, 60].

Radiology

Chest radiograph findings may include apical pleural thickening, upper zone reticulation, upwards retraction of the hilar structures and progressive upper lobe volume loss [1, 61, 62]. There may be right sided tracheal deviation due to upper lobe contraction, while lateral imaging may demonstrate anteroposterior flattening of the chest wall in keeping with platythorax [61].

The typical findings identified on high-resolution computed tomography (HRCT) imaging are well established and form a major component of the diagnostic process. The characteristic appearances are that of apical irregular bilateral pleural thickening with adjacent subpleural dense airspace consolidation and reticulation suggestive of fibrosis, which may be accompanied by traction bronchiectasis and architectural distortion in the upper lobes (Fig. 1) [1, 2, 27, 62, 63]. Lower zone involvement is typically less marked or absent, although co-existent radiological patterns including UIP and non-specific interstitial pneumonia (NSIP) may be seen [27, 39]. In addition, as previously noted, sPPFE may occur in the context of an ILD such as hypersensitivity pneumonitis, which may further complicate the interpretation of radiological findings [27, 40].

Histopathology

Histological examination of lung tissue in PPFE reveals distinctive features of upper zone visceral pleural fibrosis and subpleural intra-alveolar fibroelastosis with preservation of the lung parenchyma distant from the pleura [2, 12, 27, 28]. Additionally, there may be mild patchy lymphoplasmocytic infiltrates and fibroblastic foci in limited quantities [2, 12, 27, 28]. Fibrointimal thickening of the pulmonary vasculature is a frequent finding, while approximately 25% of cases may demonstrate features indicating co-existent pathology such as UIP or hypersensitivity pneumonitis [28].

Diagnosis

The radiological features of PPFE are well established; however, in many cases, a confident diagnosis cannot be made from imaging alone due to a lack of typical HRCT findings or the presence of features suggestive of other forms of ILD. As such, lung biopsy is often pursued to allow for histological correlation with clinical and radiological findings in order to help secure a more assured diagnosis [12, 27]. Adequate tissue samples for diagnostic use in PPFE have been acquired through a range of modalities, including surgical lung biopsy, transbronchial lung biopsy, cryobiopsy and CT-guided transthoracic biopsy [27, 39, 60, 64–66].

There are no internationally agreed diagnostic criteria for PPFE. Reddy et al. proposed diagnostic criteria which consider both radiological and histological features to inform the diagnostic process [27]. Their criteria delineate levels of diagnostic confidence in radiological and histological findings using the term "definite PPFE" where there are typical disease features and "consistent with PPFE" where features consistent with PPFE may exist with features of coexistent disease may be present or the disease distribution is atypical [27].

While the proposed criteria from Reddy et al. are frequently used to validate diagnosis in other studies, they require tissue sampling, which is not always possible due to the heightened risk of pneumothorax, air leak syndrome, exacerbation risk and the profound physiological effects of the disease in some patients, rendering them unable to tolerate such procedures [63]. Given the absence of effective treatment in PPFE, careful consideration is needed as to the benefits of pursuing lung tissue in cases, given the recognised risks.

In order to address the difficulty in obtaining histology in some cases, Watanabe et al. proposed diagnostic criteria which incorporate symptom and physiological parameters (RV/TLC % predicted and BMI) for use in cases where lung tissue cannot be obtained [63]. They reported an overall sensitivity and specificity of their criteria incorporating physiological features in the absence of histology as 87.8% and

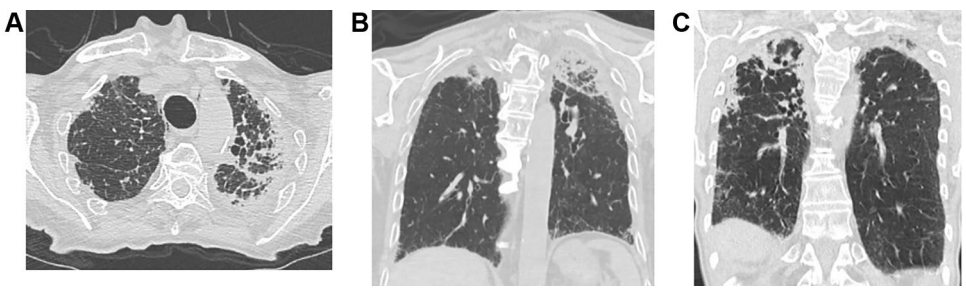

Fig. 1 **A** Axial plane computed tomography (CT) demonstrating apical pleural thickening with subpleural reticulation and consolidation in a patient with pleuroparenchymal fibroelastosis (PPFE). **B** Coronal reconstruction of the same patient as A demonstrating apical disease with sparing of the lower zones. **C** Coronal reconstruction demonstrating apical subpleural fibrosis and consolidation in a patient with PPFE

83.5% respectively [63]. A separate study undertook a retrospective analysis of 28 iPPFE patients applying the diagnostic criteria proposed by Watanabe et al., but modifying the physiological criteria to include flat chest index scores in place of RV/TLC with some success [67]. However, they noted that iPPFE patients who met the physiological criteria had a lower FVC and patients with early iPPFE may therefore not fulfil the criteria [67]. Additionally, Tetikurt et al. recently proposed a diagnostic assessment score comprising a range of clinical and radiological features of PPFE in order to determine diagnostic probability [68•].

Differential Diagnosis

The differential diagnosis for both radiological and histological findings that may be seen in PPFE is varied and complicated by the fact that sPPFE may develop secondary to co-existent ILD, occupational exposure or infection (Table 2) [27]. Multi-disciplinary team discussion is therefore vital to establish a diagnostic consensus by correlating clinical, radiological and histological findings.

Causes of upper zone predominant lung fibrosis include advanced sarcoidosis, fibrotic hypersensitivity pneumonitis, inhalational causes (including occupational exposure), post radiotherapy change, connective tissue disease and drug-induced lung disease. Differentiating radiological and histological features also seen in pleural apical cap may also be challenging [12, 69, 70]. Histological features of other forms of interstitial lung disease, such as UIP/IPF, HP and cryptogenic organising pneumonia, may overlap with typical PPFE findings [12, 27, 28].

Clinical Course and Outcomes

The clinical course in PPFE is variable, with some patients exhibiting a rapid FVC decline and early mortality, while others progress at a slower rate [51••, 52, 71]. Generally, PPFE is associated with a poor prognosis and is typically characterised by progressive breathlessness and physiological decline. The disease course is often complicated by recurrent pneumothorax and respiratory infections before the eventual development of hypercapnic respiratory failure [42, 51••, 71]. Additionally, progressive weight loss and worsening platythorax may also occur [39, 49, 55].

Reported median survival ranges from 2 to 11 years, with 5-year survival figures ranging from 29 to 38% [39, 48••, 51••, 52, 72]. Similar outcomes and survival have been

Table 2 Differential diagnosis in pleuroparenchymal fibroelastosis

Differential diagnosis	Discussion
Upper lobe predominant fibrotic lung disease • Advanced fibrotic sarcoidosis • Fibrotic HP • Occupational lung disease • Post-radiation • Connective tissue disease • Drug-induced lung disease	Lung fibrosis predominantly affecting the upper lobes may be a manifestation of a range of disease processes, with or without associated pleural thickening. A thorough medical history, including symptoms of CTD, previous treatment, occupational and environmental exposures may aid assessment. Features including mosaic attenuation and centrilobular nodules may suggest hypersensitivity pneumonitis, while sarcoidosis may present with a range of additional radiological features including lymphadenopathy and peri lymphatic nodularity. Serum autoantibodies may aid detection of connective tissue disease. Histological examination of these conditions is generally not in keeping with the typical findings in PPFE
Pleural thickening with lung fibrosis • Asbestos related lung disease • Advanced fibrotic sarcoidosis • Post-radiation • Drug-induced lung disease	Asbestosis is typically seen in a lower zone distribution but may be associated with pleural disease. Histology findings generally demonstrate more extensive architectural distortion that typically seen in PPFE [12]
Isolated apical pleural thickening with subpleural intra-alveolar fibroelastosis on histology • Pleural apical cap	Typically seen in patients of older age, low BMI and recurrent pulmonary infection. Radiological findings are those of irregular wedge-shaped apical opacification with no lower zone involvement. Pleural apical cap shares many histological features with PPFE creating a diagnostic challenge. It rarely progresses and lung function is usually preserved unlike the typical course of PPFE [12, 69, 70]
Other forms of ILD • UIP • NSIP • COP	UIP and NSIP typically, but not exclusively, favour the lower lobes, while subpleural sparing is a feature of NSIP, which is unlike typical findings of PPFE. Histological findings of UIP are generally different to those seen in PPFE in terms of distribution, while fibroblastic foci are generally seen in low number in PPFE, unlike IPF [12]. Cryptogenic organising pneumonia typically presents with migratory patchy airspace opacification on imaging, unlike the homogenous upper lobe progressive changes in PPFE although some histological features such as intra-alveolar fibroelastosis may also be seen histologically in COP [12]

CTD connective tissue disease, *PPFE* pleuroparenchymal fibroelastosis, *BMI* body mass index, *UIP* usual interstitial pneumonia, *NSIP* non-specific interstitial pneumonia, *COP* cryptogenic organising pneumonia

reported when comparing cohorts of patients with iPPFE and sPPFE [48••]. The most common cause of death is respiratory failure, with respiratory infection, acute exacerbations and pneumothorax also recorded [39, 73]. One study comparing a cohort of iPPFE patients with a cohort of IPF patients reported a more rapid decline in FVC, as well as significantly worse survival, in the iPPFE cohort [4].

The development of pulmonary hypertension is associated with a poor prognosis and may occur in up to 19% of patients [74]. There are relatively few reports of cases of lung cancer in the PPFE population, which is in contrast to IPF, and this may due to the fact that patients with PPFE are less likely to have a smoking history [39, 73].

Nakamura et al. utilised cluster analysis to identify four potential phenotypes among a cohort of iPPFE patients [51••]. Their findings revealed that males with a high symptom burden, a lower lobe UIP pattern and a history of smoking had a significantly poorer prognosis [51••]. Identified factors associated with a poor prognosis include male gender, progressive upper lobe volume loss, lower lobe UIP pattern, older age, FVC, DLCO and elevated levels of KL-6 [4, 28, 48••, 50, 51••, 52, 73, 75].

Management

There are currently no pharmacological treatments shown to be effective in PPFE and large controlled studies are lacking. As with other forms of progressive ILD, supportive measures including supplementary oxygen and palliative care intervention should be considered where indicated. Non-invasive ventilation may provide benefit for patients with daytime hypercapnia but patient tolerance may be poor [76].

Pulmonary Rehabilitation

Pulmonary rehabilitation may offer benefits to patients with PPFE and improved 6-min walking distance, symptoms and quality of life questionnaire scores have been reported in a small cohort of PPFE patients undergoing pulmonary rehabilitation [77, 78]. Attendance at pulmonary rehabilitation may be limited by recurrent pneumothorax or pneumomediastinum, although there are reports of patients with these conditions safely completing pulmonary rehabilitation courses [77].

Pharmacological Treatments

While the anti-fibrotic agent nintedanib has shown efficacy in slowing the rate of FVC decline in patients with progressive ILD, data for the use of anti-fibrotic medication in PPFE is limited, with most studies failing to demonstrate a significant benefit [71, 79–81]. A retrospective analysis of patients receiving nintedanib for at least 6 months compared 15 patients with iPPFE with 27 IPF patients, with no significant efficacy demonstrated in the PPFE group in contrast to the IPF group in whom the rate of FVC decline was significantly slowed [81]. Another study comparing 64 patients with iPPFE with additional typical UIP findings on radiology with 195 IPF patients included 8 patients prescribed nintedanib and 26 prescribed pirfenidone and again suggested limited efficacy of both drugs in PPFE [80].

In contrast, one study including 9 PPFE patients prescribed nintedanib for a minimum period of 3 months demonstrated a reduction in the annual rate of FVC decline following initiation of treatment, while an additional case report documented a good response to pirfenidone in a patient with iPPFE [82, 83•].

Although there are many reports of patients receiving steroids as treatment for PPFE, there is limited evidence of any clinical benefit and immunosuppression is not generally recommended in PPFE [4, 39, 83•]. Metformin has been shown to reduce pleural fibroelastosis in mouse models through suppression of extracellular matrix protein production and may have therapeutic potential in PPFE, although further research is required [84].

Lung Transplantation

There are reports of successful single, double and living donor lobar lung transplantation in PPFE, although data regarding long term outcomes is limited [85–87, 88••, 89]. Disease-specific issues including low BMI, pleural thickening and platythorax may complicate potential transplantation in many patients [90]. Overall post-transplant survival in iPPFE is comparable to transplant recipients with IPF, although post-transplantation FVC has been observed to be significantly lower in recipients with iPPFE when compared with those with IPF [88••]. Low BMI and platythorax often fail to improve significantly post transplantation, while disease recurrence has been reported in a patient with iPPFE 5 months post-transplantation [88••, 91].

Conclusion

The distinct clinical, radiological and histological features that characterise PPFE are now well established in medical literature. While the true incidence of PPFE is unknown, it is likely to be more common than previously thought. Despite recent advancements, much about the condition remains unknown and there remains no effective pharmacological treatment. As the use of antifibrotic medication expands in progressive forms of ILD, opportunities for larger-scale studies of their effects in

PPFE may be more feasible. The development of agreed and validated diagnostic criteria is vital to facilitating robust clinical trials in PPFE in the future. Additionally, the development of prognostic assessment tools would help better inform both clinicians and patients.

Declarations

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Conflict of Interest The author declares no competing interests.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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