OPEN ACCESS

ISSN: 2835-9496

Tetikkurt C and Tetikkurt US (2025): 1241
Ameri J Clin Med Re, 2025; 5(9): 100235
DOI: 10.71010/2835-9496.2025.AJCMR-e235

Review Article

American Journal of Clinical and Medical Research

Diagnosis and Treatment of Pleuroparenchymal Fibroelastosis: Review

(Running title: *Pleuroparenchymal Fibroelastosis: Review*)

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Citation: Tetikkurt C, Tetikkurt US (2025) Diagnosis and Treatment of Pleuroparenchymal Fibroelastosis: Review. Ameri J Clin Med Re: AJCMR-e235.

Received Date: 18 Aug, 2025; **Accepted Date:** 29 Aug, 2025; **Published Date:** 05 Sep, 2025

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare, progressive interstitial lung disease marked by fibrosis of the pleura and subpleural parenchyma. First described as a distinct pathological entity in 1992, PPFE has since gained recognition as a unique form of pulmonary fibrosis with distinguishing clinical, radiological, and pathologic features. Despite growing awareness, PPFE remains underdiagnosed while its pathogenesis, risk factors, and optimal management strategies are still obscure. The condition has since garnered attention due to its distinct pathologic and clinical features with a poor prognosis (1-4). It is characterized by fibroelastotic changes predominating in the subpleural lung parenchyma with visceral pleural fibrosis mainly involving the upper lobes. PPFE can be idiopathic or associated with a variety of secondary conditions, including connective tissue diseases, bone marrow or lung transplantation, recurrent infections, and genetic predispositions. Clinically, it manifests with progressive shortness of breath, chronic cough, and a restrictive ventilatory defect on pulmonary function tests, which can result in significant respiratory impairment over time. HRCT serves as a crucial diagnostic tool, revealing hallmark findings such as upper lobe pleural thickening, subpleural fibrosis, and volume loss. However, due to its overlapping features with other fibrotic lung diseases, particularly the idiopathic pulmonary fibrosis and chronic hypersensitivity pneumonitis, accurate diagnosis often necessitates multidisciplinary evaluation incorporating clinical history, imaging, and histopathology (3-6).

Given the rarity of PPFE, standardized treatment strategies are lacking, and they are primarily extrapolated from other forms of interstitial lung diseases. Current therapeutic approaches include supportive care, immunosuppressive therapy in selected cases and lung transplantation for advanced diseases. Emerging research suggests a potential role for antifibrotic agents, but their efficacy in PPFE remains to be fully elucidated. Prognosis varies, with some patients experiencing a slow decline, while others progress rapidly to end-stage respiratory failure. This review aims to provide a comprehensive analysis of the current understanding of PPFE, including its epidemiology, pathology, clinical and radiologic characteristics with including diagnostic challenges and treatment options. By consolidating recent advancements in research and clinical practice, our aim is to enhance awareness, improve early recognition and guide future therapeutic developments for this challenging condition to highlight the areas of uncertainty and the need for further research.

Pathogenesis and etiology

Precise pathogenesis of PPFE is still largely speculative. It is believed to arise from abnormal wound healing and dysregulated fibrosis, leading to excessive deposition of fibrous and elastotic tissue within the pleura and subpleural lung parenchyma. The involvement of the pleura is a distinguishing feature of PPFE, unlike other fibrotic lung diseases such as idiopathic pulmonary fibrosis (IPF) or non-specific interstitial pneumonia (NSIP). The upper lobes are predominantly affected, with involvement extending to the subpleural regions and occasionally, the pleura (5-8). In some cases, PPFE has been observed following a history of recurrent infections, exposure to environmental toxins, or radiation therapy (9-14). A genetic predisposition has been suggested in some studies (4-6), though the exact risk factors for developing PPFE remain elucidated. An association with other autoimmune diseases, including rheumatoid arthritis, has been noted in isolated reports. Acute or subacute lung injury precipitating an exuberant interstitial inflammation is the hallmark of the pathologic cascade leading to PPFE (15-17). Overall, PPFE appears to result from a combination of genetic susceptibility, immune dysregulation, recurrent infections, and mechanical lung injury. The exact pathogenesis is not fully understood and remains obscure that requires further research.

Clinical Presentation

Patients with PPFE typically present with progressive dyspnea, often accompanied by dry cough and fatigue. The most common symptom is gradually worsening dyspnea that typically occurs with exertion but can progress to resting dyspnea as the disease advances. A persistent dry, non-productive is another frequent manifestation in these patients. Fatigue is a common symptom, likely due to impaired lung function, the chronic nature of the disease, and usually occurs in late disease stages. As the disease progresses and lung function deteriorates, blood oxygen levels may decrease, leading to hypoxemia. This can result in cyanosis that may come out as peripheral, central, or both. Patients with advanced disease and respiratory insufficiency often present with a markedly thin body habitus, resulting from diminished appetite or increased muscular exertion associated with labored breathing. Some patients may present with wheezing, although

this is much less common than other respiratory symptoms. Finger clubbing may develop often as a sign of chronic long-standing or advanced lung disease. Pleural involvement may lead to chest discomfort or pleuritic chest pain, though it is not always prominent.

Symptoms are often insidious in onset and due to the disease rarity, initial misdiagnoses such as asthma, COPD, or IPF are common. Differential diagnosis with other more common interstitial lung diseases constitutes the hallmark step of definitive diagnosis. The distinctive clinical feature of PPFE is its predominantly upper-lobe distribution. Physical examination findings in PPFE are often nonspecific, although inspiratory crackles and clubbing may be present in the advanced stages of the disease. Suprasternal notch deepening and platythorax are unique signs of pleuroparenchymal fibroelastosis that are not observed in other interstitial lung diseases. Absence of pathologic laboratory findings and imaging manifestations like significant ground-glass opacities which are more frequent in other forms of ILD, may help distinguish PPFE from diseases like NSIP and IPF.

Diagnosis

The diagnosis of PPFE involves a combination of clinical presentation, radiologic findings, histopathologic examination, and exclusion of other potential interstitial lung diseases. Due to extreme rarity of PPFE with non-specific nature of associated findings, physical examination scarcely provides or may not reveal a useful hint for a differential or definitive diagnosis. Cyanosis, tachypnea, use of accessory, and Hoover's sign are frequent manifestations that reveal advanced disease with respiratory insufficiency. As these signs may emerge in any lung or systemic disease with respiratory failure, they lack an adequate sensitivity or specificity for PPFE. Absence of finger clubbing is crucial for differential diagnosis with other interstitial lung diseases as it is an uncommon finding in PPFE patients. Suprasternal notch deepening and platythorax are the hallmark of inspection manifestations of PPFE diagnosis that may be designated as the fundamental physical findings. Chest imaging, especially the HRCT, remains the hallmark of definitive diagnosis revealing almost specific manifestations while a through discriminative assessment with interstitial lung diseases is the non-sine qua criteria to avoid a misdiagnosis. Chest x-rays can detect PPFE in advanced stages when fibrosis peaks but they are less sensitive than HRCT, though they may still show suggestive findings. In the early stages, the abnormalities on chest X-ray may be subtle, making HRCT a more definitive diagnostic tool (4-7). The key radiologic feature of PPFE is the upper-lobe predominance of fibrosis, often with pleural thickening and honeycombing. The pleural involvement is more extensive than in other forms of fibrotic lung disease. As PPFE primarily affects the upper lobes of the lungs, chest x-ray may show more pronounced changes in this region, often revealing bilateral involvement. The upper lobes may appear more opacified compared to the lower zones. A reticular pattern may be observed in these areas that reflect fibrotic changes. The opacities are typically fine and linear, but in severe cases, they may evolve into honeycombing-like patterns. Unlike other forms of interstitial lung disease, such as idiopathic pulmonary fibrosis, ground-glass opacities are typically absent or minimal in PPFE on chest X-ray. Although pleural thickening may be present, large pleural effusions are not a characteristic finding in PPFE patients (5,6).

HRCT may reveal a reverse subpleural fibrotic pattern, where the pleura is thickened due to fibrosis, with sparing of the lung parenchyma in the early stages showing a clear upper-lobe predominance. Parenchymal fibrosis and pleural involvement are most prominent in the apical and posterior regions. This is one of the hallmark features of PPFE that helps to distinguish it from other interstitial lung diseases. Pleural thickening is a definitive characteristic of PPFE which may involve the apical pleura that extends into the adjacent lung parenchyma. The pleura may demonstrate both fibrosis and elastosis that appears as a dense, linear opacification on HRCT. In advanced cases, pleural fibrosis may contribute to a cobblestone appearance that is most prominent in the subpleural regions affecting the lung parenchyma adjacent to the pleura. This is often seen as thickening of the subpleural interstitial tissues. In more advanced stages, honeycombing may be observed in the upper lobes with cystic spaces surrounded by fibrotic tissue. However, this observation is generally less prominent than in idiopathic pulmonary fibrosis, and the extent of honeycombing is usually more limited. Unlike in IPF or other fibrotic diseases, the lower lobes are often spared or show only mild fibrosis, further supporting the diagnosis of PPFE when upper lobe involvement is prominent. Traction bronchiectasis may be present in advanced disease due to the fibrotic changes, but it is usually less pronounced compared to other fibrotic lung diseases (18-20). The imaging findings of PPFE are summarized as follows. Chest X-ray shows pleural thickening and a reticular pattern predominantly in the upper lobes; absence of significant ground-glass opacities; lack of significant pleural effusion. HRCT reveals upper-lobe predominance of fibrosis and pleural thickening with subpleural involvement, honeycombing in advanced stages, absence of significant ground-glass opacities, and sparing of the lower lobes. HRCT remains the most sensitive imaging modality for diagnosing PPFE, offering a clearer understanding of the characteristic pathologic manifestations.

Laboratory findings lack diagnostic sensitivity and specificity in PPFE patients. Most patients will demonstrate restrictive lung disease, characterized by a reduced forced vital capacity (FVC) and forced expiratory volume in one second (FEV_1). Diffusion capacity for carbon monoxide (DLCO) is often reduced, reflecting impaired gas exchange, especially in advanced disease (21). Arterial blood gas analysis shows hypoxemia and type I respiratory failure. In advanced stages of the disease, carbon dioxide retention may occur due to respiratory failure and muscle fatigue, resulting in type II respiratory failure. Definitive diagnosis of PPFE requires a pathologic examination, typically obtained via surgical lung biopsy. The characteristic findings include fibrosis and elastosis of the pleura and adjacent lung parenchyma, with relative sparing of the interlobular septa and sparing of the perivascular regions. The pathological pattern differs from that of IPF, NSIP, and other ILDs that can aid in distinguishing PPFE from these diseases (22-25). Serological tests are useful in ruling out autoimmune disorders, but they are not specific for PPFE. In some cases, the presence of autoimmune markers may suggest an underlying connective tissue disease. Urinary desmosines may be elevated in patients with idiopathic pleuroparenchymal fibroelastosis and may be used as a noninvasive diagnostic biomarker (26). TERT and TERC mutations may emerge in PPFE patients (27-29). The differential diagnosis of PPFE includes other forms of ILD, such as IPF, NSIP, chronic hypersensitivity pneumonitis, and asbestosis. The absence of significant ground-glass opacities,

which are characteristic of early IPF or NSIP, and the unique upper-lobe predominance of pleural fibrosis help to differentiate PPFE from these conditions. Additionally, the pleural thickening seen in PPFE is more marked and may extend to the apex of the lung (30-37).

Treatment

Currently, an established treatment protocol for PPFE is unavailable due to the limited number of cases and the heterogeneity of the disease. Treatment strategy is largely based on those used for other forms of ILD, but outcomes remain poor, particularly in advanced stages of disease. Drugs such as pirfenidone and nintedanib have shown efficacy in slowing the progression of IPF but their use in PPFE is under investigation (38-42). Given the commonalities in the fibrotic processes, these agents may offer some benefit, though the evidence is limited. There is no data supporting the routine use of corticosteroids or immunosuppressants in PPFE. However, in cases where an autoimmune component is suspected, these agents may be used cautiously. As the disease progresses, supplemental oxygen may be required to manage hypoxemia, especially in cases with advanced fibrosis and respiratory insufficiency. Lung transplantation remains the treatment of choice for end-stage PPFE, notably in patients with rapidly progressive disease. Lung transplantation may lead to significant morbidity or mortality due to advanced fibrosis in the lung parenchyma, severe pleural thickening, and advanced pleural adhesions.

Lung transplantation in patients with PPFE carries relatively high morbidity due to several factors: progressive respiratory failure, immunosuppressive treatment, graft dysfunction, bronchiolitis obliterans syndrome, and chronic allograft dysfunction. The mortality rate in PPFE patients undergoing lung transplantation tends to be higher compared to those with other forms of interstitial lung disease, primarily due to the following reasons: pre-existing pulmonary and pleural fibrosis, primary graft dysfunction, postoperative infections, and organ rejection. The availability of suitable and extremely limited lung donors is another significant challenge in lung transplantation for these cases. PPFE patients may have specific anatomical or functional characteristics that make finding an appropriate donor more difficult, potentially leading to prolonged waitlist duration and delayed transplantation that increases the risk of death while waiting. Even if PPFE patients survive the early postoperative period, long-term survival rates remain lower than for patients with other causes of end-stage lung disease. Many of these patients will experience chronic graft dysfunction or progressive pulmonary complications (43,44). Given the poor prognosis and lack of effective pharmacologic therapies, transplantation offers the only potential for long-term survival. However, the high morbidity and mortality associated with lung transplantation necessitate careful patient selection and management. The prognosis of PPFE is generally poor, with most patients experiencing a steady decline in lung function over time. Survival rates are lower than for other fibrotic lung diseases, and rapid progression to respiratory failure may occur. However, some patients experience a more indolent course, and the clinical outcome may be influenced by the underlying etiology and comorbid conditions. Early diagnosis and appropriate management may mitigate disease progression.

Conclusions

Pleuroparenchymal fibroelastosis (PPFE) is a rare and often underrecognized form of interstitial lung disease characterized by progressive fibrosis of the pleura and adjacent lung parenchyma, predominantly affecting the upper lobes. The pathogenesis is not yet fully elucidated, and the pathological features may resemble those of other pulmonary diseases. Clinical presentation is variable, ranging from asymptomatic cases to severe respiratory failure. The condition is usually associated with a poor prognosis displaying a progressive course leading to acute or chronic type I or type II respiratory failure. Due to its similar or indistinguishable clinical, and radiologic profile with other interstitial, granulomatous, or autoimmune lung diseases, PPFE emerges as one of the most troublesome diagnostic challenges of pulmonary medicine. Occasionally, histopathologic evaluation of the pleural and parenchymal lung samples may remain inadequately conclusive for a definitive diagnosis. The benefits of antifibrotic agents, such as pirfenidone or nintedanib, are currently under investigation with limited evidence for a beneficial affect in the long term. Currently, lung transplantation appears to be the only treatment option in advanced cases. Clinicians should maintain a high index of suspicion for PPFE, especially in patients presenting with upper-lobe predominant fibrosis on HRCT and a history of environmental exposures or autoimmune diseases. Multidisciplinary management, including the consideration of lung transplantation in suitable candidates, is critical to addressing the needs of patients with advanced disease. As the understanding of this disease continues to evolve, it is hoped that advancements in molecular pathology and clinical trials will yield more impressive treatments for this challenging and often devastating condition.

Conflicts of Interest

Cuneyt Tetikkurt does not have any conflicts of interest to declare associated with this review.

Umit Seza Tetikkurt does not have any conflicts of interest associated with this review.

Source of Funding

There is not any source of funding or financial support for the conduct of the research and/or preparation of this review design, collection, analysis, and data interpretation.

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