# Assessment score for the diagnosis of a case with pleuroparenchymal fibroelastosis

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## Abstract

Idiopathic pleuropulmonary fibroelastosis is an extremely rare lung disease characterized by the combination of fibrosis of the visceral pleura and the fibroelastotic changes transcending in the subpleural lung parenchyma that predominantly affects the upper lobes with accompanying volume loss. It is mostly idiopathic while infection, autoimmunity, bone marrow or lung transplantation and genetic predisposition may be associated with the development of PPFE. The disease is exceptionally rare as approximately ninety cases have been reported in the literature currently. A 35-year-old female presented with exertional dyspnea, dry cough and weight loss. Physical examination demonstrated platythorax, suprasternal notch deepening and fine rales over the upper lobes. Blood count, serum biochemistry, autoimmunity and serologic markers for collagen vascular diseases were within normal limits. Arterial blood gases demonstrated a low $pO_2$ (48 mm Hg) and a high $pCO_2$ (54 mm Hg) values. Chest x-ray showed bilateral parenchymal fibrotic lesions, left pneumothorax, bronchiectasis in the middle and pleural thickening in the upper lung zones while HRCT revealed bilateral apical pleural thickening, traction bronchiectasis, subpleural reticulations, ground-glass opacities and honeycombing in the upper lobes. Bronchoscopy, BAL cytology, smear and culture did not reveal any pathologic findings. Relevant with the clinical, laboratory, radiologic manifestations and the differential diagnosis with other interstitial lung diseases, PPFE was the final diagnosis. The aim of this case report was to present the clinical manifestations of our case. The second crucial objective was to establish a diagnostic scoring system relevant with the literature and the clinical manifestations of the patient.

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## Introduction

Pleuroparenchymal fibroelastosis (PPFE) is an extremely uncommon disorder that was first reported by Amitani as an idiopathic upper lung fibrosis [1,2]. Later Frankel described the disease in a more detailed pattern [3,4]. The first cases of PPFE cast in a pattern of chronic interstitial pulmonary fibrosis along with pleural involvement [1,3]. Most patients are idiopathic while little is known about the etiology. PPFE may occur following conditions like bone marrow, stem cell, lung transplantation or occupational exposure [5-11]. The disease is characterized by upper lobe prevailing progressive fibrosis, subpleural elastosis, collagenous fibrosis leading to dense intraalveolar involvement and pleural thickening [1-4]. PPFE may imitate IPF [Idiopathic pulmonary fibrosis (IPF)]. The primary difference between IPF and PPFE is the location of radiologic findings where lower lobes are involved in the former while upper lung participation is dominant in the other. The clinical outcome of PPFE on the other hand, is similar to IPF but with a slower course of progressive pulmonary fibrosis [3-6].

First aim of this case report was to evaluate the findings of the presented patient and to review the clinical manifestations of the relevant PPFE cognisance in the literature. The second and the more noteworthy target was to establish a diagnostic scoring system relevant with the clinical profile of our patient itself and the current literature to designate a definitive identification algorithm for patients in whom the clinical profile for PPFE is equivocal and the tissue biopsy is unachievable.

## Case Report

A 35-year-old female presented with exertional dyspnea, dry cough and sixteen kilograms weight loss during the last eighteen

months. The patient was a never smoker. Personal or family history did not include any significant disease of concern. She was a housewife who did not have any previous environmental, occupational agent or drug exposure. Inspection of the thorax showed platythorax and suprasternal notch deepening (Figure 1) while finger clubbing was not present. Vital signs revealed a blood pressure of 120/70 mm Hg, a 120/min resting pulse and a 24/minute respiratory rate. Lung auscultation revealed fine rales over the upper lung zones. Blood count and biochemistry were within normal limits. Serologic markers for collagen vascular diseases and vasculitis including ANA, RF, anti-dsDNA ENA, cANCA and pANCA were negative. Serum ACE was 38 U/L. ECG showed sinus tachycardia of 120 beats/minute with a normal cardiac axis. Chest x-ray demonstrated thickened pleura in the upper lung zones peripherally, left apical pneumothorax, bilateral fibrotic lesions, patchy ground-glass infiltrations in the lung parenchyma and bronchiectasis (Figure 2). High resolution computed tomography (HRCT) revealed bilateral apical pleural thickening, left apical pneumothorax, parenchymal ground-glass opacities, bronchiectasis, platythorax, subpleural and parenchymal fibrotic lesions in the upper lobes (Figure 2). Pulmonary function tests demonstrated a restrictive pattern with a $FEV_1$: 1320 ml (58%), FVC: 1.08 (28%), $FEV_1$/FVC: 122%, TLC: 2.35 (48%) and a significant decrease in DLCO/VA: 2.86 (32%) value. Arterial blood gas analysis revealed type II respiratory failure with a low $pO_2$ (48 mm Hg) and a high $pCO_2$ (54 mm Hg) in room air. Six-minute walking distance was 300 meters. Fiberoptic bronchoscopy showed normal findings. BAL smear and culture were negative for bacteria, tuberculosis and fungal agents while cytologic evaluation did not demonstrate malignant cells, evidence of infection or foreign material like asbestosis fibers. Ophthalmologic examination showed normal findings. Rheumatology consultation did not indicate any connective tissue disease or vasculitis. Invasive diagnostic procedures such as transbronchial biopsy, VATS or surgical lung biopsy were not done because of the severe type II respiratory insufficiency with a significantly decreased pulmonary functional reserve. The patient responded well to oral 32 mg/day methylprednisolone treatment. Final diagnosis was PPFE as the clinical, radiological, laboratory manifestations of the patient and the differential diagnosis for other interstitial lung diseases evaluation have pointed out.

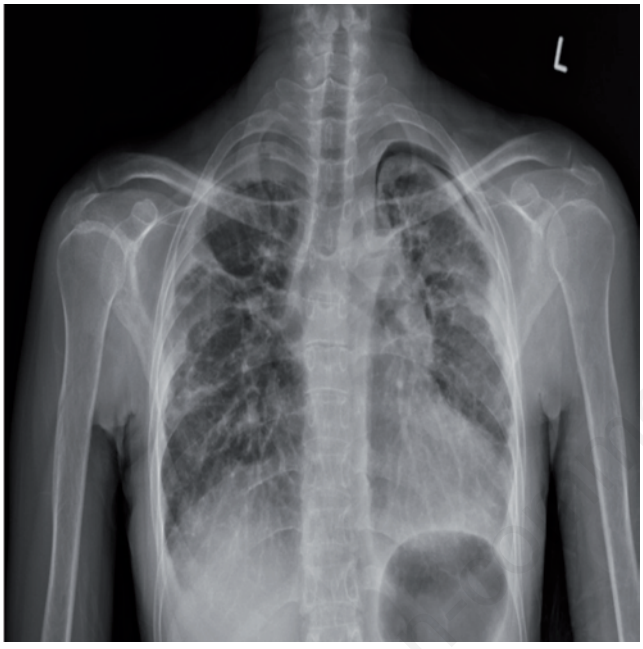


**Figure 1. Chest X-ray of the patient showing fibrotic parenchymal changes, left apical pneumothorax, ground-lass opacities and pleural thickening in both upper lung zones.**

## Discussion

PPFE is a rare disease first described by Amitani as an idiopathic lung fibrosis that leads to compact profound intra-alveolar fibrosis, significant elastosis in the alveolar walls with explicit fibrous thickening of the pleura exhibiting an intense upper zone predominance [1-5]. Most cases are idiopathic without an apparent cause, an associated explicit disease or a distinct exposure [2- 6]. Bone marrow, stem cell and lung transplantation can induce PPFE as a manifestation of graft versus host disease [7-10]. Occupational dust exposure such as asbestosis or aluminum may also elicit pleuroparenchymal fibroelastosis [11,12]. Mycobacterial disease or aspergillus infection have also been reported to precipitate PPFE [13-15]. It has been suggested that acute or subacute lung injury that leads to exuberant interstitial inflammation is the hallmark of the pathological cascade culminating with PPFE in these patients.

True incidence and prevalence of PPFE is unknown due to the uncertainties of diagnosis, absence of common identification crite-

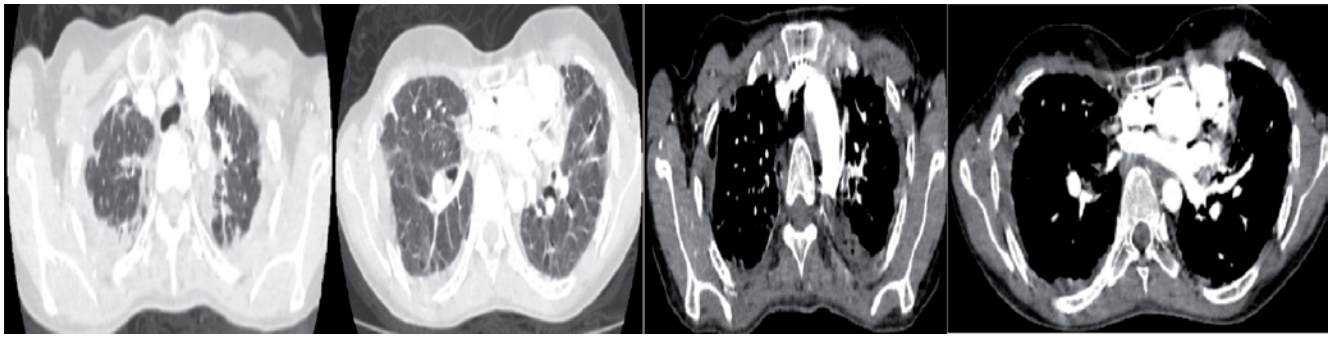

**Figure 2. Thorax CT revealing pleural thickening, fibrotic parenchymal lesions involving both upper long zones, ground-glass infiltrations, bronchiectasis and platythorax.**

ria and the rare occurrence of the disease. Most common conditions associated with PPFE include infections, bone marrow or lung transplantation while autoimmunity and genetic predisposition can contribute significantly to the development of PPFE [2-6]. Currently, there is no agreed diagnostic consensus for the identification of pleuroparenchymal fibroelastosis [4,15]. This patient was prelusively presented to put forward a diagnostic evaluation score in the light of its own clinical manifestations along with the current literature data that can guide the clinicians for an accurate diagnosis of such exclusive cases in whom tissue biopsy is unachievable.

A diagnostic assessment scoring profile including the current clinical manifestations of our case and the relevant literature data was put forward for the definitive identification of PPFE patients (Table 1). The diagnostic probability of PPFE was designated as inconsistent, low, intermediate and definitive (Table 2) according to the existence of clinical, laboratory and radiologic manifestations of the disease. The proposed diagnostic assessment scoring profile was constituted according to the PPFE manifestations revealed in literature [2-6,12,14] and of our patient itself. Diagnostic assessment scoring scale revealed significant correlation with the clinical findings of the presented case that pointed out to a definitive and a final diagnosis of PPFE. It is extremely crucial that this assessment scoring system will be highly successful, practical and convenient for confirming the definitive diagnosis in patients with a high probability of PPFE disease as it is the case in our patient.

The first algorithmic step was the absence of any interstitial disease, occupational or drug exposure in the personal history of the patient. The second hallmark was the existence of symptoms that may be relevant with any interstitial lung diseases such as dyspnea, dry cough and weight loss. The third benchmark was the existence of previous or current pneumothorax. Patient history, symptoms and the presence of pneumothorax were determined as weak diagnostic indicators for PPFE diagnosis because these features are also common manifestations of other interstitial lung diseases as well. All these attributes were all designated as one point in the diagnostic assessment score due to their low sensitivity.

The fourth triangulation point was the absence of finger clubbing in our patient which is a widespread manifestation of other interstitial lung diseases. Common factor in most types of clubbing, is digital vasodilation that results in increased blood flow to the distal portion of the digits. Whether vasodilation results from a circulating or a local vasodilator, a neural mechanism, a response to hypoxemia, a genetic predisposition or a combination of these is currently unknown [16-20]. The exact mechanism by which the increased blood flow results in changes in the vascular connective tissue under the nail bed is obscure. However, in some cases of interstitial lung diseases, hypoxia is absent in the presence of clubbing while many interstitial lung diseases with severe hypoxemia are not associated with finger clubbing. Genetic inheritance and predisposition may also play an outstanding role in digital clubbing [17-22]. The crucial hallmark is the absence of finger club-



**Table 1. Diagnostic assessment score of the clinical and radiologic manifestations of the pleuroparenchymal fibroelastosis patients.**

| Clinical and radiologic manifestations of pleuroparenchymal fibroelastosis patients | Index score |
|---|---|
| Absence of CVD, granulomatous infection, drug or occupational exposure | 1 |
| Weight loss | 1 |
| Dry cough | 1 |
| Dyspnea | 1 |
| Absence of finger clubbing | 3 |
| Suprasternal notch deepening | 3 |
| Platythorax | 3 |
| Current or previous pneumothorax | 1 |
| Restrictive pulmonary function tests | 1 |
| Low DLCO/VA | 1 |
| Decreased 6MWD | 1 |
| Hypoxemia | 1 |
| Chest x-ray findings* | 2 |
| Thorax CT manifestations** | 4 |
| TERT and TERC mutations | 3 |

CVD, collagen vascular disease; *chest X-ray findings: upper lobe involvement, bilateral pleural thickening, platythorax, decreased lung volume, pneumothorax, subpleural fibrosis, parenchymal fibrotic lesions, honeycombing, infiltrative changes and bronchiectasis; **thorax CT manifestations: upper lobe involvement, bilateral pleural thickening, platythorax, decreased lung volume, subpleural fibrosis, parenchymal fibrotic lesions, honeycombing, parenchymal infiltrations, pneumothorax, traction bronchiectasis and ground-glass opacities.

**Table 2. Clinical probability of pleuroparenchymal fibroelastosis according to the diagnostic assessment score.**

| Diagnostic assessment score | Probability of diagnosis of pleuroparenchymal fibroelastosis |
|---|---|
| DAS≤6 | Inconsistent |
| 6< DAS ≤12 | Low |
| 12< DAS ≤18 | Intermediate |
| DAS >18 | Definite |

DAS, diagnostic assessment score.

bing in PPFE patients despite the presence of long-term tissue hypoxemia as it was the case in our patient that should alert the clinician to the probable presence of PPFE rather than the existence of other interstitial lung diseases. Absence of finger clubbing emerges as a significant hallmark for the identification of PPFE which was nominated with three points in our diagnostic scale.

The fifth triangulation point was the existence of physical findings such as the suprasternal notch deepening and platythorax. Suprasternal notch deepening and platythorax appear as the most sensitive and the fundamental manifestations of PPFE since they almost never emerge as a sign of other interstitial lung diseases. Predominantly upper lung zone pleural thickening and subpleural parenchymal lung fibrosis are the relevant mechanisms that have led to these two aforementioned findings in the PPFE patients. Platythorax and suprasternal notch deepening were evaluated with three points, as they are not the expected default manifestations of other interstitial lung diseases that always indicate the unique physical examination finding for the PPFE patients. The presence of fine rales is the default manifestation of other interstitial lung diseases that was designated with only one point due to its low diagnostic significance. As hypoxia, restrictive pulmonary function tests, decreased DLCO/VA and low 6-minute walk test may occur as the ordinary laboratory manifestations of any interstitial lung disease, these findings were nominated with only one point for each.

There are no specific diagnostic laboratory tests for the PPFE patients. Inconsistently high levels of KL-6 and SP-D have been reported with equivocal consequences in PPFE [23-25]. Elevated serum autoantibodies and rheumatologic markers like rheumatoid factor and myeloperoxidase– antineutrophil cytoplasmic antibody revealed undetermined significance [3,25-28]. Increased levels of urinary desmosine have been shown by Oyama *et al.* in a preliminary study including individuals with biopsy proven PPFE compared to idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease and healthy control subjects with a potential utility of this test as a noninvasive diagnostic marker in patients with suspected but unbiopsied cases of PPFE [29]. None of these indicators are in routine clinical use due to their undetermined significance for PPFE. Consequently, the laboratory tests with equivocal significance were not included in the diagnostic assessment score scale due to their equivocal denotation that yet has to be determined.

As the sixth trig point, chest X-ray and thorax CT manifestations revealed disease unique attributes for an accurate identification of PPFE patients. The objective radiologic criteria for the indubitable PPFE diagnosis along with HRCT findings include upper or mid-lung predominance, presence of pleural thickening, subpleural or parenchymal lung fibrosis that exhibit predominanly upper lung zone involvement, ground-glass opacities, fibrotic lesions, traction bronchiectasis and platythorax. These features are almost genuine for PPFE notably when they exist in a compatible clinical setting. Such radiological manifestations are extremely rare in other interstitial lung diseases. The presence of current or previous mycobacterial, fungal infections or different diseases with a fibrotic sequela may preclude their diagnostic sensitivity. The CT findings were designated as four points while the score of the chest radiograph remained at two for PPFE diagnosis as the resolution of the thorax CT is much higher. Furthermore, the thorax and the lung parenchyma can easily be visualized in different imaging planes by CT that provides a much more elaborative image sequence, exclusively for the detection of subpleural fibrosis or other fibrotic lesions that may be readily missed with the conventional chest radiograph. Consequentially, thorax CT appears to be the most accurate diagnostic modality for the PPFE patients.

A history of familial pulmonary fibrosis is often present in PPFE patients. Existence of a familial link has been stated among 57% of these cases [1,3,28,30]. Genetic mutations can be detected even in PPE patients without an apparent family history of lung disease. A noteworthy association has been found between the TERT and TERC genes, associated with the telemore integrity and the telomerase function. A significant link has been described by Newton et al between the clinically outstanding PPFE variants and the abnormally shortened telomeres [31]. Likewise, the existence of such mutations has been also reported to be relevant with a progressive disease phenotype similar to that of UIP. These mutations have also been stated in half of a cohort PPFE patients most of whom were female with a low body mass index [32-34]. The existence of TERT and TERC mutations were designated as three points in our diagnostic assessment score since they were present in almost half of the PPFE patients. The TERT and TERC mutations were absent in our case.

Our patient exhibited virtually all the clinical, laboratory and radiologic manifestations of PPFE, revealed at Table 1, except the TERT and TERC mutations, that reached an assessment score of twenty-four points. This profile was almost the highest score that could be reached in terms of PPFE diagnosis in any case as well as our patient. The results indicate that the application of such an evaluation score can yield extremely beneficial results in terms of definite final diagnosis providing an exquisite pathway for the clinicians in practice. The assessment scoring system abstractively facilitates the diagnosis of PPE in patients who cannot undergo tissue biopsy due to various comorbid conditions. Utility of this approach will on the other hand, guide the clinicians in the right diagnostic pathway for an accurate identification of PPFE precluding the excrescent delay. The presence of platythorax and suprasternal notch deepening along with the compatible the chest x-ray and especially the thorax CT imaging manifestations of PPFE appears to be the fundamental keystone for the definitive diagnosis in our case and for other PPFE patients.

## Conclusions

PPFE is an extremely rare and yet clinically an unclassified interstitial lung disease. Diagnosis may exhibit significant challenges for the clinicians. Identification of PPFE does not pose any difficulties for clinically apparent cases in whom tissue biopsy is accessible. A diagnostic dilemma arises if the patients present with an atypical clinical profile when a diagnostic biopsy is unachievable. We believe that even if the diagnostic assessment score for any patient does not yield a definitive final diagnosis of PPFE, it will provide an exorbitant useful pathway for the clinicians by establishing the disease probability. Utility of such an application will not only preclude delay in diagnosis, but also will minimize the potential patient morbidity and mortality due to the implementation of invasive procedures.

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