Diagnosis of pleuroparenchymal fibroelastosis: a review

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Abstract

Pleuroparenchymal fibroelastosis (PPFE) is a rare lung disease with unprecedented features characterized by fibroelastotic changes in the subpleural lung parenchyma affecting the upper lobes. PPFE is usually idiopathic, but it can be caused by infection, autoimmunity, bone marrow or lung transplantation, or a genetic predisposition. Histopathologic examination of lung biopsy samples reveals homogenous subpleural fibrosis and abundant elastic fibers, allowing for a definitive diagnosis. As PPFE mimics many interstitial lung diseases, clinicians face significant difficulties in making a definitive final diagnosis. Since most disease-related comorbid conditions manifest at an advanced stage, invasive tissue sampling for histopathologic evaluation is consistently impossible. Such a patient presentation highlights the importance of an analysis based solely on clinical findings, which would provide a definitive diagnosis without the need for a biopsy. Because of its exceptional and inconceivable presentation, PPFE creates a diagnostic dilemma. In light of our two cases and the literature data, we present a diagnostic assessment score assay that relies solely on clinical manifestations without histopathological tissue verification to shed light on the diagnosis of PPFE. This review focuses on PPFE identification through the use of a diagnostic assessment analysis to improve early disease recognition without the use of invasive diagnostic interventions to obtain biopsy samples for histopathologic evaluation. This analytic approach, while not diagnostic in and of itself, may provide a useful pathway for differential diagnosis and may preclude redundant initiatives.

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Introduction

Pleuroparenchymal fibroelastosis (PPFE) is an extremely rare idiopathic interstitial lung disease with almost unique clinical features that was first enunciated by Amitani *et al*. as idiopathic upper lobe fibrosis [1]. The disease was subsequently described by Frankel *et al*. in a more detailed pattern [2]. PPFE develops as a combination of fibroelastic changes predominant in the subpleural parenchymal areas of bilateral upper lobes with accompanying visceral pleural fibrosis. Progressive volume loss, decreased body mass index, and platythorax ensue as unique disease features. Diagnosis is often achieved on the basis of clinical and explicit CT manifestations [3-5]. Although a number of disease associations have been described, no single cause of PPFE has been unequivocally identified. PPFE leads to progressive volume loss in the upper lobes and produces platythorax along with decreased body mass that follows an indispensably progressive course inducing respiratory failure [6]. PPFE has distinctive pathologic features of subpleural elastosis, intra-alveolar and visceral pleural collagenous fibrosis. It is usually idiopathic but may be associated with stem-cell, lung transplantation, or rarely ever with connective tissue disorders [3,4]. Prognosis is a variable that may follow an indolent disease course or may show a rapidly progressive disease leading to respiratory insufficiency with a fatal outcome. Treatment with steroids or immunosuppressive agents often fails and transplantation is required occasionally [6-8].

Epidemiology

Actual incidence and prevalence of PPFE are unknown, due to diagnostic uncertainties and lack of a definitive diagnostic

consensus. Approximately, 120 cases have been depicted currently. Patient age varies from 13 to 87 years with a mean of 53.0 years. The male/female ratio is 45% to 55% and there is no association with smoking [9-12]. Becker revealed that 5.9% of the 205 biopsied cases among 1622 patients undergoing ILD work up, had PPFE [8]. PPFE constituted 7.7% of IIP cases referred to a tertiary center [13]. Approximately, 25% of the patients with fibrotic ILD listed for lung transplantation had consistent imaging findings of PPFE [14].

Pathogenesis

Etiology is unknown but most cases are idiopathic [2-4,7,8]. Bone marrow, stem cell, and lung transplantation may cause PPFE due to graft *versus* host disease [15-17]. Occupational exposure to aluminum or asbestosis may induce PPFE [18]. Chemotherapy, an underlying genetic disorder, or mycobacterial or fungal infection may also cause PPFE [5-8]. An acute, or subacute lung injury such as diffuse alveolar damage may precipitate exuberant interstitial inflammation as the hallmark of the pathologic cascade culminating in PPFE. It exhibits individualized upper lobe dominant progressive fibrosis, subpleural elastosis with collagenous fibrosis causing dense intra-alveolar involvement along with pleural fibrosis and thickening [19-21]. The pathogenesis of such type of damage causing chronic well-circumscribed and subpleural elastin-rich fibrotic lesions is unknown [1-3,9-11].

Familial pulmonary fibrosis is frequent while an existence of a familial link has been stated among 57% of the PPFE patients. Genetic mutations may occur without an apparent family history of lung disease [7,22]. A significant correlation has been shown between the TERT and TERC genes, associated with telomere integrity and telomerase function [23]. Newton has revealed a notable link between PPFE variants and abnormally shortened telomeres [24]. The presence of such mutations has also been reported in patients with a progressive disease phenotype similar to UIP. The same mutations have been stated in female PPFE patients with a low body mass index [25] that may reveal a diagnostic significance for pleuroparenchymal fibroelastosis.

Pathology

Histopathologic examination is the hallmark for the final diagnosis that requires the demonstration of intra-alveolar fibrosis and elastosis with visceral pleural fibrosis. Pathology reveals predominant upper zone involvement, prominent homogenous subpleural intra-alveolar fibrosis with alveolar septal fibrosis, sparing or preservation of lung parenchyma away from the pleura, exiguous, patchy lymphoplasmacytic infiltrates, scarce fibroblastic foci along with pleural fibrosis. Intra-alveolar fibrosis and elastosis comprise dense collagenous fibrosis filling alveolar spaces with elastin deposition in the alveolar walls. Granulomatous inflammation may be present in approximately 15% of the cases but their presence may also represent a coexistent pathology such as HP or infection. Myofibroblasts in PPFE stain positively for podoplanin [9,11,12]. Interstitial lung diseases with accompanying fibrosis constitute the most important hindrance to PPFE differential diagnosis. In these cases, the histopathological assessment may be equivocal which necessitates the constellation of clinical and radiological findings that may reveal distinctive or unique PPFE features. Although histopathology is the most accurate final step for PPFE diagnosis, the drawback is that invasive procedures cannot be performed in most patients due to concomitant disease-related complications such as respiratory failure. Coexistence of other interstitial lung diseases may lead to confusion while characteristic PPFE lesions minimize this possibility, especially in the presence of typical clinical manifestations of the disease. In cases where histopathology remains equivocal introduction of clinical and radiological findings solves this problem to a large extent by providing a conclusive diagnostic contribution.

Clinical manifestations

Most of the patients present between 40 and 70 years of age but PPFE has been also reported in children and the elderly. A review of 78 cases from different series published up to 2013 revealed a bimodal age distribution ranging from 13 to 85, with a mean age of 49 years. The initial diagnostic step is the evaluation of patient history to establish the presence of previous granulomatous inflammation, CVD, medication, and occupational exposure along with a family history. A history of familial pulmonary fibrosis is often elicited from individuals with PPFE. and the presence of a familial link has been stated among 57% of the PPFE patients [1,3,21,22]. Patient symptoms and clinical manifestations constitute the most crucial landmark for diagnosis while such manifestations usually emerge in advanced cases. Duration of symptoms before admission varies from 6 to 24 months [4,5]. The most common symptom is progressive dyspnea on exertion followed by dry cough and weight loss. Progressive weight loss is frequent during the disease course that may point out to an intercurrent infection or occult malignancy [6]. Weight loss and low body mass index come out late in the disease course due to the increased workload of respiratory insufficiency. Muscle and adipose tissue loss may be associated with an unknown genetic defect or a metabolic disorder. Since these manifestations are usually belated, the most likely underlying mechanism seems to be energy loss due to increased respiratory workload. Although dyspnea, dry cough, weight loss, fatigue, and signs of respiratory failure are frequent manifestations of PPFE they do not show sufficient diagnostic sensitivity for PPFE, as they may commonly emerge as a manifestation of all systemic or lung disorders, especially the interstitial lung diseases. Symptoms of respiratory insufficiency comprising cyanosis, tachypnea, use of accessory respiratory muscles, nasal flaring, and Hoover's sign may develop in patients with advanced disease. Disease-unique inspection findings include suprasternal notch deepening and platythorax. The absence of clubbing in PPFE patients may constitute a benchmark in the differential diagnosis with other interstitial lung diseases, especially the idiopathic pulmonary fibrosis because it is an extremely rare manifestation of PPFE. The presence of these three findings emerges as an indispensable criterion for PPFE diagnosis. Auscultation may reveal inspiratory crackles in the upper lung zones that may occur commonly in many other lung disorders. Auscultation may reveal normal findings because inspiratory crackles or squawks may only be detected if the disease has extended outside the upper zones or when there is coexistent UIP, NSIP, or HP [5,6].

There are not any specific or characteristic laboratory tests that are useful for PPFE diagnosis. Restrictive pulmonary function tests decreased DLCO/VA, hypoxia, and hypercarbia may develop as late manifestations of PPFE without revealing a conclusive feature for differential diagnosis. If pleural involvement is extensive, the carbon monoxide uptake may be elevated because of extrapulmonary restriction. Patients with PPFE may develop hypoxemic respiratory failure with a typically widened alveolar–arterial gradient due to a reduced arterial oxygen pressure while arterial carbon dioxide is

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usually normal or nearly normal late until the advanced disease stage owing to hypoventilation or extrapulmonary restriction while hypercarbic death is usually uncommon. Platythorax may also lead to ventilation–perfusion mismatch [5,6].

Oyama *et al.* have shown increased levels of urinary desmosine in PPFE patients compared to patients with idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease, and healthy control subjects revealing the potential utility of this test as a non-invasive diagnostic marker in suspected PPFE cases [26]. KL-6 and SP-D may be elevated inconsistently in PPFE with unclear consequences while high levels of rheumatologic markers may exist without any significance [6,27,28]. Azoulay *et al*. have shown the existence of familial association and genetic transmission among PPFE patients [22]. A significant link has been revealed between the TERT and TERC genes that are associated with telomere integrity and telomerase function [23]. Abnormally shortened telomeres may occur among the eminent PPFE variants while the existence of these mutations was found to be relevant to a progressive disease phenotype similar to that of idiopathic pulmonary fibrosis. They have been identified in half of a cohort of PPFE patients most of whom were female with a low body mass index [23,24]. Because of the uncertainties in diagnostic sensitivity and specificity, none of the aforementioned laboratory markers are routinely used. Detection of TERT and TERC mutations may be useful in pathogenesis and diagnosis, but more research is needed to reveal their true diagnostic potential.

Radiology

Lung imaging turns out to be the foremost diagnostic utility for PPFE due to unique imaging manifestations. Chest X-ray may reveal bilateral irregular pleural thickening of the upper lungs in an otherwise normal lung. Chest X-ray carries a limited diagnostic value for early disease because of its low image resolution and display of non-specific findings. Infiltrations, bronchiectasis, ground-glass opacities, and pneumothorax may emerge as other PPFE features. Diagnostic yield of CXR increases in advanced disease when the fibrotic lesions become more evident. Platythorax as a late disease sequela can readily be detected on the lateral x-ray [5,7]. HRCT is the hallmark of clinical diagnosis that may disclose subpleural interstitial reticular opacities in the upper lung zones with almost normal middle and lower lobes revealing pleuroparenchymal thickening, sub-adjacent parenchymal fibrosis, traction bronchiectasis, bullae, cysts, ground-glass opacities, UIP, and NSIP pattern. Diagnostic HRCT criteria include upper lobe subpleural fibrosis with less marked or absent lower lobe involvement, and pleural thickening while the presence of platythorax may come out as the fundamental imaging finding [4-7]. Platythorax may be observed as a common finding due to weight loss and decreased BMI. Overlapping of the posterior tracheal border and spine along with the appearance of a highly noticeable deep suprasternal notch may develop because of reduced upper thoracic volume and progressive weight loss emerging as the other notable HRCT findings. HRCT appears to be the most distinctive imaging modality for accurate and unequivocal clinical diagnosis.

Treatment

There is no pharmacologic treatment that would prolong survival in PPFE patients. Bronchodilators, steroid treatment, and oxygen supplementation may provide temporary relief. Immunosuppressive agents are not useful in PPFE patients just as in idiopathic pulmonary fibrosis. On the other hand, pirfenidone or nintedanib may be beneficial by reducing lung fibrosis in PPFE because it shares similar pathologic mechanisms with idiopathic pulmonary fibrosis. Pirfenidone decreases fibroblast proliferation, inhibits transforming growth factor beta stimulated collagen production and reduces the production of fibrogenic mediators such as transforming growth factor beta. Pirfenidone has also been shown to reduce the production of inflammatory mediators such as tumor necrosis factor alpha and IL-1β in human peripheral blood mononuclear cells [29-31]. Nintedanib competitively inhibits tyrosine kinases (nRTKs) and receptor tyrosine kinases (RTKs). NRTK targets of nintedanib are Lck, Lyn, and Src. RTK targets of nintedanib comprise platelet-derived growth factor receptor (PDGFR) α and β; fibroblast growth factor receptor (FGFR) 1, 2, and 3; vascular endothelial growth factor receptor (VEGFR) 1, 2, and 3; and FLT3. Nintedanib inhibits PDGFR, FGFR, and VEGFR, which increase fibroblast proliferation, migration, and transformation [32-34]. These agents may also be useful in pulmonary fibrosis associated with collagen vascular diseases [31,35]. Consequently, pirfenidone and nintedanib may lead to effective and beneficial results for PPFE relevant to similar pathologic disease mechanisms. Further studies are needed to determine the exact efficacy levels of pirfenidone and nintedanib in the treatment of PPFE patients. The only treatment option is lung transplantation in patients with advanced disease but the outcome data for surgery is currently uncertain since there is not sufficient data relevant to transplantation as PPFE is an extremely rare disease.

Case #1

A 35-year-old female presented with exertional dyspnea, dry cough, and sixteen kilograms of weight loss in six months. Personal or family history did not reveal any disease of concern. There was no environmental and occupational exposure, or previous drug use. The patient had a thin body habitus with a 16.0 kg/m^2 BMI indicating adipose and muscle tissue loss. Vital signs showed a temperature of 36.6°C, blood pressure of 120/70 mm Hg, 120/min pulse, and a 24/min respiratory rate. Inspection of the thorax displayed platythorax, and suprasternal notch deepening (Figure 1). Auscultation revealed fine rales over the upper lung zones. Blood count and serum biochemistry were normal. Serologic markers for collagen vascular diseases and vasculitis including ANA, RF, anti-dsDNA ENA, cANCA, and pANCA were negative. ECG depicted a sinus tachycardia of 120 beats/minute with a normal cardiac axis.

Chest x-ray showed thickened pleura in both upper lungs, left pneumothorax, bilateral parenchymal fibrotic lesions, patchy ground-glass infiltrations, and bronchiectasis**.** 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: 1080 ml (28%), FEV_1/FVC: 122%, TLC: 2.35 (48%), and a low DLCO/VA of 2.86 (32%). ABG analysis displayed type II respiratory failure with a 48 mm Hg pO_2 and a 54 mm Hg pCO_2 on room air. 6MWD was 300 meters. TERT and TERC mutations were positive. BAL smear and culture were negative for bacteria, tuberculosis, and fungus while cytologic evaluation did not demonstrate any malignant cells, evidence of infection, or foreign material such as asbestosis. The patient responded well to oral 32 mg/day methylprednisolone treatment. The final diagnosis was pleuroparenchymal fibroelastosis

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as the clinical profile, the differential diagnosis for other interstitial lung diseases evaluation, and the diagnostic assessment score analysis have been pointed out.

Case #2

A 32-year-old male was admitted for dry cough, exertional dyspnea, and a weight loss of 10 kg in four months. His father had pulmonary embolism and his brother had died of an undiagnosed interstitial lung disease. He was a current smoker with a 6-pack-year history and did not have any previous environmental or occupational exposure, and drug use. The patient had a thin body habitus with a 16.2 m^2/kg BMI which pointed out the loss of adipose and muscle tissue (Figure 3). Vital signs showed a temperature of 36.4°C, a blood pressure of 130/80 mm Hg, a respiratory rate of 28 breaths/min, and a pulse rate of 120 beats/min. SpO_2 was 58% which increased to 95% with 1 L/min oxygen. Serum biochemistry, urine analysis, renal, and liver function tests were normal except for a high WBC count of $14x10^3/\mu L$ and a mildly elevated serum CRP level of 9.48 mg/l. ECG showed sinus tachycardia with a normal cardiac axis. ABG analysis revealed type II respiratory failure with pO_2:63 mm Hg and pCO_2: 48.5 mm Hg on room air. Serologic markers for collagen diseases or vasculitis were negative. CXR demonstrated a right pneumothorax and parenchymal ground-glass opacities in both upper lung zones. HRCT revealed bilateral irregular upper zone pleural thickening, subpleural parenchymal reticular changes, traction bronchiectasis, right pneumothorax, bilateral apical cysts, and focal glass ground opacities in the upper lobes (Figure 4). Pathologic examination of the lung wedge biopsy specimen revealed distinct subpleural fibrosis, with apparent elastosis that comprised a network of elastin deposition in the alveolar walls with intervening collagen deposition, and explicit pleural fibrosis compatible with pleuroparenchymal fibroelastosis.

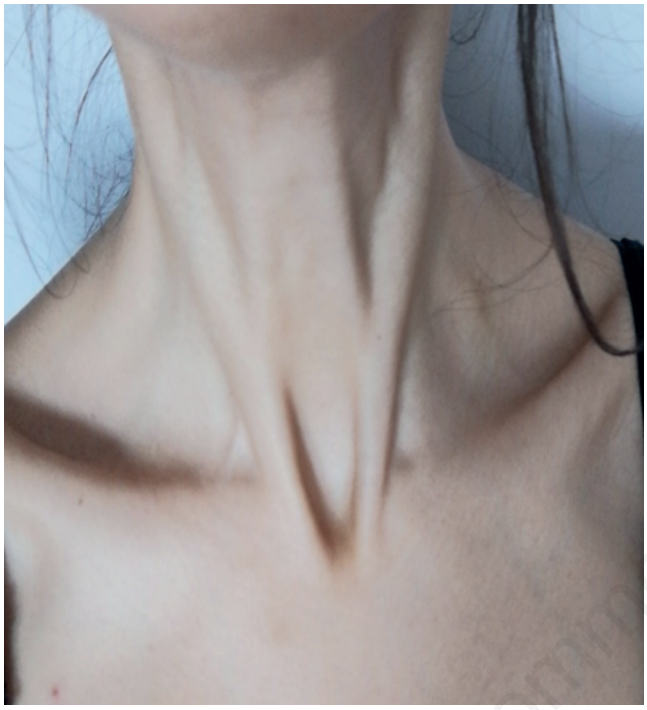

Figure 1. Deepened suprasternal notch in patient #1.

Discussion

Pleuroparenchymal fibroelastosis has been delineated as one of the rare idiopathic interstitial pneumonias that may not be as unusual as formerly presumed. There does not exist any consensus for a definitive diagnosis [6] other than the pathologic examination. Another crucial problem is the coexistence of other interstitial lung diseases in approximately 43% to 75% of the PPFE patients [3,10] which may lead to a significant dilemma in diagnosis. On the other hand, Watanabe et al have revealed that histology-proven PPFE patients may have lower lobe lesions or involvement in HRCT that may lead to a diagnostic challenge with the other interstitial lung diseases curtailing the sensitivity of CT imaging [7]. Accurate PPFE diagnosis poses a noteworthy drawback for clinicians. Achieving a

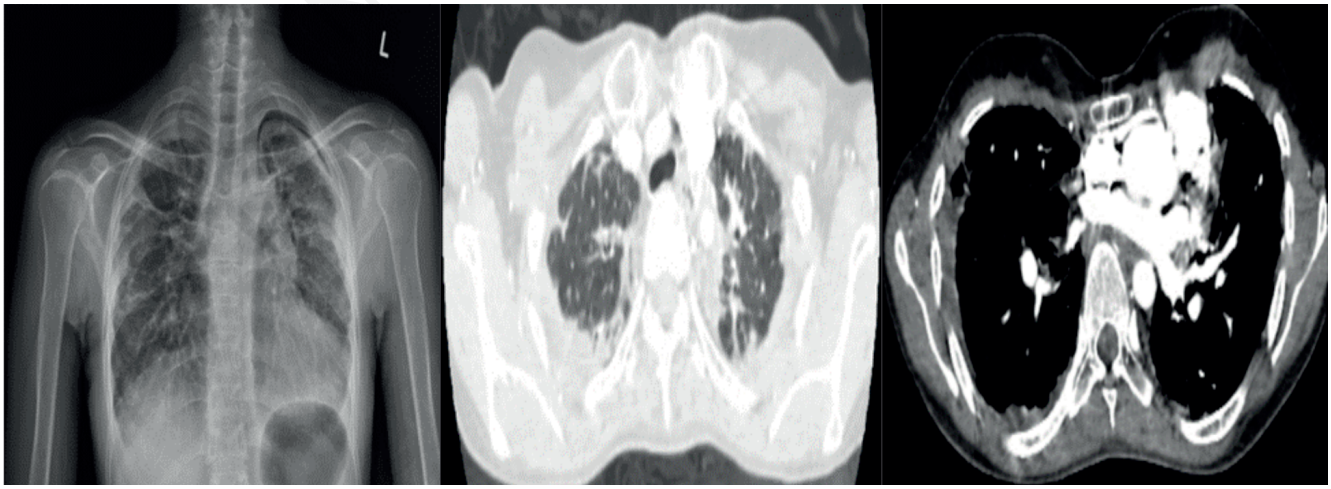

Figure 2. Chest X-ray and HRCT revealed pleural thickening, fibrotic parenchymal lesions involving both upper long zones, ground-glass opacities, bronchiectasis, and platythorax.

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definitive PPFE diagnosis, even in the presence of a biopsy, may pose a great confrontation due to the coexistence of other interstitial lung diseases. Moreover, comorbid conditions such as respiratory failure and pulmonary hypertension of advanced disease may preclude obtaining tissue samples by invasive procedures for pathologic evaluation to establish an unequivocal diagnosis.

Although characteristic imaging findings are detected by chest X-ray and HRCT, they may occasionally lead to equivocal or inconsistent conclusions for differential diagnosis with other interstitial lung diseases. Clinical findings may emerge as the cornerstone of definitive PPFE diagnosis. To ensure an accurate diagnosis, we introduced a diagnostic assessment score analysis solely based on the clinical findings (Table 1) without the need for pathological tissue examination. The new assessment score analysis includes a much better descriptive and conclusive delineation for an unequivocal diagnosis compared with the assessment protocol that we had presented previously [36]. The new protocol aims to maximize the possibility of diagnosis by the inclusion of new criteria and excluding subjective inclusions such as patient symptoms that may arise in many other lung diseases. Histopathological verification

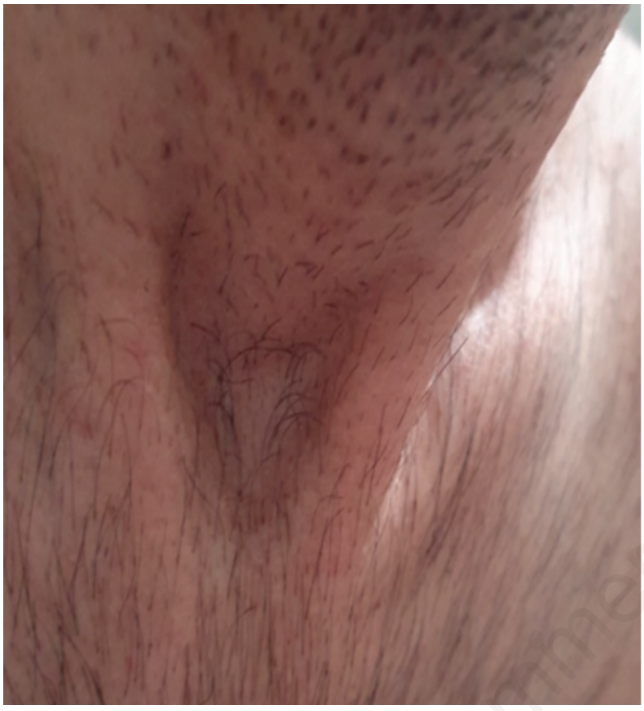

Figure 3. Deepened suprasternal notch in patient #2.

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

Clinical and radiologic manifestations of PPE	Index score
Absence of granulomatous infection, drug or occupational exposure	1
Family history	1
Exclusive lung confinement	1
BMI ≤16.2 (m^2/kg)	1
Absence of finger clubbing	2
Suprasternal notch deepening	3
Platythorax	3
Current or previous pneumothorax	1
Pulmonary function tests*	1
Laboratory findings°	1
Chest X-ray findings#	2
Thorax CT manifestations§	4
Compatible histopathology	5

*Pulmonary function tests, restrictive lung function, decreased 6MWD, hypoxia, and hypercarbia; °laboratory, KL-6, SP-D, urinary desmosine, TERT and TERC mutations; #chest-X ray, upper lobe involvement, bilateral pleural thickening, pneumothorax, platythorax, decreased lung volume, bronchiectasis, and subpleural fibrosis; §thorax CT, upper lobe involvement, bilateral pleural thickening, platythorax, decreased lung volume, subpleural fibrosis, pneumothorax, traction bronchiectasis, mosaic attenuation, suprasternal notch deepening, and UIP or NSIP pattern.

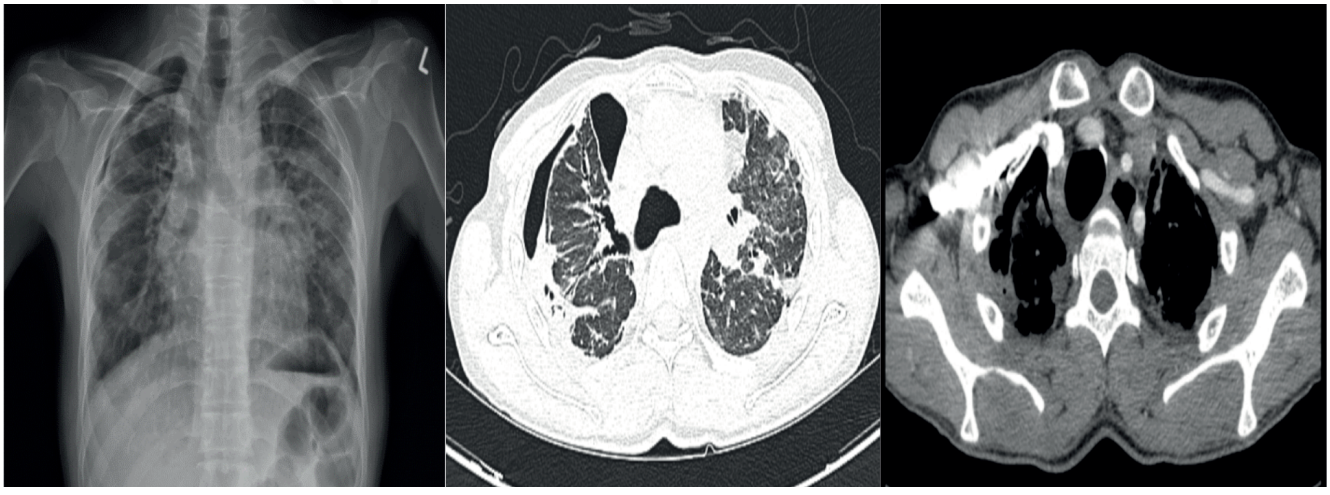

Figure 4. Chest X-ray showed right pneumothorax and parenchymal infiltrations. HRCT revealed bilateral irregular upper zone pleural thickening, subpleural parenchymal reticular fibrotic changes, traction bronchiectasis, right pneumothorax, bilateral apical cysts, and focal glass ground opacities.

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was also included in this new evaluation scale. The probability of PPFE diagnosis was put forward as inconsistent, low, intermediate, and definitive (Table 2) utilizing the clinical, laboratory, and radiological manifestations of the patients that emphasized reaching a definitive diagnosis without tissue biopsy requirement while histopathologic confirmation was also incorporated if achievable in stable patients. The proposed diagnostic assessment score was constituted based on previous literature data and the clinical findings of our two patients [2,3,6-9,19-21]. The diagnostic assessment score is depicted in Table 1 and PPFE probability is shown in Table 2. The new analytical approach established an accurate diagnosis relying solely on the clinical findings in both of our patients, one of whom had also a conclusive pathologic verification. Our results indicate that PPFE diagnosis can be achieved by applying the clinical manifestations without a biopsy requirement.

The initial step was to determine the existence of any interstitial or occupational lung disease, drug exposure, and family history. The presence of such factors was designated with only one point due to their low significance for PPFE diagnosis. The second point was exclusive confinement to the lung that was instituted with two points as only idiopathic pulmonary fibrosis would create a drawback for the differential diagnosis in regard to this criterion. The third scrutiny was the detection of a low BMI that was designated as one point because it would occur in any other lung or systemic disease. The most likely mechanism for low BMI is increased respiratory workload that emerges in the advanced stage. Normal hormonal and metabolic serum values confirmed the lack of any associated metabolic or hormonal disease in our patients indicating the increased workload of respiratory failure as the only eventual mechanism. Dyspnea, dry cough, and fatigue revealed an extremely low sensitivity as they frequently accompanied many other lung diseases and were not included for diagnosis since they emerged as common manifestations of many lung diseases and were not included in the assessment score analysis. Suprasternal notch deepening, and platythorax, appeared to be the most crucial triangulation findings for PPFE. The existence of these manifestations made the diagnosis highly probable and was assigned three points for each because they frequently came out as the unique characteristic findings of PPFE that scarcely ever develop in other lung disorders, particularly interstitial lung diseases. The absence of clubbing was assigned two points as a meaningful finding for PPFE that occurred frequently in interstitial lung diseases other than PPFE. Current or previous pneumothorax is a common manifestation of PPFE but its presence exhibits a slight contribution to diagnosis due to frequent association with other pulmonary disorders that were nominated with only one point. Signs of respiratory insufficiency such as cyanosis, tachypnea, nasal flaring, use of accessory respiratory muscles, and diaphragmatic fatigue were perceptual, intuitive or biased manifestations that were not included in the assessment analysis since they are common manifestations of many other lung diseases with respiratory failure.

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

Diagnostic assessment score	PPFE diagnosis probability
DAS ≤5	Inconsistent
6< DAS ≤11	Low
12< DAS ≤18	Intermediate
DAS >18	Definitive

DAS, diagnostic assessment score.

Restrictive pulmonary function tests, low DLCO/VA, decreased 6MWD values, hypoxemia, and hypercarbia were assigned with one point under the heading of pulmonary function tests as they revealed a low sensitivity for PPFE diagnosis that may arise in other diseases frequently as well and displayed a weak back up for PPFE patients with advanced disease only. Presence of elevated serum KL-6, SP-D, urinary desmosine levels, or the TERT and TERC mutations were designated with one point under the collective laboratory heading because of their low sensitivity along with their current unavailability for routine clinical use. Characteristic manifestations of chest X-ray are bilateral upper zone pleural thickening, parenchymal fibrosis, platythorax, alveolar infiltrations, ground-glass opacities, lobar volume loss, pneumothorax, and apical pleural caps restricted to the uppermost 5 mm of each hemithorax [6,37,38]. The presence of three or more of these findings was assigned with two points as its sensitivity was inconclusive for early disease due to low resolution and poor differential diagnostic potential of chest X-ray with other interstitial lung diseases.

CT manifestations of PPFE for definite PPFE include bilateral upper lobe pleural thickening, subpleural fibrosis, alveolar infiltrations, ground-glass opacities, traction bronchiectasis, pneumothorax, distortion of the airways within areas of PPFE, and mosaic attenuation of the lung parenchyma along with varying patterns of UIP of NSIP. Platythorax comes out as a frequent finding of PPFE correlating with weight loss and decreased BMI. Overlapping of posterior tracheal border and spine due to reduced anteroposterior thoracic depth and the appearance of a highly noticeable deep suprasternal notch resulting from reduced upper thoracic volume and progressive weight loss appear to be the other crucial CT manifestations [7,38-40]. The aforementioned CT findings are unique for PPFE diagnosis and the existence of three or more of these CT findings were appointed with four points. The ultimate endpoint for PPFE diagnosis was the presence of a histopathologic sample with compatible PPFE features that were designated with five points comprising a total score of 26 points in the assessment score analysis.

Diagnostic probability of PPFE was constituted as inconsistent, low, intermediate, and definitive (Table 2) according to the presence of clinical, laboratory, radiologic, and pathologic PPFE manifestations as revealed by literature data (2,3,6,7,37,38) and displayed by our cases. Diagnostic assessment scores revealed an inconsistent probability for scores of 5 or less and a definitive diagnosis probability of PPFE for those above 18 points (Table 2). Assessment score analysis revealed 20 points for the first and 25 points for the second patient. This approach confirmed the accurate diagnosis in both of our cases one of whom had an accurate histopathologic verification with compatible clinical findings while only the presence of clinical manifestations put forth an accurate PPFE diagnosis in the other patient.

The diagnostic assessment score approach will provide a conclusively exact diagnosis of PPFE patients without an imperative tissue biopsy. We conclude that our diagnostic assessment evaluation is practical, easily applicable, and highly authentic for confirming PPFE which is a usually diagnostic challenge in clinical practice. It is highly probable that a final unequivocal diagnosis can be achieved in almost all PPFE patients by relying solely on the clinical findings without a prerequisite invasive intervention for tissue samples by utilizing this simple analytic approach. This new assessment modality will precisely establish the accurate diagnosis by relying solely on the clinical manifestations while the availability of a compatible histopathologic analysis on the other hand will eliminate the difficulties of differential diagnosis with other or coexisting interstitial lung diseases.

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Conclusions

Pleuroparenchymal fibroelastosis is an extremely rare unclassified interstitial lung disease with unique clinical and radiologic manifestations. Although PPFE has distinctive features, it is frequently a noteworthy diagnostic challenge for clinicians with other lung disorders since most of the clinical manifestations come out late in the disease course. As most of the patients are admitted at an advanced disease stage diagnostic biopsy is often unachievable due to the coexistence of PPFE-associated respiratory insufficiency or other disease-relevant complications. The diagnostic evaluation score we have set forth presents an indispensable alternative for an accurate PPFE diagnosis, exclusively based on clinical manifestations. Even if the assessment score does not yield a definitive diagnosis, it will provide a useful pathway for disease probability that will as well preclude redundant interventions which may lead to significant morbidity and mortality in these patients. This new clinical approach provides an indubitable PPFE diagnosis in any circumstance including identification of equivocal cases, deterring inutile enterprises for tissue biopsy and implanting differential diagnosis with other interstitial lung diseases that determines almost a definitive diagnostic probability of pleuroparenchymal fibroelastosis patients.

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