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Review Article

Clinical Diagnosis of Pleuroparenchymal Fibroelastosis

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Abstract

Pleuroparenchymal fibroelastosis (PPFE) is an extremely rare interstitial lung disease (ILD) characterised by fibroelastotic changes predominating in the subpleural lung parenchyma with visceral pleural fibrosis involving the upper lobes. It has distinctive clinical, radiological, and pathological manifestations. Diagnosis constitutes literally a stalemate because of its rarity, unavailability of an agreed diagnostic consensus, and requirement of tissue biopsy for an accurate final diagnosis that can not be performed in most of the patients owing to the comorbid complications of the disease itself. Identification of PPFE may also pose great difficulties due to the coexistence of other interstitial lung diseases. PPFE usually exhibits a persistently deteriorating prognostic course culminating in fatal complications including respiratory failure, pulmonary hypertension, cor pulmonale, or pneumothorax. Presence of disease relevant complications frequently preclude invasive tissue biopsy interventions in these patients leading to a diagnostic challenge for clinicians.

This review aims to provide a definitive diagnosis based on entirely the clinical manifestatins of PPFE by shedding light on the pathogenesis, clinical, and radiologic findings of the disease. Histopathological tissue evaluation was also included in the diagnostic approach for patients whose condition was suitable for an invasive biopsy intervention. With this review, it is concluded that an approach consisting of exclusively clinical manifestations will ensure adequate support for an accurate PPFE diagnosis without any requirement for histopathological tissue examination.

Definition, pathogenesis, epidemiology, and pathology of pleuropulmonary fibroelastosis

TPleuroparenchymal Fibroelastosis (PPFE) is a rare idiopathic interstitial lung disease (ILD) with exclusive clinical manifestations. It was first described by Amitani [1] as upper lobe fibrosis that was later enunciated in more detail by Frankel [2]. The disease comes out with predominant fibroelastic lesions in the subpleural lung parenchyma perseveringly located in the lung apices [3,4]. Progressive parenchymal volume loss with eventual respiratory failue is the exemplary hallmark of PPFE prognosis in almost every patient. Etiology and pathogensis is unknown [2-4] while most cases are idiopathic [7,8] without a relevant autoimmune, vasculitic, infectious, or malignant cause. Diagnosis is often reached on the basis of clinical and the explicit computed tomography (CT) manifestations [3-7]. PPFE may develop as a consequence of many other diseases including bone marrow, stem cell, and lung transplantation due to graft versus host disease [9-11]. Asbestos and aluminum exposure may induce PPFE while chemotheraphy, genetic disorders, autoimmune or connective tissue disease, acute lung injury with a mycobacterial or a fungal infection, and chronic hypersensitivity pneumonitis may also play a role [13-16]. Acute or subacute lung injury precipitating an exuberant interstitial inflammation is the hallmark of the pathologic cascade leading to PPFE. The disease typically displays individualized upper lobe dominant subpleural elastosis with collagenous fibrosis causing dense intra-alveolar involvement, progressive fibrosis, and consequent pleural thickening. Pathogenesis of such type of damage leading to chronic well-circumscribed and subpleural elastin-rich fibrotic lesions in PPFE patients is currently unknown [17-20]. Treatment with immunosuppressive agents is not successful and the only option is lung transplantation in patients with advanced disease.

Incidence of PPFE is unknown because it is an extremely rare disease as approximately 120 cases have been reported up to now [4-6]. The uncertainty of disease incidence may also be relevant to the lack of an agreed diagnostic consensus, coexistence of other interstitial lung

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diseases, and the inability to clearly differentiate PPFE from other interstitial lung diseases. Mean age of presentation is 53 years ranging from 13 to 87 years. It is slightly more common in women, with a male to female ratio of approximately 45 to 55. PPFE is unassociated smoking [8,17,18]. Approximately 6% of the 205 biopsied cases among 1622 patients undergoing ILD work up had pathologic findings PPFE (8) while PPFE constituted 7.7% of the idiopathic interstitial pneumonia (IIP) cases referred to a tertiary center [19]. Shioya revealed that one fourth of the patients with fibrotic ILD listed for lung lung transplantation had consistent imaging findings of PPFE [20].

Occurence of hereditary pulmonary fibrosis with a familial link occurs among two thirds of the PPFE patients. Genetic mutations may be encountered in PPFE cases and a significant correlation between the TERC and TERT genes relevant to the telemore integrity or telomerase function has been revealed [21]. A noteworthy association has been revealed between PPFE and the abnormally shortened telomeres [22]. Similar or same mutations have been reported among female PPFE patients with a low body mass index (BMI) [23]. As shown in the aforementioned studies, genetic and hereditary disorders due to structural gene mutations may play a crucial role in the development of PPFE and the variability of the disease course.

PPFE has unique pathologic features consisting of subpleural elastosis and intra-alveolar collagenous fibrosis along with visceral pleural fibrosis displaying primarily upper lung involvement. Explicit homogenous subpleural alveolar and septal fibrosis with preservation of lung parenchyma away from the pleura. Scarce, patchy lymphoplasmacytic infiltrates, exigious fibroblastic foci, and pleural fibrosis may be observed. Alveolar fibrosis and elastosis occurs with dense collagenous filling of alveolar spaces along with elastin deposition in the alveolar walls. Granulomatous inflammation may exist in approximately 15% of the cases that may reveal HP or infection. Myofibroblasts in PPFE stain positively for podoplanin [17,24,25]. Progressive volume loss in the upper lung zones along with the ongoing weight loss due to respiratory failure leads to platythorax as the fundamental manifestation of PPFE patients.

Clinical manifestations and treatment

Age of onset varies between 40 and 70 with a bimodal age distribution ranging from 13 to 85 years. Initial step in the assessment of patients suspected for PPFE is to set forth the presence of previous ILD, occupational or drug exposure, granulomatous inflammation, and a relevant familial link that may occur among 57% of the PPFE patients [1-3,26,27]. Patient symptoms and clinical manifestations are the fundamental landmark for diagnosis. The mean duration of symptoms before admission ranges from approximately 6 months to 24 months as the disease is less well known similar to idiopathic pulmonary fibrosis (IPF) patients. The most frequent symptom is progressive dyspnea on exertion followed by dry cough and weight loss that emeges as a late manifestaion in most of the patients. Weight loss and low BMI come out as a sequela of advanced disease due to the energy loss of increased workload of respiratory insufficiency.

Cyanosis, tachypnea, use of accessory, and Hoover's sign are frequent manifestations of PPFE patients with advanced disease revealing the presence of respiratory insufficiency in these cases. Because they may emerge in any lugn or systemic disease with respiratory failure they do not carry an adequate sensitivity or specificty for PPFE diagnosis. Lack of finger clubbing is a crucial manifestation for PPFE in the differential diagnosis with other interstitial lung diseases as it a common finding in these patients. Presence of suprasternal notch deepening and platythorax are fundamental inspection findings for PPFE diagnosis. Consequently, existence of these manifestations appear as the prerequisite and sine qua non signs for PPFE. On the other hand, rales which may appear as auscultation findings, are of no specific diagnostic value since they may emerge in almost any other lung and systemic disease.

Unfortunately, there are no unprecedented diagnostic laboratory findings for PPFE. Restrictive pulmonary fuction tests, decreased DLCO/VA, hypoxia, and hypercarbia may occur without a conclusive or distinctive diagnostic feature for PPFE as they may come out very frequently in many other disorders, especially the ILD. PPFE patient may have increased levels of KP-6, SP-D, or rheumatologic markers [28,29] along with high levels of urinary desmosine [30]. A familial link or genetic transmission may be present in PPFE patients [31,32]. Genetic studies may detect TERT and TERC mutations and abnormally shortened telomeres have been shown in female PPFE patients with a low BMI [33,34]. Although laboratory and genetic markers can support the diagnosis in PPFE patients, their potential appear to be far from providing a significant diagnostic contribution. Another drawback about these modalities arises from the fact that they are not routinely applied since they are only used in advanced research centers.

Lung imaging turns out to be the foremost diagnostic utility for PPFE due to unique and dşsease exclusive findings. Chest x-ray may reveal bilateral irregular pleural thickening of the upper lungs in an otherwise normal lung but carries a limited diagnostic value for early disease becasuse of its low image resolution and display of non-specific findings. Infiltrations, bronchiectasis, ground-glass opacities, and pneumothorax may be observed as other radiologic findings. Diagnostic yield of chest x-ray 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]. High-resolution computed tomography (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, subadjacent parenchymal fibrosis, infiltrations, pneumothorax, traction bronchiectasis, bullae, cysts, ground-glass opacities, UIP, and NSIP pattern. The fundamental diagnostic HRCT criteria include upper lobe subpleural fibrosis with less marked or absent lung involvement in other areas along with irregular pleural thickening. Platythorax is a frequent imaging manifestation that occurs due to extreme weight loss and decreased BMI of increased workload of respiration. Posterior tracheal border and spine convergence along with a notable deep suprasternal notch appearence may develop because of reduced upper thoracic volume and progressive weight loss that emerge as the other crucial diagnostic HRCT findings [4-7]. Consequently, HRCT apeears to be the most distinctive and exclusive modality for an accurate identification of PPFE patients, especially in a compatible clinical setting along with an explicit differential diagnosis from other ILD. Radiologic spectrum of PPFE is extremely similar to IPF where imaging may introduce an unequivocal diagnosis in most of the patients. Diagnostic assessment score analysis by Tetikkurt et al has defined a new pathway for the clinical diagnosis of PPFE patients doess not require histopathological

tissue biopsy evaluation [35] while a recent version of this algorithm comprising more objective diagnostic criteria is under publication. A new diagnostic algorithm, which includes more precise and objective diagnostic criteria for a definitive and accurate diagnosis of PPFE is still under publication [36].

PPFE may show a gradual progressive course over 10–20 years but a median survival of 11 years is the usually the expected survival outcome for most of the patients [1-3,7]. A longitudinal disease behavior divergence is becoming increasingly recognized among PPFE patients with a progressive disease phenotype. Such patients have a median survival of approximately less than 5 years that is almost identical to the prognosis of IPF [6]. Rapid forced vital capacity (FVC) decline in PPFE patients may indicate a shortened survival with a worse prognosis leading to death within 2 to 3 years of diagnosis [37]. Approximately, one-third of the 36 cases died within 12 months exhibiting a cohort median survival of 24 months [38]. Patient prognosis primarily depends upon hereditary or genetic factors while outcome is usually associated with intervening disease complications such as respiratory failure, pulmonary hypertension, infection, or pneumothorax while coexisting other interstitial lung diseases may also contribute to a shortened survival.

Regarding treatment, currently there is not any pharmacological treatment option that can contribute to the survival of PPFE patients. While bronchodilator agents and steroids can only provide temporary symptomatic relief in some patients, they have do not have any effect on prognosis. As in all other similar interstitial diseases, immunosuppressive agents have not been shown to have any positive effect on life expectancy and exert a negative contribution to survival due to their serious side effects. In terms of immunosuppressive treatment, PPFE shows great similarities with IPF. Antifibrotic agents, on the other hand, can provide a prognostic contribution to patient survival by slowing down fibrosis similar to IPF. Pirfenidone decreases fibroblast proliferation, inhibits transforming growth factor beta stimulated collagen production, and reduces the production of fibrogenic mediators while may also reduce production of inflammatory mediators such as tumor necrosis factor alpha and Interleukin (IL)-1β in human peripheral blood mononuclear cells [39-41]. Nintedanib competitively inhibits tyrosine kinases and their receptors. These include 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 also inhibits PDGFR, FGFR, and VEGFR which increase fibroblast proliferation, migration, and transformation [42-44]. Nintedanib has also been useful for the treatment of pulmonary fibrosis associated with collagen vascular diseases [45]. Further large-scale studies comprising different populations with distinctive genetic features are required to define the exact effectivity adequacy of pirfenidone and nintedanib for PPFE patients. Lung transplantation seems to be the only treatment option that will be effective to prolong the survival in patients with advanced disease. Prognostic survival or outcome data for lung transplantation is currently lacking as there are not any sufficient studies relevant to surgical treatment because PPFE is an extremely rare disease, may have been misdiagnosed due to the absence of an agreed diagnostic consensus, and accompanying other interstital lung diseases that may interfere with the patient mortality.

The most definitive and accurate criteria for the diagnosis PPFE appear to be the clinical manifestations of the patients. Presence of suprasternal notch deepening and platythorax are unique for PPFE patients while absence of finger clubbing is keystone and benficial for the differential diagnosis with other ILD such as IPF [46-48]. Inspection findings of suprasternal notch deepening or platythorax are the fundamental and definitive hallmark of PPFE diagnosis (Figure 1). Laboratory findings are not sensitive for PPFE as they are frequently encountered in many lung diseases interstitial or not, along with other systemic diseases. Chest x-ray may display useful manifestations but low image resolution and appearence of these verities in advanced disease stage occurs to be the fundamental drawback or inconvenience. Thorax CT is emerges as the most useful and definitive imaging modality for PPFE and is the hallmark of clinical diagnosis.

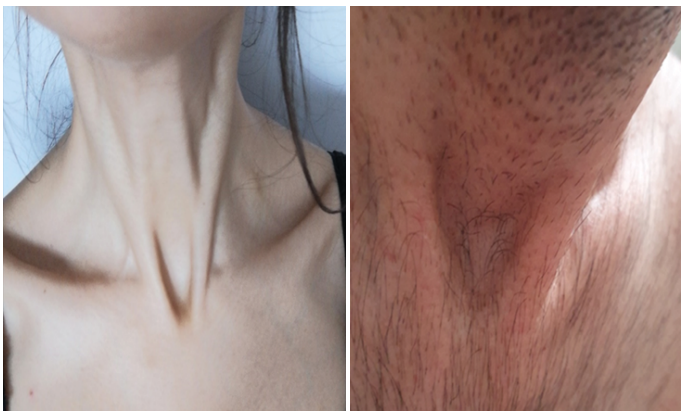

Figure 1. *Two patiens with suprasternal notch deepening [36].*

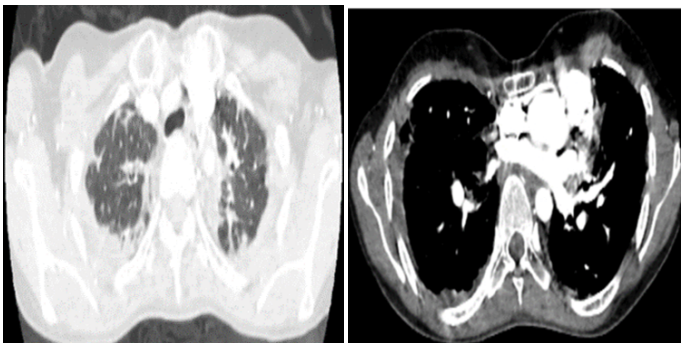

Figure 2. *Thorax CT manifestations of the PPFE revealing pleural thickening, subpleural parenchymal fibrosis, platyhorax, and suprasternal notch deepening [36].*

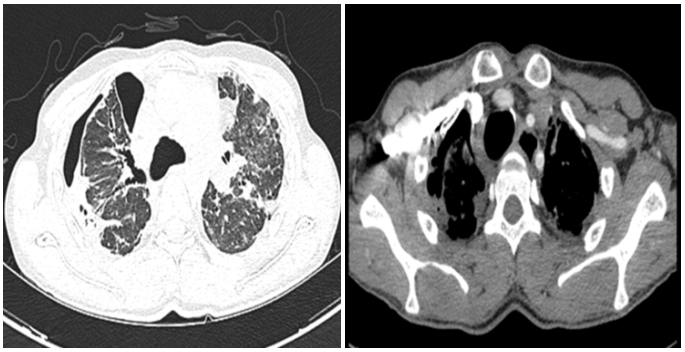

Figure 3. *Thorax CT findings of the PPFE patient showing pleural thickening, pneumothorax, subpleural fibrosis, and suprasternal notch deepening [36].*

In addition to the high image quality due to high resolution, the ability to obtain images in axial, coronal and sagittal cross sections makes thorax CT an indispensable diagnostic tool in both early and late disease stages (Figure 2,3). Furthermore to revealing the visual features of other interstitial diseases in the differential diagnosis, thorax CT is the greatest guide in both the diagnosis and differential diagnosis for detecting distinct lesions and other ILDs that may coexist. Thorax CT can also detect pathological events such as suprasternal notch deepening and platithorax that cannot be detected by physical examination or chest X-ray. An accurate definitive diagnostic identification of PPFE entails histopathologic evaluation of the tissue biopsy samples of the lung parenchyma and the pleura. Unfortunately, it is almost impossible to perform an invasive diagnostic procedure for tissue biopsy in most of the patients due to PPFE relevant natural complications. Since this situation necessitates making the diagnosis according to clinical manifestations in the vast majority of patients, the diagnostic evaluation score we have introduced provides a great support to clinicians both for the definitive diagnosis of the disease and the differential diagnosis with other ILDs. We have reached an accurate defingtive diagnosis in two PPFE patients by using the diagnostic assessment score analysis (Tables 1 and 2) without the slightest reqiurement for tissue biopsy [35,36]. This analytical approach, besides its usefulness in terms of an accurate and definitive diagnosis, provides an effective approach to clinicians by creating a diagnostic pathway for the differential diagnosis with other interstitila lung diseases and for the evaluation of suspicious pleuroparenchymal fibroelastosis cases to preclude the redundant diagnostic interventions.

Table 1. *Diagnostic assessment score for the clinical and radiologic manifestations of pleuroparenchymal fibroelastosis patients [36].*

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

CVD: collagen vascular disease
* 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, penumothorax, platythorax, decreased lung volume, bronchiectasis, and subpleural fibrosis
**** Thorax CT: upper lobe involvement, bilateral pleural thickening, platythorax, decreased lung volume, subpleural fibrosis, penumothorax, traction bronchiectais, mosaic attenuation, deep suprasternal notch deepening, and UIP or NSIP pattern

Table 2. *Probability of pleuroparenchymal fibroelastosis diagnosis [36].*

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

DAS: diagnostic assessment score

Conclusions

PPFE is an uncommon and recently described ILD for which there does not exist an agreed diagnostic consensus. Since it is an extremely rare disorder that may be also accompanied by other ILDs, it often leads to a diagnostic dilemma for the clinicians. Although the disease has unique clinical and radiological features, tissue biopsy is absolutely required for and accurate and definitive diagnosis. Complications such as respiratory failure or pulmonary hypertension that emerge due to the subsistent complications of the disease itself often precludes an invasive procedure for diagnostic tissue sampling. Invasive procedures may lead to life-threatening incidents in these patients because of the possible serious disease sequela that may have developed before biopsy or may emerge acutely due to the invasive procedure to be performed itself for obtaining tissue biopsy. An accurate diagnosis can be reached relying solely on the clinical and radiological manifestations without any requirement for invasive tissue sampling for pathologic evaluation. Biopsy may only be an option in stable patients without any respiratory or other systemic complications if equivocal or suspicious clinical findings for PPFE exist. We firmly believe that the diagnostic assessment score analysis we have introduced will obviate the drawback of definitive diagnosis dilemma that often arises in all patients that leads to a diagnostic challenge for the clinicians..

Author contribution

Cuneyt Tetikkurt designed and wrote the review

Conflicts of interest

Cuneyt Tetikkurt has no conflicts of interest to declare associated with this review..

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