Mini Review

CLINICAL INVESTIGATION

Clinical diagnosis of pleuroparenchymal fibroelastosis

Abstract

Pleuroparenchymal Fibroelastosis (PPFE) is a rare interstitial lung disease characterised by fibrosis of the visceral pleura with fibroelastotic changes predominating in the sub pleural lung parenchyma involving the upper lobes. The disease has unique clinical, radiological, and pathologic manifestations. Diagnosis is a challenge for clinicians because it is an extremely rare disease, there is no agreed consensus, and tissue biopsy is required for final diagnosis. PPFE may display a relentlessly progressive clinical course leading to an irreversible respiratory failure. PPFE diagnosis may cause serious difficulties due to the presence of other accompanying interstitial lung diseases, and comorbid sequela of the disease itself such as respiratory failure that usually precludes the diagnostic interventions for tissue biopsy.

This review focuses on the clinical PPFE profile revealing epidemiologic, physiopathologic mechanisms, clinical, radiologic, and pathologic manifestations to reach a definite diagnosis exclusively relying on the clinical findings alone without a tissue biopsy that is frequently unachievable due to the comorbid complications of pleuroparenchymal fibroelastosis.

Keywords: Pleuroparenchymal fibroelastosis • Interstitial lung disease • Intraalveolar fibrosis • PPFE

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Cuneyt Tetikkurt*

Department of Pulmonary Medicine, Cerrahpasa Medical Faculty, Istanbul Cerrahpasa University, Istanbul, Turkey

*Author for correspondence:

tetikkurt@gmail.com

Tel: +905323810900

Introduction

PPFE is a rare idiopathic interstitial lung disorder with unique clinical features that was first enunciated by Amitani and the disease was subsequently described in more detail by Frankel [1,2]. Pleuroparenchymal fibroelastosis emerges with visceral pleural fibrosis, fibroelastic changes in the sub pleural lung parenchyma, and is consistently located in the lung apices [3,4]. Progressive lung volume loss leading to eventual respiratory failure is the hallmark of PPFE. Diagnosis is often achieved on the basis of clinical and the explicit CT manifestations [3-7]. Etiology is unknown [2-4] but most cases are idiopathic while PPFE may be associated with many other disorders [7,8]. Bone marrow, stem cell, and lung transplantation may lead to PPFE due to graft versus host disease [9-11]. Occupational exposure to asbestos and aluminum may induce PPFE while chemotherapy, an underlying genetic disorder, autoimmune or connective tissue disease, acute lung injury particularly due to mycobacterial or a fungal infection, and chronic hypersensitivity pneumonitis may also culminate in PPFE [12-16]. Acute or subacute lung injury precipitating exuberant interstitial inflammation is the hallmark of the pathologic cascade leading to PPFE that exhibits individualized upper lobe dominant progressive fibrosis, sub pleural elastosis with collagenous fibrosis causing dense intra-alveolar involvement, and pleural thickening. The pathogenesis of such type of damage leading to chronic well-circumscribed and sub pleural elastin-rich fibrotic lesions is unknown [17-20].

PPFE has unique and distinctive pathologic features of collagenous visceral pleural fibrosis, sub pleural elastosis, and intra-alveolar collagenous fibrosis [17, 19, 20]. The disease causes progressive volume loss in the upper lung zones leading to platy thorax as the fundamental physical finding of the disease and follows gradual profile with consequent respiratory failure. Bronchodilators provide a temporary relief while with steroid and immunosuppressive treatment often fails. Lung transplantation seems to be the only treatment option that can increase the quality of life and life expectancy for these patients [7,8].

Actual incidence and prevalence are unknown due to the rarity of the disease, uncertainty of diagnosis, absence of an agreed diagnostic consensus, and coexistence of other interstitial lung diseases [6]. Approximately, 120 cases have been reported up to now. The age of onset ranges from 13 to 87 years, with an average of 57 years. Male female ratio is 45% to 55% and there does not exist any correlation with smoking [17-19]. Among 1622 patients undergoing ILD work up, Becker revealed that 5.9% of the 205 biopsied cases had PPFE [8]. One fourth of the patients with fibrotic ILD listed for lung lung transplantation had consistent imaging findings of pleuroparenchymal fibroelastosis [21].

A familial link has been revealed among 57% of the PPFE patients. Genetic mutations may occur without an apparent family history of lung disease [22]. A notable link between PPFE variants and the abnormally shortened telomeres has been revaled [23]. These mutations have also been shown in patients with a progressive disease phenotype similar to UIP [24]. The same mutations are present in most of the female PPFE patients with a low body mass index revealing that the presence of TERT and TERC mutations carry a notable diagnostic significance for pleuroparenchymal fibroelastosis [25]. Pathologic diagnosis requires upper visceral pleura fibrosis, homogenous subpleural intra-alveolar fibrosis sparing of lung parenchyma away from the pleura, scattered lymphoplasmacytic infiltrates with sparse fibroblastic foci [19,20]. Most common ILD to coexist with PPFE is Usual Interstitial Pneumonia (UIP), reported in one-fourth to one-half of the cases [26- 32]. Coexistent UIP and even NSIP occur most frequently in the lower lobes unlike PPFE while such a simultaneous occurence may lead to a diagnostic intricacy.

Clinical manifestations

A detailed patient history along with a meticulous physical examination are the hallmark for an accurate PPFE diagnosis. Patient history constitutes the most important step by revealing the existence of familial disease, drug or occupational exposure, and other interstitial lung diseases. Familial pulmonary fibrosis is often present and a familial link has been reported in approximately two thirds of the PPFE patients [18]. Patient symptoms and physical findings usually emerge in advanced disease with a duration of symptoms before presentation varying from 6 months to 24 months. The commonest symptom is insidous progressive dyspnea in exertion and dry cough; nonspecific chest discomfort, and pleuritic pain are reported while persisting pain is unusual in the absence of a pneumothorax [4,6,7]. Dyspnea on exertion followed by dry cough usually emerge as the initial symptoms. Progressive weight loss may raise the possibility of an intercurrent infection or an occult malignancy. Weight loss and low body mass index probably occur due to the increased respiratory workload of advanced disease relevant to pulmonary insufficiency. Other findings such as cyanosis, tachypnea, use of accessory respiratory muscles, nasal flaring, and Hoover's sign may come out in the later disease course.

Absence of clubbing, presence of plathythorax, and deepened suprasternal notch are the hallmark physical findings for PPFE diagnosis. Many patients with PPFE develop platythorax as a result of marked upper lobe volume contraction in conjunction with reduced chest wall bulk due to weight loss causing a decreased anteroposterior thoracic depth and flattening of the anterior chest wall. Significant low body mass index is an extremely common finding [21,22,23]. Distinct low body mass index is most likely due to the energy loss caused by increased respiratory workload of respiratory failure. Suprasternal notch deepens considerably that is easily detected by inspection. Chest CT may demonstrate a prominent deepened suprasternal notch radiologically. Suprasternal notch deepening is a definitive clinical manifestation in many patients due to the same physiopathologic mechanisms causing platythorax as the most significant diagnostic verity of PPFE. Absence of finger clubbing emerges as an extremely significant finding that may rule out idiopathic pulmonary fibrosis.

There does not exist any specific laboratory test for PPFE diagnosis. Restrictive pulmonary function, decreased DLCO/VA, hypoxia, and hypercarbia are the most frequent manifestations of advanced disease. KL-6 and SP-D may be elevated inconsistently in PPFE patients [17,22]. High levels of rheumatologic markers may occur without any clinical significance [2,24]. Increased urinary desmosine may have a potential utility as a non-invasive diagnostic marker in suspected PPFE cases [22]. None of the aforementioned laboratory markers are utilized routinely due to their uncertain diagnostic sensitivity and specificity. Presence of TERT, TERC mutations and the abnormally shortened telomers are frequently observed in PPFE patients [25-27].

Chest x-ray may show bilateral irregular pleural thickening in the upper lungs in an otherwise normal lung. CXR has a limited diagnostic sensitivity in early disease due to its low image resolution while its diagnostic yield increases in advanced disease when the fibrotic lesions become more evident. Platythorax is readily detected on the lateral chest x-ray. HRCT is the fundamental modality for clinical diagnosis even in early disease stages due to its high resolution that may reveal subpleural interstitial reticular opacities in the upper lung zones with almost normal middle and lower lobes while revealing pleuroparenchymal thickening, subadjacent parenchymal fibrosis, traction bronchiectasis, bullae, cysts, and UIP or nonspecific interstitial pneumonia pattern. HRCT diagnostic criteria include upper lobe pleural thickening and subpleural fibrosis with less marked or absent lower lobe involvement [4,5,6,7]. HRCT

appears to be the only imaging modality that can procure a definitive diagnosis.

Prognosis and outcome

PPFE may progres gradually over 10 years –20 years [1]. A median survival of 11 years is usually the expected outcome for most of these patients [7]. Divergence in longitudinal disease behavior is increasingly recognized in acknowledgment of a subgroup of patients who are prone to inexorably advancing disease. This progressive disease phenotype has a typical median survival of less than 5 years and it has been described in patients with PPFE [6,31]. Rapid decline of FVC in PPFE patients is associated with a shortened survival and a worse prognosis leading to death within 2 years to 3 years of diagnosis while another study revealed that one-third of the 36 cases progressed from diagnosis to death within 12 months, resulting in a cohort median survival of 24 months [33,34]. Survival may be influenced with comorbid disorders, accompanying other interstitial lung diseases, or the presence of complications such as respiratory failure, pulmonary hypertension, or pneumothorax.

Conclusion

Pleuroparenchymal fibroelastosis is an extremely rare interstitial lung disease. It appears as a diagnostic challenge for the clinicians due to its rarity, lack of an agreed diagnostic consensus, uncertain or obscure profile of the disease. Lung CT appears to be the most useful imaging modality while an accurate diagnosis is only eligible by histopathologic examination of lung biopsy that is frequently unachievable due to the cormobid complications of the disease itself. A diagnostic assessment score developed by Tetikkurt et al. can reveal the definitive PPFE identification relying solely on the clinical manifestations, without an absolute biopsy requirement. Another revised and an improved diagnostic assessment score analysis comprising the tissue biopsy evaluation for an accurate PPFE diagnosis is currently in the state of unpublished data that is under evaluation in the journal it was submitted to be published. This review will be useful for clinicians to reach an unequivocal final diagnosis of pleuroparenchymal fibroelastosis without performing any intervention for tissue biopsy that may be highly deleterious for PPFE patients due to the eventful respiratory complications of the disease. In addition, it will focus on the misconceptions of the clinicians about PPFE by presenting the unknown or invisible aspects of the disease as a clinical guide with a practical perspective.

Conflict of Interest

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

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