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Pleuro-Parenchymal Fibroelastosis (PPFE)-A Case Report

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ABSTRACT

Pleuro-parenchymal fibroelastosis (PPFE) is a rare form of interstitial lung disease with pleural and parenchymal components in the form of fibrosis and elastosis. This is often missed due to its rarity and nonspecific symptoms. Most of the cases were attributed to trivial respiratory infections in the past. Here we present a case of an elderly female who is symptomatic after COVID-19 infection and has characteristic radiological patterns in high-resolution computed tomogram (HRCT) to suggest a diagnosis of PPFE.

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Introduction

Pleuro-Parenchymal Fibroelastosis (PPFE) is a rare condition characterized by pleural and subjacent parenchymal fibrosis predominantly involving the upper lobes. PPFE is a distinct clinicopathological entity, with clinical features often leading to a link to recurrent pulmonary infection. PPFE may also present with more diffuse involvement, and coexist with different patterns of ILD. PPFE comprises of dense established intra-alveolar fibrosis, with the alveolar walls in these areas showing prominent elastosis, and dense fibrous thickening of the visceral pleura; these changes have a striking upper-zone predominance [1, 2]. PPFE was first described by Amitani et al. as idiopathic pulmonary upper lobe fibrosis. Most cases were considered idiopathic, although a few cases were familial [3].

Case Report

A 77-year-old female homemaker presented with cough and scanty expectoration progressive breathlessness and easy fatiguability for the last 10 months. There was no history of fever, chest pain or hemoptysis. There was no weight loss. She has loss of appetite and tiredness. There was no history of diabetes or hypertension. She had SARS Coronavirus 2 infection (COVID-19) in 2020 and suffered from B symptoms. She was not hospitalized or put on home oxygen supplementation. Since then she used to get recurrent respiratory symptoms in the form of cough and wheezes. These symptoms responded to symptomatic treatment.

On examination, she was moderately built and nourished. There was no clubbing or generalized lymphadenopathy. Her vitals were stable. Respiratory system examination showed end-inspiratory crackles bilaterally more in the upper lung fields. Other systems were within normal limits.

Her blood examination showed a C-reactive protein (CRP) of 18 and an erythrocyte sedimentation rate (ESR) of 32 mm fall in the first hour. Sputum gram stain, culture, and AFB stain were negative. X-ray chest PA view showed multiple nodular opacities in the lung apices, mostly subpleural (Figure 1). HRCT scan demonstrated multiple subpleural nodular opacities in both upper lobes with significant pleural thickening (Figure 2). Pleural thickening was also seen in the lower lobe areas (Figure 3).

The patient underwent a fiberoptic bronchoscopy. No intraluminal lesions were detected and bronchial lavage fluid was retrieved for culture sensitivity, acid-fast bacilli (AFB) smear, Mycobacterium tuberculosis- polymerase chain reaction (MTB-PCR), AFB culture, and fungal culture. All these investigations were reported negative. Her spirometry showed a restrictive abnormality.

Based on the history of previous viral infections and characteristic HRCT findings, pleuro-parenchymal fibroelastosis was diagnosed after ruling out the possibility of current infections.

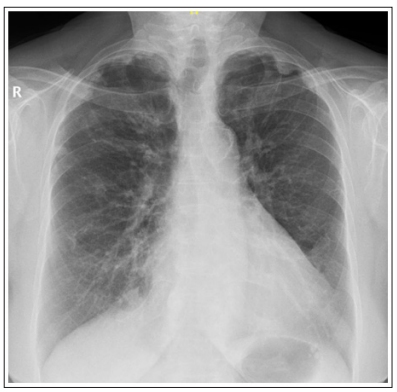

Figure 1: X-Ray Chest PA View Showing Multiple Subpleural Nodules in the Apical Region. Lung Zones Showed Increased Broncho-Vascular Markings

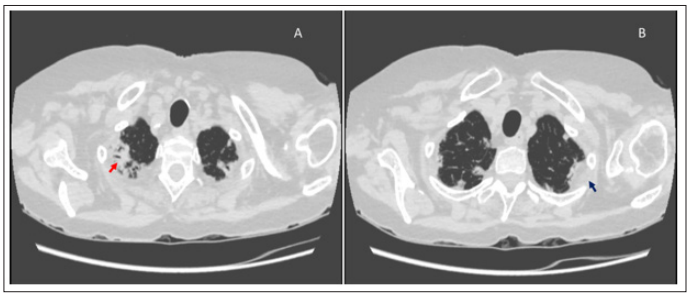

Figure 2: HRCT Axial Cut Through Upper Lobes (A & B) Showing Parenchymal Fibrosis (Red Arrow) and Pleural Thickening (Blue Arrow)

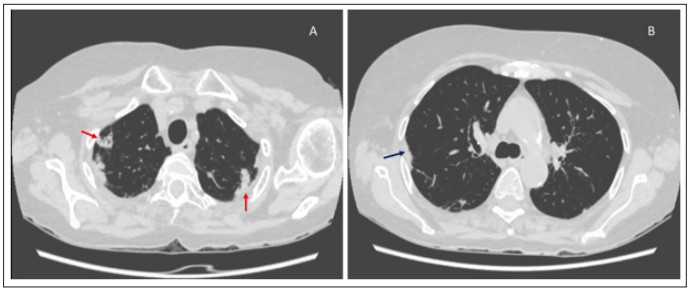

Figure 3: HRCT Axial Cut Through Upper Lobe (A) and at Carinal Level (B) Showing Pleuro-Parenchymal Fibrosis (Red Arrows) and Pleural Thickening (Blue Arrow)

Discussion

PPFE is a distinct clinicopathological entity, with clinical features often leading to a link to recurrent pulmonary infection. PPFE comprises dense established intra-alveolar fibrosis, with the alveolar walls in these areas showing prominent elastosis and dense fibrous thickening of the visceral pleura. These changes have a striking upper-zone predominance [1, 2]. Most cases are considered idiopathic, although a few cases are familial [3].

Pathogenesis

It has been suggested that acute or subacute lung injury, including diffuse alveolar damage, causing interstitial inflammation leads to a pathological cascade that culminates in PPFE [4]. However, the exact nature of the injurious stimuli triggering this process has not been identified so far. The presence of diffuse alveolar damage has also been reported in the setting of post-transplant PPFE [5]. PPFE and alveolar fibroelastosis developing in post-transplant restrictive allograft syndrome (RAS) have common pathological and gene profile characteristics

Etiology

A number of potential initiating factors for PPFE have been reported, the commonest of which are bone marrow and hematopoietic stem cell transplant as well as lung transplant [6]. A history of cancer chemotherapy, autoimmune or connective tissue disease, acute lung injury particularly with infective complications, chronic hypersensitivity pneumonitis (HP), and occupational exposure to asbestos and aluminum have also been associated with PPFE [7].

Types

1. Idiopathic PPFE
2. Non-idiopathic PPFE- This entity results from:

a) As a form of restrictive allograft syndrome complicating lung, bone marrow, and hematopoietic stem cell transplant (Restrictive chronic allograft dysfunction) [6, 7].
b) Fibrotic interstitial lung disease (e.g., usual interstitial pneumonia, hypersensitivity pneumonitis) [8, 9].
c) Chronic or recurrent bronchopulmonary infection (e.g., Aspergillus, nontuberculous mycobacteria) [10, 11].
d) Autoimmune or connective tissue disease (e.g., scleroderma, rheumatoid arthritis, inflammatory bowel disease) [12].
e) Familial history of pulmonary fibrosis
f) Anticancer/cytotoxic chemotherapy (e.g., cyclophosphamide and carmustine) and radiation therapy [8].
g) Occupational dust inhalation (e.g., asbestos and aluminum)

Clinical Features

PPFE has been reported in children and the elderly, but most patients come under the age group 40 to 70 years. 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 [13]. The majority were labeled as Pulmonary upper lobe fibrosis (PULF) rather than PPFE, and a sizable number developed PPFE after transplant rather than as an idiopathic entity. The common symptoms are progressive breathlessness and cough; nonspecific chest discomfort and pleuritic pain. However, persisting pain is unusual in the absence of pneumothorax. Progressive weight loss is frequently reported during the disease course and may raise the possibility of an intercurrent infection or occult malignancy.

Differential Diagnosis

The main differential diagnostic for PPFE include conditions associated with upper lobe disease, including hypersensitivity pneumonitis (HP), sarcoidosis, idiopathic interstitial pneumonia (IIP) with extension of disease to the upper zones (including usual interstitial pneumonia -UIP), atypical including nontuberculous mycobacterial infection, post–lung injury remodeling, pneumoconiosis, malignancy, and apical pleural cap.

Radiology

Chest radiographic findings are nonspecific or minimal. Pleural thickening and apical fibrosis may be visible. The characteristic CT findings of PPFE have been highlighted in multiple studies [6, 12]. For diagnostic purposes, cases should be examined using both standard axial and coronal reconstruction images. Reddy and coworkers proposed CT criteria for "definite" PPFE, including upper lobe pleural thickening with subpleural fibrosis and limited, if any, lower lobe involvement [12]. Tractional distortion of the airways within areas of PPFE is common, reflecting the dense surrounding fibrosis of the disease. The presence of "free-standing" bronchiectasis and mosaic attenuation of the lung parenchyma has also been reported [5, 6]. Overt lung fibrosis of varying patterns can coexist with PPFE, most frequently UIP, nonspecific interstitial pneumonitis (NSIP), or HP [9, 12]. PPFE manifesting as a lung nodule in conjunction with more usual appearances of apical fibroelastosis has also been reported. Whether this represents another rare variant of PPFE remains unclear.

Anteroposterior flattening of the chest, or platythorax, is described in PPFE and has been correlated with decreased BMI, suggesting its potential role as a surrogate marker of weight loss in PPFE. Two other observations associated with platythorax but not reported so far include: 1) "overlapping" of the posterior tracheal border and spine (a consequence of reduced anteroposterior thoracic depth) and 2) the appearance of a deep suprasternal notch resulting from reduced upper thoracic volume and progressive weight loss.

A histopathological diagnosis of PPFE requires a demonstration of intra-alveolar fibrosis and elastosis (IAFE), ideally involving visceral pleura [12]. Foci of loose fibroblastic proliferation may be present at the interface between established fibrosis and normal lung parenchyma [11]. Inflammation is typically mild and nonspecific, but intimal fibrosis may be evident, appearing prominently within the pulmonary vasculature, particularly the pulmonary veins

Pulmonary Function

The progressive reduction of lung volume in PPFE produces a characteristic restrictive ventilatory defect denoted by decreased forced vital capacity (FVC), decreased total lung capacity (TLC), and increased ratio of forced expiratory volume in 1 second to FVC. Reduced TLC may be accompanied by mild or moderately increased residual volume [14]. Patients with established or progressed PPFE have a predilection for hypoxemic respiratory failure with a typically widened alveolar–arterial gradient due to reduced arterial oxygen pressure. The arterial carbon monoxide pressure is usually normal or nearly normal but may be increased in the late stage of the disease, owing to hypoventilation or extrapulmonary restriction. Pneumothorax and pneumomediastinum are frequent complications of PPFE.

Treatment

No treatment has been shown to be effective in PPFE. Low-dose prednisolone used empirically, may have useful, although unproven, immunomodulatory effects [15]. The use of larger doses of corticosteroids or the use of immunosuppressive agents such as azathioprine or methotrexate is usually avoided in view of the heightened risk of infection in these patients. Pirfenidone, an antifibrotic agent, has been used in isolated cases of iPPFE and PPFE occurring in RAS, with varying anecdotal results.

Patients with PPFE who are prone to frequent pulmonary infections may benefit from prophylactic antibiotics. Antifungal therapy is usually reserved for those with radiological or microbiological evidence of such infection. Oxygen assessment, nutritional input, psychological support, and pulmonary rehabilitation should ideally form part of the standard of care of PPFE

Conclusion

Integration of clinical, radiological, and pathological data, can minimize misdiagnosis, particularly when the presenting abnormalities are limited in extent. Recent studies have shown that a subgroup of patients has a very poor outcome due to rapid clinical deterioration. Those with coexistent PPFE and separate fibrotic lung disease such as UIP fare badly and has poor clinical outcome. The prognostic determinants of PPFE, like its etiological factors, remain ill-defined and are the focus of ongoing studies.

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