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A Commonly Misdiagnosed Rare Pulmonary Disease: Idiopathic Pleuroparenchymal Fibroelastosis

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ABSTRACT

Awareness among clinicians about Idiopathic pleuroparenchymal fibroelastosis (PPFE) is lacking. By the time patients are diagnosed, they have been seen by multiple physicians and misdiagnosed multiple times. It is a rare condition that is characterized by fibrosis of the pleura and subpleural lung parenchyma, predominantly affecting the upper lobes. The most common cause of fibrosis in other processes is collagen predominant, but in PPFE fibrosis is usually caused by elastic fibers. A Verhoeff-Van Gieson stain from lung biopsies in patients who present with fibrosis in the upper pleural and parenchymal areas will help in establishing the diagnosis by demonstrating the elastic fibers. We also need to rule out the possibility of other lung parenchymal conditions like usual interstitial pneumonia, nonspecific interstitial pneumonitis, pulmonary apical cap, etc. We have presented a case report on PPFE to bring attention to clinicians and to add to the literature so that patients are diagnosed early.

KEYWORDS
Pleuroparenchymal fibroelastosis

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INTRODUCTION

Pleuroparenchymal fibroelastosis (PPFE) is a rare disorder, first described in the Japanese literature by AMITANI et al. as idiopathic pulmonary upper lobe fibrosis.[1,2] Most cases of PPFE are idiopathic, but occasionally, they are caused by an underlying connective tissue disease or following a bone marrow transplantation.[3] Clinical presentation of PPFE is just like any other idiopathic interstitial pneumonia, but the distinctive radiological and pathological characteristics help reach a possible diagnosis.[2,3,4] The American Thoracic Society (ATS)/European Respiratory Society (ERS) consensus classification of idiopathic interstitial pneumonias mentions PPFE as 1 of the entities but does not address specific diagnostic criteria.[5,6] Previous studies show that these patients are diagnosed months after presentation because the entity is not well known and are not referred in time to pulmonologists. Once diagnosed, it is important to follow these patients closely to determine the best therapeutic strategy, depending on the evolution of the disease. Hence, early diagnosis is vital.[4,6,7] We present a case report on this rare idiopathic interstitial pneumonia to bring attention to clinicians so that patients are diagnosed early and managed accordingly.

CASE PRESENTATION

Our patient is a 44-year-old female who is an active smoker with 25-pack-year smoking history. She was referred to the pulmonary clinic for evaluation of an abnormal chest CT scan. The patient was seen in the emergency room 3 weeks before presenting to the pulmonary clinic due to chest pain. At that time, a CT scan showed chronic bilateral right apical changes. The patient had dyspnea on moderate and severe exertion but not at rest or mild exertion. She denied any arthralgia, myalgia, eye problems, or skin problems. She endorsed on and off cough with whitish sputum but denied any recent change in the color or amount. The patient only used as-needed albuterol prescribed by her primary care physician along with weekly vitamin D. She reported that she was exposed to an unspecified chemical when she was 1 year old and was admitted to hospital along with her mother for observation. She had no childhood history of respiratory problems. She

regularly uses marijuana but denied using any other illicit substance or alcohol. Her grandfather died of mesothelioma at the age of 72, and her grandmother had a history of tobacco use disorder and severe emphysema.

A chest x-ray (Figure 1) showed mild scarring and paraseptal emphysematous changes at the apices bilaterally. A CT scan (Figure 2) showed reticular opacities bilaterally more in the right apex with similar peripheral and subpleural opacities at the superior segment of the lower lobe. A pulmonary function test revealed normal baseline spirometry with slight air trapping and a reduction in the diffusion capacity of the lung. The patient did not desaturate on a 6-minute walk test. Connective

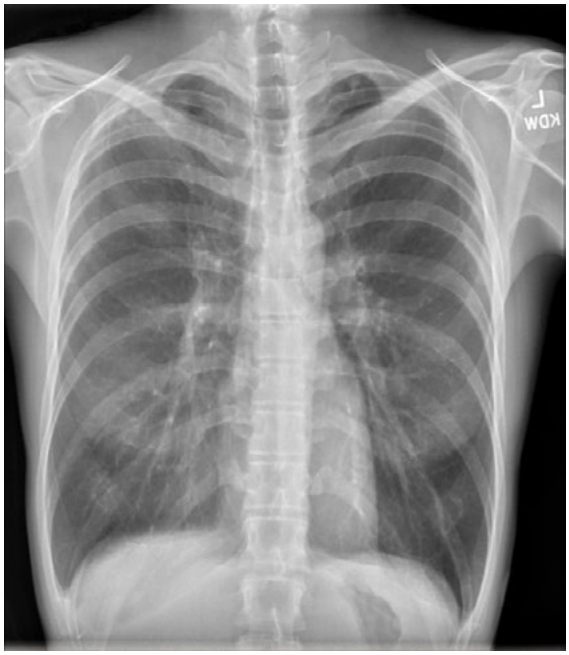

FIGURE 1: CXR showing mild scarring and paraseptal emphysematous changes at the apices bilaterally.

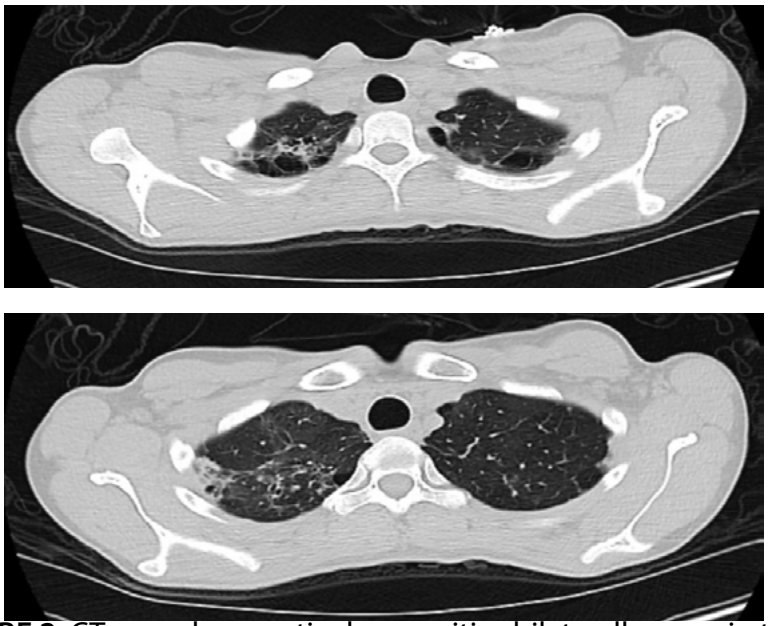

FIGURE 2: CT scan shows reticular opacities bilaterally more in the right apex involving the pleura and mild traction bronchiectasis.

tissue and vasculitis workups were negative. She underwent bronchoscopy with robotic right video-assisted thoracoscopy with lung biopsy in the upper, middle, and lower lobes. The patient did well postoperatively, and microscopic examination showed relatively well-demarcated subpleural fibroelastosis and mild chronic pleuritis. A Verhoeff-Van Gieson stain highlighted elastin deposition. Emphysematous changes and intra-alveolar pigment-laden macrophages are also noted in the lung tissue and are highly likely to be pleuroparenchymal fibroelastosis (Figure 3,4).

DISCUSSION

Idiopathic Pleuroparenchymal fibroelastosis (PPFE) is a rare condition characterized by fibrosis of the pleura and subpleural lung parenchyma, predominantly affecting the upper lobes. It was first described in 2004 by Frankel et al. in the Journal of the American College of Chest Physicians. They described 5 patients with pleural and subpleural parenchymal fibrosis, mostly in the upper lobe. The imaging and pathologic findings could not be explained by other known categories of idiopathic

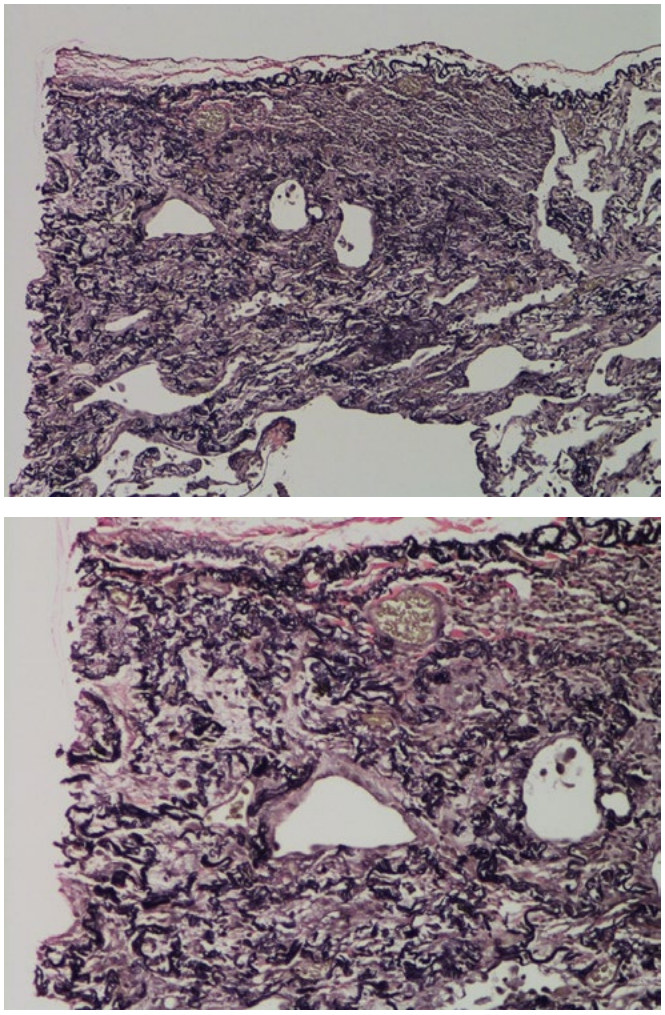

FIGURE 3: Pleuroparenchymal fibroelastosis, Verhoeff-Van Gieson stain, original magnification x40 and x100 highlights elastic fibers (dark blue to black).

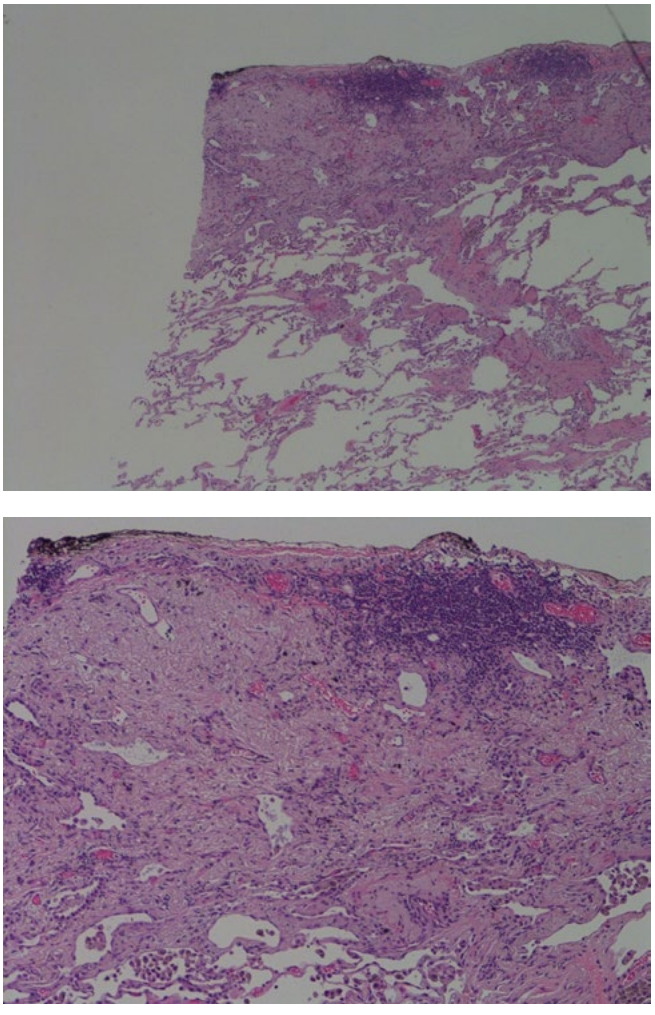

FIGURE 4: Pleuroparenchymal fibroelastosis, hematoxylin and eosin stain, original magnification x40 and x100 showing demarcated subpleural fibrosis with focal mild chronic pleuritis.

interstitial pneumonias, and the authors came up with the term PPFE. The most common cause of fibrosis in other processes is collagen predominant, but in PPFE fibrosis is usually caused by elastic fibers. Since then, there have been case reports and case series describing presentations and diagnoses of PPFE.[1]

Depending on pathologic and radiologic pictures, Reddy et al. classified patients as "definite PPFE," "consistent with PPFE," or "inconsistent with PPFE." "Definite" was assigned when there was upper zone pleural fibrosis with subjacent intra-alveolar fibrosis accompanied by alveolar septal elastosis. "Consistent with" was assigned when intra-alveolar fibrosis was present, but it was not 1) associated with significant pleural fibrosis, 2) not predominantly beneath the pleura, or 3) not in an upper lobe biopsy. "Inconsistent with" was assigned for cases that lacked the requisite features described above.[2]

Similar presentations of upper lobe subpleural fibrosis have been described in patients following lung transplantation, bone marrow transplantation, and as part of connective tissue-associated interstitial lung disease like systemic sclerosis and Sjogren's syndrome. It was also found that patients with PPFE might have concomitant idiopathic interstitial pneumonia. It is important to clinically evaluate patients suspected to have PPFE for other collagen vascular diseases.[3,4,5] Our patient was clinically evaluated for collagen vascular disease, and basic studies showed negative results.

Sometimes PPFE patients are misdiagnosed as usual interstitial pneumonia or nonspecific interstitial pneumonia, but a detailed examination of the radiologic picture and histologic studies may help differentiate these entities from PPFE. Usual interstitial pneumonia has a classic radiologic picture with subpleural reticular infiltrates and honeycombing and a UIP histologic pattern with heterogeneity.[6]

We need to rule out conditions like asbestosis, connective tissue diseases, sarcoidosis, radiation, or drug-induced lung diseases in patients who have fibrotic changes in both the pleura and the parenchyma before we label patients with a diagnosis of idiopathic PPFE.[6,7] Based on our patient's clinical presentation, laboratory, radiologic and histologic pictures, we can confidently say she has PPFE. She did not have significant asbestos exposure, and histology did not show evidence of asbestos exposure like a ferruginous body. She did not have any previous exposure to radiation or previous treatment with chemotherapy like methotrexate, cyclophosphamide, or any other medication that is associated with pleural thickening and interstitial pneumonitis with fibrosis. Another condition that we need to consider, especially in a patient with a small upper-lobe only fibro elastotic process is a pulmonary apical cap (PAC). The presence of a low number of cells with fibrosis rich in elastic fibrils is characteristic of both PPFE and PAC; however, the degree of fibrosis is diffuse in PPFE, and patients present with symptoms like dyspnea on exertion or cough in contrast to an incidental diagnosis of PAC due to its asymptomatic nature. Recent studies have suggested that including the radiological progression of disease in the diagnostic criteria for idiopathic PPFE might help in excluding PAC, but differentiating these 2 conditions may sometimes be very difficult.[8,9,10]

The presentation of PPFE is variable. One associated complication mentioned in case reports is pneumothorax; we should consider the possibility of PPFE as a differential when we find a patient with unexplained pneumothorax with suggestive radiologic pictures. It is also therapeutically challenging to appropriately treat pneumothorax in PPFE patients due to the pleural and parenchymal involvement of the disease and further complications like bronchopleural fistulas.

The pathophysiology of PPFE is not known, and treatment is challenging, especially in severe cases. There are familial cases of PPFE in a case series published previously, but no clear genetic location was demonstrated to be affected. It was suggested that Transforming Growth Factor alpha (TGF-alpha) inhibitors might be tried as a treatment, but at this time, there is no treatment other than lung transplantation.[6,9,10]

CONCLUSION

In conclusion, idiopathic pleuroparenchymal fibroelastosis is a rare progressive disease with no clear pathophysiology or treatment and needs to be detected early to prevent unnecessary work-up and treatment trials. There is no clear standardized diagnostic method, and further research is required to come up with criteria for diagnosis. Our main purpose in this paper is to bring attention to clinicians about this rare disease so that patients are diagnosed early, and health care costs are reduced.

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