Case Report
Volume 13:2, 2023

Journal of Pulmonary & Respiratory Medicine

ISSN: 2161-105X Open Access

A Commonly Misdiagnosed Condition: Idiopathic Pleuro-Parenchymal Fibroelastosis

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Abstract

Awareness among clinicians about idiopathic Pleuroparenchymal Fibroelastosis (PPFE) is lacking and by the time patients are diagnosed with it, they were 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. Most common cause of fibrosis in other processes is collagen predominant but in PPFE fibrosis is usually caused by elastic fibers. Verhoeff van Gieson stain from lung biopsies in patients who presented 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 so that patients are diagnosed early.

Keywords: Pleuroparenchymal • Fibroelastosis • Subpleural • Horacoscopy • Myalgia

Case Presentation

Patient is a 44 years old female who is an active smoker with 25 pack year smoking history referred to the pulmonary clinic for evaluation of abnormal chest CT scan. Patient was seen in the emergency room 3 weeks before presenting to the pulmonary clinic due to chest pain and at that time CT scan was done which showed chronic bilateral right apical changes. Patient has dyspnea on moderate and severe exertion but not at rest or mild exertion. Patient denied any arthralgia, myalgia, eye problems or skin problems. Patient endorses on and off cough with whitish sputum but denied any recent change in the color or amount. Patient only uses as needed albuterol which was prescribed by her primary care physician and weekly vitamin D. She also 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. No childhood history of respiratory problems. Patient regularly uses marijuana but denied using any other illicit substance or alcohol. Patient's grandfather died of mesothelioma at the age of 72 and her grandmother had history of tobacco use disorder and severe emphysema.

Chest X ray (Figure 1) showed mild scarring and para septal emphysematous changes at the apices bilaterally. 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. Pulmonary function test revealed normal baseline spirometry with slight air trapping and a reduction in diffusion capacity of the lung. Patient did not desaturate on 6 minutes walk test. Connective tissue and vasculitis workup are negative. She then underwent bronchoscopy with robotic right video assisted thoracoscopy with lung biopsy in the upper, middle, and lower lobes. Patient did well postoperatively, and microscopic examination shows relatively well demarcated subpleural fibroelastosis and mild chronic pleuritis. Verhoeff van Gieson stain highlights elastin deposition. Emphysematous changes and intra alveolar pigment laden macrophages are also noted in the lung tissue highly likely pleuroparenchymal fibroelastosis (Figures 3 and 4).

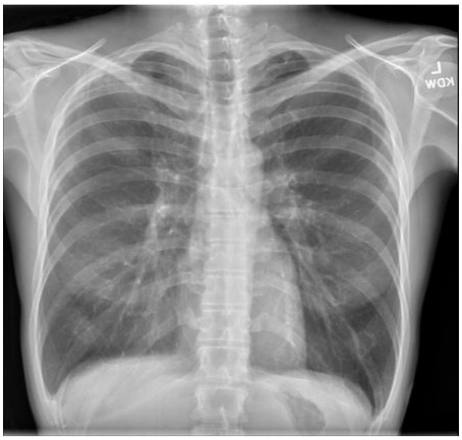

Figure 1. CXR showing mild scarring and para septal emphysematous changes at the apices bilaterally.

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Received: 23 January, 2023, Manuscript No. JPRM-23-88066; **Editor assigned:** 27 January, 2023, PreQC No. JPRM-23-88066 (PQ); **Reviewed:** 13 February, 2023, QC No. JPRM-23-88066; **Revised:** 12 April, 2023, Manuscript No. JPRM-23-88066 (R); **Published:** 20 April, 2023, DOI: 10.37421/2161-105X.2023.13.653

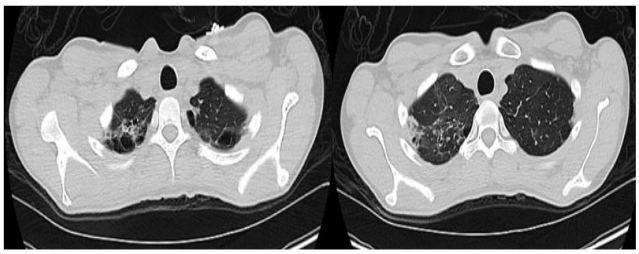

Figure 2. CT scan shows reticular opacities bilaterally more in the right apex involving the pleura and mild traction bronchiectasis.

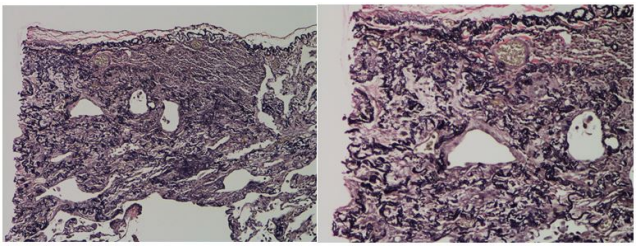

Figure 3. Pleuroparenchymal fibroelastosis, Verhoeff van Gieson stain, original magnification 40X and 100X highlights elastic fibers (dark blue to black).

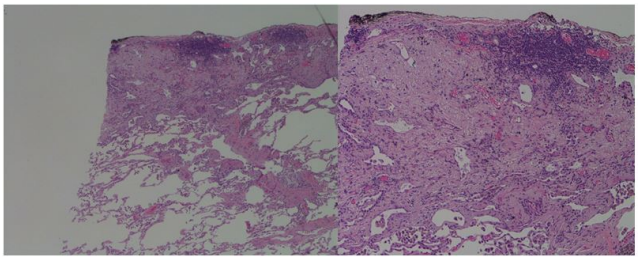

Figure 4. Pleuroparenchymal fibroelastosis, hematoxylin and eosin stain, original magnification 40X and 100X showing demarcated subpleural fibrosis with focal mild chronic pleuritis.

Results and Discussion

Idiopathic Pleuroparenchymal Fibroelastosis (PPFE) is a rare condition that is 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. on 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 interstitial pneumonias and the authors came up with the term PPFE. Most common cause of fibrosis in other processes is collagen predominant but in PPFE fibrosis is usually caused by elastic fibers. Since then, there are case reports and case series describing presentations and diagnosis of PPFE [1].

Depending on pathologic and radiologic pictures Reddy, et al. classified patients to '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:

- Associated with significant pleural fibrosis,
- Not predominantly beneath the pleura or
- 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 has 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 a concomitant idiopathic interstitial pneumonia. It is important to clinically evaluate patients who are suspected with PPFE for other collagen vascular diseases [3-5]. 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 detailed examination of the radiologic picture and histologic studies may help in differentiating 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.

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 a diagnosis of idiopathic PPFE [6,7]. In our patient, with the clinical presentation, laboratory, radiologic and histologic pictures, we can confidently say that she has PPFE. She did not have any significant exposure to asbestos and histology did not show evidence of asbestos exposure like ferruginous body. She did not have any exposure to radiation previously and no 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 low number of cells with fibrosis rich in elastic fibrils is characteristic of both PPFE and PAC but 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 study suggested that including radiological progression of disease in the diagnostic criteria for idiopathic PPFE might help in excluding PAC but differentiating these two conditions may sometimes be very difficult [8].

Presentation of PPFE is variable and one complication that is mentioned in case reports associated with it is pneumothorax and 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 disease and further complications like bronchopleural fistulas [9,10].

Conclusion

The pathophysiology of PPFE is not known and hence 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.

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How to cite this article: Raru, Yonas. "A Commonly Misdiagnosed Condition: Idiopathic Pleuro-Parenchymal Fibroelastosis." *J Pulm Respir Med* 13 (2023): 653.