Overcoming the challenges of a misdiagnosed rare lung disease – idiopathic pleuroparenchymal fibroelastosis

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Abstract

Pleuroparenchymal fibroelastosis (PPFE) is a rare condition characterized by pleural and subpleural lung fibroelastosis with an upper lobe predominance. We present the third case of idiopathic PPFE from India, as well as the second *ante-mortem* diagnosis. A 27-year-old man presented with a 1-year history of modified Medical Research Council class II shortness of breath and dry cough. He described a 15-kg weight loss. After a clinico-radiological diagnosis, he was given anti-tubercular treatment and referred because he showed no improvement. A high-resolution computed tomography of the chest revealed bilateral upper lobe bullae, parenchymal and subpleural fibrosis, and irregular pleural thickening. PPFE was found in surgical lung and pleural biopsies. He was given systemic glucocorticoids but did not respond clinically or radiologically. Pirfenidone and a lung transplant were out of reach for him. He died 9 months after being diagnosed with his condition. Finally, idiopathic PPFE is an extremely rare entity, with only three cases reported from our subcontinent. As a result, it is easily underdiagnosed or misdiagnosed; clinician awareness of this condition is critical for better diagnosis and management.

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Key words: idiopathic pleuroparenchymal fibroelastosis, pulmonary tuberculosis, pectus excavatum.

Contributions: SG, PU, AK, BS, NS, resources, data curation, writing - original draft; SG, PU, AK, NS, investigation; SG, PU, writing - review and editing; PU, supervision; SG, PU, visualization.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: no ethical committee approval was required for this case report by the Department.

Patient consent for publication: the patient gave his written permission to use his data to publish this case report and any accompanying images. Informed consent was obtained from the patient included in the study.

Funding: none.

Availability of data and materials: all data underlying the findings are fully available.

Received: 8 May 2023.
Accepted: 26 June 2023.
Early view: 2 August 2023.

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Licensee PAGEPress, Italy
Monaldi Archives for Chest Disease 2024; 94:2632
doi: 10.4081/monaldi.2023.2632

Introduction

Pleuroparenchymal fibroelastosis (PPFE) is an underdiagnosed and misdiagnosed clinicopathological entity characterized by fibroelastosis of the pleura and subpleural lung parenchyma with striking upper lobe predominance. Multiple sporadic cases and case series have been reported from all over the globe [1-6]. To the best of our knowledge, this is the third case of idiopathic PPFE (IPPFE) to be reported from our subcontinent and the second case for which the diagnosis was made *ante-mortem*. If not appropriately evaluated, it can be misdiagnosed as fibrotic hypersensitivity pneumonitis, pulmonary tuberculosis, or pulmonary tuberculosis complications [7]. Here, we present a case of a 27-year-old male misdiagnosed with pulmonary tuberculosis and later found to have IPPFE.

Case Report

A 27-year-old male electrician presented to us in September 2022 with a dry cough and shortness of breath as per the modified Medical Research Council functional class II, of 1-year duration. There was no history of fever or chest pain. He gave a history of a loss of appetite and a weight loss of 15 kg in 6 months. He denied any history of alcohol consumption or smoking. There was no history of exposure to animals, birds, inorganic dust, skin rash, or joint pain. His past history was significant for anti-tubercular drug (four-drug regimen) intake from January to June 2022 after a chest roentgenogram diagnosis without microbiological confirmation. As the patient had no symptomatic improvement with anti-

tubercular treatment, he was referred to our institute for further evaluation.

On general examination, he was thin, cachectic with a body mass index of 11.1 kg/m^2, tachypnoeic, and had pectus excavatum (Figure 1). Chest auscultation revealed decreased breath sounds bilaterally, with fine end-inspiratory crepitations more in bilateral infraclavicular and suprascapular areas. Arterial blood analysis showed a pH of 7.46, a partial pressure of carbon dioxide of 24, a partial pressure of oxygen of 96.4, HCO_3 of 19.2, and SO_2 of 97.9. A complete hemogram revealed a hemoglobin level of 10.3 g/dL, total leucocyte counts of 6,350/µL, and a platelet count of 254,000/µL. Hepatic, renal, and thyroid function tests were reported as normal. His erythrocyte sedimentation rate and C-reactive protein were 8 mm/hour and 2 mg/L, respectively. A chest roentgenogram showed bilateral upper zone cystic changes with right-side pleural thickening, costophrenic angle blunting, and cardiac shift to the left side (Figure 2).

High-resolution computed tomography (CT) of the chest showed bilateral upper lobe bullae with parenchymal and subpleural fibrosis and volume loss with irregular pleural thickening and a Haller index (ratio of thoracic width and height, measured from axial CT) of 6.7 (Figure 3). On the pulmonary function test, spirometry was consistent with a severe restrictive pattern with a forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of 88.9%, with a decreased FEV_1 of 1.6 L, 45%, and FVC 1.8 L, 40%. Given clinical, physiological, and radiological findings, differential diagnoses of familial idiopathic pulmonary fibrosis, advanced pulmonary sarcoidosis, post-tuberculosis fibrothorax, fibrotic hypersensitivity pneumonitis, pulmonary apical fibrocystic disease secondary to ankylosing spondylitis, and IPPFE were made. The patient did not give a history of any similar illnesses in his family members. He did not have any features suggestive of connective tissue disorder, and his serum anti-nuclear antibodies and rheumatoid factor were negative, ruling out connective tissue disease-associated interstitial lung disease. Due to the uncertainty in diagnosis and the non-availability of video-assisted thoracoscopic surgery, a surgical lung biopsy (SLB) was done by the cardiothoracic surgery team. On histopathology, sections from the left upper lobe showed dense collagenous fibrosis composed of hyalinized collagen and fibroelastic foci with minimal inflammation (Figure 4). Adjacent preserved lung parenchyma showed intra-alveolar hemosiderin-laden macrophages. Sections from the left lung pleura showed dense collagenous fibrosis composed of hyalinized collagen with associated reactive mesothelial hyperplasia (Figure 5). The Masson trichome special stain highlighted collagenous tissue in the section, including lung parenchyma and pleural tissue. The patient developed left-sided pneumothorax postoperatively, for which a tube thoracostomy was done with a 16 French catheter under local anesthesia. Post-tube thoracostomy, the lung did not expand (Figure 6). With a diagnosis of IPPFE, the patient was started on systemic glucocorticoids empirically, even though their benefits are unproven. There was no clinical or radiological response after 1 month. The patient was offered treatment with pirfenidone and counseled for a lung transplant, but he was not willing to do either due to financial restraints. As the patient had severe pectus excavatum, surgical correction was also advised, but the patient was not willing for that either. The patient succumbed to his condition after 9 months of diagnosis.

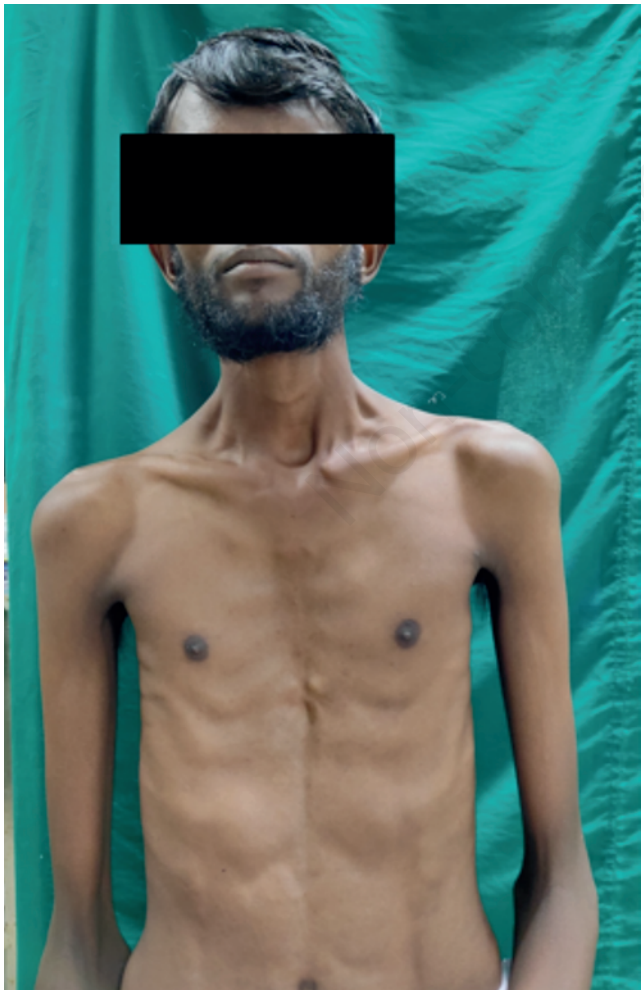

Figure 1. Anterior chest showing pectus excavatum.

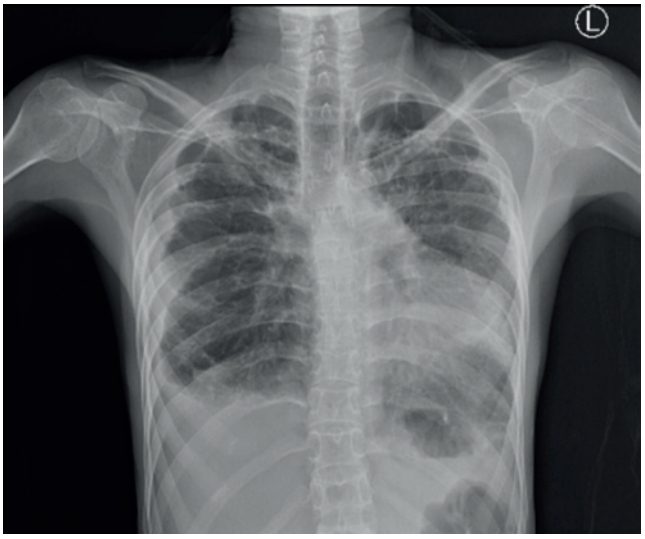

Figure 2. Chest roentgenogram posteroanterior view showing bilateral upper zone cystic changes with right side pleural thickening with costophrenic angle blunting and cardiac shift to the left side.

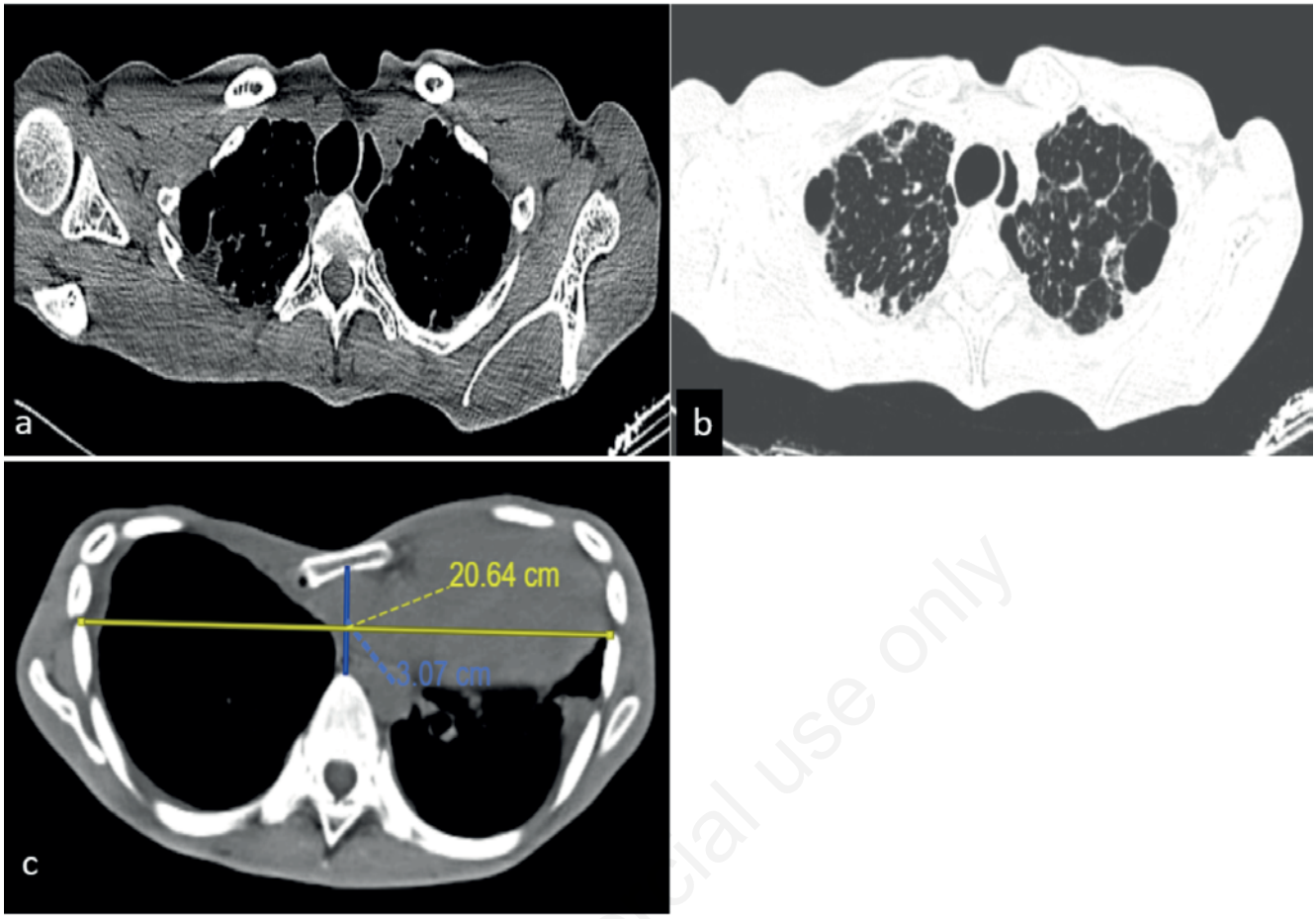

Figure 3. Transversal computed tomography of the chest. a) Bilateral pleural thickening; b) bilateral upper lobe bullous changes with interlobular septal thickening; c) severe pectus excavatum with Haller index of 6.7.

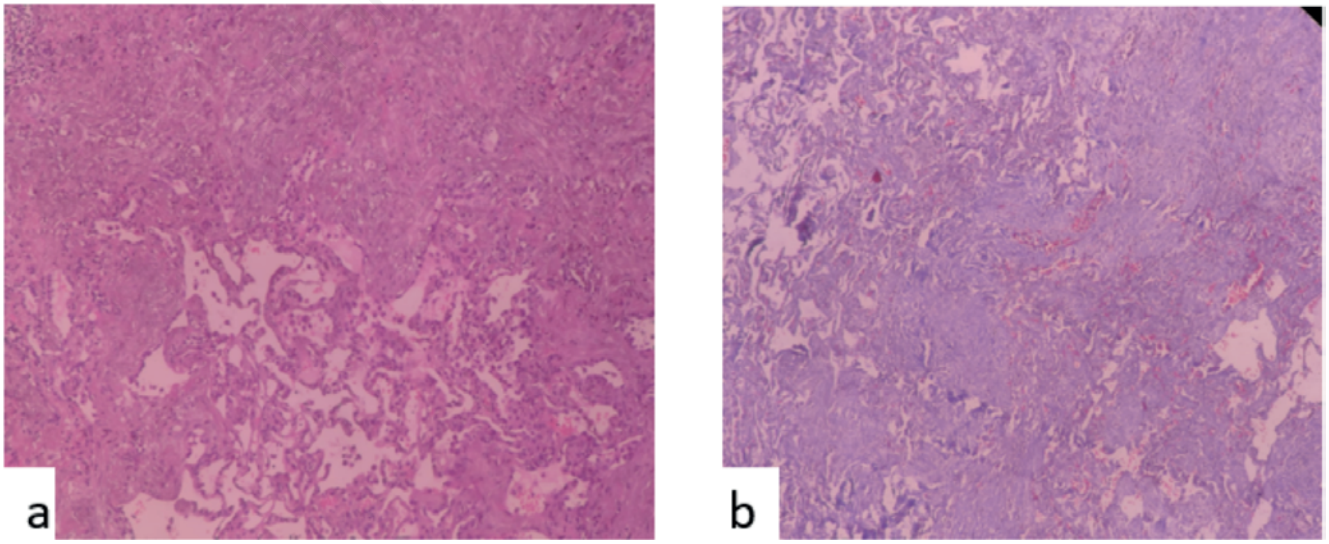

Figure 4. a) Section from lung biopsy shows sheets of collagenous fibrosis replacing the normal lung parenchyma with compressed normal alveolar spaces (H and E, ×200); b) Masson trichrome special stain highlighting the collagenous fibrosis (×200).

Discussion

The American Thoracic Society/European Respiratory Society recognized IPPFE as a separate entity in 2013; however, the description of IPPFE in the literature goes back to 1992, when Amitani *et al*. reported 13 cases of pulmonary fibrosis localized to the upper lobe and named this entity idiopathic pulmonary upper lobe fibrosis [8]. Later, in 2004, Frankel *et al*. coined the term IPPFE [9]. The first case in the Indian subcontinent was reported in 2015 by Thangakunam *et al*., where the diagnosis was made *post-mortem* [1]. Maturu *et al*., in 2019, reported the first case in which the diagnosis was established *ante-mortem* in our subcontinent [2].

In addition to IPPFE, multiple systemic conditions, most commonly hematopoietic stem or lung transplantation, chronic hypersensitivity pneumonitis, autoimmune or connective tissue disease, and occupational exposure to aluminum and asbestos, are associated with PPFE [10-13]. In a case series by Reddy *et al*., recurrent infections accounted for PPFE in half the cases [14].

As SLB is not always feasible, Watanabe *et al*. proposed three conditions for a diagnosis of PPFE without SLB: i) radiologically possible, ii) radiologically probable, and iii) radiologically and physiologically probable [15]. Radiological criteria for definite PPFE include pleural thickening with subpleural fibrosis in the upper lobes and minimal lower lobe involvement [14]. In our patient, bilateral upper lobe bullae with parenchymal and subpleural fibrosis and volume loss with irregular pleural thickening were present, predominantly in the upper lobes.

Clinical features vary, most commonly dyspnea and dry cough.

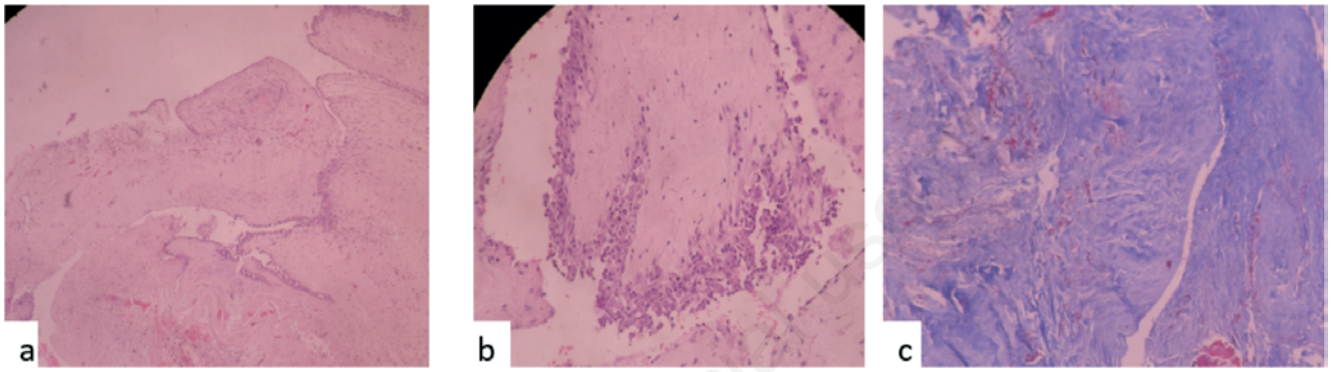

Figure 5. a) Section from the pleura shows extensive areas of collagenous fibrosis with focal mesothelial cell hyperplasia (H and E, ×200); b) at higher magnification (×400), highlighting foci of mesothelial hyperplasia; c) Masson trichrome special stain in the pleural tissue highlighting the collagenous fibrosis (×200).

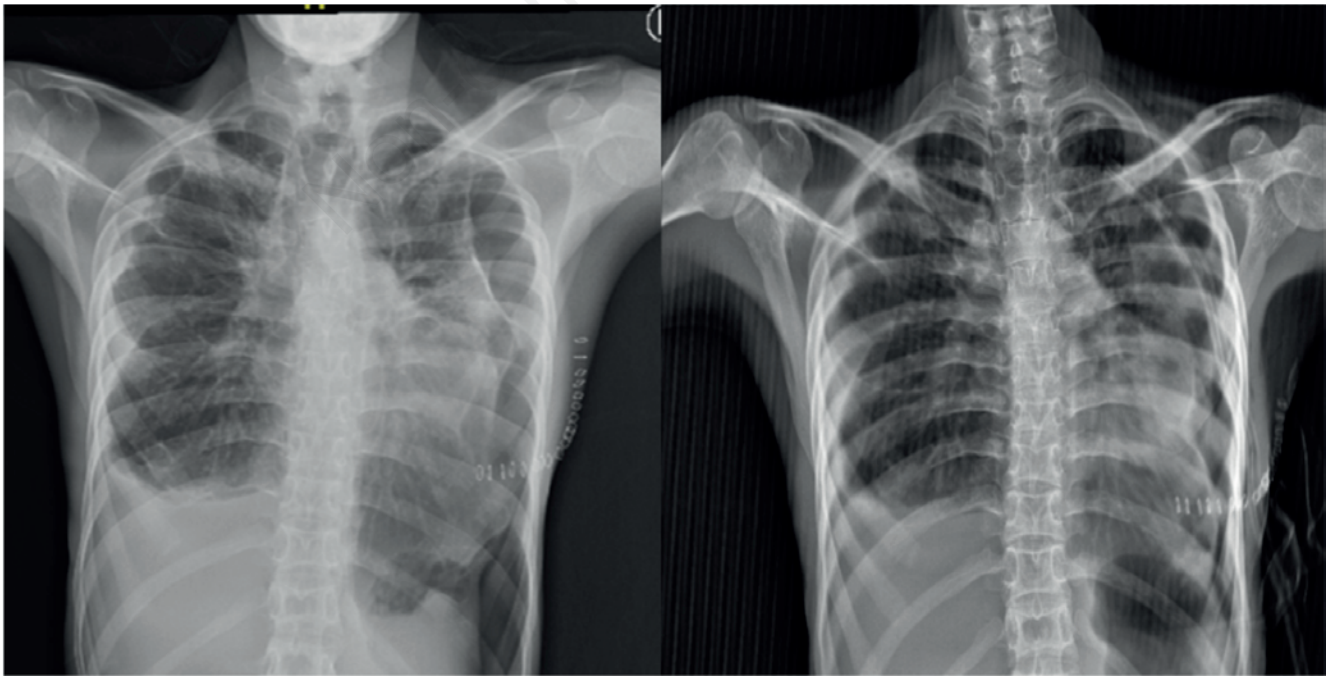

Figure 6. Chest radiograph posteroanterior view postoperatively, showing left side pneumothorax (left panel) and non-expansion of lung post-tube thoracostomy (right panel).

Spontaneous pneumothorax or pneumomediastinum has also been reported [16]. The mechanism underlying spontaneous pneumothorax or iatrogenic pneumothorax has yet to be completely understood. It has been postulated that elastic pleura offers low resistance to tear. Moreover, tissue affected after surgery may exhibit a limited healing capacity, which in turn leads to persistent bronchopleural fistulae [17]. Our patient developed pneumothorax and bronchopleural fistulae post-operatively.

Progressive weight loss is also reported during the course of the disease, which may arouse suspicion of an occult malignancy or superadded infection, as was our case. Our patient, being from a tuberculosis-prevalent country, presented with a chronic history of dyspnea and cough with significant weight loss and involvement of the upper lobe in imaging. He was naturally suspected of having a *Mycobacterium tuberculosis* infection and was started on treatment for the same. No response to the treatment prompted further investigation, leading to the diagnosis of IPPFE.

Currently, there is no consensus on treating IPPFE except for supportive care and, ultimately, lung transplantation. However, low-dose prednisolone may have a useful, although unproven, immunomodulatory effect [18]. In a case report by Sato *et al*., pirfenidone was shown to prevent the decline in pulmonary function in IPPFE patients [19]. Nintedanib may also prevent FVC decline in IPPFE, as demonstrated by the case series by Naseer *et al*. [20].

Conclusions

In conclusion, IPPFE is a very rare entity, with just three cases reported from our subcontinent. Thus, it can be easily underdiagnosed or misdiagnosed, probably due to a lack of knowledge and awareness of this entity. Our case of IPPFE was first misdiagnosed as pulmonary tuberculosis. IPPFE should be considered a differential diagnosis in patients with predominantly upper lobe pulmonary fibrosis. Awareness of this condition among clinicians is essential for better diagnosis and management.

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