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Pleuroparenchymal Fibroelastosis: A Rare Interstitial Lung Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Report

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ABSTRACT

Pleuroparenchymal fibroelastosis (PPFE) is a rare interstitial lung disease (ILD) characterized by upper-lobe predominant fibrosis involving of the pleural and subpleural lung parenchyma. It is a relatively newly recognized entity within the spectrum of ILDs. Diagnosing PPFE can be challenging due to its rarity and overlapping clinical features with other ILDs. We report the case of two patients, siblings, of first degree consanguineous parents, 37 and 32 years old, suffering from worsening dyspnea, dry cough and weight loss, the high resolution chest computer tomography objectified a platythorax, a bilateral pleural cap thickening, diffuse sub pleural reticulations with bilateral apical traction bronchiectasis, associated with septal and non-septal lines, the main scannographic lesions spared the lower lobes. After eliminating differential diagnoses, the diagnosis of PPFE in a familial form was made based on the radiological criteria proposed by Reddy and al and on according to the 2013 ATS/ERS consensus. We underline the importance of reporting these 2 cases to learn more about the disease, a rare chronic fibrosing interstitial pneumonia, and its serious prognosis in the absence of therapies.

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Keywords: Pleuroparenchymal fibroelastosis; interstitial lung disease; fibrosis; platythorax; dyspnea.

1. INTRODUCTION

Pleuroparenchymal fibroelastosis (PPFE) is a rare chronic fibrosing interstitial pneumonia which predominant in the bilateral upper lobe. The diagnosis is based mainly on high-resolution chest computer tomography, rarely on lung biopsy. We report the case of two siblings having a first degree consanguineous parents, which the diagnosis of PPFE was based on the radiological criteria proposed by Reddy and al [1] and on according to the 2013 ATS/ERS consensus.

2. CASE REPORT

CASE 1:

A 37-year-old male patient, born of a consanguineous marriage, with a history of smoking with a 24-pack-year. At the time of diagnosis, there were no reported similar cases of his condition within the family.

He consulted for a progressive worsening dyspnea becoming at less effort, a dry cough turning productive with yellowish sputum, a weight loss and anorexia since one month.

The physical examination showed a low BMI (Body Mass Index) of 17.33 kg/m², and an oxygen saturation of 97% on room air. No cyanosis or digital clubbing was observed. Right basal thoracic fluid effusion syndrome was present.

A chest X-ray was performed, revealing bilateral infiltrations predominantly at the apex, with the retraction of the hila upwards and a right diaphragmatic dome elevation (Fig. 1). A chest CT scan showed significant findings, including bilateral upper lobe pleural thickening and septal and non-septal thickening, bronchial dilatations and distortions, and evidence of mediastinal shift towards the right. These findings were associated with moderate pleural effusion on the right (Fig. 2).

The bronchoscopy examination revealed an unobstructed trachea and bilateral bronchial distortion with a minimal inflammatory state. The bronchoalveolar lavage (BAL) fluid analysis, including tuberculous bacilli smear and culture, as well as tuberculous bacilli PCR (Polymerase chain reaction) testing returned negative results.

The pleural fluid analysis revealed the presence of serosanguinous fluid containing lymphohistiocytic elements with no atypical cells identified, and pleural needle biopsy indicating thickened fibrous pleura, containing some lymphoid and fibroblastic elements with no histological signs of malignancy or tuberculosis.

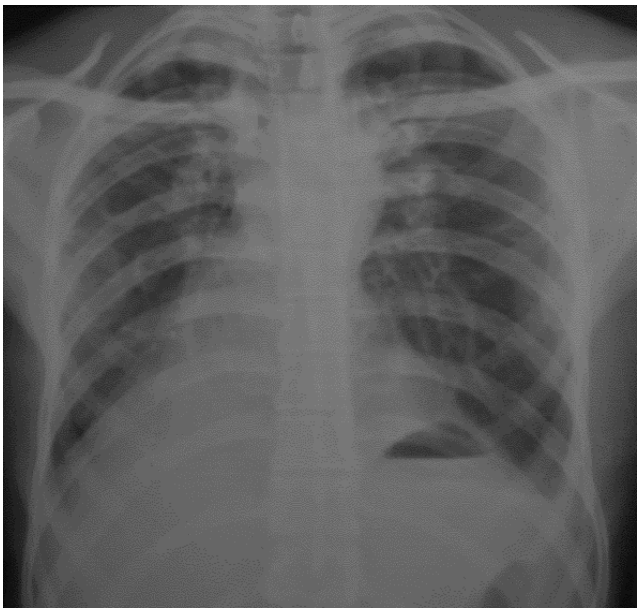

Fig. 1. Chest X-ray: bi-apical infiltrations with the retraction of the hila upwards and a right diaphragmatic dome elevation

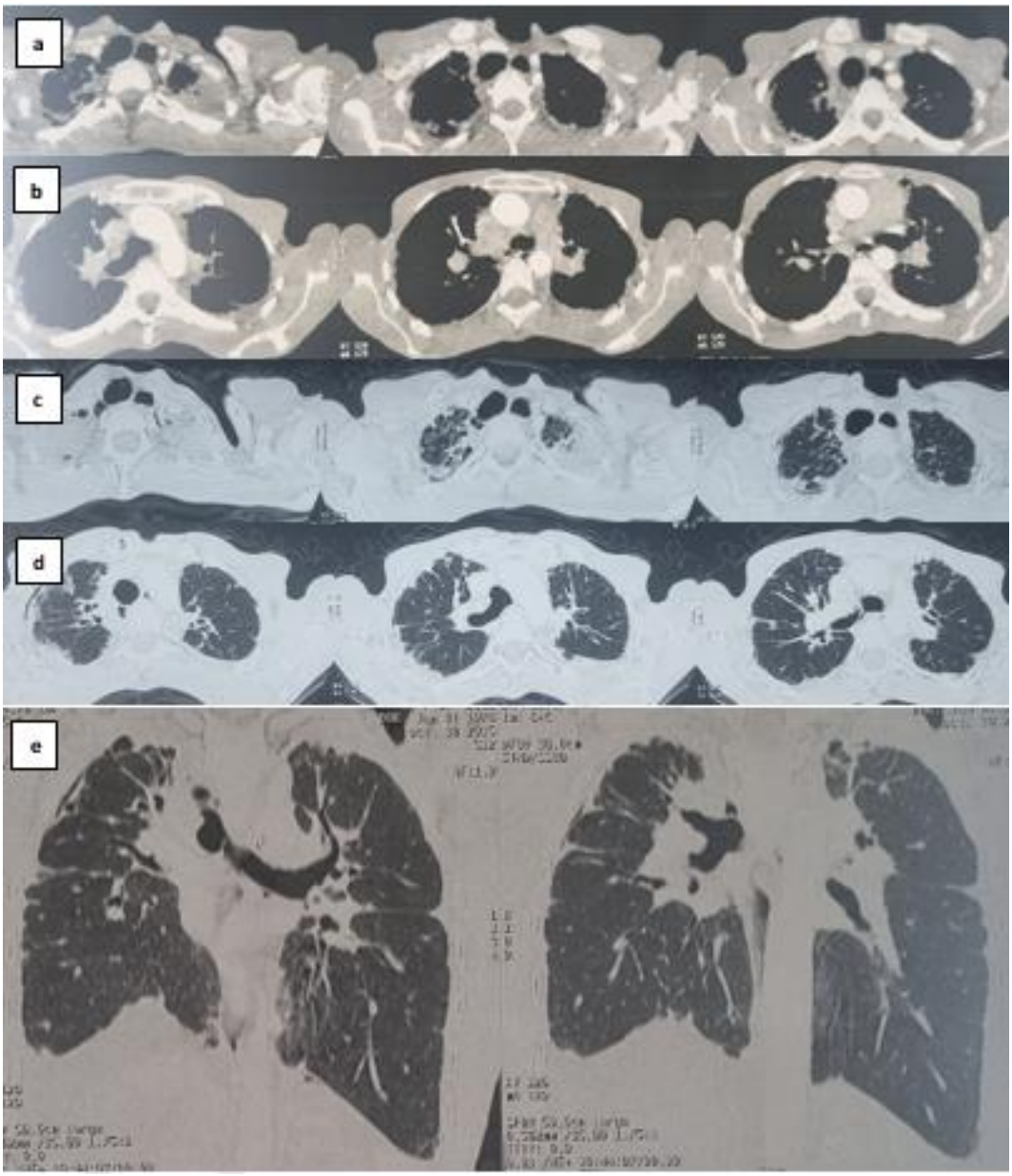

Fig 2. High-resolution thoracic computed tomography: Axial (a,b,c,d) and coronal (e) planes : bilateral apical pleural thickening and subpleural septal and non-septal thickening, bronchial dilatations and distortions, moderate right pleural effusion

Autoimmune markers and tests for sarcoidosis came back negative. Given the medical history, clinical manifestations, suggestive CT scan patterns, and histological findings, the patient was diagnosed with PPFE according to the 2013 ATS/ERS guidelines.

The patient was placed on antibiotics (amoxicillin and clavulanic acid), and had demonstrated significant improvement in his productive cough. The spirometry showed a probable severe restrictive ventilatory disorder with a significant reduction in lung volumes. An arterial blood gas analysis performed an hypercapnic respiratory failure. The patient received non-invasive ventilation (NIV), coupled with appropriate nutritional and psychological assistance, before being discharged.

Given the patient's young age and medical state, a lung transplant was proposed. Unfortunately, this procedure was unavailable inside the national healthcare system, as were antifibrotic drugs at the time. The patient passed away 2

months after discharge from the hospital, likely due to respiratory distress. Subsequently, six years following Case 1's diagnosis, his sister exhibited comparable clinical findings (Case2).

CASE 2:

A 32-year-old female patient, born of a consanguineous marriage, with a history of passive smoking exposure, a one-year history of dyspnea on exertion, and no history of occupational exposure or previous illnesses. Notably, similar cases exist within the family, including two deceased brothers: one, deceased 5 years ago at the age of 37 due to idiopathic PPFE, and the other, deceased a month prior to her admission at the age of 32, due to an unexplored respiratory pathology, possibly PPFE as showed in case 1.

She consulted for worsening of her dyspnea since two months becoming stage 4 according to the MMRC scale, a dry cough and mild-intensity lateral thoracic pain in the sub axillary region, a weight loss, anorexia and asthenia.

The physical examination showed a low BMI of 11.8 kg/m², a polypneic patient, an oxygen saturation of 93% on room air, accompanied by signs of respiratory distress. No cyanosis or digital clubbing were observed. Pulmonary auscultation revealed subcrepitant rales with predominance on the left side. The rest of the somatic examination was normal.

A chest X-ray showed diffuse reticulonodular infiltrations in both lungs and aspects of bilateral pleural caps with the retraction of the hila upwards and a right diaphragmatic dome elevation (Fig. 3). A chest CT scan showed several significant findings including platythorax with a flat chest index of 0.47 (Fig. 4), bilateral upper lobe pleural thickening and both septal and non-septal regions thickening. Notably, there was dominant traction bronchiectasis in the right upper lobe (Fig. 5). The CT scan patterns were strongly suggestive of PPFE.

The bronchoscopy revealed unobstructed trachea and bilateral bronchial distortion with a minimal inflammatory state. Unfortunately, a biopsy couldn't be performed considering the patient's dyspnea. Autoimmune markers and tests for sarcoidosis came back negative. These laboratory tests were specifically conducted to eliminate other causes of ILDs.

Given the medical and familial history, clinical manifestations, and suggestive CT scan patterns, the patient was diagnosed with PPFE according to the 2013 ATS/ERS guidelines.

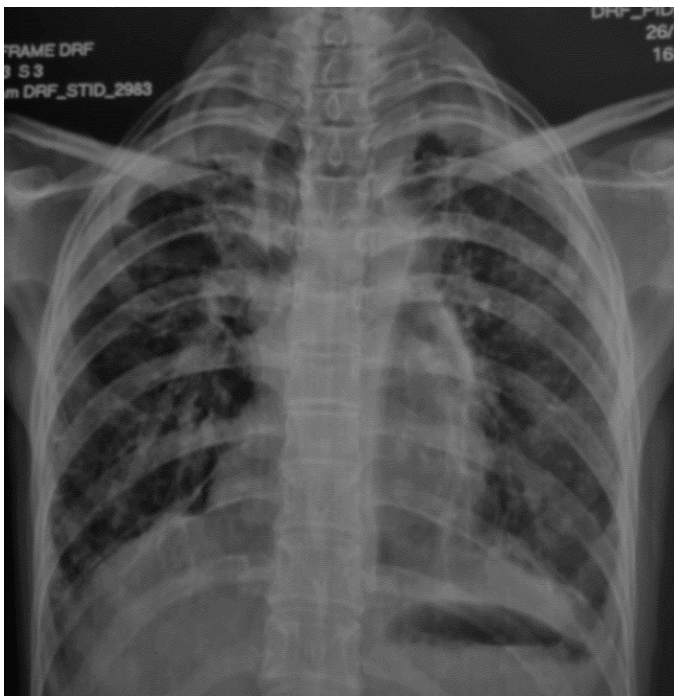

Fig. 3. Chest X ray: biapical pleural thickening and diffuse bilateral reticulonodular opacities with the retraction of the hila upwards and a right diaphragmatic dome elevation

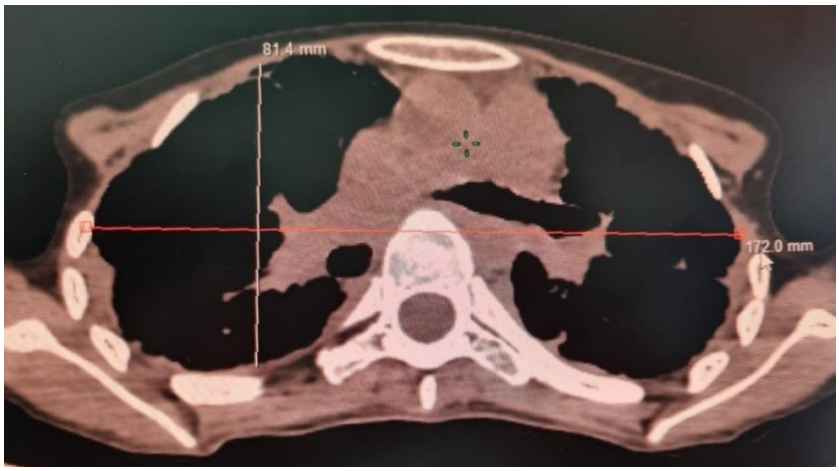

Fig. 4. Flat chest index= 0,47 [Reference value for FPI (Flat Pattern Index): 0.649 ± 0.06]

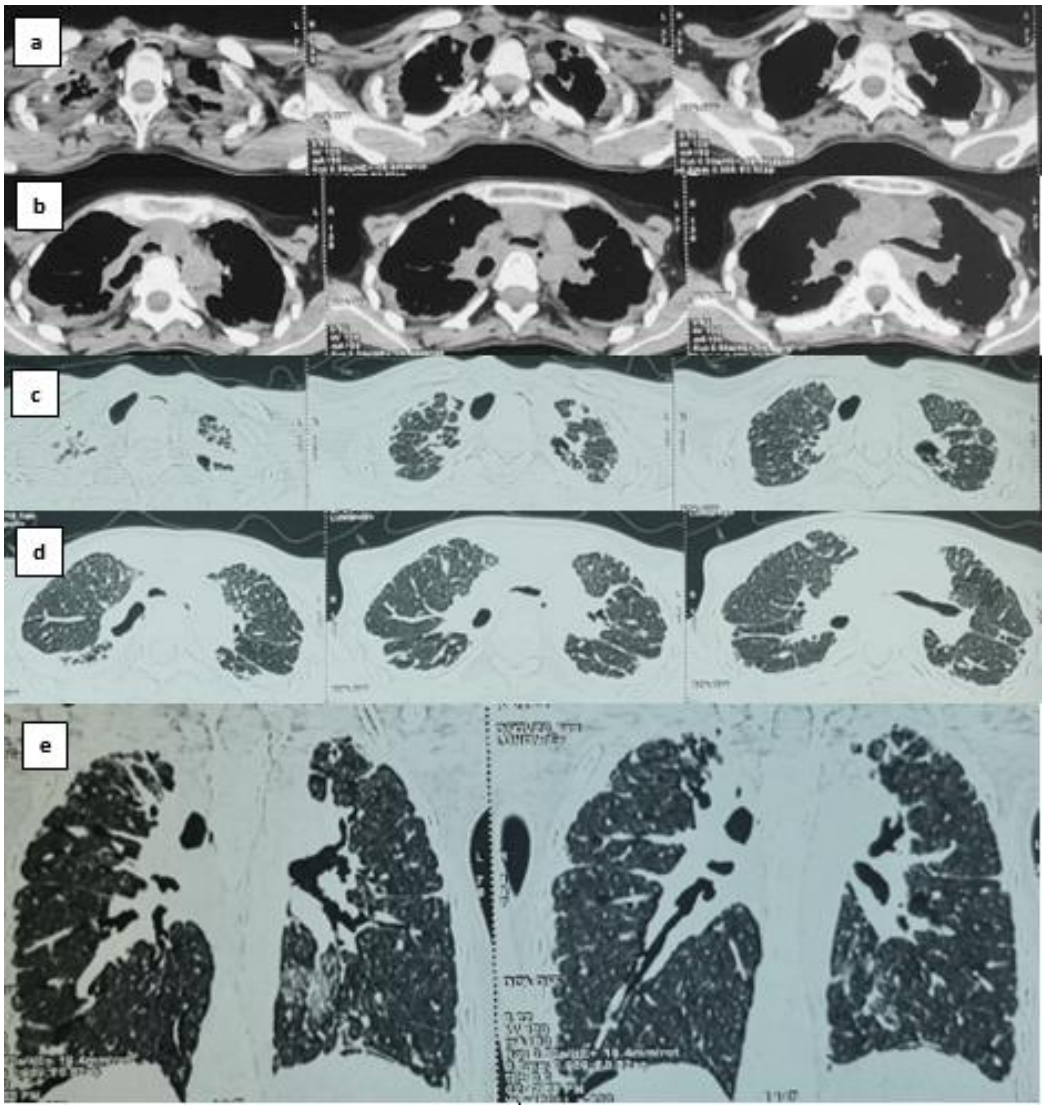

Fig. 5. HR chest CT scan: Axial (a,b,c,d) and Coronal (e): biapical pleural thickening and subpleural fibrosis, traction bronchiectasis

Due to the patient's dyspnea, a plethysmography couldn't be realised to evaluate the disease's impact on the patient's respiratory function. Instead, a 6-minute walk test was conducted, which revealed desaturation to 72% at 30 meters. Arterial blood gas analysis indicated hypercapnic respiratory failure. Electrocardiogram exam was normal and the echocardiography showed no signs of pulmonary hypertension.

Given the patient's young age and condition, a lung transplant was recommended. However, this procedure was unavailable inside the national healthcare system, and antifibrotic medications were not affordable for the patient. Genetic counseling was advised. Nevertheless, the patient received bronchodilators and NIV to assist with her respiratory challenges, along with adequate nutritional and psychological support. The patient passed away 4 months after discharge from the hospital, likely due to respiratory distress.

3. DISCUSSION

Pleuroparenchymal fibroelastosis (PPFE) is considered as a rare idiopathic interstitial pneumonia (IIP) in the revised international multidisciplinary classification of the IIPs in 2013 [1]. It is characterised by predominantly upper lobe pleural and subjacent parenchymal fibrosis, the latter being intra-alveolar with accompanying elastosis of the alveolar walls [2].

The true incidence and prevalence of PPFE are not known, because of misdiagnosis and the absence of agreed criteria for its identification [2]. First described in the Japanese literature in 1992 by Amitani et al*.* as idiopathic pulmonary upper lobe fibrosis and mentioned for the first time as PPFE in an English publication in 2004 by Frankel et al [3,4].

It can occur at any age and no gender predominance has been described in previous studies [4–6]. The main symptoms are dry cough, progressive worsening dyspnea, a constant weight loss, sometimes a sudden onset of chest pain due to pneumothorax may be the first symptom to appear, however crepitus rales and digital hippocrasis are rarely found. On physical examination, a platythorax or flattened thoracic cage it can be found in patients with PPFE [3].

The frontal chest X-ray shows a reduced lung volume with ascending hilar opacities and diaphragmatic cupolas, a bilateral apical pleural thickened. Otherwise, the parenchyma appears not very pathological [7]. The high resolution computer tomography has a major interest for the diagnosis of the PPFE, the proposed radiological criteria is definite when it shows a pleural thickening with associated subpleural fibrosis concentrated in the upper lobes with less marked or no lower lobe involvement [8]. The platythorax or the antero-posterior flattening of the chest is commonly observed in PPFE measured from the antero-posterior diameter over the transverse diameter of the thoracic cage at the level of the 6th thoracic vertebra which is smaller than the normal population [9]. Pneumothorax or pneumomediastinum may complicate the course of the disease.

The diagnosis of certainty is anatomopathological by labelling of elastin fibers with orcein or Elastic Van Gieson showing thickening of the elastin-rich pleura and clear boundaries with the healthy parenchyma, but surgical biopsy is often avoided because of a recognized risk of complications such as iatrogenic pneumothorax, pneumomediastinum or the development of a bronchopleural fistula [4].

Definitive diagnosis traditionally requires a positive histopathological examination. However, in countries with a higher prevalence of the disease, such as Japan, some studies have suggested that clinical, physiological, and imaging data may be sufficient to establish the diagnosis [9]. Due to the lack of consensus on diagnostic criteria for PPFE, multiple proposals have been suggested.

In 2012, Reddy and al. proposed a set of diagnostic criteria for PPFE based on radiological findings, categorizing them as 'definitive'; 'consistent with PPFE'; 'inconsistent with PPFE' (Table 1) [1]. In 2013, the ATS/ERS set diagnostic criteria for IPPFE based on radiological findings, regardless of whether there is histopathological confirmation.

The histological characteristics has for consequence a restrictive ventilatory disorder as the main functional abnormality. The PPFE is usually reported as an idiopathic disease, but there are many associated situations (lung transplantation, post-chemotherapy, drug therapy, bone marrow transplantation, recurrent infections). Familial forms with genetic abnormalities by TERT and TERC mutation are also observed [10,11].

Table 1. Criteria proposed for the diagnosis of pleuroparenchymal fibroelastosis

Category	Histopathology	CT high resolution
Definitive	Upper lobe pleural fibrosis with subjacent intra-alveolar fibrosis accompanied with alveolar septal elastosis	Pleural thickening with associated subpleural fibrosis in the upper lobes without involvement of the lower lobes
Consistent with PPFE	Presence of intra-alveolar fibrosis but 1) not accompanied by significant pleural fibrosis, 2) not subpleural predominance or 3) not present in a biopsy of the upper lobe	Pleural upper-lobe thickening with associated subpleural fibrosis but 1) not distributed in the upper lobes, or 2) with characteristics of coexistent disease in other sites
Inconsistent with PPFE	Absence of features of definitive and consistent diagnosis	Absence of features of definitive and consistent diagnosis

It's important to emphasize that there is no established pharmacological consensus on the treatment of PPFE. The lack of a standardized treatment presents a significant challenge for the management of PPFE patients. Nowadays, there is no specific therapy other than lung transplantation, which regarded the treatment of choice for patients with end-stage respiratory failure caused by this disease [12]. The corticosteroids are useless and the use of immunosuppressive agents such as azathioprine or methotrexate is usually avoided because of the hight risk of infection in these patients. The role of antifibrotics in treating PPFE is not yet well-established. While antifibrotic agents have shown efficacy in managing idiopathic pulmonary fibrosis, their effectiveness in treating PPFE remains controversial. Oxygen assessment, nutritional input, psychological support, and pulmonary rehabilitation should ideally be part of the standard of care of PPFE [10].

4. CONCLUSION

In conclusion, we underline the importance of reporting these 2 cases to learn more about the disease, a rare chronic fibrosing interstitial pneumonia, and its serious prognosis in the absence of therapies.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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