



Case report

Transbronchial cryobiopsy for diagnosis of pleuroparenchymal fibroelastosis

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ABSTRACT

Rationale: Pleuroparenchymal fibroelastosis (PPFE) is a rare subtype of idiopathic interstitial pneumonias. PPFE mostly affects the upper lung zones and is characterized radiologically by pleural and subpleural fibrotic thickening with a reticular pattern. There is no established treatment for PPFE but lung transplantation can be considered for advanced stage. The gold standard for the diagnosis of PPFE is surgical lung biopsy (SLB) but the bronchoscopic transbronchial cryobiopsy (TBCB) is a less invasive alternative.

Patient concerns: We report here two cases in which the diagnosis of PPFE was established with the help of TBCB.

Diagnosis and interventions: Bronchoscopy with TBCB was performed under sedation with spontaneous ventilation and the help of an uncuffed ET tube.

Outcomes: Histopathology showed intra-alveolar fibroblastic proliferation with elastosis, which confirmed the diagnosis of PPFE.

Lessons: The current report demonstrates that TBCB can be a useful and safe tool to confirm the diagnosis of PPFE. According to our knowledge, this is one of few reports that shows successful diagnosis of PPFE by TBCB.

1. Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare subtype of idiopathic interstitial pneumonias, first described by Amitani et al. [1] as a fibrosis of the upper lobes and then identified as a novel clinicopathologic entity by Frankel et al., who coined the term pleuroparenchymal fibroelastosis [2]. In 2013 PPFE was recognized as an entity in the American Thoracic Society (ATS)/ERS classification statement on idiopathic interstitial pneumonia [3]. Until now about 120 cases have been reported in the world literature [4]. Its etiology is unknown and seems to be unrelated to smoking. While 10–30% of cases are idiopathic, some cases are associated with pre- or coexisting conditions like bone marrow and lung transplantation, recurrent respiratory tract infections, auto-immune disease, alkylating chemotherapy or genetic factors [4–7, 15]. The differential diagnosis includes diseases like asbestosis, tuberculosis, sarcoidosis, chronic hypersensitivity pneumonia and

unclassifiable interstitial pneumonia [4,8]. Common presenting symptoms are dyspnea on exertion, dry cough and recurrent respiratory tract infections [8–10]. Spontaneous pneumothorax and pneumomediastinum have been reported [11–13]. The diagnosis of this disease is established on the basis of compatible radiologic and histopathologic findings. Radiologically, PPFE is characterized by pleural and subpleural fibrotic thickening with a reticular pattern, with upper lobe predominance [14]. Histopathology shows an intense elastic fibrosis of the upper lobes involving visceral pleura and subpleural parenchyma with intra-alveolar involvement [15]. The mean age at time of diagnosis is 50 years and some reports suggested that females are affected more frequently [4,8]. The disease is progressive in 60% of patients with a disease-specific mortality of 40% [3]. There is no established treatment for PPFE. Immunosuppressive drugs, acetylcysteine and even pirfenidone have not shown beneficial effects according to previous case reports [8,16,17]. Lung transplantation for end stage disease can be

Abbreviations: PPFE, Pleuroparenchymal fibroelastosis; TBCB, Transbronchial cryobiopsy; SLB, surgical lung biopsy; HRCT, High-resolution CT.

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considered [4,8]. While the gold standard for the diagnosis of PPFE is surgical lung biopsy (SLB), the current report shows that bronchoscopic transbronchial cryobiopsy is a less invasive alternative.

2. Case 1

A 73-year-old male was referred because of progressive dyspnea. The medical history included hypertension and venous thromboembolism of the lower extremity and the medication included aspirin, candesartan and metoprolol. He complained of progressive dyspnea on exertion and non-productive cough. There were no recurrent respiratory infections. History taking was not indicative of auto-immune diseases and there was no exposure to bird, pets, dust or other particular compounds associated with interstitial lung disease. There was no family history of pulmonary fibrosis and no known allergies. Physical examination revealed fine crackles bilaterally and was otherwise unremarkable. Laboratory investigation revealed no evidence of a connective tissue disease or vasculitis. Chest radiograph showed sign of reticular opacity in both lungs. Pulmonary function testing showed reduced diffusion capacity (TLco 6.22 mmol/min/kPa, 60% of predicted) and reduced total lung capacity (TLC 77% of the predicted value). Echocardiography showed normal ventricular and atrial function and no signs of pulmonary hypertension. Cardiopulmonary Exercise Testing showed near-normal peak exercise capacity and no significant impairment. High-resolution CT (HRCT) of the chest demonstrated subpleural thickening, volume loss and architectural distortion predominantly found in both lung apices and reticulation in basal region, consistent with PPFE (Fig. 1A, B). Transbronchial cryobiopsy was performed under propofol sedation with the use of an uncuffed endotracheal tube and a bronchial blocker to control bleeding. Three biopsies were obtained from segments 9 and 10 of the right lower lobe. The procedure was complicated by pneumothorax and the patient was treated with a chest drain for three days. The pathological specimen demonstrated tissue with interstitial fibroelastosis, consistent with PPFE (Fig. 2A–D). Because there was no inflammatory infiltration of alveolar septa and interstitium, NSIP was ruled out.

Follow-up with pulmonary function testing and HRCT has not shown progression in 40 months. Therefore, no treatment has been initiated.

3. Case 2

A 58-year-old engineer was referred for investigation when his breathlessness, present for four years, began to limit his capacity for physical exertion. He had never smoked, had no symptoms of a connective tissue disease (CTD) and gave no history of pertinent exposures or familial lung disease. He was taking simvastatin, perindopril and metformin, all commenced after the onset of symptoms.

Investigations revealed no antibodies against an extensive panel of CTD antigens, thermophilic moulds, *Aspergillus* or avian antigens. Lung

function tests showed ventilatory restriction with moderate to severe impairment of gas transfer factor (FVC 2.52L, 57% predicted; spirometric ratio 0.84; TLco 39% predicted). Contiguous high-resolution CT demonstrated symmetrical pleural and subpleural fibrosis at the periphery of the upper lobes (Fig. 3 A). A larger patch of fibrosis with marked traction bronchiectasis was present in the lingula with additional foci of subpleural scarring in both lower lobes (Fig. 3 B).

Bronchoalveolar lavage from the right middle lobe was notable only for trivial (17%) lymphocytosis. An MDT diagnosis of upper zonal PPFE and lower zonal unclassifiable ILD was reached. The patient was offered either surgical lung biopsy or transbronchial cryobiopsy to increase the diagnostic certainty and to guide therapeutic planning particularly with respect to anti-fibrotic treatment.

Transbronchial cryobiopsies comprising two pieces of lung tissue from each of the lingula and left lower lobe showed intra-alveolar fibroblastic proliferation with elastosis and mild chronic inflammation without granulomatous or vascular abnormalities. The biopsies did not include pleural tissue.

A diagnosis of progressive PPFE was concluded and low dose prednisolone commenced, initially to good effect. He went skiing three months after the biopsy but in the months that followed, he suffered recurrent chest infections despite ongoing prophylactic antimicrobials. He gradually developed worsening respiratory failure and succumbed whilst waiting for a lung transplant assessment.

4. Discussion

The diagnosis of PPFE is established by characteristic changes on HRCT scan and histopathology. SLB is the gold standard for obtaining adequate histological samples in idiopathic interstitial lung disease as well as PPFE. However, SLB is an invasive procedure with significant morbidities requiring hospitalization for a few days and carries a risk of postoperative complications such as prolonged air leak and pneumothorax. The rate of postoperative mortality of SLB ranges between 0% and 3.6% [18]. Recently, transbronchial lung cryobiopsy (TBCB) has emerged as a less invasive technique [19–21]. This technique allows sampling of specific areas in the lung identified on HRCT scan. Under fluoroscopic guidance, a cryoprobe is positioned the periphery of the lung, approximately 1 cm proximal of the visceral pleura. After 5–7 seconds of freezing, the lung tissue around it sticks to the probe and can be removed and subsequent bleeding is controlled with a bronchial balloon blocker [22]. With TBCB, larger tissue samples can be obtained compared to transbronchial forceps biopsy (TBLB), which is inadequate for diagnosis in most ILD cases. A sample size of 5 mm in diameter is suggested as sufficient [19].

Ravaglia C et al., published a retrospective review for 447 cases comparing TBCB with SLB, 150 cases in the SLB group and 297 cases in the TBCB group; In the SLB group, the pathologists identified histopathologic criteria sufficient to define a characteristic pattern in 148

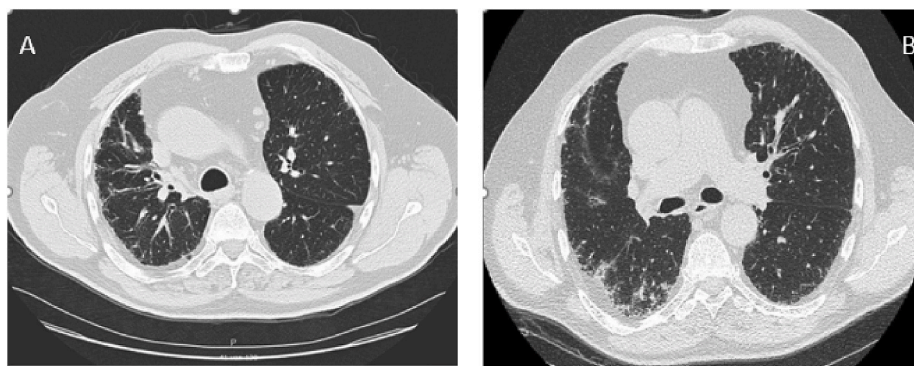


Fig. 1. HRCT images showing diffuse pleural and subpleural thickening with consolidations, architectural distortion and traction bronchiectasis accompanied by volume loss in the upper lobes (A), also in the apical segment of lower lobes (B).

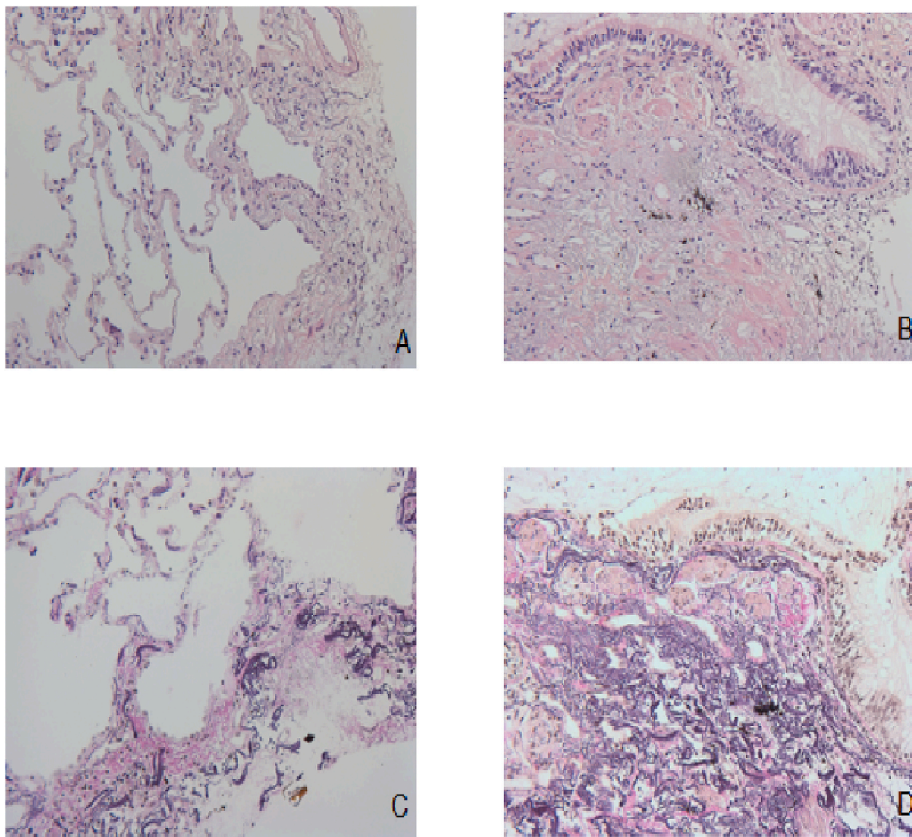


Fig. 2. Lung biopsy specimen (H&E stain, $\times 100$) and (EvG) stain X100) at low power: (A) Demonstrated the peripheral lung parenchyma with a transition of extensive elastosis with fibrosis. (B) Shows bronchiolus with metaplastic hyperplasia of smooth muscle mixed with dense elastosis and fibrosis. (C) EVG staining demonstrates elastosis and fibrosis. (D) EVG staining demonstrates extensive elastosis in the submucosa.

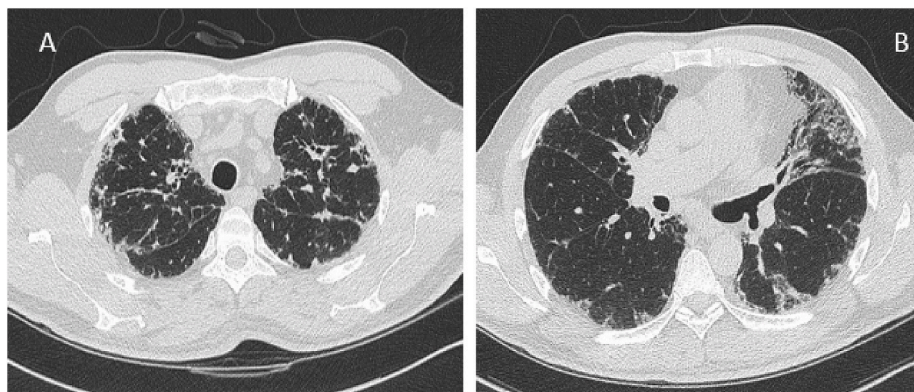


Fig. 3. High-resolution CT showed symmetrical pleural and subpleural fibrosis at the periphery of the upper lobes (A). Also a patch of fibrosis and traction bronchiectasis in the lingula with additional foci of subpleural scarring in both lower lobes (B).

patients (98.7%); in the TBCB group, a characteristic pattern was obtained in 246 cases (82.8%; $p = 0.013$) with significant decrease in number of hospital days and mortality between TBCB and SLB [20].

Therefore TBCB might be sensible first diagnostic approach for obtaining tissue in interstitial lung disease [19,20]. Recent reports have suggested that TBCB might obviate the need for surgical biopsy in most cases of interstitial lung disease [19–21].

In 2016 Kushima H et al., performed TBLB in two patients suspected of PPFE in whom SLB was contraindicated and found that the specimens in both patients showed aggregates of elastic fibers in the submucosa, consistent with PPFE [23]. The authors concluded that the TBLB can be helpful in the diagnosis of PPFE, because the anatomical distribution in the secondary lobules (in contrast to disease like UIP and NSIP) is not a crucial factor in the histopathological diagnosis of PPFE.

In many reported series, at least a third of patients with PPFE have a

co-existing ILD away from the upper lobes, most commonly usual interstitial pneumonia (UIP) or fibrotic/chronic hypersensitivity pneumonitis (CHP). Sampling of these areas by transbronchial cryobiopsy offers two advantages – obviating the need for surgical biopsy and securing pathologic information that could impact crucially on the patient's management or prognosis. Hemorrhage control can be challenging when obtaining cryobiopsies from the upper lobes because bronchial blockers are difficult to position in the upper lobe and can dislocate easily. However, these problems can be overcome by techniques such as using a biopsy forceps to position an Arndt endobronchial blocker by grabbing its guide loop and pushing it well into the target segment. At our institutions we have not experienced significant difficulties in controlling bleeding after TBCB from upper lobes.

The current report demonstrates that TBCB can be a useful and safe tool to confirm the diagnosis of PPFE. According to our knowledge, this

is one of few reports that shows successful diagnosis of PPFE by TBCB, with histopathological specimens demonstrating characteristic interstitial fibro-elastosis.

Declaration of competing interest

We have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2020.101164>.

References

- [1] R.N.A. Amitani, F. Kuse, Idiopathic pulmonary upper lobe fibrosis (IPUF), *Kokyu Junkan* 69 (1992) 3–9.
- [2] S.K. Frankel, C.D. Cool, D.A. Lynch, K.K. Brown, Idiopathic pleuroparenchymal fibroelastosis: description of a novel clinicopathologic entity, *Chest* 126 (2004) 2007–2013.
- [3] W.D. Travis, U. Costabel, D.M. Hansell, et al., ATS/ERS committee on idiopathic interstitial pneumonias. An official American Thoracic Society/European Respiratory Society statement: update of the international multidisciplinary classification of the idiopathic interstitial pneumonias, *Am. J. Respir. Crit. Care Med.* 15 (188) (2013) 733–748.
- [4] Kian Shaun, Cheng Hong, Khoo Leong Chuah, Pleuroparenchymal fibroelastosis of the lung: a review, *Arch. Pathol. Lab Med.* 140 (8) (2016) 849–853. August 2016.
- [5] F. Chen, K. Matsubara, A. Miyagawa-Hayashino, et al., Lung transplantation for pleuroparenchymal fibroelastosis after chemotherapy, *Ann. Thorac. Surg.* 98 (2014) 115–117.
- [6] F. Mariani, B. Gatti, A. Rocca, et al., Pleuroparenchymal fibroelastosis: the prevalence of secondary forms in hematopoietic stem cell and lung transplantation recipients, *Diagn. Interv. Radiol.* 22 (5) (2016) 400–406, <https://doi.org/10.5152/dir.2016.15516>.
- [7] C. Beynat-Mouterde, G. Bel t ramo, G. Lezmi, et al., Pleuroparenchymal fibroelastosis as a late complication of chemotherapy agents, *Eur. Respir. J.* 44 (2) (2014) 523–527.
- [8] M. Bonifazi, M.A. Montero, E.A. Renzoni, Idiopathic pleuroparenchymal fibroelastosis, *Curr. Pulmonol. Rep.* 6 (2017) 9.
- [9] T. Oda, T. Ogura, H. Kitamura, et al., Distinct characteristics of pleuroparenchymal fibroelastosis with usual interstitial pneumonia compared with idiopathic pulmonary fibrosis, *Chest* 146 (2014) 1248–1255.
- [10] K. Watanabe, Pleuroparenchymal fibroelastosis: its clinical characteristics, *Curr. Respir. Med. Rev.* 9 (4) (2013) 229–237.
- [11] J.C. English, J.R. Mayo, R. Levy, J. Yee, K.O. Leslie, Pleuroparenchymal fibroelastosis: a rare interstitial lung disease, *Respirol. Case Rep.* 3 (2) (2015) 82–84.
- [12] H.J. Noh, Y. Seo, S.M. Huo, T.J. Kim, H.L. Kim, J.S. Song, Idiopathic pleuroparenchymal fibroelastosis presenting in recurrent pneumothorax: a case report, *Tuberc. Respir. Dis.* 77 (4) (2014) 184–187.
- [13] Y.-Y. Lin, W.-H. Hsu, M.-H. Wu, T.-Y. Chou, Pleuroparenchymal fibroelastosis presenting with pneumothorax, *SAGE Open Med. Case Rep.* 6 (2018), 2050313X18762853.
- [14] N. Enomoto, H. Kusagaya, Y. Oyama, et al., Quantitative analysis of lung elastic fibers in idiopathic pleuroparenchymal fibroelastosis (IPPF): comparison of clinical, radiological, and pathological findings with those of idiopathic pulmonary fibrosis (IPF), *BMC Pulm. Med.* 14 (2014) 91.
- [15] J.H. Von der Thüsen, Pleuroparenchymal fibroelastosis: its pathological characteristics, *Curr. Respir. Med. Rev.* 9 (4) (2013) 238–247.
- [16] S. Sato, M. Hanibuchi, M. Takahashi, et al., A patient with idiopathic pleuroparenchymal fibroelastosis showing a sustained pulmonary function due to treatment with pirfenidone, *Intern. Med.* 55 (5) (2016) 497–501.
- [17] E.B. Boerner, U. Costabel, T.E. Wessendorf, F. Bonella, D. Theegarten, Idiopathic pleuroparenchymal fibroelastosis (PPFE) - a case study of a rare entity, *Rev. Port. Pneumol.* 23 (6) (2017) 352–355. ISSN: 2173-5115.
- [18] Benjamin Bondue, Thierry Pieters, Patrick Alexander, et al., Role of transbronchial lung cryobiopsies in diffuse parenchymal lung diseases: interest of a sequential approach, *Pulm. Med.* (2017) 201771–201773. Article ID 6794343, 7 pages.
- [19] J. Hetzel, F. Maldonado, C. Ravaglia, A.U. Wells, T.V. Colby, S. Tomassetti, J. H. Ryu, O. Fruchter, S. Piciucchi, A. Dubini, A. Cavazza, M. Chilosi, N. Sverzellati, D. Valeyre, D. Leduc, S.L.F. Walsh, S. Gasparini, M. Hetzel, L. Hagemeyer, M. Haentschel, R. Eberhardt, K. Darwiche, L.B. Yarmus, A. Torrego, G. Krishna, P. L. Shah, J.T. Annema, F.J.F. Herth, V. Poletti, Transbronchial cryobiopsies for the diagnosis of diffuse parenchymal lung diseases: expert statement from the cryobiopsy working group on safety and utility and a call for standardization of the procedure, *Respiration* 95 (2018) 188–200.
- [20] C. Ravaglia, M. Bonifazi, A.U. Well, S. Tomassetti, S. Tomassetti, C. Gurioli, et al., Safety and diagnostic yield of transbronchial lung cryobiopsy in diffuse parenchymal lung diseases: a comparative study versus video- assisted thoroscopic lung biopsy and a systematic review of the literature, *Respiration* 91 (2016) 215–217.
- [21] U.A. Gauhar, Usefulness of transbronchial cryobiopsy in interstitial lung disease, *Arch. Pulmonol. Respir. Care* 3 (2) (2017), 050-051.
- [22] R. Thomas, M.J. Phillips, Bronchoscopic cryotherapy and cryobiopsy, in: F.J. F. Herth, P.L. Shah, D. Gompelmann (Eds.), *Interventional Pulmonology (ERS Monograph)*, European Respiratory Society, Sheffield, 2017, pp. 141–161.
- [23] H. Kushima, K. Hidaka, H. Ishii, A. Nakao, R. On, Y. Kinoshita, M. Fujita, K. Watanabe, Two cases of pleuroparenchymal fibroelastosis diagnosed with transbronchial lung biopsy, *Respir. Med. Case Rep.* 19 (2016 Jul 18) 71–73, <https://doi.org/10.1016/j.rmcr.2016.07.008>.