

# Pleuroparenchymal fibroelastosis secondary to autologous hematopoietic stem cell transplantation: A case report

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**Abstract.** Pleuroparenchymal fibroelastosis (PPFE) is a rare interstitial lung disease. Although an increased number of PPFE cases have been reported recently, the characteristics of this condition have not been well described. The present study reports on the case of a 34-year-old male patient who presented with unilateral lung abnormalities. The patient was admitted due to a 9-year history of progressive cough and exertional dyspnea, as well as a history of Hodgkin's lymphoma treated by autologous hematopoietic stem cell transplantation (HSCT). The patient had been initially diagnosed with tuberculosis and received regular anti-tuberculosis therapy for 18 months; however, the symptoms progressed. Serial chest computed tomography scans indicated a gradually worsening diffuse pleural thickening, dense subpleural opacification and volume loss, associated with evidence of fibrosis in the right lung. On physical examination the patient was cachectic, with a body mass index of 18.5 kg/m<sup>2</sup>, and he had a flattened thoracic cage. Arterial blood gas analysis revealed hypoxia. Pulmonary function tests revealed restrictive ventilation dysfunction and decreased diffusion capacity. The microbiological and cytological examinations were negative. Lung biopsy revealed a thickened pleura consisting of large amounts of collagen and elastic fibers, coexisting with subpleural intra-alveolar fibrosis with alveolar septal elastosis, without inflammatory infiltrates. The patient was diagnosed with PPFE secondary to HSCT and eventually succumbed to respiratory failure and infection while waiting for a lung transplant. Physicians should be aware of the typical and atypical characteristics of this rare disease, as its clinical and radiological characteristics may lead to misdiagnosis, particularly as chronic infections. The prognosis remains poor without effective long-term treatment.

## Introduction

Pleuroparenchymal fibroelastosis (PPFE) is a rare interstitial lung disease (1), first described in 1992 by Amitani *et al* (2) as 'upper lobe pulmonary fibrosis'. PPFE is histologically characterized by a thickened, fibrotic visceral pleura with subpleural parenchymal fibrosis and elastosis, predominantly of the upper lobes. Although an increased number of PPFE cases have been reported, the characteristics of this disease have not been well described, which may lead to misdiagnosis. The present study reports on the case of a patient who presented with extensive unilateral lung abnormalities following autologous hematopoietic stem cell transplantation (HSCT) and determined the key characteristics, with the aim of helping physicians to distinguish PPFE from chronic infectious diseases.

## Case presentation

A 34-year-old male patient was admitted to the China-Japan Friendship Hospital (Beijing, China) in May 2017 due to experiencing progressive cough and exertional dyspnea for 9 years. The patient had been diagnosed with Hodgkin's lymphoma in 2011, and received chemotherapy (including adriamycin, bleomycin, vincristine and dacarbazine) and radiotherapy, followed by autologous HSCT 2 years later. The initial chest radiography after the transplantation was normal; however, 10 years prior to admission to our hospital, a follow-up chest computed tomography (CT) revealed a small right-sided pneumothorax, albeit without symptoms. At 9 years prior to admission, the patient had developed a progressive cough and exertional dyspnea, and chest CT revealed the presence of an exudative lesion in the lower right lung. A bronchoscopy and bronchoalveolar lavage (BAL) were performed 5 years prior to admission. Acid-fast bacilli were detected in the BAL fluid smear. The patient was then diagnosed with tuberculosis and received treatment with isoniazide, rifampicin, pyrazinamide and streptomycin for a total of 2 months, followed by isoniazide, rifampicin and streptomycin for a further 16 months. However, the symptoms slowly progressed. A biopsy of the right lung performed in another hospital in 2016 revealed collagenous fibers and a certain amount of normal alveolar tissue (Fig. 1). The patient was diagnosed with tuberculosis-associated lung

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destruction. The patient was a non-smoker and reported no known exposure to environmental allergens or asbestos.

On physical examination the patient was cachectic, with a body mass index of 18.5 kg/m<sup>2</sup> and had a flattened thoracic cage. The heart rate was >120 beats/min and the respiratory rate was 30 breaths/min. The breath sounds were decreased at the bottom of the right lung and arterial blood gas analysis revealed hypoxia. Pulmonary function tests revealed restrictive ventilation dysfunction and decreased diffusion capacity: The forced vital capacity (FVC) was 1.15 l (21.3% of predicted) and the ratio of the forced expiratory volume in 1 sec to the FVC was 95.14%; the total lung capacity was 2.72 l (35.7% of predicted) and the diffusion capacity of carbon monoxide was 3.35 mmol/min/kPa (27.5% of predicted). Serial chest CTs performed at the time of admission to our hospital revealed a gradually worsening diffuse pleural thickening, dense subpleural opacification and volume loss associated with evidence of fibrosis in the right lung (Fig. 2). Bronchoscopy was repeated at our hospital, with the BAL examination revealing 5.0% macrophages, 17.5% lymphocytes, 76% neutrophils and 1.5% eosinophils. The microbiological and cytological examinations were negative. Percutaneous lung puncture biopsy revealed a thickened pleura, consisting of large amounts of collagen and elastic fibers, coexisting with subpleural intra-alveolar fibrosis and alveolar septal elastosis, without inflammatory infiltrates (Fig. 3).

Based on the medical history, clinical manifestations, imaging and histological findings, the patient was diagnosed with PPFE secondary to HSCT and eventually succumbed to respiratory failure and infection while waiting for a lung transplant in August 2017.

## Discussion

PPFE is a rare form of interstitial lung disease characterized by elastic fibrosis involving the pleura and subpleural parenchyma. Since PPFE was first described by Amitani *et al* (2), >100 cases have been reported to date (3-9). PPFE may be either idiopathic or occur secondary to lung transplantation (10), marrow transplantation (3,11) or HSCT (12), representing a rare late post-transplantation complication.

The correlation between PPFE and transplantation was first reported by von der Thüsen *et al* (11), who described PPFE secondary to bone marrow transplantation. A study by Mariani *et al* (12) retrospectively reviewed high-resolution computed tomography images from 53 lung transplant recipients and 700 HSCT recipients, revealing that the prevalence of PPFE was 7.54% [95% confidence interval (CI): 0.43-14.6%] among lung transplant recipients and 0.28% (95% CI: 0.00-0.68%) among HSCT recipients. In that retrospective study, patients with secondary PPFE developed fibrosis within 2-13 years (mean, 5.3 years) post-transplantation. The case of the present study developed pleural thickening and fibrosis 9 years after HSCT, which is within the time window reported by previous studies. The mechanism by which transplantation leads to PPFE has remained to be fully elucidated. Possible causes may include reactions to chemotherapy or radiotherapy, or graft-versus-host disease (GVHD) (13). GVHD may be a likely cause, as the majority of the reported cases occurred after HSCT. However, certain patients develop PPFE after autologous bone marrow transplantation, lung transplantation or chemotherapy alone.

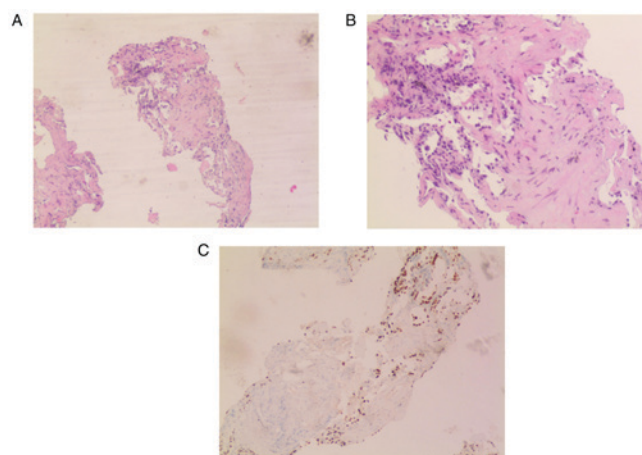


Figure 1. Histological findings of a percutaneous lung puncture biopsy performed in another hospital in 2016. (A and B) H&E staining revealed thickened pleura consisting of hyaline degeneration of connective tissue, coexisting with subpleural intra-alveolar fibrosis with alveolar septal elastosis, without any inflammatory infiltrates or granulomatous inflammation. (C) Thyroid transcription factor 1 staining revealed remaining alveoli (magnification, x40 in A and C, and x100 in B).

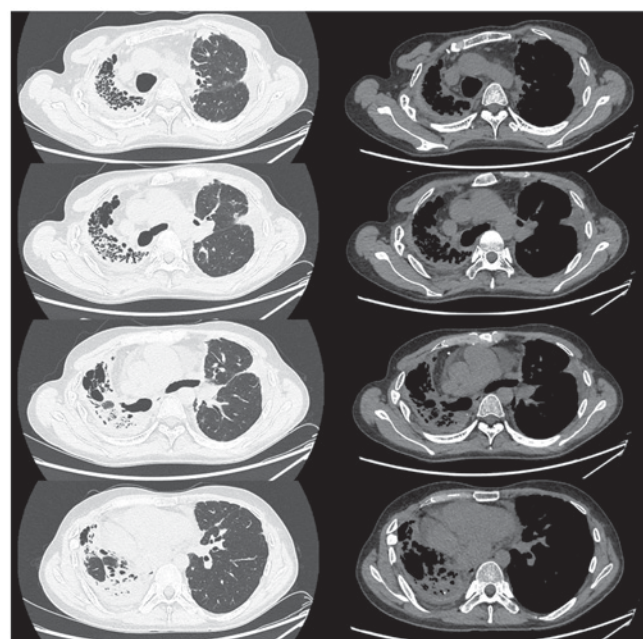


Figure 2. Axial CT performed at the time of admission to our hospital revealed diffuse pleural thickening, cystic bronchiectasis, dense subpleural opacification and volume loss associated with evidence of fibrosis involving the entire right lung including the lower zone. In the left lung, CT imaging indicated wedge-shaped interlobular pleural thickening distributed in the upper zone. CT, computed tomography.

One case developed post-HSCT PPFE and the surgical specimen exhibited characteristics of PPFE, without any evidence of GVHD (i.e. no lymphocytic inflammation or eosinophilic scarring suggestive of GVHD or obliterative bronchiolitis) (14). In this case, immunosuppressive therapy did not improve the pulmonary function (14). Those results suggest an association of PPFE with the conditioning treatment for HSCT rather than with GVHD. Therefore, PPFE after HSCT is a heterogeneous condition, with the contribution of GVHD to the development

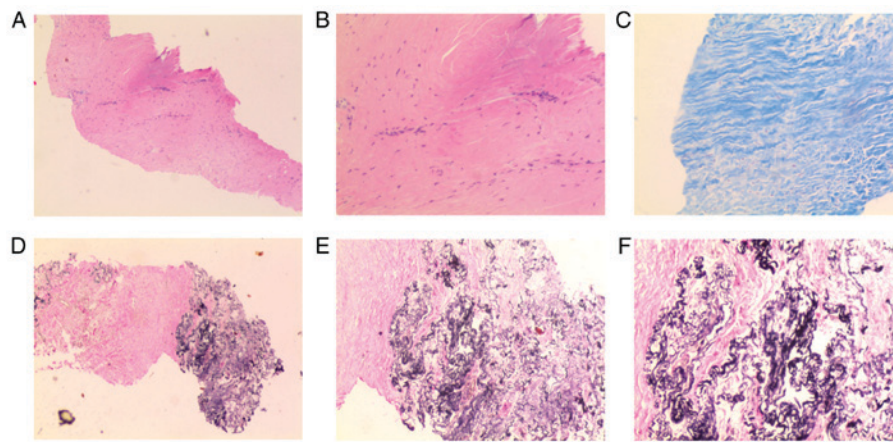


Figure 3. A percutaneous lung puncture biopsy guided by Doppler ultrasound was performed in our hospital after admission. (A and B) H&E staining revealed thickening of pleura consisting of hyaline degeneration of connective tissue. (C) Masson staining for collagen fibers and (D-F) elastic fiber staining and revealed large amounts of elastic fiber and collagen fiber, without any inflammatory infiltrates or granulomatous inflammation (magnification, x40 in A and D, x100 in B, C and E, and x200 in F).

of PPFE differing across cases. According to certain experts, in addition to lung collapse and fibrosis resulting from constrictive bronchiolitis obliterans, PPFE may be a consequence of persistent intra-alveolar organizing pneumonia (11). By histological analysis of biopsy specimens, certain studies demonstrated that diffuse alveolar damage preceded the development of PPFE in lung transplant as well as in HSCT recipients, suggesting that PPFE may represent a late complication associated with multiple factors (drugs, radiation, infection and cell-mediated immune reaction) that results in acute lung injury/diffuse alveolar damage. PPFE has also been described as a pulmonary complication following chemotherapy (15) or radiotherapy (16). The present patient received chemotherapy and radiotherapy at another hospital 17 years ago. Unfortunately, no information on the dosage of chemotherapy and radiotherapy was available, which is a limitation of the present study.

The case of the present study was diagnosed with tuberculosis-induced lung destruction prior to presenting at our hospital, and had received regular anti-tuberculosis therapy for 18 months, although the lesion on the right lung continued to progress. Possible reasons included non-tuberculosis mycobacterial infection rather than tuberculosis, and other diseases leading to structural damage of the lung. Considering that pneumothorax, which is a known clinical characteristic of PPFE, had occurred years prior to the diagnosis of tuberculosis, and that a significant deterioration with diffuse bilateral pleural thickening, albeit without inflammatory infiltrates, was observed on biopsy, the diagnosis of PPFE was favored over that of an infectious disease. Recurrent pulmonary infections may be an important risk factor for the progression of PPFE. Pulmonary infectious diseases caused by *Mycobacterium avium-intracellulare* complex (17), *Aspergillus* (18,19) or *Cytomegalovirus* (12) have been reported in patients with PPFE. These infectious diseases may coexist, but the association between these infections and PPFE has not yet been established. This calls for further investigation into whether the pathology of PPFE is induced by these infections, or whether PPFE favors the growth of these infectious pathogens.

The patient underwent a consecutive series of chest CT scans during follow-up over the 9 years prior to admission

to our hospital. However, the destruction of the lung parenchyma was attributed to tuberculosis, even after a biopsy of the right lung. A better awareness of the clinical, radiological and histological characteristics of PPFE will help physicians distinguish between this disease and chronic infections. These characteristics include typical risk factors (lung transplantation, bone marrow transplantation, HSCT, chemotherapy and inhalational exposure to aluminosilicate), slow progression, platythrax and marked thickening of the pleura with elastic fibers and dense collagen.

The prognosis for PPFE remains poor, with variable progression (18,20). The clinical course was reported to be progressive in a number of PPFE patients, despite aggressive treatment with corticosteroids, immunosuppressants or pirfenidone (19,21). Lung transplantation has been applied as a treatment in several cases of end-stage PPFE, but long-term outcome data are currently unavailable (21-23).

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#### Availability of data and materials

All the datasets generated and analyzed in the present study are available from the corresponding author on reasonable request.

## Authors' contributions

SZ and WX analyzed and interpreted the patient data and were major contributors in writing the manuscript. ZW and YT wrote the original medical record of the patient. JD performed the histological examination of the biopsy tissue. ZZ revised the manuscript. All authors have read and approved the final version of the manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Informed consent has been obtained from the patient regarding the publication of the case details and any associated images.

## Competing interests

The authors declare that they have no competing interests to disclose.

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