**Abstract:**
A 64-year-old man who presented with repeated bouts of pneumothorax was admitted to our hospital because of gradually progressive dyspnea and repeated episodes of a fever. The physiological, radiological and pathological findings were consistent with pleuroparenchymal fibroelastosis (PPFE). In addition, the serum-specific precipitating antibody for *Aspergillus* was positive. After the administration of voriconazole, a marked improvement was observed in the imaging and physiological findings. Given this clinical course, we diagnosed the patient with PPFE secondary to aspergillosis. The present case suggests that a therapeutic approach based on the cause of secondary PPFE may improve the prognosis of PPFE.

**Key words:** pleuroparenchymal fibroelastosis, chronic pulmonary aspergillosis, voriconazole, pulmonary function test

**Introduction**

Pleuroparenchymal fibroelastosis (PPFE) is a rare form of interstitial pneumonia characterized by parenchymal pulmonary fibrosis predominantly involving the upper lobe. The idiopathic form of PPFE is now listed as a rare idiopathic interstitial pneumonia in the classifications of the American Thoracic Society and the European Respiratory Society (1). A recent report by Ishii et al. described unique physiological characteristics of PPFE, such as restrictive impairment in which the forced vital capacity (FVC) is more severely reduced than the total lung capacity (TLC) but with an increased residual volume (RV)/TLC ratio (2). However, the cause is still unknown. There have been no reports in which antifungal agents were effective in PPFE patients with findings suggestive of *Aspergillus* infection (3, 4).

**Case Report**

A slender 64-year-old man presented with repeated bouts of pneumothorax, including a surgical procedure, since 18 years of age, and he had a persistent dry cough and exertional dyspnea from his 30s. He had a smoking history of 17.5 pack-years from 16 to 30 years of age. He had no history of asthma.

The patient was admitted to our hospital because of gradually progressive dyspnea on exertion and repeated episodes of a mild fever. On admission, his body mass index was 17.9 kg/m², and clubbed fingers were not seen. No rale was heard on auscultation. Chest radiograph showed thickening of the bilateral apical pleura with elevated hilar opacities (Fig. 1), and the lateral view showed an abnormally-narrowed anteroposterior diameter of the thoracic cage. Chest computed tomography (CT) demonstrated subpleural fibrotic opacities with traction bronchiectasis extending to adjacent lobes with multiple bulla and large cysts in the upper lung fields that were not seen in the middle and lower lobes (Fig. 2). The forced expiratory volume in one second (FEV₁) and FEV₁/FVC ratio were decreased (2,110 ml and 68.6%, respectively). The TLC was decreased, and the RV was increased, which resulted in an increased RV/TLC ratio (155% predicted). The serum-specific precipitating antibody for *Aspergillus* was positive, while immunoglobulin E (IgE) and IgE antibody for *Aspergillus* were negative.

Transbronchial lung biopsy specimens obtained from the left upper lobe (Elastica van Gieson staining) revealed dense aggregates of elastic fibers that were associated with intra...
alveolar fibrosis (Fig. 3A). The specimen contained a few granulomas (Fig. 3B), but there were no hyphae suggesting the presence of *Aspergillus*. The culture tests of both bronchial lavage fluid and sputum were negative. His serum C-reactive protein level was not elevated, and his Krebs von den Lungen-6 (KL-6) and surfactant protein (SP)-A levels were within the normal range (265 U/mL and 36.6 ng/mL, respectively). The serum levels of β-D-glucan and galactomannan antigen were also within the normal range. In contrast, the serum SP-D level was slightly elevated (194 ng/mL). These clinical, radiological and pathological findings were consistent with a diagnosis of PPFE (3).

The patient had a history of surgical procedure of the chest and chronic obstructive lung disease as risk factors for development of chronic pulmonary aspergillosis, in addition to a positive finding of serum-specific precipitating antibody for aspergillus and the presence of a few granulomas in the lung tissue. This was highly suggestive of a clinical diagnosis of chronic pulmonary aspergillosis based on the guidelines for aspergillosis (5). However, whether aspergillosis was the cause or result of PPFE could not be confirmed. We considered two possibilities: that aspergillosis secondarily resulted in PPFE-like lesions, or that aspergillosis was accompanied by primary PPFE.

We started the administration of antifungal agents after obtaining informed consent from the patient because no specific, effective treatment for PPFE was available at the time. Voriconazole was started at a loading dose of 600 mg/day followed by doses of 300 mg/day. One month after the initiation of voriconazole, the RV/TLC ratio had declined by 6% (149% predicted), but the values of KL-6 and SP-D did not change significantly (300 U/mL and 189 ng/mL, respectively). Another 10 months later, the RV/TLC ratio had de-
PPFE is a rare form of interstitial pneumonia characterized by parenchymal pulmonary fibrosis predominantly involving the upper lobe. Pulmonary function tests in patients with PPFE reveal mechanical restriction with a high RV/TLC ratio, causing increased partial pressure of arterial carbon dioxide and eventual hypercapnic respiratory failure (4). PPFE can occur without any underlying diseases (idiopathic PPFE) or with any of a number of conditions. However, the etiology of PPFE is unclear (6).

The underlying diseases include infections and hematopoietic stem cell transplantation, radiation, anticancer chemotherapy, some kind of autoimmune diseases and hypersensitivity pneumonia, among others. Reddy et al. reported that repeated inflammatory damage in a predisposed individual might lead to the pathology of PPFE (7). Although *Aspergillus* infection and *Mycobacterium* infection have been reported as causes of infection-related PPFE (7-9), whether the PPFE-like lesions are induced by these infections or PPFE facilitates the development of these infectious agents is unclear. There have been several reports of *Aspergillus* infection in the fibrotic lesions of PPFE (7, 9). However, Reddy et al. reported that repeated inflammatory damage in a predisposed individual might lead to the pathology of PPFE (7). In the present case, we were convinced of the presence of aspergillosis because the serum precipitating antibody with a high specificity for *Aspergillus* was positive (10).

The most important issue with PPFE is that there is no therapy targeting the inhibition of elastosis, due to the unclear underlying causes and mechanism of pathogenesis. There have been no reports of antifungal agents being effective in PPFE patients with findings suggestive of *Aspergillus* infection. This case showed marked improvements in the symptoms, the RV/TLC ratio, and the imaging findings after the administration of voriconazole. Whether or not voriconazole inhibits elastosis and/or collagenesis in addition to exerting fungicidal effects is unclear, as we did not obtain samples of lung tissue after the administration of voriconazole. However, the present case suggests that the development of PPFE might be related to aspergillosis. Distinguishing secondary PPFE from idiopathic PPFE is meaningful, as adopting a suitable therapeutic approach based on the cause of secondary PPFE may improve the prognosis of PPFE.

The present case suggests that distinguishing secondary PPFE from idiopathic PPFE is meaningful, as adopting a suitable therapeutic approach based on the cause of secondary PPFE may improve the prognosis of PPFE.

**Conclusion**

The authors state that they have no Conflict of Interest (COI).

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**References**


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