Pirfenidone-induced Eosinophilic Pleurisy

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Abstract

The patient was a 69-year-old man with idiopathic pulmonary fibrosis who was taking pirfenidone. After 7 weeks of treatment, he suffered from left-sided eosinophilic pleurisy. Medical thoracoscopy was performed and the histopathological examination of the parietal pleura revealed the massive infiltration of eosinophils and lymphoid follicles. After stopping pirfenidone therapy, the patient’s pleural effusion disappeared without additional treatment, and never recurred. This is the first case report of pirfenidone-induced pleurisy.

Key words: drug-induced pleurisy, eosinophilic pleurisy, pirfenidone, medical thoracoscopy

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Introduction

Drug-induced pleurisy is a rare adverse effect of various pharmacotherapies. The diagnosis is usually made clinically based on a history of using a prescribed drug, the exclusion of other potential etiologies, spontaneous improvement with the discontinuation of the suspected causative drug, or a re-challenge test (1, 2). A pleural fluid analysis is usually performed, but the results of thoracoscopic investigations have rarely been reported. The pleural effusion of patients with drug-induced pleurisy can show an increase in eosinophils (>10%), which represents eosinophilic pleural effusion (EPE). Pirfenidone, an oral antifibrotic agent that may reduce the progression of idiopathic pulmonary fibrosis (IPF), was approved for use in Japan in 2008, in the European Union in 2011, and in the United States in 2014. The prescription of pirfenidone was expected to increase worldwide following the 2015 change in the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association guidelines for IPF (3) from a “conditional recommendation against use” in 2011 to a “conditional recommendation for use”. To date, no reports have described pleurisy as an adverse drug reaction in patients receiving pirfenidone, including a post-marketing surveillance report of 1,371 cases from Japan (4). We herein describe a case of pirfenidone-induced eosinophilic pleurisy that was diagnosed by medical thoracoscopy.

Case Report

A 69-year-old man was started on pirfenidone (600 mg/day) for progressive dyspnea due to IPF. He had a 51 pack-year smoking history, but no occupational exposure to inhaled irritants. He had been taking omeprazole and mosapride to treat reflux esophagitis for at least 1 year. The patient had no history of allergies, respiratory disease other than IPF, or pleural disease. After 2 weeks of pirfenidone treatment, a mild elevation of serum eosinophils (380/μL) was noted. After 5 weeks of treatment, the pirfenidone dose was increased to 1,200 mg/day. After 7 weeks of treatment, he presented with worsening left-sided chest pain and was admitted to the hospital. His temperature was 36.8°C, and his peripheral oxygen saturation (SpO₂) was 90% in ambient air. During a physical examination, auscultation revealed fine crackles in the chest. The laboratory data on admission revealed elevated eosinophils (538/μL) and C-reactive protein (5 mg/dL), and an interferon-gamma release assay (QuantiFERON⁹-TB gold in tube) was positive. A parasitic disease was ruled out because the patient was negative for ova and parasites and showed a normal serum immunoglobulin (Ig)E level. The results of a...
physical examination and his serum levels of autoantibodies including antinuclear antibody (×20, nucleolar pattern) did not suggest collagen vascular disease. Chest radiography (Fig. 1) and computed tomography (CT) (Fig. 2) showed left pleural effusion, reticular opacities with traction bronchiectasis and honeycombing in the lower lobes. An analysis of the pleural fluid obtained in the first thoracentesis showed an exudative pattern with elevated lymphocytes (68%) and eosinophils (25%), and slightly elevated levels of adenosine deaminase (37.9 IU/L), without malignant cells or elevated tumor marker levels [carcinoembryonic antigen (CEA), 3.1 ng/mL; cytokeratin 19 fragment (CYFRA), 1.5 ng/mL]. These investigations revealed EPE with a usual interstitial pneumonia pattern and tuberculous pleurisy and malignant disease could not be excluded. Medical thoracoscopy showed diffuse pleural thickening with multiple translucent nodules and adhesions in the parietal pleura and diaphragm (Fig. 3). A histopathological examination of the nodule in the diaphragm revealed lymphoid follicles and the massive infiltration of eosinophils, lymphocytes, and plasma cells, without cancer cells or granuloma (Fig. 4). Cultures of sputum, pleural effusion and specimens from the parietal pleura were negative for bacteria and mycobacteria. Based on these results, we suspected pirfenidone-induced pleurisy. As a result, pirfenidone was discontinued and the patient’s chest pain and serum eosinophilia gradually improved and finally resolved. The marked spontaneous resolution of the pleural effusion was observed at eight weeks after the suspension of pirfenidone and without any additional treatment. The patient died of the progression of IPF with bacterial pneumonia 3 years later. During that time, pleural effusion did not recur, nor did serum eosinophilia or other possible etiologies of EPE, which included tuberculosis, malignancy, parasitic disease and collagen-vascular disease.

**Discussion**

Although re-challenge was not performed for ethical reasons and based on the request of the patient, we hypothesize that the pleurisy in the present case had been caused by pirfenidone.

In contrast to drug-induced pneumonia, drug-induced pleurisy is rather rare. Although over 30 drugs have been associated with pleurisy, including nitrofurantoin, dantrolene, interleukin 2, amiodarone, valproic acid, and dasatinib (1, 2, 5), drug-induced pleurisy often remains unsuspected by clinicians. One reason is that the interval between the commencement of the suspected causative agent and the appearance of pleural lesions may range from several days to more than 10 years (6). Another is that the presentations differ among the causative drugs and even among individuals who receive the same drug. Drug-induced pleurisy may be unilateral or bilateral, and lung lesions and serum or pleural eosinophilia are not always present (1, 2). Unless it is suspected, drug-induced pleurisy can be diagnosed as idiopathic.

In the present case, medical thoracoscopy revealed the massive infiltration of eosinophils and lymphoid follicles in the histopathological examination of the parietal pleura. Only 2 case reports have described drug-induced EPE in which medical thoracoscopy was performed. The causative agents in those cases were methotrexate (7) and oranzapine (8). In those 2 cases and our own pirfenidone-induced case, drug-induced EPE was reported to present with pleural thickening involving eosinophilic inflammation without other specific findings. Nodules in the pleura and lymph follicles in a pleural biopsy specimen have only been described in our case. The specificity of nodules or lymph follicles for drug-induced pleurisy remains unclear.

Medical thoracoscopy was useful for ruling out other causes of pleurisy in the present case. Medical thoracoscopy reportedly offers a safe and efficient approach for diagnosing pleurisy of unknown etiology, including EPE. EPE has non-serious etiologies such as the presence of air and/or blood in the pleural space, along with serious etiologies, including malignant disease (22.7–40.1% of all EPEs) (9, 10) and tuberculosis (2.2–15.6%) (11, 12). The diagnostic yields of medical thoracoscopy for malignant disease and pleural tuberculosis are reported to be 91-95% and 100%, respectively (13). In comparison, the analysis of pleural fluid has a relatively low diagnostic yield. One study showed the usefulness of medical thoracoscopy in detecting the etiology in 52.4% (11/21) of patients with undiagnosed EPE (14). We propose that due consideration should be given to drug-induced pleurisy in the differential diagnosis of indeterminate EPE.

To the best of our knowledge, this represents the first case report of pirfenidone-induced eosinophilic pleurisy. The histopathological examination of a specimen of the parietal pleura, which was obtained during medical thoracoscopy, re-
Figure 2. Chest CT on admission (7 weeks after starting pirfenidone) showing left pleural effusion, reticular opacities with traction bronchiectasis and honeycombing in the lower lobes. The CT images were spliced for display purposes.

Figure 3. Medical thoracoscopy revealed diffuse thickening with multiple translucent nodules (arrow) and adhesion on the parietal pleura and diaphragm.

Figure 4. The pathological examination of the left parietal pleural biopsy specimen revealed the formation of lymphoid follicles and the massive infiltration of eosinophils (Hematoxylin and Eosin staining: a: ×20, b: ×100).

revealed the massive infiltration of eosinophils and lymphoid follicles. This offered a useful tool for ruling out other causes of EPEs, particularly malignant disease and tuberculosis. Although rare, drug-induced pleurisy should be suspected as one of the differential diagnoses in patients with pleurisy of unknown etiology.

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