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Case Report

A case of drug-induced interstitial pneumonia caused by repeated exposure to bepridil

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ABSTRACT

The patient was a 78-year-old man. In August 2007, he underwent catheter ablation for atrial fibrillation after taking bepridil for 3 weeks. Soon after the ablation, he experienced frequent atrial extrasystoles and began taking bepridil again on the day he left the hospital. Six days after discharge, he was readmitted to our hospital with dyspnea and was diagnosed with acute heart failure. The patient had no recurrence of atrial fibrillation, so the administration of bepridil was stopped. His dyspnea was eased using standard therapy for heart failure and he was discharged from our hospital. In March 2011, he had a recurrence of atrial fibrillation and was readmitted to our hospital. The administration of bepridil was initiated to defibrillate the atrial fibrillation. Although bepridil stopped the atrial fibrillation by the third day, he presented with dyspnea and fever on the fourth day. A chest radiograph showed bilateral interstitial patterns that radiated from the pulmonary hilum. He was treated for acute heart failure and bacterial pneumonia, but this was ineffective. We suspected that the interstitial pneumonia was caused by bepridil. Corticosteroid therapy dramatically improved his symptoms. This was a rare case of acute drug-induced interstitial pneumonia caused by repeated exposure to bepridil.

1. Introduction

Bepridil is reported to be effective for pharmacological defibrillation of atrial fibrillation that has persisted for 3 months or more and for the maintenance of sinus rhythm after electrical defibrillation [1,2]. Like amiodarone, bepridil has been reported to cause drug-induced interstitial pneumonia in some cases [3,4]. We experienced a case of acute drug-induced interstitial pneumonia, with severe symptoms caused by short-term re-exposure to bepridil that complicated the diagnosis.

2. Case report

A 78-year-old man visited our hospital complaining of palpitations resulting from a recurrence of atrial tachycardia and atrial fibrillation in March 2011. In August 2007, he was hospitalized twice for catheter ablation of atrial fibrillation and acute heart failure at the age of 74. Bepridil was prescribed for 3 weeks before catheter ablation and for a week just after catheter ablation, for frequent extrasystoles at that time. Four years later, atrial tachycardia and fibrillation recurred, and he was admitted to our hospital for the arrhythmias. He was treated with 100 mg/day of bepridil. By the third day, the atrial fibrillation converted to sinus rhythm (Fig. 1). On the fourth day, he complained of dyspnea with exertion and his body temperature rose. Fine crackles were slightly audible in the bilateral lower lung fields. Hematology revealed high concentrations of white blood cells (WBC, 9700/μL), C-reactive protein (CRP, 10.7 mg/dL), and brain natriuretic peptide (BNP, 521 ng/dL). The alveolar-arterial oxygen difference (AaDO2) increased to 97 Torr and he was administered oxygen (partial pressure [PaO2] of 77 Torr with 3 L/min of O_2). Pulmonary function test results revealed a mild restrictive pattern (vital capacity: 67.8% of predicted), and decreasing diffusing capacity for carbon monoxide (DLCO: 67.5% of predicted). Bilateral interstitial patterns radiating from the pulmonary hilum were observed in chest radiography (Fig. 2A, B). Chest computed tomography (CT) scans revealed pleural effusion, patchy subpleural ground-glass opacities, consolidation, and diffuse linear opacity in the bilateral lung fields (Fig. 2C, D). We suspected acute heart failure because of the negative inotropic drugs he was taking and concomitant bacterial pneumonia and administered standard therapy for heart failure and antibiotics. Despite such therapy, his symptoms and radiographic findings deteriorated each day.

Upon examining his previous hospital records from 4 years prior, we found that he was diagnosed with acute heart failure at the second hospitalization 1 week after catheter ablation for atrial

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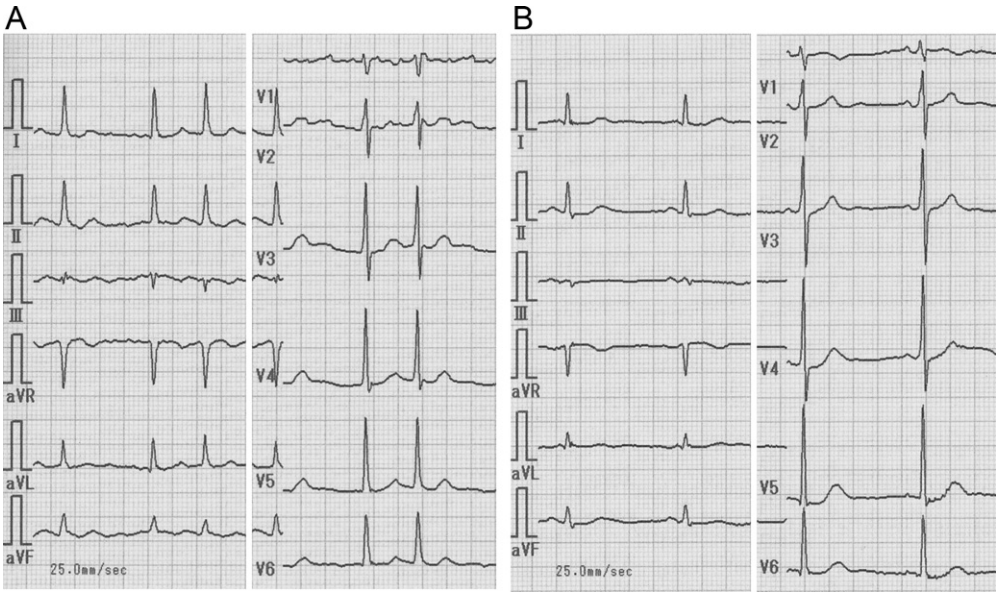

Fig. 1. Twelve-lead ECGs during atrial fibrillation and sinus rhythm. (A) Twelve-lead ECG on the first day of the third hospitalization showed recurrence of atrial fibrillation. (B) Administration of bepridil converted persistent atrial fibrillation to sinus rhythm by the third day after bepridil administration.

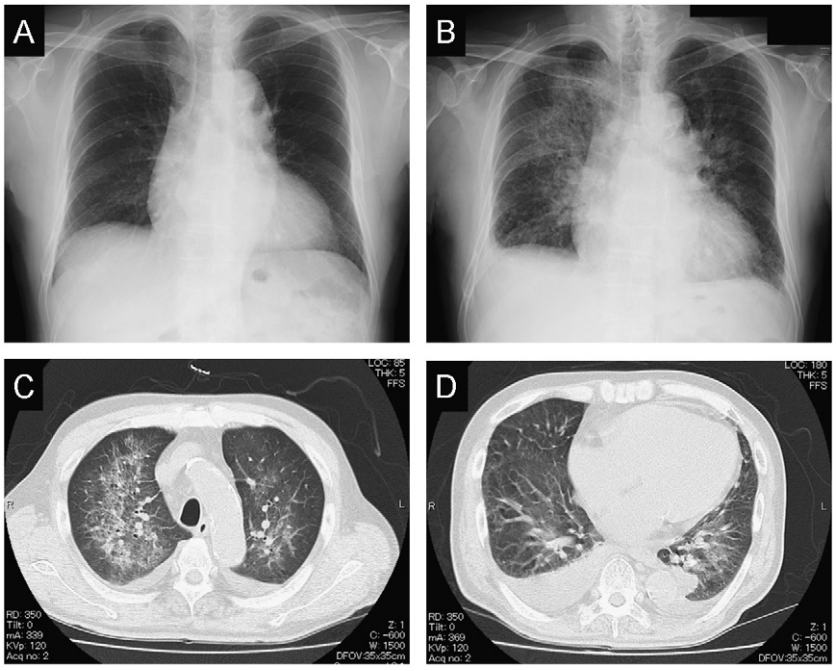

Fig. 2. Chest radiography and computed tomography. (A) Chest radiograph before bepridil administration on the third hospitalization showed cardiomegaly (cardiac to thoracic width ratio: 57%) without pleural effusions and cephalization of pulmonary vessels. (B) Chest radiograph on the 12th day after bepridil administration showed bilateral pleural effusions and an interstitial pattern dilated from the pulmonary hilum. (C, D) Chest CT scan on the 12th day after bepridil administration revealed pleural effusion, patchy subpleural ground-glass opacities, consolidation, and diffuse linear opacity in the bilateral lung fields.

fibrillation. His symptoms and chest radiographic findings had improved by standard therapy for heart failure, and the cause of the heart failure had been thought to be a complication of negative inotropic drugs or the cardiac catheter ablation, but this had not been clarified at the time. We noticed that bepridil was administered for 3 weeks before the first hospitalization for catheter ablation and bepridil (100 mg/day) was administered after the catheter ablation for 7 days prior to the second hospitalization for acute heart failure. From these details, we speculated that the diagnosis of heart failure of unknown etiology at the second hospitalization could have been due to bepridil-induced interstitial pneumonia and, therefore, was possibly relieved by the fortuitous cessation of bepridil (clinical course, medication, and laboratory data are summarized in Fig. 3).

The results of right ventricular catheterization were normal (mean pulmonary artery wedge pressure, 8 mmHg; cardiac index, 3.98 mL/min/m^2) and heart failure was ruled out. Results of blood tests after the appearance of dyspnea with exertion revealed high concentrations of surfactant protein A (SP-A, 206 ng/mL) and surfactant protein D (SP-D, 268 ng/mL), but KL-6 (311 U/mL) was still within the normal range. However, KL-6 level increased to 1132 U/mL, and SP-A and SP-D levels gradually decreased in

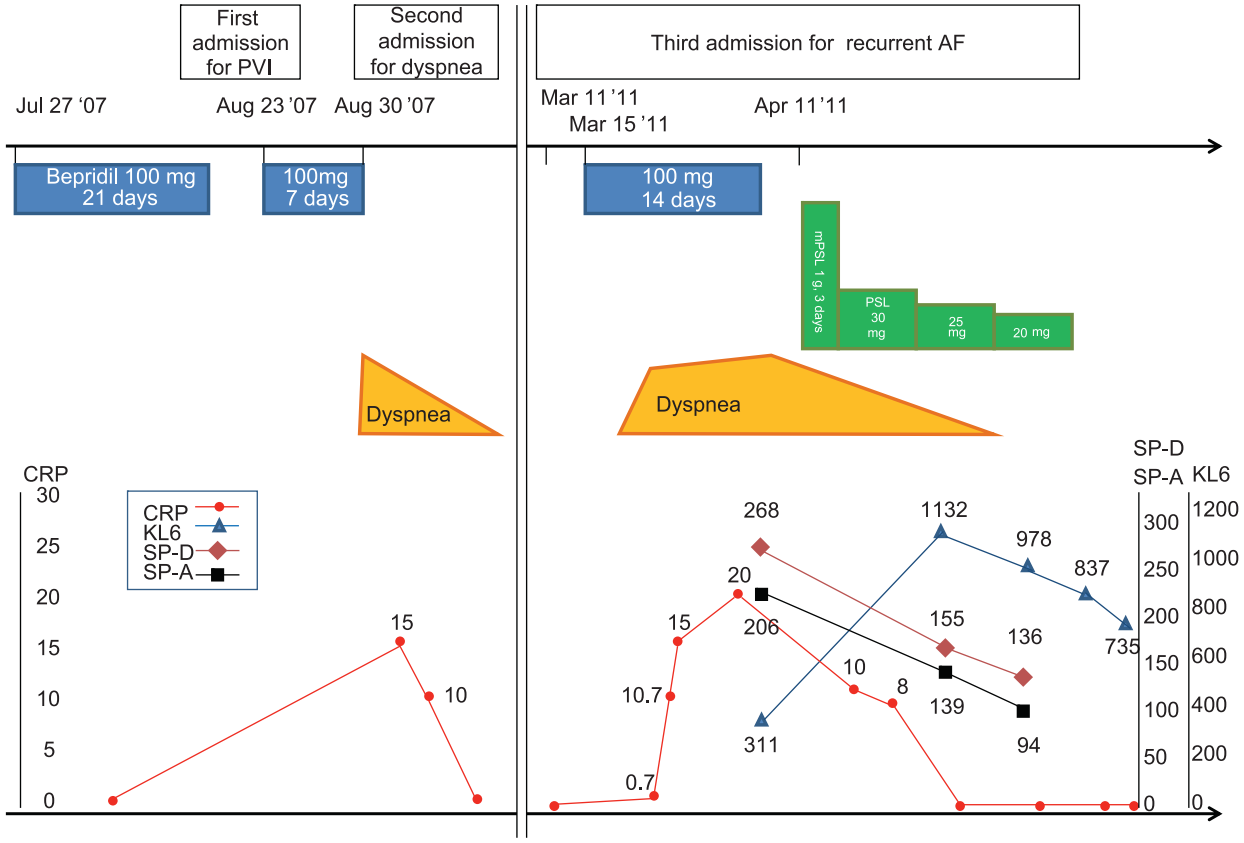

Fig. 3. Clinical course. The first administration of bepridil did not cause dyspnea and elevation of CRP levels. CRP elevation and dyspnea occurred after bepridil administration on both the second and third hospitalizations. The third administration of bepridil caused the rapid onset of dyspnea and CRP elevation, and as a result of the longer duration of administration, the interstitial pneumonia was worse than that at the second hospitalization. Although serum SP-D and SP-A levels increased in the acute phase of the interstitial pneumonia, serum KL-6 levels increased in its late phase. These serum markers for interstitial lung disease gradually decreased after the start of corticosteroid therapy. CRP, C reactive protein; mPSL, methylprednisolone; PSL, prednisolone; and PVI, pulmonary vein isolation. Normal values: KL-6, <500 U/mL; SP-D, <110 ng/mL; SP-A, <43.8 ng/mL.

the late phase of pneumonia (Fig. 3). Bronchial alveolar lavage fluid (BALF) revealed inflammatory cells (3.5×10^5/mL); increased percentages of neutrophils (13%), lymphocytes (37%), and eosinocytes (9%); decreased percentage of macrophages (41%); 59.9% $CD4^+$ lymphocytes; and 17.9% $CD8^+$ lymphocytes. The $CD4^+/CD8^+$ ratio was 3.35. Although the increases in inflammatory cells and mixed cellularity in the BALF findings indicated interstitial lung disease, this information was insufficient for making a definitive diagnosis. The drug lymphocyte stimulation test (DLST) for bepridil was negative (90%), and a previous study indicated that DLST is not always positive in bepridil-induced interstitial pneumonia [5].

Our eventual diagnosis of drug-induced interstitial pneumonia caused by bepridil was based on chest radiographic findings, chest CT, BALF, and clinical processes. We stopped bepridil administration on the 14th day and began administration of 30 mg of oral prednisolone after intravenous steroid pulse therapy (methylprednisolone, 1000 mg/day) for 3 days. The patient's symptoms and chest radiography findings improved gradually. We gradually reduced the dose of prednisolone, and 39 days after starting prednisolone therapy, his respiratory failure had improved from Hugh-Jones class V to class I and he was discharged. At the time of discharge, he was able to walk by himself.

3. Discussion

Among anti-arrhythmic drugs, amiodarone is well known to induce interstitial pneumonia [6]. In view of bepridil's blocking action on sodium, potassium, and calcium channels in cardiomyocytes, it is expected to have similar effects to amiodarone. However, the induction of interstitial pneumonia may be a rare secondary effect of bepridil, although some cases have been reported recently [3,4].

Our patient experienced respiratory symptoms and fever on the fourth day when bepridil was administered for the third time. The onset of bepridil-induced interstitial pneumonia was earlier in our case than in previously reported cases, in which patients developed bepridil-induced interstitial pneumonia at any time from 14 days to >200 days after administration of bepridil [3]. In the present case, we noted that the underlying mechanism of bepridil-induced interstitial pneumonia may have involved an immunoallergic reaction rather than pulmonary toxicity resulting from drug accumulation, as is sometimes the case with amiodarone. In the current case, the longest period of administration of bepridil was only 3 weeks before the first hospitalization. If the interstitial pneumonia had been induced by the direct pulmonary toxicity of bepridil, it would have occurred more than 3 weeks after beginning administration. At the time of the third hospitalization, the respiratory symptoms occurred after only 4 days of bepridil administration, which is too rapid to be caused by pulmonary toxicity.

The fact that interstitial pneumonia was induced at a low dose of bepridil (100 mg/day) supports an immunoallergic mechanism rather than a pulmonary toxicity mechanism. In the present case, the dose of bepridil was lower than those in previously reported cases (150–400 mg/day) [3] and it was given for a shorter period. An immunoallergic mechanism would cause a small dose of bepridil to induce interstitial pneumonia. Drug-specific antibodies tend to be produced in cases of high-dose, long-term, recurrent exposure.

In this case, recurrent exposure to bepridil may have activated an immune allergic reaction and caused rapid onset of interstitial pneumonia on the third hospitalization.

After initiating bepridil, interstitial pneumonia should be considered a secondary effect of the drug so that it is discovered early. In the repetitive, small-dose administration of bepridil, for example as a temporary medication for terminating atrial fibrillation, particular attention should be paid to respiratory symptoms and fever. If such symptoms appear, bepridil should be immediately discontinued and the patient should be examined for interstitial pneumonia through the measurement of parameters such as SP-A, SP-D, and KL-6; chest radiographs; and CT. In this case, SP-A and SP-D could be more useful for the early diagnosis of bepridil-induced interstitial pneumonia than KL-6. However, DLST may not be very useful in the diagnosis of drug-induced interstitial pneumonia as it could yield negative results as shown in some previous studies [6]. In addition, we could not perform a lung biopsy because the patient was taking warfarin for atrial fibrillation. The BALF results suggested the presence of drug-related lung injury, ruling out other problems such as common bacterial infection and congestion of the lungs in heart failure. The increase in levels of lymphocytes, neutrophils, and eosinophils in BALF also supported the diagnosis of interstitial lung disease.

In diagnosing drug-induced pneumonia, provocation testing using the suspected drug is the most reliable method for assessing the relationship between the particular drug and pneumonia [7,8]. At the second hospitalization, the patient was diagnosed with acute heart failure, and bepridil-induced interstitial pneumonia had not been suspected. Most reported cases of drug-induced lung diseases exhibit areas of consolidation, infiltrates, or interstitial lesions on radiography and CT that are entirely nonspecific and easily confused with the pulmonary abnormalities caused by congestive heart failure, pneumonia, and pulmonary infarction [9]. Because patients receiving anti-arrhythmic agents have underlying cardiac disease, discriminating between dyspnea caused by heart failure with negative inotropism and drug-induced pulmonary disease is sometimes very difficult.

This was a rare case of drug-induced interstitial pneumonia as an adverse effect of bepridil. The patient had been treated for acute heart failure at the second hospitalization when it was fortunately discontinued on admission day because no atrial extrasystoles were observed. The interstitial pneumonia was relieved in 1 month despite receiving only standard treatment for heart failure. When we diagnosed the patient with bepridil-induced interstitial pneumonia at the third hospitalization, chest radiographs and pulmonary CT scans were quite similar to those at the second hospitalization. If we had noticed drug-induced interstitial pneumonia early at the third hospitalization, it might have been resolved by stopping bepridil alone, with no need for corticosteroid therapy. We should have observed drug-induced interstitial pneumonia earlier and considered bepridil cessation. Special attention should therefore be paid to drug-induced interstitial pneumonia, even in the case of the repeated use of bepridil for brief periods.

4. Conclusions

We experienced a rare case in which the repeated short-term administration of a low dose of bepridil (100 mg/day) induced interstitial pneumonia. In medical practice, therapy with anti-arrhythmic drugs is occasionally initiated or discontinued on the basis of a patient's arrhythmic events. Short-term and low-dose administration of bepridil is possibly safer for patients than long-term and high-dose administration. However, we have to remember that repeated short-term, low-dose administration of bepridil can cause rapid occurrence of interstitial pneumonia as a result of allergic reaction, and this should be considered in daily medical practice.

5. Conflict of interest

None of the authors have any conflict of interest to disclose.

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