

Gradual Progression of Interstitial Pneumonia Induced by Bepridil

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Abstract

A 74-year-old man was administered bepridil for the treatment of atrial fibrillation since February 2008. However, he developed exertional dyspnea in October 2008. Computed tomography scans of his chest revealed extensive bilateral peribronchial consolidations. Examination of transbronchial lung biopsy specimens revealed moderate infiltration of lymphocytes. Since drug-induced pneumonia was suspected, we initiated steroid therapy. After 3 weeks of treatment, the symptoms were alleviated. In this case, the time taken for the development of dyspnea was 226 days, and the clinical course was gradual. We believe that a long-term periodic follow-up is essential in patients receiving bepridil.

Key words: bepridil, drug-induced pneumonia

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Introduction

Bepridil is a class IV antiarrhythmic drug that is used for the treatment of ventricular arrhythmia, angina, or atrial fibrillation. Recently, the role of second-line therapy for atrial fibrillation has received much attention in Japan. Bepridil-induced interstitial pneumonia is considered to be a relatively uncommon adverse effect of the drug; only 5 cases of this condition have been reported to date (1-4). In all five cases, the patients developed subacute interstitial pneumonia. Here, we report the case of a patient in whom the progression of bepridil-induced interstitial pneumonia was gradual.

Case Report

A 74-year-old Japanese man had undergone aortic valve replacement and received an implantable pacemaker for complete atrioventricular block; the patient visited our hospital for follow-ups. He had taken nifedipine and valsartan for hypertension about one decade previously. In February 2008, he was prescribed bepridil (200 mg per day) for paroxysmal atrial fibrillation. Over the next month, his sinus rhythm was maintained, and therefore, bepridil was continued. He had no previous pulmonary symptoms and no sig-

nificant radiological abnormality (Fig. 1-a). In August, a mild reticular shadow was observed in his routine follow-up chest radiograph, but this finding was overlooked because no symptoms were observed. In September 2008, he developed dyspnea when walking uphill; and the dyspnea gradually worsened. In October 2008, he was admitted to our hospital with exertional dyspnea.

His vital signs were as follows: pulse rate, 74 (regular); blood pressure, 114/72; temperature, 36.9°C; and respiratory rate, 20. He developed respiratory failure (Hugh-Jones class III). Fine crackles were audible in both lung fields, and he did not show signs of clubbed fingers. Laboratory data revealed a high concentration of KL-6 (2,745 U/mL), a slight increase in C-reactive protein (CRP) (0.77 mg/dL) and brain natriuretic peptide (BNP) (42.6 pg/mL). He tested negative for antinuclear antibody and antiextractable nuclear antigen antibody. *Legionella pneumophila* antigen in urine and *Mycoplasma pneumoniae* IgM antibody were negative, and β -D-glucan levels in the serum were within normal limits. The arterial blood gas test revealed type I respiratory failure (atmospheric conditions: PaO₂, 59 mm Hg; PaCO₂, 35.6 mmHg). A drug lymphocyte stimulation test (DLST) showed negative results for bepridil (stimulating index; 105%). His chest radiography revealed diffuse bilateral infiltration predominantly in the right and perihilar fields (Fig. 1-b). A

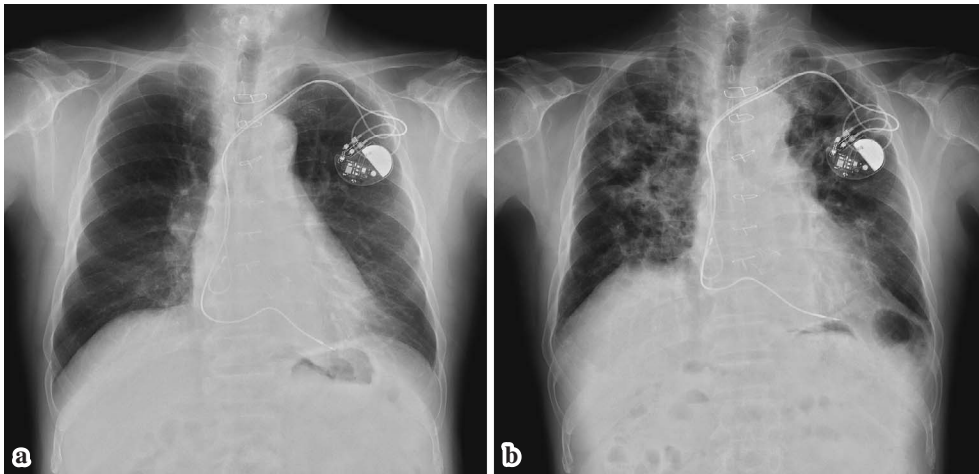


Figure 1. a. Chest radiograph before bepridil administration. No significant abnormal findings were detected. b. Chest radiograph 226 days after bepridil administration. The reticular shadow appeared in dominantly perihilar fields with lung volume loss.

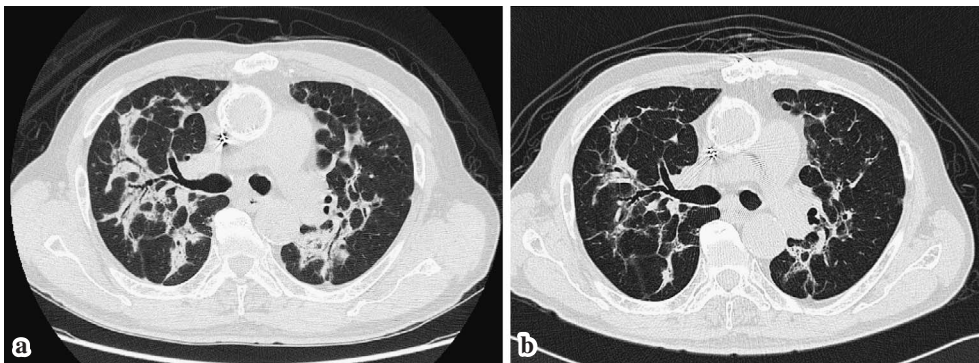


Figure 2. a. Plain CT scan of the chest shows diffuse dense consolidation with predominant peribronchial distribution. b. Plain CT scan of the chest 5 weeks after shrinkage of the consolidation as a result of steroid therapy.

chest computed tomography (CT) scan showed extensive bilateral peribronchial consolidations (Fig. 2-a). On the second hospital day, pulmonary function tests revealed a moderate restrictive pattern (vital capacity of predicted; 72%) and decreasing diffusing capacity for carbon monoxide (DLCO of predicted; 50%). Fiberoptic bronchoscopy was performed on the third hospital day. Differential cell analysis of the bronchoalveolar lavage fluid revealed 48.6% alveolar macrophages, 48.3% lymphocytes, 1.9% neutrophils, and 1.3% eosinophils. Transbronchial lung biopsy specimens showed moderate infiltration of lymphocytes and interstitial fibrosis.

From the laboratory results, we determined that the cause of his pneumonia was not an infection or autoimmune disease. Since the use of bepridil has previously induced interstitial pneumonia in several cases (1-4) and the infiltrative shadows in the radiograph were observed after the administration of bepridil, we discontinued the use of bepridil. Although the KL-6 level declined from 2,745 U/mL to 2,082 U/mL within 1 week after the discontinuation of bepridil,

the symptoms of dyspnea persisted and no significant radiological improvement was observed. Therefore, we administered steroids (1 mg/kg prednisolone). After 3 weeks of treatment, the CT findings were favorable (Fig. 2-b) and the symptoms were alleviated. After 5 weeks of treatment, the laboratory data and pulmonary function test improved; vital capacity of predicted, 95%; DLCO of predicted, 61%; KL-6, 998 U/mL and PaO₂, 76.9 mm Hg. We gradually reduced the dose of prednisolone, and at 4 months after the initiation of the medication, prednisolone was discontinued.

Discussion

We have described the gradual development of bepridil-induced interstitial pneumonia in a patient. Because there was no evidence of infection or autoimmune disease and the KL-6 levels decreased after the discontinuation of bepridil, we believed that the interstitial pneumonia was induced by bepridil, even though the drug lymphocyte stimulation test

Table 1. Clinical Features of Reported Cases of Bepridil-induced Interstitial Pneumonia

	Gender	Age (years)	Bepridil dose (mg/day)	*Period to development (days)	Arrhythmia	Therapy	Response to treatment	KL-6 (U/mL)	DLST (S.I.%)	TBLB	CT
Vasilomanolakis et al	Man	72	400	21	AF	PSL 40 mg	Improvement	Unknown	Unknown	Mononuclear infiltration and interstitial fibrosis	None
Gaku et al	Man	65	150	14	AF	mPSL 500 mg 3days	Improvement	692	Borderline 160%	Unknown	Bilateral reticular and ground-glass shadow predominantly in lower lung field
Okubo et al	Man	66	200	30	AF	PSL 30 mg	Improvement	287	Negative 93%	Alveolar septal thickening with mononuclear cell infiltration	Bilateral reticular and ground-glass shadow predominantly in the lower lung field
Watanabe et al patient 1	Man	69	200	60	AF	mPSL 1000 mg 3 days	Improvement	1230	Unknown	Unknown	Diffuse bilateral infiltration predominantly in the lower lung field
Watanabe et al patient 2	Man	72	200	40	AF	Cessation of bepridil	Improvement	3960	Unknown	Unknown	Diffuse, centrilobular, small granular infiltration predominantly in the lower lung field
Present patient	Man	74	200	226	AF	PSL 60 mg	Improvement	2745	Negative 105%	Infiltration of lymphocytes and interstitial fibrosis	Diffuse dense consolidation with predominantly peribronchial distribution

* The period between the initiation of bepridil administration and the development of dyspnea, AF: atrial fibrillation, PSL: prednisolone, mPSL: methylprednisolone, S.I.: stimulating index

was negative for bepridil. We compared our case with the other 5 reported cases of bepridil-induced interstitial pneumonia (Table 1). All of the patients were elderly men, and bepridil was administered for atrial fibrillation. The DLST was positive in 1 out of 3 patients who were examined. Histological examination of 3 patients revealed infiltration of monocytes. Five patients were examined by CT. In 4 previously reported cases, the patterns of opacities were patchy consolidations in the peripheral areas of both lung fields mainly in the lower lobes; these observations are similar to those in the case of cryptogenic organizing pneumonia (COP). In contrast, in the present case, the CT findings revealed bilateral peribronchial dense consolidations, which resembled those in the case of nonspecific interstitial pneumonia rather than COP. The dense consolidation may be ob-

served at a pulmonary fibrosis stage as a result in long-term course. In addition, the median period between the initiation of bepridil therapy and the development of dyspnea in previously reported cases was 30 days (14-60 days); all of these patients developed subacute dyspnea. However, in the present case, the time taken for the development of dyspnea was 226 days, and the clinical course was gradual. We know that for any specific drug, the clinical course and radiological pattern of drug-induced lung disease varies widely (5, 6); in the present patient, the course of development of interstitial pneumonia induced by bepridil was gradual. We believe that drug-induced interstitial pneumonia should be suspected when patients receiving bepridil complain of dyspnea, even in the case of long-term bepridil administration.

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