INTERNAL MEDICINE

□ CASE REPORT □

Drug-induced Eosinophilic Pneumonia with Pulmonary Alveolar Hemorrhage Caused by Benzbromarone

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Abstract

A 51-year-old man was admitted to our hospital with cough, hemosputum, dyspnea and chest pain. Chest high-resolution computed tomography (HRCT) revealed diffuse ground-glass opacities in both lungs with peripheral predominance. Bronchoalveolar lavage fluid was fresh-bloody and analysis indicated an increase in the eosinophil proportion. Benzbromarone-induced lymphocyte stimulation test was positive. Therefore, the patient was diagnosed as having drug-induced eosinophilic pneumonia with pulmonary alveolar hemorrhage caused by benzbromarone. After discontinuation of benzbromarone and administration of corticosteroids, chest HRCT images and respiratory manifestation improved. Here, we report this rare case of benzbromarone-induced eosinophilic pneumonia with pulmonary alveolar hemorrhage.

Key words: benzbromarone, drug-induced eosinophilic pneumonia, pulmonary alveolar hemorrhage

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Introduction

Benzbromarone (Urinorm®) is a potent uricosuric drug used in the treatment of gout and hyperuricemia. Although it has been reported that benzbromarone can be associated with hepatic injury (1, 2), to our knowledge, respiratory side effects have not been reported. However, cases of eosinophilic pneumonia with pulmonary alveolar hemorrhage induced by other drugs have been reported (3, 4). Here, we report a rare case of drug-induced eosinophilic pneumonia with pulmonary alveolar hemorrhage caused by benzbromarone.

Case Report

A 51-year-old man was admitted to our hospital with cough, hemosputum, dyspnea and chest pain. He had a medical history of Harada's disease (at age 25 years), gout (at age 45 years) and acute renal failure caused by dehydration (at age 50 years). In addition, he had smoked two and a half packs of cigarettes per day for 33 years.

He took 25 mg of diclofenac sodium as needed for a gout attack between 10 days and 6 days before admission, and took 50 mg of benzbromarone a day (total amount, 500 mg) until just before admission. Cough, hemosputum and dyspnea occurred 3 days before admission. On the day of admission, chest pain developed and dyspnea exacerbated. Physical examination on admission revealed a high body temperature (38.3℃) and fine crackles on both lower chest walls. Laboratory test results on admission were as follows (Table 1): white blood cell count, 17,500/mm^3 (98% neutrophils); C-reactive protein, 10.35 mg/dL (<0.17 mg/dL); lactate dehydrogenase, 371 IU/L (119-229 IU/L); Krebs von den Lungen (KL)-6, 594 U/mL (<500 U/mL); surfactant protein (SP)-A, 124 ng/mL (<43.8 ng/mL); and SP-D, 415 ng/mL (<110 ng/mL). Anti-nuclear antibody, proteinase 3 (PR3)-antineutrophil cytoplasmic antibody (ANCA), myeloperoxidase (MPO)-ANCA, antiglomerular basement membrane (GBM) antibody and other autoantibodies against

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Table 1.

＜Hematology＞		＜Serology＞	
WBC	17,500 /mm^3	CRP	10.35 mg/dL
Neu	98 %	IgE	9 IU/mL
Lym	1 %	IgG	1010 mg/dL
Eos	0 %	IgA	208 mg/dL
Mono	1 %	IgM	119 mg/dL
Baso	0 %	KL-6	594 U/mL
RBC	509×10^4/mm^3	SP-D	415 ng/mL
Hb	15.8 g/dL	SP-A	124 ng/mL
Ht	46.0 %	sIL2-R	737 U/mL
Plt	14.5×10^4/mm^3	RF	11 U/mL
＜Biochemistry＞		ANA	(-)
AST	28 IU/L	Anti SS-A	7.2 U/mL
ALT	19 IU/L	Anti SS-B	4.5 U/mL
LDH	371 IU/L	Anti RNP	13.9 U/mL
γGTP	32 IU/L	Anti ss-DNA	3.1 U/mL
T-Bil	1.0 mg/dL	Anti ds-DNA	2.6 U/mL
CPK	71 IU/L	Anti cardiolipin	0.8 U/mL
BUN	13 mg/dL	Anti GBM	<10 EU
CRE	0.8 mg/dL	PR3-ANCA	<10 EU
Na	142 mEq/L	MPO-ANCA	<10 EU
K	3.8 mEq/L	＜Others＞	
Cl	107 mEq/L	Mycoplasma Ab	40×
UA	2.5 mg/dL	CMV Ag(c7-HRP)	(-)
＜Blood Gas Analysis on admission＞ (O_2 7L/min mask)		C.pneumoniae IgG	(-)
		C.pneumoniae IgA	(-)
pH	7.394	Legionella Ag(urine)	(-)
PaO_2	86.6 torr	Culture of blood	(-)
$PaCO_2$	42.1 torr	Culture of sputum	(-)
HCO_3^-	25.2 mEq/L	＜BALF analysis (rt B^{4}a)＞	
BE	0.7 mmol/L	Total cell counts	6.9×10^5/mL
		Macrophage	39.3 %
		Neu	22.3 %
		Eos	31.8 %
		Lym	6.6 %
		Baso	0.0 %
		CD4/CD8	0.7

Abbreviations; ANA: anti nuclear antibody, anti GBM: anti glomerular basement membrane antibody, BALF: bronchoalveolar lavage fluid, *C. pneumoniae*: *Chlamydophilia pneumoniae*, CMV: cytomegalovirus, KL-6: Krebs von den Lungen-6, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, PR3-ANCA: proteinase 3-antineutrophil cytoplasmic antibody, RF: rheumatoid factor, sIL-2R: soluble interleukin 2 receptor, SP-A: surfactant protein-A, SP-D: surfactant protein-D

specific antigens were all negative. Arterial blood gas analysis under an O_2 mask at 7 L/min showed hypoxia (pH, 7.394; $PaCO_2$, 42.1 torr; PaO_2, 86.6 torr). Blood and sputum cultures to detect pulmonary infections by bacteria, fungi and mycobacteria were all negative. Serological tests for atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, influenza virus, RS virus and adenovirus) were all negative. Both *Legionella pneumophila* antigen in urine and cytomegalovirus antigenemia tests were also negative. Chest X-ray on admission revealed reticular shadows in all lung fields (Fig. 1A). High-resolution computed tomography (HRCT) of the chest also revealed diffuse ground-glass opacities and consolidation in both lungs with peripheral predominance and pleural effusion (Fig. 1B). Bronchoalveolar lavage was performed on the 7th day after admission. The recovered bronchoalveolar lavage fluid (BALF) was fresh-bloody and showed increased total cell counts (6.9×10^5/mL) and proportion of eosinophils (31.8%) and neutrophils (22.3%). Obvious evidence of infectious disease was not detected in BALF. Drug lymphocyte stimulation test with benzbromarone was positive (stimulation index, 223%), while that with diclofenac sodium was negative (121%).

In addition to discontinuation of benzbromarone, methylprednisolone pulse therapy (1.5 g/day intravenously) for 3 consecutive days, followed by prednisolone (PSL) (60 mg/day intravenously) and administration of ciprofloxacin for 7 days was initiated because he suffered from hemoptysis, chest pain, fever and severe dyspnea. After bronchoalveolar lavage was performed, the patient was treated with a second round of methylprednisolone pulse therapy (1 g/day intravenously) for 3 consecutive days, followed by oral PSL (60 mg/day), and panipenem/betamipron and minocycline were administered for 7 days. His symptoms and chest HRCT images subsequently improved.

Diagnosis was confirmed as drug-induced interstitial lung disease (DI-ILD) caused by benzbromarone based on clinical course, serological, radiological and microbiological findings, BALF analysis and positive lymphocyte stimulation test for benzbromarone. Therefore, we discontinued antibiotics on the 14th day after admission and continued PSL

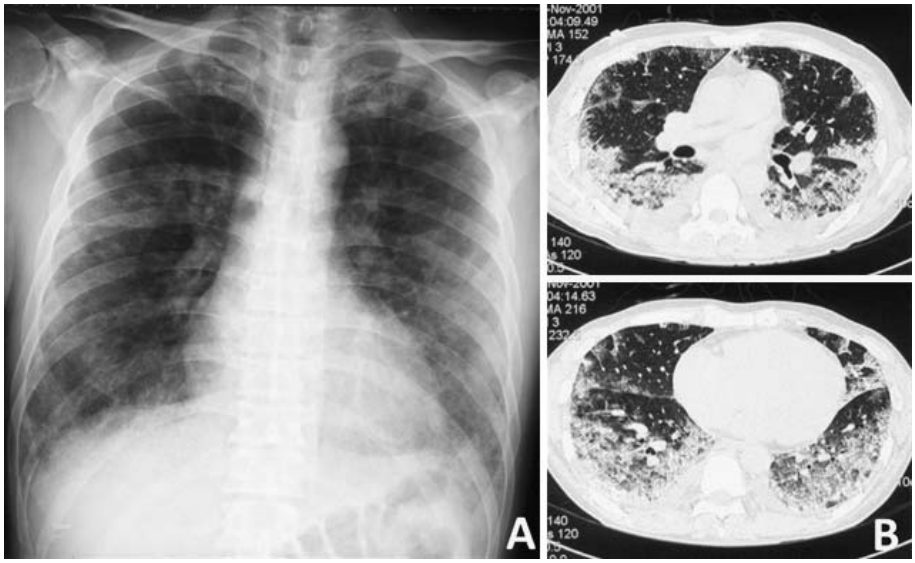

Figure 1. **Chest X-ray (A) on admission showed bilateral reticular shadows in all lung fields. Chest CT (B) showed ground-glass opacities and consolidation in both lungs, with peripheral predominance and pleural effusion.**

(60 mg/day) administration alone. Recurrence was not seen, even during PSL tapering.

Discussion

Many drugs are known to have the potential to cause DI-ILD, which exhibits a wide range of patterns similar to naturally occurring ILD. This is the first reported case of DI-ILD caused by benzbromarone.

Diagnosis of DI-ILD is often complex and is primarily made by meticulous exclusion of all other possible causes. It involves four elements: 1) clinical suspicion, including temporal association between exposure to the drug and the development of pulmonary infiltrates; 2) chest HRCT findings; 3) exclusion of other lung diseases; and 4) previously reported cases involving the suspected drug (5, 6). In the present case, HRCT images and BALF findings were consistent with DI-ILD, and other lung diseases were excluded by comprehensive examination. At first, we suspected diclofenac sodium and benzbromarone, which were given before disease onset, as the cause of DI-ILD. We thought the most likely causative drug was benzbromarone due to the following: 1) he took only small dosages of diclofenac sodium for on-demand use and his symptoms worsened when he stopped taking it at 6 days before admission; 2) he had never previously experienced any problems with similar non-steroidal anti-inflammatory drugs such as loxoprofen sodium; and 3) drug-induced lymphocyte stimulation test with benzbromarone was positive and that with diclofenac sodium was negative. Thus, although we did not perform a provocation test because of severe dyspnea and pulmonary hemorrhage, the present case was diagnosed as benzbromarone-induced eosinophilic pneumonia with pulmonary hemorrhage.

In the present case, BALF analysis revealed that eosinophils may play an important role in the pathogenesis and bloody BALF indicated that the permeability of blood vessels in the lungs was increased, although lung biopsy was not performed. From the viewpoint of pulmonary hemorrhage and increased eosinophil proportion in BALF, the patient may have had drug-induced ANCA-positive vasculitis, such as macrolide-induced Churg-Strauss syndrome (7, 8) or propylthiouracil-induced ANCA-positive vasculitis (9, 10). However, he had no particular extrapulmonary findings such as hematuria, and MPO-ANCA and PR3-ANCA were negative. Therefore, he was not diagnosed with benzbromarone-induced ANCA-positive vasculitis.

Eosinophils contain granule proteins, including major basic protein, eosinophil cationic protein, eosinophil peroxidase and eosinophil-derived neurotoxin, which are capable of inducing tissue damage and dysfunction (11, 12). Furthermore, eosinophils have been reported to synthesize and release leukotriene C4 and platelet-activating factor, which increase the permeability of small vessels (13, 14). Therefore, we expect that abundant eosinophils in the lung are a pathogenesis factor in eosinophilic pneumonia with pulmonary hemorrhage, as in the present case. In addition, another noteworthy cell fraction of BALF and peripheral blood was neutrophils. In BALF, neutrophils were similarly elevated as eosinophils. In peripheral blood, neutrophils were markedly elevated, while eosinophils were not elevated at all. Some investigators have reported that neutrophils are elevated in BALF and peripheral blood in drug-induced eosinophilic pneumonia (15, 16). They speculated that interleukin-8 and granulocyte macrophage colony-stimulating factor, which were elevated in serum and/or BALF, may contribute to the increase in neutrophils in the early stages of the disease. We herein reported a rare case with benzbromarone-induced eosinophilic pneumonia with pulmonary hemorrhage.

Acknowledgement

The authors declare that they have no potential conflicts of interest.

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