INTERNAL MEDICINE

□ CASE REPORT □

Interstitial Lung Disease Induced by Pazopanib Treatment

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Abstract

Although pneumothorax has been reported to be a major pulmonary adverse event in patients treated with pazopanib, a multikinase inhibitor, drug-induced interstitial lung disease (DILD) has not been reported. A 74-year-old Japanese man who received pazopanib for the treatment of femoral leiomyosarcoma and lung metastasis presented with dyspnea and fatigue. He had mild interstitial pneumonia when pazopanib treatment was initiated. Chest computed tomography revealed progressive bilateral ground-glass opacity (GGO) and traction bronchiectasis. We diagnosed DILD due to pazopanib. The patient's pazopanib treatment was interrupted and a steroid was administered. The symptoms and GGO were improved with treatment. Physicians should be aware of DILD due to pazopanib in patients with pre-existing interstitial lung disease.

Key words: interstitial pneumonia, pneumonitis, pazopanib, drug-induced interstitial lung disease, molecular target drug

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Introduction

Pazopanib is a multi-targeted tyrosine kinase inhibitor (TKI) that inhibits vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF) (1). A phase III study on renal cell carcinoma (2) and soft-tissue sarcomas such as leiomyosarcoma and synovial sarcoma (3) showed that pazopanib prolonged progression-free survival. Additionally, in recent years, the activity of pazopanib in several types of solid tumors including tumors of the breast, thyroid, and cervix has been reported (1).

The common adverse events of multikinase inhibitors (including pazopanib) are fatigue, diarrhea, nausea, weight loss, hand-foot skin reactions, and hypertension (4); pneumothorax has been reported as a pulmonary adverse event in patients treated with pazopanib (3, 5, 6). Drug-induced interstitial lung disease (DILD) has been reported as a serious adverse event in patients treated with epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) such as gefitinib, erlotinib, and afatinib (7, 8). Furthermore, there have been several reports of DILD due to sorafenib, another multikinase inhibitor, in recent years (9-13). However, DILD due to pazopanib has not been reported in the literature. We herein report a case of DILD due to pazopanib.

Case Report

A 74-year-old Japanese man presented with dyspnea and general fatigue. Three months previously, the patient had been diagnosed with left femoral vein leiomyosarcoma, and a chest computed tomography (CT) scan revealed multiple pulmonary metastases with bilateral mild reticular shadows (Fig. 1). He was a current smoker with a 52 pack-year habit, and quit smoking after the diagnosis of leiomyosarcoma. His Eastern Cooperative Oncology Group performance status

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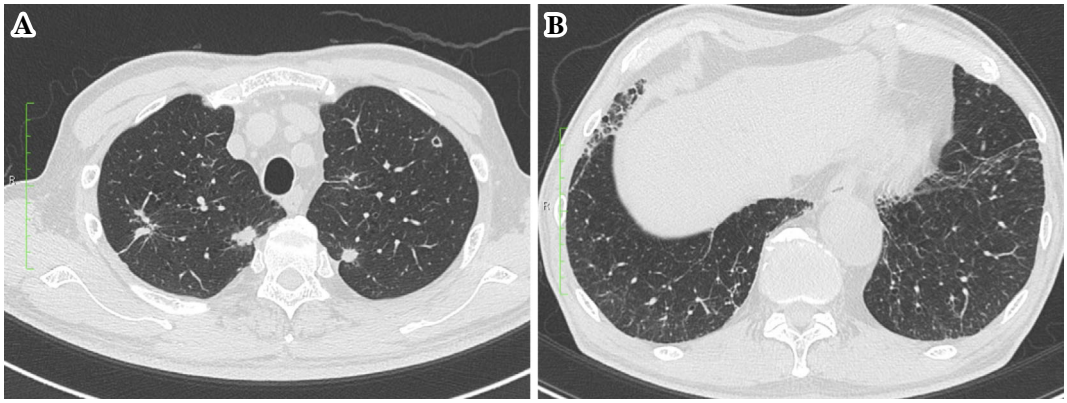

Figure 1. **Chest computed tomography from the start of pazopanib therapy. (A) Lung metastases from leiomyosarcoma and (B) pre-existing interstitial lung disease are observed.**

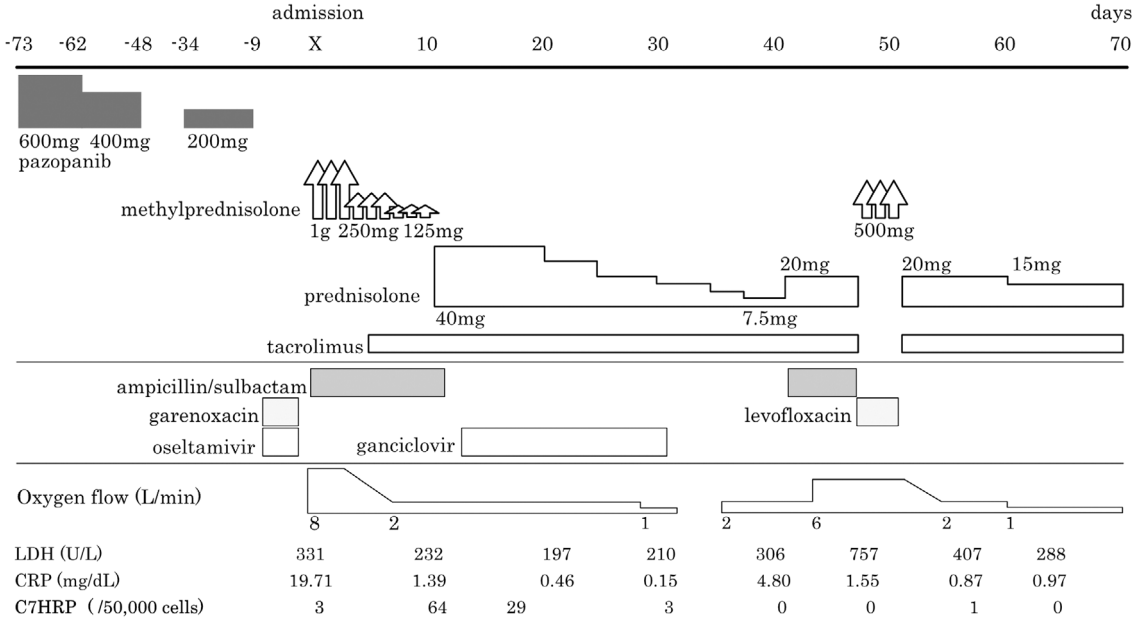

Figure 2. **The clinical course of the present case.**

score was 2. Pazopanib (600 mg) was administered; at the same time, local radiation therapy was performed to treat the patient's left femoral vein leiomyosarcoma. Twenty-five days after the start of pazopanib therapy, the patient's treatment was interrupted because of fatigue and renal function failure; pazopanib (200 mg) was re-started on day 39. Chest radiography was not performed during this period. On day 64, 25 days after the re-starting pazopanib, the patient complained of fatigue, fever, and a nonproductive cough, and pazopanib treatment was interrupted again. However, the symptoms and dyspnea became exacerbated on day 73, and he was transferred to our hospital.

The clinical course is shown in Fig. 2. On examination, his body temperature was 36.4°C, his blood pressure was 160/88 mmHg, his heart rate of 107 bpm, and his oxygen saturation was 95% (with 5 L of supplemental oxygen by mask). Fine crackles were audible in the bilateral lung fields. The results of the laboratory tests that were performed on admission are shown in Table. A chest radiograph revealed bilateral peripheral reticular shadows and ground-glass opacity (GGO), and a chest CT scan revealed bilateral GGO and traction bronchiectasis (Fig. 3A and B). Bronchoalveolar lavage was not performed due to the patient's severe hypoxia. We diagnosed the patient with DILD due to pazopanib based on the chest CT findings, the compatible clinical course, and because the laboratory tests for atypical pneumonia, opportunistic infections, and interstitial lung disease complicated by connective tissue diseases were all negative (Table). A drug-induced lymphocyte stimulation test was not evaluable because the positive control was negative. Pazopanib had already been interrupted 9 days prior to the patient's admission. High-dose methylprednisolone (1,000 mg/day for 3 days) was initiated on the day of admission, and tacrolimus was added on the 5th day after admission. His symptoms and hypoxia gradually improved, and the steroid dose was tapered. The results of a cytomegalovirus (CMV) antigenemia assay (C7HRP) changed to positive on the 9th day after admission, and ganciclovir treat-

Table. **Laboratory Data on Admission.**

Hematology			**Serology and Biochemistry**						**Rapid-Antigen Tests**		
WBC	12,600	/μL	TP	6.8	g/dL	BDG	7.8	pg/mL	*Legionella pneumophila*	(-)	
Neutro	95%		BUN	30	mg/dL	Asp-Ag	0.2	COI	*Streptococcus pneumonia*	(-)	
Lymph	2%		CRE	1.58	mg/dL	Cry-Ag	(-)		Influenza	(-)	
Mono	3%		T-Bil	0.9	mg/dL	CMV-Ag	3	/50,000 cells			
Eosino	0%		AST	78	U/L						
Baso	0%		ALT	103	U/L	ANA	< 20		**Arterial blood gas (mask with 5 L supplemental O_2)**		
RBC	3.24	× 10^6/μL	ALP	456	U/L	MPO-ANCA	< 0.1	U/mL	pH	7.435	
Hb	10.9	g/dL	LDH	331	U/L	PR3-ANCA	< 0.1	U/mL	$PaCO_2$	32.8	Torr
Hct	33.4%		γ-GTP	96	U/L	KL-6	428	U/mL	PaO_2	68.2	Torr
PLT	32.6	× 10^4/μL	GLU	120	mg/dL	SP-D	148	ng/mL	HCO_3^-	21.6	mmol/L
			CRP	19.7	mg/dL	SP-A	149.6	ng/mL	$A\text{-}aDO_2$	40.5	Torr

WBC: white blood cells, RBC: red blood cells, Hb: hemoglobin, Hct: hematocrit, PLT: platelet, TP: total protein, BUN: blood urea nitrogen, CRE: creatinine, T-Bil: total bilirubin, AST: aspartate transaminase, ALT: alanine transaminase, ALP: alkaline phosphatase, LDH: lactate dehydrogenase, g-GTP: g-glutamyl transferase, GLU: glucose, CRP: C-reactive protein, BDG: β-D-glucan, Asp-Ag: *Aspergillus* antigen, Cry-Ag: *Cryptococcus* antigen, CMV-Ag: cytomegalovirus pp65 antigenemia, ANA: anti-nuclear antibody, MPO-ANCA: myeloperoxidase-anti-neutrophil cytoplasmic antibody, PR3-ANCA: proteinase-3-anti-neutrophil cytoplasmic antibody, SP-A: surfactant protein-A, SP-D: surfactant protein-D.

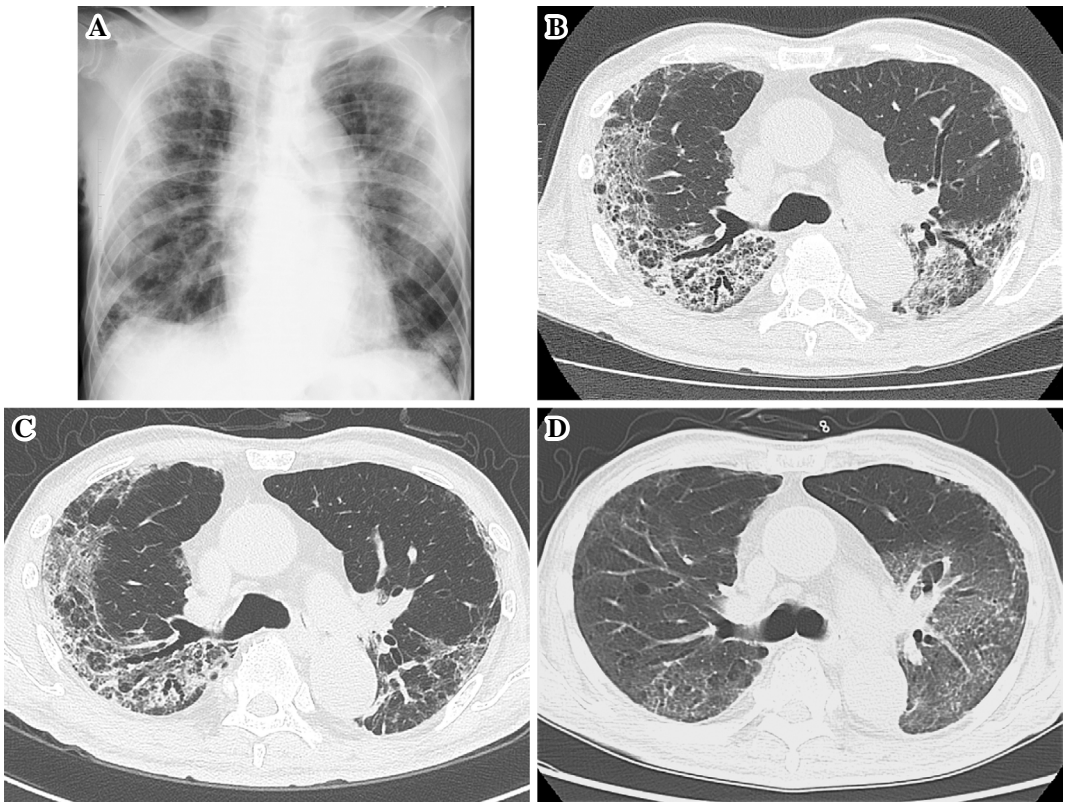

Figure 3. **The radiological findings on admission are shown. (A) Chest radiography shows bilateral peripheral reticular shadows. Chest computed tomography demonstrates bilateral diffuse ground-glass opacity and the progression of traction bronchiectasis (B) on the day of admission, (C) partial improvement on the 8th day of treatment, and (D) recurrence of interstitial pneumonia on the 42nd day.**

ment was initiated. Chest radiography and a CT scan showed partial improvement of the bilateral GGO (Fig. 3C), and he was transferred to another hospital on the 22nd day after admission. After tapering the patient's prednisolone dose on the 34th day of treatment, hypoxia and bilateral reticular shadows developed again (Fig. 3D). Since tests for C7HRP and β-D-glucan were negative, steroid and tacrolimus therapy was re-started, and the patient's DILD improved. He was transferred to a convalescent hospital to receive end-of-life care for leiomyosarcoma on the 90th day after admission.

Discussion

The present patient developed DILD due to the re-administration of pazopanib for vein leiomyosarcoma. He had mild chronic interstitial lung disease and lung metastasis when pazopanib therapy was initiated; however, chest radiography was not performed during pazopanib treatment.

DILD is a serious and important adverse effect associated with molecular targeted therapy. In particular DILD due to EGFR-TKI is relatively common (14). DILD may occur when a multikinase inhibitor, such as pazopanib, sorafenib, or sunitinib, targets the VEGF receptor (VEGFR) and PDGF receptor (PDGFR); however this occurs less frequently than DILD due to EGFR-TKI - although it should be noted that DILD due to sorafenib has been reported in recent years (as described above) (12). Only one case of Grade 1 DILD was reported among 246 patients in a phase III study on pazopanib for soft-tissue sarcoma; however, the clinical course is unknown. To our knowledge, this is the first report to describe the clinical course of a patient with DILD associated with pazopanib. Physicians should pay attention not only to pneumothorax, but also to DILD during pazopanib therapy.

Although the impairment of the alveolar repair mechanisms due to the inhibition of epidermal growth factor receptor phosphorylation may affect interstitial lung damage (15, 16), the mechanisms and risk factors of DILD due to VEGFR/PDGFR-TKI are controversial. The risk factors for DILD due to EGFR-TKI have been reported to include older age, smoking, preexisting interstitial lung disease, and a poor performance status (17-19). A post-marketing analysis of sorafenib in Japan reported that pre-existing interstitial pneumonia and pulmonary fibrosis were observed in 14% (9/62 cases) of patients with DILD (12). Our case is consistent with these characteristics; especially, pre-existing interstitial pneumonia may be associated with the development of DILD, and suggests that the application of pazopanib therapy to patients with pre-existing interstitial lung disease should be considered carefully.

In the current case, we could not completely exclude an opportunistic infection because we could not perform bronchoscopy. The C7HRP was negative on admission, but changed to positive on the 9th day after admission. The acute progression of traction bronchiectasis and GGO on chest CT implied diffuse alveolar damage (DAD); however, if DAD was induced by the reactivation of CMV, the C7HRP test should have already been positive on the day of admission. Additionally, laboratory tests such as β-D-glucan, *Aspergillus* antigen, rheumatoid factor, anti-nuclear antibody, and antineutrophil cytoplasmic antibody were all negative. After tapering the patient's prednisolone dose to 7.5 mg on the 39th day, DILD developed again. At that point, laboratory tests for opportunistic infections, including CMV, were all negative, and methylprednisolone pulse therapy was effective. The guidelines for DILD in Japan recommend that the initial prednisolone dose should be continued for 2-4 weeks and then be tapered (20) - thus, the early tapering of prednisolone might have led to the recurrence of DILD in the present case. The clinical course supports a diagnosis of DILD due to pazopanib; however, it was difficult to distinguish whether the patient's condition represented a recurrence of DILD or an exacerbation of pre-existing interstitial pneumonia.

In conclusion, the present case suggests DILD due to pazopanib developed in an older patient with pre-existing interstitial lung disease. Physicians should consider the indications of pazopanib for these patients, and carefully observe their respiratory symptoms during pazopanib treatment.

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

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