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Pazopanib-induced organizing pneumonia in a patient with leiomyosarcoma: A case report

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ABSTRACT

Pazopanib, a multityrosine kinase inhibitor used for treating malignant soft tissue tumors, rarely causes adverse events associated with the respiratory system. We report a case of a 73-year-old male with leiomyosarcoma treated with pazopanib. Four months after treatment initiation, chest computed tomography showed bilateral patchy consolidation and ground-glass opacities. Bronchoscopy revealed increased lymphocytes in the bronchoalveolar lavage fluid. Histological analysis of lung tissue demonstrated intraluminal fibrotic changes in alveolar spaces. According to these findings, we diagnosed the patient with pazopanib-induced organizing pneumonia. To best of our knowledge, this is the first report of such a case.

1. Background

Pazopanib is a multiple tyrosine kinase inhibitor-targeting fibroblast growth factor, platelet-derived growth factor, and vascular endothelial growth factor. It is used for renal cell carcinoma and malignant soft tissue tumor [1–3]. Recently, clinical trials have examined its therapeutic effects on solid cancers of the breast, thyroid, lung, and head and neck [4–11].

The most common adverse events of multiple tyrosine kinase inhibitors are fatigue, diarrhea, nausea, weight loss, and hypertension [12]. Pneumothorax is the most frequently reported respiratory system-related adverse event [13–17]. A case of pazopanib-induced lung injury presenting with a usual interstitial pneumonia pattern has already been reported; however, the patient had poor prognosis [18]. There is no known report of pathologically diagnosed pazopanib-induced organizing pneumonia.

2. Case presentation

A 73-year-old man presented with bloody urine. Imaging examination showed a tumor around the superior and inferior venae cavae, which was surgically resected. In accordance with the histological findings, the patient was diagnosed with leiomyosarcoma. A year and 5 months later, magnetic resonance imaging demonstrated local recurrence of the tumor, for which resection was performed. However, 1 year after the second surgery, computed tomography showed multiple lung metastases with local recurrence of the tumor surrounding the inferior vena cava. Because of the distant metastasis, systemic treatment using pazopanib (800 mg/day) was initiated. Most of the metastatic lung tumors were unchanged, and progression of the primary tumor and enlargement of metastatic lesions were not observed.

Chest X-ray showed bilateral peripheral consolidations, which were lower-lung-field dominant 4 months after the start of this treatment (Fig. 1). Chest computed tomography revealed non-segmental infiltration with bronchial transillumination surrounded by ground-glass

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opacities. Fine crackles were heard posteriorly over the lower portion of the lung on auscultation. Laboratory examinations showed elevated levels of KL-6, surfactant protein-A, and surfactant protein-D, which were indicative of interstitial pneumonia (Table 1). No elevation in the proportion of eosinophils in peripheral blood leukocytes was observed. Specific markers, including angiotensin converting enzyme, soluble interleukin-2 receptor, and anti-nuclear antibody, were within normal levels, which excluded the possibilities of collagen diseases and sarcoidosis. On the basis of these findings, pazopanib-induced lung injury was suspected.

Chest radiography indicates baseline image (A) and bilateral areas of consolidation mainly involving the lower lung zones after therapy (B). Computed tomography shows several pulmonary nodules before using pazopanib (C) and bilateral areas of consolidation predominantly involving the peripheral regions on the 128th day of retreatment (D).

Bronchoscopy was performed for further investigation. The percentage of lymphocytes in bronchoalveolar lavage fluid had increased. A specimen obtained by transbronchial lung biopsy was histologically analyzed using hematoxylin and eosin and elastic-van Gieson staining, which showed intraluminal fibrosis alveolar spaces consistent with the findings of organizing pneumonia (Fig. 2). Thus, the diagnosis of pazopanib-induced organizing pneumonia was confirmed.

Alveolar spaces containing Masson bodies and plugs of cellular fibrotic tissue (arrows) are evident (A: Hematoxylin and eosin staining, magnification, 200×; B: Elastica van Gieson staining, magnification, 200×).

Imaging results showed no change even after discontinuation of pazopanib. Thus, systemic treatment with an oral corticosteroid (prednisolone, 0.5 mg/kg/day) was started, resulting in gradual improvement of organizing pneumonia accompanied by a reduction in KL-6 (183 U/L). When the prednisolone dose was reduced to 12.5 mg, trabectedin [a transcription inhibitor] was initiated for the treatment of leiomyosarcoma. The patient showed no signs of remission of organizing pneumonia after discontinuing prednisolone.

3. Discussion

Organizing pneumonia is of two types: idiopathic and secondary. The latter is caused by various factors, such as drugs, infections, collagen diseases, hematological disorders, and malignancies. Typical imaging findings of sporadic infiltrative shadows in the lung are similar to those of eosinophilic pneumonia, and suggestive histological findings of alveolar organizing components are similar to the findings that indicate hypersensitivity pneumonitis. Therefore, combined examinations are needed to diagnose organizing pneumonia accurately.

Histological findings of organizing pneumonia, a specific type of interstitial lung disease, mainly comprise intraluminal organizing fibrosis and buds of granulation tissue consisting of fibroblast-myofibroblasts in distal airspaces [19]. An increased number of infiltrative lymphocytes in the alveolar spaces is also characteristic of this disease, which is indicative of an underlying immunological mechanism.

To date, there has been no report of organizing pneumonia caused by pazopanib. Moreover, interstitial lung disease is rare; however, there has been a case of a usual pattern of interstitial pneumonia with pazopanib treatment [18]. In this case, the patient required treatment with both a corticosteroid and an immunosuppressant and was re-treated with pazopanib to confirm the causal relationship. However, as the patient in our case was histologically diagnosed with organizing pneumonia, only corticosteroid was prescribed, which was effective. This indicated that pathological diagnosis is useful in establishing a prognosis and choosing the optimal therapy for pazopanib-induced interstitial pneumonia.

Corticosteroids are mostly efficacious when used as an initial treatment of organizing pneumonia [19]. Steroid pulse therapy and/or immunosuppressive drug therapy is used in limited refractory cases [20]. Some cases show spontaneous remission. In this case, steroid treatment was started because no improvement was observed after pazopanib withdrawal. A previous report of a case with life-threatening, pazopanib-induced lung injury increased the necessity of steroid treatment [18]. Steroid tapering frequently induces disease relapse, though suspected drug discontinuation might have enabled cessation of steroid therapy in the presented case.

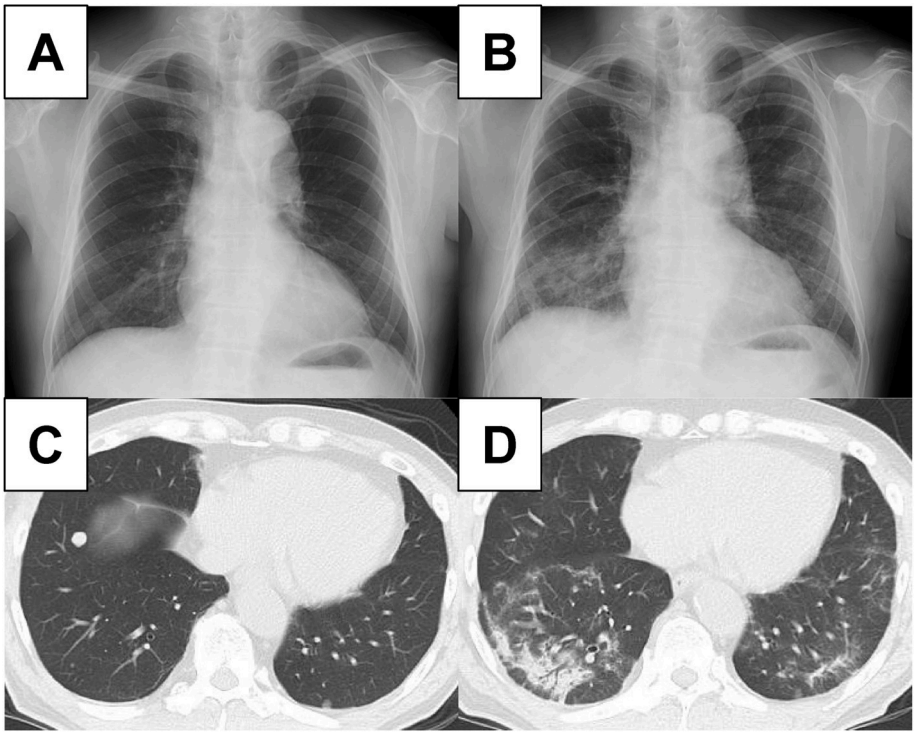

Fig. 1. Chest radiography and computed tomography findings before and after pazopanib treatment.

Table 1
Laboratory findings of patients at the first visit.

Hematological parameters			Serological and biochemical parameters					
White blood cells	4500	/uL	T-Bil	0.48	mg/dL	CRP	<0.3	mg/dL
Neutrophil	53.6	%	AST	36.0	IU/L	Procalcitonin	0.02	ng/mL
Lymphocyte	34.4	%	ALT	15.0	IU/L	ACE	11.8	IU/L
Basophil	0.4	%	LDH	209	IU/L	BNP	6.9	pg/mL
Eosinophil	4.6	%	TP	6.6	g/dL	sIL-2R	953	U/mL
Monocyte	7	%	Alb	3.6	g/dL	1-3- β-D glucan	17.0	pg/mL
Red blood cells	425	$\times 10^4/\mu L$	BUN	10.0	mg/dL	Rheumatoid Factor	<3.0	U/mL
Hemoglobin	14.1	g/dL	Cr	0.88	mg/dL	MPO ANCA	<1.0	U/mL
Hematocrit	41.7	%	KL-6	1686	U/mL	PR-3 ANCA	<1.0	U/mL
Platelets	21.9	$\times 10^4/\mu L$	SP-A	79.4	ng/mL	T-SPOT. TB	(-)	
			SP-D	361	ng/mL			

Abbreviation: KL-6, Krebs von den Lungen-6; SP-A, surfactant protein-A; SP-D, surfactant protein-D.
ACE, angiotensin converting enzyme; BNP, brain natriuretic peptide; sIL-2R, soluble interleukin-2 receptor.
MPO, myeloperoxidase; PR-3, proteinase-3; ANCA, anti-neutrophil cytoplasmic antibody.

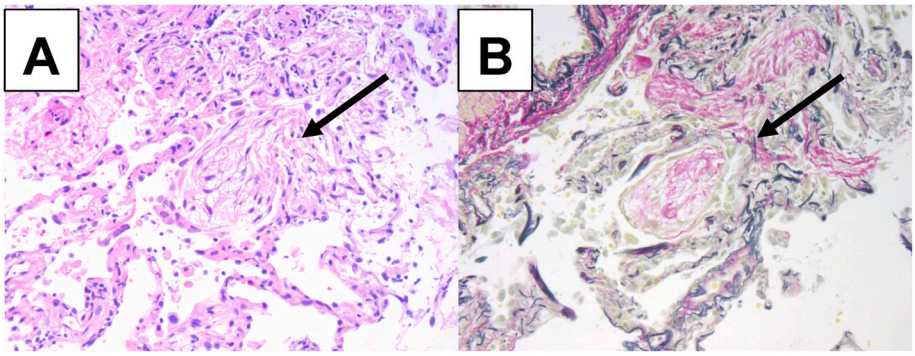

Fig. 2. Pathological analysis of transbronchial lung biopsy specimen.

Previous studies have reported cases of organizing pneumonia induced by tyrosine kinase inhibitors, including epidermal growth factor receptor tyrosine kinase inhibitor and EML4-ALK fusion tyrosine kinase inhibitor, although the frequency is low [21,22]. However, as only a small number of these cases are reported, inhibition of tyrosine kinases may not necessarily cause organizing pneumonia. Further investigation is needed to identify the mechanism.

The relationship between organizing pneumonia and multiple pulmonary metastases remains unknown. A previous study reported a case of organizing pneumonia with multiple pulmonary metastases of melanoma, indicative of a possible trigger of organizing pneumonia [23]. Additionally, atypical lung metastatic lesions might resemble organizing pneumonia, suggesting the importance of histological analysis [24].

4. Conclusion

This case report describes a rare case of drug-induced lung injury caused by pazopanib used to treat leiomyosarcoma with lung metastasis. To our knowledge, this is the first confirmed diagnosis of organizing pneumonia caused by pazopanib. As demonstrated in this report, histological analysis may be useful in establishing a diagnosis of this disease and distinguishing it from lung metastasis. Clinicians should recognize the importance of prompt diagnostic and therapeutic approaches for improving the outcome of pazopanib-related lung injury.

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Declaration of competing interest

None.

CRediT authorship contribution statement

Chie Watanabe: Conceptualization, Investigation, Data curation, Writing - original draft, Visualization. **Jun Miyata:** Writing - review & editing, Supervision. **Kotoba Esaki:** Resources, Writing - review & editing. **Ryohei Suematsu:** Resources, Writing - review & editing. **Tomoya Sano:** Resources, Writing - review & editing. **Takayuki Yamamoto:** Resources, Writing - review & editing. **Hisashi Sasaki:** Resources, Writing - review & editing. **Yohei Maki:** Resources, Writing - review & editing. **Yoichi Tagami:** Resources, Writing - review & editing. **Yoshifumi Kimizuka:** Resources, Writing - review & editing. **Yuji Fujikura:** Resources, Writing - review & editing. **Keiichi Ito:** Resources, Writing - review & editing. **Akihiko Kawana:** Resources, Writing - review & editing, Project administration.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2020.101112.

References

[1] F.A. Schutz, T.K. Choueiri, C.N. Sternberg, Pazopanib: clinical development of a potent anti-angiogenic drug, Crit. Rev. Oncol. Hematol. 77 (2011) 163–171.

[2] W.T. van der Graaf, J.Y. Blay, S.P. Chawla, et al., Pazopanib for metastatic soft-tissue sarcoma (PALETTE): a randomised, double-blind, placebo-controlled phase 3 trial, Lancet 379 (2012) 1879–1886.

[3] N. Altorki, M.E. Lane, T. Bauer, et al., Phase II proof-of-concept study of pazopanib monotherapy in treatment-naive patients with stage I/II resectable non-small-cell lung cancer, J. Clin. Oncol. 28 (2010) 3131–3137.

[4] B. Besse, J. Mazieres, L. Ribassin-Majed, et al., Pazopanib or placebo in completely resected stage I NSCLC patients: results of the phase II IFCT-0703 trial, Ann. Oncol. 28 (2017) 1078–1083.

[5] F. Koinis, S. Agelaki, V. Karavassilis, et al., Second-line pazopanib in patients with relapsed and refractory small-cell lung cancer: a multicentre phase II study of the Hellenic Oncology Research Group, Br. J. Canc. 117 (8–14) (2017).

[6] I. Messaritakis, E. Politaki, F. Koinis, et al., Dynamic changes of phenotypically different circulating tumor cells sub-populations in patients with recurrent/refractory small cell lung cancer treated with pazopanib, Sci. Rep. 8 (2018) 2238.

[7] M.E. O'Brien, R. Gaafar, B. Hasan, et al., Maintenance pazopanib versus placebo in Non-Small Cell Lung Cancer patients non-progressive after first line chemotherapy: a double blind randomised phase III study of the lung cancer group, EORTC 08092 [EudraCT: 2010-018566-23. NCT01208064], Eur. J. Canc. 51 (2015) 1511–1528.

[8] D.R. Spigel, H.A. Burris 3rd, F.A. Greco, et al., Erlotinib plus either pazopanib or placebo in patients with previously treated advanced non-small cell lung cancer: a randomized, placebo-controlled phase 2 trial with correlated serum proteomic signatures, Cancer 124 (2018) 2355–2364.

[9] J.M. Sun, K.H. Lee, B.S. Kim, et al., Pazopanib maintenance after first-line etoposide and platinum chemotherapy in patients with extensive disease small-cell lung cancer: a multicentre, randomised, placebo-controlled Phase II study (KCSG-LU12-07), Br. J. Canc. 118 (2018) 648–653.

[10] J.M. Weiss, L.C. Villaruz, M.A. Socinski, et al., A single-arm phase II trial of pazopanib in patients with advanced non-small cell lung cancer with non-squamous histology with disease progression on bevacizumab containing therapy, Lung Canc. 86 (2014) 288–290.

[11] H. Zhao, F. Yang, W. Shen, et al., Pazopanib diminishes non-small cell lung cancer [NSCLC] growth and metastases in vivo, Thorac Cancer 6 (2015) 133–140.

[12] Q. Tan, W. Wang, Y. Long, G. Chen, Therapeutic effects and associated adverse events of multikinase inhibitors in metastatic renal cell carcinoma: a meta-analysis, Exp Ther Med 9 (2015) 2275–2280.

[13] B. Çelik, Z.P. Sürücü, V. Yılmaz, H.K. Çelik, A case report of secondary simultaneous bilateral pneumothorax due to pazopanib treatment, Turk Thorac J 19 (2018) 49–51.

[14] G. Leuzzi, G. Alessandrini, V. Ferraresi, G. Ferretti, D. Forcella, F. Facciolo, Bilateral spontaneous pneumothorax and massive pneumomediastinum under Pazopanib therapy, Thorac Cancer 6 (2015) 110–111.

[15] Y. Nakahara, T. Fukui, K. Katono, et al., Pneumothorax during pazopanib treatment in patients with soft-tissue sarcoma: two case reports and a review of the literature, Case Rep Oncol 10 (2017) 333–338.

[16] K. Nakano, N. Motoi, J. Tomomatsu, et al., Risk factors for pneumothorax in advanced and/or metastatic soft tissue sarcoma patients during pazopanib treatment: a single-institute analysis, BMC Canc. 16 (2016) 750.

[17] B. Sabath, H.A. Muhammad, A. Balagani, et al., Secondary spontaneous pneumothorax in patients with sarcoma treated with Pazopanib, a case control study, BMC Canc. 18 (2018) 937.

[18] S. Ide, N. Sakamoto, S. Hara, et al., Interstitial lung disease induced by pazopanib treatment, Intern. Med. 56 (2017) 79–83.

[19] J.F. Cordier, Cryptogenic organising pneumonia, Eur. Respir. J. 28 (2006) 422–446.

[20] I.F. Purcell, S.J. Bourke, S.M. Marshall, Cyclophosphamide in severe steroid-resistant bronchiolitis obliterans organizing pneumonia, Respir. Med. 91 (1997) 175–177.

[21] N. Asai, T. Yokoi, E. Yamaguchi, A. Kubo, Successful crizotinib rechallenge after crizotinib-induced organizing pneumonia in anaplastic lymphoma kinase-rearranged non-small cell lung cancer, Case Rep Oncol 7 (2014) 681–684.

[22] H. Lee, H.Y. Lee, J.M. Sun, et al., Transient asymptomatic pulmonary opacities during osimertinib treatment and its clinical implication, J. Thorac. Oncol. 13 (2018) 1106–1112.

[23] T. Sano, H. Uhara, Y. Mikoshiba, et al., Nivolumab-induced organizing pneumonia in a melanoma patient, Jpn. J. Clin. Oncol. 46 (2016) 270–272.

[24] C. Lacerda, J. Lages, R. Rolo, Secondary organizing pneumonia mimicking pulmonary metastasis of a diffuse large cell lymphoma, Arch. Bronconeumol. 54 (2017) 386.