Polycythemia Vera Associated with Pulmonary Hypertension and Diffuse Large B-Cell Lymphoma: A Case Report

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Patient: **Male, 79-year-old**
Final Diagnosis: **Diffuse large B cell lymphoma**
Symptoms: **Dyspnea**
Medication: **—**
Clinical Procedure: **—**
Specialty: **Cardiology • Hematology • Oncology**

Objective: **Rare disease**
Background: Myeloproliferative neoplasms (MPNs), including polycythemia vera (PV), are associated with pulmonary hypertension (PH) and malignant lymphomas. Although the underlying mechanisms have not been completely clarified, it has been suggested that the Janus kinase 2 (*JAK2*) mutation, which is frequently identified in PV, can be involved in the development and/or progression of these distinct diseases in patients with MPNs. However, no reports have described the coexistence of PH and malignant lymphoma in patients with MPNs.
Case Report: A 79-year-old man being treated for PV for 27 years and PH for 5 years was hospitalized due to severe dyspnea at rest. His soluble interleukin-2 receptor levels gradually increased and the chest computed tomography showed remarkable progression of the lung lesions and an enlargement of the mediastinal and axillary lymph nodes. A lymph node biopsy was performed and the patient was diagnosed with diffuse large B-cell lymphoma (DLBCL). Owing to his poor condition, chemotherapy was not initiated, and he died on the 89th day of hospitalization. The pathological autopsy revealed the destruction of alveolar structures with neoplastic space-occupying lesions of DLBCL. Multifactorial features of PH associated with MPNs, including the intimal thickening of pulmonary arteries accompanied by megakaryocytes and obstructed pulmonary arteries with organized thrombi in the lung tissue specimens, were observed. We found a *JAK2* mutation based on a genetic analysis of the patient's bone marrow.
Conclusions: We present the rare case of a patient who had PV with a *JAK2* mutation, which coexisted with PH and DLBCL, and he developed severe refractory respiratory failure.

Keywords: **Hypertension, Pulmonary • Janus Kinase 2 • Lymphoma, Large B-Cell, Diffuse • Myeloproliferative Disorders • Polycythemia Vera**

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Background

Myeloproliferative neoplasms (MPNs) are a group of hematologic disorders caused by the clonal proliferation of the bone marrow stem cells; these include polycythemia vera (PV), essential thrombocythemia, and primary myelofibrosis [1]. Although patients with MPNs have an increased risk of thrombohemorrhagic complications, these disorders are indolent in nature [2,3]. MPNs gradually worsen and eventually lead to bone marrow fibrosis or can transform to a blast crisis, including acute leukemia.

MPNs cause pulmonary hypertension (PH) through various mechanisms, and this is associated with a poor prognosis [4]. The current PH guidelines classify PH into 5 groups based on the underlying etiology and mechanism, and MPN-associated PH is classified as PH with unclear multifactorial mechanisms (Group 5) [5]. Most patients with MPNs, especially those with PV, have a mutation in the Janus kinase 2 (*JAK2*) gene, and this contributes to the pathogenesis of MPNs [6]. Aberrant Janus kinase-signal transducer and activator of transcription (JAK-STAT) signaling mediates PH through the dysregulation of nitric oxide (NO) and cytokine levels [7]. A possible association between the *JAK2* mutation and an increased risk of non-Hodgkin lymphoma (NHL) has been reported; however, myeloid neoplasms mainly represent the subsequent hematologic neoplasms in patients with MPNs [8,9]. We report one of the first cases of a patient who had PH associated with PV and a *JAK2* V617F mutation that rapidly developed into progressive respiratory failure due to NHL. Our case report demonstrates that PV patients are at risk of developing PH and NHL and a genetic background associated with the *JAK2* mutation could be involved. This highlights the importance of managing PV patients, keeping in mind the risk of these distinct complications, especially in patients with a *JAK2* mutation.

Case Report

A 79-year-old man had an emergency admission to our hospital due to severe dyspnea at rest. He had a 27-year history of PV diagnosed at the age of 52 years, which had been well managed with hydroxycarbamide. In addition, he had a 5-year history of PH and a family history of gastric cancer. Right heart catheterization (RHC) performed at the time of diagnosis of the PH had revealed a mean pulmonary artery pressure (mPAP) of 39 mmHg, pulmonary artery wedge pressure of 9 mmHg, high cardiac output of 9.2 L/min, and a corresponding pulmonary vascular resistance (PVR) of 3.3 Wood units. He was diagnosed with PH associated with PV (Group 5) and was treated with a triple combination therapy of pulmonary vasodilators (bosentan, sildenafil, and beraprost). Anticoagulation with warfarin was initiated because a few localized ventilation-perfusion

Table 1. Laboratory data on admission.

	Value	Reference range
Blood cell count		
White blood cell (×10³/μL)	7.67	3.3-9.40
Neutrophils (%)	79.7	40.0-73.0
Lymphocytes (%)	10.3	18.0-52.0
Monocytes (%)	7.2	2.2-10.0
Eosinophils (%)	2.1	0.0-7.0
Basophils (%)	0.7	0.0-2.0
Red blood cells (×10⁶/μL)	2.6	4.4-5.6
Hemoglobin (g/dL)	8.2	13.8-17.0
Hematocrit (%)	26.9	41.0-51.0
Platelets (×10³/μL)	221	130-320
Blood biochemistry		
AST (U/L)	12	<40
ALT (U/L)	10	<40
LDH (U/L)	825	103-229
UN (mg/dL)	25	7-22
CRE (mg/dL)	0.85	0.6-1.20
CRP (mg/dL)	0.11	0.0-0.20
BNP (pg/mL)	158	<40
sIL-2R (U/mL)	1412	121-613
Arterial blood gas (O₂ 5L/min)		
pH	7.466	7.35-7.45
pCO₂ (mmHg)	40.0	35-45
pO₂ (mmHg)	39.2	86-107
HCO₃ (meq/L)	28.8	22-26
SaO₂ (%)	73.1	>96

ALT – alanine transaminase; AST – aspartate transaminase; BNP – brain natriuretic peptide; CRE – creatinine kinase; CRP – C-reactive protein; HCO₃ – bicarbonate; LDH – lactate dehydrogenase; pCO₂ – partial pressure of carbon dioxide; pO₂ – partial pressure of oxygen; SaO₂ – arterial oxygen saturation; sIL-2R – soluble interleukin-2 receptor; UN – urea nitrogen.

mismatches were noted in a ventilation/perfusion lung scan. A follow-up RHC performed 4 months before the present emergency admission revealed a persistent high cardiac output (9.3 L/min) with slight improvements in the hemodynamics (mPAP 32 mmHg and PVR 2.5 Wood units). However, he experienced a gradual worsening of the dyspnea on exertion.

On admission, his blood pressure was 94/53 mmHg, pulse rate 98 beats/min, respiratory rate 36 breaths/min, oxygen saturation 73.1% while receiving 5 L/min of oxygen, and body temperature
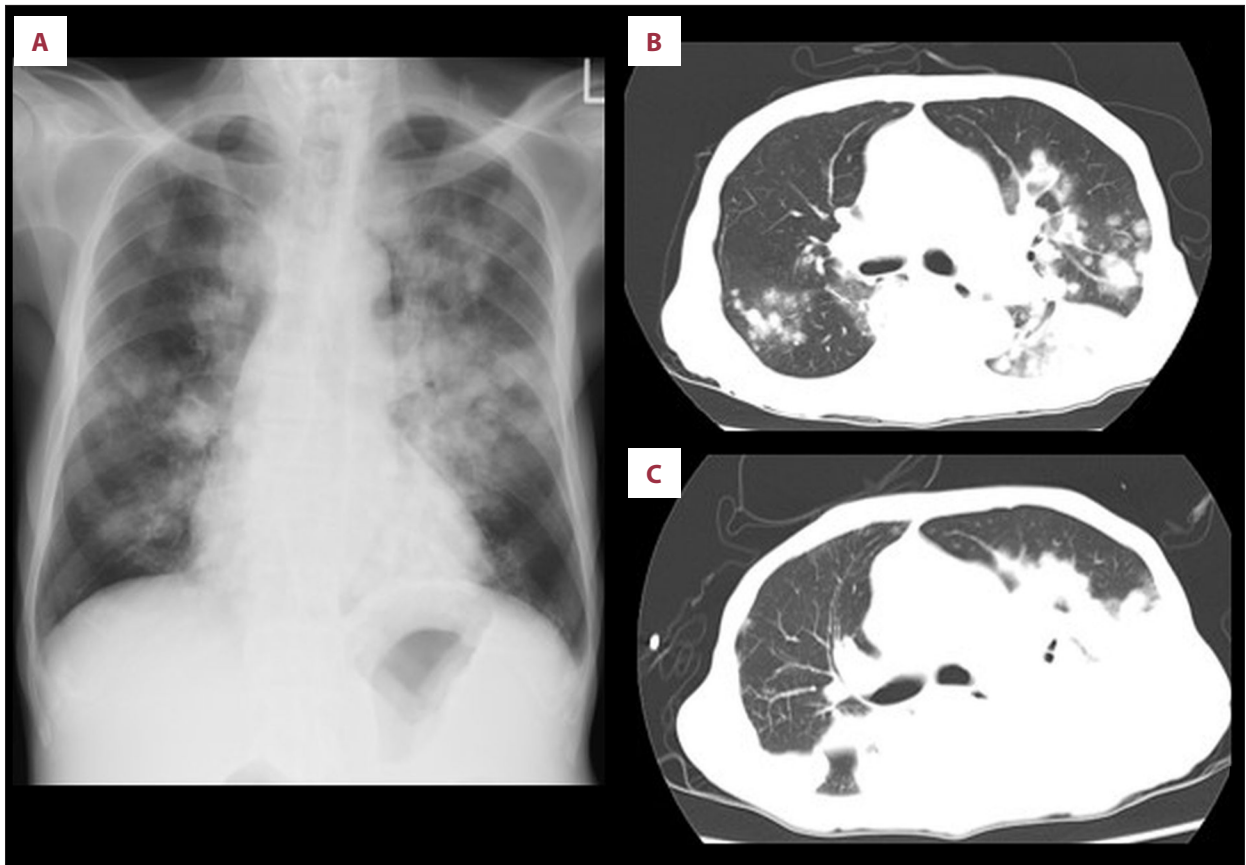
Figure 1. (**A**) Chest X-ray on admission. (**B**) Computed tomography on admission showed multiple nodules of variable sizes and consolidations with ground-glass attenuation in both lung fields. (**C**) A follow-up chest computed tomography on the 70th hospitalization day indicated remarkable progression of the lung lesions.

was 36.6°C. There was no palpable lymphadenopathy. The red blood cell count revealed anemia, although the white blood cells and platelet counts were within the normal ranges (**Table 1**). Blood biochemistry was almost normal, except for an elevated lactate dehydrogenase level, slightly elevated brain natriuretic peptide level, and mildly elevated soluble interleukin-2 receptor (sIL-2R) level. Chest radiography and computed tomography (CT) on admission revealed multiple nodules of variable sizes, and consolidations with ground-glass attenuation in both lung fields (**Figure 1A, 1B**). A bronchoscopy was planned to determine the cause of acute respiratory failure; however, we could not perform it, as the patient declined intubation. None of our therapeutic interventions (including antibiotics, steroids, and non-invasive positive pressure ventilation) were effective. His sIL-2R levels increased to 3239 IU/mL and a follow-up chest CT on the 70th day of hospitalization showed remarkable progression of the pulmonary lesions along with enlarged mediastinal and axillary lymph nodes (**Figure 1C**). An examination of the biopsy specimens obtained from the axillary lymph nodes revealed large lymphoid cells that were positive for CD20, CD79a, BCL-6, and MUM1 and negative for CD10, on immunohistochemical staining. He was diagnosed with diffuse large B-cell lymphoma (DLBCL).

Given his poor condition (performance status 4), chemotherapy was not initiated, and he died on the 89th day of hospitalization.

With the consent of his family, a pathological autopsy was performed, and this revealed the destruction of alveolar structures with neoplastic space-occupying lesions in both lungs (**Figure 2A, 2B**). Immunohistochemical staining of the specimen taken from the lung tumor confirmed the histological diagnosis of DLBCL, which was compatible with the findings from the lymph node biopsy specimen. A fibrous thickening of the intimal layer of the pulmonary arteries was seen (**Figure 3A, 3B**) in the lung tissue specimens. Plexiform lesions, which are advanced changes in the pulmonary artery and typically occur in cases of pulmonary arterial hypertension, were not detected. Some pulmonary arteries were obstructed by organized thrombi with many perforations, indicating that recanalization had commenced after pulmonary thrombosis (**Figure 3C**). Megakaryocytes were found in the lung tissue specimens, which was suggestive of extramedullary hematopoiesis (**Figure 3D**). Pulmonary veno-occlusive disease was not detected. Genetic analysis revealed that the bone marrow was positive for a *JAK2* mutation. The genetic analysis was approved by the Ethics
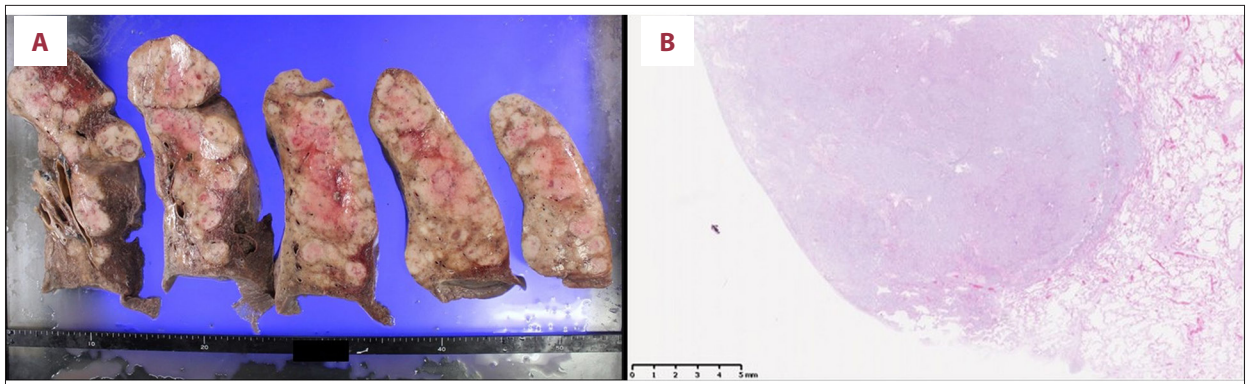
Figure 2. Pathological autopsy: Images of the lung specimen showed destroyed alveolar structures with neoplastic space-occupying lesions in both lungs: (**A**) Macroscopic images. (**B**) Microscopic images (scale bar 5 mm).
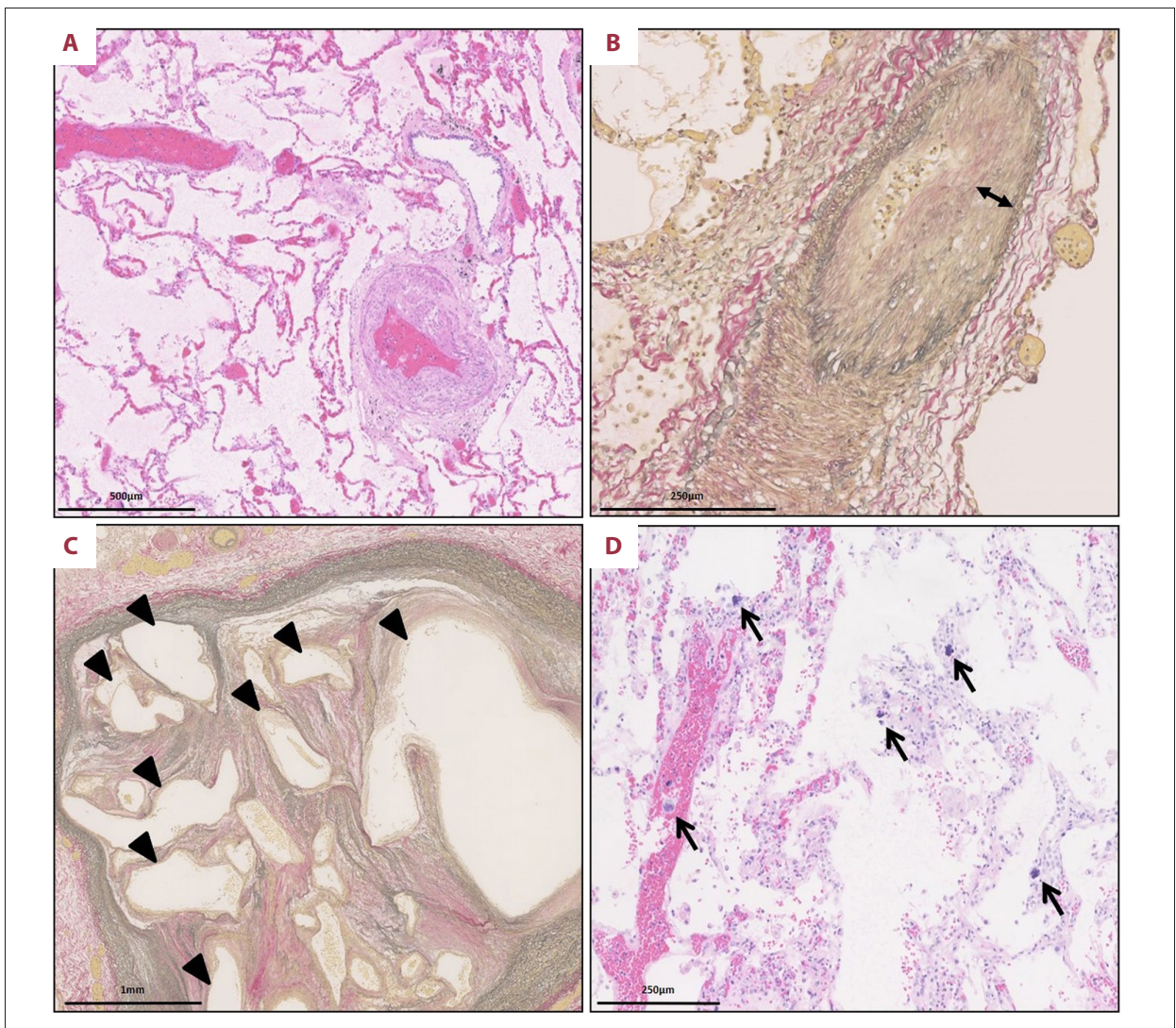

Figure 3. Microscopic findings in the pulmonary arteries: (**A**) Thickened walls of the pulmonary artery (hematoxylin-eosin stain) (scale bar 500 μm). (**B**) Elastica van Gieson staining showed intimal fibrosis (thin arrow) (scale bar 250 μm). (**C**) Elastica van Gieson staining showed thrombotic obstruction with recanalization (arrowheads) of the pulmonary arteries (scale bar 1 mm). (**D**) Megakaryocytes (thick arrows) seen in the lung tissue specimen (hematoxylin-eosin) (scale bar 250 μm).

Committee of Osaka University Hospital. It conformed to the Ethical Guidelines of Medical and Health Research involving human subjects in Japan and all the principles outlined in the Declaration of Helsinki. We obtained informed consent from the patient's family.

Discussion

We present the case of a patient with MPN-associated PH that developed into severe refractory respiratory failure. Although multifactorial PH was suspected to contribute to the patient's chronic dyspnea, aggressive NHL was finally diagnosed as the cause of fatal respiratory failure. Although PH and NHL are entirely different disease entities, we speculate that the *JAK2* mutations could have been involved in the onset and/or progression of these diseases during the course of the PV.

In patients with MPNs, PH is an important complication that is associated with poor prognosis [4]. According to the current PH guidelines, PH associated with MPNs is classified as PH with unclear multifactorial mechanisms (Group 5) [5]. Various mechanisms for MPN-associated PH have been proposed, including thromboembolism, portopulmonary hypertension, high cardiac output, and the obstruction of pulmonary microvasculature by circulating megakaryocytes. Megakaryocytes that translocate from the bone marrow to the lungs can secrete vasoactive cytokines that could lead to the development of PH [10]. The pathological evaluation of our case showed intimal thickening in the pulmonary arteries accompanied by megakaryocyte infiltration and obstructed pulmonary arteries with organized thrombi, which were compatible with the previously reported multifactorial features of PH associated with MPNs. In addition, *JAK2* mutations were detected in this case. STAT activation through hyperphosphorylation has been implicated in the pathogenesis of pulmonary arterial hypertension, as it promotes hyperproliferation of the vascular endothelial cells and angiogenesis [11]. Although a conflicting case has been reported [12], there are some case reports that have demonstrated that JAK inhibition with ruxolitinib improved MPN-associated PH [7,13]. Tabarroki et al reported that ruxolitinib therapy for patients with myelofibrosis improved PH. They demonstrated that ruxolitinib contributed to an increase in plasma-NO levels, and a reduction in the inflammatory cytokines (IL-4, IL-6, IL-8, TNF-α) and the granulocyte macrophage colony-stimulating factor, suggesting that aberrant JAK-STAT signaling can mediate PH through the dysregulation of NO and cytokine levels [7].

In contrast, patients with MPNs have an increased risk of developing a second hematologic malignancy compared to the general population [9]. Although the subsequent hematologic neoplasms were mainly myeloid leukemia, the coexistence of MPNs with a lymphocytic proliferative neoplasm (LPN) has been reported [8,9,14]. The most common combination was MPNs and chronic lymphocytic leukemia; however, the coexistence of MPNs and NHL is rare [14]. A limited number of case reports describe the association between MPNs and NHL [8,15]. Popov et al reported a case of PV with a *JAK2* mutation that was simultaneously diagnosed with DLBCL. They summarized 25 previously reported cases of PV and NHL and found that PV diagnosed at the onset with the subsequent development of B-cell lymphoma was the most representative in their case series [16]. The clinical features of our case are consistent with their findings. There are no reports that describe the coexistence of PH and NHL in patients with MPNs. To the best of our knowledge, this is the first case report where 2 distinct complications (PH and NHL) developed sequentially during the course of PV with a *JAK2* mutation. The coexistence of these complications is seldom seen, possibly because each of these complications is rare and develops at different times during the long course of MPNs.

Aberrant JAK-STAT signaling contributes to the pathogenesis of MPNs and can be involved in the development of lymphomas through the dysregulation of proliferation, differentiation, and apoptosis of hematopoietic cells [17]. The risk of developing LPN was significantly increased in patients with MPNs who had *JAK2* mutations [8]. A high rate of *JAK2* mutations has been reported in patients with MPNs who subsequently developed LPN [18]. Based on previous reports, we assume that the JAK-STAT pathway could have played a critical role in the development and/or progression of NHL and PH in our patient.

Conclusions

We present a rare case of PV with coexisting PH and NHL. JAK inhibitors play an important role in the treatment of MPNs; however, their efficacy in the treatment of PH and NHL associated with MPNs has not been established. Therefore, further studies are required to elucidate the involvement of *JAK2* mutations in the pathogenesis of PH and NHL in patients with MPNs.

Department and Institution Where Work Was Done

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Conflicts of Interest

None declared.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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