CASE REPORT

Pulmonary Hypertension Associated with Pulmonary Veno-occlusive Disease in Patients with Polycythemia Vera

Takayoshi Tachibana, Naoki Nakayama, Ayako Matsumura, Yuki Nakajima, Hiroyuki Takahashi, Takuya Miyazaki and Hideaki Nakajima

Abstract:
A 65-year-old man was diagnosed with polycythemia vera (PV) and treated with hydroxyurea. Three years later, he was admitted to our institution for severe hypoxia. Right heart catheterization revealed that the patient had pulmonary hypertension (PH). In addition, radiographic findings and resistance to pulmonary vasodilators led to the diagnosis of PH associated with pulmonary veno-occlusive disease. The administration of ruxolitinib improved his hematopoiesis and respiratory failure. While the disease is relatively common in Europe and the United States, limited data exist regarding myeloproliferative neoplasm complicated with PH in Japan. PH should be considered a potential complication and screened during the clinical care of patients with myeloproliferative neoplasms.

Key words: pulmonary hypertension, pulmonary veno-occlusive disease, polycythemia vera, ruxolitinib

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Introduction
Pulmonary hypertension (PH) is an intractable disease with various factors that can lead to persistently elevated pulmonary artery pressure. Although PH is associated with several hematological diseases, it is predominantly managed in the Department of Cardiology, and hematologists have limited opportunities to examine patients with the condition.

We herein report the case of a patient with polycythemia vera (PV) who developed PH associated with pulmonary veno-occlusive disease (PH-PVOD). In Japan, reports of patients with a myeloproliferative neoplasm (MPN) complicated by PH are rare, although they are relatively common in Europe and the United States. Hematologists should understand how to detect PH in patients with hematological diseases and report cases of patients with MPN complicated by PH.

Case Report
In 2011, a 65-year-old-man developed cerebral infarction and was diagnosed with polycythemia. His medical history was unremarkable except for cholangitis. The peripheral blood laboratory values showed a white blood cell count of 17.5×10^3/μL, a red cell count of 686×10^4/μL, hemoglobin concentration of 19.8 g/dL, hematocrit of 57.6%, mean corpuscular volume of 84.0 fl, platelet count of 61.8×10^4/μL, and lactate dehydrogenase of 401 IU/L. Neither the liver nor spleen were palpable. A Janus kinase 2 (JAK2/V617F) mutation was identified, and he was diagnosed with PV. Hydroxyurea at a dose of 1,000 mg/day was administrated. However, both the white cell and platelet counts were slowly increased, while the hemoglobin was decreased due to intestinal hemorrhaging. From the summer of 2014, he presented with dyspnea on effort and, in December, was admitted to the Department of Cardiology. The diagnosis was acute heart failure, but the patient’s condition did not improve despite furosemide administration. From the summer of 2015, he was referred to our hospital and admitted to the Department of Cardiology.

Severe hypoxia was found, with pulse oximetry results of 88% during a physical examination, and a high volume of oxygen was administered. In this condition, the partial pres-
phosphodiesterase type 5 inhibitor, intravenous epoprostenol (prostacyclin), and furosemide, were used. However, these pulmonary vasodilators induced pulmonary edema. The patient’s hypoxia worsened, and he became dependent on hyperoxygenation by heated humidified high-flow therapy in the intensive- or coronary-care unit. Characteristic CT findings and the clinical course including the resistance to pulmonary vasodilators led to the clinical diagnosis of PH-PVOD (5, 6). A lung biopsy was too invasive to perform because of severe respiratory failure.

For the refractory PV, ruxolitinib was administered at 5 mg twice a day. With the suppression of hematopoiesis, the respiratory and heart failure were slowly improved. His pulmonary pressure decreased from 34 to 27 mmHg, suggesting the effectiveness of ruxolitinib treatment. After long-term systemic and intensive rehabilitation, including the restoration of his respiratory, motor, and swallowing function, the patient was successfully discharged with home oxygen therapy. Although both PV and PH-PVOD were controlled without exacerbation with ruxolitinib, he died suddenly of an unknown cause 10 months after the PH-PVOD diagnosis.

Discussion

We herein report a case of PV complicated by PH-PVOD. PH is an intractable disease where elevation of pulmonary artery pressure occurs because of various factors. Disease progression can be complicated by right heart or respiratory failure, and the prognosis is unfavorable. Although hematologists are aware of this rare complication in paroxysmal nocturnal hemoglobinuria or sickle cell disease, we have limited opportunities to study its details (7, 8). Therefore, we should be aware of the characteristics of PH, including its manifestation and screening methods, and bear it in mind as a differential diagnosis.

In this report, we address PV and PH-PVOD from a hematologist’s point of view. PH is a condition of high blood pressure in the arteries of the lungs. Pulmonary blood pressure is separate from the systemic blood pressure and controls the pressure of the blood flow in the lungs. Pulmonary blood pressure is lower than systemic blood pressure, and normal pulmonary-artery pressure is approximately 14 mmHg at rest. If the pressure in the pulmonary artery is >25 mmHg, it is considered abnormally high and called PH (2-4). PVOD represents a rare form of PH and is characterized by the preferential involvement of the pulmonary venous system (5, 6). The pathological hallmark of the condition is the obliteration of small pulmonary veins by fibrous intimal thickening and patchy capillary proliferation (9). Therefore, PVOD is a distinct entity from idiopathic pulmonary arterial hypertension (PAH). Indeed, patients with PVOD typically demonstrate a poor response to PAH therapy, and such treatment may lead to life-threatening pulmonary edema (10).

Clinically, PH is divided into 5 broad categories accord-
United States and occurs in 5% to 48% of patients with revision of this ambiguous category in the future.

Some of the conditions in Group 5 may derive from PH-PVOD, and new evidence or knowledge may result in the revision of this ambiguous category in the future.

PH due to blood disease is categorized in Group 5, which is defined as PH-PVOD including MPN, according to previous reports (Table 2) (13-18). However, this condition is relatively rare in Japan. No comments on PH have been documented according to a large cohort study in Japan, although several case reports have been published in domestic journals (19-24). A lack of information including these clinical reports or communication with cardiologists may be one of the reasons for this situation. Furthermore, no useful predictive factors have yet been established. Careful medical care and further investigation are therefore important.

A PH diagnosis is established based on a mean pulmonary artery pressure ≥25 mmHg at rest (2-4), and right heart catheterization needs to be performed by a cardiologist. Us-

Figure 2. (A) Radiographic findings of chest X-ray. Chest X-ray showed cardiomegaly, the protrusion of the right second aortic arches, and ground-grass opacity, suggesting overburden of the right heart system. (B) Radiographic findings of chest computed tomography. Chest computed tomography indicated thickening of the interlobular septum, granular shadow, wall thickening of the bronchial branch, and ground-grass opacity, findings that were characteristic of pulmonary veno-occlusive disease. (C) Findings of cardio-ultrasonography. The dilation of the right ventricle (RV) and compression of the left ventricle (LV) wall suggested overburden of the right heart system.

Figure 3. The patient’s clinical course. FiO₂: fraction of inspiratory oxygen, HCU: high care unit, ICU: intensive care unit, CCU: coronary care unit, WBC: white blood cell, Ht: hematocrit, Plt: platelet count, PVD1: pulmonary vasodilator, including endothelin-receptor antagonist or phosphodies-terase type 5 inhibitor, PVD2 includes intravenous epoprostenol

Table 1

<table>
<thead>
<tr>
<th>PH subtypes</th>
<th>Definition</th>
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<tbody>
<tr>
<td>PH-PVOD</td>
<td>Pulmonary veno-occlusive disease</td>
</tr>
<tr>
<td>PH-PH</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>PH-MPN</td>
<td>Pulmonary hypertension associated with myeloproliferative disorders</td>
</tr>
<tr>
<td>PH-MPS</td>
<td>Pulmonary hypertension associated with myelodysplastic syndromes</td>
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Table 2

<table>
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<tr>
<th>Predictive factors</th>
<th>Values</th>
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<tbody>
<tr>
<td>Age</td>
<td>&gt;60</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Yes</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Figure 1

(A-B) Radiographic findings of chest X-ray. Chest X-ray showed cardiomegaly, the protrusion of the right second aortic arches, and ground-grass opacity, suggesting overburden of the right heart system. (B) Radiographic findings of chest computed tomography. Chest computed tomography indicated thickening of the interlobular septum, granular shadow, wall thickening of the bronchial branch, and ground-grass opacity, findings that were characteristic of pulmonary veno-occlusive disease. (C) Findings of cardio-ultrasonography. The dilation of the right ventricle (RV) and compression of the left ventricle (LV) wall suggested overburden of the right heart system.
ally leading to the development of PVOD. A histological ex-
veolar capillary diameter, has been observed in patients with
cells, which are poorly deformable and larger than the al-
cytes producing embolism in pulmonary vessels, may be as-
embolism, which consists of the translocation of megakaryo-
cies, and a normal caliber of pulmonary veins (25).

ings include interstitial edema, ground-glass opacity, inter-
glass opacities, septal lines on CT, and patients’ resistance
to pulmonary vasodilators, can also lead to a clinical diag-
nosis of PH-PVOD.

Table 1. Clinical Classification of Pulmonary Hypertension (NICE, 2013).

<table>
<thead>
<tr>
<th>1. Pulmonary arterial hypertension</th>
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<tbody>
<tr>
<td>1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis</td>
</tr>
<tr>
<td>1”. Persistent pulmonary hypertension of the newborn</td>
</tr>
<tr>
<td>2. Pulmonary hypertension owing to left heart disease</td>
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<tr>
<td>3. Pulmonary hypertension owing to lung disease and/or hypoxia</td>
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<tr>
<td>4. Chronic thromboembolic pulmonary hypertension</td>
</tr>
<tr>
<td>5. Pulmonary hypertension with unclear multifactorial mechanisms</td>
</tr>
</tbody>
</table>

Table 2. Epidemiology of PH Associated with MPN.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number</th>
<th>Diagnosis</th>
<th>Method for PH</th>
<th>Number of PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>[13]</td>
<td>30</td>
<td>18PV, 8ET, 4AMM</td>
<td>RVSP&gt;35 mmHg</td>
<td>4(13%)</td>
</tr>
<tr>
<td>[14]</td>
<td>24</td>
<td>14ET, 6AMM, 2PV, 2CML</td>
<td>RVSP&gt;35 mmHg</td>
<td>10(42%)</td>
</tr>
<tr>
<td>[15]</td>
<td>46</td>
<td>46ET</td>
<td>RVSP&gt;35 mmHg</td>
<td>22(48%)</td>
</tr>
<tr>
<td>[16]</td>
<td>25</td>
<td>14ET, 9PV, 2CML</td>
<td>RVSP&gt;35 mmHg</td>
<td>12(48%)</td>
</tr>
<tr>
<td>[17]</td>
<td>36</td>
<td>22PMF, 7MF post PV, 7MF post ET</td>
<td>RVSP&gt;35 mmHg</td>
<td>13(36%)</td>
</tr>
<tr>
<td>[18]</td>
<td>103</td>
<td>32CML, 27ET, 15MF, 26PV, 3other</td>
<td>RVSP&gt;35 mmHg</td>
<td>5(5%)</td>
</tr>
</tbody>
</table>


PH can only be reliably confirmed by a lung biopsy, but video-assisted thoracic surgery or a transbronchial lung biopsy are too invasive to perform in patients with severe respiratory failure or hemorrhagic conditions. Recently, a clinical diagnosis combining characteristic radiographic findings or clinical events has gained acceptance among experts of PVOD (5). According to the PVOD criteria specified by the Ministry of Health, Labor and Welfare in Japan, characteristic radiologic manifestations, such as centrilobular ground-glass opacities, septal lines on CT, and patients’ resistance to pulmonary vasodilators, can also lead to a clinical diagnosis of PH-PVOD.

In the present case, the patient developed acute respiratory failure and exacerbation of right heart failure due to PH after he was admitted. Indeed, the use of several pulmonary vasodilators had no effect on the patient’s condition, but his pulmonary artery pressure and peripheral blood count decreased. His hypoxia and heart failure stabilized after ruxolitinib was administered. Although splenomegaly and radiographic findings showed little improvement, the decrease in the PAH might have helped improve the patient’s acute respiratory and heart failure. The clinical course of this patient therefore suggests that ruxolitinib may be effective for the treatment of patients with PV complicated by PH. Tabaroki et al. described 15 patients with myelofibrosis and PH treated with ruxolitinib and noted that 66% experienced improvement in their pulmonary artery pressure and right ventricle function as measured by echocardiography (32). Ruxolitinib also reduced the plasma levels of N-terminal pro-brain natriuretic peptide, von Willebrand antigen, ristocetin-cofactor activity, and uric acid and increased the
nitric oxide levels.

Another concern is the onset of PH-PVOD. In the present case, the diagnosis was made at the progressive stage of PV. However, the clinical course of PH could not be clarified because the patient was transferred. The accumulation of further cases and careful care for patients with MPN following their diagnosis may be important in the future.

In the course of hospital care, several difficulties were encountered after the respiratory and heart failure were improved. The patient had a history of cerebral infarction complicated by bilateral hemiplegia and respiratory muscle paralysis. Therefore, systemic and long-term rehabilitation was required for the recovery of activities of daily living. At discharge, a variety of medical staff, including cardiologists, hematologists, physiatrists, home physicians, nurses, pharmacists, social workers, and the patient’s wife, attended a conference and discussed the patient’s medical and daily living problems. In patients with MPN related to PH, a systemic medical condition should be screened, and medical or social support should be considered.

In conclusion, in the clinical care in MPN, the complication of PH should be screened using a non-invasive and simple examination, such as echocardiography; furthermore, cardiologists should be consulted if PH is suspected. Many details of PH in patients with MPN are still unknown—particularly in Japan—so it is important to spread information, accumulate cases, and perform a comprehensive survey, including assessments of the incidence, pathophysiology, treatment, prognosis, and risk factors.

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

References


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