Resolution of myelofibrosis-associated pulmonary arterial hypertension following allogeneic hematopoietic stem cell transplantation

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Abstract: We present the case of a 62-year-old man with myelofibrosis-associated pulmonary arterial hypertension (PAH) who underwent allogeneic hematopoietic stem cell transplantation with subsequent resolution of disease and PAH. Right heart catheterization was used to guide PAH therapy before and after transplantation. Drug interactions, adverse effects, and renal insufficiency posed clinical challenges for the management of PAH-specific medications after transplantation. PAH improved soon after transplantation, and vasoactive medications were tapered off. Resolution of PAH was confirmed with repeat measurement of pulmonary hemodynamic characteristics. Although the etiology and pathophysiology for the resolution of PAH was unclear, the myelopulmonary pathophysiologic link was likely to have contributed. This is the first report describing resolution of myelofibrosis-associated PAH after allogeneic hematopoietic stem cell transplantation.

Keywords: pulmonary arterial hypertension, hematopoietic stem cell transplantation, myeloproliferative disease, myelofibrosis, cancer, pulmonary vascular disease.

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Pulmonary hypertension (PH) has been described in myeloproliferative disease (MPD). Many of these reports and series were based on echocardiographic data, as opposed to right heart catheterization (RHC), so secondary causes such as left ventricular dysfunction or a high-output state were not excluded. Pulmonary arterial hypertension (PAH) is defined hemodynamically with an RHC with the following characteristics: mean pulmonary artery pressure (mPAP) ≥25 mmHg at rest; pulmonary vascular resistance (PVR) >3 Wood units, and pulmonary capillary wedge pressure ≤15 mmHg.[1] In a small series of 10 patients, Guilpain and colleagues described two forms of PH in MPD based on RHC data: PAH and chronic thromboembolic pulmonary hypertension (CTEPH).[2] Although several potential therapies for MPD-associated PH—including cytoreductive therapy; hematological control of underlying disease; whole-lung, low-dose, external-beam radiotherapy; antithrombotic agents; and pulmonary-specific vasodilators—have been described, randomized trials are not available, and additional study is needed.[2-5]

Myelofibrosis (MF) is a type of MPD, and it is a rare disease characterized by bone marrow fibrosis, ineffective and extramedullary hematopoiesis, splenomegaly, and, rarely, PH. Ultimately, allogeneic hematopoietic stem cell transplantation (HSCT) is the only potentially curative therapy for MF, but it is associated with a significant risk of post-transplant morbidity and mortality.[6-8] The impact of PAH on the risk for HSCT or in the posttransplantation course is not well known. We describe a patient with MF-associated PAH who successfully underwent HSCT with subsequent resolution of PAH.

CASE DESCRIPTION

A 62-year-old man developed MF after a 19-year history remarkable for essential thrombocytosis. Following the diagnosis of MF, he developed splenomegaly requiring radiation to the spleen (25 Gy) and subsequently was found to have PAH 9 months after the diagnosis of MF (Table 1). Given his clinical symptomology, he was given a regimen of vasoactive medications (tadalfil, bosentan) for the treatment of his PAH. Despite multiple chemotherapies, including ruxolitinib, his MF progressed, and he became transfusion dependent. Aside from fatigue, he remained clinically asymptomatic and was referred for curative-intent HSCT. Physical examination findings were remarkable only for a firm nodular spleen palpable at 23 cm and hepatomegaly at 15 cm below the costal margin. Serological testing for collagen vascular disease, HIV infection, and hepatitis had negative results. Pulmonary function tests results and echocardiogram findings were normal. RHC confirmed PAH (Table 1).

The patient underwent matched unrelated-donor HSCT with a conditioning regimen of busulfan and fludarabine. Two weeks after transplantation, the patient developed acute renal insufficiency due to acute tubular necrosis requiring hospitalization. He transiently required hemodialysis while hospitalized, and tadalafil therapy was dis-

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Table 1. Hemodynamic parameters based on right heart catheterization

Parameter	Feb 2013, diagnosis of PH	Sep 2014, before HCST	Feb 2015, after HCST
RAP, mmHg	17	22	6
mPAP (systolic/diastolic), mmHg	47 (72/29)	36 (52/19)	28 (45/16)
PCWP, mmHg	15	11	9
PVR, Wood units	3.96	3.39	1.94
CI	3.43	3.45	5.04
Vasoreactivity with NO	Negative	Negative	Not performed
BNP, pg/mL	NA	87	233
N-terminal proBNP, pg/mL	NA	874	1,921
Medication(s)	Furosemide 20 mg qd	Bosentan 125 mg bid, tadalafil 40 mg qd, furosemide 40 mg qd	Furosemide 20 mg qd
Hemoglobin level, g/dL	9.2	9.2	9.9
Platelet count, K/uL	969	467	36
Creatinine level, mg/dL	1.4	1.33	1.34

Note: bid: twice daily; BNP: brain natriuretic peptide; CI: cardiac index, calculated as liters per minute per square meters; HCST: hematopoietic stem cell transplantation; mPAP: mean pulmonary artery pressure; NA: not available; NO: nitric oxide; PCWP: pulmonary capillary wedge pressure; PH: pulmonary hypertension; PVR: pulmonary vascular resistance; qd: once daily; RAP: right atrial pressure.

continued because of renal insufficiency. A baseline echocardiogram obtained before HSCT revealed normal left ventricular ejection fraction, but the right ventricle was dilated with right ventricular fractional area change (RVFAC) of 35% and an estimated right ventricular systolic pressure (RVSP) of 49 mmHg. Repeat RHC revealed volume overload with a decrease in PVR (Table 1). The patient's renal function slowly improved with treatment, but he continued to receive diuretics for volume overload. He also developed skin graft-versus-host disease (GVHD) that required modification of his immunosuppressive regimen. The bosentan was discontinued due to risk of interactions with tacrolimus given the improved hemodynamic characteristics. Repeat RHC 14 weeks after transplantation demonstrated markedly improved hemodynamic parameters (Table 1). Since the mPAP was elevated, a follow-up echocardiogram was obtained, and it showed a preserved left ventricular systolic function, an RVFAC of 48%, reverse remodeling of right ventricular dimensions, and an estimated RVSP of 33 mmHg. The patient's posttransplantation course was complicated by chronic refractory skin GVHD requiring photophoresis, but he remained stable from the PAH standpoint until his death 10 months later, presumably due to infection.

DISCUSSION

Resolution of PAH after treatment of the underlying inciting disorder is rare, but our case suggests PAH associated with MF may be potentially reversible. MF is characterized by stem cell–derived clonal myeloproliferation with somatic mutations involving, most notably, *JAK2*, and patients are typically *BCR-ABL 1* negative.[9] Some newer agents, including ruxolitinib, a *JAK-1* and *JAK-2* inhibitor, have shown promise in the treatment of MF, but there have been reports of both improvement and exacerbation of PH with such agents.[10,11] In those with disease refractory to chemotherapy, allogeneic HSCT currently provides the best therapeutic option for MF, but there are risks associated with this intervention.[6-8] Patient selection, timing of transplantation, and appropriate modification of risk factors remain major challenges.[12] PAH may be an added risk factor for HSCT because of the expected intravascular volume shifts associated with transplantation and the risk of medication interactions. In patients whose PAH can be optimized with medical therapy, our standard approach is to proceed with HSCT with multidisciplinary involvement. Close collaboration and coordination of care among pulmonology, cardiology, leukemia, and the HSCT services is standard for these complex cases. We typically obtain an echocardiogram and RHC before the transplantation followed by meticulous monitoring of volume status, blood pressure, and renal function before, during, and after the transplantation.

The etiology and pathophysiology of MPD-associated PAH has not been clearly elucidated. Indolent myeloid abnormalities, such as polyclonal myelofibrosis, have been reported in the bone marrow of patients with PAH.[13] In murine models, hematopoietic myeloid progenitors from patients with PAH have resulted in endothelial injury, vascular remodeling, and PAH.[14,15] Thus a myelopulmonary pathophysiologic link likely plays a role in the development of PAH in these patients.[14] Interestingly, descriptions of regression of bone marrow fibrosis after HCST in MF also suggest a complex interrelated milieu.[16] Other possible etiologic mechanisms of MPD-associated PAH may include portal hypertension, chemotherapeutic agents, tumor microembolism, extramedullary hematopoiesis, pulmonary cap-

illary obstruction with abnormal platelets or cells, acute thrombotic events, hematopoietic progenitor cell invasion of the pulmonary artery intima, and parenchymal lung disease, such as pneumonitis or fibrosis.[3,4] Interestingly, there are reports of tacrolimus, a calcineurin inhibitor, reversing dysfunctional bone morphogenetic protein receptor-2 (BMPR2) signaling and thus preventing the development of PAH in rats, so the various medications and chemotherapeutic agents may also influence the development and severity of PAH.[17] In our case, PAH was felt to be related to the underlying malignancy, although a component of portopulmonary hypertension could not be completely excluded given the patient's hepatosplenomegaly. Unfortunately, his BMPR2 status was unknown, so it is unclear whether tacrolimus may have contributed in the resolution of his PAH.

Management during the peritransplantation period can pose several challenges. In instances where volume status is unclear and right ventricular dysfunction is suspected, repeat RHC may be required to obtain the hemodynamic information needed to alter vasoactive therapy. For example, in this patient, tadalafil clearance was impaired with renal dysfunction, and it was safely discontinued after obtaining RHC data (Table 1). Similarly, drug interactions between vasoactive agents with antimicrobial therapies and/or immunosuppressive agents may require alteration of therapeutic agents or dosages. Our patient developed posttransplantation GVHD, and the known interactions between tacrolimus and bosentan made management difficult. Other common issues, such as elevated liver function test results, could be due to medication effects or GVHD, so vigilance for medication interactions and adverse effects is essential during and after HSCT. Development of PH has also been reported after HSCT due to thrombotic microangiopathy and pulmonary venoocclusive disease, so if PH worsens following HSCT, evaluation for these alternative diagnoses with CT angiogram and/or RHC should be considered.[18]

In summary, we describe the complete resolution of PAH after HSCT in a patient with MF-associated PAH. While rare, PAH may occur in MPD, and a high index of suspicion is required to promptly establish the diagnosis and institute appropriate treatment. Investigations that include RHC are required to confirm the diagnosis of PAH and exclude other potential etiologies, particularly CTEPH. HSCT may be curative for the underlying MF, and the presence of medically optimized PAH should not preclude clinically indicated HSCT. Close monitoring of hemodynamic status is essential in the peritransplant period, and management of PAH-specific vasoactive medications after transplantation may be challenging due to drug interactions, volume shifts, and renal insufficiency. Baseline and repeat echocardiograms allow serial assessments of right ventricular function and pulmonary pressures that can guide management. If clinically indicated, RHC may be repeated. When performed as a curative option for MF, HSCT may also simultaneously provide a cure for MF-associated PAH.

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