Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9811-22
Intern Med 62: 275-279, 2023
http://internmed.jp

【 CASE REPORT 】

Pulmonary Veno-occlusive Disease that Developed Following Hematopoietic Stem Cell Transplantation for Acute Myeloid Leukemia

Kenichiro Takeda[1], Akira Naito[1], Toshihiko Sugiura[1], Masaki Ishige[1], Kohei Shikano[1], Mitsuhiro Abe[1], Hajime Kasai[1], Shota Miyakuni[2], Shu Yamashita[2], Ayako Shigeta[1], Seiichiro Sakao[1] and Takuji Suzuki[1]

Abstract:

We herein report a case of pulmonary veno-occlusive disease (PVOD) induced by allo-hematopoietic stem cell transplantation (HSCT) in a 48-year-old man who was diagnosed with acute myeloid leukemia. Five months after transplantation, he developed dyspnea and was diagnosed with pulmonary hypertension based on right heart catheterization. Although he received treatment with pulmonary vasodilators, diuretics, and corticosteroids, his pulmonary artery pressure did not decrease, and his pulmonary edema worsened. Based on the clinical course, hypoxemia, diffusion impairment, and computed tomography findings, the patient was diagnosed with HSCT-related PVOD. Critical attention should be paid to dyspnea after HSCT for the early diagnosis of PVOD.

Key words: acute myeloid leukemia (AML), hematopoietic stem cell transplantation (HSCT), pulmonary veno-occlusive disease (PVOD)

(Intern Med 62: 275-279, 2023)
(DOI: 10.2169/internalmedicine.9811-22)

Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary hypertension (PH) that is characterized by venule-dominant remodeling of the pulmonary vasculature (1). The prognosis is poor, and lung or heart-lung transplantation is the only definitive therapy that may offer patients the potential for a long-term survival (1). Chemotherapy (2) and hematopoietic stem cell transplantation are known factors contributing to the onset of PVOD (3).

We herein report a patient with suspected PVOD who had undergone stem cell transplantation eight months before referral to our facility but died despite intravenous prostacyclin treatment.

Case Report

We encountered a case of PVOD in a 48-year-old man who had received allo-hematopoietic stem cell transplantation (HSCT) after being diagnosed with acute myeloid leukemia (AML) and treated with chemotherapy (including idarubicin, cytarabine, and gilteritinib, an FMS-like tyrosine kinase 3 inhibitor). Three months after the diagnosis, he underwent HSCT following a pretransplant conditioning regimen that included cyclophosphamide, cytarabine, and total-body irradiation. He then reported dyspnea five months post-transplantation, and laboratory tests and chest radiography revealed renal dysfunction and pleural effusion, respectively. Based on these findings, he was treated with corticosteroids, furosemide, tolvaptan, and eplerenone for graft-versus-host disease (GVHD) and heart failure for three

[1]Department of Respirology, Graduate School of Medicine, Chiba University, Japan and [2]Department of Cardiology, Kameda Medical Center, Japan
Received: March 20, 2022; Accepted: May 8, 2022; Advance Publication by J-STAGE: June 14, 2022
Correspondence to Dr. Kenichiro Takeda, Kenichiro.1990.0909@gmail.com

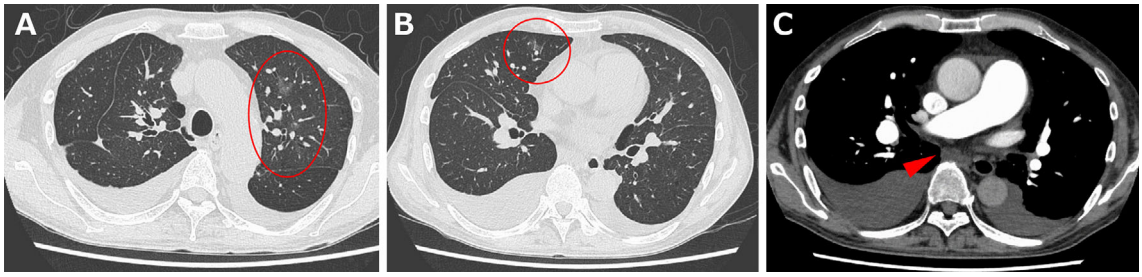

Figure 1. Chest computed tomography findings. A, B: Ground-glass opacities (round), lobar septal wall thickening, and bilateral pleural effusions are observed in the lung window. C: Mildly enlarged mediastinal lymph nodes (arrowhead) and dilated pulmonary arteries are observed in the mediastinal window.

months; however, the therapeutic effect was poor. Transthoracic echocardiography suggested pulmonary hypertension (PH) with a normal left ventricular function, and he was subsequently transferred to our hospital for a detailed PH examination and treatment.

On admission, his vitals were 36.5°C, 101/78 mmHg, 95 beats/min, and 21 breaths/min. His oxygen saturation level (SpO_2) was 98% on 4 L/min of oxygen via nasal cannula. A systolic murmur in the tricuspid valve area and lower leg edema were observed on a physical examination. An arterial blood gas analysis on room air showed his partial pressure of oxygen and carbon dioxide (PaO_2; $PaCO_2$) to be 46.9 and 33.3 mmHg, respectively, with a pH of 7.48. Laboratory investigations revealed mild anemia (hemoglobin level, 13.0 g/dL) and mild thrombocytopenia without any coagulation abnormalities, liver dysfunction, or kidney dysfunction. His brain natriuretic peptide was 1,124 pg/mL, and serological markers of connective tissue disease or human immunodeficiency virus antibodies were negative.

Pulmonary function tests revealed mild restrictive ventilatory impairment and severe diffusion impairment [vital capacity (VC) 3.1 L, 77.9% of predicted; forced expiratory volume in 1 second (FEV_1) 2.3 L, 64.7% of predicted; FEV_1% 73.6%; diffusing capacity for carbon monoxide (DL_{CO}) 4.33 mL/min/mmHg, 19.4% of predicted]. Electrocardiography revealed a high R wave in V1, suggesting a right heart burden. Furthermore, enhanced computed tomography (CT) of the chest revealed diffused ground-glass opacities, lobar septal wall thickening, bilateral pleural effusions, mildly enlarged mediastinal lymph nodes, and a dilated right heart and pulmonary artery (Fig. 1). Chest enhanced CT and lung perfusion scintigraphy excluded pulmonary emboli. Transthoracic echocardiography showed a dilated right ventricle and tricuspid regurgitant pressure gradient of 53 mmHg. In addition, echocardiography revealed no valvular disease, left myocardial dysfunction, or intracardiac shunt. Right heart catheterization revealed that the pulmonary artery pressure was 74/40 mmHg (mean 53 mmHg), pulmonary artery wedge pressure was 10 mmHg, cardiac index was 2.1 L/min/m^2, and pulmonary vascular resistance was 9.3 wood units.

Pulmonary vasodilator therapy was not immediately initiated because of the possibility of PVOD, and treatment with sufficient oxygen supplementation and diuretics was started. However, his circulatory status gradually worsened, and he was admitted to the intensive care unit on day 10. On the same day, he experienced cardiac arrest due to circulatory failure and was introduced to veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Intravenous epoprostenol (prostaglandin I_2) was started with 24-h monitoring of pulmonary artery pressure using a Swan-Ganz catheter, and the dosage was gradually increased to 20 ng/kg/min. Inhaled nitric oxide and systemic corticosteroids were also used due to the possibility of GVHD; however, the pulmonary artery pressure did not decrease, and the pulmonary edema worsened after treatment was started (Fig. 2). Drug-induced pulmonary artery hypertension (PAH) was also suspected, and despite the anti-tumor drugs for AML being discontinued, no marked changes were observed in the pulmonary artery pressure or other clinical signs. Based on these findings, we diagnosed the patient with PVOD. Despite the intensive treatment described above, the patient died on day 23.

Discussion

PVOD was first reported in 1966 as a distinct disease that caused pulmonary hypertension with venous-dominant remodeling (4, 5). In the latest definition from the 6th World Symposium on Pulmonary Hypertension (WSPH), PVOD is classified in the category of "PAH with overt features of venous/capillary involvement" (6). As PAH and PVOD usually share a broadly similar hemodynamic profile and clinical presentation, it is difficult to differentiate between them based on physical findings (7); however, some studies have revealed distinct features of PVOD. Montani et al. reported that PVOD patients have lower partial pressures of arterial blood oxygen and DL_{CO} than those with PAH (8). Mineo et al. reported that the presence of at least two relevant findings on high-resolution CT (HRCT) - septal thickening, ground glass opacities, and enlarged lymph nodes - showed a sensitivity of 95.5% and a specificity of 89% for differentiating PVOD and PAH (9). Furthermore, Ogawa et al. reported that the following 9 clinical characteristics were important for clinically diagnosing PVOD: male sex, smoking

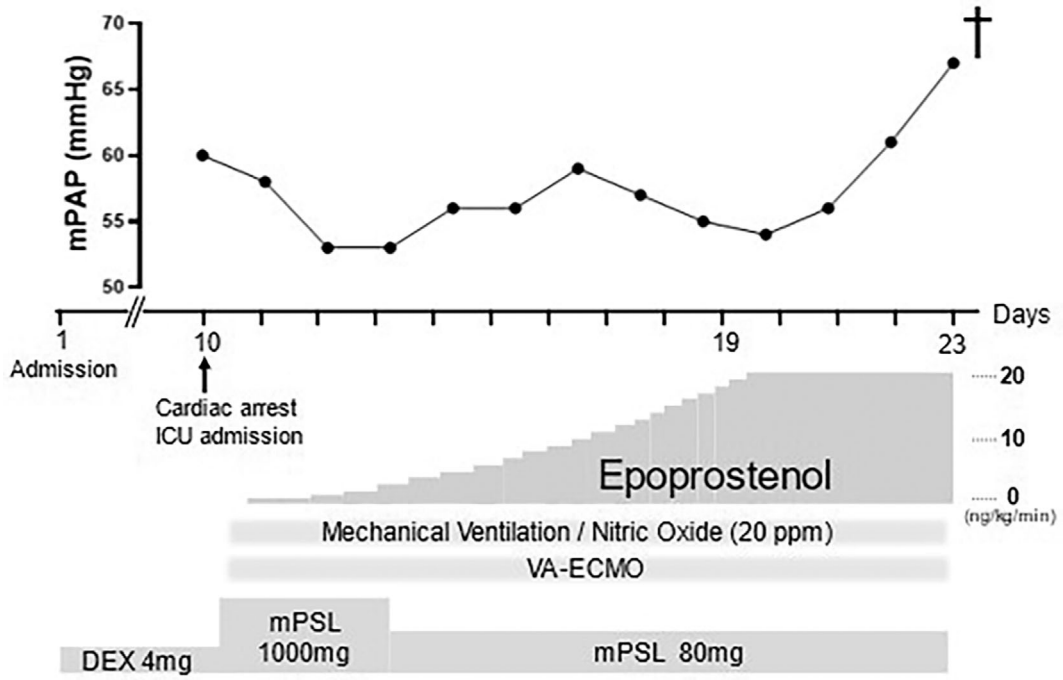

Figure 2. Trend in the mean pulmonary artery pressure after admission to the intensive care unit. DEX: dexamethasone, mPAP: mean pulmonary artery pressure, mPSL: methylprednisolone, VA-ECMO: venoarterial extracorporeal membrane oxygenation

history, 6-minute walk distance <285 m, minimum SpO_2 <92% during the 6-minute walk test, %DLco <34%, ground glass opacity and thickening of the interlobular septa on high-resolution CT, defects in the perfusion lung scan, and pulmonary edema due to vasodilators. In addition, the presence of any 5 of these factors showed 95% sensitivity and 98% specificity for predicting PVOD (10). The latest definition lists five features of PVOD: a decreased DL_{CO} and severe hypoxemia on pulmonary function testing; septal lines, centrilobular ground-glass opacities, and mediastinal lymph node enlargement on chest HRCT; a possible pulmonary edema response to PAH therapy; genetic predisposition; and occupational exposure to organic solvents (6). Our patient presented with severe hypoxemia and diffusion impairment, and his chest CT findings showed ground-glass opacities, lobar septal wall thickening, bilateral pleural effusions, and mildly enlarged mediastinal lymph nodes. Lung perfusion scintigraphy excluded pulmonary embolism, and echocardiography revealed no valvular disease, left myocardial dysfunction, or intracardiac shunt. In addition, pulmonary edema worsened with the use of pulmonary vasodilators. We did not evaluate his genetic mutations, such as EIF2AK4, and he did not have occupational exposure to organic solvents. However, his dyspnea rapidly developed five months after HSCT, and most of the features listed above were met; therefore, we diagnosed the patient with PVOD.

Eight reports (3, 11-17) of post-HSCT PVOD have been published since 2,000 (Table). The ages ranged from about 20-50 years old, with no notable trend in sex. The primary diseases were acute myelogenous leukemia (n=4), chronic myelogenous leukemia (n=1), multiple myeloma (n=1), and non-Hodgkin's lymphoma (n=2). All patients used alkylating agents, such as melphalan and cyclophosphamide. Furthermore, total-body irradiation was performed in five of the eight patients. The time from HSCT to the PVOD onset ranged from 0.4 to 10 months (median, 3 months). Right heart catheterization was performed in only four cases. Treatment for PVOD included steroids, pulmonary vasodilators (n=2), and anticoagulants (n=2). While the information available is limited, a high pulmonary artery pressure at the diagnosis indicates a poor prognosis.

Although the detailed mechanism underlying post-HSCT PVOD remains unclear, some studies have suggested that toxicity due to chemotherapeutic agents may play a role. Ranchoux et al. reported an association between alkylating agents and PVOD (2). Furthermore, transplant-associated chemotherapeutic regimens and radiation conditioning therapy are known to contribute to both vascular inflammation and endothelial cell activation. Pulmonary venular inflammation and increased capillary permeability may play an early role in PVOD, whereas pulmonary venular fibrosis and obstruction may represent later findings that manifest as pulmonary hypertension and right ventricular failure (3). Recently, Perros et al. reported that the intraperitoneal administration of mitomycin induced PVOD in rats (18), and Zhang et al. reported that mitomycin induced pulmonary vascular endothelial-to-mesenchymal transition (19). High-dose chemotherapeutic agents before HSCT can cause vascular endothelial damage, which may be a trigger for PVOD.

There is no current established treatment for PVOD. Pulmonary vasodilators, such as intravenous epoprostenol, are

Table. **Previous Reports on Post-HSCT PVOD Published since 2000.**

Ref.	Age	Sex	Primary disease	Pretransplant conditioning regimen	Duration from HSCT (Month)	MeanPAP (mmHg)	Treatment	Outcome
10	54	F	AML	Cyclophosphamide Busulfan, Fludarabine	10	21	Ambrisentan Defibrotide	Alive at 18 months
11	51	F	AML	Cyclophosphamide Fludarabine, ATG, TBI	2	29	Steroid Warfarin	Alive at 8 months
12	49	F	CML	Cyclophosphamide total body irradiation TBI	6	N/A	Steroid	Dead in a month
13	48	M	MM	Melphalan	0.4	25	None	N/A
3	21	F	AML	Cyclophosphamide Fludarabine, TBI	4.6	N/A	Prostacyclin Heparin	Alive at 33 months
14	21	M	AML	Fludarabine, Melphalan ATG, TBI	1.2	N/A	Steroid	Alive at 4 months
15	20	M	NHL	Melphalan, Thiotepa Fludarabine, ATG	3	N/A	None	Dead in a month
16	20	M	NHL	Cyclophosphamide Cytarabine. TBI	2.4	33	Steroid	Dead in 7.7 months
Our Case	48	M	AML	Cyclophosphamide Cytarabine, TBI	5	53	Epoprostenol Steroid	Dead in 3.7 months

AML: acute myelogenous leukemia, ATG: anti-thymocyte globulin, CML: chronic myelogenous leukemia, MM: multiple myeloma, N/A: not available, NHL: non-Hodgkin's lymphoma, TBI: total body irradiation

used according to the treatment algorithm of PAH, but they are known to exacerbate pulmonary edema. Although lung transplantation is thought to be the only definitive therapy for patients with PVOD (1), it is a rapidly progressive disease, and many patients do not have sufficient time to wait for a transplant. Corticosteroids are administered to target concomitant inflammatory diseases or components of interstitial pulmonary fibrosis associated with PVOD; however, their effectiveness for PVOD is unclear (3). In addition, there is a case report of defibrotide, the only approved drug for post-HSCT hepatic veno-occlusive disease, for post-HSCT PVOD (11), although there are no randomized controlled trials. In the present case, defibrotide was not administered because of the bleeding tendency caused by anticoagulation during ECMO. In addition, Ogawa et al. reported the potential effectiveness of imatinib for PVOD (20); however, its use has not yet been approved for the treatment of PVOD in Japan. Further studies are thus needed to develop a proper medical therapy strategy.

Conclusion

Post-HSCT PVOD is a rare, but rapidly progressive condition. Close attention should be paid to the development of dyspnea after HSCT for the early diagnosis, and more case reports are required to establish a treatment strategy.

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

References

1. Montani D, Lau EM, Dorfmuller P, et al. Pulmonary veno-occlusive disease. Eur Respir J **47**: 1518-1534, 2016.
2. Ranchoux B, Gunther S, Quarck R, et al. Chemotherapy-induced pulmonary hypertension: role of alkylating agents. Am J Pathol **185**: 356-371, 2015.
3. Bunte MC, Patnaik MM, Pritzker MR, Burns LJ. Pulmonary veno-occlusive disease following hematopoietic stem cell transplantation: a rare model of endothelial dysfunction. Bone Marrow Transplant **41**: 677-686, 2008.
4. Heath D, Segel N, Bishop J. Pulmonary veno-occlusive disease. Circulation **34**: 242-248, 1966.
5. Brown CH, Harrison CV. Pulmonary veno-occlusive disease. Lancet **2**: 61-65, 1966.
6. Simonneau G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J **53**: 1801913, 2019.
7. Mandel J, Mark EJ, Hales CA. Pulmonary veno-occlusive disease. Am J Respir Crit Care Med **162**: 1964-1973, 2000.
8. Montani D, Achouh L, Dorfmuller P, et al. Pulmonary veno-occlusive disease: clinical, functional, radiologic, and hemodynamic characteristics and outcome of 24 cases confirmed by histology. Medicine (Baltimore) **87**: 220-233, 2008.
9. Mineo G, Attina D, Mughetti M, et al. Pulmonary veno-occlusive disease: the role of CT. Radiol Med **119**: 667-673, 2014.
10. Ogawa A, Takahashi Y, Matsubara H. Clinical prediction score for identifying patients with pulmonary veno-occlusive disease/pulmonary capillary hemangiomatosis. J Cardiol **72**: 255-260, 2018.
11. Tissot N, Montani D, Seronde MF, Degano B, Soumagne T. Venoocclusive disease with both hepatic and pulmonary involvement. Chest **157**: e107-e109, 2020.
12. Gutman JA, Allen CT, Madtes DK, Schramm J, Delaney C. Pulmonary veno-occlusive disease following reduced-intensity cord blood transplantation. Bone Marrow Transplant **42**: 559-561, 2008.
13. Mukai M, Kondo M, Bohgaki T, Notoya A, Kohno M. Pulmonary veno-occlusive disease following allogeneic peripheral blood stem cell transplantation for chronic myeloid leukaemia. Br J Haematol **123**: 1, 2003.
14. Malhotra P, Varma S, Varma N, et al. Pulmonary veno-occlusive disease as a cause for reversible pulmonary hypertension in a patient with multiple myeloma undergoing peripheral blood stem cell transplantation. Am J Hematol **80**: 164-165, 2005.
15. Hosokawa K, Yamazaki H, Nishitsuji M, et al. Pulmonary veno-

occlusive disease following reduced-intensity allogeneic bone marrow transplantation for acute myeloid leukemia. Intern Med **51**: 195-198, 2012.

16. Zinter MS, Melton A, Sabnis AJ, et al. Pulmonary veno-occlusive disease in a pediatric hematopoietic stem cell transplant patient: a cautionary tale. Leuk Lymphoma **59**: 1494-1497, 2018.

17. Seguchi M, Hirabayashi N, Fujii Y, et al. Pulmonary hypertension associated with pulmonary occlusive vasculopathy after allogeneic bone marrow transplantation. Transplantation **69**: 177-179, 2000.

18. Perros F, Gunther S, Ranchoux B, et al. Mitomycin-induced pulmonary veno-occlusive disease: evidence from human disease and animal models. Circulation **132**: 834-847, 2015.

19. Zhang C, Lu W, Luo X, et al. Mitomycin C induces pulmonary vascular endothelial-to-mesenchymal transition and pulmonary veno-occlusive disease via Smad3-dependent pathway in rats. Br J Pharmacol **178**: 217-235, 2021.

20. Ogawa A, Miyaji K, Matsubara H. Efficacy and safety of long-term imatinib therapy for patients with pulmonary veno-occlusive disease and pulmonary capillary hemangiomatosis. Respir Med **131**: 215-219, 2017.