INTERNAL MEDICINE

□ CASE REPORT □

Pulmonary Veno-occlusive Disease Following Reduced-intensity Allogeneic Bone Marrow Transplantation for Acute Myeloid Leukemia

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Abstract

We report a case of pulmonary veno-occlusive disease (PVOD) following allogeneic bone marrow transplantation (BMT) for the treatment of acute myeloid leukemia (AML) from an HLA mismatched mother using a reduced-intensity conditioning (RIC) regimen including gemtuzumab ozogamicin. The patient was a 21-year-old male who complained of dyspnea with hypoxemia followed by loss of consciousness. The abnormalities in chest CT and echocardiography were compatible with a diagnosis of PVOD. Treatment with 1 mg/kg of oral prednisolone resolved dyspnea and hypoxemia within a few days, and chest CT abnormalities disappeared in a week. This report is the first to describe PVOD following RIC stem cell transplantation.

Key words: acute myeloid leukemia, gemtuzumab ozogamicin, pulmonary, veno-occlusive disease, reduced-intensity transplantation

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Introduction

Pulmonary veno-occlusive disease (PVOD) is characterized by postcapillary pulmonary venular obstruction leading to pulmonary vascular congestion, progressive dyspnea and right ventricular heart failure. It is classically described as a progressively fatal form of primary pulmonary artery hypertension (PAH) with a mortality rate of nearly 100% within 2 years after diagnosis. Many of the accepted treatment options for PVOD have been extrapolated from the treatment of PAH, such as vasodilators, corticosteroids, anticoagulants and thrombolytics. Overall, the current treatment options for PVOD are quite limited and generally not well defined (1). Recently, PVOD has been reported as an unusual complication of myeloablative allogeneic and autologous transplantation, suggesting that PVOD is a regimen-related toxicity (2, 3). While infection and autoimmune disorders are potential causes of PVOD (4), there is little evidence linking them to PVOD. Here, we report a case of PVOD following allogeneic bone marrow transplantation (BMT) from an HLA-A one-locus mismatched mother for the treatment of acute myeloid leukemia (AML) refractory to chemotherapy using a reduced-intensity conditioning (RIC) regimen.

Case Report

The patient was a 21-year-old man diagnosed with acute myeloid leukemia (AML M0) expressing CD7 and CD33 with complicated chromosomal abnormalities in early May 2009. After receiving induction chemotherapy consisting of idarubicin and cytosine arabinoside, *Trichosporon* fungemia developed on day 18. This complication was successfully treated with voriconazole and liposomal amphotericin B (L-AmB), despite prolonged severe neutropenia due to the failure of achieving hematologic remission. Bone marrow aspiration performed on day 32 showed 80% of cells to be leukemic. Re-induction chemotherapy consisting of daunorubicin and cytosine arabinoside failed to induce remission, although blood culture remained negative for *Trichosporon*

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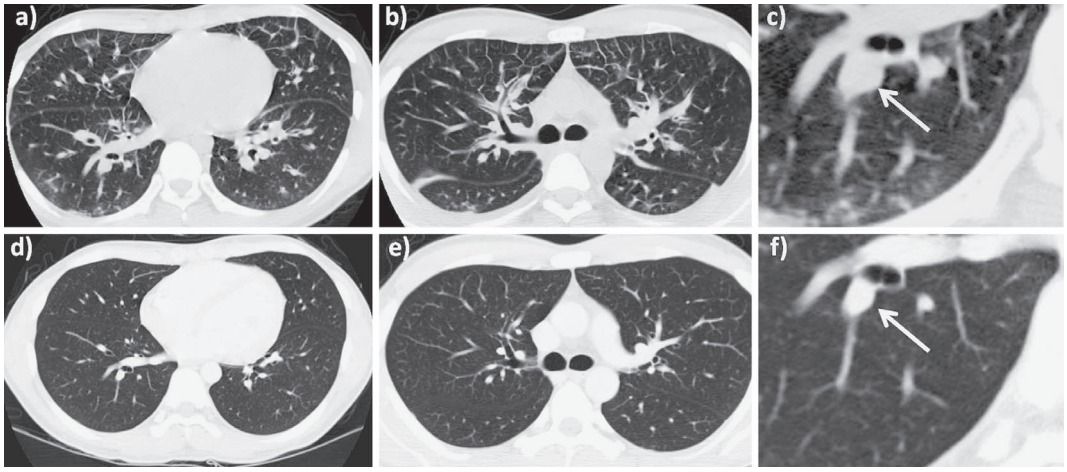

Figure 1. **Radiographic findings. a,b,c) Computed tomography at the onset of PVOD showing diffuse interlobular septal thickening, peribronchial cuffing, pulmonary arterial dilatation (arrow) with normal caliber of pulmonary veins, and ground-glass opacities with small bilateral pleural effusions. d,e,f) Computed tomography one week after treatment with oral prednisolone (1 mg/kg) under oxygen inhalation showing resolution of septal thickening, peribronchial cuffing, pulmonary arterial dilatation (arrow), ground-glass opacities, and pleural effusions.**

under voriconazole during re-induction therapy. Allogeneic stem cell transplantation (SCT) was considered to be the only curative measure for this patient due to the primary induction failure at this time point. His mother was selected as a donor because she was HLA-A one locus mismatched with the patient. Although the blood cultures remained negative for *Trichosporon*, the patient was considered intolerable to conventional myeloablative regimens because it is hard to completely cure *Trichosporon* fungemia even if voriconazole administration is continued (5-7). On the other hand, a recent prospective study suggested that GO in combination with fludarabine-based RIC regimens may be as effective as myeloablative regimens as a conditioning for patients with refractory AML (8, 9). We therefore chose the GO-combined regimen for our patient. Gemtuzumab ozogamicin (GO; 6 mg/m^2) was administered on day 24 of re-induction therapy (day -21 of BMT) and at 3 mg/m^2 on day -14 to reduce leukemic burden according to a previous study protocol (8). Peripheral leukemic cells disappeared after the GO treatment, but bone marrow aspiration performed on day -7 of BMT again showed 60% of the cells to be leukemic cells. Following a conditioning regimen consisting of fludalabine (25 mg/m^2, day -7 to day -3), melphalan (40 mg/m^2, day -3 to day -2), rabbit anti-thymocyte globulin (thymoglobulin, 0.5 mg/kg day-3, 1.25 mg/kg day-2 to day-1), and 4 Gy of total body irradiation (TBI) (day -2), 1.52×10^8 bone marrow cells/kg per patient weight from his mother was infused. Cyclosporine A and short term MTX were used for GVHD prophylaxis. Engraftment was documented on day 15 and complete donor type chimerism was confirmed on day 21.

On day 35, the patient suddenly complained of dyspnea and cough without chest pain. Five minutes later, he felt faint, but returned to consciousness within a few seconds. Systolic blood pressure was 142 mmHg, and arterial oxygen saturation measured by pulse oximetry was 86% in room air. Arterial blood gas analysis using 3 L/min of oxygen through a mask showed PaO_2 77.4 mmHg, $PaCO_2$ 44.5 mmHg, and pH 7.39. Laboratory data showed mild anemia and thrombocytopenia without any electrolyte or coagulation test abnormalities. Serologic markers of inflammation and fungal infection were negative. Chest radiographs showed no signs of pneumonia, heart failure, or pneumothorax. Electrocardiogram (ECG) at rest showed sinus tachycardia (105 beats per minute) without signs of myocardial ischemia. A chest computed tomography (CT) showed diffuse interlobular septal thickening, peribronchial cuffing, pulmonary arterial dilatation with normal caliber of pulmonary veins, ground-glass opacities, and small bilateral pleural effusions (Fig. 1a-c). Ventilation/perfusion scintigraphy showed no signs of thromboembolism. Echocardiography revealed an elevation of estimated right ventricular (RV) systolic pressure from 24 mmHg to 31 mmHg and normal-sized cardiac chambers with preserved function. These findings, in addition to sudden onset of dyspnea with hypoxemia followed by consciousness loss and typical abnormalities of chest CT and echocardiography, were consistent with PVOD.

The patient was treated with 1 mg/kg of oral prednisolone under oxygen inhalation. His dyspnea and hypoxemia were resolved within a few days and chest CT showed resolution of septal thickening, peribronchial cuffing, and pulmonary arterial dilatation in a week (Fig. 1d-f). Pulmonary function tests on the day following onset demonstrated a forced vital capacity (FVC) of 4.34 L (102% of predicted value), a forced expiratory volume (FEV1) of 3.38 L (84% of predicted value), and a corrected diffusing capacity of the lung for carbon monoxide (DLCO) of 11.8 mL/mmHg/min (36% of predicted value). Prednisolone was tapered orally by 10%

per week to 15 mg/day. Grade I acute GVHD (skin 1, gut 0, liver 0) developed on day 56 when he was on prednisolone (30 mg/day). The platelet count at the onset of PVOD was 85×10^9/L, and it gradually increased to 146×10^9/L a week after the onset of PVOD. Subsequently, the platelet count stayed at around 100×10^9/L later on. There were no apparent signs of DIC during the clinical course. Laboratory examination showed liver function abnormalities such as γ-GTP 183 IU/L soon after the use of GO and total bilirubin 1.2 mg/dL on day 15 of BMT. All these data gradually improved and normalized by day 30. There was no liver function abnormality at the onset of PVOD.

On day 164, echocardiography revealed normal right ventricular function and estimated RV systolic pressure to be 26 mmHg. FVC, FEV1, and DLCO improved to 4.53 L (107% of predicted value), 4.14 L (102% of predicted value), and 20.3 mL/mmHg/min (63% of predicted value), respectively. Repeated chest radiography and echocardiography did not reveal signs of PVOD later on. Diagnostic measures including lung biopsies and right heart catheterization were not attempted given these improvements. He eventually relapsed on day 140 and died 4 months after the third transplantation from his brother.

Discussion

Since Troussard's first report of PVOD occurring after hematopoietic stem cell transplantation (HSCT), this transplant-related complication has been anecdotally described in case reports (2, 3). Common features and risk factors of PVOD can be ascertained by reviewing reported cases (10). These reports show that the age and gender of those affected vary, although the majority of patients are younger than 25 years of age, a finding consistent with the present patient. PVOD typically occurs after several weeks to months following transplant, which is also consistent with the present case. Although somewhat nonspecific, dyspnea was a consistent early symptom in this population. The greatest risk factor for developing PVOD is endothelial injury from cytotoxic chemotherapy and irradiation. Pre-transplant conditioning regimens including cyclophosphamide (CY) and TBI/total lymphoid irradiation (TLI) have been used in many of the reported cases. CY is associated with several pulmonary complications, including interstitial pneumonitis or fibrosis and cryptogenic organizing pneumonia. In non-transplant patients, exposure to cytotoxic agents including CY has been reported as a risk factor for PVOD (11). TBI is associated with radiation-associated pneumonitis and is known to activate the vascular endothelium (12).

The pre-transplant conditioning regimens used in the present case did not include CY, and the total dose of TBI was only 4 Gy. However, GO administered to reduce the leukemic burden may have contributed to the development of PVOD. GO, a monoclonal antibody that targets the CD33 antigen expressed in approximately 90% of AML patients, is conjugated with the cytotoxin calicheamicin, which induces double-strand breaks in DNA and apoptosis in target cells. Given its limited extramedullary toxicity, GO is considered an attractive agent for debulking leukemic burden prior to allogeneic HSCT. Previous studies have reported that exposure to GO within three months before HSCT increased the risk of developing hepatic sinusoidal obstruction syndrome (SOS) (13). A recent prospective study demonstrated the safety and efficacy of administering GO two to three weeks before preconditioning with fludarabine-based RIC regimens for allogeneic HSCT (8, 9). Two groups undertook studies in attempt to determine the safety and optimal dose of GO as a preconditioning treatment. Bornhauser et al (8) assigned 6 and 3 mg/m^2 of GO on days -21 and -14, and de Lima et al (9) assigned 2 or 4 mg/m^2 of GO day -12 before HSCT. Together, both studies observed successful primary engraftment in all cases except one, and reversible hepatic SOS was documented in only two out of 83 patients with the non-relapse mortality at day 100 being approximately 20%. The present case achieved durable remission after modified HSCT despite the fact that the patient's AML was refractory to chemotherapy and the recent history of *Trichosporon* fungemia. Nonetheless, this GO-combined RIC regimen may have been associated with PVOD, although our patient did not develop hepatic SOS. PVOD is a rare complication even in patients treated with myeloablative SCT and no case of PVOD has been reported in patients who received RIC-SCT, except for one patient who underwent RIC-CBT twice (14). Accordingly, the present case report is the first to describe PVOD following RIC-SCT.

The triad of severe pulmonary arterial hypertension, radiographic evidence of pulmonary edema, and normal pulmonary artery wedge pressure (PAWP) are classical diagnostic criteria for PVOD (1). However, PAWP measurements can produce variable results, and consequently not all patients with PVOD show normal PAWP (10). Surgical lung biopsy provides the definitive diagnosis. Nevertheless, clinical and radiographic findings have been proposed as reliable identifiers of this disease when surgical lung biopsy is not applicable or unwarranted due to clinical improvement (10). Some cases were diagnosed to have PVOD without performing lung biopsy or cardiac catheter test (3, 10, 15). In the present case, typical abnormalities in the chest CT such as diffuse interlobular septal thickening, peribronchial cuffing, and pulmonary arterial dilatation with normal caliber of pulmonary veins were highly suggestive of PVOD (16). The diagnosis of PVOD was supported by an elevation of estimated RV systolic pressure, normal left ventricular function, and normal plasma brain natriuretic peptide (BNP) levels, as well as clinical improvement after steroid therapy.

Infection has been suggested to be a potential cause of PVOD. The present patient did not exhibit any obvious infection, although voriconazole was administered to prevent the recurrence of *Trichosporon* fungemia. Nonetheless, the possibility of occult viral infection contributing to PVOD cannot be ruled out. Finally, autoimmunity has also been

suggested as a mechanism underlying PVOD. Although our patient did not show apparent signs of acute GVHD, subclinical allo-antigen reactions may have contributed to his condition.

How best to treat PVOD remains controversial. Owing to the rarity of the condition, its etiology is not well defined. The disease may be difficult to differentiate from pulmonary venular obstruction, which is a milder and non-fatal condition that often undergoes spontaneous resolution. Steroids and heparin may be effective for PVOD (14); in fact, the present patient readily improved with corticosteroids alone. Corticosteroids have been used for the treatment of PVOD, presumably to target a concomitant inflammatory disease or component of interstitial pulmonary fibrosis associated with PVOD although the role and effectiveness of steroids remain poorly defined. Anticoagulant and thrombolytic therapies such as heparin have also been used for the treatment of PVOD but not as often as corticosteroids. Defibrotide and N-acetylcysteine are also appealing as potential therapeutic agents, although we are unaware of any positive data reporting their efficacy.

PVOD should thus be included in the differential diagnosis of dyspnea and hypoxia even after reduced-intensity transplantation, especially when a GO-combined RIC regimen is used. Additional case reports describing the condition may yield further insight into its etiology.

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

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