Case Report

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Pulmonary veno-occlusive disease after respiratory syncytial virus infection in a post hematopoietic stem cell transplantation patient

Tatsuo Watanabe[1,2], Kazutoshi Komori[1,2], Shoji Saito[1,2], Eriko Uchida[1,2], Takashi Kurata[1], Masatomo Kitamura[3], Hikoro Matsui[3,4], Kohta Takei[5], Yoshifumi Ogiso[6], Keiko Ohta-Ogo[7], Yozo Nakazawa[2], Kazuo Sakashita[1]

[1]Department of Hematology and Oncology, Nagano Children's Hospital, Azumino, Japan, [2]Department of Pediatrics, Shinshu University School of Medicine, Matsumoto, Japan, [3]Department of Pediatric Intensive Care Unit, Nagano Children's Hospital, Azumino, Japan, [4]Department of Pediatrics, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan, [5]Department of Pediatric Cardiology, Nagano Children's Hospital, Azumino, Japan, [6]Department of Clinical Pathology, Nagano Children's Hospital, Azumino, Japan, [7]Department of Pathology, National Cerebral and Cardiovascular Center, Suita, Japan

Abstract

Background: Pulmonary veno-occlusive disease (PVOD) is a rare but fatal complication of hematopoietic stem cell transplantation (HSCT). Although literature on PVOD post-HSCT is scarce, a recent study has indicated that this condition may be underestimated. Respiratory syncytial virus (RSV) is a common respiratory pathogen that causes common cold in healthy individuals but may lead to severe lower respiratory infection accompanied by respiratory distress in infants and immunocompromised individuals, such as post-HSCT patients. However, little is known about the relationship between PVOD and RSV infections.

Case report: A 4-year-old boy was diagnosed with metastatic neuroblastoma and underwent intensive chemotherapy, autologous HSCT, and allogeneic cord blood transplantation (CBT). He experienced PVOD on day 194 following CBT after displaying upper respiratory symptoms and positive RSV antigen test results approximately one month prior. Pathological examination of a lung biopsy specimen revealed lung injury suspected to be associated with viral infection in addition to PVOD-related findings, suggesting that RSV infection might have contributed to the onset of PVOD.

Conclusions: The patient's clinical history and histological findings indicated that RSV could have triggered the development of PVOD under potential endothelial damage caused by HSCT and other prior treatments. Common respiratory viral infections, such as RSV infection, may evoke the development of PVOD.

Key words pulmonary veno-occlusive disease, pulmonary hypertension, respiratory syncytial virus, hematopoietic stem cell transplantation, pediatric, RSV

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Correspondence: Shoji Saito, Department of Pediatrics, Shinshu University School of Medicine, 3-1-1 Asahi, Matsumoto, Nagano 390-0877, Japan, E-mail: shojis@shinshu-u.ac.jp

Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare but fatal complication following hematopoietic stem cell transplantation (HSCT) presenting as cough, dyspnea, and pulmonary hypertension (PH)[1,2]. Endothelial damage is considered the main pathophysiology of PVOD which implicates risk factors such as graft-versus-host disease (GVHD), infection, prior use of alkylating agents, and total body irradiation (TBI)[1]. Only 19 cases of PVOD after HSCT have been reported in the literature (**Table S1**). However, a recent study uncovered an unexpectedly high frequency (34.3%) of PVOD as the main cause of death in a >1-year post-HSCT autopsy review[3].

Respiratory syncytial virus (RSV) is a frequent cause of common cold in healthy individuals; however, it may lead to severe lower respiratory infections accompanied by respiratory distress in infants and immunocompromised individuals, such as post-HSCT patients[4,5]. However, little is known about the relationship between RSV infection and PVOD after HSCT.

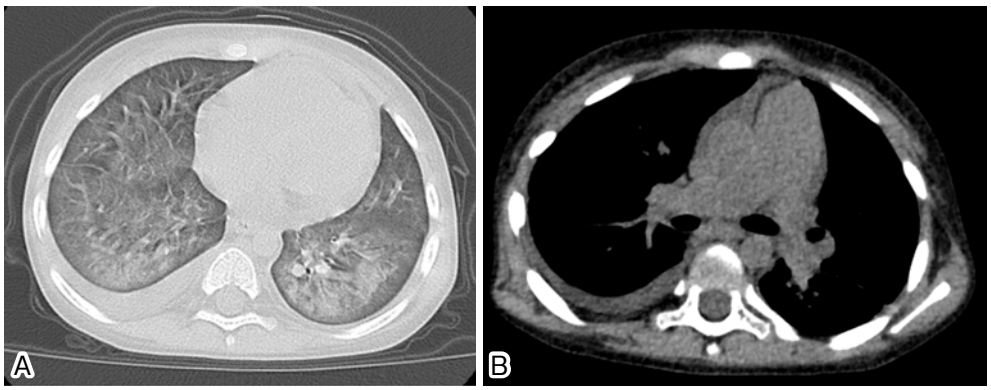

Figure 1. Chest CT findings at the onset of PVOD
Chest CT showed infiltration, ground glass opacity, and septal thickening in the bilateral lung field along with right pleural effusion (A) and dilation of pulmonary arteries (B). No mediastinal lymphadenopathy was observed. CT, computed tomography; PVOD, pulmonary veno-occlusive disease.

Herein, we describe the clinical outcomes of a pediatric patient who experienced PVOD on day 194 after allogeneic cord blood transplantation (CBT). His clinical course, in conjunction with histological lung biopsy findings, suggested RSV infection as a trigger.

Case Report

A 4-year-old boy with stage IV neuroblastoma received four cycles of chemotherapy, including high-dose chemotherapy including busulfan and melphalan, followed by autologous peripheral blood stem cell transplantation with autologous bone marrow supplementation (**Figure S1**, **Table S2**). After eight additional cycles of chemotherapy consisting of temozolomide and irinotecan, which led to stable disease, the patient underwent preparative conditioning with fludarabine (150 mg/m^2), melphalan (140 mg/m^2), and 12 Gy of TBI for subsequent allogeneic CBT (**Figure S1**, **Table S2**). The patient received tacrolimus and a short-term course of methotrexate for GVHD prophylaxis. The patient underwent engraftment on day 17. He then developed grade 3 GVHD, which was managed by increasing the prednisolone dose and was later discharged on day 85. The patient also received proton beam therapy (39.6 Gy) from days 121 to 150 post-transplantation for a right supra-mediastinum tumor with residual I^{123}-MIBG accumulation in the right adrenal gland.

The patient remained healthy with no evidence of GVHD until presentation at our hospital with a productive cough on day 159. As his older brother displayed similar cold symptoms, a rapid antigen test for RSV was performed, which revealed a positive result. His respiratory symptoms gradually worsened, and he revisited our hospital on day 194 with dyspnea and intercostal retractions. Upon admission, he was given 0.7-1.0 mg/kg of prednisolone, which failed to improve his respiratory condition. Chest computed tomography on day 231 revealed infiltration, ground-glass opacity, and septal thickening in the bilateral lung fields along with right pleural effusion (**Figure 1**, **Figure S2**). Echocardiography showed an elevated tricuspid regurgitation peak velocity of 4.1 m/s and an interventricular septum close to the isobaric, indicating the presence of PH. In addition, pericardial effusion was detected. On day 231, the patient was transferred to the pediatric intensive care unit, where mechanical ventilation and inhaled nitric oxide (NO) were initiated. Thoracoscopic lung biopsy on day 244 revealed diffuse intra-alveolar hemorrhage and edema on hematoxylin-eosin (HE)-stained samples (**Figure 2A**). Elastica van Gieson staining revealed diffuse obstructive lesions due to fibrocellular components with plump endothelial cells in the preseptal pulmonary veins and venules (**Figure 2B**). While pulmonary muscular arteries and arterioles showed mild medial hypertrophy and focal intimal thickening (Heath-Edwards Grade 2), severe stenosis with concentric intimal fibrosis or plexiform lesions was present. Based on these results, the patient was diagnosed with PVOD with mild pulmonary arterial/arteriolar lesions. Of note, HE staining also revealed enlarged type II pneumocytes with multinucleated and giant cell-like features, indicating the presence of prior lung injury that was likely attributable to his preceding viral infection (**Figure 2A**).

The patient's respiratory condition transiently improved after the initiation of inhaled NO, ambrisentan, sildenafil, and increased methylprednisolone doses. Tacrolimus was administered throughout the clinical course at target concentrations of 4-6 ng/mL for continuous infusion and 2 ng/mL for oral intake. His respiratory condition improved temporarily after increasing the dose of methylprednisolone, with PH improvement on echocardiography showing disappearance of tricus-

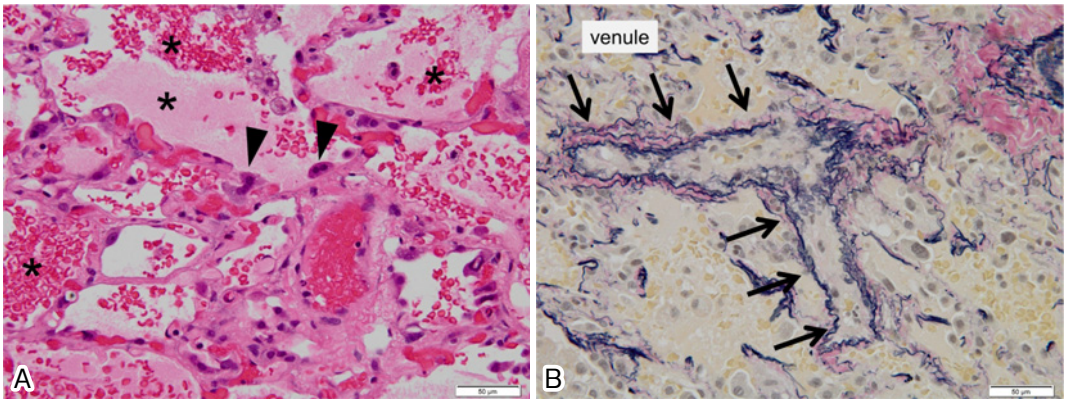

Figure 2. Histopathology of intratracheal lung biopsy showed both PVOD- and viral infection-related findings
HE (A) and EVG (B) staining of a lung biopsy specimen. (A) HE staining (original magnification x400) revealed intra-alveolar hemorrhage and edema (asterisks) along with enlarged type II pneumocytes with multi-nucleated and giant cell-like (arrowheads) morphology, indicating the presence of both PVOD and prior lung injury likely due to viral infection. (B) EVG staining identified multiple obstructive lesions due to fibrous components in pulmonary venules (arrows). PVOD, pulmonary veno-occlusive disease; HE, hematoxylin and eosin; EVG, elastica van Gieson.

pid regurgitation and rounding of the interventricular septum shape. However, he continuously required inhaled NO and high-dose prednisolone to maintain his respiratory condition (**Figure S1**, **2**).

Although mechanical ventilation with inhaled NO enabled a relatively stable respiratory status for 55 days, a metastatic relapse was identified on day 336 based on abnormal accumulations in the cranium and liver, and a right mediastinal mass was detected by I^{123}-MIBG scintigraphy. Despite no additional radiation, chemotherapy, or changes in the management of PH, the patient succumbed to respiratory failure on day 349.

Discussion

The present patient had been aggressively treated with HSCT and multiple courses of chemotherapy, including TBI and large amounts of alkylating drugs, which is consistent with other reported cases of PVOD following HSCT[1,2]. Moreover, such an extensive treatment history may have been associated with potential endothelial damage and the subsequent development of PVOD.

The patient presented with upper respiratory symptoms along with positive RSV rapid antigen test results approximately one month before the onset of PVOD. Moreover, histological examination of a lung biopsy specimen revealed lung injury findings indicative of prior viral infection, in addition to PVOD-related damage. Of note, the pathological findings of loose fibrocellular intimal thickening with swollen endothelial cells in the pulmonary veins/venules suggested subacute changes rather than long-standing alterations characterized by dense fibrous occlusions. Considering the timing of onset, these findings support the contribution of RSV in PVOD development in this case.

RSV is known to cause bronchiolitis, pneumonia, and other serious respiratory diseases in addition to long-term complications in post-HSCT patients[4,6]. However, information regarding the relationship between RSV and PVOD is scarce. Zinter et al.[7] described a 20-year-old man who experienced PVOD 77 days after HSCT (**Table S1**). Although the patient had concurrent cytomegalovirus viremia with a high viral titer (55,000 copies/mL) in the bronchoalveolar lavage, the report also mentioned upper respiratory symptoms due to RSV-A at presentation, thus implicating RSV as a possible cause of PVOD. Multiple studies have associated severe RSV infections with the development and deterioration of PH in healthy infants and patients with congenital heart disease[8]. A mouse model also showed that RSV caused PH, with histological findings of pulmonary artery medial hypertrophy accompanied by severe inflammation around both pulmonary arteries and veins[9]. Furthermore, RSV has been shown to attenuate the phosphorylation of the α-subunit of eukaryotic translation initiation factor 2 (eIF2α) by binding RSV N protein to protein kinase R to maintain the translation of cellular and viral protein[10]. Notably, this kinase encoded by the EIF2AK2 gene belongs to the same family of four eIF2α kinases, including EIF2AK4, which is the gene causing heritable and sporadic PVOD[11], although whether the changes in stress response due to attenuated eIF2α could contribute to PVOD remains unclear. Thus, RSV infection may trigger PVOD in the presence of endothelial damage.

To our knowledge, only 20 cases of PVOD post-HSCT have been reported, including the present case

(**Table S1**)[1,2]. Meanwhile, a recent study[3] identified an unexpectedly high frequency (34.3%) of PVOD as the main cause of post-HSCT death in an autopsy review in which all autopsies were performed later than day 100 transplantation. Another study[12] described that among four pediatric HSCT patients who exhibited PH under sequential echocardiogram monitoring, one had histologically proven PVOD. Therefore, the rate of PVOD may be underestimated and warrants further consideration.

A limitation of this report is that we did not evaluate the genetic predisposition to PVOD[11]; however, no family history of PVOD or PH was noted in the patient or relatives.

In conclusion, we encountered a unique case of PVOD in a post-HSCT patient following an RSV infection. Based on the patient's clinical history and histological findings, RSV was considered to have triggered the onset of PVOD. Clinicians should be aware of the possibility of late-onset complications of HSCT.

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Author Contributions

T.W. and S.S. drafted the original manuscript. S.S. contributed to the conception and design of the report. T.W., K.K., S.S., E.U., T.K., M.K., H.M., K.T., Y.N., and K.S. contributed to patient care. T.W., S.S., Y.O., and K. O-O. contributed to data interpretation. All authors drafted and critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Consent for Publication

Written informed consent for publication was obtained from the parents.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website.

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