Transfusion and Apheresis Science xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Transfusion and Apheresis Science

journal homepage: www.elsevier.com/locate/transci

Case Report

Transfusion-associated hypoxemia in pediatric patients with solid tumors after autologous peripheral blood stem cell transplantation

Ryu Yanagisawa[a,b,c,*], Seiki Abe[d], Ikuko Fujihara[e], Kazutoshi Komori[e,f], Yoshiaki Kondo[g], Kazuo Sakashita[e], Tomohiko Nakamura[a,h]

[a] Life Science Research Center, Nagano Children's Hospital, Azumino, Japan
[b] Division of Blood Transfusion, Shinshu University Hospital, Matsumoto, Japan
[c] Center for Advanced Cell Therapy, Shinshu University Hospital, Matsumoto, Japan
[d] Department of Anesthesia, Nagano Children's Hospital, Azumino, Japan
[e] Department of Hematology/Oncology, Nagano Children's Hospital, Azumino, Japan
[f] Department of Pediatrics, Shinshu University School of Medicine, Matsumoto, Japan
[g] Department of Radiology, Nagano Children's Hospital, Azumino, Japan
[h] Division of Neonatology, Nagano Children's Hospital, Azumino, Japan

ARTICLE INFO

Article history:
Received 9 June 2017
Received in revised form 7 September 2017
Accepted 11 September 2017
Available online xxx

Keywords:
Transfusion-associated circulatory overload
Transfusion-associated dyspnea
Transfusion-related acute lung injury

ABSTRACT

Background: Although several types of transfusion-related adverse reactions (TRARs) have been reported, one of the most important involves respiratory features during and after blood transfusion. Transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) are the most severe adverse events following blood transfusion, whereas transfusion-associated dyspnea (TAD) is a less severe respiratory distress. However, there exists little evidence of these factors in pediatric populations.
Case report: Here, two cases of atypical TRARs with respiratory features, in pediatric patients with solid tumors, appearing after transfusion of platelet concentrate following autologous peripheral blood stem cell transplantation are reported. Both patients developed mild hypoxemia during PC transfusion, which continued for approximately 2 weeks. Chest radiography in either patient did not reveal any abnormalities that are included in the criteria of either TRALI or TACO. Both patients recovered following oxygen administration.
Conclusion: This complication of TRARs with respiratory features may occur more frequently in pediatric populations than realized because it may be under-recognized or under-reported. Accumulation of additional cases, including non-typical cases, is necessary to fully understand the pathology of TRARs, correctly classify these reactions, and improve care of patients receiving blood transfusions.

1. Introduction

Although there are several types of transfusion-related adverse reactions (TRARs) [1], one of the most important is associated with respiratory features during and after blood transfusion. Transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) are the most severe adverse events following blood transfusion, whereas transfusion-associated dyspnea (TAD) is a less severe respiratory distress [2]. Recently, TAD was described as an adverse event, which is characterized by respiratory distress within 24 h of transfusion that does not satisfy the criteria of TRALI, TACO, or any other allergic reaction [3,4]. Respiratory distress is the most prominent clinical characteristic of TAD, and it cannot be confirmed by the patient's underlying condition or any other known cause of respiratory distress [3]. Because many pathogenesis can induce TRARs accompanied with these respiratory features, a clear understanding of the disease and correct diagnosis, management, and treatment is necessary in clinical practice. The recent development of hemovigilance systems in several countries can help to avoid underdiagnosis, underreporting, and misdiagnosis. However, further compilation of cases is necessary because there is insufficient information available for pediatric populations. Here, two pediatric patients with solid tumors accompanied with atypical TRAR with respiratory features are described. These cases did not satisfy the criteria for TRALI or TACO. Both cases had similar clinical features and clinical courses and, therefore, can be considered as having the same pathogenesis of TRARs. These

* Corresponding author at: Division of Blood Transfusion, Shinshu University Hospital 3-1-1, Asahi, Matsumoto 390-8621, Japan.
E-mail address: ryu@shinshu-u.ac.jp (R. Yanagisawa).

http://dx.doi.org/10.1016/j.transci.2017.09.003
1473-0502/

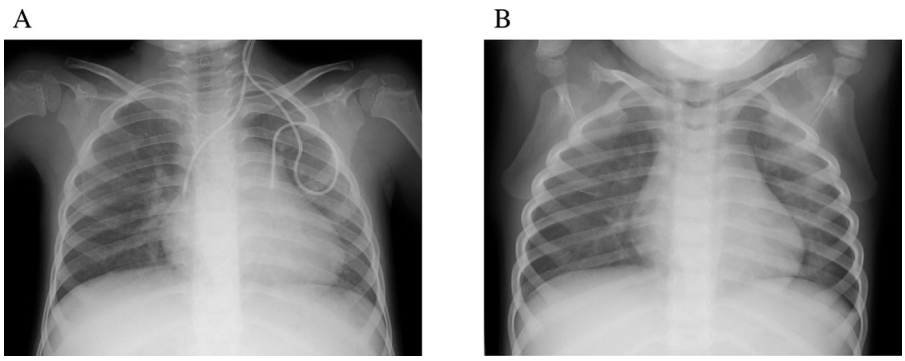

Fig. 1. (A) Chest X-rays of patient 1 showing the development of hypoxemia after transfusion of platelet concentrate (PC). (B) Chest X-rays of patient 2 the development of hypoxemia after transfusion of platelet concentrate (PC).

cases will help to further the understanding of pediatric TRARs because each can be attributed to the possibility of features and/or backgrounds unique to pediatric primary disease.

2. Case presentation

2.1. Case 1

A 5-year-old male neuroblastoma patient who was partially responsive to chemotherapy underwent autologous peripheral blood stem cell transplantation (auto-PBSCT) following a preparative regimen of busulfan (BU) and melphalan (Mel). Although he achieved engraftment of neutrophils on day 14 after SCT without apparent problems, he delayed the increment of platelet count and hemoglobin level by himself. He needed transfusions of platelet concentrate (PC) and red cell concentrate (RCC) up to days 72 and 75 based on the blood examination (indication for reference data in our institution; hemoglobin level <70 g/L, platelet count $<20 \times 10^9$/L). Because of an allergic reaction history due to PC transfusion before SCT, we prepared washed PC every time for his PC transfusions. The patient remained stable post-PBSCT and was observed on an outpatient basis after day 43. A blood examination on post-PBSCT day 62 indicated the need for a blood transfusion with both PC and RCC. At 23 min after initiation of PC transfusion, O_2 saturation (SpO_2) at rest in room air was slightly low: 92%–94%. However, there were no other physical findings. Therefore, a blood transfusion with continuous RCC was performed. The patient returned to his home on the same day 7 h later after the initiation of blood transfusion of PC with a final SpO_2 of 95% in room air. Several days later, the patient received another blood transfusion. Before starting the transfusion, SpO_2 was only 84%–88%. Although his parents reported recent fatigability, there were no other apparent abnormalities or physical findings. A chest X-ray indicated no infiltration to the lungs (Fig. 1A). Brain natriuretic peptide, electrocardiographic, and echocardiographic findings were normal. There was no evidence of infection with fungus or cytomegalovirus. Surfactant protein (SP)-A, SP-D, and Krebs von den Lungen-6 (KL-6) levels were normal. The patient's general condition remained good and his SpO_2 returned to normal around post-PBSCT day 76 with oxygen administration alone.

2.2. Case 2

A 2-year-old male medulloblastoma patient underwent auto-PBSCT following surgery and chemotherapy to achieve a complete response. The patient received a preparative regimen consisting of BU and Mel. Although his post-PBSCT interval was uneventful, at the end of transfusion with PC (approximately 5 h after the start of transfusion) on post-PBSCT day 49, he was found to be hypoxemic while sleeping, with SpO_2 of 88%–91% in room air. Although oxygen administration immediately improved these symptoms, SpO_2 remained low. Hypoxemia was significant especially while sleeping. Overnight monitoring showed periodic marked hypoxemia (SpO_2 60%–80% in room air during sleep) (Fig. 2); however, the patient was not hypoxemic when awake. There were no other apparent abnormalities or physical findings. There were no lung abnormalities on chest X-ray during this course (Fig. 1B). Also, there was no evidence of infection or an increase in KL-6. Cardiac function was also normal. The patient required oxygen administration only during sleep and his symptoms improved at about post-PBSCT day 61.

3. Discussion

The backgrounds, clinical features, and clinical courses of these two cases were similar. Although the main symptom was mild hypoxemia, there was no apparent cough or dyspnea. In addition, objective findings, such as auscultation, were normal in both cases. Both patients received the same conditioning regimen before auto-PBSCT and symptoms appeared at similar times after transplantation, but improved within comparable time frames with no residual problems for approximately 2 weeks. Because they had no history of irradiation therapies, including lung fields, these findings suggested that the chemotherapeutics used for auto-PBSCT preconditioning, particularly BU, may be responsible for the development of interstitial pneumonia [5]. A well-known noninfectious lung complication of hematopoietic SCT is idiopathic pneumonia syndrome (IPS) [6], which is primarily observed in adults. Because IPS is more frequent in allogeneic hematopoietic SCT and is associated with high mortality rates [6], these two pediatric cases may be distinct from typical IPS cases. However, other complications may be considered such as atypical pulmonary veno-occlusive disease following hematopoietic SCT [7].

Although there were differences in receiving PC products in these two patients with washed products in patient 1 compared with regular plasma rich PC products in patient 2, both cases received same Japanese unit 10 pathogen non-inactivated PC products [8]. Because transfusion with PC seemed to be a trigger in both cases, TRAR with respiratory feature also should be considered in such cases [3]. However, there was no apparent evidence of positive fluid balance indicating TACO in these cases. The criteria of TACO were not met in either case (Table 1). The presence of TRALI may be an important finding for differential diagnosis. However, neither case met the criteria for TRALI. There was no bilateral infiltration on a frontal chest radiograph in either case. Although one case presented with hypoxemia (SpO2 <90% in room air), this criteria of TRALI was not satisfied within the 6 h of transfusion [9]. Furthermore, the symptoms in these two cases seemed to be too

Please cite this article in press as: Yanagisawa R, et al. Transfusion-associated hypoxemia in pediatric patients with solid tumors after autologous peripheral blood stem cell transplantation. Transfus Apheresis Sci (2017), http://dx.doi.org/10.1016/j.transci.2017.09.003