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CASE REPORT

A case of transfusion-related acute lung injury induced by anti-human leukocyte antigen antibodies in acute leukemia

Sun Mi Jin[1], Moon Ju Jang[1], Ji Young Huh[2], Myoung Hee Park[3], Eun Young Song[3], Doyeun Oh[1]

Departments of [1]Internal Medicine and [2]Laboratory Medicine, CHA University School of Medicine, Seongnam, [3]Department of Laboratory Medicine, Seoul National University College of Medicine, Seoul, Korea

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Correspondence to
Doyeun Oh, M.D., Ph.D.
Department of Internal Medicine, CHA Bundang Medical Center, CHA University, 59, Yatap-ro, Bundang-gu, Seongnam 463-712, Korea
Tel: +82-31-780-5217
Fax: +82-31-780-5208
E-mail: doh@cha.ac.kr

Transfusion-related acute lung injury (TRALI) is a noncardiogenic pulmonary edema that occurs during or within 6 hours after transfusion. Risk factors for TRALI, which is relatively common in critically ill patients, include recent surgery, hematologic malignancy, and sepsis. Here, we report a case of TRALI induced by anti-human leukocyte antigen (anti-HLA) class II antibodies (HLA-DR) occurring after transfusion of platelet concentrates in a patient with acute leukemia. Although most patients with TRALI show improvement within 48–96 hours, our patient's condition rapidly worsened, and he did not respond to supportive treatment. TRALI is a relatively common and serious adverse transfusion reaction that requires prompt diagnosis and management.

Key Words Transfusion-related acute lung injury (TRALI), Transfusion, Anti-human leukocyte antigen (anti-HLA) antibody

INTRODUCTION

Transfusion-related acute lung injury (TRALI) is a noncardiogenic pulmonary edema that occurs during or within 6 hours after a transfusion. It was previously considered a rare complication of transfusion. However, several retrospective studies revealed that TRALI is underdiagnosed and under-reported because of the lack of recognition [1]. Newly established diagnostic criteria have increased awareness of TRALI and resulted in a recent increase in reports of TRALI. Consequently, TRALI is now recognized as a relatively common transfusion-associated complication.

TRALI is associated with plasma-containing blood products, including whole blood, packed RBC (PRBCs), fresh frozen plasma (FFP), platelet concentrates (PC), and cryoprecipitate. As critically ill patients often require transfusions, they are at high risk for TRALI. Although there are several case reports on TRALI in Korea (Table 1) [2-9], to our knowledge, ours is the first report on a patient with acute leukemia. We describe a case of TRALI induced by antibodies against human leukocyte antigen (HLA) after PC transfusion in acute leukemia.

CASE REPORT

A 79-year-old man visited the dermatology clinic with flushing of the face and hands for the previous 2 months. He had a history of coronary stent insertion because of unstable angina and a history of chronic obstructive pulmonary disease. He also had a history of cigarette smoking (50 pack-years). His prescription drugs included aspirin, beta-blocker, calcium channel blocker, and prednisolone. Complete blood cell count with differential white cell count indicated bicytopenia. He was therefore admitted to the hematology division.

On admission, his vital signs were stable. He was alert and oriented. Physical examination revealed purpura of the lower legs and pale conjunctiva. Breath sounds were normal without wheezing or crackle. Heart rate was regular without murmur. Laboratory data showed that hemoglobin level was 7.1 g/dL; platelet count, 7.0×10^9/L; WBC count, 4.0×10^9/L (neutrophils 53% and blasts 8%); blood urea nitrogen, 15.9 mg/dL; creatinine, 1.2 mg/dL; prothrombin time, 12 sec; international normalized ratio, 1.07; activated partial thromboplastin time, 36.2 sec; lactate dehydrogenase, 397 U/L.

Table 1. Case reports of TRALI in Korea.

Author	Gender/age	Underlying disease or condition	Immunologic study	Progress	Implicated blood product
Huh *et al*. [2]	M/63	Alcoholic liver cirrhosis Recent orthopedic surgery and wound infection	Not detected	Improved	PRBCs
Lee *et al*. [3]	M/69	Lung cancer	-	Improved	PRBCs
	F/68	Lung cancer	-	Improved	PRBCs
Lee *et al*. [4]	M/66	Lung cancer	Patient anti-HLA class I and II antibodies specific for donor HLA type	Could not wean off ventilator	PRBCs
	F/62	Rectal cancer	Patient anti-HLA class I and II antibodies specific for donor HLA type	-	PRBCs, PC
Lee *et al*. [5]	F/35	Pregnancy During cesarean section	-	Improved	PRBCs
Hong *et al*. [6]	M/71	Esophageal cancer Stomach cancer Heart failure	-	Improved	PRBCs
Kim *et al*. [7]	F/30	Gestational idiopathic thrombocytopenic purpura	Not detected	Improved	PC
Bae *et al*. [8]	F/23	Aplastic anemia with hemophagocytic lymphohistiocytosis	Patient serum IgM, IgG anti-neutrophil antibody	Expired (due to pulmonary hemorrhage)	PRBCs, PC
Kim *et al*. [9]	F/73	During orthopedic surgery	-	Expired	PRBCs, FFP

Abbreviations: PRBCs, Packed RBC; PC, platelet concentrate; FFP, fresh frozen plasma.

Table 2. Laboratory results and treatment.

	Before transfusion	1 hr after transfusion	2 hr after transfusion	4 hr after transfusion	5 hr after transfusion
SBP (mmHg)	120	120	90	60	50
pH/$PaCO_2$ (mmHg)/PaO_2 (mmHg)/ HCO_3 (mmol/L)/SaO_2 (%)		7.19/52/60/20/85	7.25/48/58/21/85	6.96/51/59/11/73	7.02/78/49/20/64
WBC (10^9/L)/Hb (g/dL)/platelet (10^9/L)	4.0/7.1/7.0	3.7/9.0/26.0			10.0/9.6/33.0
PT/aPTT (sec)	12/36.2	12.6/36.2			15.9/60
Na/K (mEq/L)	141/3.8	142/4.6			142/5.7
ProBNP (pg/mL)		167.6			
CK-MB/TnT (ng/mL)		1.41/0.007			5.18/0.244
BUN/Cr (mg/dL)	15.9/1.2	22.2/1.2			23.1/1.8
AST/ALT(IU/L)	16/16	16/15			551/845
Intervention and treatment		Intubation Ventilator care		Central line insertion Inotropics	CPR

Abbreviations: SBP, Systolic blood pressure; $PaCO_2$, partial pressure of carbon dioxide in the arterial blood; PaO_2, partial pressure of oxygen in the arterial blood; HCO_3, bicarbonate ion; Na, sodium; K, potassium; PT, prothrombin time; aPTT, activated partial thromboplastin time; ProBNP, probrain natriuretic peptide; CK-MB, Creatine phosphokinase MB isoenzyme; TnT, Troponin T; BUN, blood urea nitrogen; Cr, creatinine; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CPR, cardiopulmonary resuscitation.

Based on the history and laboratory findings, acute leukemia was suspected.

Because of severe thrombocytopenia and purpura, 6 units of PC were administered. Approximately 30 minutes after the transfusion, the patient suddenly developed dyspnea and began sweating. At that time, arterial oxygen saturation (SaO_2) dropped to 45%, and systolic blood pressure was 80 mmHg. Use of 100% mask oxygen inhalation did not improve his hypoxemia, resulting in stupor. Tracheal intubation was performed, and he was transferred to the intensive care unit. Complete blood count, arterial blood gas analysis, cardiac enzyme analysis, and other blood chemistry tests were performed (Table 2). Chest radiography, which had shown no active lesion 6 hours previously, revealed bilateral lung infiltrations (Fig. 1). A central venous catheter was inserted via the right subclavian vein, and the central venous pressure revealed a low possibility of cardiogenic pulmonary edema. After 1 hour, his systolic blood pressure fell below 60 mmHg. Hypotension was managed with fluid administration and dopamine infusion. His fraction of inspired oxygen (FiO_2) increased to 100%, but SaO_2 remained below 80%. Despite intensive efforts, he became asystolic and died 7 hours after

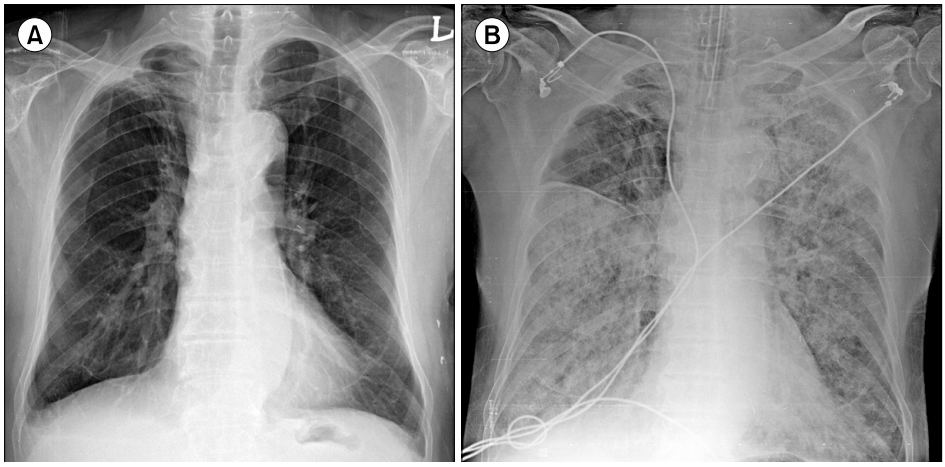

Fig. 1. Chest radiographs **(A)** 7 hours before transfusion, revealing bilateral upper lung lesions of stable pulmonary tuberculosis, **(B)** after the transfusion, revealing newly developed diffuse bilateral patch opacities in mostly the right middle and lower lung and the left whole lung without cardiomegaly or pleural effusion, suggesting pulmonary edema.

the transfusion.

We suspected acute myocardial infarction (AMI), pulmonary embolism (PE), or TRALI. However, normal electrocardiogram results and cardiac enzyme levels ruled out the possibility of AMI. PE was excluded based on the presence of bilateral extensive pulmonary infiltrates and lack of clinical evidence of deep vein thrombosis. Therefore, TRALI was highly suspected.

The patient's pre-transfusion and post-transfusion blood samples and segments from the PC bags were collected and evaluated for the presence of HLA antibodies. HLA typing of the patient was performed by sequence-based typing using SeCore A, B, C, and DRB1 Locus Sequencing Kit (Invitrogen, Brown Deer, WI, USA). HLA antibody screening and identification of the transfused PC units was performed with Luminex technology using LIFECODES LifeScreen Deluxe Kit and LIFECODES Class I and Class II Identification kits (Gen-Probe, Stamford, CT, USA). The HLA genotyping results were *A*24:02, 33:03; B*40:02, 58:01; DRB1*09:01, 13:02.* One PC unit was confirmed to contain HLA antibodies with a specificity reacting against one of the patient's HLA-DR antigens (DR13). This unit had multiple class II HLA antibodies with strong reactivity (DR4, DR8, DR11, DR12, and DR13) and moderate reactivity (DR15 and DR16). We did not evaluate anti-human neutrophil antigen (anti-HNA) antibody. Based on the results, we confirmed immune-mediated TRALI.

DISCUSSION

The pathogenesis of TRALI remains controversial; however, an antibody-mediated immune mechanism has been extensively studied. A recent systematic review of TRALI case reports in English, German, French, and Dutch showed that anti-leukocyte antibodies contributed to 80% of the cases reported [10]. Donor antibodies implicated in TRALI include anti-HLA class I, anti-HLA class II and anti-HNA antibodies [11]. We identified anti-HLA class II antibodies from one unit of PC. Contrary to HLA class I, HLA class II antibodies are not expressed on neutrophils, but on monocytes, which might contribute to TRALI. A recent study demonstrated that monocytes incubated with plasma containing anti-HLA class II antibodies (anti-DR52, anti-DR7) are stimulated to secrete high levels of cytokines and leukotriene B4 only when they express the DR antigens [12]. These cytokines might contribute to the activation of primed neutrophils in the lung, resulting in TRALI. However, although most TRALI cases are associated with the presence of anti-HLA or anti-HNA antibodies in donor plasma, fewer than 10% of TRALI cases involve the reverse mechanism in recipient anti-leukocyte antibodies against donor leukocyte antigens [13]. Furthermore, in some cases, anti-HLA or anti-HNA antibodies were not detected in the donor or the recipient [13]. Therefore, an alternative hypothesis in which biologically active lipids in blood products can also cause TRALI has been proposed. These lipids, which are breakdown products of cell membranes, normally accumulate in older cellular blood components. A lipopolysaccharide-primed animal model in which biologically active lipids from stored PRBCs caused acute lung injury (ALI) supports this hypothesis [14]. These two hypothetical causes of TRALI are not mutually exclusive and may even act synergistically [15].

TRALI is the leading cause of transfusion-related deaths worldwide and is common in critically ill patients [16]. A recent retrospective cohort study of 5,208 hospitalized patients reported that risk factors for TRALI included emergency cardiac surgery, hematologic malignancy, massive transfusion, sepsis, mechanical ventilation, and a high Acute Physiology and Chronic Health Evaluation II score [17]. Acute leukemia is also a risk factor for TRALI, as in our case. Particularly, TRALI frequently occurs during the induction phase of chemotherapy [18]. However, blood component transfusion is essential for patients with hematologic malignancy. Therefore, physicians who manage patients with hematologic malignancy must monitor TRALI development. In addition, to minimize the risk of TRALI, blood component

transfusion should be decreased and standard blood transfusion guidelines be adopted. Based on the National Blood Transfusion of Korea guideline, prophylactic platelet transfusion is required when the platelet count is less than 10,000/μL in patients with acute leukemia, except acute promyelocytic leukemia [19, 20].

Although a primary measure to prevent TRALI has been the deferral of donors implicated in TRALI, there is no consensus regarding the management of donors implicated in TRALI cases. Most implicated donors are women with a history of pregnancy. Women are exposed to paternal HLA during pregnancy, and the prevalence of HLA antibodies is increased in women who have had more pregnancies. The American Red Cross reported that antibody-positive female donors were involved in 71% of TRALI-related fatalities and 75% of TRALI cases caused by plasma transfusion [21]. For this reason, the United Kingdom disqualified multiparous females from plasma donation in 2003. UK Serious Hazards of Transfusion hemovigilance system data showed that TRALI cases associated with plasma-rich components decreased from 16 cases in 2003 to 3 cases in 2005. The Korean Red Cross has excluded all females from fresh frozen plasma donation and recommended that parous women not donate apheresis platelets since 2009. Plasma components storage also appears to be associated with the risk of TRALI. Silliman *et al.* demonstrated that lipids and non-lipid compounds (e.g., interleukin 8) generated during routine plasma components storage can prime NADPH oxidase [22]. As bioactive lipids and cytokines accumulate during storage, it is recommended that PRBCs are used within 14 days and PC within 2 days.

We conducted a literature review of TRALI in Korea since 2005. We identified 10 reports occurring in 4 men and 6 women aged between 23 and 73 years (Table 1) [2-9]. Among the 10 TRALI case reports, implicated blood products were PRBCs (6 cases), PC (1 case), PRBCs and PC (2 cases), and PRBCs and FFP (1 case). Five patients had solid cancer and 3 had undergone surgery. One patient had gestational idiopathic thrombocytopenic purpura and another had aplastic anemia with hemophagocytic lymphohistiocytosis. TRALI with acute leukemia has not been reported in Korea. Additionally, a retrospective study found that 9 of 154 patients with aneurysmal subarachnoid hemorrhage (SAH) had TRALI [23]. The study showed that the incidence of TRALI was 0.01% (9 in 836) for all transfused blood components and 0.06% (9 in 154) for all transfused patients. It also indicated that TRALI was associated with large-amount SAH and blood components transfusion exceeding 1,200 mL. Only 5 of 10 cases were evaluated by immunologic assay in TRALI reported in Korea, and anti-HLA antibodies or anti-neutrophil antibodies were found in 3 cases. In all 3 cases, antibodies were identified from patient blood. However, in our case, the anti-HLA antibody was identified from donor blood, consistent with the major pathogenesis of TRALI. A recent case-control study in the United States found that cognate anti-HLA class I and II antibodies of 12.3% and 7.8% of blood units, respectively, had been transfused to TRALI patients. Moreover, although patients were not tested for HNA type, anti-HNA antibodies were detected in 9.5% of blood units implicated for TRALI [24].

TRALI is considered to have better prognosis than ALI does (ALI mortality, 40–60%), where TRALI mortality is approximately 5–10% [1, 11]. Furthermore, most TRALI patients improve within 48–96 hours when appropriate respiratory support is provided. Among patients who survive the acute period and recover pulmonary function within a few days, long-term lung function does not appear to differ from people who never experience TRALI.

Unfortunately, our patient did not respond to supportive treatment, and his condition rapidly worsened. We presume that the severity of the underlying disease influences prognosis. Thus, although the mortality rate associated with TRALI is relatively low, clinicians should be aware that lung injury can be irreversible and fatal, and therefore should attempt to prevent it.

In summary, TRALI is a relatively common and serious adverse transfusion reaction that requires prompt diagnosis and management.

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