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【 CASE REPORT 】

Two Episodes of Transfusion-related Acute Lung Injury (TRALI) Occurring within a Short Period

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Abstract:
Transfusion-related acute lung injury (TRALI) is a non-hemolytic adverse reaction that occurs ≤ 6 hours after receiving a transfusion. A 72-year-old man with leukemia developed severe hypoxemia after platelet transfusions on two occasions within a 4-day period. During the first episode, the transfused platelet preparation was positive for anti-human-leukocyte antigen antibodies. The pathogenesis of TRALI includes an antibody-mediated mechanism and a non-antibody-mediated mechanism, in which various factors combine to activate pulmonary neutrophils. In our case, it is considered that the patient's neutrophils reached the activation threshold for the development of TRALI after the accumulation of various factors besides anti-leukocyte antibodies.

Key words: transfusion-related acute lung injury, two TRALI episodes, non-antibody-mediated TRALI, platelet transfusion

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Introduction

Transfusion-related acute lung injury (TRALI) is a type of non-hemolytic adverse transfusion reaction. It is a severe and rare condition, characterized by the development of hypoxemia and acute non-cardiac pulmonary edema within 6 hours of receiving a blood transfusion (1). The pathogenic mechanism responsible for TRALI is still not fully understood. It is reported that anti-leukocyte antibodies, including anti-human leukocyte antigen (HLA) antibodies and anti-human neutrophil antigen (HNA) antibodies, and bioactive substances, such as lipid mediators, are associated with the development of TRALI (2, 3). However, in some cases, no antibodies are detected despite TRALI being clinically suspected. A two-hit model has been suggested to explain the development of the condition: the first hit being the patient being predisposed to the condition, and the second hit being a transfusion (4, 5). In addition, a threshold model, in which pulmonary neutrophils have to be activated above a certain threshold for TRALI to develop, has been advocated. In this model, a combination of various individual risk factors activates neutrophils, and TRALI occurs after the threshold is reached (6, 7).

We experienced quite a rare case, in which TRALI occurred after platelet transfusions on two occasions within a short period. We herein discuss the pathogenesis of TRALI in our case, based on its clinical course.

Case Report

Two days before he was admitted to our hospital, a 72-year-old man developed fever and dyspnea, and was admitted to a nearby hospital under a diagnosis of pneumonia. After laboratory studies led to a suspicion of acute leukemia, he was transferred to our hospital. On admission, the patient's oxygen saturation level was 88-93% during the administration of 10 L/min oxygen. An arterial blood gas analysis revealed a pH of 7.51, a carbon dioxide partial pressure ($PaCO_2$) of 29.9 mmHg, an oxygen partial pressure (PaO_2) of 71.7 mmHg, and a PaO_2/fractional concentration of inspired oxygen (FIO_2) of 72.4. A chest radiograph revealed bilateral consolidation with ground glass opacity. He was diagnosed with acute myeloid leukemia (AML, M2, ac-

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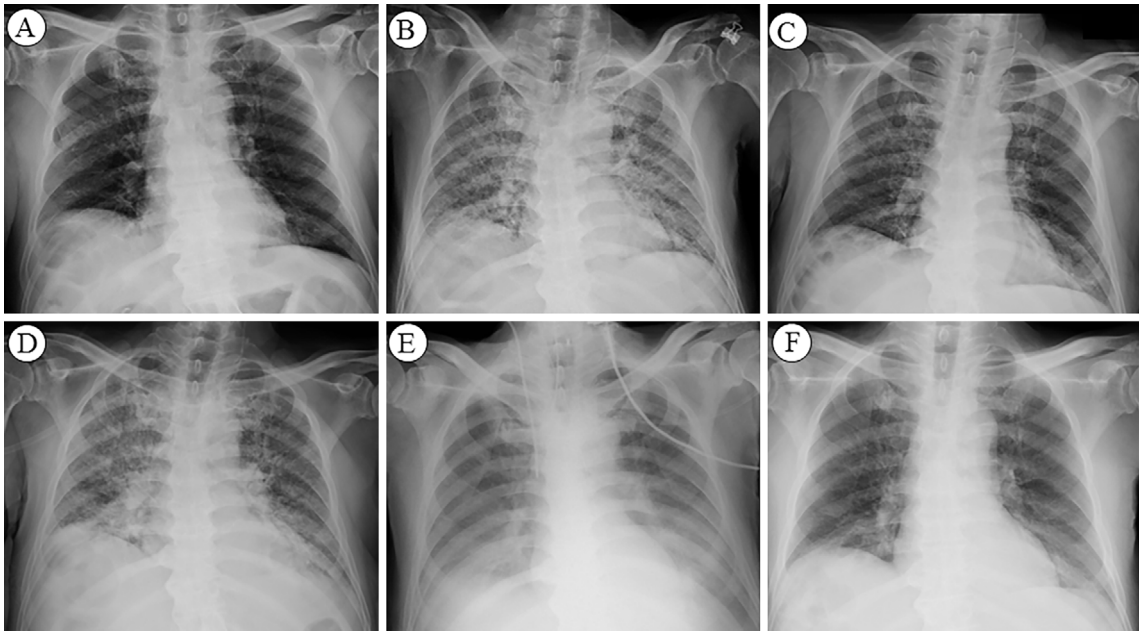

Figure 1. Chronological chest radiographs obtained after the 1st and 2nd episodes of TRALI. (A) The lungs were normal on the morning of day 9 of chemotherapy. (B) Nine hours later, TRALI occurred after a platelet transfusion. (C) The next day, the TRALI spontaneously resolved. (D) On day 12 of the chemotherapy, TRALI occurred again after a platelet transfusion. (E) The next day, the patient's pulmonary edema was ameliorated via mechanical ventilation. (F) On day 16 of the chemotherapy, the patient's lungs were nearly normal.

cording to the French-American-British cooperative group classification) based on bone marrow aspiration. He had a history of cholangitis and stroke, but no history of allergies or transfusions.

After receiving treatment for his pneumonia; i.e., at 22 days after admission, he underwent chemotherapy, involving daunorubicin and cytarabine. At that time, his body temperature was 36.7℃, his oxygen saturation level was 99% in room air, and the consolidation detected on chest radiography had improved. Laboratory tests revealed a white blood cell (WBC) count of 1,320/μL (neutrophils: 66/μL) and a C-reactive protein (CRP) level of 6.65 mg/dL. He received transfusions of red blood cells and platelets for pancytopenia just after admission, and no transfusion-related adverse events occurred at that time. On day 8 of chemotherapy, he had a fever of 37.6℃, and his laboratory data revealed a WBC count of 330/μL (neutrophils: 141/μL). He developed febrile neutropenia, and the antibiotic treatment he had been receiving since admission, which involved meropenem, teicoplanin, and liposomal amphotericin B, was continued.

On day 9, ninety minutes after a platelet transfusion was started, he developed chills and dyspnea, and his blood pressure and oxygen saturation suddenly dropped. He demonstrated a fever of 39.0℃, a heart rate of 137 beats per minute, blood pressure of 80/44 mmHg, and oxygen saturation of 89% in room air. Coarse crackles were heard in the bilateral lungs on auscultation. An arterial blood gas analysis performed after the administration of 10 L/min oxygen revealed marked hypoxemia (a pH of 7.41, a $PaCO_2$ of 37.0 mmHg, a PaO_2 of 110 mmHg, and a PaO_2/FIO_2 of 111). A chest radiograph revealed bilateral infiltration, but another chest radiograph that had been taken 9 hours earlier had not revealed any abnormalities (Fig. 1A, B). Transthoracic echocardiography showed a normal wall motion without dilatation of the inferior vena cava. These findings were compatible with non-cardiac pulmonary edema. The platelet transfusion was stopped, and the patient was administered oxygen, intramuscular adrenaline, intravenous saline, an antihistamine, and a glucocorticoid as a treatment for anaphylaxis. The continuous infusion of dopamine was started for hypotension. On the morning of day 10, his general condition improved, and the pulmonary edema seen on chest radiography had also markedly ameliorated (Fig. 1C). TRALI was suspected because of the rapid onset of hypoxemia and non-cardiac pulmonary edema after the platelet transfusion. We reported this episode to the Japanese Red Cross Society and sent the used platelet preparation and a sample of the patient's blood for examination.

On day 12, the patient's platelet count had decreased to 1.4×10^4/μL, and he had bloody sputum. A platelet transfusion was started after the administration of 5 mg of d-chlorpheniramine maleate and 100 mg of hydrocortisone to prevent anaphylaxis. Before the transfusion, his oxygen saturation level was 96% during the administration of 2 L/min oxygen. However, three hours after the transfusion was finished, he had a fever of 38℃, and his oxygen saturation level had dropped to 84% during the administration of 15 L/min oxygen. An arterial blood gas analysis revealed severe hypoxemia (a pH of 7.46, a $PaCO_2$ of 40.4 mmHg, a PaO_2 of 69 mmHg, and a PaO_2/FIO_2 of 70). Laboratory tests re-

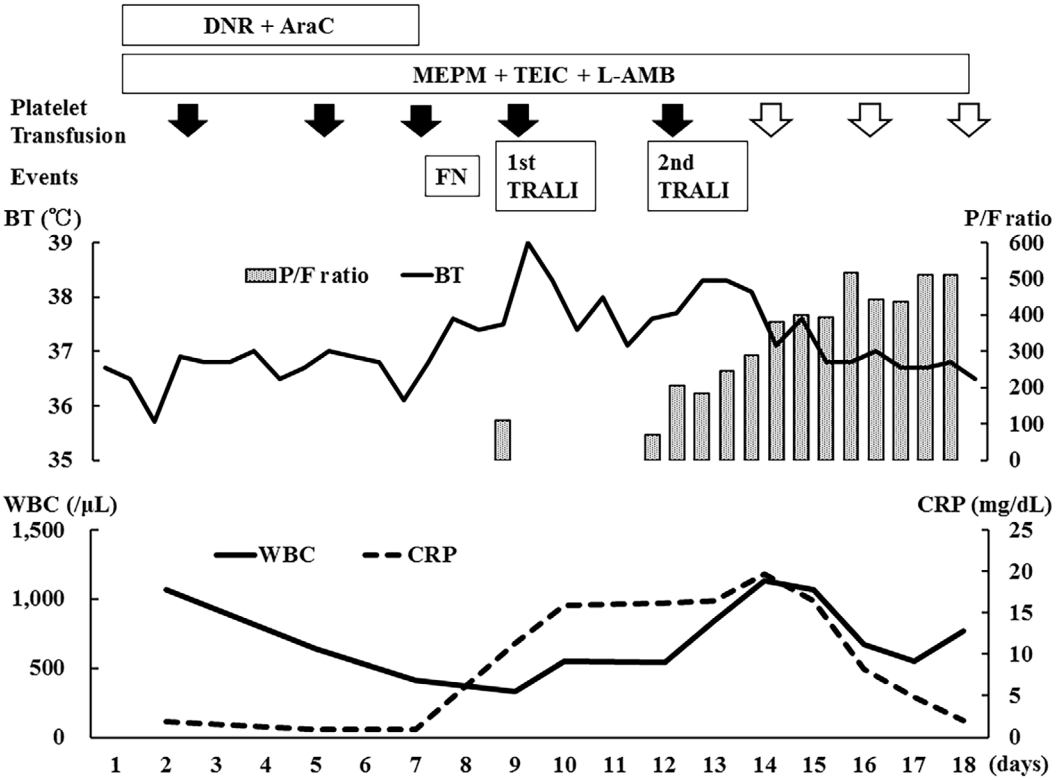

Figure 2. **The clinical course of our case. At 22 days after admission, the patient was given chemotherapy. Antibiotic treatment with meropenem, teicoplanin, and liposomal amphotericin B was administered from admission. During the chemotherapy, platelet transfusions were administered for thrombocytopenia (indicated by black arrows). On day 8, the patient developed febrile neutropenia, and his CRP level increased. The first TRALI episode occurred on day 9, and the second occurred on day 12. After the second episode, washed platelet preparations were used (indicated by white arrows). In the second episode, intubation and mechanical ventilation were required for severe hypoxemia, but the patient's oxygenation level (indicated by his P/F ratio) had already improved on day 13. AraC: cytarabine, BT: body temperature, CRP: C-reactive protein, DNR: daunorubicin, FN: febrile neutropenia, L-AMB: liposomal amphotericin B, MEPM: meropenem, P/F ratio: oxygen partial pressure/fractional concentration of inspired oxygen ratio, TEIC: teicoplanin, TRALI: transfusion-related acute lung injury, WBC: white blood cell**

vealed a WBC count of 540/μL (neutrophils: 367/μL) and a CRP level of 16.12 mg/dL. On that day, the administered infusion volume was 1,650 mL, and a 500 mL infusion was added before the transfusion because the patient was dehydrated due to diarrhea and fever. His urinary volume was 817 mL over seven hours, but it was not measured accurately due to his diarrhea and incontinence. He was admitted to the intensive care unit (ICU), as he required intubation and mechanical ventilation. A chest radiograph showed bilateral pulmonary edema, as was the case in the first episode, and pleural effusion (Fig. 1D). Left ventricular asynergy was not seen on transthoracic echocardiography. On day 13, his oxygenation level improved markedly. Washed platelet preparations were used after this episode. The patient's pulmonary edema gradually improved (Fig. 1E, F). After diuretic treatment for pleural effusion, he was extubated and left the ICU on day 16. This episode was also suspected to have been due to TRALI, but the used platelet preparation and a sample of the patient's blood could not be preserved because the onset of the condition occurred at night and during a national holiday. No further TRALI episodes occurred after we starting to use washed platelet preparations. The patient's clinical course is described in Fig. 2.

The findings of the analysis conducted by the Japanese Red Cross Society after the first episode revealed that the platelet preparation that had been given to the patient was positive for anti-HLA antibodies. A cross-matching test between the patient's T lymphocytes and the transfused blood also produced a positive result (Table). The patient's serum N-terminal pro brain natriuretic peptide (NT-proBNP) level did not increase after the transfusion, which suggested that the pulmonary edema was not cardiogenic. These findings indicated that the donor's anti-HLA antibodies had thus caused the first TRALI episode.

Table. Laboratory Findings Obtained after the First Episode of TRALI.

Tests	Results	
CRP	12 hours before TRALI	11.37 mg/dL
	Onset of TRALI	13.01 mg/dL
NT-proBNP	12 hours before TRALI	1,700 pg/mL
	Onset of TRALI	843 pg/mL
Anti-plasma protein antibody	Negative	
Plasma protein deficiency	None	
Anti-HLA antibody	Recipient	class I and class II negative
	Donor	class I and class II positive
Anti-HNA antibody	Recipient	negative
	Donor	negative
Cross-matching test between the recipient's T lymphocytes and the donor's transfused blood	Positive	

CRP: C-reactive protein, HLA: human leukocyte antigen, HNA: human neutrophil antigen, NT-proBNP: N-terminal pro-brain natriuretic peptide, TRALI: transfusion-related acute lung injury

Discussion

In our case, the first episode met the diagnostic criteria for TRALI (1), and the patient was diagnosed with TRALI based on his clinical course and laboratory findings. In the second episode, we could not examine the preparation or the patient's blood, but we strongly suspected TRALI based on the patient's clinical course. Bilateral pleural effusion and non-cardiac pulmonary edema occurred during the second TRALI episode. The patient's PaO_2/FIO_2 ratio had already improved to >250 on the day after his admission to the ICU, but it took four days for him to be extubated because gradual diuretic treatment was used to treat his pleural effusion. Although TRALI is a very rare condition, it is considered that most likely our patient developed TRALI twice within a short period of time.

A two-hit model is advocated as one of the mechanisms that causes TRALI (4, 5). The first hit involves the risk factors possessed by the patient, which can include increased levels of interleukin-8, liver surgery, chronic alcohol abuse, shock, a high peak airway pressure while being mechanically ventilated, smoking, a positive fluid balance, and/or high levels of CRP (2, 8). When a transfusion is added as the second hit, anti-leukocyte antibodies, such as anti-HLA class I or II antibodies or anti-HNA antibodies, from the donor or recipient activate pulmonary neutrophils. Consequently, the recipient develops pulmonary edema due to damage to the pulmonary endothelial cells (9, 10). This is antibody-mediated TRALI. In the first episode in our case, it is speculated that the patient had an increased CRP level caused by febrile neutropenia (the first hit), and the addition of a platelet transfusion containing anti-HLA antibodies (the second hit) caused antibody-mediated TRALI. However, in 20% of TRALI cases, no antibody is detected in either the donor or recipient. This non-antibody-mediated form of TRALI is caused by a different type of second hit, such as lipid mediators, extracellular vesicles, or aged blood cells in the transfusion (11). In our case, although the cause of the second episode could not be examined in detail, the second episode might have involved non-antibody-mediated TRALI because it was quite unlikely that two platelet preparations in a row were positive for anti-leukocyte antibodies. Moreover, the second TRALI episode only occurred three days after the first episode; therefore, it might have been associated with other factors besides the transfusion.

A threshold model has been advocated for considering individual predisposing risk factors for TRALI (6, 7). This model suggests that various factors in the donor or recipient activate pulmonary neutrophils, and TRALI occurs when the neutrophil activation level reaches the required threshold. In this model, even if individual risk factors cannot cause TRALI alone, concomitantly occurring risk factors might cause TRALI via the cumulative activation of neutrophils. This model was applied to our case. It is speculated that the patient's neutrophils were mildly activated by his AML. In the first episode, a platelet transfusion containing anti-HLA antibodies, which resulted in strong neutrophil activation, was administered, and the neutrophil activation level induced by the combination of AML and the transfusion reached the threshold; thus, antibody-mediated TRALI occurred. TRALI is said to resolve spontaneously within 96 hours (12, 13), and the activated status of the pulmonary neutrophils persists during this period. In the second episode, which occurred 72 hours after the first episode, it is likely that the patient's pulmonary neutrophils were still more strongly activated than usual due to the first TRALI episode. Therefore, even if the transfusion had not resulted in strong neutrophil activation, the cumulative neutrophil activation level induced by the additional transfusion was enough to reach the threshold, and hence, non-antibody-mediated TRALI occurred. Several months later, when the activation of the patient's neutrophils was probably only very mild, the patient did not develop TRALI despite receiv-

ing an unwashed platelet transfusion.

To prevent antibody-mediated TRALI, it is recommended that transfusions containing anti-leukocyte antibodies should be avoided, e.g., fresh frozen plasma derived only from male donors should be used (14-16) because of the high anti-leukocyte antibody positivity rate of females with a history of pregnancy, and donors that have previously been associated with TRALI should also be excluded. As well as antibodies, plasma proteins and biological response modifiers are also associated with the onset of TRALI. These are contained in plasma; therefore, it has been reported that washed platelet preparations, from which as much plasma as possible is removed, are effective for preventing TRALI (17). Actually, our patient no longer developed TRALI after we started to use washed platelets, even though it was considered that his neutrophils were still activated. However, the pathogenesis of TRALI has not yet been fully elucidated, and there are no established treatment strategies for non-antibody-mediated TRALI.

Conclusion

In our case, TRALI occurred twice in the same patient after platelet transfusions. Various factors that activate neutrophils, in addition to anti-leukocyte antibodies, are associated with the onset of TRALI. It should therefore be noted that administering platelet transfusions when a patient's neutrophils are in a highly activated state might cause TRALI.

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

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Yuina Akagi and Shogo Murata contributed equally to this work.

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