【 CASE REPORT 】

Pulmonary Involvement of Acute Myeloid Leukemia Mimicking Transfusion-related Acute Lung Injury

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Abstract:
Transfusion-related acute lung injury (TRALI) is defined as a new episode of acute lung injury (ALI) occurring during transfusion or within 6 hours of transfusion completion. A 66-year-old man suffering from acute myeloid leukemia developed acute respiratory distress syndrome after platelet transfusion. TRALI was diagnosed clinically, but an autopsy showed leukemic cells in diffuse pulmonary edema. Anti-human neutrophil antigen (HNA)-3a antibodies were detected in the donor serum, and the HNA-3 genotype of the patient was identified as a/a. This case was considered to represent pulmonary involvement of acute myeloid leukemia, rather than TRALI. A revision of the definition of TRALI accounting for hematological malignancies should therefore be considered.

Key words: transfusion-related acute lung injury, acute myeloid leukemia, autopsy

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Introduction

Transfusion-related acute lung injury (TRALI) is defined as a new episode of acute lung injury (ALI) that occurs during transfusion or within 6 hours of transfusion completion and is not temporally related to a competing etiology for ALI (1). The diagnosis of TRALI is based on clinical and radiographic findings and is not dependent on the results of laboratory tests or any proposed pathophysiological mechanisms. Inductively, TRALI is pathologically characterized by pulmonary edema with neutrophilic aggregates in the pulmonary microvasculature and the extravasation of neutrophils (2).

The pathogenesis of TRALI needs both a predisposition in the patient and mediators in the transfusate (3). Mediators in the transfusate include both antibody mediators and non-antibody mediators. The transfusion of leukocyte antibody-containing blood products increases the risk of TRALI 15-fold (4). Alloantibodies directed against human neutrophil antigen (HNA)-3a are related to fatal TRALI (5). The HNA-3 genotypes are a/a, a/b, and b/b.

Many reports have described the clinical diagnosis of TRALI in leukemia patients. However, none of those reports have been dissected. We herein report a case of acute pulmonary involvement of acute myeloid leukemia (AML) initially diagnosed with TRALI.

Case Report

A 66-year-old man was admitted to our hospital with hyperleukocytosis [white blood cell (WBC) count, 130.3×10^9/L]. Chronic myelomonocytic leukemia (CMML)-1 had been diagnosed 6 weeks prior to this admission, based on the findings of 50.2% mature monocytes and 0.6% blasts in the bone marrow and the absence of a bcr-abl1 fusion gene. After admission, AML with myelodysplasia-related changes (MRC) was diagnosed, based on the findings of 5.2% ma-
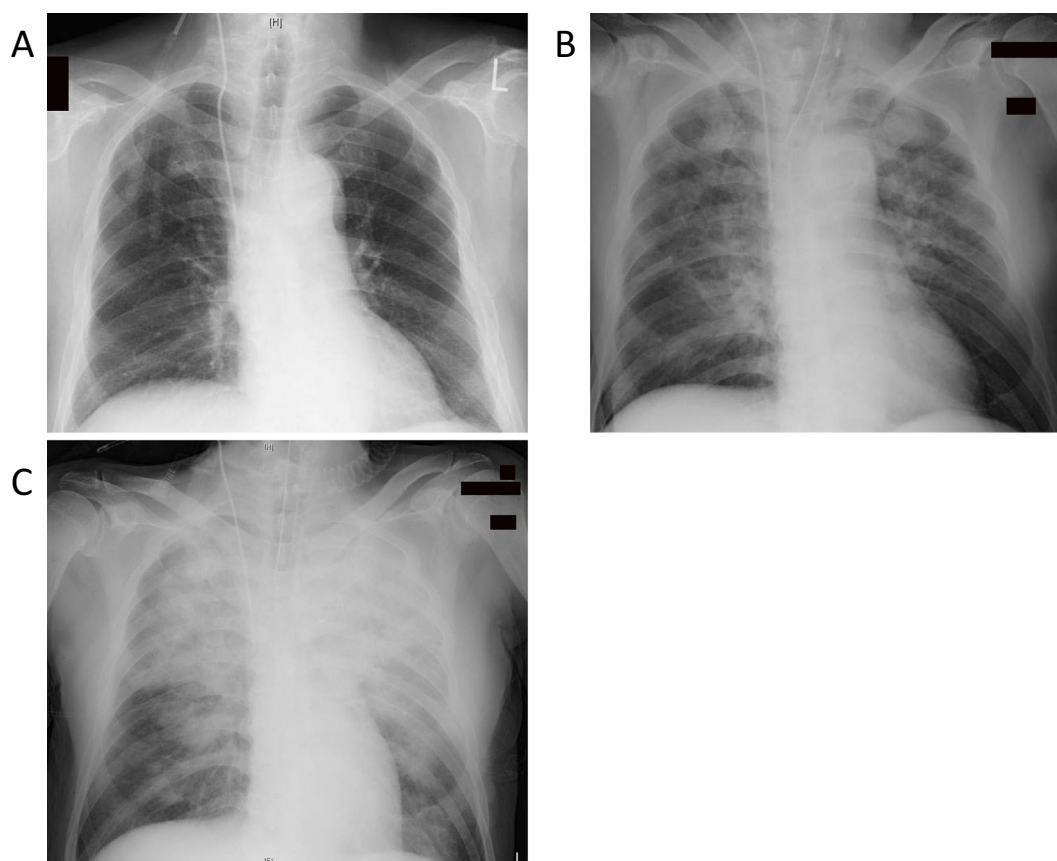
Figure 1.   Chronological chest X-rays. The lungs were normal on admission (A). Three days later, he developed dyspnea during platelet transfusion (B). The next day, he died (C).

ture monocytes, 58.2% abnormal promonocytes, 20.5% abnormal monoblasts, and 0.5% myeloblasts in the bone marrow and the history of CMML. Disseminated intravascular coagulation (DIC) was noted, in accordance with the criteria of the Japanese Ministry of Health and Welfare, and the administration of recombinant human soluble thrombomodulin was initiated.

Three days later, the patient's thrombocytopenia (platelet count, $41×10^9$/L) was found to have progressed. As acute DIC caused by acute leukemia with a platelet count <50× 10^9/L was an indication for platelet transfusion (6), a leukoreduced apheresis product with ABO-identical platelets was transfused. His WBC count was $135.3×10^9$/L, comprising 1% band neutrophils, 5.5% segmental neutrophils, 10% lymphocytes, 83% mature and immature monocytes, 0.5% polychromatic erythroblasts, and 0% myeloblasts. Thirty minutes after starting the transfusion, the patient suddenly developed dyspnea, and the room-air hemoglobin oxygen saturation as measured by pulse oximetry percutaneous oxygen saturation (SpO_2) decreased to 82% from 96% before the transfusion. We were certain that transfusion-associated circulatory overload (TACO) was not involved, as no cardiomegaly was apparent on chest X-ray and the levels of brain natriuretic peptide (BNP) were not elevated. Despite treatment for anaphylaxis, worsening hypoxemia compatible with acute respiratory distress syndrome (ARDS) (7) resulted in the requirement of intubation and mechanical ventilation. Ranimustine

was administered at 50 mg to obtain anti-leukemic effects. His WBC count was $76.2×10^9$/L at that point. The next day, the WBC count surged to $333.7×10^9$/L, and he died (Fig. 1). Sepsis was excluded based on negative results from two consecutive blood cultures.

An autopsy revealed interstitial infiltration of CD14-positive leukemic cells in diffuse pulmonary edema (Fig. 2). Furthermore, some alveoli were involved, and almost all pulmonary capillaries were occupied by leukemic cells, not neutrophils. No hyaline membrane was apparent. These findings were compatible with leukostasis, defined as the intravascular accumulation of leukemic cells occupying most or all vascular lumina, with or without the presence of fibrin. In addition, all of the main organs showed the infiltration of leukemic cells.

Anti-HNA-3a antibodies were detected in donor serum by a granulocyte immune fluorescence test (GIFT) (8) and granulocyte agglutination test (GAT) (Fig. 3) (9). The HNA-3 genotype was identified as a/a by a high-resolution melting analysis (10).

Discussion

To our knowledge, this is the first reported autopsy case of clinically diagnosed TRALI in a leukemia patient. The lungs of the patient showed the pathological involvement of CD14-positive leukemic cells in diffuse pulmonary edema.
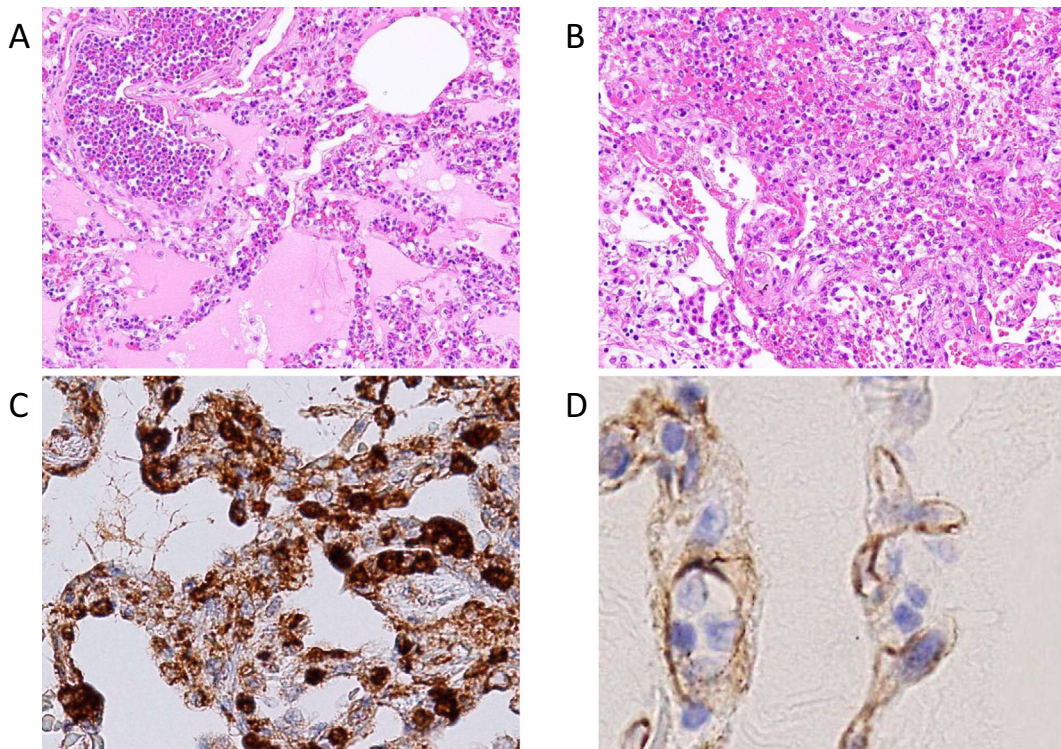
Figure 2.   Histological sections of the lung from a patient suffering acute respiratory distress syndrome. Leukemic cells are seen infiltrating the interstitium and occupying middle-sized blood vessels in diffuse pulmonary edema (A). Some alveoli are involved, with the destruction of the normal lung architecture (B). Abnormal promonocytes and monoblasts show positive staining for cluster of differentiation (CD) 14 (C). CD34 staining reveals obstruction of almost all pulmonary capillaries (D).
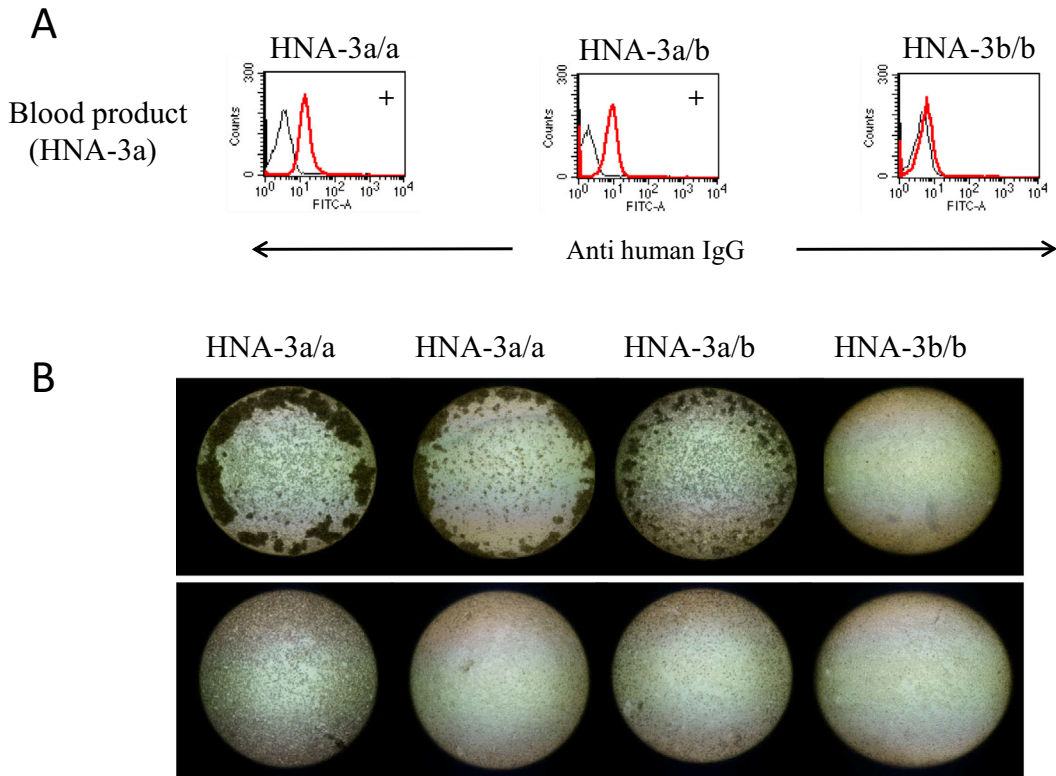

Figure 3.   Detection of anti-HNA-3a antibodies in the donor serum by a granulocyte immune fluorescence test (GIFT) (A) and granulocyte agglutination test (GAT) (B). A tendency to react to the HNA-3 genotype a/a is evident.

Anti-HNA-3a antibodies were detected in donor serum, and the HNA-3 genotype of the patient was a/a.

TRALI was diagnosed clinically, but an autopsy revealed leukemic cells in diffuse pulmonary edema. This case was therefore considered to represent pulmonary involvement of AML rather than TRALI. Admittedly, we cannot rule out TRALI entirely, as the criteria for TRALI do not include any histological findings, and the exclusive risk factors for TRALI do not include hematological malignancies (1). However, all clinical syndromes should be resolved on the basis of the pathological description of etiology. In this case, leukemic cells overwhelmed the lungs, while neither neutrophilic aggregates in the pulmonary microvasculature nor extravasation of neutrophils, as histological characteristics of TRALI, were identified. The fact that pulmonary involvement of AML with hyperleukocytosis causes ARDS is well established (11, 12). Indeed, it is difficult to distinguish between pulmonary involvement of AML and TRALI precisely because leukemic cells occasionally behave like neutrophils in TRALI. As such, revising the definition of TRALI to take hematological malignancies into consideration seems warranted.

Anti-HNA-3a antibodies were detected in donor serum and the patient showed an HNA-3 genotype of a/a. In addition, dyspnea developed during the infusion of a platelet transfusate containing anti-HNA-3a antibodies. These lines of evidence indirectly suggested TRALI. Although patients suffering from hematological malignancies are considered to be at risk of developing clinical TRALI (13), how leukemic cells behave when anti-leukocyte alloantibodies are transfused and which stage of leukocyte differentiation HNA-3 is expressed at remain unclear, because these issues have yet to be investigated pathologically.

TRALI has been investigated *in vivo* under conditions of normal neutrophil function. In the present case, neutropenia and hyperleukocytosis of CD14-positive leukemic cells were present. However, these facts do not exclude TRALI, because neutrophil depletion does not prevent mice from developing TRALI induced by anti-HNA-3a antibodies, despite alleviating the severity of lung injury (14).

This case was considered to represent pulmonary involvement of AML rather than TRALI. A revision of the definition of TRALI accounting for hematological malignancies should be considered. To reduce the risk of TRALI, plasma-removed platelet concentrate (15) and male-only fresh-frozen plasma (16, 17) should be used in the future.

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