Fatal TRALI Associated with Neutrophil Antibodies in a Recipient of Pre-Storage Leukocyte-Reduced Blood Components

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Abstract

A 53-year-old man developed possible transfusion-related acute lung injury (TRALI) after red cell component transfusion. The patient developed autoimmune neutropenia with the expression of neutrophil antibodies. Neutrophil aggregation, endothelial damage, and development of a large thrombus containing platelets were observed post mortem in his pulmonary vessels. The patient also had subacute organizing pneumonia. He received blood components treated with universal pre-storage leuko-reduction. Even though leukocytes in the blood components are reduced to a few million by this process, TRALI can be fatal, as was the case for this recipient, who had subacute organizing pneumonia in conjunction with immune-mediated neutropenia.

Key words: transfusion-related acute lung injury (TRALI), universal prestorage leukoreduction, neutrophil antibodies, autoimmune neutropenia

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Introduction

Transfusion-related acute lung injury (TRALI) is an acute lung injury that is manifested by lung edema either during or within 6 hours after blood transfusion. Reacting antibodies are detected in 60 to 90% of instances of immune-mediated TRALI, predominantly in the blood from the donors. When the antibodies present in the donor react with leukocytes in the recipient’s blood, the resulting mixed lymphocyte reaction (MLR) is often fatal (1). Nevertheless, reacting antibodies have been detected in 6% of recipient’s blood (2). Neutrophil antibodies are predominantly involved in immune-mediated TRALI. Here, we report that neutrophil antibodies in a recipient caused fatal TRALI, even though the patient received blood components that were treated with universal pre-storage leuko-reduction (ULR). TRALI caused the highest number of transfusion related fatalities reported to the Food and Drug Administration of the United States (FDA); however, autopsy cases are not frequently reported to study pathogenic aspects (3). The autopsy we performed revealed that the patient also had pulmonary tuberculosis infection as well as subacute organizing pneumonia; the association with TRALI is discussed.

Case Report

A 53-year-old man was referred to our hospital because of pancytopenia. He had been admitted to a local mental hospital with alcoholism, when he was diagnosed with aplastic anemia (AA). Medical examinations revealed that the patient also had severe primary hypothyroidism associated with chronic lymphocytic thyroiditis and complicated with myxedema. Although the myxedema did not lead to congestive heart failure, it did cause mild lung congestion, as detected by ultrasonic cardiography. With regard to his pancytopenia, his bone marrow showed normocellularity, which ruled out AA. Marked macrocytic anemia without folate or vitamin B12 deficiency indicated that his pancytopenia was associated with severe hypothyroidism. At the time, he had a hemoglobin (Hb) level of 7.6 g/dL; however, 2 months later, he was referred to us again with aggravation of Hb level to 4.2 g/dL. He complained of mild dyspnea and his percutaneous oxygen saturation (SpO2) was 92.2%
on room air. His chest X-ray demonstrated more congestion than his first visit at our hospital. He received blood transfusion of two units of red cell components (RCCs). He complained of worsening dyspnea and his blood pressure decreased from 116/66 mmHg before transfusion to 99/61 mmHg. His SpO2 1 hour and 25 minutes later was 79%. The blood transfusion was discontinued immediately and hydrocortisone and methylprednisolone were administered. However, he presented apnea and cardiac arrest 25 minutes later. Although cardiopulmonary resuscitation was initiated, the patient did not respond and he died. His chest X-ray demonstrated diffuse, severe lung edema.

Results

The samples of the patient’s blood taken before transfusion and the donor’s blood were sent to the Japan Red Cross Society (JRCS) to determine the association between the transfusion and his death. The patient was found to have neutrophil antibodies instead of human leukocyte antigen (HLA) antibodies. We were unable to identify which antigens were involved on the neutrophils in the present case. However, the donor did not have antibodies against neutrophils or HLA. Therefore, we believe that he developed possible TRALI in association with his neutrophil antibodies, according to the diagnostic criteria adapted by Kleinman et al (4). In addition, we reached a diagnosis of autoimmune neutropenia, supported by the fact that his bone marrow showed a lack of mature neutrophils (segmented neutrophils were 0.8% of nucleated cells in bone marrow). We performed autopsy with the consent of his relative. The autopsy revealed neutrophil aggregation, endothelial damage, and the formation of a large thrombus comprising platelets in the pulmonary vessels; lung atelectasis, lung edema, alveolar hemorrhage, and hyaline membrane, which suggested acute lung injury (Fig. 1). These pathological findings supported the diagnosis of TRALI. In addition, we also observed severe fibrosis in the alveolar septum indicating interstitial pneumonitis, organizing pneumonia (Fig. 2), and pulmonary tuberculosis. These pathological findings were considered to be subacute to chronic inflammatory findings. Alcian blue stain confirmed the presence of mucin in the bone marrow, myocardium, pancreas and liver, which indicated that these organs were affected with myxedema.

Discussion

The present case had all of the pathological findings that have been documented in reported cases with TRALI: lung edema, leukocyte aggregation, pneumonitis, hyaline membrane, intra-alveolar leukocyte infiltration, intra-alveolar bleeding, atelectasis, and interstitial inflammation (5). The autopsy confirmed that he was incidentally infected with pulmonary tuberculosis as well as affected with subacute organizing pneumonia, although his chest X-ray and blood test on admission did not indicate the presence of these pulmonary lesions. It is unclear when he was infected with pulmonary tuberculosis; nevertheless, this infection did not seem to be active. Subacute organizing pneumonia might promote the proinflammatory condition rather than pulmonary tuberculosis. Nine, including the present case, of ten reported cases had severe lung lesions before developing TRALI (5). Circulating neutrophils do not show their full microbicidal capacity when challenged with biological activating agents unless they have first been primed. Priming refers to a process whereby the response of neutrophils to an activating stimulus is potentiated (6). In vivo studies have demonstrated that surgical procedures and active infections induce neutrophil priming in patients (7). The activation of neutrophils is considered to be the second step in the activation of the pulmonary endothelium for sequestration of polymorphonuclear neutrophils (PMNs) in the microvasculature. The third step is the infusion of specific antibodies directed against antigens on the neutrophil or biologic response modifiers, which activate the microbicidal arsenal of the se-
questered PMNs, thus resulting in endothelial damage, capillary leak and ALI (8). This model has been confirmed in a rat lung model and in vitro using human pulmonary microvascular endothelial cells as targets (9).

The current case presented with cardiac and respiratory arrest 1 hour and 50 minutes after the RCC transfusion. We did not find any myocardial injuries, except for myxedema on autopsy. Neutrophil antibodies were detected in the blood samples from the patient both before and after the blood transfusion. We did not perform MLR between blood samples from the donor and the recipient. However, we found that the serum tryptase level in the patient increased from 5.3 μg/L before transfusion to 22.1 μg/L after transfusion. Hence, we suggest that the neutrophil antibodies in the recipient caused TRALI, although these are not identified in every instance of immune-mediated TRALI. He had chronic lymphocytic thyroiditis demonstrating high titer of antibodies against thyroid peroxidase. He had never received a blood transfusion. He had been treated with some of antipsychotics because of alcoholism. Neutrophil antibodies might be induced by this autoimmune disease (10) or medication which he received. There are some reports showing that antibodies in recipients are associated with TRALI, reducing leukocytes from the donor’s blood components before transfusion decreases the risk of developing TRALI (11). ULR of whole blood products was instituted by the JRCS in January 2007, while all blood products were irradiated before then. Overall, the leukoreduced RCCs and platelet concentrates contain less than 5×10⁶ white cells (12). It is important that, even if leukocytes were reduced to a few million per unit, this small number of leukocytes can lead to the development of TRALI when the donor leukocytes react with the recipient’s neutrophil antibodies.

Antibodies to human neutrophil alloantigen (HNA)-3a are commonly implicated in TRALI. The fact that one patient experienced TRALI on two occasions when he was transfused with platelets from a donor with anti-HNA-3a and that none of the other nine recipients of the same donor’s plasma experienced TRALI suggest that the patient’s factors contribute to neutrophil antibody-mediated transfusion reactions (13). Some reports have described recipients with autoimmune disease who developed TRALI. It is interesting to note that a recipient presenting with immune-mediated pancycopenia after reduced-intensity allogeneic bone marrow transplantation developed fatal TRALI (14). It should be noted that subacute organizing pneumonia may have increased the risk of TRALI in this patient by reacting with neutrophil antibodies in the recipient, and the autoimmune diseases of chronic lymphocytic thyroiditis and autoimmune neutropenia ultimately contributed to the fatal TRALI, even though he received pre-storage leuko-reduced blood products.

References

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