Diagnosis of Transfusion-Related Acute Lung Injury: TRALI or Not TRALI?

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Abstract. TRALI is a challenging diagnosis for both the transfusion specialist and the clinician. A Canadian consensus panel has recently proposed guidelines to better define TRALI and its implications. The guidelines recommend classifying each suspected case in one of the following 3 categories: (1) “TRALI,” (2) “Possible TRALI,” or (3) “Not TRALI.” We report the clinical presentation, laboratory evaluation, and management of 3 patients with respiratory failure (RF) following allogeneic blood transfusions. These patients all experienced RF within 6 hr post-transfusion. Based on a review of the clinical and laboratory data and applying the Canadian guidelines, the first patient, a 67-yr-old man with chronic myelomonocytic leukemia, was diagnosed as “TRALI” due to the sudden onset of RF requiring intensive resuscitation. The second patient, a 55-yr-old man with aplastic anemia, was diagnosed as “Possible TRALI” due to pre-existing RF that worsened after blood transfusion. The third patient, a 1-yr-old male, was diagnosed as transfusion associated circulatory overload (TACO) and “Possible TRALI,” although his RF improved after treatment with diuretics. In all 3 cases, the blood donor center was informed of the suspected TRALI reactions. The remaining blood products from the donors associated with these reactions were quarantined. After review of the clinical data, the donors associated with cases #1 and #3 were screened by the blood center for granulocyte and HLA antibodies. Using a Luminex flow bead array, the following class I and class II antibodies specific for patient #1 were identified in the respective donor: anti-A25, B8, B18, and anti-DR15, DR17. Subsequently, donor #1 was permanently deferred. A non-specific IgM anti-granulocyte antibody was identified in the donor associated with case #3, and this donor was subsequently disqualified from plasma and platelet donations. In conclusion, the Canadian guidelines to categorize patients suspected of TRALI provide a useful framework for evaluation of these patients and their respective blood donors.

Keywords: platelet transfusion, anti-HLA antibodies, anti-neutrophil antibodies, acute lung injury, diagnostic guidelines

Introduction

Transfusion-related acute lung injury (TRALI) is a complication of blood transfusion and has been recently reported by the FDA as the most frequent cause of transfusion-associated fatality [1]. The reported incidence of TRALI varies from 1 in 5000 to 1 in 13,000 transfusions in the United States [2]. The lack of standardized diagnostic criteria explains why the true incidence of TRALI has been uncertain. To better define the diagnosis of TRALI, a consensus panel was convened in April 2004 by the Canadian blood services and the International Society of Blood Transfusion’s Committee on Biomedical Excellence for Safer Transfusion. The panel proposed diagnostic guidelines for TRALI and recommended approaches to laboratory and
donor management. If a diagnosis of TRALI is suspected following blood transfusion, the consensus panel recommended naming it: (1) “TRALI,” (2) “Possible TRALI,” or “Not TRALI” based on clinical and radiographic criteria within 6 hr of a completed blood transfusion. Applying these guidelines [3], we report 3 suspected cases of TRALI, which all occurred at Stanford Hospital and Clinics within the span of one week. We present the results of the laboratory investigations of each of these cases.

Methods

Transfusion reaction evaluation. For each suspected transfusion reaction, the nursing staff of Stanford Hospital and Clinics are trained to stop the transfusion immediately, flush the iv site to keep the line open, ensure that the blood component was given to the correct patient, and assess and record the patient’s signs and symptoms. A transfusion reaction report form is then completed, including the patient’s diagnosis, history of previous reactions, date and time of reaction with associated symptoms, and vital signs before and after transfusion. The report is sent to the Transfusion Service (TS) along with a post-transfusion blood specimen and the blood bags. The TS technologist performs a clerical check, inspects the post-transfusion blood sample for hemolysis, and repeats ABO/Rh typing on both the transfused unit and the patient’s blood sample, along with an antibody screen and direct Coombs’ test if hemolysis is suspected. The blood products are sent for Gram staining and culture if signs of sepsis are present.

If the symptoms indicate hypoxemia and/or respiratory failure, the diagnosis of TRALI is suspected; all blood products related to the implicated unit are quarantined and the TS Medical Director is notified. Following review of the clinical history and presentation of the reaction, the TS physician evaluates the suspected TRALI reaction based on a definition of acute lung injury (ALI) used by the international pulmonary and critical care community [4]. ALI is characterized by (i) acute onset of hypoxemia (oxygen saturation <90% by pulse oximetry) for a patient who is breathing room air, or a PaO2/FiO2 ≤300 mmHg, (ii) bilateral infiltrates on frontal chest x-ray (CXR), and (iii) no evidence of circulatory overload. The TS physician reports the reactions as (1) “TRALI” if ALI occurred within 6 hr post-transfusion with no temporal relationship to another risk factor for ALI, (2) “Possible TRALI” if ALI occurred within 6 hr post-transfusion, but with alternative risk factors for ALI, or (3) “Not TRALI” [3].

Laboratory tests. In accordance with the Canadian consensus panel’s recommendations [3], the complete laboratory TRALI investigation is initiated for all patients diagnosed as “TRALI.” For patients diagnosed as “Possible TRALI,” the laboratory investigation is initiated at the discretion of the blood collection center. For the complete laboratory TRALI investigation, donor samples are tested at the Stanford Medical School Blood Center HLA Laboratory for HLA Class I and Class II antibodies using the Flow PRA (One Lambda, Canoga Park, CA) for screening, as well as the single antigen flow bead (One Lambda) for identification of antibody specificities. Neutrophil antibodies are identified at the Southeastern Wisconsin Blood Center using standard flow cytometry. Recipients are HLA-typed at the Stanford Medical School Blood Center HLA Laboratory by a DNA-based low-resolution typing method using polymerase chain reaction amplification (Labtype, One Lambda).

Donor management. The plateletpheresis donors of each case are first considered “temporally associated donors” (within 6 hr) for the suspected TRALI reaction. Then, a “temporally associated donor” is considered an “implicated donor” for the TRALI reaction if antibodies to an HLA Class I or II antigen or human neutrophil antigen are present on the respective recipient’s granulocytes defined after genotyping.

Case Reports

Case 1. This patient was a 67-yr-old man with a history of chronic myelomonocytic leukemia (CMML), progressing to acute myeloid leukemia, for which he was treated with tipifarnib, a farnesyl transferase inhibitor, as part of a clinical trial at another institution. On day 14 of tipifarnib treatment, he came to the outpatient clinic and presented with mild fatigue, no cardiorespiratory symptoms, blood hemoglobin concentration of 8.6 gm/dl, hematocrit of 25.1%, WBC of 3,300/µl, and platelet count of 3,000/µl. He received one single-donor apheresis platelet transfusion after being pre-medicated with acetaminophen (650 mg po) and diphenhydramine (25 mg po). Approximately 20 min after completion of the transfusion, the patient complained of a “tickle in throat” although his vital signs remained stable and lungs were clear. Diphenhydramine (25 mg iv) was administered. The patient initially improved, but during the next 30 min he developed coughing with frothy secretions and shortness of breath. The CXR revealed bilateral patchy opacities without enlarged cardiac shadow. In the absence of hives, wheezing, or laryngeal edema, the differential diagnosis of anaphylaxis was excluded. No infection was identified, with negative reports from cultures of urine, blood, and sputum, collected at the time of presentation. The patient required mechanical ventilation and was transferred to the intensive care
unit (ICU) where he became hypotensive and oliguric, requiring pressors and dialysis. Pulmonary capillary wedge pressures ruled out cardiogenic pulmonary edema; central venous pressures along with cardiac echo revealed severe hypovolemia due to progressive pulmonary edema and third-spacing of fluid. Despite maximal efforts of resuscitation the patient died 21 hr post-transfusion. A diagnosis of “TRALI” was highly suspected.

Case 2. This patient was a 55-yr-old man with a history of aplastic anemia treated with antithymocyte globulin and cyclosporine, who presented to the oncology clinic with neutropenic fever. Subsequently he was admitted to the hospital with sepsis and hypotension and transferred to the ICU for respiratory and cardiovascular support. On admission his blood hemoglobin concentration was 75 gm/dl, hematocrit 21.3%, WBC 500/μl, and platelet count 7,000/μl. The patient received 2 units of packed red blood cells and 2 plateletpheresis units. Approximately 2 hr after completion of the second plateletpheresis transfusion, he exhibited worsening respiratory function with tachypnea and abrupt arterial hypoxemia with a decline in the PaO₂ from 132 mmHg to 53 mmHg. The CXR showed diffuse bilateral opacities, a right pleural effusion, and no evidence of left atrial hypertension. Blood and urine cultures were negative at the time of the reaction. Despite intense respiratory and cardiovascular support, the patient’s condition progressively worsened and he died on day 21 of his admission. The etiology of respiratory failure was considered by the TS team as “Possible TRALI.”

Case 3. This patient was a 1-yr-old male who presented to the oncology clinic with a history of a small blue cell tumor on the left anterior thigh, along with pulmonary metastases. After 4 cycles of chemotherapy, he received radiation therapy to his chest and thigh. During a routine check of his blood cell count, the patient was found to have a blood hemoglobin concentration of 6.4 gm/dl and a platelet count of 7,000/μl. He was transfused with 1 whole plateletpheresis unit. Approximately 1 hr after completion of the platelet transfusion, the patient presented with increased respiratory rate from 32 to 72, cyanosis, and hypoxemia with a PaO₂ of 57 mmHg. The CXR showed bilateral pulmonary infiltrates consistent with pulmonary edema, as well as bilateral pleural effusions. The patient was admitted to the hospital for investigation and treatment of respiratory failure. The differential diagnosis at the time of admission for respiratory distress included: (1) intrinsic pulmonary pathology secondary to metastases, (2) transfusion-associated circulatory overload, (3) pneumonia, and/or (4) TRALI. The patient was intensely treated with iv furosemide to induce diuresis. Although he remained O₂-dependent via nasal cannula for about 2 weeks, he responded well to the diuretic treatment, which ameliorated the pulmonary edema on CXR. Cultures of blood, urine, and bronchoalveolar lavage were negative. It was concluded that his respiratory distress and pleural effusions were not due to infection, but more likely attributable to a combination of TACO (in the setting of slowly progressive radiation pneumonitis) and “Possible TRALI.”

Results of Laboratory Investigations

A hemolytic reaction was excluded in each of the 3 patients. Bacterial contamination from transfused products was also ruled out, based on negative cultures from transfused blood products as well as patient blood samples at the time of transfusion. Serum samples from the donors associated with patients #1 and #3 were subjected to a complete serologic evaluation for TRALI. No laboratory investigation was initiated in case #2.

Patient #1 had the following HLA phenotype: A25, AX; B8, B18, Bw4; DR15(2), DR17(3), DR51, DR52; DQ2, DQ6. For patient #1, the associated donor was a para-1 female who had both HLA Class I and Class II antibodies, but no anti-neutrophil antibodies. HLA antibodies were first screened by ID flow bead array, confirmed with the Luminex class I single antigen flow bead array, and identified for specific Class I as anti-B8, B39, B64, B65 strong reacting (8+) antibodies, as anti-B18, B35, B51, B75, B38, B71 and A25, A33, A68 weaker reacting (4+) antibodies, and as anti-B52, B53, B39, B41, B42, B54, B72, B77, B78, and A26, A66, and A69 marginally reacting (2+) antibodies.

Class II antibodies were also confirmed by
Table 1. Summary of the 3 suspected cases of TRALI.

<table>
<thead>
<tr>
<th>Case</th>
<th>Recipient (age &amp; sex)</th>
<th>Diagnosis</th>
<th>Implicated blood component</th>
<th>Reaction report</th>
<th>Donor antibody screen</th>
<th>Donor deferral</th>
</tr>
</thead>
<tbody>
<tr>
<td>#1</td>
<td>67 yr, male</td>
<td>CMML*</td>
<td>plateletapheresis</td>
<td>“TRALI”</td>
<td>A25, B8, B18, DR15, DR17</td>
<td>permanent</td>
</tr>
<tr>
<td>#2</td>
<td>55 yr, male</td>
<td>aplastic anemia</td>
<td>plateletapheresis</td>
<td>“Possible TRALI”</td>
<td>untested</td>
<td>none</td>
</tr>
<tr>
<td>#3</td>
<td>1 yr, male</td>
<td>blue cell tumor</td>
<td>plateletapheresis</td>
<td>“Possible TRALI”</td>
<td>IgM anti-PMN† broad reactivity</td>
<td>plasma and platelet donations</td>
</tr>
</tbody>
</table>

*CMML: chronic myelomonocytic leukemia.  
† PMN: polymorphonuclear neutrophil or granulocyte.

single antigen flow beads and identified as DR1-DR18 but not DR7, DR51, DR52, DQ8 and DQ9. In conclusion, the complete TRALI investigation of patient #1 confirmed that the tested donor was implicated in the TRALI reaction experienced by this patient, with patient-specific antibodies identified against HLA class I (A25, B8, B18) and against HLA class II (DR15 and DR17).

For patient #3, the associated donor was a non-transfused male who tested negative for HLA antibodies and for IgG neutrophil antibody, but positive for IgM anti-neutrophil antibody. The IgM reactivity was not specific for any neutrophil alloantigen.

Based on these findings, the plateletapheresis donor #1 was permanently deferred. No action was taken for donor #2, as no laboratory investigation took place. Finally, donor #3 was disqualified from further donation of plasma products or platelets.

The 3 suspected cases of TRALI are summarized in Table 1.

Discussion

TRALI is the most common cause of fatality related to blood transfusion and it often remains unrecognized clinically [1]. The pathophysiology of TRALI is only partially understood. In order to recognize TRALI consistently, standardized reporting mechanisms are needed. Therefore, our Blood Bank/Transfusion Service has applied the recent TRALI guidelines proposed by a consensus conference [3] to 3 suspected cases of TRALI at our institution. These patients had received chemotherapeutic agents for a hematologic disease or a soft tissue tumor and they all presented with symptoms of ALI within 2 hr after completion of a blood transfusion. Two of the patients (#1 and #3) had to be admitted to the hospital as a consequence of the suspected TRALI reaction following a plateletapheresis transfusion in the outpatient clinic. Patient #2 was already in the ICU, where his compromised respiratory function worsened after platelet transfusion.

The strength of the clinical recognition of a TRALI diagnosis guides the transfusion service in investigating the associated blood donations, potentially preventing future TRALI reactions from the same donor, and/or preventing future TRALI reactions in the same patient. After careful review of the clinical presentation, a full laboratory investigation was performed in cases #1 and #3; donor #1 was confirmed as being implicated in a TRALI reaction and became permanently deferred; donor #2 was neither tested nor deferred; and donor #3 was disqualified from donating plasma or platelets.

When the TRALI reaction was initially described by Popovsky et al [5,6] in the early 1980s, the laboratory investigations were primarily a confirmatory test with a positive crossmatch between the donor serum and the patient's
granulocytes. The current guidelines of the concensus panel recommend making a definite diagnosis of TRALI based solely on clinical information [3]. Still the clinical diagnosis of a TRALI reaction remains a challenge both for the attending clinician and the Transfusion Service physician. The diagnosis in patient #2 was “Possible TRALI,” due to underlying sepsis with respiratory failure prior to transfusion. Silliman et al [2] emphasizes that risk factors for ALI should not be regarded as criteria against TRALI, which should also be considered in patients with compromised respiratory function if worsening occurs after transfusion [2].

Thus, the laboratory investigation of a TRALI reaction does not merely confirm the TRALI reaction, but also provides an evaluation of the blood donors associated with the TRALI reaction. This evaluation should guide the blood donor center physician in managing the associated donors. The donor testing should be undertaken in all “TRALI” diagnoses made with no preexisting ALI in the patient prior to transfusion, as in case #1. Subsequently donor #1 was confirmed as implicated in TRALI reaction #1 as he had multiple HLA antibodies, some of which matched the recipient’s HLA antigens. In a look back at the donations associated with case #1 (data not shown), we did not observe any TRALI reactions after blood transfusion from the 6 previous donations of the same donor implicated with case #1, including after transfusion of the case #1-related product, which was a double plateletapheresis unit.

Interestingly, Toy et al [7] found no evidence of TRALI after transfusion of blood products from one donor with multiple HLA antibodies into 103 recipients, 25% of whom had ≥1 HLA antigen that matched the donor antibody. Kopko et al [8] reported the presence of a mild to severe respiratory syndrome in 35% of recipients receiving blood products from a donor with anti-human-neutrophil-antigen (HNA)-3a antibody. Therefore, a case of TRALI may represent an isolated event, but donor granulocyte antibodies rather than HLA antibodies seem likely to cause multiple cases of TRALI [8].

Hypothetically, TRALI reaction may be the result of two cumulative events: the first event being linked to the patient (ie, underlying sepsis, hematologic disease, and/or post-surgical status) and the second event being related to the transfusion of potential granulocyte primers (eg, inflammatory cytokines, active lipids and/or alloantibodies) [9,10]. In order to implement definite measures to prevent TRALI reactions, clinicians and transfusion specialists may have to define susceptibility criteria for TRALI in patients receiving blood transfusion.

A recent working group lead by Toy et al [11] from the National Heart, Lung, and Blood Institute (NHLBI) published guidelines to assist critical care physicians in recognizing TRALI. They limited the diagnosis of TRALI to patients with a new onset of severe hypoxemia and they recommended carefully assessing TRALI patients for pre-existing risk factors for ALI [11]. To facilitate TRALI diagnosis, Toy et al [11] gave a helpful list of TRALI-associated symptoms and laboratory findings, one of which is transient leukopenia concomitant to the onset of ALI. In patient #1, diagnosed with a “TRALI” reaction, the WBC remained within normal range, while patients #2 and #3 were neutropenic before the platelet transfusion. In response to the TRALI-Consensus Conference report [3] and the guidelines published by Toy et al [11], a new AABB interim standard was issued in June 2005 [12]. This interim standard (# 5.4.2.1) recommends evaluating blood donors implicated in TRALI or associated with multiple events of TRALI and reassessing their eligibility to donate [12].

In conclusion, application of recommended guidelines for TRALI diagnosis [3] have helped our Transfusion Service physicians to categorize the transfusion reactions in patients with symptoms of respiratory failure as “TRALI,” “Possible TRALI,” or “Not TRAL.” Preventive measures such as donor deferral and/or disqualification for plasma donations have been implemented depending on the results of neutrophil and HLA antibody screening of the associated donors.

The lack of specificity of preventive measures targeting blood donors should encourage clinicians to adhere to blood component utilization guidelines and to minimize inappropriate use of blood products. Interestingly, the 3 patients reported here were severely thrombocytopenic; although none of them was actively bleeding, platelet transfusion was indicated due to the risk of intracranial bleeding.
with platelet counts ≤10,000/µl [13]. Ultimately, specific criteria for TRALI susceptibility will need to be defined as a preventive measure.

References