Pathology Consultation on Transfusion-Related Acute Lung Injury (TRALI)

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Abstract

Transfusion-related acute lung injury (TRALI) is a serious condition characterized by respiratory distress, hypoxia, and bilateral pulmonary infiltrates, which occur within 6 hours of transfusion. Several theories have been proposed to explain the underlying pathologic mechanisms of TRALI. Immune-mediated TRALI accounts for over 80% of reported cases and is mediated by donor antibodies to HLAs and/or human neutrophil antigens (HNA). Immune-mediated TRALI is most commonly associated with donor plasma transfusion or other blood products from multiparous women, which has led many countries to reduce or exclude women from donating high-volume plasma products. This policy change has resulted in a decrease in the incidence of TRALI and highlighted the importance of nonimmune-mediated TRALI, which is thought to be caused by bioreactive lipids and other biologic response modifiers that accumulate during storage of blood products. When TRALI is suspected, clinical consultation with a transfusion medicine specialist helps differentiate it from other transfusion reactions with similar characteristics.

Consult

A 32-year-old man was taken to the operating room after a motor vehicle accident. He had sustained pulmonary contusion, and a thoracotomy was in progress to drain a left hemothorax. During surgery, the patient received 3 units of leukoreduced packed RBCs. He was hemodynamically stable before transfusion, but became hypotensive and hypoxic while receiving the third unit of RBC. The nadir blood pressure and oxygen saturations were 62/38 mm Hg and 74%, respectively. Chest radiography performed at that time showed increased bilateral opacification of the lungs. A complete blood count (CBC) collected at the time of the event was notable for leukopenia; his WBC count was 1.9 × 10^3/μL (1.9 × 10^9/L), down from 16.3 × 10^3/μL (16.3 × 10^9/L) preoperatively. A transfusion reaction workup was ordered by the trauma surgeon. No clerical errors or signs of hemolysis were found, including a negative result on direct antiglobulin test. The clinical events surrounding the transfusion were most consistent with transfusion-related acute lung injury (TRALI). The patient was given oxygen support and steadily improved over the course of hours. A TRALI investigation request was submitted to the donor center that supplied the 3 units of transfused RBC.

Questions

1. What are the clinical criteria used to diagnose TRALI? How should the patient be treated?
2. What are the proposed pathologic mechanisms of TRALI?
3. How are potential TRALI cases investigated?
4. What policies are donor centers using to reduce the risk of TRALI?

Background

According to the US Food and Drug Administration, TRALI is the current leading cause of transfusion-related mortality, accounting for 43% of all fatal transfusion reactions between 2007 and 2011. However, according to the factors for ALI such as sepsis, pneumonia, pancreatitis, and burn injury are present.6 However, according to the factors for ALI such as sepsis, pneumonia, pancreatitis, and burn injury are present.6 However, according to the factors for ALI such as sepsis, pneumonia, pancreatitis, and burn injury are present.6 However, according to the factors for ALI such as sepsis, pneumonia, pancreatitis, and burn injury are present.6

The diagnosis of TRALI is based on clinical and radiographic findings. It should be suspected when a patient develops acute respiratory distress within 6 hours of a transfusion in the absence of left atrial hypertension or circulatory overload. Transient and dramatic leukopenia/neutropenia has been observed in TRALI,9,10 and is likely secondary to sequestration of neutrophils in pulmonary capillaries (see next section).

Episodes of TRALI typically improve within 48 hours; however, in severe TRALI, pulmonary infiltrates and hypoxia can persist for up to 7 days and mechanical ventilation may be required.3,4 Treatment for TRALI is supportive care. Supplemental oxygen and fluid resuscitation with colloid may improve hypotension and tissue perfusion.10,11 Fatality rate associated with TRALI is estimated at 6% to 20% of cases.4,12,13

Proposed Pathophysiology of TRALI

Several mechanisms to explain the pathology of TRALI have been suggested. A common target in all of them is the neutrophil. Pulmonary specimens from fatal TRALI cases show predominantly neutrophilic infiltrates and alveolar edema.10

One of the first proposed mechanisms of TRALI implicated donor-derived HLA or human nuclear antigen (HNA) antibodies directed against cognate recipient antigens on neutrophils and/or endothelial cells.4,14,15 Indeed, a systematic review of TRALI cases found that 86% were caused by antileukocyte antibodies.16 Transfusion of donor antibodies is believed to activate neutrophils either directly or indirectly via interaction with HLA antigen-antibody complexes on pulmonary endothelial cells.15,17,20 Consequently, activated neutrophils are sequestered in lung capillaries where they release toxic mediators that damage the endothelium and cause loss of vascular integrity. Leakage of fluid and inflammatory cells results in pulmonary edema, a hallmark of ALI.

Two observations suggest that factors other than antibodies are involved in the pathogenesis of TRALI as well. The first comes from “look-back” studies of donors implicated in TRALI cases. They concluded that only a few recipients of transfusions with antibodies specific to their leukocyte antigens develop TRALI or other adverse reactions.21-23 The second observation is that TRALI can occur in the absence of HLA or HNA antibodies.4,24,25 These so-called nonimmune or antibody-independent cases of TRALI are likely mediated by biologic response modifiers (BRMs), soluble factors that accumulate during storage of blood products. Proposed BRMs that may potentially activate neutrophils include bioreactive lipids, CD40L, and various cytokines.24,26 BRMs were implicated in a case of TRALI after transfusion of autologous blood units.27

Thus, a “2-hit” hypothesis of TRALI has been proposed to explain the aforementioned observations. The first hit involves specific inflammatory host factors that prime neutrophils and/or pulmonary endothelium. Numerous “first hits” have been documented such as infection,
recent surgery (in particular cardiac surgery), hematologic malignancies, and massive transfusion. The second hit occurs when transfused mediators (ie, antibodies and/or BRM) cause neutrophil activation and additional damage to pulmonary endothelium.

In a recently published, prospective study of TRALI, Toy et al. used multivariate analysis to identify patient and donor risk factors. The authors found that increased interleukin 8 levels, liver surgery, alcohol abuse, shock, high peak pressure during mechanical ventilation, smoking, and positive fluid balance predisposed patients to TRALI. Donor factors associated with TRALI were female gender and the amount of transfused HLA class II or HNA antibodies.

Although the “2-hit” theory is supported by numerous clinical studies, it fails to explain why TRALI also affects noncritically ill patients. A newly described mechanism, called the threshold model, aims to merge the antibody-mediated and the 2-hit theories of TRALI. This model proposes a clinical threshold determined by a combination of donor and host factors. For example, transfusion of a blood product with low-titer antileukocyte antibodies may cause TRALI in a critically ill surgical patient (low threshold) but may have no demonstrable effect on a relatively healthy person harboring the cognate antigens (high threshold). Alternatively, transfusion of antibodies or BRMs with strong potential to cause TRALI may not necessarily require a priming event to achieve the critical TRALI threshold.

### TRALI Investigation and Laboratory Evaluation

When a TRALI reaction is suspected, the hospital blood bank/transfusion service must be contacted immediately. Consultation with a specialist in transfusion medicine will help differentiate TRALI from transfusion-associated circulatory overload (TACO). This distinction may be difficult, because TACO and TRALI have similar clinical presentations. However, the distinction is critical to ensure proper management. A CBC performed immediately that shows new leukopenia is highly suspicious for TRALI. TACO should be managed with diuretics, whereas TRALI requires ventilatory support with or without intubation.

Once it is determined that the patient has TRALI, the transfusion medicine consultant notifies the blood center, which contacts the donor(s) of the blood product(s) and initiates testing for HLA and HNA antibodies. Concurrent HLA typing of the patient should be arranged.

One of the challenges of HLA antibody screening is the high sensitivity of the commonly used flow-based assays. Consequently, the role of HLA in TRALI may be overestimated because very low concentrations of antibodies with unknown clinical relevance are detected. Donor testing for HNA antibodies is not routinely performed and only offered by a few specialized laboratories. HNA (and HLA class I) antibodies are detected in serum with the granulocyte immunofluorescence test (GIFT) and the granulocyte

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<th>TRALI Diagnostic Criteria</th>
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<td><strong>Consensus Definitions</strong></td>
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<td>ALI Acute onset; hypoxia (PaO₂/FiO₂ ≤300 mm Hg or oxygen saturation by pulse oximetry &lt;90% on room air); bilateral pulmonary infiltrates by chest radiograph; no evidence of left atrial hypertension (ie, circulatory overload)</td>
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<td>NHLBI ALI developing ≤6 hours after transfusion; no alternative ALI risk factors permissible; possible TRALI: for patients with preexisting risk factors for ALI</td>
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<td>CCC ALI developing ≤6 hours after transfusion; no alternative ALI risk factors permissible; possible TRALI: for patients with preexisting risk factors for ALI</td>
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ALI, acute lung injury; CCC, Canadian Consensus Conference; FiO₂, fraction of inspired oxygen; PaO₂, partial pressure of arterial oxygen; NHLBI, National Heart Lung and Blood Institute.

### TRALI vs TACO

<table>
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<tr>
<th>Condition</th>
<th>Signs and Symptoms</th>
<th>Supporting Data</th>
<th>Pathogenesis</th>
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<tr>
<td><strong>TRALI</strong></td>
<td>Respiratory distress; tachypnea; hypoxemia; hypotension; noncardiogenic pulmonary edema; fever; onset within 6 hours of transfusion</td>
<td>Decrease in WBC count; bilateral pulmonary infiltrates on chest radiograph</td>
<td>HLA class I or II antibodies; human neutrophil antibodies; biological response modifiers</td>
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<td><strong>TACO</strong></td>
<td>Respiratory distress; tachypnea; hypoxemia; cardiogenic pulmonary edema; hypertension; tachycardia; rapid improvement with diuretics</td>
<td>Bilateral pulmonary infiltrates on chest radiograph; increased heart size, vascular congestion, and/or pleural effusions; pulmonary artery occlusion pressure &gt;18 mm Hg; elevated BNP</td>
<td>Transfusion of large volume or rapid infusion of blood products</td>
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BNP, B-natriuretic peptide; HLA, human leukocyte antigens; TACO, transfusion-associated circulatory overload; TRALI, transfusion-related acute lung injury; WBC, white blood cell.
agglutination test (GAT). The specificity of the HNA antibody can be determined by using the GIFT and GAT assays with a panel of phenotyped neutrophils. Donors of TRALI-implicated units that have alloantibodies are permanently deferred from future donations.

Evaluation for the presence of BRMs in blood products is currently restricted to research laboratories, with the exception of neutrophil priming assays and commercial immunoassays for cytokines that may be useful in cases of nonimmune TRALI.

**TRALI Mitigation Strategies**

Antibodies were documented in over 80% of published cases of TRALI and the donors most likely to be sensitized to HLA and HNA are multiparous women. In the Leukocyte Antibody Prevalence Study (LAPS I), 7,841 donors provided pregnancy and transfusion history, and underwent testing. The results showed that the prevalence of HLA antibodies was less than 2% in nontransfused or transfused men and nulliparous women. In contrast, women with prior pregnancies had significantly higher rates of HLA sensitization, from 11.2% for those with 1 pregnancy to 32.2% for women with 4 or more pregnancies. A subset of donors was also tested for HNA antibodies, and the results showed a prevalence of 0.7%, with no difference between men and women.

Plasma products were the first targets of TRALI mitigation measures because they contain higher amounts of leukocyte antibodies. In October 2003, the United Kingdom implemented a predominantly male donor plasma program that proved to be a successful TRALI reduction strategy. In response to the increased reports of TRALI in the United States and the success in the United Kingdom, the American Association of Blood Banks (AABB) released a bulletin in 2006 recommending adoption of measures to limit collection of high-plasma volume products from donors at risk or known to be sensitized to leukocyte antigens. These measures were to be instituted by the fall of 2007 for frozen plasma and by the following year for apheresis platelets.

Most donor centers in the United States opted to also implement a predominantly male donor plasma program, which has proven to be a successful mitigation strategy. A prospective study of TRALI incidence was already under way when the AABB recommendation was issued. According to the data, the incidence of TRALI at 2 large tertiary hospitals decreased from 2.57 to 0.81 per 10,000 transfused units between 2006 and 2009. In addition, the American Red Cross reported the investigation of 32 probable TRALI cases in 2006 when 45% of the plasma units were from women, compared with only 7 cases in 2008, when 95% of the units were from men.

Implementation of strategies to reduce TRALI risk associated with apheresis platelets has been challenging. Eliminating female donors from platelet donation would critically affect the supply because women donate almost 40% of these units. Even the deferral of women with 1 pregnancy would likely decrease the available apheresis platelet inventory by 23%. An alternative method, which many donor centers currently use, is to screen female platelet donors for HLA antibodies. The increased expense of testing is balanced by a significant reduction (5%) in the female apheresis platelet donor deferral rate. At this time, screening for HNA antibodies is not routinely performed.

**Case Summary and Conclusion**

A TRALI investigation was carried out by the supplier of the 3 units of RBCs our patient received during surgery. Two of the 3 donors were located and 1 tested negative for HLA antibodies. The donor of the third unit, a 53-year-old woman with a history of 3 pregnancies, had multiple HLA antibodies, including anti-B7, anti-DR3, and anti-DQ6. HLA typing of the patient identified cognate HLA-B7, HLA-DR3, and HLA-DQ6 antigens. Thus, the investigation confirmed the suspicion of TRALI and the donor was permanently deferred.

Since the implementation of predominantly male donor plasma collection, TRALI cases associated with RBC units are implicated in almost 50% of the reports submitted to the FDA. This patient’s critical clinical condition likely predisposed him to the development of TRALI when exposed to the small concentration of HLA antibodies present in the third unit of RBCs.

TRALI should be considered when patients develop acute lung injury within 6 hours of transfusion. Although its pathogenesis is not yet completely understood, it appears to be a multifactorial process that culminates in neutrophil activation and acute lung injury. Accumulating data suggest that donor and host factors contribute to the development of TRALI. Understanding the role of these factors is of utmost importance to design mitigation strategies to decrease TRALI incidence. The incidence of TRALI has been reduced successfully through the adoption of predominantly male donor plasma, screening women for HLA antibodies, and the selective deferral of donors with antibodies. However, awareness that any blood product, including RBCs, may cause TRALI will continue to advance our understanding and optimal management of this life-threatening acute complication of transfusion. In addition, prompt recognition of TRALI by the clinical team ensures proper case management and improved prognosis.

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References


