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Transfusion-Related Acute Lung Injury (TRALI): Report of 2 Cases and a Review of the Literature

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ABSTRACT

Transfusion of allogeneic blood products is given for correction of coagulation deficits and for the improvement in oxygen-carrying capacity or delivery. Blood transfusion has become safer following the advancement in blood testing using state-of-the-art viral assays; however, there continues to exist a variety of noninfectious transfusion risks that still remain and that cannot be entirely eliminated. Research is now directed towards understanding these lesser-known, but serious transfusion-related complications. This purpose of this review is to discuss a serious noninfectious cause of acute lung injury, transfusion-related acute lung injury (TRALI), which occurred in 2 recent cases in the intensive care unit, and to review the current literature of this syndrome.

INTRODUCTION

Transfusions of allogeneic blood products are common medical interventions in the intensive care unit (ICU).[1–4] Moreover, as the population ages, together with the increasing severity of illness seen in ICU subjects, some investigators predict that the demand for these products will continue to grow.[5] Risks associated with the transfusion of allogeneic blood products include infectious risks, immunomodulation, and alloimmunization to antigens associated with the products transfused.

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INFECTIOUS RISK

Modern blood banking has dramatically reduced the risk of transmission of lipid-enveloped viruses from transfusion therapy, with the incidence approaching levels that are difficult to estimate. For example, the risk of transmitting human immunodeficiency virus (HIV) from blood products in the United States is now estimated to be anywhere from 1:1.4 million units to 1:2.4 million units transfused; for human T-lymphocyte virus (HTLV-I/II) 1:250 000 units to 1:2 million units transfused; for hepatitis C 1:872 000 units to 1:1.7 million units transfused; and for hepatitis B from 1:58 000 to 1:149 000 units transfused.[6] In contrast, blood transfusion is still unsafe in many resource-limited countries, where up to 50% of transfusions within a hospital were associated with unfavorable outcomes.[7] Currently, bacterial contamination of blood products, particularly in platelets, is one of the more significant causes of transfusion-related morbidity and mortality. Septic transfusion reactions may present with clinical symptoms similar to immune-mediated hemolytic transfusion reactions or in transfusion-related acute lung injury (TRALI). Extremely high fever and/or gastrointestinal symptoms in a transfusion recipient may be indicative of sepsis. The diagnosis is based upon culturing the same organism from both the patient and the transfused blood component.[8]

IMMUNOMODULATION

Clinical evidence for the existence of immunologic reactions to transfusion was first reported in 1973, when Opelz et al observed that allogeneic blood transfusions improved renal allograft survival.[9] Subsequent clinical and experimental animal studies confirmed these findings. In some institutions, allogeneic blood transfusions were often deliberately administered to renal allograft recipients to delay or prevent the rejection of the renal allograft. The possible beneficial effects of this form of therapy were not further investigated after the introduction of effective immunosuppressive agents such as cyclosporine.[10]

ALLOIMMUNIZATION

Allogeneic blood transfusion can be viewed as a form of temporary transplantation. Transfusion intro-

duces a multitude of foreign antigens and living cells into the recipient that will persist for a variable time. A recipient who is immunocompetent often mounts an immune response to the donor antigens, resulting in a variety of clinical consequences depending upon the blood cells and specific antigens involved. The antigens most commonly involved are HLA class I antigens, which are expressed on all nucleated cells and on anucleate platelets, and HLA class II antigens, which are found on lymphocytes, monocytes, macrophages, and endothelial cells.[1,6,11–23]

Although infectious risks are decreasing, noninfectious risks of transfusion-associated injury have emerged as the prominent risk for patients, especially in the ICU. We discuss 2 recent cases of suspected TRALI in the ICU with a review of the literature.

CASE 1

A 38-year-old woman with a history of heavy vaginal bleeding presented to Ochsner Medical Center Emergency Department with an associated history of lower abdominal cramping, dizziness, and weakness, with laboratory findings of anemia and mild pancreatitis. Her past medical history was significant for systemic hypertension, obesity, and adult-onset diabetes mellitus, now known to be risk factors for the development of endothelial dysfunction. Her past surgical history was significant for a recent history of an ovarian cyst surgically removed at a local area hospital, after which she developed postoperative sepsis with a 9-day ICU stay. During this current hospitalization, she was treated with medroxyprogesterone (Provera); however, her preoperative course was complicated by the need for packed red blood cells (pRBCs), without resolution of her vaginal bleeding, and she subsequently underwent a dilatation, curettage, and hysteroscopy under general anesthesia. During her surgery she received additional pRBCs and fresh frozen plasma (FFP). Her intraoperative course was complicated by the development of laryngospasm during emergence from general anesthesia, requiring urgent endotracheal intubation. She immediately developed signs and symptoms of acute respiratory distress syndrome (ARDS) and acute renal failure, requiring a 16-day stay in the ICU. She was discharged from Ochsner Medical Center in stable condition with a complication of probable drug-induced ototoxicity and laboratory evidence of mild pancreatitis.

CASE 2

A 33-year-old man was ejected off a motorcycle without cranial protection and urgently brought to Ochsner Medical Center Emergency Department with a diagnosis of multiple orthopedic fractures including a basilar skull fracture, with an admission Glasgow Coma Score of 3 to 4, with computed tomography (CT) findings of diffuse intraparenchymal cerebral injury and scattered traumatic subarachnoid hemorrhage, and with possible splenic laceration. Additional medical findings included a positive toxicology screen for ethanol and for amphetamines, and radiographic evidence of cardiomegaly and pulmonary contusions. He was preoperatively transfused with 2 units of pRBCs, underwent urgent surgical stabilization of his femur fracture, and was brought to the ICU for supportive care. During his initial postoperative course, the patient emerged from his coma and was weaned from positive pressure ventilation. However, ongoing laboratory findings included a decreasing hemoglobin level to a nadir of 7.6 g/dL. He underwent additional transfusion of 2 units of pRBCs and repeat abdominal CT for reevaluation of the possible splenic injury. Approximately 6 hours following administration of the second unit, the patient developed respiratory distress, was urgently reintubated, and was placed on positive pressure ventilation. He rapidly developed ARDS that progressed to Multiple Organ Dysfunction Syndrome (MODS) and died on day 18 of this admission.

In both cases, the blood donor center was informed of the suspected TRALI reactions for further investigation.

ADVERSE REACTIONS FROM ALLOGENEIC TRANSFUSIONS

A number of organizations and countries have established surveillance systems to study the risks associated with allogeneic blood products. Hemovigilance is a national system of surveillance, beginning from blood collection to the follow-up of the recipients receiving transfusion of allogeneic products with analysis of any adverse events. In the 2004 surveillance report released by the United States Department of Health and Human Services, an analysis was performed on 1322 medical treatment facilities, which reported a total of 32 128 transfusion-related adverse reactions that required diagnostic or therapeutic intervention.[24] In those adverse events, 160 were reported as TRALI, with TRALI more likely to occur in hospitals performing more than 8000 surgeries per year (see Figure 1). In contrast, adverse events related to ABO incompatibility were fewer, with only 52 occurrences reported.[24]

TRANSFUSION-RELATED ACUTE LUNG INJURY

The transfusion of blood products is often a lifesaving therapy, but transfusion can be associated with the development of acute lung injury (ALI)/ARDS, with TRALI now reported to be the leading cause of transfusion-associated fatality in the United States.[15,25–27]

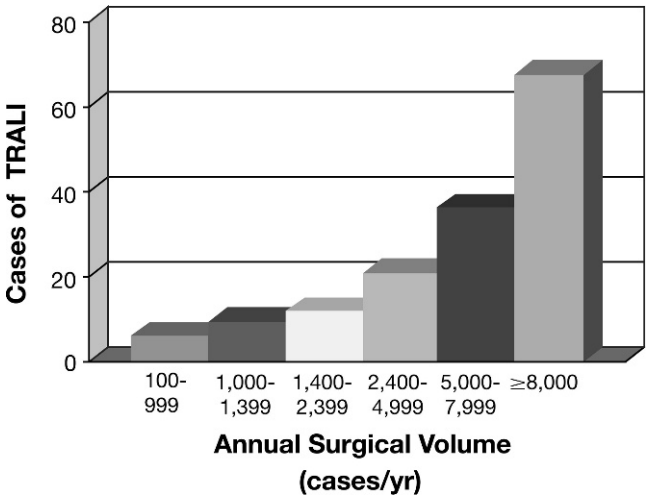

Figure 1. Number of adverse reactions (ALI) from allogeneic transfusion reported by US hospitals. Columns represent the annual surgical volume reported by those hospitals. (Data redrawn from Whitaker BI, Sullivan M. Current issues in blood transfusion. In: Whitaker BI, Sullivan M, eds. The 2005 Nationwide Blood Collection and Utilization Survey Report. Washington, DC: USDHHS; 2005:31–34.[24])

In 2005, TRALI accounted for 34% of transfusion-associated mortalities reported to the Food and Drug Administration. It produced more deaths than those attributed to sepsis from bacterial contamination in platelet or red cell components, or deaths due to hemolytic reactions following incorrect blood administration.[28]

ETIOLOGIES OF TRALI

Studies into the specific etiologies of TRALI have been limited to findings from isolated case reports, retrospective reviews, observational studies from single hospitals, and limited animal research.[29–31] In a retrospective study over a 5-year period (from 1997 to 2002), Holness et al reported transfusion-related adverse events involving 58 deaths to the Center for Biologics Evaluation and Research.[26] Cardiovascular disease, pulmonary disorders, and cancer were the most frequent diagnoses of those patients receiving allogeneic blood products. Fresh frozen plasma was implicated in approximately half of the cases, whereas pRBCs played a role in approximately one-third of the fatalities.[26] In another retrospective case-control study, by Silliman et al, the authors found that 2 groups of patients were at risk: those with hematologic malignancies, with the majority of these occurrences during their induction phase of chemotherapy, and in patients who underwent cardiopulmonary bypass for surgical correction of cardiac disease.[32] In a recently reported single-center retrospective cohort study, Khan et al studied 841 consecutive critically ill patients for the development of ALI/ARDS. These authors observed that the risk of ALI/ARDS is higher in patients who receive transfusions, especially in patients who receive plasma-rich blood products (FFP and platelets) rather than those only transfused with pRBCs.[33] Finally, in a prospective case-control trial, Gajic et al observed 901 critically ill patients who were transfused with over 6500 units of blood products in a medical ICU over a 2-year period. The authors observed that patients were more likely to develop ALI following transfusion if they had comorbidities of sepsis, liver disease, and a history of chronic alcohol abuse.[34] Furthermore, cases of ALI were more likely to have received plasma-rich products (FFP or platelets). The development of ALI following transfusion was also more likely to occur in those patients who received blood products from female donors, especially if larger volumes of plasma were used from female donors. Of the 74 patients who developed ALI, 58 required medical ventilation with a mean duration of 3.6 days (1.6 to 7.1 d), and these patients had a higher mortality rate if they developed TRALI (41%) than that of matched controls (23%). These authors concluded that both the underlying patient characteristics (first-hit phenomena) and the specific transfusion factors (second-hit phenomena) were associated with the development of TRALI.[34] Furthermore, their report indicated that TRALI is grossly underrecognized and underreported and supports this observation as stated in other studies.[27,35,36]

DIAGNOSIS

TRALI is defined as the development of lung injury occurring within 6 hours after a transfusion and with a clear temporal relationship to the transfusion.[27,37,38] The clinical characteristics described most often include marked dyspnea, tachypnea, fever, hypotension or hypertension, the appearance of frothy sputum, diffuse crackles, and decreased breath sounds, with pulmonary infiltrates noted on chest x-ray film, as well as findings of hypoxemia/hypoxia with arterial blood gas analysis. Signs of congestive heart failure, increased jugular venous pressure and/or third heart sounds are usually absent. If a pulmonary artery catheter is present, the pulmonary capillary wedge pressure is normal or decreased.[26,27,38–47] Histologic findings reveal massive lung edema, capillary granulocyte aggregation, and neutrophil extravasation into alveoli. Electron microscopy has revealed extensive capillary endothelial damage with activated granulocytes in direct contact with alveolar basement membranes.[41,48] TRALI reactions have equal gender distribution and can occur in all age groups.[2,49–51] However, TRALI is a diagnosis of exclusion, as other etiologies of

ARDS such as sepsis, aspiration, allergic reactions, atelectasis, negative pressure pulmonary edema, transfusion-associated circulatory overload, reperfusion syndrome of the newly implanted liver, or cardiogenic pulmonary edema can also occur in the ICU.[16,27,38–46,52,53]

More than 70% of patients will require mechanical ventilation because of the development of frothy secretions or diffuse alveolar hemorrhage, hypoxemia, and the observation of diffuse bilateral infiltrates on portable chest x-ray film. Most cases (70%–87%) will resolve in less than 96 hours, although mortality can occur and is reported to be in the range of 6% to 10%.[1,42,54]

The severity of TRALI may depend upon the susceptibility of the patient as a result of an underlying disease process (first-hit phenomena) and the nature of triggers in the transfused blood components (second-hit phenomena). All blood products, except albumin, have been implicated in TRALI reactions.[49,54–56]

BASIC SCIENCE OF TRALI

Two different etiologies have been proposed in the development of TRALI. The *first hypothesis* is a single antibody-mediated event that involves the transfusion of anti-HLA class I and class II or antigranulocyte antibodies into patients whose leukocytes express blood-related antigens. Antigranulocyte antibodies present in donor serum have been implicated in this pathogenesis.[26,57,58] Yang et al reported 2 interesting cases of TRALI that occurred following blood transfusion between mothers and their daughters. In the first case, a 4-month-old girl received pRBCs donated by her mother. In the second case, a 78-year-old mother received blood from her daughter. Histologic examination of the mothers' serum revealed panel-reactive cytotoxic HLA antibodies. The authors proposed that the mothers were sensitized from their earlier pregnancies and had produced HLA antibodies against the daughters' paternally derived HLA antigens.[59]

In a prospective cohort controlled study by Gajic et al, critically ill patients were closely observed for development of ALI following transfusion. Donor samples were collected from transfusion bags. Risk factors were compared between patients who did develop ALI following transfusion and transfused controls, matched by age, gender, and admission diagnosis. The authors found that 74 out of 901 transfused patients developed TRALI within 6 hours after transfusion, an incidence of 8%. However, when compared to transfused controls, ALI patients were more likely to have sepsis and have a history of chronic alcohol abuse. When adjusted for patient characteristics, transfusion of plasma from female donors, the number of pregnancies in the female donors, the number of donor units positive for antigranulocyte and HLA class II antibodies, and increases in biologically active lipids that accumulate in older, cellular blood products (mixtures of lysophosphatidylcholines generated during blood storage) in the donor product were associated with development of TRALI. The authors concluded that both patient and transfusion risk factors determine the probability of TRALI after transfusion.[34] However, antigranulocyte antibodies and/or HLA antibodies are not found in all donors' blood products used in patients who subsequently develop TRALI, nor will patients with antibody/antigen concordance with their donors' blood products develop clinical signs of ALI.[26,60–63]

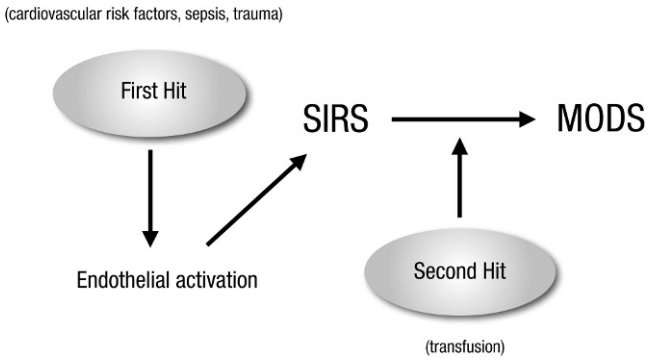

Figure 2. Simplifed Two-Hit Phenomena: A number of preexisting risk factors, in the presence of trauma or surgery, leads to SIRS (Systemic Inflammatory Response Syndrome) activation (~80% in the SICU), with additional injury (for example, transfusion, drug allergy, infection, hypoperfusion, genetic predisposition, all leading to thrombogenesis and the development of microvascular thrombosis) leading to MODS (Multiple Organ Dysfunction Syndrome).

The *second hypothesis* is a 2-event model. This alternate mechanism is termed the ''2-hit'' or ''neutrophil priming'' hypothesis and postulates that a pathway to neutrophil activation and aggregation on the endothelial cells of the capillaries can occur without the presence of leukocyte antibodies.[64–67] The *first event* (first-hit phenomenon), such as sepsis, trauma, small concentrations of bacterial endotoxins (lipopolysaccharides), by-products of the complement cascade, platelet-activating factor, or biologically active lipids can transform the endothelial phenotype from a quiescent state to an activated or inflammatory state, resulting in endothelial dysfunction, increased leukocyte–endothelial cell interactions, increased cytokine release, and increased procoagulant activities[68–71] (see Figure 2).

The *second event* (second-hit phenomenon) is the transfusion of a biologic response modifier (including lipids, lysophosphatidylcholines, antibodies, or soluble CD40 ligands, a platelet-derived proinflammatory

mediator that accumulates during platelet storage)[72] that activates adherent neutrophils, with subsequent release of their granular content upon the pulmonary endothelial cells, resulting in significant endothelial damage and capillary leak. Normally, the neutrophil response is designed to restrict the damage to the smallest possible region where pathogens are located; however, in the systemic inflammatory response syndrome (SIRS), these damaging agents inevitably leak into the surrounding areas, where they have the capacity to inflict significant and widespread tissue damage.[43,72,73] The basement membrane is also damaged during this process, which leads to additional fluid and cellular extravasation in the interstitial and alveolar spaces.[46,74]

The fundamental concept is that injury, from many etiologies, can prime the innate immune system such that a second insult provokes an unbridled systemic inflammatory response, resulting in significant organ dysfunction.[75,76]

One limitation of the ''2-hit model'' is the development of TRALI in patients who were apparently healthy prior to transfusion, such as in the setting of the use of FFP for coumadin reversal for elective surgery. It is possible that such patients have subclinical evidence of or unrecognized risk factors for endothelial dysfunction.[36] Certainly in this instance, the existence of endothelial dysfunction from cardiovascular diseases could provide the initial or first event mechanism for this model.[68–71] Alternatively, a transfused component may be able to provide both the mediators of endothelial activation and the second-hit bioactive molecules that activate neutrophils, triggering ALI.[36]

PREVENTION

To prevent further antibody-mediated cases, the evaluation of TRALI should include leukocyte antibody testing of implicated donors.[56] The American Association of Blood Banks standards require that blood centers and transfusion services evaluate donors implicated in TRALI or associated with multiple events of TRALI regarding their continued eligibility to donate.[77] The potential that modifiable transfusion risk factors such as donor gender, parity, and alloimmunization are associated with the development of ALI may have important clinical implications in the prevention of ALI in critically ill patients.[56] Some studies have shown decreased incidence of ALI in patients managed with a conservative transfusion policy, whereas in studies with a liberal blood product transfusion strategy, an increase in the development of ALI/ARDS and worse outcomes in critically ill patients were observed.[78–83] Of note, even the transfusion of autologous blood products is associated with complications of ALI, including death.[84,85]

CONCLUSION

TRALI has emerged as the most important cause of morbidity and mortality resulting from blood transfusion, due in part to the decrease in morbidity and mortality from the more common, historical concerns of transfusion, and from the increase in recognition of this syndrome.[6,27,35,86,87] Transfusion practice has been under increased scrutiny over the last 2 decades. Recent studies have investigated lower acceptable limits for transfusion triggers, as RBC transfusion does not consistently improve tissue oxygen consumption in critically ill patients, either globally or at the level of the microcirculation.[88–90] Although currently there are no clear evidence-based guidelines on the lower limits of acceptable hemoglobin or hematocrit levels, especially in ICU patients, lower transfusion targets are being advocated.[82,83,90,91] Both patient and transfusion risk factors determine the probability of the development of TRALI; while the exact etiologies are not known, the presence of endothelial dysfunction, donor-derived antileukocyte antibodies, and biologic response modifiers that accumulate during blood storage play important roles. TRALI has emerged as the dominant and serious hazard of transfusion. Improved understanding of its pathophysiology is needed to improve clinical strategies that deal with the risk. Only with continued effort toward research and education to promote recognition and prevention of complications associated with blood components can we lessen the consequences of this syndrome.

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