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Perioperative Recognition, Management, and Pathologic Diagnosis of Transfusion-related Acute Lung Injury

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THERE are many well-described complications of hemotherapy, including acute and delayed hemolytic reactions, transmission of infectious agents, and febrile and hypersensitivity reactions. Noncardiogenic pulmonary edema resulting from blood-product transfusion has been characterized as an infrequent, though serious, complication of hemotherapy resulting from immunoreactivity of certain leukocyte antibodies. Most reports have appeared in pulmonary and hematology journals; only three case reports have been published in the anesthesia literature in the last 10 yr.[1–3] Nomenclature has been descriptive, using terms such as transfusion-associated noncardiogenic pulmonary edema and transfusion-related adult respiratory distress syndrome (ARDS).[1,4]

Other investigations, including some more recent, have been more definitive, attributing this clinical syndrome to a specific antigen–antibody mechanism involving human leukocyte antigen (HLA) and granulocyte antigens, called transfusion-related acute lung injury (TRALI).[5–10] In this report, we describe a patient who developed fulminant noncardiogenic pulmonary edema after the administration of packed red blood cells in the operating room whose hematologic and clinical evaluation fulfills criteria to substantiate the diagnosis of TRALI.

Case Report

A 51-yr-old morbidly obese gravida 5, para 5 woman with atypical adenomatous endometrial hyperplasia was admitted to our hospital for total abdominal hysterectomy and bilateral salpingo-oophorectomy. Preoperative laboratory studies were normal with the exception of mild hyperglycemia. In the operating room, she lost 2,200 ml blood acutely by hemorrhage from extensive retrouterine varices; the blood loss was difficult to control. She received four units of type-specific, crossmatched packed red blood cells, as well as crystalloid and hetastarch solution (Hespan, DuPont, Wilmington, DE).

One hour after administration of the fourth unit of blood, her hemoglobin oxygen saturation measured by pulse oximetry abruptly decreased from 95% to 85% and frothy serous fluid appeared in the tracheal tube. A Foley catheter and radial artery catheter were in place. She was given intravenous furosemide, then transported to the surgical intensive care unit with her trachea intubated and fraction of inspired oxygen 1.0, manually applied continuous positive airway pressure *via* a modified Jackson-Rees circuit, and a hemoglobin oxygen saturation of 100%. A pulmonary artery catheter was inserted. Arterial blood gas evaluation revealed *p*H 7.22, carbon dioxide tension 39 mmHg, and oxygen tension 168 mmHg. A portable chest roentgenogram showed diffuse opacity of both lung fields and indistinct vasculature consistent with pulmonary edema.

A transesophageal echocardiogram demonstrated normal mitral valve function, good left ventricular function, and no evidence of left ventricular wall motion abnormality. The electrocardiogram was unchanged from a preoperative study except for increased heart rate and a slightly prolonged QT interval. Her cardiac output was 5.1 l/min, pulmonary artery occlusion pressure 16 mmHg, heart rate 130 beats/min, and systolic blood pressure 66 mmHg with infusion of dopamine and dobutamine.

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Vasopressor therapy and ventilatory support were continued, and colloid and red cell transfusions also were given to support cardiac filling pressures and arterial blood pressure. Serum evaluation of cardiac isoenzymes was within normal limits, and there was no clinical evidence of septicemia. Results of blood cultures were negative throughout her hospitalization.

The trachea was extubated on postoperative day 3 with normal arterial blood gas values and evidence of slowly resolving pulmonary edema by chest roentgenogram. The rest of her surgical recovery was uneventful and she was discharged in good condition on postoperative day 11.

Upon considering the differential diagnosis of this ARDS-like syndrome, the transfusion medicine service was contacted to address the possibility of TRALI. The patient had received four units of packed red blood cells that were traced to the blood donor center of a nearby community hospital. Two of the four blood units had been donated by multiparous women (parity of four and six), fulfilling the criteria of Popovsky *et al.*[5] necessary to further consider this pathophysiologic diagnosis. The other two donors were men without a transfusion history, and these were not investigated further. Each of the two female donors provided a clotted blood sample for HLA and granulocyte antibody studies.

The patient provided a blood sample for HLA screening and crossmatching with the donor serum. Unfortunately, there was no pretransfusion blood remaining from the patient from which to assess the presence or absence of pretransfusion anti-HLA. An HLA antibody screen on sera from the patient and donor 1 revealed 100% sensitization against a leukocyte panel. The HLA antibody screen from donor 2 was 12% reactive. Lymphocytotoxic crossmatch was positive against the patient's lymphocytes with both donor 1 and 2 sera. Granulocyte antibodies were present in the serum of donor 1 only (table 1). The result of autocrossmatching of the patient's serum and leukocytes was negative. These findings support the diagnosis of TRALI in this patient.

Discussion

This patient had a clinical syndrome consisting of respiratory distress, refractory hypotension, and low-grade fever in close temporal relation with the transfusion of packed red blood cells. The chest roentgenogram revealed diffuse pulmonary infiltrates and indistinct vascular markings without cardiac enlargement. Myocardial infarction was ruled out with serial enzyme and electrocardiogram studies. Measurements of pulmonary artery pressure and cardiac output and echocardiography eliminated a diagnosis of left ventricular failure. This clinical picture fulfills the criteria for noncardiogenic pulmonary edema or ARDS.

Table 1. Patient-Donor Hematologic Testing

Source	HLA Antibody Screen (%)*	Granulocyte Antibody†	Lymphocytotoxic Crossmatch‡
Patient	100	–	–
Donor 1	100	+	+
Donor 2	12	–	+

* Expressed as percent reactivity with leukocyte panel *versus* serum from each source.

† Presence or absence of granulocyte antibody in serum from each source.

‡ Presence or absence of lymphocytotoxic antibody in serum from three sources (patient, donor #1 and donor #2) *versus* patient lymphocytes.

ARDS is characterized by diffuse lung injury that may be precipitated by any of numerous causes including pulmonary infections, aspiration, severe trauma, pancreatitis, gram-negative septicemia, and blood product transfusion (TRALI).[11] TRALI has heretofore been a diagnosis of exclusion; that is, other more immediately diagnosable (and possibly correctable) factors leading to ARDS must be ruled out before a final diagnosis of TRALI is made. However, clinical suspicion should be high in the setting of recent blood product transfusion, and the hospital blood bank or transfusion medicine service should be notified.

TRALI is clinically indistinguishable from ARDS. Both are characterized by acute respiratory distress, diffuse bilateral alveolar and interstitial infiltrates on chest roentgenogram, and they both manifest with varying degrees of hypoxemia. Additional findings of hypotension refractory to administration of fluid and fever may be seen.[5–7,12] The onset of TRALI is usually within 1–6 h of blood product transfusion.[5,6,12] TRALI is associated with a lower mortality rate (10%) than the 50–60% overall mortality rate seen in non–transfusion-related ARDS cases[5,13] as demonstrated by the substantial clinical improvement that most patients with TRALI show within 48–96 h with prompt diagnosis and treatment.[6,13]

Approximately twenty thousand blood products are transfused yearly at our institution with an overall adverse reaction incidence of approximately 0.2% per unit transfused, but there have been no previously documented cases of TRALI. Unfortunately, we have no way of retrospectively ascertaining the number of post-transfusion cases of ARDS *versus* nontransfusion ARDS cases. The overall incidence of TRALI is unclear, although Popovsky and Moore[6] reported an incidence of 0.02% per unit and 0.16% per patient transfused. Another study reported five cases of pulmonary edema from a total of 440,000 blood products transfused (incidence 0.001%).[14] Other authors suggest that TRALI may be an underdiagnosed complication of transfusion that is usually attributed to other causes.[5–7,13,15]

The pathogenesis of TRALI is thought to result from concomitant transfer of HLA or granulocyte antibodies

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from the donor's plasma to the recipient during blood product transfusion.[5,6,8] Any plasma-containing blood product (whole blood, fresh frozen plasma, packed red blood cells, and cryoprecipitate) can cause TRALI, but most reactions are produced by transfusions of whole blood, fresh frozen plasma or packed red blood cells.[5] The volume of plasma necessary to cause such a reaction is unclear.[6] Less commonly, the recipient has been sensitized by pregnancy or previous transfusion and has antibodies in the serum that react with donor leukocytes. This usually results in a febrile transfusion reaction, but could theoretically precipitate TRALI.

Popovsky and Moore[6] reported that donor antibodies are implicated in almost 90% of TRALI cases and that multiparous women usually are the source of donor antibodies. Once infused, the antibody interacts with the recipient's marginated pool of granulocytes, the majority of which are found in the lung, activating the complement cascade. This results in further neutrophil sequestration and aggregation within the extensive microvasculature of the lung. Complement activated neutrophils release enzymes that are directly toxic to the pulmonary capillary endothelium.[5,13] The result of these reactions is manifested clinically by pulmonary edema and respiratory distress.

TRALI should be considered in a patient developing acute respiratory distress and pulmonary edema after transfusion of plasma-containing blood products. Under general anesthesia, this may only be evident by decreased hemoglobin oxygen saturation and increased inspiratory pressures. The hospital transfusion medicine service or blood bank should be notified immediately to facilitate the evaluation of this potentially life-threatening complication of transfusion. After cardiogenic causes have been excluded, the diagnosis is established by the presence of HLA or granulocyte antibodies (or both) in donor serum that react with the patient's lymphocytes or granulocytes. Multiparous women, usually with a history of three or more pregnancies, are the donors to identify when screening plasma-containing blood products implicated in potential TRALI cases.[5] However, the serum from any donor who has been transfused previously or who has been pregnant (and therefore exposed to foreign HLA or granulocyte antigen) and donates blood could theoretically precipitate TRALI, and could have played a role in the genesis of ARDS in this patient as she demonstrated anti-HLA antibody in her serum. This is difficult to interpret, however, as no pretransfusion serum was available.

In this case, we demonstrated granulocyte antibody in the serum of one of the two involved donor units. Also, HLA antibodies were found in both donor sera, and these were reactive with the patient's lymphocytes in a lymphocytotoxic assay. This immunologic finding combined with ARDS and rapid resolution of symptoms with supportive therapy confirmed the diagnosis of TRALI.

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