Transfusion Related Acute Lung Injury

Nadia Abidi, Jay Herman MD, Julie Karp MD

Department of Pathology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

Clinical Case

A 74 year old woman presented with hematemesis. Her medical history was significant for pulmonary embolism treated with warfarin anticoagulation, fibromyalgia treated with NSAIDs/steroids, and a prior bleeding event from a gastric ulcer. On admission she was stable with a hemoglobin of 8.7 g/dL and a therapeutic INR of 3.19. A type and screen determined a blood type of AB positive. In anticipation of endoscopy, the patient received one unit of red blood cells and four units of type AB plasma. Following transfusion, her INR was 1.83. The patient received an additional four units of type AB plasma to further correct her INR. Endoscopy identified a medium-sized gastric ulcer. Shortly after completion of the endoscopy, the patient became hypoxic and began experiencing dyspnea and frothy oral secretions. A chest x-ray 1 hour after the start of the reaction showed diffuse pulmonary edema without cardiomegaly (image 1). The patient was intubated within 2 hours of the reaction and a chest x-ray showed increasingly diffuse pulmonary edema with small bilateral pulmonary effusions (image 2). Ventilator and pressor support were required for several days, and the patient was extubated five days after the reaction. The clinical team and transfusion service strongly suspected Transfusion Related Acute Lung Injury (TRALI) and contacted the blood supplier. The blood supplier determined the Human Leukocyte Antigen (HLA) Class I/II type of the patient and pursued HLA antibody screening for the donors of the four plasma units transfused most proximal to the reaction. Three of the four donors were parous females and returned for HLA antibody screening, while the fourth male donor could not be contacted. Of the three tested donors, none had Human Neutrophil Antigen (HNA) antibodies. Two of the three tested donors had HLA Class I/II antibodies that were non-cognate with the patient. One of the three tested donors had extensive HLA Class I/ II antibodies which were cognate with 4 of 6 of the patient's HLA Class I antigens and 4 of 6 of the patient's Class II antigens. The implicated donor was deferred from further donation.

Image 1. X-ray at 1 hour post reaction showing diffuse pulmonary edema without cardiomegaly

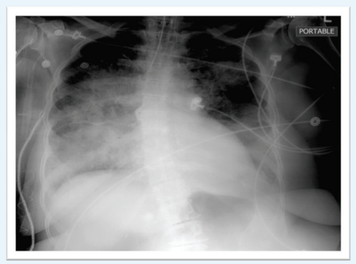
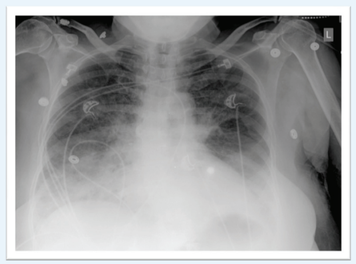


Image 2. X-ray at 2 hour post reaction showing increasingly diffuse pulmonary edema and small bilateral pulmonary effusions



INTRODUCTION

TRALI (defined in Table 1), is an under-recognized immune-mediated transfusion complication that causes non-cardiogenic pulmonary edema. From 2007 to 2011, TRALI was the leading cause of transfusion-related fatalities reported to the Federal Drug Administration and accounted for 43% of transfusion related fatalities.

Table 1. Definition of TRALI

Transfusion Related Acute Lung Injury
1. New ALI • Acute onset • Hypoxemia: PaO_2/FiO_2 ≤300mmHg or O_2 sat ≤90% on room air • Bilateral infiltrates on frontal chest radiograph • No evidence of left atrial hypertension
2. Onset of symptoms within 6 hours of transfusion
3. No preexisting ALI before transfusion

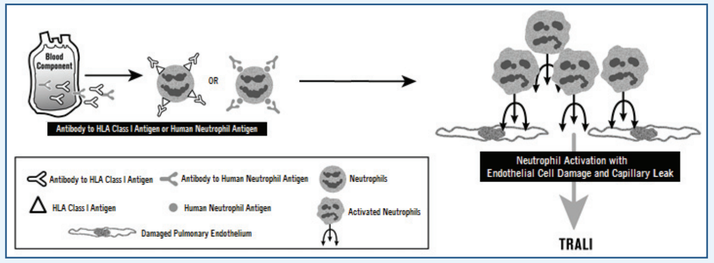
PATHOGENESIS

TRALI is an immune mediated event. The proposed mechanism for TRALI involves *donor antibodies* present in the transfused blood component reacting with cognate antigens on a recipient's neutrophils (PMNs). The donor antibodies can be anti-HLA Class I/ II or anti-HNA. Via unknown mechanisms, antibody coated PMNs localize to the pulmonary microvasculature and become primed for complement activation. Complement activation causes PMNs to release proteases, oxygen radicals, and acidic lipids, thereby damaging the pulmonary vascular endothelium. This allows for the leakage of fluids into the adjacent pulmonary interstitium and alveoli, resulting in pulmonary edema and the symptoms of TRALI (image 3). Alloimmunizing events that may cause donors to form anti-HLA or anti-HNA antibodies include pregnancy and previous blood transfusion. Strategies implemented to prevent TRALI have decreased the number of cases overall, but the risk of TRALI remains. In the case of plasma transfusion, limiting supplies to male donors only (low risk of alloimmunization) has reduced TRALI.

CLINICAL PRESENTATION

The symptoms of TRALI include hypoxemia, tachycardia, fever, mild hypotension, cyanosis, and bilateral non-cardiogenic pulmonary edema that progresses to involve the entire lung fields. Patients have a normal central venous pressure and low to normal pulmonary wedge pressure. These symptoms have a rapid onset and progression and always present within 6 hours of transfusion of plasma-containing blood components. The diagnosis of TRALI is made clinically and is confirmed by HLA typing the recipient and testing donor serum for the presence of HLA or HNA antibodies. A cognate match between a donor antibody and recipient antigen confirms the diagnosis of TRALI.

Image 3. Pathogenesis of TRALI. Transfused HLA and HNA antibodies prime and activate a recipient's neutrophils by binding to them directly causing transfusion related acute lung injury.



MANAGEMENT

Treatment of TRALI is supportive.

1) Respiratory support in the form of oxygen supplementation and/or intubation, as needed.
2) Hypotension should be treated with IV fluids and vasopressors if refractory.

A chest x-ray should be ordered and capillary wedge pressures measured. Suspected TRALI cases must be reported to the blood bank and a sample of the patient's blood taken for further investigation. As a donor antibody is the causative factor in TRALI, no special accommodations are necessary for the patient to receive future transfusions. With aggressive and prompt support, approximately 80% of TRALI patients improve within 48 to 96 hours after the original insult.

PREVENTION

TRALI prevention strategies primarily focus on limiting the use of plasma products of donors who are most likely to have HLA antibodies. Strategies include, but are not limited to:

1) Permanent deferral of donors implicated in TRALI reactions.
2) Near-exclusive use of plasma from male donors. Due to the rarity of blood type AB and the high demand for universal donor AB plasma, this exclusivity does not apply to type AB plasma products. This is demonstrated in the above case.
3) Minimize the inappropriate transfusion of blood components
4) Develop plasma-reduced components

CONCLUSION

The patient's clinical course was consistent with TRALI, with cognate patient HLA antigens and donor HLA antibodies confirming the diagnosis. Implementation of new prevention strategies is needed to address this elevated risk and further reduce TRALI cases in the future.

REFERENCES

1. Federal Drug Administration. Fatalities Reported to FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2011. Available at: http://www.fda.gov/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/ucm302847.htm Accessed April 4, 2013.
2. Kleinman, S, Kor, DJ. Transfusion-related acute lung injury (TRALI). In: *UpToDate*, Rose, BD (Ed), UpToDate, Waltham, MA, 2013
3. Mair, DC and Eastlund, T. The pathophysiology and prevention of transfusion-related acute lung injury (TRALI): a review. *Immunohematology*. 2010; 26:161-173.
4. Popovsky, MA. *Transfusion Reactions.* 4th ed. Bethesda, MD: AABB Press; 2012.