Transfusion-related Acute Lung Injury (TRALI)

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Transfusion is an inevitable event in the life of many individuals. Transfusion medicine personnel attempt to provide blood products that will result in a safe and harmless transfusion. However, this is not always possible since no laboratory test gives totally accurate and reliable results all the time and testing in routine transfusion services is devoted primarily to the identification of red blood cell problems. Thus, when patients are transfused, several possible adverse effects may occur in the transfused patient even though quality testing indicates no potential problem. These adverse events include infectious complications, hemolytic reactions, anaphylaxis, urticaria, circulatory overload, transfusion-associated graft-versus-host disease, chills and fever, immunomodulation, and transfusion-related acute lung injury (TRALI).[1]

ABBREVIATIONS: TRALI = transfusion related acute lung injury.

INDEX TERMS: TRALI; transfusion.

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CASE HISTORY

A 52-year-old white male was admitted to a local hospital emergency room (ER) for an acute upper gastrointestinal hemorrhage. He denied any other medical problems, took no medications, and stated that he did not smoke or drink alcohol. His admitting hemoglobin and hematocrit were 7.8 g/dL and 24%. He was referred by the ER physician to a gastroenterologist who performed an esophagogastroduodenoscopy (EGD) in the ER to determine the cause of the bleeding episode. During and immediately following the procedure, the patient received four units of compatible packed red blood cells (RBCs) and four units of fresh frozen plasma (FFP). His baseline vital signs were normal; however, following administration of approximately 125 mL of the fourth unit of FFP, he began to complain of nausea, chills, and difficulty breathing. The transfusion was immediately discontinued and a workup for suspected transfusion reaction was begun.

The patient's condition worsened over the next three hours with decreasing blood pressure, dyspnea, and decreased renal output. The patient was admitted to the surgical intensive care unit (SICU) and was ultimately intubated due to decreasing oxygen saturation. The patient exhibited normal central venous pressure and pulmonary wedge pressure. Normal saline was administered intravenously. No diuretic agents were administered. Chest radiographs exhibited bilateral infiltrates consistent with pulmonary edema. Approximately 48 hours later the dyspnea began to improve, and the patient was extubated at 56 hours postreaction. He continued to improve and was discharged from the hospital three days later.

CLINICAL FINDINGS

TRALI is an uncommon and often unrecognized but serious complication of transfusion that is described in the literature as a clinical constellation of signs and symptoms including dyspnea, cyanosis, hypotension, and chills and fever along with the physical and radiographic findings of bilateral pulmonary edema. These signs and symptoms usually appear within one to four hours following transfusion of any of a variety of blood products including whole blood, packed red blood cells, fresh frozen plasma, granulocytes, cryoprecipitate, platelet concentrates, apheresis platelets, allogeneic bone marrow, intravenous immunoglobulin, and peripheral blood progenitor cells.[2-5]

DIFFERENTIAL DIAGNOSIS

TRALI has been recognized as a discrete clinical entity since the early 1980s. However, this adverse effect of transfusion is receiving more widespread attention recently and has been reported to be the third most common cause of death fol-

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lowing transfusion. However, many clinicians remain unaware of the condition because TRALI must be differentiated from a number of other conditions including adult respiratory distress syndrome (ARDS), pneumonia, cardiac failure, circulatory overload, bacterial contamination, and acute hemolytic transfusion reaction. Differentiation may be difficult and is a diagnosis of exclusion based upon clinical signs and symptoms rather than laboratory testing. Other causes of respiratory and cardiac dysfunction must be ruled out as well as respiratory distress related to transfusion. The presence of donor and/or recipient leukocyte antibodies may be documented via lymphocyte crossmatch at a later point in time. Nonetheless, TRALI should be considered when a recently transfused patient develops acute respiratory distress.[3,6,7]

ETIOLOGY

The precise pathogenic mechanism of TRALI is uncertain but is thought to be primarily an immune-mediated process with multiple etiologies. A review of the literature indicates that there are three mechanisms that can precipitate TRALI: 1) HLA class I or II complement-activating antibodies or antibodies to specific granulocyte antigens in a recipient that reacts with donor leukocytes; 2) HLA class I or II complement-activating antibodies or antibodies to specific granulocyte antigens in a donor that reacts with recipient leukocytes; and 3) biologically active lipids in stored blood components. Anti-IgA antibodies have been implicated in one case of TRALI. Leukocyte antibodies in one donor have also been reported to react with the leukocytes of another donor. It is interesting that these reactions most commonly occur as the result of passively acquired donor antibody since most transfusion reactions occur as the result of recipient antibody to donor antigens. Granulocyte antibodies associated with TRALI have been identified in blood products donated by multiparous women. Antibody specificity and detection of the corresponding antigen are rarely reported in the literature.[2,3,7-10]

It is postulated that the HLA antibodies may cause the following sequence of events to occur to produce lung injury: 1) antibodies bind to and directly activate neutrophils; 2) complement is activated resulting in the production of anaphylatoxins that promote neutrophil aggregation and sequestration in the pulmonary microvasculature; 3) neutrophils marginate into the pulmonary vasculature and release enzymes, cytokines (tumor necrosis factor-alpha, interleukin-1, 6, and 8), and superoxide radicals that damage the blood vessels; and 4) endothelial cell injury occurs resulting in pulmonary edema due to the accumulation of protein and fluid due to capillary leakage. Autopsy findings in a patient who died of TRALI substantiate this mechanism.[5,11,12]

Another possible cause of TRALI is the presence of biologically active lipids in stored blood. This mechanism is proposed to cause TRALI to occur as a result of a two-event activity. The first event that may precipitate TRALI is associated with the clinical condition of the patient: cardiac disease, infection, recent surgery, cytokine administration, massive transfusion, and hematologic malignancies. The second event is the infusion of biologic response modifiers in the transfused components. Factors within the blood products involved were component age and increased levels of biologically active lipids.[3-5,11-14]

Underlying pulmonary disease is believed to prime neutrophils and result in adhesion to the pulmonary endothelium. Upon administration of blood products containing a biological mediator/priming agent (lipid), there is an augmented respiratory burst within the neutrophils with the subsequent release of the granule contents. The released products damage the endothelium resulting in capillary leakage, and noncardiogenic pulmonary edema very similar to the immune-mediated mechanism.[11-14]

TREATMENT

If acute respiratory distress occurs during transfusion, the transfusion should be halted immediately and not resumed even if the symptoms subside. Depending on the severity of the reaction, treatment may include intravenous corticosteroids, oxygen therapy, and ventilatory support. Saline infusions are recommended. Diuretics are not recommended since the pulmonary edema is not due to fluid overload but 'capillary leak syndrome'. Corticosteroids are not recommended because the underlying disorder is the microvascular insult. Recovery usually occurs within 48 to 96 hours, but severe morbidity and mortality may occur. The best outcomes are observed when TRALI is diagnosed very rapidly and treatment instituted.[2,5,11]

PREVENTION

Several approaches to the prevention of TRALI have been recommended. Among these recommendations are: 1) limit the amount of plasma transfused from implicated donors by transfusing either washed or frozen-deglycerolized red blood cells; 2) indefinitely defer donors implicated in fatal TRALI; 3) defer multiparous women as donors; 4) screen donor units for leukoagglutinins; 5) change manufacturing processes to limit accumulation of lipids during storage; and 6) identify

patients at risk for TRALI and use washed or fresh components for them.[2,11,12]

The listed preventive measures are potentially expensive and challenging to supply necessary products in a timely manner. It is likely that all of the above strategies would reduce the risk of TRALI in the patient population; however there are a number of challenges that would have to be overcome to adequately serve the transfusion patient population. Limiting infusion of plasma from implicated donors by administering washed fresh, frozen deglycerolized RBCs and reducing the amount of plasma in units would be helpful, but would increase manufacturing costs and product preparation time for acutely ill patients. Certainly, all donors implicated in fatal TRALI should be deferred; however, this action would somewhat limit the donor pool. Exclusion of multiparous women from the donor pool could potentially reduce the donor pool by 5% to 30%. However, their plasma could be fractionated into plasma protein derivatives for other uses. An additional consideration with this approach would be the problems that could arise when a multiparous female insists upon becoming a directed donor for her child. Screening donor units for leukoagglutinins is impractical to do since tests are expensive, not readily available, and have long turnaround times. Changing the manufacturing processes to limit lipid accumulation may work in the future, but the process must be designed, tested, and approved for use. Identifying patients at risk and using only fresh, washed, or frozen deglycerolized RBCs would increase the cost and reduce turnaround time for critically ill patients.

CONCLUSION

TRALI is a potential consequence of transfusion and may exhibit mild to marked signs and symptoms. When a patient exhibits acute respiratory distress syndrome within one to four hours post transfusion, TRALI should be suspected and appropriate treatment instituted.

The signs and symptoms associated with this patient suggest TRALI as a diagnosis. Investigation of the gender of the donors revealed that the donor of the fourth unit of plasma was a multiparous female. Numerous possible adaptations to the provision of blood products exist; however, these changes could potentially harm an already low donor pool, increase the cost to all patients, and markedly decrease turnaround time in provision of blood products to acutely ill patients.[1-3,11,12]

An abbreviated discussion of this case study has been accepted for publication in *ASCLS Today*.

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