Transfusion-Related Acute Lung Injury and Exudative Pleural Effusion: A Case Report

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Transfusion-related acute lung injury (TRALI) is an acute lung injury that occurs during or following transfusion. It is typified by dyspnea, cough, hypoxemia, and noncardiogenic pulmonary edema within 6 hours of transfusion. Meanwhile, pleural effusion is a common finding in critically ill patients and potentially reflects imbalances in vascular permeability, and hydrostatic and oncotic pressures across lung capillaries. If pleural fluid is available, an analysis may help in the differential diagnosis of TRALI.

Key words: transfusion-related acute lung injury, pleural effusion

Introduction

Transfusion-related acute lung injury (TRALI) is a clinical syndrome that presents as acute hypoxemia and noncardiogenic pulmonary edema during or after blood transfusion.(1) Any blood product that contains plasma has the potential to cause TRALI; however, platelet concentrates derived from whole blood are most commonly implicated, followed by fresh-frozen plasma, packed red blood cells, whole blood, granulocytes, cryoprecipitate and intravenous immunoglobulin.(2) The most common symptoms associated with TRALI are dyspnea, cough, and fever.(3,4) Other features include hypotension and transient leucopenia.(5) Symptoms associated with TRALI can be sudden and fulminant, and most commonly occur between 1 hour and 2 hours after the onset of transfusion, but may develop within 30 minutes. Almost all reactions occur within 6 hours from the start of a transfusion(4,6,7), however, some case reports have shown an incubation period of up to 48 hours.(8,9)

The true incidence of TRALI has not been well established because there is significant underreporting of cases.(10) Estimated incidence rates vary widely, ranging from 0.002% to 1.12% per product transfused and from 0.08 to 8% per patient transfused(3,7,11-17) because the definition of TRALI(3,11,15,16,18), method of surveillance(17,19) and population under investigation differ between studies.

Pleural effusions are not uncommon in critically ill patients and have the potential to reflect imbalances in vascular permeability, and hydrostatic and oncotic pressures across lung capillaries. Therefore it is helpful to distinguish between exudative pleural effusion and transudative effusion to aid in the differential diagnosis of TRALI. We present a patient with upper gastrointestinal bleeding who developed sudden onset of respiratory distress during transfusion of
red blood cells. TRALI was considered because of the presence of exudative pleural effusion and clinical manifestations.

Case Report

A 53-year-old-man presented with fresh bloody vomitus and tarry stool passage for 1 day. He was brought to the emergency department where upper gastrointestinal (UGI) bleeding and hypovolemic shock (blood pressure: 75/52 mmHg) were impressed. An intravenous infusion of 2000 ml 0.9% sodium chloride solution and four units of packed red blood cells were given, and he was admitted to the intensive care unit. The patient underwent an esophagogastroduodenoscopy, which showed an active gastric ulcer and a proton pump inhibitor was administered. However, the patient developed sudden onset of dyspnea, tachypnea (30-36 breaths/min), and hypoxemia (FiO₂: 35%, PO₂/FiO₂: 177 mmHg) during transfusion of the 4th unit of packed red blood cells. His breath sounds revealed bilateral crackles and a chest radiograph showed newly developing increased bilateral airspace infiltrations especially in the lower lung zones, and pleural effusions (Fig. 1A) compared with the admission chest radiograph (Fig. 1B).

We started diuretic therapy because of suspicion of fluid overload. Furosemide 10 mg intravenously was administered three times over the following three days and the cumulated intake minus output was a negative 3360 ml, without calculation of insensible loss. However, chest radiography showed unresolved bilateral alveolar infiltrates and pleural effusions so we performed an echo-guided thoracocentesis. Exudative pleural effusion was noted because of a high level of lactic dehydrogenase in the pleural fluid (532 IU/L, normal range: 200-500 IU/L). Also, his electrocardiogram appeared normal, a cardiac echocardiogram showed

Fig. 1 A Radiograph taken after blood transfusion shows increased infiltrates over the bilateral lung fields, especially the lower lung zones and bilateral pleural effusions
B Admission chest radiograph
no evidence of left ventricle systolic or diastolic dysfunction, and his renal function was within the normal range.

Considering the normal cardiac and renal function of this patient, the persistent pulmonary edema after a negative fluid balance, the exudative pleural effusion and the mechanism of pleural effusion production, non-cardiogenic pulmonary edema was considered. This non-cardiogenic pulmonary edema developed during blood transfusion so TRALI was considered. Later the UGI bleeding improved, and blood transfusions were no longer needed. His clinical condition gradually improved and he was smoothly discharged on day 8.

**Discussion**

**TRALI is defined as noncardiogenic pulmonary edema temporally related to the transfusion of blood products and is characterized by respiratory distress, hypoxemia and pulmonary edema in the setting of transfusion of a plasma-containing blood product.** TRALI has emerged as the leading cause of transfusion-related fatalities reported to the United States Food and Drug Administration (20).

The pathogenesis of TRALI has not been fully elucidated. Two leading mechanisms have been formulated. Both of these lead to a final common pathway of increased pulmonary microvascular permeability which results in pulmonary edema.

The leading model suggests that TRALI is caused by donor antibodies against human neutrophil antigens or human leukocyte antigens in the lungs of the recipient (3,21). The second hypothesis is called a two-event model (22-24). The first event is an inflammatory condition in the patient (e.g. sepsis, tissue injury, recent surgery) causing sequestration and priming of neutrophils in the pulmonary compartment. The second event is the transfusion, containing either antibodies or bioactive lipids that have accumulated during blood storage, stimulating the primed neutrophils to release proteases.

TRALI is a clinical diagnosis as distinguishing biomarkers are absent. A definition of TRALI based on clinical and radiological parameters was formulated during a consensus conference and by the US National Heart, Lung and Blood Institute in 2004 (25-27). The definition is derived from the widely used definition of acute lung injury (ALI) and its more severe form, acute respiratory distress syndrome (ARDS), as proposed by the North American-European Consensus Conference (NAECC) consensus (28). ALI was defined as acute onset hypoxemia (PaO\(_2\)/FiO\(_2\) <300 mmHg) with bilateral infiltrates on chest radiograph with no evidence of circulatory overload. Because patients with other risk factors for ALI often receive transfusions, the NAECC created a two-tiered definition, TRALI and possible TRALI. TRALI is ALI that occurs during or within 6 hours of transfusion, with no temporal relationship to an alternative risk factor for ALI. Possible TRALI is used when there is a clear temporal relationship to an alternative risk factor for ALI. An important limitation of this definition is that patients with circulatory overload cannot be defined as having ALI or TRALI.

The diagnosis of TRALI requires a high index of suspicion and exclusion of other types of transfusion reactions. Pulmonary transfusion reactions can be especially difficult to investigate. The differential diagnosis of respiratory distress in the setting of transfusion includes allergic/anaphylactic reactions, TRALI, transfusion associated circulatory overload (TACO), bacterial contamination, and hemolytic transfusion reaction (29). The most important of these are TACO and TRALI. They are frequently confused with one another because the clinical features are similar.
and there are no diagnostic tests that reliably discriminate between them. The fact that a patient could have both simultaneously only adds to the complexity (25,30,31).

The use of brain natriuretic peptide (BNP) levels has recently been postulated as a laboratory adjunct in the differentiation of TRALI from TACO. BNP is a polypeptide released by the ventricles and atria in response to volume or pressure overload (32). Zhou et al. (33) demonstrated 81% sensitivity, 89% specificity, a 89% positive predictive value, a 81% negative predictive value, and 87% accuracy of BNP in diagnosing TACO. When interpreting BNP levels, it is important to compare posttransfusion with pretransfusion levels. A normal BNP level may exclude TACO and posttransfusion increases in the BNP level favor TACO.

If available, protein measurements of the edema fluid and a matched plasma sample can be diagnostic of increased permeability pulmonary edema. For example, the edema fluid/plasma protein ratio is < 0.65 in hydrostatic pulmonary edema, and > 0.75 with increased permeability pulmonary edema (34,35). This method is valid only with undiluted pulmonary edema fluid, not bronchoalveolar lavage fluid. However, the utility of this method for distinguishing TRALI from TACO has not been evaluated in a formal experiment, and there are aspects to the technique (e.g., sample timing, can only be used in intubated patients) that limit its utility (30).

Other laboratory parameters may also be useful. Transient, acute neutropenia has been reported by many authors (5,36-39), and the complete blood count is a readily available, inexpensive tool to increase the likelihood of identifying TRALI. Thrombocytopenia has also been reported in TRALI and seems to be more durable than the leucopenia (38,40,41). Confirmatory and definitive evidence for the diagnosis of TRALI requires investigating the donor and recipient for passively transfused antibodies.

Our patient developed sudden onset of dyspnea, tachypnea, and hypoxemia during blood transfusion although not severe enough to require mechanical ventilation. The BNP level was not available and no acute transient leucopenia was noted. However, acute thrombocytopenia (platelets decreased from 143000/µL to 81000/µL) was noted and there was no evidence of circulatory overload, so TRALI was considered. In addition, exudative pleural effusion was aspirated. Pleural fluid is normally a microvascular filtrate from parietal pleural capillaries whose homeostasis is maintained mainly by a matching outflow via parietal lymphatic stomata (42). Experimental data shows that hydrostatic (43,44) and permeability pulmonary edema (45) are followed by pleural effusion accumulation that comes from the lung interstitium. In hydrostatic and permeability pulmonary edema models, 21-29% of the overall excess fluid formed exits the lung via the visceral pleura into the pleural space (44,45). It seems reasonable, if available, to analyze the pleural fluid to aid in the differential diagnosis of TRALI from TACO, although this method has seldom or never been proposed.

The first step in the treatment of TRALI is to make the correct diagnosis. If the suspected blood product is still being transfused, it should be discontinued immediately (46). In the majority of cases, TRALI is a self-limited condition that has a better prognosis than most causes of ALI/ARDS. For mild TRALI cases, supplemental oxygen and supportive care may be sufficient treatment. For more severe cases, intravenous fluids and mechanical ventilation are necessary. Although an optimal ventilation strategy for TRALI has not been specifically studied, smaller tidal volumes and optimization of positive end-expiratory pressure seem to improve outcomes in ALI (47). In contrast to the 40 to 60% mortality rate of ALI (48), the mortality
rate of TRALI is low, around 5 to 10\%\(^{(3,7,27,49)}\). Also, the pulmonary function of TRALI patients usually recovers without apparent structural damage such as fibrosis\(^{(49)}\) and most patients return to baseline status in a few days.

In conclusion, TRALI is a rare but serious complication of transfusion therapy. The key to the diagnosis and treatment of TRALI is high clinical suspicion and the need to exclude cardiogenic pulmonary edema or volume overload and other more common causes of ALI/ARDS. Rapid recognition when cases of TRALI occur remains vital to the further understanding and proper treatment of this complication.

References

輸血相關急性肺損傷及滲出性肋膜積液：病例報告

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輸血相關急性肺損傷是指輸血中或輸血後發生的急性肺損傷。典型的表現是輸血六個小時內出現呼吸困難、咳嗽、低氧血症及非心因性肺水腫。同時，肋膜積液是重症患者常見的臨床表現，肋膜積液也能反應出肺臟微血管中的血管通透性、靜水壓、膠體滲透壓的變化。如果可行的話，或許除了患者臨床及影像學的表現，可藉由肋膜積液的分析來協助進行輸血相關急性肺損傷的鑑別診斷。

關鍵詞：輸血相關急性肺損傷，肋膜積液