Case Report

Acute lung injury after platelet transfusion in a patient with dengue fever

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Abstract:

Transfusion-related acute lung injury (TRALI) is a serious clinical syndrome associated with the transfusion of plasma-containing blood components. Recently, TRALI has come to be recognized as the leading cause of transfusion-related mortality. This complication typically presents as shortness of breath, hypoxemia, hypotension, fever, and non cardiogenic pulmonary edema, occurring within 6 h after transfusion. Although the mechanism of TRALI has not been exactly known, it has been associated with human leukocyte antigen antibodies and with biologically active mediators in stored cellular blood components. We, hereby, present a case of a patient with dengue fever who developed acute lung injury (ALI), presumably TRALI, after transfusion of platelet concentrates. He was treated with supportive measures and mechanical ventilation. Greater knowledge and increased awareness especially amongst the clinicians regarding TRALI is needed for prevention and treatment of this potentially severe complication of blood/component transfusion.

Key words

Acute lung injury, blood transfusion, non cardiogenic pulmonary edema, transfusion-related acute lung injury

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Introduction

Transfusion-related acute lung injury (TRALI) represents acute lung injury (ALI) associated with the transfusion of one or more plasma-containing blood products. It has become the leading cause of transfusion-related morbidity and mortality.[1] The incidence of TRALI is frequently reported as one occurrence for every 5,000 blood component transfusions,[2] however, this is thought to be a vast underestimate of the true incidence, resulting from lack of recognition or underreporting particularly amongst clinicians. The TRALI syndrome is represented by a group of clinical symptoms that generally develop within 6 h after transfusion, with the manifestation of fever (increase of > 1°C in temperature), tachypnea, cyanosis, dyspnea, acute hypoxemia with arterial oxygen tension/fraction of inspired oxygen <300 mmHg and oxygen desaturation.[3,4] It may be life threatening but self limiting condition in majority of the patients. Supportive care with mechanical ventilation may be sufficient for treatment. We, hereby, present a male patient of dengue fever who developed ALI after platelet transfusion.

Case Report

A 65-year-old male, presented with history of fever with chills, arthralgia, and myalgia of 5 days duration along with vomiting and epistaxis for 1 day. There was no history of any significant past illness except that few months ago he was diagnosed to have systolic hypertension but he was not on any treatment. On examination, pulse rate was 112/min, blood pressure 120/70 mmHg, temperature 99.6°F, and respiratory rate was 18/min with 100% oxygen saturation at room air. Rest of the general examination was within normal limits except that he had mild pallor and evidence of epistaxis. Systemic examination was unremarkable. Laboratory investigations showed hemoglobin 12.2gm%, total leukocyte count 4,600/cmm, polymorphs 64%, lymphocytes 36%, hematocrit 36%, and platelet count 18,000/cmm. Other hematological and biochemical parameters that included coagulation profile, liver, and renal function tests and electrolytes were within normal limits. Dengue serology for IgM antibodies was positive. Chest radiograph at the time of admission did not show any significant abnormality [Figure 1]. After 3 hours, platelet count was repeated that showed declining trend (12,000/cmm) so transfusion of platelet concentrates was planned. The patient remained hemodynamically stable during this period [Blood pressure (BP); 120-130/70-80 mmHg, pulse rate (HR); 100-120/min, respiration rate (RR); 15-18/min, SpO_2: 100%. After about 12 hours since presentation, he was transfused 50 ml of the platelet concentrate from random plasma donor over a period of 20 minutes. Single unit platelet concentrate from random donor, which contains approximately 5.5×10^{10} platelets, was transfused. One hour after transfusion initiation, he developed cough, respiratory distress, and hypotension. He was noted to have tachycardia (pulse 146/min),

blood pressure 80/50 mmHg, tachypnea (respiratory rate 42/min), and low oxygen saturation (SpO_2 76%) described in Table 1. His neck veins were not distended and central venous pressure was 9 cm of water. Chest auscultation revealed bilateral extensive coarse rales without evidence of bronchospasm. Patient was treated with supplemental oxygen, intravenous fluids (both colloids and crystalloids), hydrocortisone and vasopressors. The fluid replacement consisted of 800 ml of crystalloid and 500 ml of hetastarch solution. Vasopressors used were dopamine: (10-20 μg/kg/min) and nor epinephrine (> 20 μg/kg/min). Two hours later, his temperature was 102°F, pulse 140/min, and blood pressure 70/50 mmHg. Chest radiograph revealed bilateral alveolar infiltrates with normal cardiac silhouette [Figure 2]. Arterial blood gas showed pH 7.34, pCO_2 46 mmHg, pO_2 62 mmHg, HCO_3 22 mmol/L. There was no evidence of circulatory overload so diuretic was not given. Subsequently, patient was managed with invasive (conventional) mechanical ventilation in a pressure regulated volume control model using low tidal volume in addition to empirically administered antibiotics. The repeated total leukocyte count was 4,200/cmm. All cultures (blood, urine, and throat swab) which were sent, reported as sterile. The specimen from platelet bag was not sent for culture. Electrocardiogram, echocardiography, and cardiac enzymes did not reveal any cardiac involvement. The condition of the patient gradually improved and was extubated in 48 hours. Chest X-ray also showed improvement [Figure 3] and he was discharged in 7 days. Patient was diagnosed as a possible case of transfusion related acute lung injury of clinical symptoms, chest radiograph, and laboratory findings that can establish the diagnosis. The platelet concentrate implicated in the ALI in our patient was derived from male donor who had history of blood transfusion in the past. No investigations of the patient and donors serum for anti-leukocyte antibody could be performed due to technical constraints.

Discussion

The term TRALI was coined by Popovsky *et al*.,[5] in 1983 referring to noncardiogenic pulmonary edema complicating transfusion. TRALI is associated with transfusion of whole blood, fresh frozen plasma (FFP), platelets, cryoprecipitate, immunoglobulin, and stem cell preparations. 10–15% incidence of TRALI has been seen in unleukodepleted blood transfusion. FFP is the blood product most frequently implicated. The clinical severity of TRALI does not appear to be related to the volume or type of blood component transfused. Stored blood components are also implicated in the increased occurrence of TRALI.[6]

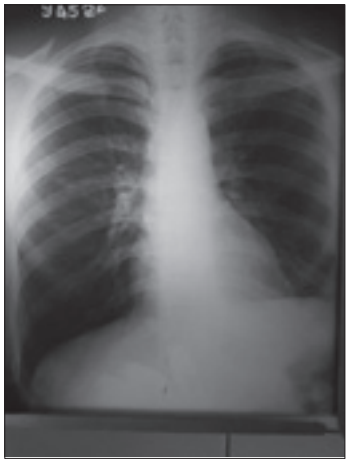

Figure 1: Pre-transfusion X-ray Chest

Table 1: Clinical parameters before and after the transfusion of platelet concentrate

Parameters	Pre transfusion	Post transfusion	After resolution
Pulse rate (beats/min)	112	146	88
Blood pressure (mmHg)	120/80	70-80/50	150/80
Temperature (°F)	99.6	102	98.4
Respiratory rate (breaths/min)	16	42	16
Central venous pressure (mm of water)	-	9	9
SpO_2 at room air (%)	100	76	100
Arterial Blood Gas analysis			
pH	7.36	7.34	7.36
pCO_2 (mmHg)	28	46	20
pO_2 (mmHg)	96	62	98
HCO_3 (mmol/L)	18	22	20

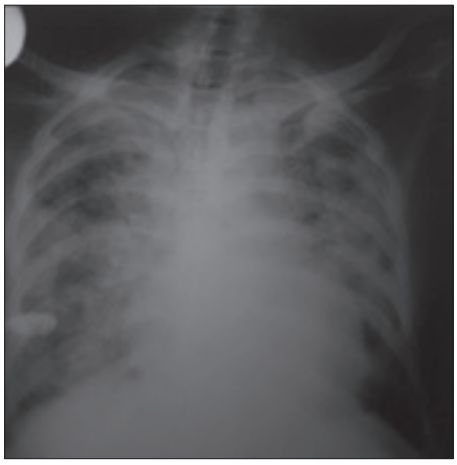

Figure 2: X-ray chest immediately after developing acute lung injury

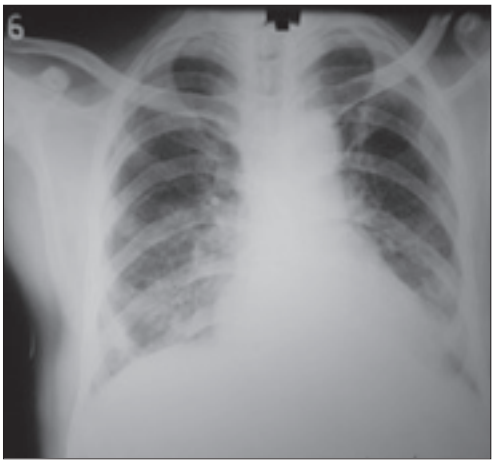

Figure 3: X-ray chest after resolution of acute lung injury

Two mechanisms have been hypothesized which may be responsible for TRALI.[7] One is immune mediated that involves an interaction between passively transferred donor human leukocyte antigen (HLA) antibodies and recipient HLA antigens. The antibody–antigen interaction leads to leukocyte activation and subsequent lung injury. Alternatively, non immune mechanism, a "two hit" hypothesis has been proposed in which biologically active substances, such as lysophosphatidylcholine species of bioactive lipids, accumulate in the red cells as the blood is stored and are transfused passively. These inflammatory lipids can subsequently induce neutrophil priming capable of producing endothelial cell damage of pulmonary capillaries, injury in the setting of systemic inflammation from another insult, such as trauma or sepsis. That is followed by capillary rupture, together with the exudation of fluids and proteins within the alveoli, which results in pulmonary edema.

TRALI was increasingly recognized as a serious adverse transfusion event in the past decades but was poorly understood. Thus, to better understand TRALI, a proper definition was required and was finally created through working group of NHLBI (National Heart Lung and Blood Institute) and Consensus Panel statement.[4,8] An NHLBI working group defined TRALI as new ALI occurring within 6 hours of the end of transfusion of one or more plasma-containing blood products in patients without other risk factors for ALI, or in patients with other risk factors for ALI if there was no pretransfusion ALI present and if the new ALI was temporally associated with the transfusion. NHLBI used the definition of ALI put forth by the North American–European Consensus Conference in 1994 [Table 2].[9] In 2004, a Consensus Panel statement titled–"Toward an understanding of TRALI" extended the criteria for diagnosing TRALI by expanding the meaning of "the presence of hypoxia" to include other clinical evidence supporting the conclusion of hypoxia, and by creating criteria for "possible TRALI," [Table 3] which is defined by the same diagnostic criteria with those of TRALI, but it refers to the case in which the patient has other acute pulmonary risk factors such as sepsis, aspiration, near drowning, disseminated intravascular coagulation, trauma, pneumonia, drug overdose, fracture, burns, and cardiopulmonary bypass in addition to a transfusion.

TRALI can be confused with other situations involving acute respiratory failure, such as acute respiratory distress syndrome (ARDS) and transfusion-related circulatory overload (TACO) and cardiogenic pulmonary edema. There was no evidence of transfusion associated circulatory overload with absence of jugular venous distension or a S3 gallop with normal central venous pressure in our patient. B-natriuretic peptide may have some value in distinguishing TACO from TRALI which could not be done. Cardiogenic pulmonary edema was ruled out because there were no signs of fluid overload, no cardiomegaly, and normal echocardiography and troponin I level. As the respiratory dysfunction was acute, blood counts were normal, and antibiotics were given since presentation, we excluded the possibility of a lung infection or septicemia due to bacterial infection. Aspiration pneumonia was excluded as patient was fully conscious and resolution was relatively rapid and complete. The reason why we diagnosed our case as "possible TRALI" was that the possibility of ALI/ ARDS due to dengue infection was still a possible differential diagnosis. Dengue hemorrhagic fever can result in ARDS.[10,11] Dengue virus antigen has been found in alveolar lining cell of the lung. Increased permeability of the alveolar-capillary membrane results in pulmonary edema. A diagnosis of possible TRALI can be made if there are preexisting risk factors for ALI other than transfusion that could not be excluded.

Table 2: The North American-European Consensus Conference definition of ALI[9]

Parameter	Finding
Timing	Acute onset
Pulmonary artery occlusion pressure	≤ 18 mm Hg when measured, or lack of clinical evidence of left atrial hypertension
Chest radiograph	Bilateral infiltrates seen on frontal chest radiograph
Hypoxemia	Ratio of PaO2/FIO2 ≤ 300 mmHg regardless of positive end-expiratory pressure level, or oxygen saturation of ≤ 90% on room air (added by National Heart, Lung, and Blood Institute (NHLBI) working group)

Table 3: Recommended criteria for TRALI and possible TRALI according to Consensus Panel Statement[8]

1. TRALI
a. ALI
i. Acute onset
ii. Hypoxemia
Research setting: PaO_2/FiO_2 ≤ 300 mmHg, or SpO_2 < 90% on room air
Non-research setting: PaO_2/FiO_2 ≤ 300 mmHg, or SpO_2 < 90% on room air or other clinical evidence of hypoxemia
iii. Bilateral infiltrates on frontal chest radiograph
iv. No evidence of left atrial hypertension (ie, circulatory overload)
b. No preexisting ALI before transfusion
c. During or within 6 h of transfusion
d. No temporal relationship to an alternative risk factor for ALI
2. Possible TRALI
a. ALI
b. No preexisting ALI before transfusion
c. During or within 6 h of transfusion
d. A clear temporal relationship to an alternative risk factor for ALI

Laboratory findings are only suggestive and not diagnostic of TRALI. Such findings include leukopenia, neutropenia, monocytopenia, and hypocomplementemia.[12] Demonstration of human leukocyte antigen (HLA) class I or class II or neutrophil-specific antibodies in donor plasma and the presence of the cognate (corresponding) antigen on recipient neutrophils strongly support, but are not required for the clinical diagnosis of TRALI. Such testing typically takes days or weeks to perform and is not helpful clinically.[13] Optimal methods for detecting these antibodies in donated products have yet to be determined. Tests for lipid priming activity or neutrophil-activating factors in the plasma from the blood component are only available on a research basis.

The treatment of TRALI is primarily supportive, based on the maintenance of the hemodynamic balance of the patient and on the necessity for the earliest possible application of ventilatory support. Patients with TRALI are euvolemic or may be hypovolemic as a result of excessive fluid leakage into the lung. Whereas rapid volume reduction with diuresis is the treatment of choice for TACO, in patients with TRALI, diuretics may cause hypovolemia. There are no data regarding the efficacy of steroids.

Unlike ARDS, TRALI generally has a good prognosis. In spite of having a favorable prognosis, TRALI mortality is estimated at

5-10% of the cases, which is still considered low when compared with ARDS, which has a mortality rate of approximately 40-50%.[14,15] In 80% of all TRALI patients, there is resolution of the pulmonary infiltration within the first 4 days. However, in a minority of patients, hypoxemia and pulmonary infiltrate can persist for more than 7 days. The resolution of TRALI frequently occurs rapidly and does not have any long-term sequelae.

Regarding prevention, multiple approaches have been proposed and are in place, including plasma from men only, resuspending pooled buffy coat platelets in plasma from men only, and screening female donors (either all, or only those donors with a history of pregnancy, transfusion, or both) for leukocyte antibodies.[16,17] Decreasing incidence of TRALI through changes in blood product policies has been supported through biovigilance data.[18] The International Society for Blood Transfusion (ISBT) published recommendations for screening donors for leukocyte antibodies.[19] Antibody detection should include antibodies against Human neutrophil antigens (HNA-1a, HNA-1b, HNA-2, and HNA-3a) and HLA class I (HLA-A2) and class II. The ISBT also recommended screening donors at risk for leukocyte antibody formation, that is, parous women, and individuals who have undergone transplantations and transfusions.[18] Blood components with high plasma fractions (plasma, aphaeresis platelets, and whole blood) should not be prepared from these donors. Lastly, those with anti-HNA-3a should not donate because of the high rate of fatality associated with this antibody.

Conclusion

TRALI is a severe complication of blood transfusion which may be life threatening. Greater knowledge and high index of suspicion on the part of clinicians regarding TRALI could be crucial in prevention and treatment. With supportive treatment (hemodynamic and ventilatory), good outcome can be expected.

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