

TRALI in a Patient with Hematological Malignancy: Complexities in the Critically Ill

Rajeswari Subramaniyan*

Department of Transfusion Medicine, Yashoda Hospital, Malakpet, Hyderabad, India

*Corresponding author: Rajeswari Subramaniyan, Department of Transfusion Medicine, Yashoda Hospital, Malakpet, Hyderabad-500036, India, Tel: 040 6777888; E-mail: arthisoundarya@gmail.com

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Abstract

Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion related mortality. It is a new lung injury occurring within 6 hours of transfusion having no alternative risk factors of acute lung injury. Here we report a patient with AML-M3, who probably had TRALI after apheresis platelet transfusion and died despite prompt resuscitation. A strong clinical suspicion of TRALI is required. Critically ill patients with hematological malignancies are at risk population for TRALI. TRALI related mortality rate in such patients is significant. TRALI risk mitigation measures should be implemented in this cohort to reduce the incidence.

Keywords: Lung injury; Acute; Transfusion; Critically ill; Hematological malignancy

Introduction

TRALI (Transfusion-related acute lung injury) remains the leading cause of transfusion-related fatalities with an incidence of 1:1200 to 1:5000 transfused products [1]. Almost all blood components have now been implicated in TRALI [2]. Critically ill patients with hematological malignancies constitute the “at risk” cohort for TRALI. TRALI associated with leukemia has been fatal in many patients. We present a case of suspected TRALI after apheresis platelet transfusion in a patient with acute myeloid leukemia prior to induction chemotherapy.

Case Report

A 38-years old female came to emergency at 2:00 AM with 7 days history of fatigability, weakness and 3 days history of vomiting. Past history was insignificant. On physical examination she was extremely pale, afebrile, pulse rate 90/min, Blood Pressure (BP) 100/70 mmHg and respiratory rate 20/min. Systemic examination was unremarkable. Complete hemogram revealed Hb -4 g/dL; platelet count-16000/ μ l; white cell count-50,400/ μ l; absolute neutrophil count: 1008/ μ l. Peripheral smear showed atypical promyelocytes (70%) and marked leucocytosis. A provisional diagnosis of acute leukemia was made and bone marrow examination was requested. Renal function, liver function and coagulation tests were within normal limits. Routine chest X-ray and ECG were normal. The patient was admitted in the intensive care unit.

By 8:00 PM, before transfusion, her urine output was 200 ml (oliguria probably due to prolonged vomiting). In view of hypovolemia, fluid resuscitation was initiated. Initial transfusion of one unit of packed red blood cell was uneventful. Subsequently (after 8 hours), one unit of SDAP (Single Donor Apheresis Platelets) was transfused. After 50 ml of transfusion for 15 minutes, the patient suddenly developed breathlessness and hypotension (BP-80/60 mmHg). Transfusion was discontinued. Her SpO₂ was 66% at room air.

Examination revealed bilateral crackles and arterial blood gas analysis showed pH=7.3, pCO₂=31.2; pO₂=65.8. Her chest roentgenogram revealed non-homogenous bilateral infiltrates and no cardiomegaly (Figure 1).

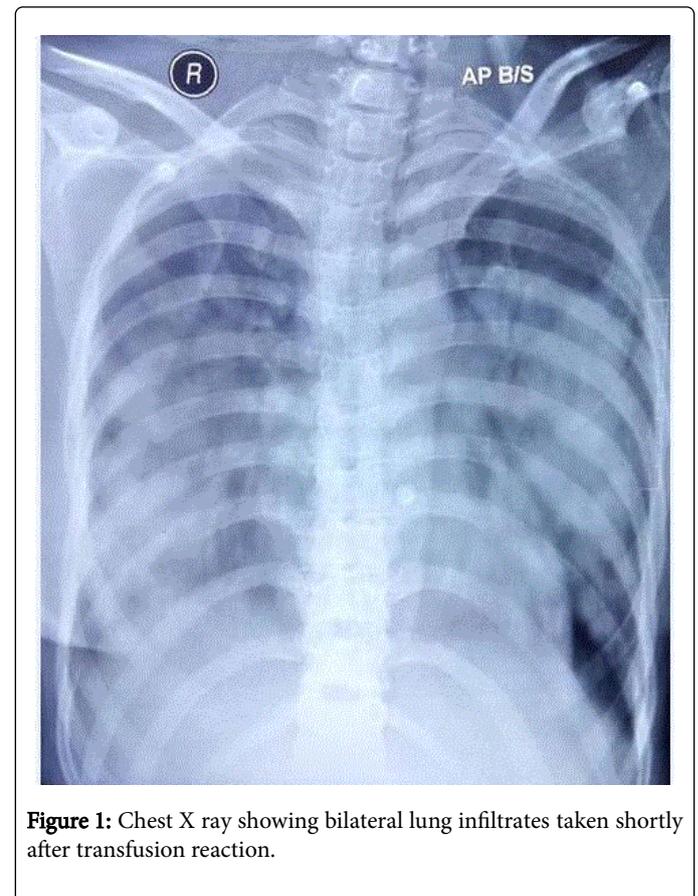


Figure 1: Chest X ray showing bilateral lung infiltrates taken shortly after transfusion reaction.

Echocardiography was normal and ejection fraction was 66%. Immediate resuscitative measures included non-invasive ventilation,

intravenous hydrocortisone, normal saline boluses, dopamine infusion and intramuscular adrenaline. Circulatory overload was ruled out, although the brain natriuretic peptide (BNP) level was 1407.88 pg/ml (normal 0 ng/ml-200 ng/ml). Meanwhile, to rule hemolytic transfusion reaction, we rechecked the patient's blood group and the blood bag that had been transfused. Direct Coombs' Test and red cell antibody screen were negative. Two hours post transfusion, she had persistent hypotension of 70-80/60 mmHg and double ionotropes were initiated (dopamine and vasopressin). During the ensuing hours, she became anuric (serum creatinine increased from 0.8 mg/dL to 4.1 mg/dL) and was started on dialysis with no benefit. Her SpO₂ dropped to less than 60% necessitating intubation and positive pressure ventilation. She succumbed to refractory shock and sudden cardiac arrest with unsuccessful cardiopulmonary resuscitation. Flow cytometry analysis was consistent with AML-M3 (Acute Myeloid Leukemia). Her pre/post-transfusion and blood bag's blood cultures were sterile (transfusion-associated bacterial sepsis was ruled out). Polymerase Chain Reaction revealed the presence of PML-RARα fusion, confirming the diagnosis of Acute Promyelocytic Leukemia (APML) in this patient. In this patient, TRALI was considered excluding the other possible causes of acute lung injury. The implicated donor was a 23 years old male volunteer. He was advised to refrain from blood donation in future. We did not have the facility to evaluate donor leucocyte antibodies.

Discussion

TRALI is an acute lung injury (ALI) occurring within 6 hours of blood transfusion in a patient with no preexisting ALI prior to transfusion. In the presence of an alternate risk factor for ALI, possible TRALI can be diagnosed as per the standard definition of consensus panel (Table 1) [3]. Pathogenesis of TRALI is centered around neutrophil activation. Among the postulated theories [4], the "two-event model" proposed by Wyman et al. [5] appears to be relevant. In patients with underlying conditions like hematological malignancy, recent cardiac surgery, massive transfusion, higher cytokine levels, chronic alcohol abuse, shock, mechanical ventilation, current smoking and positive fluid balance, a pro-inflammatory state sets in [6,7]. The activated endothelium release chemokines like IL-8, growth related oncogene- alpha (GRO-α) and epithelium derived neutrophil activating peptide-78 (ENA-78) leading to neutrophil adhesion (neutrophil priming) and sequestration (first event). After transfusion of blood and blood components containing leucocyte antibodies, cytokines or bioactive lipids (second event), these primed neutrophils activate nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby releasing excess reactive oxygen species (ROS) leading to endothelial dysfunction, capillary leak and pulmonary edema [5,8]. In up to 89% of TRALI cases, donor leucocyte antibodies were demonstrated in the recipients. This finding indicates severe form of TRALI [2].

TRALI
In patients with no evidence of acute lung injury (ALI) prior to transfusion, TRALI is diagnosed
a) if a new ALI is present:
i. Acute onset
ii. Hypoxemia
PaO ₂ / FiO ₂ ≤ 300 mm Hg or Oxygen saturation is <90% on room air or
other clinical evidence of hypoxemia
iii. Bilateral infiltrates on frontal chest radiograph
iv. No evidence of left atrial hypertension (i.e. circulatory overload)
b) No preexisting ALI before transfusion
c) No temporal relationship to an alternative risk factor for ALI
d) During or within 6 hours of completion of transfusion
Possible TRALI
a. ALI
b. No pre-existing ALI before transfusion
c. During or within 6 h of transfusion
d. A clear temporal relationship to an alternative risk factor for ALI
Alternative risk factors for ALI includes septic shock, aspiration, pneumonia, drug overdose, multiple fractures, pulmonary contusion, cardiopulmonary bypass, burns, near drowning, toxic inhalation, acute pancreatitis

Table 1: TRALI definition criteria as per consensus panel recommendation [3].

Signs and symptoms typically begin within 1-2 hrs of transfusion which includes dyspnoea, bilateral pulmonary edema, hypoxemia,

fever, and hypotension [4]. Differential diagnosis of TRALI includes: Transfusion-associated circulatory overload (TACO), anaphylaxis and

sepsis. The signs and symptoms of TRALI resemble TACO. Differentiating them in critically ill patients is challenging. TACO presents with hypoxemia, pulmonary edema associated with features of left atrial hypertension. Although elevated BNP levels are supportive of TACO, the study by Li et al. [9] questioned its utility in differentiating TRALI and TACO in critically ill patients, as conditions like anemia and renal failure have an impact on BNP levels (clearance of the peptides reduced). Before transfusion, our patient had impending renal failure that resulted in elevated BNP levels. But there were no features suggestive of TACO. Anaphylaxis was ruled out (no evidence of bronchospasm, wheeze, laryngeal edema or stridor). TRALI was suspected with a clear temporal association to transfusion (15 minutes after initiating transfusion), although pulmonary leukostasis syndrome was also considered. However, the patient had no apparent signs of respiratory distress prior to transfusion.

The incidence of TRALI per product ranges from 1 in 1200 to 5000 (1 in 625 patients transfused), several folds higher than the hemovigilance data due to underreporting. In critically ill, the incidence of TRALI ranges from 2.2% to 29% [2,7,10]. TRALI has been described in patients with acute leukemia during induction chemotherapy, consolidation and following stem cell transplantation [11,12]. Development of symptoms before initiating chemotherapy is peculiar in this case. High cytokine levels especially tumour necrosis factor- α produced by blast cells [13], positive fluid balance probably created a favourable niche for TRALI.

Mechanical ventilation and oxygenation remain the mainstay of the treatment, recovery being achieved in 48-96 hours. In general, TRALI related mortality rate is observed to be 6-20% as compared to that of 41% in critically ill. Despite intense resuscitative measures, our patient could not survive. Patient's underlying conditions had an impact on the prognosis. Hence, recipient related risk factors play a major role in TRALI [2].

Demonstration of leucocyte antibodies and inflammatory cytokines are not definitive of TRALI. Plasma rich products (fresh frozen plasma, apheresis platelets, whole blood) transfusion is an independent risk factor for TRALI. Female donors are mostly implicated in TRALI. The donor implicated in our case was a non-transfused male. However, in one study, 1% of non-transfused males had HLA (Human Leucocyte Antigen) antibodies [2]. There are no clear-cut guidelines for cases where male donors are implicated. The American Association of Blood Banks (AABB) recommends the practice of whole blood and high plasma volume components transfusion from males, nulligravida, donors with no previous history of transfusion or HLA antibodies negative parous females as TRALI risk mitigation strategies [14]. A recent meta-analysis concluded that this donor-based approach had reduced the incidence of TRALI with maximum impact amongst the critically ill [15]. Ongoing experiments on specific RBC filters to absorb the leucocyte antibodies and lipids are on the horizon as additional risk reduction measures [16].

In conclusion, TRALI is not so uncommon as it was once thought, particularly in critically ill patients. Hematological malignancy itself is a risk factor for these patients, making them an ideal target for implementing preventive measures.

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