Case Report

Transfusion-related acute lung injury induced by anti-human leukocyte antigen antibodies in the donor blood – A case report

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ABSTRACT

Transfusion-related acute lung injury (TRALI) is one of the leading causes of transfusion-related fatalities, and there are no available specific therapies. The pathophysiology of the condition is not straightforward and is poorly understood. A 2-hit model is generally attributed to underlie TRALI. In this case report, we report a case of a 72-year-old male patient with no significant history, who was transfused with packed red blood cells and developed TRALI as a consequence. He recovered in 24 h and had no sequelae. Laboratory investigations of the blood donors revealed a positive human leukocyte antigen antibody screen. Further research is required to comprehend and elucidate the pathophysiology of TRALI, for better diagnostics and therapeutic approaches for the same in the future.

Key words: Acute respiratory distress syndrome, Human leukocyte antigen antibodies, Transfusion-related acute lung injury

Transfusion-related acute lung injury (TRALI) is a clinical syndrome in which there is acute, non-cardiogenic pulmonary edema associated with hypoxia that occurs during or after a transfusion [1]. Transfusion reactions are adverse events that occur after transfusing blood products such as whole blood, fresh frozen plasma, platelets, cryoprecipitate, granulocytes, intravenous immune globulin, allogenic and autologous stem cells, and packed red blood cells (pRBCs) [2]. It is the leading cause of death from transfusion, as documented by the U.S. Food and Drug Administration at the TRALI consensus conference in Toronto [3]. Even though the current incidence is unknown, TRALI is markedly underdiagnosed and underreported. Specifically, an incident of TRALI includes 1 in 5000 units of pRBCs, 1 in 2000 plasma-containing components, and 1 in 400 units of whole-blood-derived platelet concentrates [4]. Anti-granulocyte, anti-human leukocyte antigen (HLA), anti-monocyte, and anti- immunoglobulin A antibodies and lipids in stored blood have been implicated in TRALI development. Mild-to-moderate cases of TRALI are usually misdiagnosed as other transfusion-related adverse effects and seldom reported or thoroughly investigated.

Here, we report a case of a 72-year-old man who developed TRALI following a transfusion of pRBCs. The rationale behind reporting this case lies in the fact that TRALI is often underdiagnosed or misclassified as other types of acute respiratory distress. Reporting raises clinical awareness and future recognition. Accumulated data from reported cases can help guide public health policies and recommendations regarding transfusion practices.

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CASE REPORT

A 72-year-old male patient was admitted to our hospital for severe pancytopenia secondary to B12 deficiency. He had no significant history.

On admission, the patient was hemodynamically stable with normal vital signs. His hemoglobin, however, was 3 g/dL and hence, was planned for a packed red cell transfusion. The patient's laboratory investigation report is presented in Table 1.

An uneventful transfusion of one pRBC took place. However, 4 h after a pRBC transfusion, the patient experienced a sudden onset of dyspnea, and severe hypoxemia (SpO_2 <70%; pH 7.30; pO_2 - 60 mmHg). On examination, he was tachypneic with a respiratory rate of 30 cycles/min, his blood pressure was 140/90, and he had a normal temperature. On auscultation, he had diffuse crepitations in all lung fields.

All the laboratory investigations were repeated. Electrocardiogram showed no new changes, and cardiac

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Table 1: Patient's laboratory investigation report

Patient characteristics	May 24, 2024
Hemoglobin	5.2
Total leukocyte count	7690
Platelets	23,000
Prothrombin time	12.9
International normalized ratio	1.13
Activated partial thromboplastin time	28.3
Blood urea	43.3
Creatinine	1.06
Sodium	137.1
Potassium	3.36
Chloride	96.1
Total protein	5.09
Albumin: Globulin	2.78
Bilirubin	1.1
Conjugated bilirubin	1.88
Albumin	0.62
Aspartate aminotransferase	32.5
Alanine transaminase	60.4
Alkaline phosphatase	68.1
Gamma-glutamyl transferase	50.5
Folic acid	0.31

enzymes were well within the normal range. A repeat chest X-ray showed coarse alveolar infiltrates with no evidence of cardiomegaly. A high-resolution computed tomography was done, which was reported as bilateral pleural effusions, small-to-moderate amount on right and small amount on left (Fig. 1). The patient displayed the clinical characteristics of TRALI, which included acute dyspnoea, hypoxemia, fever, hypotension, tachycardia, leukopenia, thrombocytopenia, and normal pulmonary artery occlusion pressure due to non-cardiogenic pulmonary edema. Features suggestive of pulmonary edema. An echocardiogram was done and showed normal function, with no evidence of left ventricular failure or volume overload. A clinical diagnosis of non-cardiogenic pulmonary edema was made. Bacterial cultures of the patient's blood were also negative. The patient did not undergo endoscopic examination because her stool examination did not have blood, and we had a coherent explanation of her clinical condition. In this case, anorexia and low food intake were determined to be the causes of Vitamin B12 deficiency.

Immediate management of TRALI was to stop the transfusion and notify the blood bank to screen the donor unit for anti-leukocyte antibodies, anti-HLA, or anti-neutrophil-specific antibodies. The patient was then admitted to the intensive care unit, was given a dose of diuretic, and was put on non-invasive mechanical ventilation. A few hours later, the patient's general condition improved and was de-escalated to intermittent non-invasive ventilation, which he received for 1 day. HLA antibody screening was done for the donor blood, and it was positive for HLA class 1 titers. Thus, the diagnosis of TRALI was confirmed.

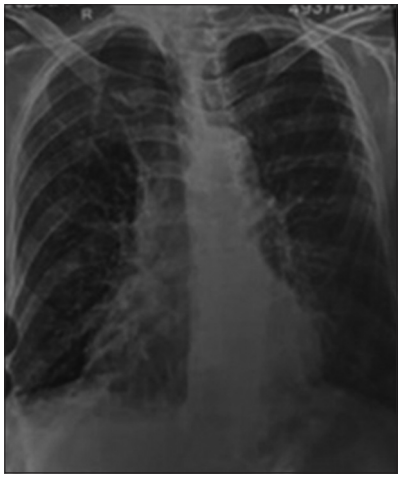

Figure 1: Chest X-ray showing coarse alveolar infiltrates with no evidence of cardiomegaly

On day 2, the patient was stabilized and was on oxygen support through nasal prongs and was shifted to step down for further monitoring. On a repeat chest radiograph, the lung opacities were cleared. The rest of his hospital stay was uneventful.

DISCUSSION

TRALI is a severe and sometimes life-threatening reaction to blood transfusion, characterized by the sudden onset of lung injury and non-cardiogenic pulmonary edema, resulting from the activation of immune cells within the lungs and leading to acute respiratory distress syndrome (ARDS) [5]. TRALI is diagnosed according to the Canadian Consensus Conference Panel [6]: Acute lung injury (ALI): Acute onset. Hypoxemia: SpO_2<90% or PaO_2/FiO_2<300 mmHg on room air, or other clinical evidence of hypoxemia. Bilateral infiltrates on frontal chest X-ray. No evidence of left atrial hypertension, such as circulatory overload. No pre-existing ALI before transfusion. Occurs during or within 6 h of transfusion. No temporal relationship to an alternative risk factor for ALI (including pneumonia, sepsis, aspiration, multiple trauma, acute pancreatitis).

The pathophysiology is assumed to have a two-hit model that underlies this condition. The first hit represents patient predisposing factors, such as inflammation. The second hit is due to HLA class I/II or human neutrophil antigen (HNA) antibodies or donor biological response modifiers (bioactive lipids, mitochondrial damage-associated molecular patterns, extracellular vesicles, or aged cellular blood products), which are present in the donor blood [7]. First-hit risk factors for TRALI include chronic alcohol abuse, liver surgery, smoking, shock, higher peak airway pressure while undergoing mechanical ventilation, and positive intravascular fluid balance.

The antibody hypothesis states that an antigen–antibody reaction triggers a series of events leading to TRALI. Most often, the causative blood component contains antibodies against recipient white blood cell (WBC) antigens. More rarely (e.g., in approximately

10% of those cases that occur through the antigen–antibody mechanism), the antibody is present in the recipient and reacts with antigens on transfused donor WBCs. Antibodies may be HLA Class I or HLA Class II or directed against HNAs. It is possible that transfused HLA antibodies may directly activate or injure pulmonary endothelial cells. Activated neutrophils, and possibly other WBCs, lodge in pulmonary capillaries either through cellular adhesive mechanisms or by physical trapping of WBC agglutinates. Such activated neutrophils release vasoactive substances, such as leukotrienes, or cytotoxic substances such as reactive oxygen metabolites. These mediators cause pulmonary endothelial leakage or damage with consequent pulmonary edema. The clinical features observed in cases of TRALI include dyspnoea, fever, hypotension, tachypnoea, tachycardia, frothy endotracheal aspirate, and requirement of mechanical ventilation to support oxygenation. Features of TRALI that are less clearly documented include hypertension, leukopenia, and hypocomplementemia.

As was the case with our patient, the treatment of TRALI is mainly supportive. However, there has been ongoing research for potential therapeutic strategies. For example, interleukin (IL)-10 therapies, C-reactive protein down-modulation, IL-8 receptor blockade, and neutrophil extracellular trap disruption. Mortality of ALI is about 40–60%, but majority of the TRALI patients improve within 48–96 h of the insult, when appropriate and prompt supportive measures are initiated. However, survival of TRALI in critically ill patients is as low as 53% compared with 83% in ALI control subjects [8]. Thus, understanding the pathophysiology requires a high degree of clinical suspicion, and the development of novel therapeutic strategies is highly significant to lessen the mortality burden of TRALI.

The differential diagnoses for TRALI include (a) transfusion-associated circulatory overload (TACO): Although TACO can present with respiratory distress and pulmonary edema, it typically shows signs of volume overload, such as elevated jugular venous pressure, hypertension, and responds well to diuretics. In this patient, there was no clinical or radiological evidence of fluid overload. (b) Cardiogenic pulmonary edema: Heart failure or left ventricular dysfunction was ruled out by normal echocardiographic findings and absence of elevated brain natriuretic peptide levels. (c) ARDS due to other causes: Infectious or inflammatory causes such as pneumonia, sepsis, aspiration, or trauma were excluded based on clinical history, laboratory investigations, and absence of alternative risk factors temporally related to lung injury. (d) Anaphylactic or severe allergic reaction: The absence of typical allergic symptoms such as urticaria, bronchospasm, or hypotension made anaphylaxis unlikely. (e) Pulmonary embolism: The patient lacked clinical features of thromboembolism, and imaging did not support this diagnosis.

CONCLUSION

TRALI is highly underrecognized and underreported. The findings of this study ignite us to explore TRALI induced by HLA-I and II antibodies, and to analyze antibody typing and source. By contributing to the literature on this entity, we intend to develop a better clinical understanding of the entity, which will possibly improve hemovigilance and can possibly contribute to better identification and preventative measures.

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