Transfusion-Related Acute Lung Injury – Case Report and Literature Review

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Abstract

Blood transfusion is a common procedure that usually goes without complications. However, adverse transfusion reactions should not be overlooked. Transfusion-related acute lung injury (TRALI) is the leading cause of transfusion-related fatalities and is characterized by the onset of acute respiratory distress in the form of non-cardiogenic pulmonary oedema. We hereby report the case of a 28 year old Jamaican lady who developed acute onset dyspnoea, tachycardia and hypoxaemia following transfusion of fresh frozen plasma and red cell concentrates.

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Introduction

TRALI is the leading cause of transfusion-related mortality and it often remains unrecognized clinically.[1] The true incidence of TRALI is unknown because of the difficulty in making the diagnosis and under-reporting especially in the intensive care setting where the development of symptoms may be attributed to multiple other disease processes or therapeutic interventions rather than transfusion. It is estimated to occur in 1:1300 to 1:5000 transfusions of plasma-containing blood products.[2] Though uncertainty remains with regards to the pathophysiology of TRALI, its development is influenced by both transfusion-related and patient-related risk factors.

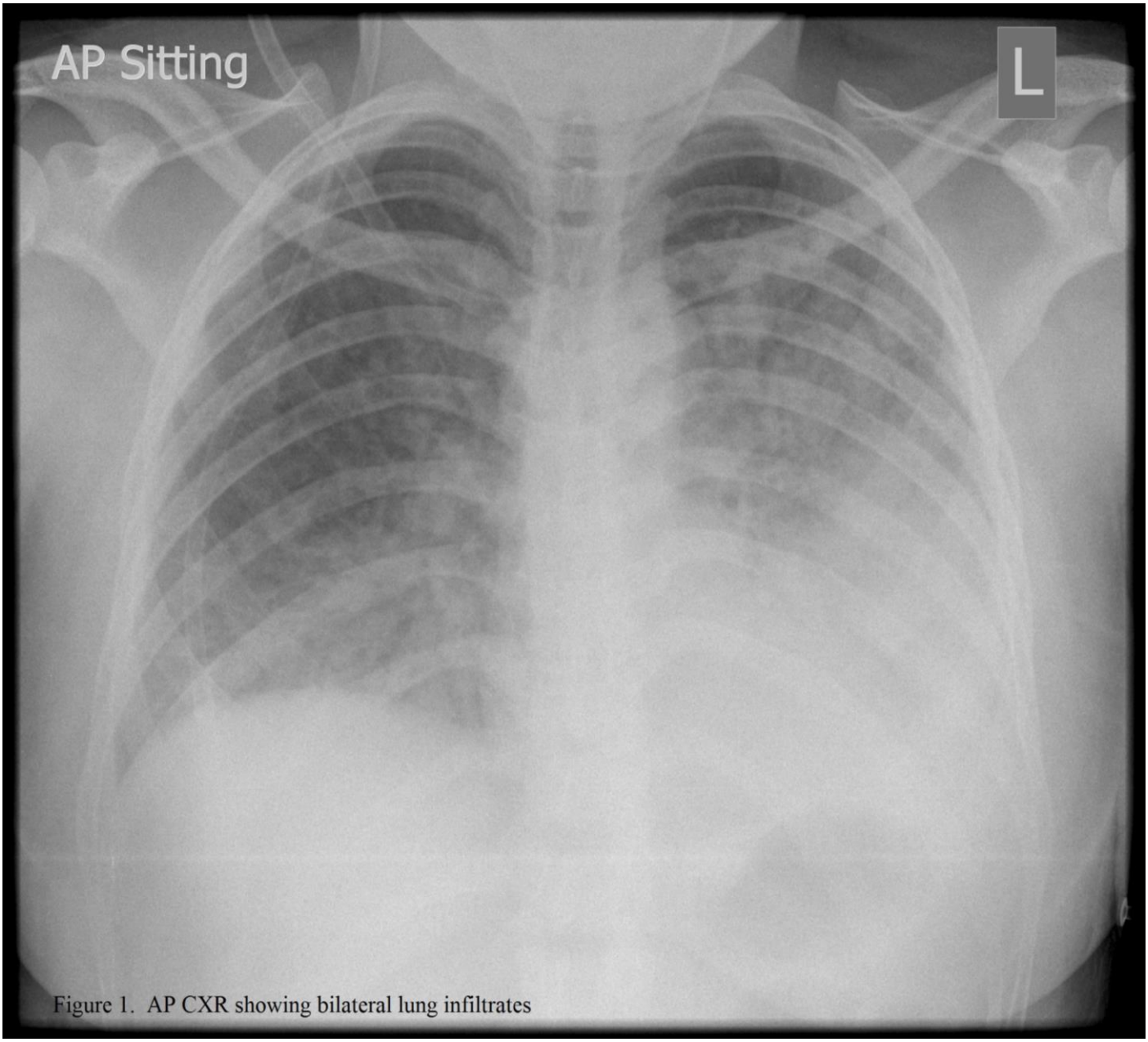
Case Report

A 28-yr old, previously healthy woman, presented to the Accident and Emergency department complaining of lower abdominal pain. A Focused Assessment with Sonography in Trauma (FAST) scan showed free fluid in the pelvis and she was subsequently diagnosed with a ruptured ovarian cyst. Laboratory investigations on presentation showed a white cell count of 6.3 x 10^9/L, haemoglobin of 7.8g/dL (normal mean corpuscular volume and mean corpuscular haemoglobin) and a platelet count of 166 x 10^9/L. Liver and renal function, glucose and coagulation screen were within normal limits. She underwent urgent laparoscopic ovarian cystectomy and was transfused four units of packed red cells

(PRCs) intra-operatively. In view of significant intra-operative bleeding she required further transfusion with fresh frozen plasma (FFP). However, whilst receiving her fourth unit of FFP, she became acutely dyspnoeic. On examination she had low-grade fever, tachycardia (145bpm) and tachypnoea with a respiratory rate of 25 breaths/minute and an oxygen saturation of 77% on room air. On auscultation of the chest, there was decreased air entry both bases with left basal crepitations. The rest of her physical examination was unremarkable.

CXR showed bilateral patchy infiltration particularly in the left lung field (Figure 1).

Figure 1*: AP CXP showing bilateral lung infiltrates*



The patient was diagnosed with transfusion-related acute lung injury and required admission to intensive care for ventilatory and haemodynamic support. The patient did not require intubation as she improved significantly with non-invasive ventilation.

Repeat laboratory investigations showed a transient leukopenia (white cell count of 3.4 x 10^9/L) followed by a leucocytosis (white cell count of 12.3 x 10^9/L) within 24 hours of her transfusion.

In view of leukopenia and the presence of infiltrates on chest x-ray, blood cultures were taken and she was also started on piperacillin/tazobactam to cover for any potential concomitant infectious pathology. The patient stabilised and made an uneventful recovery within a few days.

Definition of TRALI

TRALI has been defined by both the National Heart, Lung, and Blood Institute (NHLBI) working group as well as a Canadian Consensus Conference, as new acute lung injury (ALI)/acute respiratory distress syndrome (ARDS) occurring during or within six hours after blood product administration characterised by acute hypoxaemia, bilateral infiltrates on frontal chest radiograph and no evidence of circulatory overload/left atrial hypertension or pre-existing ALI/ARDS before transfusion.[1,3]

Pathogenesis

TRALI is postulated to develop as the result of two separate clinical events. The first or priming event is due to the patient's primary disease or condition, which results in activation of the pulmonary endothelium and the accumulation of primed, adherent neutrophils in the lung. The second event is the subsequent blood transfusion, whereby the primed neutrophils are activated by either a leucocyte antibody or biological response modifiers (BRM) present in the transfused blood product. Activation of the primed neutrophils results in augmented release of their microbicidal arsenal, which causes collateral injury to the pulmonary endothelium that manifests as capillary leak, and clinically as TRALI. Thus, the two-event mechanism proposes that both recipient and blood product factors contribute to TRALI pathogenesis.[4]

Risk Factors

All blood components have been implicated in TRALI; however, plasma containing blood components are most commonly implicated, with FFP and whole blood-derived platelet concentrates (WB-PLTs) having caused the largest number of reported cases. In most centres, the plasma is platelet-rich plasma. This use of platelet-rich plasma is significant for it allows for the infusion of platelet fragments and all endogenous growth factors and other mediators which are platelet-derived. Many of these compounds are effective activators of polymorphonuclear cells and innate immunity resulting in acute lung injury.

Certain patient risk factors have been identified as increasing the risk of TRALI.[5] These include:

- Higher IL-8 levels – may prime neutrophils and the lung endothelium[6]
- Shock – results in tissue injury possibly predisposing to TRALI through priming of the recipient's endothelium and immune cells[7]
- Liver surgery[5]
- Positive fluid balance – more likely to manifest pulmonary oedema when there is ALI[8]

- Peak airway pressure greater than 30cm of H_2O if mechanically ventilated before transfusion – increases the risk of ALI[9-10]
- Chronic alcohol abuse – results in lower levels of glutathione antioxidant in the lung[11-12]
- Current smoking[9-10]

Pearl Toy et al reported that receipt of plasma (including whole blood) from female donors is a strong risk factor, and reduction of this risk factor was concurrent with a decrease in TRALI incidence from approximately 1:4000 units to approximately 1:12000 units.[5,13] Furthermore, there is evidence that TRALI is commoner in recipients of blood products from multiparous female donors who are more likely to possess anti-HLA antibodies and anti-neutrophil-specific antibodies with increasing number of pregnancies.[14]

Following a case analysis, it was established that our patient had received blood products from ten different donors, three of which were females. Out of the female donors, one was nulliparous whilst the other two donors had a history of three or more gestations. Antibody testing of recipient and donor blood concluded that the donor with HLA antibodies with the same specificity as that of our patient was one of the multiparous females. This is in keeping with the literature data that suggests a higher risk of TRALI when receiving blood products from multiparous females.

The association between the risk of TRALI and blood product storage time has been debated for long. Whether longer RBC storage is associated with increased risk for lung injury and mortality is considered the most critical issue currently facing transfusion medicine. In a prospective case-control study by Toy et al (2012), evidence against longer storage of leuko-reduced RBC units being an important risk for TRALI was documented.[5,15] There is also conflicting data regarding the risk of TRALI with multiple transfusions. Results from the same case-control study by Toy et al had initially suggested increased risk for TRALI with increasing numbers of transfusions. However, when a multivariate analysis was carried out, no statistically significant correlation was found.[5]

Diagnosis and Management

TRALI occurs within 6 hours of transfusion with the majority of cases presenting during the transfusion or within the first 2 hours. TRALI is the insidious onset of acute pulmonary insufficiency presenting as tachypnoea, cyanosis, and dyspnoea with acute hypoxaemia, $PaO_2/FiO_2<300$ mmHg, and decreased pulmonary compliance, despite normal cardiac function.

Although the diagnosis is mainly based on clinical grounds, certain laboratory and radiographic investigations can facilitate the diagnostic challenge posed by TRALI.[14] Radiographic examination reveals diffuse, fluffy infiltrates consistent with pulmonary oedema.

Transient leukopenia has been temporally associated with the onset of TRALI (as in our case report), and serial measurements of white cell count may reveal this finding.[16,17]

Echocardiography, measurement of BNP levels and pulmonary oedema fluid protein analysis are complementary tests in helping to exclude cardiac dysfunction and volume overload as the cause of the acute symptomatology.[5,16]

As previously discussed, the precise mechanism responsible for TRALI is unknown, but the syndrome has been associated with passive transfer of leukocyte

antibodies and biologically active lipids in blood components. The majority of cases of TRALI (65-80%) are thought to be triggered by passive transfer of HLA Class I and/or neutrophil-specific antibodies[18-22] or HLA Class II antibodies[23,24] present in the plasma of the transfused blood product. In a minority of cases, the causative antibodies are present in the recipient, and react with transfused cellular material. Testing plasma samples from the implicated donor and patient for leukocyte antibodies can be very helpful in evaluation of a suspected TRALI case, however these are not found in all cases of TRALI.[5]

Toy et al found no evidence of TRALI after transfusion of blood products from one donor with multiple HLA antibodies into 103 recipients, 25% of whom had ≥1 HLA antigen that matched the donor antibody.[25] On the other hand, Kopko et al reported the presence of a mild to severe respiratory syndrome in 35% of recipients receiving blood products from a donor with anti-human-neutrophil-antigen (HNA)-3a antibody. Therefore, a case of TRALI may represent an isolated event, but donor granulocyte antibodies rather than HLA antibodies seem likely to cause multiple cases of TRALI.[18]

As with other forms of ALI/ARDS, there is no significant treatment for TRALI. If the patient is still being transfused when the diagnosis is first suspected, the transfusion should be stopped immediately. The treatment for TRALI is supportive and consists of aggressive respiratory support with supplemental oxygen and mechanical ventilation, if required, at low enough pressure and tidal volume to not induce barotraumas.[26-27] In rare cases, the hypoxemia resulting from TRALI can be so severe that extracorporeal oxygenation may be required as a temporizing measure while the lungs heal.[28,29] It is important to report any case of TRALI to the blood service so that an implicated donor can be contacted and, if appropriate, taken off the donor panel.[5]

Risk reduction strategies:

Different centres have adopted different strategies ranging from testing of allo-exposed donors for leucocyte antibodies to the exclusion of all females from donating high plasma volume products. Another strategy involves dilution of antibodies present by pooling of plasma donations of multiple donors. From a bedside view, the most important measure to prevent TRALI is to limit patients' exposure to allogenic blood products. Furthermore, recognition and awareness of the syndrome need to be heightened among clinicians.[8]

Conclusion

TRALI has been reported by haemovigilance programs to be the most frequent cause of transfusion-related mortality in the US and a leading cause of transfusion-related morbidity and mortality elsewhere. TRALI is thought to be under-diagnosed and under-reported, particularly in critical care setting where the development of symptoms may be attributed to multiple other disease processes or therapeutic interventions rather than transfusion. Thus, maintaining a high index of suspicion is crucial in making the correct diagnosis, especially when transfusing patients using fresh frozen plasma and whole blood-derived platelet concentrates.

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