

## CASE REPORT

# Transfusion related acute lung injury – TRALI: a case report

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**Abstract** - Transfusion-related acute lung injury is a serious and potentially lethal complication occurring after transfusion of blood products. Underreporting is strongly suspected because of a lack of awareness among health care providers. In this report we describe a case of TRALI and discuss definition criteria, pathogenesis and treatment options.

**Keywords** - Transfusion related acute lung injury, TRALI, pathophysiology, definition

## Introduction

Transfusion-related acute lung injury (TRALI) is the occurrence of acute lung injury (ALI) and was described in 1983 [1]. All types of blood products have been associated with TRALI, but components that contain large amounts of plasma such as fresh frozen (quarantined) plasma and platelet concentrates have been most frequently implicated [2,3].

The National Heart Lung and Blood Institute (NHLBI) definition of TRALI includes the onset of signs and symptoms of ALI during or within six hours after transfusion of blood products, in the absence of other causes of acute lung injury or circulatory overload [4]. The classic cut-off value of six hours has its limitations. In up to 25% of critically-ill patients receiving multiple blood transfusions, a delayed TRALI can occur from 6-72 hours after transfusion and is associated with a mortality of up to 40%. The risk of delayed TRALI increases along with increasing numbers of transfused blood products [5].

There is still no consensus on the incidence, pathogenesis and best method for laboratory diagnosis of TRALI. Underreporting is strongly suspected although the number of reported incidents is increasing; probably as a consequence of increased awareness among health care providers. TRALI is considered to be the leading cause of death due to transfusion, followed by bacterial contamination, and ABO-haemolytic reactions [6,7].

In this report we describe a classic case of severe TRALI which is still a difficult-to-make and under-recognized diagnosis.

## Case

A 73-year-old woman was presented to the Emergency Department at the Twenteborg Hospital with pain in the right hip

after a fall at home. Her medical history revealed an intracranial meningioma, the surgical removal of which in 1991 led to the development of partial epilepsy. In 2002 she underwent operation to place a left dynamic hip screw for a medial column fracture. The procedure was complicated by a deep vein thrombosis and paroxysmal atrial fibrillation. At presentation, she was stable on medication using acenocoumarol, valproic acid, amiodarone, diclofenac/misoprostol, and solifenacin.

Radiographic investigation of the right hip revealed a pertrochanteric femoral fracture. Routine pre-operative chest radiograph was normal (Figure 1). The following day a proximal femoral nail was positioned surgically under general anaesthesia. The procedure was uncomplicated.

However, postoperatively the haemoglobin concentration was 3.8 mmol/L (7.1-9.8 mmol/L), thrombocytes  $60 \times 10^9/L$  ( $135-385 \times 10^9/L$ ), APTT 42 sec (27-37 sec) with an INR of 1.5 (0.8-1.2). As a result, two erythrocyte concentrates and two units of fresh frozen plasma (FFP) were transfused. Within 90 minutes after the transfusion, she experienced progressive shortness of breath and hypotension. On examination we saw a dyspnoeic patient with a body temperature of 35.7 °C and a blood pressure of 76/38 mmHg. Her heart rate was 121 bpm sinus tachycardia and respiration was 30/min with an oxygen-saturation of 78 %. Pulmonary examination revealed diffuse, bilateral crackles without wheezes. No peripheral oedema was found.

Laboratory investigation showed: Hb 7.8 mmol/L (7.1-9.8 mmol/L), thrombocytes  $93 \times 10^9/L$  ( $135-385 \times 10^9/L$ ), APTT 77 sec (heparin effect; 27-37 sec), INR 1.2 (0.8-1.2), CRP 95 mg/L (0-10 mg/L), creatinine 85 µmol/L (55-90 µmol/L), urea 9.1 mmol/L (3.0-8.0 mmol/L), sodium 141 mmol/L (136-146 mmol/L), potassium 3.9 mmol/L (3.5-4.7 mmol/L), bilirubin total 19 µmol/L (1-17 µmol/L), LDH 223 U/L (125-250 U/L), haptoglobin 1.0 g/L (0.3-2.4 g/L) indicating no haemolysis. Arterial blood gas analysis without administration of oxygen showed a combination of metabolic and respiratory acidosis: pH 7.24 (7.35-7.45); pCO<sub>2</sub> 6.3 kPa (4.5-6.0

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kPa);  $\text{HCO}_3^-$  19.6 mmol/l (22-26 mmol/l);  $\text{pO}_2$  7.3 kPa (10-14 kPa);  $\text{O}_2$  saturation 84 %. Central venous pressure was 6 mmHg.

On chest radiograph diffuse bilateral pulmonary infiltrates were seen (Figure 2). There were no signs of circulatory fluid overload (no Kerley B lines or cardiomegaly and low central venous pressure) in our patient.

### Discussion.

The acute development of non-cardiogenic pulmonary oedema following transfusion of blood products, is suspect for the development of TRALI. Acute lung injury is defined according to the following four criteria [8]:

1. Timing: Acute onset.
2. Oxygenation:  $\text{PaO}_2/\text{FiO}_2 \leq 300$  mmHg (regardless of positive end-expiratory pressure (PEEP)).
3. Chest radiograph: bilateral infiltrates seen on frontal chest radiograph.
4. Pulmonary artery wedge:  $\leq 18$  mmHg when measured or no clinical evidence of left atrial hypertension.

All four criteria were present in our patient. Because signs of ALI developed within two hours after transfusion of blood products and other causes of ALI were absent, a transfusion reaction, probably TRALI, was suspected and reported to the haemovigilance officer at our hospital and to the regional blood bank. It was investigated by laboratory analyses. No blood-group serological evidence of an acute haemolytic transfusion reaction caused by the erythrocyte concentrates was found. The patient and the donors were screened for granulocyte-specific and human leukocyte antigen (HLA) antibodies. In the plasma of one of the FFP donors HLA (class I and II) antibodies as well as weak antibodies against human neutrophil antigens (HNA) were identified using complement-dependent microcytotoxicity tests, lymphocyte (LIFT) and granulocyte (GIFT) immunofluorescence

tests and leukocyte agglutination tests. HLA class I and class II antigen genotyping was performed by PCR in our patient. HLA-A24 and HLA-DR4 antigens, against which the antibodies present in the serum of the donor are directed, were positive. Cross-matching of patient lymphocytes with the serum of this donor was also positive. In this way the diagnosis of TRALI was confirmed.

The incidence of TRALI is not well established due to the lack of a clear definition, and of recognition. Based on the NHLBI criteria, TRALI occurs in 1 out of 1120-1323 transfused units [9]. Data from the Dutch TRIP (Transfusion Reactions in Patients) 2007 annual report show 2.7 reports per 1000 transfused blood products and 23 reports of TRALI from the transfusion of 700 980 blood products. In four of the reported cases of TRALI an immunological cause was identified. The estimated mortality due to TRALI is 5-10%, making it one of the leading causes of transfusion related mortality [10].

Although in this case report it has been established that the leukocyte-reactive antibodies in a female plasma donor were directed against the HLA epitopes of the patient who received the plasma product, leukocyte-reactive antibodies are not always present in donor or recipient all cases of TRALI.

Since June 2007, all female donors and previously transfused male donors in the Netherlands have been excluded from donation

**Figure 1. Chest radiograph at presentation**



**Figure 2. Two hours after transfusion**



Because of respiratory failure and the need for mechanical ventilation, the patient was transferred to intensive care and intubated. Treatment with mechanical ventilation and inotropic medication in combination with furosemide was started. Under this regimen the clinical situation stabilized and within 72 hours mechanical ventilation and inotropic agents were terminated. The patient recovered fully, and was discharged in good condition.

for plasmapheresis products for transfusion. Therefore, the risk of ALI due to transfusion of plasma-containing blood products could possibly be reduced after the release of these products. In particular, female blood donors who have been pregnant frequently have HLA antibodies with an overall prevalence of 24% and increasing prevalence related to the number of previous pregnancies [11]. However, the presence of HLA antibodies or neutrophil-specific antibodies in plasma products from male donors cannot be fully excluded and remains to be investigated in cases of TRALI.

The pathogenesis of TRALI is not completely understood. Leukocyte antibodies in donor plasma have been implicated in most cases with antibodies directed at human leukocyte antigen (HLA) class I, HLA class II or neutrophil-specific antigens, particularly HNA-3a. Transfused leucoagglutinating antibodies bind to recipients' neutrophils localized in the pulmonary endothelium resulting in activation and release of oxidases and other damaging biological response modifiers that cause capillary leakage. In a minority of TRALI cases, no antibodies are identified and it is postulated that neutrophil priming factors in the transfused component can mediate TRALI in a patient with pulmonary endothelial activation, the so-called two hit mechanism [11-15].

Because in the serum of the donor, antibodies were identified that were directed against HLA epitopes of our patient, the TRALI transfusion reaction appeared to be immune-mediated.

TRALI has been reported to occur equally in both sexes and in all ages, and is a diagnosis of exclusion [16]. Other possible aetiologies have to be ruled out before the diagnosis of TRALI can be rendered. In making the differential diagnosis of transfusion-related complications with TRALI, transfusion-associated circulatory overload (TACO), allergic/ anaphylactic reactions, bacterial contamination and haemolytic transfusion reactions must also be included [17,18].

There is no specific diagnostic study. A normal echocardiography does not rule out cardiogenic pulmonary oedema. B-natriuretic peptide (BNP) may have some value in distinguishing TACO from TRALI. TACO is suggested by an absolute BNP level of more than 100 pg/dl and a posttransfusion to pretransfusion ratio of more than 1.5 [19].

The sudden onset of dyspnoea within six hours after the start of transfusion should alert clinicians. Often fever, tachycardia and tachypnoea and hypotension are present [20]. Our patient showed no signs of circulatory fluid overload (no Kerley B lines or cardiomegaly and low central venous pressure) nor was there atrial fibrillation.

Treatment of TRALI often includes mechanical ventilation with a high oxygen concentration and PEEP, generally for a short period of time. Most patients can be weaned and extubated within 48-96 hours and chest radiographs mostly return to normal within four days. Early recognition of TRALI and increased awareness among physicians could lead to detection of milder forms of TRALI which could be treated with supplemental oxygen only [13,21].

In addition, if pulmonary oedema is present administration of a diuretic should be considered, particularly if the distinction with volume overload is not clear. A lack of clinical improvement after treatment with a diuretic supports the diagnosis of TRALI. The use of intravenous steroids has been reported in a number of case reports. There are no prospective studies regarding the use of steroids, therefore their use is not recommended [22].

In conclusion TRALI is a potentially lethal complication of transfusion of blood products with a mortality rate of 5-10%. It is often unrecognized, but if treated properly the prognosis is relatively good with no long-term sequelae.

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