# Severe Transfuse Related Acute Lung Injury (TRALI) syndrome in a 14 years old girl with a history of type I von Willebrand Disease

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*Abstract*

*Von Willebrand disease (vWD) is the most common inherited bleeding disorder based on an autosomal abnormality of von Willebrand factor. Transfusion is a lifesaving medical intervention among patients with bleeding disorders. Patients with vWD are exposed to Transfuse Related Acute Lung Injury (TRALI) when they become recipients of multiple blood products and repeated transfusions. TRALI is a non-hemolytic transfusion reaction induced by infusions of intravenous immunoglobulin, platelets (suspended in plasma), whole blood, cryoprecipitates, and fresh frozen plasma (FFP). We report a 14 years old white girl, with a history of type I von Willebrand disease (vWd), recipient of 2 units' fresh-frozen plasma (FFP) and 1 unit whole blood transfusion who developed an acute respiratory distress with severe hypoxemia and bilateral pulmonary infiltrate on chest X-ray within 3 hours of the whole blood transfusion, completely reversible after mechanical ventilation. Concluding, patients with vWd who received recurrent transfusions have an increased risk of TRALI. Physicians must be familiar with it as a cause of white lung X-ray pattern.*
***Keywords:*** *von Willebrand disease, transfusion, fresh frozen plasma, TRALI*

*Rezumat*

***Sindrom de injurie pulmonară acută legată de transfuzie (TRALI) sever la o pacientă de 14 ani cu boală von Willebrand tip I***

*Boala Von Willebrand (bvW) reprezintă cea mai frecventă coagulopatie ereditară, fiind determinată, în principal, de anomalia factorului von Willebrand. Manifestările hemoragice impun transfuzii repetate și cresc riscul de injurie acută pulmonară severă indusă transfuzional (TRALI). Incidența acestui sindrom TRALI nu este cunoscută, dar poate apărea la orice produs biologic administrat, plasma proaspăt congelată fiind cel mai frecvent implicată. Etiopatogenia sindromului TRALI este multifactorială, mecanismul imun mediat prin anticorpi anti-leucocitari și/sau anti-neutrofilici fiind incriminat adesea. Prezentăm cazul unei paciente în vârstă de 14 ani, cunoscută cu boală von Willebrad de tip I, cu menometroragie în antecedente, internată în șoc hipovolemic, cu suspiciune de torsiune de anexă stângă și hemoperitoneu, pentru care se instituie, inițial, o unitate (U) de masă eritrocitară și hemostatice și, în continuare, pentru susținerea funcțiilor vitale, 5 U crioprecipitat și 2 U plasmă proaspăt congelată. La 3 ore după ultimul produs biologic administrat apar febra, hipotensiunea, dispneea, desaturarea, plămânul alb radiologic. Diagnosticul diferențial a luat în considerare: edemul pulmonar, detresa respiratorie și T.R.A.L.I. Pacienta a răspuns favorabil după 3 ore de ventilație mecanică. În concluzie, pacienții cu boală von Willebrand au risc crescut de TRALI și, de aceea, este nevoie ca medicii să fie familiarizați cu acest sindrom post-transfuzional asociat cu plămânul „alb".*
***Cuvinte-cheie:*** *boala von Willebrand, transfuzie, plasmă proaspăt congelată, TRALI*

## Introduction

Transfusion-related acute lung injury (TRALI) is a severe complication of blood transfusion, a life-threatening adverse event of transfusion. The first case of fatal cardiogenic pulmonary oedema following blood transfusion was reported by Barnard in 1951[1]. In 1985, Popovsky et al. documented acute respiratory distress syndrome following blood transfusions as a distinct clinical entity and coined the term transfusion related acute lung injury (TRALI), which they described in the order of 1 per 5000[2] TRALI is underdiagnosed and underreported as many clinicians are not familiar with the syndrome, so the true incidence of TRALI is unknown[3-6]. In the same time, it is considered to be the most serious cause of transfusion - related morbidity and mortality[7].

A clinical definition of TRALI was established in 2004, based on acute respiratory distress which has temporal association with transfusion of blood components[3,8]. Four years after, in 2008, a distinction between classic and delayed syndrome was proposed[8]. Pathophysiology is still controversial, considering 2 major patterns of TRALI: the first one is the immune pattern mediated by the granulocyte-binding alloantibody and the second is two-event model, non-immune mediated, induced by neutrophil - priming substances such as biologically active lipids[4].

## Case report

We report the case of a 14 years old white girl, with a history of type I von-Willebrand disease (vWd), admitted in hospital for nausea, soft stools and abdominal pain, lethargy within the previous 24 hours before hospitalization. On admission, her general appearance was altered with generalized pallor, weight 53 Kg, temperature 36.6° Celsius, tachycardia (135 beats/min) with weakened peripheral pulse, hypotension (blood pressure = 75/30 mm Hg) and drowsiness as signs of hypovolemic shock.

Laboratory and initial imaging investigations revealed left ovary torsion, hemoperitoneum, type I von Willebrand disease severe form, hypovolemic shock.

Supportive measures were recommended in order to sustain her vital signs. The administration of 2 units' fresh-frozen plasma (FFP), 1 unit whole blood transfusion, and 5 U cryoprecipitate was recommended and transfusion was initiated. Within 3 hours of the last transfusion with whole blood, patient presents cyanosis, dyspnoea and tachypnea, intense

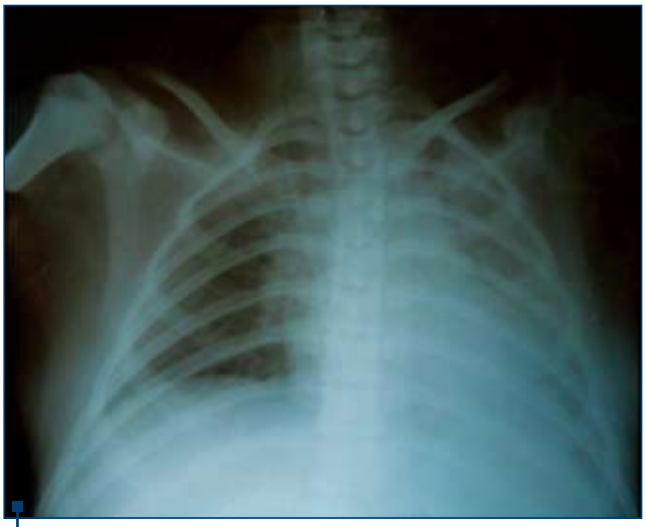

*Figure 1. Postero anterior chest X-ray reveals bilateral infiltrative lesions with white left lung*

left chest pain, relapsed hypotension, fever with acute onset. Clinical exam reveals hypoxemia ($PaO_2$ = 78%), respiratory distress and pulmonary left crackles. Chest X-ray shows evidence of bilateral pulmonary patchy infiltrates with complete "white out" left lung (Figure 1), indistinguishable from Acute Respiratory Distress Syndrome (ARDS). There was a partial response to supplemental oxygen therapy 4 L/min but mechanical ventilation was required and ICU support. The patient was mechanically ventilated for 4 hours. The patient recovers after 3 hours, oxygen saturation returned to 100%. Improvement in the chest X-ray was visible within the next 24 hours.

## Discussion

The respiratory distress syndrome associated with transfusions, called TRALI, represents a serious risk that may be presently underestimated, as it often goes unrecognized and undertreated[4]. The TRALI definition of the European Haemovigilance Network[5] and the Amendments by the TRALI Consensus Conference Committee in Toronto in 2004[6] include the following recommended clinical criteria:

- Acute onset of acute lung injury (ALI) (most cases occur within 1-2 hours of transfusion);
- Hypoxemia with Oxygen saturation < 90% on room air measured by pulse oximetry and $PaO_2$ / $FiO_2$ ≤ 300;
- Bilateral lung infiltrates on frontal chest radiography;
- No evidence of left atrial hypertension (circulatory overload);
- Occurrence during or within 6 hours after completion of transfusion;
- No temporal relationship to an alternative risk factor for ALI;
- New ALI and no other ALI risk factors present including aspiration, multiple trauma, pneumonia, cardiopulmonary bypass, burn injury, toxic inhalation, lung contusion, acute pancreatitis, drug overdose, near drowing, shock and sepsis;
- If one or more ALI risk factors are present, possible TRALI should be diagnosed.

TRALI is characterized by an acute respiratory distress and non-cardiogenic lung oedema developing during, or within 6 hours of transfusion. In its fulminant presentation, TRALI can be clinically indistinguishable from acute respiratory distress syndrome occurring as a result of other patient - related causes of respiratory failure, such as: acute respiratory distress syndrome (ARDS), pneumonia, and cardiac failure[7]. Of note, ARDS, which is accompanied by a high mortality, does not resolve in 24 hours.

Immune TRALI, which occurs mainly after the transfusion of fresh - frozen plasma and platelet concentrates, is a rare event (about one incidence per 5000 transfusions), but frequently (approximately 70%) requires mechanical ventilation (severe TRALI) and is not uncommonly fatal (6-9% of cases)[7].

There is evidence that TRALI is more frequent in recipients of blood products collected from multiparous female donors because they are more likely to possess anti-HLA antibodies and anti- neutrophil- specific antibodies[8]. Serologic evidence of TRALI consists in an HLA-match found between donor alloantibodies (anti-HLA-DR4) present in the single-donor platelet preparation and the patient's own HLA class II antigens (HLA-DR4)[9-10]. Alloantibodies are generated during pregnancy, but of course that would not explain the presence of such antibodies in men. Neutrophil alloantibodies are found in 10% to 20% of female donors and 1% to 4% of male donors, yet the incidence of TRALI is about 1:5000 transfusions[9]. Such antibodies can bind the patient's white blood cells following transfusion and induce white blood count (WBC) activation with release of proinflammatory mediators and other cytokines[9]. Sometimes, in 5 - 15% of cases, no antibody is identified in either the donor or recipient[3].

In atypical cases, TRALI can become symptomatic much later and is common after massive transfusion (40- 57%)[6]. Characteristics of the delayed TRALI syndrome are time of onset 6-72 hours after transfusion with a slow development of clinical manifestations in patients who have other risk factors for ALI (i.e. sepsis, aspiration, near-drowning, disseminated intravascular coagulation, trauma, pneumonia, drug overdose, fracture, burns and cardiopulmonary bypass)[3]. Non-immune TRALI, which occurs mainly after the transfusion of stored platelet and erythrocyte concentrates, is a two-event model and seems to be characterized by a more benign clinical course, with oxygen support sufficient as a form of therapy in most cases, and a lower mortality than immune TRALI[3,5,6].

The severity of TRALI depends upon the susceptibility of the patient to develop a more clinically significant reaction as a result of an underlying disease process, and upon the nature of triggers in the transfused blood components, including granulocyte-binding alloantibodies (immune TRALI) or neutrophil-priming substances such as biologically active lipids (non-immune TRALI)[7].

TRALI must be carefully differentiated from transfusion-associated circulatory overload (TACO)[7], severe allergic or anaphylactic reactions, bacterial contamination, acute hemolytic reaction, usually secondary to ABO incompatibility, acute event unrelated to transfusion: myocardial infarction, pulmonary embolism, sepsis, pneumonia.

Von Willebrand disease (vWD) is a bleeding disorder based on an autosomal inherited abnormality of von Willebrand

factor which lead to a disruption of primary hemostasis. Currently, vWD is divided into three types, type 1 vWD being the most common one and type 3 the most severe. Patients with vWD are a risk group exposed to TRALI during transfusions with blood products. Therefore, it is important to suspect TRALI if a respiratory distress occurs in a recipient of blood products.

By virtue of its morbidity and mortality, TRALI has become one of the most serious current complications of transfusion. Between 6 to 10% of cases are fatal and transfusion of antibodies specific for white blood cells (leukocytes) is considered to be a major cause of severe TRALI[7]. The subsequent finding of leukocyte antibodies in a donor unit, matching a recipient leukocyte antigen, may be taken as strongly supportive evidence in a suspected case. These tests may take several months to complete and are available only in a few laboratories. Occasional negative antibody tests may not exclude the condition, especially when a direct cross-match between suspect donor and recipient is not possible.

TRALI must be recognized promptly and treated appropriately by stopping the transfusion[10]. No specific laboratory tests are available for TRALI and initial diagnosis depends on a high degree of suspicion. If a donor is implicated in a TRALI syndrome, then it is recommended to be permanently deferred from any future donation because a TRALI - implicated donor may cause multiple transfusion reactions in different recipients[3].

To prevent further antibody-mediated cases, the evaluation of TRALI should include leucocyte antibody testing of implicated donors but, for technical reasons, it is not possible to test blood donors to detect them[10]. However, further studies are necessary for the prevention of this serious transfusion complication.

## Conclusion

Despite the rarity of this syndrome, physicians need to be aware of the existence of TRALI, to recognize its manifestations promptly and treat it properly. Multiple transfusions for type I von Wilebrand disease are considered to be at risk of TRALI. ■

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