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Case Report

Transfusion-Related Acute Lung Injury (TRALI) in two Thalassaemia Patients Caused by the Same Multiparous Blood Donor

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Abstract. We report two separate episodes of transfusion-related acute lung injury (TRALI) in two thalassaemia patients who received red blood cell transfusions from the same multiparous donor. Both cases had the same symptomatology and occurred within 60 minutes of transfusion. The patients presented dyspnoea, sweating, fatigue, dizziness, fever, and sense of losing consciousness. The chest x-ray showed a pulmonary oedema-like picture with both lungs filled with fluid. The patients were treated in the intensive therapy unit. They were weaned off the ventilator and discharged following hospitalization 7 and 9 days respectively. The TRALI syndrome was diagnosed to be associated with HLA-specific donor antibodies against mismatched HLA-antigens of the transfused patients. Haemovigilance improvements are essential for reducing the morbidity and mortality in transfused patients. Blood from multiparous donors should be tested for the presence of IgG HLA-Class I and –Class II antibodies before being transfused in thalassaemia and other chronically transfused patients.

Keywords: Transfusion-related acute lung injury, TRALI, Thalassaemia, Haemovigilance, Blood donors, Multiparous women.

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Introduction. The major adverse events caused by transfusions are mainly related to the transfer of non matched blood components, acute and delayed reactions, transmission of viral or bacterial infections, transfusion-related acute lung injury (TRALI) etc.[1-5]

To minimise the risk of adverse events, the donated blood is thoroughly screened for antibodies, viruses and other risk factors before storage and transfusion.

In the case of TRALI which occurs in 0.04-0.16 % of transfusions, almost all types of blood products have been associated with adverse events, such as packed red blood cells (RBC), fresh frozen plasma and platelets.[1,2] TRALI has been estimated to be the third cause of transfusion-related mortality with current mortality rates ranging in the patients affected between 5 to 25%.[4,6]

About two-thirds of the TRALI incidences are thought to be immune-mediated and involve mainly the passive transfusion of leucocyte antibodies in blood products.[7] Antibody-mediated TRALI is an important cause of transfusion-associated morbidity and is the leading cause of transfusion-related mortality.[7] Human leukocyte

antigen (HLA)-Class I, HLA-Class II or neutrophil-specific antibodies, particularly HNA-3a have been implicated in most of the reported cases of TRALI.[3,8]

The mechanism for TRALI in thalassaemia involves mainly the transfer of blood donor antibodies through contamination of the transfused RBC and reaction with the anti-HLA antigens of lymphocytes of the recipient, affecting mainly the lung endothelium of the recipient causing pulmonary oedema. Blood donor antibodies are particularly prevalent in some categories of blood donors such as multiparous women, where antibodies are formed in response to sensitisation from foetal blood infiltration during multiple pregnancies.[3]

Cases Report. Approval of the report of the cases was obtained from the committee of clinical studies of the Ministry of Health and the Bioethics Committee of Cyprus. The patients gave their informed consent for reporting the study.

Two male thalassaemia major patients of 28 (A) and 31 (B) years had separate episodes of the TRALI syndrome in 2004 and 2011 respectively, which were caused as a result of the transfusion of packed RBC from the same multiparous woman blood donor. During the period of TRALI, patient A was splenectomised with a mean rate of RBC transfusions of 186 ml/kg/year while patient B had splenomegaly (19x11cm) and was hypertransfused with a mean rate of RBC transfusions of 366 ml/kg/year. Patient A was non-iron loaded with serum ferritin 246 μg/l, magnetic resonance imaging (MRI) T2* of the heart 23.4 ms and liver 17.0 ms and other clinical complications included osteopenia, hypogonadism and cholelithiasis. Patient B was iron loaded with serum ferritin 2790 μg/l, MRI T2* of the heart 40.9 ms and liver 5.9 ms and in addition to cholecystectomy and splenomegaly, clinical complications included osteopenia and hypothyroidism. Patient A was receiving deferiprone and patient B deferoxamine for the treatment of iron overload, as well as other drugs for the treatment of other clinical complications of the underlying disease.

The diagnosis of the TRALI syndrome in each case was generally difficult because of the rarity of the complication, number of symptoms and the timing of the event. Despite the diagnostic difficulties, the symptoms in both cases were the same (**Table 1**). A difference in the timing of the initiation of the clinical symptoms due to TRALI was observed between the two patients. In the patient A, the acute respiratory distress symptoms began in about 10-15 minutes after the initiation of the transfusion involving 15-20 ml from one unit of 320 ml of packed RBC from one blood donor. In the patient B, the symptoms began at home at about 60 minutes following the transfusion of two RBC units of 300 ml and 280 ml from two different blood donors respectively.

In both cases, the patients presented a number of symptoms including dyspnoea, sweating, fatigue, dizziness, fever, and sense of losing consciousness (**Table 1**). Clinical and laboratory investigations indicated the presence of hypoxaemia with oxygen saturation in patients A and B of less than 60 % and 65 % respectively, increased respiratory rate, low blood pressure and increased pulse rate. The chest x-ray showed pulmonary oedema with both lungs filled with fluid (**Table 1, Figure 1**).

Supportive treatment included the administration of oxygen, adrenaline, cortisone, diuretics, suctioning and other symptomatic treatment before admission to the intensive therapy unit, where further deterioration of lung function was observed which led to sedation and intubation on a mechanical ventilator (**Table 1**). Improvement in the respiratory parameters including oxygenation, remission of the lung oedema, as well as RBC transfusions and other medical support allowed the patients to be weaned off the ventilator and discharged from the intensive therapy unit following the hospitalisation of a total of 7 days and 9 days for patients A and B respectively.

In both cases, the laboratory findings suggested the cause of an allergic reaction as a result of the transfusion. In the patient A, high lymphocyte count (7.83%) was detected in the transfused packed RBC. Furthermore, on the first day of the TRALI episode the T cell marker count of CD5 and CD7 increased to 48% and 54% respectively, the anti-RBC antibodies to 48% and the anti-HLA antibodies to 20%. On the second day following the episode the CD5 and CD7 counts decreased to 25% and 28% respectively, the anti-RBC antibodies to 20% and the anti-HLA antibodies remained unchanged at 20%.

In the case of patient B, HLA-typing was performed on both the patient's and the blood donors' samples, as well as HLA-specific antibody

Table 1. Clinical symptoms and treatment of the two thalassaemia patients following the TRALI episode.

Patient	Clinical symptoms	Clinical findings	Supportive treatment	Intensive therapy unit
A **28 years** **Male** **(2004)**	Respiratory distress 10 -15 minutes after the transfusion started <u>Symptoms</u> Acute chest pain, dyspnoea, cyanosis, hypotension, tachycardia, fever, cough with yellow foaming sputum, palpitations, headache, sweating, fatigue, dizziness, vomiting and sense of losing consciousness.	Hypoxaemia Chest X-rays Bilateral infiltration. Lung oedema Haemodynamically unstable.	Oxygen: 2 l/min Venturi mask Hydrocortisone 300mg iv stat Diuretics 40mg iv and antiemetics in d/w 5% iv drip Suctioning and other symptomatic supportive treatment	Hypoxaemia Oxygen saturation: 60% Sedated and intubated for 3 days. Mechanical ventilation. Other medical support 3 days after: Improvement in respiratory mechanisms as well as in oxygenation, weaned from ventilator Discharged after 7 days
B **31 years** **Male** **(2011)**	Acute respiratory distress within 60 minutes after the transfusion <u>Symptoms</u> Chest pain, dyspnoea, tachycardia, cough, bloodstained foamy sputum, dizziness, headache, fever, sweating etc.	Hypoxaemia Chest X-rays Bilateral infiltrations Lung oedema Haemodynamically unstable. Decrease in haemoglobin to 6.7 g/dl	Oxygen: 3 l/min Venturi mask. Hydrocortisone 400mg iv stat Diuretics 40 mg iv, antipyretics. Suctioning and other symptomatic supportive treatment	Hypoxaemia Oxygen saturation: 65% Sedated and intubated for 5 days. Mechanical ventilation Transfusion of a total of 9 units of RBC in 9 days Discharged after 9 days

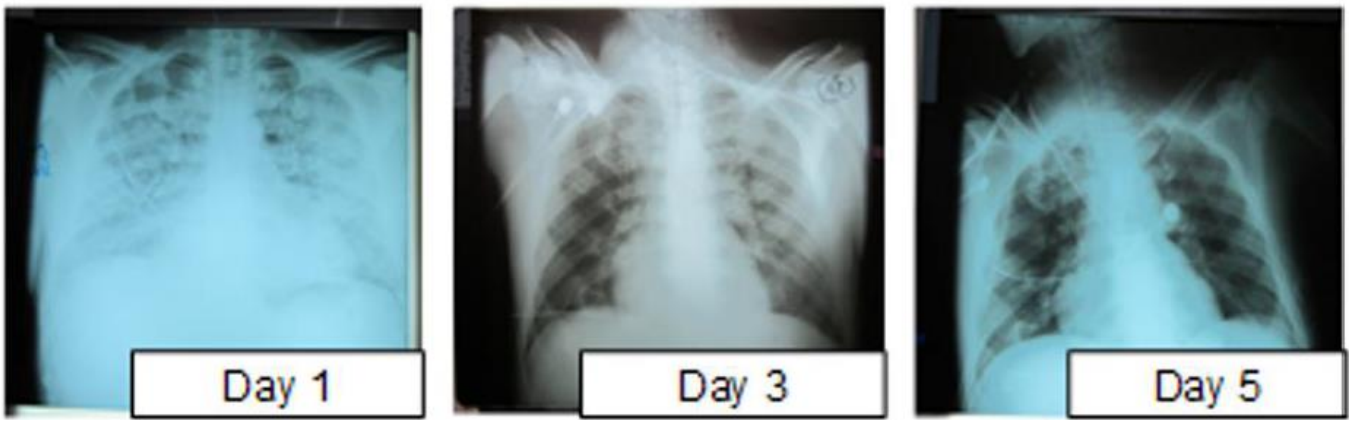

Figure 1. Acute pulmonary oedema in the thalassaemia major patient B caused by the TRALI syndrome. Bilateral pulmonary edema is shown from the X-ray images in patient B on the day of the TRALI incidence. Significant remission of bronchial infiltration is observed in subsequent X-ray images which were obtained following treatment in the intensive therapy unit on the 3rd and 5th day.

testing on the donor's serums. A multiparous woman blood donor was found to be positive for the presence of IgG HLA-Class I and –Class II antibodies against the following mismatched antigens of patient B: HLA -A30, -A33, -B8, -DR4, and -DR17. The complement cytotoxicity cross-match against the T and B patient lymphocytes was also positive.

The TRALI syndrome was diagnosed in both cases as a result of the presence of residual plasma and leucocytes in the RBC transfusion, which was associated with HLA-specific antibodies of the multiparous woman blood donor against mismatched HLA-antigens of the transfused patients A and B.

The multiparous blood donor related to the TRALI incidences was a mother of four children and had in total six pregnancies. Following the first incidence of TRALI, she was advised to terminate blood donations. However, seven years later she ignored the earlier advice and donated blood which resulted in the second TRALI incidence.

Discussion. To our knowledge, these are the first cases of thalassaemia patients who had a TRALI episode originating from the same blood donor. It

appears that despite significant efforts to eliminate or minimise the risks of toxicity associated with transfusions, the immunological toxic side effects are evident, especially in chronically transfused patients. Further improvements in haemovigilance are essential for reducing the morbidity and mortality associated with transfusions.

In the case of thalassaemia major, chronic transfusions cause alloantibody formation in response to the transfused RBC. In one study it was estimated that 22% of the thalassaemia patients have alloantibodies, with a higher rate in splenectomised (36%) compared to non-splenectomised (13%) patients.[9,10] Similarly, autoantibodies (Coombs +ve) are found in about 25% and autoantibodies with alloantibodies in 44%, which is higher in splenectomised thalassaemia patients (56%).[9,10] The presence of autoantibodies and alloantibodies appear to increase with age due to exposure to more antigens from different blood donors as a result of the increase in the number of transfusions. It is mainly observed in older thalassaemia patients, especially when considering that with the recent introduction of improved treatments life expectancy has increased and thalassaemia patients are living longer and approaching normal lifespan.[11]

Allergic and febrile reactions are common side effects of RBC transfusions in thalassaemia patients. Similarly, other common side effects include delayed haemolytic reactions and bacterial or viral (Hepatitis B and C) infections.[12]

Despite that TRALI is a rare syndrome, the symptoms are rapid and life-threatening. The patients affected by TRALI should be urgently diagnosed and receive the appropriate emergency treatment. Recipient predisposition and number of other factors appear to affect the aetiology and prognosis of individual patients with TRALI.[3,13,14]

In relation to haemovigilance and TRALI, the findings of this study signify and suggest that additional steps should be taken about the TRALI prevention measures which are commonly adopted, i.e. the prevention from plasma donation of female donors with previous pregnancies or any other donors who had received transfusions. In particular, in the light of the present findings, the permission for RBC donation of individuals from the above groups should be reconsidered since it may prove ineffective from preventing TRALI in similar cases.[2-4,13,14]

Within the context of hemovigilance, there is also a need for the preparation of further guidelines at the national and international level to minimise the incidence of TRALI. For example, a male-only strategy for RBC or other blood product donation for transfusions could decrease the incidence of TRALI in thalassaemia and other similar categories of patients.[14] Similarly, RBC and other blood component samples from multiparous women donors should be thoroughly tested for the presence of IgG HLA-Class I and –Class II antibodies and excluded from blood donation in thalassaemia or other high-risk categories of patients.[3,4,13,14]

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Dedication. This paper is dedicated to Evdoxia Mantilari Kontoghiorghe, who passed away in February 2017.

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