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Transfusion-Related Acute Lung Injury After Immunoglobulin Infusion for Kawasaki Disease: A Case Report and Literature Review

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Background

Transfusion-related acute lung injury (TRALI) is a rare life-threatening complication of transfusions, for which the true incidence remains obscure, probably due to misdiagnosis and underreporting. It was first described in 1983; however, it took 2 decades to develop a consensus definition, which remained controversial anyway.[1] Its diagnosis depends on certain criteria that were determined by the Canadian Consensus Conference Panel on TRALI in 2004 (Figure 1).[2]

It manifests as noncardiogenic pulmonary edema and presents with new-onset respiratory distress within 6 hours of the transfusion. It is mostly associated with platelets and plasma transfusions, and it is not frequently reported in immunoglobulin transfusions.

The pathogenesis of TRALI appears to be related to donor antibodies that recognize leukocyte antigens in the host (anti-HLA [human leukocyte antigen] class I and anti-HLA class II) or the infusion of lipids and other biologic response modifiers that accumulate during storage or processing of blood components. TRALI appears to be the result of at least 2 sequential events and treatment is supportive.

Case Presentation

TA was a 2-year-old child diagnosed to have Di-George syndrome since early infancy.

He came with a 5-day history of fever, spikes of high-grade fever reaching 40°C; he had a skin rash; and his mother confirmed him having cracked lips and edematous palms and soles.

On examination he had distinctive features of Di-George syndrome (micrognathia, high nasal bridge, hypertelorism with narrow palpebral fissures, and low set ears). He looked cranky and miserable. He had generalized blanching and faint maculopapular rash involving the limbs and the torso. His peripheries were edematous and he had red cracked lips. His neck examination revealed unilateral cervical lymphadenopathy. His systemic examination was otherwise unremarkable.

His past medical history was significant for tetralogy of Fallot, which was corrected surgically in the United States 16 months prior to this illness; however, his cardiac function was normal and he was not on any medications. His immune status was unknown at the time of presentation due to him being managed abroad (as no reports available), but his mother had denied recurrent or prolonged severe infections.

Family history was not significant. He had isolated speech delay but otherwise achieved his milestones. He was up to date in his vaccinations and had no allergies otherwise.

His inflammatory markers were not significantly high: white blood cells = 4.6×10^9, 40% were polymorphonuclear neutrophils and 26% were lymphocytes. In fact his lymphocytes count was low, 1.19×10^9. C-reactive protein was 43 (significant if >1), and his platelets were 91×10^9. He had no pyuria. His liver function panel was normal. His blood and urine cultures were negative and so was his echocardiography.

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Term	Definition
TRALI	Acute lung injury (defined below) occurring within 6 hours of completion of transfusion of blood product. No pre-existing acute lung injury. No other temporally-associated risk factors for acute lung injury (see below).
Possible TRALI	Acute lung injury (defined below) occurring within 6 hours of completion of transfusion of blood product. No pre-existing acute lung injury. One or more temporally-associated risk factors for acute lung injury.
Acute lung injury (ALI)	New onset. Hypoxemia SpO2 <90% or Pa02/Fi02 < 300 mm Hg on room air, or other clinical evidence of hypoxemia. Bilateral infiltrates on frontal chest X-ray.
Because the diagnosis of ALI can be difficult, it is important for the transfusion service medical director and the patient's physician to communicate to determine, in particular, whether a patient has evidence of volume overload. Although ALI and hydrostatic pulmonary edema may coexist, the latter is a more common complication of transfusion and must be excluded in order for a diagnosis of TRALI or possible TRALI to be made.	

Figure 1. Canadian consensus conference panel TRALI and ALI definitions.

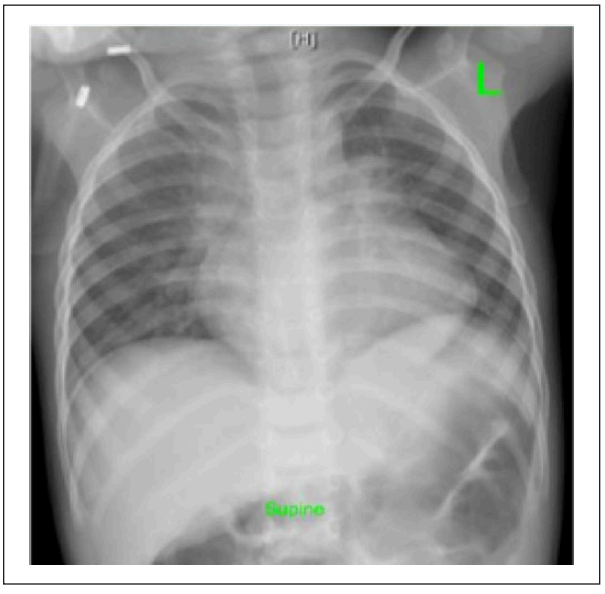

Figure 2. CXR done at admission.

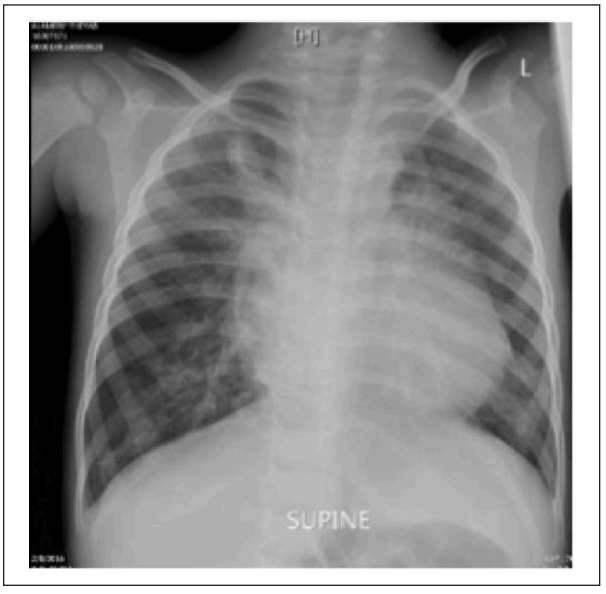

Figure 3. CXR done 2 hours after the end of the IVIG infusion shows bilateral congestion.

He was diagnosed as typical Kawasaki disease and treated with high-dose intravenous immunoglobulin (IVIG; 2 g/kg). Two hours after the end of the transfusion the child developed a new-onset rapidly progressing respiratory distress manifesting as tachypnea and low SaO_2 down to 82%, associated with fever. He was maintaining his blood pressure. There was good bilateral air entry with bilateral coarse crackles, no wheezes, and no focality noted on chest examination. Immediate chest X-ray (CXR) was done and was similar to the one done earlier in admission with more marked congestion, and normal cardiac size (Figures 2-4). His capillary blood gas showed pH 7.319, PO_2 45, and PCO_2 39 (hypoxemic).

Testing the donor and the patient's plasma for HLA antibodies and performing an HLA type on the recipient was not obtainable (laboratory limitations).

The patient was managed with supportive care in a high-dependency unit: provided supplemental oxygen, was kept NPO on intravenous fluids, and was kept under close observation. He improved and his distress slowly recovered over the next 24 to 36 hours.

Discussion

TRALI's true incidence in the pediatrics population is unknown. It is well established in the adult population, and it is reported more commonly in critically ill patients since they are transfused more commonly.[3] It is typically associated with transfusion of plasma products (fresh frozen plasma) and packed red blood cells.

There are 2 pediatric case reports from Greece wherein TRALI occurred after packed red blood cells

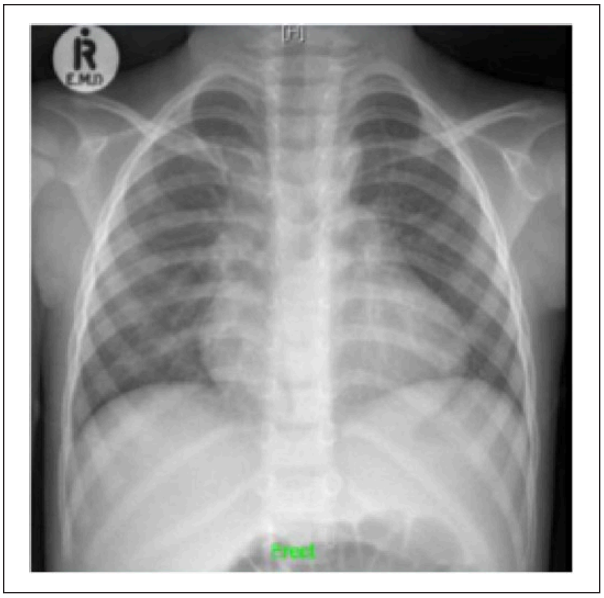

Figure 4. CXR 24 hours after the end of the IVIG infusion shows resolution of the congestion.

transfusion.[4] In both these patients, the acute lung injury was established clinically and treatment was supportive. Only one case report of TRALI after IVIG infusion has been published. Rizk et al in 2001 from the United States reported a 23-year-old man who was transfused with immunoglobulin for his multiple motor neuropathies.[5]

The cause of TRALI is currently not fully understood but suggested to be immune mediated.[6] Antibodies directed toward human leukocyte antigens or human neutrophil antigens have been found in the blood products transfused to patients suffering from TRALI, and they are thought to be the cause. These antibodies are thought to directly activate either the patient's neutrophils, monocytes, or tissue macrophages, leading to initiation of the inflammatory cascade.[7] Multiparous women develop these antibodies through exposure to fetal blood; transfusion of blood components obtained from these donors is thought to carry a higher risk of inducing immune-mediated TRALI.[8]

There are other hypotheses on the pathophysiology of TRALI. The 2-event hypothesis has been suggested where in preexisting pulmonary condition (ie, the first-event, like inflammation, surgery) leads to localization of neutrophils to the microvasculature. The second event occurs when the mediators (such as lipids and cytokines that form due to apoptosis of dead white blood cells during storage) are transfused and activate neutrophils, leading to a secondary injury and a noncardiac pulmonary edema.[1]

Another hypothesis suggested that there is a genetic predisposition to the development of acute lung injury.[9,10]

Supportive care is the mainstay of therapy in TRALI, in terms oxygen supplementation and aggressive respiratory care.

Prevention of TRALI is difficult, but proper use of blood and blood product transfusions can limit the unnecessary morbidities and mortalities. One example of initiatives to lower TRALI's incidence is a "Risk Reduction Strategy," a plan applied in Canada after the consensus conference on TRALI in concordance with AABB recommendations in 2007 and 2009. The 2-step strategy is the following: male-only plasma and apheresis platelets collected from male and nulligravida female donors. The incidence of TRALI after this change is under study.

Conclusion

TRALI is not limited to blood transfusions; it can happen with any type of transfusion. More awareness is needed regarding this complication of transfusion especially in the pediatrics age group. It is suggested that clinician using IVIG should closely monitor patients to pick up this potential fatal complication at the earliest and institute timely and appropriate supportive care. More research is needed to reach a plan to identify risk factors in donors' and recipients' plasma for TRALI.

Author Contributions

JI: Contributed to conception and design; contributed to acquisition, analysis and interpretation; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

AAA: Contributed to conception and design; contributed to analysis and interpretation;drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

GG: Contributed to conception and design; contributed to analysis and interpretation; drafted the manuscript; gave final approval; agrees to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

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