ejpmr, 2021,8(5), 747-753

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

TRANSFUSION RELATED ACUTE LUNG INJURY

Rabia Sultana, *Dr. Sattwik Das and Dr. Beduin Mahanti

School of Pharmacy, Techno India University, Salt Lake City, Sector–V, EM–4, Kolkata–700091, West Bengal, India.

***Corresponding Author: Dr. Sattwik Das**

School of Pharmacy, Techno India University, Salt Lake City, Sector–V, EM–4, Kolkata–700091, West Bengal, India.

Article Received on 21/03/2021 **Article Revised on 11/04/2021** **Article Accepted on 01/05/2021**

ABSTRACT

Transfusion Related Acute Injury (TRALI) represent Acute Lung Injury(ALI) after transfusion of one or more plasma-containing blood plasma developing within 6 hours of transfusion ,not explained by another ALI factor. The mechanisms are still unclear. In massive transfusion, the mechanism of lung injury was initially thought to be microaggregates in stored blood causing micro-pulmonary emboli and lung damage, but this theory has been discredited, since transfusion of stored blood through microaggregate filters has not prevented lung injury in animals nor in humans. Pathologically, the disease involves sequestration of activated neutrophils within the pulmonary capillaries, leading to acute lung injury. The mechanism may include factors in unit(s) of blood, such as antibody and biologic response modifiers. In addition, yet to be described factors in a patient's illness may predispose to the condition. The current incidence is estimated to be 1 in 5,000 units. Patients present with acute dyspnea, or froth in the endotracheal tube in intubated patients. Hypertension, hypotension, acute leukopenia have been described. Management is similar to that for ALI and is predominantly supportive. When TRALI is suspected, Blood banks should be notified to quarantine other components from the same donation. No special blood product is required for subsequent transfusion of a patient who has developed TRALI.

KEYWORDS: Transfusion related acute lung injury (TRALI), Blood transfusion, Acute Lung Injury.

INTRODUCTION

Transfusion Related Acute Lung Injury (TRALI) is defined as new. All which develops within 6 hours of transfusion of one or more units, not attributable to another ALI risk factor. Amongst the numerous possible complications, TRALI has emerged as the most important cause of morbidity and mortality resulting from transfusion of blood or derived of the blood components. In fact, TRALI is currently being regarded as the first cause of severe morbidity and mortality related to blood transfusion therapy. The TRALI concept was described in 1985 by Popovsky, who published a trial on surgical patients, who developed hypotension, hypoxemia and respiratory failure, in the absence of hemodynamic overload from 1-6 hours after blood transfusion. A 72% of these patients required mechanical ventilation. There was a resolution of the condition to 96h of onset of symptoms in 81% of cases. Moreover, the presence of leukocyte antibodies and anti-HLA type I was evidenced in a large percentage of donor. Two decades ago, TRALI was considered a rare complication of transfusion medicine. Nowadays, TRALI has emerged as the leading cause of transfusion-related mortality, presumably as a consequence of reaching international agreement on defining TRALI with subsequent increase recognition and reporting of TRALI cases. The consensus definition in 2004 allowed a better estimate of TRALI, and possible TRALI for populations where other risk factors for acute lung injury are often present, mostly in critically ill patients. Of note, the incidence of TRALI is 50-100 times higher in the critically ill than the general hospital population. In 2004, the consensus conference organized by the Canadian Blood Service and Hema-Quebec (Canada) established the criteria of the Canadian definition, which although very similar to those of the US consensus, introduced the difference between TRALI and possible TRALI, depending on whether or not a temporary relationship to other alternative risk factor for TRALI production.

Both of them have limitations

i) Only identify new and severe hypoxemia. The mild unidentified.

ii) TRALI forms of TRALI may pass diagnosis in patients with other ALI risk factors, requires expert clinical evaluation, and still there are indeterminate cases.

iii) The definition does not include lab tests, so the diagnosis is only based on clinical variables.

iv) The limit of 6h cannot lead to detect cases developed after this period.

Recently, Mark & Corwin, have proposed an extension of the definition of TRALI in terms of the period in which the clinical manifestations begin: classic TRALI, which starts during the first 6 hours of transfusion and

agrees with the model of immune TRALI, and late TRALI or TRALI-deferred, starting between 6 and 72h of transfusion and whose mechanism of production would poorly defined mediators.

ETOLOGY

True TRALI should not have any risk factors for acute lung injury according to diagnostic criteria. TRALI is caused by damage to pulmonary vasculature from neutrophil-mediated in forms of human neutrophil antigen (HNA) or human leukocyte antigen (HLA) antibodies in donor blood which bind to antigens of a recipient. Storage of blood products can accumulate proinflammatory mediators that can cause TRALI as well. A two-hit hypothesis applies in this clinical syndrome. Neutrophil sequestration occurs in the pulmonary vasculature, and neutrophils activate to damage the endothelial layer, causing leakage of protein and fluid into alveolar space.

EPIDEMIOLOGY

Comorbidities suggest risk factors for having TRALI, mechanical ventilation, sepsis, massive transfusion, coronary artery bypass graft, and end-stage liver disease. Higher TRALI incidence was reported with plasma from female donors because the literature found parous female donors with multiple HLA antibodies. Other literature mentioned female donor plasma has larger quantities of anti-HLA class II and HNA positive antibodies. Blood products that have high plasma contents have been associated with an increased rate of TRALI. Critically ill patients have a higher incidence of TRALI, not only because they receive more blood products, but they also have clinical manifestations that activate neutrophil sequestration before the blood transfusion which places them at a higher risk of acquiring TRALI than the general patient population.

In the US, TRALI has been responsible for at least 30% of transfusion-related deaths. While the mortality rates have dropped over the past decade, continued awareness is key and whose mechanism of production would poorly defined mediator. ATHOPHYSIOLOGY OF TRALI.

PATHOPHYSIOLOGY OF TRALI

Pathophysiology of TRALI is not fully understood at present. In the 1950s, initial reports were made on the role of antibodies in the pathogenesis of TRALI, when it was administered to a test subject, 50 ml of blood from a patient containing leukoagglutinins. The clinical manifestations following this administration included hypotension, fever, respiratory failure and bilateral pulmonary infiltrates on chest, radiography with full recovery within 3 days. There are two mechanisms, which lead to the development of the syndrome: immune-mediated and no immune- mediated TRALI.

1) Immune-mediated TRALI is caused by anti-HLA (human leukocyte antigen) antibodies class I, II and/or less frequent antibodies directed against specific antigens of granulocytes — HNA (human neutrophil antigen), which can be present in the serum of the recipient or donor, and react with the donor's or recipient's leukocytes, respectively. The Immune-mediated TRALI is estimated at 65-85% of all reported TRALI cases. Of antibody with specificity known, those directed against HNA-1a, HNA-1b, HNA-2a, HNA-3a (5b) and HLA-A2 are the most frequently documented. Moreover, the presence of antibodies directed against HLA class II has been associated with TRALI.

An argument against immune model is that some patients who underwent the transfusion procedure did not develop TRALI, despite the presence of leukocyte antigens. Some arguments that can explain this issue are:
i) heterozygosity antigen receptor recognized by the antibody;
ii) the clinical presentation of transfused patient may predispose to a greater
or lesser manifestation of pulmonary transfusion reaction,
and iii) lack of detection by clinicians and lack of diagnosis of mild cases.

2) Non-immune-mediated TRALI can be attributed to transfusion of biologically active compounds, which are accumulated in stored blood components such as bioactive lipids, proinflammatory cytokines or platelet microparticles with high procoagulant activity. In non-immune-mediated TRALI, no antibodies were detected despite the clinical symptoms. The main inflammatory cells involved in TRALI pathogenesis are the polymorphonuclear neutrophils. For TRALI development, the production of leukocyte antibodies is crucial. There is a hypothesis of a "two-hit" model postulated by Silliman et al. 1995, which assumes that TRALI onset depends on the coexistence of a factor that predisposes a recipient's reaction, as well as on the presence of leukocyte-activating compounds in transfused blood. The "first hit" is mediated by any proinflammatory condition, it is an aggression that activates the pulmonary endothelium and promotes the recruitment and adhesion of neutrophils to the capillary endothelium, and later causes a disarray of the lung alveolar-capillary permeability barrier.

The "second hit" is induced by transfusion of a blood component. These compounds induce neutrophils activation and release of cytotoxic factors that cause endothelial damage and capillary injury. Reactive neutrophils secrete proinflammatory mediators such as cytokines (IL-1, IL-6, IL-8, TNF-alpha), release proteolytic enzymes (e.g. elastase, azurocidin), and produce reactive oxygen species. These events initiate the cascade of immune reactions with the damage to the vascular endothelium, and produce pulmonary capillary fluid leakage in to the alveolar space, thus causing edema. The neutrophilic airway inflammation of the lung, and later the disruption of the lung alveolar-capillary permeability barrier, it seems to be similar to

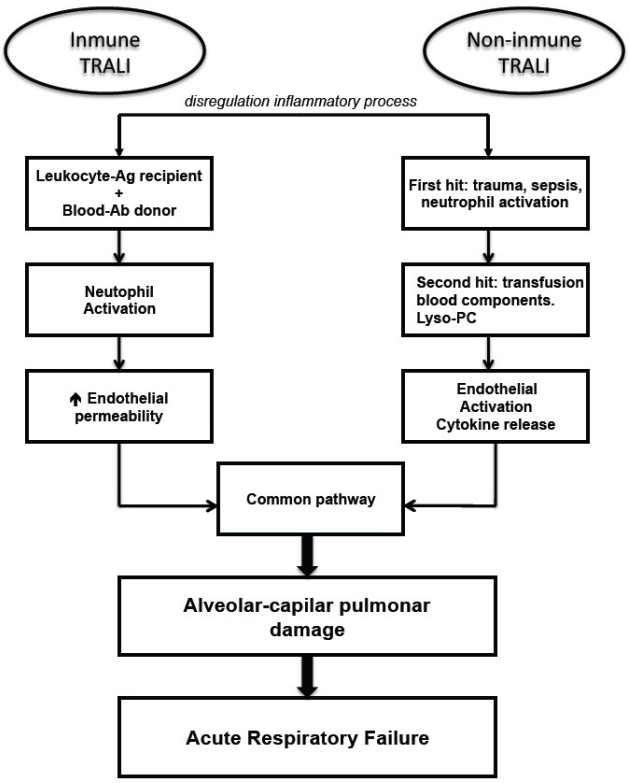
what is seen in other forms of ALI/ARDS, but with different origin.

There is a common pathway in the pathophysiology of TRALI, the damage to the alveolar-capillary membrane, where the neutrophil has been postulated as the protagonist cell for all reactions, and subsequently trigger as described above. Antibodies present in the transfused blood agglutinate to the first found neutrophils after transfusion, which are trapped in the microvasculature. It is well known that most of leukocyte antibodies of the IgG class, produce active.

neutrophils agglutination rather than passive. Neutrophils stimulated by leukocyte antibodies or biologically active lipids, liberate oxygen radicals which damage endothelial cells of the lung capillaries, leading to increased vascular permeability, and ultimately the passage of fluid and proteins into the alveoli.

EXPERIMENTAL MODELS

Animal models have disproved the microaggregate theory of acute lung injury from blood transfusions. The two major hypotheses of TRALI, passively transfused neutrophil and human leukocyte antigen antibodies, and biologically active lipids that accumulate in older, cellular blood products, have been replicated in animal models. In TRALI-related events the transfused product contain a stimulus that is insufficient to cause apulmonary transfusion reaction in the absence of one or more separate facilitating recipient factors, which can synergize with the transfused factors Ex Vivo Lung Models of TRALI In this of TRALI models, edema is produced by perfusate containing human neutrophils, human anti-granulocyte alloantibody (anti-HNA 5b), and complement. The lung edema resulted from an increase in vascular permeability and lung weight, which did not occur if the neutrophils of the perfusate were HNA 5b-negative or if any of the three components perfused was omitted. The HNA antibodies were also capable of direct neutrophil activation and reactive species oxygen (ROS) generation.



Pathophysiology of TRALI.

MECHANISMS

Although the association of transfusion with lung injury has been observed for almost 30 years, the mechanisms are still unclear. In massive transfusion, the mechanism of lung injury was initially thought to be microaggregates in stored blood causing micro-pulmonary emboli and lung damage, but this theory has been discredited, since transfusion of stored blood through microaggregate filters has not prevented lung injury in animals nor in humans. Pathologically, the disease involves sequestration of activated neutrophils within the pulmonary capillaries, leading to acute lung injury. The contribution of neutrophils to multiple types of acute lung injury is well understood and has been validated in several animal models. The major pathophysiologic question in TRALI then becomes how the transfusion is associated with or leads to wide spread neutrophil activation in these patients.

In the past two decades, two hypotheses that lead to neutrophil activation in TRALI have been proposed: antigen-antibody hypothesis versus the two-event hypothesis. Recipient factors that may be involved in the pathogenesis include the recipient's underlying condition and genetic predisposition. Donor unit factors that may be involved in the pathogenesis include leukocyte antibody, cytokines, lipids and factor(s) that increase pulmonary endothelial cell permeability. These hypotheses and factors are discussed below.

1. The antigen-antibody hypothesis: The first evidence supporting this came from observation that classic findings of TRALI (including leukopenia) developed in a healthy volunteer injected with 50 ml of blood from a patient with a strong leukoa glutinin. This healthy volunteer was not ill and his neutrophils should not have been primed. In this case, leukocyte antibody alone seemed to cause TRALI. The evidence supporting immunologic activation of neutrophils by antibody revolves around the association of this disease with the presence of anti-HLA class I and II and anti-neutrophil antibodies in the donor units implicated in TRALI. The primary hypothesis is that the alloantibodies in the donor blood product directly activate either the patient neutrophils, monocytes or tissue macrophages, leading to initiation of the inflammatory cascade. Antibodies recognizing neutrophil HNA-2a (CD177) or HNA-3 antigens have been implicated in cellular injury in both *ex vivo* perfused rat lung models and in cell culture models. In both cases, the evidence suggests direct binding of the antibodies to the neutrophils results in cellular activation leading to degranulation and respiratory burst responses, which in turn damage pulmonary endothelium. Donor alloantibodies may also attach directly to vascular endothelial cells, and thus form the equivalent of immune complexes, which in turn recruit circulating neutrophils and lead to sequestration/activation of these cells. This latter hypothesis is supported by the observation of a TRALI reaction occurring in only one lung following lung transplantation (suggesting that the alloantibodies recognized only new donor lung endothelium). This mechanism of alloantibody mediated TRALI has also been modeled in mice, where is was demonstrated that recognition of endothelial bound anti-MHC-1 mAb (the murine equivalent of anti-HLA Abs) by neutrophil Fc receptors caused neutrophil activation (degranulation/respiratory burst) and subsequent pulmonary damage. Interestingly, it has been observed that the presence of leukocyte antibodies in donors is common, while the occurrence of TRALI is uncommon, and thus antibody alone can not be the sole explanation for TRALI. The incidence of neutrophil antibody of 7.7% in blood donors and components was reported in an abstract. The incidence of HLA antibodies has been studied in female donors (not male) and the incidence is dependent on the technique used and donor parity. Using the less sensitive cytotoxity technique, Rodey found an incidence of 18.7% among donors with a history of four or more pregnancies. Densmore found HLA antibodies in 8% of female plateletphereses donors, with frequencies of 7.9% to 26.3% among those with parity between 0 and ≥3 pregnancies. Insunza found an incidence of 18.1% in female plateletpheresis donors who have had one or more pregnancies. Recently, using the sensitive Luminex flow method, investigators at Emory University found HLA antibodies in 22.5% of segments of randomly selected blood components, but the specificities of these antibodies were not defined.

2. The two-event hypothesis: Silliman et al noted an association of TRALI cases with use of aged blood products. They propose that the first event is the patient's condition (surgery, inflammation) that enhances the risk of TRALI. The second event is transfusion of mediators, such as lipids and cytokines from stored blood products, which can prime or directly activate neutrophils, leading to pulmonary damage. These lipids include lysophosphatidylcholines, which are released from apoptotic white blood cells and platelets and have the capacity to enhance neutrophil function.

3. Patient underlying condition: In both hypotheses (either direct antibody mediated activation or the two-event mechanism), it is quite likely that underlying risk factors in patients, including surgery or inflammation, enhance the risk of TRALI reactions. Inflammation has been associated with upregulation of HLA and neutrophil antigens, thus increasing the number of targets for transfused antibody and potentially increasing the probability that transfused antibodies can directly activate neutrophil function. In addition, inflammation may upregulate vascular adhesion molecules such as P, E-selectin and ICAM-1, which in turn will facilitate accumulation of neutrophils in tissues. TRALI may occur if a second hit (i.e transfusion of a lipid mediator or cytokine) enhances or directly activates neutrophil function - rapid injury of tissues, such as pulmonary parenchyma, containing the accumulated neutrophils would ensue.

4. Cytokines: Elevation of cytokines in the plasma of ALI patients, probably as a result of lung injury, has been long observed, and some cytokines are prognostic markers for patient outcome. However, it is also likely that cytokines present in donor blood products can be directly causative of ALI. Cytokines in the plasma of stored blood products are derived from two sources: leukocytes and platelets, or possibly, from a donor who was incubating an inflammatory but subclinical illness at the time of donation. Proinflammatory cytokines that accumulate with stored red cell blood products are removed by prestorage leukoreduction, while those that are released by platelet activation may not be removed by leukoreduction. TRALI decreased, but did not disappear, with the implementation of universal leukodepletion in Canada. Two reasons account for the decrease in TRALI with leukoreduction: First, the 10% of TRALI cases due to patient antibody against donor

leukocytes in the unit of blood would not occur. Second, leukoreduction reduces accumulation proinflammatory cytokines in stored blood products During storage of red cells or platelet units that are not leukoreduced, proinflammatory cytokines such as IL-1β, IL-6, IL-8 and TNFα accumulate in the supernatant plasma, and are virtually eliminated by prestorage leukoreduction. IL-8 has neutrophil priming activity that could be important in causing TRALI. Other cytokines are not reduced by leukoreduction, e.g. RANTES and TGF-β1 accumulate in platelet components during storage. RANTES (Regulated upon activation, normal T-cell expressed and presumably secreted) evokes the release of histamine from basophils, may be related to allergic reactions. There are conflicting data regarding the role of RANTES in animal models of lung injury. TGF-β1 is mostly bound in an inactive form to extracellular components, but there is evidence of a link to ALI. PAI-1 is also released by platelets, and but its levels in leukoreduced platelet products is unknown. More recently, direct priming/activation of neutrophils has been demonstrated to occur through the surface molecule CD40, which is recognized by the molecule sCD40L, a major product of platelets and found in high levels in platelet concentrates.

5. Genetic predisposition: There is new evidence that there may be genetic predispositions to the development of clinical acute lung injury. For example, polymorphisms in the *SP-B* gene have been associated with the development of ALI. Homozygosity for the deletion polymorphism in the angiotensin converting enzyme (*ACE*) gene which is associated with higher ACE levels and activity was found in an increased frequency among patients with ALI. Also, there has been some work that associated polymorphisms in the *IL-6* and *TNF-α* genes with susceptibility to sepsis and acute lung injury. Moreover, there has been a growing interest in examining whether common polymorphisms of genes that encode mediators of inflammation, innate immunity, as well as coagulation may allow for host phenotypic differences in the susceptibility to ALI, thus accounting for some of the individual susceptibility to ALI. Genetic predispositions to TRALI are thus possible but have not yet been defined.

6. Endothelial cell injury: Another contributor to TRALI reactions is the potential that transfusion products may directly injure vascular endothelial cells in the lung. Recently, Rao et al have found that supernatants from stored red blood cell units can contain a soluble, transferable factor that directly increases vascular permeability in cultured microvascular endothelial cells. The nature of such an agent, which resulted in partial endothelial cell retraction and development of increased intercellular space, remains unclear. However, the component appears to have a molecular weight greater than 100kD, ruling out common cytokines. Further investigation of the potential that stored blood products may alter vascular endothelial cell integrity is clearly warranted.

Incidence

The actual incidence of TRALI is unknown because of lack of large, current prospective studies that use a standard definition for the syndrome. The lack of such studies account for the wide range in the reported incidence of TRALI, from approximately 1 in 500 to 1 in 100,000, as reviewed at the consensus conference in Toronto in 2004, including series from University of Denver, University of Alberta, Mayo Clinic, UK, and Canada. TRALI has been reported following transfusion of all plasma-containing blood components. Estimates of the incidence of TRALI have been 1 in 5,000 components, mostly in whole blood, 1 in 7,900 units of fresh frozen plasma, and 1 in 432 units of whole blood-derived platelet concentrates. Critically ill patients may be at greater risk for TRALI because of underlying severe illness, and a retrospective study estimated the risk of TRALI and possible TRALI to be 1 in 1271 units transfused to patients in intensive care units.

Evidence for underreporting was found in a study of recipients of previous donations of donor with neutrophil 5b antibody. Some patients developed signs and symptoms of TRALI, but these cases had not been reported to the Blood Bank. Underreporting is due to several reasons. First, TRALI is acute lung injury (ALI), and there is yet no uniformly agreed upon criteria that distinguish TRALI from ALI due to other causes. Second, some clinicians attribute ALI to massive transfusion, rather than to TRALI from a single unit of blood. Third, the treatment of TRALI is currently the same as for other forms of ALI, primarily supportive with a lung protective ventilatory strategy, so clinicians who recognize the syndrome may see no reason for reporting the case to the Blood Bank. Fourth, distinguishing between intravascular fluid overload vs. TRALI is difficult. Finally, making a diagnosis of TRALI is costly to Blood Banks. The cost of a complete antibody investigation is several thousand dollars, and in addition, implicated donors may be prohibited from further donations, even if they have donated before without reported adverse reactions in recipients. The cost of investigation and loss of blood donors may understandably bias Blood Bank personnel to attribute pulmonary edema after transfusion to fluid overload rather than TRALI. These barriers to determination of the actual incidence of TRALI can be overcome. Recognizing the need for a common definition, the NHLBI Working Group on TRALI determined criteria for clinical TRALI. The common definition described earlier in this paper provides a foundation for studies of incidence. To study true incidence, large prospective studies are needed using a standard protocol. In such studies, a surveillance system is needed that does not depend on clinician reports and will capture all cases of TRALI. Also, in such studies, experts are needed to assess fluid overload vs. ALI vs. TRALI and the experts should be blinded to donor unit attributes and donor test results.

CLINICAL PRESENTATION

The acute respiratory failure is the main finding in TRALI. The central clinical symptomis dyspnea and co-occurs with tachypnea, tachycardia, cyanosis and pulmonary secretions. Another hemodynamic alterations like fever, hypotension or hypertension (rare) are also reported. All these clinical characteristics are observed during transfusion, or within 6 h of transfusion in the absence of other factors that can develop ALI, often during the first hour of a transfusion. During physical examination, the clinicians can find decreased breath sound, diffuse crackles over the lung fields, and shallow breathing. The chest radiography shows bilateral fluffy infiltrations with no cardiomegaly, and with this it can exclude cardiogenic edema. Hemodynamic monitoring helps to differentiate TRALI and cardiogenic pulmonary edema. Normal or low pulmonary capillary wedge pressure, and central venous pressure values are characteristic for TRALI. Actually, hemodynamic monitoring has been needed to exclude other causes of TRALI, because the symptoms are similar to other diseases, such as anaphylactic reaction, cardiogenic pulmonary edema, ARDS or bacterial infection.

TREATMENT

The treatment of TRALI is the support of lung function, and it does not differ from the treatment of ALI/ARDS of any other etiologies. Mild cases of ALI/ARDS could be treated with conventional measures such as oxygen therapy, and more serious cases require endotracheal intubation and mechanical ventilation strategies. The protective strategies should be applied in ALI/ ARDS, which aim to prevent the damage produced by mechanical lung ventilation. Sometimes, the presence of hemodynamic impairment requires the administration of fluids. Aggressive adminis-tration is not recommended, since as in the ALI/ARDS of other etiology, it has recently confirmed that a conservative strategy is accompanied by an improvement in pulmonary function with decreased in duration of mechanical ventilation and the ICU stay. The lack of response to fluid therapy may force the introduction introducing of the inotropes. The use of corticosteroids has been stated in some case reports, but their use in TRALI is empirical and there is no evidence of their use.

CONCLUDING REMARKS

TRALI is a distinctive clinical entity or a syndrome of ALI/ARDS, it has increased in clinical importance in recent years. Long unrecognized, and existing as only scattered reports of non-cardiogenic pulmonary edema after transfusions, TRALI remained largely undiagnosed even after a case-series report. The relative contribution of biological response modifiers, and anti-leucocyte antibodies to clinical TRALI remains unclear, and it may be difficult to answer using animals and in vitro models. It seems likely that traditional molecular mediators of inflammation are among such molecules critical for the manifestation of TRALI;

1. the action of such mediators can be inhibited by appropriate antagonists; and
2. results can be translated into therapeutic strategies for clinical use. The identification of risk factors further improves the risk-benefit assessment of a blood transfusion. Efforts to further decrease the risk of TRALI are needed to increase awareness of the syndrome among physician.

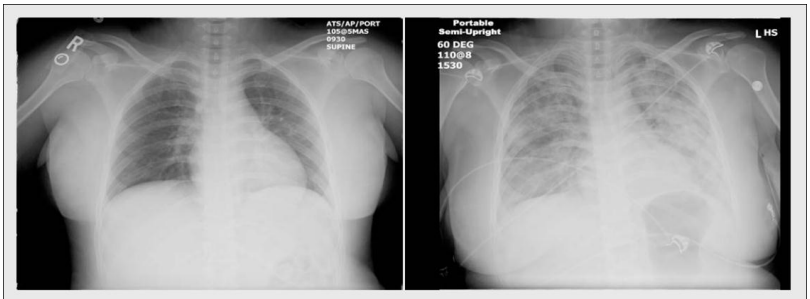


Fig 1: Pre and Post transfusion X-rays of our patient with TRALI. Bilateral Lung infiltrate with pulmonary edema is an essential criteria for the clinical diagnosis of TRALI.

CONCLUSIONS

TRALI is emerging as one of the most common causes of self-limiting, yet potentially life-threatening, transfusion associated morbidity, and diagnosis requires a high degree of suspicion. It is based primarily on exclusion of other causes and the supportive clinical picture in the setting of a temporal relation to blood product transfusates. Correct diagnosis is important aretics are contraindicated and hypovolemia needs to be corrected. Treatment is mainly supportive, with a significantly better prognosis compared to other causes of acute lung injury.

- **REFERENCES**

1. Kleinman S, Caulfield T, Chan P, Davenport R, McFarland J, McPhedran S, Meade M, Morrison D, Pinsent T, Robillard P, Sliger P. Toward an understanding of transfusionrelated acute lung injury: Statement of a consensus panel. Transfusion, 2004; 44: 1774-89.
2. Popovsky MA, Moore SB: Diagnostic and pathogenetic considerations in transfusionrelated acute lung injury. Transfusion, 1985; 25: 573-7.

3. Kopko M, Holland PV: Transfusion-related acute lung injury. Brit. J. Haematology, 1999; 105: 322-329.
4. Triulzi DJ, Kleinman S, Kakaiya RM, Busch MP, Norris PJ, Steele WR, Glynn SA, Hillyer CD, Carey P, Gottscall JL, Murphy EL, Rios JA, Ness DM, Wright DJ, Carrick D, Schreiber GB. The effect of previous pregnancy and transfusion on HLA alloimmunisation in blood donors: implications for transfusion-related lung injury risk reduction strategy. Transfusion, 2009; 49: 1825-1835.
5. Palfi M, Berg S, Ernerudh J, Berlin G: A randomised controlled trial of transfusion-related acute lung injury: is plasma from multiparous blood donors dangerous? Transfusion, 2001; 41: 317–322.
6. Benjamin RJ and Eder AF. Donor management and laboratory investigation of suspected TRALI. In: Kleinman S, Popovsky MA, eds. TRALI: Mechanisms, Management and Prevention. Bethesda, MD:AABB Press, 2008.
7. Silliman CC and McLaughlin NJD Transfusion-related acute lung injury. Blood Reviews, 2006; 20: 139-159.
8. Silliman CC, Boshkov LK, Mehdizadehkashi Z, Elzi DJ, Dickey WO, Podlosky L, Clarke G, Ambruso DR. Transfusion-related acute lung injury: epidemiology and a prospective analysis of etiologic factors. Blood, 2003; 101: 454-62.
9. Dooren MC, Ouwehand, WH, Verhoeven AJ, dem Borne A,E, Kuijpers RW. Adult respiratory distress syndrome after experimental intravenous gamma-globulin concentrate and monocyte-reactive IgG antibodies. Lancet, 1998; 352: 1601-1602.
10. Wyncoll DL, Evans TW: Acute respiratory distress syndrome. Lancet, 1999; 354: 497 - 501.
11. Nakagawa M, Toy P. Acute and transient decrease in neutrophil count in transfusionrelated lung injury:cases at one hospital. Transfusion, 2004; 44(12): 1689-1694.
12. Chapman CE, Stainsby D, Jones H, Love E, Massey E, Win N, Navarette C, Lucas G, Soni N, Morgan C, Choo L, Cohen H, Williamson L. on behalf of the Serious Hazards of Transfusion Steering Group. Ten Years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. Transfusion, 2009; 49: 440-452.
13. Rizk A, Gorson KC, Kenney L, Weinstein R: Transfusion-related acute lung injury after the infusion of IVIG. Transfusion, 2001; 41(2): 264 - 8.
14. Nicolle AL, Chapman CE, Carter V, Wallis JP. Transfusion-related acute lung injury caused by two donors with anti-human leucocyte antigen class II antibodies: a look-back investigation. Transfusion Medicine, 2004; 64: 225-230.