CASE REPORT

A prophylactic fresh frozen plasma transfusion leads to a possible case of transfusion-related acute lung injury

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SUMMARY

A 39-year-old man with cholangiocarcinoma presented with fever and abdominal pain. He was hypotensive, jaundiced and had right upper quadrant tenderness. Laboratory testing showed a leucocytosis, elevated liver function tests, total bilirubin and International Normalised Ratio (INR). Given the concern for cholangitis, the patient was given antibiotics and three units of fresh frozen plasma (FFP) before biliary drain placement. After drain placement, and within 3 h of receiving blood products, the patient became tachypnoeic and hypoxic with a chest X-ray revealing new bilateral airspace disease. The rapid development of respiratory distress was determined to most likely be transfusion-related acute lung injury (TRALI). He rapidly progressed to intubation and required 100% FiO₂, high positive-end expiratory pressure (PEEP) and intermittent-prone ventilation for 48 h but eventually recovered and was extubated. TRALI is an under-recognised aetiology for respiratory distress in the critically ill. Adopting a conservative transfusion strategy may prevent TRALI.

mask and within 1 h of onset had to be intubated for continued hypoxia.

INVESTIGATIONS

Initial laboratory data revealed a lactate of 3.6 mEq/L (normal reference range 0.3–2.2 mEq/L), a white cell count (WCC) of $21.1 \times 10^9/L$ with 57% bandemia, aspartate aminotransferase of 436 IU/L, alanine transaminase 185, total bilirubin of 15.3 mg/dL and international normalised ratio (INR) of 1.8 mg/dL. Initial chest X-ray ([figure 1](#)) did not reveal any acute cardiopulmonary process. During drain placement, frank pus was aspirated. Once the patient developed respiratory distress, a repeat chest X-ray showed new bilateral air space disease consistent with pulmonary oedema or aspiration ([figure 2](#)). An echocardiogram was performed which showed an ejection fraction of 50–55% and an estimated right ventricular systolic pressure of 29 mm Hg. Of note, the WCC dropped to 2.9 within 8 h of the transfusion while all other cell lines remained intact and the INR remained 1.8.

Antibody testing of donor plasma was conducted on two of the three donors. Neither of these two donors possessed antihuman leucocyte antigen (anti-HLA) or antihuman neutrophil (anti-HNA) antibodies.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for acute respiratory distress with bilateral infiltrates on chest X-ray in the critically ill, septic patient in the setting of recent transfusion includes the following:

- Cardiogenic
 - Congestive heart failure
 - Transfusion-associated circulatory overload (TACO)
- Non-cardiogenic
 - Sepsis with acute respiratory distress syndrome (ARDS)
 - Aspiration
 - TRALI
 - Pneumonia
 - Transfusion-related infection

TREATMENT

A diagnosis of possible TRALI was made and the patient was treated supportively with mechanical ventilation. Our patient initially required 100% FiO₂, positive-end expiratory pressure (PEEP) of 20 cm H₂O and was prone intermittently for the

BACKGROUND

Transfusion-related acute lung injury (TRALI) is a pathological condition that can have severe morbidity, high healthcare costs and potential mortality. The pathophysiological mechanism of TRALI is yet to be fully understood but new research has helped recognise associated risk factors. A deliberate transfusion strategy will help decrease the incidence of this iatrogenic disease.

CASE PRESENTATION

A 39-year-old man with a history of cholangiocarcinoma with prior resection, chemotherapy and recent biliary stent placement for obstructive jaundice presented to the emergency department with 4 days of progressive abdominal pain, vomiting, fever and deepening jaundice. On examination, he was febrile and hypotensive, requiring pressor support after initial volume resuscitation and empiric antibiotic administration. In an attempt to reverse the patient's coagulopathy for a percutaneous biliary stent placement, the patient was given vitamin K and 3 units of fresh frozen plasma (FFP). After coming back to the medical intensive care unit postprocedure, the patient was noted to be tachypnoeic and hypoxic to 85%. He was placed on a high-flow nasal canula, then a non-rebreather, then bi-level positive airway pressure and bag valve

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Figure 1 X-ray of the patient on presentation showing mild hypoventilation, but no acute cardiopulmonary process.

first 48 h. We utilised a low tidal volume strategy in ventilating him with goals of 6 cc/kg.

OUTCOME AND FOLLOW-UP

After 48 h, the patient's FiO_2 was weaned down to 50% and PEEP decreased to 10 cm H_2O and eventually he was able to be extubated on day 5 of his hospitalisation. He continued to improve and was able to be discharged home with a cholecystostomy tube in place on day 14.

DISCUSSION

TRALI is a clinical syndrome of new acute lung injury temporally related to transfusion of blood products. The definition requires onset within 6 h of a transfusion, bilateral infiltrates and hypoxaemia. There must be no evidence of fluid overload before the transfusion and no pre-existing lung injury noted. In cases where there are alternative risk factors for ARDS, the diagnosis of TRALI cannot be made, but the term 'possible TRALI' can be used.¹ The diagnosis is made on a clinical basis. The patient may have chest pain, dyspnoea, fever, chills, tachypnoea, tachycardia, hypotension with hypoxia. On examination, diffuse crackles consistent with pulmonary oedema are usually evident. Reported mortality rates are variable, but it is the cause of the most transfusion-associated deaths in the USA annually.²

Figure 2 X-ray of the patient within 4 h of fresh frozen plasma transfusion showing the development of new bilateral pulmonary infiltrates.

Table 1 Patient and product factors associated with TRALI (from Sayah *et al*)³

Patient risk factors	Product risk factors
<ul style="list-style-type: none"> ► Higher IL-8 level ► Shock ► Liver surgery (mainly transplantation) ► Chronic alcohol abuse ► Positive fluid balance ► Peak airway pressure greater than 30 cm H_2O if mechanically ventilated before transfusion ► Current smoking 	<ul style="list-style-type: none"> ► Female donor (especially multiparous) ► Strong anti-HLA-Class II ► Anti-HNA antibodies ► Whole blood ► Plasma products ► Pooled platelet products

Anti-HLA, antihuman leucocyte antigen; anti-HNA, antihuman neutrophil; IL-8, interleukin-8; TRALI, transfusion-related acute lung injury.

An arterial blood gas in the setting of suspected TRALI may be helpful for determining the degree of alveolar–arterial gradient, but is not specific to the clinical syndrome and a decreased pulse oximetry reading can usually confirm hypoxia. In addition, a brain natriuretic peptide and echocardiogram can assist in evaluating the possibility of cardiogenic pulmonary oedema. There are no specific laboratory markers of TRALI, but the diagnosis of TRALI can be supported with laboratory detection of anti-HLA antibodies or anti-HNA antibodies isolated from the donor blood. Presence of incompatible antibodies however, does not necessitate the clinical syndrome of TRALI.³ Additionally, a transient leucopenia, varying from an 8% to a 30% drop in the leucocyte count, is a highly specific occurrence.⁴ However, in the acute situation, none of these laboratory tests are useful for influencing clinical management as patients often escalate to requiring intubation within hours of onset of symptoms.

A possible immune-mediated mechanism of TRALI is implicated in 65–89% of cases through detection of HLA or HNA antibodies in the blood product.¹ It is important to note however, that despite detection of these antibodies, the specific mechanism by which TRALI develops cannot be identified with certainty as the recipient may lack the specific antigen to trigger an immune-mediated response. It is thought that these antibodies enhance recruitment of neutrophils to pulmonary endothelium and cause eventual neutrophil activation. As such, acute systemic neutropenia is commonly observed with TRALI with a concurrent increase in circulating neutrophils in the pulmonary vasculature.^{5–7}

Sachs,⁵ describes the histological finding of interstitial/intra-alveolar oedema in fatal TRALI cases and a theory regarding susceptibility to the development of TRALI called the 'threshold model.' The endothelial damage and intra-alveolar oedema has been identified on electron microscopy with degranulation along endothelium. The direct correlation is still undefined and may involve direct injury from microcidal release or mediation through reactive oxygen species. Patients with primed neutrophils or endothelial cells are at a higher risk of developing TRALI. The threshold model proposes that a lower threshold is reached between individual factors and transfusion factors for mild TRALI and a higher threshold in severe TRALI. Patient risk factors for TRALI as studied in clinical trials include liver disease, sepsis and mechanical ventilation. Transfusion factors that confer risk include plasma products, female donors (especially multiparous) and units containing leucocyte-specific antibodies or granulocyte-specific antibodies.⁸ These risk factors are presented in table 1.

There are reported cases of TRALI in neutropenic patients as well.¹⁰ Given this, there are alternative mechanisms proposed such as the production of reactive oxygen species by pulmonary

endothelial cells, platelets or monocytes which implicates patient factors in the development of TRALI, but the true mechanism of non-immune-mediated TRALI is still unknown.

Strategies to decrease the risk of TRALI have included the use of male predominant donors. The UK National Blood service has shown that by reducing the number of female FFP donations to 10–20% of all transfusions, a 79% reduction in the incidence of TRALI was observed.¹¹ Many blood banks are unable to exclude all female donors, so to reduce the risk of TRALI, most will screen platelet and plasma products for anti-HLA antibodies among these donors and exclude any donors implicated in a previous case of TRALI.¹¹ A protocol instituted by Insunza *et al*¹² where a screening strategy for screening previously pregnant donors resulted in efficacious primary prevention.

Of course, the most effective strategy in reducing the incidence of TRALI is appropriately minimising the transfusion only to cases in which there is a clear clinical benefit. In our case, a 'prophylactic' FFP transfusion was given for a mildly elevated INR before a percutaneous intervention and actually did not lead to a reduction in INR, raising the question as to whether or not the transfusion accomplished its desired goal. While it remains a very commonly held belief among physicians,¹³ there has been no evidence that this concept of 'prophylactic plasma' is effective at preventing bleeding in the patient with mild coagulopathy before procedures. Similar case reports presenting patients who have suffered TRALI after pre-procedural transfusion of FFP are published in the literature and reinforce the importance of judicious use of blood products.¹⁴ The guidelines published by the British Society of Haematology do not routinely recommend the use of FFP for the reversal of warfarin effect.¹⁵ A registry of transfusion-related adverse events, SHOT (serious hazards of transfusions) annual report recommends strict and vigilant prescribing practice for FFP.¹⁶ A number of retrospective, observational studies have shown that various procedures can be safely conducted with elevated INRs, commonly as high as 3.0,^{17 18} yet there remains a clear need for higher level evidence to establish improved guidelines regarding procedures in patients with coagulopathies. In the meantime, a combination of institutional educational programmes

and overall conservative transfusion policies have been shown to safely decrease the use of FFP and will likely contribute to the reduction in the incidence of TRALI.¹⁹

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Competing interests None.

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Learning points

- Transfusion-related acute lung injury (TRALI) is an important mechanism for respiratory distress in the critically ill and a leading cause of death after transfusions.
- Patient and product factors contribute to risk factors associated with the development of TRALI.
- Conservative transfusion strategies can decrease the incidence of TRALI.

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