

# lesson of the month

Transfusion-related acute lung injury: a rare and life-threatening complication of a common procedure

**Transfusion-related acute lung injury (TRALI) has emerged as one of the leading causes of transfusion-related morbidity and mortality and is undoubtedly under diagnosed. It is a serious pulmonary syndrome that can lead to death if not recognised and treated promptly. The diagnosis of TRALI is based primarily upon clinical signs and symptoms and is, in part, a diagnosis of exclusion.**

## Lesson

A 57-year-old lady with no past medical history presented with shortness of breath on exertion. Apart from pallor, her examination findings were unremarkable. Electrocardiogram (ECG) and chest X-ray (CXR) were normal (Fig 1). Routine blood tests showed microcytic anaemia (haemoglobin 6.8 g/dl, mean corpuscular volume 70 fl). The remainder of the blood count, renal function and liver function tests were normal. She was admitted for blood trans-

fusion and further investigation. The first unit of blood was transfused over two hours. Seventy five minutes into the second unit she became tachypnoeic, tachycardic and hypotensive. Her temperature rose to 38°C. Pulse oximetry dropped rapidly to 60% on room air. There was no erythema, urticaria or bronchospasm. Auscultation of the chest revealed bilateral, widespread crackles without rhonchi and the CXR demonstrated extensive, diffuse, bilateral pulmonary infiltrates (Fig 2). Type 2 respiratory failure was evident on arterial blood gas (ABG) estimation. Cardiac auscultation was normal and a 12-lead ECG showed sinus tachycardia with no ischaemic changes. Troponin I was marginally elevated at 0.2 ng/ml (normal range <0.06 ng/ml) and transthoracic echocardiography confirmed normal biventricular and valvular function without pericardial effusion or regional wall motion abnormality. Central venous pressure (CVP) was 6 cm H<sub>2</sub>O and blood cultures were negative.

The patient was intubated and ventilated. Inotropes were required for circulatory support and she made a rapid recovery in the intensive care unit. This was reflected in her CXR performed on day 2 (Fig 3) and there was marked improvement in oxygenation. She was extubated on day 3 and was transferred to a general medical ward the following day. A myocardial perfusion scan was normal with no suggestion of ischaemia or infarction. A chronic duodenal ulcer was found on upper gastrointestinal endoscopy. She

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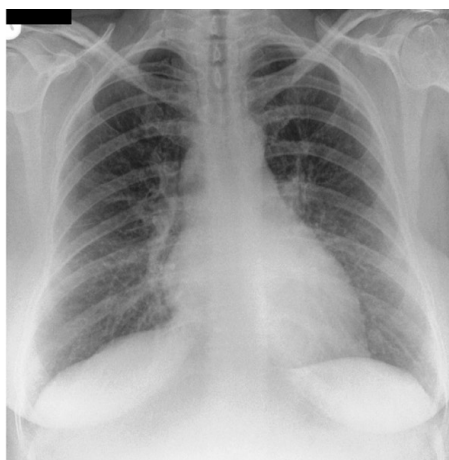


Fig 1. Chest X-ray on admission, showing clear lung fields with no cardiomegaly.

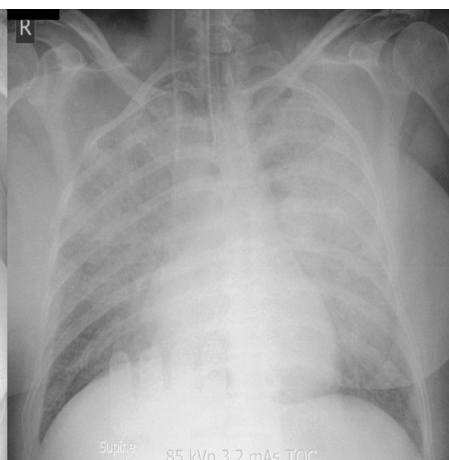


Fig 2. Chest X-ray at the time of acute pulmonary insufficiency, showing bilateral extensive diffuse pulmonary infiltrates.

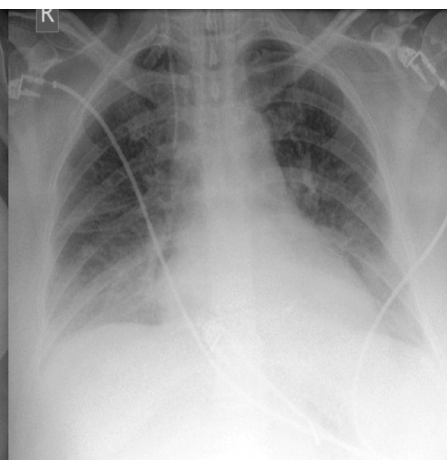


Fig 3. Chest X-ray on day 2, showing marked improvement.

refused further blood transfusions and her anaemia was corrected with intravenous iron infusion. She was discharged on oral iron supplements and a proton-pump inhibitor.

## Discussion

Transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), cardiac failure, anaphylactic reaction and transfusion-related bacterial sepsis through contamination of blood products should be considered as differential diagnosis in a patient who develops pulmonary insufficiency following transfusion.<sup>1</sup> TACO develops within minutes to hours of transfusion with respiratory distress and evidence of fluid overload such as raised CVP or gallop rhythm. Anaphylactic reaction manifests with widespread urticarial rash, wheezing and hypotension. Transfusion-related bacterial sepsis presents with respiratory failure as part of multi-organ failure due to severe sepsis. TRALI develops within six hours of transfusion with the peak of the reaction evident within the first two hours following transfusion.<sup>2-4</sup> The clinical picture is similar to acute respiratory distress syndrome (ARDS) with sudden onset respiratory distress due to noncardiogenic pulmonary oedema, hypovolaemia/hypotension (less commonly hypertension), fever (typically 1–2°C increase) and copious frothy pink pulmonary secretions.<sup>3,5-7</sup> The CXR exhibits bilateral fluffy infiltrates with type 2 respiratory failure on ABG analysis.<sup>3,5,7</sup> There is no evidence of fluid overload and the CVP and pulmonary wedge pressure are normal.<sup>7</sup> Laboratory findings may include haemoconcentration, leukopenia, neutropenia or neutrophilia, hypoalbuminemia and hypocomplementemia.<sup>8-10</sup> The more specific investigation is demonstration of antibodies to human leukocyte antigen class I/II or neutrophil-specific antibodies in donor plasma and corresponding antigen in the recipient.<sup>5,7</sup> These tests take weeks and are not widely available, making TRALI primarily a clinical diagnosis.<sup>11</sup> Investigations including blood cultures, echocardiography and myocardial perfusion imaging help exclude other differential diagnoses. The elevated troponin level in this patient could be the result of haemodynamic compromise, tachycardia and pulmonary oedema.

TRALI was first described in the 1950s. In 1951, Barnard reported the death of a patient with leukaemia following blood transfusion as an acute pulmonary reaction and in 1957 Brittingham described severe pulmonary reaction following transfusion of whole blood.<sup>12,13</sup> TRALI was recognised as a distinct clinical entity in 1983.<sup>14</sup> The pathogenesis of TRALI is not completely understood. Leukocyte antibodies in donor plasma interact with recipient neutrophils, resulting in activation and aggregation in pulmonary capillaries causing release of biologic response modifiers, leading to capillary leak and lung injury, is implicated in most cases.<sup>2</sup> The absence of these antibodies in up to 15% of cases, led to an alternative non-immune mechanism described as 'two hit' hypothesis. The first hit is the clinical condition of the patient, which causes pulmonary endothelial activation. This primes the neutrophils and leads to sequestration. The second hit is the transfusion of blood products containing biologic response modifiers such as lipids, cytokines and leukocyte

antibodies. These activate the sequestered adherent neutrophils which damage the endothelium and cause a capillary leak.<sup>15</sup> Recent surgery, active infection/inflammation, cytokine therapy and massive transfusion are considered possible predisposing risk factors.<sup>16-18</sup>

TRALI is associated with all types of blood products, including immunoglobulin preparations, but is more severe and most common with products containing larger amounts of plasma, such as fresh frozen plasma (FFP) and whole blood.<sup>3,7</sup> Ventilatory assistance and circulatory support are the mainstays of treatment. The role of corticosteroids is unclear and remains controversial. Diuretics are not indicated as the pulmonary oedema is noncardiogenic or due to fluid overload.<sup>3</sup> Most patients recover within 96 hours and there appears to be no residual pulmonary damage among survivors.<sup>3,5</sup> Mortality ranges from 5 to 13%.<sup>5,19,20</sup> This is in contrast to ARDS, which has a mortality of 40 to 50%.

Avoiding unnecessary blood transfusions will reduce the incidence of TRALI. Donors who have antibodies to high-frequency leukocyte antigens are disqualified from plasma or platelet donation to prevent occurrence of TRALI. Using only male donors to manufacture FFP, the use of pooled plasma preparations instead of single donor plasma, decreasing the amount of plasma remaining in red cell components and the use of fresher products are some of the methods undertaken to prevent the condition. There are no guidelines on re-transfusion of the patient who has already had TRALI, but the general opinion is that additional blood component therapy should not be withheld if clear indications for transfusion exist. The clinical events described illustrate the need to consider alternatives to blood products, such as intravenous iron, wherever possible. TRALI should be considered in all patients who have pulmonary insufficiency during or after transfusion. TRALI is a clinical diagnosis and timely recognition and treatment is crucial in the management.

## Reference

- 1 Silliman CC, Ambruso DR, Boshkov LK. Transfusion-related acute lung injury. *Blood* 2005;105(6):2266–73.
- 2 Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. *Transfusion* 1985;25:573–7.
- 3 Wallis JP. Transfusion-related acute lung injury (TRALI) – under-diagnosed and under-reported. *Br J Anaesth* 2003;90:573–6.
- 4 Silliman CC, Paterson AJ, Dickey WO. The association of biologically active lipids with the development of transfusion-related acute lung injury: a retrospective study. *Transfusion* 1997;37:719–26.
- 5 Hicks WA, Strait RT, Finkelman FD, Susskind BM. Transfusion-related acute lung injury (TRALI): History, Pathophysiology and role of the clinical laboratory. *ASHI Quarterly* 2004;28(3):92–5.
- 6 Ward NH. Pulmonary infiltrates associated with leukoagglutinin transfusion reactions. *Ann Intern Med* 1970;73:689–94.
- 7 Triulzi DJ. Transfusion-related acute lung injury: An update. *Hematology Am Soc Hematol Educ Program* 2006:497–501.
- 8 Nakagawa M, Toy P. Acute and transient decrease in neutrophil count in transfusion-related acute lung injury: Case at one hospital. *Transfusion* 2004;44:1689–94.
- 9 Dry SM, Bechard KM, Milford EL, Churchill WH, Benjamin RJ. The pathology of transfusion-related acute lung injury. *Am J Clin Pathol* 1999;112:216–21.

- 10 Goldman M, Webert KE, Arnold DM *et al*. Proceedings of a consensus conference: Towards and understanding of TRALI. *Transfus Med Rev* 2005;19:2–31.
- 11 Toy P, Popovsky MA, Abraham E *et al*. Transfusion-related acute lung injury: definition and review. *Crit Care Med* 2005;33(4):721–6.
- 12 Barnard RD. Indiscriminate transfusion: A critique of case reports illustrating hypersensitivity reactions. *NY State J Med* 1951;51:2399–402.
- 13 Brittingham TE. Immunological studies of leucocytes. *Vox Sang* 1957;2:242.
- 14 Popovsky MA, Abel MD, Moore SB. Transfusion-related acute lung injury associated with passive transfer of antileukocyte antibodies. *Am Rev Respir Dis* 1983;128:185–9.
- 15 Silliman CC, Kelher M. The role of endothelial activation in the pathogenesis of transfusion-related acute lung injury. *Transfusion* 2005;45:109–16.
- 16 Medeiros BC, Kogel KE, Kane MA. Transfusion-related acute lung injury (TRALI) following platelet transfusion in a patient receiving high-dose interleukin-2 for treatment of metastatic renal cell carcinoma. *Transfus Apheresis Sci* 2003;29:25–7.
- 17 Roffey P, Thangathurai D, Mikhail M, Raid M, Mogos M. TRALI and massive transfusion. *Resuscitation* 2003;58:121.
- 18 Silliman CC. Transfusion-related acute lung injury. *Transfus Med Rev* 1999;13:177–86.
- 19 Looney MR, Gropper MA, Matthay MA. Transfusion-related acute lung injury: a review. *Chest* 2004;126:249–58.
- 20 Toy P, Gajic O. Transfusion-related acute lung injury. *Anesth Analg* 2004;99:1623–4.