Chapter 47
Acute Dyspnea After Platelet Transfusion

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A 16-year-old black boy developed acute dyspnea, rigors and vomiting 20 min after receiving platelet transfusion. His vital signs showed mild fever (T: 37.5 °C), tachycardia (97–120 bpm), tachypnea (RR: 16–28), hypoxia (O_2 saturation: 82% at room air) and a mild drop in blood pressure (138/70–116/60 mmHg). The patient had no prior history of transfusion and was not premedicated prior to transfusion. He was initially treated with demerol and diphenhydramine with resolution of rigors but worsening of hypoxia.

His recent medical history was significant for acute mononucleosis diagnosed 1 week ago, complicated by idiopathic thrombocytopenia purpura (platelet count 2000/μL) requiring hospital admission for high dose parenteral steroid pulse therapy. On the day of admission, he was transfused with platelets following an episode of blood-tinged emesis. His physical examination showed bilateral cervical lymphadenopathy, bloody nasal and oral mucosa including several bleeding ulcers in the oral and pharyngeal cavities, scattered bruises, and labored breathing with fine bibasilar crackles.

Blood bank evaluation confirmed the patients' blood type (group O, Rh+): there were no clerical errors. Transfused platelets were group O. A direct antiglobulin test (DAT) was negative and serum haptoglobin was within normal range. Urinalysis was positive for blood with 3–5 RBC/hpf. A serum total IgA and brain-natriuretic protein levels were normal. Pre- and post-transfusion CBC showed no change in hemoglobin (14.6 g/dL), or platelet count, but a mild drop in WBC (15,200–10,000/μL). An ABG showed pH: 7.36, PaO_2: 97 mm Hg (100% FiO_2), $PaCO_2$: 43 mm Hg, lactate: 0.9 mmol/L (reference range: 0.5–2 mmol/L). A post-transfusion chest X-ray showed bilateral patchy and nodular opacities, more confluent and widespread in the left lung (Fig. 47.1a). A repeat chest X-ray 3 days later is shown in Fig. 47.1b.

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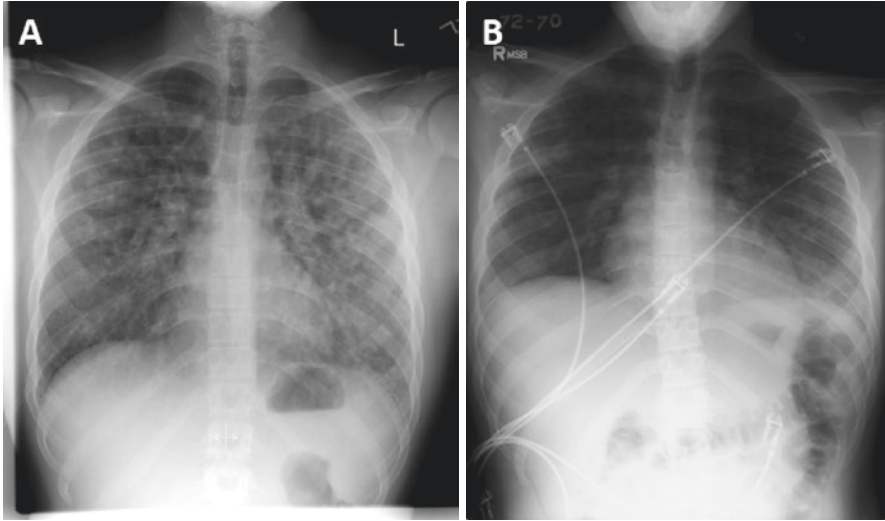e-mail: lcooling@med.umich.edu

Fig. 47.1 (**a**) Chest x-ray at the time of transfusion reaction, (**b**) and 72 h after transfusion

Q1. What is the most probable diagnosis?

A. Transfusion associated volume overload
B. Transfusion-associated lung injury
C. Septic transfusion reaction
D. Acute hemolytic transfusion reaction
E. Allergic reaction
F. Diffuse alveolar hemorrhage (DAH)

*Answer: The correct answer is **B***.

Although all of the choices listed must be considered in the differential diagnosis for this patient, the presentation, vital signs and immediate post-transfusion laboratories are most consistent with transfusion-associated lung injury (TRALI) [1]. TRALI is defined by the onset of acute, non-cardiogenic pulmonary edema within 6 h of transfusion and the *absence* of pre-existing acute lung injury [2]. Usually, TRALI occurs during or within 1–2 h of transfusion and is typically accompanied by fever, chills/rigors, and decreases in blood pressure or frank hypotension. In some cases, there may be nausea and vomiting. Diagnostic findings are hypoxia (O_2 saturation < 90% in room air), a PaO_2/FiO_2 ratio < 300 mmHg and new bilateral pulmonary infiltrates. A transient post-transfusion decrease in WBC can also be observed in many patients.

Presence of fever, decreased blood pressure and low BNP are against transfusion associated circulatory overload (TACO). Likewise, fever, lack of response to IV antihistamines and normal IgA exclude an anaphylactoid reaction due to IgA deficiency or other allergens. An acute hemolytic transfusion is excluded since: (1) transfused platelets were the same ABO type (group O) as the patient, (2) normal

haptoglobin levels, (3) absence of hemoglobinuria (as opposed to hematuria with intact RBC) and (4) stable hemoglobin levels [2]. The latter also argues against significant pulmonary hemorrhage. A septic transfusion reaction must always be considered with platelet transfusions since platelets are stored at room temperature. Septic reactions, however, typically present with fever and chills, accompanied by elevated WBC with left shift.

Q2. All of the following can precipitate this pulmonary reaction in TRALI, except:

A. Anti-HLA class 1 antibodies
B. Anti-HLA class 2 antibodies
C. Anti-granulocyte antibodies
D. Anti-IgA antibodies
E. Bioactive phospholipids

*Answer: The correct answer is **D**.*

The pathophysiology of TRALI requires an initial priming step, with increased neutrophil adhesion, rigidity and sequestration in the pulmonary microvascular [3]. This priming step is highly dependent on underlying host factors and involves endothelial activation. Blood transfusion elicits a second "hit" with frank neutrophil activation, endothelial damage and interstitial and intra-alveolar edema. Agents in blood that can induce neutrophil and endothelial activation include anti-granulocyte and HLA antibodies [3]. Anti-HLA class 1 antibodies can recognize granulocytes and endothelial cells, leading to cell activation and endothelial damage. Anti-HLA class II antibodies can bind and activate recipient monocytes that yields to the release of proinflammatory cytokines that induce endothelial and neutrophil activation. TRALI can also be precipitated by platelet-activating factor (PAF)-like, lyso-phospholipids generated by oxidation of platelet and red cell membrane phospholipids during storage [4]. These lyso-phospholipids can bind the PAF receptor on neutrophils and activate them. The activation and pulmonary sequestration of neutrophils can lead to a transient (<6 h) decrease in WBC, as was observed in this patient.

Q3. All of additional studies are useful in further evaluation of this patient, except:

A. HLA typing of the platelet donor
B. HLA typing of the patient
C. HLA and granulocyte antibody screen of the platelet donor
D. Crossmatch of patient granulocytes and donor plasma

*Answer: The correct answer is **A**.*

HLA typing of the donor is not performed, since the primary concern is donor derived, anti-WBC antibodies that are capable of recognizing the patient. Upon notification of a possible TRALI, the blood center will immediately quarantine any products from the donor that are still in inventory and initiate an investigation of the

donor, including screening donor plasma for anti-HLA and anti-granulocyte antibodies [5]. If possible, an HLA type of the patient and a crossmatch between patient granulocytes and donor serum may be requested. As part of TRALI risk-reduction strategies, all potential platelet donors with a history of pregnancy or transfusion are now prospectively screened for HLA antibodies. Several countries have also instituted "all male" plasma policies, to further eliminate the risk of TRALI from female donors [4]. As a consequence, the risk for TRALI has decreased from 1:5000 transfusions to 1.8–2 per million RBC and plasma units and 7.3 per million apheresis platelets transfusions.

In this older TRALI case, the donor was a multiparous woman (Gravid 2, Para 2) with high titer, broadly reactive HLA class I (PRA 91%) and class II (PRA 89%) antibodies. No granulocyte-specific antibodies were identified. The granulocyte crossmatch was positive by immunofluorescence and by the granulocyte agglutination assay. Of note, a retrospective review of all donations from this donor identified a prior unreported TRALI in an older female patient, who died within 1 h after being transfused with donor plasma. The donor was permanently deferred from donating any further blood products.

Q4. Which one of the following is indicated in management of this patient's condition?

A. Antihistamine
B. Furosemide
C. High dose steroids
D. Oxygen support

*Answer: The correct answer is **D**.*

Patients with TRALI require O_2 supplementation, with up to 72% requiring short-term mechanical ventilation. Symptoms usually resolve within 48–96 h, though pulmonary infiltrates may persist for a week. Surprisingly, high dose steroids have no benefit in TRALI. Because TRALI is a capillary leak syndrome, furosemide or other diuretics should be avoided since they could exacerbate hypotension, which can be unresponsive to fluid resuscitation. Antihistamines are ineffective for TRALI.

Practical Points
- TRALI is defined by the onset of acute, non-cardiogenic pulmonary edema within 6 h, usually the first 1–2 h, of transfusion and the *absence* of pre-existing acute lung injury
- Diagnostic findings are hypoxia (O_2 saturation < 90% in room air), a PaO_2/FiO_2 ratio < 300 mmHg and new bilateral pulmonary infiltrates. A transient post-transfusion decrease in WBC can also be observed in many patients
- With O_2 supplementation, up to 72% of cases of TRALI resolve within 48–96 h
- High dose steroids have no benefit in TRALI

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