# A 30-Year-Old Man With Sickle-Cell Disease and Severe Dyspnea From Transfusion-Related Acute Lung Injury

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## Introduction

Transfusion-related acute lung injury (TRALI) is a clinical syndrome of respiratory distress that develops within 6 hours of transfusion of plasma-containing blood components, with an estimated incidence of 1:5,000 transfusions and a mortality rate of 5–10%. Although rare, TRALI represents the most common cause of transfusion-related death worldwide.[1–3]

## Case Summary

A 30-year-old man with a history of sickle-cell disease (SCD) was referred to our emergency department for progressive asthenia and chest pain of 5 days' duration. On admission he was afebrile, with blood pressure of 125/80 mm/Hg, and percutaneous oxygen saturation of 96%. A supine frontal chest radiograph revealed no abnormality (Fig. 1A). The laboratory tests demonstrated a blood hemoglobin concentration of 7.5 g/dL. The patient received a blood transfusion. After 2 hours he complained of acute respiratory distress with severe dyspnea and cyanosis, and $O_2$ saturation dropped to 75%, despite the use of an oxygen non-rebreather face mask. He became febrile (body temperature, 38.2°C), tachypneic, and tachycardic (pulse 161 beats/min), with reduced blood pressure (105/60 mm/Hg), $P_{aO_2}$ of 65 mm/Hg ($P_{aO_2}/F_{IO_2} < 300$ mm Hg), and no signs of circulatory overload. The B-type natriuretic peptide was normal (80 pg/mL). The laboratory tests revealed a white-blood-cell count of 6,500 cells/$\mu$L, which was slightly decreased from the 7,200 cells/$\mu$L value detected on admission.

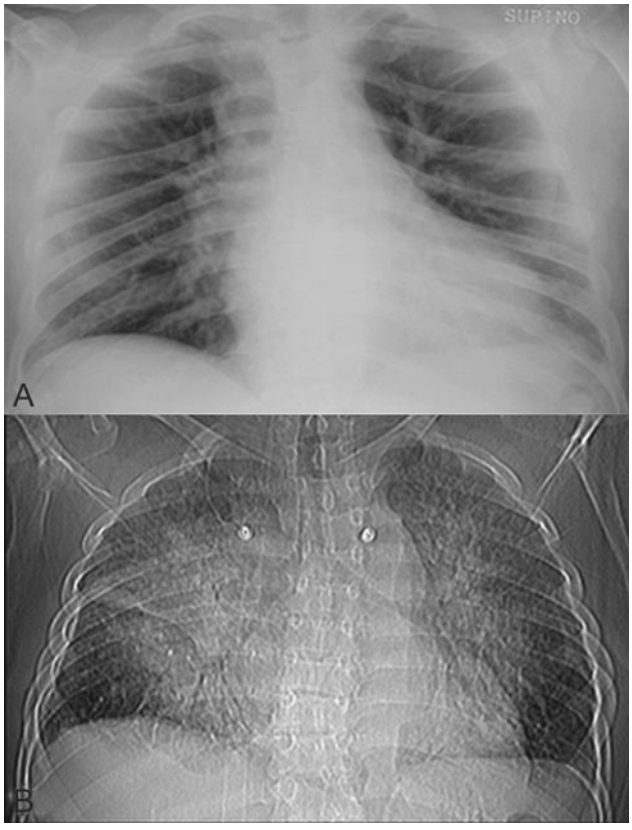


Fig. 1. Supine frontal chest radiograph on admission (A), and scout view obtained 4 hours later (B).

The patient underwent computed tomography. The scout view showed new bilateral diffuse, fluffy infiltrates consistent with pulmonary edema ("bat's wing pattern"), with no enlarged cardiac silhouette (see Fig. 1B). Multi-detector spiral contrast-enhanced computed tomography demonstrated marked symmetry of diffuse air-space consolidations with neither ground glass opacification nor gravitational anteroposterior gradient. The cortical lung was remarkably free of interstitial edema, and Kerley lines were absent. No signs of left atrial hypertension, pulmonary embolism, or pleural or pericardial effusions were seen (Fig. 2).

The patient was admitted to the ICU. He was placed on mechanical ventilation, but oxygen saturation remained

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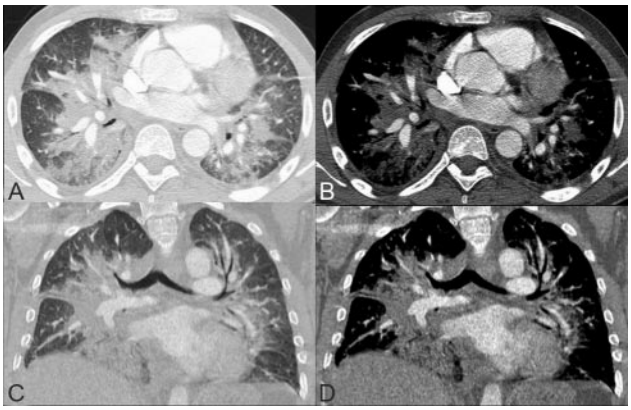


Fig. 2. Computed-tomography: axial (A and B) and coronal (C and D) reconstructions at lung (A and C) and mediastinum (B and D) window settings.

< 80%. He developed a severe hypotension unresponsive to fluids. Treatment with glucocorticoids and pressors was ineffective. Despite the intense respiratory and cardiovascular support, the patient's condition progressively worsened, and he died 1 hour later. Investigation by the blood center revealed a female donor with a history of 2 pregnancies and no transfusions. Investigation for alloreactive antibodies revealed both human leukocyte antigen (HLA) class I and class II antigens corresponding to the recipient's phenotype, implicating the donor in this TRALI case.

## Discussion

In the present case a diagnosis of TRALI was highly suspected ("possible TRALI"),[1] and subsequently supported by autopsy and histologic results that revealed lung edema, leukocyte aggregation, hyaline membrane, and intra-alveolar bleeding.[2] TRALI is a clinical syndrome of acute respiratory distress that develops within 6 hours of transfusion of plasma-containing blood components, with an estimated incidence of 1:5,000 transfusions and a mortality rate of 5–10%.[3] Most commonly it is caused by donor HLA antibodies that react with recipient antigens, as proved in our case by laboratory findings of donor and patient.[4] Although rare, TRALI represents the most common cause of transfusion-related death worldwide.[3] In the absence of a specific laboratory test, diagnosis of TRALI is based on clinical assessment and radiologic findings in patients with no preexisting ALI risk factors before transfusion.[1,5]

Diagnostic criteria include the development of dyspnea, cough, hypoxemia, hypotension, cyanosis, fever, and noncardiogenic pulmonary edema of acute onset during or within 6 hours of transfusion, with the demonstration of bilateral diffuse infiltrates on chest x-ray or computed tomography.[1,6] It is under-recognized and generally confused with other primary adverse reactions to transfusion, as transfusion-associated circulatory overload (TACO) and transfusion-associated dyspnea (usually presented as mild respiratory distress), or with other conditions such as various non-pulmonary insults leading to ARDS, and congestive heart failure.[5]

In our case, the patient experienced respiratory symptoms of acute onset within 2 hours of receiving a blood transfusion, and TACO was excluded because of his clinical presentation (with no increased blood pressure or engorgement of neck veins) and radiologic findings that demonstrated no signs of increased hydrostatic pressure edema (ie, enlarged cardiac silhouette or Kerley B lines). Moreover, the normal level of B-type natriuretic peptide was useful in establishing the condition of non-cardiogenic pulmonary edema from TACO or other conditions of congestive heart failure in such a patient with acute respiratory failure.[3,7]

In our case a preexisting alternative risk factor for ALI was present, as he had SCD. Hence, a diagnosis of "possible TRALI" was initially worded.[1] SCD is an inherited disease that causes chronic hemolytic anemia. The most common cause of hospital presentation is due to hemolytic anemia and acute painful crisis that results from vaso-occlusive events by sickled cells.[8] Acute chest syndrome (ACS) is an ALI characterized by the presence of new pulmonary infiltrates in combination with respiratory symptoms in patients with SCD.[8] ACS is often preceded by a vaso-occlusive crisis and triggered by different factors, including hypoventilation, pulmonary infectious disease, and vascular occlusions. These occlusions can be secondary to fat embolism, thrombosis, or sickling, leading to acute pulmonary hypertension.[8,9] The adults are often afebrile and complain of shortness of breath, chills, and severe pain, while severe hypoxia is unusual (18% of cases).[9] On radiologic imaging the pulmonary infiltrates are scattered and almost always involve lower lobes, with evidence of filling defects on pulmonary vessels and pulmonary hypertension.[9] These aspects are not consistent with the radiologic findings of the present case. Moreover, the autopsy did not demonstrate pulmonary thrombosis and fat embolism, the most common identifiable cause of ACS.[10,11]

The correction of anemia is a potential indication for transfusion of SCD patients presenting with severe asthenia.[8] Unfortunately, in the present case the subsequent course illustrates the dangers of transfusion. Hence, the clinicians should carefully balance the benefits and risks of transfusion, because patients with SCD who are transfused for management of their disease are at risk of developing TRALI. Blood products should be transfused to patients based on strict strategies, in order to reduce transfusion-related complications, including TRALI. Moreover, the differentiation between ACS and TRALI in SCD patients complaining of acute respiratory distress is impor-

tant, since the treatment is different. Indeed in ACS, erythrocyte transfusion or exchange transfusion may be considered to improve oxygenation.[9,11] In contrast, in the suspicion of TRALI, transfusion must be immediately stopped.[3,4] On admission we excluded a diagnosis of ALI or ARDS related to ACS because of the clinical presentation and the normal appearance of the chest radiograph. Although the occurrence of acute respiratory distress and bilateral infiltrates may be attributed to ACS, in our case TRALI was highly suspected because the onset of acute respiratory distress, associated with fever and hypotension, was temporally related to the transfusion of a blood product. TRALI is clinically indistinguishable from ARDS, which is a type of rapidly progressive and severe respiratory failure that may follow a number of direct and indirect insults to the lung. The differential diagnosis between TRALI and ARDS secondary to other causes, such as the hemolytic crisis in SCD, is essentially a clinical one.[3,4] A low $P_{aO_2}/F_{IO_2}$ ($<$ 300 mm/Hg for ALI, $<$ 200 mm/Hg for ARDS) is helpful.[1] In addition, in patients with preexisting ALI or ARDS, Higgins et al[12] suggested that the diagnosis of TRALI should be considered in the presence of a clinically important fall in $P_{aO_2}/F_{IO_2}$ ($\geq$ 20%), combined with a deterioration in the chest radiograph, during the transfusion or within 6 hours of transfusion of any plasma containing blood product. Later, investigations for leukocyte antibodies may support the diagnosis of TRALI.[1]

The management of TRALI is supportive. Supplemental oxygen is the first line of therapy. Intubation with mechanical ventilation may be necessary if the condition is severe. Intravenous fluids and pressors may be used in the setting of hypotension. Glucocorticoids are often administered empirically, although their value is not supported by data. Diuretics do not play a role in the treatment of non-cardiogenic pulmonary edema.[1–4]

Most patients with TRALI recover within 48–96 hours (80% of cases), but hypoxemia and radiological evidence of pulmonary infiltration can persist for 7 days in 20% of patients. Approximately 70% of patients require mechanical ventilation. The pulmonary lesion in TRALI patients is usually transient, and no permanent sequelae should be expected. The in-hospital mortality is estimated at 5–10%.[3,4]

In conclusion, early diagnosis of TRALI with exclusion of TACO and other conditions of ALI, along with proper treatment, improves survival and usually results in full recovery.[3,5]

### Teaching Points

- TRALI is a clinical syndrome of respiratory distress that develops within 6 hours of transfusion of plasma-containing blood components.
- This condition is usually typified by dyspnea, cough, hypoxemia, hypotension, cyanosis, fever, and non-cardiogenic pulmonary edema of acute onset. It is underrecognized and generally confused with other primary adverse reactions to transfusion such as TACO and transfusion-associated dyspnea, or with other entities such as conditions that can lead to ARDS, and congestive heart failure.
- Diagnosis is based on clinical assessment and radiologic findings in patients with no preexisting ALI risk factors before transfusion.
- Early diagnosis of TRALI with exclusion of TACO, along with proper treatment, improves survival and usually results in full recovery.

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