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Fatal transfusion-related acute lung injury type II following red blood cell transfusion in a cancer patient with suspected endocarditis: a case report

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Abstract

Transfusion-related acute lung injury (TRALI) is a potentially fatal complication of blood transfusion. The 2019 classification distinguishes TRALI type I [no acute respiratory distress syndrome (ARDS) risk factors] from type II (pre-existing or concurrent ARDS risk factors). We describe a case of TRALI type II after red blood cell (RBC) transfusion in a patient with cancer, sepsis, and suspected endocarditis. A 64-year-old woman with metastatic breast cancer on doxorubicin was hospitalized for fever and acute kidney injury. Echocardiography revealed a mobile mass on the posterior mitral leaflet with severe mitral regurgitation, and she was treated with ceftaroline and daptomycin. On hospital day 20, she received an RBC transfusion for anemia (hemoglobin 6.2 g/dL). Five hours later, she developed sudden hypoxemic respiratory failure with new bilateral infiltrates consistent with pulmonary edema, without fluid overload or cardiac decompensation. Despite non-invasive ventilation, she deteriorated and died. TRALI type II was considered the most likely diagnosis, underscoring the need for vigilance.

Key words: transfusion-related acute lung injury, anemia, pulmonary edema, case report.

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Introduction

The transfusion of blood components represents a widely utilized and essential therapeutic intervention in clinical practice. However, it can be associated with potentially life-threatening adverse events: among these, transfusion-related acute lung injury (TRALI) is a severe and potentially fatal complication, remaining one of the leading causes of transfusion-related mortality.[1]

TRALI typically presents with an acute onset (within 6 hours following transfusion) and is characterized by non-cardiogenic pulmonary edema with hypoxemia (arterial oxygen partial pressure to inspired oxygen fraction ratio ≤300 or peripheral oxygen saturation <90% on room air), bilateral pulmonary infiltrates on imaging, and the absence of any evidence of hydrostatic pulmonary edema.

Importantly, TRALI is a clinical diagnosis. According to the 2019 revised Delphi consensus, TRALI is classified into two types: type I, occurring in patients without risk factors for acute respiratory distress syndrome (ARDS), and type II, occurring in those with concurrent risk factors for ARDS or mild pre-existing ARDS.[2]

Although most cases have been associated with plasma-rich components,[3] emerging literature confirms that red blood cell (RBC) transfusions can also trigger the syndrome, especially in predisposed individuals.[4]

Despite growing awareness, TRALI type II remains underreported, particularly in oncologic patients, highlighting the need for detailed case documentation. This case exemplifies TRALI type II in a high-risk, transfused patient with multiple predisposing factors, including active cancer, sepsis, and suspected endocarditis.

Case Report

A 64-year-old woman with a history of breast cancer on doxorubicin therapy, hypertension, chronic kidney disease, and chronic obstructive pulmonary disease presented to the Emergency Department with fever, oliguria, and hypotension. Laboratory tests revealed acute-on-chronic renal failure and systemic inflammation. She was admitted to the general medicine ward, and an initial chest X-ray (Figure 1) was performed, showing accentuation of reticular-micronodular markings and basal striae on the right side, with no consolidations or effusions. Laboratory findings on admission are summarized in Table 1. During hospitalization, a transthoracic echocardiogram revealed a mobile, floating mass adherent to the atrial side of the posterior mitral leaflet, with severe mitral regurgitation, suggestive of possible infective endocarditis. Despite this, three serial blood cultures remained negative. Empiric antibiotic therapy with ceftaro-

line 600 mg BID and daptomycin 350 mg/day was initiated. On hospital day 20, the patient developed symptomatic anemia (hemoglobin 6.2 g/dL) and received one unit of leukoreduced RBCs (B positive, CCDee, kk phenotype). Approximately 5 hours post-transfusion, she developed acute dyspnea and hypotension. High-flow nasal oxygen therapy was started (inspired oxygen fraction 70%, 50 L/min), along with intravenous fluid and corticosteroids. Diuretic therapy proved to be ineffective. A repeat chest X-ray (Figure 2) showed new bilateral, confluent alveolar infiltrates, most prominent in the hilar and perihilar regions, with interstitial-alveolar involvement and basal opacities, consistent with non-cardiogenic pulmonary edema. There was no cardiomegaly, and pleural effusions were minimal. Despite escalation to non-invasive ventilation, the patient's respiratory condition worsened, and the patient succumbed to respiratory failure within 4 days.

Discussion

This case fulfills the 2019 revised Delphi criteria for TRALI type II,[2] including: i) acute onset of hypoxemia within 6 hours of transfusion; ii) new bilateral infiltrates consistent with non-cardiogenic pulmonary edema; iii) presence of concomitant risk factors (malignancy, sepsis, possible endocarditis); iv) no evidence of fluid overload or cardiac dysfunction.

In the differential diagnosis of acute respiratory distress following transfusion, distinguishing between TRALI and transfusion-associated circulatory overload (TACO) is critical, as the two entities differ significantly in both pathogenesis and management.[5] In our case, several clinical and radiographic features strongly favored TRALI over TACO. Although both conditions may present with bilateral pulmonary infiltrates and respiratory compromise within 6

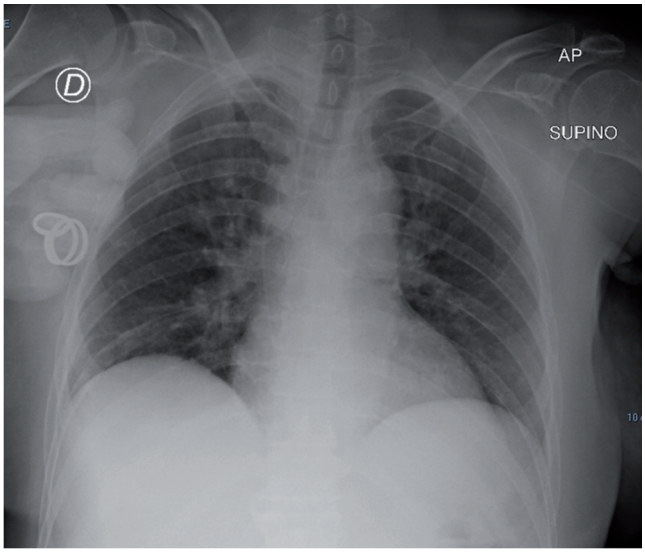

Figure 1. Chest X-ray day 1: routine chest X-ray at admission.

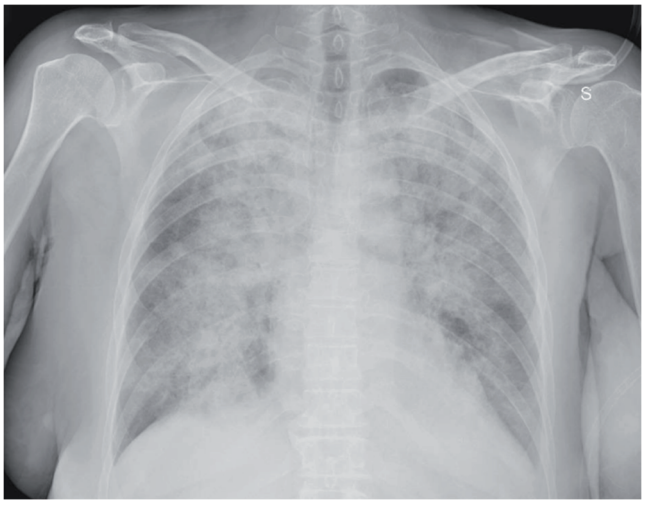

Figure 2. Chest X-ray day 20: emergency chest X-ray after pulmonary edema, confirming transfusion-related acute lung injury diagnosis.

Table 1. Initial blood test results.

Parameter	Value	Reference range
Hemoglobin	10.4 g/dL	12-16 g/dL
White blood cells	12.8×10⁹/L	4-10×10⁹/L
Neutrophils	11.75×10⁹/L	2-7×10⁹/L
Lymphocytes	0.39×10⁹/L	1-4×10⁹/L
Platelets	120×10⁹/L	150-400×10⁹/L
Creatinine	4.53 mg/dL	0.5-1.2 mg/dL
Albumin	2.4 g/dL	3.5-5.0 g/dL
C-reactive protein	38.2 mg/L	<5 mg/L
Procalcitonin	8.15 ng/mL	<0.5 ng/mL
Ferritin	2159 ng/mL	30-400 ng/mL
INR	1.24	0.9-1.2

INR, international normalized ratio.

hours of transfusion, our patient lacked key signs of circulatory overload typically seen in TACO, such as new-onset hypertension, jugular venous distension, peripheral edema, or an audible third heart sound (S3).[6] Moreover, chest radiography did not reveal cardiomegaly, which is often present in TACO due to increased cardiac preload. Diuretic therapy, a mainstay of treatment for TACO, did not yield clinical improvement, suggesting a non-hydrostatic mechanism of pulmonary edema.[7]

Although brain natriuretic peptide levels were not available in this case,[8] the overall clinical context (including the abrupt onset of hypoxemia, the absence of volume overload signs, the lack of cardiogenic findings on imaging, and the poor response to diuresis) supports a diagnosis of TRALI over TACO (Table 2). However, the ultrasound of the inferior vena cava showed no signs of congestion.

Mechanistic insight

The most widely accepted model explaining the pathogenesis of TRALI is the two-hit hypothesis.[9]

The first hit involves recipient-related factors (such as systemic inflammation, infection, or malignancy), which lead to endothelial activation and neutrophil priming.[10,11]

The second hit is mediated by bioactive substances present in transfused stored blood components, which activate primed neutrophils and other cells, including endothelial cells, monocytes, macrophages, and platelets. This process results in the release of pathogenic mediators, endothelial damage, and coagulopathy, culminating in pulmonary fluid infiltration. The second hit can be classified into antibody-dependent and -independent, based on the presence of differential pathogenic mediators in the transfused blood products. These include donor-derived anti-human leukocyte antigen or anti-human neutrophil antigen antibodies, which may bind cognate antigens on recipient neutrophils, monocytes, or endothelial cells, triggering degranulation and the release of cytotoxic mediators such as proteases, reactive oxygen species, and inflammatory cytokines.[12,13] Alternatively, non-antibody biologic response modifiers such as bioactive lipids and microparticles that accumulate during blood storage can also directly activate primed neutrophils, representing a non-immune mechanism of TRALI.[14] Evidence from *in vitro* and animal studies has identified several potential mediators, including lysophosphatidylcholines (originating from leukocytes and platelets), neutral lipids (resulting from erythrocyte membrane degradation), ceramide, soluble CD40 ligand (which accumulates during platelet storage), and microparticles derived from both platelets and RBC.[15,16]

Although the two-hit hypothesis outlines the primary framework, the pathogenesis of TRALI can be further described in three overlapping phases: i) priming of endothelial cells and neutrophils; ii) immune activation by antibody or non-antibody mediators; iii) endothelial injury and coagulopathy leading to lung damage.[17]

However, emerging perspectives suggest that the two-hit model may oversimplify the clinical reality of TRALI. A more nuanced threshold model has been proposed, in which the development of TRALI depends not merely on the presence of two discrete "hits", but rather on the cumulative inflammatory burden surpassing an individual's physiological threshold for pulmonary immune tolerance.[18]

In this view, TRALI can occur when host susceptibility (due to comorbidities, systemic inflammation, or underlying disease) and transfusion-derived stimuli (either immune or non-immune) collectively exceed a critical threshold, even in the absence of identifiable antibodies or multiple exposures (Figure 3).

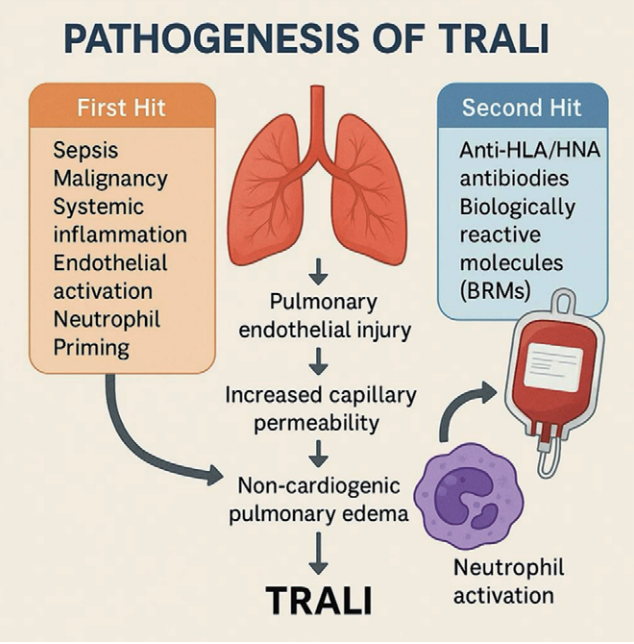

Figure 3. Schematic diagram illustrating the proposed pathogenesis of transfusion-related acute lung injury (TRALI). The first hit involves recipient-related factors (such as systemic inflammation, malignancy, or infection) leading to endothelial activation and neutrophil priming. The second hit includes transfusion-related mediators (such as anti-HLA/HNA antibodies or bioactive lipids), triggering immune activation. The threshold model suggests that when the cumulative inflammatory burden exceeds the host's tolerance, it results in pulmonary endothelial injury, capillary leak, and non-cardiogenic pulmonary edema characteristic of TRALI. BRMs, non-antibody biologic response modifiers; HLA, human leukocyte antigen; HNA, human neutrophil antigen.

Table 2. Differential diagnosis: transfusion-related acute lung injury vs. transfusion-associated circulatory overload.

Feature	TRALI (observed)	TACO (not observed)
Onset within 6 hours	✓ Present	✓ Present
Bilateral infiltrates	✓ Present	✓ Present
Signs of circulatory overload	✘ No hypertension, S3, or JVD	✓ Often present
Cardiomegaly on imaging	✘ Absent	✓ Often present
BNP elevation	Not assessed	✓ Typically elevated
Response to diuretics	✘ Not effective	✓ Diuresis improves symptoms

BNP, brain natriuretic peptide; S3, third heart sound; JVD, jugular vein distension.

In our patient, ongoing systemic inflammation from active malignancy, sepsis, and suspected endocarditis may have placed her near this threshold. The transfusion of a single leukoreduced RBC unit, though not typically associated with high immunogenicity, could have introduced sufficient biologic response modifiers to tip the balance toward acute lung injury. This model may better explain the clinical variability of TRALI and reinforces the need for heightened vigilance in high-risk patients, regardless of the specific transfused product.

Clinical and experimental evidence supports both the two-hit and threshold models, indicating that TRALI development depends on the complex interplay between transfusion-related factors and host susceptibility. Notably, most anti-human leukocyte antigen antibody-positive components do not cause TRALI, even when cognate antigens are present in the recipient, suggesting that additional recipient conditions are required to surpass the inflammatory threshold.[19]

Neutrophils remain the principal effector cells in this process.[14] In patients during the early phase of TRALI, transient neutropenia – possibly due to pulmonary sequestration – has been observed.[20] Moreover, TRALI is rarely reported in neutropenic individuals.[21]

Permanent donor deferral remains recommended for individuals implicated in confirmed TRALI cases to reduce recurrence risk.

Conclusions

The diagnosis of TRALI remains primarily clinical and radiological, and distinguishing it from other transfusion-related complications, particularly TACO, is essential for appropriate management. This case illustrates a fatal episode of TRALI type II in a patient with multiple risk factors, including active malignancy, systemic inflammation, and suspected infective endocarditis. Although TRALI is more frequently associated with plasma-rich components, this report highlights that even a single leukoreduced RBC unit may be sufficient to trigger the syndrome in susceptible hosts.

The absence of volume overload, the rapid onset of hypoxemia within 6 hours of transfusion, and the imaging findings consistent with non-cardiogenic pulmonary edema support the diagnosis. Moreover, the poor response to diuretic therapy and the lack of cardiomegaly further ruled out TACO.

Recent advances in pathophysiological understanding—including the threshold model—suggest that TRALI may result from a cumulative inflammatory burden exceeding individual immune tolerance, rather than requiring two discrete immunological events. This evolving view reinforces the need for high clinical suspicion, especially in patients with chronic inflammation or critical illness.

Clinicians must be aware that TRALI type II is underrecognized, particularly in oncologic and medically complex patients, and should remain vigilant even when transfusing leukoreduced components. Prompt identification and supportive care remain the mainstays of management, as specific targeted therapies are still lacking.

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Patient consent for publication: written informed consent for publication was obtained from the patient. The patient also provided specific written consent for the publication of anonymized clinical images.

Availability of data and materials: all data underlying the findings are fully available.