

Exploring Post-Transfusion Pulmonary Edema: Differentiating Transfusion-Associated Circulatory Overload (TACO) from Transfusion-Related Acute Lung Injury (TRALI)

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Oběhové přetížení (transfusion-associated circulatory overload, TACO) a poškození plic způsobené transfúzí (transfusion-related acute lung injury, TRALI) významnou měrou přispívají k morbiditě a mortalitě v souvislosti s transfúzí. Tato případová studie popisuje 28letou pacientku přepravenou k lékaři s dušností po transfúzi. Diagnostické vyšetření zahrnovalo fyzikální vyšetření, rentgenové vyšetření, základní laboratorní testy a echokardiografické vyšetření. Problematické bylo stanovení diagnózy, kdy bylo nutno – vzhledem k omezeným poznatkům v této oblasti, nedostatečně definovaným diagnostickým kritériím a absenci specifických léčebných intervencí – se rozhodnout mezi TACO, TRALI nebo kombinací obojího. Tyto problémy zdůrazňují potřebu přesnějšího rozpoznávání a vypracování strategií léčby těchto komplikací v souvislosti s transfúzí.

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ABSTRACT

Transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) represent significant contributors to transfusion-related morbidity and mortality. This case study involves a 28-year-old female patient presenting with shortness of breath following a transfusion. The diagnostic approach relied on physical examination, chest x-ray, basic laboratory tests, and echocardiography. The challenges included difficulty in establishing the diagnosis between TACO, TRALI, or a combination thereof due to limited awareness, poorly defined diagnostic criteria, and the lack of specific therapeutic interventions. These complexities underscore the need for enhanced recognition and management strategies for these transfusion-associated complications.

Keywords:

Lung edema

TACO

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Introduction

The pathogenesis of pulmonary transfusion reactions is increasingly understood, highlighting them as preventable medical complications. Transfusion-associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI) represent significant challenges in transfusion medicine, contributing substantially to both mortality and morbidity. These conditions commonly manifest as acute respiratory distress following blood transfusion typically within six hours, with reported prevalence rates up to 34%. These conditions are the leading causes of transfusi-

on-related death, and currently specific treatments are elusive.¹

Diagnosing TACO and TRALI also presents as considerable challenge due to inadequate awareness, poorly defined diagnostic criteria, and the absence of specific therapeutic protocols. A lack of consensus on diagnostic criteria has hindered clinical recognition and research investigation of pulmonary-related transfusion reactions. Accurate diagnosis only relies on clinical manifestation, additional examinations, and hemodynamic profile, often requiring multi-disciplinary approach from various area. Diagnostically, it is also challenging to distinguish TACO from TRALI

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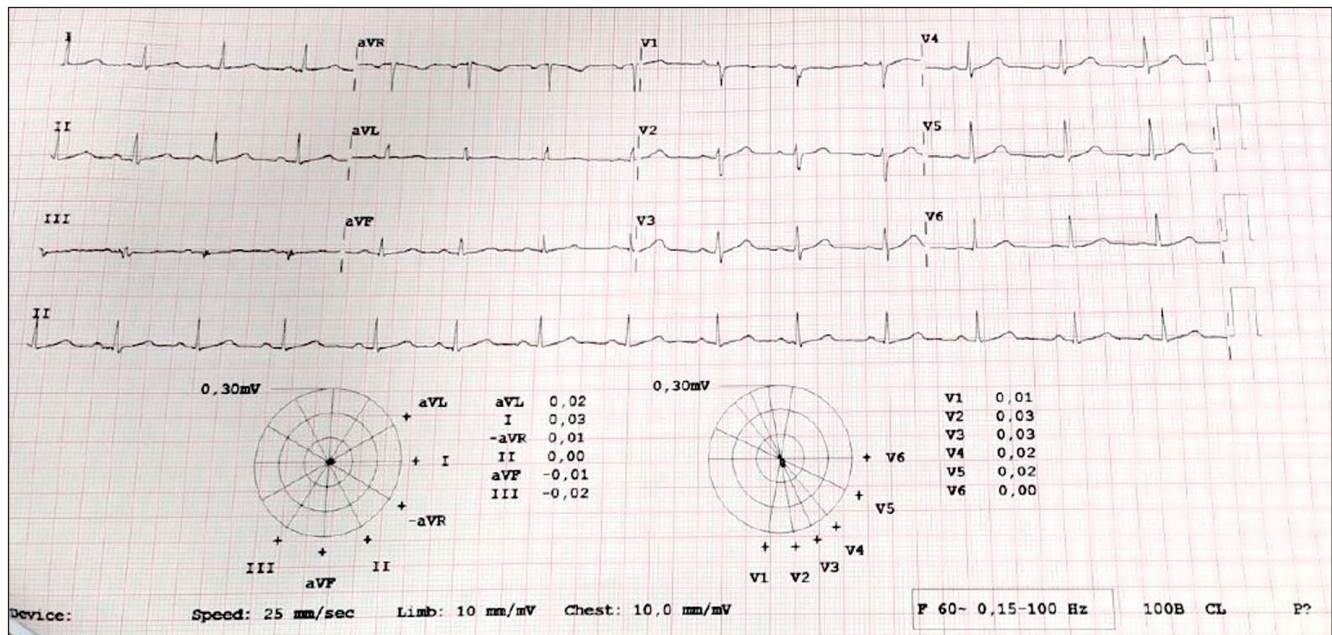


Fig. 1 – Electrocardiography revealed that sinus rhythm was found with a heart rate of 83 beats per minute.

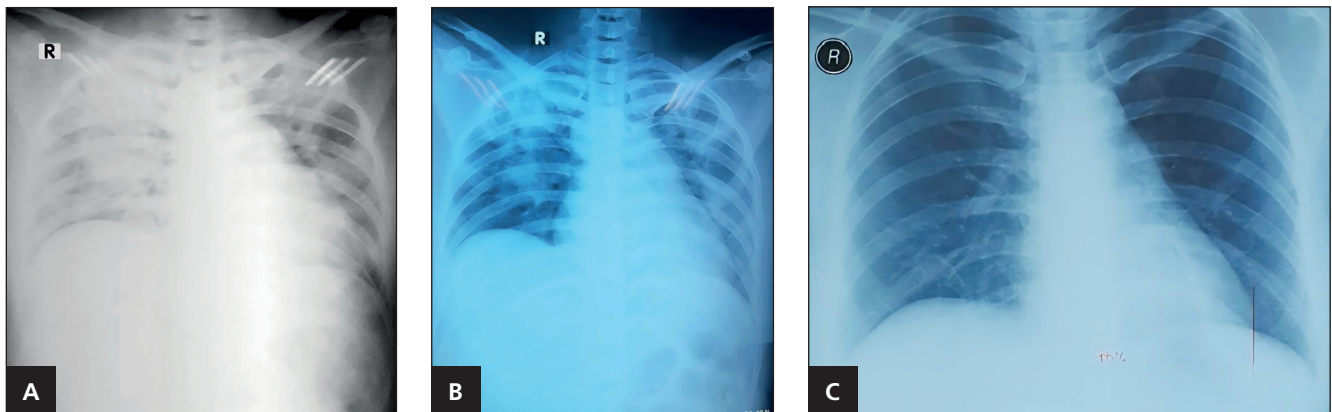


Fig. 2. – (A) Initial chest x-ray of patient at previous hospital, the heart appeared prominently and bilateral haziness was present. (B) Upon chest x-ray at the current hospital, the heart appeared prominently and inhomogeneous lung haziness at the apex and perihilar bilaterally. (C) Chest x-ray evaluation after 2 days after the admittance, the heart appeared normal in terms of shape and size, with cardiothoracic ratio of 48%. No abnormalities were observed in the lungs.

and other underlying causes of lung injury and/or fluid. In this case report, we aim to elucidate the definitions, etiology, and diagnostic approaches for differentiating TACO from TRALI. Additionally, we endeavour to equip readers with insights into management strategies and guidelines for appropriate patient referral, thereby fostering greater familiarity among medical professionals with these critical transfusion-related complications.

Case presentation

A 28-year-old woman was presented to the emergency room with shortness of breath and fever persisting for a day, occurring shortly after receiving two units of whole blood and one unit of packed red cells six hours prior. The blood transfusion was administered following a la-

parotomy procedure performed two days earlier. Her medical history did not indicate any hypertension, diabetes mellitus, coronary heart disease, stroke, kidney disease, allergies, or previous transfusions history. Treatment at a prior hospital involved a regimen of furosemide, dexamethasone, metronidazole, and ceftriaxone.

Upon arrival, the patient exhibited general weakness, with a respiratory rate of 24 breaths per minute and oxygen saturation of 99% on a non-rebreathing mask with 10 liters per minute flow rate. Initial management included administration of two doses of 20 mg furosemide and later a subsequent 20 mg of oral furosemide, alongside with monitored of fluid intake (618 cc/24 hours) and output (4500 cc/24 hours), with a deficit of 3822 cc/24 hours. Physical examination revealed signs of dyspnea, without elevated jugular venous pressure, normal cardiac physical examination, and bilateral pulmonary auscultation revealing bibasilar rales.

Electrocardiography examination indicated sinus rhythm with a heart rate of 83 beats per minute (Fig. 1). The chest x-ray was obtained from the previous hospital, showed prominent cardiac silhouette and bilateral opacities, while those obtained at the current hospital depicted prominent cardiac silhouette with heterogeneous lung opacities at the apex and perihilar regions (Fig. 2). Laboratory examination revealed abnormal hemoglobin levels (8.4 g/dL), leucocytosis (12,990/mm³), and a blood gas analysis indicated a P/F ratio of 228.57. Transthoracic echocardiography revealed left ventricular hypertrophy with preserved ejection fraction (72%), normal segmental analysis of the left ventricle, normal chamber dimensions, and mild pulmonary regurgitation. Hemodynamic parameters indicated an elevation in pulmonary capillary wedge pressure, mean pulmonary artery pressure, pulmonary vascular resistance, and estimated right atrial pressure, consistent with acute pulmonary edema.

Based on the patient's medical history, physical examination, and additional assessments, we diagnosed the patient with suspected non-cardiogenic pulmonary edema indicative of either TACO or TRALI, along with suspected pneumonia. Following recommendations from the pulmonologist, the patient received a single intravenous injection of 20 mg furosemide with antibiotics. Two days later, the patient reported no further symptoms of shortness of breath, chest pain, or palpitations. Vital signs and physical examination findings were within normal ranges. Improvement was noted in the suspected TACO or TRALI, prompting discontinuation of furosemide administration. Follow-up chest X-ray evaluation revealed a normal heart size and shape, with a cardiothoracic ratio of 48%. No abnormalities were observed in the lungs. The patient was discharged the following day without any complaints, with antibiotics prescribed for continued treatment.

Discussion

TACO and TRALI are critical complications arising from blood transfusion, characterized by the onset of acute pulmonary edema within six hours post-transfusion, accompanied with bilateral lung infiltrates on chest x-ray and hypoxia indicated by arterial blood gas or pulse oximetry results of $\text{PaO}_2/\text{FiO}_2 < 300$ and $\text{SpO}_2 < 90\%$.¹ TACO, the most common pulmonary complication of transfusion, stands as an independent risk factor for morbidity and mortality within hospital settings. As per the National Healthcare Safety Network (NHSN) 2016 criteria, TACO is defined by the emergence or worsening of at least three of the following symptoms within six hours post-transfusion: acute respiratory distress (manifesting as dyspnea, orthopnea, and cough), positive fluid balance, elevated brain natriuretic peptide levels, radiographic evidence of pulmonary edema, signs of left heart failure, and increased central venous pressure.² Conversely, the Canadian Consensus Conference in Toronto (2004) proposed a more restricted definition for TRALI. This entails the presence of acute lung injury (ALI), characterized by a sudden onset of hypoxemia with a $\text{PaO}_2/\text{FiO}_2$ ratio ≤ 300 or $\text{SpO}_2 < 90\%$ in room air, alongside bilateral infiltrates on frontal chest radiography, without evidence of left

atrial hypertension (indicating circulatory overload). TRALI diagnosis further requires the absence of pre-existing ALI prior to, during, or within six hours post-transfusion, and no temporal association with alternative risk factors for ALI. Possible TRALI, on the other hand, encompasses the same criteria but is accompanied by other risks for ALI.³

Patients who experience TACO are predominantly elderly and have a history of cardiovascular disease such as congestive heart failure and/or coronary artery disease. Other risk factors include chronic kidney disease, history of plasma transfusion, and emergency surgery. Suboptimal fluid management, inappropriate infusion practices (such as rapid infusion rates), transfusion volume, and total intraoperative fluid also increase the incidence of TACO. Clinical examination of TACO often reveals an increase in blood pressure, tachycardia, rales or S3 findings, increased pulmonary hydrostatic pressure, decreased protein in edema fluid, and response to diuretics. TRALI can be differentiated from TACO and cardiogenic pulmonary edema by the lack of circulatory overload indicators, such as normal central venous pressure (CVP) and normal pulmonary capillary wedge pressure (PCWP). To distinguish between TRALI and TACO, it is crucial to determine if there is an increased hydrostatic pressure in the lung capillaries. It is because the primary cause of pulmonary edema in TRALI is due to increased capillary permeability, while in TACO the pulmonary edema is mainly due to elevated capillary hydrostatic pressure, which is a type of non-permeability edema. Historically, pulmonary capillary wedge pressure was assessed using a pulmonary artery catheter. However, the use of these catheters has declined because they did not improve outcomes in critically ill patients. Consequently, the use of PCWP criterion was eliminated for ruling out circulatory overload. Instead, it now recommends using laboratory tests, ultrasound, and clinical factors such as fluid balance to assess circulatory overload. Hence, a positive response to diuretics typically indicates TACO rather than TRALI. Acute kidney injury and liver failure are prevalent in both TRALI and possible TRALI. Additionally, chronic alcohol abuse, tobacco use, shock before transfusion, and a positive fluid balance are associated with TRALI and possible TRALI. TRALI is more likely to be associated with signs and symptoms of inflammation, including fever, hypotension, and an exudative pulmonary infiltrate. No laboratory test is specific for diagnosing TRALI, although a transient drop in peripheral neutrophil count may be observed.^{4,5} Details regarding the comparison between TRALI and TACO is summarized in Table 1.

B-type natriuretic peptide (BNP) may differentiate TRALI from TACO, as elevated BNP levels (> 100 pg/ml) suggest cardiogenic pulmonary edema or volume overload, whereas levels under 100 pg/ml are indicative of TRALI. Echocardiography provides valuable insights into the pathogenesis of pulmonary edema post-transfusion and offers information about cardiac structure and function that cannot be assessed clinically, aiding in the definitive diagnosis of pulmonary edema post-transfusion. Evidence of increased cardiac filling pressures or systolic and/or diastolic dysfunction suggests circulatory overload and a diagnosis of TACO, whereas the absence of echo-

Table 1 – Comparison between TRALI and TACO⁶⁻⁹

Evaluated parameter	TRALI	TACO
Characteristics		
Definition	Sudden onset of hypoxemia with bilateral lung infiltrates	Pulmonary edema and signs of volume overload
Etiology	Often due to plasma products with HLA alloantibodies	Commonly due to excessive volume or rapid transfusion rate, especially in pediatric patients
Pathophysiology	Activation of neutrophils leading to capillary leakage	Rapid transfusion of large volumes of blood
Risk factors	Plasma containing blood product, particularly donated from multiparous women	Older patients with comorbidities such as congestive heart failure, chronic kidney disease
Symptoms	New onset of dyspnea, hypoxemia, hypotension, and sometimes accompanied with fever	New onset of dyspnea with symptoms of fluid overload (hypertension, peripheral edema, elevated CVP)
Onset	Within 6 hours of transfusion	Within 12 hours of transfusion
Physical examination and laboratory findings		
Hypoxemia	PaO ₂ /FiO ₂ ≤ 300 or SpO ₂ < 90% on room air	Variable, but commonly present
Blood pressure	Hypotension may be present	Hypertension may be present
Increase of CVP	No	Yes
Signs of left heart failure	No	Yes
Fluid balance	Neutral	Positive
White blood cell count	Transient leukopenia can be present	Unchanged
Chest x-ray	Diffuse bilateral infiltrates	
NT-proBNP	< 250 pg/mL	> 1200 pg/mL
Left atrial hypertension	No	Yes
Pulmonary artery occlusion pressure	< 18 mmHg	> 18 mmHg
Ejection fraction	Normal	Usually decreased
Pulmonary edema	Non-cardiogenic	Cardiogenic
Edema fluid	Transudate	Exudate
Response to diuretics	No	Yes
Treatment modalities		
Immediate cessation of transfusion	Yes	Yes
Oxygen	Yes	Yes
Intubation	Yes, if necessary	Usually not necessary
Diuretic	Usually does not respond to diuretics	Yes
Preventive strategies	Donor screening	Cardiovascular screening and fluid management

cardiographic abnormalities is central to the diagnosis of TRALI.^{6,7} The National Blood Collection and Utilization Survey reported a TACO incidence of 1 : 14,000,⁸ while literature suggests a higher incidence of TACO related to plasma transfusion and in perioperative or critically ill patients (1% to 4% of transfused patients).⁹ For TRALI, the National Blood Collection and Utilization Survey reported an incidence of 1 : 64,000, with other active surveillance estimates ranging from < 0.1% to up to 5% to 8% in intensive care unit populations.^{8,9}

The pathophysiology of TACO is akin to acute cardiogenic pulmonary edema, where blood transfusions can rapidly increase pressure in the left atrium and pulmo-

nary capillaries, leading to the transudation of fluid into the pulmonary interstitial and alveolar spaces.⁹ On the other hand, TRALI can be mediated by antibodies or non-antibodies. In antibody-mediated TRALI, donor leukocyte antibodies present in the transfused blood plasma bind to recipient antigens, causing capillary leak and lung injury. Other studies hypothesize that exposure to cognate HLA class 2 antibody and volume of HNA antibody are associated with severe and fatal cases of TRALI. Additionally, neutrophil and pulmonary endothelial cell activation in the transfusion recipient is thought to cause TRALI. Increased levels of IL-6, IL-8, and C-reactive protein before transfusion are also associated with TRALI risk. Non-anti-

body-mediated TRALI is usually caused by the absence of detectable antibodies or exposure to biologically reactive molecules in the blood.⁹

The patient complained of shortness of breath six hours post-transfusion with 2 bags of whole blood and 1 bag of packed red cells, accompanied by rales on physical examination, bilateral lung infiltrates on chest x-ray, and hypoxia (indicated by a BGA with a P/F ratio < 300), along with echocardiography indicating overload. These findings were consistent with characteristics of TACO or TRALI. Additionally, the patient had a history of emergency surgery and leukopenia. These findings tend to direct us toward TACO. However, there was also an alternative risk factor for TRALI, such as pneumonia, and no signs of cardiac involvement. IL-6 and IL-8 are important mediators in influenza pneumonia, and recent studies have shown that IL-8 is associated with disease progression among hospitalized patients with influenza, leading to a diagnosis of TRALI.

In this case, there is evidence that points to both TACO and TRALI, suggesting a mixed presentation. However, further tests, such as pulmonary hydrostatic pressure, edema fluid protein examination, NT-proBNP, leukocyte antibodies, and post-transfusion cytokine measurements, were not performed due to financial constraints.^{10–13}

Fortunately, the initial treatment for both syndromes can be started with supportive care and immediate transfusion cessation when transfusion lung injury is suspected.^{14,15} Some literature suggests that treatment for TACO includes diuretics, oxygen, and intubation, with prevention strategies focusing on screening for cardiovascular disorders, such as echocardiography or measuring NT-proBNP. For TRALI, supportive therapies can be administered, although corticosteroids have shown inconsistent results in TRALI/ARDS treatment. Routine corticosteroid use in patients with TRALI is not recommended, although successful cases have been reported. Preventive strategies for TRALI, such as donor screening based on antibody screening, history of pregnancy or transfusion, and female donors, are needed.^{1,16,17} Based on our clinical judgment, we administered furosemide injection, steroid injection, and oxygen support to the patient. The patient showed a positive response to our treatment strategy, with improvements noted both clinically and radiologically. Improved diagnostic clarity and management would be achieved through a more detailed presentation of the diagnostic criteria and treatment procedures for TACO and TRALI.

Conclusion

Following our discussion on the fundamentals of TACO and TRALI, we now grasp more thoroughly that both conditions pose substantial risks associated with transfusion, necessitating a proficient diagnostic approach. A thorough clinical assessment entails examining factors such as a history of rapid transfusion, cumulative intraoperative fluid volume, patient's sign and symptoms, fluid balance, cardiac function, NT-proBNP levels, and leukocyte antibody testing. These parameters are crucial to distinguish between TACO and TRALI accurately.

Conflict of interest

No conflict of interest.

Funding

No funding.

Ethical statement

We declare that the case report has been conducted in accordance with applied ethical standards and guidelines; the Declaration of Helsinki.

Informed consent

Appropriate permissions including written informed consent was obtained.

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