Transfusion-related acute lung injury (TRALI) following intravenous immunoglobulin infusion in a patient with myasthenia gravis

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Abstract

Transfusion-related acute lung injury (TRALI) is a rare but potentially life-threatening complication of blood product administration and has been infrequently associated with intravenous immunoglobulin (IVIG) therapy. This case report describes an 82-year-old male with myasthenia gravis who developed acute respiratory distress approximately 30 minutes after initiating high-dose IVIG. His clinical presentation included severe hypoxemia, hypotension, fever, and bilateral pulmonary infiltrates on chest imaging. Bedside ultrasound showed a collapsible inferior vena cava and normal cardiac function, supporting a non-cardiogenic etiology. The patient had no recent transfusions, pulmonary disease, or other acute lung injury risk factors. Infectious, allergic, and cardiogenic causes were excluded, and the diagnosis of TRALI was established based on established clinical criteria. The IVIG infusion was immediately stopped, and the patient required mechanical ventilation. Plasmapheresis was initiated for the underlying myasthenic crisis, and the patient showed rapid clinical improvement, with successful extubation after the second session and discharge on immunosuppressive therapy. This case underscores TRALI as a rare but serious adverse event following IVIG administration. Timely recognition using clinical and imaging criteria, along with prompt supportive care, is essential. Greater awareness is needed to improve diagnosis and reporting of this underrecognized complication, particularly in neurologic patients receiving high-dose IVIG.

Keywords: TRALI, IVIG, myasthenia gravis

Introduction

Transfusion-related acute lung injury (TRALI) is a rare but potentially life-threatening complication of blood product administration, recognized as a leading cause of transfusion-related mortality. It is characterized by acute hypoxemia and non-cardiogenic pulmonary edema within 6 hours of transfusion, without evidence of left atrial hypertension or pre-existing acute lung injury (ALI).[1] The consensus redefinition by Vlaar et al. (2019) classifies TRALI as a clinical syndrome with bilateral pulmonary infiltrates, hypoxemia ($PaO_2/FiO_2 \leq 300$ mmHg or $SpO_2 < 90\%$ on room air), and no alternative ALI risk factors, explicitly including intravenous immunoglobulin (IVIG) as a potential trigger.[1] IVIG, a pooled human plasma derivative, is widely used for immune-mediated neurologic and hematologic disorders, including myasthenia gravis. While IVIG-related complications such as hypersensitivity reactions and volume overload are well-documented, TRALI is rare and likely underdiagnosed.[3,4] Muller et al. (2020) reported 17 cases of IVIG-related TRALI, highlighting its association with neurologic conditions like myasthenia gravis and its high mortality rate (24%).[2] We present a case of TRALI following IVIG infusion in a patient with myasthenia gravis, emphasizing the importance of clinical vigilance for this uncommon but serious complication.

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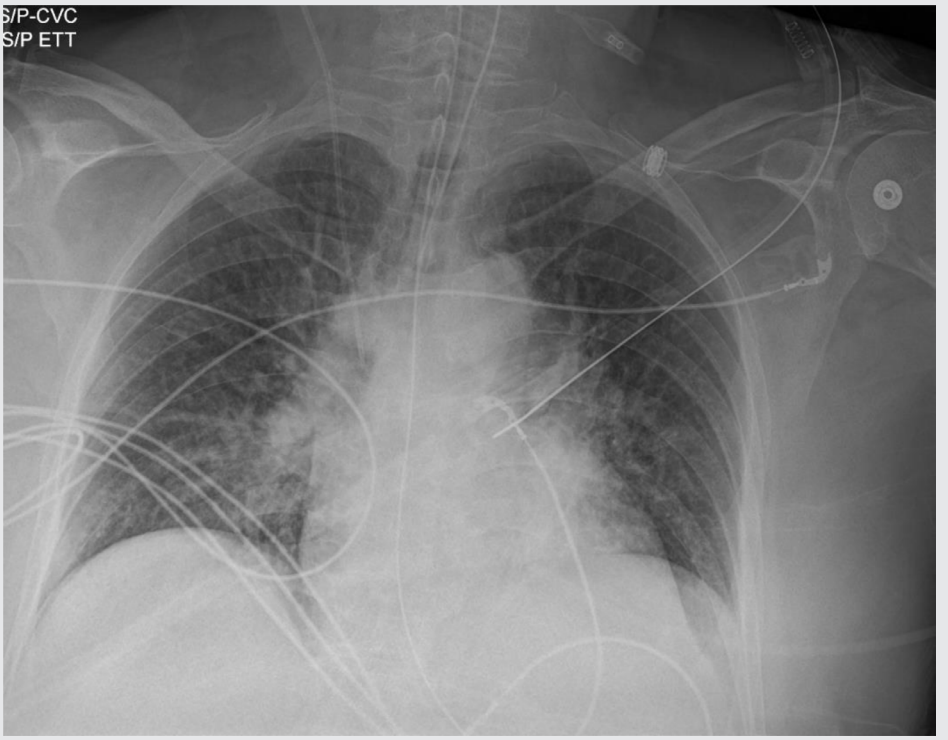

Figure 1. Bilateral interstitial prominence suggestive of pulmonary edema following 1 hr of IVIG infusion.

Case Report

An 82-year-old man with a history of ocular myasthenia gravis presented with a one-week history of worsening ptosis, diplopia, dysphagia, and progressive lower extremity weakness, suggestive of myasthenic exacerbation. These symptoms had been present for four months but acutely worsened. He had no history of recent transfusions, pulmonary disease, or other ALI risk factors (e.g., sepsis, aspiration). On admission, the patient was started on oral prednisone (10 mg daily), pyridostigmine (60 mg three times daily) and mycophenolate mofetil (500 mg twice daily. Per neurology recommendations, IVIG (1 g/kg/day, total 80 g for 80 kg body weight) was initiated, planned for administration over 4 hours. Approximately 30 minutes into the first IVIG infusion, the patient developed acute respiratory distress, high-grade fever (40.5°C), hypotension (BP 85/50 mmHg), and severe hypoxemia (SpO_2 82% on room air). He also exhibited agitation and hallucinations, as reported by family. The infusion was immediately discontinued. Chest X-ray revealed bilateral interstitial infiltrates consistent with non-cardiogenic pulmonary edema. (Figures 1 and 2) Clinical examination noted tachycardia (HR 110 bpm), respiratory distress, and no signs of jugular venous distension or S3 gallop, further supporting a non-cardiogenic etiology. Oxygen supplementation and emergent intubation were required due to worsening hypoxemia. Later, bedside ultrasound showed an inferior vena cava (IVC) diameter of 1.2 cm with >50% collapsibility, indicating no volume overload, and normal left ventricular function, ruling out left atrial hypertension.

The diagnosis of TRALI was based on the consensus criteria outlined by Vlaar et al. (2019)[1] acute onset within 30 minutes of IVIG infusion (within the 6-hour window), hypoxemia (SpO_2 < 90% on room air), bilateral infiltrates on chest X-ray, no evidence of left atrial hypertension (normal IVC diameter and cardiac function on ultrasound), no pre-existing ALI, and no alternative ALI risk factors (negative infectious workup and unremarkable brain MRI). Differential diagnoses, including transfusion-associated circulatory overload (TACO), anaphylaxis, and sepsis, were

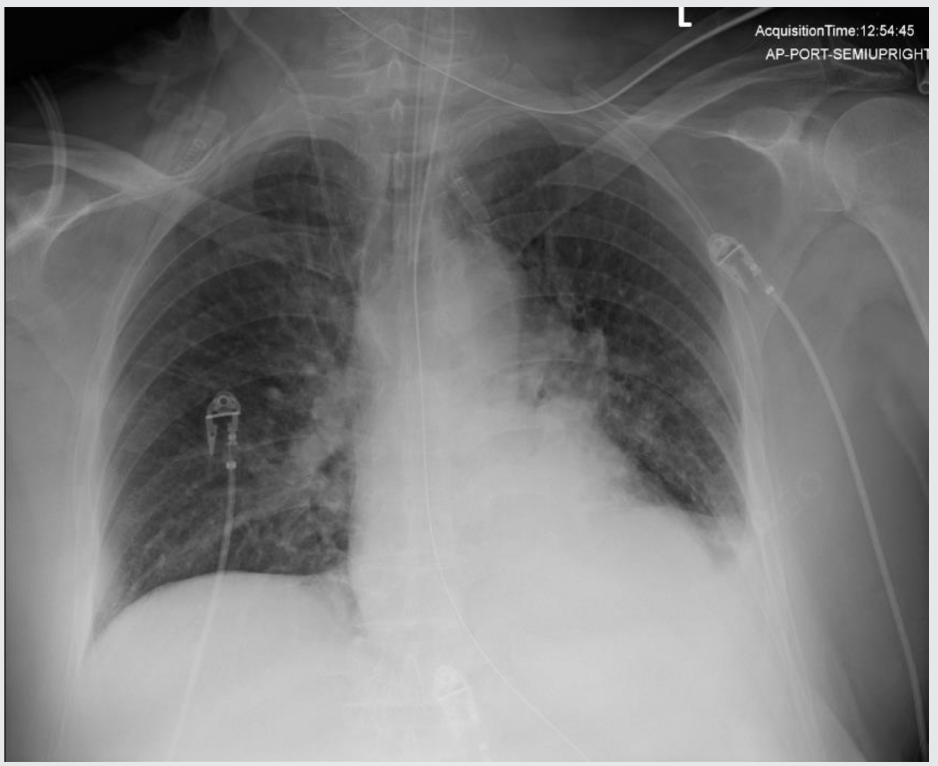

Figure 2. Bilateral interstitial prominence suggestive of pulmonary edema following 13 hrs of IVIG infusion.

excluded based on the absence of volume overload, lack of urticaria or angioedema, and negative cultures. Plasmapheresis was initiated for myasthenic crisis, with five plasma exchange sessions. After the second session, the patient was successfully extubated, with complete resolution of respiratory symptoms. He was discharged on mycophenolate mofetil 500 mg twice daily, prednisone 40 mg daily, and pyridostigmine 60 mg three times daily for ongoing management of myasthenia gravis.

Discussion

This case illustrates a rare but severe complication of IVIG therapy—TRALI—in a patient with myasthenia gravis. The diagnosis was supported by the consensus criteria from Vlaar et al., which emphasize acute hypoxemia, bilateral pulmonary infiltrates, and the absence of left atrial hypertension within 6 hours of transfusion, with IVIG explicitly included as a trigger.[1] The rapid onset of symptoms during IVIG infusion, combined with chest X-ray and bedside ultrasound findings, confirmed non-cardiogenic pulmonary edema, distinguishing TRALI from TACO.[1,2] TRALI likely results from a two-hit mechanism: patient factors (unclear in this case) prime pulmonary neutrophils (first hit), and donor-derived factors in IVIG, such as anti-HLA or anti-HNA antibodies, activate these neutrophils, causing endothelial damage and capillary leak (second hit).[1,2] Non-antibody mediators, such as bioactive lipids or microparticles, may also contribute.[1] The high IVIG dose (1 g/kg/day) may have increased the concentration of such mediators, heightening TRALI risk.[2]

Clinicians should suspect TRALI in any patient developing acute respiratory distress within 6 hours of IVIG infusion, especially with bilateral infiltrates on chest X-ray and no evidence of volume overload.[1] Bedside ultrasound, showing normal IVC diameter and cardiac function, is valuable for excluding left atrial hypertension.[1,2] The presence of fever, hypotension, and agitation aligns with findings from Muller et al. (2020), who noted fever (18%) and shock (33%) in IVIG-related TRALI cases.[2] The rarity of IVIG-related

TRALI (17 cases reported over three decades) may lead to underdiagnosis, as symptoms can mimic anaphylaxis, sepsis, or TACO.[2] The consensus redefinition simplifies diagnosis by eliminating the "possible TRALI" category and relying on clinical judgment to attribute causality.[1] In this case, chest X-ray, bedside ultrasound, and clinical examination were sufficient to meet diagnostic criteria, highlighting their utility in resource-limited settings.[1]

Immediate cessation of IVIG and supportive care, including oxygen and mechanical ventilation, were critical interventions, consistent with recommendations.[1,2] Although corticosteroids are generally not used for TRALI due to unproven efficacy,[2] they were administered in this case as a disease-modifying treatment for myasthenia gravis. Plasmapheresis, initiated for myasthenia gravis, may have incidentally removed circulating antibodies or mediators, though its direct role in TRALI resolution is unclear. It's worth noting that Muller et al. (2020) reported a 24% mortality rate in IVIG-related TRALI.[2] To help prevent TRALI, strategies include screening IVIG donors for anti-HLA/HNA antibodies or using male-only plasma. However, the pooled nature of IVIG products complicates the implementation of such measures.[1,2] Therefore, careful patient selection, slower infusion rates, and vigilant monitoring during high-dose IVIG administration are prudent, especially in patients with inflammatory conditions.[2]

The lack of antibody testing (e.g., anti-HLA/HNA) limits mechanistic insights, as such tests are not routinely available.[1,2] Future studies should explore the prevalence of antibodies in IVIG-related TRALI and non-antibody mechanisms.[1] Improved pharmacovigilance is needed to estimate incidence and risk factors,[2] and clinicians should report suspected cases to hemovigilance systems to inform safer IVIG manufacturing practices.[1,2] This case underscores the need for heightened awareness of IVIG-related TRALI, particularly in neurologic disorders requiring high-dose therapy. As IVIG use expands, clinicians must recognize this rare complication, leverage accessible diagnostic tools, and implement prompt supportive care to optimize outcomes.

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