

CLINICAL CASE CHALLENGES

Reversible Myocardial Edema Secondary to Tagraxofusp-Induced Capillary Leak Syndrome



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CD123 is the alpha subunit of the interleukin (IL)-3 receptor and is ubiquitously overexpressed in blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare and clinically aggressive hematologic malignancy. Tagraxofusp is an intravenously administered CD123-targeted diphtheria toxin (DT) conjugate drug that received a first-in-class approval by the U.S. Food and Drug Administration in 2018 for the treatment of BPDCN. The most serious toxicity of tagraxofusp is capillary leak syndrome (CLS), characterized by the constellation of hypoalbuminemia, fluid shift, and hypotension. We herein describe a case of tagraxofusp-induced, reversible myocardial edema as a manifestation of CLS.

CASE PRESENTATION

A 37-year-old Caucasian man with no history of cardiac disease was diagnosed with BPDCN involving the inguinal and external iliac lymph nodes. Baseline cardiac evaluation demonstrated sinus bradycardia on electrocardiogram and normal left ventricular (LV) wall thickness and ejection fraction (EF) with trace aortic and mitral valve regurgitation on transthoracic echocardiography. Baseline N-terminal pro-B-type natriuretic peptide was normal at 25 pg/mL. His first-line therapy was tagraxofusp 12 mcg/kg intravenously for 5 consecutive days with premedications that included intravenous (IV) methylprednisolone 50 mg daily. To mitigate the potential effects of CLS, his serum albumin was kept >3.2 g/dL and he was maintained below his dry weight with intermittent IV albumin 25% and furosemide, respectively. He was given 3 additional days of IV methylprednisolone in response to a tagraxofusp-attributed elevation in liver transaminases (peak alanine transaminase 237 U/L, peak aspartate aminotransferase 529 U/L) and discharged from hospital on day 8 of the first cycle. He presented to the emergency department 2 days later with fatigue, dyspnea, and peripheral edema. On initial evaluation, he was afebrile with a blood pressure of 114/76 mm Hg, heart rate of 115 beats/min, and an oxygen saturation below 90% on room air. Compared with a chest computed tomography from 20 days earlier, a computed tomography pulmonary angiogram showed no pulmonary emboli, but rather interval development of extensive mixed solid and ground glass pulmonary nodules, interstitial pulmonary edema, small bilateral dependent pleural effusions, and a small to moderate pericardial effusion. He was given empiric IV antibiotics for pneumonia and furosemide 40 mg IV and admitted to hospital for further investigation and management. The differential diagnosis included:

1. Drug toxicity: The leading differential diagnosis was CLS secondary to tagraxofusp.
2. Pneumonia/sepsis: Less likely given the lack of prolonged neutropenia and fever.
3. Heart failure/acute cardiomyopathy: Stress- or sepsis-induced acute cardiomyopathy.
4. Myocardial ischemia: Lowest likelihood based on absence of risk factors.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

Manuscript received June 11, 2021; revised manuscript received September 10, 2021, accepted September 10, 2021.

CLINICAL COURSE

Per detailed history, he had no viral prodrome in the preceding weeks. The patient's electrocardiogram at admission showed new inverted T waves in inferolateral leads and newly elevated cardiac biomarkers (high-sensitivity troponin T 118 ng/L [normal ≤ 18 ng/L] and N-terminal pro-B-type natriuretic peptide 3,498 pg/mL [normal ≤ 125 pg/mL]). His serum albumin level had decreased from a baseline of 4.8 to 3.2 mg/dL despite the prior prophylactic albumin infusions. His CBC demonstrated a leukocytosis of 33.2 K/ μ L, hemoconcentration (hematocrit 52%), and thrombocytopenia (platelet count 40,000/ μ L). Hyponatremia (sodium 132 mEq/L) was noted with normal renal function. His liver transaminase levels remained moderately elevated (alanine transaminase 179 U/L and aspartate aminotransferase 158 U/L). A nasopharyngeal PCR swab for common respiratory viral pathogens (including SARS-CoV-2) was negative, as were his blood and urine cultures. A repeat transthoracic echocardiogram was obtained, and compared with his baseline study from a few weeks before, there were no new segmental wall motion abnormalities nor changes in LV systolic function. However, there was an approximate 3-fold increase in the LV apical wall thickness and associated impaired myocardial relaxation with decreased mitral annular tissue Doppler velocities. The predominant appearance of the LV was very similar to apical hypertrophic cardiomyopathy. There was increased right ventricular (RV) free wall thickness as well. His peak LV global longitudinal strain had changed from a normal value of -21.3% to -15.5% ($< -18\%$ abnormal). Initial cardiovascular cardiac magnetic resonance (CMR) (1.5-T) showed normal cardiac chamber sizes with concentric LV and RV hypertrophy, normal biventricular systolic function (LVEF 63%, RVEF 50%), and the absence of regional wall motion abnormalities. The pericardium was of normal thickness with a small circumferential pericardial effusion. There was myocardial patchy late gadolinium enhancement noted with an increased T_2 value of 68 milliseconds (normal < 55 milliseconds) and increased LV mass index of 89.69 g/m² (normal < 75 g/m²) (Figure 1A). The native T_1 value measured in the midseptum was 1,462 milliseconds (normal = 1,034 \pm 39 milliseconds) with an extracellular volume fraction (ECV) of 28% (normal = 25.3% \pm 3.5%).

In light of the cardiac biomarker injury pattern and echocardiographic/CMR findings, his presentation was suspected to be a manifestation of CLS with secondary myocardial edema. He was initially treated with supplemental oxygen by nasal cannula, a furosemide infusion at 3 mg/h, methylprednisolone 125 mg IV every 6 hours, and 25 g of albumin 25% every 12 hours with a target daily negative fluid balance of 1-2 L and target trough serum albumin > 3.2 g/dL. An endomyocardial biopsy was considered, but ultimately not performed because of rapid clinical improvement. His fatigue, dyspnea, hypoxia, and peripheral edema improved over a 5-day period. A repeat limited transthoracic echocardiogram 3 days after admission showed an LVEF of 70%, and persistent wall thickening predominantly involving the apical segments. He was discharged home 7 days after admission on a tapered schedule of oral prednisone and diuretic. He was followed closely in the outpatient setting with progressive normalization of his cardiac biomarkers over 8 weeks. A repeat CMR 1 month after admission showed resolution of the previous delayed hyperenhancement with normalization of both T_2 maps (49 milliseconds) and LV mass index (74 g/m²) values (Figure 1B). The native T_1 value and the ECV decreased to 1,207 milliseconds and 21%, respectively. A repeat echocardiogram 3 months after admission demonstrated complete resolution of the previous biventricular thickness changes and pericardial effusion with normalization of tissue Doppler parameters and LV global longitudinal strain.

The patient's BPDCN-directed therapy was resumed 1 month later with a reduced dose of tagraxofusp (9 μ g/kg \times 3 days) and prophylactic daily diuretic and albumin infusions. He tolerated all 5 subsequent cycles well and proceeded to an allogeneic stem cell transplant after which he remains in complete remission over 1.5 years later.

DISCUSSION

Capillary leak syndrome (CLS) is the shared biological endpoint of vascular endothelial hyperpermeability resulting from a variety of inciting etiologies. Extravasation of plasma and proteins into the interstitial space underlies the clinical triad of hypoalbuminemia, hemoconcentration, and hypotension that, if untreated, can lead to distributive shock. The eponymous idiopathic form of CLS is known as Clarkson disease (1). CLS can also be secondary to autoimmune diseases, viral infections, and snakebites, but the most common secondary

ABBREVIATIONS AND ACRONYMS

BPDCN = blastic plasmacytoid dendritic cell neoplasm

CLS = capillary leak syndrome

CMR = cardiovascular cardiac magnetic resonance

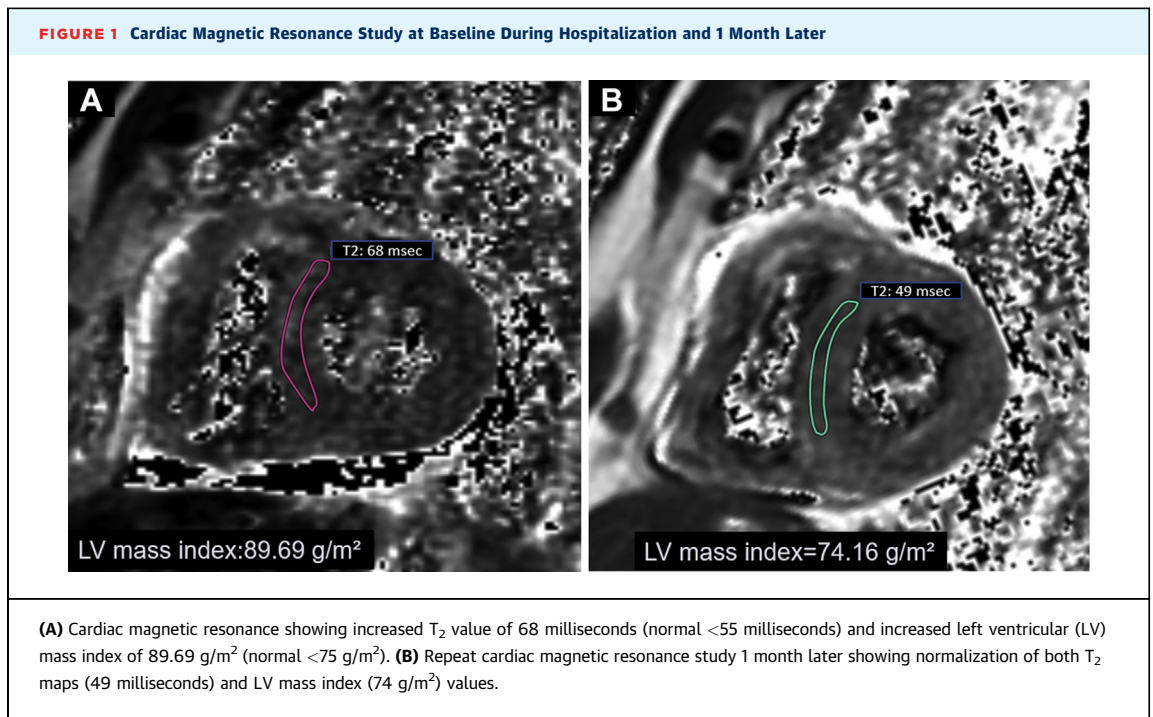
DT = diphtheria toxin

ECV = extracellular volume

EF = ejection fraction

LV = left ventricular

NT-proBNP = N-terminal pro-B-type natriuretic peptide



etiology is drugs. A total of 80% of offending agents are chemotherapy or immunomodulatory agents including gemcitabine, pemetrexed, IL-2, and others (2). Acute management involves identifying and removing any inciting agent, countering humoral inflammatory mediator effects, and reversing its oncotic effects with albumin or other colloids. Whether to employ diuresis vs intravenous fluid resuscitation requires discernment, because it depends on the anticipated risk of pulmonary edema and compartment syndrome. This, in turn, is dependent on patient comorbidities and CLS etiology; eg, pulmonary edema is much more common in drug-induced CLS (2) than Clarkson disease (1).

Myocardial edema secondary to CLS has been reported in several cases of Clarkson disease, with manifestations ranging from echocardiographic ventricular wall thickening without systolic dysfunction to cardiogenic shock with severe LV dysfunction necessitating extracorporeal life support (3-7). Critically, live and post-mortem cardiac biopsies have uniformly demonstrated diffuse edematous changes without evidence of acute inflammation or myocyte necrosis to implicate underlying myositis or infarction (3,8). Shared echocardiographic features include reversible biventricular thickening with associated systolic dysfunction only in the most severe cases. CMR enables the quantitative assessment of myocardial edema by evaluating the T_2 values and ECV. Prospective CMR examination has demonstrated higher myocardial ECV values in patients with active idiopathic CLS compared with both age-matched control subjects and patients with a history of idiopathic CLS in remission (4).

Tagraxofusp consists of recombinant human IL-3 fused to a truncated DT. Tagraxofusp-related CLS is hypothesized to be caused by uptake of the diphtheria toxin by vascular endothelium, resulting in endothelial cell apoptosis and vessel wall leakage. CLS was reported in 55% (7% \geq Grade 3) of those treated with tagraxofusp for BPDCN on clinical trial, with a median time to onset of 5 days (9). Of note, the initial U.S. Food and Drug Administration review of tagraxofusp safety data concluded that there was no attributable specific serious cardiac toxicity (10). Myocarditis is a well-known complication of respiratory diphtheria infection. However, myocarditis has not been reported with the truncated DT used in tagraxofusp.

Our patient exhibited several features analogous to the myocardial edema reported in Clarkson disease. The constellation of rapid weight gain, relative hypoalbuminemia, and hypoxemia with frank pulmonary edema without evidence of sepsis or LV systolic dysfunction occurring within days of completing his first cycle of tagraxofusp is consistent with drug-induced CLS. The concurrent echocardiographic findings of rapid-onset, reversible ventricular thickening is suggestive of transient myocardial edema. The corresponding changes

and subsequent normalization of T₂ maps, LV index, and ECV on CMR further reinforces this diagnosis. The patient had no demonstrable alternative differential. Although the possibility of undiagnosed acute myocarditis cannot be eliminated, the collective clinical presentation and cardiac imaging findings are more likely to be CLS-mediated myocardial injury.

This case illustrates the importance of recognizing myocardial edema as a rare but serious manifestation of CLS, in this case tagraxofusp-induced. Early noninvasive cardiac imaging is critical to diagnosing secondary myocardial edema and excluding alternative ischemic, inflammatory, infiltrative cardiomyopathies. The dynamic improvement this patient's baseline echocardiographic and CMR abnormalities emphasize the potentially reversible nature of CLS-related myocardial injury.

CONCLUSIONS

Tagraxofusp is an intravenously administered CD123-targeted diphtheria toxin conjugate drug used in the treatment of rare hematological malignancies. We present a case of myocardial involvement in a tagraxofusp-induced capillary leak syndrome (CLS). This case highlights the importance of using longitudinal noninvasive cardiac imaging to recognize this pattern of reversible cardiac injury as well as the early application of measures to reverse the fluid retention and oncotic effects of CLS and the successful rechallenge of the CD123-directed agent in subsequent cycles after the occurrence of CLS.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Konopleva has served as a consultant for and received research funding from Stemline Therapeutics. Dr Pemmaraju has received honoraria and research funding from Stemline Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS blastic plasmacytoid dendritic cell neoplasm, capillary leak syndrome, myocardial edema, tagraxofusp