

CASE REPORT

ADVANCED

CLINICAL CASE

Mogamulizumab-Associated Acute Myocarditis in a Patient With T-Cell Lymphoma



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ABSTRACT

A 62-year-old woman with human T-lymphotropic virus type 1 cell lymphoma developed heart failure after mogamulizumab, an immunotherapy agent. Clinical presentation and cardiac magnetic resonance imaging were consistent with myocarditis, and a recurrence of heart failure occurred after rechallenge with the therapy. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:1018–23) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

HISTORY OF PRESENTATION

A 62-year-old woman presented with weakness and was found to have hypercalcemia and a 4.7-cm anterior mediastinal mass with lymphadenopathy. She underwent lymph node and bone marrow biopsy that led to the diagnosis of T-cell lymphoma with staging showing bone and central nervous system involvement. She had a transthoracic echocardiogram (TTE) that showed a left ventricular ejection fraction

(LVEF) of 61%, mild concentric left ventricular hypertrophy, and no significant abnormalities. She received multiple rounds of chemotherapy, including 6 cycles of cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (CHOPE), but was refractory to treatment with subsequent development of bone and soft tissue lesions. Repeat TTE post-CHOPE showed a normal LVEF of 73% ([Videos 1 and 2](#)). She next underwent chemotherapy with 3 cycles of etoposide phosphate, prednisone, vincristine, cyclophosphamide, and doxorubicin; however, positron emission tomography/computed tomography showed progression of skeletal metastases. She was subsequently enrolled in a mogamulizumab trial, a humanized immunoglobulin G1 monoclonal antibody that targets C-X-C chemokine receptor type 4 (CCR4), which was recently approved for treatment of T-cell lymphoma (1).

After the first infusion of mogamulizumab, she became febrile to 101°F, tachypneic, hypotensive, tachycardic at 130 beats/min, had saturation of 100%

LEARNING OBJECTIVES

- To recognize a cardiac side effect of a novel immunotherapy agent in a cancer patient to decrease cardiovascular complications from the therapy.
- To use CMR for evaluation of cardiomyopathy in a cancer patient to diagnose the underlying process and make informed recommendations for treatment.

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on room air, and experienced rigors, chills, and chest pain that prompted a visit to the emergency department. In the emergency department, her electrocardiogram (ECG) showed sinus tachycardia with new nonspecific ST-segment and T-wave changes (Figure 1). D-dimer was elevated to 14.3 mg/l, troponin I was elevated at 0.29 ng/ml, with subsequent troponin T at 0.10 ng/ml. N-terminal pro-hormone brain natriuretic peptide was elevated at 14,548 pg/ml. TTE on this admission demonstrated a newly depressed LVEF of 32% with global hypokinesis, prompting a cardiology consultation.

PAST MEDICAL HISTORY

The patient has a history of hypertension and remote ovarian cancer, for which she underwent total abdominal hysterectomy and salpingo-oophorectomy.

DIFFERENTIAL DIAGNOSIS

Because of the temporal timing of the new immunotherapy agent, global hypokinesis, and clinical presentation, the mostly likely diagnosis was believed to be a side effect of the new cancer therapy or potentially a stress cardiomyopathy.

INVESTIGATIONS

At her cardiology evaluation, her fever, tachypnea, and hypotension had resolved. Because of her

malignancy and elevated D-dimer, she underwent chest computed tomography, which showed a possible pulmonary embolus (PE). Her examination by cardiology demonstrated a regular rhythm, absence of murmurs, rubs or gallops, decreased breath sounds at the bases, normal jugular venous pressure, and 1+ pitting edema bilaterally. Because of the elevated troponin and ECG and TTE changes, the patient underwent cardiac magnetic resonance (CMR) imaging. The CMR demonstrated decreased systolic function with a LVEF of 37% and a mildly reduced right ventricular ejection fraction of 47% (Video 3). There was diffusely increased signal intensity on T2-weighted images, with a T2 myocardial to skeletal muscle ratio of 2.4 (normal ≤ 1.9) (Figure 2A), which suggested diffuse myocardial inflammation. Late gadolinium enhancement (LGE) images demonstrated patchy mid-myocardial delayed enhancement throughout multiple areas (Figure 2B) that were consistent with a nonischemic cardiomyopathic process and with a quantitative LGE burden of 13%. These CMR findings were most consistent with myocarditis. Considering the temporal relationship of symptoms, laboratory, and imaging findings to mogamulizumab infusion, myocarditis was believed to have been caused by this immunotherapy agent.

ABBREVIATIONS AND ACRONYMS

- CCR4** = C-X-C chemokine receptor type 4
- CHOPE** = cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide
- CMR** = cardiac magnetic resonance
- ECG** = electrocardiogram
- ICI** = checkpoint inhibitor
- LGE** = late gadolinium enhancement
- LVEF** = left ventricular ejection fraction
- PE** = pulmonary embolus
- Treg** = T regulatory cells
- TTE** = transthoracic echocardiogram

FIGURE 1 Electrocardiogram Showing Sinus Tachycardia

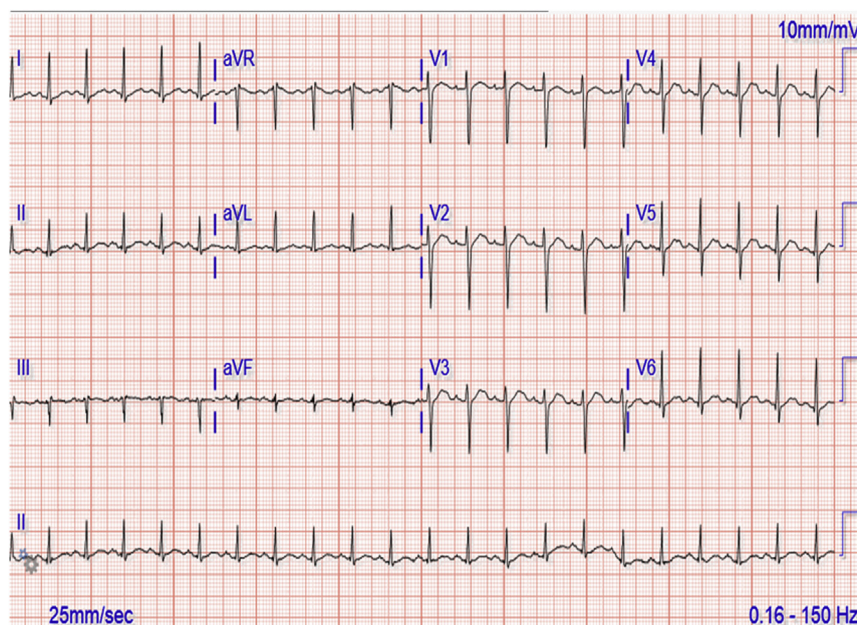
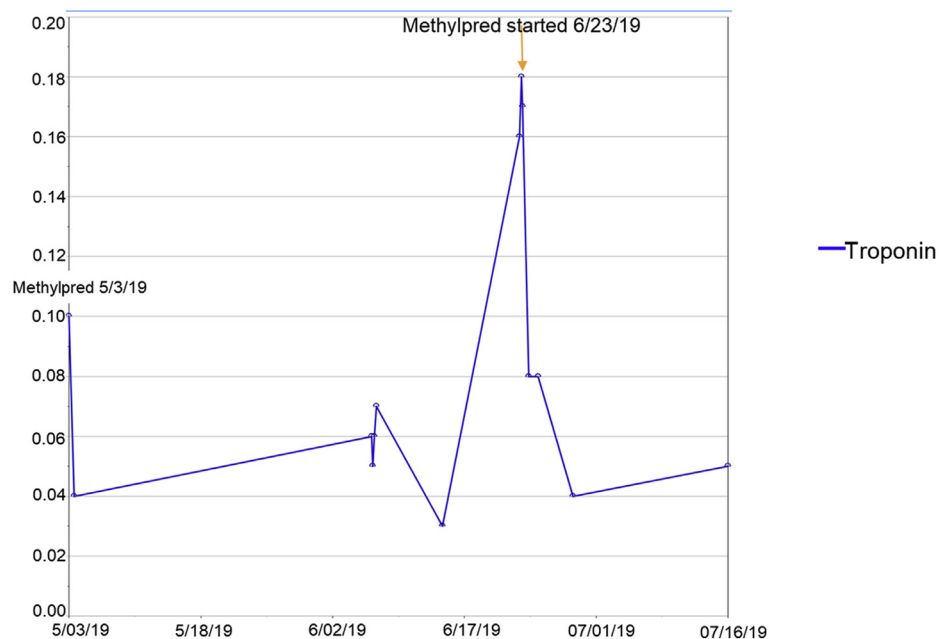


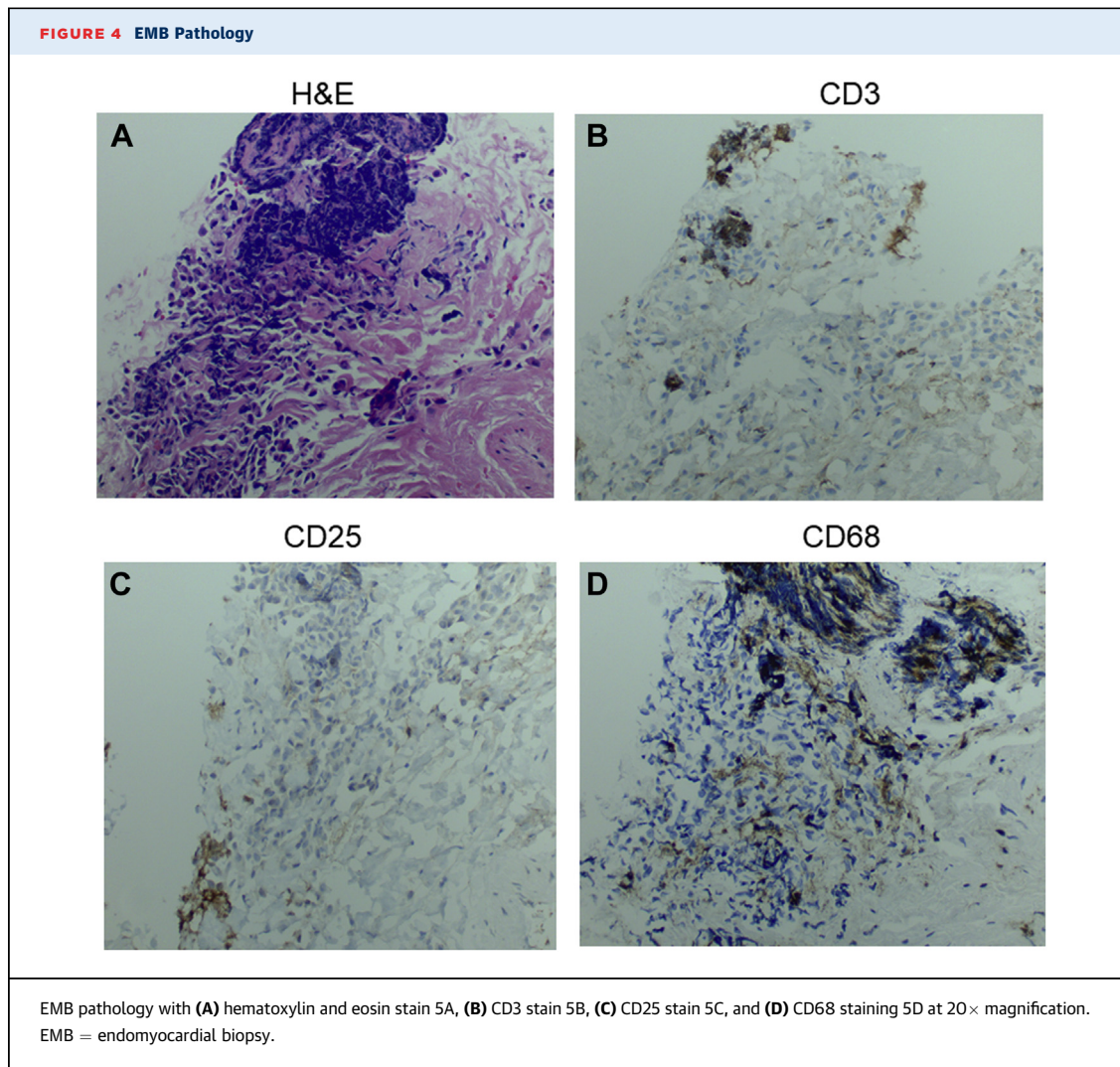
FIGURE 2 Cardiac Magnetic Resonance Obtained After Acute Heart Failure Following First Dose of Mogamulizumab**(A)** Short axis T-2 weighted image showing diffuse high-signal intensity consistent with myocardial edema. **(B)** Single-shot, short-axis late-gadolinium enhancement image showing hazy mid-myocardial delayed enhancement in the basal inferoseptal wall (arrow).

MANAGEMENT

For her possible PE, because of known brain metastases, the decision was to not anticoagulate due to concern for intracranial bleeding. For possible immune therapy-mediated myocarditis, checkpoint inhibitor (ICI)-mediated myocarditis management

was applied, and the patient was started on high-dose steroids. The patient was treated with 3 days of pulse dose steroids (1 g of methylprednisolone daily for 3 days) (2-4). With steroid therapy, the troponins down trended (Figure 3). The patient was discharged on a steroid taper and beta-blocker with follow-up in the cardio-oncology clinic. A repeat CMR 3 weeks

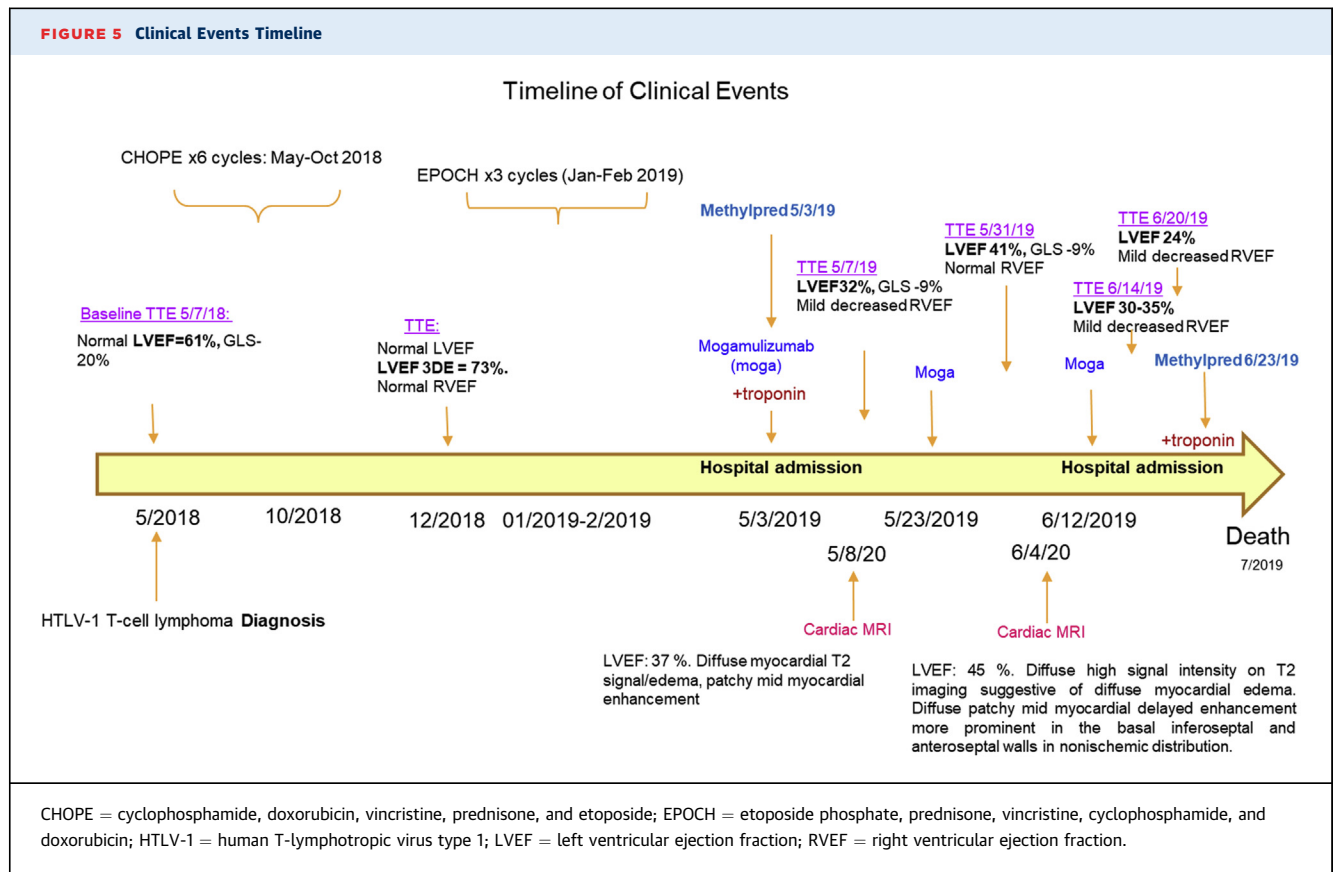
FIGURE 3 Troponin Trend and Response to Steroids



after steroids showed interval improvement of LVEF from 37% to 45% and a similar LGE extent and pattern (Video 4). In addition, monitoring chest computed tomography found a new PE, for which the patient was started on therapeutic enoxaparin.

In light of the patient's advanced cancer and lack of other treatment options, the patient received another dose of mogamulizumab, and 3 weeks later re-presented with tachycardia, hypotension, and undifferentiated shock. Infectious workup revealed a urinary source, for which she was treated with antibiotics. However, repeat TTE showed worsening of the LVEF to 24%. The main diagnostic differential for the decline in LVEF at this time included further immune-mediated cardiomyopathy due to mogamulizumab or potentially stress-induced cardiomyopathy. For concern of recurrent and/or

progressive suspected immune-mediated myocarditis, the patient was once again started on pulse dose steroids with methylprednisolone 1 g/day for 3 days and continued on a steroid taper. She then underwent right heart catheterization, with an endomyocardial biopsy showing an elevated pulmonary capillary wedge pressure of 22 mm Hg and a cardiac output of 4.6 l with a cardiac index of 2.79. Pathology specimens showed fibrous tissue without myocardial tissue identified. Hematoxylin and eosin stain showed cell aggregates (Figure 4A). The focal lymphoid aggregates of clusters had positive staining for CD3+, CD25+, and CD68+ cells in non-overlapping areas (Figures 4B to 4D), which was deemed to have uncertain significance. Overall findings were believed to be nondiagnostic, although could be considered suggestive of myocarditis.



DISCUSSION

This is the first published case of likely CCR4 inhibitor-mediated myocarditis, based on the timing of the patient's clinical presentation and course (Figure 5). CCR4 is a chemokine receptor expressed on circulating and tissue-resident T cells, as well as on other T-helper cells, including T-regulatory cells (Tregs). CCR4 is also highly expressed in T-cell lymphoma and has been shown to mediate cellular migration and proliferation (5,6). Thus, immune-mediated adverse effects on the heart may be due to immune cell activation and attack of the myocardium secondary to suppression of immune-suppressing cells such as Tregs. One other possibility could be increased tropism for T cells to the myocardium in the setting of CCR4 inhibition causing increased inflammation, cytokine release, and damage to the myocardium (6). Although extremely rare, human T-lymphotropic virus type 1 itself has been shown contribute to nonischemic cardiomyopathy (7).

Diagnosis of myocarditis normally requires clinical suspicion, positive biomarkers, imaging and/or

biopsy. Sensitivity can be low for biopsy diagnosis of myocarditis (8) and may be low due to the patchy nature of myocardial involvement (9). Imaging such as CMR can help confirm the diagnosis, and our patient met the CMR Lake Louise criteria for myocarditis, with positive edema and LGE. Diagnostic criteria has been proposed for ICI-related myocarditis, which includes the use of CMR (10,11). Although there are no studies to guide treatment of CCR4 inhibitor-mediated myocarditis, support for steroid use was drawn from recommendations for ICI-mediated myocarditis (12). Additional therapies such as mycophenolate and monoclonal antibody therapies such as alemtuzumab could have been considered (13). Although the patient received previous chemotherapy agents, they were several months before heart failure presentation. However, previous agents might have contributed to subclinical cardiotoxicity, which was not readily identified.

FOLLOW-UP

The patient's cancer continued to progress and given no further therapeutic options, the patient and family

pursued hospice care and deferred additional CMR imaging to follow-up on myocarditis progression. The patient subsequently passed away, and the family declined autopsy.

CONCLUSIONS

This is the first published case of likely CCR4 inhibitor–mediated myocarditis, and ICI-mediated myocarditis management was applied. Evidence-based treatment guidelines are needed for CCR4 inhibition–mediated myocarditis. This case also demonstrated the usefulness of CMR in diagnosis of myocarditis, as well monitoring and response to therapy. In addition to mogamulizumab, other immunotherapy agents may be associated with myocarditis. Further surveillance and research are

needed to understand the mechanisms behind cardiotoxicity and these immunotherapies.

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KEY WORDS acute heart failure, cancer, cardiomyopathy, MR sequences

APPENDIX For supplemental videos, please see the online version of this paper.