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INTERMEDIATE

CASE REPORT: CLINICAL CASE

# Lenalidomide-Induced Myocarditis, Rare But Possibly Fatal Toxicity of a Commonly Used Immunotherapy

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## ABSTRACT

A 66-year-old woman with follicular lymphoma on lenalidomide and rituximab presented with chest pain. High-sensitivity troponin T peaked at 7,566 ng/l. Cardiac biopsy revealed extensive inflammation consistent with medication-induced myocarditis. Lenalidomide was stopped with improvement in troponins and patient was initiated on high-dose corticosteroid therapy. (**Level of Difficulty: Intermediate.**) (J Am Coll Cardiol Case Rep 2020;2:2095–100) © 2020 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 66-year-old woman with low-grade follicular lymphoma, advanced stage and high tumor burden, on rituximab and lenalidomide, presented with chest pain. The patient developed acute left-sided, stabbing chest pain at rest. It persisted throughout the night. She denied shortness of breath, fever, cough, or any upper respiratory symptoms. Cancer therapy with lenalidomide (20 mg PO daily for 28-day cycle) and rituximab had been initiated approximately 1 month before presentation, with no prior chemotherapy before that.

Her vital signs on admission included a blood pressure of 143/61 mm Hg, heart rate of 56 beats/min, respiratory rate of 18 breaths/min, and temperature of 97.9°F. The physical examination was unremarkable with cardiovascular examination revealing regular rate and rhythm without murmurs, rubs, or gallops and normal jugular venous pressure.

### LEARNING OBJECTIVES

- To review the differential diagnosis of elevated troponins in a patient with chest pain.
- To highlight the importance of imaging and biopsy for diagnosis confirmation.
- To propose an algorithm when suspecting lenalidomide-induced myocarditis.
- To illustrate that lenalidomide may cause cardiotoxic effects that may affect malignancy management.

## PAST MEDICAL HISTORY

The patient had no significant history of heart disease. Her family history was negative for any heart disease as well.

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**ABBREVIATIONS AND ACRONYMS**

**hsTnT** = high-sensitivity troponin T

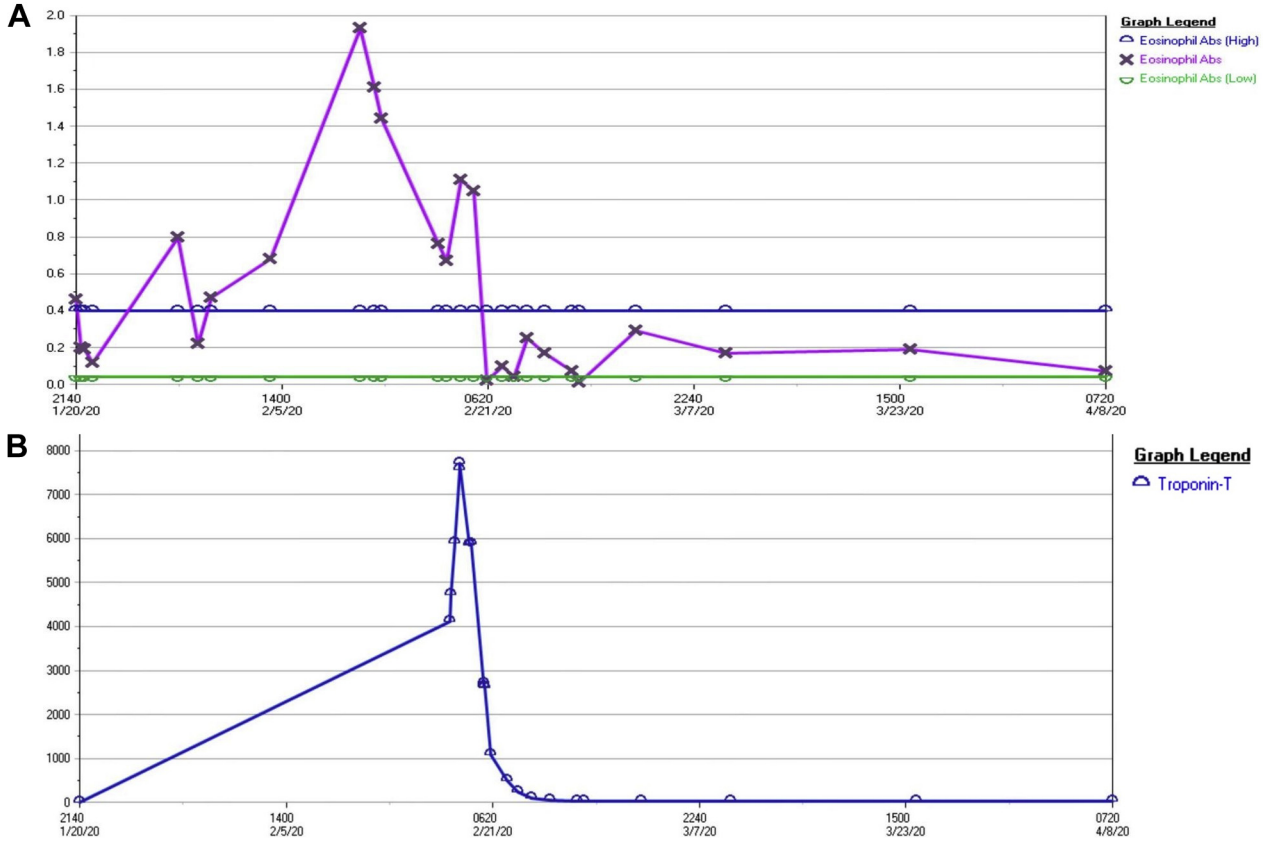
## DIFFERENTIAL DIAGNOSIS

Taking into consideration the presentation of chest pain with an elevated troponin, the initial differential diagnosis included acute coronary syndrome, stress-induced cardiomyopathy, and acute pulmonary embolism. However, initial testing with echocardiogram and coronary angiogram revealed nonobstructive coronary disease and normal left and right ventricular function. Thus, with these findings and an elevated eosinophil count, the differential expanded to include myocarditis.

## INVESTIGATIONS

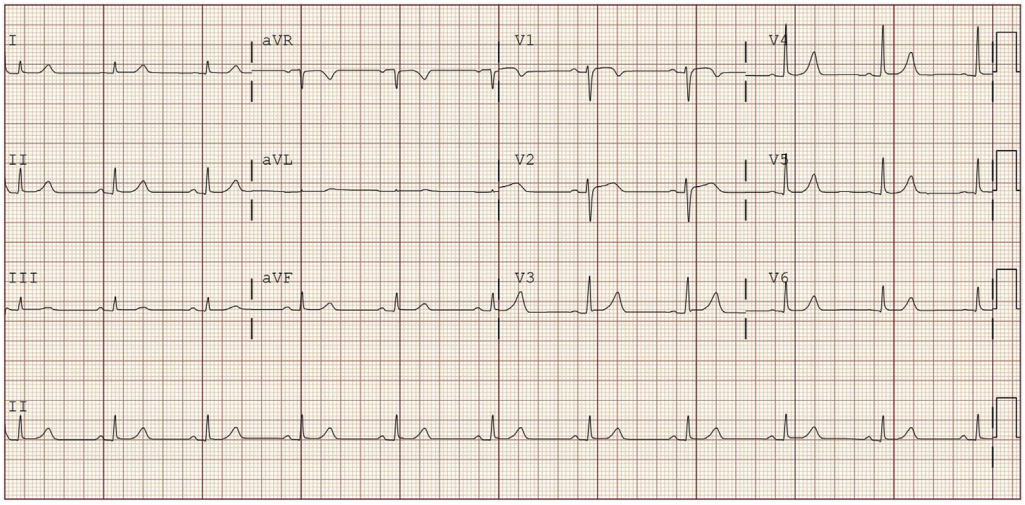
On admission, blood tests revealed a significantly elevated eosinophil count 1.11 K/μl (normal range, 0.04 to 0.40 K/μl) and high-sensitivity troponin T (hsTnT) 4,124 ng/l, both of which had been normal prior (Figures 1A and 1B). Extensive testing was performed for causes of myocarditis, including titers for parvovirus B19, *Coxiella burnetii* (Q fever), Epstein-Barr virus, cytomegalovirus, herpes simplex virus, enterovirus, adenovirus, antinuclear antibody, and Smith antibodies, which were all negative. C-reactive protein and erythrocyte sedimentation rate were normal. Of note, interleukin-2 receptor CD25 was markedly elevated at 8,990 pg/ml (normally <1,033 pg/ml), whereas all other cytokine levels (e.g., tumor necrosis factor-α, interleukin-6) were normal. Electrocardiogram showed normal sinus rhythm (Figure 2). Transthoracic echocardiogram revealed preserved ejection fraction without regional wall motion abnormalities, normal peak global longitudinal systolic strain, and minimal pericardial effusion (Figure 3). Computed tomography chest angiogram was negative for pulmonary embolism. Serial hsTnT assays peaked at 7,566 ng/l.

**FIGURE 1** Eosinophil and Troponins




**(A)** Trend of eosinophil count from initial lenalidomide dosing onward. **(B)** High-sensitivity troponin T trend from initial lenalidomide dosing onward.

**FIGURE 2** Electrocardiogram

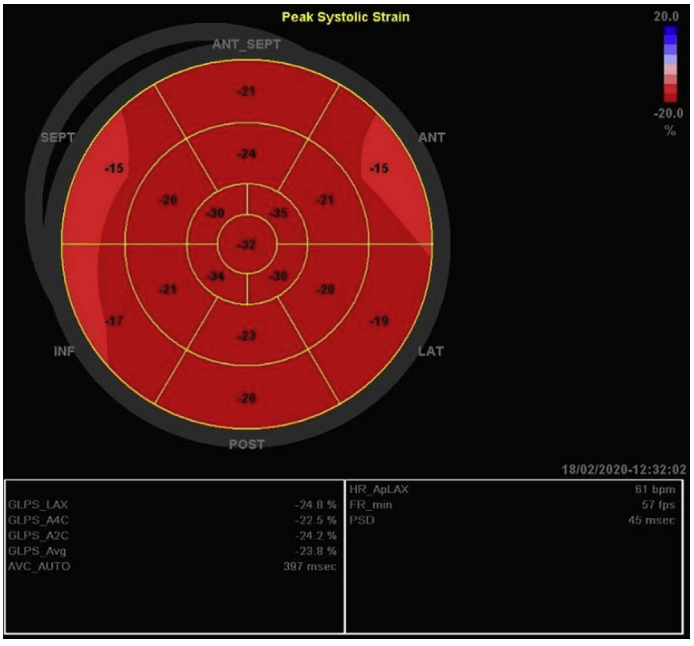



Baseline electrocardiogram on admission, normal sinus rhythm.

## MANAGEMENT

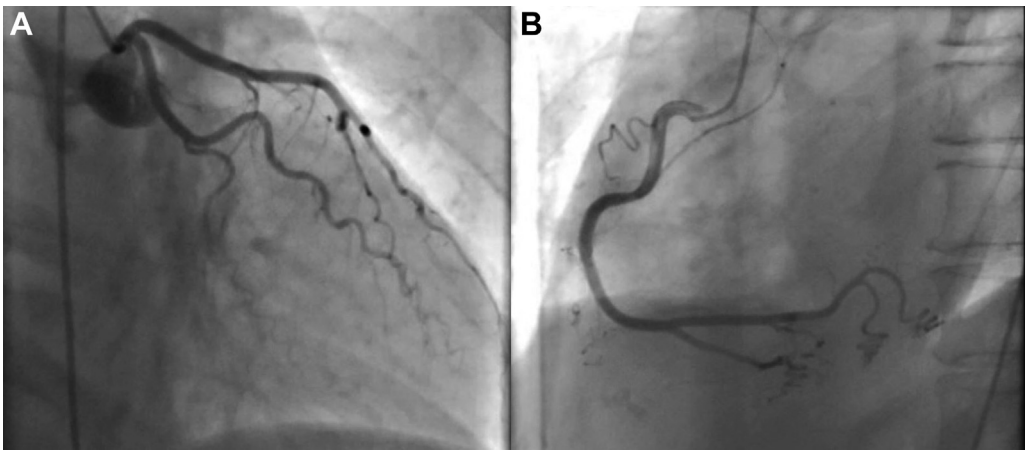
Patient was initially started on heparin drip because of concern for acute coronary syndrome. Coronary angiography revealed nonobstructive coronary artery disease (30% stenosis in mid right coronary and ostial left circumflex artery) along with left ventriculography revealing normal left ventricular function (ejection fraction >70%) (Figures 4A and 4B). Right heart catheterization showed normal intracardiac filling

**FIGURE 3** Strain Imaging




Preserved strain seen on echocardiogram imaging.

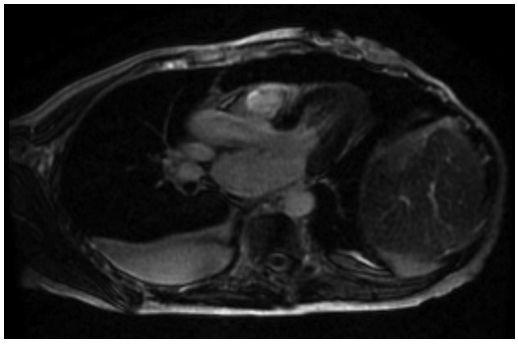
**FIGURE 4 Coronary Angiogram**




**(A)** Right anterior oblique caudal view of left coronary arteries. **(B)** Left anterior oblique caudal view of right coronary artery.

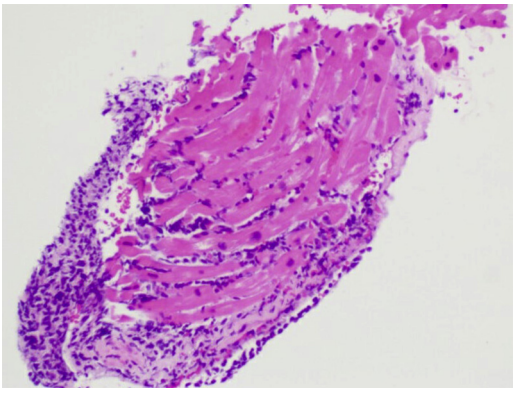
pressures (mean right atrial pressure, 5 mm Hg; mean pulmonary artery pressure, 16 mm Hg; mean pulmonary capillary wedge pressure, 6 mm Hg) and low cardiac index (2.16 l/min/m$^2$). Cardiac magnetic resonance imaging was performed to evaluate for myocarditis. T2-weighted imaging revealed hyperintensity of the right ventricular free wall with a resulting myocardial skeletal muscle signal intensity ratio of 2.73, suggesting myocardial edema. Late gadolinium enhancement images showed delayed enhancement of the right ventricular free wall in the same distribution as T2 hyperintensity signal areas (Figure 5). Endomyocardial biopsy revealed extensive, subacute lymphocytic myocarditis with multifocal lymphocytic infiltrate, ongoing cardiomyocyte necrosis, and granulation tissue response (Figure 6). Lenalidomide therapy was stopped, with improvement in clinical status and biomarkers, but during the hospitalization the patient continued to have runs of nonsustained ventricular tachycardia on telemetry that resolved after initiation of high-dose intravenous corticosteroids (500 mg intravenous methylprednisolone daily for 3 days). The corticosteroids were changed to an oral regimen and tapered off after several weeks during which the hsTnT declined to 26 ng/l and eosinophil count returned to normal.

**FIGURE 5 Cardiac Magnetic Resonance Imaging**



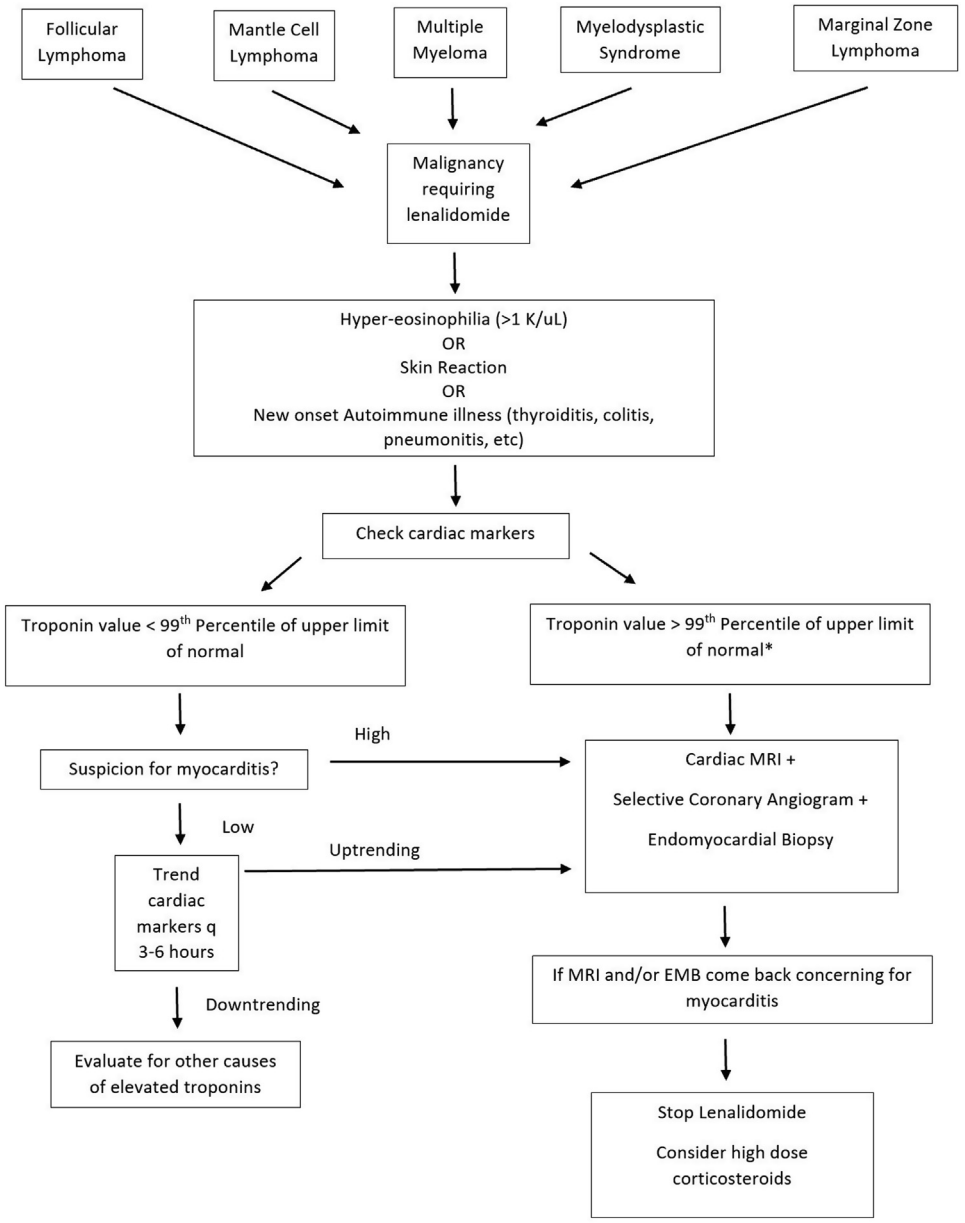
Magnetic resonance image revealing delayed gadolinium enhancement in the right ventricular wall.

**FIGURE 6 Cardiac Biopsy**



Myocardium obtained by endomyocardial biopsy showing a multifocal infiltrate of lymphocytes involving the endocardium and myocardium with focal cardiomyocyte damage and loss.

**FIGURE 7 Lenalidomide Algorithm**




An algorithm for diagnosis and management of suspected lenalidomide myocarditis. MRI = magnetic resonance imaging; EMB = endomyocardial biopsy. *If no other cause of elevated troponin, such as sepsis or severe anemia that may cause acute myocardial injury, then proceed with invasive and advanced imaging for diagnosis of myocarditis.

## DISCUSSION

Lenalidomide therapy is a second-generation immunomodulatory drug that is Food and Drug Administration approved for multiple myeloma, myelodysplastic syndrome, follicular lymphoma, marginal zone lymphoma, and mantle cell lymphoma (1). This agent is associated with side effects, such as fatigue, neutropenia, skin rash, diarrhea, and peripheral neuropathy (2). Cardiovascular toxicity has been less well documented, mostly limited to thrombosis and atrial fibrillation (3-5). Additionally, there have been case reports of pneumonitis, dermatitis, and cardiac/renal transplant rejection

from lenalidomide; myocarditis may be another unusual autoimmune side effect of the medication, similar to a reactive hypersensitivity syndrome (6,7). Previous literature postulates a predominant T-cell infiltration of the myocardium secondary to lenalidomide (8).

This is the first documented report of biopsy-confirmed myocarditis secondary to lenalidomide in a living patient. Only 1 other case report has been found in the literature confirming lenalidomide-induced myocarditis, but this was at time of autopsy (8). In our case, the offending agent was stopped immediately, while multimodality imaging and biopsy were performed promptly to confirm diagnosis.

Given the patient's age, questions arose about whether the dose of lenalidomide could have been lowered before initiating treatment. Prior studies have shown that lower dose lenalidomide is as effective and less toxic for patients with relapsed refractory multiple myeloma (9).

We propose an algorithm for the management of lenalidomide-induced myocarditis (**Figure 7**). If hypereosinophilia (>1 K/μl), skin reactions, or new-onset autoimmune illness, such as colitis or thyroiditis, develops after starting lenalidomide therapy, we recommend evaluation with cardiac biomarkers. If cardiac biomarkers are elevated (troponin value >99th percentile of upper limit of normal), we recommend selective coronary angiography to rule out significant ischemic disease, along with cardiac magnetic resonance imaging and endomyocardial biopsy if there is not another potential cause of troponin elevation (e.g., sepsis or severe anemia leading to acute myocardial injury). If results are consistent with lymphocytic myocarditis, lenalidomide therapy should be stopped immediately and high-dose corticosteroids started as soon as possible to prevent further decompensation. If symptoms improve and troponins trend down after discontinuation of lenalidomide, we propose an oral prednisone (1 mg/kg for 2 weeks and taper over 2 weeks). Higher doses (0.5 to 1 g pulse dose steroids daily for 3 days followed by 1 mg/kg for 2 weeks and taper in the subsequent 2 weeks) are recommended if symptoms persist and/or troponins trend up despite lenalidomide discontinuation.

## FOLLOW-UP

By the time of discharge, hsTnT had improved to 23 ng/l. Patient was discharged on a corticosteroid taper, which she completed over approximately 1 month. In 1-month clinic follow-up, patient was asymptomatic and repeat troponin and eosinophil count were normal. Patient continued to have a favorable response to her immunotherapy, rituximab, and lenalidomide was not reinitiated.

## CONCLUSIONS

Drug-induced myocarditis can occur from the use of lenalidomide even in low-risk patients without other cardiovascular risk factors. Early multimodality cardiovascular imaging and biopsy are essential in risk assessment and guidance of optimal management.

## AUTHOR DISCLOSURES

All authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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**KEY WORDS** cardio-oncology, cardiotoxicity, follicular lymphoma, lenalidomide, myocarditis