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CASE REPORT

ADVANCED

HEART CARE TEAM/MULTIDISCIPLINARY TEAM LIVE

Acute Myocardial Dysfunction and Hypereosinophilic Infiltrative Myocarditis Secondary to New-Onset Pediatric Acute Lymphoblastic Leukemia

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ABSTRACT

Myocardial infiltration by eosinophils leads to myocardial inflammation and fibrosis, resulting in restrictive hemodynamics. We describe an uncommon presentation of eosinophilic predominant acute lymphoblastic leukemia that manifested with hypereosinophilic infiltrative myocarditis. (**Level of Difficulty: Advanced.**) (J Am Coll Cardiol Case Rep 2021;3:991-6) © 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/).

An 11-year-old boy, with no past medical history, presented to the emergency department in fluid-refractory shock after 4 days of vomiting and 1 day of fever to 38.9°C. On physical examination, the patient was lethargic but responsive to commands. His initial heart rate was relatively low at 71 beats/min on presentation before the initiation of supportive care. Blood pressure was 80/45 mm Hg, without improvement following a total of 60 ml/kg normal saline boluses. The patient was pale, with weak pulses and delayed capillary refill.

LEARNING OBJECTIVES

- To identify paraneoplastic eosinophilic myocarditis as a rare presentation of ALL.
- To highlight the importance of early recognition and treatment of cardiogenic shock secondary to eosinophilic myocarditis.

QUESTION 1: WHAT IS THE DIFFERENTIAL DIAGNOSIS AND WHAT INITIAL TESTS WOULD YOU ORDER?

The differential diagnosis included sepsis, meningitis, toxic ingestion or exposure, and myocarditis. Laboratory evaluation revealed the following: white blood cell count, 103 × 10^9/l with 82% eosinophils; platelets, 22,000 ×10^9/l; potassium, 5.7 mEq/l; phosphorus, 6.7 mg/dl; uric acid, 5.8 mg/dl; and lactate dehydrogenase, 1,178 IU/l. The chest radiograph was normal.

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ABBREVIATIONS AND ACRONYMS

ALL = acute lymphoblastic leukemia

CMR = cardiac magnetic resonance

CT = computed tomography

EF = ejection fraction

HD = hospital day

LV = left ventricular

QUESTION 2: HOW DOES THIS INFORMATION CHANGE YOUR DIFFERENTIAL DIAGNOSIS AND MANAGEMENT?

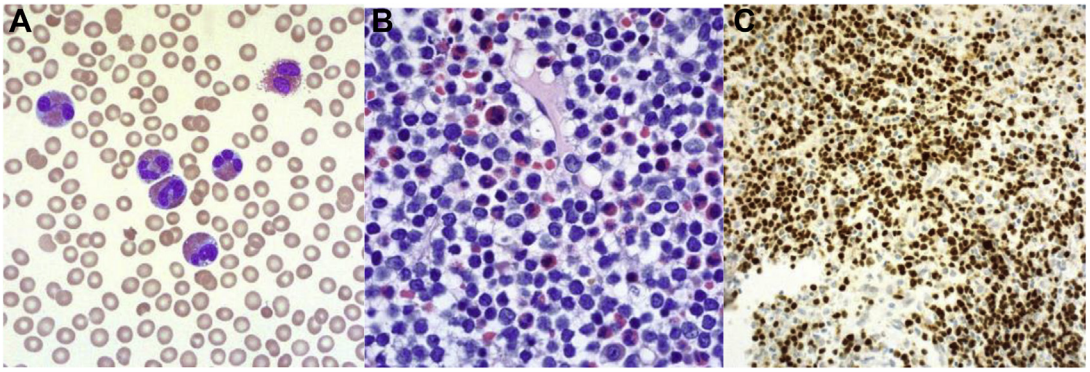
The clinical picture was consistent with acute leukemia. He was started on epinephrine to treat fluid-refractory shock, with immediate improvement in blood pressure. He was intubated for airway protection and was transferred to the pediatric intensive care unit. Bone marrow aspiration and biopsy confirmed B-cell acute lymphoblastic leukemia (ALL) with 64% lymphoblasts and marked marrow eosinophilia. Chromosomal analysis found intrachromosomal amplification of chromosome 21, a feature of high-risk ALL (1). The eosinophils were not malignant; the leukemia arose from B lymphocytes, with an associated paraneoplastic proliferation of eosinophils (**Figures 1A to 1C**). Lumbar puncture was performed, and cytarabine was administered into the spinal fluid as is standard of care for all patients with ALL, before spinal fluid analysis. Results showed no overt central nervous system involvement. Corticosteroid therapy for ALL was initiated. Computed tomography (CT) images of the chest, abdomen, and pelvis were obtained to assess disease burden. Cardiac CT revealed enhancement of the peripheral myocardium without enhancement of the subendocardium. Incidentally noted on chest CT was diffusely decreased perfusion to the left ventricular (LV) subendocardium (**Figures 2A and 2B**).

QUESTION 3: WHAT WOULD YOU EXPECT ON THE ECHOCARDIOGRAM AND ELECTROCARDIOGRAM, GIVEN THE CT FINDINGS?

A transthoracic echocardiogram, despite epinephrine, revealed low-normal systolic function (ejection fraction [EF], 56%) with stippled myocardium, suggestive of a diffuse infiltrative process (Video 1). Tissue Doppler assessment of the left ventricle suggested abnormal diastolic function. Serial electrocardiograms showed normal sinus rhythm with diffuse low voltage, complete right bundle branch block with a resultant prolonged QTc interval, and ischemic changes manifested by lateral ST-segment depression (**Figure 3**).

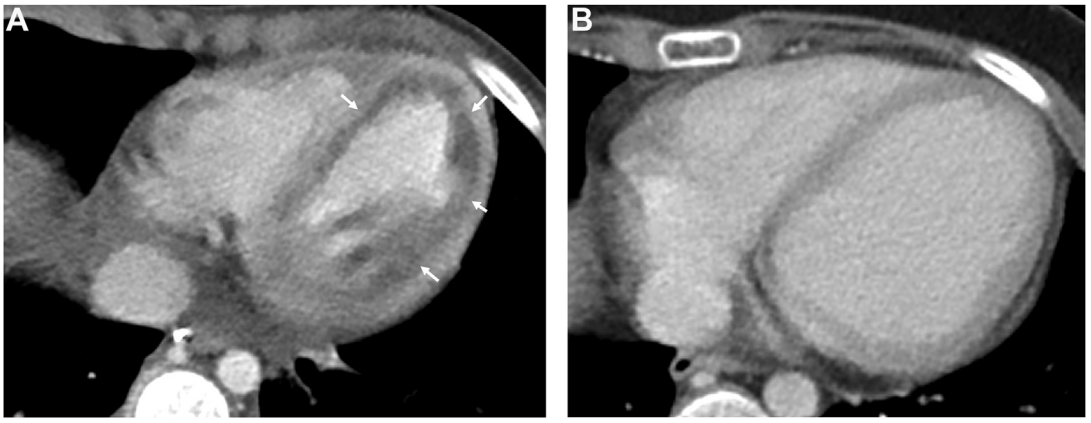
Troponin I peaked at 64 ng/ml and subsequently decreased in conjunction with resolving hypereosinophilia (**Figure 4**) and presumed improvement of myocardial eosinophilic infiltration. Milrinone was added on hospital day (HD) 5 for afterload reduction and inotropic support. Epinephrine and milrinone were discontinued on HD 10 and 14, respectively. Ventricular hypertrophy resolved over 4 weeks, although he continued to have mild LV systolic dysfunction and persistent diastolic dysfunction. Anthracycline agents were thus omitted from his induction chemotherapy, and his regimen was intensified with additional chemotherapeutic agents, including high-dose cytarabine and peg-asparaginase. At the end of induction chemotherapy, he was in remission, with no evidence of minimal residual disease. He was discharged home on HD 44.

FIGURE 1 Biopsy Findings



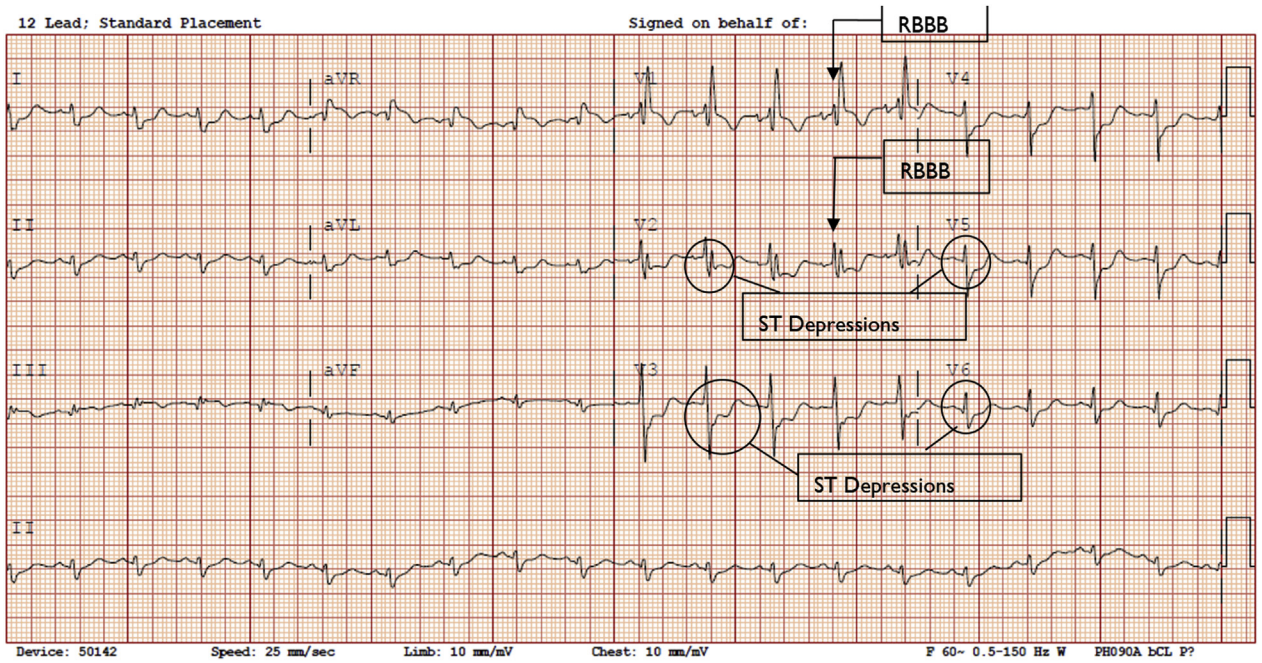
Bone marrow biopsy revealed B-cell acute lymphoblastic leukemia with 90% cellularity, including 64% lymphoblasts and 26% eosinophils. **(A)** Peripheral blood shows marked eosinophilia (bilobed cells with red granules) and thrombocytopenia. **(B)** Hypercellularity of bone marrow. **(C)** Positivity for terminal deoxynucleotidyl transferase and paired box 5 gene (B-cell markers).

FIGURE 2 **Pre- and Post-Treatment Chest Computed Tomography**



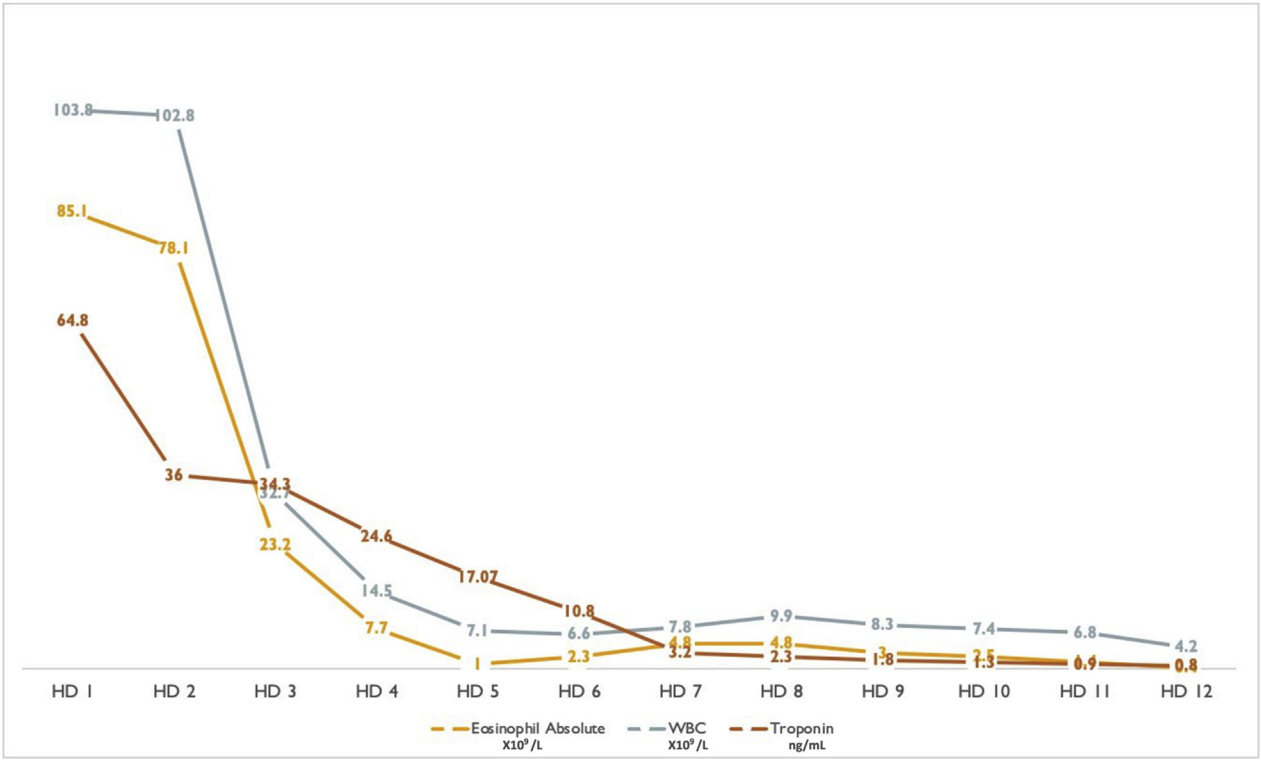
(**A)** Axial contrast-enhanced computed tomography image demonstrating diffusely abnormal left ventricular subendocardial myocardial perfusion **(white arrows)** corresponding to cardiac magnetic resonance findings. **(B)** Repeat computed tomography 6 months later, after treatment, demonstrating resolution of these findings.

FIGURE 3 **Electrocardiogram at Presentation**



The electrocardiogram shows normal sinus rhythm with diffuse low voltage, right bundle branch block (RBBB), and lateral ischemic changes manifested by ST-segment depression.

FIGURE 4 Trend of Laboratory Values



Gray = total white blood cell (WBC) count; **orange** = absolute eosinophil count; **brown** = troponin I. HD = hospital day.

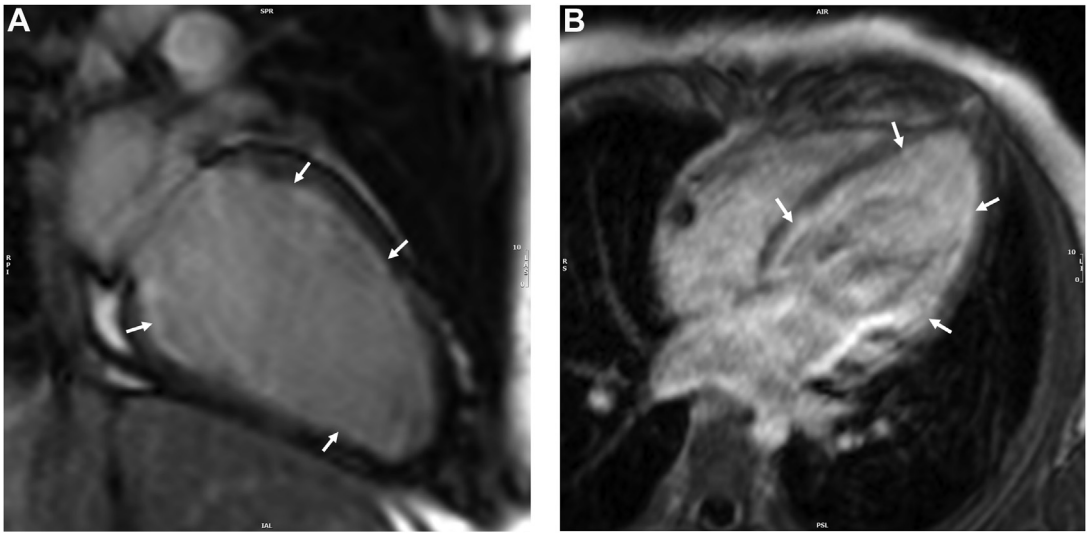
QUESTION 4: HOW HAS THE PATIENT BEEN MANAGED POST-DISCHARGE AND IN FOLLOW-UP?

Following hospital discharge, the patient received close cardiac surveillance and standard chemotherapy. Five months after the diagnosis, new mild LV dilation ($z = 2.5$ to 3) developed, with continued mild LV systolic dysfunction and new mild to moderate mitral regurgitation, presumably secondary to mitral valve annular dilation. He tolerated lisinopril and spironolactone for afterload reduction and diuresis. At 6 months after the diagnosis, cardiac magnetic resonance (CMR) revealed moderately reduced global LV function (EF 40%), with apical thinning and more severe dysfunction at the apex (Video 2). There was also mild diffuse subendocardial late gadolinium enhancement throughout the left ventricle (**Figures 5A and 5B**). Right ventricular function remained normal. During intensification chemotherapy, he received daunorubicin, 75 mg/m^2, with dexrazoxane (1:10) to ensure effective cardiac protection.

QUESTION 5: WHAT DIAGNOSIS IS CONSISTENT WITH THE CT AND CMR FINDINGS?

This patient received a diagnosis of B-ALL with paraneoplastic hypereosinophilic syndrome and infiltrative myocarditis. Given his tenuous clinical status at diagnosis, cardiac catheterization with myocardial biopsy was not performed. Instead, the stippled ventricular myocardium on echocardiogram and the CMR findings of circumferential LV subendocardial enhancement provided supportive evidence of eosinophilic infiltration.

FIGURE 5 Cardiac Magnetic Resonance Images Demonstrating Mild Diffuse Subendocardial Enhancement



The **white arrows** along the left ventricular myocardium from the base to the apex are compatible with eosinophilic myocarditis. **(A)** Post-contrast gadolinium enhanced cardiac magnetic resonance 3-dimensional T_1-weighted vertical long-axis image. **(B)** Horizontal long-axis gadolinium-enhanced post-contrast phase-sensitive inversion recovery image.

QUESTION 6: WHAT ARE THE INCIDENCE AND GENERAL OUTCOMES OF PATIENTS WITH A DIAGNOSIS OF EOSINOPHILIC MYOCARDITIS?

Eosinophilic myocarditis is an uncommon phenomenon in children, although it is associated with wide-ranging causes, including infectious, rheumatologic, immunologic, and oncological processes (2,3). Eosinophilic leukocytosis is reported in <1% of ALL cases, and hypereosinophilic myocarditis at presentation is very uncommon, although it is a determinant of significant mortality and morbidity (3-6). It has been infrequently reported, with 60 cases found in published reports (primarily pediatric patients), although few cases with high-risk features (4). Initial inflammation includes a predominance of lymphocytes and eosinophils leading to myocardial cell death, followed by an increased risk of thrombosis formation secondary to ventricular dilation and damage. Finally, fibrosis of the myocardium and valves develops, which consequently results in systolic dysfunction, valve regurgitation, and restrictive hemodynamics (2,6). Although fibrosis is typically mitigated with prompt response to the initial insult, once it occurs, the finding is irreversible.

Our patient's initial presentation in shock increased the challenge of reversing the eosinophilic infiltrative process. He had some improvement in ventricular function with reduction in hypereosinophilia, although he will likely have long-standing fibrosis-mediated myocardial damage, and he requires long-term anticongestive management with oral agents, as well as serial monitoring. Additionally, the myocardial injury required adjustments to the potentially cardiotoxic elements of his chemotherapy regimen to treat his high-risk ALL adequately, by first delaying and then minimizing the cumulative dose of anthracycline agents (7,8). His eosinophilia was reactive rather than of clonal origin, but the risk of end-organ damage and relapse still persists.

At 1 year following diagnosis, the myocardium has not normalized. Echocardiogram reveals mild mitral regurgitation without left atrial dilation, low-normal LV systolic function with EF 60%, and continued mild LV dilation (LV internal end-diastolic diameter $z = 3.4$; LV internal end-systolic diameter $z = 3.7$). Antileukemic therapy continues in the maintenance phase, as well as lisinopril and spironolactone. He has

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close subspecialty monitoring while gaining strength daily and is asymptomatic with daily activities and recreational athletics.

The diagnosis of paraneoplastic eosinophilic myocarditis should be considered in patients with ALL who present with impaired cardiac contractility and peripheral eosinophilia because prompt diagnosis informs acute management, affects subsequent oncological therapy, and may prevent the need for long-term cardiovascular support.

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KEY WORDS acute lymphoblastic leukemia, eosinophilia, myocarditis, pediatric

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

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