Hypereosinophilic Syndrome with Advanced-Stage Loeffler Endocarditis

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INTRODUCTION

Hypereosinophilic syndrome (HES) is a disease of persistent eosinophilia with end-organ damage in the absence of other causes of primary eosinophilia such as malignancy, allergic reaction, autoimmune disease, or parasitic infection.[1] Hypereosinophilic syndrome with cardiac involvement, also known as Loeffler endocarditis, is mainly characterized by eosinophilic endomyocardial infiltration. In adults with HES, the prevalence of cardiac involvement is 40%-50%.[2,3] Very few pediatric cases with cardiac involvement have been reported.[4]

CASE PRESENTATION

A previously healthy 7-year-old boy presented with a 2-month history of fever, fatigue, and weight loss. His physical exam was remarkable for tachycardia, pallor, petechiae, and hepatosplenomegaly. Laboratory workup revealed severe eosinophilia (absolute eosinophil count 40,000), anemia, thrombocytopenia, elevated troponin (TnI = 1.13 ng/mL), and elevated B-type natriuretic peptide (>3,000 pg/mL). Electrocardiogram showed sinus tachycardia. Chest x-ray was notable for pulmonary venous congestion.

A transthoracic echocardiogram (Figures 1, 2, Videos 1-3) revealed severe endomyocardial infiltrates affecting both ventricles. The right ventricular (RV) apex was nearly obliterated with extension of infiltrates into the infundibular wall. The left ventricular (LV) apex and free wall were prominently affected. Posterior mitral valve leaflet entrapment resulted in severe (visually estimated) mitral regurgitation (Figures 3-6, Videos 4-6). There was mild tricuspid regurgitation (visually estimated) with a peak velocity of 2.3 m/sec. The left atrial size was normal (22 mL/m^2, $Z = 1.25$). No RV or LV inflow or outflow obstruction was noted. There were no mobile thrombi. The LV size was normal (LV end-diastolic volume indexed = 66 mL, $Z = 1.2$). Left ventricular global systolic function was depressed (LV ejection fraction = 44%, $Z = -3.9$). Doppler evaluation showed abnormal diastolic indices (Table 1).

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Heart failure symptoms were treated with diuretics and inotropic support (milrinone). Systemic anticoagulation was started for prevention of thrombi formation. The patient was found to be FIP1L1-PDGFRA fusion gene negative and was initially treated with corticosteroids and hydroxyurea. With modest response to this treatment, imatinib was added to his regimen. After 4 weeks of treatment with imatinib, a follow-up echocardiogram demonstrated marked reduction of endomyocardial infiltrates (Figure 7). Global systolic function improved (LV ejection fraction 64%, $Z = 0$). There was notable improvement in diastolic indices (Table 1).

DISCUSSION

Hypereosinophilic syndrome is a potentially fatal disease with a prevalence of cardiac involvement of 40%-50%.[2,5,6] Cardiac complications are the leading cause of morbidity and mortality.[2] The most common presenting symptom is dyspnea in the setting of heart failure and/or mitral regurgitation.[2,7,8] Hypereosinophilic syndrome with cardiac involvement is rarely seen in the pediatric population. Only 10% of Loeffler endocarditis cases are seen in children under 16 years of age.[6]

The histopathological changes of cardiac involvement are divided into three stages. The first stage is defined by extensive tissue necrosis secondary to eosinophilic degranulation.[9] This stage is usually clinically silent, without significant findings on echocardiogram. The second stage is represented by intracardiac thrombi formation, exposing patients to a significant risk of thromboembolic complications. In the final stage, endomyocardial fibrosis prevails, with atrioventricular valve entrapment, restrictive or dilated cardiomyopathy, arrhythmia, and heart failure.[2] Interestingly, the semilunar valves are rarely affected.[10,11]

The diagnosis and staging of cardiac involvement in HES can be very challenging. Because the necrotic stage is clinically silent, most patients present in the thrombotic or fibrotic stage. Echocardiographic criteria for diagnosis and staging have been proposed, based on the presence and extent of infiltrates, valve dysfunction, and atrial and ventricular size.[12] Ultrasound-enhancing agents may be of value in patients with poor acoustic windows and have recently been approved by the Food and Drug Administration for use in children. In addition, ultrasound-enhancing agents are of particular value in the assessment of ventricular masses and create dark filling defects in the presence of thrombus. Cardiac magnetic resonance imaging is the diagnostic "reference standard" for tissue characterization and may detect patients in the silent necrotic stage. However, availability is limited, sedation is needed in younger patients, and the study involves gadolinium exposure. Endomyocardial biopsy also has the ability to diagnose patients in the necrotic stage but suffers from a high false-negative rate of up to 50%.[13]

Our patient's echocardiogram showed the pathognomonic findings of severe RV and LV endomyocardial infiltrates and mitral leaflet entrapment. Left ventricular systolic function and diastolic indices were abnormal. These changes are well described in the fibrotic stage; therefore we suspect this patient presented later in the disease

VIDEO HIGHLIGHTS

Video 1: Two-dimensional transthoracic echocardiogram, apical four-chamber view, apex down orientation with a superior-to-inferior sweep of the imaging plane to highlight the mass in the RV and LV apices. Note the characteristic echo appearance of Loeffler endocarditis with its smooth border and homogenous tissues that move with the underlying apical myocardium.

Video 2: Two-dimensional transthoracic echocardiogram, parasternal long-axis view with a rightward sweep of the imaging plane, which demonstrates the obliterated RV apex approaching the tricuspid annulus.

Video 3: Two-dimensional transthoracic echocardiogram, parasternal short-axis view with a basal-to-apical sweep of the imaging plane to emphasize the extent of the mass within the RV outflow tract.

Video 4: Two-dimensional transthoracic echocardiogram, apical four-chamber view, without and with color Doppler demonstrating the involvement of the lateral endocardium and the posterior mitral valve leaflet (PMVL). The PMVL was restricted, and this resulted in severe, eccentric posteriorly directed mitral regurgitation.

Video 5: Two-dimensional transthoracic echocardiogram, parasternal long-axis view, without and with color Doppler, demonstrating the mitral regurgitation that was interpreted as severe.

Video 6: Three-dimensional transthoracic echocardiogram volume-rendered short-axis display of the mitral valve from the perspective of the left ventricle demonstrating the mitral valve leaflet entrapment.

View the video content online at www.cvcasejournal.com.

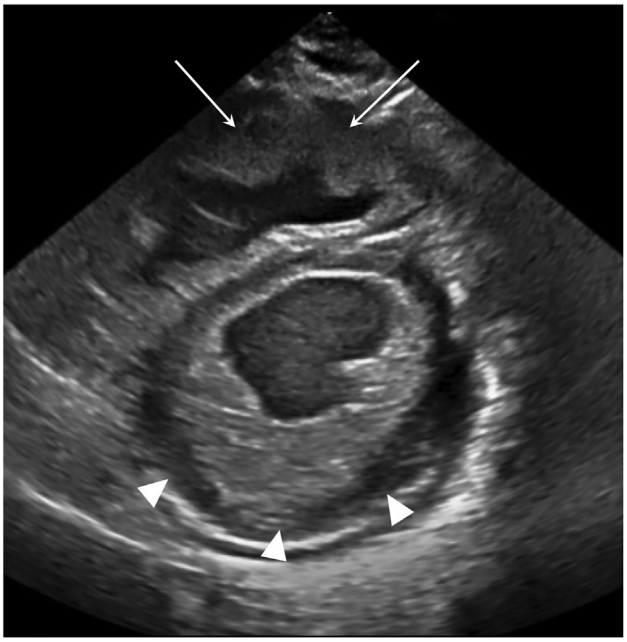

Figure 2 Parasternal short-axis view demonstrating infiltrates in the posterior left ventricle (*arrowheads*) and in the RV infundibular free wall (*arrows*).

course.[2,13] In view of the tenuous clinical condition and already established diagnosis, it was felt that the risks of cardiac magnetic resonance imaging or endomyocardial biopsy outweighed the benefits.

The treatment of HES is predominantly based on the presence of FIP1L1-PDGFRA fusion gene mutation.[5,14] Mutation-positive patients are expected to have a good response to imatinib, a tyrosine-kinase inhibitor. Mutation-negative patients are initially treated with steroids and hydroxyurea; however, some are also responsive to imatinib.[15] Heart failure symptoms are controlled with diuretics and

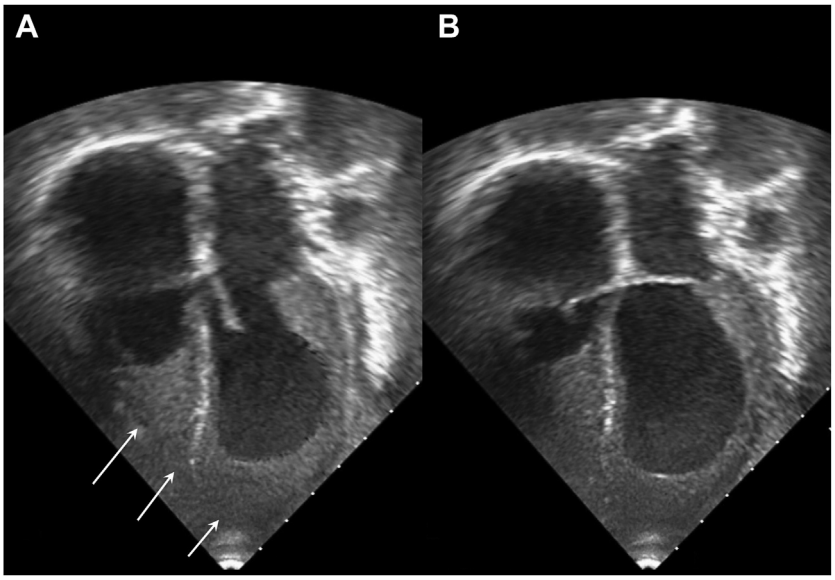

Figure 1 Apical four-chamber view in diastole **(A)** and systole **(B)** showing severe endomyocardial infiltrates within the LV and RV apex (*arrows*).

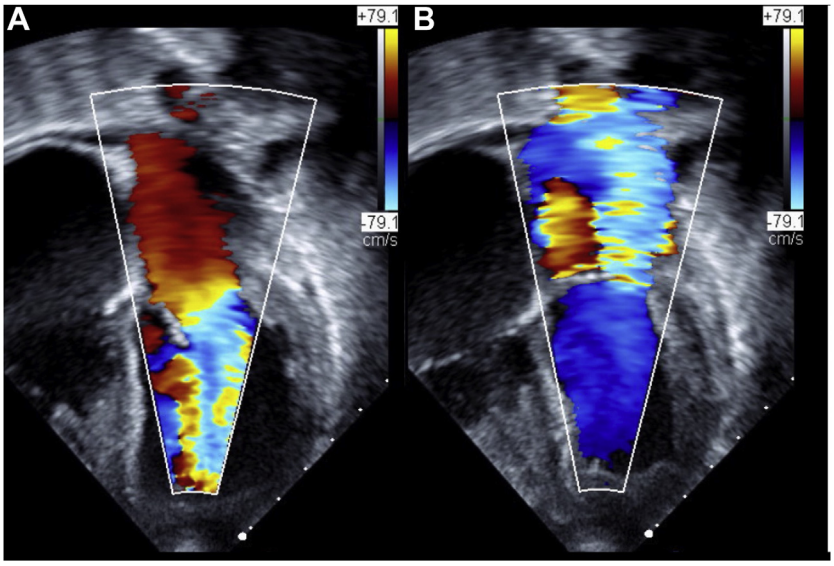

Figure 3 Apical four-chamber view in diastole **(A)** and systole **(B)** demonstrating severe mitral regurgitation.

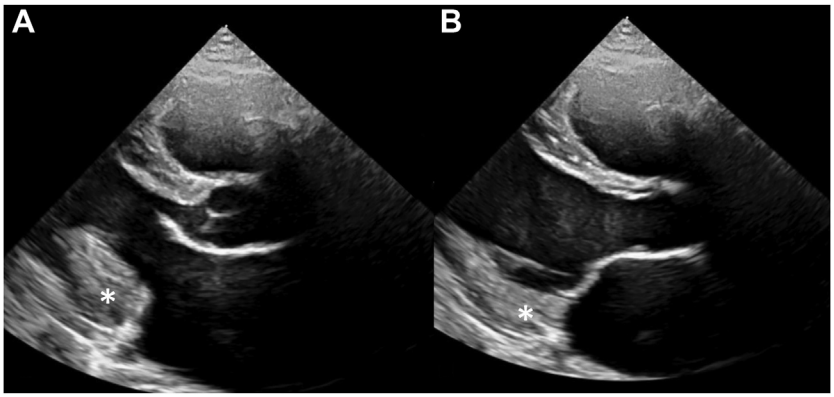

Figure 4 Parasternal long-axis view in diastole **(A)** and systole **(B)**. Note restricted movement of the posterior mitral valve leaflet in the setting of eosinophilic infiltration (*).

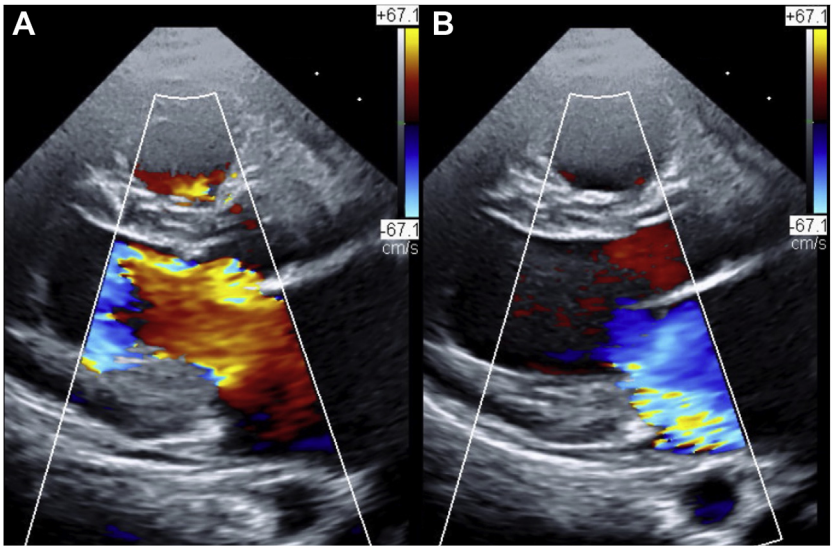

Figure 5 Parasternal long-axis view in diastole **(A)** and systole **(B)** demonstrating severe mitral regurgitation.

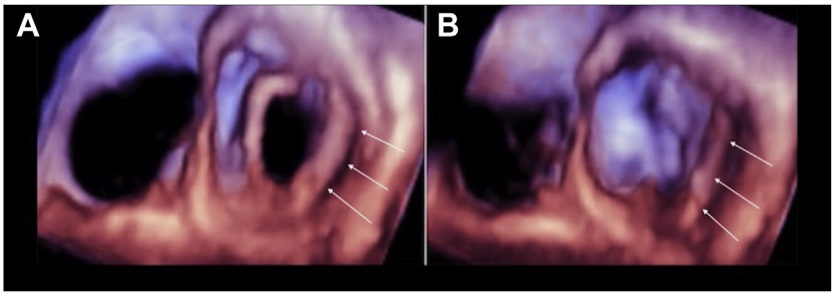

Figure 6 Three-dimensional transthoracic echocardiogram image of the mitral valve in diastole **(A)** and systole **(B)**, demonstrating restricted movement of the posterior leaflet (*arrows*).

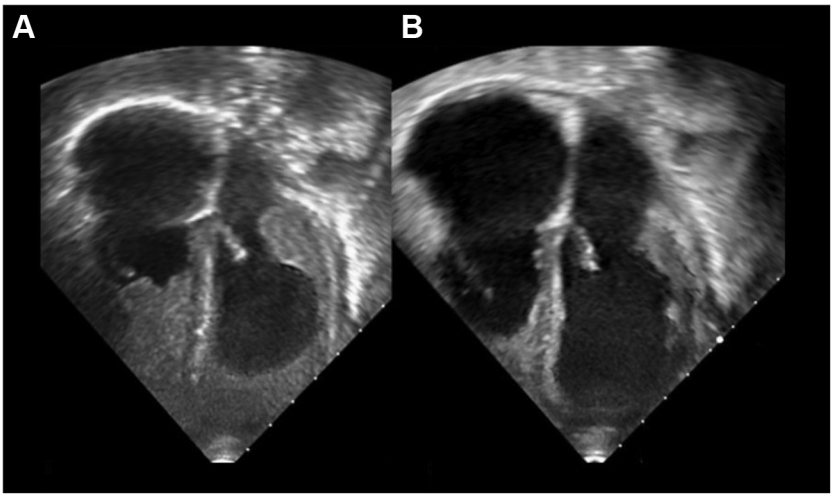

Figure 7 Comparison of infiltrates on initial **(A)** vs discharge **(B)** echocardiogram. Note partial resolution of previously extensive endomyocardial changes.

Table 1 Diastolic indices on initial versus discharge echocardiogram

	LV e', cm/sec	E/A ratio	E/e'
Initial echocardiogram	5.9	1.2	23 (Z = +11.6)
Discharge echocardiogram	11.3	1.3	16 (Z = +6.7)

inotropes. Systemic anticoagulation is an essential part of treatment as these patients are at high risk for thrombosis. The last treatment option is heart transplant. Despite the significant reduction of infiltrates and improvement in global systolic function, the patient continued to have abnormal diastolic indices and severe mitral regurgitation. He remained inotrope dependent and was transferred to a transplant center for further evaluation and management.

CONCLUSION

Cardiac involvement in HES carries a poor prognosis and significant mortality. Early detection and treatment are of utmost importance, and a multidisciplinary approach is essential. Echocardiography, an easily accessible tool, can be sufficient in the diagnosing and staging of Loeffler endocarditis.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.case.2022.02.004.

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