

Loeffler Endocarditis: A Manifestation of Hypereosinophilic Syndrome



Michael Arustamyan, DO, Jamael Hoosain, MD, Jennifer Mattson, MD, Syed Farhan Hasni, MD, Sung-Hae Cho, MD, and Paulina Gorodin Kiliddar, MD, *Philadelphia, Pennsylvania*

INTRODUCTION

Hypereosinophilia (HE) is defined as an elevated eosinophil count, $>1.5 \times 10^9/L$, on two separate tests >1 month apart, or the finding of tissue HE ($>20\%$ eosinophils) on bone marrow section.¹ Hypereosinophilic syndrome (HES) divides into hereditary, primary, or secondary (reactive); however, 75% of the time it is labeled as idiopathic. HE is a systemic disorder with various manifestations.

Loeffler endocarditis is an uncommon sequela of HE in which there is endomyocardial infiltration of eosinophils with degranulation, causing fibrosis and restrictive ventricular filling, more frequently left or biventricular involvement.² Patients typically present with weight loss, fever, cough, rash, and heart failure-associated symptoms.³ Diagnosis involves a thorough workup, especially in the evaluation of organ involvement, which helps establish HES versus HE.

Loeffler endocarditis is broken down into stages: early (necrotic), thrombotic, and fibrotic (late stage). Cardiac diagnosis begins with electrocardiography and signs and symptoms of cardiac dysfunction. Echocardiography is an important diagnostic tool in the diagnosis, and findings are dependent of the stage on patient presentation.¹

Treatment begins with high-dose corticosteroids, along with diuresis, afterload reduction, and anticoagulation. Here, we present a rare case of Loeffler endocarditis with isolated right ventricular involvement.

CASE DESCRIPTION

A 38-year-old African American woman presented with 1 week of progressive dyspnea on exertion and a diffuse rash. The rash started on the neck and progressed to involve her whole body, sparing her palms and soles. Furthermore, she endorsed new dyspnea on exertion with one block or five steps up a flight, without any previous limitations. She denied any recent travel or sick contacts. The patient also denied any chest pain or productive cough. Her medical history was significant for schizophrenia/bipolar disorder as well as a transient ischemic attack (TIA). During the evaluation of her TIA 2 months previously, a bubble study was found to be positive (Figure 1).

Home medications included risperidone and recently started naproxen. Her social history was notable for polysubstance abuse,

including extensive tobacco use as well as intranasal cocaine use in the past.

On presentation, the patient was afebrile with a blood pressure of 107/63 mm Hg, pulse rate of 114 beats/min, oxygen saturation of 99% on bilevel positive airway pressure, and a respiratory rate of 20 breaths/min. Her cardiovascular examination was unremarkable except for tachycardia, while her pulmonary examination was significant for wheezing. She had no jugular venous distention or lower extremity edema. There was no significant lymphadenopathy. Her physical examination was also notable for a diffuse, maculopapular rash, sparing the palms and soles.

Laboratory studies revealed a complete blood count significant for thrombocytopenia of 18,000, white blood cell count of 15.3, and an eosinophil count of 4,000, representing 26.2% of the differential (normal range, 0%–4%). Troponins were negative.

Clinical Impression and Differential Diagnosis

Given the patient's presentation of acute shortness of breath and sinus tachycardia, the top two diagnoses included pulmonary embolism and chronic obstructive pulmonary disease exacerbation. In addition, her HE (similar to her prior admission) and maculopapular rash prompted evaluation of other etiologies, such as autoimmune disease such as eosinophilic granulomatosis with polyangiitis, parasitic infections, HES, and secondary eosinophilia due to lymphoid or epithelial neoplasms.

Our patient was negative for influenza A. Human immunodeficiency virus was nonreactive. Hepatitis panel was negative. Antinuclear antibody was negative. Computed tomographic angiography revealed no pulmonary embolism but was significant for lung infiltrates that were likely eosinophilic and bilateral axillary and infraclavicular lymphadenopathy. Electrocardiography showed nonspecific ST-segment changes and T-wave inversions.

Transthoracic echocardiography demonstrated a dilated right ventricle with a large (2.9×2.8 cm) echodensity fixed to the right apex and a mosaic appearance with Definity (perflutren lipid microsphere; Lantheus Medical Imaging, North Billerica, MA) contrast, consistent with Loeffler endocarditis, and no left ventricular involvement (Figure 2; Videos 1-3). In addition, transthoracic echocardiography showed a flattened septum with mild tricuspid regurgitation. These findings were not present on transthoracic echocardiography done just 2 months prior during her TIA workup.

In light of these findings, hematology/oncology was consulted. Further workup for HE, including a lymphoproliferative disorder as well as possible autoimmune etiology, were pursued. *BCR-ABL*, *JAK2*, and *FIP1LI-PDGFR*A mutations were all negative. Workup for parasitic infection was also negative. Test results for perinuclear antineutrophil cytoplasmic antibody and cytoplasmic antineutrophil cytoplasmic antibody were negative ($<1:20$). The patient's immunoglobulin E level was significantly elevated at $11,733 \mu\text{g/L}$. A skin biopsy of her rash was nondiagnostic. A lymph node biopsy was performed and sent for both flow cytometry and pathology. Flow

Department of Internal Medicine (M.A.), Hahnemann University Hospital; Department of Cardiology (J.H., J.M.), Hahnemann University Hospital/Drexel University College of Medicine; and Department of Cardiology (S.F.H., S.-H.C., P.G.K.), Drexel University College of Medicine, Philadelphia, Pennsylvania.

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VIDEO HIGHLIGHTS

Video 1: Apical four-chamber view showing isolated right ventricular mass.

Video 2: Apical four-chamber with Definity contrast.

Video 3: Parasternal long-axis showing right ventricular mass.

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cytometry analysis revealed a CD45⁺ population comprising 93.6% of total cells analyzed, with mature B cells showing no aberrant immunophenotype and polyclonal with a kappa/lambda ratio of 1.1:1. The T cells also showed no loss or aberrant expression of pan-T-cell markers. The pathology report of the biopsy showed preserved nodal architecture with focal interfollicular expansion with a polymorphous population of plasma cells, few eosinophils, and small lymphocytes. There were no large Reed-Sternberg-like cells.

Management of this patient included intravenous methylprednisolone with a prolonged prednisone taper, intravenous immunoglobulin, and bridge to warfarin with a heparin drip. Her eosinophilia, rash, and dyspnea improved.

DISCUSSION

Our case is a rare presentation of an even rarer disease: Loeffler endocarditis. Moreover, the cause of our patient's HE makes this unique given the rarity of risperidone-induced HE.

Loeffler endocarditis is a rare diagnosis characterized by the unique imaging and laboratory findings as described. Eosinophilic states associated with this endocarditis include HES, lymphoma, carcinoma, and many others.⁴ There have also been reports of eosinophilic myocarditis in long-term use of antipsychotics.⁵

Our patient's endocarditis was unique in that she had isolated right ventricular involvement with no left ventricular involvement. Endomyocardial biopsy was discussed multiple times but deemed to be too dangerous given the location and worry that the thrombus would be dislodged. It was also difficult to ascertain the etiology of her HES. Her initial workup for parasites and mutations was negative. The patient underwent a punch biopsy of the skin, which was not diagnostic.

On the basis of our workup, as above, the etiology was risperidone-induced HE leading to endocarditis. Our patient was prescribed risperidone, and although she had inconsistent use in the past, she endorsed improved compliance in the 2 months between her TIA and her presentation of dyspnea.

Risperidone-induced HE is a rare phenomenon that is poorly understood. In a recent case report, Shukla and Aggarwal⁶ described HE associated with risperidone use; one possible mechanism is that risperidone blocks 5HT₂ receptors, which have an eosinophil chemoattractant profile. Considering the case of risperidone-induced HE in addition to the case series by Sahpaz *et al.*,⁵ we believe that our patient's cause can be attributed to her use of antipsychotics.

The cardiac pathology of HES is divided into three stages: the acute necrotic stage, described by HE with systemic illness; the thrombotic stage, characterized by infarcts; and the fibrotic stage, when fibrosis replaces the thrombi on the endocardium. This final stage leads to a

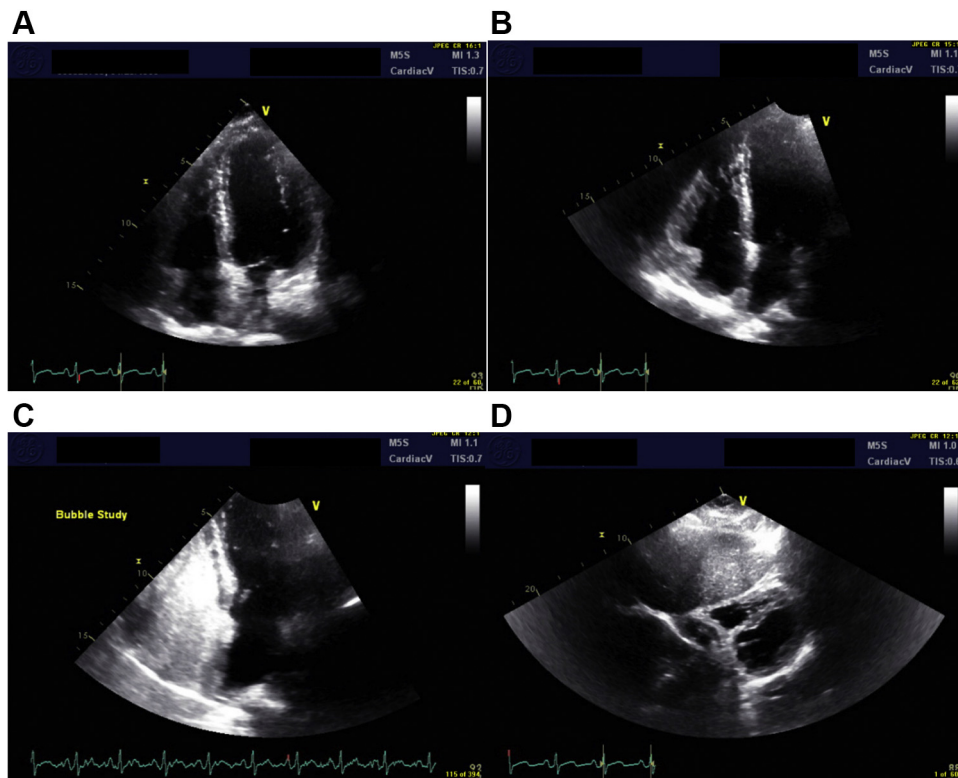


Figure 1 (A) Apical four-chamber view, (B) apical four-chamber with focus on right ventricle (no thrombus), (C) apical four-chamber view with positive bubble study, and (D) subcostal view with on thrombus in right ventricle.

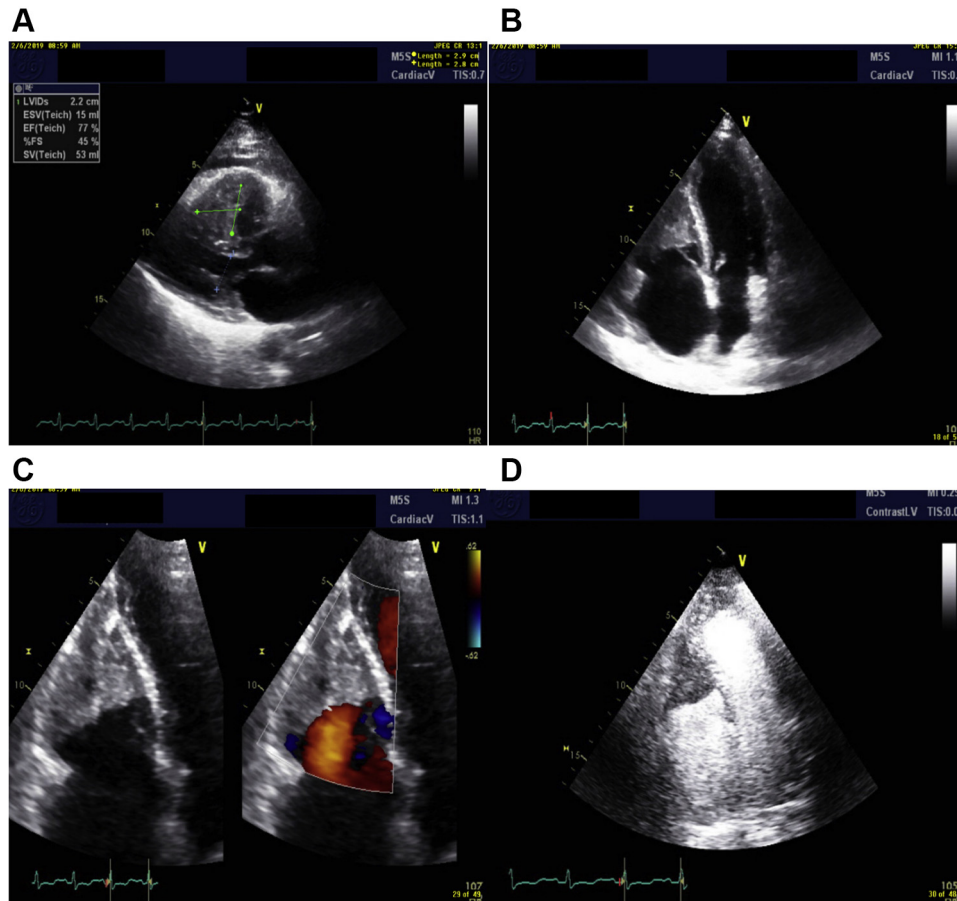


Figure 2 (A) Parasternal long-axis view with mass in right ventricle, (B) apical four-chamber view with isolated right ventricular (RV) thrombus, (C) apical four-chamber view with and without color flow Doppler, and (D) apical four-chamber view with Definity contrast demonstrating RV thrombus with no left ventricular involvement.

restrictive cardiomyopathy with symptoms of dyspnea and signs of left- or right-sided heart failure.¹

Electrocardiography, echocardiography, computed tomography, and cardiac magnetic resonance imaging are all useful in diagnosis, with endomyocardial biopsy being the most definitive. Corticosteroids are the cornerstone of therapy for HES to reduce eosinophil count. There has been some evidence that supports interferon, hydroxyurea, and other immunosuppressive medications. Once patients develop symptoms of heart failure, treatment with diuretics, β -blockers, and angiotensin-converting enzyme inhibitors is vital.⁷ Echocardiography should be used to follow the cardiac disease in intervals of <6 months. In refractory cases, especially those in the fibrotic stages, surgical intervention in the form of endocardectomy is indicated.

Our patient's symptoms did improve on high-dose steroids, and she was discharged on a prednisone taper, warfarin, and appointments to follow up with our outpatient cardiology office for serial echocardiography and cardiac magnetic resonance imaging, as well as hematology/oncology for further workup. Our case presentation also highlights the importance of early recognition of this disease, which was evaluated using a simple and cost-effective complete blood count as part of the initial test.

Follow-Up

The patient was readmitted a few months later in an adrenal crisis, as she had run out of steroids. At that point, she did undergo repeat echocardiography, which showed no change in thrombus size, which may be due to questionable compliance.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.case.2019.10.008>.

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