

Idiopathic Hypereosinophilic Syndrome Presenting as Severe Loeffler's Endocarditis

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Introduction

Loeffler's endocarditis, also known as Loeffler's endomyocardial disease, was first described by Wilhelm Loeffler in a patient with progressive heart failure due to eosinophilic infiltration of the endomyocardium, which was found to be secondary to peripheral eosinophilia¹. It appears to be a subset of hypereosinophilic syndrome (HES), in which the heart is predominantly involved, characterized by fibrous thickening of the endocardium of one or both ventricles leading to apical obliteration and restrictive pathophysiology resulting in multiple cardiovascular complications.

Case Report

A 42-year-old housewife presented with a persistent non-productive cough and dyspnea on exertion of seven-month duration, which gradually progressed to dyspnea at rest associated with orthopnea over the last 2 weeks. A history of anti-allergic medications used at the onset of symptoms was elicited, and her medical records revealed an increased peripheral eosinophilic count ($7.8 \times 10^9/l$). Detailed physical examination revealed elevated jugular venous pressure 6 cm above the angle of Louie, which was further elevated on deep inspiration. She also had bilateral pedal edema, a pansystolic murmur over the apex radiating to the axilla, fine inspiratory crackles over the lung bases and mild tenderness over the right hypochondrium. Her blood counts revealed peripheral eosinophilia ($12 \times 10^9/l$) which remained persistently elevated $>10 \times 10^9/l$ on serial blood counts (Figure 1A). Her CPK-MB was elevated but cardiac troponin levels were within normal limits. Electrocardiogram showed non-specific ST-T wave changes with delayed intraventricular conduction consistent with myocarditis. Chest radiography revealed infiltrates involving the

bilateral basal zones, extending up to the perihilar region, along with pleural effusion. Ultrasonography documented a prominent inferior vena cava and hepatic vein. Her blood sugar levels, thyroid, renal and liver function tests were all normal.

Her peripheral blood smear examination failed to reveal any parasites. Routine stool examination did not detect the presence of any ova or cysts. Immunological studies, including antinuclear antibody levels and serum IgE levels, were within normal limits. Bone marrow examination revealed a normal cellular marrow with myeloid cells seen in all stages of maturation, along with a prominence of eosinophilic precursors and no evidence of any immature cells or parasites. (Figure 1B).

On 2-D transthoracic echocardiography, the left and right atria were markedly dilated when compared to near-normal-sized ventricles. Left ventricular ejection fraction was 65%, however, the left ventricle was hypertrophied near the apex and posterior wall. A thickening of the posterior mitral leaflet was seen along with minimal pericardial effusion. Mitral inflow velocity studies showed an E/A ratio of 3.5 with a deceleration time of 95 msec, suggesting severe diastolic dysfunction. Color Doppler imaging showed significant mitral regurgitation along with tricuspid regurgitation, with no evidence of any thrombus within the endocardium. The findings were consistent with severe restrictive cardiomyopathy (Figure 2). High resolution computed tomography ruled out the involvement of lung parenchyma and/or lymph nodes.

Based on the detailed clinical evaluation and persistently elevated eosinophil counts for more than six months, supported by electrocardiographic findings suggestive of myocarditis and classical findings on 2-D echocardiogram consistent with severe restrictive cardiomyopathy, the diagnosis of Loeffler's endocarditis secondary to HES was established. The patient was treated with oral corticosteroids (1mg/kg/d) and anticoagulants, along with diuretics for congestive symptoms. She experienced symptomatic relief by the second day of treatment, but peripheral eosinophilia persisted. The dosage of oral corticosteroids was then increased to 2mg/kg/day; the patient responded well, with her eosinophil count decreasing to normal range within the next 48 hours. Electrocardiographic changes began reverting to baseline by the end of first week. Anticoagulants were discontinued due to a labile INR. There was no thrombus within the endocardium and the patient was started on a platelet inhibitor (Aspirin). Repeat echocardiography performed three weeks later showed no significant improvement in diastolic function and the patient was discharged on oral corticosteroids and diuretics and was advised to follow up regularly as an outpatient.

Keywords

Cardiomyopathy, Restrictive; Hypereosinophilic Syndrome; Mesylates.

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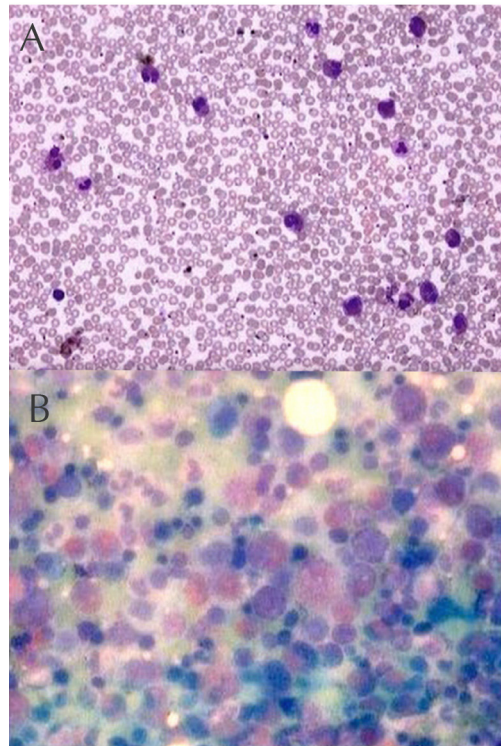


Figure 1: A - Peripheral blood smear (low power field) showing eosinophilia. B - Bone marrow picture showing myeloid cells in all stages of maturation, with prominence of eosinophilic precursors.

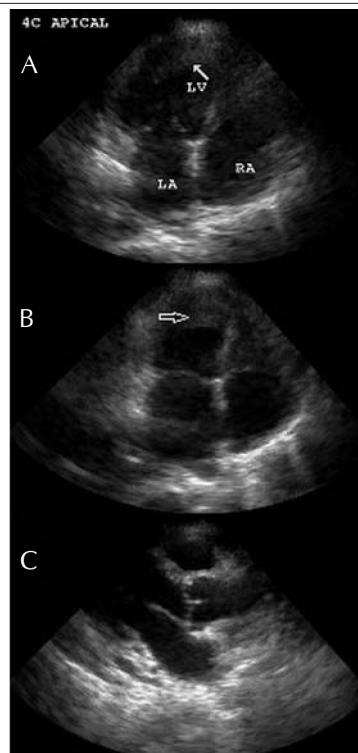


Figure 2: Echocardiography A - Apical four chamber view showing dilated left atrium (LA) and right atrium (RA) with hypertrophy of left ventricular wall (arrow). B - Oblique view showing hypertrophied left ventricular wall (arrow) with obliteration of ventricular cavity. C - Left parasternal (LPS) view showing thickening of posterior mitral leaflet.

Discussion

Idiopathic hypereosinophilic syndrome is characterized by persistent elevation of absolute eosinophil count to $1.5 \times 10^9/l$ or above for a period of at least 6 months, where the underlying cause cannot be found despite comprehensive evaluation. This condition is associated with eosinophil-mediated end organ damage, manifesting as pulmonary, cardiac and/or neurological involvement.

HES is a heterogeneous group of conditions broadly classified as (A) Primary- which is synonymous with idiopathic HES, (B) Secondary - caused by infections (most commonly parasitic and helminthic), allergic disorders, medications, autoimmune disorders, endocrinopathies and metastatic malignancies and (C) Clonal- which includes acute leukemias, chronic myeloid disorders and myeloproliferative syndromes.

Cardiac involvement is the most common extra-hematologic manifestation of HES (50-60%)². Loeffler's endomyocardial disease is a subcategory of HES where the heart is predominantly involved. Eosinophils can survive in the tissues for weeks and the degranulation of activated eosinophils is thought to be responsible for the toxic damage caused to the heart. Toxins released by the eosinophils include eosinophil-derived neurotoxin, cationic protein, major basic protein and reactive oxygen species. These toxins may damage endothelial cells and myocytes, leading to necrosis and thrombosis and eventually culminating in endomyocardial fibrosis. Valvular involvement may manifest as regurgitation involving the mitral and tricuspid valves secondary to intense inflammatory changes within the endocardium and papillary muscle dysfunction. In addition, there may be superimposed thrombus formation resulting in cardio-embolic manifestations.

The clinical presentation is characterized by a slowly progressive heart failure, secondary to restriction of the ventricles caused by fibrosis and obliteration of the ventricular chambers. This may be complicated by episodes of atrial fibrillation, thromboembolic phenomenon or acute carditis. 2-D echocardiography is the critical imaging modality for the diagnosis and follow-up of these patients. The echocardiographic hallmark of Loeffler's endocarditis includes a restrictive pattern of filling with relatively preserved left ventricular systolic function³. Other characteristic findings include thickening of the left ventricular posterior basal wall, restricted motion of the posterior leaflet of the mitral valve, apical obliteration of one or both ventricles and hyperdynamic contraction of the spared ventricular wall with bilateral atrial enlargement. Cardiac catheterization reveals markedly elevated ventricular filling pressures with mitral or tricuspid regurgitation. Cardiac magnetic resonance imaging (MRI) permits an accurate functional and anatomical study, and discriminates between tissue compositions. Gadolinium-enhanced MRI accurately identifies regions of myocardial fibrosis and can be of diagnostic assistance when a ventricular thrombus is suspected. Percutaneous endomyocardial biopsy often confirms diagnosis; however, due to patchy involvement of the endomyocardium, the results may be inconsistent.

The therapeutic approach towards this entity is normalization of peripheral eosinophilia, since it has been postulated that the cardiac damage is secondary to eosinophils'

degranulation-related toxicity rather than the underlying disease process itself. Corticosteroids are the first-line drugs. Response can occur as early as five to six hours after initiation of treatment, which is revealed as a decreased eosinophil count. In steroid-resistant patients, cytotoxic drugs such as hydroxyurea and Interferon- α are an alternative therapeutic approach⁴. Recently, the tyrosin-kinase inhibitor imatinib has emerged as an effective additional alternative causing a rapid regression of both the eosinophilic proliferation and the endomyocardial disease, especially when FIP1L1-PDGFR fusion gene mutations are present⁵. All of these individuals achieve a complete hematological and molecular remission within weeks to months of starting imatinib therapy.

The overall prognosis for patients with Loeffler's endocarditis is poor and depends on the location of involvement in the heart. In treating the eosinophilia it is possible to halt the progression of the disease, but the damage already done may be enough to result in lethal consequences. Heart failure can be managed conventionally with diuretics and vasodilators. Appropriate anticoagulation therapy, along with a corticosteroid or a cytotoxic agent, not only prevents pulmonary or systemic embolic events and thrombus growth but also limits the obliteration of the ventricular chamber, thereby inducing a favorable long-term left ventricular remodelling⁶. With an advanced restrictive process and refractory congestive heart failure, the only potential approach is endocardectomy; however, it is associated with high morbidity and mortality and does not prevent disease recurrence. Repair or replacement of mitral and tricuspid valves may be attempted, depending on the severity of valvular insufficiency.

Loeffler's endocarditis is primarily confined to the temperate belts with a predilection for males. The present case, a middle-aged female from a tropical region, represents an unusual presentation of this rare disease entity. This disease can be aggressive and fatal. A better understanding of the pathophysiological process is essential to formulate effective treatment plans, and to significantly reduce the mortality rates associated with this disease.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Aggarwal HK, Jain D; Acquisition of data: Jain D, Kaverappa V, Jain P; Analysis and interpretation of the data: Jain D, Kaverappa V, Jain P, Kumar A; Statistical analysis: Jain D, Kaverappa V, Jain P, Kumar A, Yadav S; Writing of the manuscript: Kaverappa V, Jain P, Kumar A, Yadav S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any post-graduation program.

References

1. Loeffler W. Endocarditis parietalis fibroplastica mit Bluteosinophilie, Eineigenartiges Krankheitsbild. *Schweiz Med Wochenschr.* 1936;66:817-20.
2. Weller PF, Bubley GJ. The idiopathic hypereosinophilic syndrome. *Blood.* 1994;83(10):2759-79.
3. Parrillo JE. Heart disease and the eosinophil. *N Engl J Med.* 1990;323(22):1560-1.
4. Schandene L, Roufosse F, de Lavarelle A, Stordeur P, Eflira A, Kennès B, et al. Interferon alpha prevents spontaneous apoptosis of clonal Th2 cells associated with chronic hypereosinophilia. *Blood.* 2000;96(13):4285-92.
5. Cools J, DeAngelo DJ, Gotlib J, Stover EH, Legare RD, Cortes J, et al. A tyrosine kinase created by fusion of the PDGFRA and FIP1L1 genes as a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med.* 2003;348(13):1201-14.
6. Lofiego C, Ferlito M, Rocchi G, Biagini E, Perugini E, Branzi A, et al. Ventricular remodeling in Loeffler endocarditis: implications for therapeutic decision making. *Eur J Heart Fail.* 2005;7(6):1023-6.