

Eosinophilic Heart Disease: Pathophysiology, Diagnosis, and Management – A Narrative Review

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Abstract: Eosinophilic heart disease (EHD) is an inflammatory cardiac disorder characterized by the infiltration and subsequent heart tissue damage mediated by eosinophils. The clinical manifestations of EHD vary widely, ranging from asymptomatic to severe, life-threatening conditions. Diagnosis relies on a multimodal approach, incorporating clinical presentations, laboratory findings (e.g. hypereosinophilia), and advanced imaging studies such as cardiac magnetic resonance imaging (MRI) and echocardiography. However, the gold standard for definitive diagnosis remains endomyocardial biopsy, which demonstrates eosinophilic infiltration and associated myocardial injury. Currently, there is no established consensus on specific therapeutic protocols for EHD. Management primarily targets the underlying etiology and mitigates eosinophil-induced cardiac damage. Prognosis is highly variable and largely dependent on the causative pathology, with outcomes spanning from rapidly progressive and fatal courses to indolent, chronic disease progression. Given the heterogeneity in clinical presentation and treatment responses, there is an urgent need for evidence-based clinical guidelines to standardize the management of EHD.

Keywords: eosinophilic heart disease, hypereosinophilia, clinical presentation, endomyocardial biopsy, prognosis

Introduction

Eosinophilic heart disease (EHD) is a cardiac disorder characterized by inflammatory damage and dysfunction resulting from eosinophilic infiltration and subsequent tissue injury.^{1,2} Although EHD is considered rare, its precise incidence remains difficult to ascertain due to underdiagnosis and variability in clinical presentation. There are numerous etiologies associated with EHD, such as hypersensitivity reactions,³ hypereosinophilic syndrome (HES),⁴ and eosinophilic granulomatosis with polyangiitis (EGPA),⁵ parasites infections.⁶ However, idiopathic or undefined EHD has been reported as the most prevalent form,^{1,7,8} accounting for approximately 30%.⁸ Clinical manifestations range from asymptomatic cases to life-threatening complications, with a notable in-hospital mortality rate.^{1,7,8} While the exact pathogenic mechanisms of EHD remain incompletely elucidated, current evidence suggests that eosinophil-mediated inflammatory responses play a central role in disease progression, making them a key therapeutic target.^{1,2,7,8} To date, no standardized treatment protocol exists for EHD. Management is primarily guided by the underlying etiology when identifiable. Corticosteroids are frequently employed in acute settings, while adjunctive or alternative immunosuppressive therapies may be considered in steroid-refractory cases.^{1,8,9} In this review, we provide a comprehensive overview of the clinical spectrum, underlying pathophysiological mechanisms, diagnostic approaches, and current treatment strategies for EHD, with focuses on clinically relevant aspects of EHD to facilitate early diagnosis, optimize diagnostic strategies, and guide practical management.

Clinical Presentation

EHD demonstrates a broad spectrum of clinical manifestations, ranging from asymptomatic presentation to life-threatening cardiac compromise, reflecting the disease's progressive nature and varying degrees of myocardial involvement. In the initial stages prior to overt cardiac involvement, patients frequently exhibit common cold symptoms, such as fever, sore throat, and

cough, or symptoms of allergic disorders such as bronchial asthma, rhinitis, or urticaria,^{1,2,7} or other non-specific symptoms (nausea, fatigue, myalgia, et al)¹ With disease progression and myocardial infiltration, patients may have cardiac symptoms such as chest pain, shortness of breath, chest palpitations, light headedness, heart failure and heart arrhythmias, and syncope.^{1,6–8} EHD can manifest as acute fulminant myocarditis, leading to cardiogenic shock, lethal heart failure, or sudden cardiac death (the most severe presentation). Alternatively, it may progress to chronic restrictive cardiomyopathy, indicative of extensive eosinophilic infiltration and myocardial fibrosis.^{1,6,7,10} According to the analysis in patient with histologically proven EHD by Brambatti M et al,¹ dyspnea is the most common symptom of EHD, following by chest pain and other non-specific symptoms.

Laboratory tests usually reveal hypereosinophilia, seen in over 90% patients,^{1,7,8} although elevated blood eosinophil counts may not occur during the early phase of the disorder.⁹ Other inflammatory markers, such as increased creatine kinase-MB and troponin levels, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were also observed in EHD patients.^{1,8,9} In addition, patients may also have abnormal electrocardiograms such as ST segment-T wave abnormalities.^{1,9} Reduced left ventricular ejection fraction (LVEF) and pericardial effusion can be also noticed by echocardiography, but pericardial tamponade is barely seen.¹ Due to its nonspecific presentation, EHD is frequently misdiagnosed in the absence of comprehensive diagnostic evaluation.

The clinical heterogeneity of EHD underscores the importance of maintaining high diagnostic suspicion, particularly in patients with peripheral eosinophilia who develop new cardiac symptoms.

Pathophysiology

Eosinophils play a crucial role in the immune system, primarily involving in host defense against parasites and modulating allergic reactions.¹¹ Upon activation, eosinophils release toxic proteins (eg. metalloproteinases, eosinophil peroxidase, eosinophil-derived neurotoxin, major basic protein and eosinophil cationic protein) from their granules, these proteins exert potent parasiticidal effects but can also induce collateral tissue damage when dysregulated. Additionally, eosinophils secrete reactive oxygen species (ROS)—such as hypobromite, hypobromous acid, superoxide, and peroxide—which further amplify inflammatory cascades.^{11,12} Under physiological conditions, eosinophils are predominantly localized in the gastrointestinal tract, respiratory mucosa, and skin. However, during hypereosinophilic states, they infiltrate extraneous tissues, including the myocardium.^{1,11,12} When overproduced and over-activated, eosinophils will attack seemingly normal tissue (eg. heart muscle), and thereby produce serious damage such as heart failure.^{1,11} Current evidence suggests that eosinophils infiltrate cardiac tissue during hypereosinophilic conditions, inducing inflammatory responses and subsequent myocardial damage.^{1,13} The characteristic pathological manifestations typically include myocardial edema, capillary leakage, tissue hyperemia, cellular necrosis, and ultimately fibrotic scar formation,^{1,12,13} the clinical manifestations were cardiac insufficiency (reduced LVEF) with other cardiac symptoms.

Diagnosis

Early diagnosis is critical for mitigating the progressive cardiac damage associated with EHD. Diagnosis often involves a combination of clinical presentations, blood tests (to check for eosinophilia), imaging studies like echocardiography and cardiac MRI, and endomyocardial biopsy if possible. While EHD typically presents with nonspecific clinical manifestations, the constellation of peripheral blood eosinophilia (absolute eosinophil count $> 1.5 \times 10^9/L$) with concurrent cardiac abnormalities should raise strong suspicion for this diagnosis. It is noteworthy that up to 22% of patients may demonstrate normal eosinophil counts during early disease stages, potentially delaying diagnosis.^{1,10} Image studies can provide critical evidence of cardiac involvement. For example, echocardiography typically shows poorly contracting left ventricle with or without enlarged chambers. Other findings such as left ventricular hypertrophy, involvement of the mitral and/or tricuspid valves may be present but non-specific.^{1,10,13} Cardiac MRI is very useful for diagnosing EHD. An increased signal in T2-weighted images and an increased global myocardial early enhancement ratio between myocardial and skeletal muscle in enhanced T1 images were important findings. Additionally, enhanced gadolinium uptake in the sub-endocardium was a marker of EHD.^{10,14} Endomyocardial biopsy remains the diagnostic gold standard, revealing eosinophilic infiltration to myocardia and pathological signs of cardiac damages, such as myocardial edema, capillary leakage, hyperemia, cell necrosis, or fibrosis scar formation.^{10,15,16} However, the clinical application of endomyocardial biopsy is limited by its invasive nature,

specific contraindications (including acute myocardial infarction, left ventricular thrombus, and ventricular aneurysm), and a diagnostic sensitivity of only approximately 50%—attributed to the typically focal pattern of myocardial infiltration.¹⁷ Furthermore, the procedure requires specialized technical expertise and carries increased risks in patients with significant cardiomegaly, severe heart failure, or recent infection.

Treatment

Currently, no evidence-based guidelines or consensus statements exist for the standardized management of EHD. Therapeutic strategies primarily focus on three key aspects: (1) addressing the underlying etiology of eosinophilia, (2) suppressing eosinophil-mediated cardiac inflammation, and (3) managing associated cardiac complications. When an identifiable cause is present—such as parasitic, fungal, or viral infections—targeted antiparasitic or antimicrobial therapy is typically initiated. However, in approximately 60–70% of EHD cases, the underlying etiology remains undetermined, warranting empirical immunosuppressive therapy. In such case, non-specific treatment, such as mepolizumab, azathioprine or cyclophosphamide is usually useful for managing allergic and autoimmune diseases (eg. eosinophilic granulomatosis).^{10,15} During the acute phase of EHD, high-dose glucocorticoids constitute the mainstay of treatment, followed by gradual tapering to a low-dose maintenance regimen to mitigate disease progression and prevent relapse.¹⁶ Studies indicate that corticosteroid therapy is effective in up to 85% of patients with hypereosinophilic syndrome or eosinophilic granulomatosis with polyangiitis.¹⁸ For patients who are refractory to steroids, immunosuppressive agents such as cyclophosphamide, methotrexate, or azathioprine—used either alone or in combination with steroids—have demonstrated efficacy.¹⁹ Idiopathic hypereosinophilias can be treated with corticosteroid, but alternative drug therapies include hydroxyurea or tyrosine kinase inhibitors (eg. imatinib or mepolizumab) is also recommended if they are refractory to corticosteroid therapy.^{20,21} Additionally, other biologics, such as anti-interleukin (IL)-5 and the anti-IL-5 receptor monoclonal antibodies mepolizumab and benralizumab, have been shown to be safe and effective corticosteroid-sparing agents in several trials.^{22–24}

Similar to other fulminant myocarditis, EHD can also induce life-threatening complications, such as malignant arrhythmia, cardiogenic shock or sudden death, therefore management of severe cardiac complications using mechanical adjuvant therapies (eg. ventricular assist device, intra-aortic balloon counterpulsation, and extracorporeal membrane oxygenation) are also recommended.^{12,25,26} Transition to maintenance therapy should be guided by serial echocardiographic improvement, sustained eosinophil count normalization and clinical symptom resolution. This tiered therapeutic approach balances aggressive disease control with minimization of treatment-related complications, particularly important given the frequent need for prolonged immunosuppression in EHD management.

Prognosis

The prognosis of eosinophilic heart disease (EHD) varies widely, ranging from rapidly fatal to chronic or non-fatal, depending largely on the underlying etiology. Patients with helminthic infection generally respond well to antiparasitic therapy and typically have a favorable prognosis. In contrast, acute necrotizing forms are associated with a mortality rate of up to 50%.^{1,13} The most common clinical course involves progression at a moderate pace over months to years. Beyond the rate of inflammatory myocardial injury, the prognosis of EHD is also heavily influenced by the primary disease, with the highest in-hospital mortality observed in hypersensitivity-related forms (36.1%).¹

Long-term outcomes for survivors of chronic EHD are characterized by a high risk of relapse and significant cardiac damage. Modern therapies have improved survival rates - with over 80% of patients surviving five years after diagnosis. The disease often leaves lasting, sometimes irreversible, structural cardiac damage, such as endomyocardial fibrosis (EMF), leading to chronic heart failure and a reduced long-term quality of life.

Conclusion

EHD is a rare but life-threatening disorder characterized by eosinophil-mediated myocardial injury. The clinical manifestations of EHD are highly variable and non-specific. Diagnosis involves a combination of clinical presentations, blood tests and imaging studies, but endomyocardial biopsy is the gold standard. Despite the absence of standardized treatment protocols, management focuses on addressing the underlying etiology of eosinophilia, suppressing eosinophil-

mediated inflammation, and managing associated cardiac complications. Future prospective studies and international registries are needed to define standardized diagnostic criteria and evidence- based treatment algorithms.

Data Sharing Statement

The original contributions presented in the study are included in the article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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