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Case Report

Myocarditis and Eosinophilia: Three Cases of Hypereosinophilic Syndrome and Myocarditis

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ABSTRACT

Eosinophilic infiltration is a rare and underrecognized cause of myocarditis associated with prolonged eosinophilia. Before advanced imaging and routine biopsy, patients were diagnosed with an idiopathic cardiomyopathy with subsequent diagnosis made on autopsy. We present 3 cases of eosinophilic myocarditis diagnosed by cardiac biopsy classified as hypereosinophilic syndrome. Two patients presented with severe left ventricular dysfunction, and 1 patient presented with cardioembolic stroke. All patients were successfully treated with glucocorticoid therapy. Our cases highlight the importance of early diagnosis with endomyocardial biopsy and prompt immunosuppressive treatment.

RÉSUMÉ

L'infiltration par les éosinophiles est une cause rare et non reconnue de myocardite associée à une éosinophilie prolongée. Avant l'imagerie avancée et la biopsie systématique, le diagnostic de cardiomyopathie idiopathique était posé après l'autopsie des patients. Nous présentons 3 cas de myocardite à éosinophiles dont la biopsie cardiaque a permis de poser le diagnostic de syndrome d'hyperéosinophilie. Deux patients ont présenté une dysfonction grave du ventricule gauche, et 1 patient a présenté un accident vasculaire cérébral d'origine cardio-embolique. Le traitement par glucocorticoïdes s'est avéré réussi chez tous les patients. Nos cas montrent l'importance du diagnostic précoce par biopsie endomyocardique et du traitement immunosuppresseur hâtif.

Eosinophils typically constitute between 0% and 7% of leukocytes and release cytotoxic granules that help to mediate tissue damage. Myocardial eosinophilic involvement was first reported in 1936 described as "fibroplastic parietal endocarditis with blood eosinophilia" and diffuse focal myocardial inflammation on pathology.[1] Sustained eosinophilia has reported cardiac involvement as high as 82% with a 5-year mortality at 30%.[2] We present 3 cases of hypereosinophilic syndrome (HES).

Case 1

An 81-year-old woman with asthma, reflux, and gastric erosions presents with a 4-week history of New York Heart Association (NYHA) III heart failure. Her physical examination results were remarkable for sinus tachycardia with frequent ectopy, hypotension (mean arterial pressure [MAP] of 65 mm Hg), elevated jugular venous pressure, and S3 and S4 with a holosystolic murmur radiating to her axilla. There were bibasilar crackles and pedal edema present (Fig. 1).

Her investigations were remarkable for eosinophilia (16.1 × 10^9/L), moderate to severe left ventricular (LV) systolic dysfunction, and moderate mitral regurgitation by echocardiogram. A right ventricle (RV) biopsy was performed with findings of eosinophilic myocarditis, and HES was diagnosed in the patient. She had a rapid clinical response to high-dose glucocorticoids and return to NYHA 1 functional status. Serial echocardiograms up to 3 years postdiagnosis shows stable mild LV dysfunction and mild functional mitral regurgitation. She remained on low-dose prednisone with no evidence of recurrence.

Case 2

A 67-year-old man with a history of hypertension and atopic dermatitis presents with a 3-week onset of NYHA III symptoms with sinus tachycardia and MAP of 75 mm Hg requiring 2 L of supplemental oxygen. His physical examination results revealed an elevated jugular venous pressure and S3, S4, and 2/6 holosystolic murmur at his apex. Lung fields had bilateral crackles, and pedal edema was present. He had eosinophilia (12.2 × 10^9/L), N-terminal pro–B-type natriuretic peptide of 4270 ng/dL, high-sensitivity troponin T of 112 ng/L, and severe LV dysfunction with mild functional mitral regurgitation on echocardiogram. RV biopsy showed eosinophilic infiltration, and HES was diagnosed in the patient. He had a rapid improvement on high-dose glucocorticoids and discharged in NYHA II status with improvement to mild LV function remaining on low-dose prednisone (Fig. 1).

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Ethics Statement: The anonymized case report series is submitted in accordance with the standards of the University of Calgary Research Ethics Board.

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See page 102 for disclosure information.

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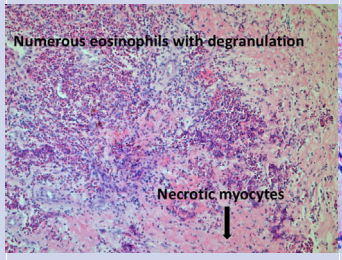
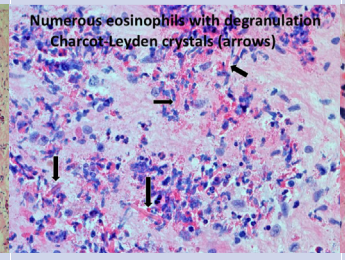
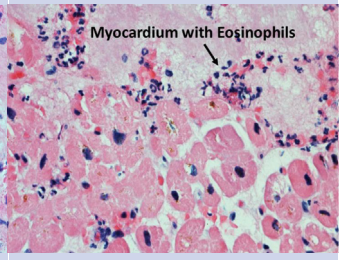
	Patient 1	Patient 2	Patient 3
Age (years)	81	67	63
Sex	Female	Male	Female
Comorbidities	Asthma Gastric Erosions	Hypertension Atopic Dermatitis	Hypertension Gout
Allergies	None	None	None
Medications	Pantoprazole Ventolin	No home medications	Perindopril Allopurinol
Presentation	NYHA III HF symptoms Atypical chest pain	NYHA III HF symptoms	Bilateral watershed and hemispheric cardio-embolic strokes
Peripheral Eosinophils	16.1 x 10^9/L	12.2 x 10^9/L	6.6 x10^9/L
NT-proBNP (ng/dL)	2370	4270	N/A
HS-Troponin T (ng/L)	453	112	1778
ECG	Sinus tachycardia with PVCs	Sinus tachycardia with RBBB	Sinus tachycardia with non-specific T wave abnormality
Echo	Moderate to severe LV dysfunction with regional variability and moderate to severe MR	Severe LV dysfunction in a regional pattern with mild functional MR	Normal LV systolic function with a small basal inferior wall motion abnormality. No hemodynamically significant valve disease
Cardiac Catheterization	Normal coronary arteries	Normal Coronary Arteries	N/A
Biopsy	Normal Bone Marrow Cardiac Biopsy: - Numerous eosinophils with degranulation - Myocyte necrosis	Normal Bone Marrow Cardiac Biopsy: - Numerous eosinophils with degranulation - Myocyte necrosis and mural thrombus	Normal Bone Marrow Cardiac Biopsy: - Numerous eosinophils with degranulation - Myocyte necrosis and mural thrombus
			
Outcome	Treated with high dose steroid with a slow taper. NYHA I functional status residual mild LV dysfunction.	Treated with high dose steroid with a slow taper. NYHA I functional status residual mild LV dysfunction.	Treated with high dose steroids with a slow taper. Preserved cardiac function. Significant motor and cognitive deficits.
Follow up	3 years	1 year	8 months

Figure 1. Characteristics, investigations, and outcomes for the patients. ECG, electrocardiogram; HF, heart failure; HS, high-sensitivity; LV, left ventricular; N/A, not available; NT-proBNP, N-terminal pro—B-type natriuretic peptide; NYHA, New York Heart Association.

Case 3

A 63-year-old woman with a history of hypertension and gout was found confused with symptoms of a stroke and found to have multiple infarcts within both cerebral hemispheres and within the posterior fossa concerning for a cardioembolic source. Her vital signs were remarkable for sinus tachycardia (110 beats/min) with a MAP of 85 mm Hg requiring 2 L of oxygen. She was hypovolemic with an otherwise unremarkable precordial examination, clear breath fields, and no peripheral edema. Her Glasgow Coma Score was 14 with weakness to her lower extremities and a positive Babinski sign. The patient's electrocardiogram was remarkable for sinus tachycardia with nonspecific ST abnormalities, and she had a peak troponin high-sensitivity troponin T of 1778 ng/L. Peripheral eosinophils peaked at 12.2 $\times$ 10^9/L with an echocardiogram that revealed preserved biventricular function. RV biopsy confirmed eosinophilic infiltration given a diagnosis of HES with normalization of her eosinophilia on high-dose steroids and

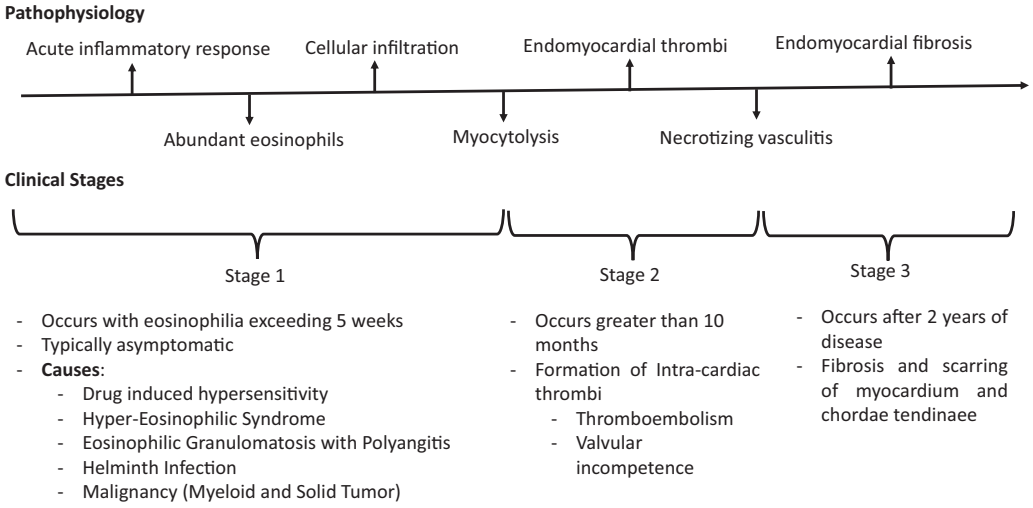


Figure 2. Pathophysiology, clinical stages, and common causes of eosinophilic myocarditis.

currently on maintenance prednisone of 5 mg daily. Unfortunately, because of her significant multi-territorial stroke, she required extensive neurorehabilitation.

Discussion

Pathogenesis of eosinophilic myocardial damage is proposed to be due to direct damage and a bystander effect. Release of cytotoxic cationic proteins increases permeability of myocytes to apoptosis, and release of major basic protein acts as a platelet stimulator contributing to thrombus formation.[1,2] Pathogenesis is thought to start with an acute inflammatory response with abundant eosinophils, followed by cellular infiltration and release of cytotoxic proteins leading to myocytolysis and development of endomyocardial thrombus. Subsequently, necrotic vasculitis and development of endomyocardial fibrosis often occur[3] (Fig. 2).

Clinical presentation matches pathology and is broken into 3 stages.[3] The acute necrotizing stage (Stage 1) is typically asymptomatic and occurs with 5 weeks. The thrombotic stage (Stage 2) results with the formation of intracardiac mural thrombi and occurs at approximately 10 months. The fibrotic stage (Stage 3) occurs after 24 months with fibrosis and scarring of myocardium progressing to a restrictive cardiomyopathy. Complications include embolic events, eosinophilic vegetations, and dysrhythmias or conduction disturbances.

Causes include drug hypersensitivity, small- and medium-sized vasculitis, myeloid, and solid malignancies. Helminth infections such as strongyloidiasis and schistosomiasis can also result in sustained eosinophilia with multiorgan involvement. In many cases, the etiology is unclear and is grouped into a syndrome coined "HES," characterized by sustained ($>$ 6 months) peripheral eosinophilia ($> 1.5 \times 10^9$/L) with evidence of end-organ injury.[2]

Peripheral eosinophilia is the only specific sign to suggest eosinophilic myocarditis with nonspecific findings with traditional biomarkers, electrocardiogram, and echocardiography. Echocardiography is the first choice for evaluating LV function with contrast allowing for identification of thrombus formation. Cardiac magnetic resonance imaging has been capable of detecting myocardial fibrosis and inflammation, and provides an early diagnosis of myocarditis and thrombi.[1,4]

Guidelines recommend the use of endomyocardial biopsy for a definite diagnosis of eosinophilic myocarditis.[5] Treatment involves standard heart failure management with early initiation of corticosteroids resulting in substantial improvements.[4] Refractory to corticosteroids, adjunctive immunosuppressants such as azathioprine have been successfully used. Currently, anticoagulation is limited to known thrombosis. Prognosis is dependent on the timing of diagnosis and early treatment, with mortality ranging from 48% to 75% if delayed.[4]

Conclusion

Eosinophilic myocarditis is a rare cause of LV dysfunction with prognosis dependent on the timing of diagnosis. Our 3 cases reveal the importance of early clinical suspicion, endomyocardial biopsy, and early initiation of treatment.

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Disclosures

The authors have no conflicts of interest to disclose.

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