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.

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. Sustained eosinophilia has reported cardiac involvement as high as 82% with a 5-year mortality rate of 30%. 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 discharged in NYHA II status with improvement to mild LV function 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).
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 x 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 a slow taper. NYHA I functional status residual mild LV dysfunction. Significant motor and cognitive deficits. Follow up

### Table 1

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

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Pathophysiology

Clinical Stages

- Acute inflammatory response
- Cellular infiltration
- Endomyocardial thrombi
- Endomyocardial fibrosis

Endomyocardial fibrosis

Stage 1
- Occurs with eosinophilia exceeding 5 weeks
- Typically asymptomatic
- Causes:
  - Drug induced hypersensitivity
  - Hyper-Eosinophilic Syndrome
  - Eosinophilic Granulomatosis with Polyangiitis
  - Helminth Infection
  - Malignancy (Myeloid and Solid Tumor)

Stage 2
- Occurs greater than 10 months
- Formation of Intra-cardiac thrombi
- Thromboembolism
- Valvular incompetence

Stage 3
- Occurs after 2 years of disease
- Fibrosis and scarring of myocardium and chordae tendineae

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. Pathogenesis is thought to start with an acute inflammatory response with abundant eosinophils, followed by cellular infiltration and release of cytotoxic proteins leading to myocyte death and development of endomyocardial thrombus. Subsequently, necrotic vasculitis and development of endomyocardial fibrosis often occur

Clinical presentation matches pathology and is broken into 3 stages. 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 x 10⁹/L) with evidence of end-organ injury.

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 thombi.

Guidelines recommend the use of endomyocardial biopsy for a definite diagnosis of eosinophilic myocarditis. Treatment involves standard heart failure management with early initiation of corticosteroids resulting in substantial improvements. 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.

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.

Acknowledgements

The authors thank Dr Yinong Wang for his help with the pathology slides.

Disclosures

The authors have no conflicts of interest to disclose.

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