Eosinophilic myocarditis (EM) is a rare disease characterized by myocardial eosinophilic infiltration. This infiltration of the myocardium has been described as a hypersensitivity response induced by a variety of causes ranging from drugs (including inotropes, vasodilators, antibiotics, diuretics, etc), parasitic infections, and neoplasia. EM is also frequently encountered in autoimmune disorders, such as Churg–Strauss syndrome and Löffler disease. In the vast majority of cases, EM is associated with hypereosinophilia (ie, eosinophils >1.5×10^9/L). Patients with EM may present with mild, moderate, or even severe heart failure symptoms sometimes accompanied with arrhythmias. EM in the absence of hypereosinophilia not only poses a great diagnostic challenge but also creates difficulty with post-treatment follow-up unless invasive procedures are used. Another difficulty in the management of this disorder is the lack of standardized therapeutic medical management. In the case below, we describe an otherwise healthy woman with no prior history of cardiac disease or allergy admitted to our hospital with recurrent arrhythmia, elevated troponin T values, and newly diagnosed reduced left ventricular ejection fraction.

Case Presentation

A 59-year-old woman with history of systemic hypertension well controlled with bisoprolol presented to our hospital with 5 months of intermittent symptomatic palpitations worsening in the past few days. An ambulatory exercise stress test (treadmill) completed 2 days before admission was normal but an echocardiogram was notable for left ventricular systolic dysfunction (ejection fraction, 35%). The initial ECG showed sinus rhythm with ventricular rate of 55 beats per minute and a new right bundle branch block. She denied chest pain or dyspnea. Blood work was notable for a positive troponin T value. Cardiac catheterization was notable for no significant coronary artery disease and left ventricular angiography confirmed the reduced left ventricular systolic function. Endomyocardial biopsy (EMB) samples were obtained during the same procedure and the patient was taken to our chest pain unit for monitoring. The next day she had nonsustained ventricular tachycardia and was transferred to our intensive care unit for treatment with amiodarone, as well as for medical management of heart failure with usage of an angiotensin-converting enzyme inhibitor, β-blocker, spironolactone, and loop diuretics. The EMB revealed myocardial eosinophilic infiltration (Figures 1 and 2). Infectious causes and giant cells were ruled out. Special stains for amyloids were negative. She then was given high-dose intravenous prednisolone combined with azathioprine daily. Prednisolone and azathioprine were administered as seen in the Table. Patient weight was 59 kg. On day 4, repeat echocardiography revealed improved systolic function (ejection fraction, 45%). No further arrhythmias occurred while in the intensive care unit. On day 7 she was transferred to a normal care unit to further optimize her heart failure therapy. She was discharged home 7 days later in good condition with a maintenance dose of azathioprine 50 mg daily and a prednisolone taper. Because the patient had no eosinophilia, there would be no means, beside biopsy, to effectively monitor outpatient therapy. She was thus readmitted 6 months later for an EMB, which showed complete histological remission (Figures 3 and 4). Repeat echocardiography at that time was notable for normalization of left ventricular systolic function (ejection fraction, 65%).

Discussion

In the early stage of EM, peripheral hypereosinophilia is not present in some patients and may not develop during the course of the illness in a subset of these patients. In many cases, the causative agent remains unclear. Myocarditis can certainly be diagnosed using, for example, MRI and if hypereosinophilia is present in peripheral blood count, EM can logically be suspected. However, it remains controversial whether therapy should be initiated on the sole basis of cardiac imaging and laboratory values without an EMB. We advocate for an EMB to confirm the diagnosis before proceeding with intensive corticosteroid treatment. The goal of corticosteroid therapy is to prevent or at least reduce eosinophil-mediated organ damage and should be commenced as soon as possible. Treatment failure or even disease relapse has occurred after a long course of high-dose steroids and, in some cases, had fatal consequences. The reasons for this nonresponsiveness to
corticosteroids are still unclear. Although the role of immunosuppressive therapy in other causes of myocarditis remains controversial, it has shown to be effective for EM. Aggarwal et al reported effective treatment of EM using a combination of steroids and azathioprine at a dose of 2 mg/kg in a patient who presented with cardiogenic shock. Two weeks later, a repeat EMB showed almost complete resolution of the eosinophilic myocardial infiltrate and remarkable clinical recovery. What remains unknown is how long to provide treatment with corticosteroids and other immunosuppressive agents. Some literature advocates for treatment for ≥1 year. However, a general recommendation cannot be made given the limited data available for this rare disease. This, together with varying treatment practices, and a relative lack of evidence-based guidelines would support efforts for a large multicenter, randomized controlled trial for optimal management of EM.

In conclusion, EM can occur in the absence of peripheral blood hypereosinophilia, which makes the diagnostic work-up and monitoring of therapeutic treatment particularly difficult. EMB remains the gold standard for diagnostic testing. In our opinion, a course of prednisone plus azathioprine for ≥6 months is necessary treatment for this disorder.

Acknowledgments
We express our heartfelt gratitude to Reinhard Kandolf, Karin Klingel, and Rajesh Mittal for their kind support.

Disclosures
None.

References

KEY WORDS: azathioprine ▪ biopsy ▪ eosinophilic enteritis ▪ heart failure ▪ myocarditis ▪ prednisone ▪ reticuloendotheliosis, familial, with eosinophilia

Table. Therapeutic Regimen

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<th>Day</th>
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<tr>
<td>8</td>
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Figure 1. Trichrome stain of an endomyocardial biopsy sample featuring massive eosinophilic infiltration.

Figure 2. Same biopsy sample with Giemsa stain.
Figure 3. Trichrome stain of an endomyocardial biopsy sample from the same previous patient after a 6-month treatment with prednisone and azathioprine.

Figure 4. Same patient with Giemsa stain, notice that the eosinophilic infiltration has disappeared.
Management of a Patient With Eosinophilic Myocarditis and Normal Peripheral Eosinophil Count: Case Report and Literature Review
Thierry Fozing, Nayef Zouri, Axel Tost, Rainer Breit, Gottfried Seeck, Charlotte Koch and Cem Oezbek

Circ Heart Fail. 2014;7:692-694
doi: 10.1161/CIRCHEARTFAILURE.114.001130
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1941-3289. Online ISSN: 1941-3297

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