CLINICAL VIGNETTE

Hypereosinophilic Syndrome with Myocarditis

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Introduction

Eosinophilic myocarditis is a rare type of myocardial inflammation associated with sustained eosinophilic infiltration. Eosinophilic activity is followed by activation of an immune stimulus, an inflammatory process, which can cause tissue damage and dysfunction. In developed countries, the most common causes are hypersensitivity or allergic reactions, and hematological diseases leading to peripheral blood eosinophilia (eosinophils > 1500/mm^3).[1] It has a variable clinical presentation, ranging from asymptomatic forms to life-threatening conditions. Most patients have marked peripheral eosinophilia. The degree of eosinophilic infiltration of cardiac tissue can determine disease severity. Severe cardiac disease can be common with profound peripheral eosinophilia, greater than 5000 mm^3. In the majority of forms, immunosuppressive therapy is the main treatment.[2]

Case

A 51-year-old female with hypertension, dyslipidemia, and hyperplastic colon polyps presents to clinic with generalized weakness. One week prior to her clinic visit, she experienced three days of diarrhea and throat discomfort with mild dysphagia. For a few days she took a variety of herbal medicine, provided by an herbalist. A few days later, she noted decreased appetite, headache, neck discomfort, numbness in the right 3rd fingertip, along with arm weakness. This was followed by facial swelling. She had no fever, chills, sweats, nasal congestion, cough, chest pain, shortness of breath, rash, abdominal pain, or dysuria. Travel history includes a trip to Israel two months prior to presentation. Her physical exam was unremarkable, except for mild distress. She was directed to the Emergency Department for further evaluation.

In the Emergency Department, EKG showed normal sinus rhythm with nonspecific T wave abnormality and she had troponin elevation of 20.8 ng/mL. Chest x-ray showed no evidence of cardiopulmonary disease. Left cardiac catheterization was performed without obstructive disease. Echocardiogram revealed mild anterior pericardial effusion without tamponade. Ejection fraction was 55 to 60% without any major structural or valvular abnormality. There was no evidence of hypereosinophilic thrombus in the left ventricle. Her white blood cell count was elevated at 29 K/uL with 48% eosinophils. CRP were elevated at 75.5 mg/L and ESR was up to 34 mm/hr. Her IgG level was 778 mg/dL. Rheumatology was consulted. ANCA testing was negative and she was presumed to have myocarditis secondary to an allergic reaction from herbal medicine and was diagnosed with hypereosinophilic syndrome. She received methylprednisolone 100mg IV for three days, with significant symptom improvement and decreasing white blood cell count, eosinophil count and troponin levels to the normal range. She was discharged home on oral prednisone 60 mg daily with a taper over two weeks. The white blood cell count decreased to 10.28 K/uL with an absolute eosinophil count of 0. Subsequent eosinophil counts remained normal. The parasitic infection evaluation was negative. Subsequent endoscopy and colonoscopy did not reveal evidence of eosinophilia. She was positive for H. pylori, which was treated. Her throat discomfort and mild dysphagia resolved after completion of H. pylori treatment. The colonoscopy was significant for seventeen hyperplastic colon polyps. Hematologic malignancy panel was negative for PDGFR A&B, ETV6, FGFR1, JAK2, CALR, MPL and BCR/ABL.

The patient remained off steroids for approximately seven months, when she developed a recurrence of facial swelling. Corticosteroid treatment restarted followed by a gradual taper. Cardiac MRI revealed mild focal myocarditis with mild inferior LV wall scarring, with normal biventricular systolic function and no evidence of pericarditis. A bone marrow biopsy was without evidence of malignancy or significant eosinophilia. PDGFRA and JAK2 tests were negative.

Six months later, generalized facial swelling recurred without angioedema. The patient was not on any corticosteroids at the time and symptoms were not responsive to antihistamines. Eosinophil count increased to over 7000 /mm^3. She was evaluated in the Emergency Department and a prednisone 40 mg daily was initiated with gradual taper. She was then started on mepolizumab, which she tolerated. Eosinophil count improved to 80 /mm^3 after the first injection. Low dose prednisone continued at 3 mg daily, with 1 mg reductions every seven to ten days. The plan was to proceed with mepolizumab injections every twenty-eight days for at least three doses.

Discussion

Myocarditis with hypereosinophilic syndrome is a rare form of inflammatory cardiomyopathy. An unselected autopsy series identified it in 0.5% of cases and in 0.1% patients biopsied for suspected myocarditis.[1] The etiologies include medications (inotropes, vasodilators, antibiotics, diuretics, non-steroidal anti-inflammatory drugs, etc), parasitic infections, and neo-

plasia. It has also been associated with autoimmune disorders, such as eosinophilic granulomatosis with polyangitis and Löffler disease.[3] Clinical manifestations vary depending on the underlying cause. Prior to the onset of myocarditis, two-thirds of reported symptoms of the common cold and one-third of patients reported allergic diseases such as bronchial asthma, rhinitis, or urticaria.[4] Symptoms are similar to other forms of myocarditis, including chest pain, dyspnea, fatigue, palpitations, or syncope.

Eosinophilic cardiac conditions range from acute myocarditis to endomyocardial fibrosis. Eosinophilic infiltration of the cardiac tissue is the first phase of the disease. This is followed by myocardial necrosis from eosinophil degranulation. The second phase is the thrombotic stage associated with a hypercoagulable state with increased levels of circulating thrombin. The final phase involves fibrotic scarring of the endocardium with the promotion of fibroblast activation, proliferation and extracellular matrix production by eosinophils.[2]

Determining the diagnosis can be challenging. Although a majority of cases have marked eosinophilia in peripheral blood, it can be absent in the early stages. Inflammatory markers including C-reactive protein levels and erythrocyte sedimentation rate as well as markers of myocardial injury such as creatine kinase or troponins are often raised. Unfortunately, their absence does not exclude myocarditis.

An EKG is indicated when suspecting myocarditis and ST-T segment abnormalities can be seen. Echocardiograms can detect a pericardial effusion and monitor changes in cardiac structure or function. Echocardiographic features in Eosinophilic Myocarditis include left ventricular systolic dysfunction, increased left ventricular wall thickness due to interstitial myocardial edema, and pericardial effusion. Given the thrombotic phase of the disease, detection of thrombus formation in the apical parts of the ventricles is crucial.[1]

An endomyocardial biopsy is needed to establish a definitive diagnosis. It can reveal eosinophilic degranulation near thrombotic and necrotic lesions. Cardiac MRI is an alternative noninvasive diagnostic modality, which can detect presence of myocardial inflammation. It can also detect endomyocardial fibrosis in the advanced stages, which typically involves the right or left ventricular apices.[1] Cardiac MRI has high specificity in diagnosing myocarditis, however, cannot identify the cause of the disease process and pathologic evaluation is still recommended.[5] In this case, a biopsy was not performed. The possibility of eosinophilic granulomatosis with polyangiitis was considered however the patient did not meet most of the criteria: marked peripheral eosinophilia >10%, paranasal sinus abnormality, bronchial asthma, pulmonary infiltrates, mononeuropathy or polyneuropathy, and extravascular eosinophil infiltration on biopsy.[6]

Management is challenging due to lack of standardized treatment. The choice of therapy also depends on the underlying etiology. If eosinophilia was drug-induced or secondary to a hypersensitivity etiology, the offending agent is discontinued. With corticosteroid therapy, the goal is to prevent or at least reduce eosinophil-mediated organ damage.[3] There is limited evidence as no clinical trials have tested steroid efficacy in patients. Corticosteroids were frequently used (77.7%), in systemic conditions where steroids have a primary indication. Examples include eosinophilic granulomatosis with polyangiitis (87.0%) and hypereosinophilic syndrome (86.7%).[7]

Conclusion

Confirming the diagnosis of Hypereosinophilic Myocarditis is challenging. In this patient's case, the etiology may have been due to a hypersensitivity reaction to herbal supplements that mimicked acute coronary syndrome. Why certain circumstances may lead to eosinophilic affinity to myocardial tissue is yet to be fully understood. With corticosteroid therapy and mepolizumab, the patient's symptoms and eosinophilia improved. Her progress continues to be monitored.

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