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CASE REPORT

Eosinophilic myocarditis: A case report of idiopathic eosinophilic myocarditis

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Summary. *Eosinophilic myocarditis (EM) is associated with syndromes that involve hypereosinophilic exposure to the heart. We describe an interesting case of idiopathic EM. A 51year old man presented with fever, dyspnea, intermittent chest discomfort and weight gain for 6–8 weeks. Physical examination was notable for jugular venous distension, bilateral bibasilar rales, 3+ pitting edema of the lower extremities, and tachycardia. Chest X-ray showed bilateral infiltrates. Inflammatory markers were elevated in his peripheral blood, including C-reactive protein and erythrocyte sedimentation rate. He had mild leukocytosis and eosinophilia. Transthoracic echocardiogram revealed low normal ejection fraction. The overall clinical picture was consistent with heart failure (HF) and he was given intravenous diuretics. He underwent endomyocardial biopsy which revealed diffuse interstitial inflammatory infiltrates, predominately eosinophils with non-caseating granulomas, consistent with EM. Systemic corticosteroid therapy was initiated. Over the next 3 days, he experienced symptomatic improvement. His ejection fraction also improved to normal and he was discharged home. This case highlights the importance of an early diagnosis of EM and the need to maintain a high degree of suspicion in the correct clinical scenario.*

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Introduction

Eosinophilic granulocytes are a subtype of myeloid cells, named after their abundant intracellular granules that stain intensely with the aniline dye eosin [1]. Eosinophils participate in hypersensitivity and allergic responses, and combat parasites [2]. The syndromes that involve eosinophilia are either reactive (asthma, infection) [3], clonal myeloid disorder and cancer [4], eosinophilic granulomatosis with polyangiitis (EGPA) [5] or idiopathic hypereosinophilic syndrome (HES) [6, 7]. The tissues commonly affected from hypereosinophilic exposure include skin, lungs and gastrointestinal tract [7, 8]. Cardiac tissue damage has been reported as a result of peripheral eosinophilia, first described by Loeffler [9]. Eosinophilic myocarditis is one of the most common cardiac manifestations of eosinophilia and ranges from mild localized disease to multifocal widespread infiltrates associated with myocardial necrosis, thrombotic complications and endomyocardial fibrosis [10, 11]. The clinical presentation may range from chest pain and palpitation to fulminant HF and death [11, 12].

Case Presentation

A 51year old man presented to the hospital with subacute symptoms of exertional dyspnea, paroxysmal nocturnal dyspnea, atypical chest pain, cough, and weight gain of approximately 30 pounds over the preceding 6–8 weeks. His past medical history included anxiety, depression and bipolar disorder. His social history was notable for buying drugs off the internet for anxiety and cough suppression. He was unable to provide the generic or trade names of the drugs, but mentioned that some of the anxiolytics were from the benzodiazepine group. He was a social alcohol drinker and had a remote history of smoking and marijuana use over 20 years ago.

At the time of presentation, he had a low grade temperature of 100.9 degrees Fahrenheit, heart rate was 116 beats per minute, blood pressure was 139/85 mmHg, respiratory rate was 16 breaths per minute with an oxygen saturation of 95% on 4 liters of supplemental oxygen via nasal cannula. Physical exam was notable for elevated jugular venous pressure of 12cm of H_20, bilateral bibasilar rales, 3+ pitting edema of the lower extremities, and tachycardia but otherwise normal heart sounds without murmurs, gallops and rubs.

Investigation and Differential Diagnoses

His electrocardiogram showed sinus tachycardia with low voltage and a prolonged QT_C interval of 496msec. Initial laboratory testing revealed leukocytosis of 15,700/mm^3, eosinophilia of 6.6% (1036 cells/mm^3), and evidence of renal dysfunction with a creatinine of 1.96. Non-specific inflammatory markers were found to be elevated: C-reactive protein level was 26 (normal values are 0.00–0.50 mg/dl) and erythrocyte sedimentation rate of 63 (0–22 mm/hr). His troponin-I level was 2.31pg/ml (normal <0.02) and brain-type natriuretic peptide was elevated at 1501 pg/ml (normal <100). Chest X-ray showed bilateral infiltrates suggestive of pulmonary vascular congestion. His transthoracic echocardiogram showed a low-normal left ventricular systolic function with an ejection fraction of 50%, mild global left ventricular wall hypokinesis, without regional wall motion abnormalities, grade 1 diastolic dysfunction and an abnormal speckled myocardial appearance on visual assessment.

The working diagnosis at the time was myocarditis of unknown etiology. Given his fever and elevated inflammatory markers, the main concerns were for autoimmune or infectious causes of myocarditis. In regards to infectious workup, all laboratory studies, including blood and urine cultures, polymerase chain reaction testing of viral antigens from the upper respiratory tract and testing of antibody titers to parasites, were negative. In regards to autoimmune evaluation, anti-neutrophil antibody, anti-myeloperoxidase antibody, and anti PR3 antibody were negative. The patient was unable to undergo non-invasive cardiac magnetic resonance imaging due to severe claustrophobia. Given his chronic respiratory symptoms, he underwent pulmonary function testing which showed moderately severe obstructive pulmonary defect without significant response to bronchodilator. FEV1 (forced expiratory volume in 1 second) was 2.15 liters (normal 3.0–4.5 liters), FVC (functional vital Capacity) was 3.37 liters (normal 3.9–5.7 liters) and FEV1/FVC ratio was 64 (normal 67.9–87.2). $FEF_{25-75\%}$ (forced

expiratory flow over the middle half of the FVC) was 2.7 liters per second (normal values 1.5–4.2 liters per second) and DLCO (diffusing capacity of the lung for carbon monoxide) was 20 milliliters per mm Hg per minute (normal 15–28 milliliters/mmHg/ minute).

The patient then underwent invasive cardiac hemodynamic measurement and endomyocardial biopsy for tissue diagnosis. Right heart catheterization revealed elevated filling pressures with a mean right atrial pressure of 12 mm Hg (normal <5), right ventricular systolic pressure of 36 mm Hg, diastolic pressure of 8 mm Hg, right ventricular end- diastolic pressure of 13, pulmonary artery systolic pressure of 30 mm Hg and diastolic pressure of 17mm Hg and mean pulmonary capillary wedge pressure of 22 (normal < 15), but cardiac output was preserved at 5.93 liters per minute by Fick's principle and 5.59 liters per minute by thermodilution technique (normal range at rest is 4–8 liters/minute). Systemic vascular resistance was elevated at 1457 dynes/sec/cm^5 (normal 800–1200 dynes/sec/cm^5) and pulmonary vascular resistance was 204 dynes/sec/cm^5 (normal 37–250dynes/sec/cm^5). Right ventricular biopsy was performed at the time of right heart catheterization. Endomyocardial biopsy revealed diffuse interstitial inflammatory infiltrates, predominately eosinophils with non-caseating granulomas, consistent with EM. Trichrome stain showed myocyte necrosis.

Treatment

The patient was started on high dose corticosteroids and heart failure medications, including diuretics and beta-blocker therapy, with significant symptomatic relief. Beta-blockers were chosen as he had a persistently elevated heart rate and evidence of diastolic dysfunction on his echocardiogram. Given renal dysfunction, initiation of angiotensin-converting-enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB) or mineralocorticoid receptor antagonist was delayed. A repeat echocardiogram performed 3days after initiation of therapy demonstrated an improvement in the patient's ejection fraction to 65 %, and the patient was discharged home with outpatient ongoing follow-up.

Discussion

Eosinophilic myocarditis was first described in the literature by Wilhelm Loeffler in 1936, when he observed endocarditis parietalis fibroplastica and peripheral eosinophilia (9). It is characterized histopathologically by eosinophil and lymphocyte infiltration into the myocardial tissue. Eosinophils contain high concentrations of hydrolases and basic proteins. Release of these proteins during degranulation result in cell death and fibrosis.

The pathology of EM is described in 3 stages [13].

Acute necrosis and myocarditis. This involves infiltration of the myocardium with eosinophils and lymphocytes which leads to clinical symptoms of acute coronary syndrome or heart failure; Thrombosis. Thrombi form at the apices of the ventricles which elevate risk for embolic complications.

Fibrotic stage. This involves endomyocardial scarring that leads to features of chronic congestive heart failure and valvular disease.

Although there are no globally accepted guidelines for the diagnosis of EM, the Japanese Circulation Society Task Force Committee on Acute and Chronic Myocarditis have published guidelines for the diagnosis and treatment of EM [14]. The essential diagnostic features include eosinophilia >500/microliter, cardiac symptoms, elevated cardiac enzymes, electrocardiogram changes and cardiac dysfunction on echocardiography, especially in the presence of unremarkable coronary angiography. EM poses a considerable mortality [15]. The proportion of EM among all cases of myocarditis is unclear, but it is suggested to be greater than previously thought [16].

There are many possible etiologies for EM. Drug hypersensitivity has been described as one of the most common causes of EM [17]. Frequently implicated drugs include methyldopa, hydrochlorothiazide, ampicillin, furosemide, digoxin, tetracycline, aminophylline, phenytoin, benzodiazepines, and tricyclic antidepressants [18]. Other causes of EM are EGPA, as well as diseases involving peripheral eosinophilia, such as idiopathic hypereosinophilic syndrome, myeloproliferative disorders, infection and cancer.

Hypersensitivity myocarditis was described by Burke et al. in 1991 [18]. It was defined by the presence of eosinophils, a mixed lymphocytic infiltrate along natural planes of separation, and an absence of fibrosis or granulation tissue in areas of infiltrate. Autopsy specimens of 69 cases were studied to determine drug association, spectrum of histologic findings, distribution of infiltrates, and correlation between degree of infiltrated and cardiac symptoms. The drugs commonly implicated were methyldopa, hydrochlorothiazide, ampicillin, furosemide, digoxin, tetracycline, aminophylline, phenytoin, benzodiaz-

epines and tricyclic anti-depressants. The patient mentioned in this case report did have access to certain anxiolytics and antitussive drugs, which included benzodiazepines. The etiology of EM in this case could have been hypersensitivity due to exposure to certain drugs that are prone to cause eosinophilia and related myocardial damage. The causative association between specific histologic findings and drugs has not been established because of the common usage of many of the drugs implicated [18]. Thus, obtaining a detailed clinical history and gathering information about the past use of drugs is essential if such a clinical syndrome is suspected.

EGPA is a necrotizing small and medium sized vasculitis with granuloma formation and eosinophilic infiltration in a patient with asthma and eosinophilia. It is a type of anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis and can be divided into ANCA positive and ANCA negative by serology testing [19]. EGPA was first described by Churg et al in 1951 as the clinical syndrome of severe asthma, eosinophilia, fever and vascular involvement in thirteen autopsy cases [20]. EGPA has some unique features when compared to other forms of vasculitis like Wegener's granulomatosis and microscopic polyangiitis. Firstly, patients with EGPA usually have a history of asthma and/or chronic sinusitis. Secondly, eosinophils are always elevated in blood or other tissues. Additionally, the organ involvement pattern is different compared to other ANCA associated vasculitis. Cardiac, ear, nose, throat and peripheral nerves are common sites of involvement, as opposed to the renal involvement seen with other ANCA associated vasculitis.

The American College of Rheumatology has developed a classification system for EGPA [21]. These include: asthma, peripheral blood eosinophilia > 10% on differential leukocyte count, mononeuropathy or polyneuropathy, migratory pulmonary infiltrate, paranasal sinus abnormality, extravascular eosinophilic infiltration of tissues on biopsy. In the appropriate clinical setting, the presence of at least four of these criteria carries a sensitivity of 85% and a specificity of 99.7% [21–23]. Symptomatic cardiac involvement is documented in 27% to 47% and usually presents in the form of myocarditis, pericarditis, endocarditis, pericardial effusion, arrhythmias, myocardial infarction, congestive heart failure, cardiogenic shock or valvular heart disease [24]. Our patient had a peripheral eosinophilia of < 10% on differential leukocyte count. His pulmonary function tests showed a moderately severe obstructive pulmonary defect, without reversibility on usage of bronchodilators, and no prior history of asthma. He did not have neuropathy, migratory pulmonary infiltrates or evidence of paranasal sinus abnormality. It is important to consider EGPA as a cause of EM, because of a high prevalence of symptomatic cardiac involvement in these patients.

Among the other causes of eosinophilia are parasitic infections. Enko et al. described a case of eosinophilic myocarditis caused by visceral larva migrans by Toxocara Canis infection [3]. In our patient, we obtained antibody titers against Toxocara, Strongyloides, Trypanosoma cruzi, Schistostoma and stool microscopic evaluation for ova and parasites. All the investigations to rule out parasitic infection were negative.

Endomyocardial biopsy is the only method currently for the definitive diagnosis of EM by confirming eosinophil infiltration in myocardium. Echocardiography, nuclear imaging with gallium-67 or indium-111 labelled antimyosin antibodies and cardiac MRI are forms of non-invasive testing that can provide supportive data, but none are diagnostic of the disease process.

After a diagnosis of EM is made, treatment is focused on providing hemodynamic stability from the cardiac standpoint and corticosteroid therapy to reduce eosinophil-induced cardiac damage. Several corticosteroid regimens have been proposed, and the overall consensus is initiation of high dose steroids and continuation over several weeks to prevent relapses [7, 25]. However, there is still lack of evidence-based guidelines for the use, dose, duration of corticosteroids and the need for maintenance therapy in patients with EM.

Conclusion

EM is an underdiagnosed subtype of myocarditis, which if not recognized early may result in irreversible myocardial damage leading to fatal outcomes. In our case, the patient had improvement in of systolic function and heart failure symptoms. This was achieved with early corticosteroid therapy, diuretic therapy for reducing preload and pulmonary vascular congestion, beta blockers and blood pressure control for afterload and diastolic CHF management. There must be an attempt to rule out common causes of EM as mentioned above. Endomyocardial biopsy is the only definite diagnostic tool. Clinicians must have a high index of suspicion to diagnose this entity in the correct clinical scenario.

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