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Acute Eosinophilic Myocarditis and Hyper IgE in HIV Infection: A Case Report

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Abstract

Context:

Eosinophilic myocarditis is a rare cause of myocarditis. It is manifested histopathologically by diffuse or focal myocardial inflammation with eosinophilic infiltration, often in association with peripheral blood eosinophilia. Patients infected with Human Immunodeficiency Virus (HIV), especially those with lower CD4 counts, can occasionally have hyperimmunoglobulinemia E (Hyper IgE) and eosinophilia.

Case Report:

We report a case of a 29-year-old patient with Acquired Immunodeficiency Syndrome (AIDS) who had a persistent elevation of eosinophil counts and elevated IgE levels for a year prior to admission. He was presented to our emergency department with chest pain and laboratory tests revealed peripheral blood eosinophilia and elevated troponins. Coronary angiogram showed nonobstructive coronary artery disease. He then underwent cardiac magnetic resonance imaging which was consistent with an infiltrative myocarditis. After being put on steroid therapy, his peripheral eosinophilia resolved and his cardiac symptoms improved.

Conclusion:

Our case highlights that eosinophilia and Hyper IgE in HIV patients has the potential to contribute to end-organ damage.

Keywords: Acute eosinophilic myocarditis, Hyper Ig-E, HIV infection

Introduction

Hyperimmunoglobulinemia E (Hyper IgE) and eosinophilia have been described in some human immunodeficiency virus (HIV)-infected patients. There is an association between immunoglobulin E (IgE) level and immune status. IgE levels (20- to 100-fold above normal) usually correlated with significant decrease in CD4 cells.

Case Presentation

A 29-year-old African-American male with a past medical history of advanced AIDS and non-compliance with medications was presented with acute onset of chest pain. The pain was associated with shortness of breath. Physical activity worsened the intensity of the pain. He denied any nausea, vomiting or diaphoresis. Physical examination was unremarkable. Laboratory work up on admission showed a troponin T level of 5.0 ng/ml (upper limit of normal = 0.10 ng/ml), white blood cell (WBC) count of 2.0 K/uL and eosinophil count 1.52 K/uL (upper limit of normal = 0.4 K/uL), hemoglobin level of 9 g/dL and platelets count of

250,000/ μ L and absolute CD4 count of 12/ mm^3 . Renal, liver and clotting profiles were all normal. The electrocardiogram (EKG) initially showed T wave inversions in the anterior leads, which were not present on prior EKGs. The troponin T level rose to a peak of 35.8 ng/ml and a repeat EKG revealed changes consistent with inferior wall myocardial ischemia. The 2D echocardiogram revealed decreased ejection fraction estimated at 30–35% with no wall motion abnormalities. Workup for hypercoagulable state including anticardiolipin antibodies, protein C, protein S, factor V Leiden and homocysteine levels tests were all negative.

Of interest, throughout the year prior to admission, the percentage of eosinophil was noted to be persistently and abnormally high. In that same period, the patient was leukopenic with WBC count ranging between 0.8 K/ μ L and 3 K/ μ L. In addition, Immunoglobulin E level was found to be elevated at 9330 IU/ml (normal <100 IU/ml). Fluorescence *in situ* Hybridization (FISH) peripheral blood analysis was negative for FIP1L1-PDGFRB translocation. Bone marrow biopsy showed slightly hypercellular tri-lineage hematopoiesis with no evidence of any pathological/clonal hematologic disorder. The anti-neutrophil cytoplasm antibodies (ANCA), anti-nuclear antibodies (ANA), rheumatoid factor, myeloperoxidase antibody, proteinase 3 antibody, anti-cyclic citrullinated peptides (CCP) were negative. Serologic studies for infection, hepatitis, toxoplasmosis, autoimmune, and paraneoplastic disease were negative. Stool analysis and blood films were negative for parasites.

On the basis of his elevated troponins and echocardiographic findings, he was initially managed for non-ST elevation myocardial infarction (NSTEMI) with aspirin, statin, clopidogrel, beta blockers and heparin. Angiography showed that our patient had a mild non-obstructive disease. A cardiac magnetic resonance imaging (CMR) was done [Figures 1 and 2] and it showed a pattern typical of eosinophilic endomyocarditis. He was started on daily methylprednisolone 1 mg/kg intravenously. On steroid treatment, the eosinophilic count decreased dramatically and his clinical state ameliorated rapidly. A repeat echocardiogram on day 10 revealed an increase in ejection fraction and systolic function confirming the therapeutic benefit of the steroid therapy.

Discussion

Since their discovery, in 1879 by Ehrlich, eosinophils have gained an increasing interest due to their ability to release multiple mediators that can recruit other cells and inflict tissue and organ damage by multiple mechanisms.[1] In normal conditions, eosinophils are found in peripheral blood with a normal count ranging between 0.05 to $0.5 \times 10^9/\text{L}$ and usually represent 1-6% of the bone marrow nucleated cells. Eosinophils are not present in other organs or tissues, with the exception of spleen, thymus, uterus, part of the GI tract and lymph nodes.[2] Their development and maturation occur in the bone marrow from interleukin (IL)-5 responsive CD34⁺ precursor cells with multiple cytokines and chemokines being involved in their growth and activation, of which IL-5, granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-3 (primarily secreted by T lymphocytes, mast cells or stromal cells) are considered the most potent. Additionally, an oncogenic mutation in tyrosine kinase, such as platelet-derived growth factor receptor A or B (PDGFRA, PDGFRB), or fibroblast growth factor receptor 1 (FGFR1) can produce clonal eosinophils.[2]

Multiple definitions of Hypereosinophilia (HE) and its associated syndromes have been proposed since the 1970s. Blood eosinophilia is defined as a blood eosinophilic count greater than $0.5 \times 10^9/\text{L}$.

Hypereosinophilic syndrome (HES) is defined as the presence of peripheral blood hypereosinophilia with the presence of HE-related organ damage in the absence of an alternative explanation of the organ damage. HES applies to any clinical presentation where documented blood HE is linked to organ damage, whether HE is due to a reactive process, neoplastic or other underlying disease. HES is classified to Idiopathic HES when there is no underlying cause for HE is found, Primary (neoplastic) HES when there is an underlying stem cell, myeloid, or eosinophilic neoplasm responsible for the HE and Secondary (reactive) HES when eosinophils are considered nonclonal cells and an underlying condition or disease is responsible for the HE (cytokine-driven).[2]

Hypereosinophilic syndrome is very rare, and under diagnosed, its true prevalence is unknown. The estimated prevalence in the United States was between 0.315 and 6.3 per 100,000.[2,3,4,5,6,7,8] Activated

TH2 cells produce multiple cytokines including IL-4, IL-5, and IL-13, which mediate eosinophilic activation, differentiation and survival with resultant eosinophilia and IgE production.[1] HIV1 infection was noticed to be associated with a shift from predominant TH1 immune response to TH2 immune response resulting in increased eosinophilic count and IgE levels. This was especially seen in patients with CD4 counts lower than 200 cells/ μ L.[3,4,5,6] It is still unknown whether this shift is a result of the effects of the virus on T cells or is it a result of the developing immunodeficiency.[1] HIV infection with the associated cytokine driven eosinophilia can be considered as a cause of secondary (reactive) HE.[4,7,8,9,10,11,12,13]

HES induced organ damage is a result of eosinophils release of multiple toxic products including eosinophil cationic protein (ECP), major basic protein (MBP), ribonuclease eosinophil derived neurotoxin (EDN), eosinophil peroxidase (EPO), free oxygen radicals and enzymes like elastase and collagenase. Additionally, eosinophils can secrete leukotrienes and prostaglandins that alter vascular and bronchial muscle tone. Release of TGF-B by activated eosinophils can cause an increased collagen synthesis and extra cellular matrix deposition resulting in a pro-fibrotic environment. HES can affect any tissue or organ; however, most clinical complications arise mostly from the nervous system, skin, heart and lungs.[9,10]

Cardiac involvement presents with signs and symptoms of heart failure, intracardiac thrombus, myocardial ischemia, arrhythmias and rarely pericarditis. Three stages of cardiac involvement have been traditionally described; acute necrosis, thrombosis and fibrosis. The acute necrotic stage, which usually occurs when the duration of illness is short (mean 5.5 weeks) results from eosinophilic infiltration of the myocardium and degranulation of toxic products causing myocardial necrosis.[11,12] Diagnosis of this stage can be difficult as the symptoms might be absent, but can be done with cardiac biopsy or CMR. This stage is followed by the development of mural thrombi that results from ventricular wall vascular damage and can lead to atrioventricular valvular incompetence; this stage is seen with a more prolonged eosinophilia of around 10 months. The late fibrotic stage is seen after around 24.5 months of disease as a result of fibrosis of the myocardium.[12] Diagnosis of cardiac involvement in HES can be late when the patient present with endocardium or chordae tendinae scarring that leads to valvular incompetence and restrictive or dilated cardiomyopathy. Multiple modalities can be used to evaluate cardiac involvement in HES that include electrocardiography, echocardiography, CMR, and endomyocardial biopsy. The EKG findings are generally non-specific. Echocardiography can show an evidence of thrombus formation, endomyocardial thickening and valvular abnormalities.[10,12] Recently, CMR has been gaining more attention in the diagnosis of cardiac involvement as it provides a non-invasive specific and sensitive tool. Late gadolinium enhancement is capable of detecting myocardial inflammation and fibrosis.[12] Endomyocardial biopsy is still the gold standard for the diagnosis, and serial biopsies might be done to provide information on the clinical course.[11] Biopsy was not performed in this case so pathology was not available. But the clinical, laboratory, and radiologic features were consistent with acute eosinophilic myocarditis secondary to HIV-related Hyper IgE/Hypereosinophilic syndrome.

Treatment of HES depends on many factors including the type of HES, degree of organ involvement and degree of hypereosinophilia. Glucocorticosteroids are the first therapy in patients who have organ involvement and do not have FIP1L1-PDGFR α fusion gene or any other tyrosine kinase sensitive mutations. Prednisone at a dose of 1 mg/kg for one to two weeks is considered as an appropriate therapy, followed by tapering dose that varies depending on the level of eosinophilia and organ involvement. A corticosteroid-sparing agent can be added once a stable maintenance dose of glucocorticoids is reached such as hydroxyurea, interferon-alpha or the newer anti-IL-5 and anti-CD52. Symptoms of congestive heart failure can be managed with conventional heart failure medications. Valvular complications might eventually need surgical intervention, with mitral valve replacement being the most performed.[11,13]

In our patient, we ruled out any stem cell, myeloid or eosinophilic neoplasm. The elevated eosinophilic count and Hyper IgE is mostly secondary to HIV infection. Our case highlights that eosinophilia and Hyper IgE in HIV patients has the potential to contribute to end-organ damage. Since hypereosinophilia and Hyper IgE in HIV patients is directly correlated with depressed CD4 count, it is reasonable to conclude that treatment of the acute end-organ damage such as myocarditis with steroids and antiretroviral therapy can reverse the HIV-associated hypereosinophilia and the associated end organ damage.

Footnotes

Source of Support: Nil.

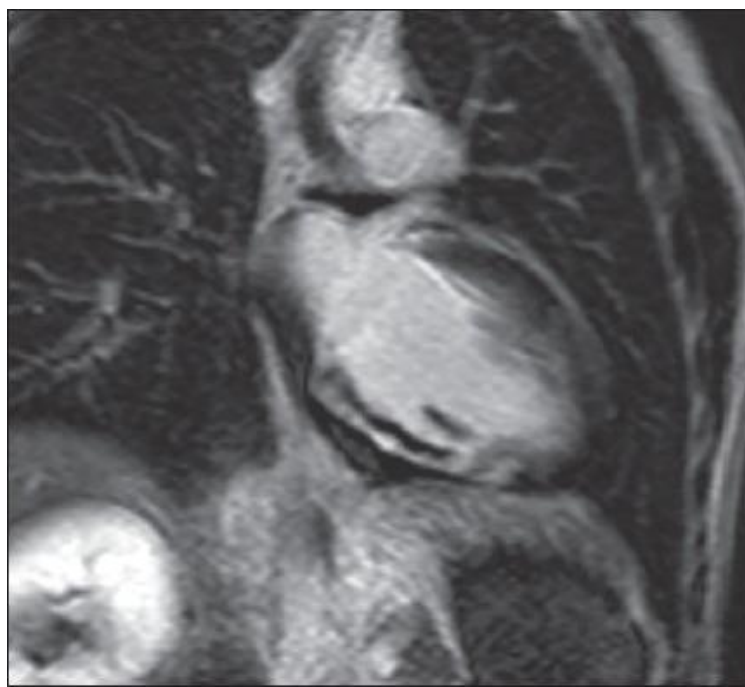
Conflict of Interest: None declared.

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Figures and Tables

Figure 1



Magnetic resonance imaging depicting circumferential subendocardial delayed enhancement on the long axis T2 weighted view

Figure 2



Short-axis T2-weighted edema images demonstrating focal myocardial edema in the subepicardium of the left ventricle

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