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Case Report

Lymphocytic variant of Hypereosinophilic syndrome complicated by myocarditis

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ABSTRACT

A 26 year-old-male with nil significant past medical history presented to us with swelling of left lower limb since 2 weeks. He has tachyapnea and tachycardia. His JVP was normal and cardiac auscultation was normal. Examination was suggestive of deep vein thrombosis (DVT) of the left lower limb. Doppler of lower limb confirmed this and patient was appropriately placed on anti-coagulation. He had persistently elevated blood eosinophil counts. Bone marrow biopsy was and mutational analysis confirmed presence of lymphocytic variant of hypereosinophilic syndrome (HES). He continued to have tachycardia and cardiac enzymes were positive. Electrocardiogram revealed sinus tachycardia and echo was normal. After ruling out the possibility of pulmonary thromboembolism with CT pulmonary angiogram, myocarditis was attributed to HES. He was promptly treated glucocorticoids which were later tapered gradually in lieu of improvement of his clinical condition and declining eosinophil counts. He was discharged and was under regular follow-up.

Key words: Hypereosinophilic syndrome, Persistent eosinophilia, Deep vein thrombosis, Myocarditis.

Key messages:

- The case is interesting for the rarity of the disease. The disease is potentially treatable and hence must be kept in mind of treating physician while dealing with a case of persistent eosinophilia.
- Hypereosinophilc syndromes can present with coagulation abnormalities, especially venous thrombosis. Active search for venous thrombosis is required in patients with suspicious clinical presentation.
- Cardiac involvement is more usually observed in myeloproliferative variant of HES. These patients usually test positive of *FIP1L1-PDGFRA*. Our patient though had lymphocytic variant of HES, had myocarditis.
- Lymphocytic variant hypereosinophilic syndrome rarely presents as myocarditis and shows good response to steroids, especially upon early diagnosis.

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INTRODUCTION

Hypereosinophilic syndrome (HES) encompasses a diverse group of hematological pathologies characterized by chronic, unexplained blood and tissue eosinophilia, with evidence of organ dysfunction attributable to the eosinophilia.[1] HES has been typically classified into myeloproliferative and lymphocytic variants based on an effective description of the elemental pathophysiological processes. Lymphocytic HES formulates from an overproduction of interleukin 5 (IL-5) by dysregulated T-lymphocytes and a reactive proliferation of eosinophils. Alternately, myeloproliferative HES variants are described by the presence of a gene rearrangement resulting in a fusion product coined FIP1L1-PDGFRA with intrinsic tyrosine kinase activity leading to clonal expansion of eosinophils.[2] This case report illustrates our patient with a lymphocytic variant of the hypereosinophilic syndromes without any dermatological manifestations, complicated by deep vein thrombosis and myocarditis, with a good response to steroids.

CASE HISTORY

A 26-year old male presented with a 5 day history of swelling and pain in his left lower limb. There is a local rise of temperature and tenderness in left leg. Systemic examination revealed tachycardia (118 beats/min), elevated jvp and a normal P2. Pulmonary area is resonant to percussion and there was no ejection systolic murmur. Electrocardiogram revealed sinus tachycardia. Echocardiogram was normal. Venous Doppler revealed left lower limb DVT and was appropriately placed on anti-coagulants. Investigations revealed leucocytosis and hypereosinophilia, an absolute eosinophil count of 32 X 10^3 per microliter, with other cell lines being normal. A peripheral smear showed 70% eosinophils with no blasts or abnormal cells. There were no symptoms suggestive of allergic rhinitis, asthma or eczema in the past. After reasonably excluding secondary causes of hypereosinophila a bone marrow biopsy was done which revealed a lymphocytic variant of hypereosinophilic syndrome (Figure 1). Molecular genetic analysis for FIP1L1-PDGFRA gene rearrangement was negative, thereby ruling out the myeloproliferative variant of hypereosinophilic syndrome. His general condition worsened, he had persistent tachycardia. He had significantly elevated troponin and repeat electrocardiogram and echocardiogram did not show any change from baseline. In view of persisting tachycardia, CT pulmonary angiogram was done which did not show pulmonary thromboembolism. Hence the diagnosis of myocarditis secondary to HES was strongly considered.

In view of inappropriate tachycardia, he was started on oral prednisolone at a dose of 1mg/kg/day. Following initiation of steroids, his tachycardia came down and showed clinical improvement. His steroids were gradually tapered as his clinical condition improved with declining eosinophil counts, decreasing heart rate. He was kept on maintenance dose of steroids and was discharged soon afterwards. He was doing fine and was under regular follow-up.

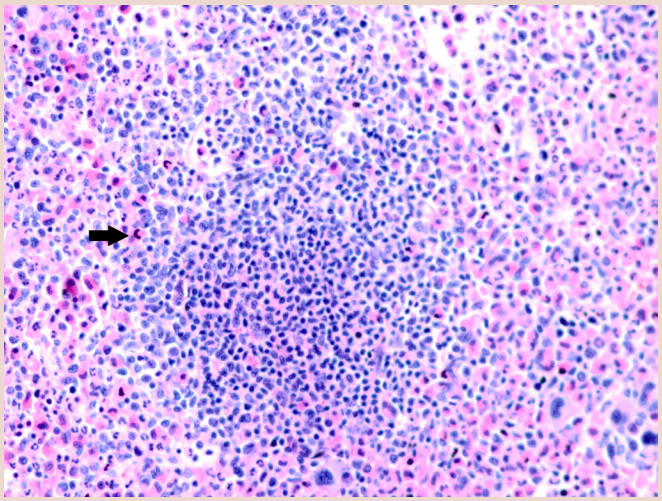

Figure 1: Bone marrow aspiration and biopsy showing lymphoid nodule (arrow) surrounded by sheets of eosinophils and its precursors (H & E stain*20).

DISCUSSION

Hardy and Anderson coined the term hypereosinophilic syndrome (HES) in 1968. In 1975, Chusid et al furnished empirical diagnostic criteria for idiopathic HES (IHES) which is implemented till date: [1]

1. Persistent eosinophilia greater than 1500 per microliter for over 6 months.
2. Lack of supportive proof of rest of the known etiologies of secondary hypereosinophilia.
3. Diverse organ involvement.

The myeloproliferative variant of HES typically involves males, with pertinent cardiac involvement, and demonstration of a frequently positive FIP1L1-PDGFRα [Fip1-Like1–Platelet Derived Growth Factor Receptor alpha] fusion gene mutation.[2] Also seen are dysplastic eosinophils on peripheral smear, serum B12 >1000 pg/mL, serum tryptase ≥12 ng/mL, anemia orthrombocytopenia, hepatosplenomegaly, bone marrow cellularity >80%, spindle-shaped mast cells in bone marrow and myelofibrosis. Patients with an elevated serum tryptase or atypical mast cells on the bone marrow biopsy must also be screened for the 816V c-kit mutation associated with systemic mastocytosis.[3]

In contrast, the lymphocytic variant of HES involves males and females equally. There are increased dermatological manifestations, including pruritus, eczema, erythroderma, urticaria, and angioedema, seen in almost all patients reported in the literature. Prior histories of atopic diseases are commonly reported with an elevated serum Ig E level. Cardiac involvement is rare despite the increased eosinophil counts. Complications of hypereosinophilia in this subset are more commonly lung and gastro-intestinal involvement.[4]

The lymphocytic variant of HES (L-HES) is characterized by an associated increased production of interleukin (IL)-5 by "type 2" T-cells, resulting in a "reactive" polyclonal eosinophil proliferation and enhancement. The effects of these Th2 cytokines on other cells (e.g., B cells) account for associated biological features of L-HES. Indeed, B cell stimulation leads to increased Ig E synthesis and polyclonal hypergammaglobulinemia. The diagnosis of L-HES fundamentally depends on increased monoclonal T-cell subsets with the abnormal expression of surface markers such as CD3−CD4+and CD3+CD4−CD8, along with a negative FIP1L1-PDGFRα fusion gene mutation.If available, increase in serum thymus and activation-regulated chemokine (TARC) might prove to be a helpful marker of L-HES.[5,6]

Eosinophil-induced cardiac dysfunction proceeds via three stages: it begins with an acute necrotic stage followed by an intermediate phase characterized by thrombus formation and endo-myocardial damage. It concludes via a fibrotic stage.[7]The initial necrotic phase is generally clinically inert and is characterized by endocardial inflammation, myocardial infiltration with eosinophils and lymphocytes, eosinophil degranulation, myocardial necrosis and the creation of sterile microabscesses. Elevations in serum troponin levels is a reliable and sensitive predictor of initial ongoing eosinophil induced myocardial destruction. Contrast-enhanced cardiac MRI accurately details every stage of eosinophil-influenced cardiac destruction; including the initial myocardial eosinophilic inflammation. Echocardiography sometimes is normal in the acute necrotic stage. Echocardiography and cardiac MRI may reveal intra-cardiac thrombi in the second stage of the disease including thrombus generation along damaged endocardial territories. Endo-myocardial biopsy might suggest definitive proof of eosinophil induced cardiac dysfunction and is usually reserved later for patients with an uncertain diagnosis. In the concluding fibrotic stage, successive scar tissue formation leads to endo-myocardial fibrosis, creating a restrictive cardiomyopathy and valvular regurgitation because of entrapment of the chordae tendineae. Echocardiography or cardiac MRI may reveal areas of fibrosis.[8]

Significant data suggests that veins and arteries might be damaged in HES, although the mechanisms are unclear. Cases are known to develop femoral artery occlusion, intracranial sinus thrombosis and digital gangrene. Microvascular thrombi and obstruction via eosinophil-mediated destruction of endothelium coupled with stimulation of the coagulation system have been documented in conjunction with acute kidney injury and cold-mediated Raynaud's phenomenon leading to digital necrosis. While eosinophils might interfere in coagulation pathways at different strata, the accurate mechanisms following up to hypercoagulability remain unclear.[9]

The aim of treatment of HES is to inhibit eosinophilopoietic cytokine production (IL-5 and IL-3, GM-CSF) by deregulated T cells and to control their proliferation and prevent end-organ destruction, thromboembolic phenomenon and malignant transformation.Anticoagulation is only justified if thrombi are present, and not for prophylactic use. For the myeloproliferative variant of HES (associated with the FIP1L1–PDGFRA fusion gene), imatinib (a tyrosine kinase inhibitor) is considered the first-line therapy. Current therapeutic choices for patients with L-HES include steroids and hydroxycarbamide, but other alternative agents like cyclosporine and methotrexate are proven beneficial in a few.[10] Trial of imatinib in L-HES remains controversial. There are reports of response to imatinib in patients negative for the FIP1L1–PDGFRA fusion gene, particularly in those unresponsive to steroids. Recent formulations include the anti-IL-5 monoclonal antibodies (e.g. mepolizumab), which has a specific role in eosinophil development and seems to mediate HES. Mepolizumab is highly specific and binds with immense affinity to free IL-5, thus inhibiting its interaction with the IL-5 receptor on the eosinophil surface. Our case highlights the importance of investigating patients with unexplained persistent eosinophilia and including this unusual syndrome in the differential diagnosis.[11]

Our case highlights that the lymphocytic variant of the hypereosinophilic syndrome can be associated with myocarditis, though this is not very commonly described in the literature. Usually, the hypereosinophilic syndromes respond very well to steroids, and in our patient, his response was good upon the initial admission, but very poor during the second time that he had presented to us. Also, our patient did not manifest with any dermatological symptoms which is seen in almost all of those with the lymphocytic variant of this condition. We also recommend that

patients who have been diagnosed with hypereosinophilic syndromes be followed up regularly with the blood eosinophil counts, as our case illustrates that relapse of the condition is very much possible. Early diagnosis and prompt treatment with steroids is quintessential in managing these patients.

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