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Case Report

Rare Case of Primary Hypereosinophilic Syndrome

Ayesha Mohan BS[1], Farzana Hoque[2]

Abstract

Hypereosinophilia is a rare collection of syndromes of various etiologies that can present incidentally or in some cases, in a life-threatening manner. This is a unique case of a 38-year-old male who presented with acute encephalopathy following a cerebrovascular event and was later found to have elevated eosinophil counts. It is crucial to have high clinical suspicion to diagnose this rare disease when a patient presents with multi-organ dysfunction with no clear etiology, especially when involving a presentation of acute onset in a relatively young patient.

Keywords: *Primary hypereosinophilia, Eosinophilic encephalopathy, FIP1L1-PDGFRA mutation, Hypereosinophilic syndrome*

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Introduction

Hypereosinophilic syndromes (HES) encompass a rare and heterogenous group of disorders defined as consistent and marked blood absolute eosinophil count (>1.5 x 10^9/L).[1] It is a diagnosis of exclusion once other etiologies of hypereosinophilia such as allergic, parasitic, and malignant disorders have been excluded. This syndrome is more common in males than females and is most often seen in young to middle-aged patients.[1] The accumulation of eosinophils can cause various target-organ damage and can involve the skin, heart, lungs, and nervous system. Approximately 75% of cases of presumed HES remain undefined and dawns the term idiopathic HES.[2] The estimated prevalence of HES was between .36 to 6.3 per 100,000.[3] In many patients, symptoms are sudden, and eosinophilia may be detected incidentally. In a small minority of patients, manifestations of HES can present as severe and life-threatening due to the rapid progression of multi-organ complications.

Case Report

We report a case of a 38-year-old Caucasian male with no significant prior medical history and non-smoker who presented to an outside hospital with an acute cerebrovascular event (CVA) characterized by multiple neurologic symptoms including fatigue, blurry vision, ataxia, headaches, and dizziness. According to the family, the patient had been experiencing intermittent episodes of numbness in various dermatomes preceding admission. MRI from the outside hospital showed "multiple small foci of high DWI/ADC signal" in the bilateral cerebral and cerebellar hemispheres consistent with small acute infarcts (Figure 1).

The etiology of the small infarcts was thought to be from cardiac or large artery emboli. CTA brain/neck was negative, and an ECHO showed normal LV systolic function along with Grade 1 diastolic dysfunction. TEE was done and showed no evidence of a cardiac source causing CVA. The patient was determined to have new-onset type II diabetes due to a glucose level of 418 on arrival. A ventilation perfusion scan demonstrated a low risk of PE and doppler studies revealed the presence of left lower leg deep vein thrombosis. The patient was evaluated by hematology/

1. Saint Louis University School of Medicine, St. Louis, MO, USA
2. Associate Professor of Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA

Corresponding Author: Dr. Farzana Hoque, Associate Professor of Medicine, Saint Louis University School of Medicine, St. Louis, MO, USA. E-mail: farzanahoquemd@gmail.com

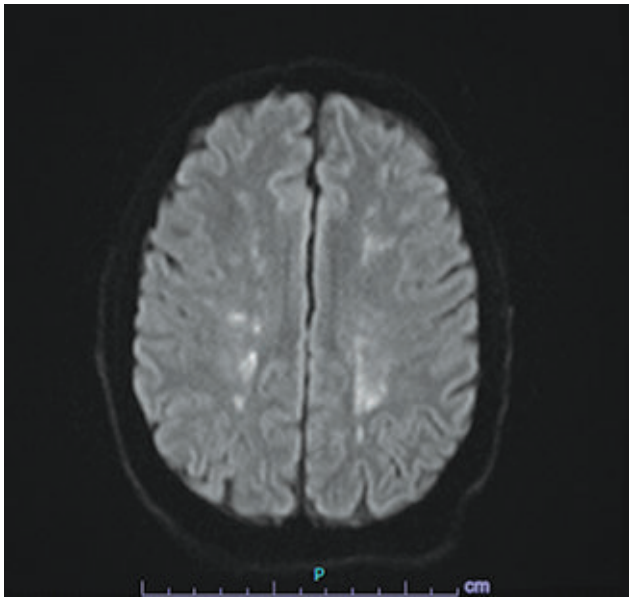

Figure 1: *MRI Brain without contrast demonstrating multiple small infarcts in bilateral cerebral and cerebellar hemispheres.*

oncology at an outside hospital where a bone marrow biopsy showed concern for hypereosinophilic syndrome with CBC with differential showing eosinophil levels near 41% and absolute eosinophil counts of 9.05 x10^9/L *(Figure 2).*

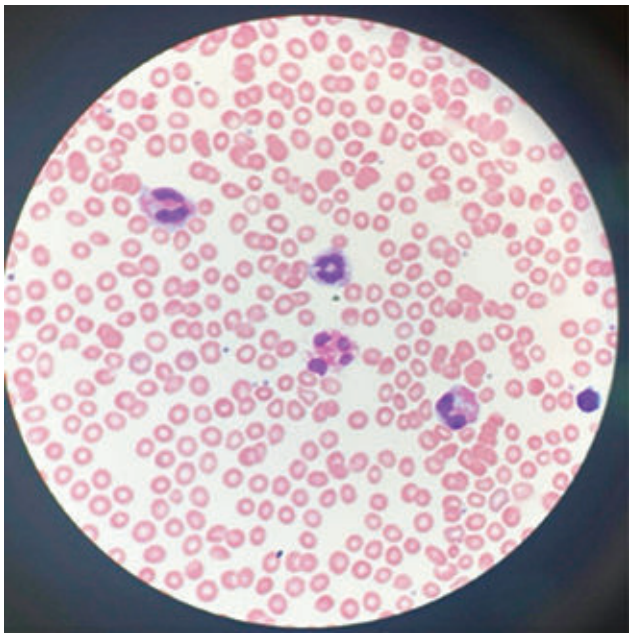

Figure 2: *Pathology finding of bone marrow specimen showing prominent eosinophilic hyperplasia.*

The patient was transferred to our facility for further hematologic workup and was started on methylprednisolone before transfer. During his hospitalization, the patient became encephalopathic with intermittent periods of aggression and marked confusion. Infectious Disease was consulted at our facility and was unable to determine infectious etiology for his presentation. CBC continued to show increasing eosinophils and was treated with IV Solumedrol, Hydroxyurea, Bactrim, Valtrex, and one-time Ivermectin to cover potential infectious causes. EEG conducted by neurology showed generalized slowing. Bone marrow biopsy completed at the outside hospital revealed marked hypereosinophilia and FIP1L1-PDGFRA rearrangement but no evidence of lymphoma or acute leukemia. FISH identified deletion of the CHIC2 gene on chromosome 4q12 resulting in the fusion of FIP1L1-PDGFRA which resulted in steroid-refractory hypereosinophilia. The patient was then started on Imatinib with significant response after 2 doses and eosinophil levels improved from 13,000 ìl to 700 ìl and white blood cell counts decreased from 45 × 10^9/L to 4.8× 10^9/L within a few days. Cardiac MRI showed no signs of eosinophilic myocarditis. The patient was admitted to acute rehab and returned home shortly after with much physical and cognitive improvement. The patient continues to have consistent hematology-oncology follow-ups and has remained on Imatinib and Eliquis to this day.

Discussion

Hypereosinophilia (HES) is a group of rare disorders characterized by peripheral blood eosinophilia greater than 1.5x10^9/L and evidence of end-organ damage attributable to the eosinophilia and not otherwise explained in the clinic setting. HES can be idiopathic or associated with a variety of underlying conditions, including allergic, rheumatologic, infectious, and neoplastic disorders. The etiology of this condition can be primary (myeloid), secondary (lymphocyte driven), or unknown. In many patients, the onset of symptoms is insidious. In a minority of patients, the initial manifestations are severe and life-threatening due to the rapid evolution of cardiovascular or neurologic complications.

There are various subsets of HES including primary, secondary, or idiopathic. Primary HES involves underlying stem cells, myeloid, or eosinophilic neoplasm. Secondary or reactive HES eosinophilic expansion is driven by parasitic infections, certain solid tumors, and T-cell lymphoma all of which can lead to marked organ damage and dysfunction. In idiopathic HES, the underlying etiology of hypereosinophilia remains unknown despite a thorough work-up. Certain subtypes of HES associated with genetic mutations such as PDGFRA, as seen in the patient at our facility, occur almost entirely in males.[4] Patients with PDGFRA-positive HES fall under the primary category and generally experience debilitating complications associated with high mortality

rates in the absence of treatment. There have been some cases where patients had minimal symptoms with little to no disease progression over several years.[5] First-line therapy for all patients with the FIP1L1-PDGFRA mutation is a tyrosine kinase inhibitor called imatinib mesylate and should be initiated immediately upon diagnosis of this subtype in order to prevent the progression of end-organ damage. If mutational analysis is not readily available, certain lab values can be used as surrogate markers for the presence of the mutation including markedly elevated serum Vitamin B12 levels (>2000 pg/mL), elevated serum tryptase level (>11.5 ng/mL), and/or splenomegaly.[6]

Among the identifiable causes of HESs, the FIP1L1-PDGFRA fusion gene is the most common and affects between 10-14% of all patients presenting with HES.[4] Patients with this mutation classically do not respond to corticosteroid therapy and are seen to have an aggressive course with poor prognosis without proper treatment with imatinib. Prompt initiation of therapy is essential to prevent irreversible complications such as endomyocardial fibrosis and sequelae of thromboembolic events.[7] The response to imatinib is rapid with the majority of patients experiencing clinical and hematological resolution of abnormalities within the first month.[8] A lack of hematologic response at 2-4 weeks is a concern for primary resistance which is a rare event.[9] If the patient is intolerant to imatinib or develops resistance, other tyrosine kinase inhibitors have demonstrated efficacy against FIP1L1/PDGFRA-positive cell lines such as nilotinib.[10] Bone marrow transplant has been used successfully in these patients but should be reserved solely for symptomatic patients who are unresponsive to tyrosine kinase inhibitors.[11] Causes for morbidity and mortality in HES primarily encompass organ dysfunction, namely cardiovascular complications such as endomyocardial fibrosis, heart failure, and infiltrative cardiomyopathy. Patients with HES are at high risk for developing thrombosis, particularly in the cardiac ventricles.[12] A cohort study involving 71 adults with HES showed that thrombotic events were common with 24% of the study population experiencing at least 1 event, which was associated with an increased risk of death. The presence of molecular aberration on next-generation sequencing, such as FIP1L1-PDGFRA, was associated with a 5-fold increase in the risk of thrombosis.[13] Although this disease is rare, prompt diagnosis and treatment lead to a better prognosis. In a retrospective study analyzing 43 patients, the overall survival rate was 80% at 5 years and 42% at 10 and 15 years following initial diagnosis.[14] This same study demonstrated that the factors most capable of impairing prognosis were the presence of a myeloproliferative syndrome, non-response of the hypereosinophilia to corticosteroids, the existence of cardiopathy, and elevated maximum eosinophilia.[14] Recent studies have shown that patients who achieve complete molecular remission and continue imatinib therapy for a prolonged period, greater than 7 years, are less likely to relapse after imatinib discontinuation. The optimal duration of therapy has not been determined but it has been recommended to continue imatinib therapy for at least 7 years to avoid relapse.[15] PCR-detectable FIP1L1-PDGFRA transcription levels can be used to determine molecular remission.

Conclusion

Hypereosinophilic syndrome is a rare condition that has the potential to lead to fatal outcomes because of the potential for end-organ damage if treatment is delayed. There are a variety of etiologies for this condition including infectious parasites, genetic mutations such as the *FIP1L1-PDGFRA* variant, underlying malignancy, and even idiopathic causes. A multidisciplinary approach with early hematology intervention is essential to ensure safe patient outcomes. Clinicians' awareness of this uncommon but highly dangerous condition is imperative to prevent devastating outcomes.

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