Case Report

Refractory Idiopathic Hypereosinophilic Syndrome Presenting with Myocarditis and Responding to Imatinib: A Case Report

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Abstract

Idiopathic hypereosinophilic syndrome (HES) is a rare disorder characterized by persistent hypereosinophilia leading to multi-organ dysfunction. Its clinical manifestations vary widely; however, cardiac and neurological involvement are the leading causes of morbidity and mortality. Corticosteroids are the initial treatment of choice, but in idiopathic HES resistant to corticosteroids, second-line therapy should be considered. Imatinib is usually reserved for patients with a positive platelet-derived growth factor receptor A (PDGFR-A) mutation; however, its use in idiopathic HES with a negative PDGFR mutation is debatable given that such patients usually respond well to high doses of corticosteroids. Here, we present a case of a young male with corticosteroid-refractory idiopathic HES successfully treated with imatinib. The patient presented with features suggestive of acute coronary syndrome and confusion. A coronary angiogram was normal. Echocardiography showed an ejection fraction of 37%, and brain imaging showed evidence of multifocal cerebral thromboembolic infarcts. During the hospital stay, the patient developed diffuse alveolar hemorrhage. Biochemically, it was noted that the patient had hypereosinophilia. Through thorough workup, a diagnosis of idiopathic HES was established. The patient was started on high-dose corticosteroid (500 mg intravenous methylprednisolone daily) followed by a maintenance dose of prednisolone (0.5 mg/kg/day), but had no response. Second-line therapy with imatinib (400 mg per oral daily for 4 days and then down-titrated to 100 mg daily) was initiated, which resulted in drastic biochemical and clinical improvements. This case report supports the efficacy of imatinib as a second-line agent in corticosteroid-resistant idiopathic HES with a negative PDGFR mutation.

Keywords: Corticosteroids, hypereosinophilia, idiopathic hypereosinophilic syndrome, imatinib, myocarditis

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INTRODUCTION

Idiopathic hypereosinophilic syndrome (HES) is a rare hematological disorder characterized by hypereosinophilia and eosinophil-related tissue damage and organ dysfunction.[1] The incidence of HES has been estimated as 0.36–6.3 per 100,000 people.[2] It mostly affects those aged 20–50 years but has also been reported in children and elderly.[3,4]

Organ damage in HES can be attributed to a variety of mechanisms including eosinophil infiltration,

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eosinophil-induced fibrosis, or eosinophil-induced hypercoagulability state.[5] The clinical symptoms of HES can be highly diverse, with the most prevalent manifestation on presentation being the involvement of the cutaneous, pulmonary, and gastrointestinal tract. Cardiac manifestations account for <5% of the cases at the time of diagnosis; however, cardiac and neurological involvement are the leading causes of morbidity and mortality.[6,7]

The diagnosis and management of HES are challenging because it necessitates the exclusion of other eosinophilic diseases. Patients who present with life-threatening manifestations, on the other hand, require prompt treatment to avoid undesirable consequences and permanent organ dysfunction.[8] In terms of cardiac involvement, patients with eosinophilic myocarditis experience fast-progressing symptoms with significant morbidity and mortality. A severe form of HES can produce acute eosinophilic necrotizing myocarditis, which results in acute systolic dysfunction.[9] Endomyocardial biopsy is considered the gold standard for diagnosis of eosinophilic myocarditis, but has a sensitivity of only 54%.[10] The use of electrocardiography, echocardiography, and cardiac biomarkers are less invasive methods that are useful in diagnosis.

Systemic corticosteroids are considered the initial treatment in most forms of HES.[8] However, in case of no response to corticosteroids, a second-line agent should be considered. Imatinib mesylate is a tyrosine kinase inhibitor having action against various tyrosine kinases receptors, including the fusion kinase *Fip1-like 1/platelet-derived growth factor receptor A* (PDGFR-A), which is responsible for PDGFR-A-associated HES. The use of imatinib mesylate therapy in HES with a negative PDGFR-A mutation is debatable, although some patients have demonstrated a response to this therapy.[11] In such cases, imatinib can be considered as a second-line agent in corticosteroid refractory disease.[12]

In this report, the authors describe a young male who presented with features of acute coronary syndrome and multiple bilateral hypodense lesions on brain imaging suggestive of infarcts, which are thromboembolic in origin and were later found to be secondary to idiopathic HES. The condition was refractory to corticosteroids, and imatinib was introduced as a salvage therapy that resulted in significant improvement in biochemistry, normalization of eosinophilic count, and, eventually, extubation. The objective of this case report is to demonstrate the efficacy of using imatinib as a second-line agent in patients with corticosteroid refractory idiopathic HES with a negative PDGFR mutation.

CASE REPORT

A 33-year-old, non-smoker male with no significant history of chronic illnesses, cardiac disease, or allergy to food or drugs presented to the emergency department of a university hospital complaining of acute typical chest pain that had started a few hours before arrival. He was noted to be restless, agitated, and confused. His electrocardiogram showed T-wave inversion in lead 3 and aVF and ST-segment depressions V_2 to V_6 [Figure 1]. His troponin I peaked at 9.89 ng/ml. Due to the patient's confusion and agitation, he was sedated and electively intubated to facilitate a coronary angiogram, the findings of which were normal. Afterwards, a non-contrast head computed tomography (CT) scan was done, which revealed multiple bilateral cortical and subcortical hypodensities encompassing both frontal and parietal lobes as well as the right caudate head [Figure 2]. Initial laboratory investigations were significant for a leukocyte count of 32,300 cells/μL, with a 58% eosinophil count. Subsequently, over the next few days, his leukocyte count continued to rise despite the septic workups being negative and exclusion of an underlying infectious process. A transthoracic echocardiogram was performed, and it showed left ventricular dysfunction with an ejection fraction of 37% and an akinetic inferior and lateral wall [Figure 3]. Cerebrospinal fluid analysis was normal.

Given that the patient was a young healthy adult with no comorbidities or high-risk health behaviors, with multi-organ dysfunction and a high eosinophil count, the possibility of HES was considered, and thus primary and secondary causes of HES were investigated. Bone marrow examination showed normal cellular bone marrow with trilineage hematopoiesis with abundant eosinophils and no blast cells. There were no clinical features suggestive of hematological malignancies (no hepatosplenomegaly or lymphadenopathy). Moreover, chromosomal analysis, BCR-ABL mutation, and HES-specific fluorescence *in situ* hybridization panel for PDGFR-A and PDGFR-B mutation were negative. A CT scan of the chest, abdomen, and pelvis, and an esophagogastroduodenoscopy were done without any remarkable findings. Stool analysis and culture were negative for any parasitic infection. Serum autoantibodies including antinuclear antibody and antineutrophil cytoplasmic antibody were also screened and were unremarkable. Serum IgE level was 73.9 (normal value 5–500 kU/L), and serum B12 was also within the normal reference range.

The constellation of signs and symptoms of cardiac involvement, multiple bilateral cortical, and subcortical hypodense lesions on head CT scans and a significant

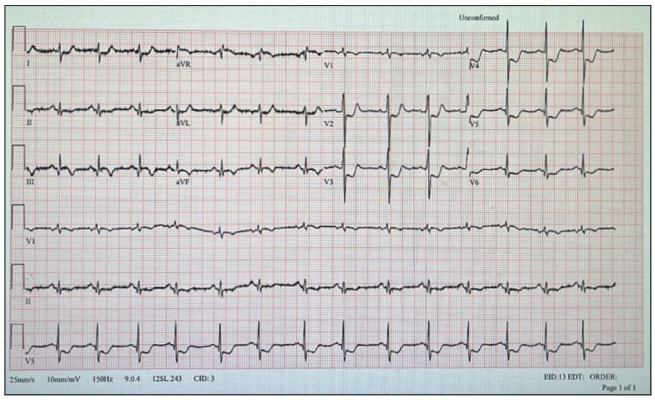

Figure 1: A 12-leads ECG showed T-wave inversion on lead 3 and aVF, ST-segment depressions V_2 to V_6

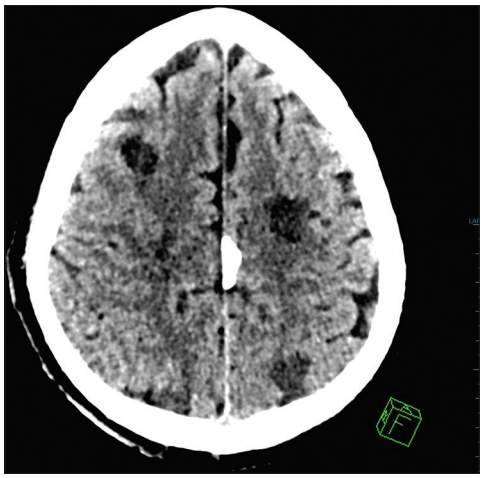

Figure 2: A noncontrast head computed tomography scan demonstrates multiple bilateral cortical and subcortical hypodensities encompassing both frontal and parietal lobes as well the right caudate head

elevation of serum eosinophils raised concern for the life-threatening presentation of HES. A trial of 3-day pulse corticosteroids (500 mg intravenous methylprednisolone daily) was initiated followed by a maintenance dose of prednisolone (0.5 mg/kg/day) after ruling out bacterial, parasitic, and fungal infections. The condition was refractory to the trial of corticosteroid, as evidenced 4 days later by the development of diffuse alveolar hemorrhage. In addition, biochemically, the eosinophilic count continued to rise.

Due to the rapid deterioration of the patient's condition, and lack of response to corticosteroids, imatinib was introduced as a salvage therapy after a multidisciplinary meeting with the hematology team. The patient was started initially on imatinib 400 mg per oral daily for 4 days and then down-titrated to 100 mg per oral daily as a maintenance dose. A substantial improvement was noted biochemically with normalization of eosinophilic count within 7 days from the initiation of imatinib [Figure 4], and shortly after, the patient was extubated and started to regain his baseline level of consciousness, and ultimately, the patient was able to mobilize and perform his activities of daily living. The patient was discharged from the hospital with full function, and at an outpatient clinic follow-up after 1 month, he retained full functioning.

DISCUSSION

There have been several classification systems for HES, including the 2006 classification by clinical phenotype as idiopathic, myeloproliferative (M-HES), lymphocytic (L-HES), overlap, associated, or familial HES.[13] The revised (2016) World Health Organization classification of eosinophilic disorders separates myeloid/lymphoid neoplasms with eosinophilia and rearrangement of PDGFR-A, PDGFR-B from chronic eosinophilic leukemia, not otherwise specified, and distinguishes between L-HES and I-HES.[13] Idiopathic HES has been reported to occur in up to 75% of the cases.[14]

The main goals of the treatment of HES are to reduce the absolute eosinophil count to a safe level, treat signs and symptoms attributed to the disease, and prevent disease-mediated organ dysfunction.[15] Corticosteroids remain the initial treatment of choice, even for patients presenting with life-threatening manifestations of the disease, including PDGFR mutation-negative HES, such as our patient. Idiopathic HES resistant to corticosteroid therapy has been reported to occur in up to 15% of the cases.[6] HES is deemed steroid sensitive when absolute eosinophil count decreases by >50% in 2–3 days.[16] However, if the desired response is not achieved after 3 days of high-dosage corticosteroid, second-line treatment, such as imatinib, hydroxyurea, vincristine, or cyclophosphamide, should be considered.

Several factors are to be considered when selecting the most appropriate second-line agent, including the acuity of the clinical manifestations, drug availability, the pharmacologic and side effect profile of the therapeutic agent, and the most likely diagnosis.[16] Such as in our case, the patient had life-threatening complications of HES in the form of acute heart failure along with thromboembolic ischemic stroke. High-dose corticosteroid was administered for 3 days followed by a maintenance of prednisolone (0.5 mg/kg/day), but with a lack of clinical and biochemical response. Subsequently, imatinib was initiated as a second-line agent for refractory idiopathic HES, which resulted in a drastic clinical and biochemical response, and a rapid reduction of serum eosinophil count to near normal levels within a 3-day period.

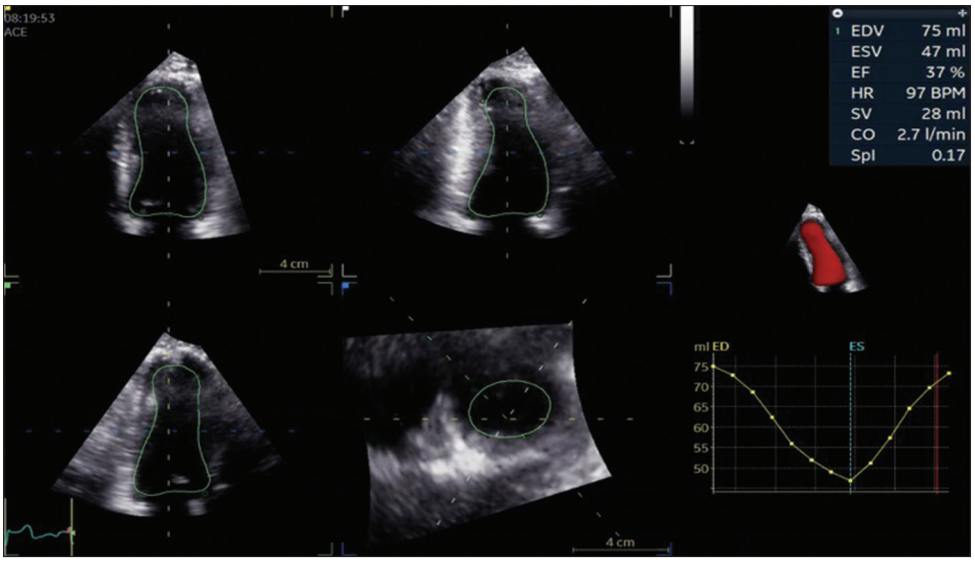

Figure 3: Apical 2 chamber and short-axis transthoracic ECHO views demonstrating an estimated left ventricular ejection fraction of 37%

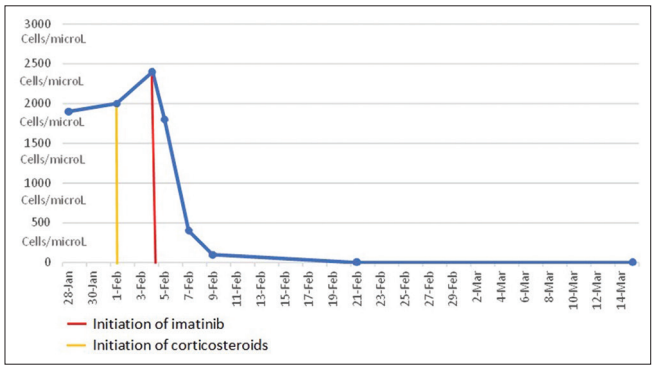

Figure 4: Dynamic changes of eosinophilic count in response to imatinib

Imatinib mesylate, a tyrosine kinase inhibitor, is the drug of choice in M-HES associated with positive PDGFR mutation. The use of imatinib in patients without a known imatinib-sensitive mutation remains controversial. However, despite a negative PDGFR mutation and no feature suggestive of M-HES, there was a strong clinical and biochemical response to imatinib in our patient. There are a few case studies of idiopathic HES unresponsive to standard therapy that showed a substantial response to imatinib, with a response rate of 9%–60%.[11,17] Ogbogu and Klion reported a similar case of a young patient who presented with chest pain and picture suggestive of ischemic coronary changes in electrocardiography who was found to have idiopathic HES. Similar to our case, a high-dose corticosteroid was not effective, after which imatinib was introduced empirically, and within 1 week, his eosinophilic count normalized.[11] It should be noted that high-dose corticosteroids should be continued with imatinib in the initial days for patients with evidence of cardiac involvement to prevent myocardial necrosis, a rare complication of imatinib.[12]

CONCLUSION

Cardiac or neurologic involvement in idiopathic hypereosinophilic syndrome are considered life-threatening manifestations that require immediate treatment to avoid disease complications and risk of death. Imatinib mesylate is the drug of choice for myeloproliferative idiopathic hypereosinophilic syndrome with a positive PDGFR mutation. However, our case report supports the efficacy of imatinib as a second-line agent in corticosteroid-resistant idiopathic hypereosinophilic syndrome with a negative PDGFR mutation.

Declaration of patient consent

The author certifies that all appropriate patient consent forms have been obtained. In the form, the patient has given his consent for his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

Ethical considerations

The Institutional Review Board of Imam Abdulrahman Bin Faisal University, Dammam, Saudi Arabia, provided ethical approval for reporting this case (Ref. no.: IRB-2024-01-057).

Peer review

This case report was peer-reviewed by two independent and anonymous reviewers.

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Conflicts of interest

There are no conflicts of interest.

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