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Chronic Eosinophilic Leukemia in an African American Man

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Abstract

The term "hypereosinophilic syndrome" refers to a rare group of disorders characterized by a persistent, marked proliferation of eosinophils with end-organ involvement. Chronic eosinophilic leukemia is a myeloproliferative variant of hypereosinophilic syndrome characterized by clonal eosinophilia, which can result in hematologic, cardiac, or pulmonary end-organ damage, among others. We present a case of chronic eosinophilic leukemia seen at our institution and discuss an approach to making the diagnosis of hypereosinophilic syndrome in general, and chronic eosinophilic leukemia in particular. We also explore treatment options in the management of hypereosinophilic syndrome/chronic eosinophilic leukemia, including novel agents like Alemtuzumab and Mepolizumab.

Keywords: Chronic eosinophilic leukemia; Hypereosinophilic syndrome; Imatinib; FIP1L1-PDGFRA

Introduction

Eosinophils are non-dividing, end stage cells that differentiate from the hematopoietic stem cell in the bone marrow. They migrate in the blood transiently and are predominantly tissue-dwelling cells [1]. Eosinophils play a pivotal role in the body's response to parasitic infections and some bacterial infections, and are also important in the etiopathogenesis of atopy and allergy reactions. Although eosinophilopoiesis and egress from the bone marrow is regulated by T cell-mediated cytokines depending on presence of allergens or infections [1], production is occasionally not controlled by these mechanisms and a hypereosinophilic state may result.

The term "hypereosinophilic syndrome"(HES) has been described to explain the finding of persistent eosinophilia of 1.5×10^9/L or higher (≥ 1500 eosinophils/mm³) lasting greater than 6 months, with evidence of organ involvement, and in the absence of other known causes of eosinophilia such as parasitic infection or allergic reaction [2]. Six clinical types of HES were described at a 2005 international consensus workshop on the treatment of HES: (i) myeloproliferative variant HES, (ii) lymphocytic variant HES, (iii) familial HES, (iv) overlap HES, (v) associated HES and (vi) idiopathic HES [2]. Chronic eosinophilic leukemia (CEL) falls within the myeloproliferative variant of HES. It is characterized by clonal eosinophilia and can be differentiated from the broad category of HES by the presence of increased peripheral blood and marrow blasts or by the demonstration of a clonal cytogenetic abnormality or a hallmark tyrosine kinase activating mutation in the myeloid lineage [3]. CEL discriminately affects men, with a male-to-female ratio estimated at 9:1 [3]. Peak incidence occurs between ages 20-50, although some cases have been reported in infants and children [3]. The clinical features seen in CEL include hepatomegaly, splenomegaly, anemia, thrombocytopenia, and bone marrow dysplasia or fibrosis. Cardiac involvement may lead to endomyocardial fibrosis and valvular insufficiency, and pulmonary involvement can cause fibrosis, effusions, emboli, and ground glass attenuation, among others. Patients can have elevated cobalamin and tryptase levels as well as increased levels of atypical mast cells [2,3].

We present a case of CEL seen at our institution and discuss an approach to the diagnosis and management of CEL in particular, and HES in general.

Case Report

The patient is a 54-year-old African-American male with history of asthma, (requiring intubation in the past for an asthma flare), who presented with sudden onset pleuritic chest pain and dyspnea. Chest x-ray was normal and cardiac work-up was negative. He was diagnosed with acute asthma exacerbation, admitted, and was treated with IV methyl prednisolone, albuterol and ipratropium nebulizers with improvement in his symptoms. He was found to have significant eosinophilia on admission, which had been longstanding (for over 3 years) on review of his medical record. Laboratories showed white blood cell count of 24.6×10^9/L with a differential of 9% neutrophils, 1% bands, 19% lymphocytes, 6% monocytes, and 45% eosinophils. Hemoglobin was 10.9 g/dL, hematocrit 33.8 %, platelets 155×10^9/L, and MCV 85.8. Hematology consultation was therefore sought for marked eosinophilia.

On evaluation by the hematology team, he denied fevers, chills, night sweats, weight loss, abdominal pain, nausea, vomiting or diarrhea. He denied recent travel abroad, camping, or exposure to unsanitary water or food. He also denied easy bruising or bleeding, allergic reactions, or history of allergy to medication. His home medications were albuterol and Advair inhalers. He endorsed a 10-pack-year history of smoking but had quit 30 years prior. He, however, did report occasional cocaine use. His family history is significant for asthma in his mother who died of asthma-related complications. His physical examination revealed diffuse inspiratory and expiratory wheezing in all lung fields and moderate splenomegaly, but was otherwise unremarkable. He had no palpable lymph nodes.

A review of his medical record revealed that he had been evaluated for hypereosinophilia on a prior admission for asthma exacerbation, 3 years before his current presentation. A bone marrow biopsy at that time had shown markedly hypercellular marrow with marked myeloid and eosinophilic hyperplasia, and florescent in-situ hybridization (FISH) had revealed the presence of the FIP1L1-PDGFRA (Fip1-like-1 fused with platelet derived growth factor receptor alpha) mutation consistent with chronic eosinophilic leukemia. Unfortunately, he was lost to follow up until this admission.

To guide management, we reviewed the patient's peripheral blood smear and he underwent a repeat bone marrow biopsy which showed a markedly hypercellular marrow (95% cellularity) with predominant eosinophilia (60% of total marrow cellularity) (Figure 1). Flow cytometry showed myeloid predominance with increased CD52+ eosino forms; and florescent in-situ hybridization (FISH) was positive for the FIP1L1-PDGFRA mutation, consistent with chronic eosinophilic leukemia. Cytogenetic analysis revealed normal karyotype. We also obtained echocardiography, CT scan of the chest and pulmonary function tests, looking for other evidence of organ involvement but these were unremarkable. His only evidence of organ involvement was the bone marrow findings, mild anemia and splenomegaly.

Given that patients with FIP1L1-PDGFRA-mutated CEL have virtually universal response to Imatinib, we encouraged the patient repeatedly on multiple occasions to begin treatment with Imatinib. Unfortunately, he declined treatment. It has been about a year since his last comprehensive hematology review. He has been readmitted twice subsequently in the interim period for asthma flares for which he received routine treatment and was discharged. We reiterated the need to receive treatment for CEL on these occasions but he remains yet unwilling. Interestingly, he showed no overt signs of deterioration in his clinical or performance status from his initial presentation.

Discussion

The term "hypereosinophilic syndrome" (HES) was first coined in 1975 by Chusid et al. to describe patients with profound eosinophilia of an unclear cause [3]. To meet criteria for this diagnosis, patients had to demonstrate: (i) Persistent eosinophilia of 1.5×10^9/L (1500/mm³) or higher for a period greater 6 months; (ii) absence of other known causes of eosinophilia; and (iii) signs and symptoms of end organ involvement. The initial criteria established in 1975 are still used in making the diagnosis today. A patient suspected of having HES owing to prolonged profound eosinophilia should first undergo rigorous evaluation to rule out secondary causes of eosinophilia including parasitic, bacterial, fungal or viral infection; allergic and drug hypersensitivity reactions; neoplasms like leukemias, lymphomas, or solid organ adenocarcinomas; and autoimmune disorders or connective tissue disease [4]. Other causes such as hypoadrenalism, radiation exposure, cholesterol embolization and IL-2 therapy should also be ruled out [4]. Failure to identify a secondary cause for the eosinophilia should then lead to a comprehensive work-up to identify end-organ damage from HES and a possible clonal population of eosinophils, as is the case with myeloproliferative variant HES and CEL.

Work-up should include routine blood studies such as complete blood count with differential and chemistries, serum troponin, echocardiogram, computed tomography scans of the chest/abdomen/pelvis, and pulmonary function tests to establish end-organ involvement. A biopsy of affected tissues can also be undertaken if feasible [4]. A review of the peripheral smear and screening of the peripheral blood for the FIP1L1-PDGFRA (F/P) mutation by FISH or reverse transcription polymerase chain reaction (RT-PCR) is crucial in identifying clonal eosinophilia, as is the case in CEL [2-5]. If screening for the F/P mutation is negative, bone marrow biopsy and cytogenetic analysis should be undertaken to look for other evidence

of clonal eosinophilia such as 5q33 and 4q12 translocations, which suggest PDGFRB (platelet derived growth factor receptor beta) and PDGFRA-rearranged clonal eosinophilia respectively [5]. These translocations portend favorable response to Imatinib [5]. Analysis may, however, reveal 8p11.2 translocation, which suggests FGFR1 (fibroblast growth factor receptor 1)-rearranged clonal eosinophilia, associated with aggressive myeloid malignancies that are refractory to current drug therapy [5]. Bone marrow evaluation is also useful because it is helpful in excluding other well-defined myeloid malignancies, which can be secondary causes of eosinophilia. Failure to identify a clonal population on bone marrow evaluation should prompt investigation for an aberrant or clonal lymphocyte population with T cell receptor (TCR) gene rearrangement studies and peripheral blood lymphocyte phenotyping [5]. Identification of an aberrant/clonal lymphocyte population in this setting makes the diagnosis of lymphocytic variant HES, whereas the failure to identify such a population suggests a diagnosis of idiopathic HES [5].

Hypereosinophilic syndromes were historically treated with corticosteroids primarily, with hydroxyurea and interferon-alpha reserved as second line therapies. However, with reports of improved survival with Imatinib in chronic myelogenous leukemia (CML) in the early 2000s, Physicians started to use it in treating patients with HES/CEL based on the hypothesis that both CML and HES/CEL share a common pathogenic mechanism [3]. The first report of Imatinib use in HES was in 2001, in a patient with HES refractory to corticosteroids, hydroxyurea, and interferon alpha. He was given Imatinib and achieved complete hematologic response after taking Imatinib 100 mg daily for only 4 days [3]. A subsequent paper documented response to Imatinib 100 mg daily in 4 of 5 patients who were treated with this regimen [6]. Yet another study showed Imatinib responsiveness despite high serum IL-5 levels, demonstrating that the level of eosinophil-associated cytokine production was not necessarily predictive of Imatinib responsiveness in HES [3,7]. Several other patients with HES/CEL also showed good response to Imatinib, and a landmark study by Cools et al later identified that the molecular basis for response to Imatinib in HES was the inhibition of a novel fusion tyrosine kinase: FIP1L1-PDGFRA (F/P) [3,8].

Patients with F/P positive CEL or PDGFR-associated CEL should be treated with Imatinib (100-400 mg by mouth daily) given that response to Imatinib in these patients is almost universal, with patients achieving complete hematologic and molecular remission within days to weeks [2]. Maintenance therapy with daily Imatinib and surveillance with FISH or RT-PCR checking for the reappearance of the FIP1L1-PDGRFA fusion transcript (molecular relapse) every 3 to 6 months is recommended [9]. PDGFR-negative HES/CEL is not as responsive to Imatinib with reported response rates ranging from 9-60 % [2]. These patients are treated traditionally with corticosteroids. If refractory to corticosteroids, however, they are treated with Imatinib, but typically require higher doses and longer duration of therapy to achieve remission [2,10]. If refractory to Imatinib as well, other possible options for therapy include hydroxyurea, interferon alpha, second-and third-generation tyrosine kinase inhibitors, and allogeneic stem cell transplantation [2]. Interferon alpha provided a good response in a patient who was treated for coexisting CEL and Hepatitis C infection, with a significant decline in his eosinophilia and improvement in his symptoms after beginning interferon therapy [11]. Lymphocytic variant HES (L-HES) is initially treated with corticosteroids. Interferon alpha is the preferred second line therapy given its effect on both eosinophils and T cells [2]. In the case of idiopathic HES, corticosteroids are also first line therapy, with hydroxyurea and interferon alpha reserved as possible second line agents [2-5].

Novel agents in the management of HES and/or CEL have been investigated and show great promise. Two of these are Alemtuzumab and Mepolizumab, both of which are humanized monoclonal antibodies.
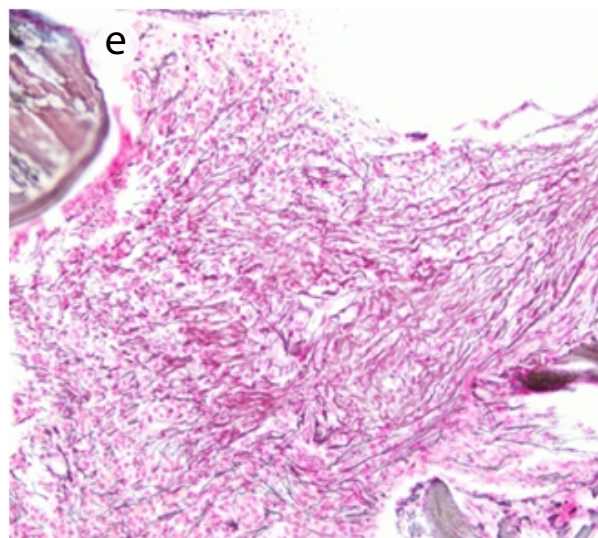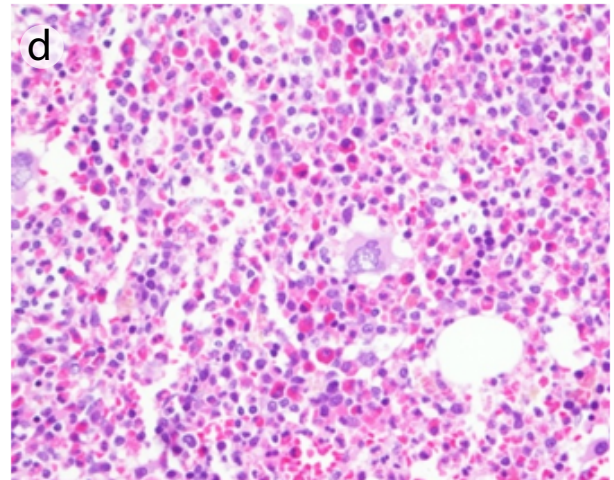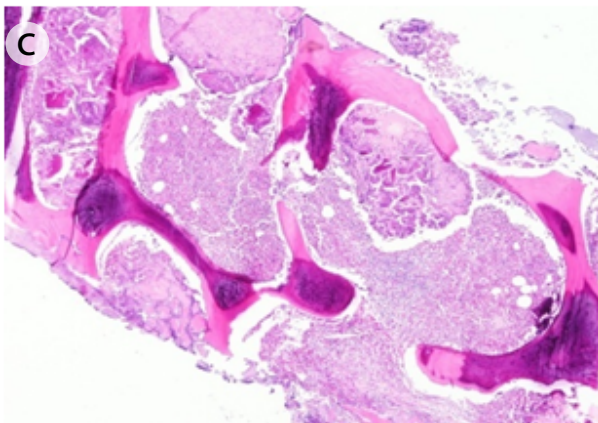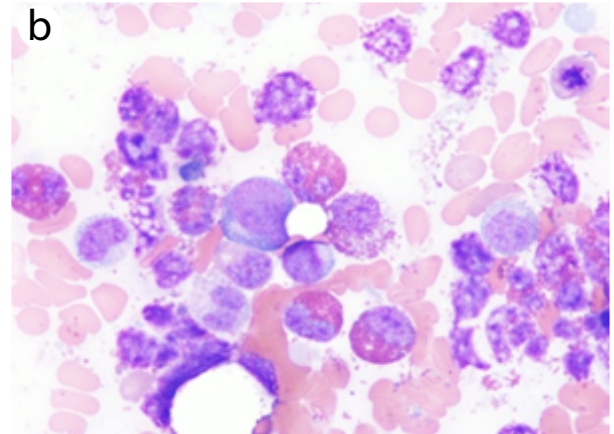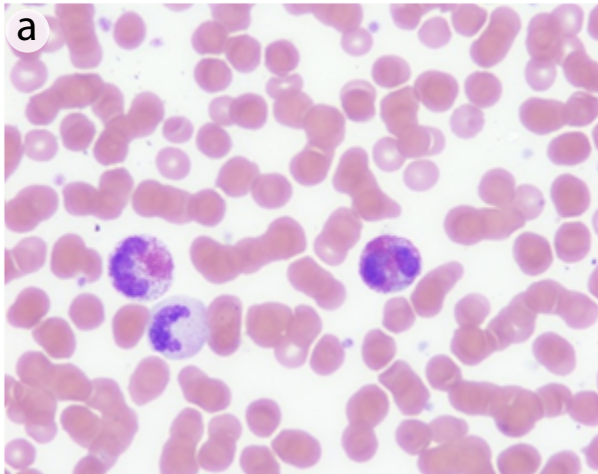
Figure 1: (a) Peripheral blood showing marked eosinophilia, with some eosinophils showing degranulation

(b) Bone marrow aspirate showing a marked increase in eosinophils and their precursors

(c) Bone marrow core biopsy showing hypercellularity with a greater than 90% cell to fat ratio

(d) Bone marrow core biopsy demonstrating sheets of eosinophils and their precursors

(e) Reticulin stain of bone marrow core biopsy showing a moderate to marked increase in reticulin fibrosis

Alemtuzumab is an anti-CD52 antibody, which was investigated as a potential effective therapy in HES due to the inherent expression of CD52 on eosinophils. A study at the MD Anderson Cancer Center in Houston, Texas, USA showed remarkable response rates and durable complete hematologic remission, especially with maintenance therapy [12]. Interestingly, some patients were able to achieve up to a third remission after repeat induction therapy with Alemtuzumab upon relapse [12]. In the case of Mepolizumab, it was postulated to be a potential therapeutic agent in HES since it binds with high affinity to IL-5, preventing it from interacting with its receptor on eosinophils. IL-5 is known to play a significant role in eosinophil maturation, differentiation, mobilization, activation, and survival [13]. A study by Rothenberg et al to evaluate the effects of mepolizumab on corticosteroid sparing and the maintenance of clinical stability in patients with HES treated with corticosteroids showed that it is effective and can result in corticosteroid-sparing for patients with FIP1L1-PDGFRA negative hypereosinophilic syndrome [13]. At the moment Alemtuzumab and Mepolizumab are only available on clinical protocols for refractory HES or on compassionate use basis and are not yet mainstream therapy for HES and/or CEL.

Conclusion

HES/CEL is a group of rare disorders characterized by a persistent marked proliferation of eosinophils with end organ involvement. Despite advances in treatment with the discovery of Imatinib in patients with the FIP1L1-PDGFRA mutation, further research is needed for the development of new therapies. Alemtuzumab and Mepolizumab are two novel agents that show promise, but are yet to become mainstream therapy for managing HES/CEL.

Declaration of Interests

The authors state no conflict of interests and have received no payment in the preparation of this paper or in conducting the study.

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