

# Fatal Idiopathic Hypereosinophilic Syndrome Presenting with Refractory Ascites: Case Report Study

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## ABSTRACT

Hypereosinophilic syndromes were a group of divergent disorders united by overproduction of eosinophils and the several organ damages ascribed to this persistent eosinophilia. Among all the presenting symptoms, gastrointestinal symptoms were the least common. We were reporting a 21 year old man with a 2 year history of refractory ascites, hepatomegaly, portal and hepatic veins thrombosis and cutaneous lesions. Bone marrow aspiration and biopsy revealed granulocytic hyperplasia with marked eosinophilia. After ruling out common causes of eosinophilia, a diagnosis of idiopathic hypereosinophilic syndrome was made. The patient was treated with corticosteroids and imatinib but due to the advanced progression of the disease, resulted in a fatal outcome. Since early diagnosis and treatment is the key for improving the prognosis of HES patients, a high clinical suspicion is necessary in the diagnosis of this condition.

**Keywords:** Eosinophilia; Hypereosinophilic syndrome (HES); Refractory ascites

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## INTRODUCTION

First described by Hardy and Anderson in 1968(1), hypereosinophilic syndrome (HES) encompasses a wide and heterogeneous group of

rare disorders characterized by excessive production of eosinophilic series by the bone marrow leading to marked and persistent elevation of eosinophils in the peripheral blood as well as infiltration of these cells into different internal organs causing potentially serious complications.

This incessant eosinophilia was associated with a spectrum of end organ dysfunction. Of these, cardiac involvement was the leading cause of mortality in HES patients(2). Cutaneous lesions may be the only presenting symptom in some patients(3). Less than 20 percent of HES cases manifest with gastrointestinal symptoms(4). We here were reporting a 21 year old patient with HES presenting with refractory ascites. To our knowledge, this is the first HES patient ever reported from Iran presenting predominantly with

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### CASE REPORT

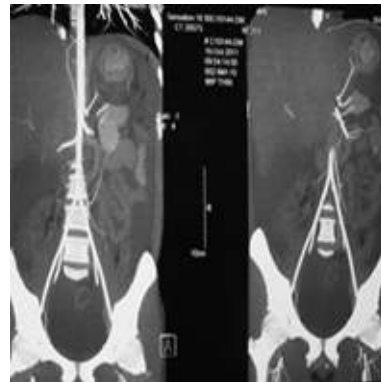
The patient was a 21 year old caucasian male seen at the gastroenterology department of our tertiary hospital in July 2011 with a 2 year history of increased abdominal girth and cervical lymphadenopathy.

For the first time in 2009, he was worked up for ascites, cutaneous lesions and cervical lymphadenopathy in another medical center. Medical records from that admission demonstrated a leukocyte count of  $30.3 \times 10^9 / L$  with eosinophils making up to more than 57%, mild microcytic anemia (Hb: 11.7 g/dL, MCV: 72 fL) with a platelet count of  $63 \times 10^9 / L$ . All serum viral markers including hepatotropic viruses were negative; but *toxoplasma gondii*-specific Immunoglobulin G antibody was elevated above the upper reference limit (URL). Microscopic analysis of the ascitic fluid showed a leukocyte differentiation of 85% lymphocytes and 15% polymorphonuclears (PMNs). Serial complete blood counts (CBCs) divulged declining RBC and platelet counts with the leukocytosis being still persistent. The bone marrow aspiration samples revealed normocellular marrow with eosinophilia. Regarding the exacerbating thrombocytopenia, the patient went through open splenectomy. A skin biopsy showed prominent papillary dermal edema with no signs of vasculitis. Further doppler ultrasonography of the abdominal vessels revealed chronic portal and hepatic vein thrombosis with partial recanalization. Upper and lower GI endoscopic studies were unremarkable. Rheumatologic studies including antiphospholipid antibodies, antinuclear antibodies (ANA), anti-cardiolipin and anti-dsDNA antibodies as well as lupus anticoagulants were all within the acceptable normal range. The patient was discharged on anticoagulant (coumadin, 5mg daily), diuretics and prophylactic antibiotic for SBP.

On the current admission, the patient appeared ill, was eupneic and afebrile with a blood pressure of 110/70 mm Hg and a pulse rate of 77/min.

He complained of fatigability but denied having chest pain, shortness of breath or altered mental status.

Physical examination revealed facial edema with cervical chain lymphadenopathy. Non-pruritic erythematous urticarial papules and plaques were evident in both upper extremities. Abdominal examination was positive for shifting dullness and fluid wave in favor of ascites. All other examinations including heart and lungs and neurologic examination



**Fig. 1:** Contrast-enhanced computerized tomographic angiography (CTA) of the abdominal vessels showing filling defect in portal vein and absent hepatic veins.

were unremarkable. Plain chest X-ray was normal.

Considering the past history of portal vein thrombosis, contrast-enhanced computerized tomographic study of the abdominal vessels (abdominal CT-angiography) was attained and unveiled marked hepatomegaly with significant ascites besides filling defects in portal and hepatic veins and a narrow inferior vena cava (IVC) (figure 1).

Subsequent lab data showed a lower than normal protein C level but with normal protein S and homocysteine levels. Based on the clinical impression of hypereosinophilic syndrome, bone marrow aspirated samples were obtained and interpreted as granulocytic hyperplasia with the proportion of eosinophils being more than 40%.

To investigate cardiac involvement, transthoracic echocardiography (TTE) was done and showed normal LV size with moderate systolic dysfunction (LVEF: 40%) and mild diastolic dysfunction without valvular heart disease or pericardial effusion.

To rule out PDGFRA-associated chronic eosinophilic leukemia (CEL), Fip1-like-platelet-derived growth factor receptor  $\alpha$  chain (FIP1L1-PDGFRA) fusion transcript test was conducted and turned out to be negative in our patient.

Based on the clinical findings and with a persistent eosinophilia for more than six months without an obvious cause, a diagnosis of idiopathic hypereosinophilic syndrome was made.

The patient was put on high dose prednisolone (40 mg daily in two divided doses), but not showing clinical improvement, imatinib (100mg daily) was added as the secondary agent.

Despite treatment, in the course of the disease, the

patient developed bradycardia, which soon turned into a cardiopulmonary arrest. All resuscitation attempts failed and the patient passed away.

## DISCUSSION

Considerable eosinophilia is commonly associated with allergic and hypersensitivity conditions, parasitic (helminthic) infections, autoimmune and collagen vascular disorders, malignancies and certain types of immunodeficiency (5). Regardless of the cause, when chronic, eosinophilia becomes leads to a spectrum of end organ damages largely attributable to eosinophil-derived mediators which have toxic effects on organ tissues.

The hypereosinophilic syndromes (HES) are a heterogeneous group of rare disorders characterized by the sustained overproduction of eosinophilic series. Originally presented in 1975 by Cushid(6) and subsequently modified, the diagnostic criteria include presence of persistent peripheral blood eosinophilia  $\geq 1.5 \times 10^9/L$ , the absence of a secondary cause of eosinophilia, and evidence of eosinophil-associated end organ damage(4). The common organ systems involved in HES are hematologic (100%), cardiovascular (58%), cutaneous (56%), neurologic (54%) and pulmonary (49%) systems(7). Liver and gastrointestinal tract are involved in less than 20% of patients(4). HES with a predominant GI symptom are very rare(8). Falade et al. reported a childhood case of HES presenting as inflammatory bowel disease(9). Also, chronic active hepatitis and eosinophilic ascites are reported as primary symptoms(10). Skin manifestations of this syndrome are not pathognomonic and might be seen as pruritic erythematous macules and papules mostly on trunk and extremities(3).

Hypereosinophilia may induce thrombosis in various organs. Although the exact mechanism was unknown but this might raise from the actions of eosinophil peroxidase in forming hypothiocyanous acid, a compound which diffuses into endothelial cells and strongly induces tissue factor expression by these cells(11). Tissue factor, believed to be crucial in thrombus formation, was also expressed by eosinophils directly(12). Ryoichi et al. reported a pediatric patient with hypereosinophilia that was complicated by central sinovenous thrombosis(13).

The prevalence of HES was not clearly described,

but in one study, Crane et al. reported an estimated prevalence of 0.36 to 6.3 per 100,000. HES is seen most commonly in the 2nd to 4th decade of life with a men to women ratio of 9:1 and a few cases reported in children(14).

Although it was a syndrome of unknown etiology, recent investigations have led to newly emerging theories about the possible causes such as primary molecular defects or the role of eosinophil-specific interleukin (IL)-5.

The so called “neoplastic hypereosinophilic syndromes”(15) are a subtype of hypereosinophilic syndromes with myeloproliferative features in which the patients usually demonstrate a chromosomal abnormality, namely The FIP1L1 - PDGFRA fusion which displays extensive tyrosine kinase activity. This fusion was believed to be associated with a poor prognosis and was commonly seen in pediatric patients(16). Our patient was reported negative for this fusion.

Idiopathic hypereosinophilic syndrome was a diagnosed by exclusion, thus all other possible causes of eosinophilia such as infections, malignancies (especially Hodgkin’s and non-Hodgkin’s disease and acute lymphocytic leukemia) have to be ruled out before making a certain diagnosis. Attempts to discover systemic organ involvements such as endomyocardial damage are to be taken into account using proper diagnostic methods and paraclinics(5).

In virtue of the lack of large multicentric clinical trials, treatment options for HES were principally based on case reports and case series; however, general consensus was that initial treatment should be commenced with high dose corticosteroids. Addition of a secondary agent was considered if the desired clinical and paraclinical improvement is not reached with steroids, but the selection of this second agent was challenging and usually controversial. Imatinib as one of the widely used additional agents was thought to have a response rate of 14–60% in patients with FIP1L1/PDGFRA-negative HESs(17).

Since early diagnosis and treatment is the key for improving the outcome of HES patients and regarding the wide scope of signs and symptoms, a high clinical suspicion is indispensable in the diagnosis of HES. In our opinion the 2 year delay in the proper diagnosis of our patient played an important role in the catastrophic fatality of the condition.

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