# SERIES OF UNFORTUNATE EVENTS: UNUSUAL MANIFESTATIONS OF IDIOPATHIC HYPEREOSINOPHILIC SYNDROME

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#### ABSTRACT

Idiopathic hypereosinophilic syndrome is a clinical condition characterized by marked overproduction of eosinophils. It is clinically defined based on the presence of three features which include sustained blood eosinophilia of greater than 1500/cu mm for more than 6 months with absence of other apparent etiologies for eosinophilia including parasitic, malignant, rheumatologic and allergic diseases and having signs and symptoms of organ involvement. It is a grave condition which manifests at any age and is fatal if left untreated. Here, we present a patient who was admitted in our hospital for urticaria and during the course of stay developed signs and symptoms of organ involvement. He was eventually started on steroids and showed marked improvement upon discharge and follow up.

Key Words: Hypereosinophilia, Corticosteroids, FIP1L1 – PDGRF

# INTRODUCTION

Hypereosinophilic syndrome is a rare clinical condition characterized by increased peripheral and tissue eosinophils, with protean clinical manifestations ranging from asymptomatic eosinophilia to life threatening organ involvement. Idiopathic hypereosinophilic syndrome is diagnosed based on the diagnostic criteria and by excluding other causes of Hypereosinophilia. The treatment is based on the type and the genetic mutations. In general they respond well to immunosuppressants. Here present a case of idiopathic hypereosinophilic syndrome admitted with dermatological manifestation and developed features of organ involvement and successfully treated with steroids.

# CASES

A 22 year old patient with no co-morbidities was admitted with complaints of reddish lesions on the trunk and extremities associated with itching for the last 2 months. He also had complaints of low grade fever associated with dry cough for the last 2 weeks. There was no history of any previous drug intake before appearance of symptoms but the patient had history of atopy as evidenced by frequent allergic symptoms. On examination, patient was febrile, had no icterus or pedal edema and vitals were stable. He had raised erythematous plaques on the trunk and extremities. Examination of the cardiac, respiratory and central nervous system was normal.

Laboratory investigations revealed hemoglobin of 13.5g/dl, total leukocyte count of 18000 cells/cmm (with a leukocyte differential showing 32% eosinophils, 59% neutrophils, 08% lymphocytes and 1% monocytes) and a platelet count of 2.5 lakhs/cmm. Absolute eosinophil count was 3200 cells/cmm and ESR was 56mm/hr. Peripheral smear showed normocytic normochromic anemia with eosinophilic leucocytosis (Figure 1).

The morphology of the eosinophils varied from classical eosinophils to variants such as hypersegmented forms and partially degranulated forms with vacuolated cytoplasm. Renal function tests, liver function tests and HbA1C were within normal limits. X ray chest taken on admission was normal. Ultrasound abdomen was also normal. Punch biopsy of the skin lesions revealed a microscopic appearance of acute

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urticaria. The patient was started on antihistamines and his skin lesions slowly disappeared, but started developing a high grade fever with sudden onset of tachycardia and respiratory distress.



Figure 1: Leishman stain -100X – Peripheral Smear showing eosinophilia

The patient was immediately shifted to the intensive care unit. As he had severe hypoxia he was mechanically ventilated (initially non-invasive and then invasive ventilation). X ray chest on day 1 of ICU stay showed bilateral infiltrates. A high resolution CT scan of the lungs showed bilateral minimal pleural effusion and bilateral patchy infiltrates (Figure 2).

Pleural fluid aspirate was exudative with increased eosinophils (91% of the total count). His blood, urine and tracheal aspirate cultures were all sterile. His serum procalcitonin was normal. Serology for Hepatitis B, Hepatitis C, and HIV and connective tissue workup including ANA/ dsDNA/ ANCA profile were also negative. Repeated examination of the stool microscopy and stool culture yielded nil results for parasites or ova and enzyme immuno assay strongyloidiasis was negative. The patient continued to have high grade fever and persistent tachycardia despite supportive therapy. On day 2 of ICU stay, he developed severe myalgia and swelling of the joints. Aspiration of synovial fluid was suggestive of reactive synovitis. On the 3rd day of ICU admission, he developed pericarditis as evidenced by a pericardial rub, ST elevation in all leads in ECG and normal Serum CK - MB and Troponin T. Echocardiogram showed mild pericardial effusion with no regional wall motion abnormality. Bone marrow aspiration and biopsy revealed a normocellular picture (Figure 3) and the myeloid series showed normoblastic maturation with increase in eosinophilic precursors such as myelocytes and metamyelocytes without any increase in blast cells (Figure 4).

Thus there were no obvious features for a myeloproliferative neoplasm. A provisional diagnosis of hypereosinophilic syndrome was arrived and we investigated him further to exclude major clonal causes for eosinophilia. Due to financial constraints, we tested for 2 of the most common and probable cytogenetic abnormalities, viz., BCR-ABL 1 fusion gene and FIP1L1 – PDGRFA gene rearrangements. Both were negative. In view of the elevated peripheral eosinophilia, organ damage (skin, musculoskeletal

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system, cardiovascular and respiratory system involvement) and bone marrow findings a diagnosis of Idiopathic Hypereosinophilic Syndrome was established.



Figure 2: HRCT of lung showing bilateral pleural effusion with bilateral patchy opacities



Figure 3: Leishman stain -100x- Bone marrow normocellular for age

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Figure 4: Leishman stain - 400 xs - Bone marrow showing numerous eosinophils & their precursors (arrows)

The patient was started on pulse methyl prednisolone 1g/day for 3 days followed by prednisolone at a dose of 1mg/kg/day. The patient improved clinically and was weaned off the ventilator. His absolute eosinophil count had reduced to 1100/cmm at discharge. His absolute eosinophil count at the end of one month was 300/cmm after which prednisolone was gradually tapered.

#### DISCUSSION

Eosinophils are one of the granular leucocytes from the bone marrow. Approximately 8 microns in diameter, they contain a bilobed nucleus with the characteristic eosinophilic granules. Eosinophils contain four types of granules; primary, small, lipid bodies, and small secretory vesicles. IL-3, IL-5, and GM-CSF stimulate eosinophil production in the bone marrow (Peter Valent *et al.*, 2012). They produce and store biologically active molecules, including Eosinophil Cationic Protein, Major Basic Protein, neurotoxin, lipid mediators, and cytokines. Once triggered, their mechanism of recruitment can be either allergic form (IgE dependent) or non allergic which is IgE independent (Peter Valent *et al.*, 2012). These cells upon massive activation can induce an inflammatory process and cause changes in the microenvironment resulting in fibrosis, thrombosis, and life- threatening end organ damage.

The normal differential count in a complete blood count for eosinophils is a range of 1-4% of the total cells. In an Absolute Eosinophil count, the normal biologic reference interval is between 50 and 500 cells/cu.mm (Peter Valent *et al.*, 2012). Eosinophilia is classified into mild, moderate and severe and this criterion has been revised recently. The absolute eosinophil counts of mild, moderate and severe eosinophilia are 450-1500 cells/cumm, 1500-5000 cells/cumm and >5000 cells/cumm respectively (Beck, 2009). Mild eosinophilia is most often associated with allergies, drugs, parasitoses, collagen diseases and skin diseases. A few malignancies which cause mild eosinophilia are Hodgkin's disease and myeloproliferative neoplasms other than chronic eosinophilic leukemia. Moderate eosinophilia occurs due to the same causes of mild eosinophilia, but of severe intensity. However, milder forms of severe

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eosinophilia can also overlap in this category. Severe eosinophilia is most often associated with nonneoplastic conditions such as dermatitis herpetiformis, eosinophilic gastropathy, tropical eosinophilia, Loffler syndrome, Churg-Strauss syndrome, Idiopathic hyper eosinophilic syndrome (IHES) etc. and neoplastic conditions such as chronic eosinophilic leukemia and myeloproliferative neoplasms associated with gene rearrangements such as PDGFRA, PDGFRB & FGFR1. The term hyper eosinophilia (HE) is used when there is blood eosinophilia along with tissue eosinophilia. When organ damage is associated with HE it is called hypereosinophilic syndrome (HES). Hyper eosinophilic syndrome is divided into the following types: i) Idiopathic HES ii) Primary (neoplastic) HES with an underlying clonal myeloid or stem cell disorder iii) Secondary or reactive HES iv) Lymphoid variant (Peter Valent *et al.*, 2012).

Our patient presented with moderate eosinophilia with atopic dermatitis whose clinical severity was not commensurate with the high eosinophil counts. He had not consumed in the recent past any of the drugs known to cause eosinophilia. His stool analysis was normal ruling out a parasitic infestation of the gut. Skin biopsy did not reveal any feature suggestive of collagen disease. Further, his ANA profile was also negative. His respiratory system was normal on admission ruling out respiratory causes. He had no lymphadenopathy to suspect Hodgkin disease. His clinical presentation was not suggestive of tropical eosinophilia and blood investigations were negative for parasites. Thus we concluded that the eosinophilia in our patient was unlikely to be of reactive nature. Although our patient subsequently developed typical end organ damage which was highly suggestive of Hypereosinophilic Syndrome (HES), we had to rule out a clonal etiology and hence further investigations such as bone marrow aspiration, bone marrow trephine biopsy and molecular studies were performed. BCR- ABL 1 fusion gene was negative, ruling out the possibility of Chronic Myeloid Leukemia. The serum Vitamin B 12 levels were normal in our patient, another factor that is needed for the diagnosis of Myeloproliferative Neoplasm with eosinophilia.

The recent WHO classification of the hematopoietic neoplasms states that there is no single or specific cytogenetic abnormality to make a diagnosis of Chronic Eosinophilic Leukemia (CEoL). The criteria are: 1) exclusion of specific cytogenetic abnormalities such as BCR- ABL 1 fusion gene (absent in this case), PDGFRA, PDGFRB & FGFR1 gene rearrangements; 2) presence of +8/i(17q) and 3) myeloblasts between 5% and 19% in the bone marrow (Swerdlow et al., 2008). Of these the first and third criteria need to be satisfied for a diagnosis. In our patient <5 % myeloblasts in the bone marrow aspiration study ruled out the possibility of CEoL. The WHO classification has brought in a new category called 'Myeloid and Lymphoid Neoplasms with Eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 (Swerdlow et al., 2008). These abnormalities also needed to be ruled out. Financial constraints weighed down testing of these cytogenetic abnormalities. Of the three types, Myeloid and Lymphoid Neoplasms with Eosinophilia and abnormality of PDGFRA was the closest differential and this was tested and the result was negative. The blood picture of Myeloid and Lymphoid Neoplasms with Eosinophilia and abnormality of PDGFRB is similar to Chronic Myelomonocytic Leukemia or atypical CML. As this was not the case here, we decided against testing for this abnormality. Myeloid and Lymphoid Neoplasms with Eosinophilia and abnormality of FGFR1 presents either as Myeloid and Lymphoid Neoplasms with Eosinophilia and abnormalities of PDGFRA or PDGFRB. This was also not tested owing to the rarity of its occurrence in literature. The presence of sustained moderate eosinophilia during the workup period, absence of an obvious cause for eosinophilia, no proof for clonality of the proliferating eosinophils and a myeloblasts percentage of <5 in the bone marrow differential, suggested that, the most plausible diagnosis was Idiopathic Hyper Eosinophilic Syndrome (IHES).

Idiopathic Hypereosinophilic Syndrome (IHES) is a hematological disorder where there is a marked overproduction of eosinophils. The diagnostic criterion is: 1. Sustained blood eosinophilia of greater than 1500/ul for more than 6 months. 2. Other apparent etiologies for eosinophilia must be absent, including parasitic, malignant, rheumatologic and allergic diseases. 3. Presence of signs and symptoms of organ involvement (Ogbogu *et al.*, 2007). Of the above, organ involvement is the most significant criteria to diagnose IHES. Vriiese *et al.* reported two cases of IHES in which they had significant end organ damage but the first criterion of eosinophilia above 1500 for six months was not found (Vriiese *et al.*, 1997). This

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was clear in our patient as he had manifestations of organ damage but the evidence of eosinophillia for 6 months was not present. Our patient presented with dermatological manifestations in the beginning and during the course of hospital stay presented with unusual manifestations of organ involvement in a short period of time.

Idiopathic hypereosinophilic syndrome can affect any system, the most common being the cardiac, respiratory and nervous systems. The most common manifestations of IHES on the heart are eosinophilic myocarditis and endomyocardial fibrosis. This occurs through three stages - the stage of acute necrosis, stage of thrombosis and the stage of fibrosis (Ogbogu *et al.*, 2007). The stage of necrosis occurs due to the release of toxic catatonic proteins from degranulating eosinophils. This is followed by thrombus formation due to the increased blood hypercoagulability and finally thrombus formed on denuded myocardium is replaced by fibrosis. Our patient however had the rare entity of pericarditis. Ogbogu *et al.*, 2007). Another study by Shevyll Arvie Tan et al also highlights the rarity of pericardial involvement among patients suffering from IHES (Tan and Duggal, 2009). The reason why some patients end with pericarditis instead of the usual pathology is unknown.

Our patient also had pulmonary involvement in the form Type 1 respiratory failure and bilateral patchy infiltrates in HRCT. According to the study conducted by Dulohery *et al.* (2011). 12 of the 49 patients reviewed had radiological findings of ground glass opacities and patchy infiltrates (Dulohery *et al.*, 2011). This study also states that the prevalence of asthma among their patients was 27%. Our patient did not have a previous history of asthma but he did have previous history of allergic symptoms. Other manifestations the patient had include myalgia and reactive synovitis. This also is unusual as the heart, CNS, skin and lungs are most commonly involved (Ogbogu *et al.*, 2007).

Corticosteroids are the drug of choice for IHES and lymphoid variant of HES. Hydroxyurea, IFN – alpha, Mepolizumab (anti IL5 antibody) can also be tried as steroid sparing agents (Klion, 2005). The treatment of reactive HES is managing underlying disorder with or without corticosteroids. Neoplastic HES usually do not respond to steroids. Tyrosine kinase inhibitors like Imatinib, Nilotinib or Dasatinib is the drug of choice in PDGRFA or PDGRFB positive neoplastic HES. But these tyrosine kinase inhibitors are not effective in neoplastic HES with PGFR1 mutation. Since this disease behaves like leukemia/lymphoma syndrome, combination chemotherapy plus allogenic stem cell transplantation is recommended (Valent *et al.*, 2012).

In summary, IHES can affect multiple organ systems and can range from mild to severe involvement. It generally responds well to immunosuppressant therapy. Prompt diagnosis and early treatment would help to significantly reduce the morbidity and mortality

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