Case report

Hypereosinophilic Syndrome: A rare differential diagnosis for profound leucocytosis:

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ABSTRACT

A broad range of disorders are present with eosinophilia and these include infectious, allergic, rheumatic, neoplastic, endocrine and idiopathic disorders which range from benign to life-threatening illnesses. All these conditions create a heterogeneous list of clinical presentation that patients may display, thus creating a diagnostic challenge for clinicians. We present a patient with a broad range of clinical features and hematological counts that fit into the diagnosis of Hypereosinophilic Syndrome (HES). He was investigated reasonably to rule the various possible differentials and subsequently started on Prednisone therapy.

Key Words: Hypereosinophilic Syndrome, FIP1L1-PDGFRA, Imatinib

CASE

A 54-year-old male was referred from one of the rural health centers with 6 months history of generalized swelling, pruritis and worsening shortness of breath on exertion and a 2-year history of back pain and lower limb pain which escalated with mobilization. Generalized swelling involved facial puffiness, abdominal distention and lower limb swelling. His itchiness was generalized but marked on the limbs. The patient described as being short of breath after about a 30 meter walk or climbing stairs.

Past history revealed that he had been investigated for chronic diarrhoea in November, 2009, was treated for amoebiasis and subsequently improved. He was diagnosed to have dyslipidemia in April, 2010, managed with Atorvastatin 40mg nocte and afterward lost to follow up. The patient was not on any regular medications at time of admission and had no known allergies and his family history revealed his father suffered from hypertension, diabetes mellitus type 2 and stroke. He worked as a farmer, did not take alcohol and cigarettes but occasionally took kava.

On examination, he was an obese man with normal vital signs. He was pale and his eyes looked puffy. There were no palpable lymph nodes. His heart sounds were normal. His respiratory examination revealed bibasal coarse crepitations. Abdominal examination was normal. Extremities revealed thickened skin in right forearm (Figure 1) and exfoliative erythematous rashes on his legs (Figure 2)

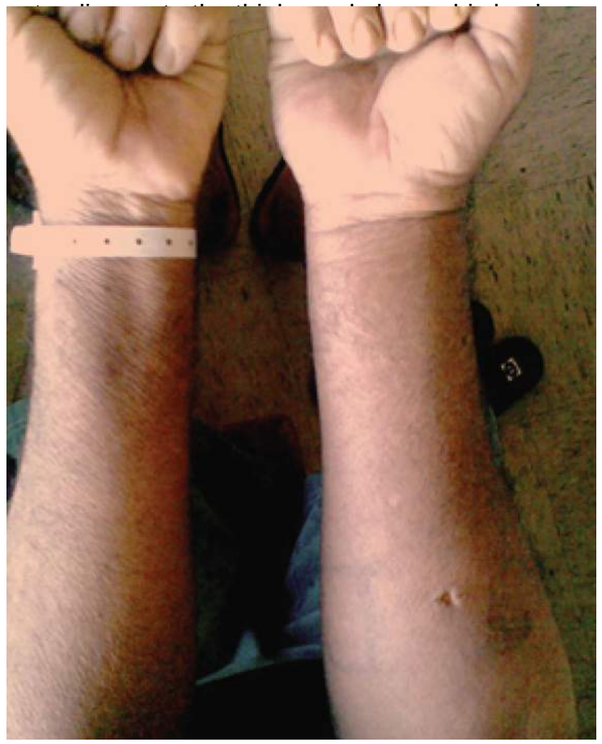

Figure 1: Thickened right forearm skin

The patient's full blood count showed normocytic anaemia with a hemoglobin of 7.9g/dL and a white cell count of 409800/µL with more than 85% eosinophils (figure 3). ESR was elevated at 100mm/hr. His kidney functions were normal and liver function tests revealed a mildly raised ALP of 211U/L. The Vitamin B12 level was low at 42ng/L. His chest x-ray showed evidence of cardiomegaly with normal lung fields and ECG had normal findings. Antinuclear antibodies (ANA) were negative.

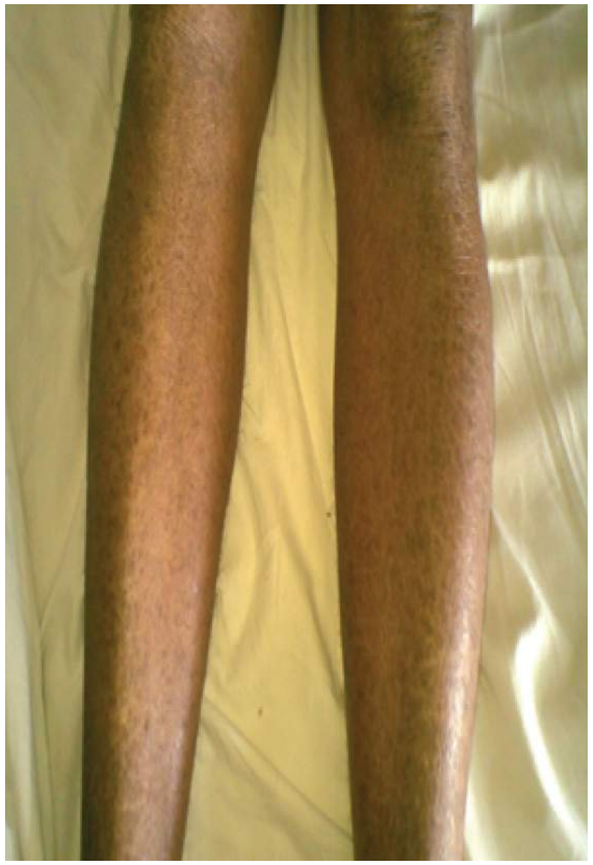

Figure 2: Erythematous exfoliative rashes in legs

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A Trans-thoracic Echocardiogram study showed impaired relaxation pattern indicative of Stage II Diastolic dysfunction.

A skin biopsy (figure 4) was taken from the thickened skin of the right forearm for histological studies which showed perivascular eosinophilc infiltration in dermis, suggestive of eosinophilicvasculitis.

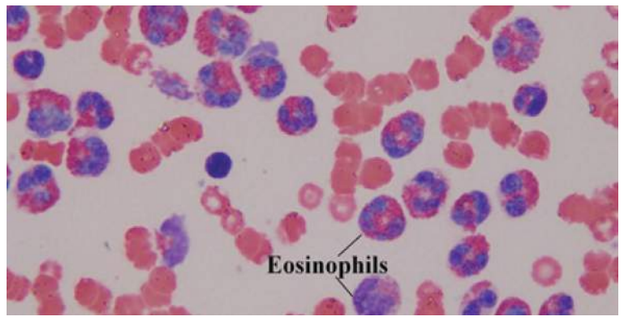

Figure 3: Peripheral Blood Smear: Shows marked eosinophilia

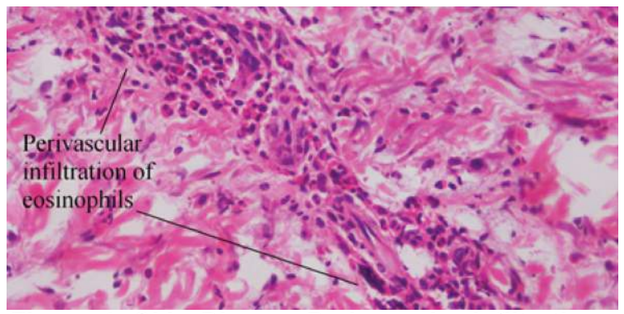

Figure 4: Skin Biopsy: Perivascular infiltration of eosinophils

Bone marrow aspirate (figure 5) and trephine biopsy was carried out and it showed hypercellular fragments due to markedly increased eosinophils and eosinophil precursors with normal maturation pattern. No increase in blasts and no dysplasia were reported in other cell lines.

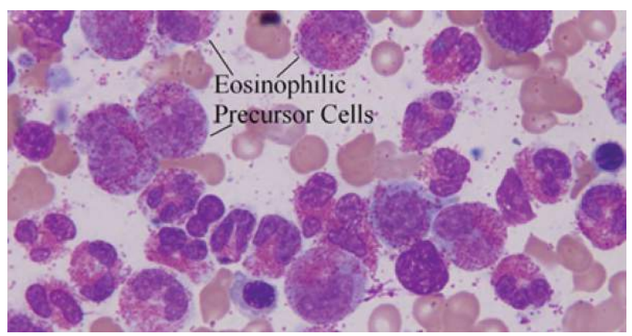

Figure 5. Bone Marrow Aspirate Smear: Eosinophils at various stages of maturation with dysplastic changes

Chromosomal studies for the bone marrow aspirate showed no BCR/ABL 1 gene rearrangement and further studies revealed no F1P1L1/CHIC2/PDGFRA gene rearrangement.

The diagnosis of hypereosinophilia was made and the differentials included hematological malignancies or idiopathic cause. The available literature on hypereosinophilia showed that allergies, infections and autoimmune processes were frequently associated with mild to moderate hypereosinophilia and the serum was negative for ANA and so these processes were ruled out. A malignant process was also ruled out since the vitamin B12 level was not elevated, chromosomal studies were negative, the bone marrow showed dysplastic changes in less than 5% of eosinophils and clinically he did not have signs or symptoms frequently associated with a malignant pathology such as weight loss and hepatosplenomegaly.

The patient was initially started on Lasix 20mg once daily with low dose aspirin for his diastolic dysfunction. Once the possible differentials were ruled out, the patient was assessed to have idiopathic hypereosinophilic syndrome (HES) and evidence suggested the use of steroids to bring down the eosinophil count to prevent further end-organ damage.

He was initiated with Prednisone of 60mg daily and reviewed a week later. His WCC dropped to 238240 cells/µL. After 2 weeks, he was less symptomatic and had a white cell count that dropped to 34370 cells/µL, so his Prednisone dose was tapered to 50mg once daily.

On his most recent review, the white cell count was 10010 cells/µL with an eosinophil count of 4905 cells/µL. He still complained of generalized itchiness but had no shortness of breath on exertion nor generalized swelling. His dose of Prednisone was reduced to 35mg once daily. In his subsequent reviews, the Prednisone dose is to be further tapered down and an immunosuppressant added.

DISCUSSION

The term hypereosinophilic syndrome (HES) is synonymous with idiopathic hypereosinophilia, was thought up in 1968 by Hardy and Anderson to describe the groups of patients with unexplained high eosinophil counts with end-organ damage***1,5,6.*** There has not been much research done on hypereosinophilic syndrome due the rarity of the condition, incidence rate of 0.036 per 100000 population,***2.*** with a male to female ration of 9:1

1. Chusid et al in 1975 used a diagnostic criteria for HES***1, 5, 6:***
2. Persistent eosinophilia of 1.5 x109/L (1500/mm3) for longer than 6 months;
3. Lack of evidence for parasitic, allergic, or other known causes of eosinophilia; and
4. Signs and symptoms of organ involvement

In a more recent literature, it has been indicated that the 6 month time period requirement is less frequently used due to advanced and accessible testing methods***2,5,6,9.*** Hypereosinophilia is categorized using the absolute eosinophil count into mild (0.5-1.5 x 109/L), moderate (1.5-5 x 109/L) and severe (> 5 x109/L)***12.***

A retrospective study had demonstrated that the most common clinical manifestations associated with hypereosinophilia were weakness and fatigue (26%), cough (24%), dyspnoea (16%), myalgias or angioedema (14%), rash or fever (12%), and rhinitis (10%)***31.***

The pathophysiology of HES is sequestration of eosinophils into organ tissues. Any organ system maybe associated with HES***1,2,8,11, 12.*** A retrospective study showed that the most common being dermatological manifestations were found in 69% of patients, 44% of patients had pulmonary manifestations, 38% had gastrointestinal and 6% had cardiac involvement which increased to 20% in subsequent follow-ups***11.*** Eosinophil derived neurotoxin, peroxidase, eosinophilic cationic protein and major basic proteins are enzymes released by eosinophils that cause endothelial damage and promote fibrosis, thrombosis and infarction.***10,12.***

The classification of Hypereosinophilic Disorders varies due to ongoing research and updates from various studies. A convenient form of classification is mentioned by Gotlib et al***1.*** and again by Tefferi et al***12:***

1. Reactive
2. Clonal
3. Idiopathic

Reactive causes of Hypereosinophilia need to be ruled out first and these include:

- Parasitic Diseases- Helminthes, tapeworm, Filiariasis etc
- Allergic Diseases- asthma, Atopic Dermatitis etc
- Immunologic Diseases- Rheumatoid Arthritis, Churg-Strauss Syndrome, Wegner's Granulama tosis etc
- Neoplasms- Mastocytosis, T-cell lymphomas, Hodgkin's Lymphoma etc***1,3,13.***

The reactive causes usually give rise to mild or moderate peripheral eosinophilia and represent a physiologic response by bone marrow to increased tissue demand for eosinophils. The eosinophilia ceases or declines with cessation of the causative disease process***13.***

Once possible reactive causes are ruled out clinically or by laboratory investigations, the attention shifts to look for clonal causes of eosinophilia which includes mainly Chronic Eosinophilic Leukemia (CEL).

The laboratory investigation for CEL is centered on determining the presence of FIP1L1/PDGFRA fusion gene. The gene is created by a deletion on the 4q12 gene leading to the creation of the fusion gene***1,2,6,7.*** The median prevalence of FIP1L1/PDGFRA fusion gene in a review of eight published studies of hypereosinophilic patients was 23% (3-56%)***24.***

Negative FIP1L1-PDGFRA fusion calls for assessment of other clonal hypereosinophilias associated with recurrent molecular defects such as PDGFRA with other fusion partners on 4q12, PDGFRB on 5q31-33, or FGFR1 on 8p11-13***2.*** Malignant clones of eosinophils are also associated with systemic mastocytosis, myelodysplastic syndromes (MDS), acute myeloid leukemia, chronic myeloid leukemia (CML) and other myeloproliferative disorders and thus need to be considered***1,2,6.***

Chronic Eosinophilic Leukemia, Not Otherwise Specified (CEL, NOS) is classified under clonal causes of eosnophilia and so should be considered if there is absence of the PDGFRA/B or FGFR1 as there may be evidence of clonality but this is not classifiable with the cytogenetic and/or morphologic studies***2.*** CEL, NOS may be distinguished from HES by the presence of a nonspecific clonal cytogenetic abnormality or increased blast cells (>2% in the peripheral blood or >5% in the bone marrow, but <20% blasts in both compartments)***1,2.***

The lymphocytic variant hypereosinophilia involves abnormal T-cells which excessively produce cytokines (e.g. IL-5) and causes excessive production of IgE, thus promoting the production of eosinophils in bone marrow***2,6.*** The condition has a combination of both reactive and clonal mechanism and thus creates a dilemma in its classification. The patients usually present with dermatological manifestations ***1,2,9.*** There is no consensus for the diagnosis of the lymphocytic variant***2.*** This condition has a prevalence of about 17% in hypereosinophilic patients***11*** and has a tendency to have malignant transformation to T-cell lymphoma or S'ezary Syndrome***2,16.***

Research has demonstrated finding T-cell clonality by detecting TCR gene rearrangements and abnormal T-cell immunophenotype (e.g. CD3-CD4+, CD3+CD4-CD8- or CD4+ CD7-). Elevated levels of IgE, thymus and activation-regulated chemokine (TARC), cytokines (esp. IL-5, IL-4 and IL-13) produced due to these abnormal T-cells provides support for lymphocytic variant***2,6,11,16,15,17.***

Anemia and thrombocytopenia are common hematological changes in addition to the raised white cell count with predominantly eosinophils ranging from 1500-400000/µL.

Smears from the blood and marrow show varying degrees of mature, immature cells and cell dysplasia. Charcot-Leyden Crystals are a common finding in bone marrow smears***2.*** Elevated levels of Vitamin B12 are common in malignancies associated with eosinophilia***6,7,11.*** Serum Tryptase levels are elevated in the CEL namely FIP1L1-PDGFRA positive, and can be used as a substitute marker if cytogenetic studies are not easily available***2,11.***

Such extensive investigations were not carried out in our setting due to limited resources, cost of tests and treatment modalities not being readily and reasonably available.

Most patients with Eosinophilia are initially classified as Idiopathic Hypereosinophilia (HES), after preliminary clinical analysis and various investigations are inconclusive. Subsequent manifestations of the disease process and/or further tests may reveal a clonal or reactive pathology***2,3,5.***

The consensus among experts is that Imatinib provides definitive treatment for PDGFRA/B rearrangements***2,7,30***. Numerous studies have shown its efficacy to produce hematologic and cytogenetic remissions***18-22,30.*** Doses from 100mg- 400mg daily produced remission and the patient may be maintained on as low as 100mg weekly***23.***

For patients with HES, CEL-NOS and lymphocytic variant hyper-eosinophilia, recommendations are to treat with steroids, such as Prednisone at 1mg/kg which rapidly reduce eosinophil counts and can be gradually tapered***24.*** The use of steroids for long periods comes with numerous side effects and so necessitates tapering to the lowest possible dose and adding other drugs that can be used alone or in conjunction to the steroid therapy.

These drugs include Hydroxyurea (most commonly used), Interferon-α (IFN-α), Vincristine, Cyclophosphamide. Imatinib used at high doses has also produced reduced eosinophilic counts in selected cases of Idiopathic HES***25,27.***

Novel approaches to treat HES are still undergoing trials with newer Tyrosine Kinase Inhibitors showcasing more potency, efficacy, fewer adverse effect profiles or ability to treat resistant cases***2, 7,4,26,28,29.***

ABBREVIATIONS

BCR/ABL1 - Breakpoint cluster region/Abelson murine leukemia
F1P1L1 - Fip1- like1
CHIC2 - Cysteine-rich hydrophobic domain 2 protein
PDGFRA- Platelet Derived Growth Factor Alpha
PDGFRB- Platelet Derived Growth Factor Beta
CEL - Chronic Eosinophilic Leukemia
CEL, NOS - Chronic Eosinophilic Leukemia, Not **Otherwise Specified**
FGFR1 - Fibroblast growth factor 1
TCR - T Cell Receptor

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