Hyperesoinophilic Syndrome with FIP1L1 PDGFRα Mutation: A Case Study

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ABSTRACT

In India, a clinical and/or a laboratory diagnosis of hypereosinophilia is very common and is usually attributed to parasitic infestations (viz helminthiasis and filariasis) or atopy. The treatment usually includes deworming or antifilarial drugs in the filaria endemic regions. We report here, a case of hypereosinophilic syndrome in a middle-aged man, who presented with features which mimicked asthma with eosinophilia that did not respond to the routine treatment measures. He was found to have a FIP1L1-PDGFR-α mutation and he improved on treatment with the small molecule, tyrosine kinase inhibitor, Imatinib that is commonly used in patients with malignant diseases of haematological origin.

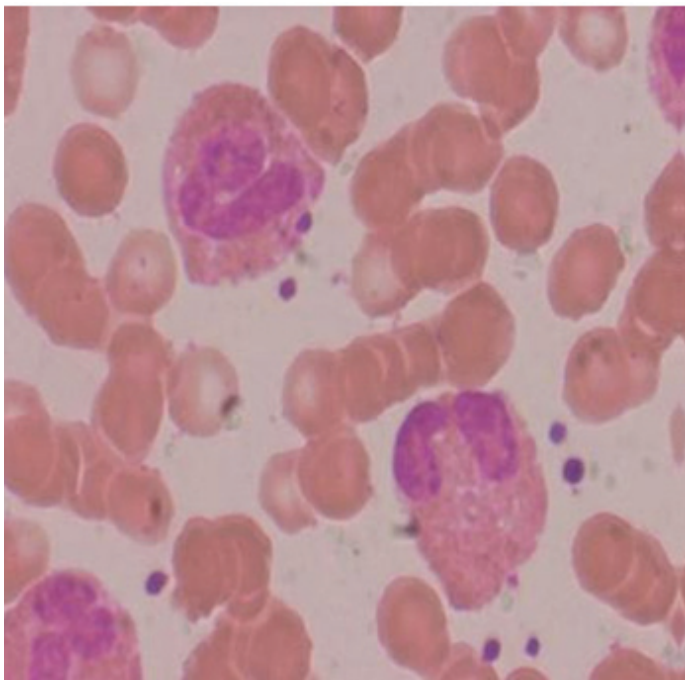
Key Words: Eosinophilia, asthma, hypereosinophilic syndrome, Imatinib

INTRODUCTION

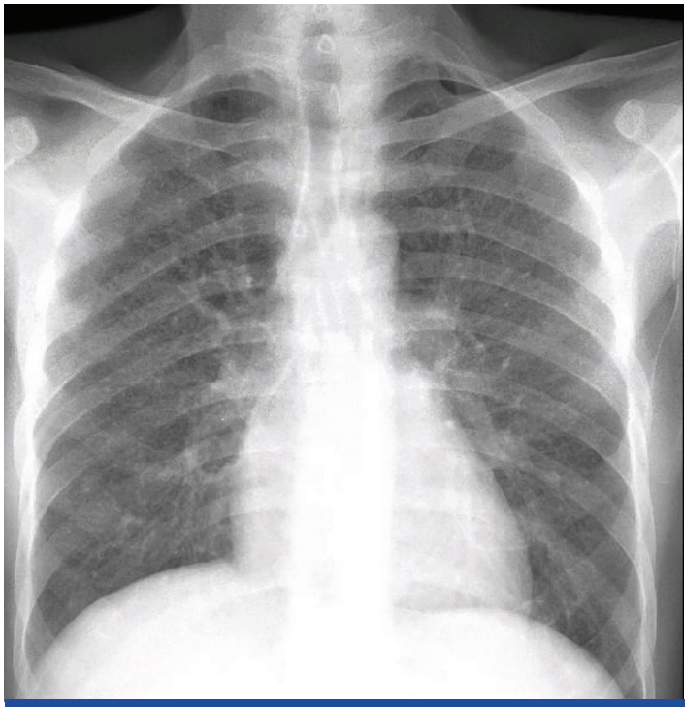
Eosinophilic diseases include various relatively uncommon conditions which are characterized by tissue-associated eosinophilic inflammation and, in some cases, peripheral blood eosinophilia, such as the eosinophilic gastrointestinal diseases (EGIDs), Churg-Strauss syndrome, and what is known as the hypereosinophilic syndrome (HES). No good method existed, to detect the molecular evidence of a myeloproliferative variant in the patients, until around 2003, with the discovery of an interstitial deletion on chromosome 4q12, that leads to the fusion of the FIP1-like 1 (FIP1L1) and the PDGFRα genes, with the fusion product encoding for a protein that has significant constitutive tyrosine kinase activity [6].The presence of this fusion protein was found to be responsible for pronounced eosinophilia in the affected patients. Patients who have this fusion mutation are now known to form most of the so-called myeolproliferative hyper-eosinophilic syndrome (M-HES) variants. Here, we are presenting one such case with the above mentioned mutation.

CASE REPORT

A 48-year-old male, a daily wage labourer and a chronic smoker (twenty pack years), presented with the complaints of wheezing and cough of three months duration. He had stopped smoking since the onset of the symptoms (three to four months). He had no history of orthopnea, fever, weight loss, allergic rhinitis, sinusitis or epistaxis. He had already received treatment of inhaled corticosteroids for three months and a week's course of oral steroids (prednisolone), without benefit. Thereafter, he had a three-week course of diethylcarbamazine (DEC) that again had no effect on his symptoms. He was referred to our center in March 2010, because of non-remitting wheezing and minimally productive cough, which was severe enough to prevent him from working. On clinical examination, he was found to have mild pallor, bilateral polyphonic wheezing, holosystolic murmur at the apex and mild splenomegaly. His lab investigation showed a haemoglobin level of 11.3 gm/dl, a total leukocyte count of 16500/mm^3 and platlet counts 197000/mm^3. His differential count showed 8% neutrophils, 9% lymphocytes, 82% eosinophils and 1% monocytes. His absolute eosinophil count was 13.43 x 109/ liter. His peripheral blood smear [Table/Fig-1] showed eosinophilia, with no immature cells. His immunoglobulin E (Ig E), anti-neutrophil cytoplasmic antibodies (ANCA) and his stool evaluation for parasites were negative. His chest radiograph [Table/Fig-2] showed prominent bronchovascular markings, with no parenchymal abnormality. He could not perform spirometry. An abdominal ultrasound confirmed splenomegaly. His 2-D echocardiography revealed severe mitral regurgitation, moderate tricuspid regurgitation and severe pulmonary artery hypertension. Oral dexamethasone (4mg twice daily) Was started, however, his blood eosinophilia persisted at 12680/mm^3. His bone marrow aspirate and trephine biopsy showed hyperproliferative marrow with eosinophilia. In view of the eosinophilia with significant cardiac



[Table/Fig-1]: Giemsa stain of peripheral blood smear (40x) showing eosinophils with bilobed nuclei and abundant eosinophilic granules in the cytoplasm. Few cells show trilobed nuclei. Admixed with these cells are small round basophilic platelets seen, normal in number and morphology.



[Table/Fig-2]: Chest X-ray. PA view showing bilateral prominent broncho-vascular markings

involvement, a diagnosis of myeloproliferative hypereosinophilic syndrome was considered. Reverse transcriptase polymerase chain reaction(RT-PCR) analysis showed a hybrid transcript for FIP1L1-PDGFRα, which confirmed a diagnosis of FIP1L1-PDGFRα which was associated myeloproliferative hypereosinophilic syndrome (M-HES), with pulmonary and cardiac involvement. He was started on 100mg of Imatinib daily. His repeat blood count after one month of the Imatinib therapy, showed a normal eosinophil count. He is on regular follow-up and has improved symptomatically.

DISCUSSION

Elevated peripheral blood eosinophil counts are usually seen with helminthic and parasitic infections, atopy and drug hypersensitivity. [1],[2] Other less common causes of eosinophila are malignancy, connective tissue disorders, tissue-associated eosinophilic inflammation, eosinophilic gastrointestinal diseases (EGIDs), the Churg-Strauss syndrome and hypereosinophilic syndrome (HES). [3], [4] In 1975, Chusid and his colleagues defined three diagnostic criteria which have remained as the basis for the modern definition of HES [5]:

1. Peripheral blood eosinophilia with the absolute eosinophil count being greater than 1500 cells/mL and it being sustained for more than 6 months.
2. No other evident cause for eosinophilia, including allergic diseases and parasitic infection.
3. Signs or symptoms of organ involvement by eosinophilic infiltration.

In general, HES is seen more commonly in men than in women, with a reported male/female ratio of 9:1. Such cases have mostly been described in adults, with the age at diagnosis usually falling between 20 and 50 years [4],[6],[7] Nonspecific constitutional symptoms can be seen as a part of HES; the National Institutes of Health case series reported that fatigue is present in 26% of the patients and fever in 12% [8]. Other presenting symptoms included cough (24%), breathlessness (16%), muscle pain (14%), angio-oedema (14%), rash (12%), and retinal lesions (10%) [7] A subset of the HES patients have an interstitial deletion in chromosome 4q12, which leads to the expression of a fusion gene, FIP1L1-PDGFRα [6],[7] Although the patients with this mutation are more adequately classified as chronic eosinophilic leukaemia (CEL) cases, given the clonal nature of the eosinophil expansion, the cells are morphologically indistinguishable from normal mature eosinophils and a large majority of the cases have a normal cytogenetic pattern. The patients therefore present clinically as typical HES cases, the only clue to the diagnosis being refractoriness to the standard modes of treatment [8, 9].

All patients who have HES, who do not respond to the initial standard therapy, should undergo an evaluation by RT-PCR or fluorescence in situ hybridization (FISH) for the presence of the FIP1L1-PDGFRα mutation, to help with the appropriate diagnosis and the guide therapy. The presence of this mutation mandates a therapy with imatinib, because these M-HES patients may be relatively refractory to corticosteroids, as was seen in our patient [10]. Imatinib selectively inhibits ABL, PDGFRα and KIT tyrosine kinases. FIP1L1-PDGFRα is particularly sensitive to Imatinib and a low initial dose is therefore appropriate. The early detection of FIP1L1-PDGFRα in patients with chronic unexplained hypereosinophilia is now considered to be critical for its optimal management, as its presence is associated with high morbidity and mortality rates. [11] There is an increased frequency of cardiac involvement in FIP1L1-PDGFRα positive HES patients [2]. The pathophysiological reason for this increased tendency for endomyocardial fibrosis in the M-HES patients is unknown [11]. It may possibly be due to an eosinophil-mediated cardiac damage. The cardiac damage evolves through three stages: the acute necrotic stage, followed by the thrombotic stage, which then progresses to the fibrotic stage [12]. In the fibrotic stage, significant intramural fibrosis occurs, that leads to impaired cardiac function and output, and significant valvular damage [2],[13]. This leads to valvular dysfunction like mitral regurgitation, as was seen in our patient. Imatinib, a tyrosine kinase inhibitor, is an effective drug in PDGFRα associated HES. The Imatinib response rate in these patients is nearly 100% [14], [15]. Generally, clinical improvement is seen within one month. Low dose imatinib (100 mg/d) is usually sufficient to control eosinophilia and its symptoms, as opposed to the higher doses of 400–800 mg which is used in chronic myeloid leukaemia. The side effects of low dose Imatinib therapy are generally mild and they rarely lead to the discontinuation of the therapy. Our patient was started on 100mg of Imatinib OD and he responded symptomatically in less than one month.

CONCLUSION

An early detection of FIP1L1-PDGFRα in patients with chronic unexplained hypereosiniphilia is critical for its optimal management and also to avoid organ damage, especially cardiac damage. The discovery of FIP1L1-PDGFRα has opened up avenues in understanding the molecular pathogenesis of HES and also the prospect of effective, molecularly targeted therapy like Imatinib.

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DECLARATION ON COMPETING INTERESTS:
No competing Interests.

Date of Submission: **Oct 01, 2010**
Date of Peer Review: **Dec 20, 2010**
Date of Acceptance: **Apr 10, 2011**
Date of Publishing: **Jun 13, 2011**