# Hypereosinophilic Syndrome in Behcet's Disease: Unearthing a Hidden Clonality

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## Abstract

**The association of hypereosinophilic syndrome (HES) and Behcet's disease is not well understood. Commonly, patients are treated with standard medications for hypereosinophilia, with variable responses. However, persistent hypereosinophilia (absolute eosinophilic count >1500 cells/μL) not responding to standard treatment may be predictive of a primary clonal haematological disorder. According to the revised World Health Organization (WHO) classification, HES has six categories; one of which is myeloproliferative neoplasm (clonal eosinophilia) associated with FIP1-like-1-platelet-derived growth factor receptor-alpha (FIP1L1-PDGFRα). We report a case of a 38-year-old Indian male with Behcet's disease with concomitant HES, who tested positive for clonal eosinophilia (FIP1L1-PDGFRα fusion) which is a rare imatinib-sensitive mutation. The patient was administered low-dose imatinib mesylate (100 mg daily), and showed an excellent response with complete resolution of HES. The causal relationship between Bechet's disease and HES requires further investigation and research. Left untreated, HES has the potential to cause severe end-organ damage and this necessitates early detection and treatment which can significantly reduce patient morbidity and mortality.**

**Keywords:** Hypereosinophilia, FIP1L1-PDGFRα, gene, Behcet's disease, imatinib

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## Introduction

The definition of Hypereosinophilic Syndrome (HES) has evolved over many decades. The modified definition of HES proposed in 2010 is widely used in clinical practice and includes the following criteria: i) absolute eosinophilic count (AEC) > 1500 cells/μL on 2 or more separate evaluations or symptomatic tissue hypereosinophilia regardless of blood AEC and ii) elimination of any secondary cause for eosinophilia.[1] There are six known variants of HES classified as: (1) Lymphocytic HES (2) Myeloproliferative HES (3) Overlap HES (AEC ≥1500 cells/μL with organ involvement) (4) Associated HES (AEC ≥1500 cells/μL linked to a known secondary cause of eosinophilia) (5) familial HES and (6) idiopathic HES. These variants have diverse clinical presentations and variable responses to treatment.

Behcet's disease, also known as Behcet's syndrome or Old Silk Route disease, is a rare autoimmune vasculitis characterised by inflammation in the blood vessels throughout the body. Autoimmune diseases such as Behcet's are one of the differential diagnoses for eosinophilia.[2] We report a patient with Behcet's disease showing a persistently high eosinophilic count not responding to standard treatment for eosinophilia.

## Case Report

A 38-year-old Indian male presented to the dermatologist with a history of recurrent painful sores in the mouth and genital area since 2016. There was no history of fever, weight loss or other constitutional symptoms. He had no other comorbidities, no recent sexual exposure and no significant family history. He was treated elsewhere with acyclovir and antibiotics, which had provided no significant relief for his symptoms. Clinical examination of the mouth revealed sharply demarcated erythematous erosions and ulcers on the soft palate, gingival and buccal mucosa, and two genital lesions (one on the glans and other on the scrotum) varying from 1 to 2 centimetres. They were extremely tender and not indurated. There was no significant lymphadenopathy. Examination of the eyes and the rest of the skin was normal. Based on these findings, a diagnosis of Behcet's disease was made. Serology for syphilis was negative. He received treatment with colchicine, topical triamcinolone acetonide (a synthetic corticosteroid) and thalidomide over the next 4 years, and it was noted that with thalidomide therapy, the sores gradually abated. For the concomitant eosinophilia, he was given diethylcarbamazine for 21 days but there was no response. AEC remained unchanged at 5,888/μL with normal haemoglobin and platelets.

The patient came to our haematology outpatient clinic for further assessment of his increasing AEC (5,888/μL to 6,134/μL) despite diethylcarbamazine treatment. There was no history of fever, weight loss, night sweats (type B symptoms) or any thrombotic events. He had no history of any other major illness, except sinusitis. There were no rashes or gastrointestinal complaints. He was not taking any drugs that are commonly associated with eosinophilia. Other secondary causes of eosinophilia, such as infection, parasites, pulmonary eosinophilia disease, allergic gastroenteritis, metabolic conditions, hepatitis markers [hepatitis B virus (HBV, HbsAg), hepatitis C virus (HCV)], anti-treponemal antibody and human immunodeficiency virus (HIV) were excluded. Flow cytometry for clonal lymphocyte subset analysis was negative. Stool culture was negative for any infectious aetiology. Chest X-Ray and 2-D echo were normal; the ultrasonography (USG) of abdomen and pelvis showed mild hepatomegaly. An IgE test for allergic bronchopulmonary aspergillosis was normal (35.8 U/mL). Since he was asymptomatic, he was given a suitable period of observation, where the repeat complete blood counts (CBC) revealed persistently high AEC as depicted in Table 1.

Therefore, a Fluorescence in situ hybridization

**Table 1: Periodic haemograms showing patient's AEC levels recorded over three years**

| | 30.05.17 | 05.12.17 | 23.12.17 | 20.02.18 | 18.04.18 **Started on Imatinib** ↓ | 09.05.18 | 02.08.18 | 12.09.18 | 30.09.18 | 03.11.18 | 23.02.19 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Hb** | 16.2 | 16.1 | 15.7 | 15.3 | 14.3 | 13.5 | 14.6 | 14.8 | 14.8 | 14.6 | 14.6 |
| **WBC** | 12.8 | 12.7 | 14.4 | 14.2 | 13.6 | 5.9 | 7.2 | 6.9 | 5.6 | 6.5 | 7.1 |
| **AEC** | 5888 | 6134 | 7842 | 7542 | 8469 | 236 | 288 | 698 | 282 | 240 | 142 |
| **Plts** | 3.77 | 2.95 | 2.71 | 3.23 | 2.64 | 3.66 | 3.75 | 3.45 | 3.22 | 1.83 | 3.1 |

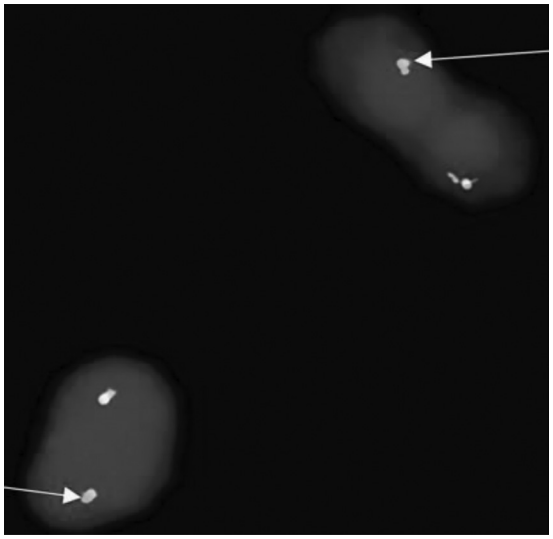

**Figure 1: FISH on interphase cells with arrows showing fusion of PDGFRα with FIP1L1 and CHIC2 deletion**

(FISH) test was done [Figure 1] which showed evidence of CHIC2 deletion followed by fusion of PDGFRα (4q12) with FIP1L1 in 180/200 (Freq 90%) interphase cells. There was no evidence of PDGFRβ (5q33) or FGFR1 (8p12) translocation/rearrangement.

FISH test for BCR-ABL1 and JAK-2 V617F mutation analysis were negative. Based on his blood counts and FISH results, the patient was diagnosed to have Hypereosinophilic Syndrome (HES) with FIP1L1-PDGFRα fusion. This is an imatinib-sensitive mutation and hence he was started on oral imatinib mesylate (100 mg) once a day.

After nearly a month's treatment with imatinib, there was a remarkable decrease in the AEC (8,469/μL to 236/μL). At 3 months follow up, CBC was repeated to evaluate the response [Table 1] and AEC level persisted in the normal range (288/μL) while on therapy. Imatinib mesylate (100 mg daily) was continued with the intention of long-term use. The patient was subsequently lost to follow-up after over a year.

## Discussion

The prevalence of HES in tropical countries is estimated to be 0.5–1 case per 100,000 population.[3] Out of six subtypes of HES, the incidence of FIP1L1-PDGFRα fusion across multiple clinical trials was low (11-16%).[4] In developing countries, ≤10% of people with HES are found to have FIP1L1-PDGFRα fusion and this rare entity is a clonal marker of myeloproliferative HES.[5,6] There is heterogeneity in the clinical presentation of primary eosinophilia, ranging from asymptomatic to showing symptoms of fatigue, dyspnoea, myalgia, pruritis, cough or fever and organ involvement [7] which our patient did not have.

Behcet's disease is a rare form of systemic autoimmune vasculitis for which the exact cause is unknown. A definitive diagnosis is made based on a patient's clinical signs and symptoms. In one of the reports from literature, a similar case of hypereosinophilia with a diagnosis of Behcet's has been documented.[8] However, despite significant advances in our understanding of the pathogenesis of HES, the exact incidence and prevalence of HES and Behcet's disease occurring together remains unknown. Our patient did not respond to the standard line of treatment for eosinophilia. Moreover, there was persistent increase in the AEC levels for which an additional test (FISH) was done and then a clonal aetiology (FIP1L1-PDGFRα fusion with CHIC2 deletion) was documented. Patients with HES often develop eosinophilic infiltration of the myocardium, which, if ignored, can lead to irreversible cardiac injury and potentially also involve other organs like kidneys, liver, lungs and intestines, which causes significant morbidity and mortality.[9]

Low dose Imatinib mesylate (a tyrosine kinase inhibitor with activity against PDGFRα) can result in a rapid and complete response of HES when administered in doses ranging from 100–400 mg daily.[10] It is considered safe with few side effects and our patient was treated with this medication with an excellent response over a period of more than one year.

## Conclusion

Eosinophilia in Behcet's disease is an important finding and must not be ignored. If the eosinophilic count is persistently high (exceeding 1500 cells/μL) and unresponsive to standard therapy, it must be taken into consideration and testing should be done to rule out myeloproliferative neoplasm. FIP1L1-PDGFRα gene fusion with CHIC2 deletion is a rare cause of hypereosinophilia occurring as a clonal abnormality in our patient. If HES remains untreated, it could lead to severe end-organ damage and hence early detection is crucial. The presence of HES in our patient with Behcet's disease may be correlated or coincidental, and the causal relationship between the two requires further research. Presently, Imatinib mesylate is the mainstay of treatment for FIP1L1-PDGFRα related HES and exhibits robust responses.

**References:**

1. Simon HU, Rothenberg ME, Bochner BS, Weller PF, Wardlaw AJ, Wechsler ME, Rosenwasser LJ, Roufosse F, Gleich GJ, Klion AD. Refining the definition of hypereosinophilic syndrome. *J Allergy Clin Immunol. 2010* Jul;126(1):45-9.

2. Seifert M, Gerth J, Gajda M, Pester F, Pfeifer R, Wolf G. Eosinophilie--eine differentialdiagnostische Herausforderung [Eosinophilia--a challenging differential diagnosis]. *Med Klin (Munich). 2008* Aug 15;103(8):591-7. German.
3. Sreedharanunni S, Varma N, Sachdeva MUS, Naseem S, Malhotra P, Bansal D, Trehan A, Varma S. The Spectrum of Hypereosinophilia and Associated Clonal Disorders - A Real-World Data Based on Combined Retrospective and Prospective Analysis from a Tropical Setting. *Mediterr J Hematol Infect Dis. 2018* Sep 1;10(1):e2018052.
4. Gotlib J, Cools J. Five years since the discovery of FIP1L1-PDGFRA: what we have learned about the fusion and other molecularly defined eosinophilias. *Leukemia. 2008* Nov;22(11):1999-2010.
5. Pardanani A, Brockman SR, Paternoster SF, Flynn HC, Ketterling RP, Lasho TL, Ho CL, Li CY, Dewald GW, Tefferi A. FIP1L1-PDGFRA fusion: prevalence and clinicopathologic correlates in 89 consecutive patients with moderate to severe eosinophilia. *Blood. 2004* Nov 15;104(10):3038-45.
6. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BH. NIH conference. The idiopathic hypereosinophilic syndrome. Clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med. 1982* Jul;97(1):78-92.
7. Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, Nutman TB, Pfab F, Ring J, Rothenberg ME, Roufosse F, Sajous MH, Sheikh J, Simon D, Simon HU, Stein ML, Wardlaw A, Weller PF, Klion AD. Hypereosinophilic syndrome: a multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol. 2009* Dec;124(6):1319-25.e3.
8. Mashaleh MA, Burgan A, Khasawneh R, Khataybeh O, Kamal N, Heresh AA. Eosinophilic Leukemia Presenting with Behçet-Like Symptoms. *Journal of the Royal Medicine Services. 2014*;21(4):79-82.
9. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF, Hellmann A, Metzgeroth G, Leiferman KM, Arock M, Butterfield JH, Sperr WR, Sotlar K, Vandenberghe P, Haferlach T, Simon HU, Reiter A, Gleich GJ. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes. *J Allergy Clin Immunol. 2012* Sep;130(3):607-612.e9.
10. Pardanani A, Ketterling RP, Li CY, Patnaik MM, Wolanskyj AP, Elliott MA, Camoriano JK, Butterfield JH, Dewald GW, Tefferi A. FIP1L1-PDGFRA in eosinophilic disorders: prevalence in routine clinical practice, long-term experience with imatinib therapy, and a critical review of the literature. *Leuk Res. 2006* Aug;30(8):965-70.