Eosinophilic Leukemia Presenting with Behçet-Like Symptoms

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ABSTRACT

We report on a 28 year old female who was diagnosed as a case of Behçet's syndrome and referred to our rheumatology clinic for further evaluation regarding unexplained fever and leukocytosis. Blood film revealed anemia and persistent eosinophilia. Bone marrow examination showed eosinophilic leukemia which is a rare condition especially in the female gender. Although Behçet syndrome can be associated with eosinophilia, the clinical picture was suggestive of myeloid neoplasm.

Key words: Behçet Syndrome, Eosinophilia, Eosinophilic leukemia

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Introduction

Persistent peripheral blood eosinophilia can be associated with variety of diseases ranging from parasitic infection, gastrointestinal disease, vasculitis to the hyper eosinophilic syndrome (HES).(1)

The term ‘eosinophilic leukaemia’ is used to describe a haematological neoplasm with raised eosinophil count; eosinophils are increased in peripheral blood and bone marrow, and are a part of the neoplastic clone. An eosinophil count greater than 1.5 × 10⁹/l is often used as one of the criteria for making this diagnosis. According to the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, eosinophilic leukemia may include a number of different disorders, defined according to or defined, at least in part, according to the underlying cytogenetic/molecular genetic abnormality.(2,3)

Case Report

We present a 28 year old female referred from general medicine clinic with the diagnosis of Behçet Syndrome for the last five months based on recurrent oro-genital ulcerations and uveitis and she was maintained on steroids and Colchicine. Reviewing the case, she had a history of painful oral and genital ulcerations, there was history of bilateral red eyes for which she was evaluated by an ophthalmologist and diagnosed as anterior uveitis. She denied gastrointestinal symptoms; there was no history of abortions or thrombosis. She had a history of fever, loss of appetite and weight loss of 10 kg in the last five months which was not explained by her disease status and that was the reason for the referral.

Physical examination revealed pallor, fever with temperature of 37.5°C, tachycardia with regular heart rate of 100/min and splenomegaly.

Our impression was that this patient had Behçet
syndrome complicated by uveitis. Uveitis responded well to steroid but the patient continued to have constitutional symptoms and progressive enlargement of spleen to a massive size. Initial laboratory data were normal apart from slight leukocytosis with a white blood count of 13X10⁹/L which later increased to 44X10⁹/L with shift to the left and an absolute eosinophilic count of 1.65X10⁹/L, normochromic normocytic anemia with hematocrit of 20% and adequate platelets count. Reticulocyte count of 1.8% was normal. Direct antiglobulin test was negative and coagulation profile was normal. Normal kidney and liver function tests except for high LDH at 712IU/L (normal range 120-240IU/L). Normal thyroid function. C-reactive protein was positive (24 mg/l). Urine analysis showed 10-12 WBCs and urine culture showed staphylococcus aureus sensitive to cloxacillin and erythromycin, blood culture showed no growth. Chest X-ray was normal and cardiac echogram was normal with no evidence of vegetations. Chest, abdomen and pelvic CT scan showed splenomegaly. Ophthalmological assessment showed uveitis which resolved on follow up evaluation. She was started on cloxacillin intravenously and continued on steroids, however; the fever continued with persistent non resolving eosinophilia. We proceeded to bone marrow study which showed hyper cellular bone marrow particles. The myeloid to erythroid ratio was 8:1. The granulocytic precursors showed granulocytic hyperplasia with increased eosinophils and eosinophilic precursors. The blasts were not increased. Megakaryocytes were adequate with unremarkable morphology with which showed features consistent with myeloproliferative neoplasm. Fluorescence in situ hybridization (FISH) study for BCR/ABL fusion gene was negative thus excluding chronic myeloid leukemia. FISH study for FIP1L1-PDGFRα rearrangement was positive. So the final diagnosis was: Myeloid neoplasm with eosinophilia, consistent with eosinophilic leukemia. The patient showed clinical response on treatment and unavailability of FIP1L1-PDGFRα FISH study in our center.

**Discussion**

Eosinophilic leukemia is one of the myeloproliferative neoplasms consisting of clonal proliferation eosinophil precursors. Males are commonly more affected than females. Patients with eosinophilic leukemia usually present with splenomegaly, hepatomegaly, thrombocytopenia, anemia, elevated B12, fatigue, skin rash, oro-genital ulcers, lymphadenopathy, cardiac infiltration and elevated serum tryptase.⁴,⁵

Behçet syndrome is an autoimmune disorder characterized by inflammation in blood vessels throughout the body. The exact cause is unknown. The inflammation leads to numerous symptoms that may initially seem unrelated.⁶ The signs and symptoms of Behçet disease commonly include oro-genital ulcerations, eye inflammation, and skin rashes. Patients usually have variable presentation with and disease course varies from mild to severe life threatening.⁷

Behçet syndrome is one of the differential diagnoses of eosinophilia.¹ In our case although the patient was diagnosed as Behçet the peripheral blood eosinophil count is more than what is expected in the typical case. Kristin et al.⁸ published a case report with update on hypereosinophilic syndrome; he presented a similar case with oral ulceration and eosinophilia and one of the top differential diagnoses was Behçet syndrome. Vandenberghe et al.⁶ reported 17 patients with this neoplasm, of which only four were females and in most of the cases the age was more than 35. The most dominant symptom was fatigue. Majority of cases had palpable spleen, whereas cardiac involvement was uncommon.⁵ None of these cases showed any element of vasculitis or Behçet disease classical presentation. Moreover, a larger study performed by Roche-Lestienne et al.⁹ showed male predominance and in only five cases out of 35 the patients' age was below 30. Majority of clinical and biological features were those of eosinophilic leukemia. Najera et al.¹⁰ reported a patient with presumed Behçet disease and found to have eosinophilic leukemia.
and this is consistent with the presentation of our patient. The uveitis responded well to steroid treatment, however the constitutional symptoms along with huge splenomegaly and eosinophilia persisted, therefore we proceed to bone marrow biopsy which confirmed the diagnosis of eosinophilic leukemia. It is still unexplained whether the uveitis in our patient was part of the initial diagnosis of Behçet disease or it was a coincidental finding of primary eye disease as it had not been reported before as one of manifestations of eosinophilic leukemia.

The key criteria for confirming the diagnosis of eosinophilic leukemia is the presence of a clonal cytogenetic or molecular genetic abnormality or blast cells that account for more than 2% in peripheral blood or more than 5% in bone marrow.\(^{(11)}\) Myeloid neoplasm with FIP1L1-PDGFRA rearrangement is a rare neoplasm. The genetic aberration is a cryptic Del\(^{(12)}\) (q12q12), an 800-kp deletion on chromosome 4q12. This entity has been defined by the 2008 World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissues as a distinct hematopoietic neoplasm.\(^{(2)}\) The age distribution varies widely in patients with this disease, seven to 75 years old, and show marked male predominance.\(^{(12,13)}\) The most common clinical and pathologic findings include persistent (more than 6 months) eosinophilia often more than 1.5x10\(^9\)/L, increased morphologically and immune-phenotypically aberrant mast cells, and marked sensitivity to treatment with low-dose (50-100 mg daily) imatinib mesylate.\(^{(12,14,15)}\)

The pathogenesis of FIP1L1-PDGFR\(\alpha\) gene fusion is similar to BCR-ABL positive chronic myeloid leukemia with constitutively increased tyrosine kinase activity of the fusion protein, potential evolution from chronic phase disease to blast crisis/secondary acute myeloid leukemia and even better response to treatment with imatinib.\(^{(12,16-21)}\) The underlying 800-Kbp cryptic deletion cannot be visualized through conventional karyotyping. Therefore, fluorescence in situ hybridization (FISH) or reverse transcriptase-polymerase chain reaction (RT)-PCR is typically used to detect the fusion gene.\(^{(22,23)}\) In 2003, Coolls et al.\(^{(14)}\) discovered the FIP1L1-PDGFR\(\alpha\) fusion gene as a recurrent genetic abnormality in patients with hypereosinophilic syndrome. This novel fusion gene results from a cryptic 4q12 interstitial deletion involving an 800 kb region between FIP1L1 and PDGFRA. It encodes a constitutively active FIP1L1-PDGFR\(\alpha\) fusion protein, the tyrosine kinase activity of which is strongly inhibited by imatinib.\(^{(4,14,16)}\)

### Conclusion

Eosinophilic leukemia is a rare myeloid neoplasm with PDGFRA gene re-arrangement. Recognition of this entity in the differential diagnosis of clonal eosinophilia specifically with the presence of overlapping signs and symptoms of Behçet syndrome is crucial as there is currently an effective targeted therapy for this condition.

### References


