Chronic Oro-Genital Ulcerations as a Presenting Feature of Chronic Eosinophilic Leukemia: A Case Report

Abstract

Hypereosinophilia can be primary, including idiopathic hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia, or secondary/reactive to various infective and non-infective stimuli. Chronic oro-genital ulcerations can occur due to various dermatological and non-dermatological disorders, and many times it serves as a useful indicator of an underlying systemic disorder. Hence, a case presenting with chronic oro-genital ulcerations needs a thorough evaluation. We are reporting an interesting case of a middle-aged male who had chronic oro-genital ulcerations as a presenting feature of chronic eosinophilic leukemia with *FIP1L1-PDGFRA* fusion (FIP1-like 1/platelet-derived growth factor receptor alpha). The patient's oro-genital ulcerations responded excellently to imatinib.

Keywords: *Chronic eosinophilic leukemia, chronic oro-genital ulcerations, hypereosinophilia, imatinib mesylate, PDGFRA gene re-arrangement*

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Introduction

Hypereosinophilia is defined as >1.5 × 10^9 eosinophils/L in peripheral blood. With adequate workup, if this is demonstrated on more than one occasion at an interval of a minimum of one month, it can be considered "persistent". If the patient does not have any signs and symptoms, then the duration of the interval should be considered as 6 months.[1] Hypereosinophilia can be primary, including idiopathic hypereosinophilic syndrome (HES) and chronic eosinophilic leukemia, or secondary/reactive to various infective and non-infective stimuli.[2] Clonal myeloid neoplasms with eosinophilia are divided into three categories: (1) myeloid/lymphoid neoplasms with eosinophilia and rearrangements of *PDGFRA* (platelet-derived growth factor receptor alpha), *PDGFRB* (beta), *FGFR1* (fibroblast growth factor receptor 1) or provisionally *PCM1-JAK2* translocation; (2) hypereosinophilia associated with another well-defined myeloid neoplasm, such as chronic myeloid leukemia (CML); and (3) chronic eosinophilic leukemia (CEL) not otherwise specified (NOS).[1] Chronic oro-genital ulceration with pain can be caused by various diseases.[3] We report a case of a middle-aged male who had chronic recurrent oro-genital ulcerations and was eventually diagnosed to have CEL with *FIP1L1-PDGFRA* fusion.

Case Report

A 36-year-old male presented with complaints of painful genital ulcers for 6 months and oral ulceration for 3 months. He had a history of tobacco chewing for the last 20 years. He had been treated for Behcet's disease and connective tissue disease with various immunosuppressive drugs including steroids, colchicine, dapsone, etc., but had no improvement. The patient had multiple superficial mucosal erosions of variable size with irregular borders and surrounding erythematous rim over the tip of the tongue, buccal mucosa, hard palate, soft palate, and over glans penis [Figure 1a and b]. His ophthalmological examination was normal. Pathergy test was negative. His previous biopsy specimen from oral mucosa demonstrated features of epithelial ulcers with chronic lymphocytic infiltrate, plasma cells and few neutrophils [Figure 2a]. As the morphology of ulcers was intriguing, we investigated the case further to rule out any systemic disease and nutritional deficiencies. He was found to have anemia,

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raised leukocyte count and very high eosinophil count, and B 12 level. Tests for viral infections like human immunodeficiency virus, and hepatitis B and C virus were non-reactive. Rapid plasma reagin test and treponema pallidum hemagglutination tests were negative for syphilis. Direct immunofluorescence study from perilesional mucosa was negative and anti-desmoglein 1 and 3 antibodies were not detected. He was referred to hemato-oncologist to be investigated for hypereosinophilia. All investigations are summarized in Table 1.

So, the final diagnosis of CEL with *PDGFRA* gene rearrangement was made and the patient was started on tyrosine kinase inhibitor imatinib mesylate (400 mg daily), prednisolone (1 mg/kg), and other supportive treatment. Within 20 days, all ulcers healed [Figure 3a and b], and the eosinophil count started to decrease. The patient has been in follow-up for the last 4 months and is doing well on imatinib.

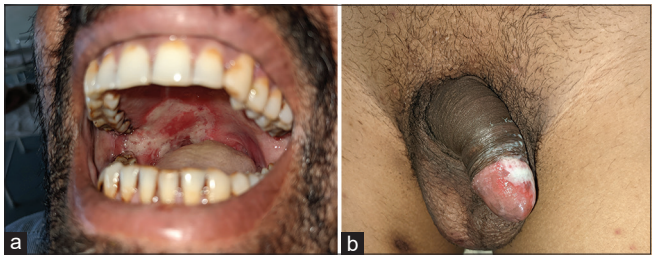

Figure 1: Coalescing ulcers with irregular borders involving (a) oral mucosa, hard palate, soft palate and (b) glans

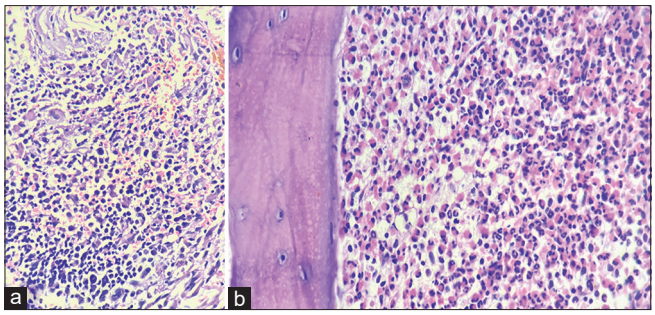

Figure 2: (a) Ulcerative epithelium with submucosal tissue infiltrated with plasma cells and lymphocytes (H and E, 400x); (b) hypercellular bone marrow with increased eosinophils and its precursors (H and E, 400x)

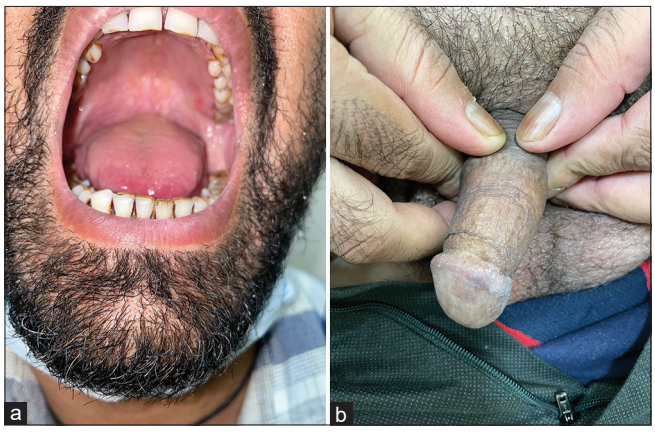

Figure 3: Healing of oral (a) and genital ulcers (b) on day 20 after starting imatinib mesylate

Discussion

The list of causes of oro-genital ulceration is exhaustive including viral infections like herpes simplex, cytomegalovirus; bacterial infections like syphilis, tuberculosis; inflammatory diseases like Behcet's disease, lichen planus, Crohn's disease, ulcerative colitis; autoinflammatory syndrome; aphthous ulcers; drugs; various hematological disorders, etc.[3] Our patient did not fulfill the diagnostic criteria of Behcet's disease. There have been reports of patients with CEL presenting with oral and penile ulcers which were treated for Behcet's disease.[4,5] Morphology of lesions in our case was not characteristic of dermatologic diseases mentioned in the above text and oral mucosal biopsy was non-specific. Hence, we investigated patients for systemic disorders.

Other cutaneous features reported in patients of CEL are pruritus, skin rash, rhinitis, eczema, angioedema, etc., which were absent in this patient. He had anemia, mild splenomegaly, mild thrombocytopenia, and remarkable eosinophilia along with a very high B12 level. Few studies have found that elevated levels of B12 have been strongly associated with *PDGFRA* gene re-arrangement.[4] This fact can be used along with other findings like anemia, eosinophilia, thrombocytopenia, hepatosplenomegaly, elevated tryptase level, systemic involvement, and skin lesions for a provisional diagnosis, which can be confirmed with genetic studies as in our case. Systemic involvement due to persistent eosinophilia can occur and may lead to organ damage.[6] However, our patient did not have any other systemic involvement except for mild splenomegaly, which improved over a period of a few days of treatment. The most common cause of mortality in such patients is fibrosis involving endomyocardial muscles. Other potentially serious conditions that can occur in CEL patients are lung fibrosis, thromboembolism, and eosinophilic gastritis. Hence, patients need to be investigated for the same and regular follow-up is necessary.

The standard treatment for CEL with the *FIP1L1-PDGFRA* fusion is imatinib mesylate in a dose of 100-400 mg/d. It is a potent inhibitor of both platelet-derived growth factor receptor alpha and beta tyrosine kinases. Imatinib can effectively suppress but cannot eliminate gene rearrangement, so ongoing treatment is recommended. In CEL-not otherwise specified and CEL associated with genetic defects other than *PDGFR,* systemic steroids are the mainstay of treatment.

Conclusion

In the absence of other cutaneous findings and no response to conventional therapies in a case of oro-genital ulcerations, the patient should be investigated thoroughly to

Table 1: Details of investigations and diagnostic workup

Investigations	Patient value	Laboratory reference range
Hemoglobin	10.30 gm/dl	13-17gm/dl
Red blood cell count	3.20 million/cu mm	4.5-5.9 million/cu mm
Hematocrit	32.5%	38-51%
Total leucocyte count	24960/cu mm	4000-11000/cu mm
Differential leukocyte count	Neutrophils - 45% Lymphocytes - 15% Monocytes - 2% Eosinophils - 38% Basophils - 0%	Neutrophils - 40-70% Lymphocytes - 20-40% Monocytes - 1-7% Eosinophils - 0-6% Basophils - 0-2%
Absolute eosinophil count	9462/µL	<500/µL
Platelet count	145000/cu mm	150000-450000/cu mm
Erythrocyte sedimentation rate	82 mm/hr	<15 mm/hr
C-reactive protein	40.65mg/L	<10mg/L
B-12 assay	>2000 pg/mL	160-950 pg/mL
Antinuclear antibody by immunofluorescence	Weak positive, cytoplasmic pattern	-
Penile doppler	Reduced arterial flow	-
Troponin level	<0.01 ng/mL	0-0.04ng/mL
Pathergy test	Negative	-
Coagulation profile, kidney, and liver function tests	Within normal limits	-
Ultrasound abdomen	Mild splenomegaly	
Chest X-ray, Electrocardiogram	No abnormalities detected	-
Biopsy from the tip of the tongue	Non-specific inflammatory infiltrates consisting of predominantly lymphocytes and plasma cells.	-
Bone marrow aspirate and biopsy [Figure 2b]	Markedly hypercellular fragments with increased eosinophils and eosinophilic precursors (59%). Megakaryocytes were present in adequate numbers with unremarkable morphology. Blasts were not increased.	-
Genetic analysis by next-generation sequencing	Pathogenic *FIP1L1-PDGFRA* (FIP1-like 1/platelet-derived growth factor receptor alpha) fusion detected (Genotype: *FLP1L1-PDGFRA*.F11P12del77.1)	-

find the etiology, especially in the presence of eosinophilia, as it could be a pointer toward a more grievous disease. Though rare, one must keep in mind that chronic eosinophilic leukemia can present as oral and genital ulcers. Advancement in genetic investigation helps to further classify this disease for therapeutic responsiveness, so whenever possible, that should be done.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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