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Chronic eosinophilic leukemia: Behçet's disease mimic

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Abstract

Report on a 53 year old male diagnosed with Behçet's syndrome over seven years duration. He came to the rheumatology & immunology clinic of Kasr Alainy hospital complaining of persistent oral and penile painful ulcers despite of compliance to treatment. Blood film revealed eosinophilia. Bone marrow examination showed eosinophilic leukemia.

This raises the question if there is an association between BD and CEL as myeloid neoplasm transformation or CEL is the original disease with Behçet's syndrome like symptoms.

Keywords

Behçet's syndrome; eosinophilic leukemia

Abbreviations

BD: Behçet's Disease; CEL: Chronic Eosinophilic Leukemia; MDS: Myelodysplastic Syndromes

Introduction

Behçet's disease (BD) is a chronic & systemic vasculitis of multifactorial etiology. It is characterized mainly by recurrent orogenital ulcers and several systemic manifestations including ocular disease, skin lesions, and gastrointestinal involvement [1]. BD in association with malignancy has been reported. Myelodysplastic syndrome is the most common clonal hematopoietic disorder while colorectal cancer is a common malignant solid neoplasm associated with BD [2].

Eosinophilic leukemia is one of the myeloproliferative neoplasms consisting of clonal proliferation in eosinophil precursors. Males are commonly more affected. Patients with eosinophilic leukemia may present with various combinations of symptoms and signs of end organ damage [3].

The 2016 World Health Organization (WHO) classification system of hematopoietic and lymphoid tissues includes a special category for myeloid and lymphoid disorder with eosinophilia and abnormalities in one of the following PDGFRA, PDGFRB gene or PCM1-JAK2 [4].

Case Report

53 year old patient complained of recurrent oro-genital ulcers and ocular affection that was described as uveitis over 7 years duration. Based on these clinical findings, the patient was diagnosed with Behçet's disease and was maintained on colchicine and steroids. Despite compliance to treatment the patient developed persistent oral and penile painful ulcers, generalized fatigue, loss of weight and

attacks of wheezy chest that made him seek medical consultation. On systematic reviewing: the patient was vitally stable, pale with BMI 19.5%. He had bilateral red eyes with single oral tender flat ulcer with red floor. Multiple well defined hyperpigmented plaques with scaling were present over elbows as well as dystrophic nails. Abdominal palpation revealed huge splenomegaly reaching the umbilicus. His peripheral blood examination revealed mild normocytic normochromic anemia (HB% 11.2 gm/dl), moderate thrombocytopenia (Plt 82) with marked leucocytosis (41x 10^9/L) and absolute eosinophilia 67%. Reticulocytic count was normal.

ESR was 90 mm/hr& CRP was 25 mg/l. Liver and kidney function tests were normal apart from elevated LDH (474mg/dl) and negative stool analysis for parasites on three successive stool specimens. Viral screening of hepatitis B, C and HIV were negative.

Serum kappa/lambda ratio was 1.8 while serum IgE was 1400 IU/ml (Reference range: up to 100) and IgG 2370(700-1600). B2 microglobulin 0.4 mg/dl (0.07-0.18).

Chest x-ray and Echocardiography were normal. Abdominal ultrasound showed hepatomegaly of diffuse pathology with portal vein dilatation and huge splenomegaly. CT chest reported few subcentemetric retrosternal, retrocaval, precarinal and tiny calcified right infra hilar lymph nodes in addition to nodular ground glass opacities suggestive of an inflammatory process. Pathergy skin test did not reveal any abnormalities. HLA-typing was HLA-B52.

Oral mucosal scrapping and skin biopsies revealed nonspecific inflammatory infiltration by neutrophils, and few eosinophils.

Bone marrow aspirate and biopsy showed packed marrow with obliteration of fat spaces and myeloid hyperplasia. Eosinophils and their precursors were increased (~ 40%). The erythroid series was relatively decreased with occasional early forms encountered. Megakaryocytic series were seen with dysplastic morphology and topography. Blasts were not increased which was confirmed by immunohistochemistry CD34. Multiple nodules formed of macrophages and mature looking lymphocyte. Those nodules showed positivity to pan T lymphoid marker CD3 in the center, surrounded by CD19 positive lymphocytes (pan B lymphoid marker). CD68 showed interstitially scattered positivity and few in the nodule (**Figure 1**).

Fluorescent in situ hybridization in the bone marrow was positive for a deletion at chromosome 4q12, resulting in fusion of the FIP1-like-1 gene and platelet-derived growth factor alpha gene, consistent with chronic eosinophilic leukemia. BCR/ABL fusion gene by FISH was negative thus excluding chronic myeloid leukemia.

The patient was advised to begin Tyrosine kinase inhibit or imatinib mesylate (Glivec 100mg once daily) and through his follow up after 3 months; he showed excellent response with healing of the mucosal ulcers, disappearance of the skin lesions. This was associated with normalization in the peripheral blood picture and eosinophilic count together with Ig E level falling off to 384 IU/ml. The follow up bone marrow biopsy showed normal cellularity for age with orderly normal Trilineage hematopoiesis. The lymphoid aggregates detected on diagnosis have much resolved and only one focus of reactionary nature mixed B and T lymphoid population was encountered. The follow up cytogenetic studies was negative for FIP1L1 -PDGFRA by Fluorescent in situ hybridization. The patient is now on

follow up.

Discussion

Behçet's syndrome is an autoimmune disorder characterized by recurrent oral aphthea with other systemic manifestations as genital ulcers, and uveitis. Behçet's syndrome is one of the differential diagnoses of eosinophilia [5].

Eosinophilic leukemia is one of the myeloproliferative neoplasms consisting of clonal proliferation in eosinophil precursors. It is a multisystem disease, and the presenting complaint can vary depending on the organ involved. Patients usually present with hepatosplenomegaly, cytopenia, fatigue, skin rash, oro-genital ulcers, cardiac infiltration and ocular affection [3].

Skin involvement can be the only presentation of CEL. Mucocutaneous manifestations occur in 25-50% of patients with chronic eosinophilic leukemia [6]. While Pruritus, urticaria, angioedema and erythematous papules, plaques, and nodules are among the common mucocutaneous manifestations, mucosal ulcerations including penile and oral ulcers were also rarely reported [7, 8]. Mucosal ulceration, which can be particularly painful and difficult to treat manifestation, may be misdiagnosed as Behçet's syndrome [9]. As for the ocular involvement, in our patient it was only conjunctivitis that responded well to topical treatments. However, it is worth mentioning that isolated bilateral uveitis was reported in a child with hypereosinophilia [10].

The key criteria for confirming the diagnosis of eosinophilic leukemia is the presence of a clonal cytogenetic or molecular genetic abnormality e.g., FIP1-like-1/platelet-derived growth factor alpha fusion, which is the most frequent. This fusion gene encodes for the *FIP1L1–PDGFR* alpha protein, the constitutively activated tyrosine kinase activity that induces eosinophilia. The standard of care for patients with the FIP1-like-1/platelet-derived growth factor alpha translocation is the tyrosine kinase inhibitor imatinib mesylate [3]. In fact after clonality was confirmed; we started to revise the presumed BD diagnosis and its possible relation with hematologic malignancies.

The profound clinical and laboratory improvement makes us believe that the case was originally chronic eosinophilic leukemia presenting predominantly with cutaneous manifestations. CEL has insidious onset and its course varies considerably among different individuals. It may remain subtle for years like our case. The nail dystrophy and skin pyoderma as well as the apparently Behçet's like clinical manifestations could be considered as paraneoplastic syndrome that precedes the expression of an occult malignancy.

So the overlapping of the symptoms between BD & eosinophilic leukemia raise the challenge for any physician to precisely define the diseases entity and to decide upon the best treatment options.

Conclusion

We are reporting CEL, presenting with an uncommon presentation of early cutaneous manifestations. Several apparently idiopathic rheumatic diseases can be early manifestations of hidden cancers. Clinicians should notice that CEL could be an alternative diagnosis in patients with refractory oral mucosal ulcerations.

Figures

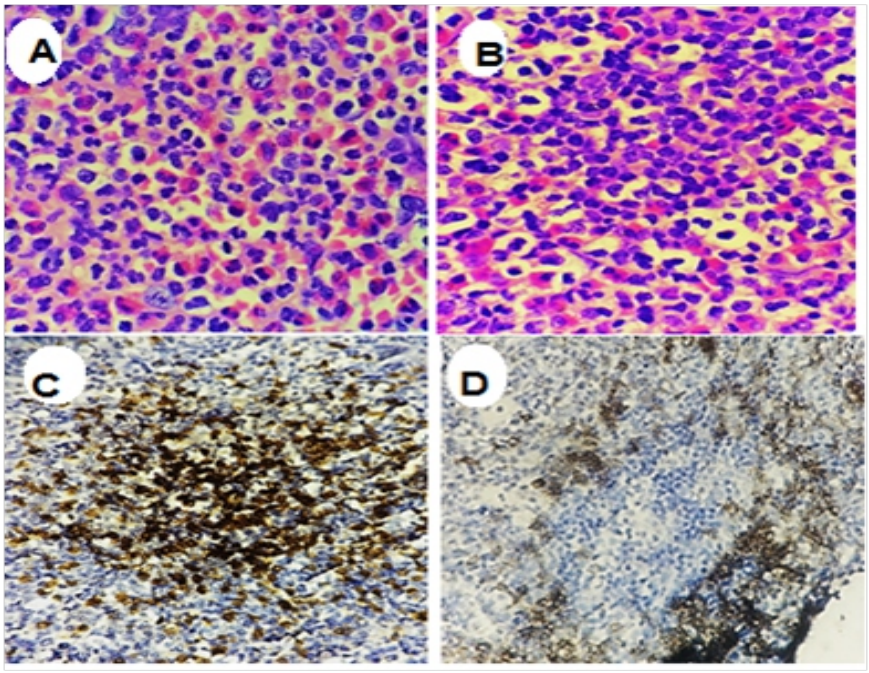

Figure 1: (A) shows Myeloid hyperplasia with marked eosinophilia**, (B)** Multiple nodules formed of macro phages and mature looking lymphocytes, **(C)** CD3 Positive mainly in the center of the nodules , few scattered interstitially, **(D)** CD 19 positive lymphocytes.

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