

Pruritus as a presenting symptom of FIP1L1-PDGFRΑ-Positive Chronic Eosinophilic Leukemia

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Abstract

Eosinophilia can be diagnosed in a wide spectrum of benign and malignant diseases, having a persistent eosinophilic count of more than 1500/mm³ obliges further workup. FIP1L1-PDGFRΑ-Positive Chronic Eosinophilic Leukemia patients can be asymptomatic at presentation or in critical status with multi-organ involvement.

Introduction:

FIP1L1-PDGFRΑ-Positive Chronic Eosinophilic Leukemia is a rare myeloproliferative neoplasm characterized by a gradual increase in circulating eosinophils persistently in peripheral blood ([?] 1.5 x 10⁹/L), bone marrow, and tissue. Before confirming the Clonality and approving the diagnosis of CEL, Secondary causes should be ruled out [1]. Infiltration of eosinophils in multiple organs and the release of the eosinophilic granules and cytokines causes significant damage and possible dysfunction to the affected organs. Patient presentations vary from serious presentation such as restrictive cardiomegaly to presenting with long-standing eosinophilia without any specific symptoms. The gastrointestinal tract, lung, and skin are the most commonly affected organs as reported in FIP1L1-PDGFRΑ-Positive Chronic Eosinophilic Leukemia patients [1]. Here we report a case of a 30-year-old male patient who was found to have FIP1L1-PDGFRΑ-Positive CEL with predominantly skin manifestation mainly severe pruritus.

Case Presentation:

A 29-year-old male patient with a background of newly developed attacks of cough and shortness of breath of few months duration diagnosed as intermittent asthma, with no similar history during childhood. The patient was referred to the Dermatology team with complaints of multiple skin lesions related to sun exposure along with persistent pruritus., the patient had an initial assessment of common causes of allergies with came back negative and patient was kept for follow up, a few months later patient Presented same complaints but it was associated with watery diarrhea and history of subjective weight loss, along with a history of severe persistent pruritus, CBC done showed elevated WBC counts with marked eosinophilia for which patient was referred to further workup. CBC showed WBC of 22 x10³/μl normal value (4.0-10.0 x10³/μl), Hb: 14.6 gm/dL normal value (13.0-17.0 gm/dL), PLT: 168 x10³/μl normal value (150-400 x10³/μl), ANC: 4.8 x10³/μl normal values (2.0-7.0 x10³/μl), Eosinophil count: 14.1 x10³/μl normal values (0.0-0.5 x10³/μl). Peripheral smear:

Showed normocytic normochromic red cells, leukocytosis with marked eosinophilia, composed mostly of mature forms, the majority of eosinophils show abnormal nuclear segmentation and or sparse cytoplasmic granulation, Platelets are adequate.

Chest x-ray was unremarkable, US abdomen came significant for mild Hepatosplenomegaly.

Bone marrow was remarkably hypercellular (almost 100% cellularity) with granulocytic hyperplasia and remarkably increased eosinophilic cells with adequate erythropoiesis and megakaryocytes with some dysplastic forms. CD117 immunostain performed on bone marrow showed increased mast cells, included some spindle-forms. These mast cells were positive for mast cell tryptase and aberrantly positive for CD 25. No increase in CD34-positive cells was noted. Reticulin stain shows areas of mildly increase reticulin fibers (MF0-1).

FISH (Fluorescence in situ hybridization) analysis using the *FIP1L1/CHIC2/PDGFR* (*4q12*) probe was consistent with a deletion of *CHIC2* resulting in the fusion of *PDGFR* and *FIP1L1* in 76% of nuclei. No BCR/ABL1 gene rearrangement. Molecular genetics revealed no *KIT* mutation. Molecular study for JAK-2, CALR, and KIT D816V mutation was negative.

The patient was started on imatinib 100 mg oral daily, with normalization of the counts within 1 month, along with significant improvement of his skin manifestations in regards to frequency and attacks and their intensity.

Discussion:

PDGFR α -associated chronic eosinophilic leukemia is a type of blood cancer that is marked by chronic unexplained eosinophilia more than 1500/mm³. CEL is described as a myeloproliferative variant of Hypereosinophilic syndrome. Myeloid and lymphoid neoplasms with eosinophilia and rearrangements of PDGFR α , PDGFR β , and FGFR1 were recognized as a specific class in the 2008 WHO classification [2]; such neoplasms are denoted by overexpression of an aberrant tyrosine kinase due to a mutation or a specific fusion gene. The cell of origin has been recognized as a mutated pluripotent (myeloid-lymphoid) stem cell.[3] Clonal eosinophilia, usually arising from PDGFR α , PDGFR β , or FGFR1 gene rearrangements or point mutations, with the formation of a FIP1L1-PDGFR α fusion gene being most abundant, [4] accounting for around 10–20% of patients with undefined eosinophilia in Western countries. Approximately 70% of patients with PDGFR α rearrangement usually present with eosinophilia [5] as a result of the interstitial deletion of 4q12 leading to FIP1L1- PDGFR α fusion.

The FIP1L1-PDGFR α fusion protein, is a receptor of platelet-derived growth factor, the fusion receptor is continuously activated despite the presence of platelet-derived growth factor since the first 29 amino acids of the FIP1L1 protein are capable of activating the kinase domain of PDGFR α . The persistent phosphorylation of the receptor on a tyrosine triggers the activation of the complete succeeding signal pathway, inducing the transformation of hematopoietic cells to an incessant growth state. [6]

The FIP1L1-PDGFR α fusion gene is deemed as the main molecular biomarker and has recently proven to be sensitive to treatment with tyrosine-kinase inhibitor drugs, such as imatinib

The rapid increase of eosinophils and their disposition in the organs such as the skin is accountable for the clinical manifestation. The most prevalent symptoms include cough, dyspnea, generalized weakness, skin rash, and rhinitis. [7] All organs can be affected by persistent eosinophilia, one of the known examples is Cardiac involvement, particularly endomyocardial fibrosis, raising the incidence of mortality. Other serious presentations including lung fibrosis, thromboembolism, and eosinophilic gastritis. [7] People with PDGFR α -associated chronic eosinophilic leukemia can also have an enlarged spleen, and elevated levels tryptase in the blood.

Manifestations presented with our case mainly were cutaneous manifestations, including multiple skin lesions reported as recurrent skin abscesses related to sun exposure which were intermittent, along with recurrent pruritus which became intense and severe at the time of diagnosis, patient had no serious systemic manifestations. Cutaneous manifestations that are commonly seen in eosinophilic leukemia include an eczema-like picture, angioedema, and multiple mucosal ulcers. [8]

At present multiple studies have proven the significant outcome with complete hematologic and molecular remission after the initiation of imatinib therapy of 100 to 400 mg daily in *FIP1L1-PDGFR* -positive patients. With the majority of patients getting complete molecular remission with 100 mg daily, Maintenance dosing adjusted to as 100- 200 mg weekly can maintain complete metabolic remission [9].

Conclusion: *FIP1L1-PDGFR α* -positive CEL can present primarily with skin manifestation rather than a systemic disease, This case was reported to increase physicians awareness of common skin manifestations, that could be a part of serious illness, bizarre presentations of skin manifestations that do not improve with usual treatment methods should trigger the need for further evaluation.

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Statement of Ethics:

Written informed consent was obtained from our patient to allow the publication of information.

Disclosure statement

The Authors have nothing to disclose.

Authors contributions:

MA: Manuscript writing, literature review, and approval of the final manuscript.

EA: Manuscript writing, literature review, and approval of the final manuscript.

MY: Case identification, and approval of the final manuscript.

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