



Pruritus as a Presenting Symptom of *FIP1L1*-*PDGFRA*-Positive Chronic Eosinophilic Leukemia

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Abstract: Eosinophilia can be found in a variety of benign and malignant conditions, and a persistent eosinophilic count of more than 1500/mm³ necessitates additional investigation. Patients with *FIP1L1*-*PDGFRA*-positive chronic eosinophilic leukemia might present as asymptomatic or in a catastrophic state with multi-organ involvement. We present the case of a young male patient who was diagnosed with *FIP1L1*-*PDGFRA* chronic eosinophilic leukemia after a long history of recurrent cutaneous symptoms with no systemic signs.

Keywords: chronic eosinophilic leukemia, *FIP1L1*-*PDGFRA*, eosinophilia, imatinib

Introduction

FIP1L1-*PDGFRA*-positive chronic eosinophilic leukemia is a rare myeloproliferative neoplasm marked by a continuous increase in circulating eosinophils ($\geq 1.5 \times 10^9/L$). Secondary causes should be ruled out before verifying clonality and confirming the CEL diagnosis.¹ The infiltration of eosinophils into many organs, as well as the production of eosinophilic granules and cytokines, cause severe damage and probable organ malfunction. Patients can report anything from serious symptoms like restricted cardiomyopathy to long-term eosinophilia with no obvious symptoms. According to patients with *FIP1L1*-*PDGFRA*-positive chronic eosinophilic leukemia, the gastrointestinal system, lungs, and skin are the most affected organs.¹ We present the case of a 30-year-old male patient who was diagnosed with *FIP1L1*-*PDGFRA*-positive CEL, which manifested mostly as severe pruritus of the skin.

Case Presentation

A 29-year-old male patient with a background of newly developed attacks of cough and shortness of breath of a few months' duration was diagnosed with 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 which came back negative, thus he was referred for further evaluation. A few months later the patient presented with the same complaints, but the later episode was associated with watery diarrhea and a history of subjective weight loss, along with a history of severe persistent pruritus. CBC showed elevated WBC counts with marked eosinophilia for which the patient was referred for further workup. CBC showed WBC of $22 \times 10^3/\mu L$ normal value ($4.0\text{--}10.0 \times 10^3/\mu L$), Hb: 14.6 gm/dL normal value (13.0–17.0 gm/dL), PLT: $168 \times 10^3/$

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μL normal value ($150\text{--}400 \times 10^3/\mu\text{L}$), ANC: $4.8 \times 10^3/\mu\text{L}$ normal values ($2.0\text{--}7.0 \times 10^3/\mu\text{L}$), eosinophil count: $14.1 \times 10^3/\mu\text{L}$ normal values ($0.0\text{--}0.5 \times 10^3/\mu\text{L}$). Peripheral smear

showed normocytic normochromic red cells, leukocytosis with marked eosinophilia, composed mostly of mature forms, the majority of eosinophils showed abnormal nuclear segmentation and or sparse cytoplasmic granulation, platelets were adequate.

Chest X-ray was unremarkable, abdomen US was significant for mild hepatosplenomegaly.

IgE levels were within normal limits. 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, including 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 showed areas of mildly increased reticulin fibers (MF0-1). FISH (fluorescence in situ hybridization) analysis using the *FIP1L1/CHIC2/PDGFR A (4q12)* probe was consistent with a deletion of *CHIC2* resulting in the fusion of *PDGFR A* and *FIP1L1* in 76% of nuclei. There was no BCR/ABL1 gene rearrangement. Molecular genetics revealed no *KIT* mutation. The molecular studies for JAK-2, CALR, and KIT D816V mutation were negative.

The patient was started on imatinib 100 mg orally once a day, and his numbers were normalized within a month, along with a considerable improvement in his skin manifestations in terms of frequency, episodes, and intensity.

Discussion

Eosinophilia is described as an increase in the number of eosinophils in the peripheral blood, with an absolute count of greater than 500 eosinophils $\times 10^3/\mu\text{L}$. Hypereosinophilic syndrome is defined as an elevated eosinophil count (>1500 eosinophils $\times 10^3/\text{L}$) that lasts longer than 6 months (HES). Nonetheless, in 2011, the working conference on eosinophil disorders and syndromes proposed that at least two episodes of eosinophilia separated by at least four weeks can be classified as persistent, indicating that there is no identifiable etiology for eosinophilia and that patients had signs and symptoms of organ involvement.^{1,2}

Chronic unexplained eosinophilia greater than 1500/ mm^3 is a hallmark of PDGFRA-associated chronic eosinophilic leukemia, a type of blood cancer. Persistent eosinophilia ($1.5 \times 10^9/\text{L}$) in the absence of reactive causes,

followed by a positive peripheral blood screening for the FIP1L1-PDGFR A gene fusion (via RT-PCR or interphase/metaphase FISH), is classified as myeloid/lymphoid neoplasms associated with eosinophilia and PDGFRA rearrangement, according to the WHO 2017 classification. The real incidence of chronic eosinophilic leukemia, not otherwise described, is unknown due to the difficulties in separating it from the idiopathic hypereosinophilic syndrome.¹

CEL is classified as a myeloproliferative subtype of hypereosinophilic syndrome. Eosinophilic myeloid and lymphoid neoplasms with PDGFRA, PDGFRB, and FGFR1 rearrangements were classified as a distinct class in the 2008 WHO classification;³ these neoplasms are defined by overexpression of an abnormal tyrosine kinase caused by a mutation or a particular fusion gene. A mutant pluripotent (myeloid-lymphoid) stem cell has been identified as the cell of origin.⁴ Clonal eosinophilia is caused by gene rearrangements or point mutations in the PDGFRA, PDGFRB, or FGFR1 genes, with the creation of a FIP1L1-PDGFR A fusion gene being the most common,⁵ accounting for 10–20% of patients with unexplained eosinophilia in Western countries. As a result of the interstitial deletion of 4q12 that leads to FIP1L1-PDGFR A fusion, approximately 70% of patients with PDGFRA rearrangement have eosinophilia.⁶

The FIP1L1-PDGFR A fusion protein is a platelet-derived growth factor receptor that remains active even when platelet-derived growth factor is present because the first 29 amino acids of the FIP1L1 protein can activate the PDGFR α kinase domain. The activation of the entire subsequent signaling pathway is triggered by the continual phosphorylation of the receptor on a tyrosine, causing the change of hematopoietic cells to an endless growth state.⁷

The FIP1L1-PDGFR A fusion gene is considered the most important molecular biomarker, and it has recently been shown to be susceptible to tyrosine-kinase inhibitor medications like imatinib.

The clinical manifestation is caused by a rapid increase in eosinophils and their distribution in organs such as the skin. Cough, dyspnea, generalized weakness, skin rash, and rhinitis are the most common symptoms.⁸ Persistent eosinophilia can affect any organ; one well-known example is cardiac involvement, notably endomyocardial fibrosis, which increases the risk of death. Lung fibrosis, thromboembolism, and eosinophilic gastritis are some of the most serious symptoms.⁸ In addition to an enlarged spleen and higher tryptase levels in the blood, those with PDGFRA-associated chronic eosinophilic leukemia may have an enlarged spleen.

Our patient's symptoms were mostly cutaneous, with several skin lesions reported as recurrent skin abscesses connected to intermittent sun exposure, as well as recurrent pruritus that became prominent and severe at the time of diagnosis. There were no major systemic manifestations. Eczema-like symptoms, angioedema, and numerous mucosal ulcers are all common cutaneous signs of eosinophilic leukemia.⁹ Currently, many studies have demonstrated a significant outcome with complete hematologic and molecular remission in FIP1L1-PDGFR α -positive patients after initiating imatinib therapy of 100 to 400 mg daily.² A maintenance dose of 100–200 mg weekly can maintain total metabolic remission, with the majority of patients achieving complete molecular remission with 100 mg daily.¹⁰

Conclusion

FIP1L1-PDGFR α -positive CEL can manifest primarily as a skin symptom rather than a systemic disease; this case was reported to raise physician awareness of a common skin symptom that could be a sign of a serious illness; unusual presentations of skin symptoms that do not improve with standard treatment methods should prompt further evaluation.

Abbreviations

PDGFR α , platelet-derived growth factor receptor A; PDGFR β , platelet-derived growth factor receptor Beta; FGFR1, fibroblast growth factor receptor 1; TKI, tyrosine kinase inhibitor; DM, diabetes mellitus; ANC, absolute neutrophil count; FISH, fluorescence in situ hybridization; HES, hypereosinophilic syndrome; CML, Chronic Myelogenous Leukemia; CBC, complete blood count; MPN, myeloproliferative neoplasm.

Statement of Ethics

The case was approved by Hamad Medical Corporation Research Center with reference number MRC-04-20-997.

Consent

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

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Disclosure

The authors report no conflict of interest in this work.

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