

## Case Report

# Severe Eosinophilia Associated with FIP1L1/PDGFR A Rearrangement Presenting with Yamaguchi Syndrome

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**Abstract**

FIP1L1/PDGFR A is a rare genetic rearrangement, presenting most commonly as Chronic Eosinophilic Leukemia (CEL), but may also be associated with other myeloid and lymphoid neoplasms. The peripheral blood and bone marrow exhibit a striking eosinophilia, often associated with an increased number of mast cells on trephine biopsy. Tissue infiltration by eosinophils and release of cytokines from eosinophilic granules mediate multi-organ tissue damage. The tyrosine kinase inhibitor Imatinib has been shown to induce rapid and complete clinical and haematological responses in patients harboring the mutation. We present the case of a young patient with CEL associated with PDGFR A rearrangement, presenting with severe eosinophilia and evidence of multi-organ damage (cardiac, renal, endocrine and respiratory). The peripheral blood and bone marrow displayed a striking eosinophilia, and FISH analysis for FIP1L1/PDGFR A revealed a positive fusion signal in 92% of the nuclei examined. Echocardiography showed left ventricular apical hypertrophy (Yamaguchi syndrome), which has previously not been reported in this subset of patients. He was managed with supportive care, along with low-dose imatinib (100mg/day initially), to which he achieved a rapid clinical and haematological response. Currently, five months from the initial diagnosis, he is doing well on low dose imatinib (100 mg) twice a week.

**Keywords:** Eosinophilia; Chronic eosinophilic leukemia; FIPL1/PDGFR A

**Abbreviations**

AEC: Absolute Eosinophil Count; CEL: Chronic Eosinophilic Leukemia

**Background**

Eosinophilia is a common clinical finding encountered in a wide range of diseases, including allergic disorders, infections, drugs and haematological malignancies. Haematological conditions associated with eosinophilia include lymphomas, acute myeloid leukemia, myelodysplastic syndromes, chronic eosinophilic leukemia NOS, myeloid/lymphoid neoplasms associated with rearrangement of PDGFR A, PDGFR B, FGFR1 and PCMI-JAK2 genes, and hypereosinophilic syndrome. In this report, we present the case of a young patient who presented with hyperleucocytosis (TLC  $147.57 \times 10^9/L$ ) and severe eosinophilia (absolute eosinophil count  $63.5 \times 10^9/L$ ), who was later found to have rearrangement in FIP1L1/PDGFR A gene.

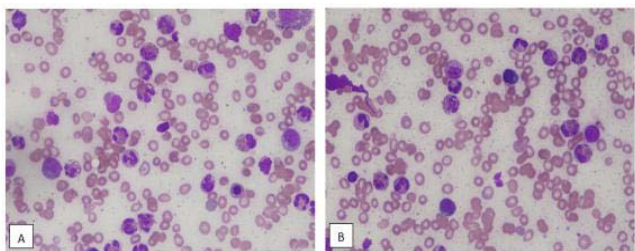
Myeloid/ Lymphoid neoplasms associated with PDGFR A rearrangement is a rare disease entity characterized by a cryptic deletion resulting in fusion of PDGFR A and FIP1L1 genes [1]. This rearrangement confers on haematopoietic precursor cells commitment to eosinophilic differentiation [2]. The usual presentation is as Chronic Eosinophilic Leukemia (CEL), but patients may also present with acute myeloid leukemia and/or T lymphoblastic leukemia/lymphoma [3,4]. There is a marked predisposition to male sex (male: female ratio is 17:1) and median age of onset is in late 40s [3]. Tissue infiltration by eosinophils and

release of cytokines from eosinophilic granules mediate multi-organ tissue damage. Hence, patients usually present with constitutional symptoms, accompanied by respiratory, cardiac, gastrointestinal and dermatological manifestations. The peripheral blood displays striking eosinophilia with mature morphology [3]. A range of morphological abnormalities can be observed in eosinophils, including sparse granulation, cytoplasmic vacuolation and nuclear hyper- or hypo-segmentation. The bone marrow is hypercellular with increased numbers of eosinophils and usually with a normal blast percentage. Bone marrow mast cells are often increased on trephine biopsy. The clonal eosinophils may show evidence of activation in terms of the immunophenotypic expression of CD23, CD25 and CD69.

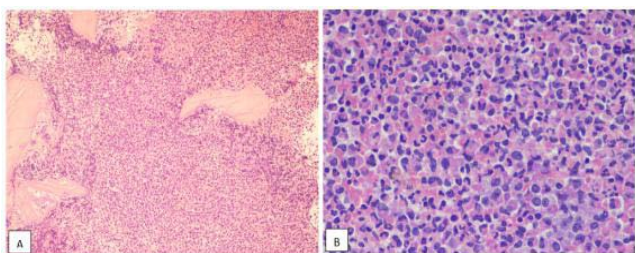
The long-term prognosis of the disorder is still unclear, as its responsiveness to imatinib was not known until 2003 [5]. Nonetheless, if imatinib treatment is available and cardiac damage has not occurred, current evidence suggests the prognosis to be favorable. Imatinib has been shown to induce rapid and complete clinical and haematological responses at doses ranging from 100-400 mg/day [6].

**Case Presentation**

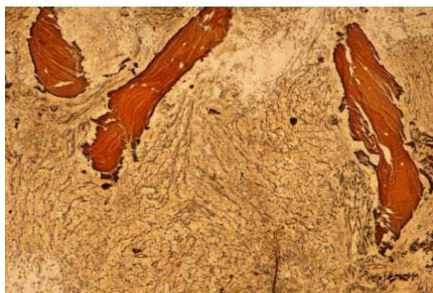
A 30 year old male patient with no prior comorbidities presented with complaints of intermittent fever, progressive shortness of breath and pedal edema since 1 month. On general review, he had tachycardia (pulse rate 97/min), tachypnea (respiratory rate 20/min), postural hypotension and bilateral lower limb edema up to mid-thigh and hydrocele. Abdominal examination showed hepatosplenomegaly. Chest examination showed normal vesicular breathing in all areas with no cardiac murmur in areas of cardiac auscultation.



**Figure 1:** Bone marrow aspirate showing prominent eosinophilia and nuclear hypersegmentation.

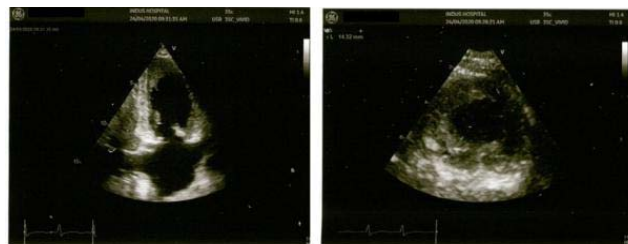


**Figure 2:** Low power (A) high power (B) views of bone marrow trephine showing hypercellular marrow with prominent eosinophilia.



**Figure 3:** Reticulin stain showing Grade 1 myelofibrosis (loose network of reticulin with many intersections) (WHO classification, 2017<sup>3</sup>).

CBC showed bicytopenia and hyperleucocytosis (Hb 5.4 g/dl, TLC  $147.57 \times 10^9/L$ , Plt  $44 \times 10^9/L$ ). Peripheral film examination revealed a striking eosinophilia (43% eosinophils) with mature morphology, leucoerythroblastic blood picture and no significant blast cells. Bone marrow examination showed a hypercellular marrow exhibiting 95-100% cellularity and marked eosinophilic hyperplasia with all stages of differentiation. Scattered megakaryocytes were seen. There was no evidence of excess blasts, mast cells, significant dysplasia, granuloma, necrosis or metastatic disease in the available material. Reticulin stain showed Grade 1 myelofibrosis (loose network of reticulin with many intersections). On further workup, he was found to have prolonged INR (1.65), normal aPTT, deranged renal profile (urea 83mg/dl, creatinine 1.77 mg/dl, microalbuminuria 24.0mg/L) and liver function tests (total bilirubin 2.6mg/dl, direct bilirubin 1.64mg/dl, GGT 199U/L, ALT 634U/L, alkaline phosphatase 771U/L) and raised serum LDH (444 U/L). Serum TSH level was slightly low (0.347mIU/L; reference range 0.4-4.2 mIU/L), but free T3 and T4 levels were within normal limits. Ultrasound Abdomen showed significant hepatosplenomegaly (liver 19.5cm, spleen 18.3cm) and fatty infiltration of the liver. Chest



**Figure 4:** Echocardiogram showing apical myocardial hypertrophy.

X-ray showed two well defined densities in the right upper zone, resembling granulomas. Echocardiography showed left ventricular apical hypertrophy (Yamaguchi syndrome), and moderate tricuspid and mitral regurgitation. High sensitivity troponin I (103ng/L) and NT-proBNP (6403pg/ml) were raised. Thus, the patient had severe eosinophilia associated with evidence of multiorgan damage (cardiac, renal, endocrine and respiratory). He was initially managed with supportive care (hematinics, packed red cell transfusions, DVT prophylaxis, high protein diet, albumin replacement) and was started on Prednisolone 1mg/kg/day and Hydroxyurea 1g/day.

The following differential diagnosis were considered: chronic eosinophilic leukemia NOS, myeloid neoplasms with gene rearrangements (PDGFRA, PDGFRB, FGFR1 and PCM1-JAK2 genes), idiopathic hypereosinophilic syndrome and secondary causes of eosinophilia (infections, connective tissue disorders, etc.).

Bone marrow karyotyping revealed 46 chromosomes in all 20 cells counted and no significant abnormality. FISH analysis for FIP1L1/PDGFRB revealed a positive fusion signal in 92% of the nuclei examined. The patient was thus diagnosed a case of Myeloid neoplasm with PDGFRA rearrangement presenting as chronic eosinophilic leukemia (WHO Classification 2017)<sup>3</sup>. He was later started on low dose imatinib 100mg/day. Two weeks after commencement of imatinib, the patient reported improvement in constitutional symptoms, but serial CBC monitoring showed pancytopenia (Hb 6.8g/dl, TLC  $2.0 \times 10^9/L$  with 2% Eosinophils, Platelets  $54 \times 10^9/L$ ). His dose was reduced, and currently five months from the initial diagnosis, he is doing well on Imatinib 100 mg/day twice a week.

## Discussion and Conclusion

Our patient is a case of chronic eosinophilic leukemia associated with PDGFRA rearrangement, presenting with severe eosinophilia and evidence of multi-organ damage. Several case reports and case series of patients with eosinophilia associated with FIP1L1/PDGFRB rearrangement, have been published from various countries [7-18]. In addition to the more common presentations, they have described the clinical features and outcome of this rare disease entity in paediatric patients, the occurrence of rare FIP1L1 breakpoint (located outside the usual breakpoint region) and atypical presentation of the disease with thrombotic thrombocytopenia purpura. In a case series comprising of 22 patients with mutated FIP1L1/PDGFRB, all patients were male with absolute eosinophil counts ranging from  $1-110 \times 10^9/L$  [17]. Most patients presented with constitutional symptoms, with evidence of organ involvement (skin, cardiac, pulmonary, gastrointestinal, neurologic) in a variable proportion of patients. Cardiac involvement, characterized by congestive heart failure, left ventricular thrombus

and characteristic echocardiographic findings, was noted in 7 (32%) of patients. Three patients were retrospectively identified, and they had not received imatinib treatment; in the remaining 19 patients, imatinib was started in 18 patients. Of the patients who received imatinib, complete haematological response was obtained in 17 patients; the remaining patient discontinued imatinib on account of intolerance, and was asymptomatic off-treatment, with an AEC of  $1-1.5 \times 10^9/L$ .

In another case series comprising of 33 patients with CEL associated with PDGFRA rearrangement, cardiac involvement was present in 22% of patients, and manifested as endomyocardial fibrosis, valvular abnormalities and mural thrombosis [18]. To our knowledge, this is the first case of apical hypertrophic cardiomyopathy (Yamaguchi syndrome) presenting in association with a clonal eosinophilia. Our patient displayed a rapid haematological response to imatinib in terms of reduction in his white cell count. It has been shown that a single weekly dose of imatinib, ranging from 100-200 mg/week is sufficient to maintain remission in patients with CEL harboring the FIP1L1/PDGFR mutation [19].

### Clinical Practice Points

- FIP1L1/PDGFR is a rare genetic rearrangement, presenting most commonly as Chronic Eosinophilic Leukemia (CEL), but may also be associated with other myeloid and lymphoid neoplasms.
- Tissue infiltration by eosinophils and release of cytokines from eosinophilic granules mediate multi-organ tissue damage.
- The tyrosine kinase inhibitor Imatinib has been shown to induce rapid and complete clinical and haematological responses in patients harboring the mutation. A dose of 100-200 mg/week has been shown to be sufficient in maintaining remission.

### Authors' Contributions

ZA analyzed and interpreted the patient's data and managed the patient. FM analyzed and interpreted the peripheral blood and bone marrow aspirate and trephine biopsy findings of the patient. HMH performed the bone marrow biopsy procedure, and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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