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Case Report

FIP1L1– PDGFRA positive chronic eosinophilic leukemia: A case report

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ABSTRACT

Chronic eosinophilic leukemia (CEL) is a rare type of leukemia which is characterized by persistently increased number of eosinophils in peripheral blood and bone-marrow alongwith evidence of clonal proliferation of eosinophils with tissue infiltration by eosinophils leading to organ damage and causing systemic manifestations. An accurate diagnosis of CEL is essential as these patients show excellent response to imatinib mesylate. Use of technique like FISH (fluorescent in-situ hybridization) & RTPCR (Reverse Transcriptase) helps in proving the clonality of eosinophils. We report a case of CEL with FIP1L1 (Fip1-Like-1) PDGFRA (Platelet Derived Growth Factor Receptor – Alpha Gene) mutation in 29-year old male presenting with persistent eosinophilia. Rarity of this entity definitely needs a space in literature.

1. Case Report

The patient was a 29-year old male with no significant past family or personal medical history. He was referred to our Hospital for work-up of persistent eosinophilia. No past history of any allergy or exposure to toxin, pesticides or any addiction history or history of any recent travel. On physical examination, the patient was not having fever and had mild pallor. There was no hepatomegaly, lymphoadenopathy, rashes on skin or icterus.

On investigation, his haemogram showed haemoglobin 11.7 g/dl, TLC – 13.0 x 10^9 L and eosinophil count 8.0 x 10^9/L and platelet count – 241 x 10^9/L and LDH – 136 U/L. Red Blood Cell population was predominantly normocytic Hypochromic with a few microcytes. Differential count showed fair number of eosinophils with dysplasia and a few myeloid precursors were also present in the peripheral blood smear (Figure 1). ESR was raised (32 mm) Liver Function Tests and Renal Function Tests were within normal limits. No abnormality was detected in urine examination. In stool examination, parasitic ova and cyst were not found. Serum Electrolytes were normal. Serological markers for Hepatitis A, B or E and HIV were negative. ECG was normal. PET Scan showed Low FDG uptake in prevascular, paratracheal and axillary lymphnodes. There was increased FDG uptake in Bone-marrow which was suggestive of marrow infiltrative disease. Bone-marrow aspirate showed myeloid proliferation with increased eosinophilic precursors (Figure 2). Bone-marrow trephine biopsy showed myeloid proliferation with increased eosinophilic granulopoiesis & grade II reticulin fibrosis.

Cytogenetic analysis revealed karyotype (46, XY) with no visible chromosomal abnormality molecular cytogenetic abnormalities FISH for BCR – ABL 1, JAK2V617F, JAK2EXON12, CALR and MPL were negative. FISH showed CHIC 2 deletion with fusion of PDGFRA – FIP1L1 in 190/200 cells and negative for PDGFRB and FGFR1 (Figure 3). In view of absence of secondary causes of Eosinophilia, presence of FIP1L1 – PDGFRA rearrangement with CHIC2 deletion and with no organ damage. The diagnosis of FIP1L1 – PDGFRA positive

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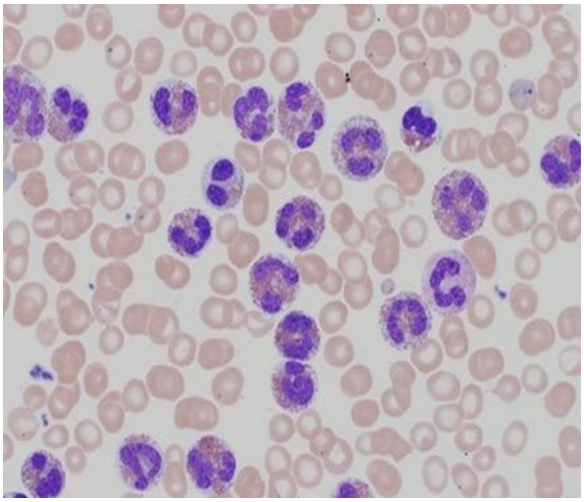

Figure 1: Esoinophilia (8.0x10^9/L) was observed in Peripheral Blood (Wright-Giema, x100)

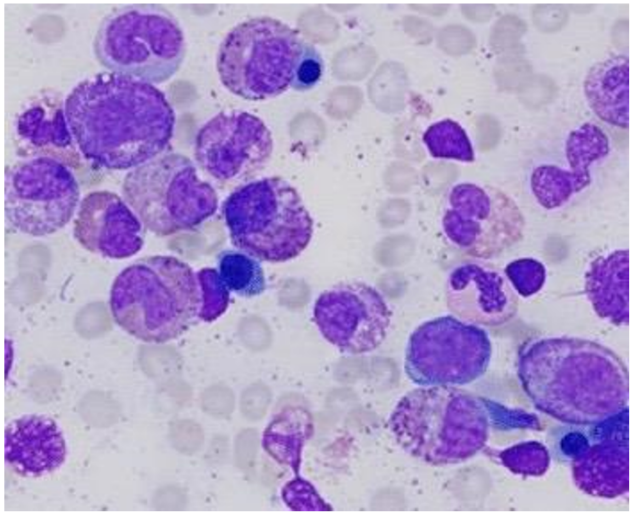

Figure 2: Myeloid proliferation with eosinophilic granulopoesis seen in bone marrow aspiration (x100)

chronic Eosinophilic leukemia was finally made and patient was started on 100 mg imatinib.

2. Discussion

Hypereosinophilia is defined as an eosinophil count of >1.5 x10^9/L. In an individual presenting with eosinophilia reactive/secondary causes of eosinophilia must be ruled out first.[1] Eosinophilia encompass hematologic and non-haematological disorder. Tissue infiltration of eosinophils and release of its contents lead to organ damage which can be life-threatening.[2] Identifying the cause of eosinophilia is of utmost importance as it decides the disease outcome.

CEL is a rare leukemia which is considered to be a type of Idiopathic Hyper Eosinophilic Syndrome (IHES)

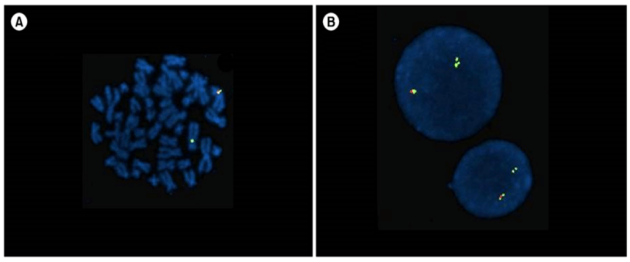

Figure 3: Fluorescence in situ hybridization (FISH) for the FIP1L1-PDGFRA rearrangement. CHIC2 is labeled in orange, FIP1L1-PDGFRA in green. Loss of orange signal suggests deletion of the 4q12 region on metaphase FISH (**A**) and interphase FISH (**B**)

by some authors, whereas many consider it as a separate entity.[2–4] Secondary causes of eosinophilia like allergy, parasitic infestation and others must be excluded before considering CEL as a diagnosis. An evidence of genetic clonality of eosinophils is mandatory for diagnosis of CEL. Myeloproliferative neoplasm with eosinophilia and platelet derived growth factor receptor-alpha gene and Fip1-like-1 gene mutation (FIP1L1-PDGFRA; F/P) shows complete hematological response and resolution of organ damage with imatinib therapy.[5]

The clinical presentation varies from being asymptomatic to severe systemic manifestations like eosinophilic endomyocarditis or restrictive lung disease.[1,6]

Persistent eosinophilia may cause tissue infiltration of any organ system.[7] The most common cause of mortality among these patients is eosinophilic mediated organ injury to heart leading to progressive heart failure.[1,6] Firstly, the secondary causes of eosinophilia must be excluded followed by evaluation of primary eosinophilia by careful study of peripheral blood-smear and bone-marrow, cytogenetics, FISH, flowcytometry and RTPCR. Eosinophilia with genetic abnormalities in particular FIP1L1-PDGFRA fusion is among the most common molecular abnormality. This encodes aberrant constitutively activated tyrosine kinase which without any growth stimuli leads to eosinophil proliferation.[8] CEL is marked by presence of increase in number of blast in the bone-marrow with proven clonality of eosinophils.

3. Conclusion

FIP1L1 – PDGFRA positive CEL is a rarely reported entity from India. An accurate CEL diagnosis is essential as these patients greatly benefit from a specific treatment with imatinib. Thus sophisticated techniques like FISH, and RTPCR are crucial in understanding the cellular and molecular oriented classification of eosinophilia which carries therapeutic implication. This case warrants its mention to further emphasize the need of awareness among clinicians about this rare but treatable entity which can

otherwise be life-threatening.

4. Source of Funding

None.

5. Conflict of Interest

None.

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