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Pathology

"CHALLENGES IN INTERPRETATION OF EOSINOPHILIA ASSOCIATED WITH LEUKEMIA: CASE REPORT OF TWO CASES"

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ABSTRACT Eosinophilia is a condition that develops when bone marrow makes too many eosinophils. It can be reactive or caused by a new genetic mutation. Here we are discussing two cases, one is idiopathic hypereosinophilic syndrome (HES) and other case is acute myeloid leukemia associated with eosinophilia (AMLEo). In AMLEo, causative role and impact of eosinophilia was uncertain. Cytogenetic and molecular genetic techniques do help for the evidence of clonality of the eosinophils and for identifying patient with respect to imatinib sensitivity and resistance. Eosinophils in patients with myeloid or stem cell derived neoplasm usually belong to the malignant clone. But in a resource limited settings, it is challenging for a pathologist for proper diagnosis of such cases wheather to overlooked or ignore such eosinophilia present in a leukemia and to differentiate HES from chronic eosinophilic leukemia.

KEYWORDS : Chronic eosinophilic leukemia, Hypereosinophilic syndrome, Imatinib, Myeloid leukemia with eosinophilia

INTRODUCTION

Hypereosinophilic syndrome (HES) is a rare hematologic disorder which is difficult to differentiate from eosinophilic leukemia on peripheral blood examination. Bone marrow (BM) examination does help in some cases, but in many cases cytogenetic or molecular testing is required for confirmation of diagnosis. Other case is acute myeloid leukemia with eosinophilia (AMLEo) in which immature and abnormal eosinophilic precursors noted in BM aspiration smears. BM biopsy section showed plenty of eosinophils. In the second case, there was a dilemma that should we ignore or emphasize the presence of significant eosinophilia in bone marrow of this patient of acute myeloid leukemia. Here we stand in a need of reviewing the current concepts in the pathogenesis of eosinophilia associated leukemias.

Case History

Case report 1

A 40 year old woman presented with skin manifestation like livedoreticularis and cardiomyopathy. Patient had unexplained hyperosinophilia for more than 5 months duration. On peripheral blood smears, eosinophils were more than 60% and total leucocyte count was 25,900/ cumm, but blast cells were not found. [Figure1].

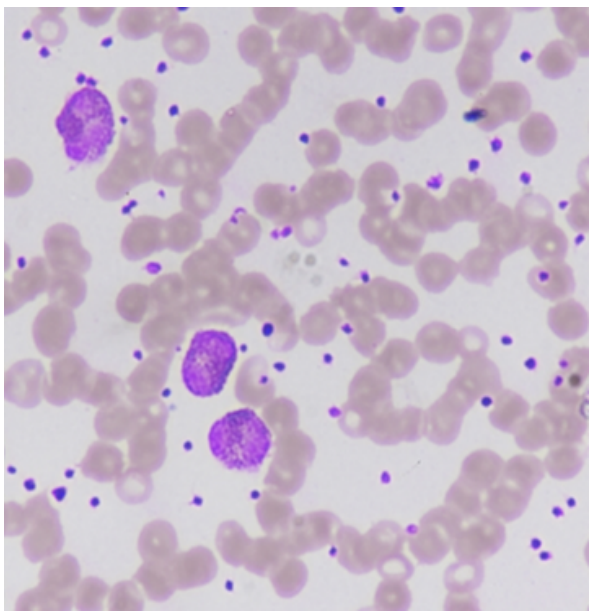

Figure 1 - Hypereosinophilic syndrome: Eosinophils in peripheral blood smear (x400, Leishman stain)

Bone marrow examination revealed eosinophils and their precursors were upto 9.5%, and blast were upto 2% [Figure 2 and 3]

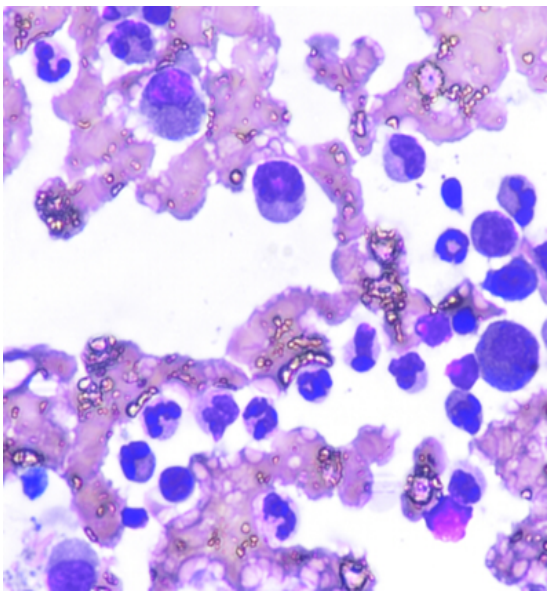

Figure 2- Hypereosinophilic syndrome: Bone marrow aspiration smear (x400, MGG)

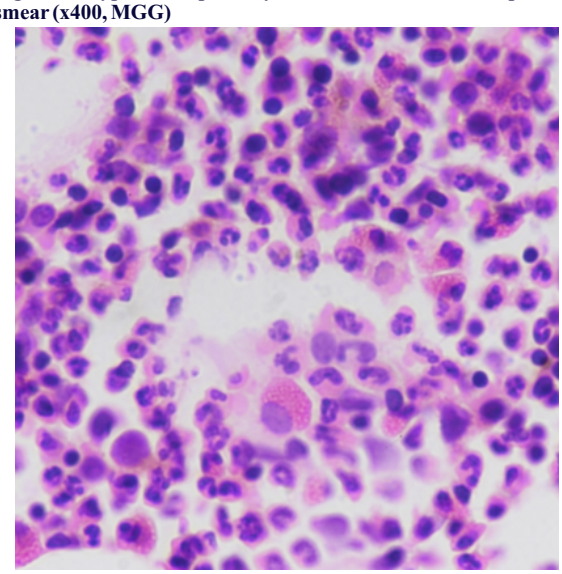

Figure 3- Hypereosinophilic syndrome: Bone marrow biopsy section show increased number of eosinophils (x400, H& E).

Based on these findings a diagnosis of idiopathic hypereosinophilic syndrome was made. Cytogenetic analysis was done to exclude chronic eosinophilic leukaemia, viz. PDGFRA which was negative. On follow up she was on Imatinib therapy and was responding well to therapy.

Case report 2

An 11 year old male patient presented with a progressive fatiguability, intermittent fever and loss of appetite since 1 month and petechial rash since 1 week. He was apparently asymptomatic 6 months back. On examination patient was pale with no organomegaly or lymphadenopathy. Complete blood count revealed anaemia (Hb-9gm/dl) and thrombocytopenia (Platelet count-36,000/cumm) with normal total leucocyte count (9,430/cumm), however the peripheral blood smear examination revealed 65% blasts consistent with acute myeloid leukemia. Bone marrow aspiration showed 56% blasts and the eosinophils with its precursors about 7.0% which included a few immature forms [Figure 4].

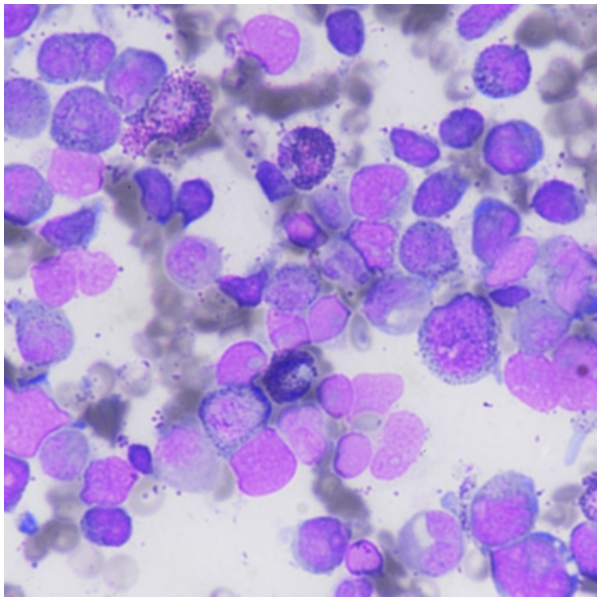

Figure 4- Acute myeloid leukemia with eosinophilia: Increased number of blasts and eosinophilic precursors in bone marrow aspiration smear (x400, MGG)

Bone marrow biopsy section showed many eosinophils along with blast[Figure 5 and figure 6].

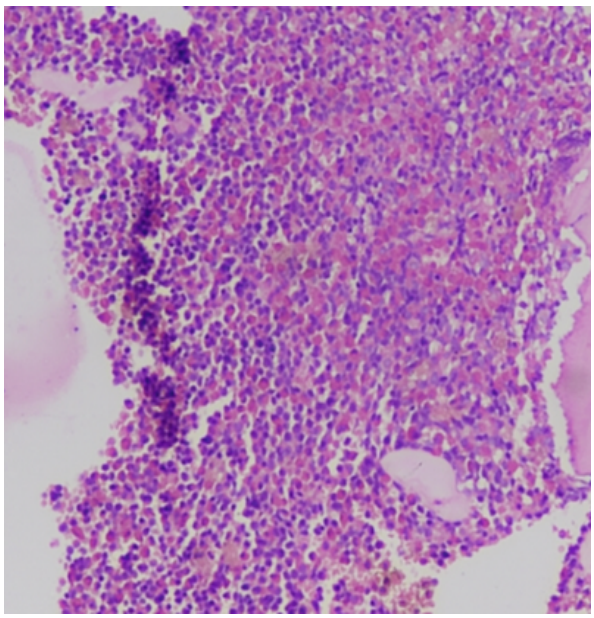

Figure 5- Acute myeloid leukemia with eosinophilia: bone marrow biopsy section (x100, H& E)

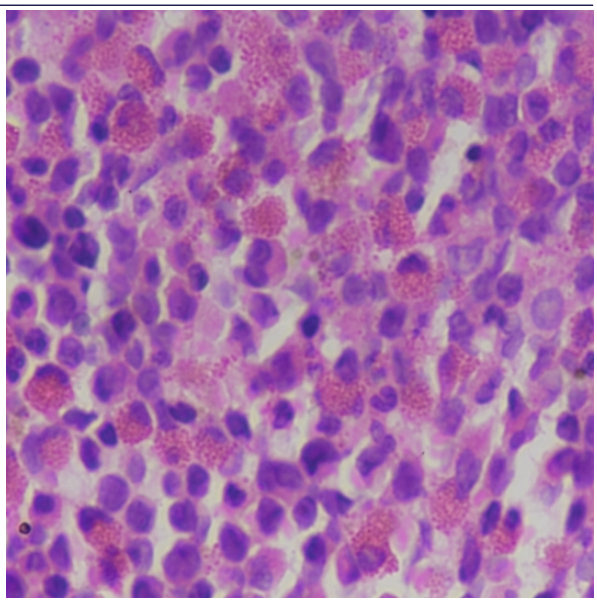

Figure 6- Acute myeloid leukemia with eosinophilia: bone marrow biopsy section (x400, H& E)

Flow-cytometry revealed blast cells expressed CD45, CD19, CD56, CD13, CD33, CD117, CD34, HLA DR, and the diagnosis was acute myelogenous leukemia with CD19 and D56 co-expression. Unfortunately, cytogenetics of this patient was not done.

DISCUSSION

Based on these two cases, we review the recent literature about current concepts of hematological disorders presenting with eosinophilia and significance of Imatinib therapy in eosinophilia. In HES, peripheral blood eosinophilia count is > 1500/ul for > 6 months and occurs in the absence of other causes of eosinophilia, viz. allergies, parasitic infections and immune dysregulation.[1],[2],[3] Total leucocyte counts in peripheral blood are usually less than 25,000/uL and bone marrow showing increased eosinophils ranging from 30 to 60%, with or without myeloblasts.[2] The prevalence of the syndrome is not clearly known. HES predominantly affects males, with an estimated male-to-female ratio ranging up to 9:1.[3] Cardiopulmonary and neurologic dysfunction are the predominant causes of illness and death.[1], [2], [3] The basic cause of organ damage in HES is due to release of eosinophil-derived neurotoxin and major basic protein by eosinophils, which causes endothelial damage promoting fibrosis, thrombosis and infarction. [5] Though bone marrow examination is mandatory to differentiate between HES and CEL, routine immunophenotyping may also need, but cytogenetics can help to confirm the diagnosis in some cases.[2], [6] On follow-up, this patient was found responding to imatinib despite negative cytogenetic test for PDGFR beta, although imatinib is less effective in PDGFR beta negative patients. Thus imatinib can be started with or without availability of molecular findings, in the appropriate clinical context.[3] Investigations like FISH or nested RT-PCR and cytogenetic analysis should be performed to exclude a possibility of underlying lymphoma or the lymphocytic variant of hypereosinophilic syndrome. Reactive eosinophilia can occur in B-cell and T-cell lymphoproliferative disorders.[3] In these disorders, eosinophilia is said to be primary when eosinophils are part of the neoplastic clone. To rule out differential diagnosis like chronic eosinophilic leukemia or systemic mastocytosis, serum tryptase estimation should be performed.[3] However serum tryptase estimation was not done in this case.

Allogenic hematopoietic stem cell transplantation (HSCT) has been found to provide prolonged remission in a debilitating HES. In upto 10 -20% cases of chronic eosinophilic leukemia (CEL), the FIP1L1 fusion gene and related cytogenetic surrogate CHIC2 deletion by FISH is detected, but in the remaining 80 to 90% cases it is really difficult to diagnose. In such cases a trial of imatinib therapy may be offered.[3]

In patients with eosinophilic leukemia or other myeloid neoplasm, eosinophils can be immature and they may display atypical morphology but not always on MGG or Wright-Giemsa stained aspirate smear.[5] Here the question was whether eosinophilia and eosinophilia with morphologically atypical eosinophils and/or its

precursors in cases of AML has any prognostic significance.[7]

Eosinophils in patients with myeloid or stem cell derived neoplasm usually belong to the malignant clone.[3],[8],[9] But exclusion of an abnormal T-cell population with abnormal cytokine production is need to be excluded.[2] Sometimes AML-Eo may represent transformation of a myeloproliferative neoplasm (MPN) with rearrangement of PDGFRA, PDGFRB or FGFR1. [3] PDGFRA translocation in AML shows very good response to imatinib therapy. But in many instances such PDGFRA associated AML present with other concurrent cytogenetic abnormalities which shows imatinib resistance.[3]

Cases with FGFR1 rearrangement or with another rare translocation viz. ETV6-ABL1, shows an aggressive clinical course and limited response to imatinib.[5],[7],[10] Unfortunately in our case cytogenetic study was not available as is true in several resource limited centres.

Further studies with bigger cohorts are needed to establish better cut offs in eosinophil counts, clinical parameters which could be surrogate markers of an underlying leukemia. CEL is important to differentiate as it can develop later into acute myeloid leukemia, so such cases may require long term follow-up. In leukemia with hypereosinophilia, molecular studies may be indicated for early and appropriate treatment.

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