Persistent Eosinophilia: A Diagnostic Dilemma

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ABSTRACT

Chronic eosinophilic leukaemia-not otherwise specified (CEL-NOS) is a myeloproliferative neoplasm associated with an autonomous, clonal proliferation of eosinophilic precursors resulting in persistent eosinophilia.

A 50-year-old female presented with easy fatigability, cough and generalised swelling of the body. Investigations revealed anaemia with leucocytosis (56.150 x 10^3/ul) and 88% eosinophils (absolute eosinophil count was 49412/ul). Peripheral smear showed abnormal eosinophils exhibiting abnormal granulation and nuclear lobation. Reactive causes were ruled out and a bone marrow aspiration/biopsy revealed mildly hypercellular marrow with increased number of eosinophils and their precursors, 7% blasts along with dysplastic megakaryocytes - hypolobated and occasional segmented forms. Molecular studies including chromosomal and gene analysis were done. A combination of the clinical picture, laboratory and molecular studies led us to a diagnosis of CEL-NOS.

The causes for eosinophilia are myriad and range from reactive causes like parasitic infestations to neoplasms in which eosinophils are a part of the neoplastic population/ are cytokine-mediated reactive component in the background of another neoplasm.

The incidence of CEL-NOS is obscure due to significant overlap with Idiopathic Hypereosinophilic eosinophilia (IHES). While CEL-NOS is a myeloproliferative neoplasm and its diagnosis can be made provided evidence of a clonality is present, IHES is a diagnosis of exclusion. It is important to differentiate the two entities as they carry different prognosis and modes of treatment.

Keywords: Eosinophilia, Chronic Eosinophilic Leukaemia, Idiopathic Hypereosinophilic Syndrome.

Introduction

Chronic eosinophilic leukemia is a myeloproliferative neoplasm characterized by clonal expansion of eosinophilic precursors resulting in persistently elevated numbers of eosinophils in the bone marrow, peripheral blood as well as tissues. The diagnosis of CEL depends on criteria that relies heavily on cytogenetics and molecular studies put forward in the WHO fascicle after ruling out causes of secondary eosinophilia. In the absence of such evidence, the diagnosis of IHES may be made, which is a diagnosis of exclusion.

Case Report

A 50-year-old female presented with easy fatigability, cough and generalised swelling of the body of 15 days duration. She had history of intermittent skin rashes over sun exposed areas, and two episodes of loss of consciousness following hot water bath.

General examination showed pallor with bilateral pitting edema of upper and lower limbs. There was generalised thickening of the skin which was particularly prominent over the lower back. Features of dermographism was also present.

Routine blood investigations showed haemoglobin of 8.9 g/dl, with a total leucocyte count of 56.150 x 10^3/ul with 88% eosinophils (the absolute eosinophil count being 49412/ul) and the erythrocyte sedimentation rate (ESR) was raised (106mm in the first hour). The peripheral smear showed absolute eosinophilia with a few abnormal eosinophils exhibiting abnormal granulation and nuclear lobation (Fig 1), blood smears did not reveal any haemoparasites. Urinalysis and stool examination were unremarkable. IgE was found to be raised (781 IU/ml), however anti-nuclear antibodies and alpha-1-antitrypsin were within normal limits. Serology for HIV, HBsAg and VDRL were non-reactive. The conditions associated with secondary eosinophilia were ruled out.

Ultrasonography of the abdomen revealed mild splenomegaly, and HRCT of the thorax showed cardiomegaly with a thin rim of pericardial effusion while echocardiogram showed right atrial, right ventricular and IVC dilatation.

Bone marrow aspiration revealed increased number of eosinophils and their precursors along with 7% blasts (Figs 2&3) and biopsy (Fig 4) showed mildly hypercellular marrow and abnormal megakaryocyte clustering along
with dysplastic megakaryocytes (Fig 4) showing hypolobation and occasional segmented forms (pawn ball megakaryocytes).

In view of the aforementioned findings, molecular studies were done. Chromosomal analysis was interpreted as 'normal female karyotype’, and FISH was negative for PDGFRA deletion/rearrangement. Gene analysis for BCR-ABL fusion transcripts, JAK2 (exons 12 and 14), MPL (exon 10) and CALR (exon 9) were found to be negative, as were evidence of monoclonal B-cell or T-cell population.

Thus, a diagnosis of CEL-NOS was made based on clinical, laboratory and molecular studies.

Discussion

The general consensus for the upper limit of absolute eosinophil count is $0.5 \times 10^9/l$. Essentially, the severity of eosinophilia has been divided into mild, moderate and severe with the AEC being $0.5-1.5 \times 10^9/l$, $1.5-5 \times 10^9/l$ and $>5 \times 10^9/l$ respectively. Abnormal accumulation of eosinophils can have profound and deleterious effects on health by end organ damage due to eosinophil activation and release of various cytokines.

Eosinophilia has been broadly classified into familial and acquired. Familial eosinophilia is an autosomal dominant disorder characterised by eosinophilia that may result in...
end organ damage in some affected family members. An underlying genetic defect is rarely responsible for eosinophil activation. Acquired eosinophilia is classified into secondary (reactive causes), primary (clonal) and idiopathic including hypereosinophilic syndrome.

The path to working up patients with hypereosinophilia is arduous, requiring a number of tests to arrive at an accurate diagnosis. A systematic approach with the patients' presenting features serving as a guide would be pragmatic. A detailed history including drugs, travel history and allergies is mandatory, as many studies implicate intake of herbal medication in eosinophilia. Various parasites such as Strongyloides stercoralis, Ankylostoma duodenale, Schistosoma species etc may cause eosinophilia and must be ruled out. A diagnosis of CEL can be made if there is evidence of clonality or increased blasts in the peripheral blood/bone marrow, while IHES is a diagnosis of exclusion.

The current WHO guidelines gives weightage to cytogenetic and molecular studies as its primary criteria without a definite outline for morphologic criteria. This becomes problematic especially in cases of CEL without proof of clonality in whom a false diagnosis of Idiopathic HES may be made according to the current guidelines.

An update to this classification was formulated in 2011 at The Working Conference on Eosinophil Disorders and Syndromes in Vienna, Austria. Essentially, a multidisciplinary team proposed new definitions and criteria in the hope that it might streamline the current WHO guidelines. More emphasis was given on histomorphology, as many cases tend to fall in the grey zone between CEL and IHES as the diagnosis is based primarily and solely on cytogenetics and molecular studies.

Wang et al studied 139 patients diagnosed with CEL (n=17) and IHES (n=122), and found that 16/17 (94%) cases with CEL and 24/122 (20%) cases with IHES had abnormal bone marrow morphology. They assessed the bone marrow for cellularity, morphology and numbers of all lineages, myeloid: erythroid ratio and fibrosis, and concluded that the most common aberrations were hypercellularity, abnormal eosinophils, abnormal megakaryocytes, elevated myeloid: erythroid ratio (>10), fibrosis (moderate to marked), dysgranulopoiesis and dyserythropoiesis.

**Conclusion**

We present this case report of chronic eosinophilic leukemia as an attempt to highlight the arduous process of working up a patient with hypereosinophilia. A systematic and thorough evaluation, including a detailed history, clinical examination and laboratory investigations will aid in coming to an accurate diagnosis as it is important to differentiate between chronic eosinophilic leukemia and hypereosinophilic syndrome, as they confer different therapeutic and prognostic implications.

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**Competing Interests**

The authors declare that they have no competing interests.

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