International Journal of Allied Medical Sciences and Clinical Research (IJAMSCR)

ISSN:2347-6567

*IJAMSCR |Volume 5 | Issue 1 | Jan - Mar - 2017*
**www.ijamscr.com**

*Review article* *Medical research*

# Chronic eosinophilic leukemia – Not otherwise specified with literature review

**Sohaila Fatima[1]*, Wajih Ahmed Siddiqui[2] and AbdulRahman Alshehri[3]**

*1 Department of Pathology, King Khalid University, Abha KSA*
*[2, 3]Department of Internal Medicine, Hemato-Oncology unit, Aseer Central Hospital, Abha KSA.*
***Corresponding Author**: **Sohaila Fatima***
**Email id**: **sohailafatima@gmail.com**

## ABSTRACT

Chronic eosinophilic leukemia−not otherwise specified (CEL−NOS) is a rare disorder with hypereosinophilia and an increased number of blood or bone marrow blasts (<20%) or an evidence of eosinophilic clonality. It constitutes a new entity in the 2008 revised World Health Organization classification (WHO). We report a case of CEL−NOS in an 18 year old male who presented with extensive thromboembolism.

**Keywords:** *CEL-NOS, HES, Thrombosis.*

## INTRODUCTION

Chronic eosinophilic leukemia−not otherwise specified (CEL−NOS) is a rare hematological malignancy and is put in the category of myeloproliferative neoplasms under revised WHO classification of myeloid neoplasms and acute leukemia. [1]. It is an aggressive disorder whose true incidence is not known. Hyper eosinophilia has varied causes making diagnosis challenging and difficult at times. Secondary/reactive eosinophilia is more common than primary/neoplastic disorders .CEL-NOS which is attributed to an autonomous clonal proliferation of eosinophil precursors is quite uncommon.

## CASE REPORT

An 18 year old male presented with generalized itching, anorexia, weight loss (3 Kg) for past 6 months. He had right lower limb pain and swelling for 2 months, abdominal pain for 15 days. He was not taking any medications, had no reported allergies, no history of an infectious process. On examination the patient had right lower limb tenderness and edema. Complete blood count showed hemoglobin (Hb):148 g/L, white blood count (WBC): 104× $10^9$/L, platelets: 206 × $10^9$/L, absolute eosinophil count: 83.2 × $10^9$/L. Peripheral blood smear findings revealed marked eosinophilia(80%) with few immature forms with differential count of 80% eosinophils, 4% neutrophils, 9 % lymphocytes, 4% monocytes, 1% basophils and 2% myelocytes. Prothrombin time-13 seconds and activated partial thromboplastin time was 38 seconds. Bone marrow (BM) examination demonstrated an active marrow hypercellular for age, relative reduction of normal appearing erythroid series, myeloid hyperplasia with eosinophilic dominance ( 51%) with immature eosinophils and increased number of myeloblasts

(10%) megakaryocytes with normal lobulation and granularity.(Figure 1) BM biopsy showed similar findings with prominence of eosinophils and eosinophilic myelocytes. Cytogenetic abnormalities were not detected by conventional karyotyping, BCR/ABL rearrangement; Fip 1–like 1 platelet−derived growth factor receptor alpha (FIP1L1−PDGFR α) fusion gene and JAK2V617F mutations were negative. Biochemical parameters were within normal range. Urine and stool were negative for parasites. Ultrasonography (USG) abdomen revealed hepatomegaly and splenomegaly with a span of 12cm and 14cm respectively. USG doppler scan revealed thrombosis of right popliteal vein.(Figure 2A) Computed tomography scan revealed filling defects involving infrarenal inferior venacava extending to left femoral vein, left internal jugular vein and innominate vein. Multiple wedge shaped areas of patchy pneumonitis involving posterior segment of right lower lobe and superior lingula representing pulmonary infarcts and hypodense areas in enlarged spleen consistent with splenic infarction were visualized.(Figure 2B) Electrocardiography and echocardiography were normal. Based on history, clinical findings and investigations a diagnosis of CEL-NOS with extensive thromboembolism was made. Our patient was started on imatinib (tyrosine kinase inhibitor) 200mg once daily, pegylated interferon alfa-2a 90ug once weekly ,tinzaparin (anticoagulant) 175units/Kg/day subcutaneously, antihistaminics (loratidine, ranitidine) and his WBC count dropped to $40\times 10^{9}$/l in a week and $17.4\times 10^{9}$/l after 2 weeks and his general condition improved. He was discharged from the hospital with regular follow up advice.

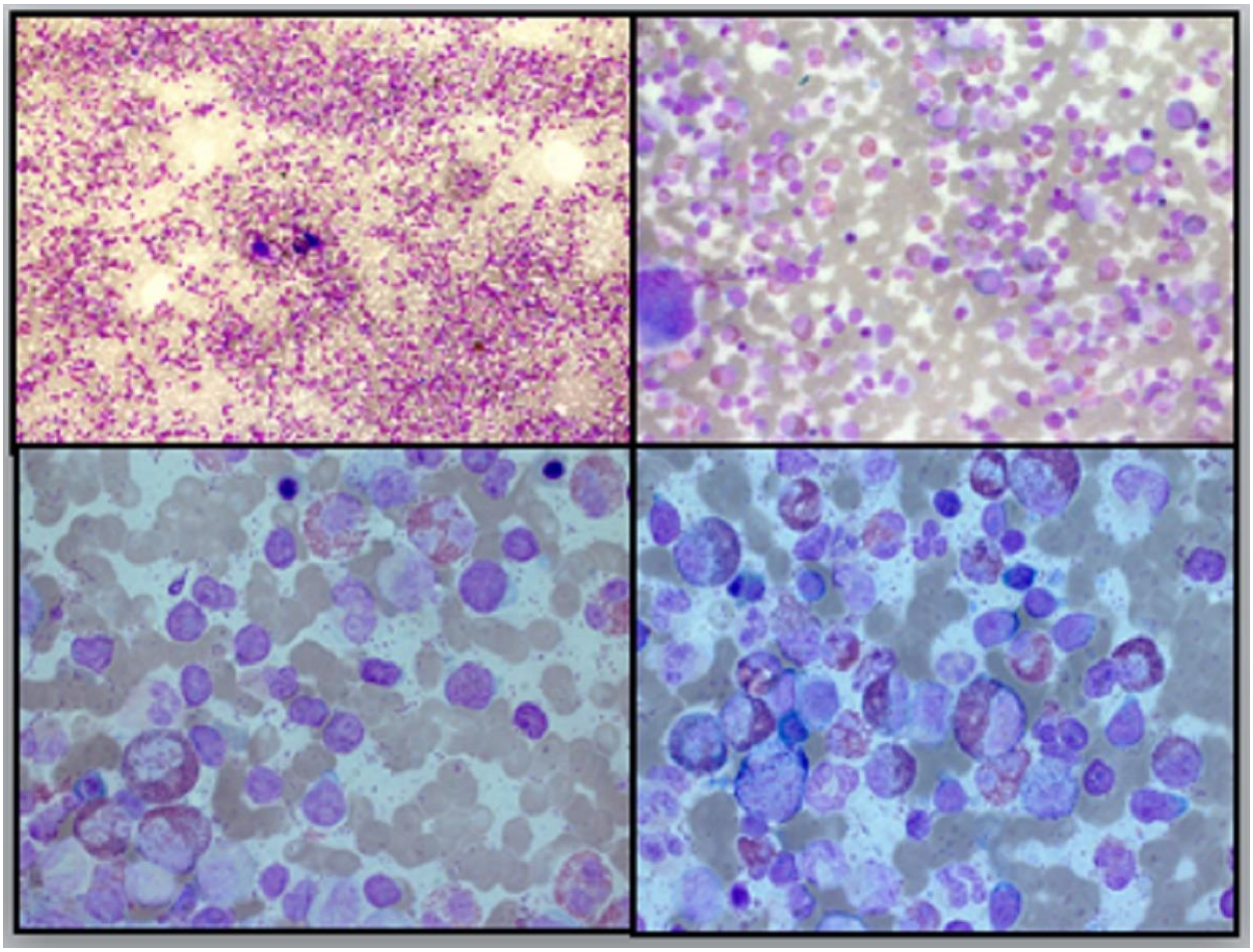

**Figure 1: Bone marrow aspirate smear showing predominance of eosinophilic precursors alongwith myeloblasts.**

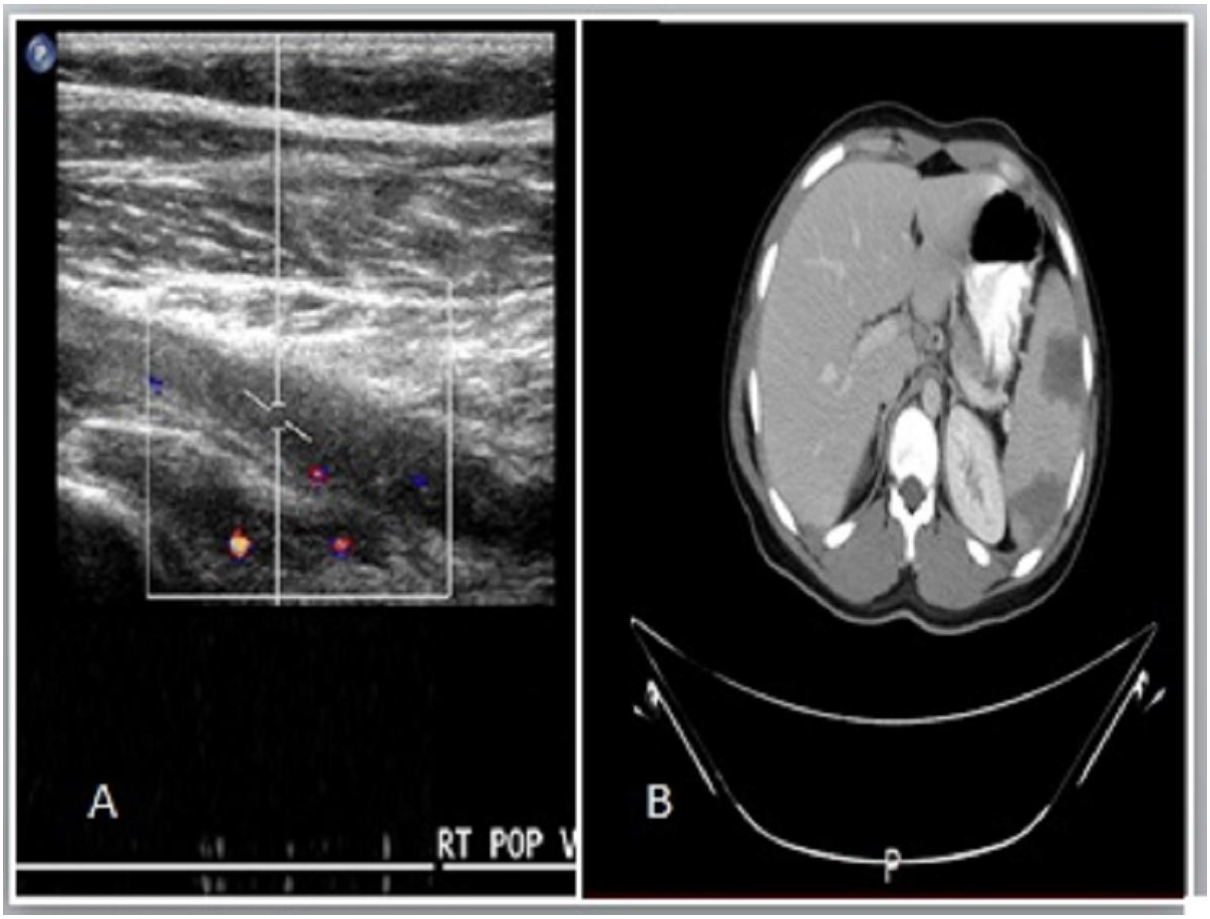


**Figure 2:A. Doppler USG of right popliteal fossa showing thrombus filling popliteal vein with absence of color filling. B.CT scan of the abdomen showing large splenic wedge shaped hypodensities consistent with splenic infarcts.**

## DISCUSSION

Eosinophilia is seen in various neoplastic and nonneoplastic (infections, hypersensitivity conditions, drug reactions, connective tissue disorders) conditions .The term "hypereosinophilic syndrome"(HES) was coined in 1968 to describe patients with prolonged eosinophilia of unknown cause. [2] It was first defined in 1975 as peripheral blood eosinophils $>1.5\times10^9$/L blood on 2 examinations (interval ≥1month), organ damage or dysfunction attributable to tissue HE and exclusion of other disorders as major reason for organ damage.[3] It could be idiopathic(no underlying cause),primary/neoplastic (underlying stem cell, myeloid or eosinophilic neoplasm) or secondary/reactive. [4] Neoplastic conditions associated with eosinophilia could be myeloid neoplasms variably chronic myeloid leukemia, other myeloproliferative neoplasms (MPNs), distinct variants of acute myeloid leukemia, rare forms of myelodysplastic syndromes (MDSs), some MDS/ MPN disorders, and a subset of patients with (advanced) systemic mastocytosis .[5]

The 2001 WHO classification system placed CEL/HES under chronic myeloproliferative disorder category of chronic myeloid neoplasms .[6 ] According to 2008 revised WHO classification CEL-NOS comes under the category of myeloproliferative neoplasms .Some cases previously diagnosed as CEL may now be put in a new subgroup, "Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1.[1] CEL-NOS is diagnosed if it fulfills criteria of eosinophil count 1.5 x $10^9$/L or greater, blasts being less than 20% in the peripheral blood and bone marrow, absence of BCR-ABL1 fusion gene and no evidence of another MPN or MDS/MPN. There should be a clonal, myeloid-related cytogenetic or molecular

genetic abnormality or blast cells should be more than 2% in the peripheral blood or 5% in the bone marrow. Cases with eosinophilia that lack evidence of clonality may be diagnosed as idiopathic HES after all causes of reactive/secondary eosinophilia have been excluded.[1] Our case fulfilled the above mentioned criteria and was diagnosed as CEL-NOS.

Eosinophils originate from CD34+ hematopoietic precursor cells. The most potent growth factors for eosinophils are IL-5, Granulocyte Monocyte-Colony Stimulating Factor, and IL-3 which are primarily produced by activated T lymphocytes, mast cells, and stromal cells. Eosinophils produce and store a number of biologically active molecules in their granules, such as eosinophil peroxidase, eosinophil cationic protein,major basic protein, and numerous cytokines, including TGF-β.Under various conditions, eosinophils are activated to release their mediators and thereby influence tissue homeostasis and integrity. In the setting of massive and persistent activation, eosinophils cause profound changes in the microenvironment often with resultant fibrosis, thrombosis or both and thus severe organ damage.[5,8] In patients with eosinophilic leukemia serious complications like endomyocardial fibrosis, thrombosis are more common. [5,7] Our patient presented with multiple life threatening thromboembolic episodes.

The estimated age-adjusted incidence rate for HES/CEL is 0.036/100,000 person-years (based on Surveillance Epidemiology and End Results data from 2001 to 2005). The median age at HES diagnosis is 52.5 years, with a male-to-female ratio ranging from 1.47 to 9.[9,10] However our patient was a young 18 year old male.

The most common genetic abnormality seen in 10–20% of all patients of primary eosinophilia results from a deletion of genetic material from chromosome 4 bringing together part of the Platelet Derived Growth Factor Receptor (PDGFR) gene and part of the FIP1L1 gene creating the FIP1L1-PDGFR alpha fusion protein which is constitutively active tyrosine kinase and can be inhibited by Imatinib and other TKIs) [11]. Other genetic abnormalities include fusions of fibroblast growth factor receptor 1 (FGFR1) or PDGFRβ, each occurring in less than 1% of patients of HES/CEL. These have been given a separate category of 'Myeloid and lymphoid neoplasms associated with eosinophilia and abnormalities of PDGFRA, PDGFRB or FGFR1 'under WHO classification [1]. So many patients who were previously diagnosed as HES/CEL are now placed in this category.

No general consensus has been reached on the ideal treatment algorithm for CEL-NOS. Due to its rarity recommendations are largely based on case reports and data extracted from the treatment of HES. CEL-NOS can be treated with a variety of modalities including glucocorticoids, hydroxyurea, interferon-α, allogeneic stem cell transplantation and TKIs. [12] Novel agents Alemtuzumab and Mepolizumab which are humanized monoclonal antibodies have been investigated and shown great promise .Alemtuzumab is an anti-CD52 antibody which acts due to the inherent expression of CD52 on eosinophils. [13] Mepolizumab binds with high affinity to IL-5 preventing it from interacting with its receptor on eosinophils. [14] Our patient was started on low dose imatinib, pegylated interferon alfa-2a and symptomatic treatment with good response.

This case highlights the role and significance of hematological parameters and cytogenetics in attaining a diagnosis of a rare disease and facilitating appropriate management in this unique subset of hematological malignancy. The patients should be placed on close regular follow up because of the aggressive nature of disease process and its transformation into acute leukemia. Further studies are needed to detect new molecular targets and novel agents that improve patient outcome.

**Conflict of interest: None**

## REFERENCES

[1]. Swerdlow S, Campo E, Harris NL, Elias Campo, Steven H. Swerdlow, Nancy L. Harris, et.al. Editors. World Health Organisation Classification of Tumours of Haematopoietic and Lymphoid Tissue. Lyon, France: International Agency for Research on Cancer; 2008.

[2]. Hardy WR, Anderson RE: The hypereosinophilic syndromes. Ann Intern Med, 68, 1968, 1220-1229.

[3]. Chusid MJ, Dale DC, West BC, Wolff SM. The hypereosinophilic syndrome: Analysis of fourteen cases with review of the literature. Medicine (Baltimore) 54, 1975, 1-27.
[4]. Valent P, Klion AD, Horny HP, Roufosse F, Gotlib J, Weller PF. Contemporary consensus proposal on criteria and classification of eosinophilic disorders and related syndromes.J Allergy Clin Immunol, 130(3), 2012, 607–612.
[5]. Valent P. Pathogenesis, classification, and therapy of eosinophilia and eosinophilic disorders. Blood Rev. 23, 2009, 157–165.
[6]. Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC; 2001.
[7]. Bain BJ, Fletcher SH. Chronic eosinophilic leukemias and the myeloproliferative variant of the hypereosinophilic syndrome. Immunol Allergy Clin North Am, 27, 2007, 377-388.
[8]. Ackerman SJ, Bochner BS. Mechanisms of eosinophilia in the pathogenesis of hypereosinophilic disorders. Immunol Allergy Clin North Am. 27, 2007, 357–375.
[9]. Crane MM, Chang CM, Kobayashi MG, Weller PF. Incidence of myeloproliferative hypereosinophilic syndrome in the United States and an estimate of all hypereosinophilic syndrome incidence. The Journal of Allergy and Clinical Immunology. 126(1), 2010, 179-181.
[10]. Roufosse FE, Goldman M, Cogan E. Hypereosinophilic syndromes. Orphanet journal of rare diseases. 2, 2007, 37.
[11]. Gotlib J, Cools J, Malone JM, Schrier SL, Gilliland DG. The FIP1L1-PDGFRalpha fusion tyrosine kinase in hypereosinophilic syndrome and chronic eosinophilic leukemia: implications for diagnosis, classification, and management. Blood. 103, 2004.
[12]. Butterfield JH, Weiler CR. Treatment of hypereosinophilic syndromes—the first 100 years. Semin Hematol.; 49(2), 2012, 182-191.
[13]. Strati P, Cortes J, Faderl S, Kantarjian H, Verstovsek S: Long-term follow-up of patients with hypereosinophilic syndrome treated with Alemtuzumab, an anti-CD52 antibody. Clin Lymphoma Myeloma Leuk .13, 2013, 287-291.
[14]. Rothenberg ME, Klion AD, Roufosse FE, Kahn JE, Weller PF, et al. Treatment of Patients with the Hypereosinophilic Syndrome with Mepolizumab; N Engl J Med 358, 2008, 1215-1228.

**How to cite this article:** Sohaila Fatima, Wajih Ahmed Siddiqui and AbdulRahman Alshehri. Chronic eosinophilic leukemia – Not otherwise specified with literature review. Int J of Allied Med Sci and Clin Res 2017; 5(1): 204-208.
**Source of Support:** Nil. **Conflict of Interest:** None declared.