

Case Report

## A Rare Case Report on Chronic Neutrophilic Leukemia with Review of Literature

Priyanka Gupta<sup>1</sup>, Kishore Shaw<sup>2</sup>, Raka Hota<sup>1</sup>, Sukumar Chakravarty<sup>3</sup>

<sup>1</sup>2nd Year PG Student, Department of Pathology, Hi Tech Medical College & Hospital, Bhubaneswar, Odisha.

<sup>2</sup>Clinical Tutor, Department of Medicine, College of Medicine & JNM Hospital, Kalyani, West Bengal.

<sup>3</sup>Professor, Department of Pathology, Hi Tech Medical College & Hospital, Bhubaneswar, Odisha.

Corresponding Author: Priyanka Gupta

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### ABSTRACT

Chronic neutrophilic leukemia (CNL) is a very rare myeloproliferative neoplasm (MPN) of elderly characterized by sustained neutrophilic leucocytosis (>25000/cumm). Considering its rare entity, herein we report a case of CNL in an 80year old man who presented with dyspnoea, pleurisy and PUO. Persistent neutrophilic leukocytosis in a case of PUO in an elderly patient similar to this case can lead to a mistaken underdiagnosis. Suspicion is therefore required, to diagnose a case as CNL, if a patient presents with sustained neutrophilic leukocytosis without any underlying cause, not responding to higher antibiotics.

**Keywords:** CNL, MPN, PUO, Sustained neutrophilic leukocytosis.

### INTRODUCTION

Chronic neutrophilic leukemia is a rare chronic myeloproliferative malignancy characterized by hepatosplenomegaly, sustained neutrophilic leukocytosis, high NAP score and negative BCR-ABL1 translocation. The etiology of CNL is unknown, but association with plasma cell dyscrasias is seen in 20%-30% cases. The true incidence of CNL is not known, but based on literature survey, only 200 cases have been reported till date.

### CASE REPORT

An 80 year old male diabetic patient was referred to our hospital ICU in an unconscious state, with septic shock for 15 days duration. Clinical examination revealed enlarged firm liver (3.5 cm) and spleen was just palpable. The patient had pallor. Blood investigations showed WBC-20000/cumm, Hb-7.2 gm%, platelet couny-

1.88 lakh/cumm, DC-N88.6 L5.9 M3 E2 B0.3. The absolute neutrophil count was 17800/cumm. Polymorphs and some stab form exhibit toxic granules. Myeloblasts were not seen in peripheral smear. Biochemistry parameters revealed RBS-306mg/dl, S.Urea-53mg/dl, S.creatinine-1mg/dl and hypernatremia with S. Na-154.7 mg/dl. Blood culture was negative, but the urine culture showed candida infection. USG abdomen revealed hepatomegaly, mild splenomegaly and grade 2 prostatomegaly. Patient was given complete course of higher antibiotics empirically since blood and urine culture were negative for pathogens. But the patient's clinical condition didn't improve and there was persistent pyrexia. Follow up peripheral blood examination was done which revealed progressive leukocytosis with sustained neutrophilia without absolute or relative monocytosis, eosinophilia or basophilia. The leucocytes rose to

39000/cumm with absolute neutrophil count 34000/cumm, in spite of higher antibiotics. So he was diagnosed as a case of PUO and bone marrow study was done. Aspiration was easy and adequate and revealed hypercellular marrow. There was grossly accelerated granulopoiesis. Stab form and neutrophils constituted 70% of all myeloid cells. Megakaryocytes were normal. Marrow picture was suggestive of chronic myeloproliferative neoplasm with possibility of chronic neutrophilic variant. So, NAP score and BCR-ABL were advised. The NAP score was high, 310(normal 35-100). BCR-ABL was negative by FISH. With this history and investigations, diagnosis of CNL was made. Patient was immediately started on Hydroxyurea and Imatinib to control the blood count. Total leucocyte count came down to 13100/cumm with absolute neutrophil count of 10,073 with decrease in platelet count to 80000 within a span of one week. At present the patient's blood count and hydroxyurea dose are being monitored regularly in order to prolong his survival, but still the platelet count is fluctuating in lower range. Other cytogenetic study like "exclusion gene arrangement" could not be carried out due to poor economic condition of the patient.

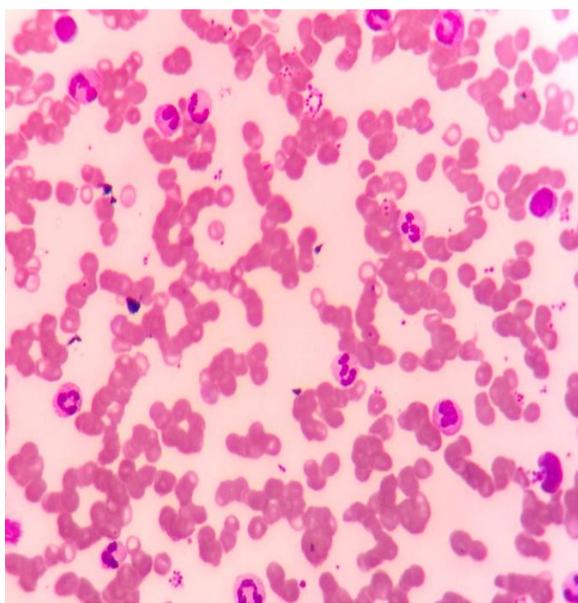


Figure 1: Peripheral blood smear showing leukocytosis with neutrophilia without left shift (Wright-Giemsa stain, 400x original magnifications).

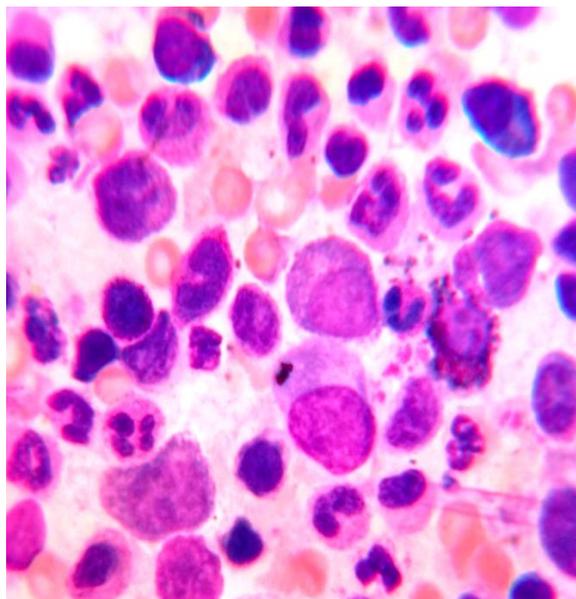


Figure 2: Bone marrow aspirate smear showing maturing granulopoiesis without increase in blasts (Wright-Giemsa stain, original magnification 1000x). The megakaryocytes are normal in morphology

## DISCUSSION

The myeloproliferative neoplasms (MPNs) include chronic myeloproliferative disorders and overlap myelodysplastic / myeloproliferative syndromes (MDS/MPNs).<sup>[1]</sup> Both MPNs and overlap MDS/MPNs are clonal neoplasms which show marrow hypercellularity, maturation of the specific cell lineages and organomegaly. Of the MPNs, there are four common disorders, recognized as common myelogenous leukemia (CML) with its characteristic 9; 22 translocation and BCR-ABL fusion protein, and three non-CML MPNs: Polycythemia vera (PV), Essential thrombocythemia (ET), and Primary myelofibrosis (PMF).<sup>[1]</sup>

All the three non-CML MPNs (PV, ET, PMF) show acquired point mutation in JAK2 kinase.<sup>[1]</sup> Apart from this mutation, each has specific WHO criteria for diagnosis. WHO diagnostic criteria for PV is Hb >18.5gm/dl in men, >16.5 gm/dl in women or evidence of increased red cell volume.<sup>[1]</sup> The diagnostic criteria for PMF is atypical megakaryocytic hyperplasia, often accompanied by reticulin and/or collagen fibrosis or in absence of fibrosis, megakaryocytic atypia and marrow hypercellularity with granulocytic and erythroid hyperplasia.<sup>[1]</sup> The diagnostic

criteria for ET is sustained platelet count  $\geq 450 \times 10^9/L$ , with bone marrow biopsy showing proliferation of enlarged mature megakaryocytes, without significant increase or left shift of granulopoiesis or erythropoiesis. [1]

The MPNs also include a number of uncommon or atypical disorder like chronic eosinophilic leukemia not otherwise specified (CEL), systemic mastocytosis (SM), and chronic neutrophilic leukemia (CNL). [3]

Diagnostic criteria of CNL (WHO,2008) is WBC persistently  $\geq 25 \times 10^9/L$  with  $> 80\%$  cells being segmented neutrophils & bands without dysplasia in peripheral smear; immature granulocytes  $< 10\%$  of WBC; bone marrow demonstrates hypercellularity with increase percentage of neutrophilic granulocytes which show normal maturation pattern, no increase in blasts, and normal or left shifted megakaryocytes; hepatosplenomegaly; no Philadelphia chromosome or BCR-ABL1; no rearrangement of PDGFRA, PDGFRB, or FGFR1; no evidence of another myeloproliferative neoplasm (PV,PMF,ET); no evidence of MDS or an MDS/MPN; and either the exclusion of a physiologic neutrophilia (infection, inflammation, underlying malignancy) or molecular or cytogenetic evidence of clonality within myeloid cells. [1] Unlike CML, eosinophilia and basophilia are absent.

A variety of reactive causes like infections, inflammatory disorders and malignancies can be associated with neutrophilia. The main differential diagnosis of CNL are these reactive causes, leukamoid reactions, a CML, plasma cell dyscrasia associated neutrophilia and neutrophilic CML (CML-N). [2]

First case of CNL was reported by Tuohy in 1920 in a female patient with massive splenomegaly & neutrophilic leukocytosis. [3] CNL's leukemic nature could not be established at that time. Subsequent studies showed CNL as a variant of CML. [4] It was not recognized by

FAB classification because of its rarity. [5] The diagnostic criteria of CNL, which was basically diagnosis of exclusion was first published by 2001 WHO classification. [6] These criterias were later updated by 2008 WHO classification. It included some additional criteria, specifically the exclusion gene rearrangement of PDGFRA, PDGFRB or FGFR1. [7] Recently it has been reported, that these cases are frequently associated with oncogenetic mutation in gene for the colony stimulating factor 3 receptor (CSF3R). [8]

Based on literature survey, approximately 200 cases of CNL have been reported till date. [7] Probably  $< 40\%$  of reported cases meet the current WHO diagnostic criteria, [9] as it has been refined recently.

In majority of the cases, cytogenetic studies showed a normal karyotype. [7]

One review series reported cytogenetic abnormalities in 37% cases of CNL. [9]

“The reported abnormalities included trisomy 8, trisomy 21, deletion 11q and deletion 20q. The most frequent cytogenetic abnormality was deletion 20q.20q deletions are not specific for CNL and have been reported in other MPNs.” [2]

Since the initial discovery of the JAK2 V617F mutation, a few cases of CNL with this mutation have been published. [10,11]

## CONCLUSION

Because of infrequent incidence of CNL, similar cases should be properly and exhaustively worked out so that it will not be under diagnosed and appropriate treatment can be initiated in time.

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