# Chronic Neutrophilic Leukemia: A Rare Heterogenous Myeloproliferative Disorder

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**ABSTRACT:**

Chronic Neutrophilic Leukemia (CNL) is a rare, infrequently recognized, myeloproliferative disorder. It usually manifests as a leukemoid reaction, with mostly mature granulocytes in the peripheral blood, with rare to occasional immature forms, and sometimes with normoblasts. Because this disease entity is very rare, and because it is typically a diagnosis of exclusion, it is important for pathologists and hematologists to, be familiar with Chronic Neutrophilic Leukemia (CNL) when approaching the patient with a myeloproliferative clinical picture. Thus, the objectives of this report are: 1) to detail the clinical case of a 52 year old male patient with initial presentation of hyperleukocytosis, 2) to review the differential diagnosis of a granulocytic myeloproliferative presentation and demonstrate the laboratory and clinical criteria utilized to establish a diagnosis of CNL in this case, and 3) to briefly review the current literature on the diagnosis and treatment of CNL.

**Key-words:** Chronic neutrophilic leukemia, myeloproliferative disorder.

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## INTRODUCTION:

Chronic neutrophilic leukemia (CNL) is a rare chronic myeloproliferative disorder that presents as a sustained, mature neutrophilic leukocytosis with few or no circulating immature granulocytes.[1] The clinical manifestations also include hepatosplenomegaly, elevated leukocytic alkaline phosphatase, elevated serum vitamin B12 and serum vitamin B12 binder ("R" fraction), elevated serum uric acid[2] and absence of Philadelphia chromosome. The first case of CNL was reported by Tuohy in 1920. The term 'chronic neutrophilic leukaemia' was first used by Tanzer et al in 1964.[3] Among all reported cases, 90% have been over 60 years of age. Cytogenetic and molecular analyses are negative for the Philadelphia chromosome and its molecular counterpart, the BCR/ABL fusion gene. These features distinguish CNL from chronic myelogenous leukemia (CML), atypical chronic myeloid leukemia, and chronic myelomonocytic leukemia. It should also be differentiated from the recently described neutrophilic-CML (CML-N), in which the Philadelphia chromosome is present but is associated with a novel BCR/ABL molecular rearrangement (c3/a2 junction) that encodes for a 230 kDa fusion protein rather than the usual 210 kDa fusion protein associated with classic CML.[1] Because this disease entity is very rare, and because it is typically a diagnosis of exclusion, it is important for pathologists and hematologists to, be familiar with Chronic Neutrophilic Leukemia.

## CASE REPORT:

A 52 year old male patient presented with complaints of fatigue and lump in the

left hypochondrium region of one month duration. There was no history of pain, fever and bleeding manifestations. On general physical examination patient had palor. Abdominal examination revealed enlarged liver, about 3 cms below the costal margin, which was firm and tender. Spleen was palpable 5cms below the coastal margin. No peripheral lymphadenopathy observed. Systemic examination was within normal limits.

Hematological investigations revealed hemoglobin–9.5 GM/dl, Total Leukocyte Count–45X10$^{9}$/L. Peripheral blood smear showed normocytic normochromic anaemia with a Differential Count of Polymorphs-88%, Lymphocytes-06%, Eosinophils-015, Basophils-01%, Myelocytes-02%, Meta-myelocytes-02%. No toxic granules were present. Platelets were within normal limits. No abnormal cells were observed. Elevated leukocytic alkaline phosphatase was seen-340 (control 180).

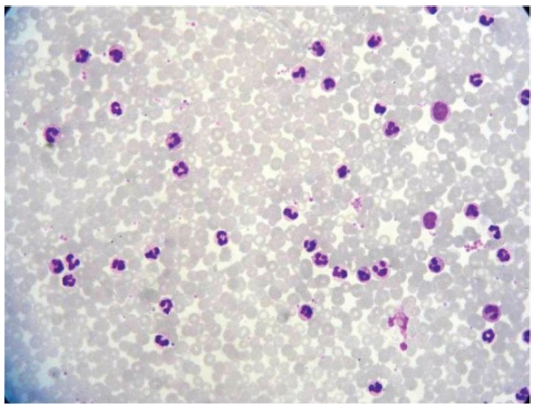

**Fig-1: Peripheral blood film showing increased number of neutrophils**

Bone marrow examination showed hypercellular marrow with increased M:E ratio of 15:1. Myeloid series revealed a marked degree of myeloid hyperplasia with more than 80% of the segmented forms along with the few immature myeloid cells.

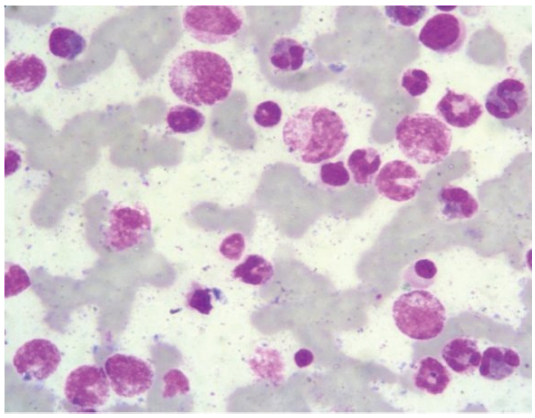

**Fig-2: Bone marrow aspirate showing shift to left in myeloid series**

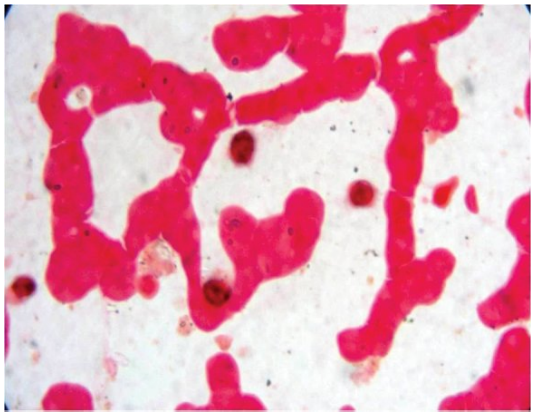

**Fig-3: Elevated leukocytic alkaline phosphatase**

No dysplastic changes were observed in myeloid series. Erythroid series showed normoblastic maturation. Megakaryocytes were normal in number and morphology. Iron staining showed normal to increased in iron storage. Diagnosis of myeloid hyperplasia with increased iron stores was made. The patient was treated with antibiotics, but did not respond to the treatment and presented with the same complaints. The patient was reevaluated after a chromosomal analysis revealing the absence of Philadelphia chromosome (Ph), which suggested a chronic myelo-proliferative disorder with the likely possibility of chronic neutrophilic leukemia. Then the patient was put on chemotherapeutic agents. The patient responded well and is on regular follow up.

**DISCUSSION:**

Chronic neutrophilic leukemia has been reported as a rare entity characterized by persistent mature neutrophilia in association with hepatosplenomegaly, elevated serum B12 levels, hyperuricaemia and raised alkaline phosphatase. There should be no dysplasia or striking reticulin fibrosis. These together with absence of basophilia, monocytosis and absence of bcr-abl transcript define the disease. WHO classification of haematopoeitic malignancies has identified chronic neutophilic leukemia as a distinct entity.[4] It's a disease of the elderly. The clinical presentation of an elderly male with hyperleukocytosis consisting primarily of mature neutrophils was most consistent with a myeloproliferative neoplasm and was at first highly suspicious for CML.[5] Several morphologic features argued against this representing CML at the time of bone marrow biopsy, namely: 1) the vast majority of megakaryocytes showed normal morphology as opposed to the micromegakaryocytes characteristic of CML, 2) there was an absence of basophilia and intermediate and less mature myeloid forms in the peripheral blood as would be expected in CML, and 3) there was no evidence of increased cell turnover in the form of sea-blue histiocytes as is typically seen in CML. Finally, in the absence of the Philadelphia chromosome and BCR-ABL1 fusion transcript, the diagnosis of CML is highly unlikely.

Low serum G-CSF levels have been documented by a number of groups, suggesting that the neoplastic granulopoiesis can exert a suppressor effect on G-CSF synthesis. Interestingly, CML patients, in contrast to those with CNL, invariably have low LAP scores and yet both disorders have a significantly low G-CSF levels. It would seem therefore that, while serum G-CSF may be an important cause, it is unlikely to be the sole reason for the induction and/or stabilization of LAP activity. Neutrophil function can be elevated, as defined by increased phagocytosis, superoxide production and nitroblue tetrazolium (NBT) reduction activity, although paradoxically intracellular bactericidal activity may be reduced.[3] Most patients are not anaemic or thrombocytopenic at presentation but have peripheral leucocytosis with predominant segmented and band cells. Serum vitamin B12 and uric acid levels are usually increased and they have high neutrophilic alkaline phosphatase. Bone marrow biopsies reveal hypercellular marrow with marked neutrophilic proliferation with no unusual distribution pattern.[4] Cytogenetic abnormalities include trisomy 8, trisomy 21, del (20q) and t (1;20). Familial occurrence of chronic neutrophilic leukemia has also been reported. Transformation to acute leukemia is common and seen in 20% of patients. Death is usually due to cerebral haemorrhage, blastic transformation or fulminant infection.[6] Differential diagnosis includes reactive leukocytosis, leukemoid reaction, chronic myeloid leukemia, other chronic myeloproliferative disorders and myelodysplastic syndromes. Chemo-therapeutic agents, such as hydroxyurea, may temporarily control leucocytosis and splenomegaly, and the use of interferon-α may induce long standing clinical remission. So far, allogeneic bone marrow transplantation represents the only treatment modality with curative potential.[7]

**CONCLUSION:**

Chronic neutrophilic leukemia is an uncommon chronic myeloproliferative disorder of the granulocytic lineage. It should be distinguished from other chronic processes that have a neutrophilic component, other chronic myeloproliferative disorders, and myelodysplastic syndromes, including chronic myelomonocytic leukemia. Management decisions will have to be based on reports from therapeutic strategies effective in similar chronic clonal myeloid disorders.

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