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CASE REPORT

Chronic Neutrophilic Leukemia in a 32-Year-Old Female: A Rare Discovery, Diagnostic Dilemma and Review of the Current Literature

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Abstract: Chronic neutrophilic leukemia (CNL) is a rare disease, with an annual incidence of about 1 new case per million people, a little male preponderance and a median diagnostic age of approximately 65. The disease's clinical manifestations can range from asymptomatic to extremely symptomatic, with severe splenomegaly and constitutional symptoms. Most of CNL patients succumb from disease-related complications or progress to acute myeloid leukemia, which leaves their prognosis poor. A 32-year-old female experienced heartbeat awareness for 4 months, worsening over time, with fever, headache, dizziness, joint stiffness, pain, reduced joint movement, and body weakness. After initial evaluation and investigations, a diagnosis of CNL was reached with differential diagnoses of reactive neutrophilia/leukemoid reaction, chronic myeloid leukemia (CML), neutrophilic-CML (CML-N). Clinicians should have a high index of suspicion to diagnose and differentiate them. Immediate treatment was initiated to stabilize the patient before further diagnostic workups but disease rapid progression and the impact limited diagnostic investigations on patient outcomes. Therefore, a streamlined approach to managing CNL is crucial in time-sensitive situations, as it ensures prompt accurate diagnosis and intervention.

Keywords; Chronic neutrophilic leukemia, myeloproliferative neoplasm, CSF3R-SETBP1-ASXL1, allogeneic HSCT.

1. INTRODUCTION

Chronic neutrophilic leukemia (CNL) is a potentially aggressive, myeloproliferative (MPM) disorder characterized by increased cellularity in the bone marrow involving one or more cell lines. This is often accompanied by specific somatic mutations. It has been classified among the BCR/ABL-negative myeloproliferative neoplasms. It is characterized by significant leukocytosis with absolute mature neutrophilia, neutrophils usually display toxic granulation, nuclear hyper segmentation, and an elevated leukocyte alkaline phosphatase (LAP) score (Figure **2**) (Table **1**). Also, manifestations of CNL feature a normal platelet count, absence of peripheral blood monocytosis, basophilia or eosinophilia [1]. Based on statistics from the Surveillance, Epidemiology, and End Results Program (SEER) of the National Cancer Institute for 2022, CNL is still considered a rare neoplasm, with an undetermined true incidence [2]. CNL management often involves a multidisciplinary approach, including hematologists, oncologists, other specialists and supportive care. Traditional treatments include hydroxyurea and interferon-alpha, but emerging targeted therapies, such as JAK inhibitors are promising [3]. This case report raises critical considerations

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regarding the challenges associated with rapid disease progression and the limitations of diagnostic investigations in time-sensitive situations. In this instance, the patient's clinical deterioration and subsequent demise within 36 hours post-admission emphasize the urgent need for expedited diagnostics and prompt initiation of therapeutic interventions.

Table 1. WHO diagnostic criteria for chronic neutrophilic leukemia.

1.	Peripherial blood WBC $\geq 25 \times 10^9$/L
	Segmented neutrophilis plus band forms $\geq$ 80% of WBCs
	Neutrophil precursors (promyelocytes, myelocytes, and metamyelocytes) <10% of WBC
	Myeloblasts rarely observed
	Monocyte count $<1 \times 10^9$/L
	No dysgranulopoiesis
2.	Hypercellular bone marrow
	Neutrophil granulocytes increased in percentage and number
	Neutrophil maturation appears normal
	Myelobasts <5% of nucleated cells
3	Not meeting WHO criteria for BCR-ABL1$^+$ CML, PV, ET or PMF
4	No rearrangement of PDGFRA, PDGFRB or FGFR1, or PCM1-JAK2
5	Presence of CSF3R T618I or other activating CSF3R mutation
	Or
	In the absence of a CSFR3R mutation, persistent neutrophilia (at least 3 months), splenomegaly and no identifiable cause of reactive neutrophilia including absence of a plasma cell neoplasm or, if present, demonstration of clonality of myeloid cells by cytogenetic or molecular studies
	The diagnosis of chronic neutrophilic leukemia requires all five criteria

Abbreviations: CML: chronic myeloid leukemia; ET: essential thrombocythemia; PV: polycythemia vera; PMF: primary myelofibrosis; WBC: white blood cell count; WHO: World Health Organization

2. CASE DESCRIPTION

A 32-year-old female presented at emergency medicine department (EMD) as a referral from a neighboring regional level hospital, informant was her mother and patient herself; she presented with chief complaint of heartbeat awareness for the past 4 months which was associated with gradual onset worsening with time easy fatiguability and shortness of breathing, initially on exertion but later even at rest which was accompanied by fever, headache, dizziness, generalized joint stiffness and pain, reduced joint movement and body weakness, however there was no history of convulsions or loss of consciousness. No history of cough, chest pain, drenching night sweats or history of tuberculosis contact. No history of joint swelling. The patient also reported history of abdominal pain associated with nausea, 2-3 episodes of non-projectile vomiting per day for 3 days prior to admission but no history of diarrhea or abdominal swelling. No history of abnormal per vaginal bleeding or discharge. In the course of this illness 3 weeks prior to admission she was taken to a neighboring regional level hospital, transfused 3 units of blood and referred to our setting for further evaluation and management. Past medical history; She has history of multiple hospital visits treated as urinary tract infections. 4 months prior to this admission (September 2023), she was investigated in at a referring hospital and the documented complete blood count results showed Leukocytosis of 47.16 X10^9/l with an absolute Neutrophil count of 40.08X 10^9/l, Platelets 303 x 10^9/L, Haemoglobin of 12.0g/dl (Table **2**), blood and urine for culture revealed no bacteria growth. She was then treated symptomatically where constitution symptoms temporarily subsided. No history of surgery, no known food or drug allergy. Family and social history; She is the first born in family of 4 children, the siblings are alive and well. She is housewife with two kids. No history of hereditary diseases in the family. The rest of the history was unremarkable. Physical examination on admission; She was ill looking young

woman, drowsy, cachectic, conscious – oriented to people, place and time, afebrile, dyspneic at rest, tachycardic, conjunctiva and pale skin mucosa, no rash, no subcutaneous bleeding or ecchymosis, not jaundiced, not cyanosed and no palpable lymphadenopathy. With some dehydration and generalized severe joints tenderness. Vital signs; Blood pressure 79/61mmHg MAP 65, Pulse rate 109 beats per minute, Respiratory rate 39 breath per minute, SpO2 85% on room air. Cardiovascular system; Warm extremities, cap refill 2 secs, thread pulse, regular-regular, non-collapsing, synchronized with the contralateral limb, no JVD, but had precordial hyperactivity, apex beat located in 5th intercoastal space along the left midclavicular line, heart sounds 1 and 2 heard with no murmur. Per abdomen; scaphoid abdomen moved with respiration, no hepatomegaly but spleen was palpable 4 cm below left costal margin. Relevant investigations were completed after admission and the findings comprised the following: Complete blood count revealed Leukocytosis of 90.25 X10^9/l with an absolute Neutrophil count of 83.66 X 10^9/l, Platelets 372 x 10^9/L, Haemoglobin of 9.4 g/dl, Peripheral blood smear; Normocytic hypochromic anaemia with marked leukocytosis, marked neutrophilia band neutrophils, toxic granulated neutrophils and marked segmented neutrophils seen predominant and adequate platelets seen. Cytomorphology is suggestive of Chronic neutrophilic leukaemia (CNL). ESR 140 mm/lh, Uric acid 257.74 µmol/L, Lactate Dehydrogenase (LD) 204.23 U/l, S-Calcium total 4.32 mmol/l, S-Phosphate Inorganic 2.54 mmol/l, S-Potassium 3.18 mmol/L, S-Sodium 155.05 mmol/L, Alanine Aminotransferase (ALT) 9.13 U/l and Aspartate Transaminase (AST) 15.20 U/l (Table **2**). Routine electrocardiogram showed sinus tachycardia, abdominal pelvic ultrasound scan only showed splenomegaly. Chest X-ray report; Normal heart size, normal pulmonary vasculature, macro/micronodules scattered all over the lung fields, mixed infiltrates are also seen in the lung fields, features suggestive of Metastatic lung disease (Figure **1**). Further investigations done to rule out chronic infection were negative. Based on the clinical manifestations, physical examination and related investigations results; a possible diagnosis of chronic neutrophilic leukemia was made, with potentially confounding differential diagnoses of reactive neutrophilia/leukemoid reaction, chronic myeloid leukemia (CML), neutrophilic-CML (CML-N), MPN/myelodysplastic (MDS) overlap disorders such as atypical chronic myeloid leukemia (aCML) and chronic myelomonocytic leukaemia (CMML). Patient was immediately started on Hydroxyurea, Allopurinol tablets and hydration as supportive managements, but unfortunately while proceeding with other diagnostic workouts patient passed away within 36 hours of hospital stay (Figure **3**).

Table 2. Laboratory investigations of the patient.

Complete Blood Count	**Sep/2023**	**Jan/2024**	**Unit**	**Reference Range**
Leucocyte Count	47.16	90.25	× 10^^{9}/L	4.00 - 11.00
Erythrocyte Count	4.5	3.20	× 10^^{12}/L	4.60 - 6.50
Haemoglobin	12.0	9.4	g/dl	13.0 - 18.0
HCT	36.2	30.3	%	40.0 - 54.0
MCV	80.6	94.7	fL	80.0 - 100.0
MCH	27.1	29.4	pg	27.0 - 32.0
MCHC	33.3	31.1	g/dL	32.0 - 36.0
RDW	22	20.9	%	11.0 - 16.0
Platelet Count	303	372	× 10^^{9}/L	150 - 500
Mean Platelet Volume	10.0	9.0	um^^{3}	6.0 - 11.0
Platelet Distribution Width	12.4	16.3	%	11.0 - 18.0
Differential	**Sep/2023**	**Jan/2024**	**Unit**	**Reference Range**
Neutrophils	40.08	83.66	× 10^^{9}/l	2.00 - 6.90
Lymphocytes	3.77	4.06	× 10^^{9}/l	0.60 - 3.40
Monocytes	1.88	1.71	× 10^^{9}/l	0.00 - 0.90
Eosinophils	0.94	0.81	× 10^^{9}/l	0.00 - 0.70
ESR	140 mm/lh			0 — 29

Jan/2024

Test	Result	Reference Range
Uric Acid	257.74 µmol/L	202.30 - 416.50
S-Sodium	155.05 mmol/L	136.00 - 145.00
S-Potassium	3.18 mmol/L	3.50 - 5.10
S-Calcium total	4.32 mmol/l	2.15 - 2.55
Lactate Dehydrogenase (LD)	204.23 U/l	240.00 - 480.00
Alanine Aminotransferase (ALT)	9.13 U/l	2.00 - 41.00
Aspartate Transaminase (AST)	15.20 U/l	2.00 - 40.00
S-Phosphate Inorganic	2.54 mmol/l	0.87 - 1.45

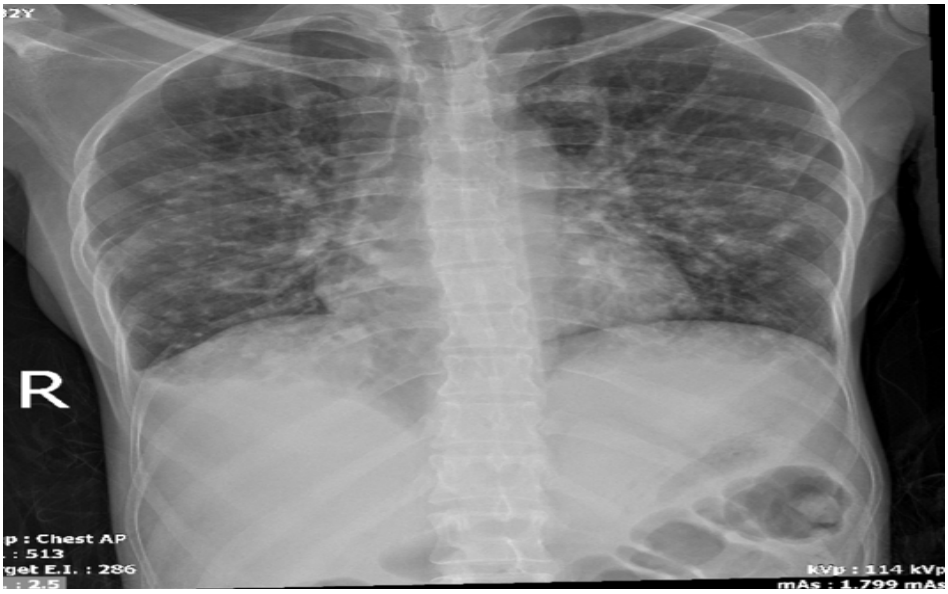

Figure 1. Chest x-ray; macro/micronodules scattered all over and mixed infiltrates in the lung fields.

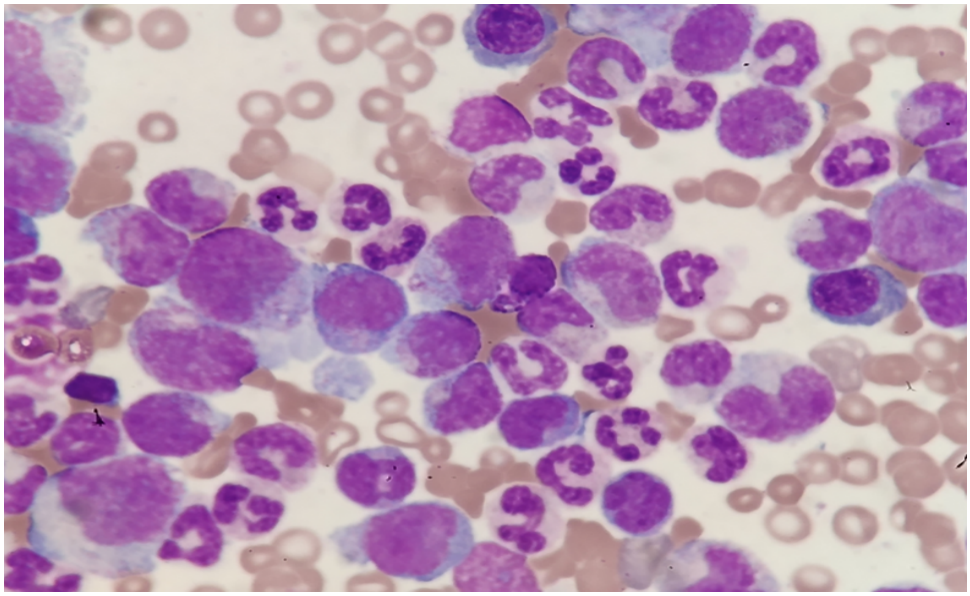

Figure 2. Leukocytosis with a predominance of mature neutrophils on a peripheral blood smear.

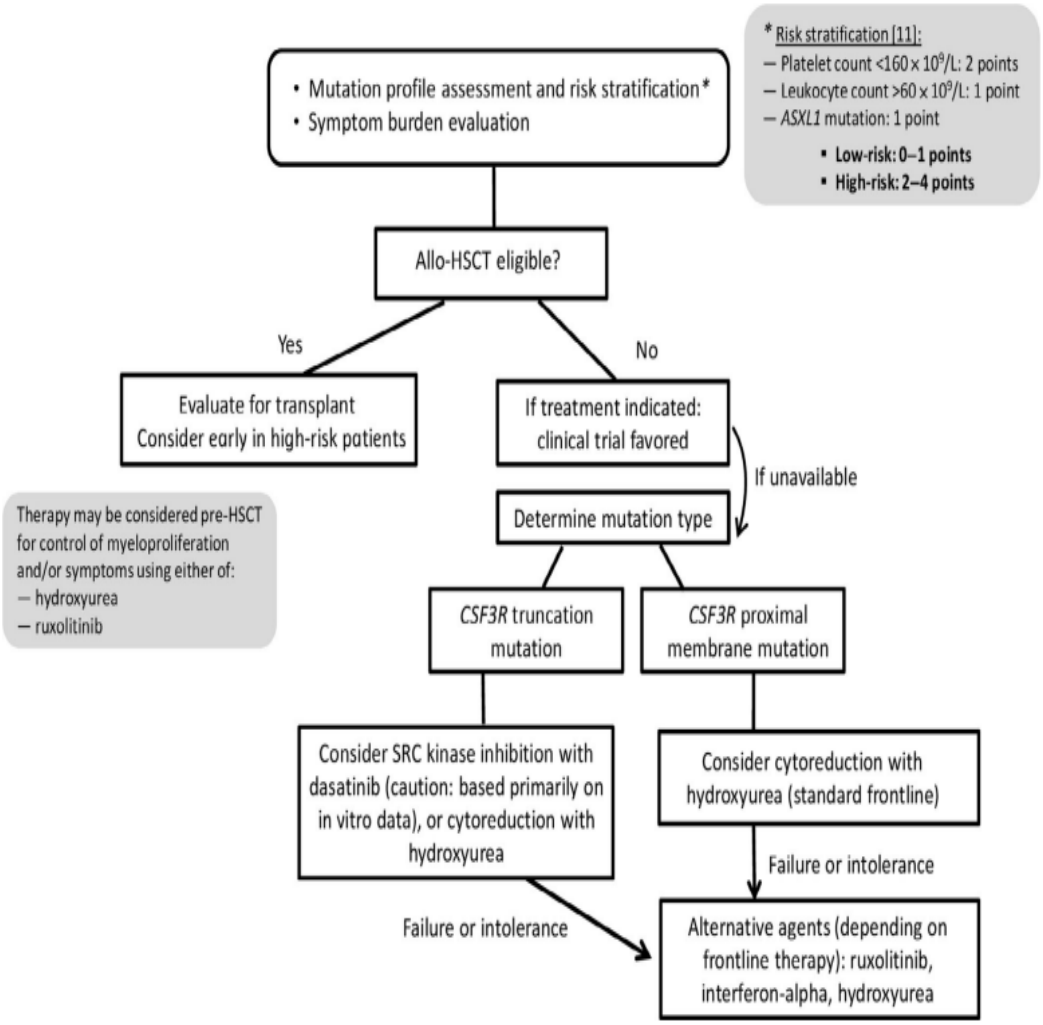

Figure 3. Algorithm for management of chronic neutrophilic leukemia. **Abbreviation:** Allo-HSCT, allogeneic hematopoietic stem cell transplant.

3. DISCUSSION

CNL was originally referred to as "polymorphonuclear neutrophil hyperleukocytosis" in 1920 [4]. There are currently about 200 CNL cases published in the literature; however, many of these cases may fail to meet the WHO's diagnostic criteria [3,5]. In the past, correct diagnosis has been significantly challenging by the absence of chromosomal markers. The WHO modified its diagnostic criteria in 2016 as a result of the recent discovery of oncogenic driver mutations in CSF3R [5-6]. Case reports and a few case series studies constitute almost all of the literature on the disease. It is yet unclear exactly the incidence and epidemiological characteristics of CNL are. There are no recognized racial or geographic distinctions. Globally, the prevalence of CNL has been quite low and hasn't been trending upward [7]. CNL generally presents as substantial enlargement of the liver and spleen, bone marrow granulocyte hyperplasia, and persistent mature neutrophils and leukocytosis in peripheral blood [7-8]. Apart from the specific symptoms, anemia, exhaustion, bleeding tendency, gout, and metabolic arthritis are also non-specific symptoms of CNL. Even the B symptoms of lymphoma, such as cutaneous itching, nocturnal sweats, and weight loss, can occur in patients with CNL [9]. When diagnosed with CNL, some patients might experience no symptoms at all. The only presentation can be an incidental neutropenia finding [7]. As of currently, there is no recognized standard of care for CNL treatment. Hydroxyurea was the first-line treatment for the majority of the patients in the literature. For patients who are not responding to first-line treatments, interferon-α,

imatinib and JAK inhibitors have been prescribed [10]. No treatment has been demonstrated to significantly increase survival, with the possible exception of HSCT, which is only available to a small percentage of eligible patients [3]. The patient in this case report was admitted to the hospital with heartbeat awareness, easy fatiguability, shortness of breath, fever, generalized joints and all limb pain and other constitutional symptoms as the primary symptoms. This shows how diverse the clinical manifestations of CNL can be. Though nonspecific, these features prompted a comprehensive diagnostic workup, considering the urgency of the case. The diagnosis of CNL requires all the five WHO 2016 revised diagnostic criteria. The decision to perform a limited set of diagnostic investigations in this patient, highlights the challenges faced in resource-constrained or time-sensitive situations. While these tests provided essential baseline information, the absence of molecular and cytogenetic analyses, including the evaluation of specific mutations such as CSF3R, SETBP1, and ASXL1, limited the depth of understanding of the disease biology.

4. IMPLICATIONS FOR FUTURE PRACTICE

In time-sensitive situations, the critical importance of a streamlined approach in managing CNL is evident, ensuring the timely and efficient diagnosis and intervention.

CONCLUSION

With a median survival of about 24 months, chronic neutrophilic leukemia is a rare but potentially fatal myeloproliferative malignancy. The rapid deterioration and death of the patient within 36 hours of admission exemplify the aggressive nature of CNL. The urgency of the clinical scenario necessitates a reconsideration of diagnostic prioritization to allow for more rapid and comprehensive assessments. In this case report time constraints have hindered the implementation of cytogenetic analysis and molecular profiling in CNL diagnosis, thereby limiting the identification of specific mutations. We have highlighted the challenges posed by the rapid progression of CNL and the impact of limited diagnostic investigations on patient outcomes. Further research and discussion are warranted to develop strategies for expedited diagnostic pathways in situations where time is of the essence, aiming to enhance the management of aggressive CNL.

AUTHOR CONTRIBUTIONS

J.H.K conceptualized the manuscript and did data curation. J.H.K wrote the first draft of the manuscript. E.W.M and K.G.K. reviewed and edited the first draft of the manuscript. J.H.K administered the project. All authors reviewed the final version of the manuscript and approved for submission. K.G.K. supervised the whole process.

DATA AVAILABILITY

Not Applicable.

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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ETHICS APPROVAL

Our institution does not require ethical approval for reporting individual cases or case series.

INFORMED CONSENT

Written informed consent was obtained from both, the patient and her mother for their anonymized information to be published in this article.

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