

Chronic neutrophilic leukemia

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ABSTRACT

Chronic neutrophilic leukemia is a rare myeloproliferative disorder characterized by a sustained peripheral blood neutrophilia, absence of the BCR/ABL oncoprotein, bone marrow hypercellularity with less than 5% myeloblasts and normal neutrophil maturation, and no dysplasia. This leukemia has been associated with mutations in the colony-stimulating factor 3 receptor (*CSF3R*) that may activate this receptor, leading to the proliferation of neutrophils that are the hallmark of chronic neutrophilic leukemia. We present a case of chronic neutrophilic leukemia and discuss the criteria for diagnosis and the significance of mutations found in this leukemia.

KEYWORDS Chronic neutrophilic leukemia; *CSF3R*; myeloproliferative disorder; *RUNX1*; *SETBP1*; *SRSF2*

CASE PRESENTATION

A 53-year-old man presented to the emergency room with abdominal pain. He was a previous smoker (50 pack-years) and stated that he had recently been experiencing night sweats. The past history was otherwise unremarkable. Blood work at the time revealed a leukocytosis of $40 \times 10^9/L$ (Figure 1a) and hyperuricemia (10.1 mg/dL). Mild splenomegaly was present. Flow cytometry detected a very small (0.1) population of kappa clonal plasma cells. A bone marrow examination showed a hypercellular (100%) marrow with granulocytic hyperplasia and numerous polymorphonuclear cells (Figures 1b and 1c). A plasma cell infiltrate was not appreciated. Subsequent lab work revealed the absence of the BCR/ABL oncoprotein but the presence of colony-stimulating factor 3 receptor (*CSF3R*) and set binding protein 1 (*SETBP1*) mutations. These findings were consistent with a diagnosis of chronic neutrophilic leukemia (CNL). The patient was started on ruxolitinib and scheduled for follow-up.

Follow-up at 1 month showed a slight drop in the white blood cell count and uric acid as well as an improvement in appetite and decrease in night sweats. A second bone marrow aspirate was still hypercellular with granulocytic hyperplasia with less than 10% immature granulocytes and no increase in blasts. A repeat mutation panel now revealed a serine/arginine-rich splicing factor 2 (*SRSF2*) mutation and a variant *RUNX1* mutation of undetermined significance. The mutations for *CSF3R* and *SETBP1* were

not detected on this analysis. The patient is currently stable with a sustained moderate leukocytosis and remains on ruxolitinib. He is being considered for a hematopoietic stem cell transplant.

DISCUSSION

In 2016, the World Health Organization classification of hematologic malignancies was updated to reflect advances in the understanding of CNL.¹ In CNL, the presence of kinase mutations that activated kinase signaling to promote the expansion of neutrophils has been incorporated into the diagnostic criteria.¹ A high prevalence of *CSF3R* is found in about 80% of cases.^{2,3} Also common are mutations in *SETBP1* (14%–50%) and various spliceosome proteins.^{2,4,5} Both *CSF3R* and *SETBP1* were found in our case, which is very supportive of a diagnosis of CNL. Patients can still be classified as having CNL in the absence of activating mutations if they meet other criteria such as neutrophilic leukocytosis $>25 \times 10^9/L$ for at least 3 months, hypercellular bone marrow with granulocytic hyperplasia and no dysplasia, splenomegaly, absence of the BCR/ABL oncoprotein, and no detectable underlying reason for a reactive neutrophilia.¹ Reactive neutrophilia has been associated with underlying plasma cell neoplasms.⁶ In the case of a plasma cell neoplasm, the diagnosis of CNL can still be made if there is evidence of myeloid cell clonality. Our case had a very minute population of clonal plasma cells (0.1%), which may be coincidental monoclonal gammopathy of undetermined significance given the tiny population

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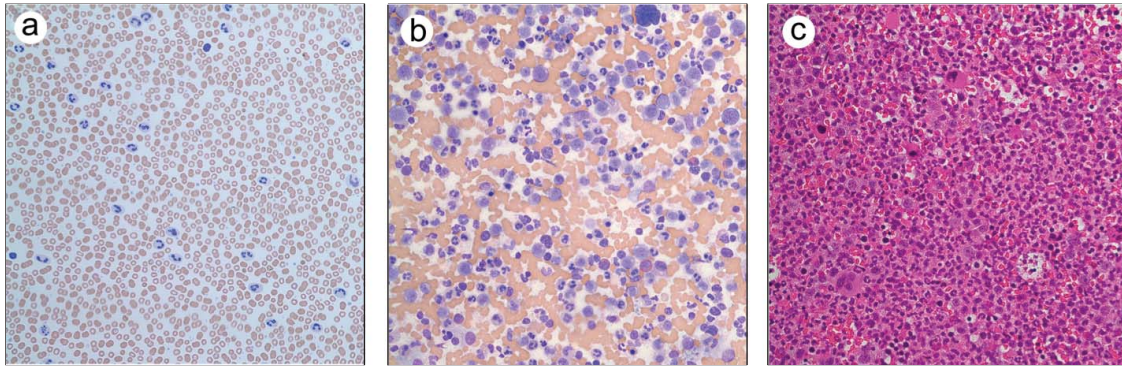


Figure 1. (a) Peripheral blood (Wrights, ×500). (b) Bone marrow aspirate (Wrights, ×500). (c) Bone marrow core biopsy (hematoxylin and eosin, ×400).

of plasma cells. Our case also had *CSF3R* and *SETBP1* mutations, which support the diagnosis of CNL. Because mutant *CSF3R* has been associated with dysregulated Janus kinase/signal transducers and activators of transcription signaling, it has been suggested that ruxolitinib may be efficacious in treating CNL, and there are some anecdotal cases suggesting some clinical benefit of ruxolitinib.^{4,5} However, there have been other cases in which a *CSF3R* mutation was present but there was no response to ruxolitinib which suggests that additional genetic events such as an *SETBP1* mutation may abrogate the response.^{7–9} It is also interesting that on the patient's last bone marrow biopsy, an *SRSF2* mutation and *RUNX1* gene variant were detected. It is known that both *SRSF2* and *RUNX1* abnormalities have been found in early stages of myelodysplastic syndromes.^{10,11} The significance of these findings remains to be seen in this patient. Further studies are necessary on the occurrence of these mutations and their interactions in CNL that will provide insight into the biogenics and therapeutic targeting of this rare but serious myeloid malignancy.

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127(20):2391–2405. doi:10.1182/blood-2016-03-643544.
2. Pardanani A, Lasho TL, Laborde RR, et al. *CSF3R* T618I is a highly prevalent and specific mutation in chronic neutrophilic leukemia. *Leukemia*. 2013;27(9):1870–1873. doi:10.1038/leu.2013.122.

3. Maxson JE, Gotlib J, Pollyea DA, et al. Oncogenic *CSF3R* mutations in chronic neutrophilic leukemia and atypical CML. *N Engl J Med*. 2013;368(19):1781–1790. doi:10.1056/NEJMoa1214514.
4. Gotlib J, Maxson JE, George TI, Tyner JW. The new genetics of chronic neutrophilic leukemia and atypical CML: implications for diagnosis and treatment. *Blood*. 2013;122(10):1707–1711. doi:10.1182/blood-2013-05-500959.
5. Cui Y, Li B, Gale RP, et al. *CSF3R*, *SETBP1* and *CALR* mutations in chronic neutrophilic leukemia. *J Hematol Oncol*. 2014;7(1):77–81. doi:10.1186/s13045-014-0077-1.
6. Dincol G, Nalcaci M, Dogan O, et al. Coexistence of chronic neutrophilic leukemia with multiple myeloma. *Leuk Lymphoma*. 2002;43(3):649–651. doi:10.1080/10428190290012218.
7. Ammatuna E, Eefting M, van Lom K, Kavelaars FG, Valk PJ, Touw IP. Atypical chronic myeloid leukemia with concomitant *CSF3R* T616I and *SETBP1* mutations unresponsive to the JAK inhibitor ruxolitinib. *Ann Hematol*. 2015;94(5):879–880. doi:10.1007/s00277-014-2272-0.
8. Lasho TL, Mims A, Elliott MA, Finke C, Pardanani A, Tefferi A. Chronic neutrophilic leukemia with concurrent *CSF3R* and *SETBP1* mutations: single colony clonality studies, in vitro sensitivity to JAK inhibitors and lack of treatment response to ruxolitinib. *Leukemia*. 2014;28(6):1363–1365. doi:10.1038/leu.2014.39.
9. Maxson JE, Tyner JW. Genomics of chronic neutrophilic leukemia. *Blood*. 2017;129(6):715–722. doi:10.1182/blood-2016-10-695981.
10. Ouyang Y, Qiao C, Chen Y, Zhang SJ. Clinical significance of *CSF3R*, *SRSF2* and *SETBP1* mutations in chronic neutrophilic leukemia and chronic myelomonocytic leukemia. *Oncotarget*. 2017;8(13):20834–20841. PMID:28209919.
11. Sood R, Kamikubo Y, Liu P. Role of *RUNX1* in hematological malignancies. *Blood*. 2017;129(15):2070–2082. doi:10.1182/blood-2016-10-687830.