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Clinical response to ruxolitinib in *CSF3R T618*-mutated chronic neutrophilic leukemia

Maximilian Stahl[1], **Mina L. Xu**[1], **David P. Steensma**[2], **Raajit Rampal**[3], **Melissa Much**[1], **Amer M Zeidan**[1]

[1]Department of Pathology, Brady Memorial Laboratory, Yale School of Medicine, 310 Cedar Street, New Haven, CT 06510, USA

[2]Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215, USA

[3]Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA

Dear Editor,

Chronic neutrophilic leukemia (CNL) is a rare myeloproliferative neoplasm (MPN) that includes only about 200 patients described to date meeting the World Health Organization (WHO) criteria and the recently reported *CSF3R* T618I mutation. Diagnosis of CNL using the World Health Organization 2008 criteria[1] requires a WBC count of ≥25 × 10^9/L, ≥80 % segmented/band neutrophils, absence of dysgranulopoiesis, exclusion of genetic drivers that are known to occur in others MPNs (such as *BCR-ABL1*, *PDGFRA/B*, or *FGFR1* rearrangements), and <10 % immature myeloid cells [2]. Previously, CNL was often confused with chronic myeloid leukemia (CML), atypical CML (aCML), or chronic myelomonocytic leukemia (CMML); however, this changed with the identification of oncogenic mutations in the granulocyte colony-stimulating 3 factor receptor (*CSF3R*) gene in approximately 83 % of WHO-defined CNL patients [3]. *CSF3R* mutations in CNL are either nonsense or frameshift mutations truncating the cytoplasmic tail (truncation mutations) or point mutations in the extracellular domain (membrane proximal mutations) [3, 4]. Truncation mutations are sensitive to dasatinib in vitro, while membrane proximal mutations show ligand-independent signaling through the JAKSTAT pathway and cells harboring this mutation are sensitive to Jak1/2 inhibitors in vitro. Additional observations from Mayo Clinic showed that concomitant *SETBP1* and *ASXL1* mutations in CNL patients with a CSF3R mutation help to further distinguish CNL from aCML and are associated with poorer outcomes [5]. There is as yet limited clinical experience with ruxolitinib in patients

Maximilian Stahl, maximilian.stahl@yale.edu.

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Mina Xu contributed in the figures, study design, data collection, and writing.
David P. Steensma contributed in the data interpretation and writing.
Raajit Rampal contributed in the data interpretation and writing.
Melissa Much contributed in the figures, study design, data collection, and writing.
Amer M Zeidan contributed in the literature search, figures, study design, data collection, data analysis, data interpretation, and writing.

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with CNL, given the low prevalence of the disease [6, 7]. After the initial case reported by Maxson et al., Dao et al. presented the case of another patient with CNL and a CSF3RT618I mutation who experienced reduction in hepatosplenomegaly and improvement in blood counts and constitutional symptoms with ruxolitinib, but there was no reduction in *CSF3R T618I* allele frequency or overall bone marrow cellularity after 3 months of treatment [6]. This argues for the inability of ruxolitinib to cytoreduce the malignant clone in the short-term. Dao et al. described a double-mutated CNL patient (*CSF3R*T618I and SETBP1 D868N) who was refractory to the treatment with both ruxolitinib and hydroxyurea both in vitro and in vivo [7]. The authors speculated that the co-expression of *SETBP1* in these CSF3R T618I mutations in a patient with CNL might have contributed to the ineffectiveness of JAK inhibitor therapy in CNL. We report the case of a patient with a *CSF3R* and SETBP1 mutation, who responded to ruxolitinib, at least for a brief period of time.

Our patient is a 76-year-old man, who presented with a new sharp intermittent left upper quadrant (LUQ) abdominal pain and fatigue without other constitutional symptoms. Complete blood count (CBC) showed a white blood cell count (WBC) of 147×10^9/L, hemoglobin (Hb) 9.7 g/dL, MCV 104, and platelet count 235×10^9/L. The differential count included 73 % neutrophils, 4 % lymphocytes, 1 % monocytes, 1 % myelocytes, 5 % promyelocytes, and 2 % blasts. Blood smear showed dysgranulopoiesis (Fig. 1a). A CBC done 7 months earlier was normal. Examination demonstrated mild LUQ tenderness without organomegaly or lymphadenopathy. Uric acid and LDH were elevated while liver enzymes and kidney function were normal. Computed tomography (CT) scan of the abdomen and pelvis showed hepatomegaly (18.4 cm) and splenomegaly 15.5 cm), which was absent on prior CT in 2012, as well as a wedge-shaped splenic hypodensity possibly representing a splenic infarct (Fig. 2a, b, c). Marrow biopsy was 100 % cellular with profound erythropoietic hypoplasia, mild myeloid dysplasia, and diffused interstitial reticulin fibrosis (Fig. 1b). No aspirate could be obtained. Flow cytometric studies of blood confirmed the majority of cells being mature neutrophils and less than 1 % of cells being CD34+ CD117+ myeloblasts. There was no increase in monocytes and no evidence for monoclonal lymphocytosis.

The patient was treated with hydroxyurea while awaiting results of florescence in situ hybridization (FISH) and polymerase chain reaction (PCR) studies for *t*(9; 22) and *BCR-ABL* fusion, respectively, which were negative. Supportive care with rasburicase, allopurinol, and fluids was administered. FISH showed three copies of chromosome 8q in 10 % of the bone marrow cells. Molecular profiling demonstrated no mutations of *CEBPA*, *NPM1*, *FLT3*, *KIT*, *JAK2*, *PDFGR*, *FGR1*, or *CALR*. CSF3R T618I mutation was present, suggestive of a diagnosis of chronic neutrophilic leukemia (CNL)[5]; *SETBP1* (SETBP1 G870S) and *ASXL1* (ASXL1 R404 and Y700) mutations, both of which have been reported to be associated with worse outcomes and resistance to JAK2 inhibitor therapy in patients with CNL, were also present [7–9]. The patient declined allogeneic stem cell transplant. Ruxolitinib was started at 5 mg twice daily and the dose increased in 5-mg increments to 20 mg twice daily (Fig. 3). On follow-up 3 months after initiation of ruxolitinib therapy, symptoms resolved, the patient was able to resume strenuous physical activity, and the CBC markedly improved (Fig. 3). Additionally, he achieved a dramatic reduction in spleen size (11.6 cm in length from previously 15.5 cm) and moderate reduction in liver size (17.6 cm in

length from previously 18.4 cm) (Fig. 2 a, b, c). Five months after initiating ruxolitinib, he lost response with increasing WBC and worsening platelet count and Hb, so hydoxyurea was added with stabilization of his WBC count (Fig. 3).

The response in our case suggests that patients with *SETBP1* mutations may respond to ruxolitinib, at least for a brief period of time. An ongoing small clinical trial is evaluating the impact of ruxolitinib on natural history of CNL (Clinicaltrial.gov NCT02092324). As ruxolitinib therapy has not been shown to change the natural history of CNL, ASCT should be considered for transplant-eligible patients with CNL.

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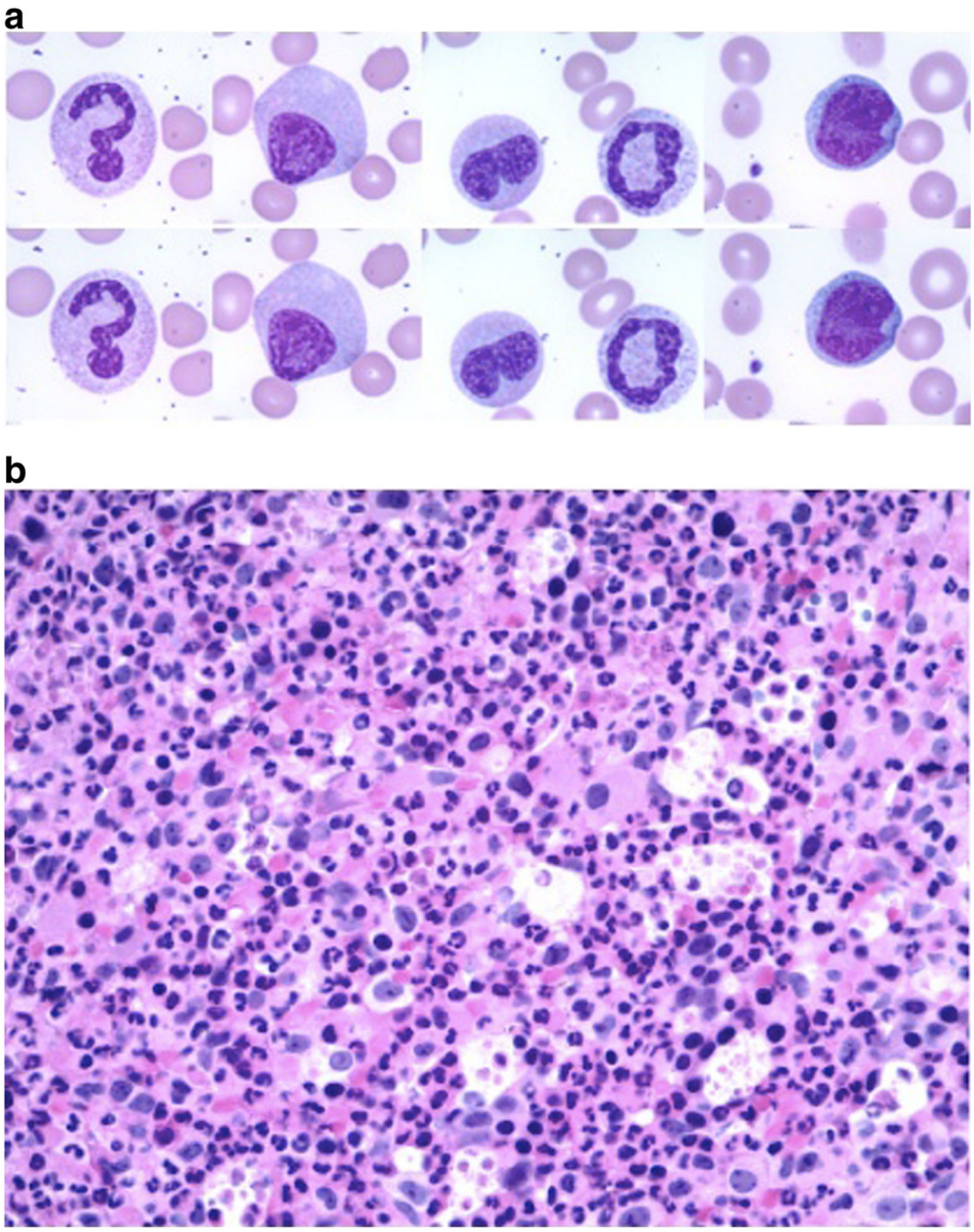

Fig. 1.

a Wright-Giemsa-stained blood smear (x400) demonstrating dysgranulopoiesis. **b** Bone marrow biopsy with myeloid hyperplasia and multilineage dysplasia (x100)

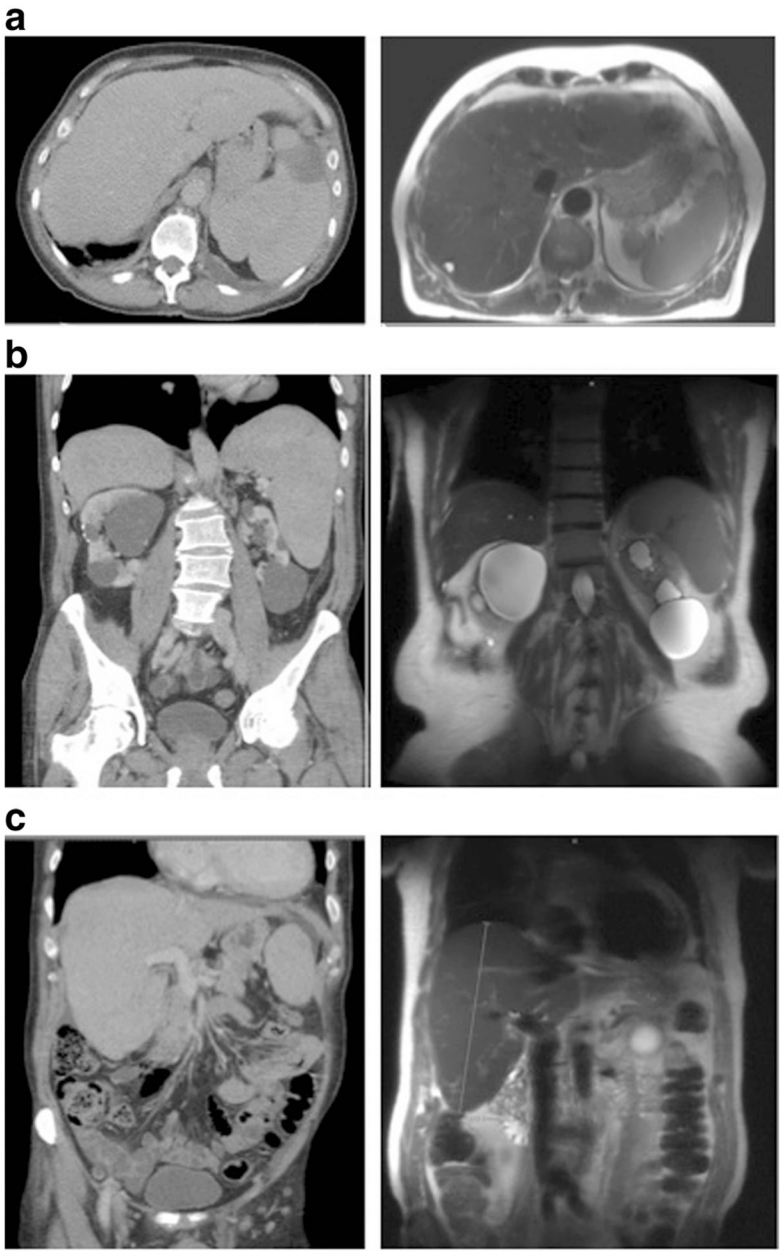

Fig. 2.

Pre- and post-ruxolitinib therapy contrast-enhanced CT scans. **a** Axial view pre- and post-treatment. **b** Coronal view splenomegaly preand post-treatment. **c** Coronal view hepatomegaly pre- and post-treatment

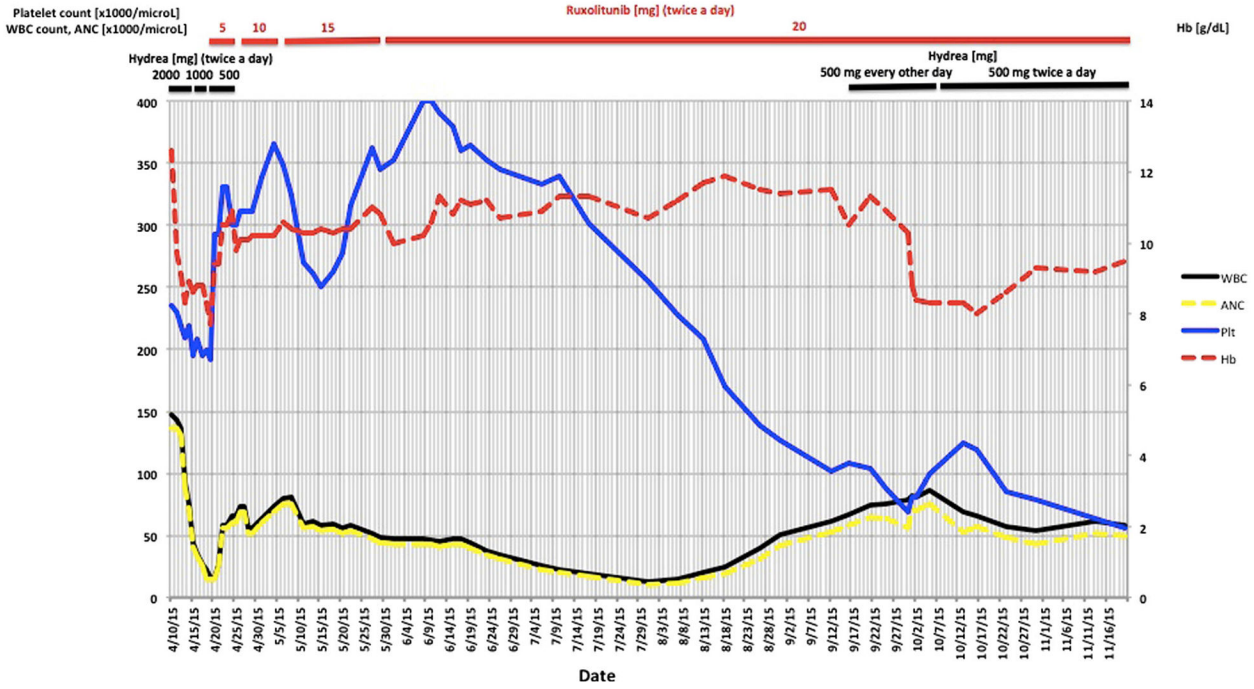

Fig. 3.

WBC, ANC, Hb, and platelet count upon presentation and during treatment with hydroxyurea and ruxolitinib