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Ammatuna, Emanuele; Eefting, Matthias; van Lom, Kirsten; Kavelaars, François F.; Valk, Peter J.M.; Touw, Ivo P.

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LETTER TO THE EDITOR

Atypical chronic myeloid leukemia with concomitant CSF3R T618I and SETBP1 mutations unresponsive to the JAK inhibitor ruxolitinib

Emanuele Ammatuna · Matthias Eefting · Kirsten van Lom · François F. Kavelaars · Peter J. M. Valk · Ivo P. Touw

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Dear Editor,

In the 2008 WHO classification, atypical chronic myeloid leukemia (aCML) is defined as a chronic leukemic disorder with myeloproliferative as well as myelodysplastic features. Colony-stimulating factor 3 receptor gene (*CSF3R*) mutations have been recently identified in patients diagnosed as chronic neutrophilic leukemia (CNL) or aCML [1]. The most frequent *CSF3R* mutation in CNL/aCML occurs in the membrane proximal region, resulting in the constitutively active mutant CSF3R T618I. Importantly, in both mouse models and patients, this mutant CSF3R has been shown to be sensitive to the JAK inhibitor ruxolitinib [2]. In addition to *CSF3R* mutations, about 25 % of patients with aCML have mutations in the SET binding protein-1 (SETBP1) [3]. Here, we describe a patient with aCML and concomitant CSF3R T618I and SETBP1 G870S mutations who did not respond to ruxolitinib.

A 57-year-old male presented in September 2013 with a deep venous thrombosis of the left popliteal vein. Physical examination revealed a massive splenomegaly. Total blood cell count showed a low Hb level (7.36 g/dL), low platelet count (127×10^9/L) and leukocytosis (97×10^9/L). A peripheral blood smear showed 1 % blasts and clear signs of dysgranulopoiesis such as Pelger-Huët and other bizarre nuclear abnormalities. Bone marrow examination revealed hypercellularity, 2 % blasts, dysgranulopoiesis, such as those founded in the peripheral blood and megakaryocyte dysplasia. Cytogenetic analysis showed a normal male karyotype. Molecular analyses revealed the presence of the CSF3R T618I and the SETBP1 G870S mutations (Fig. 1). *BCR-ABL1*, JAK2 V617F, and *CALR* abnormalities were negative. The patient was initially treated with hydroxyurea. WBC decreased to 25×10^9/L. At this time, ruxolitinib at a dosage of 15 mg twice daily was added to the therapy. After 1 week, WBC decreased to 5.8×10^9/L and HU was suspended. Two weeks later, WBC had increased to 74×10^9/L. Because of the lack of response, both HU and ruxolitinib were discontinued and an intensive chemotherapy was initiated.

Similarly to a case of CNL recently described by Lasho and colleagues [4], our aCML patient, with concomitant CSF3R T618I and SETBP1 G870S mutations, was refractory to ruxolitinib therapy. A significant clinical response to ruxolitinib has been reported in a case of aCML with CSF3R T618I, but lacking a concomitant *SETBP1* mutation [5]. Although the CSF3R T618I mutation has originally been reported in 70 % CNL and 29 % aCML, Pardadani et al. found this specific mutation only in CNL patients and not in 9 strictly WHO defined aCML cases [6]. This result was confirmed by Wang and coworkers, who investigated the presence of the CSF3R T618I mutation in a cohort of 65 aCML cases [7]. Our case fulfilled all the 2008 WHO definitions of aCML and expressed the CSF3R T618I mutation. Like the occurrence of the JAK2 V617F mutation across three clinically distinct disorders, i.e., polycythemia vera, essential thrombocytosis, and primary myelofibrosis, the disease phenotype of CSF3R T618I-mutated chronic neoplasms may be modified by host genetic

E. Ammatuna (✉) · M. Eefting · K. van Lom · F. F. Kavelaars · P. J. M. Valk · I. P. Touw
Department of Hematology, Erasmus University Medical Center, Cancer Institute Daniel den Hoed, Groene Hilledijk 301, 3075 Rotterdam, The Netherlands
e-mail: ammatuna@gmail.com

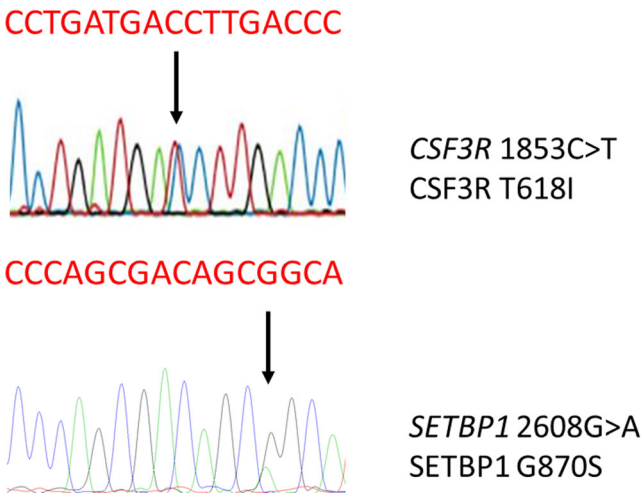

Fig. 1 Sanger sequences of regions of the *CSF3R* and *SETBP1* genes. The *bold arrows* indicate the 1853C>T *CSF3R* (T618I) and the 2608G>A *SETBP1* (G870S) mutations

factors or additional molecular alterations such as those involving the SETBP1 gene, resulting in variable sensitivity to JAK inhibitors. In this regard, it would be interesting to investigate the presence of additional mutations in the aCML cases described by Maxson and coworkers in their original paper [1].

Conflict of interest The authors declare that they have no conflict of interest.

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