Letter to the Editor

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Development of chronic myeloid leukemia in a patient previously diagnosed with a JAK2-positive myeloproliferative neoplasm

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To the Editor,

Myeloproliferative neoplasms (MPNs) are a heterogeneous group of clonal hematopoietic disorders including chronic myeloid leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) [1, 2]. CML is characterized by the chromosomal translocation t(9;22)(q34.1;q11.2). This leads to the formation of the Philadelphia (Ph) chromosome which contains the BCR-ABL1 fusion gene [2]. The other MPNs, all Ph-negative, are frequently characterized by driver mutations in JAK2, CALR, and MPL. While PV is defined by the somatic JAK2 V617F gain-of-function mutation or another functionally similar JAK2 mutation, JAK2, CALR, and MPL are recurrently mutated in ET (incidence of 55, 25, and 3%, respectively) and PMF (incidence 50–60, 24, and 8%, respectively) [2]. Despite initial studies in which JAK2 mutations and BCR-ABL1 were considered as mutually exclusive, some researchers already reported the coexistence of BCR-ABL1 and other MPN markers (JAK2, CALR, or MPL mutations) [3, 4]. Here, we describe a patient with an unusual clinical course wherein CML developed in a patient who was initially diagnosed with a JAK2-positive MPN.

In 2016, a 59-year old woman was referred to the hematology department with several symptoms such as temporary vision changes, headache, sweats and restless legs, in combination with persistent thrombocytosis (>450 × 10^9/L). At the time of diagnosis, the platelet count was 516 × 10^9/L without any evidence for an underlying reactive phenomenon. In addition, a discrete leukocytosis was noted (11 × 10^9/L). Hematocrit, red blood cell mass and hemoglobin levels were all within the normal range. The peripheral blood film showed the presence of mature granulocytes and the absence of a leukoerythroblastic picture. Clinical examination revealed no palpable spleen enlargement. Chromosome analysis showed no anomalies in the patient’s karyotype. Quantitative polymerase chain reaction (qPCR) revealed a V617F mutation in the JAK2 gene (variant allele frequency of 3.6% JAK2 V617F/total JAK2). No other mutations were identified in a next generation sequencing (NGS) analysis with a 68 gene panel. Since both the bone marrow aspirate as well as the bone biopsy were of insufficient quality to allow conclusive assessments, the strictly defined WHO diagnostic criteria for ET could not be fully met and a presumptive diagnosis of JAK2-positive ET was made. The patient was treated with acetylsalicylic acid only. In 2018, the platelet count increased to >700 × 10^9/L and hydroxyurea (500 mg/day) was started.

Two years later, the patient presented with a progressive and pronounced leukocytosis. At the time of consultation, the peripheral blood film showed a leukocytosis of 39 × 10^9/L with myeloid precursors and absolute eosinophilia and basophilia. Platelet and hemoglobin levels were normal. Both bone marrow aspirate and bone biopsy appeared to be hypercellular with marked granulocytic proliferation and a maturation pattern similar to that in the blood without significant dysplasia and without blast excess. Eosinophils were increased in number. The proportion of erythroid...
precursors was significantly decreased and the megakaryocytes appeared to be smaller than normal with signs of hypersegmentation. In addition, the biopsy showed a grade 1 fibrosis (0–3 scale). Ultrasound imaging was negative for hepatosplenomegaly. Molecular testing showed a strong presence of the BCR-ABL1 fusion gene (p210 BCR-ABL1/ABL ratio of 2.99, international scale 176.88%) and disappearance of the JAK2 mutation (sensitivity 1%). No evidence for other MPN related clonality could be observed using NGS. It was hypothesized that the patient evolved from a JAK2-positive ET to the chronic phase of BCR-ABL1 CML over a course of four years. Therapy with dasatinib (70–100 mg/day) was started and the patient reached complete hematologic remission within the first month of treatment. Retrospective fluorescence in situ hybridization (FISH) on the initial diagnostic sample from 2016 appeared to be negative for BCR-ABL1.

ET is characterized by its indolent nature and long symptom-free intervals occasionally complicated by life-threatening thromboembolic or hemorrhagic events. However, in a minority of ET patients, fibrotic (4–11% of cases) or leukemic transformation (2.1–5.3%) will shorten life expectancy [5]. The development of CML during the course of disease in ET patients can be considered as a rather unique finding and could serve as a warning not to take a previous diagnosis as the cause for the symptoms. Furthermore, our case illustrates potential pitfalls in the diagnosis of MPNs since one of the major diagnostic WHO criteria for ET is that the criteria for BCR-ABL1-positive CML or other myeloid neoplasms are not met [2]. While a handful of reports have described the occurrence of CML in JAK2-negative ET patients [6], and dozens of cases have described the concomitant existence of a JAK2-positive MPN and CML [7], very few reports have described the ‘transformation’ of a JAK2-positive ET to CML [8, 9]. Various explanations can be put forward for this atypical case. First, the patient could already had a CML diagnosis with the thrombocytosis at initial diagnosis reflecting preferential megakaryocytic differentiation of the small clone of BCR-ABL1 positive cells [10]. Concomitant detection of BCR-ABL1 and JAK2 V617F have been reported in patients with MPNs at the time of diagnosis [3]. However, as stated earlier, cytogenetic analysis showed a normal karyotype and FISH analysis identified normal BCR and ABL signal patterns. Secondly, the patient could have an ET with the Ph chromosome occurring in a stem cell that was part of the ET clone (i.e. a subclone). Nevertheless, this scenario is unlikely since it would be expected to have a strong simultaneous appearance of both the JAK2 mutation and the BCR-ABL1 fusion gene. Last, it could be hypothesized that the patient had a JAK2-positive ET in combination with the independent transformation of a normal stem cell to CML [10]. In this specific case, several arguments are in favor for the last hypothesis. Nonetheless, whether this transformation is due to the development of a second clone or a sequel of a single clone that acquires a ‘second hit’ cannot be determined with certainty. However, the fact that a disappearance of the JAK2 mutation occurred in combination with a strong positive BCR-ABL1 result is indicative for the co-existence of two independent clones with final masking of the JAK2-positive clone. Concerning the latter, retesting of the sample using a more sensitive droplet digital PCR (ddPCR, sensitivity 0.04%) unraveled a very weak positive JAK2 V617F signal (0.32%, clinical cut-off 0.5–5%). Furthermore, spontaneous normalization of the platelet counts in parallel with increasing leukocyte levels most likely reflects the growth of a dominant Ph-positive clone. Therefore, it was of importance to monitor JAK2 mutation status and evolution of platelet counts during the course of dasatinib treatment, which inhibits the growth of the CML cell line overexpressing BCR-ABL1. As can be derived from Figure 1, five weeks after initiation of dasatinib a recurrence of thrombocytosis could be observed. Moreover, nine weeks after treatment initiation, reappearance of

Figure 1: Evolution of platelets, white blood cells (WBCs), BCR-ABL1 and JAK2 V617F quantifications during the course of disease. IS, international scale; ddPCR, droplet digital polymerase chain reaction; FISH, fluorescence in situ hybridization; qPCR, quantitative polymerase chain reaction.
the JAK2 mutation (ddPCR 6.3%) and an early molecular response of BCR-ABL1 was noted (p210 BCR-ABL1/ABL ratio of 0.062, international scale 4.06%). These evolutions form strong arguments for the co-existence of two independent clones. A previous study that performed continuous quantitative assessments of BCR-ABL1 and JAK2 V617F in 18 MPN patients already demonstrated that, in the majority of cases, opposing kinetics strongly indicate the existence of two different clones which are not only independent of each other, but are also able to compete with each other [4]. No flow cytometric analyses has been performed, so it is unclear if the two populations carry a specific leukemia associated immune phenotype, which could help in the discrimination between the two clones. Alternatively, single cell PCR could be used to prove the existence of individual clones.

We can conclude that one should keep in mind that concomitant existence of JAK2-positive MPNs and CML may occur and is potentially underdiagnosed. Furthermore, since Ph-positive and Ph-negative MPNs differ substantially in their treatment regimes, this rare case underlines the value of molecular testing for both diagnostic and treatment purposes in MPN cases with a rather atypical clinical course.

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References