Two Cases of Myeloproliferative Neoplasm with a Concurrent JAK2V617F Mutation and BCR/ABL Translocation without Chronic Myelogenous Leukemia Phenotype Acquisition during Hydroxyurea Treatment

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Dear Editor

Myeloproliferative neoplasms (MPNs) are categorized on the basis of BCR/ABL translocation occurrence as either Philadelphia-positive CML or Philadelphia-negative MPNs (Ph-MPNs). MPNs include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) \[1\]. The JAK2V617F mutation, which is specific for Ph-MPN, occurs in more than 95% PV cases and in approximately 50% ET and PMF cases \[1\]. The 2008 revision of the WHO classifies MPNs into 2 categories, BCR/ABL-positive CML and Ph-MPNs, on the basis of the presence or absence of the Philadelphia chromosome \[2\]. Although the 2008 WHO classification does not include MPNs with more than 1 genetic aberration as a distinct disease entity, some cases with coexistence of JAK2V617F mutation and BCR/ABL translocation have been recently reported and up to 28 cases have been previously reported \[3-20\]. Among these reports, the majority of the patients either had pre-existing BCR/ABL-positive CML and developed JAK2V617F mutation while undergoing tyrosine kinase inhibitor treatment \[4-7\] or developed BCR/ABL-positive CML with a pre-existing JAK2V617F mutation-positive MPN \[8-12\]. In contrast, a small number of patients showed simultaneous occurrence of both JAK2V617F mutation and BCR/ABL translocation, with a CML phenotype in the bone marrow (BM) with development of symptoms or morphology associated with JAK2V617F mutation, and with MPN only after imatinib treatment \[3, 6, 13-15\]. We report 2 MPN cases that were simultaneously positive for both JAK2V617F mutation and BCR/ABL translocation and that did not acquire the CML phenotype during hydroxyurea (Korea United Pharm, Seoul, Korea) treatment.

Case 1 was a 36-yr-old man who was admitted in November 2009 with severe thrombocytosis. The patient’s hemogram results at admission were as follows: white blood cells, 9.4×10⁹/L, Hb, 13.8 g/dL, and platelets, 830×10⁹/L. The peripheral blood smear (PBS) and BM biopsy revealed a marked increase in the platelet and the clustered megakaryocyte numbers (9.2/high power field) without evidence of dysplasia. Allele-specific PCR for JAK2V617F mutation detection and reverse-transcriptase PCR (RT-PCR) for BCR/ABL fusion transcript detection using custom-designed primers was performed. The PCR and the RT-PCR analyses showed that the patient was positive for JAK2V617F heterozygous mutation and the BCR/ABL fusion transcript (b3a2...
Subsequently, the JAK2V617F mutation allele burden was quantified by real-time quantitative PCR using JAK2 MutQuant™ (Ipsogen, Marseille, France). The JAK2V617F mutation allele burden was calculated as the percentage of the V617F copy number to the sum of V617F and wild-type copy number. The JAK2V617F mutation allele burden was quantified to be 27.91% (7,200/25,800) at diagnosis. The major BCR/ABL fusion transcripts quantitation was also performed by real-time PCR using the LightCycler t(9;22) Quantification kit (Roche Diagnostics, Mannheim, Germany) and the normalized copy number (NCN) was 0.02 at diagnosis. The patient’s karyotype was determined to be 46,XY [20]; however, his interphase FISH analysis result was nuc ish(ABL1x3,BCRx2)(ABL1 con BCRx1)[61/200], representing cryptic BCR/ABL fusion on der(22)t(9;22) in 30.5% of the total cells.

Thus, on the basis of these findings, the patient was diagnosed to have ET with a major BCR/ABL fusion transcript. The patient was treated with hydroxyurea and the initial response during the first year of treatment was promising (BCR/ABL fusion transcript maintained in the range of 0.005 NCN to 0.01 NCN). However, despite continuing treatment, the number of BCR/ABL fusion transcripts increased to 5.0 NCN in the second year of follow-up, which indicated treatment failure. Interestingly, the patient did not show morphological evidence of CML during the follow-up period.

Case 2 was a 58-yr-old man diagnosed with leukocytosis and splenomegaly on admission. The patient’s hemogram results at admission were as follows: white blood cells, 19.7 × 10⁹/L, Hb, 13.0 g/dL, and platelets, 285 × 10⁹/L. The PBS showed an occasional presence of tear-drop cells and immature granulocytes with blasts (Fig. 1A). The BM biopsy showed extensive myelofibrosis (grade 2-3) with a cellularity of 90% and an increased number of dysplastic megakaryocytes (Fig. 1B). The myelofibrosis was demonstrated by the reticulin silver stain (Fig. 1C). At diagnosis, the JAK2V617F mutation analysis showed a heterozygous mutation (Fig. 1D) and the JAK2V617F mutation allele burden was quantified to be 69.66% (2,640/3,790). The RT-PCR analysis revealed the presence of BCR/ABL fusion transcript (b3a2 type) (Fig. 1E). The patient’s karyotype was determined to be 46,XY,
In addition, the 2 patients showed different outcomes according to both the initial level of BCR/ABL fusion transcripts and the introduction of a tyrosine kinase inhibitor during the hydroxyurea treatment. The patient with low initial BCR/ABL fusion transcript levels experienced a relatively good initial response to hydroxyurea treatment, although the treatment failed 2 years later. In contrast, the patient with high BCR/ABL fusion transcript levels did not initially respond well to hydroxyurea treatment, but a dramatic response was achieved after a treatment change to dasatinib. On the basis of these findings, we speculate that treatment with a tyrosine kinase inhibitor can be effective and therefore recommend this approach in JAK2(V617F)-positive MPN patients with a concurrent BCR/ABL translocation, particularly if the initial BCR/ABL fusion transcript level is high.

In conclusion, we report 2 cases of MPN with concurrent JAK2(V617F) mutation and BCR/ABL translocation without CML phenotype acquisition during the hydroxyurea treatment. Treatment with tyrosine kinase inhibitors can be effective, particularly if the initial BCR/ABL fusion transcript level is high in these patients. Further molecular genetic analysis is needed to elucidate the pathogenesis of these hematological chimeras.

Authors’ Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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