**To the editor:**

**BCR-ABL1 is a secondary event after JAK2V617F in patients with polycythemia vera who develop chronic myeloid leukemia**

Two patients with a history of JAK2V617F+ polycythemia vera (PV) without a family history of a myeloproliferative neoplasms developed chronic myeloid leukemia (CML) 12 and 18 years after their initial presentation. Only patient 1 received myelosuppressive therapy (hydroxyurea). To understand the relationship between the acquisition of JAK2V617F and BCR-ABL1, we performed genotypic analyses of hematopoietic progenitor cells (HPCs) assayed from these patients.

As shown in Figure 1A, all 48 hematopoietic colonies (HCs) cloned in semisolid medium from patient 1 were homozygous for JAK2V617F, and 4 of 48 (8%) HCs contained both JAK2V617F and BCR-ABL1. Each of the 33 HCs from patient 2 contained JAK2V617F, whereas the BCR-ABL1 fusion was identified in 18% of colonies heterozygous for JAK2V617F and in 58% colonies homozygous for JAK2V617F. JAK2 wild-type HCs were not identified even in the presence of a high concentration of erythropoietin in either patient. HCs with BCR-ABL1 without JAK2V617F were also not observed (Figure 1A).

Single-cell analyses were used to exclude the possibility that the coexistence of BCR-ABL1 fusion and JAK2V617F mutation in a single HC generated in semisolud medium might be the result of cells migrating from one colony to another. Clonal evolution can be inferred using such single-cell studies. As shown in Figure 1B, the distribution of genotypes of the colonies cloned from a single CD34+ cell from these 2 patients was similar to that of HCs generated in semisolid medium. These studies suggest that the acquisition of BCR-ABL1 occurred after JAK2V617F and that the development of CML is a secondary event that may occur in either heterozygous (patient 2) or homozygous (patient 1) JAK2V617F+/H11001 HPCs.

Bocchia et al reported a similar patient with PV who developed CML in whom JAK2V617F and BCR-ABL coexisted in HPCs.

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**Figure 1. Simultaneous genotyping for JAK2V617F and BCR-ABL1 of individual CFU-GM, BFU-E, and mixed CFUs assayed in semisolid medium and in colonies generated from single CD34+ cells in liquid cultures.** CD34+ cells were assayed in semisolid medium (A) or in single-cell liquid cultures (B), supplemented with SCF, thrombopoietin, IL-3, IL-6, and G-CSF, each at 100 ng/mL, and 4 units/mL of erythropoietin (Amgen). Individual HCs were plucked from semisolid media or from liquid cultures of single CD34+ cells. The colonies were divided into 2 parts. Half were analyzed for JAK2V617F using a nested allele-specific PCR and the other half were analyzed for the presence of BCR-ABL1 using interphase FISH. Each HC contained either heterozygous or homozygous JAK2V617F, whereas the BCR-ABL1 was demonstrated only in a fraction of these HCs. JAK2 wild-type HCs and BCR-ABL1+ HCs without JAK2V617F were not observed in either patient.
committed to multiple hematopoietic lineages. In contrast, Cambier et al provided evidence in another PV patient who developed CML that the PV and CML originated from distinct clones. Our findings indicate that both the JAK2V617F mutation and BCR-ABL1 can occur concurrently in both CFU-GM and BFU-E and that JAK2V617F occurs before the acquisition of BCR-ABL1. The clinical phenotype of myeloproliferative neoplasms frequently evolves over time. Although this progression can be enhanced by the use of chemotherapeutic agents, it represents the natural clonal evolution of these malignancies. The development of CML in PV occurs much less frequently than myelofibrosis or acute myeloid leukemia, but should be considered in patients with PV who develop extreme leukocytosis. The contribution of BCR-ABL1 to disease progression appears to be greater than that of JAK2V617F, because these patients display a clinical phenotype that is consistent with CML rather than PV. These clinical observations represent an example of clonal evolution in which the initial genetic event is a mutation leading to the activation of a tyrosine kinase (JAK2), which is then followed by either a second genetic event leading to the acquisition of a fusion protein resulting in activation of another protein kinase (BCR-ABL1) or by homologous recombination resulting in JAK2V617F-homozygous HPCs that lack BCR-ABL1. Subsequently, the JAK2V617F-heterozygous HPCs with BCR-ABL1 can also undergo homologous recombination and become homozygous for JAK2V617F.

To the editor:

Hemichorea in a patient with JAK2V617F blood cells

Chorea has been reported in patients with polycythemia vera (PV). JAK2V617F is a molecular marker used for the diagnosis of PV. Occasionally, patients have insufficient clinical criteria to establish a diagnosis of PV or only possess some disease features without having overt hematologic manifestations. We present a case of an elderly woman with subacute hemichorea who was found to have normal hematologic profile and JAK2V617F+ hematopoiesis. Hemichorea completely resolved after therapeutic phlebotomy and hydroxyurea therapy.

A previously active, healthy 87-year-old woman experienced an episode of dizziness and a week later dysarthria and facial asymmetry. An MRI/MRA of the brain was unrevealing. Three weeks later, she developed involuntary movements of the left arm, face, and leg that progressively worsened in intensity and frequency. Neurologic examination revealed left hemichorea with motor impersistence and “milkmaid’s grip.” Chorea was activated by rapid alternating movements and walking. There were no signs of Parkinsonism or dystonia.

Palpable splenomegaly was absent on examination. Blood work was notable for a hemoglobin of 15.6 g/dL, hematocrit of 44.2%, WBC count of 8.6 x 10^9/L, platelet count of 281 x 10^9/L, mean corpuscular volume of 95.7 fL, normal iron studies, and a serum erythropoietin of 12.7 mIU/mL. Her peripheral blood JAK2V617F granulocyte allele burden was 35% as determined by allele-specific PCR. The patient refused a BM biopsy.

References
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