LETTER TO EDITOR / EDITÖRE MEKTUP

Coexistence of JAK2V617F mutation and BCR/ABL translocation in one patient

Aynı hastada JAK2V617F mutasyonu ve BCR/ABL translokatıyonu birlikteliği

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Dear Editor,

The myeloproliferative disorders (MPDs) constitute a subcategory of chronic myeloid disorders and include chronic myeloid leukemia (CML), essential thrombocytopenia (ET), polycythemia vera (PV) and myelofibrosis (MF). In 1960, the discovery of the Philadelphia chromosome (Ph) became a cornerstone in CML treatment and led to the development of molecular targeted therapy. Recently, an acquired mutation in the Janus kinase 2 (JAK2) gene has been discovered in nearly all patients with PV and approximately half of the patients with primary MF and ET. Subsequently, the mutation has been demonstrated in atypical MPDs (chronic neutrophilic leukemia, unclassified), de novo myelodysplastic syndrome or acute myeloid leukemia.¹ It has been hoped that targeted inhibition of JAK2V617F should achieve similar disease control as thyrosine kinases has produced in CML.

A gain-of-function mutation at codon 617 (V617F) of the JAK2 gene causes constitutive activation of the JAK-STAT pathway which in turn leads to uncontrolled hematopoietic cell proliferation.² In mice, JAK2V617F induces a PV-like disease with erythrocytosis, low serum erythropoietin (Epo) level, splenomegaly, extramedullary hematopoiesis, megakaryocytic hyperplasia, and anemia.² ³ Tef-
reference values [3.6 mU/mL (4.5–33 mU/mL)]. Hydroxyurea and allopurinol were started for decreasing cell load and additionally hydration was supplied. Hematocrite levels were lowered as 45% via flebotomies.

Histopathologic examination of bone marrow biopsy revealed 95% cellularity, markedly increased myeloid series, decreased blast ratio (<0.05), increased myeloid/erythroid ratio (5/1) and increased dismature megacyocytes. Immunohistochemical staining with prussian blue revealed decreased iron deposits and stage 0 CML was reported in according to reticulin fibrosis score. Abdominal ultrasound examination has no pathologic findings related with spleen, liver and the other organs. Cyto genetic analysis revealed no cytogenetic abnormality. The examination of peripheral blood samples by using PCR revealed that BCR-ABL (P210) was 0.01. Translocation (t 9;22) was found 8% positive in FISH study by using BCR-ABL translocation probe. As a part of diagnostic evaluation of MPDs, JAK2V617F mutation analysis was performed and was found to be positive in according to Rotor gen real time PCR analysis in peripheral blood. Therefore, the coexistence of JAK2 mutation and Philadelphia chromosome (Ph+) was observed in a single patient. These results revealed the diagnosis of a myeloproliferative disease (CML/PV) and imatinib therapy was started at 400 mg/day.

There is a debate as to whether MPD and CML arise separately from each other, representing independent development from a normal stem cell, or whether the Ph chromosome arises in a stem cell of a MPD clone.11

The unexpected hematological responses (including thrombocytosis),7 or erythrocytosis,8,9 evolving myelofibrosis,10,11 and/or persisting spleen enlargement,7,12 under imatinib mesylate treatment led some physicians to detect for JAK2 mutation in either peripheral blood or bone marrow. Probably, imatinib therapy suppresses the BCR-ABL clone, enabling the proliferation of JAK2V617F mutated cells. It is likely that the dominance of JAK2 positive clone obtain an escape effect which may explain the mechanism of bone marrow fibrosis and also hematological changes. Campiotti et al. have prospectively detected JAK2 mutation positivity in one patient among 13 new cases of Ph+ positive CML.13 In contrast with other reports;7,12 after the partial cytogenetic response to imatinib treatment, JAK2 mutation was disappeared. Therefore, they have firstly hypothesized that imatinib treatment have caused the regression of CML clone, as well as JAK2 mutated cells, and that JAK2 mutation can be acquired by Ph+ cells.13 But in most cases, as described previously, imatinib mesylate therapy did not effect the coexisting and/or acquired JAK2 clone.7,12 Moreover, owing to a proliferative advantage, JAK2 mutated hematopoiesis could overwhelm the BCR-ABL translocated hematopoiesis. To our knowledge, it seems more likely that there are two independent growing aberrant stem cell clones.

On the other hand, some patients with preexisting JAK2V617F positive MPD were found to have Philadelphia translocation in the literature.11,14–16 Krämer et al. showed retrospectively that the JAK2V617F mutation was already present at initial diagnosis of BCR-ABL positive CML. And after the successful treatment of CML with imatinib, JAK2V617F might have been responsible for the development of myelofibrosis.11

Eventhough the JAK2V617F mutation has been excluded in a large cohort of BCR-ABL patients, the present report gives evidence that the coexistence of these two disease-specific mutations is possible. Physicians have to keep in mind that unexpected hematological responses, evolving myelofibrosis, and/or persisting spleen enlargement during effective treatment of Ph+ CML may be caused by an underlying JAK2 positive hematopoietic clone.

REFERENCES

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