Klinik ve Deneysel Araştırmalar Dergisi
Journal of Clinical and Experimental Investigations
Cilt/Vol 1, No 2, 138-140

LETTER TO EDITOR / EDİTÖRE MEKTUP

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

Aynı hastada JAK2V617F mutasyonu ve BCR/ABL translokasyonu birlikteliği

Osman Yokuş[1], Fatih Kurnaz[2], Özlem Şahin Balçık[3], Burak Uz[4], Murat Albayrak[5]

J Clin Exp Invest 2010; 1(2): 138-140

Key words: JAK2V617F mutation, BCR/ABL translocation, miyeloproliferative disorders, myelofibrosis

Klin Den Ar Derg 2010; 1(2): 138-140

Anahtar kelimeler: JAK2V617F mutasyonu, BCR/ABL translokasyonu, miyeloproliferatif bozukluklar, miyelofibroz

Dear Editor,

The myeloproliferative disorders (MPDs) constitute a subcategory of chronic myeloid disorders and include chronic myeloid leukemia (CML), essential thrombocytemia (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 moleculary targeted therapy. Recently, an acquired mutation in the Janus kinase 2 (JAK2) gene has been discovered in nearly all patents 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] Teffери suggested that JAK2V617F mutation probably leads to a PV-weighted MPD phenotype.[1]

Jelinek et al. reported no mutated cases for JAK21849G>T in 99 CML patients, including 55 imatinib-resistant subjects.[4] Similarly, Bock et al. did not detect JAK2 mutation in 5 Ph^+ CML patients in a previous report.[5] In contrast with these reports, more recently, several cases with the coexistence of BCR-ABL fusion gene and JAK2V617F mutation in blood and bone marrow samples were reported.[6–13] We report here a new case with concomitant BCR-ABL rearrangement and JAK2V617F mutation, and compare our findings with those of similar reports.

A 58-year-old female patient presented with ruddy face, dizziness, flushing and pruritis. Physical examination was normal with no palpable spleen enlargement. The hematological parameters were as follows: white blood cells, $20.3x10^9$/L with a differential count of 83% neutrophils; hemoglobin, 16.9g/dL; hematocrite, %56,4; platelets $387x10^3$/µl. Peripheral smear revealed thrombocytosis and left shift of the myeloid series. Iron deficiency and inflammation were ruled out. The leukocyte alkaline phosphatase (LAP) score was below 10%. Arterial blood gas analysis revealed a normal oxygen saturation. Serum Epo levels were found lower than

[1]*Sema Hospital, Department of Hematology, İstanbul;* [2]*Erciyes University Department of Hematology, Kayseri;* [3]*Fatih University Department of Hematology, Ankara,* [4]*Hacettepe University Department of Hematology, Ankara;* [5]*Dışkapı Yıldırım Beyazıt Education and Research Hospital, Department of Hematology, Ankara, Turkey*

Yazışma Adresi /Correspondence: *Burak Uz MD*

Hacettepe University Medical School, Department of Internal Medicine, Division of Hematology **E-mail:** burakuz@yahoo.com

Geliş Tarihi / Received 19.06.2010, Kabul Tarihi /Accepted: 18.07.2010

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 megacaryocytes. Immünohistochemical 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. Cytogenetic 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,[4] the present report gives evidence that the coexistence of these two disease-spesific 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

1. Tefferi A. Classification, diagnosis and management of myeloproliferative disorders in the JAK2V617F era. Hematology Am Soc Hematol Educ Program 2006;240–5.
2. James C, Ugo V, Le Couedic JP et al. A unique clonal JAK2 mutation leading to constitutive signalling causes polycythaemia vera. Nature 2005;434:1144–8.
3. Wernig G, Mercher T, Okabe R, Levine RL, Lee BH, Gilliland DG. Expression of Jak2V617F causes a polycthemia vera-like disease with associated myelofibrosis in a murine bone marrow transplant model. Blood 2006;107:4274–81.
4. Jelinek J, Oki Y, Gharibyan V et al. JAK2 mutation 1849G>T is rare in acute leukemias but can be found in CMML, Philadelphia chromosome-negative CML, and megakaryocytic leukemia. Blood 2005;106:3370–3.
5. Bock O, Büsche G, Koop C, Schröter S, Buhr T, Kreipe H. Detection of the single hotspot mutation in the JH2 pseudokinase domain of janus kinase 2 in bone marrow tre-

phine biopsies derived from chronic myeloproliferative disorders. Journal of Molecular Diagnostics 2006; 8:170-7.

6. Krämer A. JAK2-V617F and BCR-ABL-double Jeopardy? Leukemia Res 2008;32:1489–90.
7. Pardini S, Fozza C, Contini S et al. A case of coexistence between JAK2V617F and BCR/ABL. Eur J Hematol 2008; 81.75–6.
8. Inami M, Inokuchi K, Okabe M et al. Polycthemia associated with the JAK2V617F mutation emerged during treatment of chronic mylogeneous leukemia. Leukemia 2007;21:1103–4.
9. Cambier N, Renneville A, Cazaentre T et al. JAK2V617F-positive polycythemia vera and philadelphia chromosome-positive chronic myeloid leukemia: one patient with two distinct myeloproliferative disorders. Leukemia 2008;22:1454–5.
10. Hussein K, Bock O, Seegers E et al. Myelofibrosis evolving during imatinib treatment of a chronic myeloproliferative disorder with coexisting BCR-ABL translocation and JAK2V617F mutation. Blood 2007;109:4106–7.
11. Krämer A, Reiter A, Kruth J et al. JAK2-V617F mutation in a patient with Philadelphia-chromosome-positive chronic myeloid leukemia. Lancet 2007;8:658–60.
12. Veronese L, Tchirkov A, Richard-Pebrel C et al. A thrombocytosis occuring in Philadelphia positive CML in molecular response to imatinib can reveal an underlying JAK2V617F myeloproliferative neoplasm. Leuk Res 2010;34:94–6.
13. Campiotti L, Appio L, Solbiati F, AgenoW, Venco A. JAK2-V617F mutation and Philadelphia positive chronic myeloid leukemia. Leukemia Research 2009; 33.212–3.
14. Jallades L, Hateyye S, Tigaud I et al. Emergence of therapy-unrelated CML on a backgraund of BCR-ABL-negative JAK2V617F-positive chronic idiopathic myelofibrosis. Leuk Res 2008;32:1608–10.
15. Bornhäuser M, Mohr B, Oelschlaegel U et al. Concurrent JAK2(V617F) mutation and BCR-ABL translocation within committed myeloid progenitors in myelofibrosis. Leukemia 2007; 21:1824–6.
16. Curtin NJ, Campbell PJ, Green AR. The Philadelphia translocation and pre-existing myeloproliferative disorders. Br J Haematol 2005;128:730–6.