JAK2 Negative Polycythemia Vera

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ABSTRACT

Polycythemia vera (PV) is a stem cell disorder, characterized as a panhyperplastic, malignant, and neoplastic marrow disorder. Several reasons suggest that a mutation on the Janus kinase-2 gene (JAK2) is the most probable candidate gene involved in PV pathogenesis, as JAK2 is directly involved in intracellular signaling, following its exposure to cytokines, to which PV progenitor cells display hypersensitivity. A recurrent unique acquired clonal mutation in JAK2 was found in most patients with PV and other myeloproliferative diseases (MPDs). A female patient of age 50 years, presented with hemiplegia, diplopia, and had a consistent rise in hemoglobin and hematocrit. Serum Erythropoietin (Epo) was decreased. JAK2 mutation analysis was found to be negative. A diagnosis of polycythemia vera was made on the basis of the British Committee for Standards in Hematology (BCSH) guidelines.

Keywords: JAK 2 V617F mutation, polycythemia vera, BCSH guidelines

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INTRODUCTION

Polycythemia vera is a rare disorder, with a minimum incidence of 2.6 per 100000.[1] In early 2005, a novel Janus kinase 2 (JAK2) mutation was described in association with PV, Essential thrombocythemia (ET), and primary myelofibrosis. JAK’s are cytoplasmic tyrosine kinases that mediate signaling from cytokine receptors to the cell nucleus. Mutational frequencies using sensitive detection techniques on either peripheral blood or bone marrow are estimated at 95% for PV and greater than 50% for ET.[2] However, it is very clear that some patients with classical PV lack JAK2V617F mutation, while some patients with other MPDs such as Idiopathic Myelofibrosis (IMF) and ET also express the JAK2V617F mutation.[3] The molecular basis of JAK2 V617F negative PV is unknown.[4] Here is a case report of JAK2V617F negative polycythemia vera.

CASE REPORT

A female patient of age 50 years presented with hemiplegia to the medical ward along with visual disturbances. The patient had a history of generalized weakness since two years. There was no history of smoking or alcohol intake and the patient was not hypertensive. The respiratory system and cardiovascular system were normal. Previous investigations showed a consistent rise in hemoglobin and hematocrit, with normal total leucocyte count and platelet count. On examination, the patient had mild splenomegaly confirmed on sonography; laboratory investigation revealed Hb% 19.6 gm%, hematocrit 0.62, TLC 9,200 cells/cumm, and a platelet count of 3.29 lakhs /cmm. Coagulation assays were normal, kidney and liver function tests were normal, arterial blood gas analysis was normal, and bone marrow showed a normoblastic appearance, with slight erythroid dominance. Serum Epo level was 3.09 mIU/ml. CT and MRI of the brain revealed multiple white matter infarcts. Secondary causes of erythrocytosis were ruled out. Cytogenetic analysis for JAK2V617 mutation was done, which was negative.

A diagnosis of polycythemia vera was made on the basis of the British Committee for Standards in Hematology (BCSH) guidelines. The discovery of JAK2 mutation in the majority of patients with PV allowed revision and simplification of the diagnostic criteria.[4] These criteria were as given in Table 1. Diagnosis of PV was made as A1 + A2 + A3 and B3 + B4, as present in our case. The patient underwent phlebotomy and was put on hydroxyurea. The patient symptomatically responded well to the treatment.
DISCUSSION

JAK2 gene is located on the short arm of chromosome 9, and loss of heterozygosity on chromosome 9p due to uniparental disomy is the most common cytogenetic abnormality in PV. Only a minority of sporadic patients with PV do not carry JAK2, and the proportion of familial cases of PV that are negative is definitely higher. The discovery of JAK2 mutations in the majority of patients with PV simply showed the presence of clonal disease. This allowed for revision and simplification of the diagnostic criteria in those with a JAK2 mutation. The amendment to the guidelines for the diagnosis was adopted by the BCSH and the criteria are as shown in Table 1. The WHO also revised their criteria, which is abnormally low in more than 90% of patients with PV. If the results of both the tests are suggestive of PV, the diagnosis is likely; bone marrow examination is encouraged, but not essential for making the diagnosis.

Diagnostic criteria for PV were originally devised by the Polycythemia vera study group in the USA, in 1960. They required increased red cell mass and additional diagnostic criteria. They also included tests that were obsolete, such as, increased leucocyte alkaline phosphate or unbound B12 binding capacity. The World Health Organization (WHO) introduced criteria for diagnosis in 2001. These criteria were over-permissive, as they allowed a diagnosis with an Hb that would be considered within the normal range. Some of the criteria were tests that were only available in a few laboratories and were not validated, such as, endogenous erythroid colony formation. In the UK, Pearson defined criteria that were designed to include only patients who were likely to have the diagnosis and be able to make a diagnosis using tests that were widely available. These criteria were adopted in the British Committee for Standards in Hematology (BCSH) guidelines for diagnosis and management. The discovery of JAK2 mutations in the majority of patients with PV simply showed the presence of clonal disease. This allowed for revision and simplification of the diagnostic criteria in those with a JAK2 mutation. The amendment to the guidelines for the diagnosis was adopted by the BCSH and the criteria are as shown in Table 1. The WHO also revised their criteria in view of the presence of JAK2 mutations in the majority of patients.

BCSH criteria are the most accurate diagnostic criteria for PV as they have an acceptable level of sensitivity and specificity for PV as they have an acceptable level of sensitivity and specificity for PV. Other diagnostic criteria that were proposed were the JAK2 mutation. The amendment to the guidelines for the diagnosis was adopted by the BCSH and the criteria are as shown in Table 1. The WHO also revised their criteria in view of the presence of JAK2 mutations in the majority of patients.

In the newly proposed diagnostic criteria for PV, the presence of JAK2V617F mutation has been integrated as a major criterion. It has been suggested that JAK2V617F mutation analysis can be used to screen individuals with polycythemia. There is no significant difference in the clinical presentation of the JAK2 mutation in positive and negative PV patients. In general, patients who do express JAK2V617F are older than those who do not, but they do not have a longer duration of disease.

In recent times, mutations of JAK2 exon 12 have been described in JAK2V617F negative patients with PV. Most patients with PV, carrying an exon 12 mutation, had isolated erythrocytosis at clinical onset, unlike patients with JAK2 positive PV, who had elevations in leucocytes and platelet counts. Both leucocytes and platelet counts were within normal limits in the present case. A detection method for exon12 mutation is currently available at limited centers.

Of late, the Medical Research Council Primary Thrombocytopenia-1 Trial studied the effect of JAK2 mutation on the treatment outcome in PV and ET patients, demonstrating that JAK2 mutation in positive patients was more sensitive to hydroxyurea and not to anagrelide, than in those without JAK2 mutation. Furthermore, the rate of arterial thrombosis appeared to be lower in JAK2 positive patients receiving hydroxyurea compared to those receiving anagrelide, an effect that was not evident in JAK2 negative patients. These results support the concept of classifying PV or ET as JAK2 positive or negative during diagnosis.

Table 1: Diagnostic criteria for polycythemia vera

| JAK2-positive polycythemia vera | JAK2-negative polycythemia vera |
|--------------------------------|--------------------------------|
| A1. High hematocrit (>0.52 in men, >0.48 in women) or raised red cell mass (>25% above predicted) | A1. Raised red cell mass (>25% above predicted) or hematocrit ≥ 0.60 in men, ≥ 0.56 in women |
| A2. Mutation in JAK2 | A2. Absence of a mutation in JAK2 |
| A3. No case of secondary erythrocytosis | A3. No case of secondary erythrocytosis |
| A4. Palpable splenomegaly | A4. Palpable splenomegaly |
| A5. Presence of an acquired genetic abnormality (excluding BCR-ABL) in the hematopoietic cells | A5. Presence of an acquired genetic abnormality (excluding BCR-ABL) in the hematopoietic cells |
| B1. Thrombocytosis (platelet count >450 × 10^9/l) | B1. Thrombocytosis (platelet count >450 × 10^9/l) |
| B2. Neutrophil leucytosis (neutrophil count >10 × 10^9/l in non smokers, >12.5 × 10^9/l in smokers) | B2. Neutrophil leucytosis (neutrophil count >10 × 10^9/l in non smokers, >12.5 × 10^9/l in smokers) |
| B3. Radiological evidence of splenomegaly | B3. Radiological evidence of splenomegaly |
| B4. Endogenous erythroid colonies or low serum erythropoietin | B4. Endogenous erythroid colonies or low serum erythropoietin |

Diagnosis requires A1 + A2 + A3 + either one other A or two B criteria.
and designing treatment strategies. This case is presented because of its rarity and to highlight the importance of JAK2 mutation in polycythemia vera.

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