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Casos clínicos

Concurrent MPL515 and JAK2V617F mutations in a patient with chronic idiopathic myelofibrosis. Case report and review of the literature

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RESUMEN

Se describe el caso de un paciente con una neoplasia mieloproliferativa compatible con mielofibrosis primaria, con la mutación coexistente de MPL515 y JAK2V617F. Se hace una breve revisión y discusión de la bibliografía.
Palabras clave: neoplasia mieloproliferativa, mielofibrosis primaria, mutación MPL515 y JAK2V617F.

ABSTRACT

Here we describe the case of a patient with a myeloproliferative neoplasia consonant with myelofiobrosis who was found to display a concurrent MPL515 and JAK2V617F mutations A brief review and discussion of the literature is made.
Key words: Myeloproliferative neoplasia, myelofiobrosis, mutations MPL515 and JAK2V617F.

Chronic idiopathic myelofibrosis (MF) or agnogenic myeloid metaplasia is the least common of the major myeloproliferative neoplasias (MPN) and carries the poorest prognosis. The annual incidence is reported at 0.2-1.5 cases per 100,000 persons per year, with a predominance of men older than 50 years of age. The median survival is 3.5-5.5 years, although the natural history of IMF is quite unpredictable, depending on the presence or absence of poor prognostic features. A subset of low-risk patients will live longer than 10 years and require minimal active management. The median age at diagnosis of IMF is approximately 65 years, with 70% of cases diagnosed beyond 60 years of age and approximately 10% younger than 45 years of age. Although IMF has been sporadically associated to radiation and benzene exposures, no common etiologic factor has been identified.[1]

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Two novel somatic mutations, one involving a cytoplasmic tyrosine kinase and the other a corresponding cytokine receptor, have been designated in MPD and both were shown to induce constitutive JAK-STAT activation as well as impart relevant disease phenotype in mouse transplant models.[2] The first of these two mutations, JAK2V617F, is present in nearly all patients with polycythemia vera (PV) but also in approximately 50% of those with either essential thrombocythemia (ET) or IMF. Furthermore, compared with ET, PV is characterized by a significant higher JAK2V617F/wild type JAK2 allelic ratio as well as JAK2V617F mRNA burden.[3] The second mutation involves MPL515, either W515L or W515K (MPLW515L/K), and is much less prevalent but more specific than JAK2V617F: the mutational frequency is approximately 5% in IMF, 1% in ET and 0% in PV (4). Curiously, some patients with either IMF or ET feature both MPL515 and JAK2V617F mutations in their granulocyte-derived DNA.[4]

CASE REPORT

79 year old mexican mestizo female, allergic to penicillin, with a previous diagnosis of hypertension in pharmacological control. On June 2009, in another center, she was diagnosed as a myelodisplastic syndrome and received treatment with erythropoietin. On August 2009 symptoms such as nausea, anorexia , arthralgias and cough developed. Then she was refered to our center on February 2010 when

the patient referred loss of weight of 14 kg in 14 months approximately and on the physical examination she had splenomegaly of 4cm under costal margin. The CBC of February 2010, reported hemoglobin of 10.6 g/dL, Hematocrit 33%, reticulocytes 10% leukocytes of 23 000 , and platelets 139 000. The V617F JAK2 mutation was reported as Positive, and also the W515 L/K mutation of the MPL gene. The diagnosis of primary myelofibrosis was established and corroborated with a bone marrow biopsy, which reported a hypercellular bone marrow with primary myelofibrosis in fibrotic stage. We began treatment with danazol 100 mg PO every 24 h, and we have recommended INCB18424, an oral selective JAK 2 inhibitor. The patient has also received red cell transfusions and darbopoietin. Most recent labs of April 16 reported: hemoglobin 11.8 g/dl, hematocrit 37% ,reticulocytes 4.3 %, leukocytes 34,300, platelets 235,000. She has been well and the symptoms have improved.

DISCUSSION

We have conducted a study in a group of 36 Mexican mestizo patients with MPN and studied five molecular markers: The BCR/ABL1 fusion gene, the JAK2 V617F mutation, the JAK2 exon 12 mutations, the MPL W515L mutation and the MPL W515K mutation; 17 patients with ET, eight with PV, four with MF, five with undifferentiated MPN, one with primary erythrocytosis and one with familial thrombocytosis. Patients with the BCR/ABL1 fusion gene were excluded. Twelve individuals with the JAK2 V617F mutation were found; 11 of them had been clinically classified as PV and one had been classified as MF. One patient with the MPL W515L was identified with a clinical picture of ET. No individuals with either the MPL W515K mutation or the JAK2 exon 12 mutations were identified. Of the 17 individuals with ET, six (35%) had the JAK2 V617F mutation and one (6%) was found to have the MPL W515L mutation. Of the eight individuals with PV, five displayed the JAK2 V617F mutation, whereas of the four patients with MF, one had the JAK2 V617F mutation. The most consistent relationship was that between PV and the JAK2 V617F mutation (p=0.08).[5]

The patient described here displays concurrent MPL515 and JAK2V617F mutations. Based on the observations by Lasho et al,[6] the current mutation represent separate secondary clones arising from a common progenitor clone that currently remains molecularly undefined. The observations by Lasho are consistent with the results of a study that demonstrated a larger size of clonal myelopoiesis than could be accounted for by JAK2V617F allele burden in ET and PV.[7] However the observations by Lasho et al[6] do not support the contention that JAK2V617F is a late genetic event and instead suggest the possibility that mutant allele burden, instead of the mere presence of a specific mutation, might be important in the determination of phenotype in MPD. They also found that the MPL515 mutant allele burden was much lower in two other MPLW515L-positive patients with ET, a scenario that mirrors the JAK2V617F mutation pattern in ET and PV, respectively.[8] Lasho et al observed an occasional fluctuation in both MPL515 and JAK2617 mutant allele burdens, a phenomenon that might have arisen from either changes in BM cellular composition or allele burden that was below the detection limit of their assay. Their results in the correlation of changes in MPLW515L/K allele burden with either treatment or clinical features were inconclusive. More studies are needed to understand the clinical significance and prognosis of the concurrent MPL515 and JAK2V617F mutations.

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