The role of JAK2 gene mutations in the etiologic diagnosis of splanchnic vein thrombosis

Dear Editor,

Two clinical reports, both related to the association of a portal or mesenteric vein thrombosis and an hereditary thrombophilic disorder, have been recently published in this journal (1,2). Both suggest the need, in this clinical setting, of performing a thrombophilic study including G20210A factor II gene mutation, factor V Leyden mutation, activated protein C resistance, lupus anticoagulant, antcardiolipin antibodies, protein C and S deficiencies, antithrombin deficiency and plasmatic homocysteine.

Nevertheless, the most frequent cause of splanchnic thrombosis, either portal thrombosis (PT) or Budd-Chiari syndrome (BCS), is not the existence of one of those thrombophilic factors, but the presence of an underlying myeloproliferative disorder (MPD). This entity does not seem to have been taken into account in any of the two clinical cases. The MPD, identified using conventional criteria, is present in about 30% of the cases of PT and 50% of BCS, being this percentage at least similar to that of the whole group of the aforementioned thrombophilic disorders (3). The identification of a MPD in these patients is of paramount importance since the management of this disease is completely different to that of the patients with an abdominal thrombosis without a MPD. However, in this clinical setting the clinical suspicion of a MPD is hampered since the splenomegaly and the anemia induced by hemorrhage may induce normal values in blood cellular counts. This might have been the situation in the case report presented by Chirinos et al. (1) in which hemorrhagic phenomena were the main clinical feature. Thus, it is necessary to routinely evaluate patients with splanchnic thrombosis to rule out an “occult” MPD.

An association between MPD and point mutations in the JAK2 tyrosine kinase gene has recently been described (4,5). The first mutation to be described, the JAK2V617F, has been identified in 90% of patients with polycitemia vera (PV) and in 50% of those with essential thrombocytopenia or idiopathic myelofibrosis (6). If the recently described exon 12 mutations are considered, JAK2 gene mutations are present in virtually all patients with PV, thus constituting a sensitive diagnostic marker of the disease. This has led to a proposal for the modification of the WHO MPD diagnostic criteria, in order to include JAK2 mutations as major diagnostic criteria (8).

Patients with a MPD and the JAK2V617F mutation have an increased risk of thrombosis compared to those without the mutation (6). The JAK2 mutation even seems to confer some additional risk specifically for the development of splanchnic thrombosis, but not for the rest of locations (9). This mutation has been described in 40-50% of patients with polycitemia vera and in 17-36% of patients with PV (10,11). A recent study about patients that had developed a massive abdominal thrombosis leading to a visceral transplantation (liver or bowel) showed a 17% prevalence of the JAK2 mutation (12). Therefore, in the clinical setting of a patient with splanchnic thrombosis, the detection of JAK2 mutation may help to the identification of an occult MPD. For instance, in the study of Patel et al. (13) in patients with BCS, the JAK2 mutation was positive in 24 out of 41 patients, none of them fulfilling the classical MPD diagnostic criteria.

The presence of another thrombophilic factor, as it occurs in these case reports, does not exclude the possibility of finding an associated MPD. In the report by Kiladjian et al. (14), 11% of patients with PT and JAK2 mutation had an antiphospholipid antibody associated, 8% a protein S deficiency and 5% a factor II G20210A mutation. In the Prigminani et al. report (11), 32.3% of patients with a JAK2 mutation had another associated thrombophilic disorder. Our group has also described a patient with a BCS who presented an association of the JAK2V617F mutation and a factor V Leyden mutation (15).
In conclusion, nowadays, in the etiologic diagnostic work-up of a splanchnic thrombosis, the detection of JAK2 mutations and mainly the JAK2V617F, should be included, even in the presence of other possible etiologic factors and despite there is not any other laboratory parameter to suspect the presence of a MPD (14-16).

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References