Portal vein thrombosis as the first sign of a primary myeloproliferative disorder : diagnostic interest of the V617F JAK-2 mutation. A report of 2 cases

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Abstract

Portal vein thrombosis is, in some cases, related to a myeloproliferative disorder but the diagnosis of the latent forms may be difficult in case of normal blood counts. We report two cases of patient with portal vein thrombosis of unknown origin in whom the presence of the V617F mutation of the Janus Kinase 2 gene lead to the diagnosis of primary myeloproliferative disorder, confirmed on bone marrow examination. The search of the V617F mutation of the Janus Kinase 2 gene has to be performed in all cases of portal vein thrombosis of unknown origin. (Acta gastroenterol. belg., **2008**, 71, **39-41**).

Introduction

Since the widespread use of abdominal Doppler-ultrasonography and abdominal CT, the diagnosis of portal vein thrombosis (PVT) has become easier and more frequent. Therefore, the diagnostic challenge is to identify the cause of PVT.

The occurrence of PVT can be influenced by both local and systemic factors. Local factors include injury to the portal venous system (after surgery or splenectomy), disorders leading to decreased portal flow such as cirrhosis, hepatobiliary and pancreatic malignancies, and inflammatory diseases involving organs within the portal venous territory such as appendicitis, diverticulitis, inflammatory bowel diseases, pancreatitis, cholangitis and colon neoplasia. Systemic risk factors are represented by all the thrombophilic states such as primary myeloproliferative disorders (MPD), antiphospholipid syndrome, paroxystic nocturnal hemoglobinuria, hyperhomocysteinemia, and genetic coagulation abnormalities (eg, C or S protein deficiency, antithrombin deficiency, factor V Leiden mutation, prothrombin gene mutation, C677T MTHFR polymorphism) or auto-immune disorders (1,2,3). In a population of 23.796 autopsies, the prevalence of PVT was of 1,1% (4). Of the 254 patients with PVT, 44% had secondary hepatobiliary malignancies, 28% had cirrhosis, 10% had a major abdominal infectious or inflammatory disease and 3% had a MPD. For 14%, no cause was found.

In case of PVT related to MPD, blood count abnormalities and conventional criteria for MPD are frequently absent at the time of the diagnosis of PVT (2). Recently, the V617F mutation of the Janus Kinase 2 gene (JAK-2) was described in the majority of patients with polycythemia vera and in the other MPD (5-8). We report the case of two patients with PVT of unknown origin in who the presence of the V617F JAK-2 mutation lead to the diagnosis of polycythemia vera in the first and essential thrombocythemia in the second.

Case reports

Case 1

A 49-year-old man was seen in April 2006 because he complained of diffuse abdominal pain since 3 months. He had normal stools, a weight loss of 7 to 8 kg and nocturnal sudations. He had a past history of ischemic cardiomyopathy. He drank 20 to 30 beers a week. He took venlafaxin once a day and ibuprofen. Clinical examination only showed slight hepatosplenomegaly.

Biochemical analysis showed normal hemogram, no inflammatory syndrome and normal renal function. Liver enzymes were as follow : AST were normal, ALT 59 mU/ml (normal range : 0-41), alkaline phosphatases 164 mU/ml (normal range : 40-129), gamma GT 262 mU/ml (normal range : 8-61). Total bilirubin was normal. Anti-HCV antibodies, HBs antigen, anti-HBs antibodies, anti-nuclear, anti- smooth muscle and anti-liver kidney microsomes antibodies were negative.

Oesogastroduodenoscopy and colonoscopy were normal. Abdominal CT-scan showed a slight atrophy of the hepatic left lobe, slight splenomegaly and portal and superior mesenteric vein thrombosis with a portal cavernoma.

The hepatic venous pressure gradient was normal (3 mmHg). Transjugular liver biopsy showed macrovacuolar steatosis but no portal or sinusoidal fibrosis nor cirrhosis.

Following the discovery of the portal vein thrombosis, additional biochemical tests were performed. Coagulation screening tests, including fibrinogen, thrombin time, APTT, INR, antithrombin, C-protein, S-protein antigen, APCR, factor VIII, lupus like anticoagulant and anti-cardiolipin antibodies, were normal. The prothrombin G20210A mutation was also excluded.

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Homocystein level was normal. The D-dimer level was elevated at 0,68 µg/ml (normal range : 0,00-0,50). Paroxystic nocturnal hemoglobinuria was excluded. Leucoconcentrate was normal.

Cytogenetic analysis on peripheral blood leukocytes showed no BCR-ABL fusion transcript but demonstrated the presence of the V617F JAK-2 mutation.

Bone marrow examination showed an overgrowth of the 3 precursor's populations, suggestive of MPD such as polycythemia vera.

Anticoagulant therapy was started with acenocoumarol.

Case 2

In March 2001, a 72-year-old woman complaining of abdominal pain since 1 week was hospitalized. PVT was diagnosed on CT scan. Clinical examination was normal. Hemogram, coagulation screening tests and liver enzymes were normal. No thrombophilic state and no clue for MPD were found. No causes of PVT were found. Anticoagulant therapy with acenocoumarol was started.

In February 2007, cytogenetic analysis on peripheral blood leukocytes was performed and the V617F JAK-2 mutation was detected. Consequently, a bone marrow biopsy revealed essential thrombocythemia despite the fact that blood count was always normal during the 6 years follow-up.

Discussion

Portal vein thrombosis is frequently the first sign of a myeloproliferative disorder, in a latent form or at an early stage, in young patients (9). At the time of the diagnosis of PVT, blood count abnormalities and conventional criteria for MPD are frequently absent (2,9, 10). Bone marrow morphology and growth factor-independent megakaryocyte and erythroid colony growth in vitro lead to the diagnosis of MPD in more than 30% of patients with PVT (9).

The mechanism linking overt primary MPD and hepatic or portal vein thrombosis is thought to involve high blood viscosity due to high hematocrit value or raised count of abnormal platelets. But in our cases, these two changes were absent at the time of diagnosis of PVT. The pooling of blood cells in an enlarged spleen due to portal hypertension, decreased production or increased destruction of the blood cells, previous gastrointestinal bleeding or occult blood losses and dilution of blood cells by an increased plasma volume due to portal hypertension may explain the absence of peripheral blood changes typical of a primary MPD (9).

Clinicians need for biological markers to diagnose MPD in case of normal blood count and to perform bone marrow examination in only selected cases.

In 2005, an acquired single mutation V617F of the JAK-2 gene was described in the majority of patients with polycythemia vera (5-8) but also in 57% of patients with essential thrombocytemia and in 50% of patients with idiopathic myelofibrosis (8). This mutation was not found in the control populations and in patients with secondary polycythemia. It was concluded that V617F JAK-2 mutation is a 100% specific clue to a distinct clonal MPD (11). However, it seems that this mutation is not sufficient in itself for the MPD phenotype and additional acquired mutations are probably mandatory for the occurrence of MPD (12). A bone marrow biopsy must also be performed in V617F JAK-2 mutation positive patients to assist in the diagnosis of the underlying MPD that may have different prognoses and treatment (13).

JAK-2 is a cytoplasmic tyrosine kinase that intermediates between growth factor receptors on the haematopoietic progenitor cell surface (eg, erythropoietin and interleukin-3) and cytoplasmic signalling molecules (eg, STAT5 and PI3 kinase). JAK-2 possesses an active kinase domain (JH1), which is negatively regulated by an inactive pseudokinase domain (JH2). A guanine-to-thymidine mutation encoding a valine-to-phenylalanine substitution at position 617 (V617F) in the JH2 domain of JAK-2 disrupts the autoinhibitory function of JH2 and leads to constitutive JH1 tyrosine kinase activity (12). This "gain of function" mutation of JAK-2 gives haematopoietic precursors proliferative and survival advantages, with growth factor hypersensitivity.

The V617F JAK-2 mutation can be detected by PCR-direct sequencing using DNA from the granulocyte lineage or with increased sensitivity by amplification refractory mutation system using DNA from unfractionated blood (14).

Recently, the V617F JAK-2 mutation was found in 17,2 to 41,3% of patients with PVT (13,15,16). In the trial from Colaizzo et al., seven of the 17 patients carrying the mutation had a diagnosis of MPD at the occurrence of the venous thrombotic event. Three of the 10 others with the V617F JAK-2 mutation but without conventional criteria of MPD developed a MPD after a median follow-up of 41 months (15).

The V617F JAK-2 mutation was also found in 40 to 58,5% of patients with hepatic vein thrombosis (12,13,16). In the trial from Patel et *al.*, eleven of the 41 patients developed overt MPD after the diagnosis of Budd Chiari syndrome after a median follow-up of 49 months (12). In 91% of them the mutation was detected.

This mutation is a reliable non invasive molecular marker for MPD and should be viewed as the first test for the diagnosis of splanchnic vein thrombosis associated with MPD (13). But larger studies are required to establish the usefulness of JAK-2 mutation screening in all case of PVT before it is routinely performed (17).

In conclusion, we presented 2 cases of a PVT associated with a MPD and a normal blood count without conventional criteria, for whom the search for the V617F JAK-2 mutation was the diagnostic key. The search for the V617F JAK-2 mutation should be a part of the initial

check-up in all cases of PVT of unknown origin even years after the occurrence of PVT as demonstrated in case 2.

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