Transient ischemic attacks as the first presentation of *JAK2*-V617F positive chronic myeloproliferative neoplasm

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Abstract

Several studies have shown that thrombotic events may underlie a latent or subclinical myeloproliferative neoplasm (MPN) and precede its definite diagnosis by 1-2 years. An early diagnosis of patients with MPN, especially those with thrombotic events in the latent MPN phase, would be beneficial for their management, preventing further morbidity and improving their quality of life. For the majority of these cases, the location of thrombosis is mainly in the splanchnic major veins, while ischemic stroke and cerebral venous thrombosis are rarely observed. In this report, we present a female patient with transient ischemic attacks who suffered from a latent MPN, on the basis of a positive testing for the *JAK2*-V617F mutation.

Introduction

Thrombosis represents a harmful complication in patients with myeloproliferative neoplasms (MPN) and the leading cause of their increased morbidity and mortality.¹⁻³ Indeed, 12-39% of patients subsequently diagnosed with polycythemia vera (PV) and 11-25% of those diagnosed with essential thrombocythemia (ET) initially presented with a thrombotic attack (arterial, venous, or micro-circulatory).¹⁻³ Several studies have shown that thrombotic events may underlie a latent or subclinical MPN (MPN without increased blood counts) and precede its definite diagnosis by 1-2 years.^{4,5} Recently, a mutation in the *JAK2* gene (V617F), which is present but does not differentiate the different types of MPN (PV, ET and primary myelofibrosis),^{2,6} has been detected in a proportion of patients with unexplained thrombosis or thrombosis in unexpected sites, providing further evidence that these patients have a latent MPN.^{4,5} For the majority of these cases, the location of thrombosis is mainly in the splanchnic major

veins,^{4,5,7,8} while ischemic stroke and cerebral venous thrombosis are rare.^{9,10} In this report, we describe the rare case of a female patient who presented with transient ischemic attacks with latent MPN on the basis of a positive molecular testing for the *JAK2*-V617F mutation.

Case Report

A 45-year old woman was referred to our Department in February 2011 for a thrombophilia workup. The patient reported transient dysarthria one year previously but had no other neurological symptoms and signs, and was prescribed aspirin for three months by a neurologist. Fifteen days before coming to the hospital, she experienced sudden loss of sight from her left eye that lasted approximately 30 min. The patient reported no family or personal history of thrombotic events. She was not taking oral contraceptives and was not using alcohol or tobacco. Clinical examination was normal. Laboratory studies revealed a white blood count of $8.2 \times 10^9/L$, hemoglobin 15.3 gr/dL, and platelets $457 \times 10^9/L$. White cell count differential was neutrophils 78%, lymphocytes 18%, monocytes 4%, without the presence of blasts.

Coagulopathy workup showed INR 1.06, APTT 23.1 seconds (s), fibrinogen 305 mg/dL, D-Dimers 432 ng/mL, AT-III 118.9%, protein C 115%, protein S (total) 97.1%, protein S (free) 78.7%. Renal and liver function, electrolytes, uric acid and homocysteine levels were normal. The magnetic resonance imaging (MRI) of the brain revealed global ischemic encephalopathy, without major ischemic infarcts.

Triplex ultrasound examination of carotid and vertebral arteries did not reveal thrombotic plaques. Tests for rheumatoid factor, antinuclear and antiphospholipid antibodies (including anti-cardiolipin and anti-beta2 glycoprotein I) were all negative. Molecular analyses for the detection of FV Leiden and FII-G20210A mutations showed the presence of the wild-type alleles.

Considering the presence of borderline thrombocytosis ($>450 \times 10^9/L$), a more detailed medical history revealed that she had also noted an increase in her hemoglobin and hematocrit values the year before; the hemoglobin value had risen from 12.0 to 15.3 gr/dL. Furthermore, platelet counts remained above $400 \times 10^9/L$ over the previous year (range 402-457 $\times 10^9/L$). Therefore, further molecular analyses were performed, demonstrating the absence of BCRABL1 rearrangement and the presence of the *JAK2*-V617F mutation in the peripheral blood (Figure 1). Subsequent bone marrow aspiration and biopsy showed a slight increase in cellularity, characterized mainly by an

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increased number of megakaryocytes (with atypical nuclear morphology and a remarkable variation in their size) and myeloid cell hyperplasia, without fibrosis (Figure 2). Ultimately, erythropoietin levels were 6.1 U/mL (reference range 4-33 U/mL).

Taking into account the presence of the thrombocytosis, the *JAK2*-V617F mutation and the bone marrow findings, the diagnosis of an MPN (ET) was made according to the recent WHO criteria,¹¹ and the patient was put on hydroxyurea (500 mg per day) and aspirin (100 mg per day). To date, she is followed-up as an outpatient and is in excellent health.

Discussion

The detection of the *JAK2*-V617F mutation is a very useful tool for MPN diagnosis since it is present in more than 90% of patients with PV, in 50-70% with ET and in 30-58% with primary myelofibrosis,^{2,6} while it is absent in healthy individuals.¹² For this reason, it has been incorporated in the recent diagnostic criteria of MPN.^{6,11} Furthermore, the detection of the *JAK2*-V617F mutation has been used for the early diagnosis of MPN, especially for patients

Figure 1. *JAK2-V617F* mutation was detected by allele-specific PCR, as described.² In brief, the allele-specific polymerase chain reaction (PCR) protocol amplifies a 364 bp product (both mutant and wild-type alleles and serves as an internal control) and a 203 bp product (when the patient carries the *JAK2-V617F* mutation). M: E-Gel Low Range Quantitative DNA Ladder (Invitrogen, UK). Lane 1: patient's sample positive for *JAK2-V617F* mutation. Lane 2: negative control (patient with monoclonal gammopathy of undetermined significance). Lane 3: positive control (patient with polycythemia vera). Lane 4: negative PCR control. The PCR products were analyzed in 2% TBE agarose gels.

Figure 2. Histological section from bone marrow trephine shows trilineage hemopoiesis including megakaryocytes (indicated by arrows) with atypical nuclear morphology and variation in their size (Hematoxylin and Eosin stain, original magnification $\times 40$).

with thrombotic events in the latent MPN phase. It is obvious that for such patients, an early diagnosis could be beneficial for their management, preventing further morbidity and improving their quality of life.

According to the data presented here, our patient displayed transient ischemic attacks accompanied by mild (but not sustained) thrombocytosis along with an increase, although in normal ranges, of her hematocrit and hemoglobin values the year preceding referral. We consider that our patient suffered from *JAK2-V617F* positive ET, according to the new WHO diagnostic criteria.¹¹

It is well known that the presence of the *JAK2-V617F* mutation in ET patients has been associated with clinical and laboratory findings characteristic of PV, with higher hemoglobin and hematocrit levels, lower platelet count, lower erythropoietin levels and a higher incidence of thrombotic events, than ET patients without the mutation.^{2,13} Considering also that ET is a heterogeneous entity, it has been proposed that *JAK2-V617F*-positive ET and PV may form a biological continuum, since ET patients with high hemoglobin values are more similar to PV and may eventually progress to true PV in the future.^{2,12} Ultimately, we based our therapeutic decision on the data presented in the literature where the administration of hydroxyurea has been shown to be beneficial for MPN patients with thrombotic events carrying the *JAK2-V617F* mutation.¹³

For the majority of patients with MPN and thrombotic events, the location of thrombosis is mainly in the splanchnic major veins, as in Budd-Chiari syndrome and portal vein thrombosis.^{4,5,7,8} Indeed, 30-50% of patients with Budd-Chiari syndrome and 18-53% with intra-abdominal thrombosis have been shown to suffer from a latent MPN, on the basis of a posi-

tive testing for *JAK2-V617F*, in contrast to only 2% of patients with non-splanchnic venous thrombosis.^{5,7,14-16} As a result, it has been suggested that patients with splanchnic vein thrombosis should be evaluated for the *JAK2-V617F* irrespective of their blood cell count. On the other hand, there are not sufficient data to support the detection of the *JAK2-V617F* mutation in all the patients with cerebral venous thrombosis or stroke, since they are quite rare events during the latent MPN phase. In particular, Xavier *et al.* reported that only 2 out of 178 patients with ischemic stroke and none out of 44 with cerebral venous thrombosis carried the *JAK2-V617F* mutation, implying a latent MPN in less than 1% of such cases.⁹

Similarly, Pardanani *et al.* demonstrated that only one out of 138 patients with stroke (frequency $<1\%$) was positive for the *JAK2-V617F* mutation.¹⁰ Finally, in a larger series of 664 consecutive patients with either venous thromboembolism, or stroke, or myocardial infarction at a young age, only 6 patients ($<1\%$) were found positive for the *JAK2-V617F* mutation, confirming the relative rarity of latent MPN in patients with non-splanchnic venous thrombosis.¹⁷

However, in our patient, the presence of mild thrombocytosis, the increase in hemoglobin and hematocrit values over the previous year (although still within normal ranges), and the absence of any other inherited or acquired thrombophilia predisposition, raised the suspicion of MPN, which was confirmed by the detection of the *JAK2-V617F* mutation. Consequently, in selected cases, where there is evidence of laboratory signs suggestive of MPN, the detection of the *JAK2-V617F* mutation provides an early diagnosis of the disease.

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