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The Evolution of an Essential Thrombocythemia Diagnosed During an Ischemic Stroke

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Abstract: It is unfortunate that many patients with essential thrombocythemia are diagnosed during a thrombotic event (sometimes with disabling consequences) and are not detected by regular screening actions made by family physicians. We present the case of a female patient who developed ischemic stroke, during which a thrombocytosis was detected. The investigations led to the diagnosis of essential thrombocythemia with *JAK2V617F* mutation present in heterozygous version. The treatment with hydroxycarbamide produced liver cytolysis and that with anagrelide - blood pressure increase. Combining the two drugs allowed to reduce the doses and to obtain the disappearance of side effects. The role of chronic inflammation and therapeutic possibilities in essential thrombocythemia are discussed. The long time compliance of patient to active monitoring and treatment is essential for longue time survival without complications.
Keywords: Anagrelide, Atherosclerosis, Essential thrombocythemia, Genomic instability, Hydroxycarbamide, Ischemic stroke, Interferon, *JAK2V617F*, Statin, Thrombocythosis.

INTRODUCTION

Thrombotic accidents at various sites may be the occasion to discover an essential thrombocythemia (ET). Early descovery and treatment of ET could be a way to prevent atherosclerosis with various locations development and, thereby, its complications - ischemic stroke, myocardial infarction, episodes of acute peripheral ischemia and arterial and venous thromboses in other locations. In addition, by the correct treatment of ET we make the prophylaxis of bleeding and genomic instability, which could be the cause of disease progression towards secondary myelofibrosis and / or acute leukemia or other malignancies. We present the case of a female patient who was diagnosed with ET during an ischemic stroke.

CASE REPORT

A female patient, aged 60, was diagnosed 11 years ago with ET, with the occasion of an ischemic stroke which produced a left hemiparesis. The high level of platelets (1,321,000/mm3), the myelogram aspect (the proliferation of megakaryocytic series and the presence of mature, large megakaryocytes) and, subsequently, the discover of *JAK2V617F* mutation in heterozygous variant were arguments to support the diagnosis. We did not discover other causes of thrombocytosis. In addition, the patient had hypertension, hypercholesterolemia and ischemic heart disease. Due to the fact that she had a thrombotic event in the past, cytoreductive treatment was indicated to her. According to treatment guidelines, the first-line therapy indicated for ET is with hydroxycarbamide. Aspirin (75 mg / day) was added for the prophylaxis of arterial thrombosis. Our patient did not tolerate the treatment with hydroxycarbamide very well – she presented liver cytolysis with ALT values above 100 IU/l. For this reason the drug was replaced with anagrelide (an inhibitor of phosphodiesterase III, acting only on megakaryocytic series) during which she presented hypertension flare and epistaxis. The increase of doses of antihypertensive drugs could also not normalize blood pressure values. We note that interferon-alpha is not reimbursed for this disease în our country. We opted for the combined administration of hydroxycarbamide and anagrelide, which allowed reducing the doses of each product (500 mg/day, respectively, 2.5 mg/day) and disappearance of side effects. In this way, transaminases normalized and blood pressure could be managed. Under treatment with simvastatin (which has also antithrombotic effect) the cholesterol value was corrected, too. The patient showed a high degree of compliance to regular medical checks and treatment. She has never had thrombotic events, and the disease has not progressed to myelofibrosis or acute leukemia in those 11 years of follow-up.

DISCUSSION

ET was diagnosed in our patient during an ischemic stroke. How could this thrombotic event be prevent? A periodical screening (perhaps annually) of blood count performed by the family doctor would have allowed the discovery of a thrombocytosis, which could later be investigated by a hematologist. But if the discovered thrombocytosis were below 1,500,000/mm^3 (as in the case of our patient), it would not have had indication for cytoreductive therapy (according to current guidelines), so we could not prevent ischemic stroke occurrence.

In other words, if patients do not have thrombotic risk factors (platelets over 1,500,000/mm^3, age above 60 years, history of thrombosis, or leukocytosis above 11,000/mm^3) is it always fair to expect that they make an ischemic attack (even if the risk to develop it is considered to be low) to start treatment? This is a challenge for physicians, which is worth to be explored in the future. Perhaps the study of thrombin generation, increased in ET compared to control patients [1] (that assesses thrombotic status, as a result of pro- and anti-coagulant factors involved in this process) may constitute an objective criteria for estimating the thrombotic risk of these patients at a moment, and dynamic tracking of thrombin generation could determine the right moment to start the therapy. In addition, ADP-induced platelet aggregation is higher compared to controls [1]. Only long-term studies can evaluate the effectiveness of such a step and can answer this question.

Perhaps it is not coincidentally that our patient has coronary heart disease. There is a chronic inflammation in ET [2], which promotes the development of atherosclerosis at various sites, including that at the coronary level. The atheroma plaque is friable and prone to be break, a situation that favors the appearance of a thrombus on the plaque, the mechanism involved in the pathogenesis of major coronary accident. The statin used by our patient is useful for combating chronic inflammation [2] and hypercholesterolemia (which she shows); it has also antithrombotic and vascular pleiotropic effects. The increase of transaminases is not a side effect of statin, due to the fact that it disappeared after the reduction of hydroxycarbamide dose.

Our patient began the cytoreductive treatment with hydroxycarbamide, which was associated with aspirin. It has been found that the combination of hydroxycarbamide with aspirin (at dose of antiplatelet agent) is superior comparing to the combination of anagrelide with aspirin (at the same low dose) if the patient is at high risk to develop thrombotic vascular injury [3]. But a more recent study conducted on a group of 259 hygh-risk patients with ET found that anagrelide is not inferior to hydroxycarbamide on the prevention of thrombotic events in these patients [4]. Due to the fact that our patient showed increased transaminase values during the treatment with hydroxycarbamide, we reduced the doses and associated anagrelide as it is also recommended in forms with significant thrombocytosis. This allowed us to reduce the possible adverse effects. The value of JAK inhibitor drugs when hydroxycarbamide has been ineffective is limited [5].

Interferon-alpha could be another solution for our patient, but it is not reimbursed in our country. In patients with myeloproliferative neoplasms it can lead to complete hematologic remissions and, in particular, to those with ET platelet count drops rapidly and this decrease is durable without treatment for different time periods [6].

It is believed that the emergence of mutations that may initiate disease in hematopoietic stem cells of some patients with myeloproliferative neoplasms may be the result of an intrinsic genomic instability that was not appreciated before [7]. The fact that our patient presents *JAK2V617F* mutation increases the risk of thrombosis, especially visceral thrombosis. Patients with abdominal thrombosis have not always peripheral blood cell counts which can distinguish them from those without this mutation [8]. Recently it was accepted that the presence of *JAK2V617F* mutation and of cardiovascular risk factors are also thrombotic risk factors in ET [5]. The presence of this mutation before the diagnosis of ET may be an indicator of risk for arterial and venous thrombotic events, but during the monitoring of patients with ET this mutation is rather linked to venous thrombosis [9]. The same recent meta-analysis cited above which included 2922 patients with ET, established that this mutation confers higher odd risks for arterial and venous thrombosis, and the patients were predisposed to higher risk of microcirculatory disorders, compared to those who are not carriers of this mutation [9]. *JAK2V617F* mutation does not influence the rate of death of patients compared to those *JA2V617F* negative [10] and it is believed that the mutation does not have essential role for acute leukemia transformation [10, 11].

CONCLUSION

The treatment of patients with ET has to be adapted according to individual tolerance. In addition to cytoreduction, the treatment must be completed in order to target chronic inflammation present in ET, making in this way the prophylaxis (even secondary) of atherosclerosis and genomic instability.

The patient compliance to treatment is essential for a long survival without thrombotic or bleeding complications.

It is necessary to undertake studies to help to improve treatment initiation criteria in order to avoid the occurrence of complications that can endanger the life.

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