RIGHT TRANSVERSE SINUS THROMBOSIS AND BILATERAL PCA STROKE IN A PATIENT WITH A HYPERCOAGULABLE STATE

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ABSTRACT

Essential thrombocythosis (ET) is a myeloproliferative disorder (MPD) associated with an increase number of circulating platelets due to megakaryocyte proliferation. We report on a 72 years old man who was admitted in our department for headache and visual impairment. Brain imaging revealed bilateral occipital infarction and right transverse sinus thrombosis. The patient had common cardiovascular risk factors, recurrent deep vein thrombosis and sustained elevation of platelet counts in the past 8 years.

Key words: cerebral venous thrombosis, occipital stroke, thrombocytosis, essential thrombocythemia, myeloprolipherative disorder, hypercoagulable state

Abreviations

APC	activated protein C
CVCT	cerebral venous system thrombosis
CBC	complete blood cell
ET	essential thrombocythemia/thrombocytosis
MPD	myeloproliferative disorder
NO	nitric oxid
PCA	posterior cerebral artery
PV	polycytemia vera

BACKGROUND

Thrombocytosis is a pathological condition in which peripheral blood has a higher than normal number of platelets. It may be primary in myeloprolipherative disorders (essential thrombocythemia, polycytemia vera, chronic myelogenous leukemia, myelodysplasia) or secondary, reactive to chronic infections like rheumatoid arthritis, inflammatory bowel disease, acute bacterial diseases, malignancy, splenectomy, iron deficiency, nephrotic syndrome.

Essential thrombocytemia (thrombocythosis) is an acquired chronic myeloproliferative disorder characterized by a sustained elevation of platelets number, megakaryocyte hyperplasia, and a tendency for thrombotic/hemorrhagic events. It is more frequent in older patients and usually diagnosed between 50 and 70 years old (1). The predisposing factors for the development of this condition and the complex pathogenesis of its complications are still not completely understood.

It is a diagnosis of exclusion. In 2008 World Health Organization (WHO) proposed diagnostic criteria for ET: 1) persistent thrombocytosis (>400.000/uL) in the absence of a reactive cause, 2) absence of iron deficiency (normal serum ferritin for sex), 3) JAK2 V617 F assay (peripheral blood), absence does not exclude MPD, 4) hemoglobin less than 16 g/dL in a man or less than 14 g/dL in a woman (hematocrit< 47% in a man or <44% in a woman) in the absence of splenomegaly; otherwise red cell mass and plasma volume determinations are mandatory if a JAK2 V617 F assay is positive 5) negative Bcr-Abl FISH if a JAK2 V617 F assay is negative. 6) If there is anemia, macrocytosis, or

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leukopenia, or evidence of extramedullary hematopoiesis, a bone marrow examination (including cytometry and cytogenetics) is mandatory regardless of the JAK2 V617 F expression status (2).

High-risk patients for thrombotic complications are those over 60 years old, with thrombosis history, JAK2V61F and cardiovascular risk factors. The recommended treatment is cytoreductive drugs like hydroxyurea and low-dose aspirin. Busulfan or interferon-alfa may be used in hydroxiurea failures. In low risk patients low-dose aspirin is recommended (3).

CASE PRESENTATION

A hypertensive and dyslipidemia 72 years old male, treated by antihypertensive medication, with a history of recurrent left leg deep vein thrombosis, inconstant on oral anticoagulant therapy, was admitted in our department for headache and visual impairment.

From his medical history we noticed complex abdominal surgery (appendicitis and peritonitis) in 2005. The laboratory data available showed biological inflammatory syndrome and thrombocytosis, at that time interpreted as being reactive in the inflammatory context. Shortly after surgery the patient presents deep vein thrombosis on his left leg and follows treatment with oral anticoagulant for two months and then with sulodexide. Two years later was diagnosed with essential hypertension and his laboratory data showed thrombocytosis (570x1000/uL) without biological inflammatory syndrome. No further investigation on possible etiology of thrombocitosys was done.

In 2012 he was evaluated for right inguinal lymphadenopathy and laboratory samples disclosed thrombocytosis and biological inflammatory syndrome. Abdominal ultrasound was normal except hepathospenomegaly without focal processes or lymphadenopathy. Colonoscopy examination was normal. He was diagnosed with low urinary infection and treated with antibiotics. Also in 2012 the patient had a relapse of left leg deep vein thrombosis and oral anticoagulant therapy was recommended again.

In 2013 patient was admitted in our department for headache and visual impairment. Symptoms started suddenly three weeks ago when he noticed visual abnormality and after a week associated occipital headache. The symptoms were initially ignored by the family and considered to be caused by his chronic alcohol consumption. Because of the aggravations of the visual impairment three days before admission, the patient performed an ophtalmologic examination. No signs of raised intracranial pressure were found and he was advised to perform brain imaging. Cerebral computerized axial tomography (CT scan) disclosed bilateral occipital infarction and right transverse sinus thrombosis and he was referred to the neurologist. For several days before admission in our department the patient stopped his treatment with oral anticoagulant (INR 1.09). On physical exam blood pressure was 170/80 mmHg, with facial hyperemia, unremarkable for the rest. Neurological examination showed severe visual disturbances and cortical blindness with bilateral pupillary photomotor reflex, no motor or sensitive impairment, and no other focal neurological signs. He was aware of his deficit and developed a reactive depression syndrome.

Cerebral CT scan disclosed hypodensity in the occipital lobes suggesting acute stroke in right occipital lobe (right PCA territory) and subacute stroke in left occipital lobe (left PCA territory) (Figure 1). Cerebral AngioCT scan was performed and reveals – normal, contrast opacificated arteries in the absence of conspicuous atheromatous lesions, stenosis or any other malformation (Figure 2), and negative signs of cerebral venous thrombosis: – lack of contrast opacification in the right transverse sinus (Figure 3, Figure 4). MRI T2-weighted images shows hyperintensity on the right transverse sinus and hyperintense signal in both occipital lobes (Figure 5). Diffusion-weighted MRI shows restricted diffusion in the right occipital lobe (Figure 6).

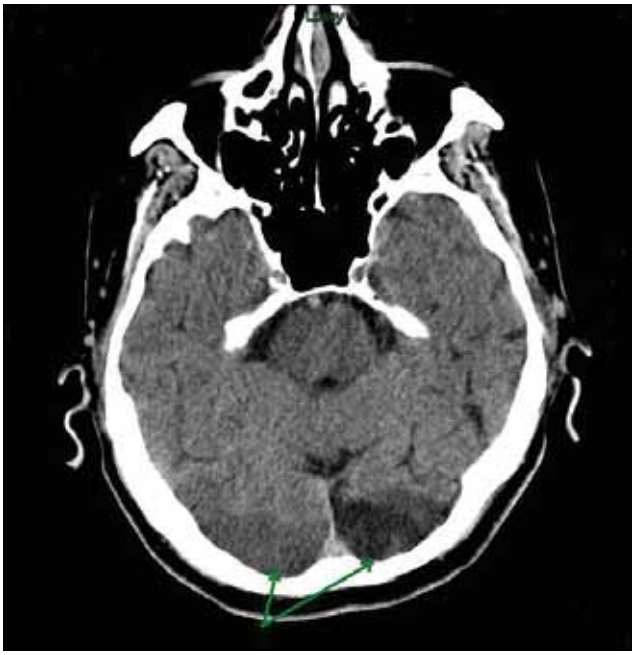

FIGURE 1. *CT scan – hypodensity in both occipital lobes suggesting acute stroke in right occipital lobe and subacute stroke in left occipital lobe*

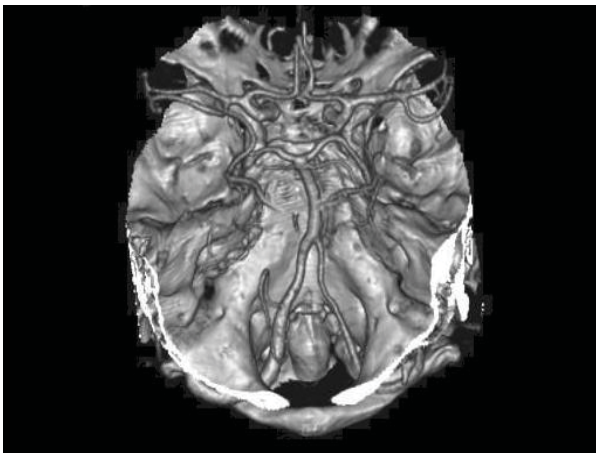

FIGURE 2. *Normal aspects on angioCT scan – arterial sequences*

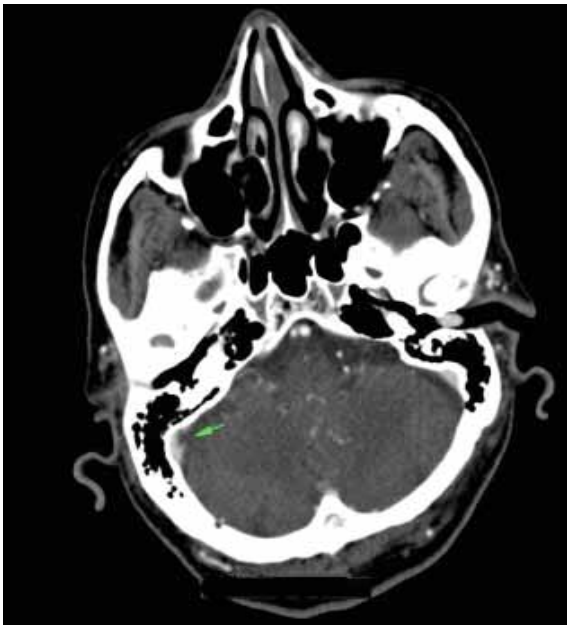

FIGURE 3. *AngioCT scan venous sequences – lack of contrast opacification in the right transverse sinus*

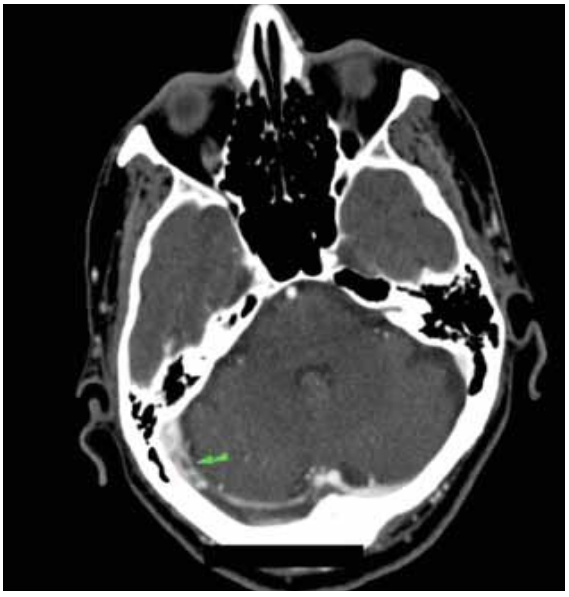

FIGURE 4*. AngioCT scan venous sequences – lack of contrast opacification in the right transverse sinus*

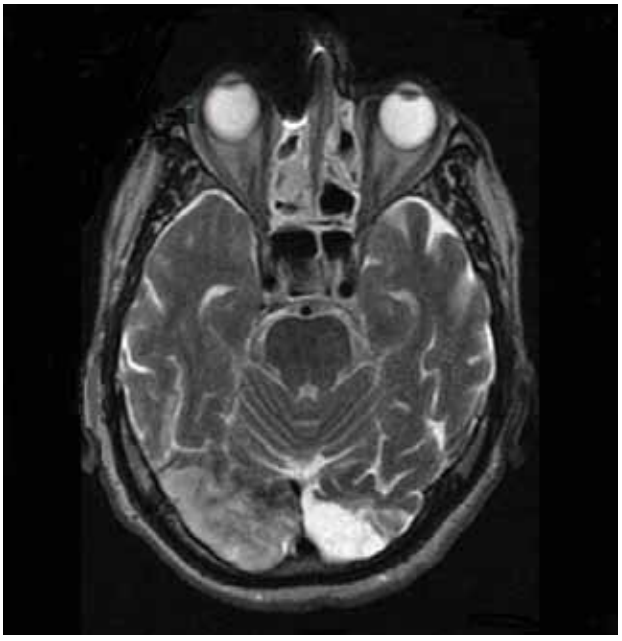

FIGURE 5. *Axial MRI- T2 weighted image-hyperintense signal in both occipital lobes.*

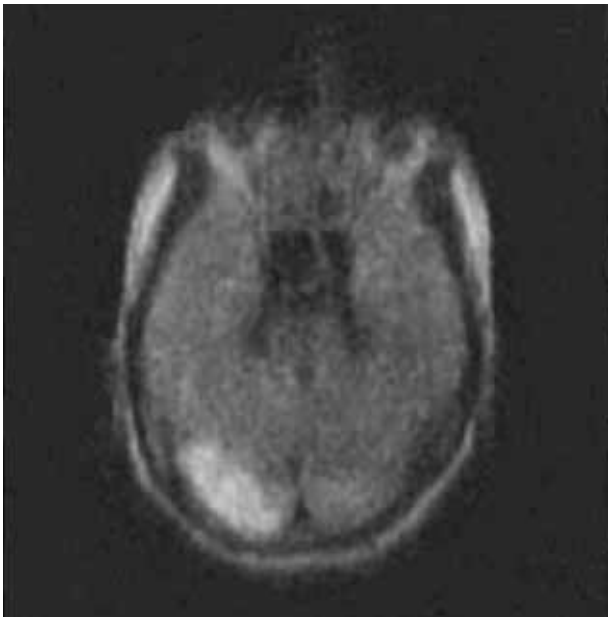

FIGURE 6*. MRI diffusion-weighted image – restricted diffusion in the right occipital lobe.*

Doppler ultrasonography of precerebral vessels was normal except a small atheromatous plaque on left ACC. His electrocardiography showed no abnormality. The routine transthoracic echocardiography showed left ventricular hypertrophy with normal left ventricular ejection, mild mitral regurgitation, no pericardial effusion. 24-hour Holter monitoring showed no arrhythmias. His repeated CBC revealed a slight leukocytosis, an increased number of platelets: 495-610x1000/uL (normal range 150-450x1000/uL) with normal serum levels of hemoglobin and hematocrit. Inflammatory tests

(ESR, CRP, fibrinogen) were in normal range and he had hypercholesterolemia. Thrombofilic tests (antithrombin, protein C, protein S, anticardiolopin antibody, antibeta2GPI) were normal except lupus anticoagulant and resistance to activated protein C. No serum iron deficiency was found. Regarding the possibility of an underlying neoplastic process the paraclinic investigations were completed with tumor markers and serum ferittin which had normal values. Abdominal ultrasound revealed hepatosplenomegaly with no signs of focal processes and of lymphadenopathy. Chest X-ray was normal.

We choose anticoagulant therapy for this patient with history of recurrent vein thrombosis, who received inconstant acenocumarol (INR outside therapeutic range in the last year) and had cerebral sinus thrombosis. We started with intravenous infusion of unfractionated heparine at therapeutic doses and then oral acenocumarol. He also received depletive treatment (mannitol), antihypertensive drugs, statine, intravenous infusion of hydration solutions and selective serotonin reuptake inhibitors (SSRIs). His clinical evolution was good with no other thrombotic events during hospitalization but the neurological disability (cortical blindness) persisted.

In the absence of any obvious solid malignancy, biological inflammatory syndrome or any other cause of reactive thrombocytosis, the patient was referred to the hemathology department for further investigations under suspicion of essential thrombocytosis.

DISCUSSION

We presented a case in which both arterial and venous thrombosis occurred in a 72 years old male with sustained elevation of platelet counts. The first event was probably stroke in the left PCA territory with homonymous right hemianopia and shortly after right PCA territory ischemia with severe visual disturbance, and right transverse sinus thrombosis. Regarding his medical history and after we excluded possible causes of reactive thrombocytosis we raised the suspicion of a myeloprolipherative disorder. In additional to hyperviscosity, ET patients developed an acquired hypercoagulable state resulting in thrombosis involving the cerebrovascular, coronary and peripheral arterial circulation, but also deep vein circulation, pulmonary embolism. Vascular occlusive events can also occur in the micro-vessels where they cause erythromelalgia, transient ischemic attacks, visual or hearing transitory deficites, recurrent headache, and peripheral paresthesia (4).

Ischemic events in the cerebral venous system has been rarely reported (5, 6).

Cerebral arterial ischemic events were reported mostly in patients with stenotic lesions and at least two vascular risk factors. No correlation was found between the platelets number and the occurrence of stroke (7, 8).

Literature data suggest that thrombosis complicate the clinical course in about 30% of patients diagnosed with ET. Abnormalities of circulating blood cells and endothelial cells are responsible for a hypercoagulability state characterized by increased thrombin generation and high circulating levels of procoagulant factors synthesized by the activated cells. Injury of the endothelium release specific markers which can bind platelets, activated them and made them capable to aggregate. So activated endothelial cells favor platelet and leukocyte adhesion and in situ production of procoagulant factors. The platelets suffer both quantitative and qualitative changes and expose on their surface the anionic phosphatidylserine which favor the generation of thrombin. Also an increased production of thrombin are due to an acquired resistance to activated protein C (APC). This acquired deficit was demonstrated in ET patients. Activated leukocytes form platelet-leukocyte aggregates and interact with endothelium cells and coagulation system. In addition endogenous nitric oxid (NO) who inhibits platelet adhesion, activation, secretion and aggregation are found to have low plasma levels in ET patients. The observation of high levels of plasma NO in patients treated with cytoreductive agents support the hypothesis of NO implication in thrombosis pathogenesis (4, 9, 10). JAK 2 mutation are of particular interest in MPD both for diagnosis and clinical evolution. This mutation has been detected in 23 to 57% of ET but initially described in PV (polycytemia vera) patients, where it has been observed in 65% to 97% of the cases. It cannot make the difference between types of MPD and his absence does not exclude the diagnosis but its presence was associated with a more frequent occurrence of both venous and arterial thrombosis (1, 11, 12).

Our patient had resistance to activated protein C and associated lupus anticoagulant that we considered an autoimmune epiphenomena and increase the risk for ischemic events especially venous thrombosis. An increased prevalence of antiphospholipid antibodies in ET was described in the literature (13).

We started the anticoagulant therapy in this case because of the cerebral venous sinus thrombosis

and thrombophilia risk factors but we emphasize that proper therapy with inhibitors of platelet aggregation and/or cytoreductive agents must be considered if the ET is confirmed by the hematologyst. Regarding the venous thrombosis, the guides recommends anticoagulant therapy with oral anticoagulant for 6-12 months if the patient has an idiopathic cerebral venous system thrombosis (CVST) and a slight form of thrombophilia, a long time therapy if the patient has a severe thrombophilia, with an increased risk of recurrence, or for unlimited time if patient has two or more idiopathic episodes of extracerebral venous thrombosis, or two or more episodes of CVST, or a single CVST with severe thrombophilia (14).

There are several reports in the literature which showed that anticoagulant treatment initiated for various reasons in patients with ET did not prevent further complications and after a variable period of time etiological cytoreductive therapy must be initiated (15). There are no available data regarding for how long to maintain oral anticoagulant but it seems also reasonable to consider antiplatelet-anticoagulant association in selected cases if Has- Bled score permitted.

CONCLUSIONS

Presence of sustained elevated platelet counts must be careful investigated for any possible reactive cause of thrombocytosis. No treatment is required for reactive thrombocytosis. In contrast patients with myeloproliferative disorders have an increased risk for thrombotic complications especially when associated cardiovascular risk factors, and needed specific treatment. Screening for thrombophilia must be performed in cases of recurrent deep vein thrombosis. Essential thrombocytosis is a diagnosis of exclusion and the patient who suspect this disorder must be referred to the hematologyst for further investigations and proper therapy in order to prevent severe complications resulting in permanent debilitating neurological sequelae.

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