Case Report

Recurrent cerebral venous sinus thrombosis in a young man- A case report of *JAK2*-negative polycythemia vera

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Abstract

Polycythemia vera (PV) is a myeloproliferative disorder most commonly associated with *JAK2V617F* mutation. Cerebral venous sinus thrombosis (CVST) has a wide range of etiologies and PV is one of them. CVST associated with PV has a poor prognosis. Some patients with classical PV lack *JAK2V617F* mutation and the molecular basis of *JAK2V617F*-negative PV is not known. We hereby report a case of a young man who presented with headache, vomiting and altered sensorium and was found to have recurrent CSVT. The patient had primary polycythemia and was subsequently diagnosed to have *JAK2*-negative PV.

Keywords: Cerebral venous sinus thrombosis, *JAK2V617F* negative, polycythemia vera

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare variety of cerebrovascular disease that can occur at any age.[1] It has wide range of aetiologies like hypercoagulable disorders and myeloproliferative disorders (MPD). It generally has a favourable outcome, but poor outcome has been documented with polycythemia as an underlying aetiology.[2] *JAK2V617F* is the most common mutation associated with MPD.[3] However, some patients with classical PV lack *JAK2V617F* mutation.[4] We report a case of young man with recurrent CVST and subsequently diagnosed to have *JAK2*-negative polycythemia vera (PV).

Case Report

A 21-year-old man presented with headache for 6 days, associated with projectile vomiting and altered sensorium since 3 days. There was no history of smoking or alcohol consumption. On examination, the GCS was E2M4V1. His pulse rate and blood pressure were 72/min and 130/80 mm Hg respectively. On central nervous system examination, plantar reflex were mute bilaterally and fundus examination revealed hyperemic disc with blurred margins with multiple dot haemorrhage and papilledema. Rest of the general and systemic examination was within normal limit.

Laboratory investigation revealed haemoglobin of 18.3 gm/dL, platelet count of 2.5 lac, elevated total leucocyte count (27,800/mm^3) and elevated packed cell volume (PCV-61). Peripheral smear showed RBCs that were normocytic normochromic with neutrophilic leucocytosis. Liver function tests and kidney function tests were normal. NCCT (Non contrast computed tomography) of head was done which showed multiple areas of haemorrhage in bilateral cerebral hemispheres, largest 74 × 57 mm in left frontal lobe [Figure 1]. Prothrombin time/International normalised ratio was normal. Blood cultures and urine cultures were sterile. Anti-Hbs Ag, anti-HCV, and HIV were non-reactive. Antinuclear antibody (ANA) and rheumatoid factor were negative.

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MRI (magnetic resonance imaging) and MR venography of brain showed Superior sagittal sinus thrombosis with partial thrombosis of right transverse sinus with a large bleed in left frontal region causing mass effect and midline shift. It also showed bleed in right occipital and right frontal lobe [Figure 2]. Thrombophilia profile (Factor 5 leiden, prothrombin mutation) and Antiphospholipid antibody were negative. Homocysteine levels- 48.03 μmol/l (n = 5.46-16.20) were raised.

Patient had similar episode of headache and vomiting, 3 months back for which he was admitted in a hospital. The patient's NCCT head was done 3 months back which showed multiple hemorrhages in right temporal (largest 67 × 37 mm), occipital and parietal lobes with associated peri lesional edema and midline shift. CT angiography brain was also done 3 months back which showed right transverse and right sigmoid sinus thrombosis with right temporoparietal lobe haemorrhagic infarction with mass effect. The patient was advised treatment but he was not compliant.

In view of elevated packed cell volume, erythropoietin level was measured and it was low, that is 1.68 (n = 5.4-31 mIU/ml) thus signifying primary polycythemia. Bone marrow aspirate showed leucocytosis with neutrophilia with normoblastic erythroid reaction. *JAK2V617F* mutation was not detected. So, finally the patient was diagnosed as CVST associated with intracranial haemorrhage (ICH) with underlying aetiology of *JAK2*-negative PV. *JAK2*-negative PV was diagnosed on basis of British Committee for Standards in Hematology (BCSH) guidelines 2007 [Table 1][5] according to which our patient satisfied A1, A2, A3, B2, and B4 criteria. Patient was started on T. warfarin with bridging Inj Enoxaparin to achieve therapeutic INR. Phlebotomy was done to reduce the haematocrit and other supportive measures were given. Patient regained consciousness by day 3 and was discharged on oral warfarin.

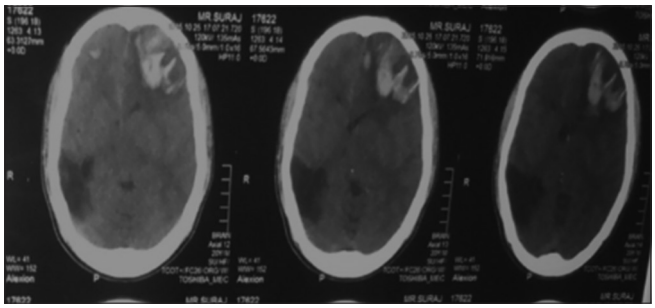

Figure 1: NCCT brain of patient showing the areas of haemorrhage in bilateral cerebral hemispheres, with largest 74 × 57 mm in left frontal lobe and with midline shift of 13 mm to right side

Discussion

Thrombosis is a serious complication of polycythemia and can lead to death in up to 8.3% of patients.[6] PV leads to primary polycythemia which is usually associated with mutation in *JAK2* gene.[7] There is no significant difference in the presentation of *JAK2*-positive and *JAK2*-negative PV, but *JAK2*-positive PV has a worse prognosis.[8]

Polycythemia causes stasis of blood that result in hyperviscosity leading to the development of thrombosis. Thrombosis of cerebral veins or sinuses results in raised venular and capillary pressure. As local venous pressure rises, there is a decrease in cerebral perfusion causing ischemic injury and cytotoxic edema and capillary rupture culminates in parenchymal haemorrhage.[9]

The BCSH criteria are considered the most accurate with the acceptable level of sensitivity and ability to differentiate PV and other causes of erythrocytosis.[10] The management of PV is phlebotomy combined with aspirin. Cytoreductive chemotherapy is recommended in patients in whom phlebotomy is poorly tolerated and those with high thrombotic risk.[11]

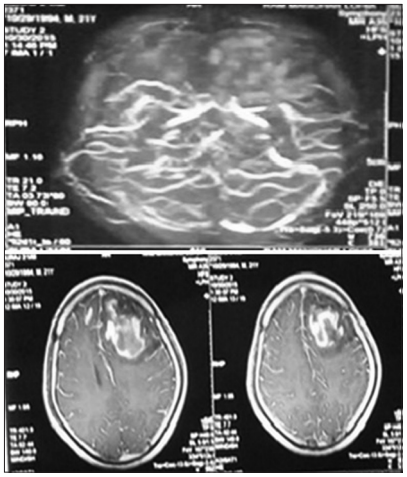

Figure 2: MRI and MR venography brain showing Superior sagittal sinus thrombosis with partial thrombosis of right transverse sinus with a large bleed in left frontal region causing mass effect and midline shift

Table 1: Diagnostic criteria for *JAK2*-negative PV [British Committee for Standards in Hematology (BCSH) guidelines 2007][5]

S.no	Criteria	S.no	Criteria
A1	Raised red cell mass (>25% above predicted) or hematocrit ≥0.60 in men, ≥ 0.56 in women	B1	Thrombocytosis (platelet count >4505 × 109/l)
A2	Absence of a mutation in *JAK2*	B2	Neutrophil leucocytosis (neutrophil count >10 × 109/l in non-smokers, >12.5×109/l in smokers
A3	No case of secondary erythocytosis	B3	Radiological evidence of splenomegaly
A4	Palpable splenomegaly	B4	Endogenous erythroid colonies or low serum erythropoietin
A5	Presence of an acquired genetic abnormality		

Diagnosis requires A1 + A2 + A3+either one other A or two B criteria

Anti-coagulation (AC) is used almost universally on the rationale of reversing the causal thrombotic process. Owing to the presence of a hemorrhagic element in 40% of CSVT, the administration of anticoagulant treatment still remains controversial,[12] although several studies have demonstrated AC treatment to be beneficial rather than hazardous. However, repeating a CT after at least 1 day from onset of symptoms to confirm that ICH is regressing or at least not progressing may be advisable before starting AC.[13]

Conclusion

Patients with CVST secondary to PV have an overall worse prognosis in comparison to other aetiologies. Thus, this case has been presented to sensitize the common physician towards the common symptoms which are frequently misdiagnosed. Early diagnosis and treatment of CVST can prevent lethal complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There is no conflicts of interest.

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