Cerebral venous sinus thrombosis in polycythemia vera patients with JAK2V617F mutation

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To the Editor: Polycythemia vera (PV) is a chronic progressive myeloproliferative neoplasm (MPN) characterized by clonal proliferation of myeloid cells. This condition presents with a high number of abnormal erythrocytosis, leukocytosis, and thrombocytosis, which may lead to venous thromboembolism. Cerebral venous sinus thrombosis (CVST) is a rare presentation of PV in clinical practice. Symptoms of PV are often insidious during the onset, and a lack of specific clinical manifestations of CVST may lead to delayed diagnosis. To date, diagnosis and management of CVST in PV remain a challenge due to the low incidence and limited evidence. In this study, we presented five cases of PV with JAK2V617F mutation, and CVST was the first manifestation of PV. The detailed characteristics are summarized in Table 1. The Institute Ethics Committee of Xuanwu Hospital, Capital Medical University approved this study (approval number 20191119). The authors certify that they have obtained all appropriate patient consent forms.

All CVST events occurred before PV diagnosis. CVST was diagnosed according to the established criteria and confirmed via magnetic resonance venography (MRV), computed tomography venography (CTV), or cerebral digital subtraction angiography (DSA). All patients underwent magnetic resonance imaging (MRI) and MRV, one patient underwent CTV, and three patients underwent DSA. The diagnosis of PV was defined according to the criteria described by the World Health Organization. The most common symptom of CVST was acute or subacute refractory and a diffuse headache was presented initially in all patients. Increased intracranial pressure (ICP), papilledema, and JAK2V617F mutation were confirmed in five patients. MRI revealed parenchymal lesions in four cases with cerebral infarction. Meanwhile, MRV or cerebral DSA showed that multiple sinuses were simultaneously involved in four patients. Transverse sinus was the leading site of involvement (all five patients) followed by sigmoid sinus (four patients). There was no other organ thrombotic event in the five patients. All patients were treated with low molecular weight heparin (LMWH, 90 U/kg each time, subcutaneously, twice daily), followed by oral anticoagulation, including warfarin in three or dabigatran in two patients. Moreover, two patients received endovascular thrombectomy due to deterioration despite anticoagulation. The two patients underwent cerebral DSA, suggesting multiple thromboses in venous sinuses. The thrombus was repeatedly drawn with a thrombus removal stent (8.0 × 20 mm, Boston Sterling, Natick, Massachusetts, USA) and the catheter negative pressure was used to attract the thrombus. Re-examination of the angiography showed that venous sinus was unobstructed and there were no complications after surgery. For PV, all five patients were treated with hydroxyurea. After treatment, the clinical symptoms of these patients were alleviated (eg, headache symptoms disappeared or improved). Most patients (four of five patients) had a favorable outcome and no one recurred at the last follow-up.

Herein, one case was presented in detail (case 4 in this study); the clinical course of CVST with PV. The fourth patient, a 52-year-old woman, complained of nausea and headache for 2 months, which was initially considered as antral gastritis; however, her symptoms progressed. She began to develop blurred and double vision a month later. Neurological examination revealed limited abduction of the right eye and papilledema. Lumbar puncture showed a high ICP together with normal cerebral spinal fluid. Abdominal ultrasound revealed splenomegaly. Furthermore, erythrocyte (5.51–6.26 × 1012/L) and hemoglobin level (156–175 g/L) were noted. Bone marrow biopsy and
gene examination confirmed JAK2V617F mutation. MRI demonstrated thrombosis of the bilateral transverse sinus, left sigmoid sinus, and left jugular vein together with bilateral parietal cerebral venous infarction. DSA revealed stenosis of bilateral transverse sinus, reflux disturbance of left sigmoid sinus, and internal jugular vein. The patient was administered antithrombotic therapy (LMWH, warfarin, and aspirin) and cytoreductive treatment (hydroxyurea and interferon-α [IFN-α]). Moreover, optic nerve sheath fenestration (ONSF) was performed due to markedly high ICP and visual impairment. Her symptoms were improved gradually. No CVST events occurred in the subsequent 2 years of follow-up.

PV is characterized by a high number of abnormal erythrocytosis, which might be prone to venous thromboembolism, and CVST is a rare initial presentation of PV. However, the precise mechanism for thrombosis in PV has not yet been comprehensively elucidated. All of our PV patients with CVST were confirmed to be positive for the JAK2V617F mutation. The JAK2V617F mutation status has been linked with PV and identified in 75% to 98% of the patients, which might be associated with an additional venous thrombosis risk.[3] Unfortunately, due to technical limitations, we were unable to determine the JAK2V617F allele burden, which is more effective when predicting the risk of thrombosis. Clinical studies investigated how the JAK2V617F allele burden, a measure of "gene dosage" for the mutation that is most often measured in granulocyte DNA, correlated with certain clinical features. In addition, JAK2V617F mutation may be related to the treatment effect. The previous publication showed that MPN JAK2V617F positive patients had a statistically higher percentage of reticulated platelets than JAK2 negative patients and cytoreductive therapy with hydroxyurea appeared to decrease reticulated platelets in JAK2 positive patients.

Clinical manifestations of CVST are highly variable,[4] while the clinical course of PV is often indolent, which

| Parameters | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 |
|------------|--------|--------|--------|--------|--------|
| Age (years)/sex | 50/male | 58/female | 64/female | 52/female | 42/female |
| Family history | No | No | No | No | Yes∗ |
| Index event | CVST | CVST | CVST | CVST | CVST |
| Duration of CVST (days) | 365 | 75 | 5 | 73 | 20 |
| Interval between symptoms and diagnosis of CVST (days) | 210 | 62 | 30 | 43 | 30 |
| Presentations | Headache, nausea/ vomiting, blurred vision | Headache, nausea/ vomiting, blurred vision | Headache, nausea, blurred vision, diplopia | Headache, mild hemiparesis, seizure |
| Past history | Hypertension | Hypertension | No special | No special | Headache |
| Papilledema | Yes | Yes | Yes | Yes | Yes |
| Splenomegaly | None | None | None | None | None |
| Erythrocyte (×10^{12}/L) | 5.83–7.11 | 3.81–6.35 | 4.04–5.76 | 5.51–6.26 | 3.84–5.15 |
| Hemoglobin (g/L) | 151–185 | 118–169 | 126–180 | 156–175 | 132–172 |
| JAK2V617F mutation | Positive | Positive | Positive | Positive | Positive |
| Bone marrow biopsy | MH | MH | Bilateral frontal, parietal, occipital CVI | Bilateral occipital CVI | Bilateral parietal CVI |
| MR findings | Bilateral occipital CVI | Normal | Bilateral frontal, parietal, occipital CVI | Bilateral occipital CVI | Bilateral parietal CVI |
| Site of CVST on MRV | Right TS, right SiS, right JV | SSS, SS, bilateral TS | SSS, SS, left TS, left SiS | bilateral TS, left SiS, left JV | SSS, ISS, left SiS, SS, bilateral TS, bilateral CV |
| Treatment | LMWH, warfarin, hydroxyurea | LMWH, dabigatran, hydroxyurea | LMWH, warfarin, hydroxyurea, endovascular thrombectomy | LMWH, warfarin, hydroxyurea, IFN-α, ONSF | LMWH, dabigatran, aspirin, hydroxyurea, endovascular thrombectomy |
| Duration of follow-up (months) | 18 | 22 | 36 | 24 | 6 |
| Outcome of CVST | Improved | Improved | Improved | Impaired vision | Improved |

∗The patient’s mother has polycythemia vera. CV: Cortical vein; CVI: Cerebral venous infarction; CVST: Cerebral venous sinus thrombosis; IFN: interferon; ISS: Inferior sagittal sinus; JV: Jugular vein; LMWH: Low molecular weight heparin; MH: Myelodysplastic hyperplasia; MR: Magnetic resonance; MRV: Magnetic resonance venography; ONSF: Optic nerve sheath fenestration; PV: Polycythemia vera; SiS: Sigmoid sinus; SS: Straight sinus; SSS: Superior sagittal sinus; TS: Transverse sinus.
often leads to missed or delayed diagnosis. Generally, CVST is a multi-factorial and uncommon cerebrovascular disorder that occurs in young patients. Additionally, our findings indicated that headache is the first and most common CVST presentation, which is often accompanied by intracranial hypertension syndromes, including nausea/vomiting, blurred vision or papilledema or other focal neurological deficits, and epileptic seizure. Therefore, the diagnosis of CVST should be considered in idiopathic intracranial hypertension PV patients complaining of a severe unexplained headache or young patients presenting with stroke symptoms or overlapping clinical presentation of these conditions. Finally, multiple sinus thrombosis is a frequent occurrence and is confirmed by MRV. CVST location is frequently associated with predisposing causes. Cavernous sinus thrombosis was more common in patients with infection-associated CVST, and non-infectious CVST is more common in the superior sagittal sinus and transverse sinus, suggesting that the risk factors may be non-inflammatory diseases, such as PV, when the thrombus occurs in the aforementioned sinuses.

PV is treated to control symptoms and reduces the risk of thrombosis complications. In addition to LMWH, all our patients received indefinite sequential warfarin or dabigatran as systemic anticoagulation for CVST.[3] Meanwhile, two patients received endovascular therapy and the symptoms improved with no recurrence during follow-up. This result provided further evidence that endovascular treatment might be a safe and viable option for PV patients with PV who fail to respond to anticoagulant therapy or have clinical deterioration. Moreover, ONSF was performed in case 4 for markedly high ICP and visual impairment, where the eyesight improved slowly. For these patients, ONSF may be a safe and effective alternative to protect vision function.

Since a previous history of thrombosis has been identified as a risk factor for thromboembolism recurrence; therefore, it is also critical to prevent CVST recurrence. The treatment regimen for PV can be determined based on the probability of thrombotic complications, which was estimated using two risk-based models of the thrombosis risk stratification system: low risk and high risk. The patients were classified into high-risk PV patients based on the complication of CVST and mutation of JAK2V617F. In addition to standardized anticoagulant therapy, cytoreductive treatment is currently recommended in high-risk PV patients. The five patients received both systemic anticoagulation and cytoreductive therapy (hydroxyurea or IFN-α), which achieved favorable long-term outcomes except for case 4 with visual impairment. Fortunately, similar to CVST in the general population, most CVST cases in PV have a relatively favorable prognosis after treatment. Consequently, a majority of patients improved after aggressive treatment, with no PV and CVST relapse reported during the follow-up period.

In conclusion, CVST could be the initial presentation of PV due to hypercoagulability. The JAK2V617F mutation can be used as a diagnostic marker or parameter to stratify the risk of thrombosis. Anticoagulant and cytoreductive treatments prevented the recurrence of CVST in PV with JAK2V617F mutation.

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**Conflicts of interest**

None.

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