Renal Vein and Cerebral Venous Sinus Thrombosis Caused by JAK2 V617F-Mutated Myeloproliferative Neoplasm

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ABSTRACT

This case report describes a 33-year man who sequentially developed renal vein thrombosis (RVT) and cerebral venous sinus thrombosis (CVST) over two years. Initially presenting with RVT, the patient was treated with thrombus aspiration and anticoagulation. Two years later, he presented with CVST, confirmed by imaging and lumbar puncture. Despite initial inconclusive laboratory findings, persistent thrombocytosis led to further investigation, revealing a JAK2 V617F-mutated myeloproliferative neoplasm (MPN) through bone marrow biopsy. This mutation, rarely associated with CVST, was identified as the underlying cause of his recurrent thrombotic events. The patient was successfully managed with β-interferon and rivaroxaban, achieving normalised platelet counts and preventing further thrombosis. This case underscores the importance of screening for JAK2 V617F mutation in young patients with unexplained or recurrent venous thrombosis, particularly in atypical sites, to guide appropriate treatment and prevent recurrence. It also highlights the complex and diverse aetiologies of CVST, emphasising the need for thorough diagnostic evaluation to identify underlying causes, such as MPN, in atypical presentations.

Key Words: *Venous sinus thrombosis, Renal vein thrombosis, JAK2 V617F mutation, Myeloproliferative neoplasm, Aetiology*.

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INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is an unusual and frequently unrecognised cerebrovascular condition accounting for approximately 0.5–1% of all strokes.[1,2] It has an estimated annual incidence of 2-5 per 100,000.[2] The causes of CVST include genetic/acquired hypercoagulable states, infections, inflammatory diseases, haematologic disorders, oral contraceptives, and trauma.[2] Here, the authors report a case involving a young man who sequentially manifested renal vein thrombosis (RVT) and CVST. When diagnosed with CVST, while there were several confounding potential aetiological diagnoses, JAK2 V617F-positive myeloproliferative neoplasm (MPN), eventually came to light during the regular follow-ups. This case highlights the importance of screening for JAK2 V617F to determine the aetiology of CVST, especially in patients with a history of venous thrombosis in uncommon sites. Identifying the correct aetiology can help choose appropriate treatment and prevention strategies.

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CASE REPORT

A 33-year man presented to the Department of Neurology with a 5-day history of headache accompanied by nausea, vomiting, and loss of appetite. He did not have limb weakness, seizures, fever, or altered consciousness. However, his medical history indicated that two years ago, he was admitted for lower back pain. Abdominal contrast-enhanced computed tomography (CT) revealed left RVT, and left RVT aspiration and balloon angioplasty were performed. After the surgery, the patient was prescribed oral rivaroxaban 20 mg qd. Three months later, the follow-up ultrasound revealed that the renal vein was recanalised, so rivaroxaban was discontinued. He had no other relevant family history. There was no obvious abnormality in the neurological examination. After admission, brain magnetic resonance imaging (MRI) showed abnormal signals in the left caudate nucleus, lentiform nucleus, and thalamus, indicative of a potential venous infarction (Figure 1A, B). Brain magnetic resonance angiography (MRA) found no significant abnormality (Figure 1C). However, brain magnetic resonance venography (MRV) failed to visualise the inferior sagittal sinus, straight sinus, left transverse sinus, sigmoid sinus, and jugular venous bulb, suggestive of occlusion (Figure 1D, E). Subsequent lumbar puncture disclosed cerebrospinal fluid under normal pressure of 145 mm H_2O, alongside a white blood cell count of 1×10^6/L (normal range: 0-5×10^6/L) and an elevated protein concentration of 469.95 mg/L (normal range: 200-400 mg/L).

Non-infectious CVST was diagnosed, and low molecular weight heparin (LMWH), 4250 IU, q12h, was given subcutaneously. The headache was gradually alleviated. We then wanted to understand why did he develop RVT and CVST in two consecutive years. The laboratory tests detected the following abnormalities: Platelet count 458×10^9/L (normal range: $125\text{-}350\times10^9$/L), but reactive thrombocytosis could not be ruled out, and the haematologist recommended regular follow-up of platelet levels. Plasma protein S was 68.8% (normal range: 75-130%), and its activity was reduced. According to the diagnostic criteria for protein S deficiency, it needed to be retested at least 6 weeks after the onset of thrombosis. Anti-β2 Glycoprotein-I antibody (anti-β2-GP1Ab) was 73.74 RU/ml (normal range: 0-20 RU/ml). There were no significant abnormalities in tumour markers, lupus anticoagulant, anti-nuclear antibody (ANA) spectrum, and antineutrophil cytoplasmic antibodies (ANCAs). Hence, the aetiology of CVST could not be determined. The anticoagulation regimen was adjusted to oral rivaroxaban after discharge.

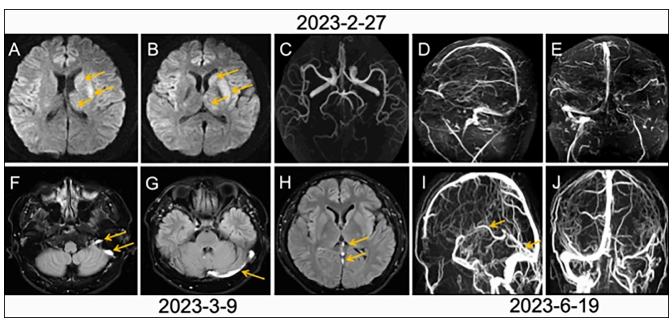

Figure 1: Brain magnetic resonance imaging findings. (A-E) Brain MR findings on 27 Feb 2023. (A, B) DWI indicates a high signal in the left caudate nucleus, lentiform nucleus, and thalamus (orange arrows). (C) Brain MRA shows no significant abnormality. (D, E) Brain MRV showed the occlusion of the inferior sagittal sinus, straight sinus, left transverse sinus, sigmoid sinus, and jugular venous bulb. (F-H) Brain MR findings on 9 Mar 2023. T2 FLAIR shows the thrombus in the straight sinus, left transverse sinus, sigmoid sinus, and jugular venous bulb (orange arrows). (I, J) Brain MR findings on 19 Jun 2023. Brain MRV shows recanalisation of the vein of Galen, internal cerebral veins, and straight sinus (orange arrows), as well as partial visualisation of the left transverse sinus, sigmoid sinus, and jugular venous bulb.

DWI, Diffusion-weighted imaging; FLAIR, Fluid-attenuated inversion-recovery; MR, Magnetic resonance; MRA, Magnetic resonance angiography; MRV, Magnetic resonance venography.

Following three months of anticoagulant therapy, the patient underwent a follow-up. He had no headache. The brain MRV showed recanalisation of the Galen vein, internal cerebral veins, and straight sinus, as well as partial visualisation of the left transverse sinus, sigmoid sinus, and jugular venous bulb (Figure 1I, J). The laboratory findings revealed restoration of plasma protein S level to normal level (97.5%) and a reduction in the anti-β2-GP1Ab titre to 15.08 RU/ml. These findings effectively ruled out protein S deficiency and antiphospholipid antibody syndrome, respectively. However, the persistent elevation in platelet count, measuring at 513×10^9/L (normal range: 125-350), prompted a sustained vigilance. One month later, the patient's platelet count increased to 660×10^9/L, and a bone marrow biopsy was performed, which showed an MPN (Figure 2). An increased number of megakaryocytes with abnormal morphology was detected. Polymerase chain reaction (PCR) for the JAK2 V617F point mutation was positive, and quantitative real-time PCR analyses for BCR: ABL1 P210 and P230 were negative. These findings identified MPN with JAK2 V617F mutation in an uncommon site as the aetiology for his recurrent venous thrombosis. The patient is currently receiving treatment with β-interferon and rivaroxaban. This treatment regimen has not only helped maintain a normalised platelet count but has also effectively precluded the recurrence of thrombotic events in other sites.

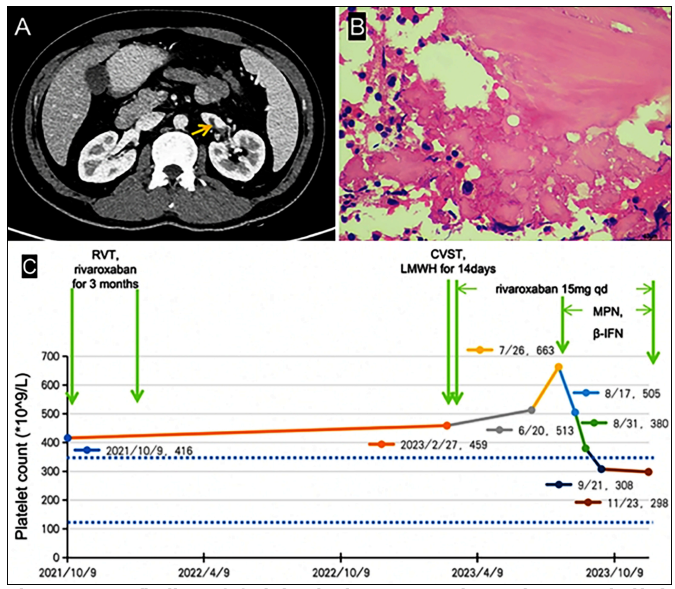

Figure 2: Case findings. (A) Abdominal contrast-enhanced CT revealed left renal venous thrombosis (orange arrows). (B) Bone marrow biopsy revealed the presence of a myeloproliferative tumour. The number of megakaryocytes was significantly increased, and they exhibited abnormal morphology, being scattered or clustered, with mainly lobulated nuclei. Some nuclei had increased lobulation, some had extremely irregular nuclear shapes, and chromatin was concentrated. (Scale bar = 40 μm). (C) The 2-year trend of platelet levels and the course of diagnosis and treatment in our patient.

CT, Computed tomography; CVST, Cerebral venous sinus thrombosis; IFN, Interferon; MPN, Myeloproliferative neoplasm; RVT, Renal vein thrombosis.

DISCUSSION

To the best of our knowledge, this is the first reported case of RVT and CVST caused by JAK2 V617F-mutation MPN in a young man.

The risk factors and aetiologies of CVST are complicated and diverse. A large registry study of patients with CVST found thrombophilia in 34.1%, genetic thrombophilic disorders (antithrombin III deficiency, protein C deficiency, protein S deficiency, and factor V Leiden) in 22.4%, antiphospholipid antibodies in 5.9%, and haematological disorders (anaemia, polycythaemia, and thrombocythaemia) in 12% of the cases.[3] Prevention and treatment of CVST vary depending on the aetiology. Therefore, determining the underlying cause is critical for preventing recurrence.

Studies have shown that JAK2 V617F is a risk factor for MPN and is closely associated with abdominal vein thrombosis.[4-6] However, data on the association between CVST and JAK2

V617F one scarce. De Stefano *et al*. have reported a small number of patients with CVST who are carriers of the JAK2 V617F mutation but do not present with MPN.[5] Similarly, our patient had no systemic symptoms, splenomegaly, or anaemia before diagnosis but repeatedly experienced venous thrombosis in atypical sites.

In conclusion, the aetiologies of CVST are tangled and complicated. The present case emphasises the importance of accurately determining the aetiology, especially in young patients with a history of venous thrombosis, recurrent CVST, or venous thrombosis in unusual sites. In such cases, screening for the JAK2 V617F mutation should be considered to determine the aetiology of CVST.

PATIENT'S CONSENT:
Written consent was obtained from the patient.

COMPETING INTEREST:
The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:
YW: Reported idea and design and manuscript writing.
LW: Writing of the manuscript and literature review.
CZ: Revising the manuscript critically for important intellectual content.
All authors approved the final version of the manuscript to be published.

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