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Case Report

Endovascular treatment for severe cerebral venous sinus thrombosis in a patient with polycythemia vera and nephrotic syndrome: a case report

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Abstract: Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease that can occur at any age and generally has a good prognosis. Polycythemia vera and nephrotic syndrome are uncommon risk factors for cerebral venous sinus thrombosis. A dilemma exists in the treatment of cerebral venous sinus thrombosis with polycythemia vera and nephrotic syndrome, as some cases are refractory to first-line therapy. Here, we report a patient with CVST who presented with a generalized seizure and was found to have bilateral frontal lobe hemorrhage and subarachnoid hemorrhage. Brain magnetic resonance venography showed extensive cerebral venous sinus thrombosis extending from the superior sagittal sinus to the left internal jugular vein. Further testing revealed that the patient had polycythemia vera and nephrotic syndrome. Anticoagulation therapy had limited effects. He underwent endovascular intervention, including stent thrombectomy, intermediate catheter aspiration, balloon dilatation, and local intravenous thrombolysis, to achieve revascularization. After 9 months of follow-up, the patient had recovered well without any sequelae. This case shows that in patients with critical cerebral venous sinus thrombosis who fail to respond to anticoagulant therapy, stent thrombectomy combined with intermediate catheter aspiration, balloon dilation, and local thrombolysis may be a viable option. This strategy can quickly resolve venous sinus obstruction and improve the prognosis of patients with critical cerebral venous sinus thrombosis.

Keywords: Cerebral venous sinus thrombosis, polycythemia vera, nephrotic syndrome, intravascular thrombolysis, stent thrombectomy

Introduction

Cerebral venous sinus thrombosis (CVST) is a rare cerebrovascular disease characterized by thrombosis of the cerebral venous or dural sinuses, and it usually causes nonhemorrhagic and hemorrhagic stroke. It has a wide range of etiologies, including hereditary thrombosis, acquired prethrombotic conditions, autoimmune diseases, infection, and local causes [1-3].

Polycythemia vera is a myeloproliferative tumor that causes an increase in red blood cells with hyperviscosity, making the patient prone to complications of thrombotic disease. CVST as its presenting symptom is relatively rare. The nephrotic syndrome also causes hypercoagulability, which often results in clots in the deep veins of the lower extremities and the renal veins [4]. Polycythemia vera and nephrotic syndrome are both rare causes of CVST [5-7].

In randomized clinical trials, anticoagulation therapy is the only treatment with a high level of evidence for CVST [8-10]. Endovascular treatment has been used only in severe cases whose clinical worsening was unresponsive to systemic heparin and progressed to intracranial hemorrhage, mental condition disorder, coma, or deep cerebral venous thrombosis [11-14]. This article reports a severe CVST patient with both polycythemia vera and nephrotic syndrome who did not respond to anticoagulation and was referred for emergent endovascular treatment.

Case presentation

A 48-year-old male, an airport ground staff member, was sent to our hospital because of

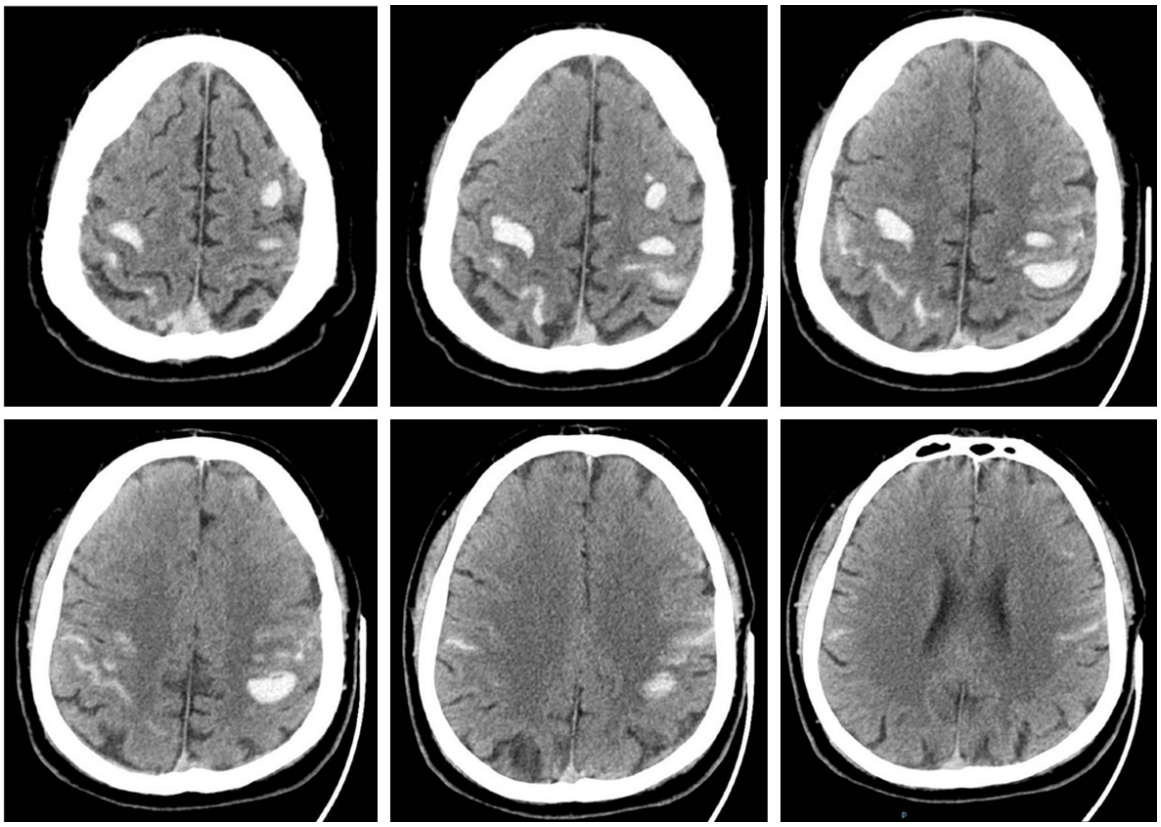

Figure 1. A brain CT scan showed multiple high-density lesions in the bilateral frontal lobes with clear boundaries, and linear high-density lesions were seen in the sulcus of the bilateral frontal and parietal lobes.

generalized seizure. The patient had 2 generalized seizures within 13 hours before admission. He did not have fever or diarrhea. He was a regular smoker and drinker. The patient had a 20-year history of hypertension (grade III) and a 2-year history of type 2 diabetes, which were well controlled by oral telmisartan and daglizin, respectively. None of his family members showed similar symptoms. On admission, his vital signs were normal, and intellectual function was consistent with his age. Nervous system examination showed that the cranial nerve was normal, the left upper limb muscle strength was 0/5 (proximal and distal muscles), the left lower limb and the right upper limb muscle strengths were 3/5 (proximal and distal muscles), and the right lower limb muscle strength was 4/5 (proximal and distal muscles). Sensory function and deep tendon reflexes were present and symmetrical. His bilateral plantar response was normal. His other physical examination results were normal.

Brain computed tomography (CT) at admission showed multiple high-density lesions in the bilateral frontal lobes with clear boundaries. Linear high-density lesions were seen in the sulcus of the bilateral frontal and parietal lobes (**Figure 1**). Brain magnetic resonance angiography (MRA) results were normal. Brain magnetic resonance venography (MRV) results showed no visualization of either the superior or inferior sagittal sinuses, or the right transverse sinus, or the sigmoid sinus, or the straight sinus (**Figure 2**). Hematologic data revealed high hemoglobin (215.0 g/L; reference value: 120.0-160.0 g/L) and red blood cell levels (6.12 × 10^{12}/L; reference value: 4.00-5.50 × 10^{12}/L) and a hematocrit of 0.650 L/L (reference value: 0.400-0.500). Total leukocyte and platelet counts were normal. Hepatic and lipid tests showed hypoproteinemia (26.46 g/L; reference value: 35.00-52.00 g/L) and hyperlipidemia (triglycerides 4.10 mmol/L; reference value: < 1.70 mmol/L). His fasting blood glucose was 15.86 mmol/L (reference value: 3.90-6.10 mmol/L), and his HbA1c was 7.50% (reference value: 4.60-6.10%). His 24-hour urinary protein was 8.928 g (reference value: 0.00-0.15 g). Serum creatinine (58.2 mmol/L; reference

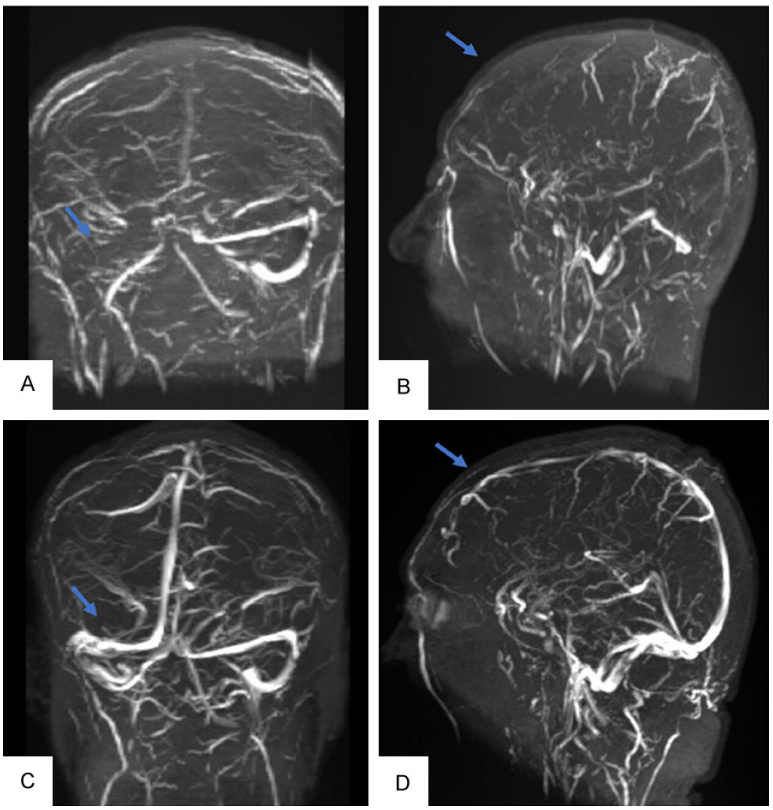

Figure 2. Brain MRV showed nonvisualization of the superior sagittal sinus, inferior sagittal sinus, right transverse sinus, sigmoid sinus and straight sinus at onset (A and B). Brain MRV showed an unobstructed superior sagittal sinus, right transverse sinus, sigmoid sinus, and internal jugular vein at the 3-month follow-up (C and D).

value: 58-110 mmol/L) and urea nitrogen (3.2 mmol/L; reference value: 3.2-7.1 mmol/L) were normal. Tumor markers, thyroid function tests, and serum electrolytes were also normal. Cardiac Doppler ultrasound, chest CT and abdominal CT were normal. The patient underwent a workup for hypercoagulable disorders and polycythemia vera. The coagulation profile was normal. Serum protein C activity, protein S activity, antithrombin III activity, plasminogen activity, lupus anticoagulant silica clotting time (SCT) and Russell viper venom time (RVVT) were normal. TPPA antibodies against syphilis and HIV were negative. Antiphospholipid antibodies, antinuclear antibodies, and antineutrophil cytoplasmic antibodies were negative. Erythropoietin was 2.68 IU/L, which was slightly below the reference range of 5.40-31.00 IU/L. Homocysteine was 35.6 μmol/L (reference value: 0.00-10.00 μmol/L). Bone marrow examination showed hypercellularity and trilineage myeloproliferation with pleomorphic, mature megakaryocytes (differences in size). The JAK2V617F, CALR (NM-004-343), BCR-ABL1 and MPL mutations were all negative.

The patient was diagnosed with CVST, secondary epilepsy, nephrotic syndrome, polycythemia vera, hypertension, and type 2 diabetes. The cause of the nephrotic syndrome was thought to be DM. For the treatment of nephrotic syndrome, the patient was given intermittent intravenous infusions of albumin, oral hydrochlorothiazide, and regular hypoglycemic therapy. According to the 2016 WHO diagnostic criteria, the patient was diagnosed with polycythemia vera and given hydroxyurea [15]. In addition, he received heparin anticoagulation (enoxaparin sodium, a type of low-molecular-weight heparin), anti-edema measures (mannitol, glycerol fructose), anti-epileptic medication (sodium valproate), and antihypertensive and hypoglycemic therapy.

The patient had another seizure on the day after admission. After intravenous injection of diazepam, no improvement was observed. After diazepam was given for a sustained period of time, the symptoms were relieved. On the second day after admission, the patient developed drowsiness and intermittent seizures and continued antiepileptic therapy with diazepam and intramuscular injection of phenobarbital. On the 4th day after admission, the patient's disturbance of consciousness worsened, manifested as moderate coma, and he went into a state of continuous epilepsy. This worsening condition induced us to do a head CT scan, which indicated increased intracranial hemorrhage in his bilateral parietal lobes (**Figure 3**). After 3 days of systematic anticoagulant therapy, the patient's condition worsened, with disturbance of consciousness and persistent seizures, and imaging study indicated an increase in intracranial hemorrhage, so endovascular therapy was initiated on the 4th day after onset. A dual-channel angiography was con-

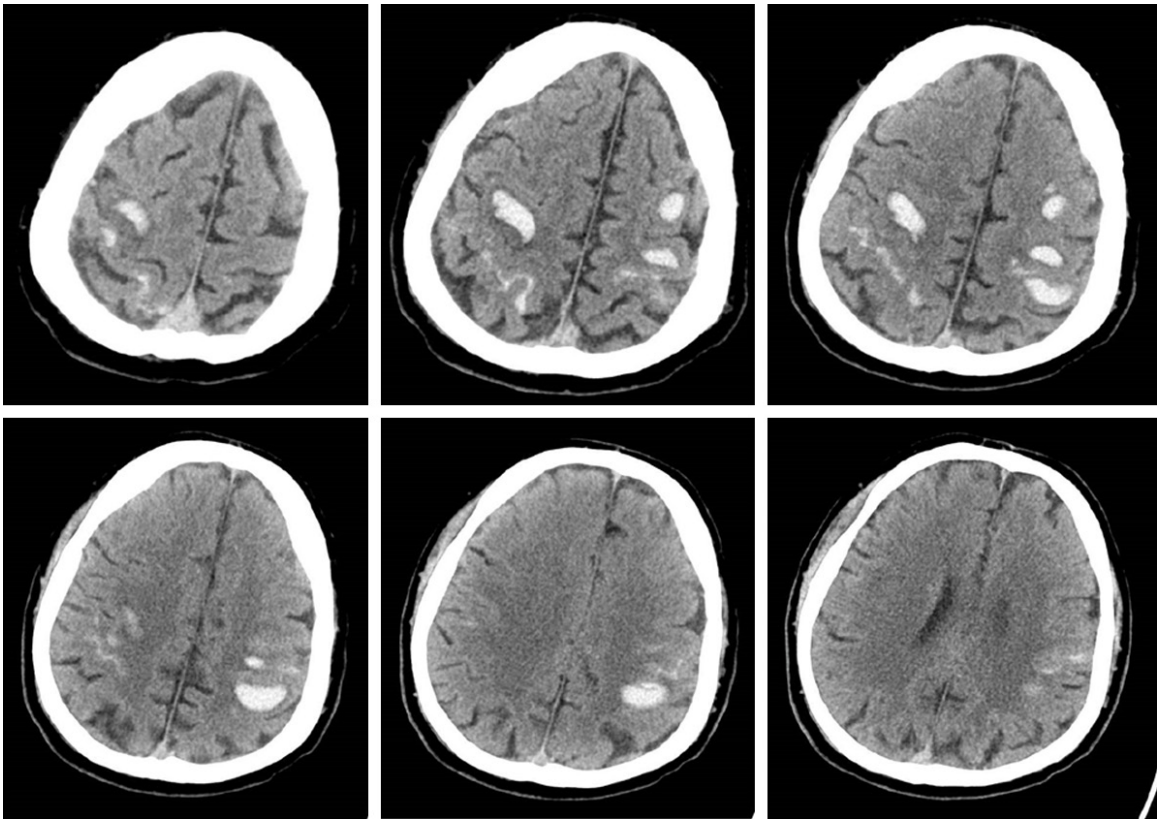

Figure 3. A brain CT scan showed multiple high-density lesions in the bilateral frontal and parietal lobes, and linear high-density lesions were seen in the sulcus of the bilateral frontal and parietal lobes.

ducted on the patient, including an antegrade arteriography and a retrograde venography. Brain digital subtraction angiography revealed reflux disturbance of the superior sagittal sinus, right transverse sinus, right sigmoid sinus, and right internal jugular vein. Guided by the microguide wire, an intermediate catheter (AXS catalyst 6 0.06 in × 132 cm, Stryker, Fremont, CA) was placed in the right transverse sinus, and a Solitaire FR (6 mm × 30 mm Micro Therapeutics Inc. dba ev3 Neurovascular) stent was implanted in the distal segment of the occluded superior sagittal sinus. Thrombus in the superior sagittal sinus distal segments was removed with intermediate catheter aspiration and a stent retrieval device. However, the middle and proximal segments of the superior sagittal sinus remained obstructed. Nonetheless, the patient still suffered from significant vessel stenosis in the superior sagittal sinus, which affected the flow of venous blood. Using a microguide wire, a balloon (Quantum Maverick 4.0 × 12 mm, Boston Scientific) was delivered and expanded from the distal to proximal end of the superior sagittal sinus. Again the superior sagittal sinus showed a shallow display. We delivered another Solitaire FR stent (6 mm × 30 mm Micro Therapeutics Inc. dba ev3 Neurovascular) to the mesial segment of the superior sagittal sinus, and many dark-red thrombi appeared as the stent was withdrawn. Then, a Rebar 18 microcatheter was placed into the distal end of the superior sagittal sinus, and urokinase (200,000 U) was administered continuously. After local thrombolytic therapy with urokinase, cerebral angiography was performed again to show the recovery of superior sagittal sinus blood flow, and the operation was concluded (**Figure 4**).

After operation, the patient's symptoms improved. After 3 weeks of anticoagulation treatment, the patient's progress was favorable, and close neurological monitoring was performed, with clinical improvement, progressive correction of the hematological values, and absorption of the hemorrhage (**Figure 5**). After discharge, the patient took rivaroxaban orally regularly, and his head MRV showed an unobstructed superior sagittal sinus, right trans-

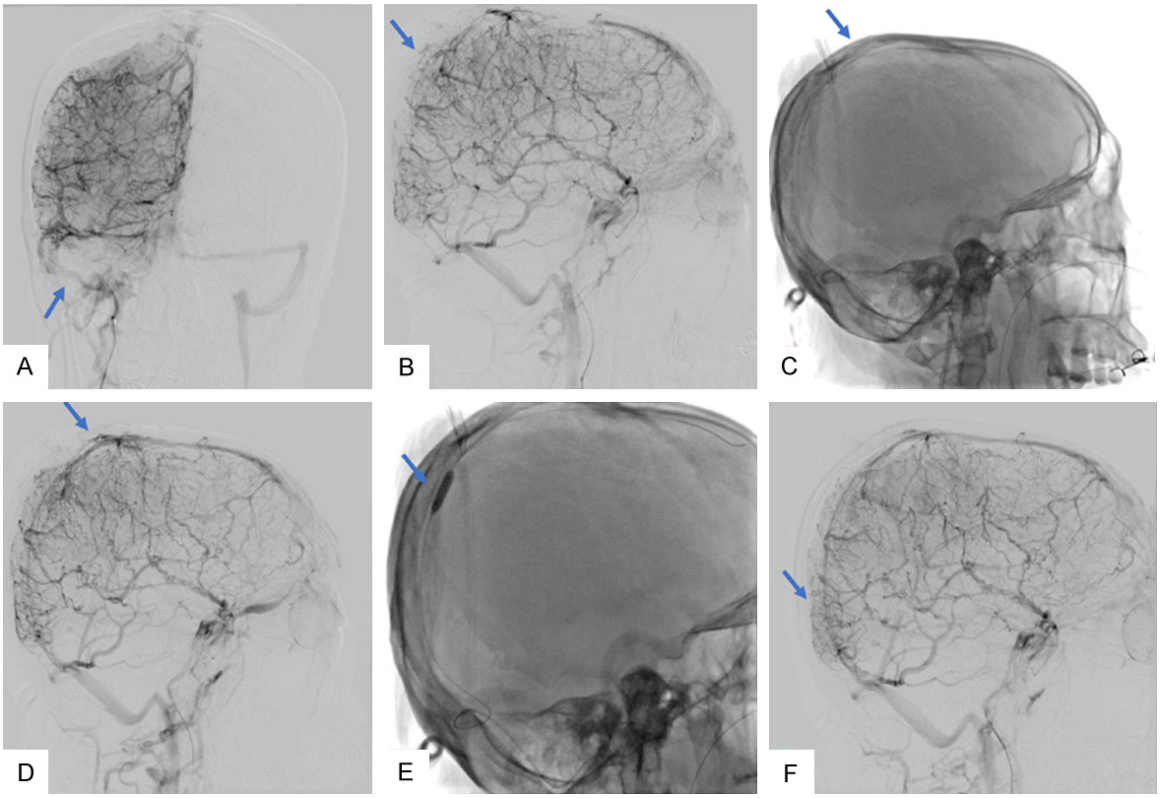

Figure 4. Brain digital subtraction angiography revealed reflux disturbance of the superior sagittal sinus, right transverse sinus, right sigmoid sinus, and right internal jugular vein (A and B). A Solitaire FR (6 mm × 30 mm Micro Therapeutics Inc. dba ev3 Neurovascular) stent was placed in the distal segment of the superior sagittal sinus occlusion (C). The thrombus in the distal segments of the superior sagittal sinus was removed using intermediate catheter aspiration combined with a stent retriever. However, the middle and proximal segments of the superior sagittal sinus remained obstructed (D). A balloon (Boston Scientific Quantum Maverick 4.0 × 12 mm) was delivered under the guidance of a microguide wire (E). Angiography showed that the superior sagittal sinus was unobstructed (F).

verse sinus, sigmoid sinus, and internal jugular vein at the 3-month follow-up (**Figure 2**). Encouragingly, the patient recovered well and returned to work after 9 months of follow-up.

Discussion and conclusions

Cerebrovascular sinus thrombosis (CVST) is a unique type of cerebrovascular insult, accounting for 0.5%-1% of all strokes. The pathogenesis of CVST is complex. It can be caused by abnormal venous blood flow dynamics, inflammatory reaction, or exudation of the venous wall, or changes in the coagulation state. The patient, who had both nephrotic syndrome and polycythemia vera, developed CVST due to the following factors. First, patients with nephrotic syndrome have high proteinuria. A large amount of protein excreted in the urine leads to a decrease in serum albumin, which in turn leads to a decrease in plasma colloid osmotic pressure, a decrease in effective circulating blood volume, and a reduced blood concentration. Thromboembolic events are 2.5-fold more likely to occur in individuals with albumin levels under 28 g/L, according to Lionaki et al. [16]. Second, another characteristic of nephrotic syndrome is hypoproteinemia. Hypoproteinemia promotes an increase in lipid synthesis in the liver and decreases the decomposition of lipids, leading to hyperlipidemia and increased blood viscosity and blood stasis. Third, the elevated hematocrit in polycythemia vera patients leads to increased intravascular viscosity. Under low shear conditions, this leads to blood flow disturbances and increases the stagnation of the venous system [17]. Hematocrit > 45% has been associated with an increased risk of cardiovascular embolism events, while our patient had a much higher hematocrit of 65%. One study showed that a strict reduction of the hematocrit below 45% is

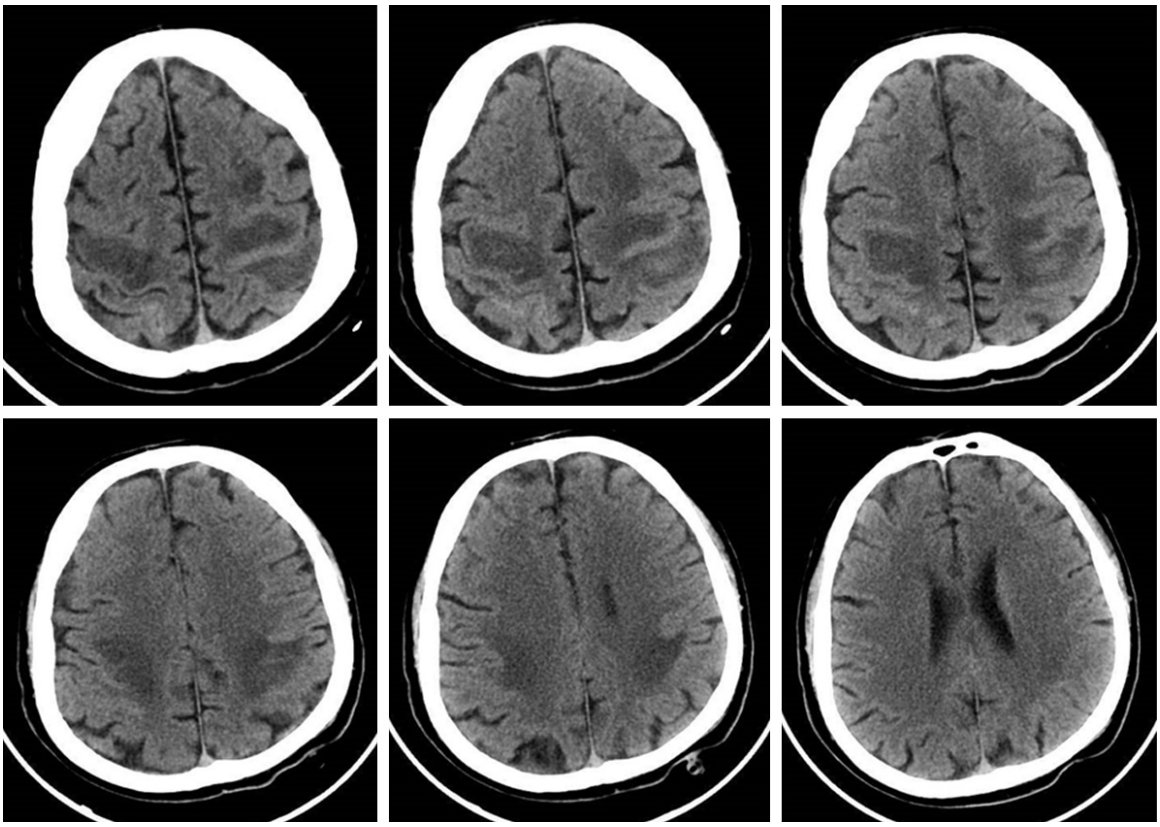

Figure 5. A brain CT scan showed that the area and density of hemorrhage in the bilateral frontal and parietal lobes were significantly reduced, the edema zone around some lesions was increased, and the subarachnoid hemorrhage was reduced.

related to a low thrombosis rate in polycythemia vera [18]. In this patient, CVST developed under the combined action of the above factors.

At present, there are few cases reported of intracranial venous sinus thrombosis in polycythemia vera and nephrotic syndrome [6, 19]. When intracranial venous sinus thrombosis is secondary to polycythemia vera, its specific signs may not be obvious. CVST can occur at any stage of nephrotic syndrome, and it lacks specific clinical manifestations, leading to missed and delayed diagnoses [6]. Therefore, systematic and comprehensive etiological screening should be carried out for patients with venous sinus thrombosis in clinical work. Based on the pathophysiologic characteristics of polycythemia vera and nephrotic syndrome, when CVST is present, treatment with dehydration and reduction of intracranial pressure may further increase the blood viscosity and cause exacerbation rather than remission. All the above factors contribute to the difficult diagnosis and treatment of polycythemia vera and nephrotic syndrome patients with CVST. Our patient was initially treated with antiedema approaches, and although he was treated with anticoagulation, his condition continued to deteriorate, which we think was related to the exacerbation of hypercoagulability.

For the treatment of venous sinus thrombosis, anticoagulation therapy is currently recognized as first-line therapy, and it can significantly improve the prognosis. However, approximately 9-13% of patients with CVST continue to experience worsening symptoms after anticoagulant therapy [1]. International guidelines indicate that intravascular therapy with local thrombolysis and/or mechanical thrombolysis techniques may be an option for patients whose clinical condition has worsened or are comatose despite anticoagulant therapy [2, 8, 20]. The optimal endovascular treatment strategy for CVST patients is not yet clear, and currently, the endovascular treatment of CVST is based on the endovascular treatment strategy

of acute ischemic stroke [21-25]. Our patient was treated with a thrombectomy stent, intermediate catheter aspiration, balloon dilatation, and local urokinase thrombolytic therapy. The patient did not achieve complete recanalization at that time despite multiple endovascular strategies. Fortunately, the patient's head MRV 3 months later showed an unobstructed superior sagittal sinus, right transverse sinus, sigmoid sinus, and internal jugular vein. In addition, intracerebral hemorrhage (ICH) should not be considered as a contraindication for thrombolysis in CVST patients. Local thrombolysis can clear residual thrombosis in the venous sinus and recanalize residual thrombosis in the cortical veins. One study also showed that regional thrombolysis improves clinical and radiologic outcomes of CVST cases coupled with ICH [26].

There are some limitations to our study. In the evaluation of the patient, only a subset of systemic diseases that cause acquired hypercoagulability, such as lupus, antiphospholipid antibody syndrome, and rheumatoid disease, were considered. Although the patient's current examination revealed no evidence of malignancy, close follow-up was necessary. Overall, this patient needs regular follow-up to monitor the course of the disease. Despite the above limitations of this case report, endovascular treatment may be considered a salvage treatment for severe CVST patients who do not respond to heparin during the acute phase. Further research is needed to confirm its safety and efficacy.

CVST is a unique type of cerebrovascular disease. This patient's condition suggests that, for patients with venous sinus thrombosis, a systematic and standardized physical examination should be performed to carefully screen for the cause. We hope this case report will improve clinicians' understanding of the rare etiology of CVST and lead them to a treatment of the underlying cause that will help patients recover from the disease. Stent thrombectomy combined with intermediate catheter aspiration, balloon dilation, and local thrombolytic therapy may be a good choice for rapid and effective recanalization of the occlusive venous sinus in patients with critical CVST who are insensitive to anticoagulant therapy.

Disclosure of conflict of interest

None.

Abbreviations

CT, computed tomography; CVST, cerebral venous sinus thrombosis; ICH, intracerebral hemorrhage; MRA, magnetic resonance angiography; MRV, magnetic resonance venography; SCT, silica clotting time; RVVT, Russell viper venom time.

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