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Pregnancy-related intracranial venous sinus thrombosis secondary to cryptococcal meningoencephalitis: a case report and literature review

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Abstract

Background Cerebral venous sinus thrombosis (CVST), a serious cerebrovascular and neurological emergency, is common in pregnant individuals and accounts for approximately 0.5–1.0% of all cerebrovascular diseases. However, CVST with cryptococcal meningoencephalitis in immunocompetent pregnant patients is rare.

Case presentation A 30-year-old woman who was 33 weeks pregnant presented with recurrent dizziness, headache, and vomiting as the main clinical manifestations, all of which were initially nonspecific. After assessment of the cerebrospinal fluid, skull computerized tomography, magnetic resonance imaging, and other laboratory and imaging examinations, the patient was diagnosed with secondary pregnancy-related CVST with cryptococcal meningoencephalitis. Despite receiving potent anticoagulant and antifungal treatment, the patient's condition deteriorated, and the patient's family opted to cease treatment.

Conclusions We present a rare case of CVST with cryptococcal meningoencephalitis in an immunocompetent pregnant patient. The difficulty of diagnosing and treating secondary pregnancy-related CVST caused by cryptococcal meningoencephalitis, as well as the great challenges faced at present are highlighted. One crucial lesson from the present case is that when clinical and imaging signs are unusual for CVST during pregnancy, it is essential to account for the possibility of other central nervous system (CNS) diseases, such as CNS infections with *Cryptococcus*, which may cause CVST.

Keywords Cerebral venous sinus thrombosis, Cryptococcal meningoencephalitis, Pregnancy, Magnetic resonance venography, Case report

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Introduction

Cerebral venous sinus thrombosis (CVST) is a rare vascular disorder that affects the cerebral venous system. CVST was first described in the early 19th century and can be caused by a variety of factors. This condition is more common in young and middle-aged adults and has a low incidence rate of only 5 cases per 1 million individuals in the general population. It accounts for 0.5–1.0% of all strokes [1, 2]. CVST is primarily categorized as having either infectious or noninfectious origins. Among noninfectious conditions, oral contraceptives and pregnancy/puerperium are both major risk factors, so the incidence of noninfectious CVST is high in young women [3]. Reports suggest that pregnancy-related CVST results in mortality rates of 5–30%. However, research on this subject in an Asian population is lacking [4]. Importantly, central nervous system infection is one of the most common causes of CVST. Meningococci and meningoencephalitis can affect the central nervous system. Although Cryptococcus is a rare cause of central nervous system infection in affluent countries, adult cryptococcal meningitis is more likely in populations with high HIV infection rates [5]. While CVST is a rare complication of cryptococcal meningoencephalitis (CM), it can lead to a large increase in intracranial pressure, affecting both the disease prognosis and the patient's clinical state. This article describes the clinical diagnosis and treatment of a patient with pregnancy-related CVST caused by CM and subarachnoid bleeding, as well as an analysis of the disease etiology, clinical manifestations, imaging characteristics, diagnosis, and treatment methods based on a literature review. This case study can serve as a reference for the diagnosis and treatment of similar patients.

Case presentation

On September 9, 2023, a 30-year-old woman who was 29 weeks pregnant began to experience symptoms of dizziness, headache, nausea and vomiting. She was first hospitalized in the obstetrics department of our hospital. The patient had no chills, fever, or edema during pregnancy. Magnetic resonance imaging (MRI), diffusion-weighted imaging and magnetic resonance angiography revealed pituitary swelling but no abnormalities in the brain. After 10 days of symptomatic therapy, the patient experienced slight improvement but rejected further examination and treatment and left the hospital against the physicians' recommendations. The patient's clinical symptoms persisted and worsened on October 8, 2023, with the addition of lower abdominal pain, and she was readmitted to the hospital. Physical examination revealed normal findings. A complete blood examination upon admission to the hospital revealed the following: white blood cell count: 8.21×10^9/L; neutrophil ratio: 83.3%; hemoglobin: 117 g/L; platelet (PLT) count: 224×10^9/L; total C-reactive protein: 5.77 mg/L; activated partial thromboplastin time (APTT): 32.3 s; prothrombin time (PT): 15.1 s; thrombin time (TT): 14.7 s; fibrinogen: 5.30 g/L; and NT-proBNP: 34.9 pg/mL. Liver and kidney function, electrolytes, rheumatic immunity (rheumatoid factor, antinuclear antibodies, anti-double-stranded DNA antibodies, etc.), and myocardial zymology, as well as virological testing for HIV, SARS-CoV-2, type A/B influenza, and hepatitis viruses, revealed no abnormalities. Brain magnetic resonance venography (MRV) examinations indicated the possibility of cerebral venous sinus thrombosis.

On the basis of these medical history and examination findings, the patient was given a primary diagnosis of CVST. The patient initially received anticoagulant therapy with enoxaparin (low-molecular-weight heparin) at a dose of 6000 AxaIU administered subcutaneously twice daily. The PLT count and anti-Xa were monitored. Subsequent interventions included glycerin fructose and mannitol treatment to relieve intracranial hypertension and prophylactic antibiotic therapy with cefazolin. On October 10, the patient presented with a fever of 38.5 °C, and an obstetric color ultrasound examination revealed fetal intrauterine distress, leading to an emergency cesarean section, followed by transfer to the intensive care unit (ICU). The anticoagulant therapy was changed to a single intravenous injection of 6000 U of heparin sodium, followed by a low-dose continuous intravenous infusion of 600 U/h with closer monitoring of coagulation function via anti-Xa, APTT, PT, TT, and FIB. The APTT increased by 1.41–2.52 times the baseline value, and the anti-Xa concentration ranged from 0.2 to 0.6 IU/mL. The PLT count ranged from 224×10^9/L to 357×10^9/L. However, the patient's condition worsened the following day, characterized by a respiratory rate of 130 breaths per minute and a blood pressure of 187/126 mmHg, and the patient developed a shallow coma with a Glasgow Coma Scale (GCS) score of 2T: E1VTM1, unequal bilateral pupils and nuchal rigidity. Brain computed tomography (CT) angiography/venography/perfusion and magnetic resonance imaging (MRI)/MRV examinations revealed thrombosis in the superior sagittal sinus, venous sinus, bilateral transverse sinus and sigmoid sinus (Fig. 1A-F). Inflammatory and infectious lesions were indicated by multiple abnormal signal shadows in the basal ganglia, lateral ventricles, and cerebellum with lower T1WI, higher T2WI, and higher DWI signals (Fig. 1G-L). On October 11, the results of the cerebrospinal fluid (CSF) examination were as follows: color: red; opacity; Pandey test: ++; total number of cells: 30,750×10^6/L; white blood cells: 750×10^6/L; mononuclear cells: 60%; and multiple nuclear cells: 40%. The CSF biochemical results were as follows: chlorine: 122.70 mmol/L; CSF glucose: 2.00 mmol/L; CSF microalbumin: 729.80 mg/L; CSF

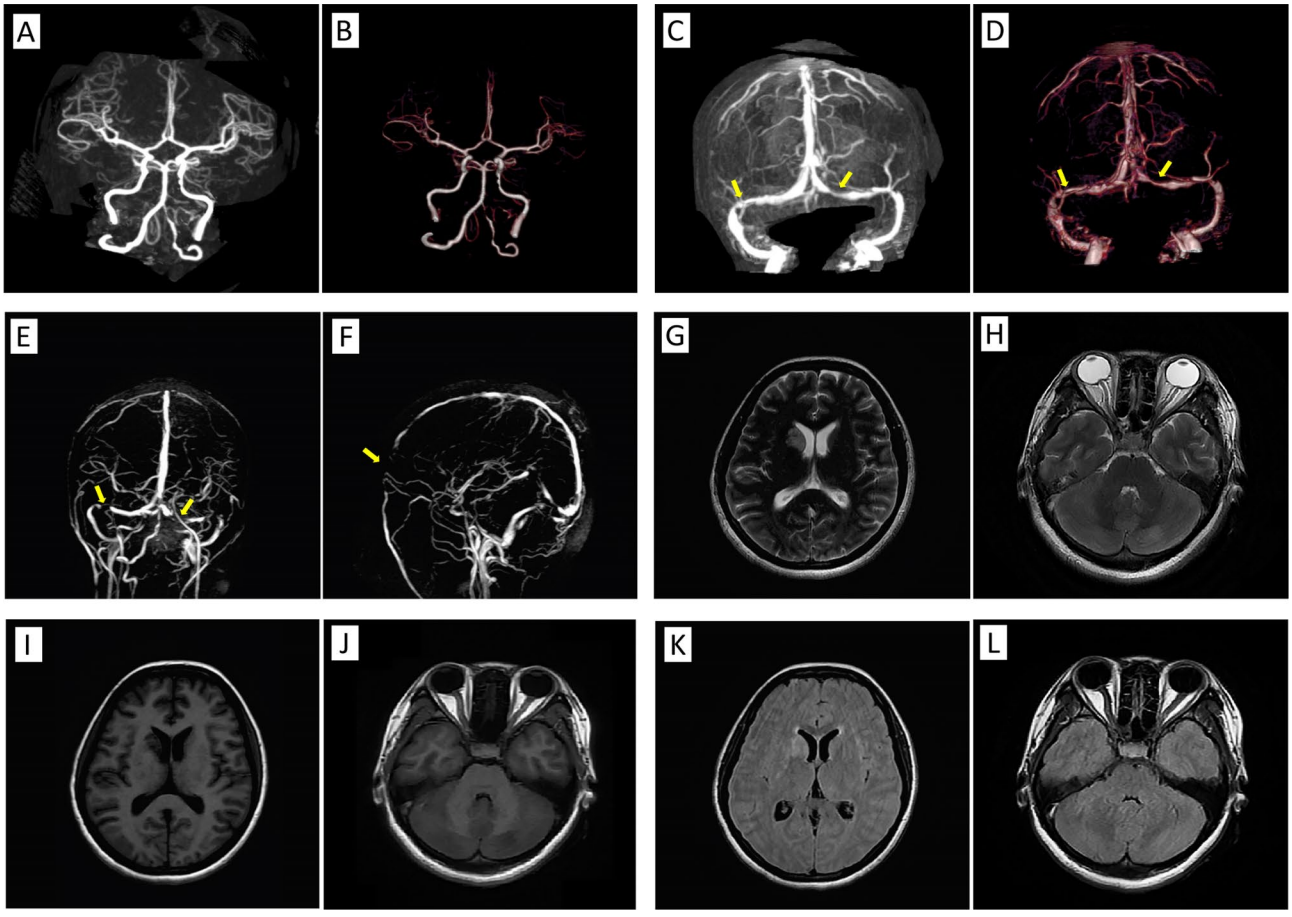

Fig. 1 Imaging results of the patient on October 11. (**A**, **B**) Cranial CT angiography (CTA) and three-dimensional reconstruction; (**C**, **D**) Cranial CT venography and three-dimensional reconstruction reveal cerebral venous sinus thrombosis (arrows shown); (**E**, **F**) Brain magnetic resonance venous (MRV) imaging. The left transverse sinus is partially unclear. The left sigmoid sinus was slightly smaller than the opposite side, and display clearly. The junction between the right transverse sinus and the sigmoid sinus was not clearly displayed, and the filling defects in the superior sagittal sinus increased compared to before. (**G-J**) MRI T1 and T2 weighted images of the head; (**K**, **L**) FLAIR (brain magnetic resonance imaging fluid attenuation reversal recovery sequence). Multiple abnormal signal shadows with a slightly lower T1-weighted image (T1WI) signal, a slightly higher T2WI signal, and a higher DWI signal exist in the right basal ganglia, bilateral lateral ventricles, centrum semiovale, bilateral cerebellar hemispheres, and left basal ganglia, which hint inflammatory and infectious lesions

micrototal protein: 1,636.50 mg/L; and CSF adenosine deaminase: 2.40 U/L. The results of cerebrospinal fluid smear ink staining indicated the presence of *Cryptococcus neoformans*. Amphotericin B cholesterol sulfate complex (150 mg, intravenously once daily) and meropenem (1.0 g, intravenously every 8 h) were subsequently added to the patient's treatment regimen for antifungal therapy. Regrettably, the patient's condition deteriorated, manifesting as changes in pupil size that culminated in bilateral dilation on October 13. Subsequent analysis of placenta, blood, and cerebrospinal fluid cultures revealed an infection with *Cryptococcus neoformans*. A re-examination of the cranial CT on October 15 revealed multiple new high-density shadows in the sulci and cistern, which indicated subarachnoid hemorrhage (Fig. 2). A definitive diagnosis of *Cryptococcus neoformans* sepsis, cryptococcal meningoencephalitis, septic shock, cerebral venous sinus thrombosis, cerebral herniation, brainstem failure, subarachnoid hemorrhage and cerebral infarction was confirmed. The patient subsequently presented with cardiogenic shock, left heart failure, and acute pulmonary edema. In light of the gravity of the situation, the patient's family opted to cease treatment and authorize discharge.

Discussion

Cerebral venous sinus thrombosis (CVST) is a rare and serious neurological emergency that interrupts blood flow to the brain by increasing pressure in veins and capillaries, which can cause cerebral infarction [6]. CVST occurs less frequently than other cerebrovascular disorders and often presents with nonspecific symptoms and signs, making clinical diagnosis difficult [7]. CVST is primarily categorized into infectious or noninfectious origins. The predominant noninfectious cause is associated

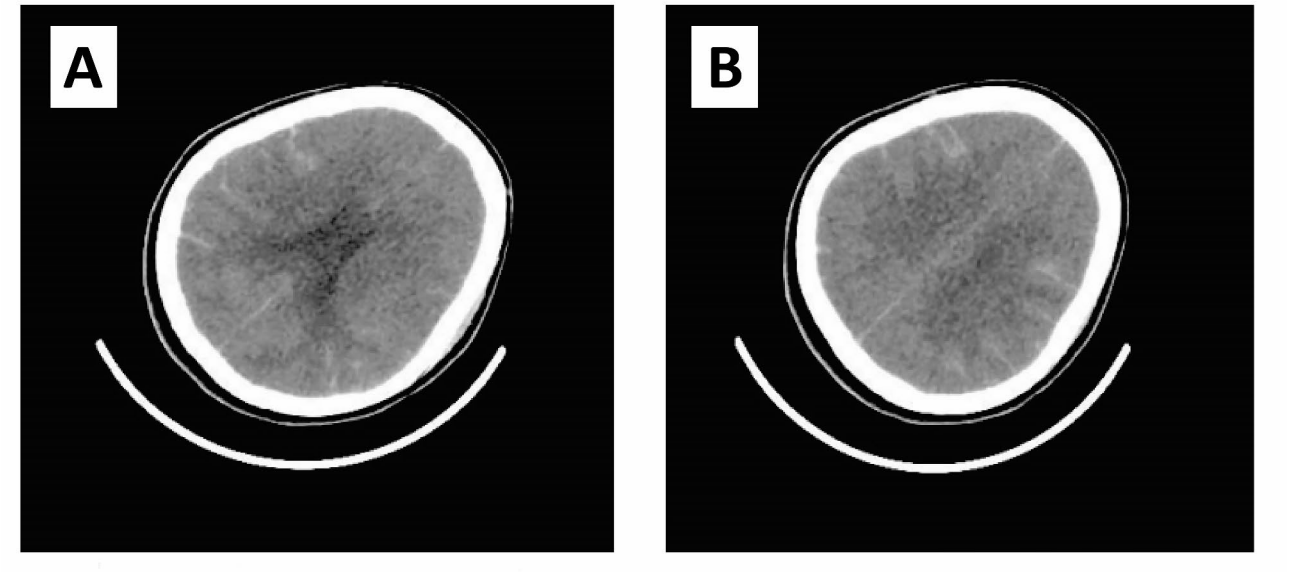

Fig. 2 Imaging results of the patient on October 15. (**A**, **B**) CT of the brain. There are multiple high-density shadows in the cisterna of the new sulcus, which indicate subarachnoid hemorrhage. Additionally, there are unclear hypodense shadows in the original right basal ganglia-right lateral paraventricular and left frontal lobe patchy, and no expansion of the supratentorial ventricles

with hereditary and acquired thrombotic disorders, antiphospholipid syndrome, and prethrombotic risk factors such as pregnancy and the puerperal period. The third trimester of pregnancy and the initial postpartum month are identified as high-risk intervals for pregnancy-related CVST [8]. Importantly, although central nervous system infections represent a small proportion (2.1%) of all cases, they are significantly correlated with unfavorable clinical outcomes [9].

The diagnosis of CVST can present challenges due to the overlapping clinical manifestations with pregnancy. Common symptoms such as headache, drowsiness, vomiting, and nausea should prompt the consideration of CVST as a potential diagnosis, particularly if they are persistent or progressive [10]. Imaging plays a crucial role in diagnosing CVST, including CT/CT venous imaging (CTV), brain MRI/magnetic resonance venous imaging (MRV), DWI, magnetically sensitive weighted imaging or 3D T2 variable flip angle weighted rapid spin−echo imaging, enhanced 3D premagnetized fast gradient echo imaging, and 3D T1-weighted vortex echo black blood sequence, which are essential tools for diagnosing CVST [11]. A CT scan of patients with CVST typically reveals high-density lesions, cerebral infarction, edema, and hemorrhage. Importantly, the radiation associated with this procedure may have detrimental effects on pregnant women [10, 11]. Furthermore, MRI can distinguish between CVST and tumors, whereas MRV can identify occlusion of the venous sinuses. Invasive intracranial angiography can detect CVST and exclude other vascular abnormalities, such as aneurysms, arteriovenous fistulas, and arteriovenous malformations [11, 12]. Given that MRI and MRV are noninvasive and do not involve radiation, they are considered the optimal methods for evaluating suspected CVST in pregnant women. During the first hospitalization, the patient experienced slight improvement but rejected further examination, and she left the hospital against the physicians' recommendations. Despite the absence of abnormalities in the brain MRI, it is still unclear whether CVST or cryptococcal meningoencephalitis was present during this period. Anticoagulation treatment is the primary approach for controlling CVST, as it prevents further thrombus formation, facilitates thrombus resolution, and minimizes intracranial and extracranial hemorrhage [13]. Rapid and effective anticoagulant therapy was conducted when the diagnosis of CVST was established through MRI and MRV at admission.

Cryptococcal infection, a prevalent opportunistic infection in AIDS patients that primarily presents as cryptococcal meningoencephalitis (CM), is a leading cause of death in HIV patients [14–16]. It rarely occurs in those with normal immune function [17]. In this case report, we presented an immunocompetent pregnant patient who developed CVST and an intracranial *Cryptococcus* infection. Pregnant women may be more susceptible to *Cryptococcus* infection because they are relatively immunocompromised [14, 17]. We cannot determine the causal relationship between intracranial *Cryptococcus* infection and CVST. However, one report indicated that CM is a rare cause of CVST [18]. CM may cause CVST by disrupting CSF circulation and venous drainage due to

high intracranial pressure; however, it may occur either independently or sequentially. Despite rapid and effective anticoagulant therapy for CVST at admission, the patient was at significant risk of mortality due to the delayed diagnosis of cryptococcal meningoencephalitis. Lumbar puncture and CSF examination were not performed until the patient appeared to have symptoms of infection and became worse, which ultimately revealed the presence of *Cryptococcus neoformans*. Generally, we rarely consider intracranial infection if a patient has no recurring infection symptoms or central nervous system (CNS) signs. CNS infection has been identified as an indicator of poor prognosis in the international study of CVST, and sepsis has one of the strongest unfavorable prognostic associations [19]. In particular, sepsis-associated thrombosis in the superior sagittal and cavernous sinuses is closely associated with a significantly high death rate [20]. Despite receiving potent anticoagulant and antifungal treatment, the patient eventually developed septic shock, numerous organ failures, and brain herniation. Therefore, medical staff should be aware of the potential occurrence of CNS infection, especially cryptococcal meningoencephalitis, in pregnant patients with CVST. If pregnant patients with CVST become infected or present with symptoms of infection, lumbar puncture and CSF examination should be performed.

Conclusions

We report a rare case of CVST with cryptococcal meningoencephalitis in an immunocompetent pregnant patient. Both CVST and other CNS diseases should be evaluated in pregnant women with signs of intracranial hypertension or neurological dysfunction. One important lesson from the present case is that when clinical and imaging signs are unusual for CVST during pregnancy, it is essential to account for the possibility of other CNS disorders, such as CNS infections with *Cryptococcus*, which may lead to CVST.

Abbreviations

CVST	Cerebral venous sinus thrombosis
CM	Cryptococcal meningoencephalitis
GCS	Glasgow Coma Scale
CT	Computed tomography
DAVF	Dural arteriovenous fistula
MRV	Magnetic resonance venous imaging
MRI	Magnetic resonance imaging

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Not applicable.

Author contributions

JH and QL contribute to conceptualization; JH, YH, YQ, LL and MX contribute to data. LL and MX contribute to software and visualization; MX and JH contribute to funding acquisition, project administration and supervision. JH, YH and YQ contribute to writing original draft; JH and QL contribute to review and editing. All authors have read and agreed to the published version of the manuscript.

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Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki, and approved by the Ethical Committee of Jieyang People's Hospital. Written informed consent was obtained from the individual(s) for participation in this study.

Consent for publication

Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this study.

Competing interests

The authors declare no competing interests.

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