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Atypical clinical and pathological findings in a patient with isolated cortical vein thrombosis★

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Abstract
Isolated cortical vein thrombosis often produces a focal lesion. Because of the rapid development of collateral circulation, increased intracranial pressure has never been reported in a patient with isolated cortical vein thrombosis. The diagnosis of isolated cortical vein thrombosis is based mainly on MRI, catheter digital subtraction angiography, and histological findings, but may be challenging. We report a patient who presented with intermittent seizures and left-sided limb weakness. Her symptoms gradually progressed, and she eventually developed signs of increased intracranial pressure. Imaging studies showed a space-occupying lesion in the right frontal lobe of the brain. As we could not diagnose isolated cortical vein thrombosis based on the preoperative findings, surgical excision of the lesion was performed under general anesthesia. Histological examination showed destruction of the brain parenchyma with infiltration of macrophages, proliferation of reactive astrocytes and small vessels, and foci of hemorrhage. Further examination found that a number of small vessels in both the subarachnoid space and brain parenchyma were filled with thrombus, some of which was organized. Elastic fiber staining showed that the obstructed vessels were veins. We diagnosed isolated cortical vein thrombosis with atypical clinical features.

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Key Words
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Research Highlights
(1) A patient with isolated cortical vein thrombosis presented with intermittent seizures and left-sided limb weakness. Her symptoms progressed gradually, and she eventually developed signs of increased intracranial pressure. Imaging studies showed a space-occupying lesion in the right frontal lobe of the brain, which was excised under general anesthesia.
(2) Postoperative pathological examination showed isolated cortical vein thrombosis. We were not able to diagnose cortical vein thrombosis based on the atypical preoperative findings.

Abbreviations
ICP, increased intracranial pressure; MRV, magnetic resonance venography; DSA, catheter digital subtraction angiography; CSF, cerebrospinal fluid

INTRODUCTION

Cerebral venous thrombosis accounts for less than 1% of all strokes[1]. The three main types of cerebral venous thrombosis are venous sinus thrombosis, cortical vein thrombosis, and venous sinus thrombosis associated with cortical vein thrombosis. The first two types are the most common and are well recognized. Cortical vein thrombosis may be secondary to venous sinus thrombosis, with the thrombosis progressing from the venous sinuses to the cortical veins. However, isolated cortical vein thrombosis develops without venous sinus thrombosis or deep venous thrombosis[2]. As there are few studies and case reports describing isolated cortical vein thrombosis, it remains poorly understood. The most common manifestations of isolated cortical vein thrombosis include seizures, motor and sensory deficits, aphasia, and hemianopia[3-4].

Isolated cortical vein thrombosis typically produces a focal lesion with rapid development of collateral circulation. Symptoms of increased intracranial pressure (ICP) such as headache, vomiting, and blurred vision caused by papilledema have never been reported. Routine imaging studies including MRI, magnetic resonance venography (MRV), and catheter digital subtraction angiography (DSA) show the parenchymal lesions caused by isolated cortical vein thrombosis but do not directly show the venous thrombosis. Diagnosis of isolated cortical vein thrombosis is therefore challenging.

Previous researches (PubMed) for isolated cortical vein thrombosis are as follows:

Title	First author	Journal	Country	Year of publication
The clinico-radiological spectrum of isolated cortical vein thrombosis	Rathakrishnan R	J Clin Neurosci	Singapore	2011
Isolated cortical vein thrombosis after epidural anesthesia: report of three cases	Yildiz OK	Int J Neurosci	Turkey	2010
Subarachnoid hemorrhage in isolated cortical vein thrombosis: are presentation of an unusual condition	Bittencourt LK	Arq Neuropsiquiatr	USA	2009
Isolated cortical vein thrombosis in a patient with arteriovenous malformation	Rathakrishnan R	J Clin Neurosci	Singapore	2009
Isolated cortical vein thrombosis - the cord sign	Sharma VK	J Radiol Case Rep	Singapore	2009
MR imaging features of isolated cortical vein thrombosis: diagnosis and follow-up	Boukobza M	AJNR Am J Neuroradiol	France	2009
Case of the month #140 Isolated cortical vein thrombosis of left vein of Labbe	Chakraborty S	Can Assoc Radiol J	Canada	2008
Isolated cortical vein thrombosis: report of two cases	Miranda VH	Rev Med Chil	Chile	2007
Spontaneous intracranial hypotension with isolated cortical vein thrombosis and subarachnoid haemorrhage	Wang YF	Cephalalgia	Taiwan, China	2007
A case of spontaneous intracranial hypotension complicated by isolated cortical vein thrombosis and cerebral venous infarction	Lai PH	Cephalalgia	Taiwan, China	2007
Isolated cortical vein thrombosis Clinical and neuroradiological aspects	Müller-Forell W	Radiologe	Germany	2007
Clinical and neuroradiological spectrum of isolated cortical vein thrombosis	Urban PP	J Neurol	Germany	2005
Isolated cortical vein thrombosis and the cord sign	Rubí J	Headache	Spain	2005
Imaging of cerebral isolated cortical vein thrombosis	Duncan IC	AJR Am J Roentgenol	South Africa	2005
A case with an isolated cortical vein thrombosis	Adachi T	Rinsho Shinkeigaku	Japan	1996
Isolated cortical vein thrombosis and activated protein C resistance	Vuillier F	Stroke	France	1996

Scarce previous case reports had described a diagnosis of isolated cortical vein thrombosis based on histological findings; the others made the diagnosis based on imaging studies. With advances in medical radiology, isolated cortical vein thrombosis is sometimes diagnosed by MRI or DSA. However, many researchers believe that isolated cortical vein thrombosis is almost always overlooked, probably because of the difficulty of definitive *in vivo* diagnosis[2-3].

A middle-aged female with a history of intermittent seizures and left-sided limb weakness was recently admitted to our hospital. Her initial brain MRI was normal, and repeat MRI approximately 3 months later showed a massive mixed-signal lesion with nodular hemorrhage and edema, and no enhancement, in the right frontal lobe. The differential diagnosis included primary angiitis of the central nervous system, tumor, infection, and venous sinus thrombosis.

Further investigation, including tissue biopsy, led to a pathological diagnosis of isolated cortical vein thrombosis. This patient presented with clinical manifestations and imaging findings unlike those reported in previous cases of isolated cortical vein thrombosis. Her symptoms were intermittent and gradually progressive, and she eventually developed signs of increased intracranial pressure. Imaging studies showed a space-occupying lesion.

CASE REPORT

A 51-year-old female was admitted to our hospital with a 3-month history of tonic-clonic seizures lasting up to 20 minutes each, and left-sided limb weakness. Her family reported that she did not sustain any head injuries during her seizures, and always recovered completely without fever, headache, or cognitive dysfunction.

Past history

Prior to admission to our hospital, she had been admitted to another hospital on several occasions. Following her first seizure, which was 20 minutes in duration, she was assessed at a clinic. At presentation, her vital signs were normal, and head CT, MRI, and electroencephalography were normal. She was diagnosed with epilepsy. As no abnormalities were detected on imaging studies and she had no previous history of seizures, she was not started on prophylactic anticonvulsive medication. She was asymptomatic until 25 days later, when she had a tonic-clonic seizure lasting approximately 10 minutes. She was assessed at the emergency department. Head CT showed a low-density lesion in the right frontal lobe, and MRI showed an area of abnormal signal in the right frontal lobe. However, magnetic resonance angiography of the head was normal. Full body positron emission tomography demonstrated decreased uptake of fluorodeoxyglucose in the right frontal lobe.

She was admitted to hospital. Her vital signs were normal. Serum electrolyte, blood urea nitrogen, creatinine, glucose, albumin, bilirubin, alkaline phosphatase, aspartate aminotransferase, cholesterol, triglyceride, and low-density lipoprotein cholesterol levels, and red blood cell and platelet counts, were normal. She was diagnosed with epilepsy and treated with intravenous fluids, mannitol, and anticonvulsant medication (sodium valproate). She improved significantly over the course of her admission. Although she still had occasional seizures, she was discharged home on the 7th day after admission on sodium valproate 0.2 mg, three times daily.

For the first 14 days after discharge, she was seizure-free, but gradually developed left-sided limb weakness. On the 15th day, she could no longer move her left arm and leg, and was readmitted to the same hospital. Her blood pressure was 142/98 mmHg (1 mmHg = 0.133 kPa) and her other vital signs were normal. Head CT showed enlargement of the right frontal lobe lesion. Brain MRI showed a right frontal lobe lesion with mixed low and intermediate signal intensity on T1-weighted images, high signal intensity on T2-weighted images, massive edema, insignificant compression of the right lateral ventricle, and no enhancement (Figures 1A–D). Lumbar puncture showed a normal cerebrospinal fluid (CSF) opening pressure. CSF analysis showed normal white blood cell count, red blood cell count, protein, glucose, herpes simplex virus and Epstein-Barr virus polymerase chain reaction, toxoplasma titer, and oligoclonal bands. She was still thought to have epilepsy. She was treated with intravenous fluids and mannitol, and sodium valproate was continued. After 7 days, her limb weakness had resolved and she could walk without assistance. She was discharged 15 days after admission. Five days after discharge, her left-sided hemiplegia returned, and she complained of a mild to moderate right-sided headache. She was readmitted to the same hospital. Head CT showed massive edema in the right frontal lobe, with nodular hemorrhage (Figures 2A, B). Brain MRI showed enlargement of the right frontal lobe lesion, and also showed a new lesion with low signal intensity on both T1-

and T2-weighted images and diffuse small hemorrhages in the juxtacortical areas, with significant compression of the right lateral ventricle and deviation of the midline to the left (Figures 1E–H). She was still thought to have epilepsy, and was treated with mannitol and sodium valproate. However, her symptoms did not resolve.

Approximately 3 months after the first seizure, she was transferred to our hospital. On reviewing her past history, we learned that she was a farmer, and had a history of type II diabetes mellitus and hypertension, both diagnosed 5 years previously. Both her blood glucose level and blood pressure had been well controlled. She denied the use of tobacco, alcohol, or illicit drugs. Her last menstrual period was 2 years ago, and she did not use any contraceptive medication. She denied any similar symptoms in other family members.

Medical examination

On physical examination, her blood pressure was 150/90 mm Hg, and other vital signs were normal. She was alert and oriented, and her speech was fluent. Her pupils were equal, round, and reactive to light. Fundus examination revealed bilateral edema and hemorrhage. Examination of the other cranial nerves was normal. Muscle strength was grade 2 in the left arm and grade 0 in the left leg. She had a positive Babinski sign on the left side. The remainder of the neurological examination was within normal limits.

Diagnosis

The differential diagnosis included primary angiitis of the central nervous system, tumor, infection, and venous sinus thrombosis. Autoimmune markers (erythrocyte sedimentation rate, rheumatoid factor, antineutrophil cytoplasmic antibody, antiphospholipid antibody, antinuclear antibody), tumor-related antibodies (carcinoembryonic antigen, CA-125, CA-199, CA-724), and coagulation protein levels (antithrombin III, protein C, protein S, lupus anticoagulant, factor V) were all normal. Serological tests for human immunodeficiency virus, Borrelia, and syphilis were negative.

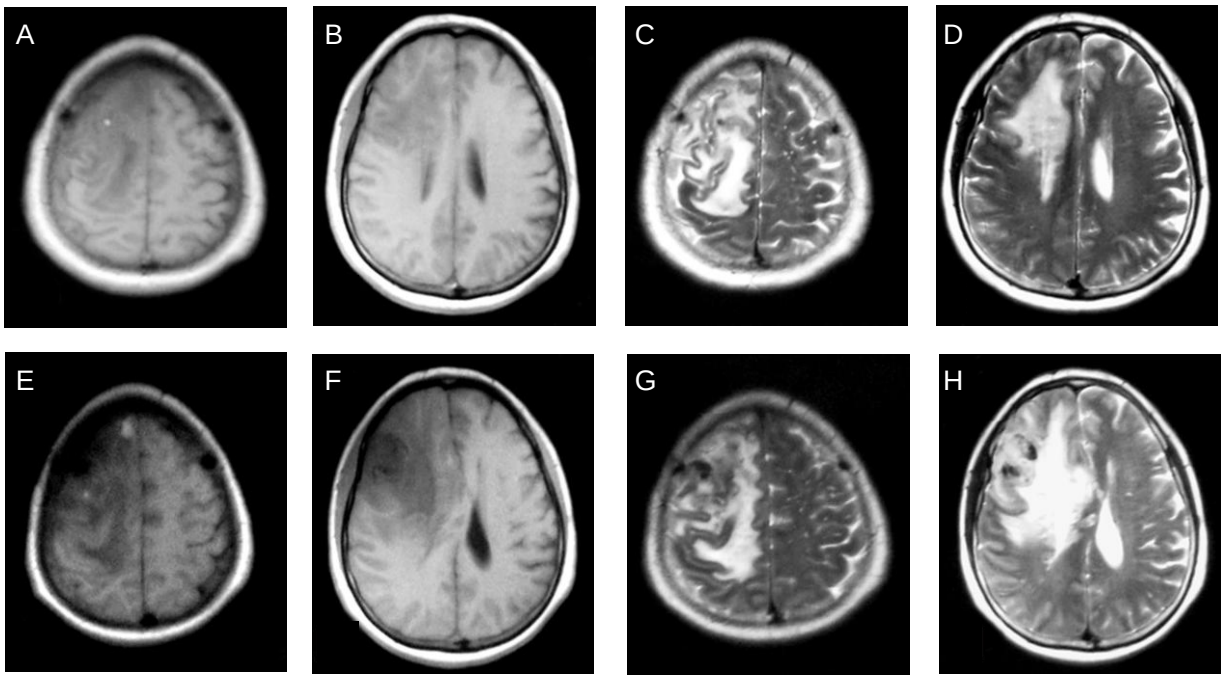

Figure 1 Brain MRI of a patient with isolated cortical vein thrombosis.

(A–D) Brain MRI of our patient with atypical presentation of isolated cortical vein thrombosis, showing mixed low and intermediate signal intensity on T1-weighted images and high signal intensity on T2-weighted images.

There is massive edema in the right frontal lobe, with insignificant compression of the right lateral ventricle, and no enhancement.

(E–H) Repeat MRI after 20 days, showing an enlarged lesion with a necrotic center, and significant compression of the right lateral ventricle with deviation of the midline to the left.

Lumbar puncture showed a CSF opening pressure of 304 kPa. CSF analysis showed a total cell count of 10 × 10^6/L, white blood cell count of 6 × 10^6/L, and elevated protein level of 63 mg/dL (normal: 15–45 mg/dL). CSF glucose and chloride levels, oligoclonal bands, 24-hour IgG synthesis rate, and cytology were all normal, and CSF virus antibody testing was negative. Electrocardiography and echocardiography were normal, and brain magnetic resonance venography was normal. Our laboratory and imaging findings did not indicate a diagnosis of isolated cortical vein thrombosis.

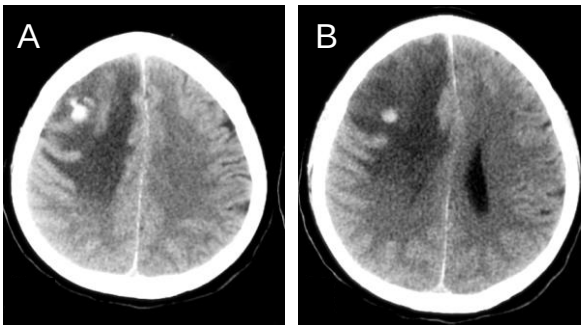

Figure 2 Cerebral CT of a patient with isolated cortical vein thrombosis.

(A, B) Head CT of our patient with atypical presentation of isolated cortical vein thrombosis, showing massive edema in the right frontal lobe and nodular hemorrhage.

Treatment

After the lumbar puncture and blood draw, she was treated with mannitol. Sodium valproate 0.2 mg, three times daily, was continued. There was no further deterioration. Two weeks after admission, surgical excision of the right frontal lobe lesion was performed under general anesthesia.

Postoperative histological examination of the surgical specimen showed destruction of brain parenchyma with infiltration of macrophages and proliferation of reactive astrocytes and small vessels. There were foci of hemorrhage in the lesion (Figure 3). Further examination found that a number of small vessels in both the subarachnoid space and brain parenchyma were filled with thrombus, some of which was organized. Elastic fiber staining showed that the obstructed vessels were veins.

The patient recovered gradually after surgery. She had residual mild left-sided hemiparesis and occasional tonic-clonic seizures. After 1 month of rehabilitation, she was able to live on her own. DSA at 2 weeks after surgery was normal. At her 9-month follow-up appointment, she still had mild left-sided hemiparesis. She continued taking sodium valproate (0.2 mg, three times daily) and had experienced one tonic-clonic seizure since discharge. All the routine tests that were performed during her initial presentation were repeated, and the results were normal. Brain MRI did not show any new lesions.

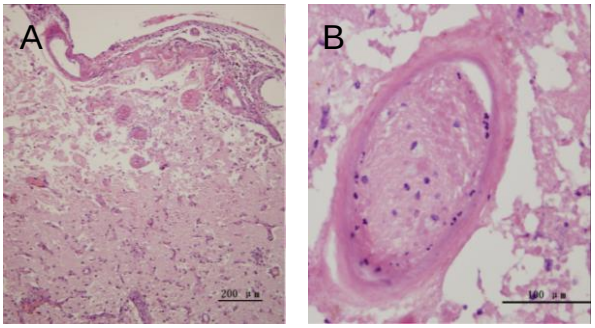

Figure 3 Histopathological examination of the surgical specimen of our patient with isolated cortical vein thrombosis (hematoxylin-eosin staining, light microscopye).

(A) Destruction of brain parenchyma, especially near the pia mater, with proliferation of small vessels (bar: 200 μm). (B) Thrombus within a vein (bar: 100 μm).

DISCUSSION

As early diagnosis of isolated cortical vein thrombosis is difficult, few cases have been reported. In spite of research to increase our understanding of the causes of this condition, the cause of nearly one third of isolated cortical vein thrombosis cases remains unknown. The acknowledged probable causes include local anatomical characteristics, thin venous walls, lack of valves and muscle fibers in veins, and veins entering the superior sagittal sinus at an acute angle with low pressure. All these features lead to slow blood flow or reflux, thereby increasing the risk of thrombus formation[5].

Many systemic factors may also cause isolated cortical vein thrombosis, such as pregnancy, dehydration, infection, oral contraception[6], coagulopathy, and autoimmune disease[7]. Some cases of isolated cortical vein thrombosis secondary to low increased intracranial pressure have been reported[8].

The clinical presentation of isolated cortical vein thrombosis is variable[9], which may be because of variability in the size and location of the cerebral cortical veins compared with the cerebral arteries[10]. The most

common symptom in reported cases is focal seizures, sometimes with secondary generalized seizures[4-5, 11-14]. Focal seizures associated with sensorimotor deficits often indicate a lesion near the central sulcus[14]. The seizures may be caused by irritation secondary to the localized venous hypertension.

The most common symptom of cerebral venous or sinus thrombosis is headache[15]. However, isolated cortical vein thrombosis has not been reported to cause symptoms of increased intracranial pressure such as headache, vomiting, or blurred vision. A reduced level of consciousness associated with deep venous involvement has also not been reported in isolated cortical vein thrombosis. Focal neurological manifestations reported in previous isolated cortical vein thrombosis cases include motor and sensory deficits[13, 16-17], aphasia[18], dyslexia, and agraphia[19].

Our patient initially presented with a tonic-clonic seizure, with no complaint of headache or neurological deficit. This initial presentation was consistent with previously reported presentations of patients with isolated cortical vein thrombosis. She subsequently developed limb weakness and signs of increased intracranial pressure, related to enlargement of the lesion. Repeat DSA did not show evidence of venous sinus thrombosis. The possibility of isolated cortical vein thrombosis with a secondary increase in increased intracranial pressure was considered. However, increased intracranial pressure and enlargement of the lesion have not previously been reported in patients with isolated cortical vein thrombosis. The delayed development of signs of increased intracranial pressure may have been because of gradual enlargement of the lesion. Importantly, parenchymal hemorrhage or subarachnoid hemorrhage[20] was visible on both CT and MRI when the lesion enlarged. The hemorrhage resulting from venous cerebral infarction is caused by increased venous pressure and injury to the vascular epithelium, both of which promote extravasation of blood[14].

Imaging studies play an important role in the diagnosis of isolated cortical vein thrombosis[9-21]. MRI is considered to be the most appropriate imaging modality[18, 22], and typically enables direct visualization of the thrombosed cortical vein, as well as visualization of secondary changes in the brain parenchyma resulting from venous outflow disturbance[23]. The T2*-weighted gradient-echo sequence is currently considered to be the most sensitive for the detection of isolated cortical vein thrombosis[14]. Unfortunately, we did not perform T2*-weighted gradient-echo sequence imaging in this patient, and regular brain MRI did not show specific changes suggesting isolated cortical vein thrombosis, except a massive lesion with edema and hemorrhage. Physicians should consider isolated cortical vein thrombosis in patients with an enlarging isolated lesion at the surface of the brain associated with edema and hemorrhage.

In our patient, MRV and DSA after surgery were normal. Although DSA did not assist in the diagnosis of isolated cortical vein thrombosis, it did allow exclusion of a diagnosis of venous sinus thrombosis.

The clinical manifestations and imaging findings in isolated cortical vein thrombosis are nonspecific. It is therefore necessary to perform a biopsy if isolated cortical vein thrombosis is suspected. In patients with isolated cortical vein thrombosis and increased intracranial pressure, surgery can both decrease increased intracranial pressure and provide a pathological diagnosis.

Considering that the risk factors for isolated cortical vein thrombosis are similar to those of intracranial venous thrombosis, patients can be given similar treatment. Further research is needed to elucidate effective medical treatment modalities for isolated cortical vein thrombosis. Our patient recovered gradually following surgery, without any further treatment other than sodium valproate. At 9 months after surgery, she had residual mild left-sided hemiparesis and had experienced one tonic-clonic seizure since discharge. These symptoms were probably sequelae of infarction and surgery.

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Author contributions: Yan Ding was responsible for the study concept and design, and wrote the manuscript. Vance Fredrickson and Yicong Lin helped write the manuscript. Yueshan Piao, Xiangbo Wang, Dehong Lu, and Cunjiang Li were responsible for data acquisition, integration, and supervision of the study.

Conflicts of interest: None declared.

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