Cerebral Venous Thrombosis Mimicking Acute Ischemic Stroke in the Emergency Assessment of Thrombolysis Eligibility: Learning from a Misdiagnosed Case

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Abstract

Purpose: Cerebral venous thrombosis (CVT) occasionally presents with acute focal neurologic signs, mimicking arterial stroke syndrome. Diagnosing CVT in the setting of thrombolysis eligibility evaluation is challenging. We reported this case to discuss the promptly recognizing CVT in the setting of thrombolysis eligibility evaluation, and review the literature of thrombolytic therapy in CVT patients.

Case report: A 57-year-old man presented with acute-onset right upper extremity monoparesis, right facial palsy, and aphasia. He underwent emergent thrombolysis with recombinant tissue plasminogen activator according to American Stroke Association guidelines. Subsequently, CVT was identified on multiphase computed tomography (CT) angiography. His symptoms initially improved but subsequently deteriorated because of intracranial hemorrhage. Cryoprecipitate and tranexamic acid were immediately administered. Anticoagulation was started 24 hours after the onset of hemorrhage. His modified Rankin Scale score was 4 at 120 days after the hemorrhage.

Conclusion: Patients with CVT have a higher risk of thrombolysis-related intracranial hemorrhage than other stroke mimics. A greater focus on noncontrast brain CT and the venous phase of CT angiography help identifying this stroke mimic before thrombolysis.

Keywords: cerebral venous thrombosis, hyperemia, intracranial hemorrhages, noncontrast computed tomography, stroke mimic

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INTRODUCTION

Cerebral venous thrombosis (CVT) is an uncommon cause of stroke and is frequently unrecognized in the emergency department. The presentation of CVT is highly variable and includes headache, seizure, altered mental status, and focal neurologic signs, depending on the location of the thrombus. CVT incidence has been increasing and its prognosis has been improving. This change in epidemiology is possibly due to the universal use of magnetic resonance image (MRI) with venography, by which mild CVT is diagnosed [(1)].

Patients with CVT occasionally present with acute focal neurologic signs mimicking arterial stroke syndrome. Diagnosing CVT in the setting of thrombolysis eligibility evaluation is challenging because current American Stroke Association (ASA) guidelines for diagnosing ischemic stroke are essentially based on clinical symptoms. Brain image study protocols, such as noncontrast brain computed tomography (CT), are straightforward and time-efficient methods for excluding intracranial hemorrhage (ICH) prior to thrombolysis[(2)]. Here we report a patient with CVT mimicking arterial acute ischemic stroke syndrome who received thrombolysis and had subsequent ICH. Strategies for promptly recognizing CVT in thrombolysis eligibility evaluation and the outcomes of thrombolysis in CVT were reviewed. The case report was approved by the Institutional Review Board, National Cheng Kung University Hospital (IRB No. B-EC-109-012).

CASE REPORT

A 57-year-old man presented with sudden-onset right upper limb monoparesis. He had no headache, neck pain, or chest discomfort. He had no known systemic disease, and he was not a smoker. He arrived at the emergency department 22 minutes after symptom onset. On examination, he had tachycardia (118 bpm) and elevated blood pressure (159/100 mmHg). Neurologic examination revealed impaired language fluency and comprehension, right facial palsy, and right upper limb monoparesis (muscle power shoulder abduction, 4; grasping, 4). His National Institute of Health Stroke Scale was 4.

The clinical course, diagnostic workup, and therapeutic intervention were summarized in Table 1. An electrocardiogram revealed sinus tachycardia. Noncontrast brain CT indicated no ICH and no early infarction sign but hyperdense superior sagittal sinus (Fig 1A–C), which might be related to hemoconcentration or thrombosis. Laboratory tests revealed elevated serum hemoglobin (17.7 g/dL). Platelet count, prothrombin time, activated partial thromboplastin time, and blood glucose level were all within normal limits. Clinical diagnosis was acute ischemic stroke in the partial left middle cerebral artery territory. Thus, the patient received intravenous recombinant tissue plasminogen activator (rt-PA) thrombolysis therapy with a dosage of 0.9 mg/kg (total dosage = 70 mg, loading dose [7 mg] administered at 1 h 20 minutes after symptom onset, with the remaining 63 mg infused within 1 h). The patient's language and muscle strength improved within 10 minutes after the rt-PA was administered.

Subsequently, he underwent eligibility evaluation for prompt endovascular thrombectomy. Multiphase CT angiography of the brain revealed no large vessel occlusion, but thrombosis was observed in the superior

Table 1. The clinical course, diagnostic workup, and therapeutic measures of the patient. (NIHSS, National Institute of Health Stroke Scale; rt-PA, recombinant tissue plasminogen activator; CT, computed tomography; ICH, intracranial hemorrhage; MRI, magnetic resonance image)

-22 min	Sudden onset right upper limb monoparesis.
0 min	Hospital arrival. Language disturbance found. NIHSS 4.
58 min	Thrombolysis with rt-PA 0.9mg/kg.
68 min	Symptom improved.
69 min	Multiphase CT angiography. Cerebral venous thrombosis diagnosed.
168 min	Symptomatic ICH. Cryoprecipitate, tranexamic acid, blood pressure control.
24 hr	MRI showed no hematoma expansion. Administered low molecular weight heparin.
1 month	Modified Rankin Scale 5.
4 months	Modified Rankin Scale 4. Mild stuttering, mild right hemiparesis.

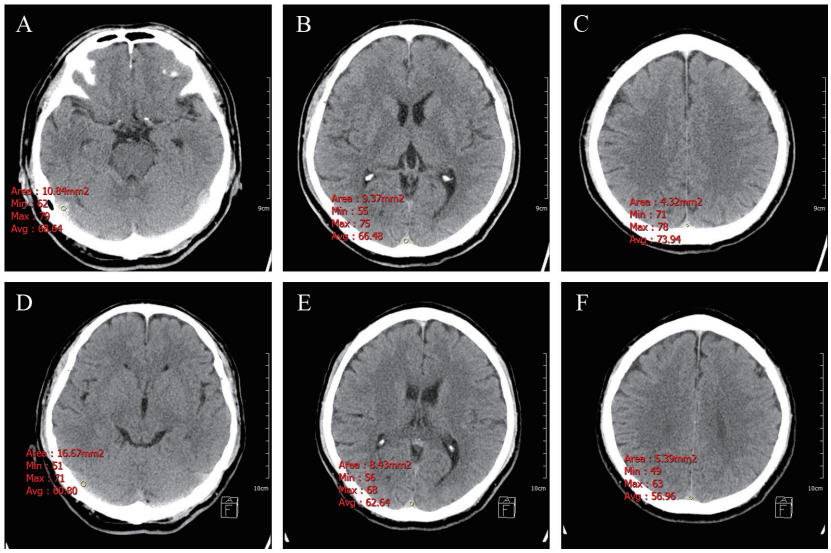

Figure 1. Noncontrast brain CT before and after rt-PA infusion. (A–C) Initial noncontrast brain CT revealed no intracranial hemorrhage and no early infarction sign. However, high attenuation was observed in the superior sagittal sinus and the right transverse sinus. (D–F) The attenuations in the venous sinuses decreased after rt-PA infusion, which may suggest partial recannalization of the superior sinus and the right transverse sinus. The average attenuations before rt-PA were 68.6HU in transverse sinus (A), 66.5HU and 73.9HU in superior sagittal sinus (B, C), and became 60.8HU in transverse sinus (D), 62.6HU and 56.9HU in superior sagittal sinus (E, F) after rt-PA. (CT, computed tomography; rt-PA, recombinant tissue plasminogen activator; HU, hounsfield unit; min, minimum; max, maximum; avg, average)

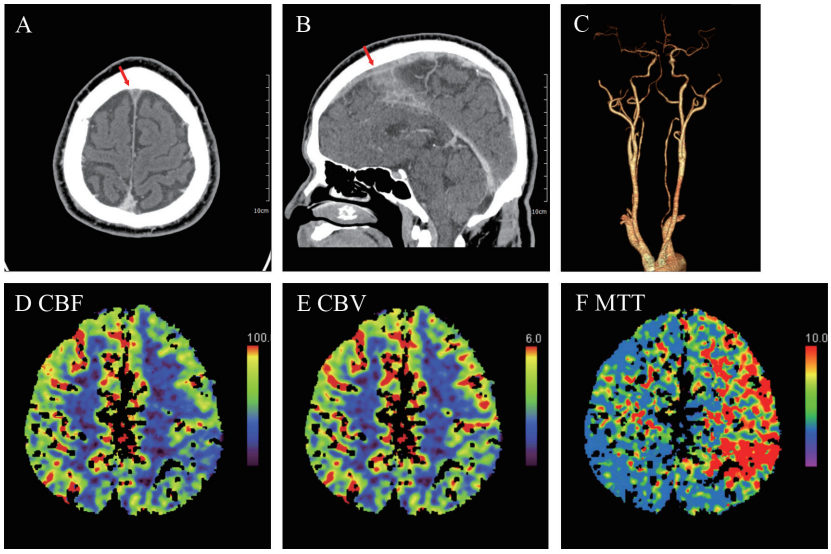

Figure 2. Multiphase CT angiography and CT perfusion. Axial (A) and sagittal (B) images from the third phase of the CT angiography revealed empty delta sign in the anterior part of the superior sagittal sinus. (C) 3D reconstruction image of cerebral arteries indicated no large vessel occlusion. (D–F) Prolonged MTT was observed in the left frontoparietal lobes and the right high frontal lobe (F), without associated changes on CBF (D) and CBV (E), suggesting venous congestion. (CT, computed tomography; 3D, three-dimensional; CBF, cerebral blood flow; CBV, cerebral blood volume; MTT, mean transient time.)

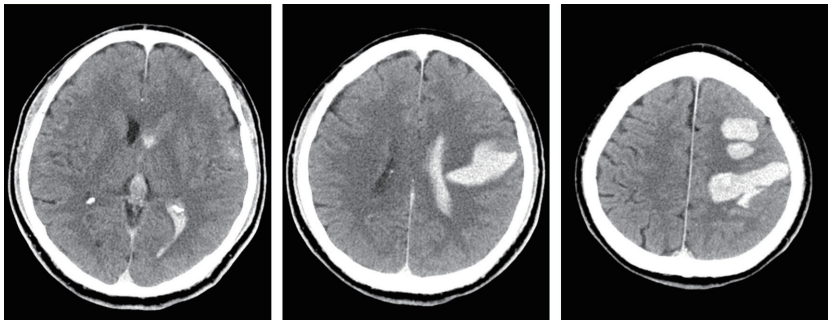

Figure 3. Follow-up noncontrast brain CT after rt-PA infusion. Intracerebral hemorrhage was observed in the left frontoparietal lobes with perifocal edema and intraventricular hemorrhage. The region of the hemorrhage was consistent with the area of venous congestion on the CT perfusion scan (see Fig 2). (CT, computed tomography; rt-PA, recombinant tissue plasminogen activator.)

sagittal sinus with empty delta sign (Fig 2A–C). A CT perfusion scan revealed increased mean transient time in the left frontoparietal lobes and the right high frontal lobe, suggesting venous congestion (Fig 2D–F). Thus, the endovascular thrombectomy was suspended and CVT was diagnosed.

One hour and fifty minutes after rt-PA was administered, the patient became agitated. His eyes deviated to the right conjugately, and the right hemiparesis reappeared. Noncontrast brain CT indicated intracerebral hemorrhage in the left frontoparietal lobes with perifocal edema and intraventricular hemorrhage (Fig 3). The location of the hematoma was consistent with the region of venous congestion observed on the CT perfusion scan 110 minutes previously. We treated the patient with 12 U cryoprecipitate transfusion and 1000 mg tranexamic acid to stop the rt-PA-related hemorrhage. Blood pressure was strictly controlled below 140/90 mmHg.

One day after the hemorrhage, the size of the hematoma was unchanged on brain MRI. Thus, we administered low-molecular-weight heparin and then warfarin for CVT. One month after the hemorrhage, the patient exhibited coherent but nonfluent speech, dense right hemiplegia, and a score of 5 on the modified Rankin Scale (mRS). Four months after the hemorrhage, the patient exhibited some improvements (mRS = 4). Mild stuttering and right hemiparesis remained.

DISCUSSION

CVT mimicking acute ischemic stroke is a clinical challenge in the expeditious assessment of thrombolysis eligibility. Although CVT is not listed on the exclusion criteria of ASA guidelines for thrombolytic therapy for acute ischemic stroke[2], the risk of ICH might be higher than thrombolysis in other stroke mimic[3,4] . Recognizing patients with this stroke mimic who are at a high risk of developing ICH prior to thrombolysis therapy prompts effective risk communication between clinician and patient. In addition, appropriate therapy with anticoagulation rather than systemic thrombolysis should be applied earlier. Because of the time-sensitive assessment for thrombolysis eligibility, the following discussion focuses on a readily available, easily applied, and broadly used tool in emergency settings to identify patients with CVT prior to thrombolytic therapy.

In the current thrombolysis eligibility assessment system, noncontrast brain CT and hematocrit may help in identifying CVT. On noncontrast brain CT, direct signs of a thrombus, such as a dense clot sign, cord sign of the cortical vein, and dural venous sinus sign, as well as indirect signs, such as intracerebral hemorrhage, subdural hemorrhage, subarachnoid hemorrhage, cerebral edema, and venous infarction, facilitate the diagnosis [5]. Several studies have quantified the CT attenuation of the venous sinus and inferred a cut-off value for the diagnosis of CVT. Buyck et al. [6] compared the diagnostic accuracy of various parameters of noncontrast brain CT for CVT, including attenuation of 62 Hounsfield unit (HU), HU-to-hematocrit ratio (H:H) of 1.52, and attenuation of affected: unaffected sinus of 1.3. The three diagnostic cutoffs, attenuation of 62 HU (sensitivity 0.6, specificity

0.78), H:H of 1.52 (sensitivity 0.65, specificity 0.74), and attenuation of affected/unaffected sinus of 1.3 (sensitivity 0.61, specificity 0.90), exhibited moderate sensitivity and specificity in diagnosing acute CVT, which was comparable to that of visual assessment by an experienced reader (sensitivity 0.46–0.72, specificity 0.98–1.00).

Regarding other image protocols for diagnosing CVT, the empty delta sign on contrast-enhanced CT and venous phase of multiphase CT angiography are also useful. In the absence of both time-of-flight and contrast MR venography, brain MRI with the simplest protocol still enables clinicians to identify a fat sinus sign (enlarged dural sinus with convex margin), disappearing flow void due to a blood clot, gyral swelling/parenchymal hyperintensity on T2-weighted and fluid-attenuated inversion recovery imaging, blooming on T2* imaging, and parenchymal venous ischemia on diffusion-weighted imaging [5]. However, the aforementioned imaging tools might not be promptly available in the thrombolysis eligibility evaluation system.

D-dimer might provide supporting evidence of CVT. Dentali et al. [7] systematically reviewed the role of D-dimer in discriminating patients with and without CVT; the mean sensitivity was 93.9% and the weighted mean specificity was 89.7%. Patients with CVT with isolated headache, longer duration of symptoms, and limited sinus involvement may have a false negative result of D-dimer; however, this group of patients would not be presented in the emergency assessment of thrombolysis eligibility for acute stroke. D-dimer is also elevated in acute ischemic stroke, particularly in patients with cardioembolic stroke and cancer-related stroke [8]. No single parameter can inform a CVT diagnosis. The suitability of D-dimer in conjunction with noncontrast brain CT in discriminating arterial stroke and CVT requires further study.

Although CVT is not currently listed as a contraindication of rt-PA, the use of systemic thrombolysis in CVT is controversial. The 2011 ASA guidelines for CVT suggest that thrombolysis can be considered in a patient with CVT who exhibits increased intracranial pressure or clinical signs despite anticoagulation and other management approaches [9]. However, the 2017 guidelines from the European Stroke Organization recommend a more conservative approach to thrombolysis in CVT [10]. In patients with acute CVT with a CVT risk score < 3, systemic thrombolysis is not required [11].a

Thrombolysis is considered relatively safe in most stroke mimics [4]. However, the patient we reported here had a poor outcome. A similar case involved a 33-year-old woman who was clinically diagnosed with pure motor lacunar stroke [12]. Her symptoms were partially alleviated after rt-PA infusion. However, headache, nausea, vomiting, and disturbance of consciousness developed within 1 h. A brain CT revealed right frontal hematoma, and a brain MRI revealed CVT in the superior sagittal sinus and bilateral transverse sinuses. The patient immediately underwent recanalization with a mechanical thrombectomy. Anticoagulation resumed 1 day later. The patient exhibited a good recovery at 1-year follow-up. Another patient, a 29-year-old man, was at the opposite end of CVT. He was clinically diagnosed with an in-hospital left middle cerebral artery stroke after undergoing diagnostic angiography for his CVT [13]. The catheter-related ischemic stroke was improved after rt-PA infusion, and follow-up imaging indicated significant sinus recanalization without intracranial hemorrhage. The patient received anticoagulation therapy 1 day after rt-PA. In addition to the aforementioned 2 patients who received a similar dosage of rt-PA to our patient, Viegas et al. [3] systematically reviewed 26 published cases of CVT treated with systemic thrombolysis. Prior to the thrombolysis, 7.2% (2/26) of patients had ICH. The rate of newly developed ICH after systemic thrombolytic therapy was 11.5% (3/26); 2 of the 3 patients (7.7%) had symptomatic ICH. However, the regimens of patients in this review were disparate. Twenty-five out of 26 cases did not follow the standard dosage of rt-PA for acute ischemic stroke. They received various dosages of urokinase (20 cases), streptokinase (3 cases), and rt-PA (2 cases) with various administration routes, infusion rates, and treatment duration. This diverse spectrum of therapeutic strategies for thrombolysis impedes the drawing of conclusions. Although the incidence of CVT is much less than that of arterial stroke, these patients can present as stroke mimics in the thrombolysis eligibility evaluation system. Understanding the advantages and disadvantages of rt-PA in patients with CVT is imperative because it determines whether a timely diagnosis of CVT prior to rt-PA infusion is necessary.

No high-quality evidence is available regarding

treating intracranial hemorrhage after thrombolysis in patients with CVT. Intracranial hemorrhage in CVT is caused by increased venular and capillary pressure and blood–brain barrier disruption due to ischemia [14]. Recanalization might be the solution for intracranial hemorrhage in CVT. Therefore, both the US and European guidelines recommend using anticoagulation even if the patient has presented with hemorrhage [9, 10]. However, consumptive coagulopathy after thrombolysis is less predictable than that after anticoagulation treatment [15]. Therefore, on the basis of pathophysiology and the management of reported cases, first reversing thrombolysis-related coagulopathy appears reasonable, followed by standard anticoagulation therapy for CVT. Mechanical thrombectomy might be a useful adjunctive treatment in such circumstances.

To the best of our knowledge, this is the third reported case of a patient with CVT who had thrombolytic treatment according to stroke regiment. We report this case to increase vigilance regarding CVT as an acute ischemic stroke mimic. In conclusion, evaluating the venous system on noncontrast brain CT, considering the venous phase of multiphase CT angiography, and measuring hematocrit and D-dimer may help clinicians recognize CVT, a stroke mimic with poorer outcome after thrombolysis than others.

aThe CVT risk score considers the following factors: malignancy, coma, mental status disturbance, thrombosis of the deep venous system, male sex, and intracranial hemorrhage.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

PYL drafted the manuscript. YCC provided critical interpretation and design the presentation of medical image. YTS made major revision and complete the final version of the manuscript. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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