

Remote Intracerebral Hemorrhage Following Intravenous Thrombolysis in Pregnancy at 31 Weeks Gestation

A Case Report and Review of the Literature

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Introduction: Intravenous recombinant tissue-type plasminogen activator thrombolysis in pregnancy for acute ischemic stroke is infrequent. As a rare complication of thrombolysis, remote intracerebral hemorrhage (rICH) whose mechanisms are unclear has not gained enough attention until now.

Case Report: We present here a case of 26-year-old pregnant woman at 31 weeks gestation who suffered from sudden onset right-sided hemiparesis and slurred speech. She successfully received intravenous recombinant tissue-type plasminogen activator thrombolysis within 2.5 hours from stroke onset. Further workup demonstrated multiple and bilateral acute cerebral infarcts due to cardioembolism. At 6 hours after thrombolysis, multifocal intracerebral hemorrhages were developed in her left cerebellum and right temporal cortex, remote from the initial infarct areas. However, the patient achieved a final complete recovery of symptoms. Despite diffusion-weighted imaging could not confirm infarct in the areas of hemorrhages, multiple cerebral embolism was suggested to be involved in the etiology of rICH.

Conclusions: rICH is different from local intracerebral hemorrhage in its risk factors, neurological outcomes, and underlying mechanisms. Patients with rICH may have favorable outcomes and multiple cerebral embolism is still one of the important mechanisms for postthrombotic rICH.

Key Words: ischemic stroke, pregnancy, thrombolysis, complication, remote intracerebral hemorrhage

(*The Neurologist* 2018;23:19–22)

Ischemic stroke is a devastating event for a pregnant woman that can result in long-term disability or death. The relative hypercoagulable state in pregnancy makes ischemic cerebral events more frequent in pregnant females than in nonpregnant females.¹ Although its efficacy and safety have been tested in a series of case reports, there is no definite conclusion about the use of recombinant tissue-type plasminogen activator (r-tPA) in acute ischemic stroke during pregnancy because of a lack of results from large controlled trials.² Remote intracerebral

hemorrhage (rICH) is a rare complication of thrombolytic therapy in ischemic strokes. The underlying mechanisms of rICH are still uncertain.

Here, we present an infrequent case of successful intravenous r-tPA thrombolysis that was accompanied with multiple rICH but resulted in a complete recovery of symptoms in a woman at the third trimester of pregnancy. We then summarize the recent literature focusing on postthrombotic rICH.

CASE REPORT

A 26-year-old woman presented to the emergency room in our hospital with a chief complaint of sudden onset right-sided hemiparesis and mild slurred speech, and her National Institutes of Health Stroke Scale (NIHSS) was 6 points. She presented 1.5 hours after last known well and was 31 weeks pregnant (G2P1). She had an unremarkable head computed tomography (CT) scan and was clinically diagnosed with an ischemic stroke. Her platelet count, coagulation values, and serum glucose were all normal. Her medical history revealed rheumatic fever in childhood without subsequent follow-up. We then found a systolic mitral murmur during the physical examination. The etiology of her stroke, therefore, was presumed to be a cardioembolism.

After assessment by obstetricians, the patient was admitted to our comprehensive stroke center for close monitoring and r-tPA treatment at standard dosage within 2.5 hours from stroke onset. Endovascular therapy was foregone because of no significant main arterial occlusions in her CT angiogram. At 2 hours postthrombolysis, the patient was significantly improved to an NIHSS score of 3. At 6 hours postthrombolysis, however, the patient felt dizzy and vomited once. A physical examination revealed nystagmus and ataxia in her left limbs, but her hemiparesis did not deteriorate. Her NIHSS score rose to 4 points. An urgent head CT scan revealed multifocal small intracerebral hemorrhages in her left cerebellar hemisphere and right temporal cortex (Figs. 1A, B), remote from the supposed infarct areas. Obstetrical monitoring was normal and no more neurological deficits presented. We did not administer urgent treatment except close monitoring because it had been 6 hours since r-tPA administration, and the hemorrhage was considered asymptomatic according to the ECASS II and mSITS-MOST rICH definitions.³

Brain diffusion-weighted magnetic resonance imaging (DWI) then demonstrated multiple and bilateral acute infarcts in the right caput nuclei caudati, left basal ganglia, and left corona radiata (Fig. 1C), corresponding to multiple cardioembolism. Cardiac ultrasonography confirmed mitral valve prolapse and insufficiency. The remainder of her workup, including vascular imaging studies, autoimmune profile, anti-phospholipid antibodies, and protein C and S, was normal. By hospital day 4, her neurological symptoms were almost completely resolved. Obstetrical evaluation did not reveal any complications with the placenta or fetus. The patient was then discharged on daily low molecular weight heparin therapy for the remainder of her pregnancy, with close obstetrical and neurological follow-up. At term, she delivered a healthy male infant vaginally with no obstetrical or fetal complications. At her most recent evaluation, the patient was fully independent in all activities of daily living, achieving a final modified Rankin Scale Score of 0. The patient was placed on long-term warfarin therapy and cardiological follow-up.

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Supported by the National Natural Science Foundation of China (grant no. 81400994).

The authors declare no conflict of interest.

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ISSN: 1074-7931/18/2301-0019

DOI: 10.1097/NRL.0000000000000165

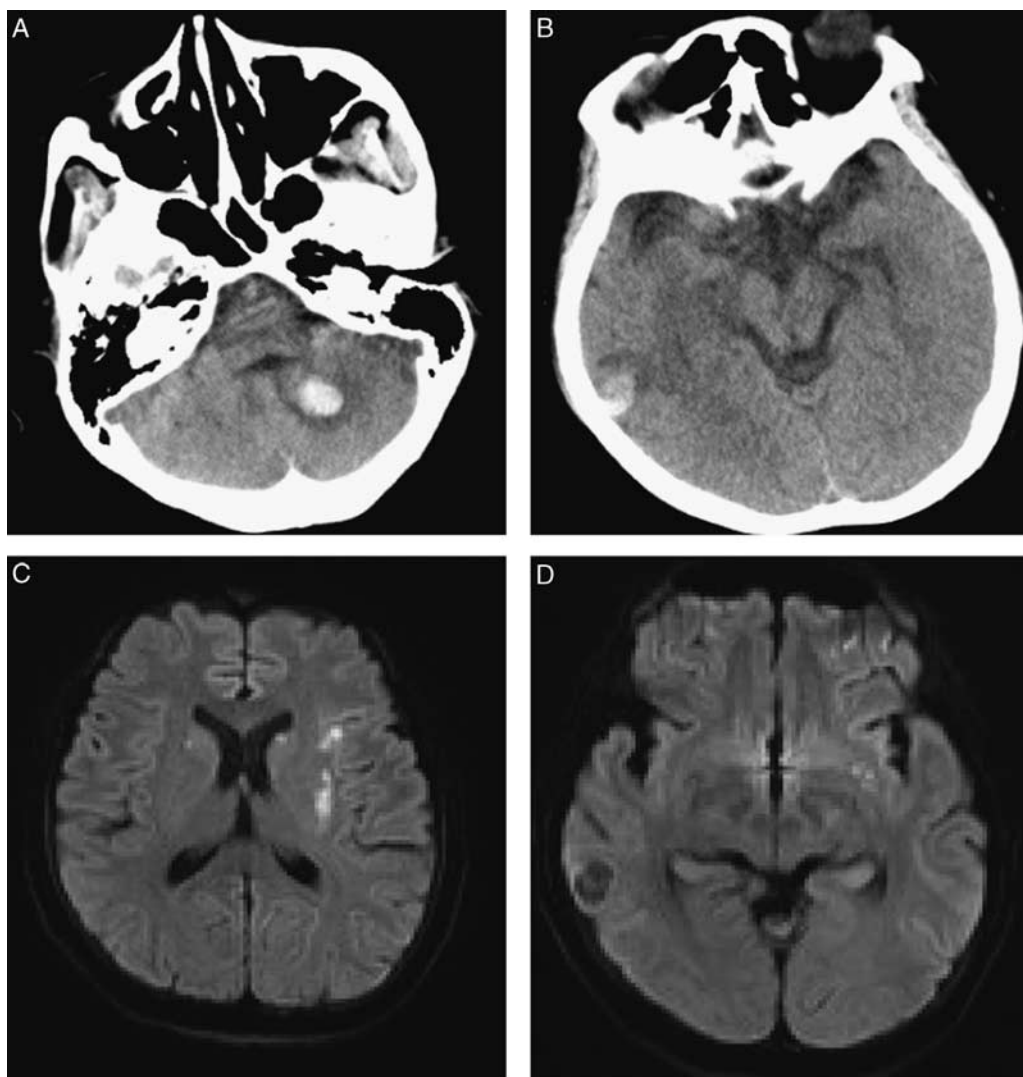


FIGURE 1. Multiple remote intracerebral hemorrhages after intravenous recombinant tissue-type plasminogen activator thrombolysis in a pregnant woman of acute ischemic stroke. A, B, Computed tomographic scan revealed intracerebral hemorrhages in left cerebellum and right temporal cortex 6 hours after thrombolysis. C, Diffusion-weighted imaging demonstrated multifocal and bilateral acute infarcts in the areas remote from the hemorrhages. D, No significant restricted diffusion in the area of right temporal hematoma.

DISCUSSION

Stroke in pregnancy remains rare, and clinical trial data regarding thrombolytic therapy in pregnant women are absent due to pregnancy always being an exclusion criterion in randomized controlled trials.⁴ However, the available published data suggest that thrombolysis in pregnancy has a safe and successful record in individual case reports or series^{5–11} and as such should not be withheld for ischemic stroke. It was reported that complication rates in systemic thrombolysis in pregnancy using r-tPA were similar to those in the nonpregnant population.^{12–14} In a retrospective study, 1 of 15 (6.7%) women had a symptomatic intracranial hemorrhage,¹⁵ comparable with what has been reported in the literature for r-tPA treatment in general.¹⁶ At the same time, r-tPA molecules are too large (72,000 kD) to cross the placenta and thus are not known to be teratogenic.¹⁴ In addition, intravenously delivered r-tPA has a half-life of only 4 to 5 minutes, which also contributes to its safety when used at recommended therapeutic doses in pregnancy. Thus, the American Heart Association and the American

Stroke Association guidelines recommend the use of r-tPA for moderate to severe strokes in pregnancy when the benefit justifies the potential risk to the fetus and the potential for uterine bleeding.¹⁷

Despite complete recovery from symptoms, the patient discussed here developed multiple rICH after thrombolysis. Thus far, there is no similar report about multiple rICH after thrombolysis in pregnant patients. Whether there is any relationship between rICH and pregnancy is unclear. Intracerebral hemorrhage after treatment with intravenous r-tPA for ischemic stroke can occur at the site of ischemic brain tissue as well as in brain areas remote from infarcted tissue. rICH postthrombolysis can be solitary or multiple and is defined as hemorrhages that appear in brain regions without visible ischemic changes.¹⁸ rICH is an infrequent complication after intravenous thrombolysis compared with local/intraischemic intracerebral hemorrhage (iICH). The risk of rICH postthrombolysis has been reported as occurring in ~1.3% to 3.7% of patients.^{18–20} The multifocal rICH, as presented in our patient, only represented

9% of all postthrombolytic hemorrhages and the overall incidence was 0.6% in the ECASS III study.²¹

From 2 cohort studies,^{22,23} postthrombolytic rICH had been found to be associated with higher age, female patients, and a history of previous stroke (> 3 mo before). Atrial fibrillation, hyperdense cerebral artery signs on CT, and elevated blood glucose were suggested to be associated with iICH but not with rICH.²² It was reported that the prognosis of rICH was poor with early deterioration and unfavorable neurological outcomes.²⁴ A recent multicenter study supports the notion that rICH increases the risk of long-term functional dependence and mortality compared with patients without any rICH or iICH.²⁵ However, when compared with patients with iICH, the patients with rICH might have better clinical outcomes and a lower 3 month mortality rate.²² Thus, despite being as likely as iICH to cause significant neurological deterioration, rICH may be associated with a more favorable outcome compared with iICH. In line with previous reports,^{22,23} the patient presented here developed multifocal rICH, but the neurological outcome was favorable; therefore, all rICH developments may not necessarily be serious life-threatening events. Regarding the location of rICH, only a small sample size study indicated that cerebellar vermis might be a vulnerable location for rICH after thrombolysis.²⁶

The pathogenesis underlying rICH is not yet fully understood. As rICH occurs outside of the infarct area, reperfusion injury may not completely explain the underlying pathophysiology. Traditionally, remote hematomas tend to be hemorrhagic transformations at a distant unrecognized focus of recent infarction or occur as a result of preexisting coagulopathies.¹⁸ However, in the cohort study from the Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Register (SITS-ISTR),²² recent previous stroke (<3 mo) was not found to be a risk factor for rICH. Another result from France found that recent silent cerebral infarcts on prethrombolysis magnetic resonance imaging did not show any association with postthrombolysis rICH.²⁷ It was also reported that rICH occurred at the site where no evidence of ischemia was found on DWI.²⁸ Nevertheless, a recent multicenter study clearly demonstrates that multiple acute embolic ischemic lesions are strongly associated with rICH. In our current case, even though DWI could not confirm infarct in the areas of hemorrhages (Fig. 1D) and there were also no clinical signs of cerebellar or right temporal ischemia before thrombolysis, it remains highly possible that the multifocal rICH was due to multiple cardiogenic emboli that were unrecognized in the hemorrhagic areas. There is a possibility that the initial DWI abnormalities in the areas of the hemorrhages were covered up by hematomas or that small ischemic lesions were missed because of current technical limitations such as slice thickness and imaging resolution. After all, a cardioembolic source has been reported as an independent risk factor for an unrecognized cerebral infarct.²⁹ Therefore, multiple cerebral embolism may still be one of the important mechanisms giving rise to the formation of rICH.

Recently, increasing data support the notion that cerebral small vessel disease, which commonly includes hypertensive arteriopathy and cerebral amyloid angiopathy (CAA), may be the leading underlying pathology in rICH.^{22,23,30} Cerebral microbleeds (CMBs) and white matter lesions (WMLs) are the imaging surrogates of cerebral small vessel disease.³¹ Meta-analyses have suggested that CMBs significantly increase the risk of any postthrombolytic symptomatic intracerebral hemorrhage,³² and postthrombolytic rICH has been previously documented to occur at the site of a CMB.³³ In agreement with

this meta-analysis, patients with preexisting lobar CMBs before thrombolysis more frequently had rICH after r-tPA treatment.²⁵ Interestingly, radiographic studies have demonstrated that new CMBs were developed in 5% to 13% of acute ischemic strokes after thrombolysis,^{34–36} and meta-analysis revealed that patients who developed new CMBs had a significantly increased risk of postthrombolytic rICH.³⁰ Therefore, thrombolysis-induced new CMBs might be the cause underlying a proportion of rICH in acute ischemic stroke.³⁰ Moreover, it has been reported that WMLs doubled the risk of symptomatic intracerebral hemorrhage after intravenous r-tPA treatment.³⁷ A recent cohort study indicates that severe WMLs predominantly increase the risk of rICH but not the occurrence of iICH.³⁸ The fact that patients with CAA tend to be older and more often female is consistent with the finding that higher age and female sex had a stronger association with rICH.²² Similarly, in thrombolysis for acute myocardial infarction, multifocal hematomas had been related to preexisting brain pathology including CAA.³⁹ Thus, rICH may be a complication of a preexisting or newly evolved microangiopathy in ischemic stroke after thrombolysis.

It has also been mentioned that rICH may be associated with the toxic effects of r-tPA, which has been suggested to induce degradation of the extracellular matrix, endothelial cell death, and blood-brain barrier leakage.⁴⁰ rICH has not been previously reported in association with other thrombolytic agents such as tenecteplase, suggesting that r-tPA has a specific class effect.^{23,40}

Thus, rICH, despite its infrequent occurrence, may present an independent mechanism different from iICH in the complications of thrombolytic therapy and thereby should be given more importance. Multiple cerebral embolism, preexisting or thrombolysis-induced cerebral small vessel pathology, and potential toxic effects of r-tPA are suggested to play a role in the mechanisms of rICH. Additional research that incorporates a comprehensive assessment of both clinical and pathologic features of rICH may be needed in the future.

ETHICS STATEMENT

This study was approved by the Institutional Review Board at the Second Xiangya Hospital of Central South University, Changsha, Hunan, China. A written informed consent was given by the patient for publication of this study and any accompanying images.

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