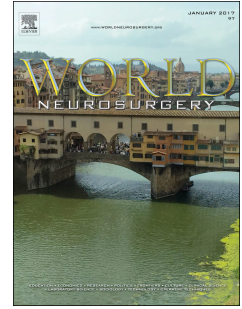


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A case of rapid malignant brain swelling subacutely after reperfusion therapy for internal carotid arterial occlusion: A case report

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Key words: acute brain swelling, acute ischemic stroke, mechanical thrombectomy, perfusion pressure breakthrough, second-impact syndrome, t-PA

Abbreviations list

blood-brain barrier (BBB), computed tomography (CT), internal carotid arterial (ICA), magnetic resonance imaging (MRI), middle cerebral artery (MCA), postoperative day (POD), rapid malignant brain swelling (RMBS), second-impact syndrome (SIS),

subarachnoid hemorrhage (SAH)

ACCEPTED MANUSCRIPT

Abstract

Background: Severe complications after reperfusion therapy for acute major vessel occlusion are not well-described. We present an extremely rare case of a patient with rapid malignant brain swelling subacutely after acute ischemic stroke.

Case Description: An 84-year old man underwent reperfusion therapy for acute left internal carotid arterial occlusion, and complete reperfusion was achieved. Although magnetic resonance imaging on postoperative day (POD) 1 revealed a small hemorrhagic infarction and subarachnoid hemorrhage (SAH) unrelated to a left middle cerebral arterial aneurysm in the left frontal lobe, neurological deficits resolved completely. On POD 5, the patient developed a fever and sudden consciousness disorder with right hemiparesis. He was diagnosed as having urosepsis, and computed tomography (CT) revealed massive hemorrhagic infarction in the left frontal lobe and diffuse SAH. Emergent hematoma evacuation and clipping were performed. Although the aneurysm was unruptured, brain swelling was severe despite a patent middle cerebral artery. CT performed immediately postoperatively (within 6 hours after preoperative CT) showed severe left brain swelling with midline shift. The patient unfortunately died on POD 15. **Conclusions:** This case has some similarities to both second-impact syndrome after head trauma and perfusion breakthrough phenomenon. In our patient, initial ischemic damage following reperfusion therapy and damage secondary to sepsis and SAH might have led to rapid malignant brain swelling. Careful management is important for patients receiving reperfusion therapy.

Introduction

Ischemic stroke is a leading cause of mortality and morbidity, and the treatment target for patients with acute ischemic stroke is immediate and efficacious recanalization of the occluded artery. Remarkable progress in the development of endovascular devices has enabled rapid recanalization and high recanalization rates, thereby providing favorable outcomes for patients with acute major arterial occlusion.¹ After reperfusion therapy, secondary prevention of stroke and rehabilitation are important. Direct oral anticoagulants have replaced warfarin for preventing cardiogenic infarction in many patients because these agents can prevent cardiogenic infarction equal to warfarin with fewer hemorrhagic complications.²⁻⁵ Older patients have worse long-term outcomes, reflecting the higher burden of comorbidities and complications after stroke.⁶ Therefore, preventing complications after stroke is especially important in these patients. We report an extremely rare case of a patient with rapid malignant brain swelling (RMBS) subacutely after acute ischemic stroke. The patient had urosepsis and massive hemorrhagic infarction with subarachnoid hemorrhage (SAH) while taking rivaroxaban. We also discuss the etiology of RMBS. To our knowledge, ours is the first report of RMBS subacutely after ischemic stroke.

Case Presentation

An 84-year old man with a history of hypertension was transported to a local hospital by ambulance approximately 30 minutes after symptom onset. Neurological examination on arrival revealed consciousness disorder, right hemiparesis, and aphasia. The patient scored 8 points on the Glasgow Coma Scale (E1V3M4) and 24 points on the National Institutes of Health Stroke Scale. Magnetic resonance imaging (MRI) showed

acute cerebral infarction in the left frontal lobe and left internal capsule (Fig. 1A). Magnetic resonance angiography showed left internal carotid arterial (ICA) occlusion. After tissue-plasminogen activator infusion 114 minutes from symptom onset, the patient was transported to our hospital by helicopter. His symptoms did not improve, and endovascular treatment was performed. Mechanical thrombectomy using a 6 × 30-mm Solitaire FR (Medtronic, Minneapolis, MN, USA) and a Penumbra 5MAX ACE catheter (Penumbra Inc., Alameda, CA, USA) was performed with a balloon-guided catheter. Initial digital subtraction angiography showed left ICA occlusion (Fig. 1B), with the distal edge of the thrombus at the middle portion of the left M1 segment. First, we fully deployed the Solitaire FR from the distal portion of the left M1 and retracted it into the Penumbra 5MAX ACE, retrieving a red thrombus. After first passage using a stent retriever, left internal carotid arteriography showed left middle cerebral artery (MCA) distal M1 occlusion. Another remnant thrombus was retrieved using a direct aspiration first-pass technique with the Penumbra 5MAX ACE. Complete reperfusion was achieved, and an aneurysm was found at the MCA bifurcation (Fig. 1C). The patient's Thrombolysis In Cerebral Infarction score was grade 3 flow. The time from onset to reperfusion was 328 minutes. The next day, postoperative day (POD) 1, MRI revealed a small hemorrhagic infarction in the frontal lobe, infarction in the left internal capsule, and a small SAH in the left Sylvian fissure (Fig. 1D and E). The patient's symptoms had resolved completely. However, his electrocardiogram showed paroxysmal atrial fibrillation, and MRI on POD1 showed that the hemorrhagic infarction with SAH was not severe; therefore, we prescribed rivaroxaban from POD 2. Computed tomographic (CT) angiography on POD 3 showed a 3-mm aneurysm at the left MCA bifurcation without stenosis or reocclusion of major vessels (Fig. 1F) and no

increase in the size of the hemorrhagic infarction and SAH. The morning of POD 5, the patient remained asymptomatic; however, by noon, he had developed a fever and sudden consciousness disorder with right hemiparesis. Laboratory testing revealed increased C-reactive protein (9.78 mg/dl) and procalcitonin (5.870 ng/ml) levels, and bacteriuria accompanied with an elevated white blood cell count. Although prothrombin time was not prolonged compared with admission (12.8 s vs. 11.9 s; POD 5 vs admission, respectively), CT revealed increased SAH and cerebral hemorrhage in the left frontal lobe at the site of previous hemorrhagic infarction seen on MRI or CT (Fig. 2A and B). Meropenem was administrated, and emergent operation was performed. Intraoperative findings showed that the MCA aneurysm was unruptured (Fig. 2C) and indocyanine green video angiography after clipping confirmed patency of the left MCA (Fig. 2D). Because the patient's brain swelling was severe during intracranial surgery, we did not replace the free bone flap. Postoperatively, physical examination revealed anisocoria, and CT performed immediately postoperatively revealed severe left hemispheric brain swelling and midline shift (Fig. 2E and F). Laboratory testing the next day revealed an increased white blood cell count ($10600/\text{mm}^2$), and C-reactive protein (19.9 mg/dl) and procalcitonin (> 100.0 ng/ml) levels. Also, *Citrobacter koseri* was isolated from blood and urine. Although intensive care was performed, the patient unfortunately died on POD 15.

Discussion

Our patient experienced acute brain swelling after urosepsis and recurrent massive hemorrhagic infarction with increased SAH subacutely, then finally died secondary to cerebral herniation. It is noteworthy that the patient experienced rapid brain swelling that led to cerebral herniation within 6 hours after symptom onset, and sudden

consciousness disorder, on POD 5. Although recurrent left ICA occlusion or venous congestion in the left hemisphere was a possible differential diagnosis, the patient's operative findings and therapeutic course after reperfusion therapy might rule out these diseases. In our patient, left internal carotid arteriography after successful reperfusion revealed bilateral anterior cerebral artery and left MCA aneurysm. This area, fed by the left ICA, was consistent with the area of rapid brain swelling, suggesting that reperfusion in the left ICA feeding territory affects rapid brain swelling. This rare condition has similarities to second-impact syndrome (SIS) after head trauma regarding the development of RMBS after the second event;⁷ therefore, the mechanism of RMBS in our patient and SIS might have common characteristics. SIS was first reported by Richard Schneider in 1973,⁸ and is characterized by rapid and profound brain swelling following second-collision impact during a short period. Although the existence of SIS and its mechanism remain controversial and unclear, a proposed hypothesis is that of brain vulnerability and dysfunctional cerebral autoregulation induced by nonsevere first head injury or repeated nonsevere head injury leading to rapid brain swelling combined with catecholamine surge following secondary nonsevere head injury over a short period.⁷ In mild head injury, brain vulnerability is caused by neurometabolic changes in glutamate and ions following changes in glucose metabolism,^{9,10} mitochondrial dysfunction,^{11,12} and oxidative stress.¹³ These injuries are also found following brain ischemia,^{14,15} which damages the blood-brain barrier (BBB) and leads to dysfunctional cerebral autoregulation.¹⁶⁻¹⁸ In our patient, complete reperfusion was achieved 5.5 hours from symptom onset, and a potentially large lesion in the left hemisphere escaped cerebral infarction with only small hemorrhagic infarctions. We consider this injury "first impact". Although postoperative MRI revealed small infarctions, a large left

hemisphere lesion would be damaged by ischemia and reperfusion because BBB damage begins as soon as 2 hours after the onset of ischemia.¹⁹ Also, administering tissue-type plasminogen activator and mechanical thrombectomy damages the BBB in vessels feeding the left hemisphere²⁰ and might induce cerebral autoregulation dysfunction on the left side. Before full recovery from ischemic damage, sepsis caused by Gram-negative bacteria and SAH associated with recurrent massive hemorrhagic infarction occurred in our patient. We consider this “second impact”. A concern with sepsis is that it may cause hyperperfusion.²¹ Lipopolysaccharide, which is an endotoxin produced by Gram-negative bacteria, could also induce BBB breakdown,²² and the effects of sepsis on the brain are amplified in patients with concomitant brain injury.²³ Prothrombin times are often normal in patients on therapeutic doses of rivaroxaban, and this test may be more informative at higher drug plasma levels.²⁴ In our patient, prothrombin time was not prolonged; however, we were not able to measure anti-Xa activity. Therefore, to what degree rivaroxaban use affected the recurrent massive hemorrhagic infarction is unknown. Diffuse SAH associated with hemorrhagic infarction might induce adrenal surge.^{25,26} Although we saw no chronic ischemia or chronic hypoperfusion in our patient, perfusion breakthrough phenomenon or hyperperfusion might affect RMBS, and could also explain our patient’s clinical course. Perfusion breakthrough or hyperperfusion are related to cerebral autoregulation dysfunction.^{27,28} This impairment also occurs after acute reperfusion with IV tPA and mechanical thrombectomy. Some AIS patients undergoing successful recanalization by mechanical thrombectomy experienced intracranial hemorrhage secondary to hyperperfusion, but no reports discuss severe rapid brain swelling.²⁹ In addition to these conditions, adrenal surge caused by SAH and hyperperfusion by sepsis also might affect

RMBS.^{21,25,26} Multiple factors could have contributed to RMBS in our patient.

Conclusions

Acute ischemic stroke could be a cause of second-impact syndrome-like phenomenon. When treating acute ischemic stroke, preventing complications and treating comorbidities are important considerations.

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Informed consent

Written informed consent was obtained from the patient's family to publish this manuscript.

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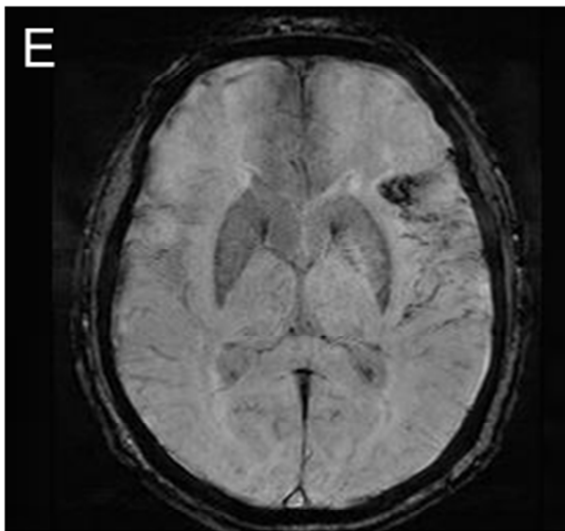
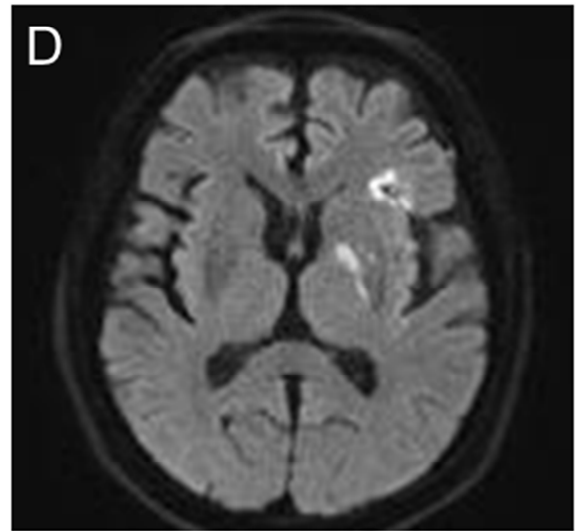
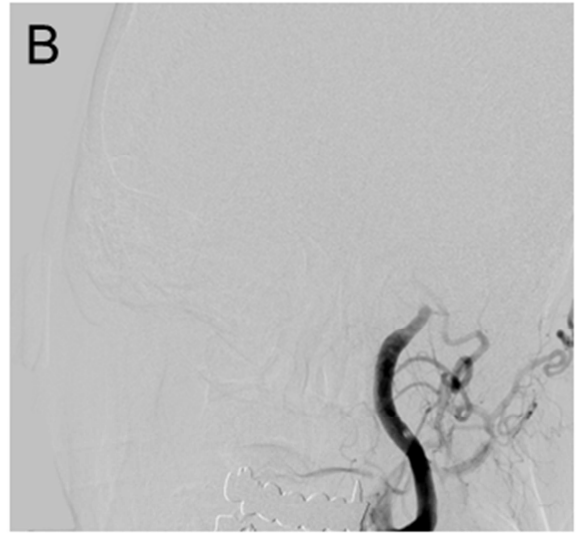
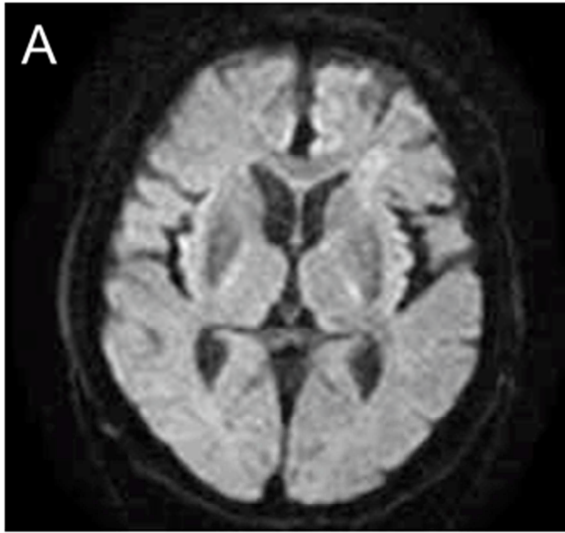
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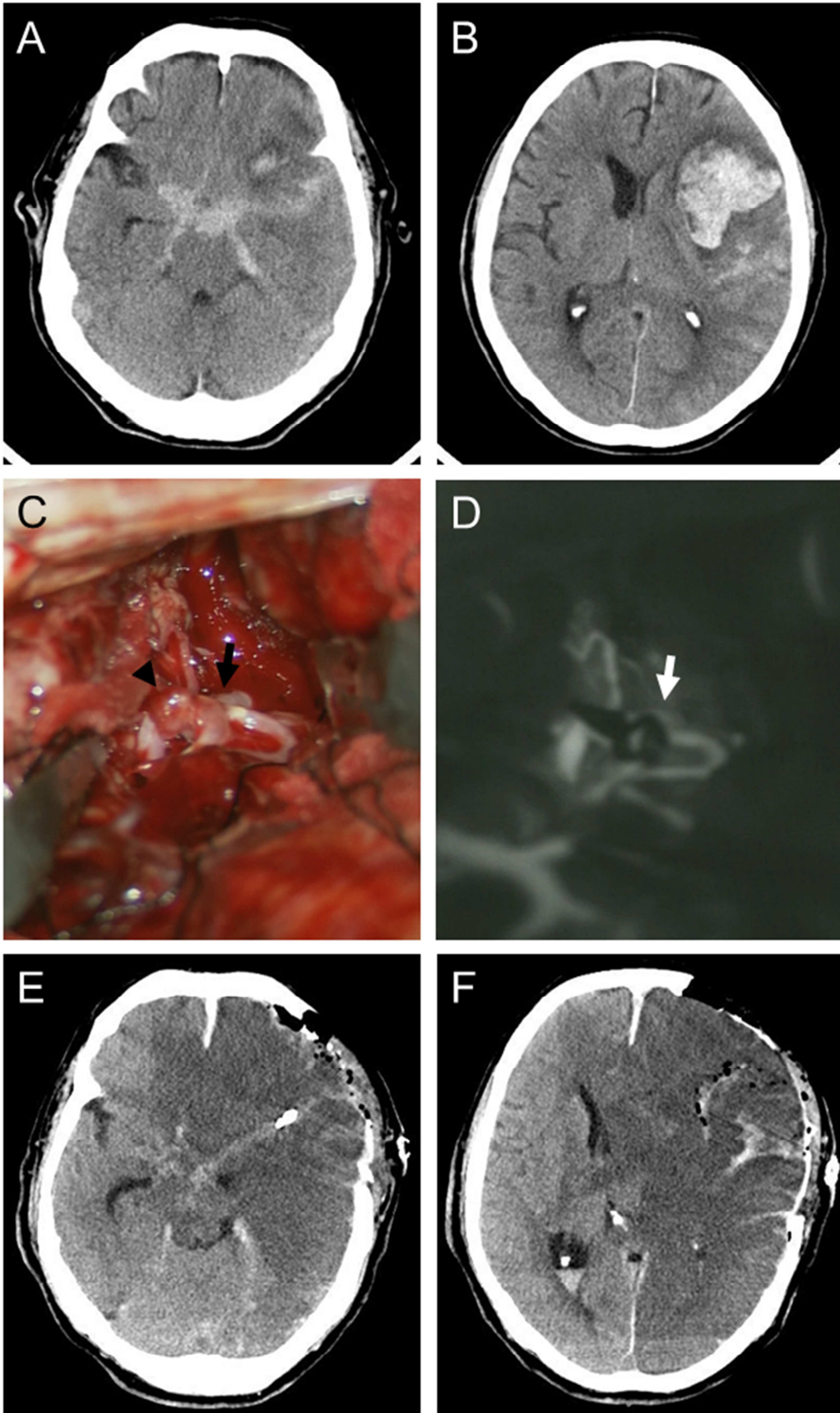
Figure legends

Figure 1: **A:** Initial diffusion-weighted magnetic resonance image showing hyperintensity in the left frontal lobe and posterior limb of the internal capsule. **B:** Initial left common carotid arteriography showed left internal arterial occlusion. **C:** Final internal carotid arteriography showing complete reperfusion and an aneurysm at the bifurcation of the left middle cerebral artery (arrow). **D:** Diffusion-weighted magnetic resonance image on postoperative day (POD) 2 showing hyperintensity in the

left frontal lobe and internal capsule. **E**: Susceptibility-weighted magnetic resonance imaging on POD 2 showing hypointensity in the left frontal lobe and left Sylvian fissure. **F**: Computed tomographic angiography on POD 3 showing no stenosis or reocclusion of major vessels.

Figure 2: A, B: Computed tomography on postoperative day 5 showing increased subarachnoid hemorrhage (A) and massive hemorrhage in the left frontal lobe (B). **C**: Intraoperative view showing an unruptured aneurysm in the left middle cerebral artery (aneurysm (arrowhead); M1 (arrow)). **D**: Indocyanine green video angiography after clipping showing the patent left middle cerebral artery (M1 (arrow)). **E, F**: Computed tomographic imaging performed just after emergent operation showing midline shift and severe brain edema in the left hemisphere.





Highlights

Complications after reperfusion therapy could be critical.

Brain ischemia is a cause of subacute rapid brain swelling.

Rapid subacute brain swelling after reperfusion resembles second-impact syndrome.

Perfusion pressure breakthrough might affect rapid subacute brain swelling.

Disclosure-Conflict of Interest

Conflicts of interest: None.

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