Bleeding from an Unruptured Cerebral Aneurysm following the Local Intra-arterial Administration of Urokinase: A Case Report

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Abstract

A 57-year-old woman with a wide-necked anterior communicating artery (Acom) aneurysm underwent stent-assisted coiling (SAC) due to aneurysm enlargement. Dual antiplatelet therapy was initiated 7 days before the operation, and systemic heparinization was performed while maintaining an activated clotting time (ACT) of approximately 300 s during the procedure. SAC was performed using a laser-cut closed-cell stent and bare platinum coils. At the end of the procedure, the Acom and right anterior cerebral artery (ACA) were occluded by in-stent thrombosis. Following local intra-arterial administration of 480000 U of urokinase, the Acom and right ACA were recanalized, accompanied by extravasation around the Acom aneurysm. A computed tomography (CT) scan revealed a right frontal hematoma, which did not enlarge after the administration of protamine sulfate. The hematoma disappeared spontaneously, and the patient recovered without any neurological deficits. Local administration of urokinase is an effective treatment for in-stent thrombosis. However, because the devices for SAC may cause mechanical injuries to the aneurysms, urokinase should be used cautiously for cerebral aneurysms, even if unruptured.

Keywords: unruptured cerebral aneurysm, urokinase, stent-assisted coiling, in-stent thrombosis, thrombolysis

Introduction

Stent-assisted coiling (SAC) is a safe and effective endovascular treatment for wide-necked and/or large cerebral aneurysms and has had good long-term outcomes.[1–3] However, thromboembolic complications are serious sequelae of SAC for cerebral aneurysms.[4–8] For the elective endovascular treatment of an unruptured aneurysm, preoperative oral administration of dual antiplatelet therapy for at least 5–7 days and systemic heparinization during the procedure are considered mandatory.[5,8] Regardless of these preoperative prevention strategies against thromboembolic complications, when the parent artery is occluded due to thrombosis, intra-arterial or intravenous thrombolysis with urokinase or tissue plasminogen activators, or intravenous bolus and continuous infusion of glycoprotein IIb/IIIa antagonists,[9,10] are recommended, although there is a risk of hemorrhagic complications.

Herein, we report a patient with an unruptured wide-necked anterior communicating artery (Acom) aneurysm who underwent SAC and complicated in-stent occlusion, received local administration of urokinase, and then experienced extravasation from the Acom aneurysm. We discuss the mechanism of thrombus formation and extravasation as well as the management of aneurysmal bleeding after thrombolysis.

Case Report

A 57-year-old woman with multiple aneurysms of the left distal anterior cerebral artery (ACA), Acom, and left internal carotid-posterior communicating artery (Pcom), experienced subarachnoid hemorrhage (SAH) due to rupture of the left distal ACA aneurysm before 3 years. Because the small right frontal hematoma involved the aneurysmal dome, the origin
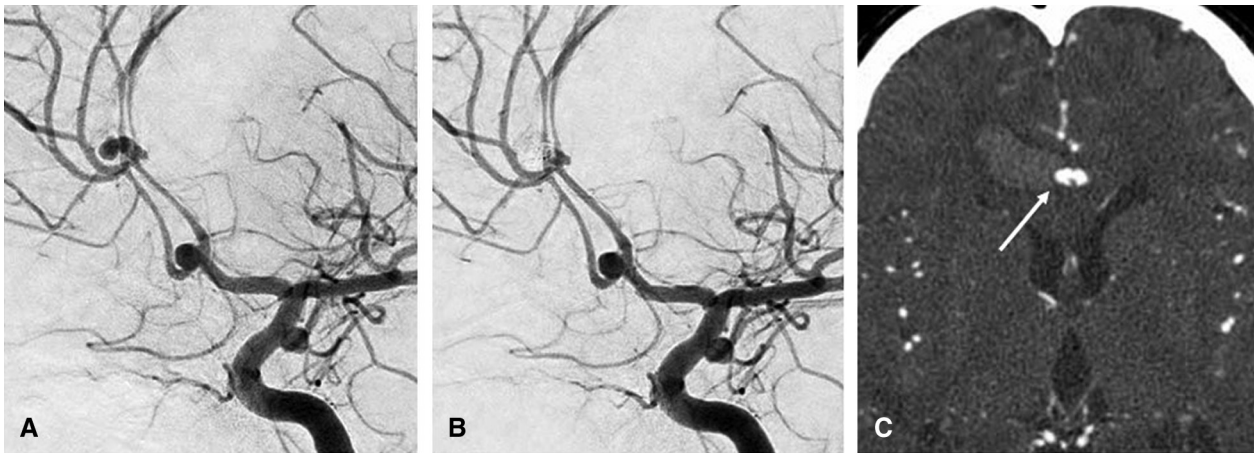
Fig. 1 (A) Left internal carotid angiogram after 7 days of SAH, 3 years prior, showing the left distal ACA, Acom, and left internal carotid-Pcom aneurysms. (B) Post-embolization of the left distal ACA aneurysm. (C) CTA showing the small intracerebral hematoma including the dome of the distal ACA aneurysm. ACA: anterior cerebral artery, Acom: anterior communicating artery, CTA: computed tomography angiography, Pcom: posterior communicating artery, SAH: subarachnoid hemorrhage.
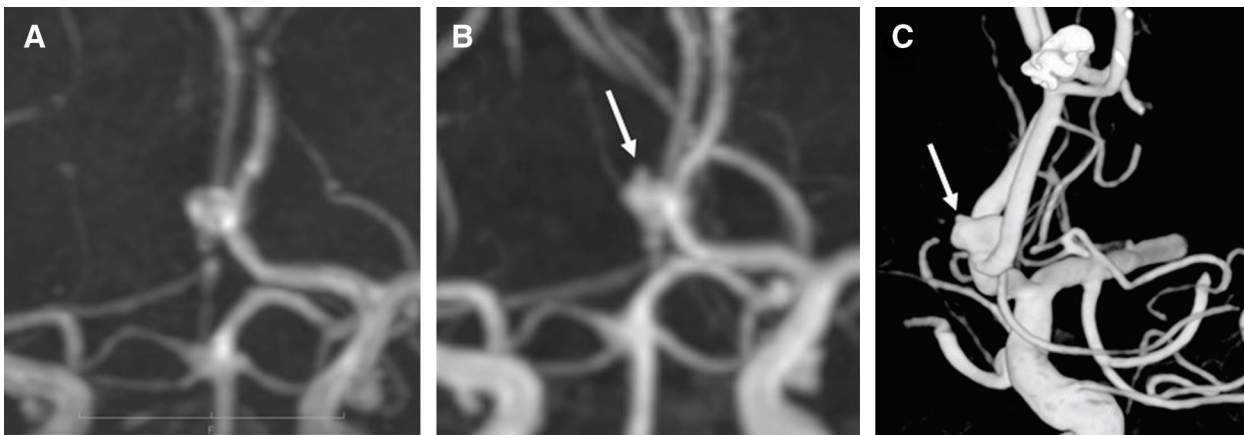

Fig. 2 (A) MRA, 3 years prior. (B) MRA, 6 months prior. (C) Three-dimensional digital subtraction angiogram, 6 months prior. The arrows demonstrate an aneurysmal bleb growing on the wall of the Acom aneurysm. MRA: magnetic resonance angiography.

of bleeding was confirmed to be the distal ACA aneurysm (Fig. 1). Following coil embolization of the distal ACA aneurysm, the remaining two unruptured aneurysms were followed up using magnetic resonance angiography (MRA). SAC was scheduled due to enlargement of the wide-necked Acom aneurysm (Fig. 2), which was noticed around 6 months ago. In the previous 3 years, she had no history other than the SAH, and her routine preoperative evaluation results were within the normal ranges.

Dual antiplatelet treatment (oral clopidogrel [75 mg] and aspirin [100 mg] per day) was started 7 days before the operation. On the day of the operation, the VerifyNow assay (ITC, Edison, NJ, USA) was performed, the results of which revealed an aspirin reaction unit

of 461, P2Y12 reaction unit of 65, and 23% inhibition. Following femoral sheath insertion under general anesthesia, systemic heparinization was initiated until an activated clotting time (ACT) of around 300 s was achieved. Using the jailing technique, a closed-cell laser-cut stent, Enterprise2 vascular reconstruction device (VRD) (4.0 mm/23 mm; Cerenovus, Irvine, CA, USA), was deployed from the right A2 segment (diameter, 1.8 mm) to the left A1 segment (diameter, 2.3 mm). The right A1 segment was aplastic, and the bilateral distal ACAs were perfused from the left A1 segment. Five Target detachable coils (Stryker, Fremont, CA, USA) were inserted into the aneurysm and the volume embolization ratio[11] was calculated as 27.1%. Following the insertion of the fifth coil, an angiogram
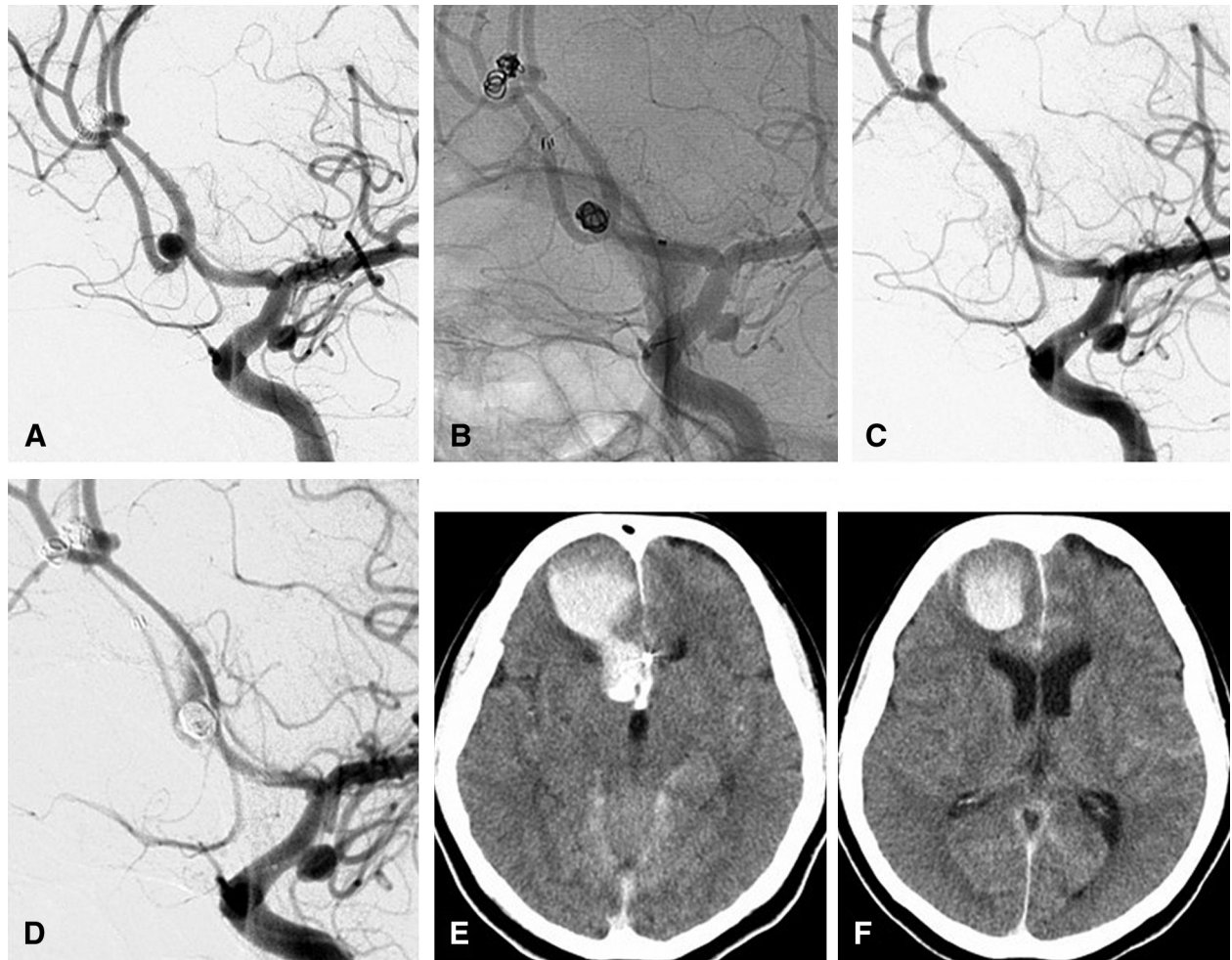
Fig. 3 (A) Pre-embolization of the Acom aneurysm. **(B)** Deployment of Enterprise2 VRD and a first coil. **(C)** In-stent thrombosis and occlusion of the Acom and right ACA following the insertion of the fifth coil. **(D)** Recanalization of the Acom and right ACA, and extravasation from the Acom aneurysm, following the administration of 480000 U urokinase. **(E, F)** CT scan following the intravenous administration of protamine sulfate, showing right frontal hematoma draining into the right lateral ventricle. ACA: anterior cerebral artery, VRD: vascular reconstruction device.

revealed in-stent thrombosis and occlusion of the Acom and right ACA (Fig. 3).

After the fifth coil was removed, an angiogram revealed incomplete recanalization of the Acom and right ACA, and no extravasation was seen. An angiogram 10 minutes later showed complete re-occlusion of these arteries. Therefore, focal administration of urokinase was started at a rate of 10000 U/min using a microcatheter placed around the aneurysmal neck. The systemic blood pressure increased from 113/62 mmHg to 155/90 mmHg following the occlusion of the Acom and right ACA, and it gradually decreased to 135/80 mmHg during the continuous infusion of urokinase. Although the angiogram revealed no recanalization after the infusion of 180000 U urokinase, recanalization of the Acom and right ACA, accompanied by extravasation

around the Acom aneurysm (Fig. 3), was observed on completing the administration of 480000 U urokinase. Subsequently, protamine sulfate (50 mg) was slowly administered intravenously to reverse the systemic heparinization. A brain computed tomography (CT) scan revealed a right frontal intra-cerebral hematoma that drained into the lateral ventricles (Figs. 3E and 3F).

Postoperatively, tracheal intubation and sedation were continued to control systemic blood pressure until the following day. Her lethargy and left arm weakness gradually improved. On the following day, a brain CT scan revealed no increase in hematoma size, and an angiogram showed complete obliteration of the Acom aneurysm and recanalization of the Acom and right ACA without extravasation. Dual antiplatelet therapy was continued from the next
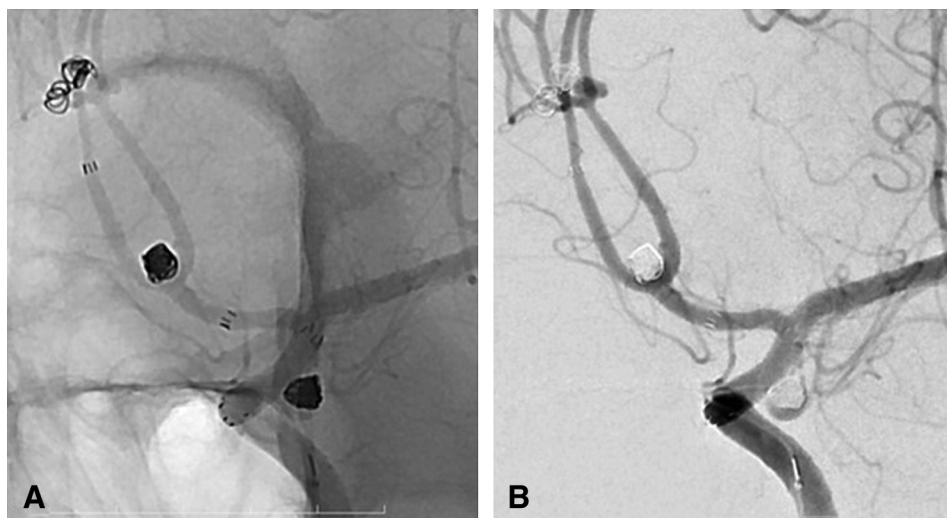
Fig. 4 (A, B) Left internal carotid angiogram after 1 year, showing the complete obliteration of the Acom aneurysm and no in-stent stenosis along the left A1 and right A2 segments. The left internal carotid–Pcom aneurysm was also treated using SAC. SAC: stent-assisted coiling.

day of operation. She recovered without any neurological deficits and returned to her work as a nurse after 3 months. An angiogram after 1 year of endovascular treatment (Fig. 4) confirmed the complete occlusion of the Acom aneurysm and good recanalization of the Acom and right ACA without any in-stent stenosis. The left internal carotid–Pcom aneurysm was also treated using SAC uneventfully.

Discussion

This report presents a rare, and to the best of our knowledge, the first case of the rupture of an unruptured cerebral aneurysm following local intra-arterial administration of urokinase. Owing to the thrombolytic action of urokinase,[12] the cause of bleeding in this case could be attributed to a spontaneous aneurysm rupture, or the advanced mechanical injuries within the parent arteries and aneurysms following the deployment of devices for endovascular treatment.

Cronqvist et al.[9] reported continuous intra-arterial injections of urokinase in 19 patients who developed thromboemboli during endovascular treatment of intracerebral aneurysms. Although one patient among the 19 cases died due to an acutely ruptured aneurysm with a large intracerebral hematoma that developed after fibrinolysis, no bleeding of the unruptured aneurysms was reported due to this treatment. Feng et al.[13] also reported on intra-arterial infusion of tirofiban and urokinase for ruptured aneurysms, coil embolization, and thromboembolic complications, and one patient died because of aneurysmal rupture. However, no studies have

reported the rupture of unruptured cerebral aneurysms because of intra-arterial infusion of urokinase.

Urokinase activates plasminogen directly following first-order kinetics to produce plasmin. Free circulating plasmin degrades both fibrinogen and fibrin, and inactivates prothrombin, factor V, and factor VIII, thereby inhibiting the coagulant phase of thrombus formation.[12] Owing to this mode of action, the initiation of bleeding following the intra-arterial administration of urokinase requires an advanced injury to the wall of the aneurysm or the parent artery, such as a perforation without any extravasation. The manipulation of the microguidewire and microcatheter, and/or the placement of the stent, may inflict silent injuries on the aneurysmal wall without any extravasation. However, the video recording of the entire endovascular procedure for this patient revealed no actions that could have resulted in mechanical injuries, such as perforation. The patient's blood pressure was maintained within the normal range during the endovascular treatment under general anesthesia, although the systolic blood pressure was somewhat elevated for a short time during the occlusion of the Acom and right A2 segment.

In-stent thrombosis during the SAC has been reported to occur in 5%–7% of cases,[4–7,10] and the preoperative use of dual antiplatelet therapy, sensitivity assays, and systemic heparinization are effective in preventing in-stent thrombosis.[5,8,14] In this case, the preoperative dual antiplatelet therapy was started 7 days before the SAC, and the VerifyNow assay revealed that the dual antiplatelet therapy was effective on the day of SAC. The ACT after systemic heparinization had also reached around 300 s during

the entire SAC procedure. Therefore, the in-stent thrombosis could be due to other reasons, such as the placement of too many coils and protrusion of the coil loops, malapposition of the stent strut to the intima of the parent artery due to the jailing technique and the tortuous parent artery, and the relatively small diameter of the parent arteries.[7,8]

The diameter of the parent artery of the Acom aneurysm in this case was approximately 2.0 mm or less. Although Nii et al.[7] reported that the mean stent diameter was significantly smaller in patients with in-stent thrombosis than in those without, Chung et al.[15] reported the successful placement of closed-cell stents in arteries less than 2 mm in diameter and obtained good results, except when the angle of the parent artery was not acute. Kühn et al.[16] also reported good long-term patency of small parent vessels following SAC treatment. In our case, we assume that the combined effects of the small diameter and the slight tortuosity of the parent artery, and the malapposition of the stent due to the jailing technique, may have contributed to in-stent thrombosis.

We administered protamine sulfate to reverse the systemic heparinization on recognizing extravasation around the Acom aneurysm. Alternative treatment strategies include proximal flow control using a balloon catheter, or internal trapping of the Acom using platinum coils to stop the bleeding. However, balloon flow control or internal trapping may again produce thrombosis of the parent artery and may result in severe neurological deficits. Therefore, we decided against flow control and prepared for open surgery to remove the intracerebral hematoma if it enlarged to reach a life-threatening size. Fortunately, because the right frontal hematoma did not enlarge and disappeared spontaneously, open surgery was unnecessary.

We selected urokinase as a thrombolytic agent because of the first author's experience of middle cerebral artery embolism local fibrinolytic intervention trial (MELT) conducted in Japan.[17] When we recognized the in-stent thrombosis, the ACT was over 300 s, and the preoperative VerifyNow assay showed effective results of the dual antiplatelet therapy. Therefore, we did not add heparin injection or antiplatelet drugs. Our protocol included an angiogram taken after every 240000 U of urokinase infused. However, we omitted the angiogram at the point of 240000 U because of the result at 180000 U. Therefore, we did not confirm an angiogram result for the 30 minutes between 180000 U and 480000 U infused. This interval may be too long.

Even if the cerebral aneurysms treated using SAC are unruptured, devices such as coils, stents,

microguidewires, and microcatheters may create mechanical injuries within the parent arteries and aneurysms. Therefore, we must recognize that bleeding could occur from those mechanical injuries and be exacerbated by urokinase. We must use urokinase with careful attention to vital signs and repeat angiograms at short intervals, for instance, at every 120,000 U of urokinase infused.

Conflicts of Interest Disclosure

None of the authors has conflicts of interest to declare.

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