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Case Report

Gamma knife surgery-induced aneurysm rupture associated with tissue plasminogen activator injection: A case report and literature review

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ABSTRACT

Background: Cases involving delayed development of intracranial aneurysms related to gamma knife surgery (GKS) have been recently reported. Here, we present a rare case of GKS-induced aneurysm rupture after intravenous injection of tissue plasminogen activator (t-PA) for occlusion of the middle cerebral artery (MCA). To the best of our knowledge, this is the first case in which t-PA-induced rupture of a GKS-related unruptured aneurysm.

Case Description: A 56-year-old woman underwent GKS for left trigeminal neuralgia. Eighteen years later, she suddenly experienced MCA occlusion with consciousness disturbance and right hemiparesis. She received an intravenous injection of t-PA and then was transferred to our hospital. We confirmed residual thrombus, and she underwent mechanical thrombectomy successfully. A postthrombectomy brain computed tomography scan revealed subarachnoid hemorrhage with a hematoma in the left cerebellar hemisphere. Cerebral angiography revealed a small irregular-shaped aneurysm at the branching site of the left circumflex branch at the distal position of the anterior inferior cerebellar artery, which was not detected on initial imaging. Coil embolization was performed. One month after the ischemic attack, she was transferred to a rehabilitation hospital, with a modified Rankin Scale score of 5.

Conclusions: The tendency to rupture is greater for GKS-induced aneurysms than for intrinsic unruptured aneurysms, according to previous reports. When performing acute treatment for cerebral infarction in patients with a history of GKS, the presence of aneurysms should be evaluated and we should keep in mind that GKS aneurysms are very small and tend to rupture.

Keywords: Aneurysm rupture, Gamma knife surgery, Tissue plasminogen activator

INTRODUCTION

With the increase in the number of patients treated using gamma knife surgery (GKS), recent cases involving delayed development of intracranial aneurysms related to GKS have been reported.[1-3,6-14] Recently, tissue plasminogen activator (t-PA) injection for patients with unruptured aneurysms has been considered safe.[4,5] Here, we present a rare case of GKS-induced aneurysm rupture after intravenous injection of t-PA for occlusion of the middle cerebral artery

(MCA). To the best of our knowledge, this is the first case in which t-PA-induced rupture of a GKS-related unruptured aneurysm.

CASE REPORT

A 56-year-old woman had experienced trigeminal neuralgia (TN) and was treated using GKS. She received 45 Gy at 50% isodose at the proximal cisternal extent of the left trigeminal nerve [Figure 1]. After GKS, she showed no symptoms for 18 years.

She experienced a sudden onset of consciousness disturbance and right hemiparesis (National Institutes of Health Stroke Scale score = 20 points). Brain magnetic resonance imaging was performed at the primary hospital. Diffusion-weighted images revealed a hyperintensity in the left insular cortex and a slight hyperintensity in the left MCA territory [Figure 2a]. Magnetic resonance angiography (MRA) revealed occlusion of the horizontal segment of the left MCA [Figure 2b]. She received an intravenous injection of t-PA (Alteplase: 0.6 mg/kg) and was transferred to our hospital. At the time of arrival, no intracranial hemorrhage was noted on brain computed tomography (CT). We subsequently performed digital subtraction angiography (DSA) for only the left internal carotid artery and confirmed the presence of MCA occlusion, even after t-PA injection [Figure 2c]. Mechanical thrombectomy was then performed using the Solitaire FR/2 revascularization device (Medtronic, Minneapolis, MN, USA; onset to reperfusion time: 3 h 13 min), and complete recanalization was achieved [Figure 2d]. Brain CT performed immediately after mechanical thrombectomy revealed subarachnoid hemorrhage (SAH) with a hematoma in the left cerebellar hemisphere [Figure 3a and b]. As CT angiography (CTA) could not confirm the presence of an aneurysm [Figure 3c and d], DSA of the posterior cerebral circulation was performed, and it revealed a small irregular-shaped aneurysm at the branching site of the left circumflex branch of the anterior inferior cerebellar artery [Figure 4a]. Since the aneurysm was located at the radiation field of the previous GKS, it was considered as a GKS-induced aneurysm, and it represented the bleeding source. Thus, we treated it using coil embolization [Figure 4b and c] and performed surgical hematoma removal and decompressive craniectomy. One month after the ischemic attack, she was transferred to a rehabilitation hospital, with a modified Rankin Scale score of 5.

The patient's family provided consent for the publication of this case report.

DISCUSSION

GKS, which irradiate high-dose radiation to the target lesion, is one of the treatment options for intracranial arteriovenous malformations (AVMs), brain tumors, and TN. Radiation

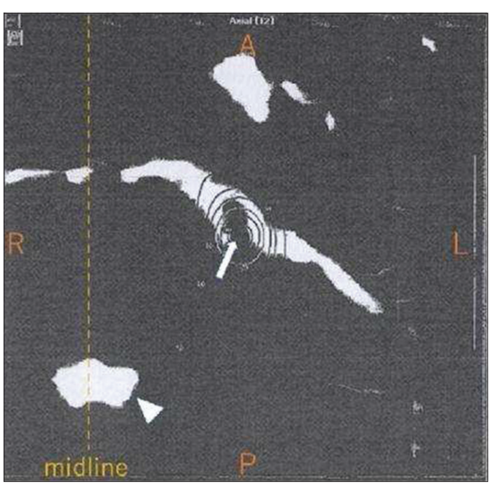

Figure 1: Dose distribution of planning axial heavy T2-weighted magnetic resonance imaging for treatment planning to the left trigeminal nerve (arrow) from a copy of printed images from old medical records. Fourth ventricle (arrow head).

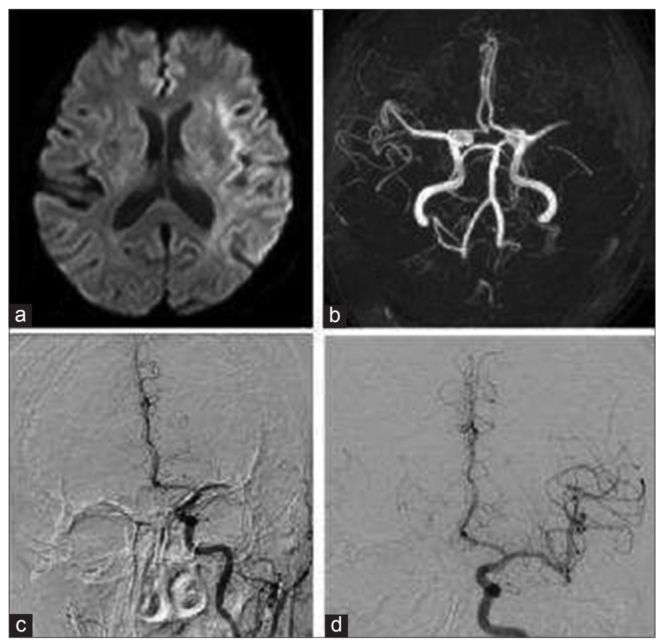

Figure 2: Magnetic resonance imaging (a and b) at the first emergency department, and digital subtraction angiography before (c) and after (d) mechanical embolectomy. Diffusion-weighted image (a) shows a hyperintensity in the left insular cortex and a slight hyperintensity in the left middle cerebral artery territory. Magnetic resonance angiography (b) shows occlusion in the horizontal segment of the left middle cerebral artery. Digital subtraction angiography shows occlusion of the horizontal segment of the left middle cerebral artery (c). Complete recanalization is performed using the Solitaire FR/2 revascularization device (d). Onset to needle time: 1 h 30 min, onset to reperfusion time: 3 h 13 min, puncture to reperfusion time: 0 h 18 min.

is known to be a factor in the delayed development of aneurysms. GKS-induced aneurysm formation is considered rare, but recently, the reported cases are increasing; Uchikawa *et al.* reported that delayed development of intracranial aneurysms following GKS was noted in 0.90% of patients.[13] As the number of patients receiving GKS treatment increases, the number of aneurysms might increase. Fourteen cases of GKS-related aneurysms have been described previously, including our case [Table 1]. In 2006, Takao *et al.*[12] presented the first case of aneurysmal SAH in a patient who underwent GKS, and 10 of the 14 (about 72%) reported cases showed SAH, which is a relatively high rate. GKS-induced delayed development of intracranial aneurysms is rare, but these aneurysms tend to rupture [Table 1]. Thus, a long follow-up is required in these patients.

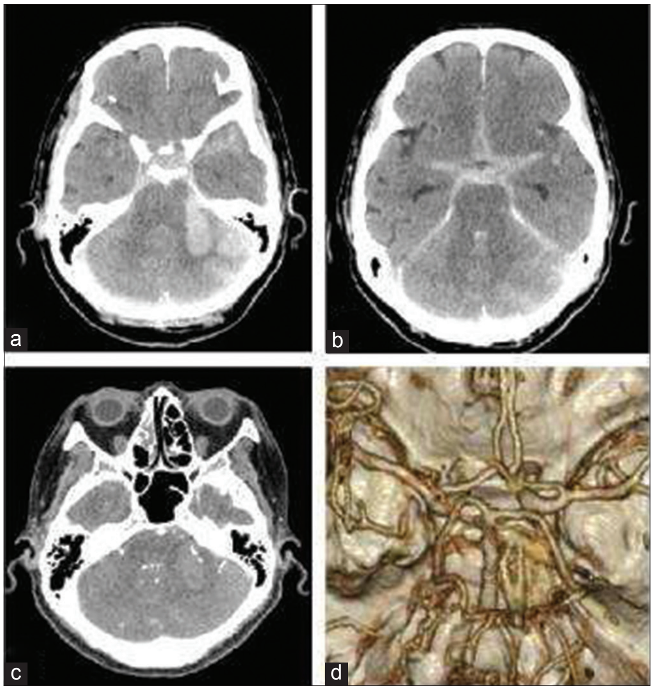

Figure 3: Computed tomography just after thrombectomy shows subarachnoid hemorrhage and a hematoma in the left cerebellar hemisphere (a and b). Computed tomography angiography could not confirm the presence of aneurysms (c and d).

There are few pathological studies on GKS-induced vasculopathy. Akamatsu *et al.* described that the wall of the arterial aneurysm exhibited a pseudoaneurysm-like structure formed with thin collagen fibers lacking elastic fibers and a tunica media, without atherosclerotic changes.[2] Akai *et al.* described that adventitial fibrosis is caused by radiation.[1] The critical radiation dose for aneurysm formation has been inconsistent across studies, varying from a low dose to a high dose [Table 1]. However, radiation-related aneurysms are more prone to damage than intrinsic cerebral aneurysms due to adventitial fibrosis. Recently, it has been reported that the presence of an intracranial aneurysm might not contraindicate intravenous injection of t-PA.[4,5] Indeed, some reports investigated the safety of intravenous injection of t-PA in patients with unruptured aneurysms and noted that unruptured aneurysms were not associated with an increased risk of intracranial hemorrhage after t-PA injection.[4,5]

However, in the present case, a GKS-induced aneurysm ruptured after intravenous injection of t-PA. We consider that the rupture tendency is greater for GKS-induced aneurysms than for intrinsic unruptured aneurysms, as plasmin activated by t-PA acts on fibrin that is a component of the vessel wall of GKS-induced aneurysms. In AVMs and TN, major artery branches might be directly affected by irradiation. In TN, which is characterized by arteries directly touching the trigeminal nerve, avoidance of a high dose of radiation exposure to surrounding arteries could be technically difficult.[13] In contrast to TN, if the AVM feeding

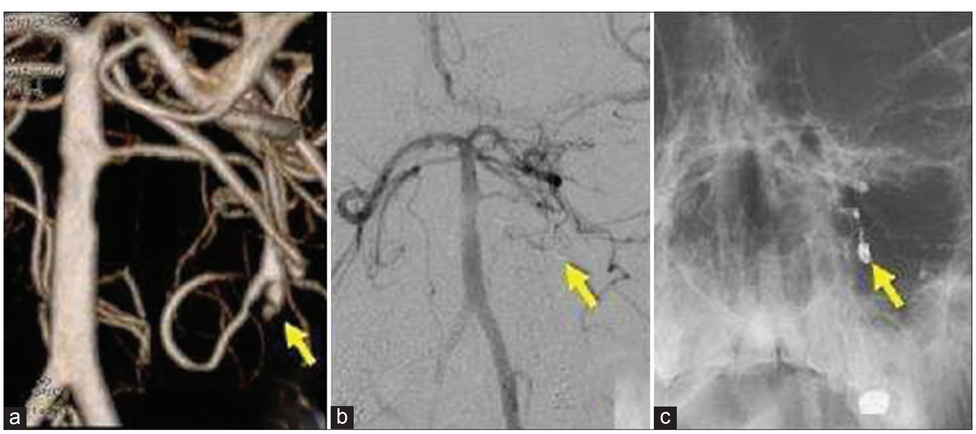

Figure 4: Cerebral angiography of the posterior cerebral circulation performed after computed tomography shows aneurysm-like dilatation in the peripheral portion of the left circumflex branch at the distal position of the anterior inferior cerebellar artery. Coil embolization is performed for aneurysmal dilatation. (a) Cerebral angiography shows aneurysm-like dilatation (arrow). (b and c) Postembolization angiography shows complete obliteration of the aneurysm (arrow).

Table 1: Reported cases of intracranial aneurysms induced by gamma knife surgery.

Study	Age/Sex (at RT)	Site	Size (mm)	Rupture	Interval (years)	Diagnosis	RT dose (Gy)	Treatment	GOS
Huang *et al*. 2001	19/F	ACA		–	0.8	AVM	25 at 50% isodose	Coil embolisation	GR
Takao *et al*. 2006	63/F	AICA		+	6	VS	12 at 50% isodose	PAO	GR
Akamatsu *et al*. 2009	75/F	AICA		+	8	VS	12 at 50% isodose	Trapping	-
Park *et al*. 2009	69/F	AICA	3.3	+	5	VS	12 at 50% isodose	Conservative	GR
Yamaguchi *et al*. 2009	67/F	AICA	3	+	6	VS	25 at 50% isodose	Trapping	GR
Sunderland *et al*. 2014	50/F	AICA		+	10	VS	25 at 50% isodose	PAO	SD
Kellner *et al*. 2015	58/F	AICA	6	–	10	Meningioma	16 at 80% isodose	PAO	GR
Akai *et al*. 2015	50/M	MCA	15	–	15	AVM	40 (marginal dose)	Resection	GR
Mascitelli *et al*. 2016	59/M	AICA		+	6	VS	-	PAO	GR
Murakami *et al*. 2016	61/M	AICA	3	+	12	VS	18 at 50% isodose	PAO	GR
Uchikawa *et al*. 2016	64/M	AICA	8	+	8	TN	23 at 30% isodose	-	Dead
Uchikawa *et al*. 2016	63/F	SCA	4	+	9	TN	64 at 85% isodose	PAO	GR
Chen *et al*. 2017	79/M	SCA	8	–	11	TN	90	Coil embolisation	GR
This case	56/F	BA branch	2	+	18	TN	45 at 50% isodose	Coil embolisation	VS

RT: Radiotherapy, F: Female, M: Male, AICA: Anterior inferior cerebellar artery, SCA: Superior cerebellar artery, BA: Basilar artery, PAO: Parent artery occlusion, AVM: Arteriovenous malformations, VS: Vestibular schwannoma, TN: Trigeminal neuralgia, GOS: Glasgow outcome scale, GR: Good recovery, SD: Severe disability, VS: Vegetative state

artery develops aneurysmal changes, the risk of rupture/aneurysmal growth is considered low because the distal side of these arteries will be occluded as nidus disappearance.

In this case, we could not find the aneurysm by MRA and CTA, because it was very small and irregularly shaped. In fact, most ruptured aneurysms have a size of under 5 mm [Table 1]. Furthermore, we did not perform DSA of posterior circulation at mechanical thrombectomy, because we did not find any aneurysm on MRA. We should keep in mind that GKS aneurysms are very small and tend to rupture. History of GKS might be a risk factor of a ruptured aneurysm that should take the cerebrovascular investigation by DSA into account when considering intravenous injection of t-PA.

CONCLUSION

GKS-induced aneurysms are vulnerable, small size and have a greater tendency to rupture than intrinsic unruptured aneurysms. When performing acute treatment for cerebral infarction in patients with a history of GKS, the presence of aneurysms should be evaluated and we should keep in mind that GKS aneurysms are very small and tend to rupture.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient family has given her consent for her images and other clinical information to be reported in the journal. The patient family understands that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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