Case Report

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

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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
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.

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 3](image1.png)  
**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).

![Figure 4](image2.png)  
**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).
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 unraptured 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.

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 branch     | BA           | 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
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Nil.

Conflicts of interest
There are no conflicts of interest.

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