Refractory De Novo Multiple Cerebral Aneurysms After Radiotherapy and Multistaged “Open” Surgical Treatment for Low-Grade Glioma During Long-Term Follow-Up: A Case Report and Review of the Literature

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INTRODUCTION

High-dose ionizing radiation therapy is effective and plays an important role in the standard treatment regimen for brain tumors and vascular malformations. As a result of the evolving technology of modified radiotherapy, long-term survival has increasingly been achieved in patients with brain tumors and vascular malformations. However, such advances have revealed an increased risk of cerebrovascular diseases such as vascular occlusions and aneurysm formation among survivors. Radiation can induce pathological vascular changes, such as internal hyperplasia and thrombosis with subsequent vessel stenosis and occlusion. Compared with radiation-induced occlusive changes, radiation-induced intracerebral aneurysms are less common.1–7 Previous reports have described radiation-induced aneurysms, detailing predisposing diseases treated by radiation, the locations of aneurysms, pathological findings, and clinical outcomes. Some patients have been treated successfully without additional neurological deficits.4,5,9–16 However, some aneurysms have proved difficult to treat, resulting in dismal clinical outcomes.2,3,6,7,23

To the best of our knowledge, multistaged surgery for refractory multiple aneurysms after radiotherapy has only been described in 3 cases.4,11,13 Thus, we have reported the case of repeated appearance and treatment of de novo cerebral aneurysms after radiotherapy for a low-grade glioma with its long-term clinical course and discussed the clinical features, pathogenesis, and implications for optimal therapeutic strategy.

CASE DESCRIPTION

A 31-year-old woman presented with intraventricular hemorrhage due to rupture of a right internal carotid artery (ICA) aneurysm that developed 17 years after surgical resection of a low-grade glioma in the right frontal lobe and postoperative radiotherapy (focal, 50 Gy/25 fractions). During glioma follow-up, salvage surgery with adjuvant gamma knife therapy and chemotherapy (ranimustine, vincristine, temozolomide) were performed for recurrence of the glioma. The aneurysm was treated with endovascular coil embolization. However, she experienced repeated intraventricular hemorrhages, and angiography revealed a de novo ICA aneurysm. The de novo aneurysms were treated with endovascular surgery using coil embolization and stenting. Despite multistaged endovascular surgery for the ICA aneurysm, she experienced repeated subarachnoid and intraventricular hemorrhages. Angiography revealed a de novo aneurysm of the right posterior cerebral artery and basilar trunk. She underwent coil embolization and stenting. Despite active management with endovascular surgery and close follow-up, she died after an eighth consecutive intraventricular and intracerebral hemorrhage caused by a de novo large aneurysm of the posterior cerebral artery.

CONCLUSIONS: To the best of our knowledge, the present study is the first to report on refractory and recurring de novo aneurysms treated by multistaged endovascular surgery during a long-term follow-up after radiotherapy and multistaged craniotomy for glioma.
low-grade glioma in the right inferior frontal gyrus that had extending to the frontobasal surface and postoperative radiotherapy (focal, 50 Gy/25 fractions) focused to the right frontobasal area at the age of 14 years (Figure 1). During tumor resection, the right carotid artery near the orifice of the posterior communicating artery was injured and repaired using an encircling clip. At 4 years after radiotherapy, the tumor had recurred at the same site, and she underwent gamma knife surgery, with 50 Gy delivered to the core of the lesion located in right inferior frontal gyrus.

At 7 years after the initial surgery, she had undergone a second operation for glioma recurrence with malignant transformation. The histological diagnosis was anaplastic astrocytoma. At 1 month after this last surgery, she experienced a sudden onset of headache. Computed tomography (CT) revealed the presence of intraventricular hemorrhage (Figure 2A). Right carotid angiography revealed an aneurysm arising from the siphon of the right internal carotid artery (ICA), slightly distal to the repaired site (Figure 2B). The neck of the aneurysm was considered to be quite difficult to access via craniotomy owing to the previous clipping and tumor removal. Therefore, we completely obliterated the aneurysm by endovascular embolization surgery (Figure 2C). Later, a ventriculoperitoneal shunt was placed for the hydrocephalus that had subsequently developed.

From the histological findings after the second surgery, the patient received

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Figure 1. The clinical course of the present case. BA, basilar trunk; IC, internal carotid artery; MCNU, ranimustine; P1, posterior cerebral artery; TMZ, temozolomide; VCR, vincristine; V-P shunt, ventriculoperitoneal shunt.
temozolomide (TMZ; 150 mg/m² in 15 cycles for 16 months) as postoperative adjuvant therapy; however, the TMZ was suspended because of lymphocytopenia. At 2 weeks after the last administration of TMZ, she again experienced a sudden onset of headache, and CT again revealed intraventricular hemorrhage (Figure 2D).

Urgently performed right carotid angiography showed an aneurysm arising from the distal side of the previous aneurysmal neck on the right ICA (Figure 2E). The aneurysm was treated by coil embolization, with complete obliteration confirmed postoperatively.

At 5 years after the second surgery, a third subarachnoid hemorrhage due to recurrent right ICA aneurysm occurred, and the aneurysm was again completely obliterated by endovascular surgery. Two years after this third hemorrhage, the surgical wound became dehiscent, probably owing to an occult wound infection. That required epicranial soft tissue reconstruction, performed by plastic surgeons using a vascularized skin flap.

At 2 years after the plastic surgery, she again experienced headache of sudden onset, and CT revealed a recurrent subarachnoid hemorrhage (fourth hemorrhage). Angiography demonstrated a de novo aneurysm near the previously embolized aneurysm of the right ICA. We again performed coil embolization. One month later, another recanalized aneurysm (right ICA bifurcation aneurysm) was embolized again with coils and a stent.

At 4 years after the fourth hemorrhage, she again experienced headache of sudden onset and a repeated right lateral ventricular hemorrhage (fifth in a sequence) was seen on the CT scan. Initial angiography did not reveal an aneurysm of the carotid artery. Therefore, the patient was treated conservatively and observed. However, the intraventricular hemorrhage recurred in the right lateral ventricle (sixth hemorrhage) 18 days later (Figure 3A). The repeated angiography showed an aneurysm with an irregular, expanded wall on both the trunks of the basilar and posterior cerebral artery (Pt portion; Figure 3B). The aneurysm was also treated by coil embolization (Figure 3C). Three days later, the intraventricular hemorrhage in the right lateral ventricle had recurred (seventh hemorrhage), and the aneurysm in the Pt, which was located in a different portion from the previous site, were completely obliterated by coils and stenting, with obliteration confirmed by angiography.

However, 7 months after the seventh rupture of an aneurysm, she developed a sudden severe headache and went into deep coma. The CT scan revealed a huge
hematoma in the right thalamus extending to the right peduncle of the midbrain with massive edema of the hemisphere causing uncal herniation (eighth hemorrhage; Figure 3D). Angiography demonstrated a large aneurysm in the right P1 that had originated from the wall uncovered by the stent (Figure 3E). Therefore, the PCA was occluded by coil embolization (Figure 3F). Although the parent artery was occluded, the aneurysm in the right P1 had ruptured again, and the patient died. An autopsy was not performed.

**DISCUSSION**

The clinical course of the patient is shown in Figure 1. The patient experienced aneurysm ruptures 8 times and, thus, the present case is the first reported case of such a clinical evolution. The pathogenesis of recurrent de novo aneurysms, such as in the present case, remains unclear. During the initial surgery for astrocytoma, the first hemorrhage might have been caused by a pseudoaneurysm, by what was considered an inadvertent injury of the carotid artery. Although we had confirmed the complete obliteration of the aneurysm on follow-up angiography after each hemorrhage, a recurrent ventricular hemorrhage occurred several years after clipping and coil embolization.

It is remarkable that the interval from the first to the fourth rupture caused by ICA aneurysm was longer than that from the fifth to the eighth, caused by the basilar artery—P1 aneurysm. The aneurysm responsible for the fifth and sixth ruptures might have remained undetected, because of the extremely short interval to repeat rupture. On diagnostic angiography just 3 months before the fifth bleeding episode, de novo aneurysms were not found on the basilar artery or P1. Repeated de novo aneurysms on the basilar trunk and right P1 were treated by stent-coil embolization, and complete obliteration had been confirmed on postoperative angiography each time. Unexpectedly, a large aneurysm on the distal side of the right P1, which had been treated by stent-coiling, ruptured 7 months after the eighth rupture, resulting in the fatal outcome. The basilar trunk—right P1 area is supposed to be slightly away from the radiation fields and the isocenter of gamma knife treatment for the glioma in the right frontobasal brain areas. The mechanisms of sequential appearance of de novo multiple aneurysms within such a short period remain to be elucidated.
| Investigator         | Pt. No. | Age at RT (years) | Sex | Aneurysm Location                          | Ruptured or Unruptured | Aneurysm Treatment | Aneurysm Treatment | Histological Examination of Aneurysm | Predisposing Disease Treated by Radiation | Interval Between Radiation and Aneurysm Detection | Radiation Dose | Clinical Outcome         |
|----------------------|---------|-------------------|-----|--------------------------------------------|------------------------|-------------------|-------------------|--------------------------------------|-----------------------------------------------|-----------------------------------------------|---------------|------------------------|
| Azzarelli et al., 18 | 1       | 12                | F   | Rt ICA, BA, Rt VA—BA junction, Rt ACA     | Rupture               | No                | Conservative follow-up | Yes; autopsy                     | Suprasellar germinoma                        | 3.6 years                        | 40 Gy WBRT, 12.2 Gy focal | Died 5 years after RT |
| Gomori et al., 1987 | 2       | 44                | M   | BA                                         | ND                    | Yes               | Conservative follow-up | No                                  | Nasopharyngeal carcinoma                    | 3 years                          | 60 Gy                      | Died             |
| Nishi et al., 24     | 3       | 48                | M   | ICA (bifurcation) and 3 fusiform aneurysms | Unrupture             | No                | Wrapping            | No                                  | Pituitary adenoma                         | 9 years                          | 50 Gy                      | Bitemporal hemianopsia, which resolved |
| Benson et al., 1989  | 4       | 2                 | M   | Rt PCA                                     | Rupture               | No                | Conservative follow-up | Yes; autopsy                     | Medulloblastoma                           | 19 years                         | 30.66 Gy, 16.56-Gy boost | Died 19 years after RT |
| Benson et al., 1989  | 5       | 14                | F   | Lt PCA                                     | Rupture               | No                | Conservative follow-up | Yes; autopsy                     | Medulloblastoma                           | 17 years                         | 34.96 Gy, 15-Gy boost | Died 17 years after RT |
| Benson et al., 1989  | 6       | 5                 | M   | Lt PCA                                     | Rupture               | No                | Conservative follow-up | Yes; autopsy                     | Medulloblastoma                           | 9 years                           | 35.04 Gy, 15-Gy boost | Died 9 years after RT  |
| Scodary et al., 1990 | 7       | 47                | M   | ACA, distal ACA, irregular ACA             | Rupture               | No                | Conservative follow-up | No                                  | Astrocytoma                                | 15 years                          | 65 Gy                       | Died             |
| Thun et al., 1991    | 8       | 22                | M   | ICA (infraclinoid)                        | Unrupture             | No                | Bypass surgery       | No                                  | Pituitary adenoma                        | 8 years                           | Yttrium implants | No neurological deficit |
| John et al., 1993    | 9       | 50                | M   | ICA                                        | Rupture               | No                | Coil embolization    | No                                  | Nasopharyngeal carcinoma                 | 5 years                           | 66 Gy                       | Died             |
| Casey et al., 1993   | 10      | 65                | F   | Lt MCA (bifurcation)                      | Rupture               | No                | Wrapping            | No                                  | Astrocytoma                                | 3.5 years                         | 60 Gy                       | Hemiparesis and dysphagia |
| Casey et al., 1993   | 11      | 23                | M   | Rt distal MCA                             | Rupture               | No                | Neck clipping       | No                                  | Arteriovenous malformation               | 21 years                          | 40 Gy                       | No neurological deficit |
| McConachie et al., 1994 | 12     | 34                | F   | Bilateral ICA (cavernous)                 | Unrupture             | No                | Rt ICA ligated in neck and clipping distal to aneurysm | No                                  | Pituitary adenoma                        | 17 years                         | Yttrium implants | No additional deficits |
| Holden et al., 1996  | 13      | 62                | F   | BA top, BA-SCA, A-com A, MCA-LSA          | Rupture               | No                | Conservative follow-up | Yes; autopsy                     | Metastasis (breast cancer)              | 7 months                          | 31.8 Gy                     | Died             |
| Jenson et al., 1997  | 14      | 9                 | M   | Rt distal ACA                             | Rupture               | No                | Neck clipping       | No                                  | Medulloblastoma                           | 10 months                         | 40 Gy WBRT, 8 Gy focal | Died 2 years after RT of metastasis |

Pt. No., patient number; RT, radiotherapy; F, female; Rt, right; ICA, internal carotid artery; BA, basilar artery; VA, vertebral artery; ACA, anterior cerebral artery; WBRt, whole brain radiotherapy; M, male; ND, not described; PCA, posterior cerebral artery; Lt, left; MCA, middle cerebral artery; LSA, lenticulostriate artery; SCA, superior cerebellar artery; NR, not reported; GKS, gamma knife surgery; IC-PC, internal carotid—posterior communicating arteries; A-com, anterior communicating artery; AICA, anterior inferior cerebellar artery; mRS, modified Rankin scale.

Continues
| Investigator          | Pt. No. | Age at RT (years) | Sex | Aneurysm Location               | Ruptured or Unruptured | Aneurysm Treatment | Histological Examination of Aneurysm | Predisposing Disease Treated by Radiation | Interval Between Radiation and Aneurysm Detection | Radiation Dose | Clinical Outcome                  |
|-----------------------|---------|------------------|-----|--------------------------------|------------------------|-------------------|-------------------------------------|-------------------------------------------|-------------------------------------------------|----------------|-------------------------------|
| Maruyama et al., 2000 | 15      | 0.4              | F   | ICA, ACA                       | Rupture                | No                | Neck clipping (ICA)/wrapping (ACA) | No                                       | Optic glioma                              | 15 years       | 70 Gy, 40 Gy                 | No additional deficits |
| Aichholzer et al., 2001 | 16      | 1                | M   | A-com A                        | Rupture                | No                | Neck clipping                       | Yes; autopsy                              | Pituitary astrocytoma                       | 9 years         | 54 Gy                        | Died 13 years after RT |
| Cheng et al., 2001    | 17      | 47               | M   | ICA (petrous)                  | Rupture                | No                | Coil embolization                   | No                                       | Nasopharyngeal carcinoma                   | 7 years         | 60 Gy                        | No neurological deficit |
| Cheng et al., 2001    | 18      | 33               | M   | ICA (petrous)                  | Rupture                | No                | Stent                               | No                                       | Nasopharyngeal carcinoma                   | 2 years         | 60 Gy                        | No neurological deficit |
| Huang et al., 2001    | 19      | 19               | F   | Distal ACA                     | Unrupture              | No                | NR                                  | No                                       | Arteriovenous malformation                 | 9 months        | 20 Gy GKS                    | n.d.                        |
| Murakami et al., 2002 | 20      | 11               | M   | IC-PC, BA                      | Unrupture              | no                | Wrapping (IC-PC)/coil embolization (BA) | No                                       | Craniopharyngioma                          | 19 years        | 60 Gy                        | No additional deficits |
| Pereira et al., 2002  | 21      | 14               | F   | ICA (bifurcation)              | Unrupture              | No                | Planned coil embolization; aborted because of reduced aneurysm | No                                       | Craniopharyngioma                          | 5 years         | 54 Gy                        | No neurological deficit |
| Louis et al., 2003    | 22      | 34               | M   | Lt ICA (cavernous)             | Unrupture              | No                | ND                                  | No                                       | Hodgkin disease                            | 27 years        | 43.5 Gy                      | Diplopia                   |
| Gabriel et al., 2004  | 23      | 31               | F   | Rt ICA (partially thrombosed giant) | Unrupture              | No                | Trapping of IC by balloon occlusion | No                                       | Pituitary adenoma                          | 29 years        | Yttrium implants             | Delayed mild left hemiparesis |
| Younesy et al., 2004  | 24      | 36               | F   | A-com A                        | rupture                | No                | Neck clipping                       | yes                                      | Optic glioma                                | 6 years         | n.d.                         | No neurological deficit |
| Takao et al., 2006    | 25      | 63               | F   | Distal AICA                    | Rupture                | No                | Coil embolization                   | No                                       | Vestibular schwannoma                      | 6 years         | 12 Gy GKS                    | No additional deficits |
| Gonzalez-Portillo et al., 2006 | 26 | 0.4              | M   | Rt ACA (A1)                    | Rupture                | No                | Neck clipping                       | No                                       | Retinoblastoma                              | 11.8 years      | ND                           | No neurological deficit |
| Akamatsu et al., 2009 | 27      | 75               | F   | Lt AICA                        | Rupture                | No                | Trapped and removed                 | Yes                                      | Vestibular schwannoma                      | 8 years         | 12 Gy GKS, 50% isodose line | No neurological deficit |
| Moriyama et al., 2009 | 28      | 50               | F   | Rt MCA (trifurcation and 3 distal), PCA | Rupture                | No                | Conservative follow-up             | No                                       | Pituitary adenoma                          | 1 year          | 50 Gy                        | Died 8 weeks after diagnosis of aneurysms |
| Park et al., 2009     | 29      | 69               | F   | Distal AICA                    | Rupture                | No                | Coil embolization (attempted)       | No                                       | Vestibular schwannoma                      | 5 years         | 12 Gy GKS                    | ND                         |
| Yamaguchi et al., 2009 | 30    | 67               | F   | Rt distal AICA                 | Rupture                | No                | Trapping and removed                | Yes                                      | Vestibular schwannoma                      | 6 years         | 50 Gy GKS                    | Moderate right hemifacial palsy |
Including the present case, we identified 39 reports of intracranial aneurysms after radiotherapy for cranial lesions (Table 1). The patients included 20 men and 19 women, with a mean age of 35.8 ± 23.3 years (range, 4 months to 75 years). The ruptured and unruptured aneurysms included 27 cases and 11 cases, respectively. The diseases that led to radiotherapy included pituitary adenomas (n = 5),\textsuperscript{5,6,15,24,27} medulloblastomas (n = 4),\textsuperscript{5,21} nasopharyngeal carcinomas (n = 4),\textsuperscript{2,10,22} astrocytomas (n = 4),\textsuperscript{1,17,23} optic gliomas (n = 2),\textsuperscript{4,16} germinoma (n = 2),\textsuperscript{12,18} breast cancer metastasis (n = 1),\textsuperscript{20} Hodgkin disease (n = 1),\textsuperscript{26} vestibular schwannomas (n = 7),\textsuperscript{7,9,29,30,33,35} a cerebellopontine angle meningioma (n = 1),\textsuperscript{31} and de novo aneurysms and arteriovenous malformations (n = 4).\textsuperscript{1,25,31,34}

In general, the location of radiation-induced aneurysms will correspond to the region of irradiated fields, except for in 1 patient with an aneurysm on the distal right middle cerebral artery after gamma knife treatment for left parietal arteriovenous malformation. Since Takao et al.\textsuperscript{28} described the first case in 2006, distal anterior inferior cerebellar artery aneurysms after gamma knife surgery for vestibular schwannoma have been reported.\textsuperscript{7,9,29,30,33,35} De novo aneurysmal formation should be considered even after standard gamma knife therapy.

The pathogenesis of radiation-induced vasculopathy is not fully understood. The histological changes seen in radiation-induced aneurysms have been described previously.\textsuperscript{1,9,17,20,30,34} Radiation-induced vasculopathy and aneurysm formation have been related to an initial endothelial damage. At more advanced stages, histological findings have demonstrated arterial walls covered with hyaline fibrosis associated with damage to the endothelial lineage, surrounding gliosis, and lymphocyte infiltration.

Sciubba et al.\textsuperscript{8} reported that various molecules such as ceramide, tumor necrosis factor-\textalpha, E-selectin, and intercellular adhesion molecule-1 were involved in radiation-induced endothelial apoptosis that precipitate chronic changes in vessel walls and could lead to vasculopathy and aneurysm formation after radiation.
and pseudoaneurysms. Murakami et al. 13 reported that radiation-induced aneurysms differ from congenital saccular aneurysms in terms of shape and location, arise directly from a segment of a major artery, and are associated with atherosclerotic changes in neighboring arteries located within the radiation field. Radiation-induced aneurysms, therefore, often have a broad neck, and direct clipping can be difficult. In the present patient, we had to select coil embolization for subsequent repeated de novo aneurysm treatment after the initial direct clipping because of the involvement of the same location.

High-dose focal radiation, such as radiotherapy combining the confocal and gamma knife technique, might accelerate the damage to the vessel wall and endothelial cells, resulting in aneurysmal formation during long-term follow-up. Owing to the nature of their formation from severely damaged vessel walls, radiation-induced aneurysms, themselves, might, therefore, be more fragile and prone to rupture than congenital aneurysms. 3,11,12

Given that the interval between radiotherapy and aneurysm detection ranged from 7 months to 31 years (mean, 10.4 ± 7.8 years) for the present review, most cases involved benign diseases such as arteriovenous malformations and benign brain tumors. This finding suggests that patients with long-term survival after radiotherapy had the necessary time for the de novo aneurysms to be revealed by hemorrhage and reflect the real probability of developing such lesions.

We must consider the possible contribution of other mechanisms such as wound infection, glioma chemotherapy effects, and the patient’s genetic background, in addition to the use of radiation. The possibility of recanalization or de novo aneurysm formation must be considered, not only because of focal arterial injury from radiation, but also because of coexisting regional vasculopathy. Rapid aneurysm development after radiation has been reported in a patient with Ehlers-Danlos syndrome. The fibrotic healing response in arteries could have been damaged by radiation, especially in patients with defects in collagen synthesis, such as in those with Ehlers-Danlos syndrome. 20 Although the patient in the present case did not have Ehlers-Danlos syndrome, she might have had some defect in the collagen response to combined high-dose radiotherapy and long-term postoperative chemotherapy.

In addition, the surgical trauma of repeated craniotomy for clipping of the aneurysm and removal of the recurrent tumor, in addition to the focal high-intensity radiation, including gamma knife therapy, might have resulted in the fragility of the walls of the parent arteries. Another possibility might have been the formation of a pseudoaneurysm caused by infection associated with the scalp and wound dehiscence after multistaged craniotomy, which required scalp reconstruction using a vascularized skin flap. Multistaged surgical trauma might have been associated with long-term exposure to occult infections causing wound dehiscence, leading to vessel walls that are more sensitive and fragile, with an increased risk of repeated de novo aneurysm formation.

Careful, periodic, long-term follow-up with magnetic resonance angiography should be required for patients with long survival after repeated craniotomy, chemotherapy, or wound infection, in addition to cranial radiation for vascular malformations and benign brain tumors.

CONCLUSION

To best of our knowledge, the present study is the first report of refractory and recurring de novo aneurysms treated by multistaged endovascular surgery during a long-term follow-up period after multistaged craniotomy and radiotherapy for glioma. The pathogenesis of refractory and recurring de novo aneurysms is unknown. The surgical trauma of the arterial wall, focal high-dose radiation, including gamma knife therapy, and infection associated with the scalp and wound dehiscence might have resulted in fragility of the walls of the arteries. Careful long-term follow-up with magnetic resonance angiography should be required for patients with long survival after repeated craniotomy, radiation, chemotherapy, or wound infection for the identification of de novo aneurysms.

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