Recurrent late cerebral necrosis with aggressive characteristics after radiosurgical treatment of an arteriovenous malformation

Case report

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✓ Late cerebral radiation necrosis usually occurs within 3 years of stereotactic radiosurgery. The authors report on a case of recurrent radiation necrosis with rapid clinical deterioration and imaging findings resembling those of a malignant glioma. This 68-year-old man, who had a history of a left posterior temporal and thalamic arteriovenous malformation (AVM) treated with linear accelerator radiosurgery 13 years before presentation and complicated by radiation necrosis 11 years before presentation, exhibited new-onset mixed aphasia, right hemiparesis, and right hemineglect. Imaging studies demonstrated hemorrhage and an enlarging, heterogeneously enhancing mass in the region of the previously treated AVM. The patient was treated medically with corticosteroid agents, and stabilized temporarily. Unfortunately, his condition worsened precipitously soon thereafter, requiring the placement of a shunt for relief of obstructive hydrocephalus. Further surgical intervention was offered, but the patient's family opted for hospice care instead. The patient died 10 weeks after initially presenting to the authors' institution, and the results of an autopsy demonstrated radiation necrosis.

Symptomatic radiation necrosis can occur more than a decade after stereotactic radiosurgery, necessitating patient follow up during a longer period of time than currently practiced. Furthermore, there is a need for more careful reporting on the natural history of such cases to clarify the pathogenesis of very late and recurrent radiation necrosis after radiosurgery and to define patient groups with a higher risk for these entities.

KEY WORDS • arteriovenous malformation • radiation necrosis • stereotactic radiosurgery

S INCE the initial report by Steiner, et al.,²⁸ in 1972, stereotactic radiosurgery has become an increasingly common modality for the treatment of AVMs. The stereotactic delivery of radiation held the promise of sparing healthy tissue adjacent to lesions; however, delayed radiation-induced complications remain a significant problem in some patients treated with radiosurgery. The majority of these adverse events occur within 3 years of radiosurgical treatment.³⁸ More recently, focus has shifted to identifying the long-term risks of radiosurgery in an effort to define better the optimal patient population for this therapeutic option. We report on a case of histologically proven delayed cerebral radionecrosis reappearing 11 years after an initial episode and 13 years after the radiosurgical treatment of an AVM. To our knowledge, this case has the longest interval between treatment and the manifestation of radionecrosis reported thus far. Furthermore, there have been no previously reported cases of recurrent cerebral necrosis after stereotactic radiosurgery.

Case Report

History and Examination. This 68-year-old man initially presented with a sudden headache in December 1990. A head CT scan showed intraventricular hemorrhage, and subsequent angiography studies demonstrated a large left posterior temporal and thalamic AVM and a left superior cerebellar artery aneurysm. An initial intervention in March 1991 involved microsurgical clip repair of the aneurysm, which resulted in a full recovery postoperatively. In July 1991, the AVM was treated with embolization, followed by LINAC radiosurgery 2 months later in September 1991. Imaging studies obtained at the time of radiosurgery are featured in Fig. 1. Because of the size (3.8 cm at its greatest diameter) and location (near the thalamus) of the AVM, a dual

Abbreviations used in this paper: AVM = arteriovenous malformation; CT = computed tomography; FLAIR = fluid-attenuated inversion-recovery; LINAC = linear accelerator; MR = magnetic resonance; PCA = posterior cerebral artery; PET = positron emission tomography.



FIG. 1. Imaging studies obtained at the time of LINAC radiosurgery in September 1991. Anteroposterior (A) and lateral (B) left vertebral artery injection angiograms demonstrating an approximately $3 \times 3 \times 2$ -cm AVM nidus supplied by the left PCA with deep venous drainage. Axial enhanced CT scan (C) revealing the left posterotemporooccipital/thalamic AVM nidus in intimate association with the left lateral ventricle. Enlarged deep draining veins are present.

isocenter approach involving the delivery of a 1900-cGy dose to the 90% isodose line was prescribed. Using Boston arcs to each isocenter, radiation was delivered to the 100 and 70% isodose lines using 3.5- and 2-cm collimators, respectively. In April 1993 (19 months later), the patient was rehospitalized after a homonymous hemianopia and a mixed dysphasia had developed. Imaging studies revealed changes consistent with radiation necrosis together with associated edema and mass effect. A 3-week course of steroid therapy successfully reversed the symptoms, and a follow-up cerebral angiogram obtained 6 months thereafter (October 1993) demonstrated no residual arteriovenous shunting but did show possible arteritis involving the left PCA branches. Because the patient's clinical status had improved, no tissue samples were obtained at that time. In the subsequent 11 years, the patient was neurologically stable with only a mild short-term memory deficit. In November 2004, the patient presented to our institution with a history of hypertension and new-onset aphasia accompanied by right hemiparesis and neglect. He was awake but oriented only to his own identity and had a slow verbal response time.

First Hospital Course. He was admitted to the neurosurgical intensive care unit and treated with steroid agents. Magnetic resonance images revealed hemorrhage with surrounding edema, signal abnormality, and enhancement centered in the left thalamus, involving the left basal ganglia and medial temporal lobe (Fig. 2A–C). These imaging findings were consistent with a malignant glioma, radiation necrosis, or radiation-induced vasculitis. A cerebral angiogram revealed a paucity of vessels in the region of the hematoma, with no evidence of arteriovenous shunting (Fig. 2D–G). It also demonstrated occlusion of the distal left PCA with proximal irregularity. The patient was discharged in stable condition to a local rehabilitation center 1 week later with plans for further evaluation of the cause of the cerebral hemorrhage.

Second Hospital Course. Sixteen days later, the patient was readmitted for a worsening mental status. He was awake but unable consistently to follow commands. Magnetic resonance imaging studies obtained at this time were notable for worsening hydrocephalus with probable trapping of the left temporal horn and increased vasogenic edema, enhancement, and mass effect in the left hemisphere (Fig. 2H–J). A ventriculoperitoneal shunt was inserted into the left temporal horn. Postoperative CT scans demonstrated resolution of the hydrocephalus, and the patient returned to his baseline mental status. A PET scan did not reveal hypermetabolic activity in the region of the hematoma. The patient was again discharged to the local rehabilitation center on a 4-week steroid taper.

During the next month, in January 2005, the patient's condition steadily deteriorated. He became obtunded with no coherent speech or ability to follow commands. Concurrently, he suffered progressive quadriparesis. Computed tomography and MR imaging studies were notable for stable dilation of the left temporal horn but increased edema and a left-to-right midline shift (Fig. 2K). The patient's family decided to forgo additional surgery and instead sought hospice care. The patient died 1 week later.

Pathological Examination. Because it was unclear whether a tumor or radiation necrosis was responsible for the patient's rapid demise, a brain autopsy was performed. On gross examination, left subfalcine (3 mm), left uncal (3 mm), and bilateral orbital gyrus (6 mm) herniation was noted along with a hemorrhagic lesion situated directly deep to the left insular cortex and measuring 4 cm at its greatest diameter. This lesion consisted of tortuous blood vessels and necrotic tissue. On microscopic examination, abnormal arteries and veins were visualized, some with abnormally thickened vessel walls (Fig. 3A). Extensive necrosis with gliosis and edema of the surrounding tissue was also noted, but there was no evidence of any neoplastic process in the lesion or adjacent tissue (Fig. 3B and C). No antibody staining was deemed necessary given the lack of evidence for neoplasia. After review by the neuropathology department personnel, the final diagnosis was designated "arteriovenous malformation, extensively necrotic.3

Discussion

The long-term complications of stereotactic radiosurgery, including necrosis, hemorrhage, cyst formation, increased seizure frequency, and arterial stenosis,^{11,25} have been reported to occur in 3.2 to 19.8% of patients undergoing treatment for AVMs.³⁸ Of these late effects, perhaps the most

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FIG. 2. Axial FLAIR MR image (A) obtained in November 2004, demonstrating hemorrhage and signal abnormality within the left thalamus, the striatocapsular and subinsular regions, and the splenium of the corpus callosum with surrounding vasogenic edema. There is mild mass effect in the left hemisphere, manifested by sulcal effacement and shift of the third ventricle to the right. Axial unenhanced (B) and Gd-enhanced (C) T₁-weighted MR images obtained in November 2004, revealing hemorrhage in the posteromedial left temporal lobe together with mild circumferential enhancement and trapping of the left temporal horn. Anteroposterior (D) and lateral (E) left vertebral artery and anteroposterior (F) and lateral (G) left common carotid artery digital subtraction angiograms showing no AVM nidus. Left vertebral artery injections exhibited a distally occluded left PCA. Mild areas of narrowing and irregularity appear within the proximal left PCA branches, possibly caused by arteritis. Axial FLAIR image (H) obtained in December 2004, demonstrating worsening hydrocephalus with marked dilation of the left temporal horn. Residual hemorrhage is apparent in the left medial posterior temporal lobe together with increased vasogenic edema in the left hemisphere. New signal abnormality has developed in the midbrain. Axial FLAIR MR image (I) obtained at the level of the lateral ventricles in December 2004, revealing worsened vasogenic edema in the left hemisphere about the residual hematoma with increased compression of the left lateral ventricle and midline shift. Axial Gd-enhanced T₁-weighted MR image (J) obtained in December 2004, demonstrating enhancement surrounding the hematoma, particularly extending medially into the thalamus as well as the corpus callosum. Axial FLAIR MR image (K) obtained in January 2005, exhibiting residual hematoma as well as extensive surrounding edema, severe hydrocephalus, and pronounced mass effect with increased midline shift.

devastating is delayed cerebral radiation necrosis, which typically manifests as cognitive dysfunction, language impairment, focal weakness, sensory loss, or apraxia.⁵ This entity has been well described in the field of conventional radiotherapy, and cases of necrosis have been reported to occur even two to three decades after the initial treatment.^{9,19,32} With respect to radiosurgery, the literature on cerebral radionecrosis is more limited. Whereas necrosis may be histologically evident in up to 33% of patients,¹ the inci-

dence of symptomatic necrosis ranges from 1.7 to 7.6%.¹¹ Although complications after radiosurgery can occur up to 10 years after treatment,¹¹ the majority of observed cases of radiation necrosis have appeared within 3 years of radiosurgical intervention.^{12,14,22,23,26,27,30,31} One notable exception is the case presented by Yamamoto, et al.,³⁷ of a necrotic white matter lesion appearing 7 years after radiosurgical treatment of an AVM.

In the present report, a necrotic lesion associated with in-



FIG. 3. Photomicrographs of the patient's vascular lesion demonstrating abnormal arteries (A, *arrowhead*) and veins (A, *arrow*) and some necrosis (B, *arrow*). Photomicrograph (C) showing extensive necrosis adjacent to gliotic, edematous brain tissue (*arrow*) and numerous hemosiderin-laden macrophages (*arrowhead*). H & E, original magnification \times 100.

tracerebral hemorrhage arose 13 years after the patient had undergone LINAC radiosurgery for an AVM in the same region as a lesion radiographically diagnosed as radiation necrosis 11 years prior. Three features of this case deserve special emphasis. First, although rare cases of recurrent cerebral necrosis exist in the conventional radiotherapy literature,^{7,13,36} we believe that this is the first report of such a diagnosis after radiosurgery. Second, the interval between radiation treatment and the presentation of cerebral necrosis is, to our knowledge, the longest yet reported for stereotactic radiosurgery. Third, the patient's condition deteriorated with surprising rapidity; his admission to our institution in November 2004 was separated from his death in January 2005 by merely 10 weeks. In its growth characteristics and appearance on imaging studies, the lesion closely mimicked a malignant growth. A suspected tumor was the reason that a PET scan was obtained during the patient's second hospitalization. However, there was absolutely no sign of neoplastic cells on histological analysis in or around the lesion. Although remnants of abnormal vessels were seen on pathological analysis, the absence of arteriovenous shunting on multiple cerebral angiograms suggested that the vessels did not represent an active AVM nidus.

The most widely accepted theory on the pathogenesis of delayed cerebral radiation necrosis centers on endothelial cell damage. Consistent with this theory are the histological changes associated with radiation necrosis. Early on, fibrinoid necrosis of blood vessel walls occurs; late changes include vessel wall thickening, hyalinization, and telangiectasia.³² Some of these changes can be seen in Fig. 3. In vitro evidence suggests that radiation alters the production of hemostatic factors by endothelial cells, skewing the hemostatic balance toward platelet aggregation and thrombosis.³ The disruption of the microvasculature subsequently leads to astrocyte hypertrophy and hyperplasia, perivascular edema, and ischemia. Moreover, an influx of leukocytes to damaged areas leads to the expression of various cytokines that, among other effects, induce oligodendrocyte apoptosis.^{6,18} Ultimately, injury from ischemia and reperfusion along with axonal demyelination results in white matter necrosis.8 Alternative theories involve the induction of an autoimmune vasculitis and the perturbation of the fibrinolytic system by radiation effects.24

The patient in the present case had an increased risk of late radiation necrosis because of the large area treated,^{2,4,15,} ^{20,21,35} which required two isocenters, and his history of hypertension. Other risk factors not seen in this patient include repeated radiosurgery for the same lesion, treatment of gliomas rather than metastases or benign tumors, and the inclusion of healthy brain tissue within the treatment volume.^{2,34} However, it remains unclear why radiation necrosis can develop either within a few months or, as in this case, more than one decade after treatment. Similarly, the triggers that activate an aggressive, rapidly progressive recurrence of necrosis are currently unknown. No differences in the rate of the development of late complications have been reported among the various types of stereotactic radiosurgery, although the treatment of AVMs with heavy particle radiosurgery has not been studied extensively.

As demonstrated in the present report, the differentiation of radiation necrosis from tumor growth can be difficult with conventional imaging. On MR images, changes associated with necrosis can be most easily seen on T₂-weighted or FLAIR sequences.⁵ These lesions usually enhance following Gd administration, as would be expected given the breakdown of the blood–brain barrier that accompanies necrosis. The Swiss-cheese and soap-bubble patterns have

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been ascribed to radiation necrosis,¹⁷ but these appearances are not specific enough for the purposes of a definitive diagnosis. Perfusion-sensitive imaging²⁹ and diffusion-weighted imaging³³ have been suggested to increase the diagnostic sensitivity and specificity of MR imaging. Magnetic resonance spectroscopy,¹⁴ single-photon emission computed tomography,¹⁶ and PET¹⁰ have also been found to be useful in differentiating radiation necrosis from tumor, but concerns about their specificity remain.⁵ In the case presented here, hemorrhage in the lesion bed posed a significant technical obstacle to spectroscopy and perfusion imaging. At the present time, no diagnostic modality has proved superior to the others, and the choice of which test to perform remains a matter of clinical judgment and availability.

Conclusions

We report on a patient in whom fulminant cerebral radiation necrosis developed 13 years after LINAC radiosurgery for an AVM and 11 years after a previous episode of radionecrosis. This case is significant because of the appearance of recurrent necrosis more than one decade after both the initial treatment and a previous episode of necrosis and also because of the speed with which the patient's condition worsened. In its rapid progression and its appearance on imaging studies, the lesion resembled a malignant glioma. However, results of a brain autopsy confirmed the diagnosis of radiation necrosis while definitively ruling out tumor. Although delayed radiation necrosis most often occurs within 3 years of stereotactic radiosurgery, the present report indicates that such complications can be seen at much later times. With this in mind, it may be prudent to monitor radiosurgically treated patients for very late occurrences of radiation necrosis. We agree with the assertion by Tandon, et al.,³¹ that a cooperative multicenter database of the outcomes of stereotactic radiosurgery is needed to better define patient risk factors and to decrease the incidence of very late radiation necrosis.

References

- Chang S, Shuster DL, Steinberg GK, Levy RP, Frankel K: Stereotactic radiosurgery of arteriovenous malformations: pathologic changes in resected tissue. Clin Neuropathol 16:111–116, 1997
- Chin L, Ma L, DiBiase S: Radiation necrosis following gamma knife surgery: a case-controlled comparison of treatment parameters and long-term clinical follow up. J Neurosurg 94:899–904, 2001
- Eldor A, Fuks Z, Matzner Y, Witte LD, Vlodavsky I: Perturbation of endothelial function by ionizing irradiation: effects on prostaglandins, chemoattractants and mitogens. Semin Thromb Hemost 15:215–225, 1989
- Flickinger J: An integrated logistic formula for prediction of complications from radiosurgery. Int J Radiat Oncol Biol Phys 17: 879–885, 1989
- Giglio P, Gilbert MR: Cerebral radiation necrosis. Neurologist 9: 180–188, 2003
- Gridley DS, Loredo LN, Slater JD, Archambeau JO, Bedros AA, Andrew ML, et al: Pilot evaluation of cytokine levels in patients undergoing radiotherapy for brain tumor. Cancer Detect Prev 22:20–29, 1998
- Hillemanns A, Kortmann DR, Herrlinger U, Skalej M, Krapf H: Recurrent delayed brain hemorrhage over years after irradiation and chemotherapy for astrocytoma. Eur Radiol 13:1891–1894, 2003

- Hopewell J, van der Kogel A: Pathophysiological mechanisms leading to the development of late radiation-induced damage to the central nervous system, in Wiegel T, Hinkelbein W, Brock M, Hoell T (eds): Controversies in Neuro-Oncology. Frontiers of Radiation Therapy and Oncology, Vol 33. Basel, Switzerland: Karger, 1999, pp 265–275
- Hoshi M, Hayashi T, Kagami H, Murase I, Nakatsukasa M: Late bilateral temporal lobe necrosis after conventional radiotherapy. Neurol Med Chir (Tokyo) 43:213–216, 2003
- Hustinx R, Pourdehand M, Kaschten B, Alavi A: PET imaging for differentiating recurrent brain tumor from radiation necrosis. Radiol Clin N Am 43:35–47, 2005
- Izawa M, Hayashi M, Chernov M, Nakaya K, Ochiai T, Murata N, et al: Long-term complications after gamma knife surgery for arteriovenous malformations. J Neurosurg (Suppl) 102:34–37, 2005
- Jagannathan J, Petit J, Balsara K, Hudes R, Chin L: Long-term survival after gamma knife radiosurgery for primary and metastatic brain tumors. Am J Clin Oncol 27:441–444, 2004
- Kawamoto H, Kiya K, Yuki K, Uozumi T: Delayed cerebral radiation necrosis occurring twice at different regions and times in a patient with a metastatic brain tumor. Acta Neurochir (Wien) 142:599–600, 2000
- Kimura T, Sako K, Tohyama Y, Aizawa S, Yoshida H, Aburano T, et al: Diagnosis and treatment of progressive space-occupying radiation necrosis following stereotactic radiosurgery for brain metastasis: value of proton magnetic resonance spectroscopy. Acta Neurochir (Wien) 145:557–564, 2003
- Kjellberg R, Abe M: Stereotactic Bragg peak proton beam therapy results, in Lunsford D (ed): Modern Stereotactic Neurosurgery. Boston: Martinus Nijhoff, 1988, pp 463–470
- Kline JL, Noto RB, Glantz M: Single-photon emission CT in the evaluation of recurrent brain tumor in patients treated with gamma knife radiosurgery or conventional radiation therapy. AJNR Am J Neuroradiol 17:1681–1686, 1996
- Kumar AJ, Leeds NE, Fuller GN: Malignant gliomas: MR imaging spectrum of radiation therapy- and chemotherapy-induced necrosis of the brain after treatment. Radiology 217:377–384, 2000
- Kureshi SA, Hofman FM, Schneider JH, Chin LS, Apuzzo MLJ, Hinton DR: Cytokine expression in radiation-induced delayed cerebral injury. Neurosurgery 35:822–830, 1994
- Lee J, Chelvarajah R, King A, David KM: Rare presentations of delayed radiation injury: a lobar hematoma and a cystic space-occupying lesion appearing more than 15 years after cranial radiotherapy: report of two cases. Neurosurgery 54:1013–1014, 2004
- Ling CC, Lo YC, Larson DA: Radiobiophysical aspects of stereotaxic radiation treatment of central nervous system diseases. Semin Radiat Oncol 5:192–196, 1995
- Marks LB, Spencer DP: The influence of volume on the tolerance of the brain to radiosurgery. J Neurosurg 75:177–180, 1991
- Okun MS, Stover NP, Subramanian T, Gearing M, Wainer BH, Holder CA, et al: Complications of gamma knife surgery for Parkinson disease. Arch Neurol 58:1995–2002, 2001
- Plowman P: Stereotactic radiosurgery VIII. The classification of postradiation reactions. Br J Neurosurg 13:256–264, 1999
- Sawaya R: The fibrinolytic enzymes in the biology of brain tumors, in Sawaya M (ed): Fibrinolysis and the Central Nervous System. Philadelphia: Hanley & Belfus, 1990, pp 106–126
- Schlienger M, Atlan D, Lefkopoulos D, Merienne L, Touboul E, Missir O, et al: Linac radiosurgery for cerebral arteriovenous malformations: results in 169 patients. Int J Radiat Oncol Biol Phys 46:1135–1142, 2000
- Shenouda G, Souhami L, Podgorsak EB, Bahary JP, Villemure JG, Caron JL, et al: Radiosurgery and accelerated radiotherapy for patients with glioblastoma. Can J Neurol Sci 24:110–115, 1997
- Statham P, Macpherson P, Johnston R, Forster DM, Adams JH, Todd NV: Cerebral radiation necrosis complicating stereotactic radiosurgery for arterovenous malformation. J Neurol Neurosurg Psychiatry 53:476–479, 1990
- 28. Steiner L, Leksell L, Greitz T, Forster DM, Backlund EO: Stereo-

taxic radiosurgery for cerebral arteriovenous malformations. Report of a case. Acta Chir Scand 138:459–464, 1972

- 29. Šugahara T, Korogi Y, Tomiguchi S, Shigematsu Y, Ikushima I, Kira T, et al: Posttherapeutic intraaxial brain tumor: the value of perfusion-sensitive contrast-enhanced MR imaging for differentiating tumor recurrence from nonneoplastic contrast-enhancing tissue. AJNR Am J Neuroradiol 21:901–909, 2000
- Takenaka N, Imanishi T, Sasaki H, Shimazaki K, Sugiura H, Kitagawa Y, et al: Delayed radiation necrosis with extensive brain edema after gamma knife radiosurgery for multiple cerebral cavernous malformations. Case report. Neurol Med Chir (Tokyo) 43:391–395, 2003
- Tandon N, Vollmer DG, New PZ, Hevezi JM, Herman T, Kagan-Hallet K, et al: Fulminant radiation-induced necrosis after stereotactic radiation therapy to the posterior fossa. Case report and review of the literature. J Neurosurg 95:507–512, 2001
- Tran TA, Fuller GN, Whitman GJ, Schomer DF: Radiologic– pathologic conferences of the University of Texas M. D. Anderson Cancer Center. Delayed cerebral radiation necrosis. AJR Am J Roentgenol 180:70, 2003
- 33. Tsui EYK, Chan JHM, Ramsey RG, Leung TW, Cheung YK, Luk SH, et al: Late temporal lobe necrosis in patients with nasopharyngeal carcinoma: evaluation with combined multi-section diffusion weighted and perfusion weighted MR imaging. Eur J Radiol 39:133–138, 2001

- Valéry CA, Cornu P, Noël G, Duyme M, Boisserie G, Sakka LJ, et al: Predictive factors of radiation necrosis after radiosurgery for cerebral metastases. Stereotact Funct Neurosurg 81:115–119, 2003
- Voges J, Treuer H, Sturm V, Büchner C, Lehrke R, Kocher M, et al: Risk analysis of linear accelerator radiosurgery. Int J Radiat Oncol Biol Phys 36:1055–1063, 1996
- 36. Wong E: Recurrent cystic radiation necrosis of the brain. **Oncol Rep 5:**685–687, 1998
- Yamamoto M, Ban S, Ide M, Jimbo M: A diffuse white matter ischemic lesion appearing 7 years after stereotactic radiosurgery for cerebral arteriovenous malformation: case report. Neurosurgery 41:1405–1409, 1997
- Yamamoto M, Hara M, Ide M, Ono Y, Jimbo M, Saito I: Radiation-related adverse effects observed on neuro-imaging several years after radiosurgery for cerebral arteriovenous malformations. Surg Neurol 49:385–398, 1998

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