

## Intracranial aneurysm following radiation therapy during childhood for a brain tumor

### Case report and review of the literature

DANIEL M. SCIUBBA, M.D., GARY L. GALLIA, M.D., PH.D., PABLO RECINOS, B.A., IRA M. GARONZIK, M.D., AND RICHARD E. CLATTERBUCK, M.D., PH.D.

*Department of Neurosurgery, The Johns Hopkins School of Medicine, Baltimore, Maryland*

✓ Ionizing radiation therapy is associated with pathological vascular changes in intracranial vessels, most commonly in the form of vessel thrombosis and occlusion. The development of an intracranial aneurysm following such therapy, however, is far less common. In this report the authors describe a 24-year-old man in whom a distal middle cerebral artery aneurysm developed 15 years after radiotherapy, which was given as adjuvant treatment following resection of a medulloblastoma. The patient underwent a craniotomy for microsurgical trapping of the aneurysm and was discharged without any neurological deficit. This case serves to remind clinicians of the possibility, albeit rare, that intracranial aneurysms may form following cranial radiotherapy.

**KEY WORDS • radiation therapy • intracranial aneurysm • vasculopathy • medulloblastoma • pediatric neurosurgery**

**H**IGH-dose ionizing radiation therapy is a reliable and effective part of the standard treatment regimen for a number of head, neck, and brain tumors, regardless of whether it is used as adjuvant or primary therapy. It is well established, however, that the application of radiation can induce a number of different pathological vascular changes, most notably intimal hyperplasia and thrombosis, with subsequent vessel stenosis and occlusion.<sup>21</sup> These changes affect capillaries, sinusoids, and small arteries, with relatively less damage done to large arteries and veins.<sup>7</sup> Although radiation-induced occlusive changes are well documented, the incidence of radiation-induced intracerebral aneurysms is far less common. In total, 25 cases of intracranial aneurysms have been reported in the literature.<sup>1,2,4–6,8,9,11–13,15–20,24,27–29</sup> In this report, we present the case of a man in whom a distal left MCA fusiform aneurysm developed longer than a decade after he underwent high-dose radiation therapy for a medulloblastoma treated during childhood.

### Case Report

**History.** This 24-year-old man was found to harbor a posterior fossa medulloblastoma when he was 9 years of age.

**Abbreviations used in this paper:** ACA = anterior cerebral artery; BA = basilar artery; CT = computed tomography; EC = endothelial cell; ICA = internal carotid artery; MCA = middle cerebral artery; MR = magnetic resonance; SAH = subarachnoid hemorrhage.

He underwent gross-total tumor resection at that time without an adverse event and later craniospinal radiotherapy (total dose 55.8 Gy) as adjuvant treatment. He was clinically monitored throughout the next 15 years with serial MR imaging. During this time, he demonstrated no new neurological deficit, and none of the MR images showed any sign of residual tumor.

**Examination.** When the patient was 23 years old, an axial T<sub>2</sub>-weighted MR image revealed an 8-mm hypointense lesion in the right sylvian fissure, which was consistent with the presence of a vascular flow void (Fig. 1 *upper*). The same lesion was associated with robust contrast enhancement on T<sub>1</sub>-weighted MR images after administration of Gd; on these images small enhancing vessels were observed to course into and away from the enhancing nodule (Fig. 1 *lower*). A review of serial MR images suggested that the lesion had enlarged over time.

The patient underwent four-vessel cerebral angiography, which revealed a fusiform aneurysm of the right distal MCA (Fig. 2). No other vascular abnormalities were noted. Computed tomography angiography (performed for import into the neuronavigation system) confirmed the presence of a right distal MCA aneurysm (Fig. 3).

**Operation.** The patient underwent a right frontotemporal craniotomy and the aneurysm was localized in the superior temporal sulcus (Fig. 4). The temporooccipital artery entered the base of the aneurysm and exited its upper surface, a find-

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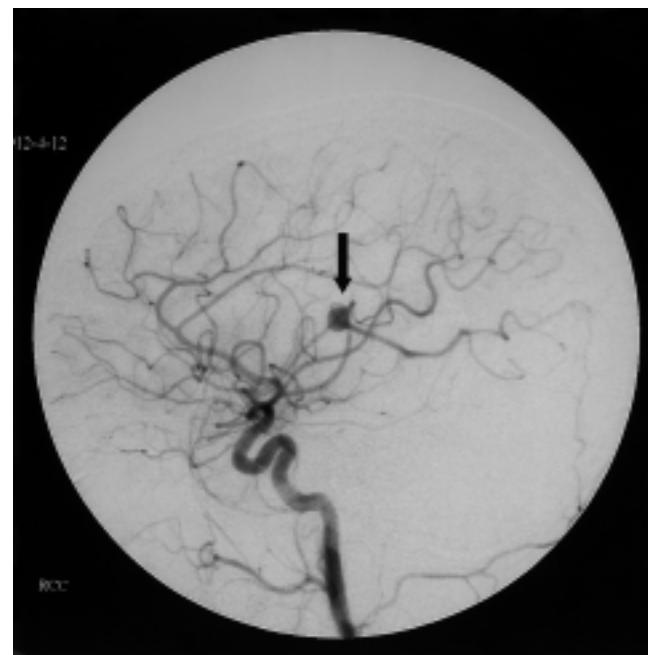
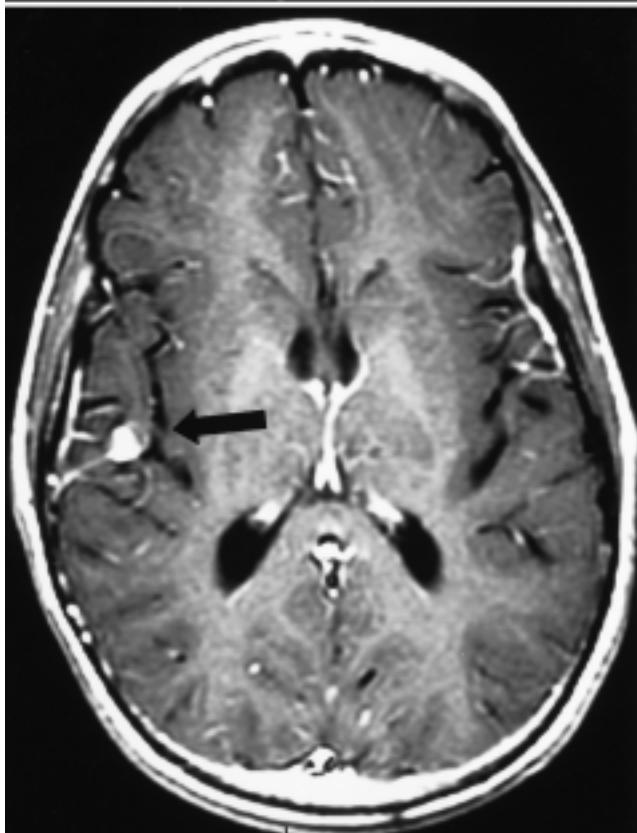
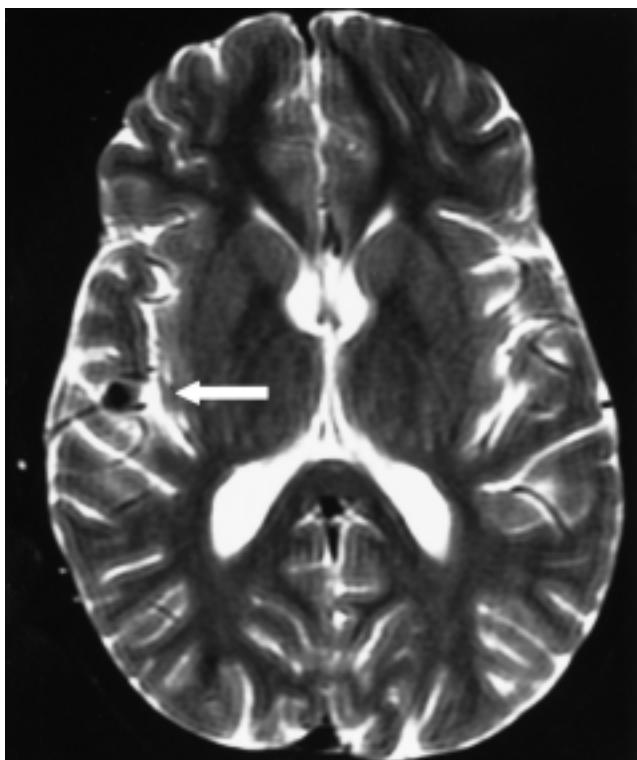


FIG. 2. Lateral angiogram obtained following a right ICA injection. A 6-mm fusiform aneurysm is present in the temporooccipital branch of the right MCA (arrow).

ing consistent with the lesion's fusiform appearance observed on angiography. A temporary clip was applied to the temporooccipital artery, with deflation of the aneurysm and no subsequent electrophysiological changes detected. Back bleeding was next assessed and believed to be adequate. Thus, the decision was made not to perform a bypass, and the aneurysm was trapped between two permanent aneurysm clips. Intraoperative angiography demonstrated no filling of the aneurysm with the contrast agent. The patient's neurological state immediately postoperatively was the same as that at baseline. Two days after the procedure, because the man reported a postoperative headache, a non-contrast-enhanced CT scan of the head was obtained (Fig. 5). This scan revealed a region of hypodensity in the right parietal and temporal lobes, which was consistent with a subacute infarct in the distribution of the superior division of the right MCA. There were no new neurological deficits associated with this infarct, and the patient was discharged on the 4th postoperative day in stable condition. Additional neurocognitive testing was conducted after discharge. It was the opinion of the neurologist that the patient's cognitive deficits were most consistent with his history of craniospinal radiotherapy.

### Discussion

Intracerebral occlusive vasculopathy associated with high-dose radiation therapy to the head, neck, and brain is a well-described phenomenon, with more than 50 cases reported in the literature.<sup>21</sup> Although radiation-induced aneurysms occur less frequently, some investigators have postulated that postradiotherapy occlusive vasculopathy and aneurysm formation share a common origin in which endothelial damage precipitates chronic changes in vessel walls.<sup>16</sup> Histological-

FIG. 1. Axial MR images of the brain. *Upper*: A T<sub>2</sub>-weighted MR image (TR 3000 msec, TE 95 msec) revealing a lesion in the right sylvian fissure that is consistent with a vascular flow void (white arrow). *Lower*: A Gd-enhanced T<sub>1</sub>-weighted image (TR 500 msec, TE 15 msec) depicting small enhancing vessels leading to and away from the enhancing nodule (black arrow).

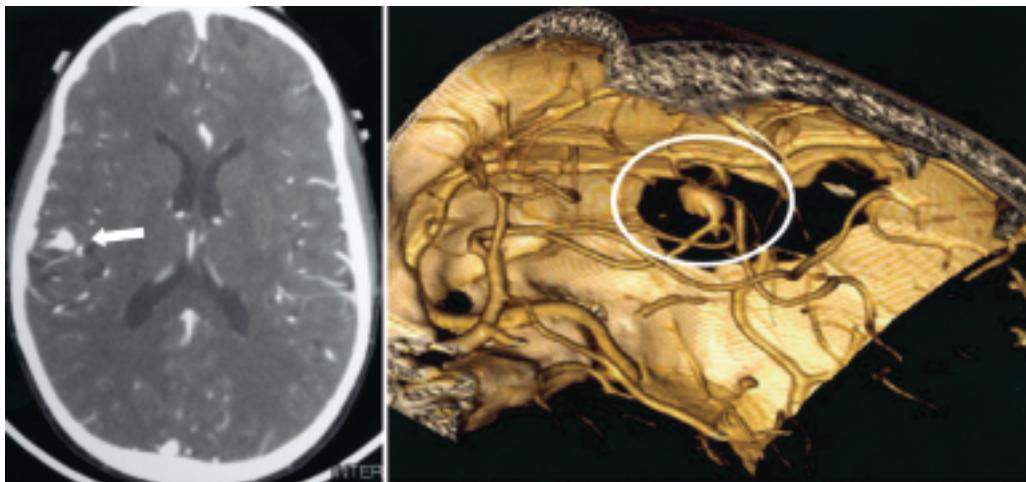


FIG. 3. *Left:* Axial contrast-enhanced CT scan revealing an aneurysm in the right sylvian fissure (arrow). *Right:* Three-dimensional reconstructed image of the right MCA aneurysm (outlined by the circle) derived from axial CT scans.

ly, these changes in small vessels are characterized by fibrin deposition surrounding the vessels, damage to the endothelial lining, gliosis, and lymphocytic infiltration. This endothelial damage leads to thrombosis and intimal narrowing, either of which may produce ischemic changes if hemodynamically significant. In addition, exposure to radiation may accelerate the rate of atherosclerosis in all these vessels, and thus may further increase the degree of vessel stenosis.<sup>6</sup>

The process by which ECs become uniquely susceptible to radiation-induced damage is still not completely understood.<sup>7</sup> Some postulate that radiation-induced DNA damage leads directly to morphological changes in the endothelium.<sup>7,21</sup> The most susceptible vessels are capillaries, sinusoids, and small arteries which appear to exhibit the most significant morphological endothelial changes of all cerebral vessels in response to radiation treatment in animal studies. Larger arteries tend to be more resistant to the effects of radiation, and veins are generally the least sensitive vessels, with only rare cases of chronic vessel wall fibrosis.<sup>21</sup> Vascular changes have been documented to occur in three distinct stages: early morphological changes in ECs of the vessels are first identified, followed by progressive sloughing of ECs and eventually vessel thrombosis and occlusion. Early sloughing of ECs from the basement membrane is believed to be primarily the product of an apoptotic mechanism.

Ionizing radiation can directly damage individual cells at the molecular level, creating cross-links and other changes in a cell's DNA, which potentially lead to the initiation of apoptotic mechanisms if the damage cannot be repaired.<sup>14</sup> Nevertheless, the specific molecular mechanisms underlying radiation-induced vascular changes still remain unclear. One possible mechanism includes an increase in intracellular ceramide, which has been postulated to be a mediator of apoptosis, via upregulation of acid sphingomyelinase expression. Notably, mice deficient in the acid sphingomyelinase pathway do not exhibit radiation-induced endothelial apoptosis, nor do they demonstrate an elevation in intracellular ceramide as is typically seen in control mice exposed to radiation.<sup>3,23,26</sup> Interestingly, Peña, et al.,<sup>23</sup> have shown that basic fibroblast growth factor can decrease production of

ceramide in rats exposed to radiation, giving this molecule therapeutic potential as a modulator of radiation-induced endothelial changes. Another possible mediator of radiation-induced pathological processes of vessels is the cytokine tumor necrosis factor- $\alpha$ , a putative mediator of apoptosis that is produced in increased amounts by irradiated leukocytes that adhere to the vessel endothelium after exposure to radiation.<sup>3,10,25</sup> In addition, upregulation of a number of different cellular adhesion molecules, most notably E-selectin, intercellular adhesion molecule-1, CD31, and vascular adhesion molecule-1, may play a role in this leukocyte adhesion and in tumor necrosis factor- $\alpha$  induced apoptosis.<sup>3,10,25</sup> It has been shown that after exposure to radiation there is early and prolonged increased expression of intercellular adhesion molecule-1, followed by transient expression of vascular adhesion molecule-1 and late upregulation of CD31.<sup>10</sup> With regard to the late consequences of irradiation, including platelet aggregation, increased collagen production, and EC proliferation, no molecular mechanisms have yet been described.<sup>3</sup>

Omura and colleagues<sup>22</sup> described 32 patients in whom

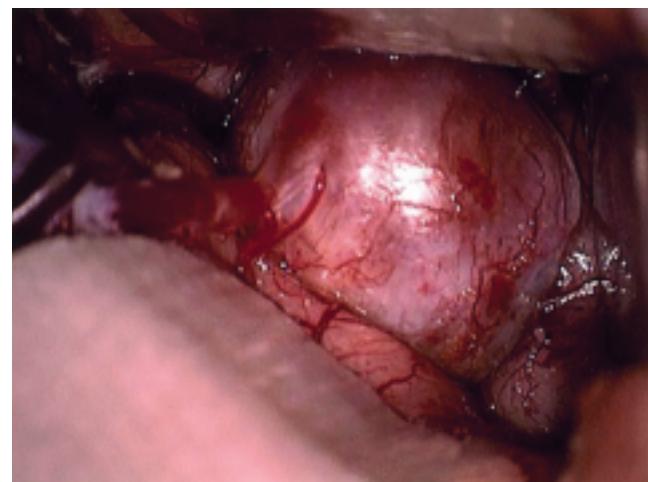


FIG. 4. Intraoperative photograph showing the distal MCA aneurysm in the right superior temporal sulcus.

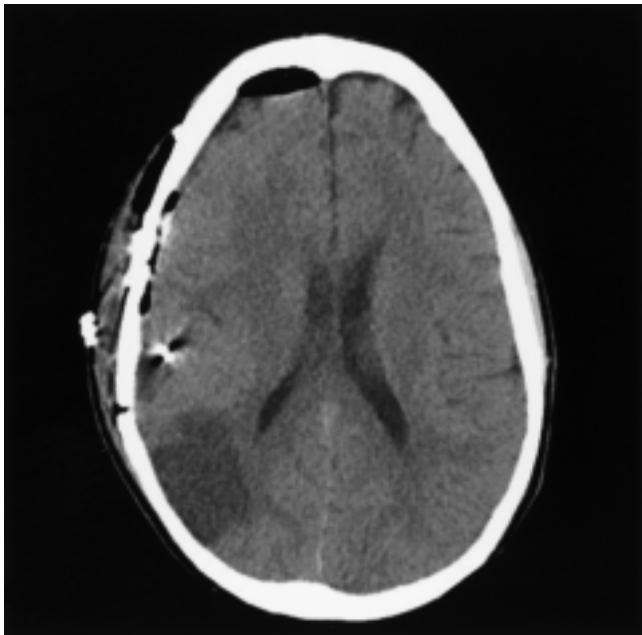


FIG. 5. Axial CT scan of the brain revealing a region of hypodensity in the right parietal and temporal lobes, a finding consistent with a subacute infarct.

the circle of Willis and major intracerebral vessels received direct radiation exposure as adjuvant therapy after tumor resection. Large vessel occlusive disease was found in approximately 20% of these patients. Changes were most often seen in the circle of Willis, terminal ICA, proximal ACA, and MCA. The time to onset of symptoms ranged from 2.5 to 12 years after radiotherapy. Although there is no clear threshold of irradiation after which vasculopathy becomes evident, all patients who exhibited vascular stenosis in this series received at least 50 cGy ionizing radiation.<sup>22</sup> Cerebral angiography in these patients revealed focal stenosis of the cerebral arteries, netlike vessels at the brain base, and anastomoses connecting the cerebral and meningeal arteries, similar to angiographic findings in cases of moyamoya disease.<sup>15,16,22,24</sup>

Much rarer than development of occlusive disease is the appearance of cerebral aneurysms following cranial irradiation. The exact cause of these aneurysmal changes is unknown, although some investigators have postulated that the pathogenetic mechanism may be similar to that found in radiation-induced occlusive vasculopathy; that is, initial damage to ECs predisposes vessels to aneurysmal changes. Including the current case, there are only 26 cases of aneurysms of cerebral vessels following cranial irradiation reported in the international literature.<sup>1,2,4–6,8,9,11–13,15–20,24,27–29</sup> Findings reported in these papers also suggest that such aneurysms tend to develop in vessels most affected by atherosclerotic changes, a late complication of radiation therapy.<sup>6</sup> Histological examinations of these aneurysms have demonstrated that their endothelial linings are heavily disrupted and fragmented, with a focal loss of ECs, findings that support the theory that the EC is an important factor in the process of aneurysm formation following radiotherapy.<sup>16</sup>

In the current case, a fusiform aneurysm involving the distal MCA developed in a patient who had received radi-

ation therapy for a medulloblastoma when he was a child. Several features of the aneurysm suggest that its occurrence was related to radiotherapy, including the lesion's position within the irradiated field, its distal location, and its fusiform structure.<sup>16</sup> Although the patient did well clinically after aneurysm surgery, it is possible that the perioperative stroke could have been avoided if a bypass procedure had been performed. In general, if a bypass is considered and can be accomplished with a low risk of morbidity, this procedure should be performed if there is any question of inadequate flow in the supplied territory.

Despite the rarity of aneurysm formation after cranial irradiation, a number of such cases have been described in the literature, the first of which was reported by Azzarelli, et al.,<sup>2</sup> in 1984. In that report the authors described the case of a 12-year-old girl with a suprasellar germinoma, who underwent resection and cranial radiotherapy (40 Gy plus a 12.2-Gy boost to the tumor bed). Three years and eight months after radiation treatment, a contrast-enhanced CT scan and a cerebral angiogram revealed multiple fusiform intracranial aneurysms involving the BA, ICA, and ACA. These aneurysms were not treated, and the patient, at the age of 17 years, died 5 years after the initial radiation treatment due to complications associated with aneurysmal SAH.

Including the case that we are reporting, we have identified 26 reported cases of intracranial aneurysms following cranial radiotherapy (Table 1). The primary intracranial diseases for which these patients received radiotherapy included the following: pituitary adenoma (six cases), medulloblastoma (five cases), nasopharyngeal carcinoma (four cases), astrocytoma (three cases), craniopharyngioma (two cases), optic glioma (two cases), germinoma (one case), breast cancer metastasis (one case), Hodgkin disease (one case), and arteriovenous malformation (one case). The mean age of the patients undergoing radiotherapy was 28.6 years (range 0.4–62 years), and the mean interval between radiation treatment and the diagnosis of an intracranial aneurysm was 10.6 years (range 7 months–29 years). The mean radiation dose for patients receiving standard craniospinal radiotherapy was 61 Gy (range 31.8–120 Gy). Those cases in which the radiation source was yttrium seeds were not included in this average because the radiation dose delivered to the field from such seeds cannot be accurately calculated. Sixteen (61.5%) of the 26 patients presented with aneurysmal SAH. Treatment for aneurysms in these 26 patients included: surgical treatment (clip placement or wrapping of the artery) in 12 patients (46%); endovascular treatment (coil embolization and/or insertion of a stent) in four patients (15.3%); no treatment or supportive care in nine patients (34.6%); and unknown therapy in one patient (3.8%). Eleven patients (42.3%) died; 10 of these had presented with SAH, one with progression of the primary disease, and one with myocardial infarction. The diagnosis was confirmed with the aid of cerebral angiography in 23 patients (88.5%), MR imaging in one patient (3.8%), intraoperative diagnosis in one patient (3.8%), and at autopsy in one patient (3.8%).

After we combined all the previously reported cases with our current case, we found that 10 (38.5%) of the 26 patients were 14 years of age or younger when first treated with cranial radiotherapy. Given that the average interval of time between cranial irradiation and the eventual diagnosis of an aneurysm is roughly 10 years in this review, an argument

TABLE 1  
*Cases of intracranial aneurysms following cranial irradiation reported in the literature\**

Authors & Year	Case No.	Disease	Age (yrs),†	Interval to Diagnosis	Radiation Dose‡	Aneurysm Location	Rupture	Treatment	Outcome
Azzarelli, et al., 1984	1	suprasellar germinoma	12, F	3.6 yrs	40 Gy WB, 12.2 Gy tumor, cone-down tech	ICA, BA, VA/BA junction, ACA	yes	conservative	died 5 yrs after RT
Gomori, et al., 1987	2	NPC	44, M	3 yrs	60 Gy	ICA bifurcation & 3 fusiform aneurysms	unclear	conservative	died
Nishi, et al., 1987	3	pituitary adenoma	48, M	9 yrs	50 Gy	PCA, MCA	no	wrapping	bitemporal hemianopsia, which resolved
Benson & Sung, 1989	4	cMB	2, M	19 yrs	30.66 Gy, 16.56-Gy boost, IT <sup>198</sup> Au, 30 mCi	PCA	yes	conservative	died
	5	cMB	14, F	17 yrs	34.96 Gy, 15-Gy boost, IT <sup>198</sup> Au, 45 mCi	PCA	yes	conservative	died
	6	cMB	5, M	9 yrs	35.04 Gy, 15-Gy boost, IT <sup>198</sup> Au, 30 mCi	PCA	yes	conservative	died
Scodary, et al., 1990	7	temporoparietal astrocytoma	47, M	15 yrs	65 Gy	ACA, pericallosal artery, irregular PCA	yes	conservative	died
Moriyama, et al., 1992	8	pituitary adenoma	50, F	1 yr	50 Gy	MCA (trifurcation & 3 distal), PCA	yes	conservative	died
Thun & Lanfermann, 1991	9	pituitary adenoma	22, M	8 yrs	90 Yt seeds; 35 mCi	infraclinoid ICA	no	bypass	alive, no residual symptoms
Casey, et al., 1993	10	pituitary adenoma	42, M	11 yrs	90 Yt seeds; 45 mCi	intrasellar aneurysm	no	bypass	survived op residual hemiparesis & dysphagia
	11	astrocytoma	62, F	3.5 yrs	60 Gy	MCA bifurcation	yes	wrapped	
John, et al., 1993	12	It parietal AVM	23, M	21 yrs	40 Gy	rt distal MCA	yes	clip appl	
McConaughay & Jacobson, 1994	13	NPC	50, M	5 yrs	66 Gy	ICA	yes	coil emb	
	14	pituitary adenoma	34, F	17 yrs	90 Yt	bilat cavernous ICA	no	& clip appl distal to aneurysm	full recovery
Hodolny, et al., 1996	15	breast metastasis, history of Ehlers-Danlos syndrome	62, F	7 mos	31.8 Gy	basilar tip, BA-PCoA-SCA, ACA-ACoA-ACA, MCA-lenticulostriate artery (2)	yes	clip appl	
Jensen & Wagner, 1997	16	cMB	9, M	10 mos	40 Gy WB, 8-Gy boost	ACA	yes	clip appl (ACA), wrapped (ACA)	died of metastatic disease 2 yrs after RT
Maruyama, et al., 2000	17	optic glioma	0.4, F	15 yrs	70 Gy & 40 Gy	ICA, ACA	yes	coil emb	no additional deficits
Cheng, et al., 2001	18	NPC	47, M	7 yrs	60 Gy & 60 Gy	petrous ICA	yes	no deficit, 3 mos postop	
	19	NPC	33, M	2 yrs	60 Gy & 60 Gy	petrous ICA	yes	no deficit, 5 mos postop	
Aichholzer, et al., 2001	20	pirocystic astrocytoma	1, M	9 yrs	54 Gy	ACoA	yes	clip appl	
Murakami, et al., 2002	21	cranipharyngioma	11, M	19 yrs	60 Gy	PCoA, BA	no	wrapped (PCoA), coil alive	
Pereira, et al., 2002	22	cranipharyngioma	14, F	5 yrs	54 Gy	ICA bifurcation	no	planned coil emb,	
Louis, et al., 2003	23	Hodgkin disease	34, M	27 yrs	43.5 Gy	cavernous ICA	no	aborted due to reduced aneurysm	
Yucesoy, et al., 2004	24	optic glioma	36, F	6 yrs	NR	ACoA	yes	NR alive w/ diplopia	
Gabriel, et al., 2004	25	pituitary adenoma	31, F	29 yrs	90 Yt	ICA	no	full recovery	
present case	26	cMB	9, M	15 yrs	55.8 Gy	distal MCA	no	delayed mild It hemiparesis	
								clip appl	no neurological deficit

\* ACoA = anterior communicating artery; appl = applied; AVM = arteriovenous malformation; cMB = cerebellar medulloblastoma; emb = embolism; IT = intrathecal; MI = myocardial infarction; NPC = nasopharyngeal carcinoma; NR = not reported; PCA = posterior communicating artery; PCoA = posterior communicating artery; RT = radiation therapy; SCA = superior cerebellar artery; VA = vertebral artery; WB = whole brain.

† Age at time of cranial irradiation.

‡ Radiation doses converted to Gray (Gy); except in the case of yttrium-90 (<sup>90</sup>Y) seed implantation.

## Radiation-induced aneurysm

may be made for radiographic screening to continue beyond this period. Although aneurysm formation following cranial irradiation is uncommon, this review reinforces the fact that aneurysmal rupture is often the initial presenting sign of an underlying cerebral aneurysm, and that such a rupture is associated with a high risk of mortality. Patients who are long-term survivors following cranial irradiation should undergo follow-up MR imaging periodically for their oncological disease. Although the use of additional advanced imaging, such as cerebral angiography, for screening patients is likely unnecessary, physicians caring for survivors of childhood cancers who have undergone craniospinal radiotherapy should consider aneurysm formation as a possibility when conducting follow-up imaging.

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Address reprint requests to: Richard E. Clatterbuck, M.D., Ph.D., Department of Neurosurgery, The Johns Hopkins School of Medicine, 600 North Wolfe Street, Meyer 8-181, Baltimore, Maryland 21287. email: rclatte1@jhmi.edu.