Characterization of radiation-induced cavernous malformations and comparison with a nonradiation cavernous malformation cohort

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OBJECT The objective of this study was to characterize the clinical features of radiation-induced cavernous malformations (RICMs).

METHODS The authors retrospectively reviewed the clinical and radiological characteristics of patients with RICMs. The features of these RICMs were then compared with features of nonradiation cavernous malformations (CMs) in 270 patients.

RESULTS Thirty-two patients with RICMs were identified (56.2% men), with a median age of 31.1 years at RICM diagnosis. The median latency from radiation treatment to RICM diagnosis was 12.0 years (interquartile range 5.0–19.6 years). RICMs were always within the previous radiation port. RICMs were symptomatic at diagnosis in 46.9%, and were associated with symptomatic intracranial hemorrhage at any time in 43.8%. Older age at the time of radiation treatment and higher radiation dose were associated with shorter latency. RICMs tended to be diagnosed at a younger age than nonradiation CMs (median 31.1 vs 42.4 years, respectively; $p = 0.054$) but were significantly less likely to be symptomatic at the time of diagnosis (46.9% vs 65.8%, respectively; $p = 0.036$). RICMs were more likely to be multiple CMs than nonradiation CMs ($p = 0.0002$). Prospectively, the risk of symptomatic hemorrhage was 4.2% for RICMs and 2.3% for nonradiation CMs per person-year ($p = 0.556$). In the absence of symptoms at presentation, the risk of hemorrhage for RICMs was higher than for nonradiation CMs (4.2% vs 0.35%, respectively; $p = 0.118$).

CONCLUSIONS In this patient population, RICMs occurred within the radiation port approximately 12 years after radiation treatment. Compared with nonradiation CMs, RICMs were more likely to occur as multiple CMs, to present at a younger age, and were at least as likely to cause symptomatic hemorrhage.

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KEY WORDS cavernous angioma; cavernous malformation; hemorrhage; radiation; vascular disorders

CAVERNOUS malformations (CMs) are well-circumscribed, multilobulated, angiographically occult vascular malformations that may be sporadic or associated with genetic mutations in *CCM1*, *CCM2*, or *CCM3*. In patients with a genetic predisposition, it is hypothesized that a “second hit” is required to develop CM. The nature of the second hit has been debated, with hypothesized mechanisms including infection, inflammation, additional genetic mutations, or radiation.¹⁵ In the sporadic or acquired form, the etiology of CM is not clear, but CMs have been noted in combination with develop-

mental venous anomalies^{6,7} and in patients with prior brain irradiation or biopsy.²⁹

The first explicit link between brain irradiation and de novo CM was proposed in 1992.⁴⁰ However, a 1987 report of intracerebral hemorrhage from a vascular malformation in a patient who underwent radiation treatment 8 years earlier for nasopharyngeal squamous cell carcinoma has a pathological description strikingly similar to CM,⁴¹ and may, in fact, be the first reported case of a radiation-induced cavernous malformation (RICM). The mechanism of de novo development of an RICM in response to radia-

ABBREVIATIONS CM = cavernous malformation; GRE = gradient echo; mRS = modified Rankin Scale; RICM = radiation-induced CM; RIT = radiation-induced telangiectasia; SWI = susceptibility-weighted imaging.

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tion therapy probably involves vascular injury, proliferation and dilation of vascular endothelium, hyalinization and fibrinoid necrosis of blood vessel walls, and finally ischemia and infarction due to narrowing of the vascular lumen.^{19,22} Evidence of this pathogenetic process includes a rat model of late radiation injury of the CNS that showed increased expression of vascular endothelial growth factor in response to radiation exposure.³⁷

The radiological and pathological appearances of individual RICMs are indistinguishable from sporadic or familial CMs (i.e., nonradiation CMs), but uncertainty exists as to whether these are clinically distinct entities. There are multiple reports that RICMs have a higher risk of hemorrhage than sporadic CMs,^{9,13,22,28,33,38} but the definition of hemorrhage (clinically symptomatic vs radiological only) has varied among studies, and hemorrhage risk calculations for RICMs have all been retrospective. Patient age and radiation dose may also influence the natural history of RICMs.

The natural history of RICMs remains poorly defined because these vascular lesions have been reported mostly as single case reports or in small patient series. The majority of reported cases have involved radiation treatment in childhood, with CMs discovered years or decades later. Only 22 cases of intracerebral RICMs^{2,3,5,10,13,16,17,23,24,26,28,30–33,35,39–41} and 5 cases of spinal RICMs^{8,18,21} in patients who received radiation therapy as adults have been previously reported, and these adult RICMs have never been compared directly with pediatric RICMs. Likewise, there has been no large-scale direct comparison of RICMs and nonradiation CMs. In this study we sought to determine the demographic factors, time from irradiation to CM diagnosis, and natural history of RICMs in comparison with nonradiation CMs, including the first calculations of prospective hemorrhage risk.

Methods

Selection of Patients with RICMs

Patients were identified from the authors' (G.L., M.J.L., and K.D.F.) clinical CM databases at Mayo Clinic, a large tertiary referral center whose Institutional Review Board approved the study protocol. Patients with CMs were included if they had brain, head/neck, or chest/thorax irradiation preceding the diagnosis of intracerebral or spinal CM. Patients were excluded if radiation was given to treat a presumed CM or if surgical pathology revealed an alternative diagnosis. Age at the start of radiation treatment was used to classify cases as adult RICMs (at least 18 years of age) or pediatric RICMs (younger than 18 years of age).

Nonradiation CM Patient Comparison

A cohort of patients with well-defined CMs has previously been reported by the senior author (K.D.F.) and derives from a database of 292 patients with a radiological diagnosis of intracerebral CM between 1989 and 1999 at our institution.¹² Excluding those patients with a history of craniospinal irradiation from this database left 270 nonradiation CM cases.

Data Collection

Data were abstracted from medical records onto a stan-

dardized form and entered into a computerized database. Demographic information, personal and family medical history, initial clinical presentation, CM treatment, and functional outcome were recorded. Symptomatic hemorrhage was defined as a clinical event involving acute or subacute focal symptoms and radiological, pathological, or surgical evidence of recent extra- or intralesional hemorrhage, as previously described.¹ Data regarding radiation treatment history included age at radiation therapy, dose and port of radiation, and indication for radiation treatment. The time from radiation treatment to RICM diagnosis (latency) was calculated as the difference between age at the start of radiation treatment and age at RICM diagnosis. The age at RICM diagnosis was established either by the date of first symptoms leading to RICM visualization if symptoms were due to the RICM, or by the date of the first MRI showing the RICM if symptoms were present but not due to the RICM, or if MRI was performed only for surveillance purposes in asymptomatic patients, as for those with prior history of brain tumor. Total duration of follow-up was calculated from the age at radiation treatment to the last clinical contact.

Radiological Data

One of the investigators (J.K.C.G.) reviewed all brain MR images of the patients with RICMs, ranging from 1 to 29 imaging studies per patient. The imaging study closest to the time of RICM diagnosis was reviewed in detail, as was the most recent MR image. Cavernous malformations were classified as Type I, II, III, or IV, as previously described.^{25,42} The number of CMs was determined on susceptibility-weighted imaging (SWI) when available ($n = 3$). If SWI was not available, then gradient echo (GRE) sequences were preferred ($n = 9$), followed by standard T2 sequences ($n = 20$) if neither GRE nor SWI was available. The anterior-posterior diameter and location of symptomatic CMs were determined on standard T2 sequences. When multiple CMs were present, the location and size of symptomatic lesions were recorded. If there were multiple lesions but no symptomatic lesion, the largest lesion was used. The association of a CM with a developmental venous anomaly or other vascular malformation was also recorded when contrasted-enhanced studies were available.

Statistical Analysis

Descriptive statistics including means, medians, and frequencies were used for patient characteristics and presenting symptoms. Comparisons of proportions for nominal and ordinal variables were performed using the Pearson chi-square test (preferred) or 2-tailed Fisher exact test depending on sample size for the given comparison. Comparisons of proportions for continuous variables were performed with the t-test, z-test, or ANOVA. In all cases, significance was set at $p < 0.05$ and analyses were performed with JMP statistical software (version 10.0.0, SAS Institute Inc.). For all statistical analyses, CM location was categorized as cortical, supratentorial-subcortical, infratentorial, or spinal.

To calculate prospective hemorrhage risk, only symptomatic (clinical) hemorrhages that occurred after CM di-

agnosis were counted. Person-years of prospective follow-up were calculated from the time of CM diagnosis to the last clinical contact, distinct from total follow-up calculated from the time of radiation therapy. For those patients whose CMs were treated, follow-up duration was censored at the time of surgical removal of the CM unless only stereotactic radiosurgery was performed, in which case there was no censoring. The annual hemorrhage rate was calculated as the number of hemorrhages during the prospective follow-up period divided by the number of person-years of follow-up. Hemorrhage risk was also stratified according to mode of initial presentation (hemorrhage vs symptoms not due to CM vs asymptomatic).

Results

Thirty-two patients (18 males and 14 females) met the inclusion criteria for RICMs, with a median age of 31.1 years at RICH diagnosis (range 11.1–73.1 years). Individual patient data are shown in Table 1. RICMs were always within the previous radiation port and were most common in the temporal cortex and brainstem. All but 1 RICH was intracerebral. The only spinal RICH occurred in the cervical cord after radiation therapy for squamous cell carcinoma of the neck. RICMs were diagnosed at a median of 12.0 years (range 0.01–60.7 years) after irradiation (Fig. 1). Radiation modality was external beam radiation therapy in 29 patients, stereotactic radiosurgery in 1, proton beam therapy followed by stereotactic radiosurgery in 1, and unknown in 1. RICMs were commonly multiple CMs at diagnosis, with a mean of 8.2 lesions (range 2–48 lesions) per patient when multiple. Slightly less than half of the patients with RICMs (46.9%) were symptomatic at diagnosis, and 43.8% had ever experienced a symptomatic hemorrhage. The median total follow-up duration since radiation treatment was 22.5 years (range 11.3–30.5 years), and the median prospective follow-up duration since RICH diagnosis was 4.3 years (range 1.0–10.1 years). The median radiation dose delivered in patients who developed RICH was 50 Gy (range 12–84 Gy). Surgical intervention for RICMs was pursued in 9 patients, achieving complete resection in 5 and partial resection in 4. All other RICMs were managed conservatively. No RICH was treated with stereotactic radiosurgery. Clinical features of the RICH cohort are summarized in Table 2.

Within the RICH cohort, younger age at radiation treatment was associated with longer latency to RICH diagnosis ($p = 0.015$) but was not predictive of presence of symptoms, risk of hemorrhage, or RICH location. Younger age at radiation treatment was also associated with higher likelihood of multiple RICMs ($p = 0.027$), the only variable found to be linked to CM multiplicity. Higher radiation dose was associated with a trend toward shorter latency of RICH ($p = 0.100$), but again, not with presence of symptoms, risk of hemorrhage, or RICH location. RICMs in cortical locations were less likely to be symptomatic at the time of diagnosis ($p = 0.049$) and had a lower risk of hemorrhage ($p = 0.020$). Finally, there was a trend toward shorter latency to diagnosis of RICMs in infratentorial locations ($p = 0.070$), even though RICMs in this location were not significantly more likely to be symptomatic ($p = 0.149$) or to cause hemorrhage ($p = 0.242$).

Comparison of Adult and Pediatric RICMs

Thirteen patients underwent radiation treatment as adults, and 19 as children (Table 3). RICH diagnosis occurred at a significantly younger age for pediatric patients with RICMs than for adult patients with RICMs (median 24.0 vs 49.4 years, $p = 0.008$). As in the full RICH cohort, latency to RICH diagnosis was significantly shorter for adult RICH than for pediatric RICH ($p = 0.007$). According to a modified Rankin Scale (mRS) score of 0 or 1, signifying no symptoms or no significant disability despite symptoms, functional outcome was more likely to be good at the time of diagnosis for pediatric RICMs compared with adult RICMs ($p = 0.021$). This difference in functional level did not remain statistically significant at the time of the last follow-up evaluation. Total duration of follow-up was significantly longer for pediatric RICH patients, although prospective follow-up, which was used to calculate hemorrhage risk, was not significantly different for pediatric and adult RICH patients. Otherwise, there were no significant differences between the adult and pediatric RICH groups, including similar rates of symptoms due to RICH, risk of hemorrhage, and CM multiplicity, size, and location. Adult and pediatric RICH comparisons are summarized in Table 3.

Comparison of RICMs and Nonradiation CMs

In comparison with a cohort not receiving radiation, those patients with RICMs tended to be diagnosed at a younger age (median 31.1 vs 42.4 years, $p = 0.054$) but were significantly less likely to be symptomatic at the time of diagnosis (46.9% vs 65.8%, $p = 0.036$). RICMs were more likely to be multiple than were nonradiation CMs ($p = 0.0002$). There were no significant differences in CM size, location, or MRI appearance, and similar proportions of patients with and without RICMs had good functional outcomes. Prospectively, the overall risk of hemorrhage was 4.2% per person-year for RICMs and 2.3% per person-year for nonradiation CMs, which was not a statistically significant difference ($p = 0.556$). For those patients with hemorrhage at presentation, the prospective risk of recurrent hemorrhage was relatively high (and not significantly different) in RICMs and nonradiation CMs (11.0% per person-year vs 5.5%, respectively; $p = 0.529$). For patients who were asymptomatic at the time of CM diagnosis, however, there was a trend toward higher prospective hemorrhage risk for RICMs than for nonradiation CMs (4.2% per person-year vs 0.35%, respectively; $p = 0.118$). RICH and nonradiation CM comparisons are summarized in Table 4.

Illustrative Case

Case 11

In several patients with multiple follow-up MR images, an imaging pattern evolved that may be important in the pathogenesis of these lesions. For example, the patient in Case 11 underwent craniospinal irradiation at 24 years of age for germ-cell dysgerminoma of the optic chiasm. At age 31, a right parietooccipital lesion with a mixed T2 signal appeared in a previously normal region of brain (Fig. 2A). This lesion expanded slightly on serial imaging,

TABLE 1: Patients with CMs and previous craniospinal irradiation

Case No.	Age at Radiation Treatment (yrs), Sex	Indication for Irradiation	Radiation Dose (Gy)	Age at R1CM Diagnosis (yrs)	Latency (yrs)	Location of Largest/ Presenting R1CM	MRI T2 Appearance	No. of R1CMs at Diagnosis	Symptoms Due to R1CM at Diagnosis	ICH During Prospective Follow-Up
1	71, M	Thyroid carcinoma	37.5*	73	2.1	TL	Type II	1	—	No
2	47, F	Astrocytoma	—	56	8.7	OL	Type II	1	—	No
3	47, M	Parotid carcinoma	66	54	6.8	Brainstem	Type II†	1	ICH, Diplopia	Yes†
4	45, F	Meningioma	30§	56	11.2	Brainstem	Type II	1	ICH, FND	No
5	43, M	Astrocytoma	60*	55	12.0	TL	Type I	2	—	No
6	33, M	Choriocarcinoma	48*	34	1.1	TL	Type II	1	—	Yes
7	31, F	AVM	32§¶	57	26.0	Basal Ganglia	Type II	1	—	No
8	30, M	SCC	55.8	49	19.4	Spinal	Type IV	1	—	No
9	29, M	Brainstem glioma	50*	29	0.0	Brainstem	Type I	1	FND	No
10	29, M	Pituitary adenoma	50.4*	33	3.7	Brainstem	Type II	1	Diplopia	Yes
11	24, F	Germinoma	30.6*	31	6.1	PL	Type III	1	—	Yes
12	22, F	Burkitt lymphoma	—*	31	9.2	Brainstem	Type II	2	—	No
13	21, F	PNET	68*	25	3.6	PL	Type I	5	ICH, seizure	No
14	16, M	Pineal germinoma	50*	21	5.0	Brainstem	Type II	20	—	Yes†
15	14, F	ALL	12*	19	5.0	Brainstem	Type I	1	ICH	No
16	13, M	Astrocytoma	60	13	0.2	PL	Type II	2	Seizure	No†
17	13, M	Astrocytoma	—	31	17.9	TL	Type II†	1	Seizure	No†
18	12, F	Astrocytoma	50*	27	15.4	TL	Type II	2	—	No
19	10, M	Oligodendroglioma	—	42	32.0	Thalamus	Type II	48	ICH, FND	No
20	9, F	Astrocytoma	—	37	28.5	TL	Type II	1	—	No
21	7, M	Medulloblastoma	44.3*	24	17.3	Cerebellum	Type I	1	—	No
22	7, F	Orbital tumor	—	61	54.4	FL	Type II	1	—	No†
23	6, F	Chronic earache	—	67	60.7	TL	Type II	2	—	No
24	6, M	Medulloblastoma	50.8*	23	17.0	Cerebellum	Type II	1	—	No
25	5, F	ALL	18*	35	30.4	TL	Type III	2	—	No
26	5, F	Brainstem mass	54	26	21.0	Brainstem	Type II	1	FND	No
27	4, M	Medulloblastoma	84*	11	7.1	TL	Type III	1	—	No
28	4, F	ALL	24*	22	17.9	Brainstem	Type I	3	FND	No
29	4, M	ALL	18*	24	19.6	FL	Type II†	4	ICH, seizure	No
30	3, M	ALL	69*	15	11.5	Thalamus	Type II	2	ICH, FND	No
31	2, M	ALL	—*	20	18.0	TL	Type II	13	Seizure	No
32	—, M	Tonsils	—**	66	2.1	Brainstem	Type I	1	ICH	Yes

ALL = acute lymphocytic leukemia; AVM = arteriovenous malformation; FL = frontal lobe; FND = focal neurological deficit (nonhemorrhagic); ICH = intracranial hemorrhage; OL = occipital lobe; PL = parietal lobe; PNET = primitive neuroectodermal tumor; SCC = squamous cell carcinoma; TL = temporal lobe.

* Whole-brain radiation with or without a local boost.

† Developmental venous anomaly associated with R1CM.

‡ R1CM completely resected.

§ Stereotactic radiosurgery.

¶ Proton beam therapy.

** Unknown radiation modality.

FIG. 1. Kaplan-Meier plot of time from radiation treatment until the development of a first CM.

acquiring the appearance of a Type II CM, but remained solitary and asymptomatic until an acute symptomatic hemorrhage at age 34 (Fig. 2B). This hemorrhage was managed conservatively. A GRE abnormality appeared in the left pons at age 35 (Fig. 2C) and then bled acutely at age 37. At the time of her second hemorrhage, a third GRE abnormality appeared in the subcortical white matter near the head of the left caudate (Fig. 2D). This lesion has not yet bled. She has no known family history of CM and is not of Hispanic descent. Her multiple CMs are presumed to be caused by radiation therapy.

Discussion

We found that RICH may occur in the brain or spinal cord, with latency to CM diagnosis inversely correlated with age at radiation treatment. A comparison of patients with RICH to those with nonradiation CM showed that RICHs were diagnosed at a younger age, were less likely to be symptomatic at the time of diagnosis, and were more likely to be multiple CMs. Importantly, the prospective risk of hemorrhage in patients with RICH was similar to that in nonradiation CM, except for those that were initially asymptomatic at presentation.

Several reports suggest that children are more susceptible than adults to the development of RICHs,^{16,19,20,22,27,33} and some authors have demonstrated an inverse relationship between radiation dose and latency to RICH diagnosis.^{16,20} Strenger and colleagues, who reported 8 RICHs in a series of 171 pediatric patients with cancer, found RICH to be more likely and have shorter latency if radiation therapy occurred in the first 10 years of life.³⁶ Taking together patients of all ages with RICH, our finding of a median latency of 12 years from radiation therapy to CM diagnosis is consistent with data from Keezer and Del Maestro, who gathered the majority of previously reported RICH cases ($n = 84$) and added 1 of their own in a 2009 report in which the mean and median latencies were 10.3 and 8 years, respectively.²⁰

In a stratified comparison of pediatric and adult RICH, we found that radiation treatment at a younger age makes

TABLE 2: Clinical and radiological features of RICHs

RICH feature	Value
Median age at radiation treatment in yrs (IQR)	13.0 (6.0–30.0)
Median age at RICH diagnosis in yrs (IQR)	31.1 (23.1–54.7)
Median latency to RICH diagnosis in yrs (IQR)	12.0 (5.0–19.6)
Median radiation dose in Gy (IQR)	50.0 (30.6–60.0)
RICHs symptomatic at time of diagnosis (%)	15 (46.9)
RICHs symptomatic ever (%)	19 (59.4)
RICHs ever associated with symptomatic ICH (%)	14 (43.8)
RICH diagnosis on imaging obtained for symptoms not due to CM (%)	12 (37.5)
RICH diagnosis on surveillance imaging in absence of symptoms (%)	5 (15.6)
No. of RICHs at initial diagnosis (%)	
Single	19 (59.4)
Multiple	13 (40.6); mean 8.2
Associated venous angioma (%)	3 (11.1)*
Location of presenting or largest CM (%)	
Cortical	16 (50.0)
Frontal	2 (6.3)
Temporal	10 (31.3)
Parietal	3 (9.4)
Occipital	1 (3.1)
Supratentorial-subcortical	3 (9.4)
Basal ganglia	1 (3.1)
Thalamus	2 (6.3)
Infratentorial	12 (37.5)
Brainstem	10 (31.3)
Cerebellum	2 (6.3)
Spinal	1 (3.1)
Median total duration of follow-up in yrs (IQR)	22.5 (11.3–30.5)
Median duration of prospective follow-up in yrs (IQR)	4.3 (1.0–10.1)

IQR = interquartile range.

* Five patients did not have contrast-enhanced images available.

multiple RICHs more likely. Previous series have shown multiplicity of RICHs in 41%²⁰ to 63%¹¹ of affected patients, but did not show any correlation with age at radiation treatment. In most cases, symptoms could be attributed to a single dominant lesion.

It is unclear if the significantly younger age at diagnosis of RICH by more than a decade compared with nonradiation CM reflects a mechanistic radiation effect or is due to more frequent surveillance MR images in patients previously treated with radiation. Evidence for the latter was our finding that RICHs were less likely to be symptomatic at diagnosis than were nonradiation CMs (46.9% vs 65.8%, $p = 0.036$), and we found that the presence or absence of symptoms had a bearing on their clinical course.

Perhaps the most concerning feature of vascular malformations, CMs and RICHs included, is their risk of hemorrhage. In this paper we report the first prospective estimate of RICH hemorrhage risk. Prospective hemorrhage rates

TABLE 3: Comparison of adult and pediatric RICMs*

Patient or RICM feature	Adult RICMs (n = 13)	Pediatric RICMs (n = 19)	p Value†	Statistical Test
Median age at diagnosis of RICM in yrs (IQR)	49.4 (30.7–55.9)	24.0 (19.7–35.9)	0.008	t-test
Median latency to RICM diagnosis in yrs (IQR)	6.8 (2.8–11.6)	17.9 (10.4–28.9)	0.007	t-test
RICMs symptomatic at time of diagnosis (%)	5 (38.5)	9 (50.0)	0.524	Pearson chi-square
RICMs symptomatic ever (%)	8 (61.5)	10 (55.6)	0.739	Pearson chi-square
Symptomatic ICH ever (%)	7 (53.9)	6 (33.3)	0.253	Pearson chi-square
CM multiplicity (%)	3 (23.1)	10 (55.6)	0.139	Fisher exact
Cortical location of RICM (%)	6 (46.2)	10 (55.6)	0.605	Pearson chi-square
Supratentorial-subcortical location of RICM (%)	1 (7.7)	2 (11.1)	1.000	Fisher exact
Infratentorial location of RICM (%)	5 (38.5)	6 (33.3)	0.768	Pearson chi-square
Good functional level (mRS score 0–1) at time of diagnosis (%)	5 (38.5)	15 (83.3)	0.021	Fisher exact
Good functional level (mRS score 0–1) at last follow-up (%)	6 (46.2)	13 (72.2)	0.142	Pearson chi-square
Median total duration of follow-up in yrs (IQR)	12.1 (9.1–19.9)	28.8 (22.8–37.2)	0.000	t-test
Median duration of prospective follow-up in yrs (IQR)	3.1 (1.1–8.5)	4.8 (1.4–11.5)	0.232	t-test
Prospective risk of ICH (% per person-year)	9.2	2.0	0.355	z-test
Prospective risk of ICH if ICH at presentation (% per person-year)	4.9	5.3	0.984	z-test
Prospective risk of ICH if asymptomatic at presentation (% per person-year)	16.0	1.2	0.291	z-test

* Case 32 was excluded from all calculations in Table 3 because the exact age at radiation treatment was unknown.

† Values in bold are statistically significant.

for RICMs and nonradiation CMs were not significantly different if the manner of presentation was not taken into account. Previous work has shown that the risk of hemorrhage in nonradiation CMs is considerably higher if the CM has previously bled, especially in the first 2 years after hemorrhage.¹² Subgroup analyses comparing our patients with RICMs (n = 8) and patients with nonradiation CMs

(n = 75) with hemorrhage at presentation showed similarly elevated hemorrhage risk during the prospective period. For patients asymptomatic at the time of RICM (n = 17) or nonradiation CM (n = 103) diagnosis, hemorrhage risk was nonsignificantly higher for patients with RICMs (4.2% per patient-year) compared with patients with nonradiation CMs (0.35% per patient-year, p = 0.118).

TABLE 4: Comparison of RICMs and nonradiation CMs

Patient or CM feature	RICMs	Nonradiation CMs*	p Value†	Statistical Test
Median age at diagnosis of CM in yrs (IQR)	31.1 (23.1–54.7)	42.4 (27.4–60.1)	0.054	t-test
CM symptomatic at time of diagnosis (%)	15 (46.9)	167 (65.8)	0.036	Pearson chi-square
CM symptomatic ever (%)	19 (59.4)	169 (67.6)	0.353	Pearson chi-square
Symptomatic ICH ever (%)	14 (43.8)	90 (33.3)	0.241	Pearson chi-square
CM multiplicity (%)	13 (40.6)	38 (14.4)	0.000	Pearson chi-square
CM Type (%)				
I	7 (21.9)	33 (13.9)	0.235	Pearson chi-square
II	21 (65.6)	167 (70.5)	0.575	Pearson chi-square
III	3 (9.4)	37 (15.6)	0.438	Fisher exact
IV	1 (3.1)	0 (0.0)	0.119	Fisher exact
Associated venous angioma (%)	3 (11.1)	57 (21.1)	0.315	Fisher exact
Cortical location of CM (%)	16 (50.0)	154 (57.0)	0.448	Pearson chi-square
Supratentorial-subcortical location of CM (%)	3 (9.4)	38 (14.1)	0.593	Fisher exact
Infratentorial location of CM (%)	12 (37.5)	78 (28.9)	0.314	Pearson chi-square
Median duration of prospective follow-up in yrs (IQR)	4.3 (1.0–9.8)	6.0 (1.3–8.2)	0.996	t-test
Prospective risk of ICH (% per person-year)	4.2	2.3	0.556	z-test
Prospective risk of ICH if ICH at presentation (% per person-year)	11.0	5.5	0.529	z-test
Prospective risk of ICH if asymptomatic at presentation (% per person-year)	4.2	0.35	0.118	z-test

* Some data not available for every patient in the nonradiation cohort.

† Values in bold are statistically significant.

FIG. 2. Case 11. **A:** Axial T2-weighted MR images of the patient at age 31 show pontine atrophy without intraparenchymal signal abnormality (**left**) and a new asymptomatic area of mixed signal intensity (**arrow**) in the right parietooccipital region (**right**) consistent with a CM. **B:** The pons is still without evidence of CM on axial T2-weighted MRI at age 34 (**left**). Axial T2-weighted MRI shows acute hemorrhage from the right parietooccipital CM (**center**). Axial GRE MRI shows the same right parietooccipital hemorrhage and no evidence of abnormality in the left caudate (**right**). **C:** Axial T2-weighted MRI obtained at age 35 shows a new hypointense lesion (**arrow**) in the posterior left pons (**left**). Stable encephalomalacia related to prior hemorrhage is observed around the right parietooccipital CM (**center**). Axial GRE MRI is still without abnormality in the left caudate (**right**). **D:** Axial T2-weighted MRI at age 37 shows acute hemorrhage from the pontine CM (**left**). Encephalomalacia in the right parietooccipital region is unchanged (**center**). Axial GRE MRI shows a new focal hypointensity in the subcortical white matter (**arrow**) near the head of the left caudate (**right**).

Previous RICM series have reported a mixture of symptomatic (clinical) and asymptomatic (radiological only) hemorrhages occurring at rates of 40%²⁰ to 56%⁹ per patient. In a series of 6 children with RICMs, Larson and

colleagues reported symptomatic hemorrhage in 50%²² of patients, or 6.7% per patient-year if these were assumed to have formed *de novo* after radiation treatment. All previous reports of RICM hemorrhage risk have been retrospective calculations, which assume the lesions are congenital and may overestimate the risk of hemorrhage.

Radiation-induced telangiectasias (RITs) may have a similar MRI appearance to Type IV CMs (visible on GRE or SWI only), but there are no established radiological criteria to distinguish the two. Pathologically, telangiectasia and CM differ only in the presence or absence, respectively, of intervening brain parenchyma among the dilated, thin-walled vascular channels. Because of these similarities and because transitional forms of these vascular malformations have been observed in some patients, RIT and RICM have been proposed to exist along a spectrum driven by a common proliferative pathway.^{19,22,34} Consistent with the hypothesis that RIT precedes RICM, Gaensler and colleagues reported a series of 20 patients with RITs (6 proven pathologically) for whom the latency from irradiation to RIT development was 2.7 years (shorter than all series of RICMs) and hemorrhage risk was 25% per patient (lower than all series of RICMs).¹⁴

Due to their radiological similarities, it is possible that some of our patients harbored RITs rather than RICMs. We believe this is unlikely, however, because all of our patients except the patient with spinal RICM (Case 8) had a largest or symptomatic lesion with appearance of Type I, II, or III CM, which are radiologically distinct from RITs. While the total number of RICMs was preferentially counted on SWI and therefore may have included RITs and overestimated the multiplicity of RICM lesions, all of the other natural history data, hemorrhage estimates, and comparisons in our study were based on the largest or symptomatic lesion that, in all but the spinal case, was radiologically an RICM and not possibly an RIT.

Of note, two patients underwent radiation treatment as children (at ages 6 and 7 years) but were not diagnosed with CM until 54 and 61 years later. The radiation dose was unknown in both cases. Even though the CM appeared within the radiation port, it is possible that these were sporadic CMs unrelated to the previous radiation therapy. We believe this is unlikely, especially because the patient with the longest latency had two CMs within the radiation port, no CM anywhere else in the brain, and no family history of CMs. Also, RICMs have previously been reported as long as 52 years after cerebral irradiation for a posterior fossa astrocytoma.⁴ Finally, the statistically significant association between age at radiation treatment and latency to RICM diagnosis persisted even after these outlier patients were excluded from repeat analysis.

In several patients, a pattern of *de novo* appearance of RICM was observed. This pattern may provide clues to the pathogenesis of these lesions and may also represent a population in which future potential medical interventions could prove beneficial. More specifically, in Case 11, surgical removal of the symptomatic lesion would not have prevented the second hemorrhage, which arose from a separate brainstem CM that was not amenable to resection. Fasudil and simvastatin in murine models have been shown to disrupt RhoA activity in endothelial cells and

may thereby stabilize CMs. In future medication trials, this group of patients with prior brain irradiation who develop a small GRE or SWI lesion may be candidates for such therapy.

Limitations of our study include the retrospective nature of the chart review and its inherent biases. In the absence of prospective screening of all patients with previous radiation treatment, symptomatic RICMs are more likely to be detected and we cannot necessarily generalize our findings to all RICMs. Tertiary referral (selection) bias may have led to more significantly symptomatic patients; in particular, patients referred from neurosurgery may overrepresent hemorrhagic RICM. Finally, due to the evolution of MRI sequences over the time frame of this study, specifically SWI, we may have underestimated the number of patients with multiple lesions.

Conclusions

In this study we add 32 cases to the evolving literature on RICMs. These lesions occurred years after radiation treatment, with a longer latency and higher likelihood of multiplicity if radiation was administered at a younger age. Our prospective estimates of hemorrhage risk might inform surgical decision making in patients with CM. Initially asymptomatic RICMs have a natural history distinct from nonradiation CMs, and further study will be necessary to determine the most appropriate management steps to minimize their substantial risk of hemorrhage.

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