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CASE REPORT - BRAIN TUMORS

De novo cavernous malformation arising in the wall of vestibular schwannoma following stereotactic radiosurgery: case report and review of the literature

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Abstract

We report a novel case of a radiation-induced cavernous malformation developing in a vestibular schwannoma previously treated with stereotactic radiosurgery. Eleven years after treatment, the patient presented with a large predominantly cystic lesion in the cerebellopontine angle. We performed surgery, and a solid vascular lesion was identified within the schwannoma, which was determined to be a cavernous malformation after histopathological analysis. We review the literature of radiation-induced cavernous lesions, illustrating that while rare, these lesions do pose concern as a long-term complication of brain radiation therapy. We also discuss the possibility that radiation-induced cavernous malformation-like lesions are pathologically distinct from cavernous malformations.

Keywords Cavernous malformation · Radiation therapy · Stereotactic radiosurgery · Vestibular schwannoma

Abbreviations

SRS	Stereotactic radiosurgery
RICM	Radiation-induced cavernous malformation
CM	Cavernous malformations
CPA	Cerebellopontine angle
Gy	Gray
MRI	Magnetic resonance imaging
WBRT	Whole brain radiotherapy

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Background and importance

Whole brain radiation therapy is a mainstay of brain cancer treatment, and stereotactic radiosurgery (SRS) allows for targeted control of intracranial metastases and other brain tumors [4, 21]. However, these approaches can lead to radiation-induced cavernous malformations (RICMs), especially in children [6]. The majority of RICMs have been described following treatment of pediatric medulloblastomas and gliomas [12], and they are most frequently located in the deep white matter and frontal and temporal lobes [3]. Subarachnoid non-radiation-induced cavernous malformations (CMs) are also extremely rare [9], and to our knowledge, subarachnoid (or other extra-axial) RICMs have only been described in one study following gamma knife radiosurgery [20]. Furthermore, while RICMs are almost always within the radiation field [12], there are few reported cases of RICMs occurring within the tumor itself [6].

There are no reported cases of RICMs forming in the wall of a vestibular schwannoma following linear accelerator-mediated (LINAC) SRS, despite the fact that SRS has become a primary treatment option for vestibular schwannomas [15]. We report a novel case of successful surgical excision of an RICM that had formed in the wall of a vestibular schwannoma 11 years after LINAC SRS and review the literature

concerning both RICMs and CMs of the cerebellopontine angle (CPA) and subarachnoid space.

Clinical presentation

In 2006, a 42-year-old female patient presented with hearing loss and facial numbness. She had no significant family or medical history. The patient underwent magnetic resonance imaging (MRI), which revealed a 2.2 × 2.3 × 2.4-cm mass centered in her left CPA (Figs. 1 and 2). The patient was diagnosed with vestibular schwannoma and treated with 25 Gray (Gy) of Cyberknife (Accuray, California) LINAC SRS (five fractions of 5 Gy), treated to 70% isodose line and covering 95% volume. Following radiation treatment, the patient experienced a progressive decrease in tumor size and central cavitation as seen on follow-up MRI (Fig. 3).

However, in 2017, the patient developed increasing facial numbness. A follow-up MRI showed a large cystic lesion with peripheral enhancement that was likely putting pressure on her trigeminal nerve (Figs. 4 and 5); this lesion had increased in size within the cerebellopontine angle compared to prior imaging, and a more solid component was noted at the upper pole of the tumor in proximity to the trigeminal nerve.

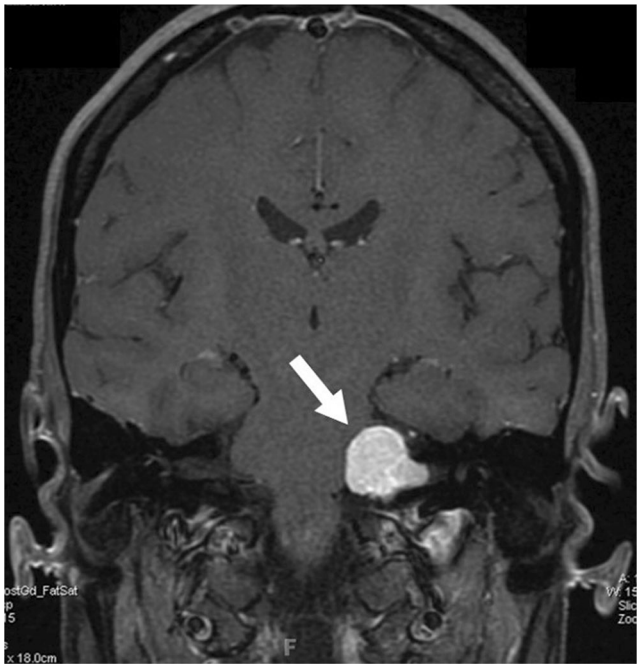

Fig. 2 Coronal T1-weighted post-contrast MRI from 2006 showing lesion (arrow) involving the left internal auditory canal (IAC) and left CPA; lesion is homogenous in enhancement

In retrospect, hemosiderin (blooming artifact), associated with focal nodular enhancement at the upper pole, was present on MRI (Fig. 6). Surgical exploration through a retrosigmoid craniotomy unexpectedly revealed a CM at the upper pole of

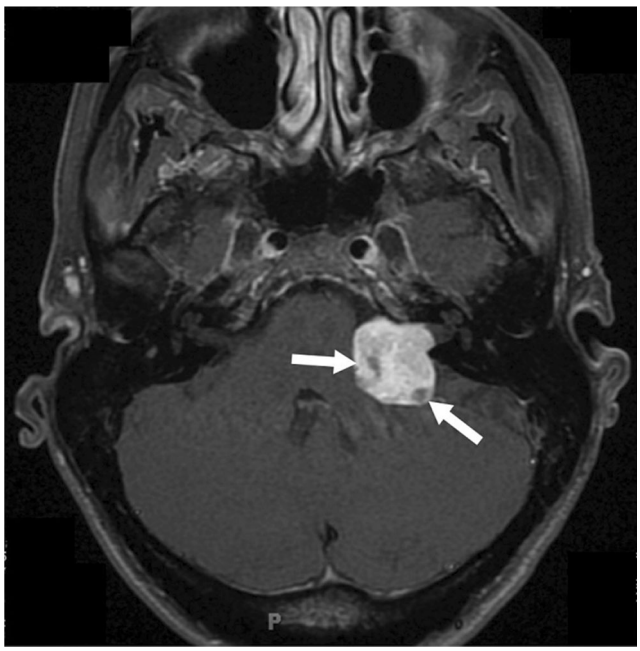

Fig. 1 Axial T1-weighted post-contrast MRI from 2006 demonstrating intensely enhancing lesion centered at the left cerebellopontine angle (CPA), widening the ipsilateral auditory canal, with indentation and medial displacement of the left middle cerebral peduncle and pons. Note the two relatively small areas of mild heterogeneous enhancement (arrows)

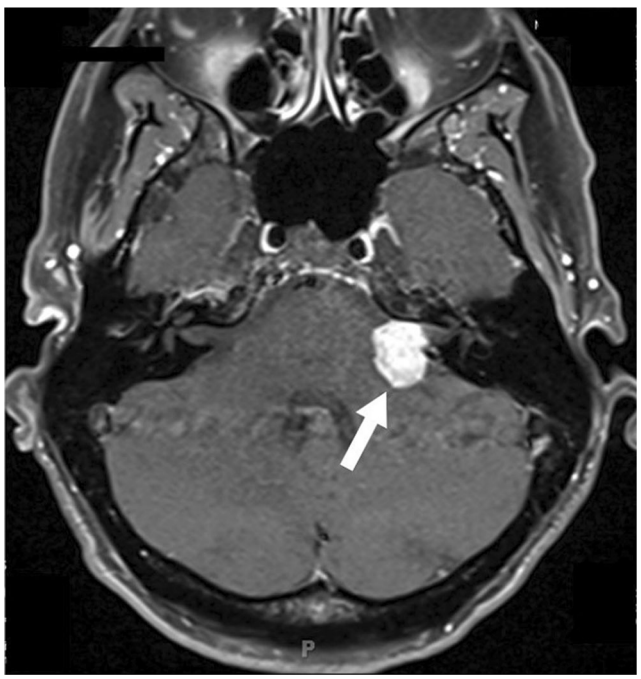

Fig. 3 Follow-up of 2006 treatment with stereotactic radiosurgery (SRS). Axial T1-weighted image demonstrates marked interval shrinkage of the tumor (arrow) with near total resolution of mass effect and compression of adjacent brain stem

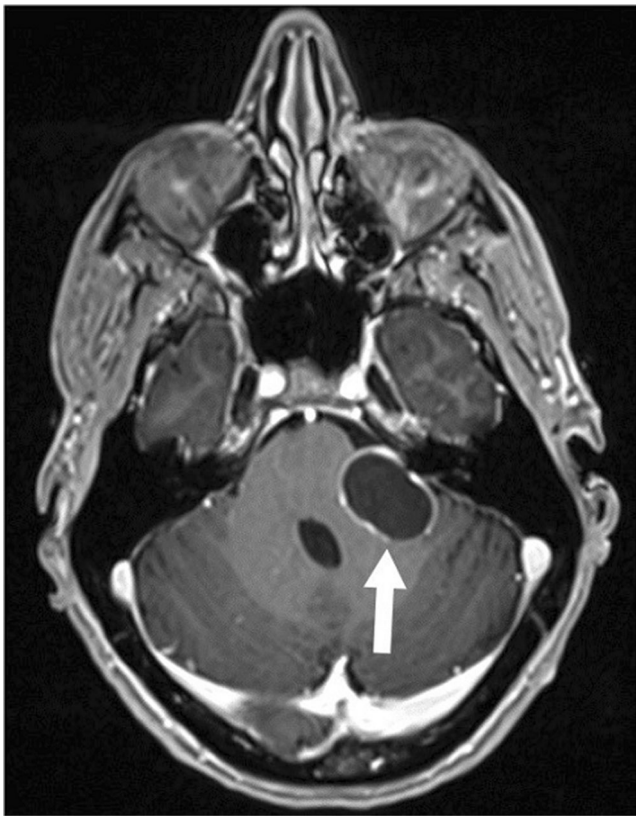

Fig. 4 Eleven years after SRS. Axial T1-weighted MRI slightly superior to IAC demonstrating interval development of a cyst-like lesion with peripheral enhancement (arrow) and central components isointense to cerebral-spinal fluid

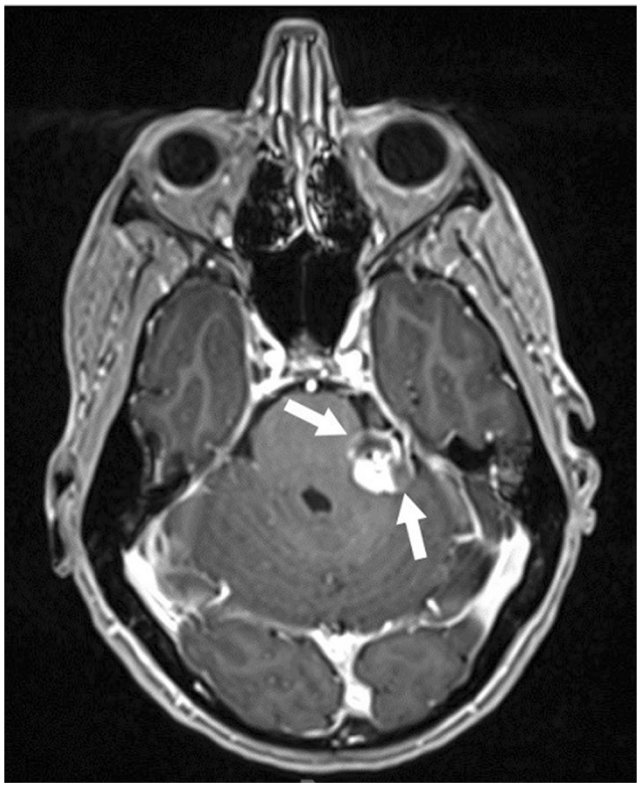

Fig. 5 Axial T1-weighted cephalad to Fig. 4 showing heterogeneous enhancement (arrows) suggesting cavernous malformation in the upper pole of the vestibular schwannoma

the tumor; the lesion was surgically removed and the cyst opened (Fig. 7). Following surgery, the patient's symptoms improved with no new deficits. The patient was discharged from the hospital 4 days after surgery with improved facial numbness and stable severe hearing loss. Histological analysis showed irregular channels with variably hyalinized interfaces, macrophages, and collagen at the interface with the schwannoma (Fig. 8a–e). At 3-week follow-up, the patient showed continued improvement.

Discussion

Our case provides insight into the development of RICMs in non-malignant tumors [16] and represents the first reported instance of a subarachnoid RICM following LINAC SRS. Our case also demonstrates typical signs of CMs on imaging that should be accounted for in treatment decisions, and the good outcome of the retrosigmoid approach for surgical resection. Below, we discuss the RICM location, the influence of radiation type and dose on RICM latency (Fig. 9), and the symptoms and treatment of CMs of the CPA.

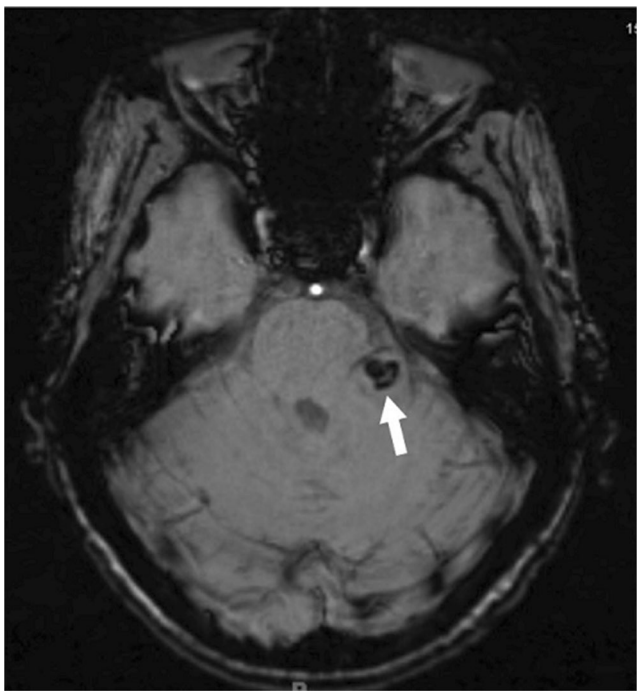

Fig. 6 Axial susceptibility-weighted MRI in 2017 showing susceptibility within the solid component of the tumor (arrow) suggesting hemosiderin deposition

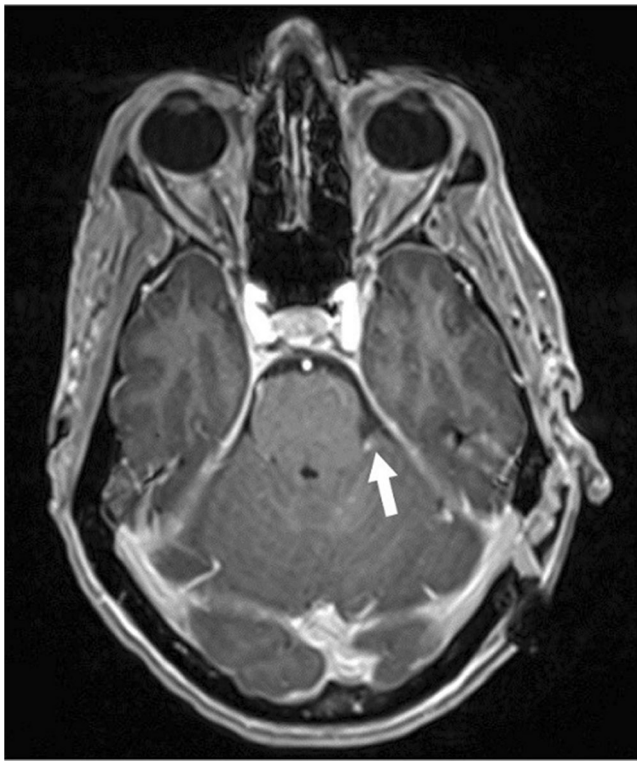

Fig. 7 Post-operative axial T1-weighted MRI demonstrating interval resection of the tumor (arrow)

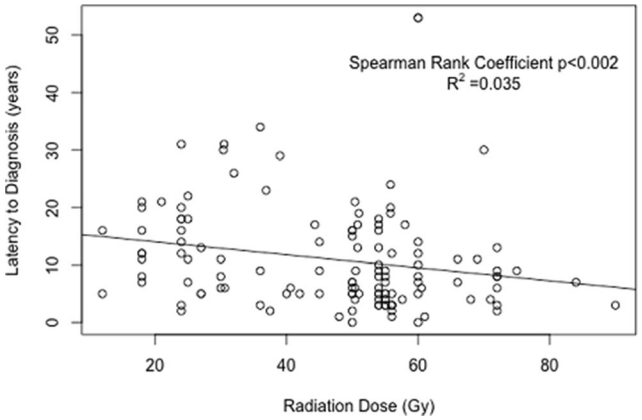

Fig. 9 One hundred twenty-five-case analysis showing an inverse correlation between total radiation dose and latency to RICM diagnosis

Literature review

We completed a literature review of RICMs reported since the most recent review was conducted by Keezer et al. in 2009 [6]; findings are aggregated in Table 1. We found 140 reported cases of RICMs in addition to our case, and collected data on the primary lesions, symptoms, locations, latency, and type and dose of radiation (Supplementary Materials, Table 2). RICMs occurred following SRS in 31 patients (22%), following whole brain radiotherapy (WBRT) in 59 patients (42%), and following targeted radiotherapy (defined as WBRT with a region-specific boost dose or region-specific radiation therapy apart from SRS) in 23 patients (16%); 27 cases (19%) did not specify the type of radiation treatment. The median age of patients at irradiation was 10.0 (range 1–78), the median RICM latency was 7.0 years, and the median radiation dose for cases with specific dose measurements was 42.5 Gy. Most primary tumors were medulloblastomas (39/140, 28%) or gliomas (30/140, 21%); of the 105 cases for which symptoms were reported, 11 had intracranial hemorrhage (11%), 22 had

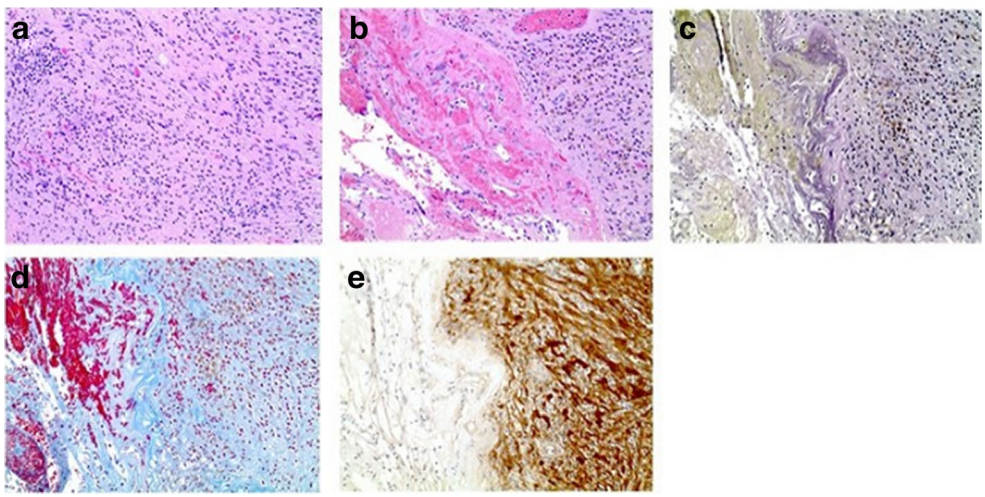

Fig. 8 Original magnification for all photomicrographs is × 200. **a** Hematoxylin and eosin (H&E) stain illustrating a typical region within the recurrent vestibular schwannoma. No vascular malformation is present in this panel. **b** H&E stain illustrating vascular malformation on the left, with irregular vascular channels with irregular endothelial lining and variably hyalinized interface with schwannoma (upper right portion of image), which contains an infiltrate of pigmented macrophages (arrow). **c** Elastic stains highlighting the boundary between vascular malformation (left) and recurrent schwannoma (right). **d** Trichrome stain demonstrating wispy blue collagen (arrow) at the interface between vascular malformation and schwannoma. **e** Immunohistochemical stain of S100 showing strong immunoreactivity within schwannoma (right) and no immunoreactivity in the vascular malformation (left)

Table 1 Patient characteristics

Median age at irradiation (range), years	10.0 (1–78)
Median latency (range), years	7.0 (0–61)
Patients receiving, *n* (%)	
SRS	31 (22.1)
Targeted radiotherapy*	23 (16.4)
WBRT	59 (42.1)
Not reported	27 (19.3)
Median radiation dose (range), Gy**	42.5 (12–84)
SRS dose	12.0 (11–32)
Targeted radiotherapy dose	54.0 (24–66)
WBRT dose	50.0 (12–84)
Median latency (range), years	
SRS latency	10.0 (0–27)
Targeted radiotherapy latency	6.0 (0–20)
WBRT latency	6.0 (0–31)
Initial lesion, *n* (%)	
Medulloblastoma	39 (27.9)
Glioma (incl. astrocytoma)	30 (21.4)
Acute lymphoblastic leukemia	8 (5.7)
Meningioma	6 (4.3)
Ependymoma	6 (4.3)
Germinoma	8 (5.7)
Burkitt's lymphoma	2 (1.4)
Carcinoma	7 (5.0)
Arteriovenous malformation	5 (3.6)
Cavernous malformation	2 (1.4)
Vestibular schwannoma	7 (5.0)
Trigeminal schwannoma	2 (1.4)
Other	18 (12.9)
Symptoms, *n* (%)‡	
Not reported	46
Asymptomatic	47 (44.8)
ICH	11 (10.5)
Cranial nerve deficit	22 (21.0)
Seizure	15 (14.3)
Headache	6 (4.3)
Ataxia	4 (2.9)
Location of cavernous malformation(s), *n*§	
Supratentorial	134
Frontal lobe	34
Parietal lobe	19
Temporal lobe	37
Occipital lobe	11
Basal ganglia	16
Thalamus	5
Internal capsule	3
Putamen	2
Other	7
Infratentorial	40
Brainstem	11
Pons	4
Midbrain	2
Cerebellum	9
Posterior fossa	6
Cerebellopontine angle	6
Prepontine cistern	2
Spine	1
Not reported	12

SRS stereotactic radiosurgery, *WBRT* whole brain radiation therapy

*This category includes WBRT with a boost dose targeted at a specific lesion, as well as all targeted radiotherapies other than SRS

**Exact SRS dose reported in only 3 cases, targeted radiotherapy dose in 10 cases, and WBRT in 25 cases

‡ For patients with multiple symptoms, all symptoms are reported. The denominator for symptoms does not include cases for which symptoms were not reported

§ For patients with cavernous malformations in multiple regions, all involved regions were reported; thus, region totals add up to more than the number of total patients

cranial nerve deficits (21%), and 15 had seizures (14%), though nearly half of patients were asymptomatic (47/105, 45%). Many patients had several lesions; of 161 RICMs, 134 (77%) were supratentorial; 1 (1%) was spinal, and 40 (23%) were infratentorial, mostly in the brainstem (11/40, 28%) or cerebellum (9/40, 23%) (see Table 1).

While the incidence of RICMs varies depending on age and tumor type, RICMs were generally found following treatment for primary brain tumors within 10 years in 34–43% of pediatric patients [3, 8]. In an observational study, over 60% of lesions were supratentorial and 30% were in the brainstem. Roughly 40% of patients had more than one RICM, and the majority of patients were male [2]. Another review added that 66% of patients were ≤ 10 years old at the time of radiation treatment; a correlation between multiple RICMs and age at radiation treatment has led to the theory that RICM formation could be a radiation-induced genetic mutation [12].

Statistical analyses

We did not find a significant correlation between latency and dose, age at irradiation, or sex. Average latencies were 10.0 years for SRS, 6.0 years for targeted radiotherapy, and 6.0 years for WBRT. Using a Mann-Whitney-Wilcoxon test, we found no significant difference in latencies across types of radiation therapy (SRS, WBRT, and targeted radiation). Dosages were not reported for all cases, and dosage variations may have influenced the latencies for SRS with respect to other treatments (Table 1). In most of the reviewed cases, radiation was reported as total dose, expressed in Gray. Dose per fraction would be a better parameter to report and analyze, as fractionation can impact the effect of overall radiation dose

on cells [11]. Therefore, future publications of RICMs or CM-like lesions should include dose per fraction and number of fractions.

Radiation-induced lesions within schwannomas

Post-radiation intratumoral CM has only been documented in one study prior to our case review [20]. Brain tumor vasculature is notable for tortuosity, hyperpermeability, and disorganized angiogenesis [17]. Increased endothelial necrosis and dose-dependent decreases in tumor vascular volume have been observed in tumors following SRS or other radiation therapies [14]. However, apart from increased rates of hyalinization [22], no RICM pathogenic factor such as fibrinoid necrosis, telangiectasia, or cavitary lesion creation has been recognized as typical of brain tumor vasculature. This may explain the extreme rarity of RICMs within tumors. Research concerning RICM formation within tumors is therefore lacking.

Cavernous malformations in the CPA

Our case represents the second study illustrating RICM found in the CPA, as most radiation-induced lesions are supratentorial and almost all are intraparenchymal [2]. However, rare instances of non-radiation-induced CMs have been reported in the CPA and subarachnoid space [18, 19]. Extra-axial RICMs have noticeably different features than intraparenchymal RICMs [13]. Non-radiation-induced CMs are linked to genetic predispositions and are generally multiloculated with hemosiderin rims; RICMs may have lower symptoms and hemorrhage rates [2, 3, 6, 8]. Non-radiation-induced CMs of the CPA are also extremely rare [9], but are associated with hearing loss in 87% of cases and progress rapidly, with subsequent facial paresis in 54% of cases [13]. Surgical resection is indicated to preserve facial nerve function, as many CPA CMs are tethered to the VII/VIII nerve complex [13]. There is a low rate of subarachnoid hemorrhage [14], and surgical resection of symptomatic and hemorrhagic lesions is found to have a high rate of positive outcomes [5].

Radiation-induced cerebrovascular complications

Growing evidence suggests that cerebrovascular changes induced by radiation may induce distinct lesions that are pathologically distinct from CMs. Radiation-induced CM-like lesions have been described as instances of chronic minor hemorrhage due to vascular injury that then underwent revascularization, forming a cohesive mass mimicking a CM [7]. Edema, vasodilation, necrosis, and gliosis occur after radiation treatment, which may lead to the formation of a CM-like lesion [1, 10, 20]. Neuroimaging features of CMs and radiation-induced CM-like lesions overlap. A recent study performed an investigation to compare the histological features of CMs to radiation-induced CM-like lesions [7]. Both radiation- and non-radiation-induced lesions contain adjacent vascular caverns with wall hyalinization and similar degrees of calcification. True CMs contain little interspersed glial tissue and frequently contain hemosiderin pigment and reactive gliosis at the perimeter. CMs also express CD34 in the channel perimeters and uniform ERG staining, indicative of vascular cell nuclei. In contrast, radiation-induced CM-like lesions typically have thinner, poorly defined walls and lack SMA immunoreactivity due to the absence of smooth muscle fibers. Most radiation-induced CM-like lesions express CD34 and more prevalent ERG in the organizing vascular spaces. Thus, radiation-induced CM-like lesions, including what have been traditionally and perhaps inaccurately termed RICMs, are pathologically distinct from non-radiation-induced CMs. In the present case, histological analysis showed irregular channels with variably hyalinized interfaces and macrophages with wispy collagen, characteristics more frequently observed in radiation-induced coagulum-like malformations [7].

Conclusion

To our knowledge, this case is the second reported case of an extra-axial RICM, and the first RICM following LINAC SRS for a vestibular schwannoma. After reviewing the literature, we found that treatment with SRS did not significantly affect RICM latency, when compared to treatment with WBRT and targeted radiotherapy. Surgical excision is recommended for symptomatic and hemorrhagic RICMs and has positive outcomes with high rates of symptom resolution.

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Compliance with ethical standards

Disclosures Kevin Kallmes holds equity in and works for Superior Medical Experts.

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study, formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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