Underappreciated delayed late complication of adult brain irradiation: development of cerebral cavernous malformations

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Background: Cerebral cavernous malformations (CCM) are an uncommon delayed late complication of brain radiotherapy in adults. **Aim:** Describe an adult treated for a malignant glioma with chemotherapy and radiotherapy who subsequently presented with multiple CCM. Methods: Case report and literature review of CCM. **Results:** Multiple CCM were discovered in an adult following presentation with a symptomatic intracranial hemorrhage. **Conclusion:** The occurrence of CCM is an unusual delayed late radiation side effect following treatment of CNS tumors. Gradient echo MRI should be considered as a standard sequence in patients with previously treated brain tumors.

Cerebral cavernous malformations (CCMs) are vascular lesions defined by abnormally enlarged vascular cavities without intervening brain parenchyma [1]. The prevalence of CCM is approximately 0.05% in the general population [1–3]. CCMs may occur in either a sporadic or familial form [1–7]. Additionally, CCMs are a rare consequence of brain irradiation administered to children [8–13]. We describe a case of multiple CCM in a Caucasian adult with a high-grade glioma occurring many years after initial brain irradiation and not apparent until presentation with a symptomatic intracerebral hemorrhage.

Case report

A normotensive 40-year-old Caucasian man with a previously treated left frontotemporal anaplastic astrocytoma presented with a cluster of seizures despite previous excellent control and new-onset headache, prompting repeat MRI (**Figures 1A–C**). He was diagnosed with an anaplastic astrocytoma 7 years ago, which was completely resected and image-verified. Following surgery, he received whole-brain irradiation (59 Gy) and adjuvant chemotherapy (carboplatin, vincristine and etoposide) for 6 months.

He had been followed neuroradiographically with standard spin echo (SE) MRI with and without contrast every 6 months with no evidence of tumor recurrence. The patient had been seizure-free since original surgery.

Repeat MRI scans following a cluster of seizures demonstrated a right frontal intracerebral hemorrhage that was suggestive of hemorrhage due to a CCM. Gradient echo (GRE) MRI was performed and was consistent with multiple CCM. Owing to symptomatic hemorrhage (new onset headaches and seizures), a decision was made to evacuate the hematoma (confirmed at time of surgery), which was accomplished uneventfully and without further seizures. The surgical pathology is illustrated in **Figures 2A & 2B**. The patient's family history is notable for the absence of epilepsy, cancer and cerebral vascular malformations. No genetic testing was performed for CCM [1–3], as the family history was unremarkable with respect to disease of the CNS and his racial background suggested a nonfamilial form of CCM.

Discussion

CCMs or hemangiomas are common and represent 10–20% of all cerebral vascular lesions [1]. Symptomatic disease is considerably less common. Single or multiple CCMs may develop, which can lead to focal neurological deficits, hemorrhagic strokes, seizures or death. The natural history of CCM is best defined for sporadic forms, although recent studies have characterized the familial pattern [1–7]. Familial CCMs have been characterized genetically and three loci are presently identified (**Table 1**). The *de novo* development of CCM after brain irradiation in children is uncommon but well recognized and often multiple [8–13]. Similar reports in adults are sparse. Postradiotherapy CCM is most closely aligned with the familial form and appears to be a dynamic vascular process radiographically with the appearance of acute hemorrhage (as in our patient), frequent changes in the size and signal intensity of pre-existing CCM and the appearance of new CCM. Studies of patients with the familial form of CCM suggest that the appearance of new lesions occurs at a rate of 0.4 lesions per year [4–7]. The rate of appearance of new lesions in postradiation forms is unknown, but is likely to be similar. In both sporadic and familial forms, the single

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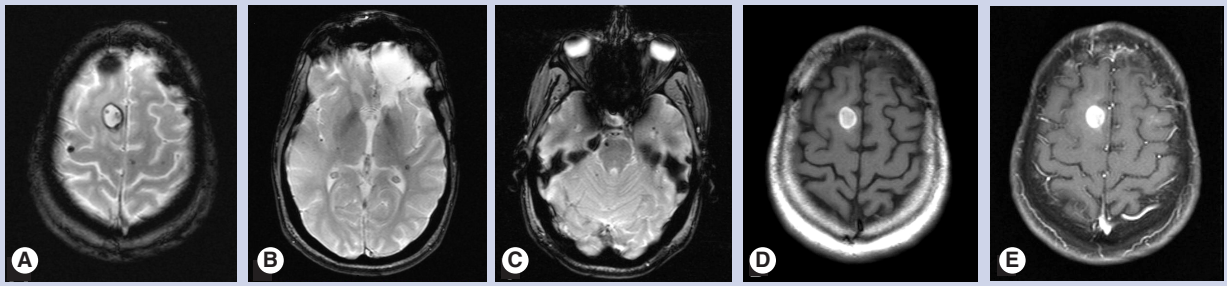
Figure 1. MRI sequences of multiple cerebral cavernous malformations.

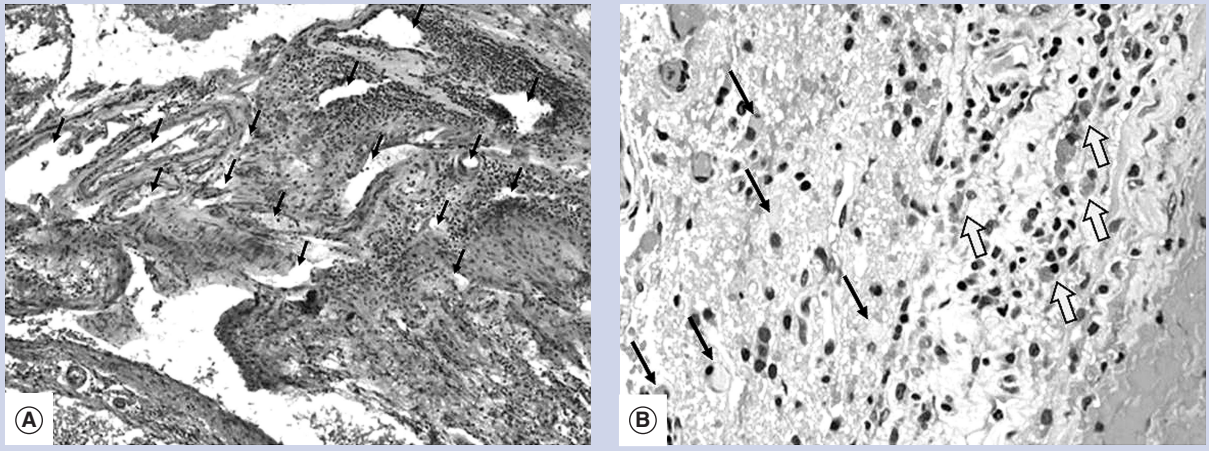


(A) Gradient echo axial images revealing a mesial right frontal high-signal intensity well circumscribed lesion with a hemosiderin rim. **(B)** Gradient echo axial images revealed scattered areas of hemosiderin deposition throughout both hemispheres indicative of multiple cavernous malformations. **(C)** Gradient echo axial image again revealing multiple foci of cavernous involvement and also a focus in the right pons. **(D)** Spin echo axial T1W noncontrast image demonstrating right frontal intracerebral hemorrhage. **(E)** Spin echo axial T1W contrast-enhanced image demonstrating right frontal intracerebral hemorrhage.

lesion hemorrhage rate is similar (i.e., 0.6% per year) [4–7]. However, in both the familial and post-radiotherapy CCM, multiple lesions are common (mean number of lesions in familial CCM is seven) and consequently, the annual hemorrhage rate is 0.6% multiplied by the number of CCMs identified by MRI. Therefore, the annual risk for hemorrhage may be substantial in patients with multiple CCM.

Zabramski *et al.* have suggested a MRI classification of familial CCM that includes four types (I–IV) [4,15]. Differentiation is based on signal characteristics seen with either SE or GRE MRI (Table 2). Our patient had Type IV lesions that were apparent only when GRE MR was performed. The histopathology of these lesions is not certain and Rigamonti has suggested that these may represent either CCM or capillary telangiectasia, lesions they consider a spectrum within a single pathological entity [16]. The natural history of these lesions (Type III and IV) may be different from those described above, which are based on Type I and IV lesions.

Figure 2. Histopathology of a resected hemorrhagic cerebral cavernous malformations.



(A) The specimen consisted of a collection of dilated vascular channels of varying caliber (arrows). The vessels are predominantly venous with hyalinization of the walls and lack of elastic laminae. There is minimal intervening glial tissue with reactive changes and a chronic inflammatory infiltrate. Haematoxylin and eosin stained section. Original magnification ×40. **(B)** At its periphery the lesion has a rim of gliosis with scattered gemistocytic astrocytes (black arrows) as well as deposits of hemosiderin both within the parenchyma and within macrophages (white arrows). Haematoxylin and eosin stained section. Original magnification ×100.

Table 1. Familial cerebral cavernous malformations.

Type	Chromosome	Gene product	Incidence (%)
CCM 1	7q	Krit 1	40–50
CCM 2	7p	Malcaverin	12–15
CCM 3	3q	PDCD 10	40

CMM: Cerebral cavernous malformations; PCDC: Programmed cell death.

Far less is known regarding postradiation CCM (as compared with sporadic and familial CCM) and in particular their etiopathogenesis [8–16]. The *de novo* development of cavernous hemangioma after brain (or spine) irradiation in adults for astrocytic tumors is uncommon [8–11,14,16]. Most *de novo* postradiation CCM cases described are in the pediatric literature. The authors are not aware of any reported cases of CCM without prior radiotherapy (nearly always administered as a large treatment field, i.e., whole brain). Not known is whether concomitant or postradiotherapy chemotherapy amplifies the effect of radiotherapy resulting in CCM; however, gliomas are predominantly treated with alkylator-based chemotherapy, therapy that is not generally considered neurotoxic. A dose of radiotherapy may affect time to appearance of CCM with shorter CCM induction time for higher doses of radiotherapy (i.e., brain radiation doses >30Gy) [8–11]. As stated above, postradiation CCMs are most often observed in young patients. This may reflect the enhanced radiation neurotoxicity in the growing brain, longer survivorship following brain radiotherapy used in the treatment of acute lymphoblastic leukemia, medulloblastoma or low-grade glioma and the time required for appearance of CCM. The time course between administration of radiotherapy and appearance of CCM is unknown, but has been estimated at 4–5 years [8–11]. Capillary telangiectasia, commonly seen following radiotherapy, are seen earlier than CCM (mean time to appearance 1–2 years) and may represent the earliest proliferative radiation-induced vasculopathy, which, as mentioned above, then evolve into CCM [17]. The delay in recognition of CCM may, in part, reflect the insensitivity of standard SE MRI most often employed to monitor such patients.

Intracerebral hemorrhage in a patient with a prior history of malignant gliomas is most often a reflection of the primary disease. However, in patients with glioma and a hemorrhage at a site distant from the primary tumor, CCM should be considered. CCMs are best visualized with GRE MRI, a MR sequence not commonly used at all centers in the management of patients with previously treated gliomas. Whether to incorporate GRE MRI as part of standard imaging follow-up for patients treated with gliomas is uncertain, as clinical management of multiple CCM is poorly defined. Utilizing GRE MRI in patients with previously irradiated gliomas may permit better identification of this entity and answer questions as to frequency, evolution and conversion from asymptomatic to symptomatic CCM.

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Table 2. Magnetic resonance characteristics of cerebral cavernous malformations.

Type	Magnetic resonance signal	Pathology
I	SE T1: hyperintense core SE T2: hyperintense or hypointense core	Subacute hemorrhage
II	SE T1 : reticulated mixed core SE T2 : reticulated mixed core (popcorn) with surrounding hypointense rim	Hemorrhage and thrombosis of varying age
III	SE T1: iso or hypointense SE T2: hypointense lesion with hypointense rim	Chronic hemorrhage with hemosiderin staining within and around lesion
IV	SE T1 : not seen SE T2 : not seen GRE : punctate hypointense lesion	Tiny lesion May represent CCM or capillary telangiectasia

CCM: Cerebral cavernous malformations; GRE: Gradient echo; SE: Spin echo MRI sequence.
Adapted from [4].

Executive summary

- A case report of an adult treated with brain-directed radiotherapy who developed a symptomatic intracranial hemorrhage secondary to the development of multiple cerebral cavernous malformations (CCMs).
- The occurrence of CCM is an unusual delayed late radiation side effect and is most often reported following treatment of childhood brain tumors.
- Radiation-induced CCMs, similar to familial CCMs, are multiple and evolve over time.
- Gradient echo MRI should be considered as a standard MRI sequence in patients with previously treated brain tumors.

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