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Case Report

Bilateral cavernous malformations resulting from cranial irradiation of a choroid plexus papilloma

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We report a case of multiple parietal cavernous malformations in a thirteen year old female who received cranial irradiation following incomplete resection of a choroid plexus papilloma. The cavernous malformations, which developed within the prior parietal radiation ports, were diagnosed nine years after the patients' radiation treatment when the patient presented with increasing frequency of seizures. Family history was negative for familial cavernous malformations. Due to the worsening frequency of seizures, the patient underwent resection of these two cavernous malformations with diagnosis confirmed by pathology. Post-operative, there was a significant reduction in seizure frequency. The origin and pathophysiology of cavernous malformations remains controversial. Cranial radiation treatment for tumors, particularly in children, may possibly lead to the development of these lesions, as occurred in this case. This is, to our knowledge, the first case of multiple cavernous malformations occurring within a previous radiation field following radiotherapy for a neoplasm. [Neurol Res 1998; **20**: 529–532]

Keywords: Cranial irradiation; cavernous malformation; pediatric; tumor

INTRODUCTION

Cavernous malformations are a class of vascular malformations that are angiographically occult, but have a propensity to bleed, provoke seizures, and/or enlarge with time^{1,2}. Recent literature on cavernous malformations in pediatric populations focuses on their origin, natural history, and treatment^{2–11}. While all the pediatric series are small, there appears to be a subset of children with cavernous malformation who have had previous cranial irradiation for a brain tumor. Others have proposed that the radiation resulted in the formations of these cavernous malformations^{2,3,12,13}. We report the case of a thirteen year old female treated with cranial irradiation following a subtotal resection of a choroid plexus papilloma. She developed bilateral cavernous malformations and the residual choroid plexus papilloma were successfully removed, with the patient retaining a stable neurologic exam.

CASE REPORT

A female presented at one year of age with lethargy and emesis. Neurologic exam was notable for a bulging anterior fontanelle. The remainder of her general exam and all lab tests were normal. She was evaluated at an outside institution with a CT scan which showed hydrocephalus secondary to a tumor located in the trigonal region of the left lateral ventricle. No cavernous malformations were noted at this time.

The patient had a subtotal resection of the tumor performed through a left parietal craniotomy. Pathology was consistent with a choroid plexus papilloma (*Figure* 1). The patient improved post-operatively with resolution of emesis and lethargy, but had persistent hydrocephalus requiring placement of a ventriculo-peritoneal shunt. She subsequently developed seizures and was placed on anticonvulsants with good response. The patient was referred for cranial irradiation, and received 3600 GyE over a six week course. Her radiation was given by bilateral opposing transparietal radiation ports. She was subsequently followed with serial MRI scans every one to two years, with no reports indicating the presence of cavernous malformations.

Nine years following cranial irradiation the patient developed headaches associated with an increase in seuzure frequency and presented to our institution. An MRI scan was notable for the new appearance of bilateral lesions within the parietal lobes along the path of the cranial irradiation. These had the characteristic appearance of cavernous malformations, with T1 central hyperintensity surrounded by a hemosiderin ring (*Figure 2*). Family history was negative for any other members with cavernous malformations. Due to increasing

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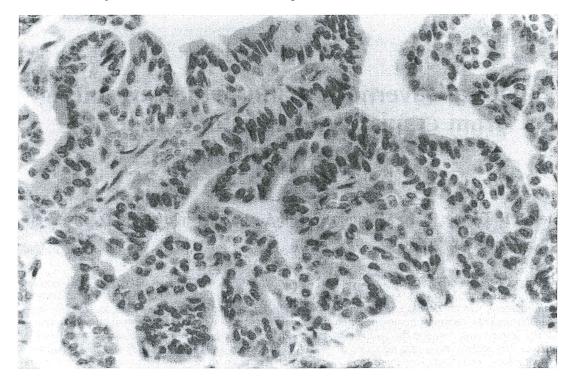


Figure 1: Photomicrograph of the tumor reveals features of a choroid plexus papilloma. H & E, magnification ×160

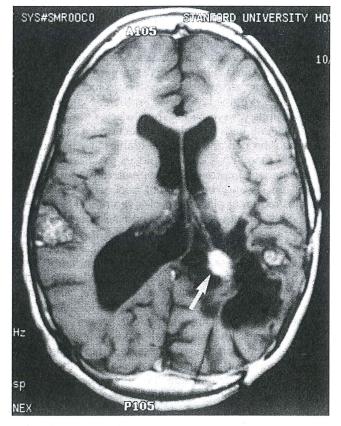


Figure 2: Follow-up MRI scan nine years following the patients cranial irradiation showed bilateral cavernous malformations, seen on a gadolinium enhanced axial T1 image. Residual choroid plexus papilloma is shown (arrow)

number of seizures despite adequate trials of anticonvulsants, and the possibility of a future clinical hemorrhage, the patient underwent resection of both of the cavernous malformations and the residual choroid plexus papilloma through two staged surgeries. Pathology confirmed cavernous malformations (*Figure 3*). Currently, she remains mildly developmentally retarded with a marked decrease in her seizure frequency.

DISCUSSION

Cavernous malformations, originally described by Crawford and Russel in 1956¹, were, until recently, thought to be rare in the pediatric population. The advent of new imaging techniques, including CT and MRI scans, led to an increase in the identification of these lesions³⁻¹¹. Despite the better recognition of these lesions, their origins remain unclear. In some cases, cavernous malformations are congenital, particularly in the familial forms and those lesions occurring in young in-fants^{6,10,14,15}. Others have proposed that the majority of cavernous malformations in both adults and children are acquired². Several reports of cavernous malformations that developed after cranial irradiation for tumors have been discussed^{2,3,12,13,16,17}. Ciricillo reported on a series of 37 children with cavernous malformations treated over a 10-year period³. Seven of these patients had previous cranial irradiation. The average radiation dose administered was 4.9 GyE (range 2.4–7.2 GyE), the average patient age was 5.8 years (range 2-12), and the average time from cranial irradiation to identification of the cavernous malformation was 6.1 years (range 1.5Cavernous malformation resulting from tumor irradiation: Steven D. Chang et al.

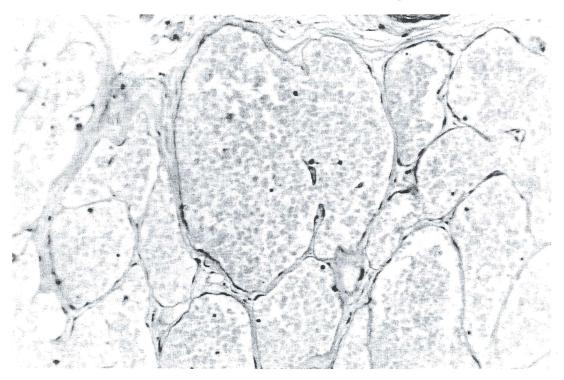


Figure 3: Photomicrograph showing the cavernous angioma with back to back vascular channels without internal elastic lamina and without intervening neural parenchyma. EVG, magnification $\times 100$

16). Only one of the seven patients was symptomatic (hemorrhage). Pozzati reviewed his series of 145 cavernous malformations, and focused on 18 patients with cavernous malformations that demonstrated aggressive behavior based on *de novo* appearance, growth, or recurrent overt bleeding¹⁷. Three of these patients (2 children) had been previously treated with cranial irradiation for tumors; a fourth patient treated with stereotactic radiosurgery while a teenager developed a *de novo* cavernous malformation. Additionally, a cavernous malformation has been implicated in a case of an apoplectic intracerebral hemorrhage that occurred 7.5 years following irradiation for a nasopharyngeal tumor¹³.

In this patient, bilateral cavernous malformations developed along the path of her radiation treatment. Previous MRI reports, obtained to follow the residual choroid plexus papilloma, failed to demonstrate any cavernous malformation. The dose of radiation received, the age of the patient, and the interval from radiation to development of both cavernous malformations all mirror those cases reported by Ciricillo. The patient, however, is to the best of our knowledge, the only reported pediatric case demonstrating the development of multiple cavernous malformations following cranial irradiation. The presence of bilateral cavernous malformations corresponding to the opposing parietal radiation ports strengthens the likelihood of de novo cavernous malformation development secondary to cranial irradiation. If children are at risk of developing such malformations following radiotherapy, they may require serial MRI

scans every one to two years for at least ten years to rule out the development of any cavernous malformations. Whether the frequency of cavernous malformation development is enough to warrant serial scanning of most children after radiotherapy is unknown.

The pathophysiology of the development of these cavernous malformations is unclear. Some authors have proposed that radiation induced capillary proliferation and fibrinoid necrosis of vascular walls leads to development of cavernous malformations². Microhemorrhages from friable, radiation-treated vessels may induce angiogenic factors resulting in vascular malformation development^{16,18}. Perivascular lymphocytes, thought to have anticoagulation potential, are common within the walls of radiated vessels, and may contribute to cavernous malformation growth². The case report of an apoplectic intracerebral hemorrhage that occurred 7.5 years following irradiation for a nasopharyngeal tumor supports these findings¹³. Further studies are needed, as only a few pathologic reviews have been reported.

The treatment for cavernous malformations is less controversial, with surgery being the method of choice. Pediatric cavernous malformation series have shown that children with previously undiagnosed cavernous malformations present with hemorrhage (27-45%), seizures (35-45%), and progressive neurologic deficits $(11-19\%)^{3,5}$. For these reasons, complete surgical excision is the goal of treatment^{2,11,19}, with the exception of lesions located in surgically inaccessible regions. Investigators have commented that radiation

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induced cavernous malformations may have a more benign clinical course, noting that seizures are much less common in this subset of patients, and hence recommend withholding surgery until symptomatic hemorrhage occurs³. Yet others report that the natural history of these *de novo* cavernous malformations are aggressive, with hemorrhages early in the clinical course¹⁷. In light of the persistent seizure disorder in our patient, and given prior reports of hemorrhage in these radiation-induced cavernous malformations^{3,13}, resection was performed. Radiosurgery is proposed as a treatment for cavernous malformations^{20,21}, but given the uncertain natural history of these lesions after radiosurgery^{22–25}, and the above reports of radiation induced cavernous malformations, it is not recommended for surgically accessible lesions.

CONCLUSION

While recent advances in imaging make cavernous malformations more common than previously thought, it appears that some cavernous malformations are acquired lesions. The present case of bilateral cavernous malformations along the path of cranial irradiation for the treatment of a choroid plexus papilloma provides a clear example of a likely causal relationship. Given the propensity of these cavernous malformations to cause hemorrhage, seizures, and progressive neurologic deficits, it may be prudent to follow children who have received cranial irradiation for intracranial tumors with serial MRI scans in order to detect and treat these lesions.

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