AVERNOUS malformations are vascular malformations composed of thin-walled, dilated capillary spaces with little intervening brain tissue. They occur in patients of all ages, but are relatively rare in children. Cavernous malformations are presumed to be congenital; however, this theory remains unproven. The lack of documented scientific information regarding the pathogenesis of cavernous malformations has hampered a clear understanding of their natural history.

In this study, we describe six cases of intracerebral cavernous malformations identified in patients after radiation therapy was administered to the brain for central nervous system (CNS) neoplasia. We review the treatment and clinical courses of these patients to understand more clearly the pathogenesis of cavernous malformations and the effect of radiation on their formation.

Clinical Material and Methods

In this retrospective review, six patients who were treated at the Children’s Hospital Medical Center between January 1988 and January 1995 were found to have developed a cerebral cavernous malformation after they received brain radiation therapy.

The patients (four boys and two girls) ranged in age from 2 to 15 years at the time of diagnosis of the neoplasia. Three patients had acute lymphocytic leukemia, two had a posterior fossa astrocytoma, and one patient had a posterior fossa medulloblastoma (Table 1). The treatment for these lesions varied: two patients underwent surgery and received radiation and chemotherapy; one patient underwent surgery and radiation treatment; and three patients received radiation and chemotherapy. The patients were followed clinically and radiographically at different intervals depending on the natural history of their disease.

Results

Six patients developed cavernous malformations after they underwent radiation treatment for CNS neoplasia (Table 2). The cavernous malformations were diagnosed 45 to 120 months after the radiation treatment: in two patients, the malformations were found incidentally on follow-up magnetic resonance (MR) images. Three patients...
presented with seizures and one patient with headaches. Three patients underwent surgical resection and three patients are currently being observed for their cavernous malformations.

**Illustrative Cases**

**Case 1**

This 6-year-old boy presented with erythematous skin lesions on his extremities. After hematological evaluation indicated he had acute lymphocytic leukemia, the patient was treated with chemotherapy and 1800 cGy of whole-brain radiation therapy (WBRT). He responded well to the treatment and stabilized in remission.

Eighty-seven months after completing the radiation treatment, the patient suffered a grand mal seizure followed by a brief loss of consciousness. When he awoke he had a right hemianopsia. Magnetic resonance imaging showed a left occipital lobe hemorrhage (Fig. 1 upper). The boy underwent surgical resection of the lesion; histological diagnosis showed a cavernous malformation next to an area of capillary telangiectasia (Fig. 2). Postoperatively, he had a partial right hemianopsia. He suffered another seizure 12 months later (99 months after radiation treatment). Magnetic resonance imaging revealed a lesion deep in the right parietal lobe with characteristics that were similar to the previous lesion and consistent with a cavernous malformation (Fig. 1 lower). This lesion was not present on previous MR images. The patient was treated with anticonvulsant medication for his seizures and is being followed with frequent neurological evaluations.

**Case 4**

This 9-year-old girl presented with a 3-week history of frontal headaches and vomiting. On examination she had bilateral papilledema and ataxia. Computerized tomography scanning of the head showed a posterior fossa mass extending into the fourth ventricle. Magnetic resonance imaging of the brain showed a mass in the posterior fossa that was suggestive of a medulloblastoma.

A gross-total resection of the lesion was performed and the histopathological diagnosis was medulloblastoma. Postoperatively, the patient received 3600 cGy of whole brain and spinal radiation with 5400 cGy radiation to the posterior fossa fractionated over 6 weeks. She received chemotherapy for 1 year after completion of radiation therapy.

The patient was followed closely with semiannual neurological evaluations and annual MR imaging studies. No cavernous malformation was present on the initial MR images (Fig. 3 left). At her 45-month follow-up evaluation, she was neurologically stable; MR imaging performed at that time showed an acute hemorrhage in her left temporal lobe adjacent to the temporal horn at the lateral ventricle (Fig. 3 center). This finding was thought to be either a cavernous malformation or disseminated medulloblastoma because it was located adjacent to the lateral ventricle. The patient has been followed with close observation and MR imaging studies. She remains asymptomatic and follow-up MR imaging performed at 63 months postsurgery shows evolution of the hemorrhage that is consistent with the natural history of a cavernous malformation (Fig. 3 right).

**Discussion**

In this study we document that intracerebral cavernous malformations can occur after radiation treatment of the brain for CNS neoplasia. We conclude that these findings show a correlation between radiation treatment and the pathophysiological development of cavernous malformations.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs),†</th>
<th>Gender</th>
<th>CNS Neoplasm</th>
<th>Symptom(s)</th>
<th>Treatment Location</th>
<th>Radiation (cGy), Location</th>
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<tbody>
<tr>
<td>1</td>
<td>6, M</td>
<td>ALL</td>
<td>erythematous lesions</td>
<td>RT/CT</td>
<td>1800, whole brain</td>
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<tr>
<td>2</td>
<td>2, M</td>
<td>ALL</td>
<td>coldlike symptoms, fever</td>
<td>RT/CT</td>
<td>2400, whole brain</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>7, M</td>
<td>ALL</td>
<td>fever</td>
<td>RT/CT</td>
<td>1800, whole brain</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>9, F</td>
<td>posterior fossa medulloblastoma</td>
<td>headache, vomiting</td>
<td>S-TR/RT/CT</td>
<td>3600, craniospinal</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>7, F</td>
<td>cerebellar astrocytoma</td>
<td>headache, vomiting, ataxia</td>
<td>S-TR/RT</td>
<td>5400, posterior fossa</td>
<td></td>
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<tr>
<td>6</td>
<td>15, M</td>
<td>pontine glioma</td>
<td>headache, diplopia</td>
<td>S-B/RT/CT</td>
<td>5400, posterior fossa</td>
<td></td>
</tr>
</tbody>
</table>

*ALL = acute lymphocytic leukemia; CT = chemotherapy; RT = radiation therapy; S-B = surgery: biopsy; S-TR = surgery: total resection.
† Age at diagnosis and treatment.

**TABLE 2**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Location of Malformation</th>
<th>RT Latency (mos)</th>
<th>Symptoms</th>
<th>Clinically Significant Hemorrhage</th>
<th>Treatment of Malformation</th>
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<tr>
<td>1</td>
<td>lt occipital</td>
<td>87</td>
<td>seizure, LOC, visual loss</td>
<td>yes</td>
<td>surgery</td>
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<td></td>
<td>rt parietal</td>
<td>99</td>
<td>seizure</td>
<td>yes</td>
<td>observation</td>
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<tr>
<td>2</td>
<td>multiple supratentorial</td>
<td>94</td>
<td>seizure</td>
<td>no</td>
<td>observation</td>
</tr>
<tr>
<td>3</td>
<td>rt parietal</td>
<td>120</td>
<td>seizure</td>
<td>yes</td>
<td>surgery</td>
</tr>
<tr>
<td>4</td>
<td>lt temporal</td>
<td>45</td>
<td>asymptomatic</td>
<td>no</td>
<td>observation</td>
</tr>
<tr>
<td>5</td>
<td>rt temporal</td>
<td>46</td>
<td>headache, vomiting</td>
<td>no</td>
<td>surgery</td>
</tr>
<tr>
<td>6</td>
<td>rt parietal</td>
<td>48</td>
<td>asymptomatic</td>
<td>no</td>
<td>observation</td>
</tr>
</tbody>
</table>

*LOC = loss of consciousness; RT = radiation therapy.
Effects of Radiation on Normal Brain

To explain how cavernous malformations might form after a patient has received radiation therapy, the known deleterious effects of radiation therapy on the normal brain must be considered. The early primary effect is vasogenic edema, which is secondary to increased capillary permeability and vasodilation. This effect can be recognized 1 to 6 weeks after radiation therapy.

The delayed effects of radiation are less well understood, but can include cerebral atrophy, white matter necrosis, demyelination, gliosis, and vasculopathy. Reports of mutagenesis resulting in meningiomas, gliomas, and sarcomas after radiation are well documented.

Vascular Changes Associated With Radiation

Vascular injury induced by radiation results from
Radiosurgery has recently been advocated for the treatment of cavernous malformations. Kondziolka, et al., reported a reduced risk of hemorrhage from cavernous malformations after stereotactic radiosurgery in which the mean age of the patient during treatment was 39 years. In our series, the mean age at presentation was 7.7 years for patients who developed cavernous malformations after they received radiation treatment for CNS neoplasia. This finding suggests that radiation may have a greater deleterious effect on the developing nervous system of a child than on the mature nervous system of an adult. Radiation may trigger the development of a cerebral cavernous malformation from a precursor lesion in children, but may actually stabilize a cavernous malformation in adults, protecting it from hemorrhage.

It was unclear if the cavernous malformations in our patients formed de novo in response to the radiation or if they had been present, but radiographically occult, at the time of radiation treatment and then hemorrhaged in response to it. Both concepts are possible and further studies are needed to clarify the cause. Radiation-induced cavernous malformations may result from a proliferative vasculopathy, which begins with capillary telangiectasias that are triggered by radiation injury to the cerebral microcirculation.

Genetic Defects in Cerebral Cavernous Malformations

Although the pathogenesis of cerebral cavernous malformations is unknown, genetic linkage studies have mapped a gene causing cerebral cavernous malformations to the CCM1 locus on the long arm of chromosome 7. Data from these studies were derived from a total of seven kindreds, four of which are composed of Hispanic Americans. Further linkage studies on non-Hispanic kindreds demonstrated the absence of linkage of cerebral cavernous malformations with the CCM1 locus on 7q21–22. This finding suggests genetic heterogeneity among cerebral cavernous malformations in which more than one locus may be involved in the formation of these lesions. It is unclear what role radiation may play in the steps between genetic mutation and phenotypic expression of cerebral cavernous malformations.

Differential Diagnosis

The presence of a new intracerebral lesion in cases of CNS neoplasia raises concern about the dissemination of neoplasia in the CNS. We have considered this possibility in some of our patients. Case 4 illustrates the difficulty in differentiating some cavernous malformations from disseminated disease. Magnetic resonance imaging is a sensitive modality for use in the diagnosis of cavernous malformations. A characteristic such as a peripheral rim of hemosiderin surrounding a reticulated core of heterogeneous signal is typical of a cavernous malformation. Because these malformations have little or no surrounding vasogenic edema, they can be differentiated from a hemorrhagic neoplasm.

Histopathological Composition of Cavernous Malformations and Capillary Telangiectasias

Cavernous malformations are compact vascular malfor-
Cavernous malformations after brain irradiation

The natural history of cerebral cavernous malformations is relatively benign. The incidence of hemorrhage from cavernous malformations varies from 0.25 to 0.7% per year. In our six patients with radiation-induced cavernous malformations, three patients (50%) developed a clinically significant hemorrhage. One patient (Case 1) required surgery for a focal deficit related to mass effect from the hemorrhage; one patient (Case 3) underwent surgery for an acute right parietal hemorrhage that caused mass effect and seizures; and the third (Case 5) underwent surgery because it was unclear whether the hemorrhage occurred in a metastatic lesion. Our current policy for patients who develop cavernous malformations after receiving CNS radiation therapy is to follow them clinically and radiographically with MR imaging unless the cause of the hemorrhage is unknown or the hemorrhage causes a neurological deficit that could be alleviated with resection. This policy is evolving as the natural history of cavernous malformations is better understood.

Conclusions

Cranial radiation is a common treatment for pediatric patients with CNS neoplasia. In this study, six patients developed intracerebral cavernous malformations after undergoing radiation treatment for CNS neoplasia. Our findings support the hypothesis that cavernous malformations can evolve from capillary telangiectasias and that this evolution may be induced by radiation. This concept should lead to a future clarification of the natural history of cavernous malformations and their treatment strategies.

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References


