Cavernous hemangiomas (cavernoma, cavernous angioma, cavernous malformation, cryptic vascular malformation) are mulberry-like assemblages of vascular sinusoids that are lined by a single endothelial layer. A lack of intervening parenchyma distinguishes these lesions from other types of vascular malformations. They contain blood products at various stages of thrombosis and degradation and are often surrounded by varied quantities of hemosiderin, gliosis and calcification. They may be found in any location in the central nervous system, including the spinal cord and ventricles. Cavernous hemangiomas have been found to be as prevalent as 0.6% in some large prospective cohorts.

These malformations were initially thought to be congenital, with some known instances of familial cases. In 1990, Wilson hypothesized that cavernous hemangiomas could be acquired following cranial irradiation. In 1994, Circillo et al presented seven such cases. A further 82 cases have since been described. However, in spite of the increasing number of cases considered to be radiation-induced, there is ongoing debate about whether these lesions represent a true acquired entity or whether they may represent previously misdiagnosed examples of congenital malformations.

The case of a 51-year-old man diagnosed with two acquired cavernous hemangiomas 17 years after cranial irradiation for a cerebellar astrocytoma is reported. A review of 84 cases of radiation-induced cavernous hemangiomas found in the literature is presented. In this series the mean age at the time of irradiation (±SD) was 10.4 ± 2.0 years (median = 8 years), while the mean time to cavernous hemangioma diagnosis (±SD) was 10.3 ± 1.9 years (median = 8 years). Time to cavernous hemangioma diagnosis was found to be inversely related to radiation dose. Hemorrhage from radiation-induced cavernous hemangiomas was found in 40.0% of patients, with an incidence of 3.9% per patient year. An inverse trend was identified between radiation dose and symptomatic presentation, cavernous hemangioma hemorrhage or surgical resection. This review of radiation-induced cavernous hemangiomas confirms that both younger patients and those who received a larger dose of radiation are at increased risk of radiation-induced cavernous hemangiomas. Our results suggest that, based on an assessment of CT or MR images, there may be an increased risk of hemorrhage when comparing radiation-induced to congenital cavernous hemangiomas. Increasing radiation doses appear to stabilize these lesions, decreasing the risk of a symptomatic presentation, cavernous hemangioma hemorrhage and surgical intervention.
reported cases the mechanism(s) of their formation is poorly understood.

This report describes the case of a man irradiated for the treatment of a cerebellar astrocytoma who, 17 years after treatment, demonstrated radiographic evidence of two distinct cavernous hemangiomas illustrating the long-term evolution of this disorder. Previous authors have suggested a relationship between radiation-induced cavernous hemangiomas to patient age and radiation dose. An increased incidence of hemorrhage in radiation-induced as compared to familial or sporadic cavernous hemangiomas has been commented on. However, these reports have included small numbers of patients which makes their results difficult to generalize to all patients with radiation-induced cavernous hemangiomas.

This report reviews the cases of radiation-induced cavernous hemangiomas reported in the literature. Using methods of statistical analysis, factors influencing: 1) the time interval between irradiation and the initial diagnosis of the cavernous hemangioma(s); 2) the number of identified acquired cavernous hemangiomas; 3) the presence of associated symptoms, cavernous hemangioma hemorrhage and the prevalence of surgical intervention have been assessed. The hypothesis that radiation induces cavernous hemangiomas via a two-hit mechanism, occurring in a variety of different radiation induced genetic micro-environments, involving both endothelial and other periluminal cells, is discussed.

**CASE REPORT**

A 14-year-old, right handed, boy presented to the Montreal Neurological Hospital in April, 1970 with sudden occipital headache and emesis followed by rapidly progressing somnolence. Angiography revealed a space-occupying lesion in the left cerebellar hemisphere. The patient underwent subtotal resection of a tumour, due to extension into the brainstem, and the neuropathological diagnosis was consistent with a Grade I cerebellar astrocytoma. As a result of the subtotal resection, the patient subsequently received a dose of 58 Gy to the residual tumour through opposing fields.

Follow-up CT scans performed in 1979 and 1984 revealed no evidence of any tumour progression. In 1987, 17 years after the initial irradiation, the patient complained of increasing difficulty walking as well as associated episodes of dizziness. Magnetic resonance imaging revealed a recurrent left hemispheric multicystic cerebellar tumour. A subtotal resection was performed in May, 1987 and neuropathology confirmed the presence of a recurrent Grade I cerebellar astrocytoma. The MRI also revealed two new, well-defined areas of increased signal intensity surrounded by regions of signal void in the right temporal and right parietal lobes (Figure 1). These were felt to be radiographically consistent with the diagnosis of cavernous hemangiomas. In 1988 the patient reported episodes of transient left temporal field blurring. In 1989 he began to have episodes of transient left hemianopsia associated with disturbances in left arm movement and sensation lasting five to ten minutes. In 2002,
32 years after his initial presentation, he suffered two generalized seizures. Since that time his seizures have been well controlled on anti-convulsant therapy. No hemorrhage or other changes in the cavernous hemangiomas have been identified since the lesions were initially diagnosed.

**Literature Analysis: Patients and Methods**

MEDLINE and EMBASE were searched (1966 to March 2006) using two keywords: cavernous hemangioma and radiation-induced neoplasms. Additional cases were included from the bibliographic references of the identified articles. Cases were included whether the cavernous hemangioma(s) were identified by histological examination or radiographic imaging.

The data collected from each case included: patient sex, age at irradiation, total radiation dose, presenting cavernous hemangioma symptoms, latency to cavernous hemangioma(s) diagnosis, number of cavernous hemangiomas identified, as well as the presence of hemorrhage on neuro-imaging and surgical intervention. When evaluating irradiation dose, the irradiation dose delivered to the area which subsequently gave rise to the cavernous hemangioma(s) was considered. Our assumption was that radiation-induced lesions require direct exposure to radiation in order to develop. Due to incomplete data present in the literature no distinction could be made between symptomatic and asymptomatic hemorrhagic events.

The Spearman rank correlation was used to explore the relationship between radiation dose and latency to diagnosis, as well as the age at irradiation and the latency to diagnosis. Statistical significance was defined as a p value <0.05.

The two-sided Wilcoxon rank-sum test was used to evaluate the relationship between latency to diagnosis, cavernous hemangiomas hemorrhage and the presence of multiple cavernous hemangiomas. The relationship between age at irradiation and hemorrhage or multiple cavernous hemangiomas was examined. The relationship between radiation dose and symptomatic presentation, cavernous hemangioma hemorrhage, surgical intervention or the presence of multiple cavernous hemangiomas were also assessed. Statistical significance was defined as a p value <0.05.

**Literature Analysis: Results**

Eighty-nine cases of radiation-induced cavernous hemangiomas were identified in the literature. Of these, five were excluded because they were not clearly identified and/or characterized by the authors. Thus, 85 cases were included in the analysis (84 derived from the literature, one from the current report) the details of which are described in Table 1. The demographics of these cases are summarized in Table 2. Two or more cavernous hemangiomas were found in 41% of patients. Forty percent of patients had evidence of hemorrhage on their investigations resulting in an estimated incidence of 3.9% per patient year [(34 events of hemorrhage)/(874 patient years of latency)]. Thirty-nine percent of patients underwent surgical intervention, predominately for the management of symptomatic cavernous hemangioma hemorrhage.

**Age at Irradiation and Time to Diagnosis**

Figure 2 illustrates the age distribution of the cases reviewed at the time of irradiation and the latency in years to cavernous hemangioma(s) diagnosis. Mean age at the time of radiation (±SD) was 10.4 ±2.0 years (median eight years) while the mean time latency to diagnosis (±SD) was 10.3 ±1.9 years (median eight years). Table 3 outlines the presenting symptoms of the 85 cases. Fifty-eight percent of patients were asymptomatic at the
Time Latency to Cavernous Hemangioma Diagnosis

There was a significant decrease in latency to diagnosis with increasing radiation dose, as demonstrated in Figure 3 (R² = 0.10, p = 0.015). Conversely, age at the time of tumour irradiation did not have a significant relationship with latency to diagnosis, as shown in Figure 4 (R² < 0.003, p = 0.124).

Symptomatology, Hemorrhage and Surgical Intervention

A significant inverse trend appeared to exist between radiation dose and the presence of symptoms, cavernous hemangioma hemorrhage or surgical intervention. Among those patients who presented without significant symptoms, the mean radiation dose ± SD received by each patient was 53.4 ± 14.4 Gy as opposed to 42.2 ± 16.3 Gy among patients who were symptomatic (p = 0.011). Those with no reported cavernous hemangioma hemorrhage received a mean radiation dose ± SD of 51.6 ± 15.7 Gy as opposed to those found to have cavernous hemangioma hemorrhage who had a mean radiation dose ± SD of 44.0 ± 16.0 Gy (p = 0.062). Finally, among those patients who did not undergo surgery, the mean radiation dose ± SD was 51.4 ± 15.9 Gy as compared to 43.9 ± 15.7 Gy among those who did undergo surgical treatment (p = 0.065).

Multiple Cavernomas

There was no significant relationship between the development of multiple cavernous hemangiomas and radiation dose, age at irradiation, or latency to diagnosis (p = 0.702, p = 0.103, p = 0.42).

Discussion

Cavernous hemangiomas are a well-recognized vascular malformation. Current research suggests that radiation-induced cavernous hemangiomas are common sequela of radiotherapy. In a recent series, Lew et al demonstrated a cumulative incidence of 5.6, 14 and 43% at three, five and ten years after irradiation in pediatric medulloblastoma patients.21 These results highlight the importance of gaining a better understanding of this disorder.

Age at Irradiation

Previous authors have proposed that children demonstrate a greater susceptibility to the development of radiation-induced cavernous hemangiomas.15,18,20,27,31 Our review confirms these findings. The average age at irradiation was 10.4 years (median age eight years). Of the 85 cases reviewed, only seven were patients irradiated at ≥20 years of age (8.2%), while 56 were irradiated at ≤10 years of age (65.9%). The reason that the immature brain rather than the adult brain responds to radiation by the more frequent formation of cavernous hemangiomas over extended periods of time is unknown. This could be related to a differential response of the immature brain to radiation injury in a background of vastly different gene expression profiles.23 It has
also been suggested that patients irradiated at younger ages develop cavernous hemangiomas at a faster rate (i.e. with a faster latency).\textsuperscript{15,35} Our study does not support this concept since it demonstrates that the age at irradiation bears no direct relationship to the latency to diagnosis. The fact that some pediatric CNS tumours tend to follow a more benign course may explain why the majority of radiation-induced cavernous hemangiomas occur in the young where the prognosis is sufficiently extended to allow for the consequences of radiation therapy to be fully realized.

**Radiation Dose**

Previous authors have demonstrated an inverse relationship between radiation dose and latency to diagnosis and our results are consistent with this finding.\textsuperscript{15} The proposed mechanisms include more extensive damage to nervous tissue with increasing radiation doses, hence the more rapid development of vascular malformations such as cavernous hemangiomas. However, increased radiation doses are associated with patients who are less likely to present with symptoms, to demonstrate evidence of cavernous hemangioma hemorrhage or require surgical intervention. This would suggest that patients who receive increased doses of radiation develop cavernous hemangiomas more quickly, but the cavernous hemangiomas that these patients do develop are less likely to have a significant impact on their clinical condition.

It has been suggested that low radiation doses are more efficient at inducing cavernous hemangiomas. The literature supporting this concept includes the observation that cavernous hemangiomas usually arise at the fringe of the main radiation field as opposed to the center, as seen in this case report.\textsuperscript{35} This potentially reflects the fact that the radiation delivered at the center of the field may result in extensive cellular apoptosis thus preventing subsequent cavernous hemangiomas formation. The periphery of the field is subject to radiation doses that alter genetic stability without substantial cell apoptosis.

**Hemorrhage**

Interest in radiation-induced cavernomas is related to the possibility that they represent a significantly greater risk of spontaneous hemorrhage than sporadic cavernous hemangiomas.\textsuperscript{14,20,28,31,35,36} The reported rate of hemorrhage among sporadic cases of cavernous hemangiomas has ranged from 0.25\% to 3.1\% per patient year.\textsuperscript{38-42} This review has found that 40.0\% of reported radiation-induced cavernous hemangiomas demonstrated evidence of hemorrhage on CT or MRI resulting in an incidence of 3.9\% per patient year. Because

| Table 2: The characteristics of the 85 cases of cavernous hemangiomas reviewed |
|----------------------------------|--------------------------|
| **Characteristic** | **Value** |
| Sex | 57.0\% male |
| >1 Cavernous Hemangioma | 41.2\% |
| Cavernous hemangioma hemorrhage | 40.0\% |
| Surgical intervention | 38.8\% |
| Radiation dose | Mean ±SD = 48.5 ±3.5 Gy  
Median = 54 |
| Age at irradiation | Mean ±SD = 10.4 ±2.0 yrs  
Median = 8 |
| Age at cavernoma diagnosis | Mean ±SD = 20.6 ±2.7 yrs  
Median = 17 |
| Latency to diagnosis | Mean ±SD = 10.3 ±1.9 yrs  
Median = 8 |

**yrs=years**

| Table 3: Presenting symptoms of the 85 cases of cavernous hemangiomas reviewed |
|----------------------------------|--------------------------|
| **Symptom** | **Prevalence** |
| Asymptomatic | 49 (57.6\%) |
| Seizure | 14 (16.4\%) |
| Headache | 8 (9.4\%) |
| Motor dysfunction | 6 (7.1\%) |
| Emesis | 5 (5.9\%) |
| Symptomatic hemorrhage | 4 (4.7\%) |
| Bulbar signs & symptoms | 4 (4.7\%) |
| Sensory dysfunction | 3 (3.5\%) |
| Syncope | 2 (2.4\%) |
| Back pain/stiffness | 1 (1.2\%) |
of an incomplete data set we were unable to quantify asymptomatic and symptomatic hemorrhages in this study. However the incidence of asymptomatic and symptomatic hemorrhage identified suggests that radiation-induced cavernous hemangiomas may be at greater risk of hemorrhage than congenital cavernous hemangiomas. In fact, our estimate of 3.9% per patient year is an under-estimation considering that these radiation-induced cavernomas almost certainly did not develop immediately following patient irradiation. Therefore during only a portion of those 874 years of latency (see results) was there a cavernoma to undergo hemorrhage.

A publication bias may exist where those patients with symptomatic hemorrhage are more likely to be reported in the literature. However, we believe that this bias would be small considering that post-radiation patients generally receive very thorough medical follow-up including repeat neuro-imaging.

Lew et al, in a large case series, suggested that the overwhelming majority of radiation-induced cavernous hemangiomas do not result in symptomatic hemorrhage and do not require surgical intervention. However, in addition to a small sample limited to medulloblastoma patients less than 21 years of age, the mean follow-up time in that case series was 7.2 years. This review demonstrates a mean latency to cavernous hemangiomas diagnosis of 10.3 years, implying that the follow-up period in Lew et al report may have been too short.

The very definition of hemorrhage remains controversial. Some authors have proposed radiological definitions while others have suggested that neurological deterioration should be used as an indicator of cavernous hemangioma hemorrhage, irrespective of radiographic evidence of hemorrhage. Although we acknowledge this controversy, we believe that radiological evidence of hemorrhage remains the most accepted means of detecting hemorrhage, the method used by all of the studies cited in this review.

**Multiple Cavernous Hemangiomas**

Results reported by Baumgartner et al supported the possibility that patients irradiated at younger ages are more likely to develop multiple cavernomas. Duhem et al suggested that certain patients develop multiple cavernomas due to genetic predispositions. This review demonstrates that multiple cavernous hemangiomas occur independently of age at irradiation, latency to diagnosis or radiation dose. These findings suggest that individual patient factors including genetic predisposition to radiation may be critical in the development of multiple cavernous hemangiomas.

Pozzatti et al have described two cases of cavernous hemangiomas with associated venous malformations. A possible association between these two vascular malformations and radiation has been previously reported. Unfortunately, the information present in the studies we reviewed does not allow us to make a comment on the frequency in which venous malformations are seen after radiation injury with or without the presence of cavernous hemangiomas.

**Etiology**

The data in the literature is most consistent with a two-hit hypothesis in the pathogenesis of radiation-induced cavernous hemangiomas. In mouse models, cavernous hemangioma have been shown to develop only after a gene mutation in CCM1/KRIT-1, one of the genes responsible for hereditary cavernous hemangiomas which is involved in endothelial cell-junction integrity, is associated with a second cellular mutation in p53, a tumour-suppressor gene involved in apoptosis.  

One possible model for radiation-induced cavernous hemangioma development would be that at the time of irradiation, some periluminal cells have a pre-existing mutation/alteration in the p53 gene resulting in a genetic susceptibility to cavernous hemangiomation. The irradiation then facilitates the development of this malformation by inducing a mutation in CCM1/KRIT-1 or another of the known (CCM2/MGC4607 and CCM3/PDCD10 genes) or unknown genes responsible for hereditary cavernous hemangioma development. Mutations in p53 are common in CNS neoplasms, with a prevalence ranging from 1% in medulloblastomas to 42% in low-grade astrocytomas. The higher rate of p53 mutations in low-grade astrocytomas may partially explain why cavernous hemangiomas have been found with a variety of low grade tumours. Cavernous hemangiomas have also been reported associated with low grade astrocytomas, oligodendrogliomas, schwannomas and a rare lesion called angioglioma.

A pre-existing genetic predisposition with a mutation or epigenetic alteration in CCM1, CCM2 or CCM3 gene(s) associated with a radiation-induced p53 mutation may also result in a genetic environment necessary for the development of cavernous hemangiomas. The possibility that both of these events could be induced by irradiation alone is unknown.

Another possible model of radiation-induced cavernous hemangioma pathogenesis may involve a germ line mutation in
CCM1 (or CCM2 and CCM3) that is associated with a radiation-induced somatic line mutation in one of these three genes. Gault et al demonstrated evidence in humans supporting a two-hit hypothesis where a cavernous hemangioma possessed both a germ as well as a somatic line CCM1 mutation.49

The hypothesis that radiation induced cavernous hemangiomas occur in a variety of different radiation induced genetic micro-environments involving both endothelial and other periluminal cells appears to be most consistent with the present knowledge base. The possibility that immunological mechanisms may be involved in the continuing growth of these lesions has been proposed.50

CONCLUSION

Cavernous hemangiomas are important sequelae of radiotherapy, particularly in the pediatric population. An understanding of the development and unique characteristics of radiation-induced cavernous hemangiomas is important for clinicians delivering radiotherapy, involved in subsequent patient medical follow-up and managing any discovered acquired cavernous hemangiomas. Further investigations, in the form of prospective clinical trials, are required to conclusively identify and characterize those patients who are at risk, the natural history of these acquired lesions and the most appropriate management.

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