

Incidental Resolution of a Radiation-Induced Cavernous Hemangioma of the Brain following the Use of Bevacizumab in a Child with Recurrent Medulloblastoma

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Key Words

Bevacizumab · Hemangioma, cavernous · Radiation-induced malformation

Abstract

Radiation-induced cavernous hemangiomas (RICH) are a known complication of radiation exposure, especially in young children. The current treatment approaches to these lesions include observation and surgical resection. We report the case of a 4-year-old male with recurrent medulloblastoma who had resolution of an incidental RICH lesion while being treated with bevacizumab for his recurrent brain tumor. There was no evidence of worsening hemorrhage with this therapy and the RICH did not recur upon discontinuation of the chemotherapy regimen. This is the first documented case of a RICH lesion responding to antiangiogenic therapy, suggesting the possible use of this class of agents in the treatment of symptomatic patients who are not considered appropriate candidates for surgical resection. Although the risk of bleeding must be taken into consideration, antiangiogenic therapies have the potential to be a novel treatment modality for symptomatic RICH lesions.

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Introduction

The overall survival of all childhood brain tumors is approximately 74% at 5 years, therefore close monitoring for long-term sequelae is of great importance [1]. One of the main treatment modalities for pediatric central nervous system (CNS) tumors is radiation therapy. Well-known complications and late effects of radiation therapy include endocrine dysfunction, cognitive deterioration, ototoxicity and secondary malignancies. Another potential complication of radiation therapy is the risk of developing cavernous hemangiomas. Cavernous hemangiomas are abnormal collections of vascular sinusoids that are lined by a single endothelial layer and lack intervening brain parenchyma. They often contain blood and blood products at various stages of clotting and degeneration. These lesions can often be surrounded by hemosiderin, gliosis and calcification and can be located throughout the CNS. There are only a few case series reporting key information on radiation-induced cavernous hemangiomas (RICH). The literature suggests that the median age of radiation is approximately 11 years and the median dose of radiation is approximately 6,000 cGy. Typically, the diagnosis of RICH is made at a median of

8.9 years from radiation exposure [2]. Some data suggest that younger age (children less than 10 years old) at the time of radiation exposure is a risk factor for developing RICH [3]. Radiation doses greater than 3,000 cGy have demonstrated a shorter latency period compared to doses less than 3,000 cGy [4].

In a study of 171 patients who received cranial irradiation, 8 patients (4.6%) developed cavernous hemangiomas between 2.9 and 18 years after radiation exposure. The lesions ranged in size from 5 to 30 mm, and half of them were single whereas the remainder presented with 2 or more lesions. The cumulative incidence increased up to 5% at 15 years after radiation exposure. In children less than 10 years old at the time of radiation, the cumulative incidence has been reported to be as high as 8.5% at 15 years, suggesting that age is truly a key risk factor for the development of RICH [3]. This is in sharp contrast to a prevalence of only 0.3–0.7% among the general population without any radiation exposure [5].

The majority of the patients who develop RICH are asymptomatic, and RICH lesions are most commonly diagnosed by surveillance imaging studies performed for other reasons such as tumor monitoring or routine follow-up. Less commonly, patients will present with symptoms such as seizures, headaches, motor dysfunction and emesis [6]. The true frequency of symptomatic RICH lesions is yet unclear. On imaging, most cavernous hemangiomas have a distinctive appearance of a well-demarcated lesion with very little to no surrounding edema; however, a hemorrhage within the RICH can make the radiographic appearance less clear. Typically, though, these lesions can be diagnosed by imaging characteristics alone. MRI most commonly reveals a reticulated core of heterogeneous signal intensity with a dark peripheral rim of hemosiderin, giving it a typical ‘popcorn’ appearance whereas a CT usually reveals a ring-like calcification with a core reticulation [7].

The most common location of these lesions is outside the radiation field exposed to the highest cumulative radiation doses. One possible explanation is that at the highest radiation doses, apoptosis is induced in the endothelial cells; however, although there is injury to the cells at moderate radiation doses, it is insufficient enough to induce significant apoptosis.

Bevacizumab (Avastin, Genentech, San Francisco, Calif., USA) is a monoclonal antibody directed against vascular endothelial growth factor (VEGF). VEGF is an essential regulator of normal and abnormal blood vessel growth. Currently, bevacizumab is approved by the FDA for the treatment of metastatic colon cancer, renal cell

carcinoma, non-small-cell lung cancer, metastatic breast cancer and recurrent glioblastoma multiforme [8–10]. It is also undergoing evaluation in the treatment of a variety of pediatric and adult malignancies in ongoing phase I and II clinical trials. We report the incidental finding of a response of a RICH in a child with recurrent medulloblastoma who was being treated with a combination of bevacizumab and irinotecan.

Case Report

The patient is a 3-year-old male originally diagnosed as having M3 medulloblastoma, with bulky metastatic disease noted in the spine on MRI imaging at diagnosis. There was no evidence on MRI of preexisting vascular malformations prior to starting therapy on his diagnostic CT or MRIs. He completed initial therapy with intensity-modulated radiation therapy following the treatment strategy of the Children’s Cancer Group 99701 protocol which included craniospinal irradiation to 36 Gy with boost to the primary sites. The protocol also evaluated the use of concomitant doses of daily carboplatin (35 mg/m²/day) given as a radiosensitizer. He also received weekly vincristine during radiation therapy. Subsequently, he was treated with maintenance chemotherapy with vincristine, cisplatin and cyclophosphamide for a total of 6 cycles, again as per the guidelines of the Children’s Cancer Group 99701 trial; however, he was not enrolled in the official trial as the study had already been closed to accrual upon his diagnosis. The patient had a complete radiographic response at the completion of therapy. Although the patient was asymptomatic, routine tumor surveillance imaging 3 months after the completion of initial therapy revealed relapsed medulloblastoma throughout the leptomeninges and subsequent positive lumbar cytology. Additionally, a brain MRI demonstrated a new lesion measuring 6 mm in the greatest axial diameter in the left posterior temporal lobe. The lesion was heterogeneous with a rim of peripheral T₂-weighted/FLAIR hyperintensity and central hypointensity. There was also evidence of susceptibility artifact on the b0 echo-planar imaging diffusion images. The appearance suggested hemorrhage into a cavernous hemangioma. Based on evaluation of the radiation mapping and dose distribution, this region of the temporal lobe received approximately 3,600 cGy of total irradiation.

Recurrent medulloblastoma, especially after full-dose craniospinal irradiation, is very difficult to cure [11]. The primary treating team did not feel that this patient was a good candidate for high-dose chemotherapy followed by autologous hematopoietic cell rescue for a variety of reasons, including ongoing myelosuppression, history of severe life-threatening infections during previous chemotherapy and low likelihood for cure given the history of full-dose craniospinal radiation therapy. Therefore, an experimental regimen utilizing bevacizumab 10 mg/kg i.v. and irinotecan 125–150 mg/m² i.v. both given every 2 weeks was initiated. At that time, this therapy was also being utilized in an ongoing Pediatric Brain Tumor Consortium Trial No. 22; however, due to ongoing myelosuppression, our patient was not eligible for enrollment in the official trial.

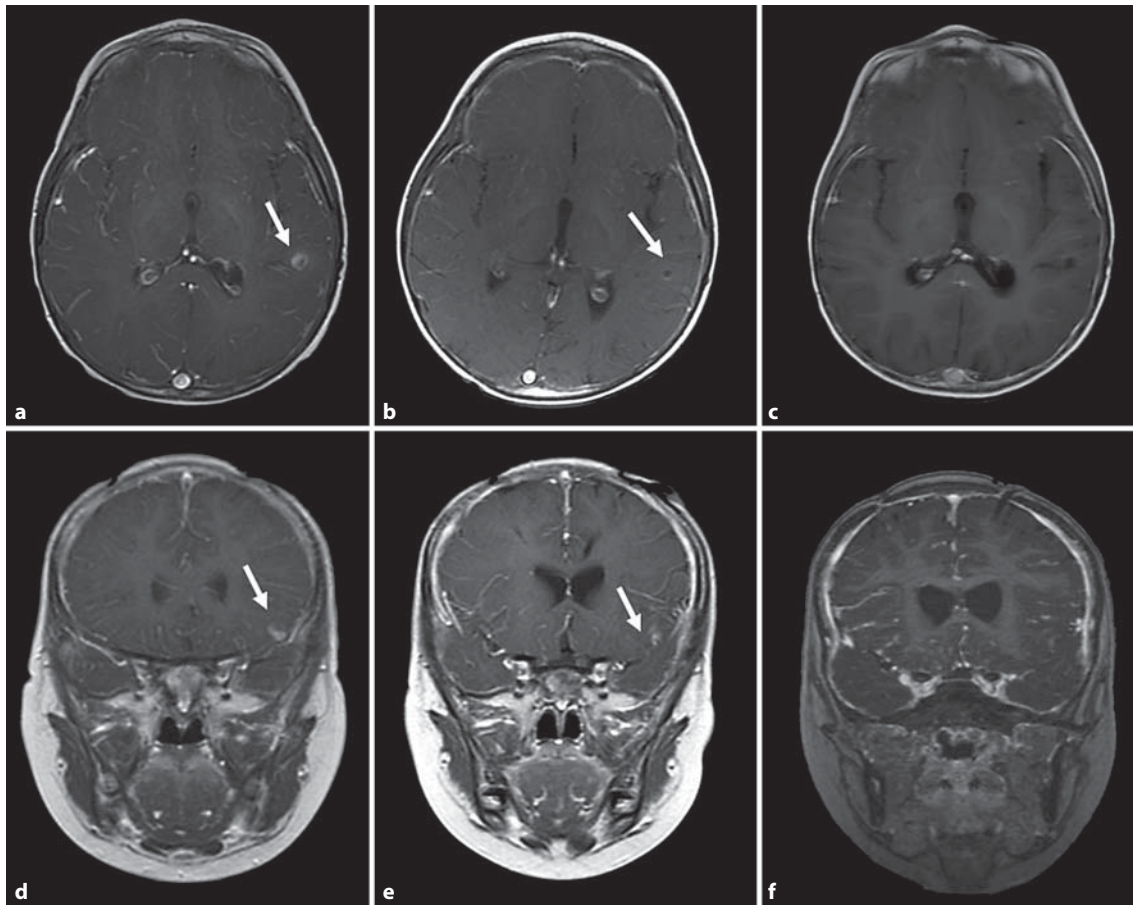


Fig. 1. MRI of brain. **a** T₁-weighted axial diagnosis of RICH: the lesion was heterogeneous with a rim of peripheral T₂-weighted/FLAIR hyperintensity and central hypointensity suggestive of cavernous hemangioma. **b** Three-month therapy with bevacizumab shows decrease in size by 33%. **c** After 6 months of bevacizumab therapy complete resolution of RICH. **d** MRI of brain after T₁-weighted coronal sections with diagnosis of RICH. **e** Three months of therapy with bevacizumab. **f** Six months of bevacizumab therapy.

After completion of 3 months of therapy, the cavernous hemangioma size and appearance had changed. There was interval decrease in size of the lesion which now measured 4 mm in greatest axial diameter. The signal characteristics of the lesion also changed, and it now demonstrated T₂-weighted hypointensity and predominantly T₁-weighted hypointensity with a thin rim of T₁-weighted hyperintensity. There was no signal abnormality identified in the surrounding brain parenchyma. The findings were compatible with the continued evolution of a hemorrhagic cavernous hemangioma (fig. 1).

After completion of 6 months of therapy, the cavernous hemangioma was no longer visible on the T₁-weighted and postcontrast MRI and could only be appreciated as seen on gradient echo imaging sequences suggestive of resolving blood products (fig. 2). The patient's recurrent tumor remained stable on the bevacizumab and irinotecan regimen for over 1 year; however, approximately 18 months after initiating the therapy, a surveillance image revealed progressive disease in the thecal sac. Although he was then

switched to an alternative experimental therapy, he died of progressive disease 5 months later. The cavernous malformation did not reappear once the chemotherapy was switched from bevacizumab and irinotecan to an alternative regimen.

Discussion

We have presented the incidental finding of a RICH that had a significant response to therapy with bevacizumab in a child with relapsed medulloblastoma. RICH should be included in the differential diagnosis of any patient who has previously received radiation therapy and presents with a new incidental and/or hemorrhagic lesion in the CNS. The mechanism of formation of RICH

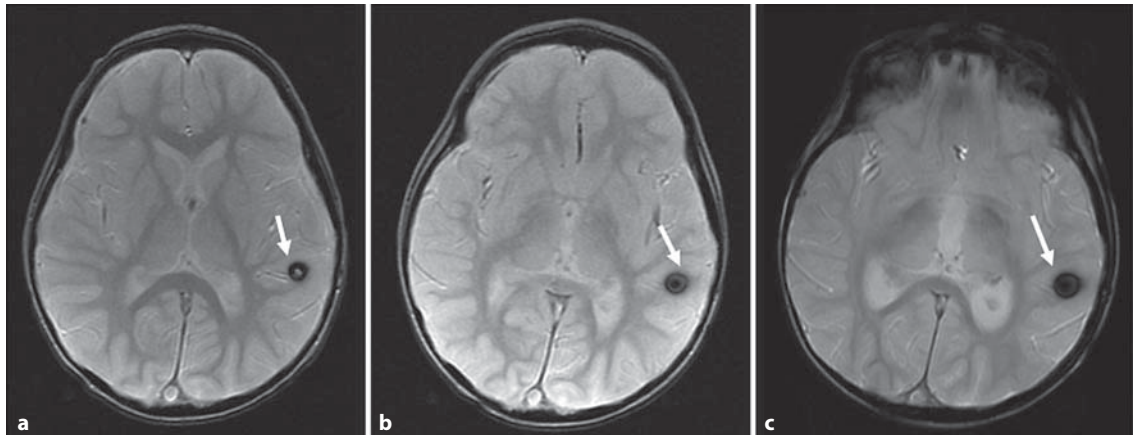


Fig. 2. MRI of brain T₂-weighted axial gradient echo sequence. **a** At diagnosis. **b** After 3 months of therapy with bevacizumab. **c** After 6 months of bevacizumab therapy. Persistent signal abnormality despite resolution in conventional MRI sequences.

is not clear; however, there are a few hypotheses. First, there is the possibility that there are preexisting occult cavernomas that cannot be identified with standard imaging studies. Second, radiation-induced injury may lead to proliferative vasculopathy that starts with the development of capillary telangiectasias [12]. Radiation causes hyalinization and fibrinoid necrosis of small vessels, including arteries and arterioles, with narrowing of the vessel lumen and endothelial proliferation. Additionally, the production of angiogenic factors such as VEGF, basic fibroblast growth factor and transforming growth factor α may also contribute to RICH formation [13, 14]. Histological studies have also reported radiation-induced venous restriction leading to an increase in the venous pressure with subsequent development of the cavernous malformation [15].

Currently, the most common treatment modality for RICH lesions includes observation with surveillance imaging and surgical resection. Resection is typically utilized if there is increase in size, new symptoms or evidence of bleeding. The best time to operate varies from patient to patient according to the opinion of the treating team; however, the major criteria for intervention include a change in size, hemorrhage or symptom development. In a series of 8 patients previously reported who developed RICH, 3 underwent surgery, all secondary to an increase in size of the lesions [3]. The risk of spontaneous bleeding has been reported from 0.5 to 3% each year but it is most likely influenced by other factors such as location and ongoing morbidities. The risk of bleeding has been reported to be higher in other published reports. In

a series of 76 patients, 37 had evidence of hemorrhage, and, among these, 54% required surgical intervention [2]. Recently, Keezer and Del Maestro [6] reported that 40% of RICH demonstrated hemorrhage in imaging studies resulting in an incidence of 3.9% per patient per year. Interestingly, there are fewer reports of bleeding when radiation dose was a mean of 5,100 cGy versus a higher incidence of bleeding in those whose dose was a mean of 4,400 cGy [6]. Additionally, the epileptiform risk is increased if the lesion is located in the frontal or temporal lobes. This risk has been estimated to be approximately 4.5–11% each year [5].

Factors that predispose patients who are exposed to radiation to develop RICH are not well understood; however, recent progress in understanding the development of vascular malformations of the brain could provide some insight. Several genes and genetic risk factors have been described to play a role in formation or regression of vessels within a preexisting vascular bed including *CCM1*, *CCM2* and *CCM3*. Their roles include stabilization of interendothelial junctions associated with actin stress fibers, cellular responses to osmotic stress, cellular proliferation and transformation and modulating the extracellular signal-regulated kinase. These proteins are expressed in the vascular endothelium and can bind into a complex that is associated with interendothelial junction and cytoskeletal proteins and other components in specific signaling pathways [16]. Investigators have proposed a 2-hit mechanism for the development of a cavernous malformation whereas an inherited mutation in 1 copy of a vascular malformation gene may be followed by a so-

matic mutation in a second copy [17]. The second hit can be environmental and perhaps is where radiation may play a contributing role. Cavernous malformations have been shown to exhibit activated angiogenesis with up-regulation of several factors. The expression of these factors can vary in adults compared to children. Expression of VEGF is more predominant in adults and appears to play a lesser role in pediatrics; however, these findings need further investigation. Other characteristics commonly found in RICH lesions include endoglin overexpression, a component of the receptor complex of the transforming growth factor β_1 and β_3 , higher MIB-1 and high expression of proliferating cell nuclear antigen [18]. However, the current understanding does not yet explain whether there are differences in expression of biological markers in spontaneous cavernous hemangiomas versus those induced by radiation.

The incidental reduction in the size of a liver hemangioma after the use of bevacizumab has also been recently described [19]. Other reports have described the use of bevacizumab in the vitreal cavity for the treatment of ret-

inal capillary hemangiomas in patients with Von Hippel-Lindau disease, which stopped the growth and perhaps inhibited the development of new hemangiomas in the treated eye [20].

We have reported the incidental finding of a significant response of RICH during therapy with bevacizumab for the treatment of relapsed medulloblastoma. It is unknown if the use of bevacizumab in this setting alters the risk of bleeding upon these vascular lesions. Although this finding is intriguing and may prompt further investigation, many questions remain unanswered. For example, what length of therapy is appropriate and would these lesions respond to differing doses of bevacizumab? Also it is unclear if these lesions would recur with time once antiangiogenic therapy has been discontinued. Our experience reveals that bevacizumab has the potential to induce a response in radiation-induced hemangiomas. Of course, this is a limited and specific case, and therefore future evaluation of this therapy may be warranted, especially in patients in whom surgical resection is not an appropriate or safe option.

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