Durable response of intracranial cellular hemangioma to bevacizumab and temozolomide

Case report

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Cellular hemangioma is a subtype of hemangioma that is associated with cellular immaturity and the potential for recurrence. Intracranial location of these lesions is extremely rare, and definitive treatment often requires radical neurosurgical resection. The authors report a case of a 12-year-old boy with a subtemporal cellular hemangioma. He underwent gross-total resection of the tumor, but within 1.5 months the tumor recurred, necessitating a second resection. Because of its proximity to vascular structures, only subtotal resection was possible. Repeat MRI 1 month after the second surgery showed significant tumor recurrence. Given the tumor’s demonstrated capacity for recurrence and its proximity to the vein of Labbé and sigmoid sinus, further resection was not indicated. In an effort to limit radiation therapy for this young patient, treatment with bevacizumab and temozolomide was chosen and achieved a complete response that has proven durable for 36 months after cessation of therapy. This is the first report of the successful use of chemotherapy to treat an intracranial hemangioma, a rare condition with limited therapeutic options.

KEY WORDS • intracranial cellular hemangioma • bevacizumab • temozolomide • treatment • oncology
and a few days later the patient underwent gross-total resection of the tumor. The initial pathological diagnosis was “consistent with capillary hemangioma, with no malignant features.” The patient recovered well from surgery and was discharged home.

Six weeks after surgery, a follow-up MR image revealed significant recurrence of the tumor with surrounding edema and dural enhancement. The patient again underwent surgery, this time a subtotal resection. At the time of this second surgery, the neurosurgeon noted a well-circumscribed vascular mass in the posterolateral tumor cavity, with direct invasion of the sigmoid sinus. Consequently, the mass was removed only down to the level of the sinus; the level of suspicion that disease involved the wall of the sinus was high. Postoperative MRI confirmed residual tumor measuring $14 \times 6$ mm. Given the difficulty of obtaining a definitive diagnosis and given the rapid regrowth of tumor, the department of neurooncology was consulted, and the surgical specimen was sent for second opinions on its pathology. After a comprehensive review involving 3 pathology departments, the most applicable pathological classification was of cellular hemangioma with a relatively high proliferative index but no malignant features.

The lesion was described as consisting of well-formed, closely packed vascular channels with plump, bland-appearing endothelial cells and pericytes (Fig. 1). Sizes of the channels varied somewhat, but most were small. There was no pleomorphism, and the proliferative index was approximately 10%. The monolayer endothelium was highlighted by CD31 and CD34, and the well-developed pericytic layer was positive for smooth muscle actin. The tumor cells were negative for S100 protein, epithelial membrane antigen, neuron-specific enolase, and inhibin. The entire appearance suggested a benign vasoproliferative lesion for which a well-accepted name is lacking in the current nomenclature. Some experts would deem this lesion to be consistent with cellular hemangioma, although of the type more often encountered in bone.

Given that the success rate of radiation therapy for preventing recurrence of these lesions is modest and that the potential neurocognitive effects of radiation to the temporal lobe are significant, the recommendation was made to undertake treatment with the vascular endothelial growth factor inhibitor bevacizumab and the alkylating agent temozolomide in an attempt to shrink the tumor and delay or avoid radiation therapy. It was hoped that should radiotherapy become necessary, a more limited field could be achieved by reducing the tumor volume. Before therapy was started, MRI showed rapid growth of the tumor, to $17 \times 14.5$ mm (Fig. 2). Treatment was initiated with intravenous bevacizumab at 10 mg/kg once every 2 weeks and oral metronomic temozolomide at 75 mg/m$^2$ daily. After 2 months of this treatment, MRI showed a good response to therapy, with a 30% decrease in the greatest bidimensional measurements. Follow-up MRI every 2 months showed a progressive decrease in tumor size; by 6 months after initiation of therapy, MRI indicated no evidence of tumor. The patient completed a 48-week course of therapy and tolerated the medications well with no significant side effects. At 36 months after cessation of therapy, the patient was clinically well and MR images showed no evidence of tumor recurrence (Fig. 3).
Discussion

Cellular hemangioma is widely believed to be a form of capillary hemangioma. Histologically, cellular hemangioma shows a combination of well-canalized and poorly canalized vessels. As the lesion matures, the endothelium flattens and the histological appearance resembles that of capillary hemangioma. Both lesions belong in the category of vascular neoplasm and tumorlike lesions. Other lesions in this group include papillary endothelial hyperplasia/Masson vegetant hemangioendothelioma, epithelioid hemangioendothelioma, hemangiopericytoma, and angiosarcoma.9 Capillary hemangiomas, cellular hemangiomas, and papillary endothelial hyperplasia are considered benign; epithelioid hemangioendotheliomas are considered low-grade to intermediate-grade malignancies; and hemangiopericytomas and angiosarcomas are considered malignant.6

Intracranial hemangiomas are extremely rare; only 20 biopsy-proven cases were found in the literature.1,2,5,8,10,11,13,17,18,20–24 With the exception of 4 cases11,20,23, the reported primary mode of treatment was neurosurgical resection, of which complete resection was achieved in 12 of the 16 cases. In the other 4 cases,13,17 only subtotal resection was possible, and additional surgery or radiotherapy was needed to achieve tumor control. One of these 4 cases, reported by Simon et al.,17 involved a 31-year-old woman with a left tentorial hemangioma. She underwent a near-total resection to treat invasion of the lesion into the left transverse sinus. Approximately 6 months later, she reported intractable headaches; the tumor had...
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recovered. She subsequently underwent 2 additional resections; the third surgery involved resection of the left transverse sinus. Of the 3 other cases, reported by Morace et al.,13 2 patients underwent CyberKnife radiotherapy at 5 months and 7 months postsurgery, respectively, and the other underwent CT-guided radiotherapy at 1 year postsurgery. For the 4 patients for whom neurosurgical resection was not used as the primary mode of treatment,15,20,23 stereotactic radiotherapy was successful in 2,20 1 died before initiation of treatment,13 and 1 received no further intervention.23 Among all 20 cases, there were no reports of spontaneous regression, and the histological subtypes were all reported to be capillary hemangioma, as was the initial pathological diagnosis for the patient reported here. The difficulty obtaining a definitive pathological diagnosis made our therapeutic management decisions much more challenging because the literature seems to indicate that therapy should differ between capillary and cellular hemangiomas.2,7,23 This issue seems to stem from the lack of universally accepted nomenclature for these benign vasoproliferative lesions.15 Although the final pathological diagnoses for the case reported here and the previously reported cases differ, the pattern of rapid recurrence of incompletely resected lesions seems similar, especially for the case reported by Simon et al.17

It is evident from the literature that stereotactic radiotherapy can successfully treat residual or unresectable intracranial hemangiomas. However, all the reported patients who received radiotherapy were adults, who are at less risk for neurocognitive sequelae. It is well established that conventional intracranial radiotherapy leads to significant neurocognitive decline, which varies according to patient age and radiation volume and dose.19 For the patient reported here, we planned to use stereotactic radiotherapy only if a trial of chemotherapy was unsuccessful, hoping to avoid the deleterious effects of radiation to the temporal lobe in a child.

For all 20 cases reported in the literature, no chemotherapeutic agents, except for steroids and interferon alpha, were used. Bevacizumab is a recombinant humanized monoclonal antibody directed against vascular endothelial growth factor, and it is used for multiple cancers including colorectal, lung, brain, and renal carcinomas.7,12 For numerous cases, use of bevacizumab to treat primary malignancies has reportedly produced incidental resolution of visceral hemangioma.4,12 Common side effects of bevacizumab include hypertension, bleeding, and proteinuria. Temozolomide is an oral alkylating agent that acts by methylating DNA, leading to DNA breakage and apoptosis in actively dividing cells.3,10 Temozolomide has been shown to have survival benefits in adult patients with newly diagnosed glioblastoma multiforme, but the literature contains no reports with regard to its use for hemangioma. Adverse effects of temozolomide include myelosuppression, fatigue, and alopecia. To reduce the likelihood of these side effects, we used a low-dose metronomic dosing regimen. Rare cases of secondary malignancies have also been reported. We felt that the combination of bevacizumab and temozolomide, with which we were familiar in our neurooncology practice, represented a relatively safer alternative to radiation therapy. This case demonstrates the durable success of bevacizumab and temozolomide treatment for recurrent intracranial hemangioma in a child. For a disease that has classically been treated with radical neurosurgical resections and radiation therapy, this case report presents a potentially safer alternative. Although we do not definitively know which agent was responsible for this response, or if both are necessary for successful treatment, our experience calls for further investigation of the role of bevacizumab and temozolomide in the treatment of visceral hemangioma, specifically intracranial hemangioma.

Disclosure

The authors report no conflict of interest concerning the material or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Concept and design: Rood. Acquisition of data: Puscasu. Analysis and interpretation of data: Yeo. Drafting the article: Yeo, Puscasu. Critically revising the article: all authors. Reviewed submitted version of manuscript: Rood, Keating. Approved the final version of the manuscript on behalf of all authors: Rood. Study supervision: Rood.

Acknowledgment

The authors thank Dr. Christopher D. Fletcher for his contribution to the pathological diagnosis for this patient.

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Accepted February 7, 2013. 
Please include this information when citing this paper: published online March 29, 2013; DOI: 10.3171/2013.2.PEDS12421. 
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