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Use of thalidomide to diminish growth velocity in a life-threatening congenital intracranial hemangioma

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Abstract

Infantile or capillary hemangioma is the most common vascular tumor of childhood. The tumors most frequently affect the head and neck area, but rare cases of intracranial lesions have been reported. Their natural history is marked by initial rapid growth velocity followed by a plateau and, in most cases, subsequent involution. Although the lesions are considered benign, 10% of affected children develop life-threatening complications (mortality rate 20–80% in this subgroup). When surgical intervention or other methods of local control are not possible, therapeutic options are limited. Corticosteroids have been the mainstay of therapy but therapeutic response is not predictable and the infectious risk is not negligible. Interferon α -2a may also be effective but has significant toxicities.

Vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) have been implicated in the pathogenesis of hemangiomas, and antiangiogenesis agents are being evaluated in the treatment of these tumors. Thalidomide may be an ideal therapy for life-threatening hemangiomas because it inhibits new blood vessel formation by antagonizing both the bFGF and VEGF pathways and has a more acceptable toxicity profile than other agents. The authors present the case of an infant born with a life-threatening, unresectable intracranial hemangioma in which treatment with thalidomide resulted in a good clinical outcome.

Keywords

intracranial hemangioma; thalidomide; vascular endothelial growth factor

Infantile hemangiomas are the most common vascular tumors of childhood and are distinct from vascular malformations. Hemangiomas continue to grow in size until the infants are 8–12 months old, when tumor growth rate plateaus and lesions often undergo spontaneous

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involution.¹⁹ Although these tumors are histologically benign, 10% of affected children develop life-threatening complications such as high-output heart failure as seen in those with large hepatic hemangiomas or airway obstruction in those with oropharyngeal or tracheal hemangiomas. The associated mortality rate ranges from 20 to 80% in this subgroup.^{5,18} Rare intracranial lesions have been described and are frequently associated with PHACE syndrome (posterior fossa malformations, facial hemangiomas, and arterial, cardiac, and eye abnormalities).^{2,11,20}

For infants and children who develop serious complications and are not surgical candidates, therapeutic options are limited. Initial therapy consists of oral or intralesional steroids, with improvement occurring in 30% of patients within 1 week. In an equal number of patients, there is little or no response, and no clear method exists to distinguish responders and nonresponders. The consequences of high-dose corticosteroid therapy in young infants, including excessive weight gain, adrenal suppression, and infectious risk, cannot be disregarded.¹⁴ Alternative therapies include interferon α -2a and -2b which may be effective in managing life-threatening hemangiomas.^{4,15,20} Considerable toxicities have been reported with the use of interferon in infants. The most common immediate side effects include leukopenia and neutropenia; prolonged therapy has been associated with thin hair and slow weight gain.²⁰ The toxicity of most concern is spastic diplegia. Barlow et al.¹ reported the development of spastic diplegia in 20% of infants (5 of 26) treated with interferon for life-threatening hemangiomas with less than half (2 of 5) recovering. We present here the case of an infant born with a life-threatening, unresectable intracranial hemangioma successfully treated with thalidomide.

Case Report

Presentation and History

This female infant, one of 3 triplets born after 33 weeks of gestation, presented for evaluation of an intracranial mass during the first day after birth. She weighed 1829 g at birth. Pregnancy was complicated by trichorionic triplet gestation, preterm labor, discordant fetal growth, and prenatal diagnosis of intracranial hemorrhage in the patient (the triplet who presented to us). The pregnancy was conceived by hormonally induced ovulation and intrauterine insemination. An older sibling had a truncal, cutaneous hemangioma as an infant that completely regressed. Also of note: an extremity cutaneous hemangioma developed in one of the other triplets; this lesion resolved by her second birthday.

Examination

Physical examination showed a left cranial nerve VII palsy. No laboratory abnormalities were noted. Magnetic resonance imaging of the brain and cranial sonography demonstrated a large heterogeneous mass spanning the middle cranial fossa, temporal bone, and posterior fossa, and extending through the skull base (Fig. 1). The bulk of the mass was hyperintense on T2-weighted MR images. Areas of T1-weighted signal hyperintensity and T2*-weighted signal loss were interpreted as hemorrhage. Computed tomography revealed a hyperdense mass centered on the petrous bone that induced aggressive osseous reaction. Initial concern was for a neoplasm in the temporal bone such as a primitive neuroectodermal tumor, atypical teratoid rhabdoid tumor, or metastatic neuroblastoma. Angiography was not performed due to the patient's weight and gestational age.

Biopsy and Postoperative Course

The patient was taken to the operating room for an ultrasound-guided biopsy. Biopsy forceps were used to obtain samples. Hemorrhage developed intraoperatively, requiring the administration of packed red cells, fresh frozen plasma, platelets, and cryoprecipitate. A postoperative CT scan showed new hemorrhage within the tumor as well as the left lateral

ventricle. Histopathological findings revealed papillary endothelial hyperplasia, suggestive of hemangioma (Fig. 2).

The vascular appearance of the specimen prompted urine and CSF analysis for vascular growth factors. The CSF and urinary levels of bFGF were elevated at 4.7 pg/ml and 4.1 pg/ml (normal = 0 pg/ml). The CSF level of VEGF was 499.9 pg/ml (historic normal for patients < 20 years is < 10 pg/ml). The urinary level of VEGF was also elevated at 578 pg/ml (normal < 232.1 pg/ml).

The patient's course was complicated by hydrocephalus and ventriculoperitoneal shunt placement. She required observation in the neonatal intensive care unit due to apnea and suspected seizures.

An MR imaging study performed when the patient was 1 month of age demonstrated a 12% increase in tumor size. The neonatal, neurosurgical, and oncology physicians were concerned for the risk of herniation or death as the tumor continued to grow. Surgical resection was not feasible in light of the patient's age and weight. Due to the vascular appearance of the tumor on imaging and histopathological examination and the presence of elevated VEGF and bFGF, we pursued antiangiogenic therapy using thalidomide.

Thalidomide Treatment and Clinical Course

Treatment with 4 mg/kg of thalidomide (12.5 mg) was initiated after informed consent was obtained when the patient was 35 days old. The dose was increased every 2 weeks by 12.5 mg to a maximum of 50 mg. The planned duration of treatment was 12 months, with dose escalations for weight gain. The main symptoms of toxicity noted were sleepiness and constipation. The maximum dose attempted was 150 mg, but that dose caused severe constipation. No hematological toxicity or evidence of peripheral neuropathy developed. No other potentially therapeutic agents including corticosteroids or interferon were administered.

An MR imaging study of the brain was performed every 2–3 months, and the patient was examined monthly to monitor for tumor progression and thalidomide toxicity. The MR images obtained at 20 months after presentation demonstrated a dramatic reduction in the hemangioma volume when compared with its maximum volume at 5 months after the patient's birth (Fig. 3). During the infant's first 3 months of life, the tumor increased in volume by 178% (relative to its size at her birth). Over the next 2 months, overall tumor volume increased by another 47%—an increase of 307% from birth. By the time the patient was 8 months old, the tumor volume had decreased by 16% from its maximum volume. Over the next 3 months, the volume continued to diminish and was 57% of the maximum when the child was 11 months of age (Fig. 4). During thalidomide therapy, urinary VEGF levels were monitored. After 3 months of therapy, the VEGF level was 538.9 pg/ml (< 75.3 pg/ml reference). After 9 months of therapy, it decreased to 205.4 pg/ml (< 130 pg/ml reference).

Examination findings remained stable with a left cranial nerve VII palsy, left complete sensorineural hearing loss, and no visual perception in the left eye. The patient demonstrated global developmental delay but with improving motor development. She was unable to sit without support at 6 months of age. At 11 months of age, she developed infantile spasms and ACTH therapy was initiated. Treatment with ACTH began after the most dramatic decrease in hemangioma size and lasted for only 1 month. By the time the patient was 14 months old, ACTH therapy had been discontinued with no seizure recurrence and her development corresponded to that of a 6-month old.

The patient was 24 months old at the time of last follow-up, and she had met the 18-month gross motor development milestones. She had received aggressive speech, occupational, and

physical therapy. She had recently said her first word and could run and climb. The audiogram performed at that time detected hearing to 10 db in her left ear. Her verbal developmental is about 6 months behind that of her triplet siblings.

Discussion

Imaging of infantile hemangiomas is used to assess the extent of disease during lesion proliferation and planning of palliative interventions intended to limit complications. The lesions typically demonstrate T2-weighted signal hyperintensity relative to muscle and avidly enhance following contrast administration; T1-weighted signal hyperintensity and T2*-weighted MR signal loss likely represents hemorrhage within the lesion, a common feature of hemangiomas. During involution, whether spontaneous or therapeutically induced, dramatic reductions in the extent and enhancement of the lesion are typical. The aggressive osseous reaction of the petrous bone in the early imaging studies in this case is atypical for hemangiomas, which usually produce smoothly marginated erosions. The findings on subsequent imaging studies was more typical for involution. Computed tomography scans 19 months after presentation demonstrated replacement of the osseous reaction with mature, dense bone, as is expected with hemangioma involution. Complete resolution is common, but it may take years for the imaging appearance to fully normalize.

Understanding angiogenesis and its role in cellular proliferation has lead to the development of mechanism-specific therapies. Thalidomide, first approved as a sedative, became best known for its teratogenicity.^{16,17} Limb malformations resulting from in utero exposure to thalidomide are due to inhibition of new blood vessel formation through the VEGF/bFGF pathway.³ Thalidomide has been rediscovered as an antiangiogenic agent. Common therapeutic indications include multiple myeloma and pediatric brain tumors.¹³

The number of medications acting directly on the VEGF/bFGF pathway, whether by downregulation of production or by receptor blockade, is rapidly expanding, with thalidomide becoming the prototype. Animal experiments demonstrate the ability of thalidomide to inhibit VEGF-stimulated neovascularization of the cornea in both the mouse and the rabbit.^{3,12} The use of thalidomide, alone or in combination with other agents, has become routine in the treatment of hematological malignancies and solid tumors in children and adults. Multiple Phase I and II studies have been published regarding the efficacy of thalidomide in cancer and more are currently ongoing. The greatest safety concern is the risk of dysmelia or limb malformations due to in utero exposure.

The VEGF/bFGF pathway has been implicated in the pathogenesis of hemangiomas.^{6,10} Cutaneous hemangiomas consistently overexpress VEGF and HIF-2 α .⁹ Proliferating hemangiomas are associated with serum VEGF levels that are significantly higher than those found in association with involuting hemangiomas and other vascular malformations.^{7,22} Levels of VEGF and bFGF have not been studied in association with intracranial hemangioma, but no evidence suggests that they would be different from the levels found in patients with other hemangiomas. This case report is the first to correlate intracranial hemangioma growth with measurements of VEGF and bFGF. More recently other antiangiogenic agents, such as interferon α -2a and -2b, have been investigated in the treatment of hemangiomas.⁸ Because interferon α has significant toxicities, the search for an effective and safe agent for use in children continues.

The evaluation of therapeutic effectiveness in patients with hemangiomas is difficult because it is well understood that these lesions will undergo regression on their own. Unlike the anticipated response to the administration of traditional cytotoxic chemotherapy, the response to thalidomide should not be expected to entail rapid regression. Treatment with

antiangiogenesis agents is characterized by a delay in the onset of action as the tumor must outgrow its existing blood supply before diminishing in size. In the case presented in this paper, the tumor initially grew with significant velocity, slowing after 4 months of therapy with evidence of decreased growth before the patient reached 8 months of age. Regression does not usually begin until after a plateau phase, which was not seen in this patient. Once regression began, it was rapid and nearly complete before the child reached 2 years of age. The percentage increase in volume, a measure of growth velocity, of periorbital hemangiomas has been reported to range from 4 to 931% between imaging studies during the growth phase.²¹ A systematic evaluation of average growth velocities based on age for hemangiomas has not been described. This is probably due to the mostly benign nature of the lesions as well as the expense and inconvenience of serial MR imaging to assess tumor volume and continued variability in nomenclature. The lack of a plateau phase in growth and the early onset of tumor regression in our patient strongly suggest that thalidomide treatment had a positive effect on the course of her disease.

We have presented the case of a child diagnosed with a life-threatening intracranial hemangioma managed by VEGF/bFGF-targeted therapy using thalidomide. There was minimal toxicity with thalidomide therapy and the neurological outcome has been better than expected. The excellent clinical outcome and toxicity profile using the mechanism-specific therapy described in this case warrants further clinical investigation and offers a new therapeutic option in the management of other life-threatening hemangiomas.

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Abbreviations used in this paper

ACTH	adrenocorticotrophic hormone
bFGF	basic fibroblast growth factor
CSF	cerebrospinal fluid
VEGF	vascular endothelial growth factor

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Fig. 1.

Contrast-enhanced T1-weighted axial (A) and coronal (B) MR images and coronal sonogram (C) demonstrating a $4.2 \times 4.2 \times 4.1$ -cm mass centered at the left petrous bone. The mass displaced the brainstem to the right (*black arrow*) and extended transtentorially into the middle cranial fossa (*upper white arrow*) and through the skull base into the infratemporal fossa (*lower white arrow*). The mass enhanced heterogeneously after contrast administration. The areas that enhanced poorly roughly correspond to areas of reduced ultrasonographic echogenicity (*white arrowheads*).

Fig. 2. Photomicrographs demonstrating histological and immunohistochemical findings. Staining with H & E (*upper*) revealed a hypervascular lesion with hyalinized vessels and scattered calcifications. Immunohistochemical studies (*lower*) revealed that the majority of cells within the lesion were hypertrophic CD31- and CD34-reactive endothelial cells. In contrast, the CD68 stain shows only scattered histiocytes. The differential diagnosis based on these findings included hemangioma versus a reactive vascular proliferation.

Fig. 3.

Contrast-enhanced T1-weighted axial (*left*) and coronal (*right*) MR images obtained 20 months after initial presentation. The hemangioma has almost resolved. An ill-defined $1.3 \times 1.6 \times 1.5$ -cm area of enhancement persists in the left temporal lobe (*arrows*). This represents a $> 95\%$ reduction in the volume of the area of enhancement from the pretreatment evaluation. There is residual enhancement within the petrous bone and along the tentorium (*right*).

Fig. 4. Graph showing change in total tumor volume over time. The hemangioma was measured in the anteroposterior, transverse, and craniocaudal dimensions.