Treatment of an Ulcerated Hemangioma With Recombinant Platelet-Derived Growth Factor

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

We report a case of a 7-month-old girl with a large facial hemangioma whose ulceration was successfully treated with 0.01% becaplermin (Regranex [Ortho-McNeil Pharmaceutical, Raritan, NJ], recombinant human platelet-derived growth factor-BB) gel. She was noted to have a hemangioma precursor on her face and a heart murmur at the time of birth. After further evaluation, she was found to have a type 1 interrupted aortic arch, ventricular septic defect, and patent ductus arteriosis, and she subsequently underwent surgery to correct her cardiac anomalies. These associated abnormalities are part of PHACE syndrome: the association of posterior fossa brain malformations, hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, and eye abnormalities.1

Her hemangioma continued to grow rapidly, progressively obstructing the vision in her right eye, and at age 3 months she was started on oral corticosteroid therapy (prednisolone, 4 mg/kg daily, tapered to 4 mg/kg every other day, and then to 2 mg/kg every other day over 2 months). Her hemangioma initially appeared to improve, but ulceration developed at age 5 months (Figure 1), worsening despite an increase in the prednisolone dosage to 3.5 mg/kg daily. The hemangioma bled focally and oozed serosanguineous fluid, and the patient experienced increasing pain. Initially, wound cultures were negative for bacterial growth and home wound care consisted of bacitracin zinc-polymyxin B sulfate (Polysporin; Glaxo Wellcome Inc, Research Triangle Park, NC) and non-stick dressings that were changed every 3 days for approximately 6 weeks. Subsequently, dressings were changed to topical metronidazole gel and Mepilex Saftec (Mölnlycke Health Care, Göteborg, Sweden) dressings that were changed every other day.

Because of worsening ulceration, she was admitted to the University of California, San Francisco Hospital to receive intravenous antibiotics, adequate pain control (with conscious sedation with midazolam and morphine for dressing changes), and more aggressive wound care. A second culture of her ulcerated hemangioma yielded coryneform gram-positive rods. On admission, her physical examination revealed a vigorous young infant with a large hemangioma measuring approximately 9 × 8 cm, encompassing nearly the entire upper forehead and medial aspects of her right nose, including extensive involvement of the upper eyelid, causing partial closure of the right eye. The 4.5 × 6-cm ulceration, which extended into the subcutaneous tissue overlying the right eyebrow, had a friable oozing surface (Figure 2).
The challenge was to heal the ulcerated portion of the hemangioma to control pain and prevent further extension and scarring.

SOLUTION

The decision was made to start applying becaplermin to the ulcerated portion of the hemangioma. The ulcer was gently debrided with half-strength hydrogen peroxide and saline 2 times daily. A thin coat of becaplermin was applied to the ulcer in the morning, and metronidazole gel was applied in the evening. These were covered with a hydrogel (Inerpan [Sherwood Medical, St Louis, Mo] or Vigilon [Bard Urological, Covington, Ga] and Telfa [Kendall Healthcare, Mansfield, Mass) dressing. Therapy with prednisolone was also tapered to 2.5 mg/kg every other day and eventually discontinued. Within 5 days, the ulcerated portion shrank to 4.2 × 4.0 cm and began to improve rapidly. At a 6-week follow-up at age 8.5 months, it was completely reepithelialized (Figure 3).

COMMENT

Becaplermin, a commercially available form of platelet-derived growth factor (PDGF), is approved by the Food and Drug Administration for the treatment of cutaneous diabetic ulcers and also has been reported to facilitate the healing of pressure ulcers and mixed arteriovenous diabetic ulcers.2,3 Playing a critical role in tissue repair and wound healing, PDGF acts as a potent mitogen for fibroblasts and smooth muscle and endothelial cells, as well as a chemotactic factor for inflammatory cells.5,6 In addition, PDGF has also been shown to induce vessel formation and to promote tumor growth by stimulation of angiogenesis.6,7 Although fibroblasts and smooth muscle cells of resting tissues contain low levels of PDGF receptors, the βPDGF receptor is markedly up-regulated in inflammatory tissue, leading to increased responsiveness to PDGF.8

Ulceration is the most common complication of hemangiomas, occurring in up to 10% of cases.9 In many cases, ulcerations are relatively minor, but when severe, as in our case, they can become a major management problem, causing soft tissue destruction, functional impairment, and pain, as well as being complicated by bleeding and infection. In our patient, corticosteroids and topical treatments were ineffective in healing the ulceration, and the wound was believed to be too fibrous and exudative to be effectively penetrated by pulsed dye laser (another treatment for ulcerated hemangiomas), which therefore was not an option.

Because becaplermin works at least in part by promoting angiogenesis, we were concerned about the possibility that it might cause further proliferation of the hemangioma, but given the severity of the ulceration, its proximity to the eyelid margin, and the observation that the ulcerated portion no longer appeared to be in a proliferative phase (there was no hemangioma visible at the base of the ulcer), we decided to proceed. Fortunately, it promoted healing of the ulcer and had no appreciable effect on proliferation of the hemangioma.

There are several possible reasons why becaplermin was effective without causing hemangioma growth. The
depth of ulceration appeared to extend to subcutaneous tissue, without any visible evidence of hemangioma at the ulcer base, and it is possible that the proliferative potential of the lesion had been destroyed by the ulceration itself. In addition, the patient was receiving therapy with systemic steroids at the time the medication was used. This may have blunted any potential stimulatory effect of becaplermin on the hemangioma by contributing to the down-regulation of PDGF, an effect that has been demonstrated in at least 1 case of a hemangioma treated with intralesional corticosteroid. In addition, other factors, such as antibiotics and more aggressive wound care while in the hospital, may have contributed to more rapid healing of the ulceration.

Finally, an intriguing (though unproven) possibility is that the granulation tissue promoted by becaplermin arises through a different angiogenic pathway than the hemangioma itself. There is evidence for biological differences among granulation tissue, hemangioma tissue, and chronic wounds at the molecular level. For example, the erythrocyte-type glucose transporter protein (GLUT-1) is highly expressed in endothelial cells of hemangiomas of infancy but is absent from other benign vascular proliferations including granulation tissue. In addition, PDGF expression is down-regulated in chronic compared with acute wounds. Thus, becaplermin might act specifically to promote the healing of the ulcerated portion of the hemangioma without stimulating proliferation of the tumor vasculature.

Our case illustrates that becaplermin may be useful in the treatment of ulcerated hemangiomas that have not responded to conservative therapy. Although we remain concerned about the possibility that becaplermin could stimulate hemangioma growth, its use may be considered in cases of ulcerated hemangioma that have the potential for significant morbidity and have failed conventional treatment.

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Editorial Comment: Hemangiomas are the most common tumor of infancy, developing in 4% to 10% of neonates. Most are uncomplicated and appropriately managed with monitoring and counseling, anticipating eventual spontaneous involution with acceptable outcome. However, a significant minority of infants develop associated complications. While caregivers are often concerned about the potential for bleeding, hemorrhage is not common, although disfigurement and ulceration are. These complications often pose a considerable therapeutic challenge. The pain associated with ulceration can be significant enough to disrupt family life. Ulceration is a nidus for infection and precursor to an inevitable scar. Sugarman et al present a particularly challenging case and a novel approach to treatment with commercially available recombinant human platelet-derived growth factor-BB (becaplermin [0.01% Regranex gel]). This product is approved for the treatment of lower extremity diabetic neuropathic ulcers.

Becaplermin is not approved for use in children, but absorption has been minimal in adult studies. The rationale for using becaplermin in this case was to promote tissue repair and wound healing. Although this infant's refractory ulceration responded rapidly after initial application of becaplermin, other variables may have played an important role in wound healing, including hospitalization, more aggressive wound care, intravenous antibiotics, and adequate pain control. Anyone considering this treatment should heed the authors' concerns about the potential to stimulate hemangioma growth.

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