Infantile Hemangioma

Clinical Resolution With 5% Imiquimod Cream

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

A 7-month-old boy in otherwise excellent health presented for consultation at the Clínica las Americas in San Juan, Puerto Rico, with an infantile (juvenile) hemangioma on the frontal scalp (3.0 x 2.5 cm; Figure 1). The hemangioma, protuberant and dusky red with a cutaneous and a subcutaneous component, was noticed by his mother at age 2 months and enlarged rapidly. Magnetic resonance imaging showed a soft tissue mass extending to the outer table of the skull, suggestive of infantile hemangioma.

CASE 2

A 4-month-old otherwise healthy girl presented to the same clinic with a red-gray bulbous hemangioma, 4.5 cm in diameter, on the frontal scalp that appeared at 1 month of age and grew rapidly. Findings of magnetic resonance imaging supported the clinical diagnosis of infantile hemangioma.

THERAPEUTIC CHALLENGE

The parents of both patients expressed interest in some form of active treatment but found conventional therapies, including laser surgery and intralesional corticosteroid injections, overly aggressive.

SOLUTION

The option of topical 5% imiquimod cream 3 times per week was offered. This was found acceptable by both parents, who fully understood that this was an off-label use of the medication.

In patient 1, aged 7 months, the lesion appeared less protuberant after 4 weeks of 3-times-weekly application of imiquimod, consistent with partial regression. Because of inflammation of the area with erythema and crusting (Figure 2), a resting period of 2 weeks was given. A similar inflammatory effect has been reported in other imiquimod-treated skin conditions. At the end of this 2-week period, there was no inflammation, and a marked reduction in the size of the hemangioma was observed.

Treatment was then restarted, increasing the frequency to every other day and continuing for 2 weeks. Inflammation with crusting reappeared. Treatment was again suspended, and follow-up examination 4 weeks later showed virtually complete clinical regression of the hemangioma with return to normal skin color. The patient at this time was 10 months old. Healing occurred without scarring and without affecting the growth of hair at the site where the hemangioma had been present. Other than local inflammation and crusting during therapy, no other adverse effect was noted. Findings from a neurologic examination were normal at the time of therapy cessation. At the most recent follow-up visit, 4 months after stopping therapy, the patient, now 14 months old, was in excellent health with no neurologic abnormalities and no recurrence of the lesion (Figure 3).

In patient 2, aged 4 months, topical application of imiquimod was started 3 times weekly. However, after 3 weeks of therapy the mother became concerned about the development of crusting and discontinued the medication. During the next 2 months, the lesion grew rapidly, and the patient returned to the clinic for reevaluation. Imiquimod therapy was then restarted at increased frequency of application (every other day), to be continued for a full 6 weeks. This course of therapy was completed despite recurrence of erythema and crusting. At
follow-up examination 4 weeks after termination of therapy, at which time the patient was 9 months old, there was nearly complete regression of the lesion with normal hairs covering the area and no evidence of scarring. At last follow-up at age 16 months, findings of the patient’s neurologic examination remained normal, and there was no evidence of recurrence of the hemangioma.

**COMMENT**

We report here for the first time to our knowledge the apparent efficacy of topical application of the immune-response modifier imiquimod in the treatment of infantile hemangioma. Infantile hemangioma is a distinct category of benign vascular tumor characterized by presentation within the first few weeks of life and rapid growth during the first year followed by a variable degree of spontaneous involution over a period of several years. The true infantile hemangioma often first appears as a pale, blanched area of the skin, which then reddens and progressively enlarges. Recent studies have shown that infantile hemangiomas possess a distinct vascular phenotype shared by placental vessels but not by other types of vascular tumors. Lesions of this unique type are clearly different than “congenital hemangiomas,” which are fully formed at birth and have been reported in some cases to show more rapid involution. The lesions described in this report are clinically typical infantile hemangiomas, appearing after birth and showing the dramatic postnatal growth characteristic of this entity. Their regression during imiquimod treatment, therefore, does not reflect the rapid spontaneous involution associated with congenital hemangiomas.

Without treatment, most infantile hemangiomas exhibit spontaneous involution over the course of years. However, many leave unsightly fibrofatty residua or scars or cause more serious complications such as airway obstruction, amblyopia, and deformation of anatomic structures during their course of development. For these reasons, active therapeutic interventions are often required. Current therapies such as laser treatment, surgical resection, intrallesional and systemic corticosteroids, and, for life-threatening hemangiomas, systemic interferon alfa therapy are in many cases incompletely effective or are associated with adverse effects and patient discomfort. Unquestionably, there is need for a more definitive and highly effective medical therapy without significant adverse effects.

Imiquimod—an imidazoquinoline amine—is an immune-response modifier that acts by affecting the innate and acquired immune response to challenges. It has been shown to be useful in the treatment of genital warts, superficial basal cell carcinoma, squamous cell carcinoma in situ, actinic keratoses, and other lesions. Successful treatment of lentigo maligna has also been reported. These entities have responded, as best understood, on the basis of enhanced immunologic reactions in the skin. The effect on innate immunity is achieved through successful production of a large number of cytokines, including interferon (IFN) α, interleukin (IL) 6, and tumor necrosis factor alpha (TNF-α) among others. Natural killer cell activity is increased, as is activation of macrophages resulting in production of nitric oxide. There is likewise stimulation of B-cell proliferation and maturation. Acquired
immunity is enhanced through production of interleukins such as IL-1, IL-5, IL-8, IL-10, and IL-12 as well as granulocyte and macrophage stimulatory factor. The production of IL-12 results in an increase in cytotoxic T lymphocytes and the release of IFN-γ.10

Interferon alpha, administered through systemic means, has been shown in the literature to be an effective treatment of hemangiomas.11 The exact mechanism of action is not fully understood. However, this route of administration has been associated with the occurrence of significant neurologic complications, especially spastic diplegia.12 Locally produced by imiquimod, IFN-α may clearly be one of the active agents responsible for the regression of the hemangiomas cited in this report. However, recent reports concerning the tumor-suppressive and antiangiogenic effects of IL-1213,14 suggest that this cytokine may also be important in the response of hemangiomas to imiquimod.

In nude mice and rats, topical application of 1% and 5% cream has been shown to result in a local increase in IFN-α and TNF-α.15 In a polyoma virus-induced hemangioendothelioma model, topical imiquimod has been shown to result in an increased number of intratumoral mast cells as well as elevated levels of tissue inhibitor of metalloproteinase type 1 (TIMP-1) and TNF-α with evidence of increased apoptosis.16 Increased density of mast cells and increased expression of TIMP-1 have also been reported in involutive-phase hemangiomas compared with proliferative-phase lesions.17 Thus, imiquimod treatment may hypothetically be causing a recapitulation of the natural involutive process of infantile hemangiomas.

A variety of studies in rodents, monkeys, and humans using in vivo and in vitro techniques (including splenic cultures of human lymphocytes treated with imiquimod) have shown the production of other cytokines, including IL-2 and IFN-γ, as a result of IL-12 production.18 Activation of natural killer cells by IFN-γ has the potential to cause destruction of hemangioma cells. Interferon gamma-inducible IP-10 may in turn have a direct antiangiogenic effect, as has been shown in experimental tumor models.19 Clearly, a variety of mechanisms may reasonably be involved in imiquimod-induced regression of infantile hemangiomas, and further clinical and experimental studies are warranted.

In summary, we have successfully used topical imiquimod to treat 2 patients with typical infantile hemangiomas of postnatal onset. These lesions in the proliferative phase completely resolved within 3 to 5 months of therapy initiation. There was no evidence of recurrence at a median of 6 months following the last treatment. This remarkable response, albeit of a small number of patients, with minimal adverse effects, warrants further clinical investigation. To this end, we have launched a larger clinical study with pathologic correlation and a mechanism-oriented investigation.

Accepted for publication March 17, 2002.

A patent to protect the subject of this article has been applied for.

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Emangiomas are the most common tumor affecting infants. Common complications include disfigurement, ulceration, and significant pain. Despite the prevalence of this tumor, its epidemiology is not well documented, its pathogenesis is unclear, and a uniform approach to therapy has not been defined.\(^1\) Topical or systemic corticosteroids are often prescribed during the rapid-growth phase in the first year of life with the expectation of controlling tumor growth. Sixty percent of infantile hemangiomas respond to treatment with corticoids.\(^2\) Minimal to moderate shrinkage can occur, but brisk involution does not. Insidious adverse effects include irritability, hypertension, and a recent concern about neurodevelopmental impairment.\(^3\) Clearly, there is a need for a safe, effective alternative treatment. The use of imiquimod cream for the treatment of infantile hemangiomas is intriguing, and the response observed by these authors impressed them enough to apply for a use patent. However, clinicians must be very cautious about indiscriminately recommending imiquimod cream for this off-label application. Imiquimod has been used anecdotally to treat molluscum, common warts, and condyloma in children without reports of significant adverse effects, but it has not been used extensively in infants, a group at highest risk of percutaneous toxic effects. In addition, the occurrence of erythema and crusting reported in these cases suggests a risk of inducing prolonged ulceration, a complication that has been described in infantile hemangiomas treated with pulsed-dye laser. Until more data are available on the safety and efficacy of this treatment, the optimal candidate for a trial of imiquimod cream is an otherwise healthy infant with 1 or more small, superficial, focal hemangiomas that do not involve high-risk sites (face, hands, feet, or diaper area). Infants should be carefully monitored for quantity of medication, ulceration, pain, and central nervous system adverse effects.

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