Imiquimod Treatment of Exuberant Granulation Tissue in a Nonhealing Diabetic Ulcer

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 62-year-old white woman presented with a 1-year history of a recalcitrant diabetic foot ulcer on the plantar aspect of her left foot. She had recently seen an orthopedic surgeon who recommended amputation. The dermatology service was consulted after the patient refused to undergo surgery.

The ulcer first developed during cast placement for Charcot arthropathy. After failing to respond to treatment with numerous topical debriding and antibacterial agents (concomitantly with wet-to-dry dressings), the patient underwent her first surgical debridement approximately 7 months before she presented to our clinic. She subsequently underwent 2 additional surgical debridements of the ulcer, at 3 and then 2 months, before she was seen in the dermatology department. Histopathologic review of all excised tissue failed to show evidence of malignancy. Two of the debridements were performed with the patient under general anesthesia. Of note, the use of chemical cauterizing agents, such as silver nitrate, was not attempted in the outpatient setting in this case.

See also pages 1373 and 1449

On physical examination, a 6-cm ulcer was observed on the medial aspect of the left heel and instep, with granulation tissue rising 2 to 3 cm above the plane of the foot (**Figure 1**). The epidermal border was yellow and thickened, with no surrounding induration or fluctuance. The cutaneous surface was anesthetic owing to the marked peripheral neuropathy.

THERAPEUTIC CHALLENGE

The patient had already received all of the standard treatments to control granulation tissue. Her desire to avoid amputation prompted investigational therapy based on a proposed mechanism of action against other vascular proliferations.

SOLUTION

At the patient's initial visit, the epidermal border of her ulcer was curretted to viable, bleeding epithelium. She was instructed to apply 5% imiquimod cream to the ulcer and its border at night Monday through Thursday. She applied a commonly used debriding agent (Accuzyme; CORIA Laboratories Ltd, San Antonio, Tex) containing papain and urea the other 3 nights, with mupirocin applied in the morning. She dressed the ulcer twice daily with an absorbent nonadherent pad (Telfa) secured with gauze (Kerlix; Kendall Healthcare Products, Dallas, Tex) and tape. She received follow-up every 6 weeks. The ulcer was inspected at each visit for signs of infection or malignancy; the epidermal border was curetted to viability; and prescriptions for the medications were renewed. As seen in **Figure 2**, the exuberant granulation tissue slowly regressed, allowing the epidermis to recover and the ulcer to shrink.

After approximately 7 months of therapy, the ulcer was completely healed (**Figure 3**). The patient started to ambulate again after being wheelchair bound for the previous year. She is extraordinarily pleased with the results. She did not complain of any adverse reaction during the therapy. While local pain and discomfort would have been blunted by her diabetic neuropathy, she did not experience any adverse systemic effects. Her treatment regimen, which consisted of 4 days of imiquimod and 3 days of enzymatic healing-debriding ointment (Accuzyme), allowed adequate time for both imiquimod-induced devitalization of the tissue and subsequent enzymatic debridement without causing excessive irritation or further ulceration of the tissue.

Figure 1. Six-centimeter diabetic foot ulcer with excessive granulation tissue and thickened epidermal border on the medial plantar surface of the left foot.
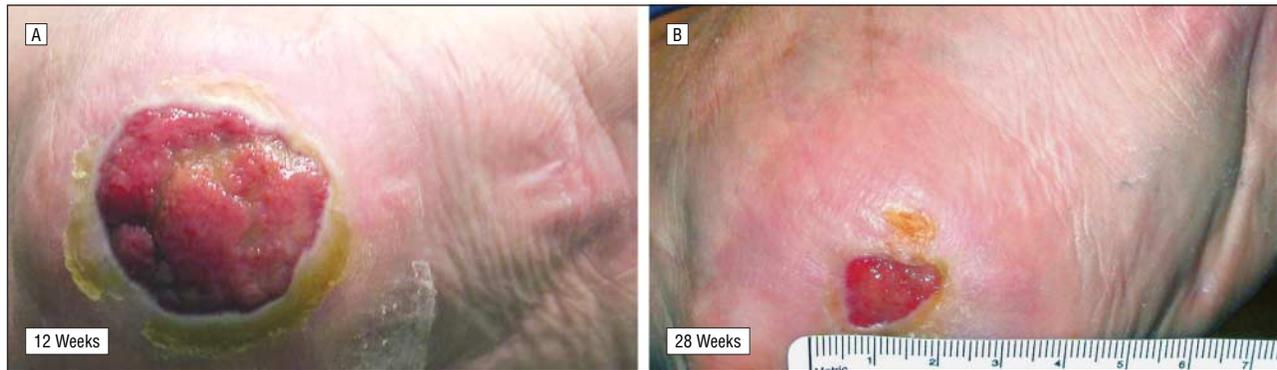
Figure 2. Improvement in ulcer size, with marked reduction of granulation tissue, after imiquimod treatment for 12 (A) and 28 (B) weeks. Ruler is in centimeters.

COMMENT

Imiquimod, first approved by the Food and Drug Administration in 1997 for the treatment of external genital and perianal warts, has since been approved for treatment of actinic keratoses and has shown activity against basal cell and squamous cell cancers, melanoma, other verrucae, keloids, cutaneous T-cell lymphoma, morphea, and other viral infections.[1-10] To our knowledge, this is the first report of the use of imiquimod for the successful treatment of exuberant granulation tissue within a nonhealing ulcer in a patient with diabetes.

The mechanism of action of imiquimod has been well described. As a synthetic ligand for toll-like receptor 7 at therapeutic doses (and toll-like receptor 8 at supratherapeutic doses), imiquimod acts to stimulate immature, plasmacytoid dendritic cells.[11] This activation has the important consequence of causing plasmacytoid dendritic cells to secrete very large amounts of interferon.[12] Although imiquimod promotes a T-helper 1 paradigm of cytokine differentiation, it also acts as a maturation factor for the plasmacytoid dendritic cells, causing them to express the costimulatory molecules CD40, CD80, and CD86, which allow for T-cell stimulation. Thus, the "master cytokine" interferon provides a link between the innate and the adaptive immune systems, an event that is related to the application of imiquimod.[13]

While most clinicians believe that it is this immune system activation that drives the anticancer and antiviral effects of imiquimod, it is more likely that another property of interferon secretion caused the improvement in the case described herein. As a commonly used chemotherapeutic agent, interferon's efficacy derives from its antiproliferative, immunomodulatory, and antiangiogenic effects. It is most likely the latter that led to the improvement in our patient.

Angiogenesis, whether in tumors or as part of wound healing, requires the correct cytokine milieu, including vascular endothelial growth factor, matrix metalloproteinase 9, basic fibroblastic growth factor, and tissue inhibitor of matrix metalloproteinase 1. Indeed, interferon achieves its antiangiogenic effects by tilting this balance of cytokines to decrease those cytokines that favor angiogenesis, such as vascular endothelial growth factor and matrix metalloproteinase 9, and promote those

Figure 3. Completely healed ulcer, shown 2 weeks after discontinuation of imiquimod therapy. The patient is no longer wheelchair bound.

that cause vessel involution, such as tissue inhibitor of matrix metalloproteinase 1.[14]

These actions are clearly elucidated in studies involving both surgical wound healing and imiquimod's action on vascular tumor growth. Regarding the proangiogenic properties of vascular endothelial growth factor, researchers have shown that antibody depletion of this cytokine in a surgical wound precludes the formation of granulation tissue altogether. Interferon's ability to deplete vascular endothelial growth factor occurs at the level of gene transcription.[15,16]

The effect of imiquimod on hemangiomas provided the initial impetus for the drug's use in our patient. Using a mouse hemangioendothelioma model, researchers have shown that application of topical imiquimod leads to involution of the tumor. Concomitant with and integral to this involution, researchers have found increased expression of tissue inhibitor of matrix metalloproteinase, further tipping the balance against angiogenesis.[14]

Imiquimod, therefore, through its activation of toll-like receptor 7 on plasmacytoid dendritic cells, promotes the secretion of very large amounts of alpha and beta interferon. Through its effect of decreasing expression of angiogenic cytokines, and by increasing the levels of antiangiogenic cytokines, interferon has been shown to be a potent antagonist of vessel formation and viability. While dermatologists have used imiquimod for this antiangiogenic effect in other vessel-rich neoplasms, such as was recently reported with hemangiomas,[17] this is the first case demonstrating the effectiveness of imiquimod therapy for unwanted, excessive granulation tissue, which

impaired the healing of a cutaneous ulcer in a patient with diabetes.

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REFERENCES

1. Edwards L, Ferenczy A, Eron L, et al. Self-administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol.* 1998;134:25-30.
2. Lebwohl M, Dinehart S, Whiting D, et al. Imiquimod 5% cream for the treatment of actinic keratosis: results from two phase III, randomized, double-blind, parallel group, vehicle-controlled trials. *J Am Acad Dermatol.* 2004; 50:714-721.
3. Geisse J, Caro I, Lindholm J, Golitz L, Stampone P, Owens M. Imiquimod 5% cream for the treatment of superficial basal cell carcinoma: results from two phase III, randomized, vehicle-controlled studies. *J Am Acad Dermatol.* 2004;50: 722-733.
4. Mackenzie-Wood A, Kossard S, de Launey J, Wilkinson B, Owens ML. Imiquimod 5% cream in the treatment of Bowen's disease. *J Am Acad Dermatol.* 2001;44:462-470.
5. Powell AM, Russell-Jones R, Barlow RJ. Topical imiquimod immunotherapy in the management of lentigo maligna. *Clin Exp Dermatol.* 2004;29:15-21.
6. Schwab R, Elston D. Topical imiquimod for recalcitrant flat warts. *Cutis.* 2000;65: 160-163.
7. Berman B, Villa A. Imiquimod 5% cream for keloid management. *Dermatol Surg.* 2003;29:1050-1051.
8. Suchin KR, Junkins-Hopkins JM, Rook AH. Treatment of stage IA cutaneous T-cell lymphoma with topical application of the immune response modifier imiquimod. *Arch Dermatol.* 2002;138:1137-1139.
9. Man J, Dytoc MT. Use of imiquimod cream 5% in the treatment of localized morphea. *J Cutan Med Surg.* 2004;8:166-169.
10. Skinner RB. Treatment of molluscum contagiosum with imiquimod 5% cream. *J Am Acad Dermatol.* 2002;47:S221-S224.
11. Hemmi H, Kaisho T, Takeuchi S, et al. Small anti-viral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway. *Nat Immunol.* 2002; 3:196-200.
12. Gibson SJ, Lindh JM, Riter TR, et al. Plasmacytoid dendritic cells produce cytokines and mature in response to the TLR7 agonists, imiquimod and resiquimod. *Cell Immunol.* 2002;218:74-86.
13. Tough DF. Type I interferon as a link between innate and adaptive immunity through dendritic cell stimulation. *Leuk Lymphoma.* 2004;45:257-264.
14. Sidbury R, Neuschler N, Neuschler E, et al. Topically applied imiquimod inhibits vascular tumor growth in vivo. *J Invest Dermatol.* 2003;121:1205-1209.
15. von Marschall Z, Scholz A, Cramer T, et al. Effects of interferon alpha on vascular endothelial growth factor gene transcription and tumor angiogenesis. *J Natl Cancer Inst.* 2003;95:437-448.
16. Howdieshell TR, Callaway D, Webb WL, et al. Antibody neutralization of vascular endothelial growth factor inhibits wound granulation tissue formation. *J Surg Res.* 2001;96:173-182.
17. Welsh O, Olazaran Z, Gomez M, Salas J, Berman B. Treatment of infantile hemangiomas with short-term application of imiquimod 5% cream. *J Am Acad Dermatol.* 2004;51:639-642.

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