Topical Imiquimod to Treat Intraepidermal Carcinoma

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF CASES

CASE 1

An 82-year-old man with severe cardiac arrhythmia and recurrent heart failure presented with a 3-year history of erythematous plaques on the left orbita and on the chest. The lesion on his left eye was a hypertrophic actinic keratosis (2 × 1.5 cm), a scaly erythematous plaque on the saddle of the nose extending to the opening of the left lacrimal duct. The chest lesion consisted of a 5 × 2.5-cm plaque with a hemorrhagic crust that caused recurrent itching. On histologic examination, the epidermal cells in the lower epidermis were atypical and showed large, hyperchromatic nuclei and abnormal mitoses (Figure 1A). The biopsy specimen tested positive for human papillomavirus (HPV) type 33 using consensus primers and polymerase chain reaction.1

CASE 2

A 52-year-old woman who previously underwent cryotherapy for a 4-mm shiny papule on the right side of the osseous part of the nose presented with a recurrence (Figure 2). On histologic examination, the lesion showed irregular keratinocytes with some dyskeratosis, increased mitoses, focal horn pearls, and a lymphohistiocytic infiltrate.

THERAPEUTIC CHALLENGE

Given the high prevalence of actinic keratoses and Bowen disease and the potential for malignant transformation,2,3 there remains a need for convenient treatments. Currently used therapies, such as cryotherapy, laser vaporization, excision, Mohs surgery, chemical peel, trichloroacetic acid, photodynamic therapy, or fluorouracil, are associated with substantial patient discomfort and significant tissue destruction.

SOLUTION

We evaluated the novel topical immune response modifier imiquimod (1-(2-methylpropyl)-1H-imidazo[4,5-c]quinoline-4-amine; 3M, St Paul, Minn) as a therapeutic alternative in 2 difficult-to-treat patients with intraepidermal carcinoma. Imiquimod was applied as 5% cream 3 times per week in an amount that could be rubbed in. In patient 1, treatment was continued for 17 weeks, when both lesions resolved. The patient did not experience any adverse effects such as erythema or discomfort while receiving treatment. A control biopsy specimen of
the chest, taken 8 months after the initial presentation, showed a scar with an increased number of blood vessels without evidence of carcinoma (Figure 1B). At the time of this report (15 months after treatment), there had been no recurrence.

Patient 2 experienced an erythema and small erosions in the treated area at week 9 (Figure 2). Treatment was stopped, and 3 weeks later, the lesion had healed without sequelae (Figure 2). During 12 months of follow-up, there was no recurrence.

COMMENT

Since actinic keratoses have a rate of progression to invasive squamous cell carcinoma of about 0.085% per lesion per year, with an even higher risk for Bowen disease, adequate treatment is necessary.

Imiquimod belongs to the new class of topical immune response modifiers. It has been successfully used for the treatment of viral infections, such as condyloma, warts, mollusca, and genital herpes, and, most recently, for basal cell carcinoma. Its mechanism of action in humans is not completely understood, but several studies suggest that it involves stimulation of the cellular immune system, including the induction of cytokines, such as interferon alpha, tumor necrosis factor alpha, and interleukin 12 (IL-12), from monocytes and macrophages. Through the induction of interferon alpha, imiquimod could enhance antigen presentation by increasing the expression of major histocompatibility complex class I and thus, together with IL-12, augment the development of a Th1-type immune response. Other cytokines that are induced by imiquimod from the epidermis, such as IL-1 and IL-6, may contribute to lesion regression by maturation and migration of Langerhans cells, increasing T-cell trafficking to the epidermis, enhancing natural killer cell cytotoxic effects, and stimulating B-cell proliferation. The local skin reactions noted with imiquimod are most likely a consequence of cytokine-induced inflammation, which is also observed with ablative therapies, such as trichloroacetic acid or fluorouracil.

The relatively long time to clinical efficacy suggests a cell-mediated immune response either against the HPV type associated with the cancerous lesion or directly against the malignant cells. This mode of action distinguishes the new class of immune response modifiers from conventional ablative techniques. Whether early forms of cutaneous neoplasia, such as actinic (solar) keratoses and Bowen disease, are associated with HPV infection is currently under debate.

Patient-applied imiquimod, the first topical immune response modifier, represents a new drug with potential for treating initial squamous cell cancers of the epidermis in selected patients. While treatment is convenient, it may be associated with erythema and erosions and infrequent scarring. Our initial observations suggest the need for larger trials to confirm this potential novel indication.

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REFERENCES


**Submissions**

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in “Instructions for Authors.” Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017. Reprints are not available.

**ARCHIVES Web Quiz Winner**

Congratulations to our January Web quiz winner, Sheila Au, MD, of the University of British Columbia, Vancouver. The correct answer to the January challenge was cylindroma. For a complete discussion of this case, see the Off-Center Fold section in the February ARCHIVES (Salvan D, Nguyen RCL, Wassel M, Portier F, Enjolras O, Hadjean E, Tran Ba Huy P. Multiple and disseminated scalp nodules. Arch Dermatol. 2001;137:219-224).

Be sure to visit the Archives of Dermatology World Wide Web site (http://www.archdermatol.com) to try your hand at the Interactive Quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the Archives. The first visitor to e-mail our Web editors with the correct answer will be recognized in the print journal and on our Web site.