Imiquimod Induces Sustained Remission of Actinic Damage: A Case Report Spanning One Decade of Observation

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Practice Points

- Topical immunomodulators such as imiquimod and topical chemotherapeutics such as 5-fluorouracil are effective in the field treatment of actinic keratoses.
- Prior topical immunomodulator use for nonmelanoma skin cancer may induce a sustained remission of actinic damage.
- The field effect of imiquimod treatment in actinically damaged skin may persist for several years.

Actinic keratosis (AK), basal cell carcinoma (BCC), and squamous cell carcinoma (SCC) are strongly linked to chronic UV radiation exposure. Although surgical treatment is necessary for advanced skin cancers, the use of topical 5-fluorouracil (5-FU) and imiquimod are well established for treatment of early skin cancers and as field therapy for diffuse actinic damage. We present the case of a patient who underwent field therapy with topical 5-FU for diffuse actinic damage and AKs and showed no inflammatory response within the perimeter of a prior BCC that had been treated with imiquimod 10 years prior. In addition to the drug effects of imiquimod on atypical keratinocytes, it also may have photoprotective effects.

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Sun damage and chronic exposure to UV radiation have been recognized as causative factors for the development of squamous cell carcinoma (SCC), its precursor actinic keratosis (AK), and basal cell carcinoma (BCC). Although surgical treatment is necessary for most advanced cases of skin cancer, several other therapeutic approaches have been described including the use of topical chemotherapy agents such as 5-fluorouracil (5-FU) and topical immunomodulators such as imiquimod. Unlike surgery, these agents provide the added benefit of treating larger fields of photodamaged skin. With the increasing prevalence of nonmelanoma skin cancers (NMSCs), the use of multiple topical agents for treatment will continue to become more common.

We present the case of a patient who underwent field therapy with topical 5-FU for diffuse actinic damage and AKs. There was no subsequent inflammatory response within the perimeter of a BCC that had been treated with imiquimod 10 years prior.

Case Report

An otherwise healthy 58-year-old man with a history of long-standing diffuse sun damage and multiple prior NMSCs presented for treatment of a recurrent BCC on the right cheek. The patient reported that the BCC had initially been biopsied and excised by his primary care physician. Two months later local recurrence was noted by the primary care physician and the patient was subsequently referred to our dermatology office. A 2-month treatment course with daily imiquimod cream 5% was initiated. This treatment caused extensive inflammation of the right cheek but was otherwise well tolerated (Figure 1).

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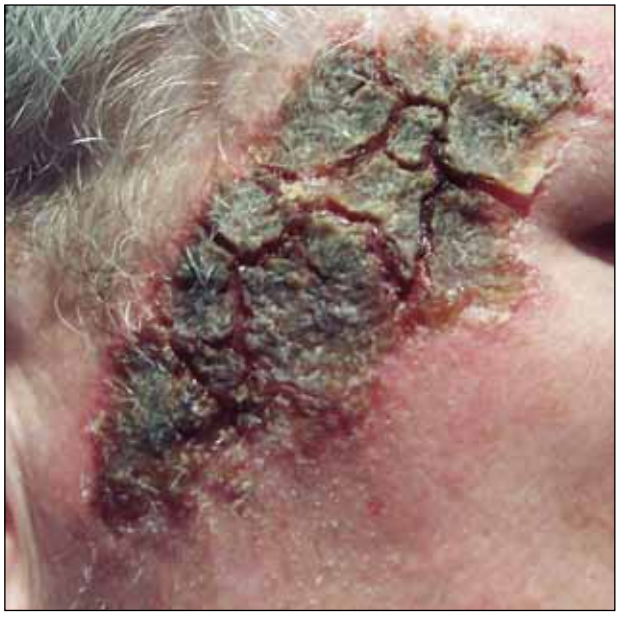

Figure 1. Extensive inflammation following application of imiquimod cream 5% for treatment of basal cell carcinoma.

During a routine skin cancer screening 10 years later, no recurrence of the BCC was noted on the right cheek; however, the patient had developed multiple AKs on the face. Therapeutic options were discussed with the patient; he agreed to topical field therapy with 5-FU cream 0.5%. The patient applied the 5-FU cream to the entire face nightly for 1 month. During this time he experienced a brisk inflammatory response with painful cracking and redness of the skin. On follow-up, it was noted that the area on the right cheek that had been treated with imiquimod 10 years prior showed no inflammatory response despite nightly application of 5-FU cream to the area (Figure 2). The patient denied any routine use of sunscreen or other sun-protective practices.

Comment

Basal cell carcinoma is the most common skin cancer in the United States with an incidence of 1.4% to 2% per year. It has become more prevalent in recent decades, likely due to genetic predisposition and increasing cumulative sun exposure.[1-4] A variety of treatment options are available. Surgical interventions include destruction via electrodesiccation and curettage, local excision, and Mohs micrographic surgery. One of the challenges in the management of BCC, as was the case in our patient, is the treatment of tumors that arise in cosmetically or functionally sensitive areas. Approaches that minimize the amount of tissue removed while ensuring the highest possible cure rate are favorable. In addition to surgery, topical imiquimod has been established as a potential treatment of BCC. Imiquimod, a nucleoside analogue of the imidazoquinoline family, is an agonist of toll-like receptors 7 and 8 that promotes cytokine-induced cell death via nuclear factor κB and a helper T cell T_H1-weighted antitumor inflammatory response.[5,6] Although clearance rates with imiquimod vary by drug regimen, success rates of 43% to 100% for superficial BCCs, 42% to 100% for nodular BCCs, and 56% to 63% for infiltrative BCCs have been reported.[7] In a 2007 randomized study of imiquimod cream 5%, 5-FU ointment 5%, or cryosurgery for the treatment of AK, imiquimod resulted in superior and more reliable clearance with lower recurrence rates.[8]

Similar to BCC, AK is closely linked to lifetime cumulative sun exposure.[9] Actinic keratoses have

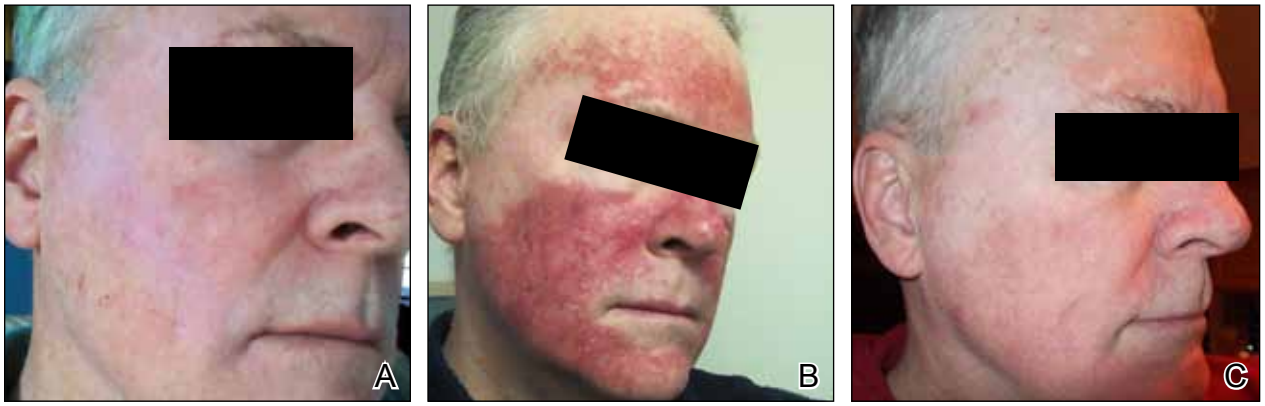

Figure 2. Right side of the patient's face on day 1 (A) and day 30 (B) of treatment with 5-fluorouracil cream 0.5% as well as 15 days posttreatment (C), with no inflammatory response on the area that was previously treated with imiquimod.

been well established as precursors to SCC, and some researchers advocate for their reclassification as early SCC in situ.[10] The incidence of malignant conversion of AK to SCC has been estimated at 0.025% to 16% annually, with an estimated lifetime risk for malignant transformation of 8% per individual AK.[11,12] Cryotherapy has been a mainstay for the treatment of isolated AK, and alternative therapies including curettage, photodynamic therapy, and laser therapy have been employed. Field-directed therapy has become a popular alternative that targets multiple lesions and field cancerization.[8,13,14] Field cancerization implies that if one cell in the patient's epidermis has been exposed to enough UV radiation to develop into a precancerous lesion or early skin cancer, then many other cells in the same environment likely have some degree of UV radiation–induced atypia.[15] 5-Fluorouacil is a pyrimidine analogue chemotherapeutic agent that inhibits thymidylate synthase and interferes with DNA synthesis.[16] This mechanism of 5-FU commonly causes an inflammatory response characterized by burning, dryness, and redness, but these effects rarely force early discontinuation of treatment. A randomized controlled trial comparing 5-FU cream 0.5% to a placebo found that complete clearance rates at 4 weeks posttreatment were significantly higher in the treatment group (47.5%) versus placebo (3.4%)($P<.001$).[13] Additional trials have established no significant superiority of 5-FU cream 5% over 5-FU cream 0.5%, with a decrease in side effects noted in patients treated with the lower concentration.[17]

Our patient had a history of a recurrent BCC and was previously treated with imiquimod. He showed no inflammatory response to field therapy with 5-FU within the perimeter of prior immunomodulatory therapy. Although no frank scaling or crusting papules consistent with AK were observed in the previously treated area prior to 5-FU therapy, subclinical field damage in that area was expected because 10 years of additional sun exposure had accumulated since imiquimod therapy was completed. Several conclusions can be drawn from this observation. Primarily, no new clinically significant actinic lesions occurred on the previously treated skin. This observation is consistent with 12-month follow-up data on AKs treated with either 5-FU, imiquimod, or cryosurgery that identified imiquimod as having the lowest recurrence rate.[8] Thus, a photoprotective effect may be ascribed to imiquimod therapy that extends beyond its drug effects on atypical keratinocytes. It has been one author's personal experience (M.Q.) that patients treated with 5-FU experience recurrence of AKs within 3 to 5 years versus 10 years of remission with imiquimod. In our patient, imiquimod therapy seemed to reset the patient's skin at the location of the prior BCC and surrounding field cancerization.

Studies with long-term follow-up are needed to investigate the need for re-treatment with imiquimod or 5-FU. The longevity of imiquimod treatment may be of importance beyond the treatment of AKs or NMSCs. For instance, during the treatment of lentigo maligna with imiquimod, Metcalf et al[18] found a significant reduction in solar elastosis ($P=.0036$), normalization of epidermal thickness ($P=.0073$), and increased papillary dermal fibroplasia in pre- and posttreatment biopsies ($P<.0001$), which have been described as antiaging effects in the laypress. Some of these mechanisms appear to be implicated in the observations noted in our patient. The 10-year period between the 2 courses of therapy in our patient suggests that imiquimod may cause sustained healing of skin that was previously classified both clinically and microscopically as UV damaged.

Conclusion

Both topical immunomodulators such as imiquimod and topical chemotherapeutic agents such as 5-FU have a role in the field treatment of AK and the focal treatment of superficial BCC and SCC. As multiple topical immunomodulators continue to be evaluated, long-term studies assessing the need for re-treatment as well as the degree of sustained remission of sun damage will be necessary. We expect that their individual roles will continue to become more precisely defined and distinct in the coming years.

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