Successful Treatment of Invasive Squamous Cell Carcinoma Using Topical Imiquimod

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 65-year-old man with a history of renal transplantation, chronic renal insufficiency after graft failure, and hemodialysis presented with a red palpable lesion on his right temple that had developed over a 3-year period (Figure 1A). The 4 × 3-cm erythematous hyperkeratotic plaque was located at the hair rim. On palpation, some induration and several papules were noted. Histologic examination of a 5-mm punch biopsy specimen showed tumor cells with variably irregular nuclei and several atypical mitoses that extended into the dermis (Figure 2A).

The patient’s medical history was remarkable for metastatic prostate cancer and 5 years of hemodialysis because of chronic renal failure. Because of prostate cancer that had been diagnosed in 1998 and had metastasized to the seventh right rib, the patient was not undergoing chemotherapy. His most recent prostate-specific antigen level was within normal limits. His current medications were furosemide, simvastatin, and epoetin alfa.

THERAPEUTIC CHALLENGE

Our challenge was to use a noninvasive, conservative treatment in a patient with chronic renal failure and prostate cancer. Therapeutic modalities such as cryotherapy, excision, photodynamic therapy, and radiotherapy are associated with tissue destruction and/or substantial patient discomfort. The recent success of topical immunomodulatory therapy with imiquimod for basal cell cancer, in situ carcinoma (Morbus Bowen), and actinic keratosis, prompted us to start the patient on a self-applied regimen of 5% imiquimod cream to be applied 3 times per week and left on overnight for 8 hours.

After 3 weeks of treatment, the lesion showed initial signs of regression at the borders, while the central erythema persisted (Figure 1B). The treatment was terminated at week 12. The patient reported no adverse effects other than some scaling. At week 16, he presented with a scar at the initial site of the lesion (Figure 1C), but there was no evidence of squamous cell carcinoma (SCC) in the biopsy specimens obtained from the borders and center of the area (Figure 2B).

COMMENT

While several studies have shown the efficacy of imiquimod therapy for basal cell cancer, in situ carcinoma (Morbus Bowen), and actinic keratosis, the present article reports the first case of invasive SCC successfully treated with topical imiquimod in a patient with chronic renal failure and prostate cancer. The histologic findings at the completion of treatment and the recurrence-free follow-up of 16 months suggest clinical cure.

Imiquimod belongs to a new class of topical immune response modifiers. It has been approved for the treatment of condylomata acuminata and has also shown efficacy in the treatment of other viral lesions, such as common warts, mollusca, and genital herpes. The mechanism of action in humans is not completely understood, but it involves the stimulation of the cellular immune system after interaction with toll-like receptor 7, leading to the induction of several cytokines, such as interferon alfa, tumor necrosis factor alpha, and interleukin 12, from monocytes and macrophages. Current thinking suggests that through the induction of interferon alfa, imiquimod may enhance antigen presentation by increasing the expression of mature histocompatibility class I and therefore, along with interleukin 12, augmenting the development of a type 1 helper T-cell immune response. Also, the maturation and migration of Langerhans cells may contribute to improved antigen processing and presentation.

In our patient, the 12-week treatment period was comparable to the length of imiquimod therapy needed to treat viral diseases. Since SCCs are not infrequently associated with human papillomavirus (HPV) in lesions in immunocompromised (84%) or immunocompetent patients, a cell-mediated immune response against HPV seems possible. Alternatively, cancerous antigens may serve as immunologic targets. In this regard, SCC antigens 1 and 2, which belong to the high-molecular-weight serine protease in-
hibitor (serpin) superfamily, may serve as tumor antigens. Usually, SCC antigens 1 and 2 are coexpressed in the suprabasal layers of stratified squamous epithelium of the tongue, tonsils, esophagus, uterine cervix, and vagina. However, they were recently detected in SCCs of the lungs and in cancers of the head and neck, where they were coexpressed in moderately to well-differentiated tumors, as in our case. An alternative theory suggests that imiquimod directly induces apoptosis of tumor cells, as has recently been demonstrated in a study of basal cell carcinomas. In that study, imiquimod was found to induce several mediators of apoptosis (eg, Fas, caspase 10, TRAF1, and TRADD) besides the up-regulation of interferon-inducible genes (eg, MxA and MxB and STAT1 and STAT2), antigen-processing and presentation molecules (eg, PA28, TAP-1, PSMB6, and PSMB10), and immune-activation markers (CD40, CD86, LAG-3, RANTES, MIP-1R, and CCR7R).

The role of HPV in SCC in immunocompromised patients is still unclear. An extremely diverse group of HPV types, mainly consisting of epidermodysplasia verruciformis–associated HPV types, can be detected in benign, premalignant, and malignant skin lesions in organ transplant recipients. Frequently, there are multiple HPV types present in single skin biopsy specimens. A comparison of transplant recipients with and without skin cancer, however, showed an equally high prevalence of epidermodysplasia verruciformis HPV DNA. The E6 protein from a range of cutaneous HPV types effectively inhibits apoptosis in response to UV-light–induced damage. It is therefore conceivable that individuals who are infected by epidermodysplasia verruciformis HPV are at an increased risk of developing SCC, possibly by chronically preventing UV-light–induced apoptosis in conjunction with their iatrogenic immunosuppression.

Our report also shows that topical immunomodulatory treatment is possible in severely compromised patients with renal failure and prostate cancer, indicating the intact quality of the skin-derived immune system under these conditions. However, the treatment should be
reserved for selected patients and should be based on history of skin cancer, immune status, age, compliance, and reduced physical performance. While the potential for nonsurgical, patient-administered treatment of cutaneous malignant neoplasms in selected patients is great, extreme caution should be executed in clinical and histologic follow-up. Careful follow-up is strongly advised to detect lesions that are suggestive of recurrence. Histologic samples should be analyzed for response and margins. Furthermore, carefully designed studies are necessary to establish the usefulness of topical immunomodulatory therapy for SCC of the skin.

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