An Atypical Presentation of Squamous Cell Carcinoma in Situ Treated Successfully with Imiquimod Cream

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Abstract

Squamous cell carcinoma in situ (SCCIS), also known as Bowen disease, is a histologic diagnosis.1 It is the earliest, non-invasive form of squamous cell carcinoma (SCC). “In situ” indicates that the cancer cells are confined only to the epidermis and have not invaded the dermis.2,3 If untreated, SCCIS can sometimes progress to an invasive squamous cell carcinoma.4 Herein, we describe a patient with an unusual presentation of SCCIS, treated successfully with imiquimod 5% cream applied in multiple short bursts over a five-month time frame.

Case Report

An 84-year-old Caucasian woman presented with a red cheek of 10 years’ duration. She stated that she had been applying topical triamcinolone 0.1% cream on the area for three to four weeks without change. On exam, she had a 6.0 cm x 6.0 cm erythematous, indurated, non-scaling, smooth plaque involving her entire right cheek from the lower eyelid to the nasolabial fold. There was a profound difference in skin texture when compared to her left cheek. Her left cheek appeared consistent with her age, while her right cheek had mild edema, but the lack of scale and actinic damage were typically associated with SCCIS; we opted to treat her with imiquimod 5% cream.

In anticipation of an exaggerated response, she began treatment with imiquimod 5% cream two nights per week with a plan to adjust application frequency based on her response and tolerance. The patient returned to the clinic five weeks later with an anticipated brisk, erythematous, crustured eruption. She was instructed to stop applications for four weeks, after which time we planned to restart her at two nights per week. At her follow-up appointment, her face had healed well, and she only had an erythematous patch in the treatment field. She restarted applications two nights per week in six-week intervals with a four-week break between cycles. With each cycle, her response became less intense until the point where she had only a minimal response. At this point, she had completed four six-week cycles. She was instructed to stop all applications to allow the area to heal, anticipating re-biopsy of the area to see if the treatment was successful. She returned in six weeks. Clinically, her right cheek had mild erythema with decreased induration and decreased fullness. Three additional scouting punch biopsies were taken from the center and periphery of the treatment area. All three biopsies were free of tumor without any epidermal atypia. She was free of disease at her six-month follow-up.

Discussion

Squamous cell carcinoma in situ (SCCIS), also known as Bowen disease, is a histologic diagnosis.1 It is the earliest, non-invasive form of squamous cell carcinoma (SCC). “In situ” denotes that the cancer cells are confined only to the epidermis and have not invaded the dermis.2,3 Like most other skin cancers, the major risk factor is excessive sun exposure, though arsenic exposure and human papilloma virus (HPV) are also risk factors.3 If untreated, SCCIS can sometimes progress to an invasive squamous cell carcinoma.4 Clinically, SCCIS usually appears as asymptomatic, reddish, scaly patches that trend toward centrifugal spreading.3 The epidermis may become atrophic or hyperkeratotic, and a cutaneous horn may develop over the lesion.2,3 Our patient’s SCCIS, however, did not present as such. The induration and rosy glow on her cheek may have been from underlying inflammation and edema, but the lack of scale and actinic damage typically associated with SCCIS were lacking. To our knowledge, this is the first report of a patient presenting with SCCIS in this manner.

Histologically, SCCIS shows atypical keratinocytes with hyperchromatic nuclei, nuclear pleomorphism, disordered maturation, multiple apoptotic keratinocytes, loss of the granular layer, parakeratosis and increased numbers of mitotic figures.2,4 The epidermis may show a “wind-blown” appearance of the abnormal keratinocytes caused by loss of orderly maturation.3 One may also see extension of the atypical cells down hair follicles. In early SCCIS, atypical keratinocytes are confined to the basal and suprabasal layers of the lower one third of the epidermis. The follicular structure is uninvolved. As lesions progress, atypical keratinocytes extend into the upper two thirds of the epidermis. Buds of keratinocytes in

Figure 1

Figure 2

Figure 3
the upper papillary dermis are also commonly found. Most pathologists define SCCIS at the point when atypical keratinocytes extend to more than two thirds of the full thickness of the epidermis and involve the epithelia of the hair follicle.

Imiquimod, a nucleoside analogue of the imidazoquinoline family, is a topical immune-response modifier. It enhances both the innate and acquired immune responses, in particular the cell-mediated immune pathway. The major biologic actions of imiquimod are thought to be mediated through agonistic activity on toll-like receptors (TLR) 7 and 8 and, simultaneously, activation of nuclear factor-kappa B (NF-kappa B). As a result of this activity, the induction of pro-inflammatory cytokines, chemokines and other mediators including IFN-alpha, IL-1, -6, -8, -10, -12, and TNF-alpha results in the activation of nuclear factor-kappa B (NF-kappa B). Furthermore, independent of TLR-7 and TLR-8, imiquimod appears to interfere with adenosine-receptor signaling pathways, and the compound causes receptor-independent reduction of adenylyl cyclase activity. This unique mechanism may augment the pro-inflammatory activity of the compound through suppression of a negative regulatory feedback mechanism that normally limits inflammatory responses. Finally, imiquimod induces apoptosis of tumor cells at higher concentrations. The pro-apoptotic activity of imiquimod involves caspase activation and appears to depend on B cell lymphoma/leukemia 2 (BCL)-2 protein. Imiquimod cream is only approved for use as a topical therapy in the treatment of Bowen’s disease, condyloma acuminata and vulgaris. The indications for use are not limited to patients with immunosuppressed conditions, and the majority of patients receiving treatment are immunocompetent. Other indications for use include basal cell carcinoma (BCC), actinic keratoses (AK) on the face or scalp in immunocompetent adults; biopsy-confirmed, typical, non-hyperkeratotic, non-hypertrophic primary superficial basal cell carcinoma (sBCC) in immunocompetent adults with a maximum tumor diameter of 2.0 cm on the trunk, neck, or extremities (excluding hands and feet) only when surgical methods are medically less appropriate and patient follow-up can be reasonably assured; and external genital and perianal warts/condyoma acuminata in patients 12 years of age or older.

SCCIS is a precursor to invasive squamous cell carcinoma. Therefore, it should be treated before invasive cancer develops. Treatment can involve both surgical and nonsurgical methods. Many articles describe the use of surgical excision, electrodessication and curettage, cryotherapy, 5-fluorouracil, imiquimod, radiation, photodynamic therapy, and lasers. Although imiquimod is off-label for this purpose, there are reports of its successful use in treating SCCIS. Patel et al. performed a placebo-controlled trial of 15 patients and showed clearance in 11 of the 15 lesions versus zero in the placebo-controlled group. Schroeder et al. and Cook-Bolden et al. found it to be a successful treatment in 14 of 15 SCCISs of the lower limbs. Furthermore, Smith et al. demonstrated successful use in combination with a COX inhibitor in the treatment of SCCIS in immunosuppressed patients. Finally, there is also a report of successful treatment of SCCIS with a combination of imiquimod, 5-fluorouracil, and tazarotene to the dorsal hands. Imiquimod 5% cream was the best option for our patient because we were able to tailor her treatment according to her response to and tolerance of the medication. It worked well to rid her of the condition.

There are still many unanswered questions, though. Our patient’s clinical presentation was unusual, and perhaps imiquimod was more effective in our patient owing to enhanced penetration from decreased keratinization. Although additional, blinded studies with larger sample sizes are needed, imiquimod may be another treatment option for SCCIS when surgery or radiation therapy are not optimal choices.

References