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CASE AND RESEARCH LETTERS

Erythema Multiforme Due to 5% Imiquimod Cream

Eritema multiforme por imiquimod 5% crema

To the Editor:

Imiquimod 5% cream (Aldara, 3M Pharmaceuticals) is a topical immunomodulator approved for the treatment of genital warts, actinic keratoses, and superficial basal cell carcinoma, although it is also used off-label in clinical practice for other dermatologic conditions. Although local side effects are most frequent, it can also produce systemic side effects. We describe the case of a patient who presented with exudative erythema multiforme that coincided with imiquimod treatment.

The 66-year-old woman, with a history of hypertension, depression, and osteoarthritis, had been on treatment for many years with amiloride plus hydrochlorothiazide, lorazepam, citalopram, and dexibuprofen. She came to the outpatient clinic with facial lesions, evident actinic damage, several actinic keratoses on the dorsum of the nose and the upper lip, and a superficial basal cell carcinoma measuring 0.7 cm on the left cheek. Treatment with imiquimod cream was prescribed for all the lesions, to be applied to the actinic keratoses 3 times a week (alternate days) for 4 weeks, and to the superficial basal cell carcinoma 5 times a week for 6 weeks. At the end of the second week of treatment, the patient had developed an intense local reaction at the sites of application, presenting as crusting, edema, and erythema; treatment with imiquimod was interrupted. It was recommenced 7 days later, but within 14 days lesions appeared on the chest, forearms, hands, and legs, accompanied by a burning sensation, a worsening of the facial lesions, a feeling of fever, and general malaise. Physical examination revealed the whole of the nose, the upper lip, and the left cheek to be covered by extensive areas of crusting that left erosions when lifted, and several round erythematous papules, measuring between 0.5 cm and 0.8 cm, in the central upper chest area, on the extensor surfaces of the forearms and lower legs, and on the dorsum of the hands; some of these papules had central erosions and others presented a target morphology (Figures 1 and 2). There was no involvement of the palms, soles, or mucosas. The patient denied having taken any drugs other than her usual medication, or having previously had herpes simplex or any other infection. Biopsy of a papule revealed epidermal necrosis, involvement of the dermal-epidermal interphase with damage to the basal layer, and perivascular lymphocytic inflammation in the papillary dermis, all consistent with exudative erythema multiforme (Figure 3). Treatment with imiquimod was suspended, and the lesions were treated with topical antibiotics; her usual medication was maintained. The patient responded well, with complete resolution of the systemic and cutaneous alterations within a few days.

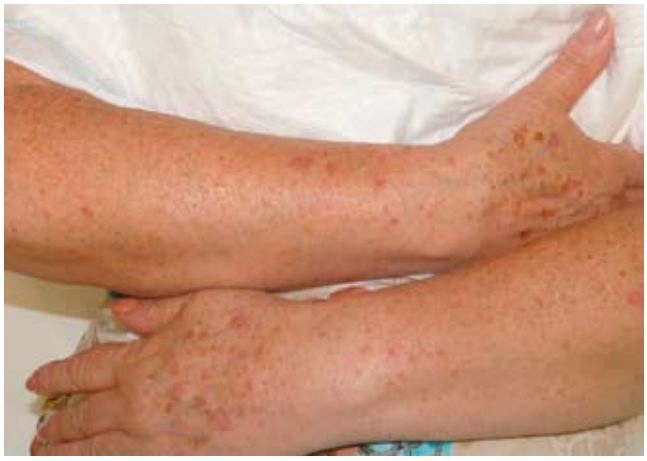

Figure 1 Erythematous papules on the extensor surfaces of both forearms, some with central erosions.

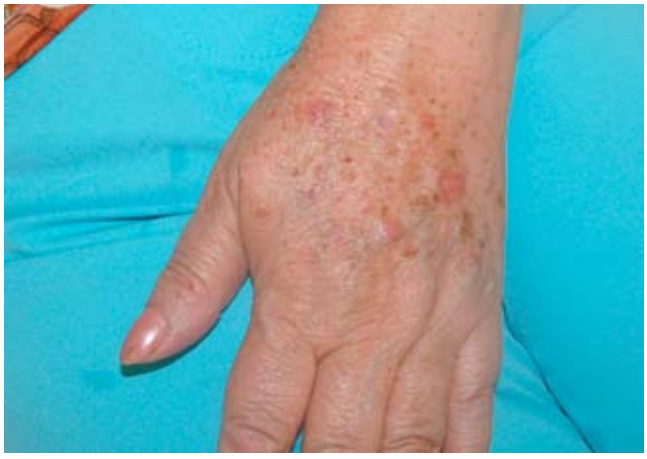

Figure 2 Detail of erythematous papules on the dorsum of the hand on skin with actinic damage.

Imiquimod is a topical immunomodulator whose antitumoral and antiviral activity results from its capacity to stimulate both innate and acquired immune responses. Although its precise

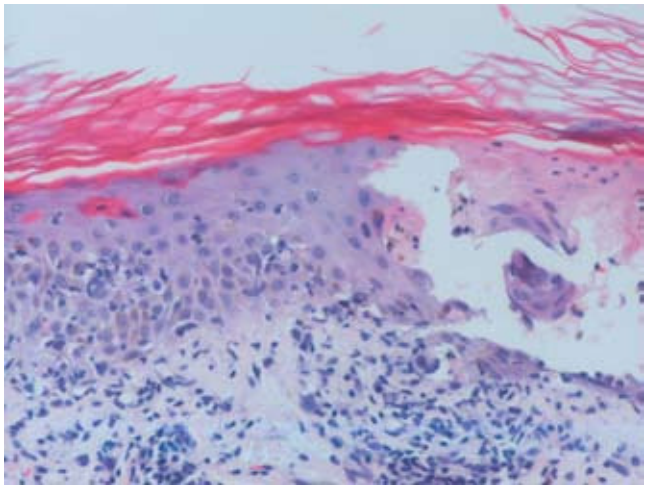

Figure 3 Skin with hyperkeratosis, involvement of the dermal-epidermal interphase, subepidermal vesiculation, mononuclear inflammatory cells, and necrosis of the overlying epidermis. There are signs of local regeneration and a superficial perivascular lymphohistiocytic infiltrate in the dermis (hematoxylin-eosin, original magnification ×10).

mechanism of action is not fully understood, it is known that it acts through the toll-like receptors 7 and 8. Activation of these receptors leads to the secretion of proinflammatory and antimicrobial cytokines, particularly tumor necrosis factor α, interferon α, and interleukins 6 and 8, which stimulate T-helper 1 and inhibit T-helper 2 lymphocytes. Clinically this causes acute local inflammation, with destruction of tumors and virus-infected cells. Most adverse reactions are local rather than systemic. Cutaneous adverse reactions consisting of erythema, crusting, edema, vesicles, or ulcers are frequently observed in the area of application and resolve with satisfactory cosmetic results; patients also often complain of pruritus and a burning sensation. Possible systemic reactions include an influenza-like syndrome, with asthenia, fever, joint and muscle pain, headache, nausea, and diarrhea.[1] Other local skin reactions have been reported, such as changes in pigmentation (hypopigmentation and hyperpigmentation), the isolated appearance of vitiligo-type lesions with poliosis, eruptive epidermoid cysts, worsening of previous granuloma annulare lesions, satellite inflammatory papules, eruptive keratoacanthomas, aphthosis, pemphigus foliaceus, and pemphigus vegetans. More rarely, there have been reports of distant lesions due to the exacerbation of previous skin disorders such as psoriasis,[2] eczema, and pityriasis rubra pilaris, and the de novo appearance of pemphigus vulgaris,[3] a morbilliform exanthem in an immunosuppressed patient,[4] angioedema, and urticaria.[5,6] Extracutaneous reactions, such as chronic neuropathic pain at the site of application,[7] spondyloarthropathy, and changes in blood cell counts[8] have also been reported. According to the summary of product characteristics, skin reactions, including exudative erythema multiforme, distant to the site of application have been reported in clinical trials. Cases of exudative erythema multiforme have been notified post-authorization, and also severe cases of Stevens-Johnson syndrome and cutaneous lupus, although the number of patients affected and their clinical details are not reported. Only 1 case similar to ours has been reported at a conference[9] and no cases have been reported in the literature.

In general, the systemic adverse effects appear to be due to cytokines being released from the skin into the blood stream rather than to imiquimod itself, as imiquimod absorption is minimal after topical application (mere nanograms are detected in the blood). Severity may be related to the frequency of application, the extent of the skin reaction, or ulceration; consequently, low doses of imiquimod are recommended for patients with extensive or numerous lesions. It should be borne in mind, nevertheless, that there is marked variability in skin and systemic reactions between individuals, even in patients using the same therapeutic regimen.

There have also been reports of exudative erythema multiforme resulting from contact with a number of allergens, such as topical drugs, chemical substances, and plants. The list of allergens includes topical corticosteroids, nonsteroidal anti-inflammatory drugs, glyceryl trinitrate skin patches, povidone iodine, paraphenylenediamine, rubber gloves, nickel, herbicides, and mixed fragrances. The pathogenesis of the disorder is unknown, but in cases like ours it would appear to be the result of systemic absorption associated with immunological phenomena with type III and IV hypersensitivity reactions.

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