Acta Dermatovenerol APA

Acta Dermatovenerologica
Alpina, Pannonica et Adriatica

2020;29:47-49
doi: 10.15570/actaapa.2020.11

Imiquimod-associated erythema multiforme

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Abstract

Patients with multiple actinic keratoses are frequently treated with topical agents such as imiquimod, an immune-response modifying agent. Adverse effects associated with imiquimod therapy are mainly limited to the application site and include erythema, crusting, scaling, and ulceration. Systemic adverse reactions such as erythema multiforme are rare. Here we report a case of a 77-year-old patient that developed erythema multiforme after treatment of actinic keratoses with imiquimod. Cessation of imiquimod and treatment with local corticosteroids led to rapid regression of erythema multiforme lesions. Residual actinic keratoses were treated with cryotherapy.

Keywords: cutaneous adverse drug reaction, topical immunomodulators, malignant epithelial tumors

Received: 13 January 2020 | **Returned for modification:** 15 February 2020 | **Accepted:** 15 March 2020

Introduction

Erythema multiforme is an acute, immune-mediated, self-limited disorder triggered by certain infections, medications, or other various agents. It is considered a type IV hypersensitivity reaction and it is characterized by symmetrically distributed targetoid lesions that can be accompanied by mucosal erosions (1, 2). The most common causes are herpes simplex virus (HSV) and *Mycoplasma pneumoniae* infection (3, 4). Systemic drugs are the second most frequent causative agents (1). Topical drugs rarely cause erythema multiforme or erythema multiforme-like reactions (5). Here we report the case of a 77-year-old patient that developed erythema multiforme after treatment of actinic keratoses with imiquimod.

Case report

A 77-year-old man with light skin presented with a 4-year history of persistent scaly papules and plaques on his bald head. In the past he was diagnosed with actinic keratoses and was treated once with cryotherapy. He was otherwise healthy. On physical examination, pigmented thickened papules and plaques with a scaly surface were found. Based on clinical appearance, a diagnosis of actinic keratoses was made. We prescribed him 5% imiquimod cream and he started applying the cream three times per week to the affected skin. After 3 weeks a prominent local reaction developed at the application site and new lesions appeared on the upper extremities, back, and lips. On physical examination, symmetrically distributed round macules, some with central vesicles on the upper extremities and neck, erosions on the lips, and hyperkeratotic crusts on his scalp were found (Figs. 1–4). A physical examination revealed no further anomalies. Histopathological examination of a skin lesion specimen from the upper extremity showed keratinocyte necrosis with the formation of intraepidermal gap under necrosis and interface dermatitis with an inflammatory, predominantly lymphohistiocytic infiltrate in the papillary dermis (Fig. 5). Polymerase chain reaction (PCR) for HSV-1 and HSV-2 from a swab of a lip lesion was negative.

Based on the clinical features and histopathological findings, a diagnosis of erythema multiforme was made. Because other common causes for erythema multiforme were ruled out, we concluded that imiquimod was the most likely cause. Therapy with imiquimod was stopped. The patient was treated with topical corticosteriod cream, and after 20 days of therapy all erythema multiforme lesions disappeared. Residual actinic keratoses were treated with cryotherapy.

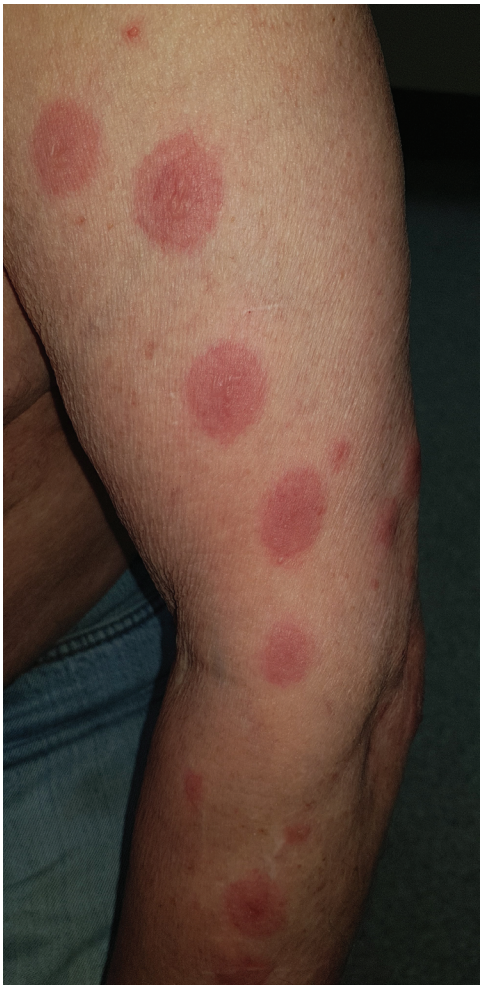

Figure 1| Targetoid lesions distributed symmetrically on the upper extremities.

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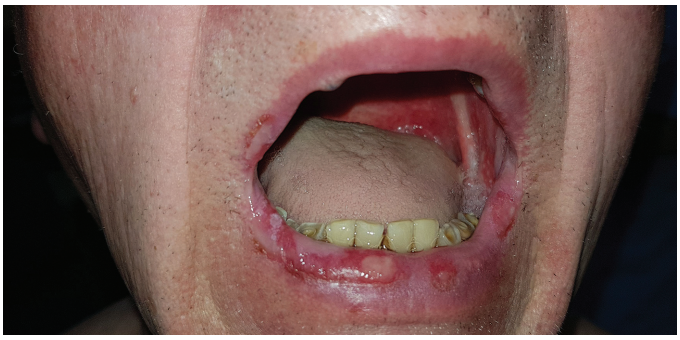

Figure 2 | Mucosal erosions.

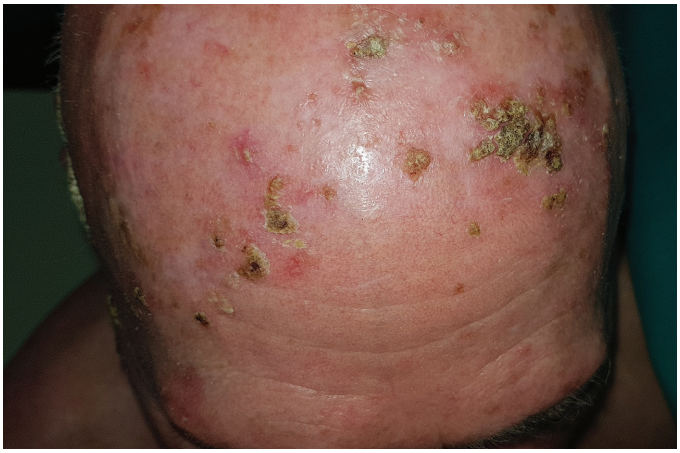

Figure 3 | Moderate inflammation with erythema and crusting on the scalp.

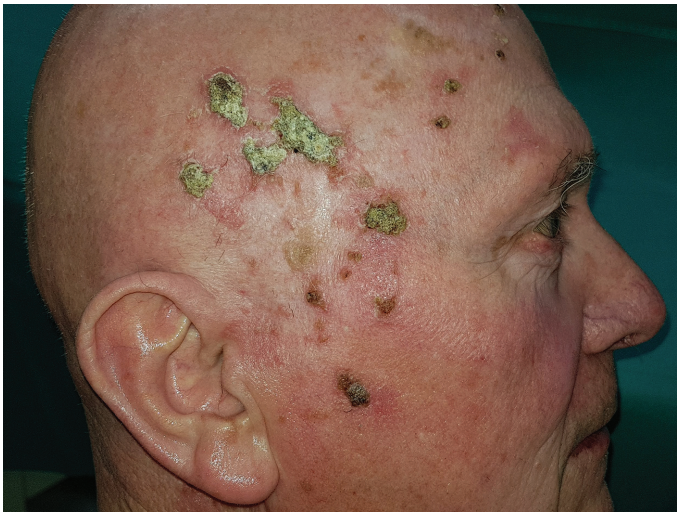

Figure 4 | Moderate inflammation with erythema and crusting on the scalp.

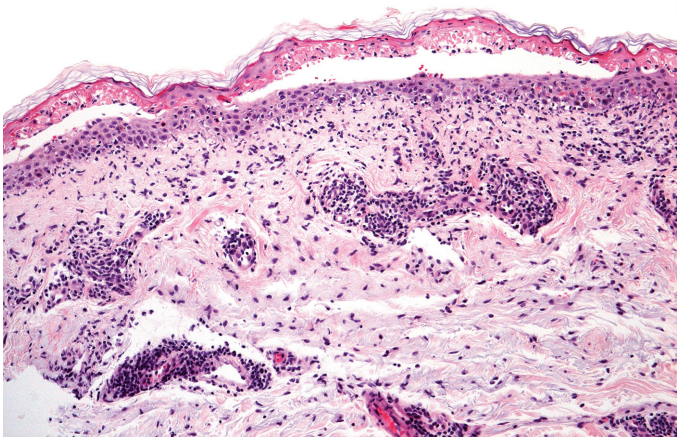

Figure 5 | Intraepidermal blistering with completely necrotic roof of the blister, marked apoptosis and hydropic degeneration of the basal cell layer.

Discussion

Imiquimod is approved for the treatment of actinic keratoses, superficial basal cell carcinomas, and genital warts. It activates both the innate and the acquired immune system (6). Through stimulation of toll-like receptor 7 on the surface of antigen-presenting cells, imiquimod induces the production and secretion of various proinflammatory and antimicrobial cytokines, such as interferon-α and -γ, tumor necrosis factor-α, and interleukins 1, 6, 8, 10, and 12, resulting in stimulation of T-helper 1 cells and cytotoxic T lymphocytes (7, 8). Clinically, this reaction manifests itself with acute local inflammation, which leads to elimination of cells with neoplastic changes, as well as virus-infected cells. The intense local reaction may result in a better treatment outcome (9). There have been reports of rare adverse cutaneous effects after imiquimod therapy, such as aphthous ulcers, eczema, alopecia, hyperpigmentation, vitiligo-like pigmentation, subacute cutaneous lupus erythematosus, pemphigus foliaceus, pemphigus vulgaris, linear IgA bullous dermatosis, eruptive epidermoid cysts, keratoacanthoma, lichen planus, lichen sclerosus, psoriasis-like dermatitis, angioedema, urticaria, morbilliform exanthema in an immunosuppressed patient, and lymphoedema (10–26). Other dermatological disorders associated with imiquimod are exacerbation of previous dermatoses such as psoriasis and pityriasis rubra pilaris (27, 28).

Frequent systemic adverse reactions include flu-like symptoms, fever, arthralgia, or myalgia (29). The systemic adverse effects are probably due to systemic cytokine release because imiquimod absorption is minimal across intact skin (29, 30). Only a few cases of erythema multiforme due to imiquimod have previously been reported (31–36). The pathogenesis of erythema multiforme is not fully understood. Current evidence suggests that it is most likely the result of cell-mediated immune reactions that occur in the setting of various triggering factors, including drugs in predisposed individuals (37, 38).

After reviewing the literature, the majority of patients with erythema multiforme due to imiquimod developed intense local inflammation at the application site. It has been hypothesized that the absorption of imiquimod through very inflamed skin may have been greater than expected from earlier studies and that the application of the drug to skin wounds, mucous membranes, or skin with impaired barrier function may enhance the risk of a serious systemic reaction, such as Stevens–Johnson syndrome, toxic epidermal necrolysis, and anaphylaxis (39, 40). It has been speculated that systemic absorption of the drug and a subsequent type III or IV hypersensitivity reaction lead to development of erythema multiforme (34, 37). In our patient, local inflammation was mild to moderate, and no systemic symptoms were observed. Thus, the development of erythema multiforme in our patient could be related to the large treatment area and possible systemic absorption of the drug.

To conclude, in the reported case the patient developed erythema multiforme in the setting of imiquimod treatment. Clinicians should be aware of this rare but serious adverse effect. Patients with extensive actinic keratoses or intense local inflammation may have a greater risk of developing erythema multiforme.

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