

RESIDENT COMPETITION RESEARCH ARTICLES

Erythema Multiforme Major Caused by Topical ImiquimodAlexandra Edelman MD,¹ J. Mark Jackson MD,¹ Alfred Knable MD¹¹Division of Dermatology, University of Louisville, Louisville, KY**INTRODUCTION**

Erythema multiforme (EM) is an acute, self-limited inflammatory skin disease that is associated with an immune reaction to various triggers, such as herpes simplex virus, *Mycoplasma pneumoniae*, and medications. Commonly implicated drugs include nonsteroidal anti-inflammatories, allopurinol, phenobarbital, phenytoin, and sulfonamides.¹ Topically applied medications are a rare cause of EM or EM-like eruptions.¹ We report one patient with EM major from imiquimod 5% topical cream.

CASE REPORT

A 65 year-old male with no significant past medical history presented with a biopsy proven squamous cell carcinoma in-situ on his right upper arm (Figure 1A). He was instructed to apply imiquimod 5% topical cream to the area for five days using a once-daily Monday to Friday regimen for a total of six weeks. He had never applied imiquimod before and was not on any other prescription or over the counter medications. There was no past history of HSV, and no viral or bacterial processes prior to the eruption.

Two weeks after beginning the imiquimod, he developed erythema, crusting, and scabbing on the right upper arm. At the same time, the patient developed painful erosions in his

mouth. The following day he developed a rash on his palms that continued to worsen and spread up his arms over the next three days. He discontinued imiquimod at this time as recommended by his dermatologist. The rash continued to progress with worsening stomatitis and the patient was subsequently admitted to the hospital.

Physical exam revealed dusky targetoid lesions on his palms (Figure 2A), erythematous papules on his arms, and crusted plaques and erosions on his buccal mucosa, lips and hard palate (Figure 2B). There was marked crusting, erythema and tenderness at the site of imiquimod application on his right upper arm (Figure 1B) and also in areas of actinic damage at other sites such as his nose and cheeks where he had not applied the imiquimod. Genital and ocular mucosae were not affected.

Other potential causes of erythema multiforme were ruled out as the patient denied the use of any new medications other than imiquimod, denied any recent illnesses or a history of HSV infection. HSV swab was negative in the hospital. With the combination of oral steroids, supportive care and topical steroids, the rash resolved over the next three weeks.

Figure 1. Squamous cell carcinoma in situ on right upper arm of patient (A) before biopsy and (B) two weeks after imiquimod treatment, coinciding with onset of erythema multiforme.

(A)

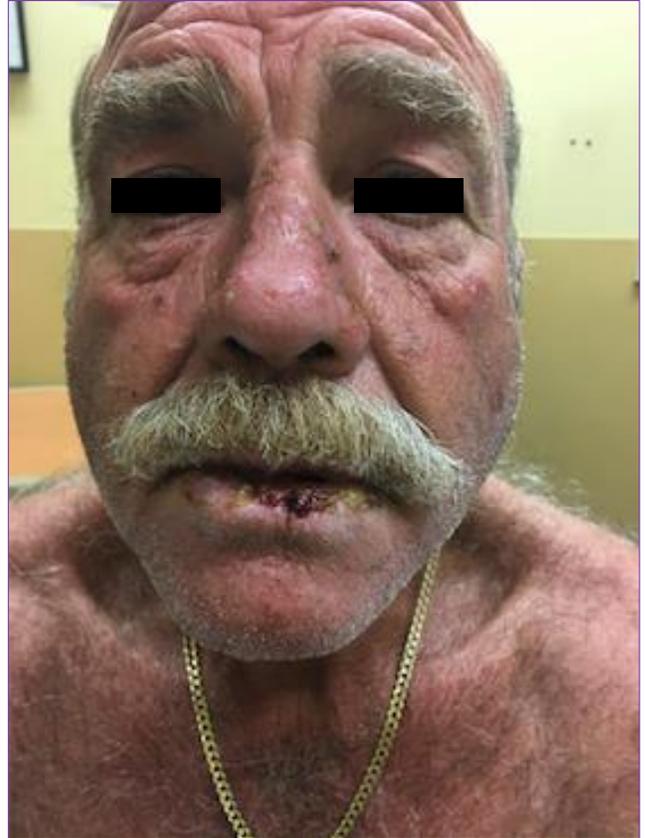


(B)



Figure 2. Stomatitis (A) and targetoid lesions on the palms (B).

(A)



(B)



DISCUSSION

Imiquimod 5% cream is a toll-like receptor (TLR)-agonist approved for the treatment of actinic keratosis, squamous cell carcinoma in-situ, basal cell carcinomas, and genital warts. The most common side effects of imiquimod include localized erythema, tenderness, scabbing, ulceration and occasionally flu-like symptoms.³ After reviewing the relevant literature, we found eight cases of erythema multiforme induced by topical imiquimod.³⁻⁸ Of the eight cases of Imiquimod-induced EM, seven patients had a significant local reaction that subsequently led to the more distant cutaneous manifestations of erythema multiforme.³⁻⁸

The pathogenesis of imiquimod-induced EM is not completely understood. Imiquimod acts on both the innate and acquired immune system by activating toll-like receptor 7 leading to the secretion of proinflammatory cytokines, particular tumor necrosis factor, interferon, IL 6 and 8, which in turn stimulates T-helper lymphocytes.¹⁻² This TLR activation cascade leading to a systemic release of cytokines is a potential mechanism of drug-induced EM.² It is also speculated that topical imiquimod produces systemic absorption, triggering a type III or IV hypersensitivity reaction leading to erythema multiforme.⁴

In conclusion, we present a case of topical imiquimod-induced EM. Imiquimod is a commonly used topical treatment for a variety of dermatologic conditions and clinicians must be aware of this rare but serious complication. Furthermore, patients with an exuberant local reaction to imiquimod may be at higher risk of developing EM.

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