Permanent Imiquimod-induced Depigmentation

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Abstract
Imiquimod may be used as a topical therapy for actinic keratosis.1 We report on a patient treated with imiquimod for actinic keratoses who developed an inflammatory reaction, which subsequently resulted in depigmentation of the skin at the sites of imiquimod application. At nine-year follow-up, the patient still had skin depigmentation. We hope to increase awareness amongst dermatologists of this rare but potentially permanent adverse effect of imiquimod and discuss the possible mechanisms by which depigmentation may occur.

Introduction
Imiquimod is a topical immune-response modifier commonly used in dermatology. It is approved by the U.S. Food and Drug Administration (FDA) for the treatment of condyloma acuminata; non-hyperkeratotic, non-hypertrophic actinic keratosis; and superficial basal-cell carcinomas less than 2 cm in diameter located on the trunk (excluding anogenital area), neck, or extremities (excluding hands and feet).1

The most frequently reported dermatologic adverse reactions include localized erythema, xeroderma, and crusted skin.1 Pigmentary changes secondary to imiquimod use have been previously reported and are therefore mentioned as a possible side effect on the package.2 However, there are relatively few clinical cases available in the literature, and there is a lack of multi-year follow-up to determine the duration of depigmentation. The FDA lists 68 reports of pigmentary changes out of a total of 1,257 reports related to imiquimod from 1997 to 2003.3 In this case, we report an unusual presentation of imiquimod-induced depigmentation with nine years of follow-up, supporting the possibility that this adverse effect may be permanent.

Case Report
A 57-year-old woman presented with multiple actinic keratoses at various locations including the nose, right upper lip, and chest. She was prescribed imiquimod 5% cream to apply to the lesions Monday, Wednesday, and Friday nights. After one month, this was increased to application every night for three weeks. Five days after starting the nightly application, the patient called complaining of swelling and blistering around her lips, swelling around her eyes, and erythema where she had applied the imiquimod. She was instructed to stop the imiquimod and return to office for evaluation. On evaluation, the patient was noted to have erythema, edema, and crusting on facial and chest application sites. The patient was instructed to use petroleum jelly three times a day and continue the discontinuation of topical imiquimod. At the follow-up two months later, the patient had developed areas of depigmentation on the chest from the imiquimod. Nine years after use of imiquimod cream, the patient continues to have areas of depigmentation on her chest (Figure 1).

Discussion
Imiquimod-induced depigmentation is a rare side effect. In our case, depigmentation continued at nine years post imiquimod therapy, providing valuable insight suggesting that the depigmentation can be permanent. A literature review revealed the development of imiquimod-induced depigmentation in a limited number of previously published case reports.3-15 The nine-year follow-up in our case supports that this effect may be long-lasting and of cosmetic significance to patients.

The possible mechanism of the pigmentary changes secondary to imiquimod use relates to its properties as an immune-response modifier. Imiquimod stimulates cytokine production (interferon-alpha, interferon-gamma, and interleukin-12), thereby leading to cell-mediated immunity including anti-viral and anti-tumor activity.14,15 This creates an inflammatory reaction, such as the erythema that our patient initially experienced where she applied the imiquimod cream. Thus, the depigmentation may be analogous to post-inflammatory hypopigmentation.

Additional mechanisms may also play a role. Imiquimod may further cause depigmentation via a mechanism similar to the pathogenesis of vitiligo. Imiquimod promotes cytokine release, which results in the activation of cytotoxic T cells and antigen presentation by Langerhans cells.17 Depigmentation in vitiligo occurs with the presentation of autoantigens by Langerhans cells leading to activation of cytotoxic T cells to destroy melanocytes. Melanocytes also have increased sensitivity to the oxidative stress that may be mediated by imiquimod.18 Depigmentation may
be a result of direct effects on melanocytes. One study demonstrated that imiquimod induces apoptosis of melanocytes.\(^{19}\) Therefore, the desirable therapeutic anti-viral and anti-tumor effects of imiquimod, through a mechanism involving inflammation and Langerhans cells antigen presentation, may also lead to the undesirable side effect of depigmentation.

Imiquimod may also lead to depigmentation via its signaling of the innate immune system through toll-like receptor 7 (TLR7).\(^{20}\) Melanocytes treated with imiquimod led to reduced pigmentation, suggesting TLRs in melanocytes play a role in inflammation-related pigmentary changes.

**Conclusion**

Given that imiquimod is a commonly used therapy, dermatologists should be aware of the potential side effect of depigmentation that may be permanent. Patients should be educated about their treatment options and informed about this possible side effect before deciding whether or not to use imiquimod therapy. Alternative treatments such as cryosurgery may also result in depigmentation; in fact, in a small study comparing cryotherapy to imiquimod therapy for actinic keratosis, the cosmetic outcome was better with imiquimod, with significantly fewer patients experiencing hypopigmentation.\(^{21}\) The mechanism leading to imiquimod-induced depigmentation likely involves post-inflammatory hypopigmentation as well as immune-mediated effects on melanocytes.

**References**


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