Imiquimod-Induced Hypopigmentation Following Treatment of Periungual Verruca Vulgaris

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PRACTICE **POINTS**

- Imiquimod commonly is used off label to treat viral and neoplastic processes.
- Clinicians should be aware of the potential for dyspigmentation or depigmentation as a side effect from treatment.

Imiquimod is a topical immunomodulating medication approved by the US Food and Drug Administration for the treatment of condyloma acuminata, actinic keratoses (AKs), and superficial basal cell carcinoma (BCC). Imiquimod commonly is used off label for its antiviral and antitumoral effects. We present a case of a 51-year-old man with vitiligolike depigmentation following treatment of periungual verruca vulgaris with imiquimod therapy.

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Imiquimod is derived from the imidazoquinoline family and works by activating both innate and adaptive immune pathways. Imiquimod binds to toll-like receptor 7 located on monocytes, macrophages, and dendritic cells,[1] which allows nuclear factor κβ light chain enhancer of activated B cells to induce production of proinflammatory cytokines, including IFN-α and tumor necrosis factor α, as well as IL-1, IL-6, IL-8, IL-10, and IL-12.[2] These proinflammatory cytokines play a role in the innate immunity, triggering upregulation of the adaptive immune pathway and activating type 1 helper T cells, cytotoxic T cells, and natural killer cells. These cells have antiviral and antitumoral effects that lend to their significance in coordinating innate and adaptive immune mechanisms.[3] More specifically, imiquimod enhances dendritic cell migration to regional lymph nodes and induces apoptosis via activation of proapoptotic B-cell lymphoma 2 proteins.[1,2] Imiquimod has been approved by the US Food and Drug Administration (FDA) to treat external genitalia and perianal condyloma acuminata, actinic keratoses (AKs), and superficial basal cell carcinoma (BCC). It often is used off label for antiviral or antitumoral therapy in Bowen disease, squamous cell carcinoma, lentigo maligna, vulvar intraepithelial neoplasia, molluscum contagiosum, common warts, and leishmaniasis.[1,2] Imiquimod is generally well tolerated; erythema and irritation at the application site are the most common side effects, with pigmentary change being less common.

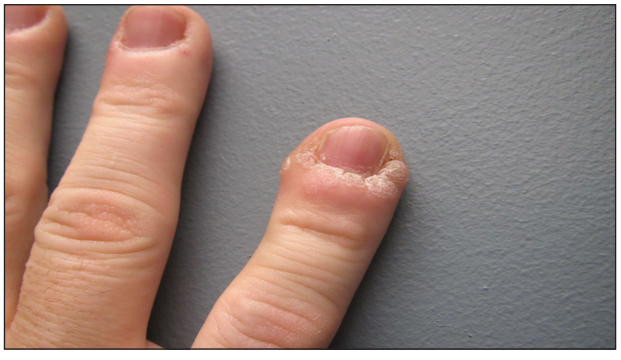

FIGURE 1. Periungual verruca vulgaris of the right fifth digit.

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The authors report no conflict of interest.

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Case Report

A 51-year-old man with a medical history of vitamin D deficiency, vitamin B_{12} deficiency, tinea pedis, and BCC presented with periungual verruca vulgaris on the right fifth digit and left thumb (Figure 1). The patient was prescribed imiquimod cream 5% to be applied 3 times weekly for 3 months. At 5-month follow-up the patient reported new-onset vitiligolike patches of depigmentation on the hands and feet that abruptly began 3 months after initiating treatment with imiquimod. On examination he had several depigmented patches with well-defined irregular borders on the bilateral dorsal hands and right foot as well as the right elbow (Figure 2). There was no personal or family history of vitiligo, thyroid disease, or autoimmune disease. Thyroid function studies and autoimmune panel were unremarkable. The patient also denied applying imiquimod to areas other than the periungual region of the right fifth digit and left thumb. He declined a biopsy of the lesions and was given a prescription for tacrolimus ointment 0.1% for twice-daily application. At 3-month follow-up the depigmented patches had spread. The patient is currently on 5-fluorouracil cream 5%. Despite loss of pigmentation, the periungual verruca vulgaris has persisted as well as depigmentation.

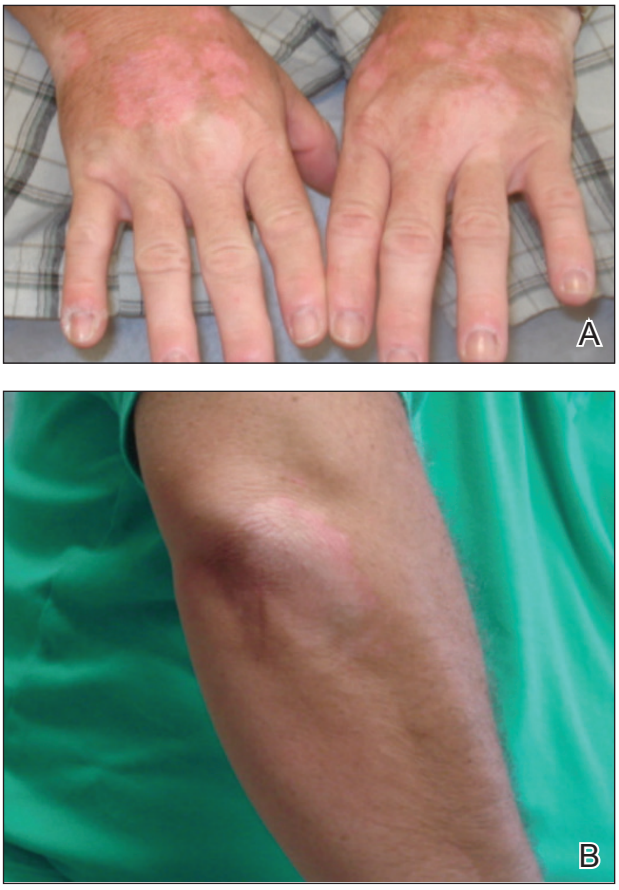

FIGURE 2. Several scattered depigmented patches with well-defined irregular borders on the bilateral dorsal hands (A) and the right elbow (B).

Comment

Imiquimod therapy is commonly used to treat conditions for which an antiviral or antitumor immune response is necessary for treatment and full resolution of skin conditions. It can yield positive results in conditions that are difficult to treat, such as periungual verruca vulgaris.[4] The most common adverse effects of imiquimod include localized inflammation and application-site reactions. Pigment changes, though less common, also have been reported. From 1997 to 2003, 1257 cases of imiquimod adverse effects were reported to the FDA. There were 68 reported cases of pigmentary change, of which 51 documented vitiligo, hypopigmentation, or depigmentation. The others reported hyperpigmentation following imiquimod use.[4] The imiquimod package insert lists application-site hypopigmentation as a possible adverse effect.[5] Imiquimod-induced hypopigmentation and depigmentation have been reported in the peer-reviewed literature.[4,6-14] Pigment loss has been reported in imiquimod treatment of condyloma acuminata, superficial BCC, nodular BCC, and extramammary Paget disease.[6-8] Duration of therapy to onset of pigment loss ranged from 7 to 28 weeks.[9] Imiquimod dosing varied among reported cases, ranging from 3 times weekly to daily application. Interestingly, hypopigmentation or depigmentation are not commonly associated with imiquimod use for the treatment of AKs, which Burnett and Kouba[9] proposed may be due to the twice weekly imiquimod dosing regimen recommended by the FDA for the treatment of AK (below the minimum threshold for pigment loss). Our patient applied imiquimod cream 5% to periungual verruca vulgaris 3 times weekly for 3 months and may have developed vitiligolike depigmentation because he met this theoretical dosage threshold. Further research is necessary to confirm a dosage-related threshold for the development of depigmentation. Imiquimod-induced pigment loss has mainly been limited to the site of application.

Depigmentation was limited to the application site the majority of the time; however, depigmentation at adjacent sites has been reported.[10] This finding was consistent with the proposed notion that cytokines induced by imiquimod have localized paracrine activity.[11] Our patient was unique in that his depigmentation was present at the site of application, adjacent to the site of application, and at distant sites. He applied imiquimod only to the periungual area of the right fifth digit and left thumb but experienced depigmentation at several other sites. Although it is possible that our patient unintentionally spread imiquimod on the distant sites, it is less likely that the application would have been sufficient to cause depigmentation. Although systemic absorption of topical medications varies depending on multiple factors, the systemic absorption of imiquimod is minimal with mild

systemic side effects reported, including headache, myalgia, and influenzalike symptoms.[5] Thus, it is possible that our patient developed distant vitiligolike depigmentation as a systemic side effect of imiquimod therapy. Although our patient declined to have a biopsy performed, Gowda et al[15] reported biopsy-proven vitiligo, demonstrating the absence of melanin and melanocytes following the use of imiquimod.

Several mechanisms have been proposed for imiquimod-induced depigmentation. For example, imiquimod may induce melanocyte apoptosis by increasing the levels of several proinflammatory and proapoptotic cytokines.[16] Imiquimod-induced melanocyte apoptosis appears to involve elevated caspase-3, decreased B-cell lymphoma 2, altered mitogen-activated protein kinase expression, and ubiquitin-mediated proteolysis.[13,17] Additionally, increased levels of IL-6 appear to increase melanocyte-binding molecules and increase melanocyte-leukocyte interactions. Another proposed theory targets toll-like receptor 7 on melanocytes that are acted on directly by imiquimod.[11,17] In contrast, development of vitiligo following trauma (Koebner phenomenon) is not uncommon, and the immune effects induced by imiquimod may mimic those seen with trauma.[14] Further research is needed to elucidate the mechanism by which imiquimod causes vitiligolike depigmentation.

Unfortunately, the depigmentation seen with imiquimod generally is permanent. Stefanaki et al[10] showed repigmentation on cessation of imiquimod use. Our patient's depigmentation remains unchanged despite treatment with tacrolimus ointment. Although it is possible for vitiligo to occur de novo without obvious inciting event or laboratory abnormality, the timeline and number of other cases in the literature make ours highly suspect for imiquimod-induced depigmentation.

Conclusion

Imiquimod is a commonly used immune-enhancing medication with an increasing list of off-label uses. Prior to prescribing imiquimod for a benign skin condition, clinicians should be cognizant of the potential for localized or possibly even distant depigmentation. We report a case of distant depigmentation following the use of imiquimod for periungual verruca vulgaris.

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