Imiquimod Induced Hypopigmentation Following Treatment of Periungual Verruca Vulgaris

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CASE REPORT

A 51-year-old Caucasian male with past medical history significant for vitamin D deficiency, vitamin B12 deficiency, tinea pedis, and basal cell carcinoma presented to the clinic with periungual verruca. The patient was prescribed imiquimod 5% cream to be applied 3 times weekly for 3 months. At his 5-month follow-up examination, the patient complained of new-onset, vitiligo-like patches of hypopigmentation involving his hands and feet. The patient reported that the hypopigmentation began abruptly, 3 months after initiating treatment with imiquimod. On exam, he had several hypopigmented patches with well-defined irregular borders on bilateral dorsal hands and feet (Figures 1 and 2). The patient denied any personal or family history of vitiligo, thyroid, or autoimmune disease. Thyroid function and autoimmune panels were unremarkable. The patient denied applying imiquimod to areas other than the periungual verruca. The patient declined a biopsy of the lesions. He was prescribed tacrolimus to be applied twice daily to hypopigmented areas. At follow-up, the hypopigmented patches were spread. Despite hypopigmentation, the periungual verruca persisted.

DISCUSSION

Imiquimod is a topical, immune-modifying medication with antiviral and antitumoral properties commonly used to treat skin conditions. The most common adverse effect of imiquimod is application site reaction/inflammation. Pigmentary changes, though less common, have also been reported. From 1997 to 2003, there were 51 reported cases of vitiligo, hypopigmentation, or depigmentation associated with imiquimod. The imiquimod package insert indicates that all adverse effects are more frequent and severe with daily application as compared to three times weekly application. Several cases of imiquimod-induced hypopigmentation have been reported in the literature.

To date, hypopigmentation has been reported in imiquimod treatment of condyloma acuminate, superficial and nodular basal cell carcinoma, and extramammary Paget’s disease. Reported duration of therapy to onset of hypopigmentation ranged from 7-28 weeks in the literature. Interestingly, no cases of hypopigmentation have been reported with imiquimod use for the treatment of actinic keratoses. It has been proposed that this may be due to the FDA-recommended twice weekly imiquimod dosing regimen for the treatment of actinic keratosis, which may be below the minimum threshold for hypopigmentation. Our patient, applied 5% imiquimod to periungual verruca vulgaris 3 times weekly for 3 months which may have met the dosing threshold for depigmentation.

Imiquimod-induced hypopigmentation has primarily been limited to the site of drug application. However, one case in the literature reported “spreading” of hypopigmentation to an area adjacent to the application site. This finding supports the notion that cytokines induced by imiquimod have localized paracrine activity. Our patient had unique findings of hypopigmentation present at the application site, adjacent to application site, and at distant sites. Although it is possible that our patient unintentionally spread imiquimod to these distant sites, it is less likely that this would have been sufficient enough over time to cause hypopigmentation. Though systemic absorption of topical medications varies depending upon multiple factors, the systemic absorption of imiquimod is reported as minimal.

The distant vitiligo-like hypopigmentation in our patient was possibly a systemic side effect of imiquimod therapy. Several mechanisms have been proposed for this depigmentation including upregulation of proinflammatory and proapoptotic cytokines. Imiquimod-induced melanocyte apoptosis specifically involves elevated caspase 3, decreased Bcl-2, altered mitogen activated protein kinase expression, and ubiquitin-mediated proteolysis. Additionally, increased levels of IL-6 appear to increase melanocyte binding molecules (ICAM) and increase melanocyte-leukocyte interactions. Another proposed theory targets TLR-7 receptors on melanocytes which are acted upon directly by imiquimod. In contrast, vitiligo following trauma (Koebner phenomenon) is not uncommon and the immune effects induced by imiquimod may mimic those simply seen with trauma. Unfortunately, the depigmentation associated with imiquimod is generally permanent. Only one case in the literature has shown repigmentation upon cessation of imiquimod use. Our patient’s hypopigmentation remains unchanged despite treatment with tacrolimus ointment.

FIGURES

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CONCLUSION

Additional research is needed to further investigate the association of imiquimod and vitiligo-like hypopigmentation. Additionally, it is imperative that clinicians are aware of the potential for hypopigmentation with imiquimod therapy and carefully consider the risk when prescribing this medication.