Induction of Vitiligo-like Hypopigmentation with Use of Topical Imiquimod for Superficial and Nodular Basal Cell Carcinomas

Roxanne Rajaii, DO,* Elizabeth Young, DO,** Sean Stephenson, DO,*** Michelle Legacy, DO,*** Lynn Sikorski, DO****

*Dermatology Resident, PGY3, Beaumont Hospital – Farmington Hills, Farmington Hills, MI
**Traditional Rotating Intern, Capital Region Medical Center – Jefferson City, MO
***Dermatopathologist, Dermatopathology Laboratory of Central States – Troy, MI
****Dermatologist, Beaumont Hospital – Farmington Hills, Farmington Hills, MI

Abstract

This case report presents a 60-year-old Caucasian male who had been treated with imiquimod 5% cream for numerous superficial and nodular basal cell carcinomas, with treatments five times per week for six weeks, resulting in vitiligo-like hypopigmentation that eventually extended beyond the borders of the treatment area. Imiquimod is an immune-response modulator currently FDA-approved for the treatment of external anogenital warts, actinic keratoses, and superficial basal cell carcinomas. Hypopigmentation is a rare side effect of topical imiquimod use, but it has been noted in previous literature of imiquimod treatment for both condylomata acuminata and superficial and nodular basal cell carcinomas. Previous studies report this phenomenon being attributed to the drug’s Th1-stimulating activity. With this striking patient presentation, we aim to demonstrate the importance of discussing this rare side effect with any patient who is to be treated with imiquimod, particularly in cases involving younger patients or lesions in cosmetically sensitive areas.

Introduction

Topical imiquimod 5% is an immune-response-modifying cream that induces cellular immune responses like local release of pro-inflammatory cytokines and stimulation of antigen-presenting cells. These effects make it a treatment modality for condyloma acuminata, actinic keratoses, and basal cell carcinoma, particularly the superficial subtype. The side-effect profile of topical imiquimod is well known, and the more common potential adverse reactions of erythema, xeroderma, crusting, and irritation are regularly discussed. One of the least common side effects, dyspigmentation, particularly hypopigmentation, is dramatic when it occurs but seldom encountered, so it is often not discussed with patients prior to treatment. Our case discusses a patient who experienced hypopigmentation not only at the treatment site but also beyond the well-circumscribed treatment area.

Case Report

This case presents a 60-year-old Caucasian male at our clinic with a significant history of numerous, biopsy-proven, superficial and nodular basal cell carcinomas dated from August 2010 to present. They were located on his arms, chest, and back and were treated with topical imiquimod 5% cream five times per week for a total treatment course of six weeks to each lesion. On examination, the patient had multiple hypopigmented macules coalescing into large hypopigmented patches involving and extending locally far beyond the treatment site. The patient reported that approximately two weeks following every six-week treatment course, he observed hypopigmented macules developing at the site of application. He stated that these hypopigmented macules were initially the size of the initial lesion but that after a full course of therapy, the macules began to coalesce and enlarge to form patches several times the size of the initial lesion and beyond the area of cream application. The most striking areas of involvement included the arms and chest (Figures 1-3).

The patient denied any other significant irritation and side effects with topical application of imiquimod but did recall having feelings “similar to having the flu” during each treatment course. He denied use of any other topical treatments, including over-the-counter therapies, to the areas being treated with imiquimod. In this patient, despite discontinuation of imiquimod and over several years of follow-up, repigmentation in these areas was not observed. Furthermore, the patient experienced the same side effect with each application of imiquimod. Although topical therapies to help with repigmentation of these lesions were offered to the patient, he refused treatment for the hypopigmented areas and denied being bothered by their appearance.

The patient’s medical history included osteoarthritis and hyperlipidemia. He denied any personal or family history of autoimmune disorders and depigmenting diseases such as vitiligo, thyroid disease, Addison’s disease, and alopecia areata. The patient also denied any personal or family history of diabetes with the exception of his father, who suffered from diabetes mellitus type II. The patient’s surgical history was significant for bilateral knee surgery. The patient denied any tobacco use. His medications included simvastatin.

Two punch biopsies were taken from affected areas on the left anterior shoulder and left anterior proximal upper arm, respectively, in order to distinguish between hypopigmentation and true depigmentation. On histopathological examination, both areas showed evidence of mild post-inflammatory hypopigmentation (Figures 4a-d) with some retained melanocytes at the dermoeipidermal junction.

Figures 1-3. Patient with multiple hypopigmented macules coalescing into large hypopigmented patches at the site of topical imiquimod therapy.

Figures 4a-d. (H&E, 2x-20x) Biopsy of a hypopigmented patch showing retained melanocytes at the dermoeipidermal junction.
melanocytes at the dermoepidermal junction. MITF-1 showed positively staining melanocytes at the dermoepidermal junction (Figures 5a-b). A periodic acid-Schiff stain showed no fungi.

Discussion
Vitiligo-like hypopigmentation is a rare side effect of topical imiquimod application. Of the few cases that have been reported, the majority occurred following treatment of condyloma acuminata, and a small subset followed treatment of basal cell carcinomas.  

The mechanism of the hypopigmentation, often with concurrent poliosis, has been debated, and several theories are currently in favor. Imiquimod’s stimulation of toll-like receptor 7 with up-regulation of nuclear factor-kappaB and subsequent induction of multiple pro-inflammatory cytokines, along with stimulation of antigen-presenting cells and other cellular immune-response mediators, is responsible for the treatment’s efficacy. The T-helper-1 subset population of lymphocytes induces further proliferation of T-helper cells and cytotoxic T-cells. Pro-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interferon (IFN)-α, interleukin (IL)-6, IL-8, IL-10, and IL-12 are produced. IL-12 stimulates the existing T-helper-cell subset to produce more IFN-α and IL-2, further ensuring a cascade of pro-inflammatory cytokines and activated T-lymphocytes. IFN-α, IL-6, IL-8, and IL-10 are known mediators in the pathogenesis of vitiligo, and it is logical to believe imiquimod could induce similar pigmentary changes.  

With this robust increase of the T-lymphocyte population, a small subset of autoreactive cytotoxic T-cells against melanocytes can be observed. The autoreactive T-cells’ destruction of the local melanocyte population is believed to cause of some cases of vitiligo-like hypopigmentation following imiquimod use. This mechanism would also explain the extension of pigmentation change beyond our patient’s treatment area, as well as reports of halo phenomena occurring around pre-existing nevi with imiquimod treatment of distant sites. Melanocytes have also been shown to activate toll-like receptor 7, the target of imiquimod, which could further explain the apoptosis and depletion of the local melanocyte population.  

Permanent reduction in the local melanocyte population may explain the persistent nature of the pigmentary change. In a study of patients with vitiligo-like hypopigmentation following imiquimod treatment, all but one case was found to be permanent. Stefanaki C. et al. observed a case of 2% repigmentation in a patient with vitiligo-like hypopigmentation following imiquimod treatment for condyloma. One proposed non-immunological mechanism of repigmentation following imiquimod use is the benzyl alcohol found in the cream vehicle inducing a contact leukoderma.  

Hypopigmentation is an exceedingly uncommon side effect, and the extension beyond the circumscribed treatment area is even rarer; we believe this supports an immunologic mechanism for pigmentary change following imiquimod use. There are no case reports of repigmentation in areas of basal cell carcinomas treated with imiquimod complicated by vitiligo-like hypopigmentation. This further necessitates a thorough prescribing discussion so a patient can make an informed decision before undergoing treatment with imiquimod.

Conclusion
In conclusion, vitiligo-like hypopigmentation following topical imiquimod use is a rare side effect and one uncommonly discussed with patients before treatment. Even less likely is extension of the hypopigmentation beyond the confines of the treatment area. Considering the striking and often persistent course of the hypopigmentation, we recommend more practitioners have detailed discussions of imiquimod’s extensive side-effect profile with patients before recommending its use, particularly in patients concerned with cosmesis.

References
Acknowledgment
Author contributions: Drs. Rajaii and Young had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Drs. Rajaii, Young, Legacy, and Sikorski

Acquisition, analysis, and interpretation of data: Drs. Rajaii, Stephenson, Legacy, and Sikorski

Drafting of the manuscript: Drs. Rajaii, Young, Stephenson, Legacy, and Sikorski

Critical revision of the manuscript for important intellectual content: Drs. Rajaii, Young, Stephenson, Legacy, Sikorski, and Lacasse

Abbreviations and acronyms
IL: Interleukin
INF: Interferon
TNF: Tumor necrosis factor