Possible mechanisms in the induction of vitiligo-like hypopigmentation by topical imiquimod

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Summary
The pathogenesis of vitiligo was examined for clues to the pigmentary changes that may occur after treatment with topical imiquimod. The literature varies on the pigmentary changes induced by topical use of imiquimod. The US Food and Drugs Administration lists 68 reports of pigmentary changes out of a total of 1257 reports related to imiquimod lodged from 1997 to 2003. Some studies describe vitiligo-like hypopigmentation associated with imiquimod treatment of genital warts (as with the patient described in this report), molluscum contagiosum, basal cell carcinoma, extramammary Paget’s disease and murine melanoma. Other studies report hyperpigmentation associated with imiquimod. The possible mechanisms of hypopigmentation associated with imiquimod treatment are discussed, including antibodies found in sera of patients with vitiligo to nonpigment cell antigens, cytoplasmic pigment cell antigens and pigment cell-surface antigens; stimulation by imiquimod of both the innate immune response and cell-mediated adaptive immunity; and increased sensitivity of melanocytes to oxidative stress. The vitiligo-like hypopigmentation following topical imiquimod treatment is in line with the mode of action of this drug.

Several case reports and studies describe vitiligo-like hypopigmentation associated with imiquimod treatment, and other studies report hyperpigmentation. The US Food and Drugs Administration lists 68 reports of pigmentary changes out of a total of 1257 reports related to imiquimod lodged from 1997 to 2003: 51 of depigmentation, 7 of vitiligo, 1 of hypopigmentation and 17 of hyperpigmentation. Treatment of condyloma acumina for 17 months with imiquimod in one of our patients resulted in almost complete disappearance of the warts but the persistence of a few hypopigmented vitiligo-like lesions. Previous treatment modalities such as cryotherapy were unsuccessful, but they did not cause pigmentary changes. The patient refused our request for biopsies of these lesions and refused to have them photographed.

Hypomelanosis can be congenital or acquired, circumscribed or generalized, and partially or completely hypomelanotic. It can be classified into three categories: (i) melanocytopenic disorders that have a reduced number of melanocytes, (ii) melanopenic disorders with a decrease in melanin and (iii) nonmelanotic disorders that are not related to melanin pigmentation.

Several mechanisms have been proposed for the vitiligo-like hypopigmentation that may occur after topical imiquimod treatment. Antibodies to non-pigment cell antigens, cytoplasmic pigment cell antigens and pigment cell-surface antigens are found in the sera of patients with vitiligo. The perilesional infiltrate comprises CD4- and CD8+ T cells, with an increased CD8/CD4 ratio. A reduction in the number of CD4+ T cells and subsequent augmentation of CD8+ T cells in conjunction with interleukin (IL)-12 induces vitiligo. Vitiligo is associated with an increase in local cytokine production, including IL-2; interferon (IFN)-γ, which is
an apoptosis mediator that in turn enhances T-cell trafficking to the skin by increasing intercellular cell adhesion molecule-1; IFN-α, which can cause induction of antimelanocyte autoantibodies or activation of cytotoxic T cells; IL-6 and IL-8, which are pro-inflammatory cytokines that also cause B-cell activation; tumour necrosis factor (TNF)-α, an apoptosis mediator and melanocyte proliferation and melanogenesis inhibitor; and IL-10, another apoptosis mediator. Another possible mechanism of vitiligo is the increased sensitivity of melanocytes to oxidative stress.

The mode of action of imiquimod involves stimulation of the innate immune response and the cell-mediated adaptive immunity. Imiquimod binds to the Toll-like receptors (TLR) 7 and 8, which are cell-surface receptors recognizing ligands associated with pathogenic organisms. TLR7 activates a signalling cascade involving the myeloid differentiation factor 88-dependent pathway, upregulation of nuclear factor-κB and protein kinases. These signals evoke the T-helper (Th1) response and increase production of pro-inflammatory cytokines, mainly IFN-α, TNF-α and IL-12, all of which play a role in the pathogenesis of vitiligo. In addition, imiquimod promotes secretion of IL-6, IL-8 and IL-10, which are pro-inflammatory and pro-apoptosis cytokines that can cause vitiligo.

The stimulation of the Th1 pathway results in a predominantly perilesional CD4+ T cell infiltrate and many CD8+ T cells. The CD4+ cells are stimulated by IL-12 to produce IFN-α and IL-2, which are known to play a role in the pathogenesis of vitiligo, and which activate CD8+ cells to become cytotoxic T cells. In a trial of imiquimod use for superficial basal cell carcinoma, the CD4+ cells reached their peak by 1 week of treatment, and CD8+ cells reached their peak by 4 weeks of treatment, by which time the ratio of CD4 : CD8 resembled that seen in vitiligo.

A recent study showed that imiquimod enhanced the antimalanoma effect of recombinant Listeria monocytogenes vaccine: 3 weeks were required for this to transpire, during which the persistent TLR signalling required for bypassing regulatory T cell-induced tolerance to self antigens allowed vitiligo to develop. In a report of successful treatment of lentigo maligna with imiquimod, the inflammatory infiltrate contained predominantly CD8+ T cells.

Several authors report treating melanoma with imiquimod. Both melanoma and vitiligo exhibit a breakdown of tolerance, as suggested by the presence of cytotoxic T lymphocytes directed at self antigens shared by melanoma cells and normal melanocytes. Melanocyte-specific CD8+ T lymphocytes were observed in vitiligo and melanoma lesions and in the peripheral blood in both diseases. The reactivity to vitiligo melanocytes could be the effective variant of the often ineffective response in melanoma. A high percentage of melanoma patients responding to IL-2 treatment developed vitiligo parallel with the melanoma regression, providing further evidence of the ability of imiquimod to cause vitiligo.

In view of the mode of action of imiquimod, vitiligo-like hypopigmentation following a course of topical imiquimod treatment is therefore not unexpected.

References


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