Treatment of Atypical Nevi With Imiquimod 5% Cream

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Background: 5% Imiquimod cream is a topical immune response modifier that has been used off-label to treat malignant melanocytic proliferations such as lentigo maligna. To our knowledge, imiquimod has not been previously used to treat atypical nevi (AN).

Observations: Three patients each with 1 selected clinically AN were treated with imiquimod 5 nights per week for 12 weeks. The lesions were subsequently excised and sent for routine histologic and immunohistochemical analysis. None of the lesions cleared. Two were consistent with atypical compound nevus on excisional biopsy and demonstrated inflammation, while the third showed congenital features and demonstrated minimal inflammation. The AN were initially interpreted as displaying more severe histologic atypia on excisional biopsy than was present at baseline. Immunohistochemical studies revealed that the AN but not the congenital-like nevus exhibited increased staining for CD4+ and CD8+ cells and for a surrogate marker of interferon expression.

Conclusions: Twelve weeks of imiquimod treatment failed to cause lesional resolution. A differential inflammatory response was observed between the AN and the congenital-like nevus. The character of the inflammatory infiltrate was similar to that observed with halo nevi. Uncertainties remain concerning imiquimod use for chemoprevention of AN, and the posttreatment histologic features may be misinterpreted as severe melanocytic atypia or melanoma.

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The presence of atypical nevi (AN) is an independent risk factor for the development of melanoma.1,2 Atypical nevi may be precursors to melanoma, with both occurring in histologic contiguity in up to 50% of cases.3 Close follow-up, digital monitoring, and timely excision are used to manage suspicious nevi. Unlike the many therapies that are used to eliminate premalignant actinic keratoses, there are no widely accepted therapeutic alternatives for the removal of AN other than complete excision. Therefore, individuals with AN may undergo numerous surgical procedures over their lifetime.

Certain inflammatory conditions may disrupt nevus formation. For example, individuals with active atopic dermatitis have fewer nevi than do nonatopic controls.4,5 Cytokines involved in active dermatitis, such as interleukin (IL)-1, IL-4, IL-5, IL-6, interferon (IFN)-α, and tumor necrosis factor α, can inhibit melanocyte growth and proliferation in vitro.6 Also, halo nevi are thought to represent an immunologic response to antigenically altered nevus cells associated with dysplasia. Some have antibodies directed against the cytoplasm of melanoma cells.7,8 CD8+ T cells have been identified as potential effectors mediating the destruction of nevomelanocytes.9,10 Because proinflammatory responses in atopic dermatitis and halo nevi are able to disrupt nevus formation, we postulated that imiquimod application might stimulate immune recognition of atypical melanocytes and that the proinflammatory responses elicited could completely or partially eliminate melanocytes within AN.

5% Imiquimod cream (Aldara; 3M Pharmaceuticals, St Paul, Minn) is an immune response modifier that functions through stimulation of Toll-like receptor 7 on B cells and plasmacytoid and myeloid dendritic cells to induce transcription of Th1 cytokines (eg, tumor necrosis factor α, IFN-γ, IFN-α, and IL-12), resulting in antitumor immune responses.11,12 Although imiquimod has demonstrated therapeutic efficacy in a variety of dermatologic conditions, approval of the Food and Drug Administration for its use in atypical nevi has not been forthcoming.
Administration and Health Canada is presently confined to the treatment of genital warts, multiple actinic keratoses, and superficial basal cell carcinomas. Several cases involving the successful use of imiquimod for lentigo maligna and cutaneous melanoma metastases have been reported in the literature.\textsuperscript{13-26} We describe 3 patients in whom imiquimod was applied to clinically AN.

### METHODS

Three patients with numerous common and clinically AN were seen in our clinic between January and April 2005. None had a personal or family history of melanoma. One nevus clinically evaluated as mild to moderately atypical was selected from each patient for treatment after the risks and benefits were explained and informed consent was obtained. In each case, the nevus was relatively flat.

Baseline photographs and measurements were taken. A 2-mm punch biopsy specimen was obtained from the periphery of each nevus to confirm the diagnosis. One week later (after the biopsy site had healed), imiquimod 5% cream was applied to the lesion and a surrounding 5-mm perimeter 5 nights per week for a total of 12 weeks. Patients could reduce the frequency of application in the event of severe inflammation and irritation.

Treatment response and adverse effects were evaluated at 4, 8, and 12 weeks after the start of treatment. Follow-up photographs were taken at each visit. The treated lesion was completely excised for histologic evaluation 1 week after the end of the treatment period. Hematoxylin-eosin–stained posttreatment biopsy specimens were reviewed by a panel of 3 dermatopathologists (M.M., R.I.C., and Nigel Ball, MD, FRCP). Immunohistochemical stains were performed on paraffin-embedded tissue to look for the presence of CD4\(^+\) and CD8\(^+\) cells. Staining was also performed for MxA (myxovirus resistance 1), a surrogate marker of local type I IFN (\(\alpha/\beta\)) production (V. A. Migounov, MD, oral communication, March 2005). Images were captured with a color camera (SPOT RT; Diagnostic Instruments, Sterling Heights, Mich) using a motorized epifluorescence microscope (Olympus BX-61; Olympus Optical Co GmbH, Hamburg, Germany).

### REPORT OF CASES

All patients completed their treatment course without interruption despite brisk inflammation, erosion, and crusting in 1 patient. None reported systemic adverse effects. On clinical examination, none of the lesions had cleared after 12 weeks of treatment.

#### CASE 1

A 57-year-old man presented with a large, clinically AN on her left arm. The findings of the baseline histologic examination showed a compound nevus with mild atypia (Figure 1A). Baseline histologic examination showed a compound melanocytic nevus with severe atypia (Figure 1A). Clinically, mild to moderate inflammation was evident after 8 weeks of treatment. At 12 weeks, there was no significant clinical change from baseline. An excisional biopsy specimen at that time (Figure 1B) showed a symmetrical proliferation with nested melanocytes predominating over single cells; however, there was lentiginous single-cell proliferation, which was mostly confined to the elongated rete ridges. Pagetoid upward spread was less focal and not associated with uniform cytologic atypia.

Rete ridge bridging, fibrosis, inflammation, and neovascularization were prominent. Inflammation was diffusely present at the level of the papillary dermis. Mitotic figures were absent. Overall, the architectural and cytologically atypical features were consistent with an AN.

#### CASE 2

A 36-year-old man presented with a large clinically AN on the lower left thorax (Figure 2A). Baseline histologic examination showed a compound nevus with mild atypia (Figure 2D). The patient experienced significant inflammation within the first few weeks of therapy (Figure 2B). The posttreatment excisional biopsy specimen (Figure 2E) showed a broad but symmetrical compound melanocytic proliferation obscured in some areas by a lichenoid lymphocytic infiltrate, which made assessment of the architectural and cytologic features difficult. The epidermal component was rather poorly circumscribed and consisted of predominantly single cells; however, pagetoid spread was only very focally apparent. There was dermal architectural and cytologic maturation. Dermal mitotic figures were not identified. There was a significant degree of epidermal and superficial dermal cytologic atypia, most pronounced in areas of intense inflammation. It was thought that the inflammatory changes could represent areas of regression of a previous melanocytic component.

#### CASE 3

A 32-year-old woman presented with a clinically AN on her left arm. The findings of the baseline histologic examination were consistent with a benign junctional nevus (Figure 3A). Minimal inflammation occurred during the course of treatment, and the lesion persisted unchanged. The posttreatment biopsy specimen (Figure 3B) showed a symmetrical melanocytic proliferation consistent with a congenital-like nevus. Cytologic pleomorphism was present, but cytologic atypia was “random.” Rete ridge bridging and fibrosis were evident. Inflammation, unlike the diffuse infiltration seen in the biopsy specimens from patients 1 and 2, was confined entirely to the previous baseline 2-mm biopsy site. Immunohistochemical staining showed increased numbers of CD4\(^+\) and CD8\(^+\)-positive cells in posttreatment biopsy specimens from patients 1 (Figure 1D and F) and 2 (Figure 2G and I) compared with baseline. Staining for CD8\(^+\) cells was greater than staining for CD4\(^+\) cells in case 1, while the reverse was true in case 2. By comparison, there was a sparse inflammatory cell infiltrate in the posttreatment biopsy specimen from patient 3, without significant increases in CD4\(^+\)- or CD8\(^+\)-positive staining (Figure 3D and F). MxA staining increased in posttreatment biopsy specimens from patients 1 and 2 (Figure 1H and Figure 2K) but not in the biopsy specimen from patient 3 (Figure 3H).

### COMMENT

Imiquimod therapy 5 days per week for 12 weeks was insufficient to clear the nevi. This regimen was selected
based on treatment protocols for lentigo maligna, most of which use daily imiquimod for 3 to 4 months. Given the depth of melanocytic nesting, treatment of compound nevi may require longer than a 3- to 4-month course. Successful use of daily to twice-daily imiquimod cream under occlusion for 12 to 28 weeks for cutaneous melanoma metastases lends support to the potential efficacy of a lengthier treatment protocol. 

Although all the nevi in our study were clinically atypical, patient 3 did not experience any significant clinical or histologic inflammation. This differential response may have been attributable to a lesser degree of atypia in patient 3’s nevus. According to the pharmaceutical company (V. A. Migounov, MD, oral communication, March 2005), imiquimod cream does not cause inflammation when applied to normal skin. Perhaps the same is true...
Figure 2. Case 2. Clinical images and baseline and posttreatment histologic sections. Nevus before (A), during (B), and after (C) imiquimod 5% cream treatment. Marked inflammation occurred at week 8. Baseline (D) and posttreatment (E) sections show mildly atypical compound nevus, with marked lymphocytic response in the latter. CD4 (G), CD8 (J), and MxA (K) staining is increased after 5% imiquimod treatment compared with baseline CD4 (F), CD8 (H), and MxA (I) staining (hematoxylin-eosin [D and E], CD4 [F and G], CD8 [H and J], and MxA [I and K], original magnification \( \times 100 \) [D-H and J] and \( \times 200 \) [I and K]).
of benign nevi. Because imiquimod-induced antitumor T_{H}1 responses are directed toward antigenically altered cells, one would expect to find a gradient of inflammatory responses based on the degree of cytologic atypia. Therefore, it may theoretically be possible to use imiquimod as a diagnostic tool to highlight immunologic differences between 2 nevi that appear to be similar clinically and histologically. To the best of our knowledge, there are no reports of imiquimod therapy inducing inflammation in benign nevi. Vitiligo is believed to occur secondarily after imiquimod application to genital warts.

MxA has recently been demonstrated to be a highly specific marker for IFN-α and to correlate with numbers of infiltrating T lymphocytes and chemokine receptor CXCR3 expression, which is characteristic for T_{H}1-biased immune responses. Increased MxA staining is seen in peritumoral infiltrates and lesional epidermal structures of cutaneous malignant neoplasms that have been treated with imiquimod. Expression is also increased within halo nevi, dysplastic nevi, and melanomas but not in normal control skin or benign congenital nevi, suggesting an intrinsic T_{H}1 immunologic bias within these lesions in the presence of antigenically altered melanocytes. Also, halo nevi are infiltrated with CD4+ and CD8+ cells with a proportionately increased population of CD8+ cells when compared with dysplastic nevi.

Figure 3. Case 3. Baseline and posttreatment histologic sections. Baseline (A) section showing benign junctional nevus and posttreatment (B) congenital-like nevus without atypia. CD4 (D), CD8 (F), and MxA (H) staining is increased after imiquimod 5% cream treatment compared with baseline CD4 (C), CD8 (E), and MxA (G) staining (hematoxylin-eosin [A and B], CD4 [C and D], CD8 [E and F], and MxA [G and H]; original magnification ×100 [A-F] and ×200 [G and H]).
CD8+ cells are thought to recognize and target antigenically altered melanocytes.10 The biopsy specimens in cases 1 and 2 showed immunophenotypic similarities to halo nevi with increased CD4+ and CD8+ cells and increased MxA staining. This immunophenotypic profile is also similar to that seen after imiquimod application to basal cell carcinomas, cutaneous melanoma metastases, and cutaneous breast cancer metastases.32

The posttreatment biopsy specimens in all cases were initially interpreted as displaying severe atypia, and only after careful review by a panel of expert dermatopathologists were the findings judged to be analogous to those seen in halo or regressing nevi. Areas of greatest atypia were confined to sites of intense inflammation. The most instructive point from this study is to recognize that the findings of histologic examination of nevi immediately after treatment with imiquimod may be misinterpreted as severe atypia or melanoma. It may be prudent to advise the consulting dermatopathologist when nevi are excised from sites of field treatment with imiquimod. In our study, there was no evidence to suggest that treatment with imiquimod induces atypia.

Imiquimod treatment of clinically AN is controversial. In particular, there are safety concerns associated with treating (or more importantly, partially treating) AN of uncertain biologic behavior. Also, the lengthy treatment course and the intensity of inflammation necessary to achieve clearance may result in greater inconvenience and discomfort than would simple excision. However, in some individuals with numerous nevi in whom melanoma is not suspected, imiquimod therapy may prove to be an interesting and helpful alternative to surgical excision. Recently, a small case series, involving 10 patients, was published in which nevi were treated with imiquimod thrice weekly for 16 weeks, without clinical change.34 Four of 14 nevi showed features of partial regression on histologic examination at week 20. The findings of that study are similar to ours except for our observation of increased atypia in the posttreatment period. It is possible that our baseline 2-mm biopsy specimens did not capture an area of greater atypia that was already present at baseline.

CONCLUSIONS

Our findings demonstrate that imiquimod treatment of AN can produce an inflammatory response. The intensity of the response and the corresponding histologic changes may be misinterpreted as severe melanocytic atypia or melanoma. Therefore, the use of imiquimod cream to treat AN cannot be recommended at this time.

We observed increased Mxa staining after imiquimod application only in the AN, which suggests that these nevi are also atypical from an immunologic standpoint. The same conclusion appears to apply to halo nevi, in which Mxa staining is intrinsically increased. This increase in staining is not seen in other benign melanocytic lesions. Consequently, imiquimod may prove to be a useful tool to evaluate immunologic atypia in melanocytic proliferations.

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