α-Melanocyte-Stimulating Hormone–Induced Eruptive Nevi

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**Background:** Synthetic peptides that target proopiomelanocortin receptors are being investigated as a novel and safe way to tan. It has been postulated that synthetic α-melanocyte-stimulating hormone (α-MSH) peptides may have protective effects against the development of melanoma because of their melanogenic activity. Their ultimate biological effect, however, especially in patients with dysplastic nevi or previous melanoma, has yet to be determined.

**Observations:** A 40-year-old white man with a history of melanoma and multiple dysplastic nevi self-administered synthetic α-MSH. He developed crops of new pigmented nevi, many of which had atypical clinical and histopathologic features. The preexisting nevi became darker and acquired growth features. After α-MSH use was discontinued, the nevi progressively lightened and lost their growth features.

**Conclusions:** Synthetic α-MSH peptides can drive proliferation of neoplastic melanocytic cells in predisposed patients. This could present an increased risk for melanoma development.

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A **known physiologic regulator** of pigmentation, α-melanocyte-stimulating hormone (α-MSH), is mitogenic for melanocytes, induces dispersion of melanosomes, increases tyrosinase activity and melanin synthesis, and, consequently, protects against UV-mediated DNA damage. Mutations in the melanocortin 1 receptor MC1R, and the resultant inability to respond to α-MSH, are associated with enhanced cytotoxic effects of UV-B and predisposition for melanoma formation. Superpotent, long-acting, synthetic analogues of α-MSH are being developed as a strategy for melanoma prevention. Although not approved by the US Food and Drug Administration, synthetic α-MSH analogues have gained popularity for enhancing tanning.

**REPORT OF A CASE**

A 40-year-old white man visited the Pigmented Lesion Clinic at Duke University Medical Center for rapidly growing new moles, several of which were irregularly shaped. He was being followed up regularly because of atypical nevi and his history of melanoma (Clark level II and Breslow depth of 0.25 mm, completely excised, approximately 9 years earlier). There was no family history of melanoma or eruptive nevi. Six weeks before the present clinic visit, the patient had started injecting himself with an α-MSH analogue (Melanotan II; Melanocorp Inc, Hendersonville, Tennessee; http://www.melanocorp.com) subcutaneously twice weekly, according to the manufacturer's recommendations, as a tanning agent. He had learned about α-MSH and its effects from fellow bodybuilders and had purchased the peptide online. It was important for him to be tan for the bodybuilding competition, but he was aware of the negative consequences of UV light tanning and thought that α-MSH would be a good option.

Three weeks after starting treatment, he noticed new moles on his trunk, neck, and arms. These, and the old nevi, began to darken, to grow rapidly, and to appear more irregular, prompting him to discontinue treatment. He did not report any other adverse effects.

On physical examination, the patient had scattered new pigmented nevi on
his neck, trunk, and extremities, confirmed by comparison with photographs taken 1 year earlier (Figure 1). Peripheral dots and “pseudopod-like” structures were found at the edges of many of the lesions, suggesting active growth (Figure 2 and Figure 3). There was no recurrence of pigmentation at the melanoma site or at the sites of previously excised melanocytic nevi. No mucosal pigmented lesions were noted. There was no evidence of lymphadenopathy. He felt well.

One lesion on his left upper middle back just medial to the midline had clinical and dermoscopic features worrisome for melanoma (Figure 2). Histopathologic findings were interpreted by the Department of Pathology, Duke University Medical Center, to reveal a compound nevus with moderate to severe architectural and cytologic atypia extending to the margins (Figure 2). There was a marked presence of pigment-laden keratinocytes and occasional pagetoid melanocytes in the epidermis. The nevocytes in the superficial dermis exhibited melanin pigmentation. The area was excised again, and no residual nevus was noted. A second biopsy of a lesion on his left abdomen revealed a moderately dysplastic compound nevus.

During the next 9 months, there was progressive lightening of the nevi. Growth features disappeared as well. He continues to have regular follow-up without further complications.

COMMENT

α-MSH is a melanotropic cytokine produced by several types of cells, including neural cells, endothelial cells, macrophages, and keratinocytes. It acts by activation of the melanocortin 1 receptor, which increases melanogenesis and enhances DNA repair in melanocytes, and is important in the regulation of pigmentation. Pituitary extracts of an α-MSH induce darkening of integument of different vertebrates in vivo. It is therefore an attractive target for inducing protective tanning without the deleterious effects of UV exposure.

Melanotan I and melanotan II are synthetic peptide analogues that are up to 1000 times more potent than endogenous α-MSH, with melanotan II being the more potent of the two. Early phase 1 and phase 2 trials confirmed that subcutaneous delivery of these peptides exaggerates the tanning response to UV-B and increases the eumelanin level and tanning without additional UV exposure. This response may be enhanced in persons with melanocortin 1 receptor variants. Because of its ability to bind to other melanocortin receptors and its effects on other cells, melanotan II is also being developed as a treatment for erectile dysfunction, obesity, and insulin resistance. No tumorigenesis has been documented in previous studies. Neither has the effect of these potent melanocortins on patients with atypical nevi or a history of melanoma been addressed. To our knowledge, this is the first documented case of eruptive atypical nevi secondary to exogenous melanocortin administration.

The phenomenon of eruptive nevi is well described in the literature and may be caused by stimulatory cytokines or by immunosuppression. Severe bullous diseases, such as toxic epidermal necrolysis and erythema multiforme, have preceded the appearance of eruptive nevi, presumably resulting from melanocytic hyperplasia during the healing process of denuded areas of skin. A case of eruptive Spitz nevi during pregnancy has also been reported. Eruptive nevi have been described in patients who develop AIDS and in patients with cancer receiving chemotherapy. In some
In some cases, the eruptive nevi were followed by the development of melanoma.\textsuperscript{13} Decreased immunosurveillance is thought to play a role because eruptive nevi have been observed to fade after interruption of chemotherapy.\textsuperscript{14} Immunosuppressed patients with renal allografts have been documented to have eruptive nevi with peripheral rims of globules on dermoscopy, similar to what we had documented in our patient.\textsuperscript{15}

The \(\alpha\)-MSH may induce eruptive nevi in susceptible patients owing to its direct stimulatory activity on the melanocyte and through immunoregulatory effects. The \(\alpha\)-MSH and its analogues are mitogenic for human melanocytes.\textsuperscript{16} It has been shown to induce changes in cell shape and to increase the dendricity of melanocytes and melanoma cells.\textsuperscript{17} In addition, \(\alpha\)-MSH is thought to exert a profound immunosuppressive effect, inhibiting nuclear factor–\(\kappa\)B activation and tumor necrosis factor–induced intracellular adhesion molecule expression in melanocytes and melanoma cells.\textsuperscript{18,19} The \(\alpha\)-MSH decreases T-cell–melanoma interaction in vitro,\textsuperscript{20} possibly allowing escape from immune detection and enhancing survival. Decreased levels of \(\alpha\)-MSH and other immunosuppressive cytokines, such as interleukin 10 and transforming growth factor \(\beta\), were good prognostic factors for response to immunotherapy of melanoma.\textsuperscript{21}

Although the biological mechanisms of acquired nevus development are still being elucidated, it is reasonable to assume that melanocytes, nevi, and melanomas are derived from a melanocytic precursor (stem) cell.\textsuperscript{22} The existence and location of these cells in the dermis (or epidermis) have yet to be fully determined. We propose that administration of a superpotent \(\alpha\)-MSH analogue in our patient, who had a background of melanoma and atypical nevi, may have driven his already genetically mutated melanocytic stem cells to produce several new, atypical nevi. Because withdrawal of the cytokine resulted in fading and loss of growth features in our patient’s atypical nevi, we suggest that the precursor cells stimulated to generate the nevi depended on the excessive \(\alpha\)-MSH stimulation to continue to drive growth and prevent regression.

The development of synthetic \(\alpha\)-MSH analogues has been valuable in studying melanocyte biological mechanisms, and they hold potential therapeutic applications.\textsuperscript{3} However, caution must be exercised in pursuing the use of these potent melanocortins in patients because their biological effect on the develop-

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  \caption{Clinical (A) and dermoscopic (B) photographs of a melanocytic lesion on the patient’s upper back that was a concern for melanoma. Histopathologic review of the entire lesion revealed a compound nevus with moderate to severe architectural and cytologic atypia of the melanocytic cells. C and D, Histopathologic analyses also revealed marked pigment accumulation in the keratinocytes and an occasional pagetoid melanocyte. Bars denote 100 \(\mu\)m.}
\end{figure}
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REFERENCES


Figure 3. Dermoscopic features of the patient’s nevi. A, C, E, and G, Features at consultation including dark brown pigmentation with peripheral pigment extensions (pseudopods) and peripheral dots; B, D, F, and H, fading of these features 6 months later.

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