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Topical Imiquimod in the Treatment of Metastatic Melanoma to Skin

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REPORT OF CASES

CASE 1

An 86-year-old woman presented in 1999 with a malignant melanoma (Clark level IV; Breslow thickness, 1.9 mm) on her right knee, which was initially treated with wide excision. In August 2000, several skin lesions of metastatic melanoma were noted on the right lower leg. These were treated with carbon-dioxide laser ablation. Multiple new skin-colored, brownish red, and dark blue smooth-surfaced and eroded papules and nodules of metastatic melanoma appeared on the whole right lower leg in December 2000 (**Figure 1**A). A large ulcerated nodule (2 cm in diameter) was noted on the right lateral crural region (**Figure 2**A). Two lesions were excised and metastatic melanoma was confirmed histopathologically. No lymph node or visceral metastases were found after staging procedures (x-ray of the thorax and sonography of the abdomen and the regional lymph nodes) were performed.

CASE 2

A 49-year-old man presented in February 2000 with melanoma (Clark level IV; Breslow thickness, 1.8 mm) on the left parietal region of the scalp. The melanoma was treated with wide and deep resection followed by split-thickness skin graft repair. A sentinel node was positive (micrometastases of melanoma) and radical lymph node dissection of the neck was performed. Other lymph nodes did not contain metastasis and there was no evidence of systemic disease. The patient received adjuvant low-dose interferon alfa-2b (3 million IU 3 times per week for 3 months) and chemotherapy (dacarbazine [DTIC-Dome; Bayer, Leverkusen, Germany], carboplatin, and fotemustine).

In July 2000, multiple local recurrences appeared around the surgical scar. Despite several treatment modalities, including excision, carbon-dioxide laser vaporation, and regional hyperthermia combined with x-ray treatment, new recurrences and in-transit metastases developed. In January 2001, we found multiple pigmented papules forming clusters and large confluent black plaques around the left ear and in the left parieto-occipital region (**Figure 3**A shows state after 1 month of treatment).

HISTOPATHOLOGY

The primary tumors of both patients had histopathologic features typical of malignant melanoma. In patient 1 (**Figure 4**A), 2 biopsy specimens of skin lesions from the right lower leg, and in patient 2, 1 biopsy specimen of a retroauricular pigmented papule, showed metastatic melanoma with sheets of neoplastic melanocytes situated mainly in the upper dermis.

THERAPEUTIC CHALLENGE

In view of her age and cardiac insufficiency, patient 1 elected a less aggressive therapy for the melanoma metastases. Several treatment modalities had been attempted for patient 2, without success. The challenge was to find a therapeutic alternative for these patients.

SOLUTION

The 2 patients were enrolled in our study after giving their informed oral consent.

The novel topical immune response modifier imiquimod (Aldara; 3M Pharmaceuticals, St Paul, Minn) was used as a 5% cream, 3 times per week on Monday, Wednesday, and Friday in the evening and washed off in the morning. The cream was applied to the papules and nodules of metastatic melanoma with a 1-cm surrounding margin.

In patient 1, treatment was carried out for 4 months, and the lesions showed complete clearing with superficial scars and residual hyperpigmentation (Figures 1B and 2B). A control biopsy specimen from the right leg, obtained 4 months after the initial therapy, showed a thinned epidermis with a perivascular lymphoid infiltrate, mild fibrosis, and an increase of ectatic vessels (Figure 4B). The large ulcerated nodule showed complete clinical resolution (Figure 2B). No adverse effects occurred except

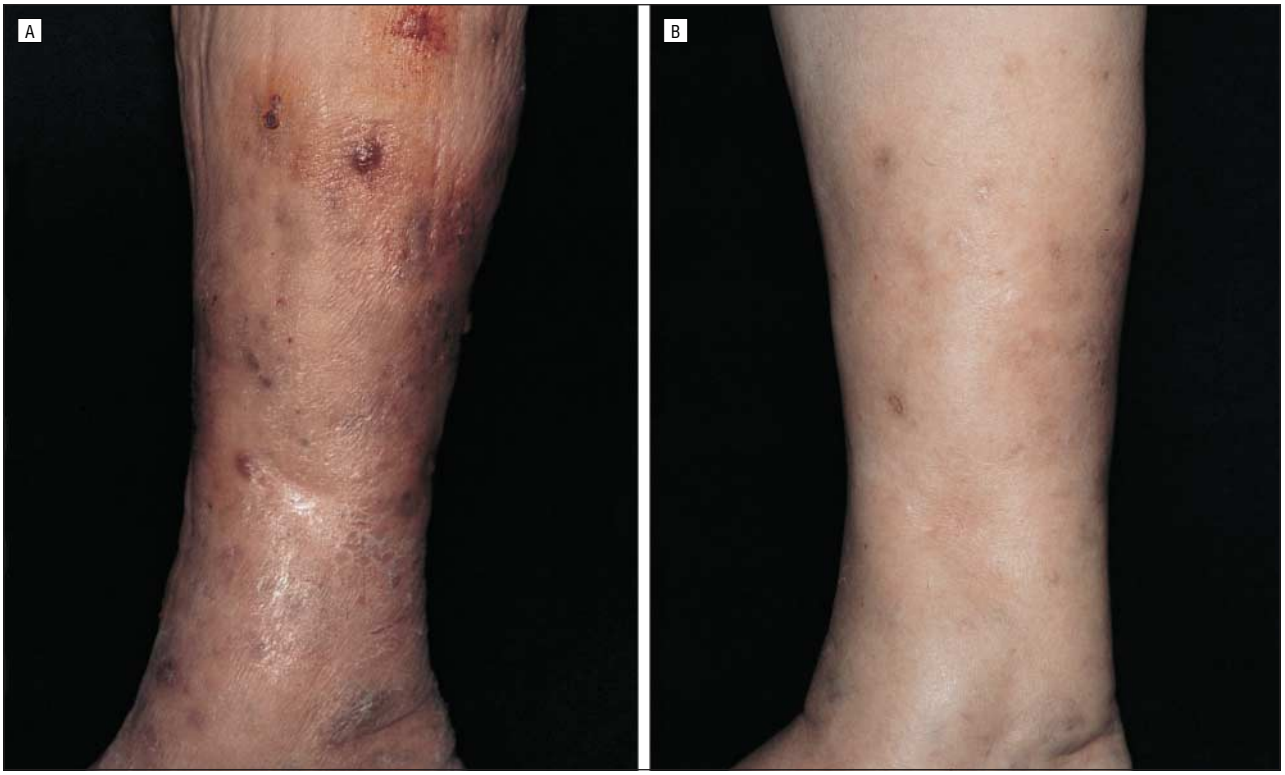

Figure 1. Patient 1. A, Right lower leg (medial aspect) with multiple cutaneous melanoma metastases. B, After 4 months of treatment with 5% imiquimod cream, metastatic papules are completely cleared.

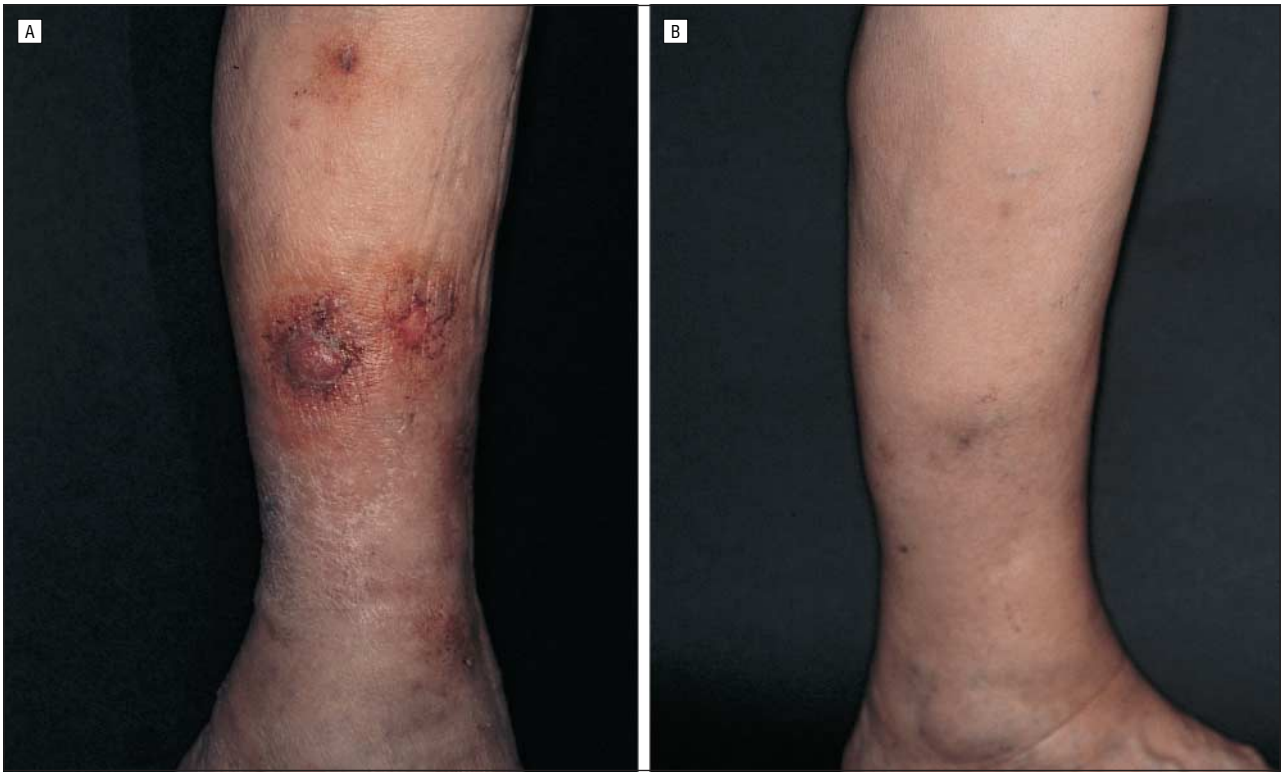

Figure 2. Patient 1. A, Right lower leg (lateral aspect) showing multiple papules and an ulcerated nodule of cutaneous melanoma metastases. B, After 4 months of treatment with 5% imiquimod cream, complete remission with residual hyperpigmentation is seen.

mild peritumoral erythema. As of this writing, the patient has been followed up for 15 months without clinical evidence of recurrence.

Patient 2 also showed complete clearing of the skin lesions after 8 months of treatment with 5% imiquimod cream (3 times per week; the cream was also applied in

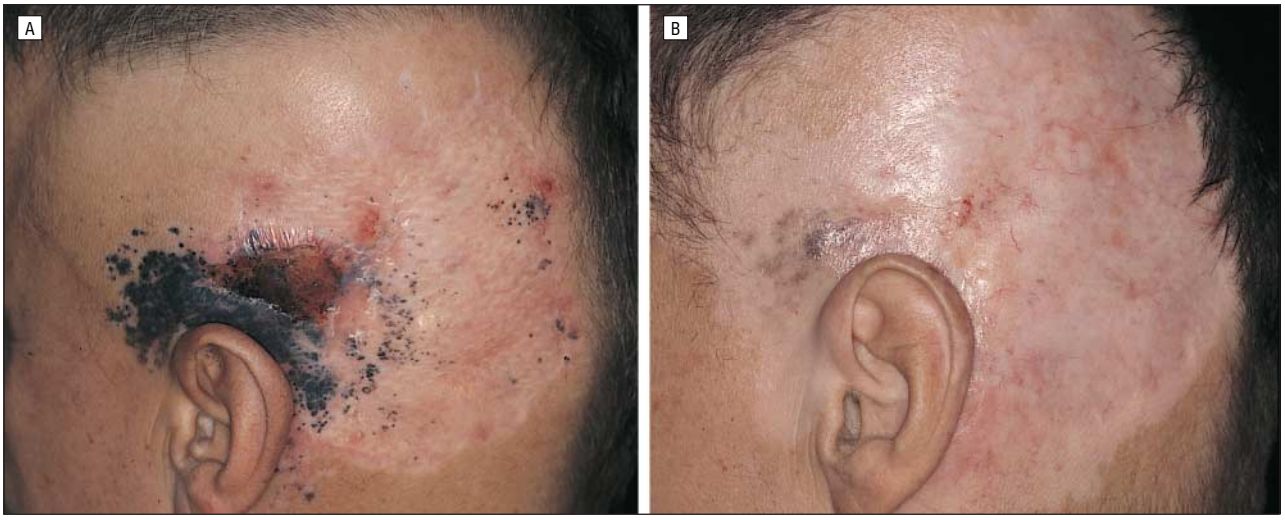

Figure 3. Patient 2. A, Clinical aspect of cutaneous melanoma metastases during treatment with 5% imiquimod cream (after 1 month). Erosions are noted as an adverse effect of the cream. B, Eight months after therapy, complete clearing can be observed. The gray-brown area (arrow) represents histologically proved regression with melanophages.

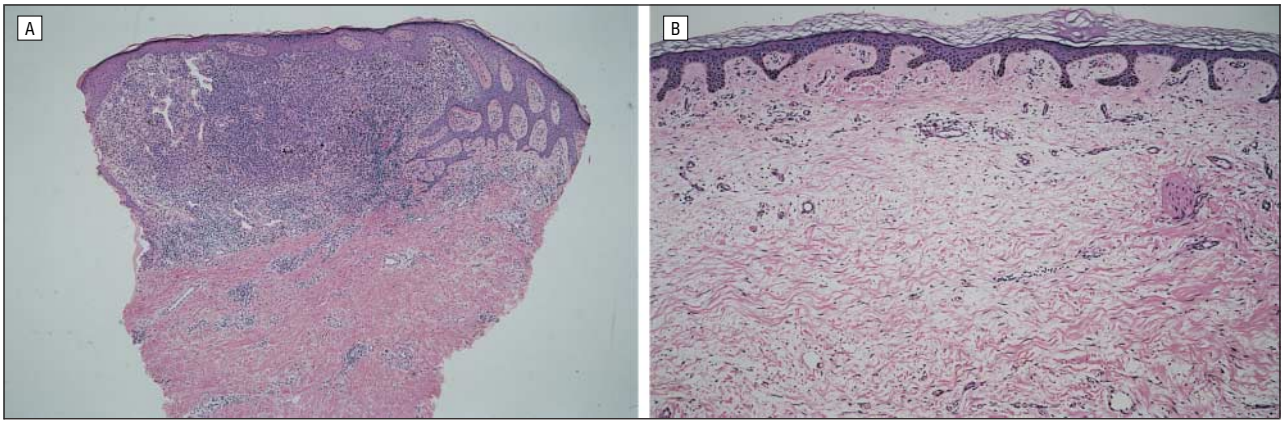

Figure 4. Patient 1. A, Histopathologic findings of metastatic melanoma to skin (hematoxylin-eosin, original magnification ×10). B, A biopsy specimen obtained after imiquimod treatment shows atrophic epidermis, a perivascular lymphoid infiltrate, mild fibrosis, and an increase of ectatic vessels (hematoxylin-eosin, original magnification ×40).

the evening on the papules and plaques and washed off in the morning). At one of the target sites, we noticed erosions after 1 month (Figure 3A); these healed rapidly after therapy was discontinued in this area for a short time. Results of follow-up examinations 4 months and 8 months later showed no evidence of recurrence of melanoma metastases (Figure 3B). In a control biopsy specimen from the gray-brown area above the left ear, we found a thickened papillary dermis marked by fibroplasia and a band of melanophages. Residual melanoma cells could not be detected.

COMMENT

Metastatic melanoma of the skin is extremely difficult to treat. Despite a variety of available options, including surgery, immunotherapy, chemotherapy, x-ray therapy, regional hyperthermia, and carbon-dioxide laser ablation, treatment is often unsuccessful.

We evaluated the efficacy of imiquimod, which has been formulated as a 5% cream, in 2 patients with metastases of melanoma to the skin. Chemically, imiquimod is a 1-(2-methylpropyl)-1*H*-imidazol[4,5-*c*]quinolin-4-amine with a molecular formula of $C_{14}H_{16}N_4$. Imiquimod enhances the immune system by inducing the release of several cytokines, including interferon α, interleukin 12, and tumor necrosis factor α.[1]

In their preliminary report on the treatment of a cutaneous melanoma metastasis, Steinmann et al[2] suggested that the application of imiquimod might result in the induction of melanoma-specific cytotoxic T cells by cross-presentation of melanoma antigens by dendritic cells.[2]

Imiquimod was introduced especially for the treatment of external genital warts (including those in children) and has subsequently been found to be useful for the treatment of molluscum contagiosum, verrucae planae, herpes simplex virus 2 infection, stucco keratoses, basal cell carcinoma, superficial squamous cell carcinoma, and actinic keratoses.[3-13]

We observed complete clinical and histopathologic remission of papules, plaques, and nodules in 2 patients with metastatic melanoma to the skin. Our findings indicate that topical imiquimod is a novel and

potentially promising therapeutic approach for the local treatment of cutaneous melanoma metastases.

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Submissions

Clinicians, local and regional societies, residents, and fellows are invited to submit cases of challenges in management and therapeutics to this section. Cases should follow the established pattern. Submit 4 double-spaced copies of the manuscript with right margins nonjustified and 4 sets of the illustrations. Photomicrographs and illustrations must be clear and submitted as positive color transparencies (35-mm slides) or black-and-white prints. Do not submit color prints unless accompanied by original transparencies. Material should be accompanied by the required copyright transfer statement, as noted in "Instructions for Authors." Material for this section should be submitted to George J. Hruza, MD, Laser and Dermatologic Surgery Center Inc, 14377 Woodlake Dr, Suite 111, St Louis, MO 63017.