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Treatment of Lentigo Maligna (Melanoma In Situ) With the Immune Response Modifier Imiquimod FREE

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ABSTRACT

Background Surgical excision is the treatment of choice for lentigo maligna (LM), or melanoma in situ. Topical application of imiquimod, a local immune response modifier, is a novel therapeutic approach that leads to LM tumor clearance. This pilot, open-label, nonrandomized study evaluates the efficacy of imiquimod in patients with LM and other systemic problems that make them poor surgical risks.

Observations Six biopsy-proven cases of LM from 5 patients (age range, 67-80 years) in whom standard surgical therapy was contraindicated were enrolled in the study. Five tumors were located on the face and 1 on the right shoulder. Imiquimod was used as a 5% cream once a day for a maximum of 13 weeks. Immediate clinical responses and follow-up, as well as histopathologic changes and immunohistologic parameters (in 2 patients), were analyzed. The complete response rate for all LM cases was 100%. Time to complete clearing varied from 5 to 13 weeks based on both clinical and histopathologic findings. The inflammatory infiltrate following imiquimod treatment consisted of T-helper lymphocytes mixed with a significant number of cytotoxic cells and monocytes or macrophages. These results indicate that imiquimod induces a cytotoxic T-cell–mediated immune response. In all patients, erythema and erosions occurred at the treated area 2 to 4 weeks after initiation of imiquimod therapy. The patients have been followed up for 3 to 18 months without evidence of recurrences.

Conclusions Topical imiquimod appears to be an excellent therapeutic option for LM. Close evaluation of patients, including posttherapy histopathologic investigation, is essential. Imiquimod can be added to the list of therapeutic approaches for carefully selected patients with LM.

The term *lentigo maligna* (LM) is used as a synonym for melanoma in situ of sun-damaged skin. It occurs most commonly on the face in elderly patients. Clinically, LM usually develops as a slowly growing asymmetric macule with brown to black variations and irregular indented borders. Histopathologically, it is characterized by a proliferation of atypical melanocytes arranged in solitary units and small nests at the dermoepidermal junction and above it.

Complete surgical excision is recommended as the treatment of choice for LM to allow accurate histologic assessment and to avoid recurrence. In special circumstances, other therapeutic options must be considered in the treatment of patients with LM. In this study, the efficacy of topically applied imiquimod (Aldara; 3M Pharmaceuticals, St Paul, Minn) was evaluated in selected patients with LM on the face and

trunk.

METHODS

Five patients with 6 biopsy-proven cases of LM, in whom standard surgical therapy was contraindicated, were enrolled in our study. All patients gave their informed consent. The clinical data of the patients are given in the Table. Imiquimod was used as a 5% cream once a day in the evening and washed off in the morning. The cream was applied to the pigmented areas of LM with a 0.5- to 1-cm surrounding margin. Treatment with imiquimod was performed for 5 to 13 weeks. Biopsy specimens were obtained from representative areas from all patients before and after treatment. In 2 patients (patients 4 and 5), 1 additional biopsy was performed during treatment.

Table. Clinical Characteristics of Patients With Lentigo Maligna (LM) Treated With Imiquimod

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Sections from formalin-fixed and paraffin-embedded biopsy specimens were stained with hematoxylin-eosin. In addition, sections from 2 biopsy specimens (patients 4 and 5) performed 3 weeks after initiation of imiquimod treatment were evaluated with both routine histologic and immunohistochemical analysis following appropriate antigen retrieval, as previously described.[1] To characterize the inflammatory cellular infiltrate, a panel of antibodies was used, including CD3 (dilution, 1:100; Novocastra Laboratories Ltd, Newcastle Upon Tyne, England), CD4 (dilution, 1:30; Novocastra), CD8 (dilution 1:25; DakoCytomation Denmark A/S, Glostrup, Denmark), CD20 (dilution, 1:20; DakoCytomation), CD30 (dilution, 1:20; DakoCytomation), CD56 (dilution, 1:20; Novocastra), S100 (dilution, 1:25; DakoCytomation), KP-1 (dilution, 1:25; DakoCytomation) and PGM-1 (dilution, 1:25; DakoCytomation), and CD56 (dilution, 1:20; Novocastra). For demonstration of formalin-resistant epitopes of cytotoxic cell proteins, T-cell intracellular antigen 1 (Immunotech, Marseille, France) and granzyme B (Sanbio bv, Uden, the Netherlands) were investigated.

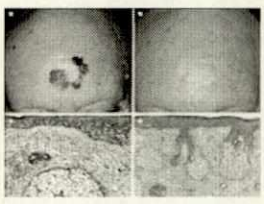
RESULTS

CLINICAL FINDINGS AND OUTCOMES

In all 6 cases of LM from the 5 patients complete clinical resolution was observed (Figure 1B). Patient 3 (Table), who presented with a recurrent amelanotic LM on her right cheek, was difficult to treat because involved margins were not clearly defined. Application of imiquimod far beyond the clinical suspected areas resulted in complete clearance; significant aesthetic disfigurement by surgery was avoided.

Figure 1.

Patient 1 with lentigo maligna. A, Large lentigo maligna on the forehead. B, Complete remission. A 5% imiquimod cream was applied for 9 weeks. The treatment site is almost imperceptible. C, Histopathologic findings before treatment reveal melanoma in situ (hematoxylin-eosin, original magnification ×250). D, A biopsy specimen obtained after imiquimod therapy shows complete resolution (hematoxylin-eosin, original magnification ×100).



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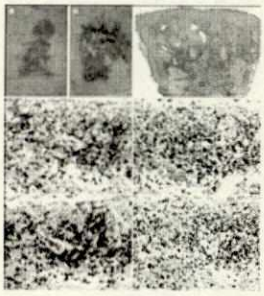
In all patients, irritation of the treated areas occurred after 2 to 4 weeks with erythema and erosions (Figure 2B). The imiquimod treatment was discontinued for a few days and then resumed with the same regimen after the irritation had subsided. Patient 3 reported fatigue and fever at the beginning of her treatment as a

systemic adverse event. Time to complete remission varied from 5 to 13 weeks. The patients have been followed up for 3 to 18 months without evidence of recurrences.

Figure 2.

Patient 4 with lentigo maligna. A, Lentigo maligna on the forehead. B, Large erosive lesion after 4 weeks of treatment with 5% imiquimod cream at the application site. C, Histopathologic findings of the erosive lesion during treatment; a superficial ulcer with a dense inflammatory infiltrate is present (hematoxylin-eosin, original magnification ×50). D, Immunohistologic investigations showed predominance of T lymphocytes (CD3) with both helper (CD4) and cytotoxic (CD8, T-cell intracellular antigen 1 [TIA-1]) phenotypes (immunoperoxidase, original magnification ×400).



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HISTOPATHOLOGIC FINDINGS

Biopsy examination confirmed the diagnosis of melanoma in situ in severely sun-damaged skin in all patients (Figure 1C). Melanocytes with atypical nuclei were present as solitary units and in small nests along the dermoepidermal junction, scattered above it, and focally within epithelial structures of adnexa.

Biopsy specimens obtained before treatment from patient 1 also revealed lymphoid infiltrates and an accumulation of melanophages in the upper dermis. In pretreatment biopsy specimens from the other patients (patients 2-5), only scant inflammatory infiltrates were present.

Control biopsy specimens obtained 9 weeks (patient 1), 13 weeks (patient 2), 5 weeks (patient 3), 12 weeks (patient 4), and 10 weeks (patient 5) after the initial therapy showed normal epidermis and only a few perivascular lymphocytes, mild fibrosis, and focally an increase of ectatic vessels. Signs of melanoma in situ were not present (Figure 1D).

Biopsy specimens from the local skin reaction at the application site obtained after 3 weeks (patients 4 and 5) showed erosions with a dense inflammatory infiltrate within the dermis (Figure 2C).

IMMUNOHISTOLOGIC FINDINGS

Immunohistologic staining performed in biopsy specimens obtained 3 weeks after imiquimod treatment (patients 4 and 5) revealed an inflammatory infiltrate composed of T-helper lymphocytes with a significant proportion of monocytes and macrophages. In addition, a distinct portion of the infiltrate consisted of cytotoxic T lymphocytes ($CD8^+$, positive T-cell intracellular antigen 1, and positive granzyme B) (Figure 2D). By contrast, only a few B lymphocytes and scattered natural killer cells and Langerhans cells were detectable. In biopsy specimens analyzed before and after imiquimod treatment, only a few T-helper lymphocytes ($CD3^+$, $CD4^+$, $CD8^-$) could be observed.

COMMENT

Alternatives to surgical excision for the treatment of LM in patients with underlying disorders that make them poor surgical risks include cryosurgery, x-ray therapy, and laser therapy. Recently, several case reports have indicated that topical application of a 5% imiquimod cream may be effective in LM[2-7] and also in metastatic melanoma to skin.[8] In a pilot study that included a large number of patients with LM,[9] an initial response rate of 93% was found.

Imiquimod is a novel therapeutic approach that was initially introduced for the treatment of external genital warts but subsequently has been found to be useful in treating many other conditions, such as molluscum contagiosum, verrucae planae, basal cell carcinoma, superficial squamous cell carcinoma, and actinic keratoses. The drug belongs to a group of immune response modifiers with antiviral and antitumor

activity. The principal pharmacologic effect is augmentation of both innate and adaptive immune responses.[10] It can activate a new receptor family, the so-called Toll-like receptors, leading to the production of cytokines and chemokines, such as interferons, interleukins, and growth factors.[11-14] Imiquimod also induces Langerhans cell migration.[15] Furthermore, the topical application of imiquimod induces apoptosis[16] and inhibits vascular tumor growth in the mouse model.[17]

We evaluated the efficacy of topically applied imiquimod in 6 LM cases from 5 patients and observed complete clinical and histopathologic remission in all cases. Local adverse effects (inflammation, erosion) were regularly observed, usually after 3 weeks. Patients were treated for 5 to 13 weeks. All treated areas have remained clear 3 to 18 months after imiquimod therapy. To better elucidate the nature of the cellular infiltrate during the application of imiquimod, we also studied immunohistologic markers at various time points in 2 patients. The inflammatory infiltrate induced by imiquimod contains primarily T-helper lymphocytes admixed with a significant number of cytotoxic cells and monocytes or macrophages. A similar immunohistologic pattern has also been found in basal cell carcinoma after treatment with imiquimod.[14,18] Our results are consistent with previous data that indicate that imiquimod stimulates a cytotoxic T-cell–mediated immune response, which may be responsible for eliciting apoptosis of neoplastic melanocytes and tumor destruction. Monocytes and macrophages also seem to be important.[14,19]

We have demonstrated that local application of 5% imiquimod cream is a valid treatment modality for LM in patients who cannot undergo surgical excision because of advanced age, very large lesions, ill-defined margins, cosmetically precarious anatomic location, or systemic disorders that make them poor surgical risks. Because imiquimod can be easily applied far beyond the clinically suspicious areas, it might also be useful in patients with LM where the excision margins cannot be clearly identified to avoid large flaps and skin grafts. Accurate posttreatment assessment, including histologic follow-up, is recommended for patients with LM treated with imiquimod.

ARTICLE INFORMATION

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