Lentigo Maligna (Melanoma In Situ) Treated With Imiquimod Cream 5%: 12 Case Reports

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Lentigo maligna (LM) is an in situ variant of melanoma. Although LM has the potential for invasion, it often has a greatly protracted radial growth phase and may remain indolent for years. The current standard of care is surgical excision, but this often results in substantial morbidity; thus, nonsurgical approaches continue to be investigated. Imiquimod cream 5% is an immunomodulatory agent that previously has been reported to successfully eradicate LM.

We evaluated the treatment course of topical imiquimod in 12 patients with LM. Data from patients with biopsy-proven LM were collected retrospectively, reviewed, and summarized. Patients ranged in age from 54 to 83 years. Most patients chose imiquimod cream as their initial form of treatment; however, other patients had a history of LM recurrence after excision or had positive histologic margins at the time of excision. Initial application regimens varied from 2 to 7 times weekly. The average duration of treatment was 15.7 weeks but ranged from 7 to 44 weeks. Results of posttreatment biopsies of the most clinically suspicious areas in 6 patients showed histologic clearance; 2 patients demonstrated single atypical melanocytes and 4 patients demonstrated clinical clearance without histologic confirmation. These findings suggest that imiquimod cream 5% may be an effective alternative treatment for LM.

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Lentigo maligna (LM) is an in situ variant of melanoma typically found on the head and neck of elderly patients. These tumors tend to be indolent for years but retain the potential to metastasize.[1] The current standard of care is either surgical excision via Mohs micrographic surgery or standard surgical excision with 5-mm margins. Because these tumors most commonly are found on the head and neck of elderly patients, potential surgical morbidity must be considered. In addition, histologic evidence of disease often extends beyond clinical margins, and differentiating the tumor from background actinic damage can be challenging.[2] Recurrence, even after Mohs micrographic surgery, is not uncommon.[3-5]

Imiquimod cream 5% is an immunomodulatory agent that has antiviral and antineoplastic effects, and several reports of its successful use in the treatment of LM recently have appeared in the literature.[6-8] This case series highlights the topical imiquimod treatment course of an additional 12 patients with LM.

Patients and Methods

Data from 12 patients with biopsy-proven LM who were treated with imiquimod cream were collected retrospectively for 4 years (2001–2004) from

Patient Demographics and Imiquimod Treatment Data*

Case No.	Age, y	Sex	Lesion Location	Reason for Treatment	Application Frequency	Treatment Duration, wk	Posttreatment Histologic Evaluation	Follow-up, mo†
1	79	F	R nasal ala	Initial treatment	5–7×/wk for 6 wk, then 3×/wk for 8 wk followed by a 6-wk break	14	Not performed	21
2	69	F	R cheek	Initial treatment	7×/wk for 2 wk, then 3×/wk for 5 wk	7	No evidence of LM	21
3	64	M	L nasal sidewall	Initial treatment	7×/wk for 15 wk followed by a 24-wk break	15	Not performed	12
4	70	F	R cheek	Recurrence	2–4×/wk for 5 mo followed by a 1-mo break, then 1×/wk for 1 mo followed by a 1-mo break, then 1×/wk for 1 wk	28	No evidence of LM	16
5	82	F	L nasal ala	Margins positive	3–5×/wk for 3 wk followed by a 1-wk break, then 3–5×/wk for 7 wk	11	Not performed	21
6	54	F	R cheek	Margins positive	3–5×/wk for 8 wk followed by a 1-wk break, then 3–5×/wk for 3 wk followed by a 5-mo break, then 2×/d for 3 wk	15	Single atypical melanocytes, no evidence of LM	16
7	80	F	R cheek	Recurrence	3×/wk for 3 wk, then 7×/wk for 5 wk	8	Not performed	23
8	68	F	L upper dorsal nose	Initial treatment	2–5×/wk for 5 wk followed by a 1-wk break, then 2–3×/wk for 6 wk	12	Inflammation, no evidence of LM	14
9	83	M	L lower cutaneous lip	Initial treatment	3–5×/wk followed by a single 5-day break	10	Patchy interface dermatitis, no evidence of LM	10
10	56	F	R central forehead	Initial treatment	Daily for 6 wk, then gradually decreasing in frequency over next 6 wk	12	Atypical junctional melanocytic proliferation less atypical than previous LM	9
11	64	F	R cheek	Recurrence	3–5×/wk	44	No evidence of LM	48
12	77	M	L cheek	Initial treatment	3–4×/wk	12	No evidence of LM	9

*F indicates female; R, right; LM, lentigo maligna; M, male; L, left.

†At follow-up, all patients had no evidence of lentigo maligna.

3 dermatology centers (Table). The patients ranged in age from 54 to 83 years.

Results

Although most patients (7/12) chose imiquimod cream as their initial form of treatment after all options were considered, 5 patients had a history of LM recurrence after excision or had positive histologic margins at the time of excision. Initial application regimens varied from 2 to 7 times weekly. The frequency of applications fluctuated according to symptoms and therapeutic response. Many patients experienced excessive irritation, and most patients averaged an application course of 3 times weekly. The average duration of treatment was 15.7 weeks but ranged from 7 to 44 weeks. The average follow-up period was 18.3 months.

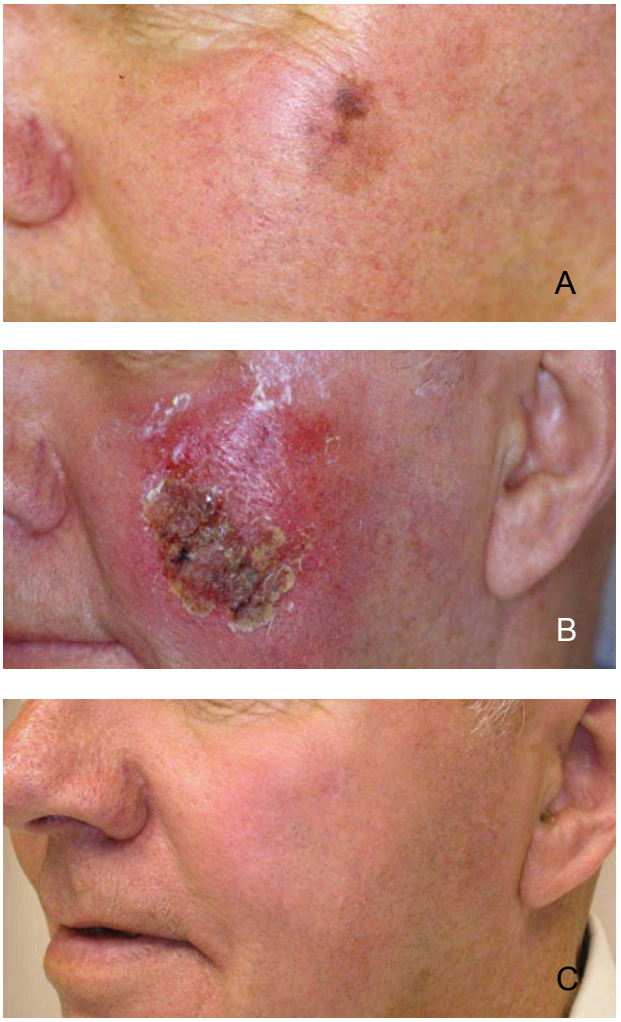
Results of posttreatment biopsies of the most clinically suspicious areas in 6 patients showed histologic clearance. In 2 patients, single atypical melanocytes were seen, but a confirmatory diagnosis of LM was not made. Four patients declined undergoing a follow-up biopsy but did demonstrate clinical clearance without histologic confirmation. Case 12 shows a typical clinical course of imiquimod therapy for LM (Figure).

Comment

LM rarely metastasizes but may become locally invasive if neglected or incompletely eradicated. Because many of these lesions occur on the face and require multiple therapeutic procedures, surgical removal not only poses oncologic concerns but also raises functional and cosmetic issues. Additionally, the sun-damaged skin of patients with LM often contains atypical melanocytes, making accurate determination of histologic margins difficult. Because of these shortcomings, nonsurgical treatment approaches continue to be evaluated.

In 2000, Ahmed and Berth-Jones[6] reported the first case of LM successfully treated with imiquimod therapy. Other single case reports have followed.[7,8] Imiquimod also appears to have an effect on invasive melanoma and metastatic disease.[9,10]

The first prospective study of imiquimod for the treatment of LM was reported by Naylor et al.[11] In their study, 26 of 28 subjects (93%) had LM tumors that cleared after 12 weeks of daily imiquimod application. A smaller study and case report series followed. Some subjects failed to respond to therapy and were offered standard surgical excision.[12] To date, the 5-year recurrence rate is unknown. There is a single case in which treatment with imiquimod cleared a large LM; the clearing was followed by the discovery of a nodular melanoma within the LM patch.



A 77-year-old man before (A) and after 12 weeks of treatment with imiquimod cream 5% applied 3 to 4 times weekly (B). At 6 months posttreatment, there is no evidence of lentigo maligna (C).

Fisher and Lang[13] believed that imiquimod stimulated the growth of this nodular component.

In 2 case studies,[8,12] imiquimod was used in elderly or infirm patients who were poor surgical candidates or who had had a recurrence of LM after surgical excision. Other patients preferred an initial trial of imiquimod to minimize scarring and disfigurement.[6,7,12] The clearance rates in these studies are impressive, but because the sample sizes are small, the data must be interpreted cautiously.

Imiquimod is a topical imidazoquinoline, which acts as an immune response modifier through the toll-like receptor 7.[14] As a result, T_H1 cytokines involved in cellular immune responses, including interleukin 12, interferon α, and tumor necrosis factor α, are preferentially induced. Imiquimod has been shown to be effective for the treatment of verruca vulgaris[15] and other viral infections,[16,17] as

well as for actinic keratoses,[18,19] Bowen disease,[20] and superficial basal cell carcinoma.[21,22] As our understanding of the mechanism of action of imiquimod and other immune response modifiers expands, it is reasonable to expect that these agents may be routinely used for other conditions.

Conclusion

This case report series provides continuity to support medical or nonsurgical treatment of melanoma in situ and stimulates further study on this matter. This case series, along with other recent reports in the literature, suggests that nonsurgical treatment of LM may provide a realistic option in the appropriate clinical setting and that further study is warranted.

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