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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Drs. Spenny, Walford, Werchniak, Beltrani, Brennick, Storm, and Perry report no conflict of interest. Dr. Chapman has performed clinical trials for, is a consultant and speaker for, and has received research grants from Graceway Pharmaceuticals, LLC.

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

*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\textsuperscript{6} reported the first case of LM successfully treated with imiquimod therapy. Other single case reports have followed.\textsuperscript{7,8} Imiquimod also appears to have an effect on invasive melanoma and metastatic disease.\textsuperscript{9,10}

The first prospective study of imiquimod for the treatment of LM was reported by Naylor et al.\textsuperscript{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.\textsuperscript{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. Fisher and Lang\textsuperscript{13} believed that imiquimod stimulated the growth of this nodular component.

In 2 case studies,\textsuperscript{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.\textsuperscript{6,7,11} 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.\textsuperscript{14} As a result, T\textsubscript{1}\textsuperscript{1} cytokines involved in cellular immune responses, including interleukin 12, interferon \( \alpha \), and tumor necrosis factor \( \alpha \), are preferentially induced. Imiquimod has been shown to be effective for the treatment of verruca vulgaris\textsuperscript{15} and other viral infections,\textsuperscript{16,17} as
well as for actinic keratoses, Bowen disease, and superficial basal cell carcinoma. 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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REFERENCES