OBSERVATION

Lentigo Maligna With Spread Onto Oral Mucosa

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Background: Lentigo maligna (LM) is a form of melanoma in situ most often seen in white patients on sun-exposed areas, primarily the head and neck. Spread of LM onto the conjunctiva has been reported. There have been no reports of LM extending onto oral mucosa.

Observations: We report 4 cases of LM in white women with contiguous spread from perioral areas to oral mucosa. The locations of the primary lesions were the vermilion of the lip, vermilion and perioral skin, cheek, and cutaneous aspect of the lip. Three cases showed focal histopathologic evidence of invasion during the course of the disease. The lesions ran a prolonged course characterized by repeated recurrences after surgery. Three of the cases required a complicated reconstruction after surgical excision. Mohs surgery with rush permanent (paraffin-embedded) sections resulted in a long remission in 2 cases, while in 1 patient, treatment with carbon dioxide laser was unsuccessful.

Conclusions: In a perioral distribution, LM can spread onto oral mucosa. This clinical presentation may cause significant long-term morbidity, as indicated by a high recurrence rate and/or progression to invasive melanoma. The oral mucosa should be examined in patients with atypical pigmented perioral lesions.

Arch Dermatol. 2002;138:1216-1220

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LENTIGO MALIGNA (LM) is a type of melanoma in situ with unique clinical and histopathologic features.[1] It occurs almost exclusively in whites and shows a slight female preponderance.[2] Lentigo maligna usually presents as a poorly circumscribed, variably colored patch on sun-exposed areas, primarily the head and neck. The cheek is the most common site. The margins of LM are often difficult to evaluate as a result of mottled pigmentation and a background of solar lentigines and chronic photodamage.[2] Long-term cumulative UV radiation is the most widely recognized risk factor for the development of LM.[3,4]

Lentigo maligna melanoma (LMM), the invasive form of LM, is the most common subtype of malignant melanoma on the face.[5] Lentigo maligna occurs less commonly on the trunk and extremities. Lesions previously reported on the subungual area,[6,7] fingers,[8,9] toes,[10] hand,[11] foot,[11] scrotum,[12] penis,[13] and oral mucosa[14,15] would be classified today as acral lentiginous melanoma or another histologic type.[16,17] The conjunctiva may be involved when LM on the eyelids and/or periorbital areas spreads onto conjunctival mucosa.[18-20] A case of melanoma in situ involving the oral mucosa, lips, and perioral skin was reported and was believed to have spread from the oral mucosa to the perioral skin.[21] One of us (L.M.C.) recently reported extension of recurrent LM of the cheek onto buccal mucosa (case 3 in this series).[22]

Herein, we report 4 cases of LM with contiguous spread from perioral skin and/or vermilion of the lip onto oral mucosa. To our knowledge, this clinical presentation has not been previously reported. All patients experienced significant morbidity. We review the complicated course and prognosis of these patients and discuss treatment options and the challenge of permanent cure. The clinical data and response to treatment in the cases studied are summarized in the **Table**.

REPORT OF CASES

CASE 1

Biopsy specimens of the primary and recurrent lesions (the latter shown in **Figure 1** and **Figure 2**) demonstrated LM. The recurrent lesions were treated with carbon dioxide laser excision fol-

Clinical Data and Response to Treatment in the Cases Studied*

Patient No./ Sex/Age, y	Initial Lesion	Treatment	Recurrent Lesions	Progression to LMM	Patient Outcome
1/F/70	Lower lip 20 y ago	Excision, negative margins	Upper and lower lips and buccal mucosa	Yes	Carbon dioxide laser, positive margins
2/F/57	Long-standing lesion on right oral commissure, lips, and adjacent skin	Narrow excision with RPS, negative margins	Buccal and labial mucosa	No	Excision with RPS, no recurrences in 5 y
3/F/51	Left cheek 20 y ago	Excision, negative margins	Recurrences on flap scars, oral commissure, upper lip, buccal mucosa	Yes	Excision with RPS, no recurrences in 6 y
4/F/81	Left upper lip 12 y ago; to commissure, vermilion, labial mucosa 1 y later	Narrow excision, negative margins	Recurrences on upper lip, cheek, melolabial fold	Yes	Excision, positive margins

*RPS indicates rush permanent section; LMM, lentigo maligna melanoma.

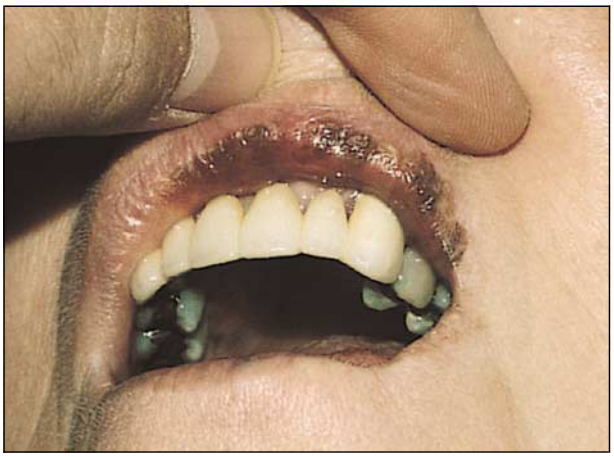

Figure 1. Irregularly pigmented lesion from case 1 on the left upper lip extending onto the labial mucosa.

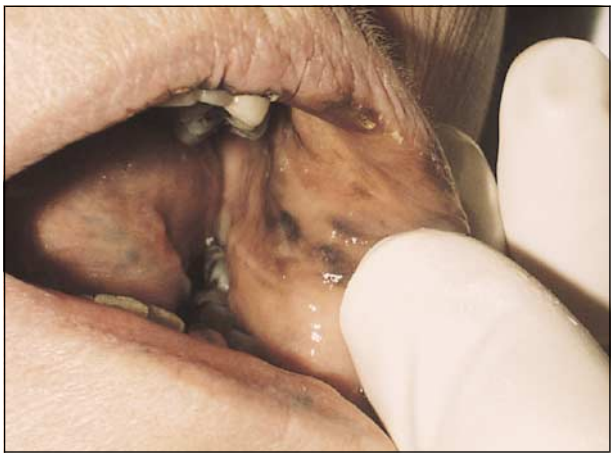

Figure 2. A group of pigmented papules from case 1 on the left midanterior buccal mucosa extending to the commissure.

lowed by peripheral vaporization. The buccal mucosal specimen removed during the laser excision revealed extensive LMM in vertical growth phase with an invasive desmoplastic component and positive margins. Three months later, biopsy specimens from residual pigmented oral lesions taken by repeat laser excision showed residual LM in the oral commissure.

CASE 2

Biopsy specimens of the primary lesion (**Figure 3**) revealed LM. The lesion was excised with a 5-mm margin using rush permanent sections. The upper lip was repaired with a rhombic flap and the lower lip, with an advancement flap. Two years later, 3 tan to brown pigmented patches were noted on the right buccal mucosa and lower labial mucosa (**Figure 4**). Biopsy specimens confirmed recurrent LM. Negative margins were obtained after 3 stages of excision with rush permanent sections, and the defect was repaired with a full-thickness skin graft from the groin. No recurrences or new atypical lesions have been noted 5 years after excision.

CASE 3

A biopsy specimen of the primary lesion on the left cheek showed LM. The lesion recurred several times and was

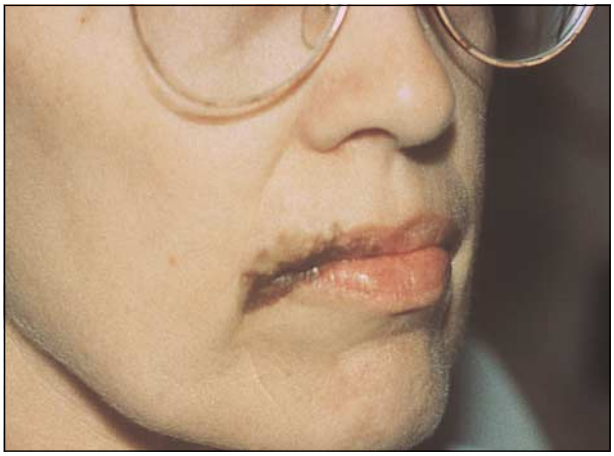

Figure 3. A long-standing pigmented plaque from case 2 involving the lips, right commissure, and perioral skin.

excised after each recurrence; advancement flap was used once for the repair. Ten years after the appearance of the primary lesion, a recurrent lesion was noted on the left cheek and oral commissure. This was treated with wide excision and reconstruction with a cervicofacial rotation flap. Pathologic analysis showed a 3-mm-thick LMM, but the margins were ambiguous. Three years later, extensive pigmentation was noted along the scar from the

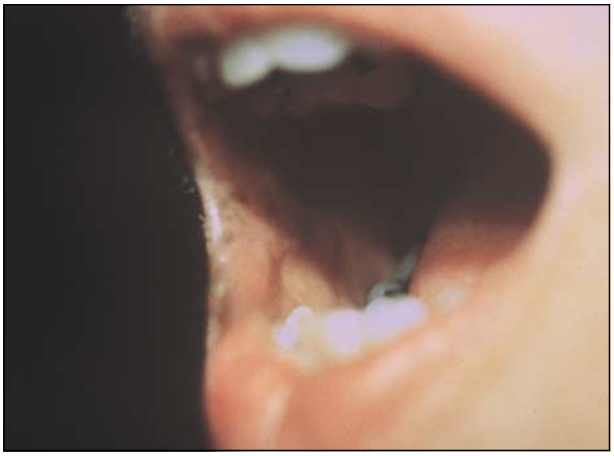

Figure 4. Tan to brown pigmented macules from case 2 on the right midanterior buccal mucosa and lower labial mucosa.

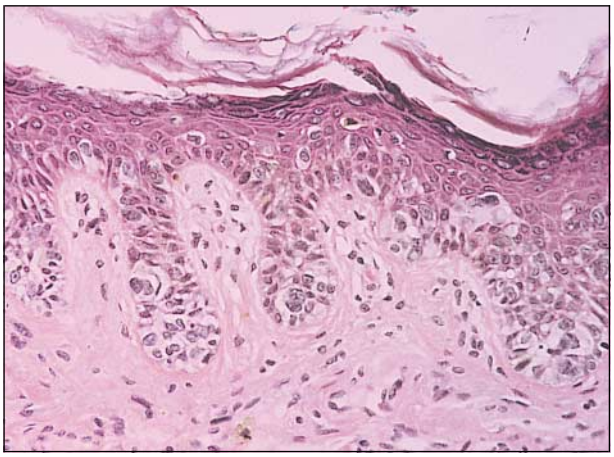

Figure 5. Biopsy specimen taken from a recurrent lesion in case 4 demonstrates pleomorphic melanocytes with large, irregular hyperchromatic nuclei and areas of pagetoid spread (original magnification ×200).

previous cervicofacial flap that involved the advanced portions of the flap and left oral commissure. The tumor extended onto the upper lip, oral commissure, and buccal mucosa. All affected areas were excised using rush permanent sections. The commissure was reconstructed with an intraoral rotation flap, the lower lip with simple undermining and advancement, and the cheek with a prefabricated supraclavicular flap. To date, there have been no recurrences or new atypical lesions.

CASE 4

The primary lesion on the left upper lip extended onto the left oral commissure, vermilion, and labial mucosa of the upper lip, and vermilion of the lower lip. A biopsy specimen showed LM. The lesion was removed with narrow margins, and the subsequent reconstruction used cheek advancement and lip rotation flaps. Within the next 6 years, several recurrent lesions were noted on the left upper lip and melolabial fold. For reconstruction, rotation flaps, a cervicofacial myocutaneous platysma flap, and a myocutaneous orbicularis flap were used. Two years later, a biopsy specimen of another recurrent lesion on the left cheek and upper lip revealed a 0.43-mm-thick

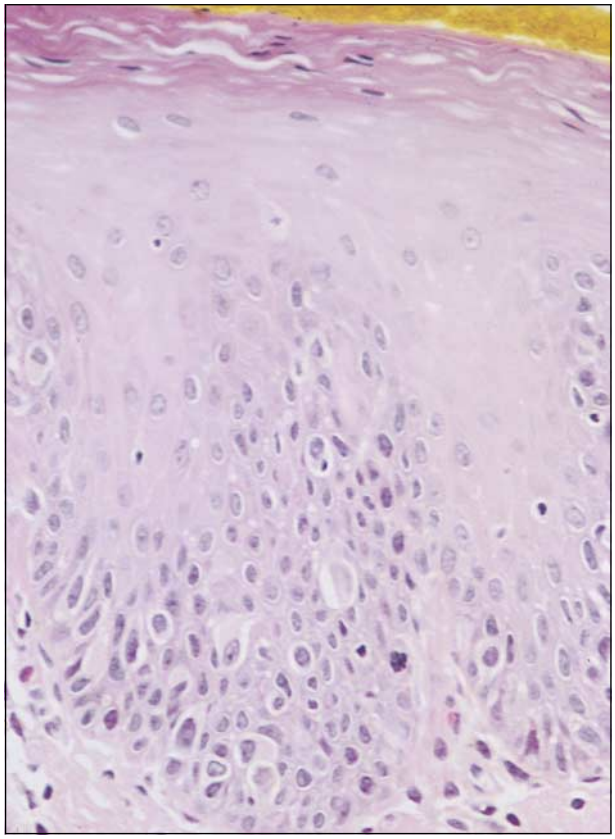

Figure 6. Biopsy specimen taken from the oral lesion in case 3 shows a proliferation of pleomorphic melanocytes with enlarged hyperchromatic nuclei along the basal layer with focal upward growth (original magnification ×400).

LMM. This was excised with a 1-cm margin; a large cheek rotation flap was used for reconstruction. The biopsy specimen showed negative margins. Recently, another recurrent lesion on the left cheek and upper lip was excised twice with positive margins.

HISTOPATHOLOGIC FINDINGS

All biopsy specimens from LM lesions revealed similar histopathologic features. Microscopic examination from a recurrent lesion from case 4 revealed an atypical intraepidermal melanocytic proliferation over a scar (**Figure 5**). The pleomorphic melanocytes were arranged as single units and small nests along the dermoepidermal junction. In some areas, there was elongation of the rete ridges, whereas in others, there was epidermal atrophy. Solar elastosis was noted. The atypical cells showed hyperchromatic, enlarged, irregular nuclei and areas of pagetoid spread.

Biopsy specimens from the oral mucosal lesions of case 3 showed a proliferation of solitary, pleomorphic melanocytes with hyperchromatic nuclei along the basal and suprabasal layers (**Figure 6**). Biopsy specimens from one of the oral lesions of case 1 (shown in Figure 2) demonstrated confluent nests of atypical melanocytes within the lower portion of the epithelium (**Figure 7**). Focal pagetoid spread was noted. In another biopsy specimen from the buccal mucosa, a dermal spindle cell neoplasm was

identified extending from the intraepidermal component. Patchy inflammation and numerous melanophages were seen in the papillary dermis. The lesion was positive for S100, consistent with desmoplastic melanoma.

COMMENT

Lentigo maligna occurs in white patients on sun-exposed areas, predominantly the head and neck. Extension onto mucosal surfaces such as the conjunctiva has been exceptional.[18-20] Herein, we report 4 cases of LM with spread from perioral areas onto oral mucosa.

All patients had cutaneous lesions for several years before development of intraoral involvement. The lesions ran a chronic course complicated by several recurrences after surgery. Two of the patients never achieved complete remission, and all experienced significant long-term morbidity. Primary melanoma of the oral cavity can be excluded in our patients primarily by history. Metastatic melanoma from the skin to the oral cavity is extremely rare and can be ruled out by the absence of advanced primary skin tumor. Benign pigmented lesions such as melanocytic nevi, oral melanoacanthomas, and oral and labial melanotic macules can be excluded by the atypical histopathologic features.

The skin lesions showed typical histopathologic features of LM[2,23] such as solitary and small nests of atypical melanocytes along the basal layer of the epidermis and adnexal structures, epidermal atrophy, and solar elastosis. Pagetoid spread, melanophages, and a dermal lymphohistiocytic infiltrate were sometimes seen. The histopathologic characteristics of the oral lesions were consistent with contiguous spread of the tumor from perioral skin areas.

Histopathologic evidence of invasion (LMM) was seen in 3 of the 4 patients at some point during their long course. While this is a small sample size, this suggests a higher than previously hypothesized progression of LM to LMM.[24] The lesions may have progressed to an invasive stage because of prolonged radial growth phases secondary to incomplete cure after each recurrence. It has been shown that the risk for LMM increases proportionately with lesional diameter.[25] Furthermore, LM may have progressed to LMM in areas that were not visible to the patient, thus being unnoticed for long periods of time. As seen in case 1, an invasive component was diagnosed in an oral LM of which the patient was not aware. Although development of invasive areas may occur slowly and gradually, there have been reports of rapid progression to LMM despite careful clinical follow-up.[26,27]

The recurrence of LM has been attributed to several factors, including migration of malignant melanocytes from adjacent epidermis or migration of deep periadnexal melanocytes to the epidermal surface.[1,2] Most authors believe that surgical excision is the treatment of choice, but the optimal surgical management of LM is still being defined. The recurrence rate with standard surgical excision (9%) is lower than that reported with destructive methods (35%-55%).[28,29] The failure rate of standard excision may be due to microscopic extension of LM by as much as 1.5 to 3 cm beyond the clinical margins.[30,31] In most cases presented herein, conventional surgery, even with wide margins, failed to eradicate the tumor completely and caused significant disfigurement.

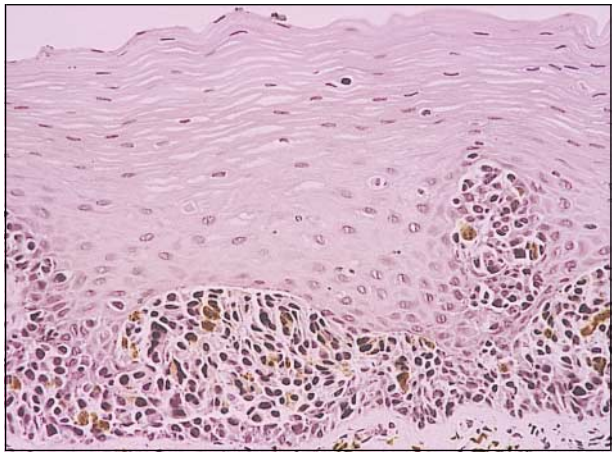

Figure 7. Biopsy specimen taken from one of the oral lesions in case 1 (shown in Figure 2) demonstrates pleomorphic, hyperchromatic melanocytes forming horizontal confluent nests within the lower portion of the epithelium (original magnification ×200).

The advocates of Mohs micrographic surgery for LM argue that this technique has a high cure rate, spares normal tissue, and allows examination of 100% of surgical margins.[32] However, the value of frozen vs rush permanent sections is debatable.[31-37] While some authors[33] suggest that frozen sections are sensitive and specific for the diagnosis of melanoma, others[32] argue that frozen sections contain artifacts and are often difficult to interpret. The use of rush permanent sections[34,35] may eliminate these problems but carries the disadvantage that only 1 stage per day can be performed. A recent study[32] recommended that if only frozen sections are to be performed, the final stage of surgery should be submitted for analysis of permanent sections prior to closing the wound. This ensures complete removal of the tumor while requiring only 2 to 3 mm of additional tissue. In this study, rush permanent sections were performed in cases 2 and 3 with excellent results.

In summary, we report 4 cases of cutaneous LM with extension onto oral mucosa. The significant morbidity associated with this clinical presentation is highlighted by the numerous recurrences and, in many instances, the need for major reconstruction with subsequent cosmetic disfigurement. This clinical presentation requires a high index of suspicion by the clinician. Examination of the oral mucosa should be performed in all patients with atypical pigmented perioral lesions. Furthermore, patients with perioral LM require long-term follow-up because there is a high probability of recurrence and/or progression to LMM.

Accepted for publication January 24, 2002.

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REFERENCES

1. Cohen LM. Lentigo maligna and lentigo maligna melanoma. *J Am Acad Dermatol.* 1995;33:923-936.
2. Cohen LM. What's new in lentigo maligna. *Adv Dermatol.* 1999;15:203-231.
3. Holman CDJ, Armstrong BK. Cutaneous malignant melanoma and indicators of

total accumulated exposure to the sun: an analysis separating histogenetic types. *J Natl Cancer Inst.* 1984;73:75-82.
4. Elwood JM, Gallagher RP, Worth AJ, Wood WS, Pearson JC. Etiological differences between subtypes of cutaneous malignant melanoma: Western Canada melanoma study. *J Natl Cancer Inst.* 1987;78:37-44.
5. Newell GR, Sider JG, Bergfelt L, Kripke ML. Incidence of cutaneous melanoma in the United States by histology with special reference to the face. *Cancer Res.* 1988;48:5036-5041.
6. Runne U, Tritsch H. Subunguale Lentigo Maligna mit streifenförmiger Nagelpigmentierung: diagnostik und operative Behandlung. *Z Hautkr.* 1978;53:899-904.
7. Clouse WE, Sanders LJ. Subungual lentigo maligna. *Cutis.* 1985;36:153-155.
8. Miescher G. Über melanotische Präcancerose. *Oncologia.* 1954;7:92-94.
9. Lupulescu A, Pinkus H, Birmingham DJ, Usndek HE, Posch JL. Lentigo maligna of the fingertip: clinical histologic, and ultrastructural studies of two cases. *Arch Dermatol.* 1973;107:717-722.
10. Morishima T, Ishikawa T, Endo M, Tsujiguchi Y. Pagetoid malignant melanoma and lentigo maligna melanoma of toe: a study with the fluorescence method (Falck and Hillarp). *Arch Dermatol Res.* 1978;262:275-283.
11. Rippey JJ, Rippey E. Malignant melanoma with adjacent Hutchinson's melanotic freckle in black Africans. *Pathology.* 1977;9:105-109.
12. Steigleder G-K. Pseudo-Paget des skrotums. *Dermatologica.* 1958;117:165-172.
13. Aronson PJ, Whitney DH, Soltani K, Medencia M. Cryosurgical treatment of dysplastic lentigo of the glans penis. *J Dermatol Surg Oncol.* 1984;10:60-62.
14. de Graciansky R, Mouly R, Timsit E, Guilaine J, Queran J, Larregue M. Dubreuilh's melanosis of the buccal mucosa. *Bull Soc Fr Dermatol Syph.* 1967;74:176-178.
15. Robinson L, Hukill PB. Hutchinson's melanotic freckle in oral mucous membrane. *Cancer.* 1970;26:297-302.
16. Arrington JH III, Reed RI, Ichinose H, Krementz ET. Plantar lentiginous melanoma: a distinctive variant of human cutaneous melanoma. *Am J Surg Pathol.* 1977;1:131-143.
17. Paladugu RR, Winberg CD, Yonemoto RH. Acral lentiginous melanoma: a clinicopathologic study of 36 patients. *Cancer.* 1983;52:161-168.
18. Cohen LM, Zax RH. Recurrent lentigo maligna invading a skin graft successfully treated with Mohs micrographic surgery. *Cutis.* 1996;57:175-178.
19. Hutchinson J. On tissue dotage. *Arch Surg (London).* 1892;3:315-322.
20. Hicks C, Liu C, Hiranandani M, Garner A, Hungerford J. Conjunctival melanoma after excision of a lentigo maligna melanoma in the ipsilateral eyelid skin. *Br J Ophthalmol.* 1994;78:317-318.
21. Horiuchi N, Tsunoda T, Suetake T, Kato T. Oral mucosa malignant melanoma in situ with involvement of the perioral skin. *Dermatology.* 1994;188:66-68.
22. Cohen LM. Mohs surgery for lentigo maligna and melanoma. *Facial Plast Surg Clin North Am.* 1998;6:309-317.
23. Cohen LM. The starbust giant cell is useful for distinguishing lentigo maligna from photodamaged skin. *J Am Acad Dermatol.* 1996;35:962-968.
24. Weinstock MA, Sober AJ. The risk of progression of lentigo maligna to lentigo maligna melanoma. *Br J Dermatol.* 1987;116:303-310.
25. Wayte DM, Helwig EB. Melanotic freckle of Hutchinson. *Cancer.* 1968;21:893-911.
26. Michalik EE, Fitzpatrick TB, Sober AJ. Rapid progression of lentigo maligna to deeply invasive lentigo maligna melanoma. *Arch Dermatol.* 1983;119:831-835.
27. Kelly JW. Following lentigo maligna may not prevent the development of life-threatening melanoma. *Arch Dermatol.* 1992;128:657-660.
28. Pitman GH, Kopf AW, Bart RS, Gasson PR. Treatment of lentigo maligna and lentigo maligna melanoma. *J Dermatol Surg Oncol.* 1979;5:727-737.
29. Coleman WP 3rd, Davis RS, Reed RJ, Krementz ET. Treatment of lentigo maligna and lentigo maligna melanoma. *J Dermatol Surg Oncol.* 1980;6:476-479.
30. Grande DJ, Koranda FC, Whitaker DC. Surgery of extensive, subclinical lentigo maligna. *J Dermatol Surg Oncol.* 1982;8:493-496.
31. Cohen LM, McCall MW, Hodge SJ, Freedman JD, Callen JP, Zax RH. Successful treatment of lentigo maligna and lentigo maligna melanoma with Mohs micrographic surgery aided by rush permanent sections. *Cancer.* 1994;73:2964-2970.
32. Cohen LM, McCall MW, Zax RH. Mohs micrographic surgery for lentigo maligna and lentigo maligna melanoma. *Dermatol Surg.* 1998;24:673-677.
33. Zitelli JA. Mohs surgery for lentigo maligna [letter]. *Arch Dermatol.* 1991;127:1729.
34. Dhawan SS, Wolf DJ, Rabinovitz HS, Poulos E. Lentigo maligna: the use of rush permanent sections in therapy. *Arch Dermatol.* 1990;126:928-930.
35. Stonecipher MR, Leshin B, Patrick J, White WL. Management of lentigo maligna and lentigo maligna melanoma with paraffin-embedded tangential sections: utility of immunoperoxidase staining and supplemental vertical sections. *J Am Acad Dermatol.* 1993;29:589-594.
36. Johnson TM, Headington JT, Baker SR, Lowe L. Usefulness of the staged excision for lentigo maligna and lentigo maligna melanoma: the "square" procedure. *J Am Acad Dermatol.* 1997;37:758-764.
37. Robinson JK. Margin control for lentigo maligna. *J Am Acad Dermatol.* 1994;31:79-85.