Lentigo Maligna/Lentigo Maligna Melanoma: Current State of Diagnosis and Treatment

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BACKGROUND Lentigo maligna (LM) is a subtype of melanoma in situ that typically develops on sun-damaged skin. Presentation may be quite subtle and delayed diagnosis is common. Clinical margins are often ill defined. Histologic evaluation can be difficult due to the widespread atypical melanocytes that are present in the background of long-standing sun damage. Recurrence following standard therapies is common.

OBJECTIVE To review the clinical features, histopathology, and treatment options for LM. Emphasis is placed on recent advances in the treatment of LM.

METHODS AND MATERIALS Literature review.

RESULTS The estimated lifetime risk of LM progressing to LM melanoma is 5%. Standard excision of LM with 5 mm margins is insufficient in 50% of cases. The recurrence rate with standard excision ranges from 8 to 20%. Mohs surgery and staged excision may offer better margin control and lower recurrence rates (4–5%). Estimates of recurrence rates following nonsurgical therapies such as cryosurgery, radiotherapy, electrodessication and curettage, laser surgery, and topical medications range from 20 to 100% at 5 years.

CONCLUSIONS Adequate treatment of LM requires a comprehensive knowledge of the diagnostic features, histopathology, and treatment options. Surgical modalities with meticulous evaluation of tissue margins appears to offer the lowest rates of disease recurrence.

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Lentigo maligna (LM) and invasive, lentigo maligna melanoma (LMM) represent one of the four main subtypes of melanoma. LMM comprises an estimated 4–15%,1,2 of invasive melanoma types that also include superficial spreading (70%),3 nodular (10–15%),1,4-6 and oral-acral melanoma (<5%).1,7,8 The clinical and histologic features that distinguish LM and LMM from other melanoma subtypes may lead to great difficulty with local recurrences. This paper will review the clinical, histologic, and biologic features that make LM and LMM distinct and present various treatment options currently in use. A critical review of the literature reveals the absence of robust prospective randomized trials. However, a review of case series may allow for the formulation of treatment plans that provide an adequate cure rate with reasonable consideration given to cosmesis.

Clinical Presentation

LM presents most commonly in chronically sun-exposed areas of the middle aged and elderly1,2 and is generally not associated with precursor melanocytic nevi.9 Historically known by the eponym Hutchinson’s melanotic freckle,10 LM appears as a large patch that expands centrifugally with variable shades of tan, brown, dark brown, or black. The lesion often contains net-like black pigmentation (Figure 1). The clinical observations of the growth characteristics of LM suggest an initial and prolonged two-dimensional centrifugal growth pattern confined to the dermal-epidermal junction. Over time the lesion may acquire...
a dermal component and is then reclassified as an LMM. The latency period between LM and LMM may be long, but rapid progression from LM to LMM has been observed, and biannual examinations of LM may not prevent occasional cases of deeply invasive LMM. Another important consideration for the practitioner is that desmoplastic malignant melanoma can occur adjacent to a lentigo or LM-like patch.

The exact percentage of LM cases that progress to LMM is unknown, and various estimates range widely. An epidemiologic analysis by Weinstock and Sobek estimated an approximate 5% lifetime risk of LMM in patients diagnosed with LM at age 45. However, in two series of 85 LM excisions, more than 50% contained occult invasive foci of melanoma, and, in a more recent report of 92 consecutive cases, 16% of LM lesions undergoing staged excisions harbored unexpected foci of invasion.

Prompted by an individual with metastasizing melanoma in situ (MIS), Megahed and colleagues reported that of 104 cases of MIS (diagnosis confirmed by reviewing histopathologic slides), 30 (29%) had invasive tumors with Melan-A/MART-1 immunohistochemical staining. The risk for LMM may be proportional to the size of the lesion, and large lesions frequently harbor small foci of invasions. Features that may herald malignant transformation from a lentigo to LM/LMM include increasing variation in color, expanding surface area, increasing border irregularity, elevation, and white macular areas overlying possible sites of regression.

The clinical exam of LM may frequently be complicated by prior therapeutic interventions, most commonly cryosurgery for a presumed benign solar lentigo. Cryosurgery and other ablative procedures depigment portions of the original lesion. In such cases, patients are often unclear about their treatment history. LM may be quite subtle, and a lesion that has been previously frozen may present with a vexing lack of diagnostic features. Suspicious melanotic patches confounded by other color and scar changes, including depigmentation, may represent arising LMM; therefore, it is important to have a low threshold for biopsy of pigmented facial lesions.

**Histology**

The histology of LM is distinct from other melanoma subtypes in several respects. The most reproducible histologic feature is atypical junctional melanocytic hyperplasia combined with underlying photodamage. Most dermatopathologists consider all LM to be MIS, whereas others make a distinction between LM and LM with MIS based on the extent and number of atypical pleomorphic melanocytes. The majority of lesions demonstrate a proliferation of atypical melanocytes in confluence along the dermal-epidermal junction with bridging of the rete pegs, epidermal atrophy, extension of melanocytes down adnexal structures, and extensive underlying solar elastosis (Figure 2). Other supportive features of a diagnosis of LM include melanocyte atypia and nonuniform pigmentation or distribution of melanocytes. This is unlike superficial
spreading melanoma, which features pagetoid spread of atypical melanocytes upwards from the basal cell layer into the epidermis. In contrast, the proliferation of melanocytes in LM tends to be located along the basal layer with minimal pagetoid spread. Extension down follicular structures is common to LM and likely leads to the high recurrence rates associated with ablative treatments.

**Diagnosis**

Excisional biopsy is the most accurate sampling method for LM. Because LM tends to be large, excisional biopsies can rarely be done. Incisional biopsies, such as multiple punch biopsies, run the risk of sampling error where invasive foci may be missed, but the clinician’s hand is often forced into this type of partial biopsy.

Punch biopsies are quick and easy and should be performed in the most clinically suspicious areas such as palpable foci that may correspond with invasion. Although selecting the highest risk areas for incisional biopsy seems intuitive, there is still potential for sampling error as clinical and histologic correlation in LM is an assumption that may or may not hold true, i.e., that the darkest pigment foci most likely overlie areas of invasion. To decrease the risk of sampling error, some pathologists prefer longer surface areas for examination (as opposed to multiple small punch biopsies from random sites). Broader surface areas can be submitted to the pathologist by performing long, thin, fusiform incisional biopsies spanning the length of the center of the tumor.

In general, shave biopsies are not recommended for biopsy of a potential melanoma due to the possibility of transecting the tumor and thereby losing the ability to measure and assign a reliable Breslow depth. In the case of LM, however, the tumors are nearly uniformly superficial, and, when LMM is present, it is usually of low-level invasiveness. A deep saucerization shave biopsy therefore rarely transects the invasive component if present.

**Treatment**

Once the diagnosis of LM has been made, the great challenge for the clinician is to strike an appropriate balance of the risk-benefit ratio for an individual patient. The majority of LM cases remain in situ. The cases that prove to be LMM, after confirming invasion, are rarely high-risk tumors in terms of depth and level of invasion. However, when one controls for depth of invasion, the prognosis for LMM is the same as for other types of melanoma.

Ideally, treatment should be minimally morbid if the lesion is in situ. The most exasperating feature of LM is the tendency of repeated recurrence following seemingly adequate treatment. Estimates of recurrence rates following superficial destructive therapies, such as cryosurgery, radiotherapy, electrodessication and curettage, laser surgery, topical 5-fluorouracil, and azelaic acid, range from 20 to 100% at 5 years. In a review of 1,351 cases of histologically confirmed MIS from the University of Graz, Austria, the 5-year recurrence rate for surgical excision was 6.8 ± 1.3%, whereas the recurrence rate for combined nonsurgical interventions was 31.3 ± 8.5%.
These data support the belief that, when feasible, surgical excision remains the treatment of choice. However, due to the occurrence of LM in a predominantly elderly population, surgery is not always an option. Nonsurgical therapies have been reported in a limited number of cases, but long-term follow-up is lacking. Most recurrences are in situ and pose no immediate threat to the patient; however, the first sign of recurrence may be invasive melanoma, in which case the consequences are more serious (Figure 3).

There are several explanations for the high recurrence rates following destructive/ablative therapies for LM. The simplest explanation is treatment of an inadequate surface area followed by perimeter recurrences. Using a Wood’s lamp to more clearly define tumor borders before treatment may be of some benefit in these cases.22 Secondly, LM frequently involves hair follicles, and surface treatments may fail to reach a depth sufficient for destruction of the deep peri-appendageal melanocyte population.23,24 A third possibility is that the atypical melanocytes in LM may be variably resistant to destructive therapies, such as laser ablation. Melanocytes may also lose the ability to produce pigment and consequently may not respond to pigment-specific wavelengths.10,23 In some cases of LM there may be a “field effect” where multiple atypical melanocytes are dispersed over a large area leading to multifocal disease with skip areas in between.25-27

Destructive/Ablative Therapies

Cryotherapy

Liquid nitrogen has been used to treat LM with varying degrees of success. In one study of 30 patients, the reported 3-year recurrence rate was 6.6%.26 However, other studies have reported a 5-year recurrence rate of 34%.21 One problem with visual assessment of cure following cryosurgery is that the treated areas often feature varying degrees of dyspigmentation. It is therefore sometimes difficult to know if the lesion has been cured or if the patient continues to have residual disease.

Laser Therapy

The argon, Q-switched Nd:YAG, ruby, alexandrite, and short pulsed dye lasers have been used successfully on a variety of benign pigmented lesions.29-42 Lasers have also been used as primary therapy for LM, but to date no large series with long-term follow-up have been published. In one case report, argon laser treatment for LM43 was reported with an initial apparent complete response followed by recurrence 4 years later.44 Two patients with single large atypical lentigines (clinical diagnoses without biopsies) achieved complete clinical responses with a Q-switched ruby laser yet both ultimately recurred: one case as LM and the other as LMM.23 There have been other reports of LM incompletely treated with alexandrite and ruby lasers.45 Some academic centers use laser therapy as the primary treatment modality in poor surgical candidates, and long-term data on recurrence rates are

Figure 3. Potentially fatal deeply invasive lentigo maligna melanoma presenting as a blue subcutaneous nodule 7 years following apparent complete excision of lentigo maligna. Lesion was invasive into multiple facial nerve branches.
anticipated. At present, laser therapy should be considered suboptimal until further evidence is provided.

**Radiation Therapy**

Radiation therapy is widely utilized for treatment of LM outside of the United States, and several studies suggest that radiation therapy for LM may be efficacious. In a German study, radiotherapy was used as primary therapy for 42 patients with LM and as adjuvant therapy for 22 LMM patients. In the case of LMM, the invasive tumor had been removed surgically but an in situ component remained postoperatively and was treated with adjuvant radiation therapy. With a mean follow-up of 23 months (median = 15 months), there were no recurrences of LM and two in situ recurrences of the LMM cases. The short-term cosmetic results were good to excellent in all cases, and the morbidity of surgery in elderly persons was avoided. The largest series to date is from Farshad and colleagues. They retrospectively analyzed 150 patients treated with Grenz or soft X-rays for LM and LMM. Ninety-three patients had LM and 57 had LMM. One hundred and one patients were followed up for at least 2 years after radiotherapy (mean 8 years). The mean time to recurrence was 45.6 months, and the recurrence rate was 7% (7 of 101). Longer follow-up is needed to evaluate radiotherapy efficacy as both primary treatment in LM and adjuvant treatment in LMM as recurrences in both can be delayed. Radiotherapy does appear to be a reasonable choice of treatment in patients who are not operative candidates.

**Immunotherapy**

A recently reported approach to the treatment of LM is intraleisional or topical application of an immune response modifier. The topical agent most frequently reported to date is imiquimod 5% cream. Naylor and colleagues demonstrated that 26 of 28 biopsy-proven LM cases treated with topical 5% imiquimod cream achieved a clinical complete response confirmed by four-quadrant post-treatment biopsies. Although encouraging, this and all previous reports suffer from short follow-up periods. Only one study to date has used imiquimod followed by surgical excision to confirm the absence of residual tumor in six patients. Four patients had a complete, or nearly complete, clearance of pigmentation with minimal residual histologic evidence of LM. One patient showed no clinical or histologic improvement, and the remaining patient had almost no residual pigmentation after treatment, yet histology revealed residual LM. Invasive disease with satellite metastases has occurred during therapy with imiquimod. This patient was alive 17 months after surgical removal of satellite tumors and topical imiquimod treatment to areas of remaining MIS. As with many other topical therapies, the development of an amelanotic recurrence is always a concern. It is likely that the use of imiquimod for LM will increase, especially for broad lesions in poor operative candidates. In addition, imiquimod is a suitable alternative in patients where surgical excision would be associated with a high level of operative morbidity (Figure 4).

The main criticism leveled at destructive therapies for LM is that destruction does not allow for the detection of invasive LMM. In addition the hypopigmentation often associated with destructive techniques can lead to delays in the diagnosis of recurrence. The proponents of destructive therapy point out the generally good cosmetic results with little
morbidity compared with surgical approaches.

**Surgical Treatments**

**Conventional Excision**

The highest sustained cure rates for LM are with surgical excision, and excision should be considered the treatment of choice for LM when feasible. The National Comprehensive Cancer Network (NCCN) recommends 5–10 mm margins of excision for melanoma in situ. However, conventional surgery using 5 mm margins for tissue sparing and standard vertical section postoperative margin control is inadequate for many cases of LM. The recurrence rates for standard excision of LM range from 8 to 20%. This is likely due to several factors, including failure to treat subclinical peripheral disease, atypical junctional melanocytes in the deep adnexal structures, and the inadequacy of histologic visualization. For example, when a 1 cm specimen is completely sectioned by breadloafing, to make 7-μm-thick sections, nearly 1,500 sections are necessary to view the entire specimen. With standard breadloafing, less than 1% of the margins are actually visualized. Even when a section is well represented, a clear definition of what constitutes a negative surgical margin is lacking. With respect to margin diameter, recent work by Bricca and Zitelli showed that Mohs micrographic surgery allowed for complete excision of head and neck melanoma in only 83% of cases when a 6 mm margin was used. Based on their data in 331 cases of melanoma in situ, they found that 9 mm margins would be required to achieve complete excision in 97% of cases. An alternative to conventional excision is a staged excision that involves meticulous evaluation of the perimeter margins. There are several variations of staged excisional techniques with a similar final goal: rigorous intra- or postoperative margin evaluation to confirm negative margins prior to repair. Although true long-term outcomes are not yet adequately represented in the literature, it would appear that the following methods represent a step forward over conventional excision and lead to a higher rate of success and a lower level of significant recurrence.

**Staged “Square” Excisions with Permanent Sections**

The staged excision technique for LM/LMM was described by Dhawan and colleagues in 1990. He excised LM by Mohs micrographic surgery and followed this by rush permanent sections. Johnson and colleagues modified this procedure and coined the term “square” technique. In this procedure, the lesion is carefully examined and delineated. Starting with a 5 mm margin, a polygonal shape is drawn around the lesion. Then using a double-bladed hair transplant scalpel, a 5 mm margin is excised around the delineated surgical margin (Figure 5). The resulting circumferential band of exposed adipose tissue surrounding the tumor may then be closed with a loose running surface suture while the peripheral margins are evaluated by en face permanent sections. The perimeter pieces are separated like the four sides of a picture frame and sectioned from the outside edge in. Positive areas are marked on a map, and the patient returns for subsequent excision iterations until negative en face perimeter margins are confirmed histologically. Then the central portion of the tumor is excised and submitted for vertical sections, and the wound is repaired. When a lesion is suspicious for LMM, the central portion can be submitted concurrently with the perimeter sections. This can help to assure that adequate staging is achieved.

In the series by Johnson and colleagues, no recurrences were observed in 35 patients reported, with short-term follow-up. The main advantages of this technique are avoidance of open wounds between stages, and the high-quality permanent sections that are obtained for histologic review. The disadvantage of this technique is the requirement for multiple trips for the patient to the doctor for subsequent stages and repair.

There are different ways to process the tissue after a staged procedure. The tissue can be oriented and sectioned en face (vertically)
Bub and colleagues recently published 5-year data (median follow-up 54 months) in 59 patients, with 62 lesions of LM and LMM, using staged excision with radially cut sections. Over this follow-up period, they had 95% disease-free survival. Variations of staged excision with permanent sections are utilized by many surgeons who feel that only with permanent sections can MIS/LM be read reliably on histology slides. Many physicians simply excise the entire lesion and submit the specimen for en face margins of the periphery and vertical radial sections of the central portion of the lesion. Usually with good cooperation between surgeon and dermatopathologist, the repair can be done within 24 hours following the original excision (Figure 6). Despite the use of high-quality permanent sections, there are difficulties in establishing negative margins in LM. The presence of increased numbers of basal melanocytes, some of them atypical, is often seen in sun-exposed areas of the skin. Distinguishing isolated melanocyte atypia consequent to sun exposure from residual LM is a difficult problem for histopathologists. A recent study showed that interobserver concordance between five histopathologists was only moderate for identifying negative and positive margins. Peripheral margins were categorized as straightforward or difficult. Straightforward positive margins showed obvious LM while straightforward negative margins lacked a significant

**Figure 5.** Lentigo maligna (LM): the square procedure. (A) LM, left arm with margin delineated and polygonal 5 mm excision margin inscribed. (B) A double-bladed scalpel is used to excise the delineated surgical margin. (C) The perimeter specimens are submitted for en face sectioning, while the central specimen is vertically sectioned.
melanocytic proliferation. The typical difficult peripheral margin contained atypical melanocytes, not diagnostic of melanoma, and frequently showed other diagnostic abnormalities that complicated interpretation such as epidermal spongiosis or actinic keratosis. For difficult cases, a control biopsy from similarly sun-damaged skin, in the form of an excisional strip, statistically improved diagnostic concordance between pathologists. A punch biopsy as a control specimen was not useful due to the limited surface area of epidermis rendered by that technique. Overall, this study demonstrated that even in very capable hands, and with good histology sections, the delineation of negative operative margins is subject to interpretation.

Recently, Agarwal-Antal and colleagues reported on 92 consecutive patients with biopsy-confirmed LM treated with staged excisions using the square technique with permanent sections. In this study, the central portions of the tumors were submitted with the first stage of excision, and 16% of the tumors had areas of invasion not detected with incisional biopsies. The more guarded prognosis associated with LMM affects the surgical recommendations in that the standard of care for excision, of LMM requires excision through adnexal structure in deep adipose tissue. A

Figure 6. Lentigo maligna (LM): excision with delayed closure. (A) Subtle multifocal nasal LM. (B) Excision of entire dorsal nasal subunit and tip subunit. (C) Delayed closure at 2 days with full thickness skin graft. (D) Final result at 3 months.
benefit of discovering an invasive focus prior to reconstruction is the potential for enrollment in clinical trials involving lymphatic mapping and sentinel lymph node biopsy and/or adjuvant therapy.

**Mohs Micrographic Surgery**

An alternative to staged excisions with paraffin-embedded permanent sections is the use of Mohs surgery with frozen sections, sometimes augmented by the use of rush permanent sections and/or immunostains. Many surgeons and pathologists consider frozen sections inferior to permanent sections. As previously discussed, the challenge of separating atypical melanocytes in sun-damaged skin from true LM can be extremely difficult even for expert dermatopathologists. Adjuvant immunostains, such as HMB-45 or MART-1, may help identify junctional melanocytes but do not necessarily help in making distinctions regarding cellular atypia. However, some argue that in skilled hands, where very high-quality frozen sections are available and the surgeon and/or the dermatopathologist is experienced at evaluating melanocytic atypia on frozen sections, a Mohs microscopic surgical approach can be effective. Cohen and colleagues performed Mohs micrographic surgery using frozen sections and rush permanent sections on 45 patients with LM and LMM and have reported on a median follow-up of 58 months with only one recurrence in a patient with five prior recurrences before MMS was performed. It is important to note that rush permanent sections were used in this study, which require overnight processing; therefore, one of the main advantages over staged excisions is lost, namely avoiding return visits to the clinic for further stages and/or repair.

Whether using permanent sections or frozen sections, making a distinction between residual LM in a margin versus atypical junctional melanocytic hyperplasia, the submission of a control biopsy may be helpful. In cases where patchy hyper- and hypopigmented skin is clinically evident in the area around the LM, a control should be sampled some distance away from the LM (usually a contralateral site if the photodamage is roughly symmetrical on the face). Long, thin fusiform specimens are preferred to punch biopsies in order to increase the surface area of the dermal-epidermal junction available for evaluation. Even with a control, in some cases it is simply not possible to confidently identify clear tumor margins, and the dermatopathologist and the surgeon must mutually agree on a stopping point for the surgery and select a potential postoperative adjuvant therapy such as an immune-response modifier versus careful observation.

Although staged surgical excisions have significantly reduced recurrence rates for LM and LMM, there are still perimeter recurrences and potential problems with surgical disfigurement. A multidisciplinary approach can be

![Figure 7. Subclinical extension of a recurrent LM. (A) Lesion prior to staged excision. (B) Dramatic operative wound following complete tumor extirpation. (C) Repair with full thickness skin grafts. (D) Repair at 1 year.](image-url)
a valuable asset to the practitioner and the patient in situations where large surgical defects are anticipated. Particularly problematic are tumors with large surface areas or those with a history of multiple prior destructive and/or surgical procedures. A consistent finding on staged approaches to sizeable LM is that less than 50% of tumors have negative margins after a 5 mm margin is attempted. Particularly problematic in these cases is that large surgical defects are anticipated. Particularly problematic in these cases is that large surgical defects are anticipated.

With staged excisions, subsequent stages often enroach upon tissue on the nose, eyelids, ears, and lips, which require complex repairs and increase postsurgical morbidities. The subclinical extension of some lesions of LM can be quite dramatic (Figure 7).

Future Directions
It is difficult to predict what recommendations for treatment of LM will be in a textbook 10 years from now. The challenge for the clinician today is to make a careful assessment as to the risks and benefits of a given therapeutic approach and strike a proper balance for an individual patient based on age, health status, and predicted tumor biology in the cases of LMM. Until more high-level evidence is available from randomized prospective studies comparing current therapeutic approaches, evidence-based medicine best supports surgical removal with careful intra- or postoperative histologic evaluation for margin control, no matter how large the operative wound becomes. One would hope for less disfiguring yet effective treatment strategies in the future.

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