Diagnosis and management of lentigo maligna: a review

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Abstract

Lentigo maligna is a melanocytic neoplasm occurring on sun-exposed skin, usually on the head and neck, of middle-aged and elderly patients. It is thought to represent the *in situ* phase of lentigo maligna melanoma. The ill-defined nature and potentially large size of lesions can pose significant diagnostic and treatment challenges. The goal of therapy is to cure the lesions in order to prevent development of invasive disease, and surgical excision is the treatment of choice to achieve clear histological margins. Nonsurgical treatment modalities have been reported; however, evidence is lacking to support their use. Age, general health, and comorbidities need to be taken into account when deciding the right treatment modality for each individual patient.

Background of lentigo maligna

History

Sir Jonathan Hutchinson first described the concept of lentigo maligna in 1890. He noted a 'senile freckle' with progressive radial growth that he speculated had an infectious origin. The condition was subsequently further characterized as 'circumscribed precancerous melanosis' by Debreuilh in 1912 [1].

Clinical presentation, risk factors, and genetics

Lentigo maligna most commonly presents on the head and neck region of elderly patients, with the highest incidence in the seventh and eighth decades of life. It usually starts as a tan-brown macule or patch, but can have a variegated pigmentation with dark black or even amelanotic features (Figure 1A). It is slow-growing and usually progresses in a prolonged radial growth phase before entering into a vertical growth phase. Lentigo maligna can develop *de novo* or within a pre-existing solar lentigo. Patients typically present with a chief complaint of a new, asymptomatic pigmented macule or patch on the head or neck region, or a freckle that has changed in size, shape, or color.

Risk factors for development of lentigo maligna include the following: a history of sunburns, a history of nonmelanoma skin cancers, advanced age, lighter skin types, and tendency to form solar lentigines. Although lentigo maligna occurs on chronically sun-damaged skin, it is thought that intermittent sunburns, rather than cumulative sun exposure, are a risk factor for lentigo maligna [2].

Studies have shown that lentigo maligna has a different genetic make-up than other types of melanoma. Unlike the other types of melanoma, a genetic propensity to form atypical nevi is not seen in lentigo maligna. In lentigo maligna, there is a higher incidence of *p53* mutations compared with *BRAF* mutations. *BRAF* may not play a significant role in lentigo maligna as it does with other types of melanoma [3–5].

Risk of progression and recurrence

Historically, lentigo maligna has been described as a premalignant precursor to invasive melanoma, and variations in nomenclature have caused confusion regarding its malignant potential [6]. In addition, early case series suggested that lentigo maligna melanoma carried a better prognosis than other types of melanoma [7]. However, it is now widely accepted that lentigo maligna represents the *in situ* phase of lentigo maligna melanoma, which is staged in the same way as

other types of melanoma using the American Joint Committee on Cancer (AJCC) guidelines, and its prognosis is directly related to the depth of invasion and other adverse features, such as high mitotic rate and ulceration [8].

No prospective study has been performed to examine the risk of progression of lentigo maligna to lentigo maligna melanoma. Limited data suggest that, if left untreated, lentigo maligna may progress to invasive melanoma in 30–50% of cases [9]. Some authors, however, postulate that this is an overestimation of progression. Weinstock and Sober performed an epidemiologic statistical analysis of the incidence and prevalence of melanoma [10]. They determined that a patient with a new diagnosis of lentigo maligna at the age of 45 would have a 3.3% risk of developing melanoma by the age of 75. Such a risk would be reduced to 1.2% if the new diagnosis was made at the age of 65. They hypothesized that one reason for the overestimation of progression is due to the fact that lentigo maligna is slow-growing, and patients typically only present when a new dramatic feature develops within the lesion. The true risk of progression is unknown, and a prospective study with a large cohort and a long follow-up duration is warranted to address this problem.

Similar to the risk of progression, the rate of progression of lentigo maligna to lentigo maligna melanoma has not been well-studied and has been estimated to range from 10 to 50 years. However, there are isolated case reports of rapid progression to invasive and metastatic melanoma from a few months to a few years [11–13].

Lentigo maligna recurrence rate varies with the treatment modality. The lowest rates of recurrence are quoted with microscopically controlled excision, which will be discussed in detail below. Recurrence is related to the fact that atypical melanocytes have subclinical extension beyond the clinical margin, which is only detected on a microscopic level. Numerous studies have shown that 5 mm margins excised around lentigo maligna are often insufficient to obtain margin control [14–26]. Agarwal et al. [15] sought to determine if 5 mm margins were adequate to excise lentigo maligna in 92 cases. They found that 58% of cases required wider excisions than 5 mm. DeBloom et al. [16] illustrated the consequences of incomplete margin control; 22% (19/84) of melanoma *in situ* recurred as invasive (average Breslow depth of 0.94 mm) and 33% (8/24) of invasive melanoma recurred thicker (Breslow depth went from 1.53 to 2.83 mm). In a prospectively collected series of 1072 patients with 1120 melanoma *in situ* treated with Mohs micrographic surgery (MMS), Kunishige et al. showed that 6 mm margin excision achieved 86% clear margin, while 9 mm achieved 98.7% clear margin [17]. This study suggests that even melanoma *in situ* on the trunk and extremities should be excised with a 9 mm margin rather than a 5 or 6 mm margin to provide the higher cure rate.

Diagnosis

The diagnosis of lentigo maligna is challenging, as the clinical presentation can be subtle and varied. Early detection of lentigo maligna relies on a high clinical suspicion index. Several noninvasive methods are employed to facilitate early diagnosis of lentigo maligna, including dermoscopy, Wood's lamp examination, and reflectance confocal microscopy. Histological evaluation, aided by immunohistochemistry staining if indicated, remains the gold standard for the confirmation of the diagnosis.

Dermoscopy

Dermoscopy utilizes a conventional or polarized light source to examine lesions with 10X magnification. The differential diagnosis of lentigo maligna includes pigmented actinic keratoses, benign solar lentigo, pigmented seborrheic keratoses, and lichen planus-like keratoses [27]. Also, early lentigo maligna may not exhibit the telltale signs of an evolving melanoma (changes in asymmetry, border, color, diameter), and it is often difficult to distinguish from surrounding sun-damaged skin [28]. Dermoscopy can help aid the clinician in the differentiation between benign entities and lentigo maligna.

Studies have shown improved diagnosis of lentigo maligna with dermoscopy. Tschandi et al. performed a prospective study of 240 flat, pigmented facial lesions to better characterize dermatoscopic patterns of these lesions. Twenty-four of these lesions were histopathologically lentigo maligna [29]. The positive predictive value for lentigo maligna was highest for a pattern of circles. In addition, the presence of a gray color is a clue to malignancy regardless of pattern [29]. Other features that have been noted to be found with lentigo maligna include the following: asymmetric pigmented follicular openings, dark rhomboidal structures, slate-gray globules, dots and streaks, annular-granular pattern, and black blotches [28,30].

Of note, pigmented actinic keratoses on the face are frequently diagnosed as lentigo maligna as both share many dermatoscopic features. This can result in unnecessary biopsy. Nascimento et al. [31] sought to further investigate the significance of an inner gray halo to help differentiate between pigmented actinic keratoses and lentigo maligna. The inner gray halo is a subtle gray or beige halo that surrounds follicular openings and meshes with the pseudonetwork that is characteristic of pigmented actinic keratoses.

Overall, dermoscopy can be a helpful tool to help differentiate lentigo maligna from other entities; however, sensitivity and specificity depends on the level of clinician expertise [32]. Therefore, all clinical factors need to be taken into account before the decision is made to perform biopsy.

Wood's lamp examination

The Wood's light was invented in 1903 and has since been a useful tool in the evaluation of pigmented lesions. The light is produced through the use of a filter that is opaque to all radiation except for a wavelength between 320 nm and 400 nm, with a peak at 365 nm. Melanin absorbs wavelengths of

Figure 1A. Lentigo maligna was diagnosed with a 4 mm punch biopsy on the left cheek. Close examination under the Wood's lamp showed that the small biopsy was within a large brown patch with color variegation and ill-defined margin, and multiple scattered brown macules.

Figure 1B. Multiple scouting biopsies were taken from the pigmented patch and macules for histological evaluation. Among twelve sampled areas, five were lentigo maligna, one was atypical junctional melanocytic proliferation, and the rest were pigmented actinic keratoses.

Figure 1C. Design for the first stage slow Mohs excision. A 3 mm margin debulking excision was taken down to subcutaneous fat for evaluation of Breslow depth via vertical sectioning, and another 3 mm margin was taken down to deep subcutaneous fat or fascia for complete margin evaluation via horizontal en-face sectioning.

Figure 1D. Defect after the first stage slow Mohs excision.

Figure 1E. Partial simple closure after the first stage slow Mohs excision before the patient was discharged home.

Figure 1F. A narrow strip of control skin was taken from the contralateral, normal appearing, sun-damaged area and submitted for en-face sectioning.

Figure 1G. Defect after the second stage slow Mohs excision. Noted that additional peripheral margin was taken around the tumor involved margin by the temple hair line.

Figure 1H. Three weeks post a large cervical facial flap reconstruction (courtesy of Dr. Bradley Manning).

radiation from 350 to 1200 nm, which spans visible, infrared, and ultraviolet light. Observation of melanin under visible light is suboptimal to discern between normal skin and lightly pigmented lesions. Visible light contains longer wavelengths, which have a deeper penetration into the dermis; these longer wavelengths are scattered by the dermis, which lowers the contrast of the pigment perceived by the naked eye. Lesions possessing an increased concentration of epidermal melanin will appear darker and fluoresce under Wood's light. This occurs because the Wood's light utilizes only shorter wavelengths, which improves the contrast between epidermal melanin and normal skin [33].

Since the true margins of lentigo maligna can exist far beyond the margins seen with visible light, the Wood's light is used to improve margin delineation. The depth of melanin determines the amount of fluorescence seen with the Wood's light. Shorter wavelengths do not penetrate the dermis; therefore, dermal melanin is not accentuated [34]. For maximum effect, the Wood's light should be used in a dark, windowless room. It is also very useful for examination of pigment recurrence in scars from previous lentigo maligna excisions [35].

Reflectance confocal microscopy

Reflectance confocal microscopy (RCM) is a noninvasive imaging technique that can detect characteristic histological features related to lentigo maligna. Confocal microscopes image thin sections of living, intact tissue with high contrast and resolution that is comparable to standard histology. These optical sections are obtained with a 100X microscope objective. This allows for evaluation of tissue architecture at the nuclear and cellular level without a biopsy [36].

Tannous et al. [37] described findings from RCM in cases of lentigo maligna compared with normal skin. In clinically normal skin, melanocytes have a bright cytoplasm and are small, with a small nuclear to cytoplasmic ratio and round nuclei. Normal melanocytes are dispersed widely as single cells at the level of the basal layer of the epidermis. In lentigo maligna, there is an increased number of larger melanocytes present as single cells at the dermoepidermal junction; these have large, angulated nuclei with a high nuclear to cytoplasmic ratio. Discrete nests and pagetoid spread of atypical melanocytes can be seen. Lentigo maligna and lentigo maligna melanoma exhibit an intraepidermal proliferation of dendritic cells, characterized by folliculotropism. This feature is rarely seen in benign lesions. Lentigo maligna and lentigo maligna melanoma can also exhibit unique 'medusa-head like structures' under confocal microscopy. These structures consist of elongated buds that extend from the hair follicle and are populated by dendritic or pleomorphic cells. They typically correspond to clinical asymmetric follicular pigmentation or a pseudonetwork [38].

One limitation is that the maximum depth of imaging is up to the upper reticular dermis, making it inadequate to evaluate invasive melanoma. Another limitation is the lack of availability and the need for specialized training in order to interpret images. Histological analysis of the tissue remains the gold standard for diagnosis of lentigo maligna. However, RCM could potentially act as an adjunctive tool to minimize the sampling error associated with biopsy [39].

Biopsy

Excisional biopsy is ideal for diagnosis of lentigo maligna [40]. In theory, excisional biopsy removes the whole clinical lesion down to subcutaneous fat with a 1–3 mm margin. This potentially allows for complete evaluation of depth and peripheral involvement. Excisional biopsy, however, is often not feasible for lentigo maligna because the
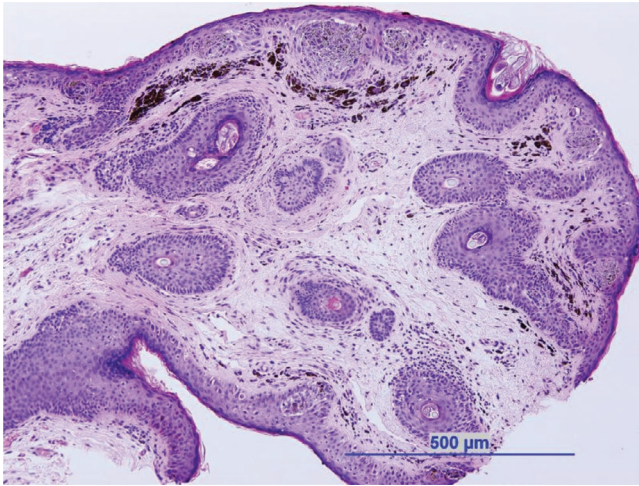
Figure 2A. Hematoxylin and eosin stain of the original biopsy of an eyelid lentigo maligna demonstrated classic lentigo maligna or melanoma *in situ*. There are an increased number of melanocytes at the dermoepidermal junction forming nests, as well as presenting as single cells with mildly enlarged, hyperchromatic nuclei (10X).
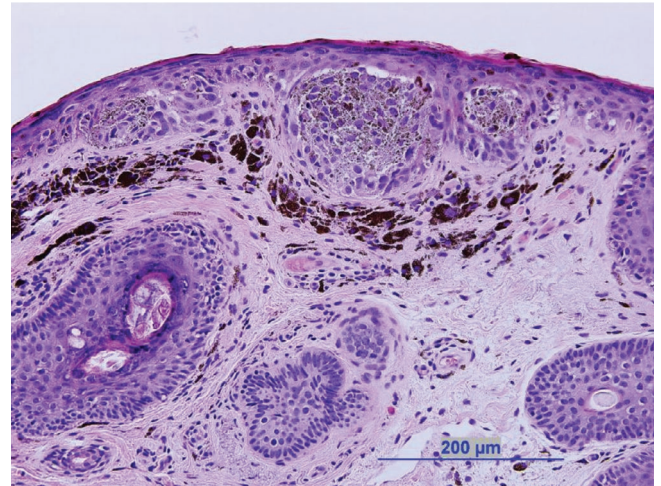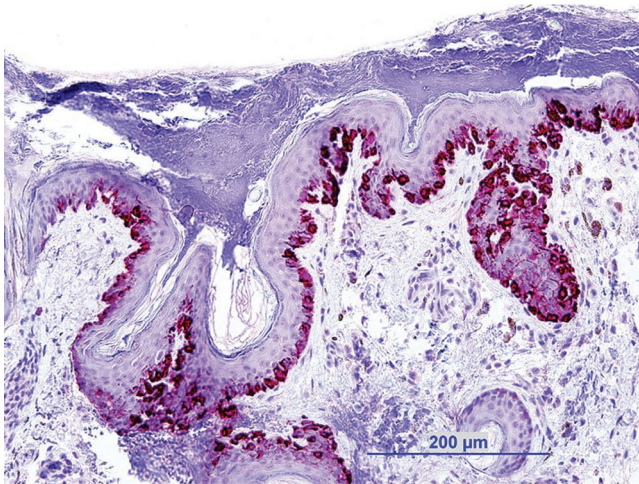

Figure 2B. The higher power of 2A (20X).

Figure 2C. An example of positive histological margin of lentigo maligna following slow Mohs excision. Immunohisto-chemistry stains using MART-1 (and MiTF, another melanocytic marker; photos not shown) strongly highlight an increased number of melanocytes at the dermoepidermal junction. There is multifocal confluence and there are scattered small nests. There is also prominent extension along adnexal epithelium.
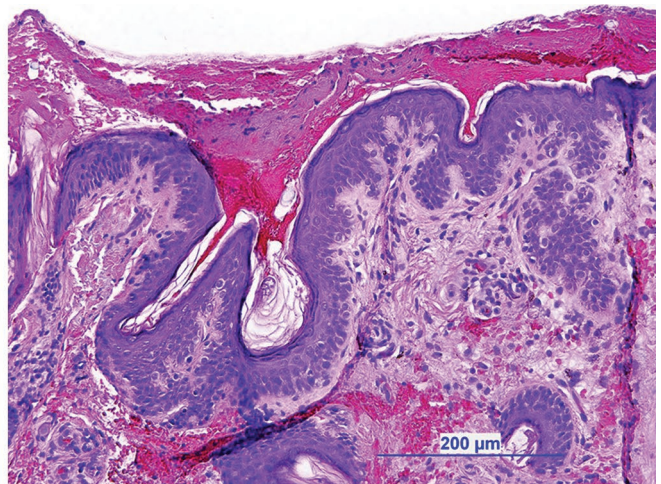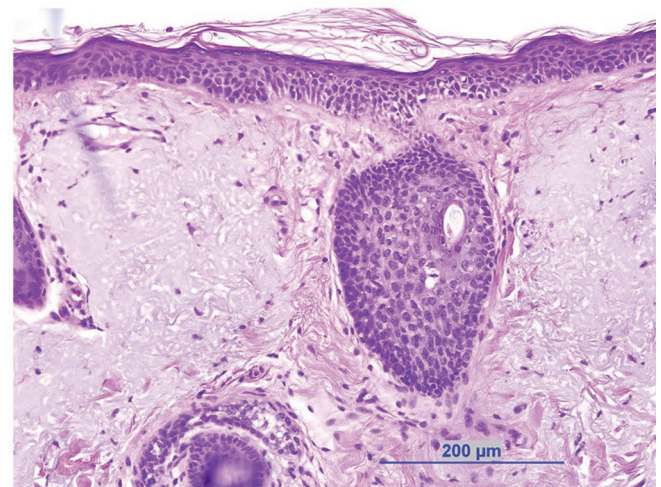

Figure 2D. An example of histological morphology of normal appearing, chronically sun-exposed skin taken from the patient's contralateral cheek. In this control skin, there is also a moderately increased number of melanocytes, some of which confluent, but there are no nests or pagetoid spreads.

lesions are typically ill-defined, widespread, and located in cosmetically sensitive areas. If the size of the lesion limits the ability to perform an excisional biopsy, scouting shave or punch biopsies can be performed (Figure 1B). Scouting biopsies should include samples from the darkest part, or most concerning part of the lesion, which will minimize the sampling error. They can also be taken from the periphery of the lesion to help delineate the peripheral margin involvement (Figure 1B).

Histological examination

Microscopic findings of lentigo maligna are characterized by the following features: atypical melanocytic hyperplasia at the dermoepidermal junction, confluence of atypical melanocytes and angulated nuclei replacing the basal layer, and nesting of atypical melanocytes with occasional pagetoid spread (Figures 2A and 2B). The cells often show cytoplasmic retraction, and there is adnexal involvement of atypical melanocytes. There can be rete ridge effacement and epidermal atrophy, but these features are not required for diagnosis of lentigo maligna [41].

Histopathologic diagnosis has been historically challenging due to the fact that it is difficult to distinguish lentigo maligna from sun-induced melanocytic hyperplasia that is naturally present on sun-damaged skin [42]. Biopsy taken from normal appearing, sun-damaged skin helps the pathologist to establish the baseline melanocytic hyperplasia for each particular patient.

Immunohistochemical (IHC) stains are often used to aid in the diagnosis of lentigo maligna. Melanoma antigen recognized by T cells (MART-1 also known as Melan A) and microophthalmia transcription factor (MiTF) are the two stains regularly used at our institution. MiTF is expressed in the nucleus of melanocytes. It accurately highlights the number of melanocytes seen in the epidermis and lesions of lentigo maligna. MART-1 may cause overestimation of the number of melanocytes in the epidermis due to the fact that MART-1 stains the cytoplasm of melanocytes, dendritic processes, and occasional keratinocytes [43]. Of note, MiTF and MART-1 are expressed in both benign and malignant melanocytes, further complicating the histological picture for the dermatopathologist [44]. Sox10 is also a useful tissue biomarker in melanocytic lesions [45,46]. It is present in the nucleus and regulates MiTF expression; therefore, similar to MiTF, it facilitates identification of melanocytes in the epidermis and chronically sun-damaged skin. MiTF and Sox10 have both been shown to be useful to distinguish lentigo maligna from pigmented actinic keratosis [47].

One promising, recently reported, IHC stain utilizes an antibody against soluble adenylyl cyclase (R21). Soluble adenylyl cyclase (sAC) is over-expressed in the nuclei of lentigo maligna, but not in native melanocytes [48]. With R21, nuclear expression of sAC is detected in almost 90% cases of lentigo maligna, but not in

nevi. However, 25–30% of melanocytic hyperplasia in benign lentigines can show nuclear staining of sAC, which then needs to be distinguished from lentigo maligna with the hematoxylin and eosin stain [49]. R21 is not widely used currently, but may become a promising adjunct to stains such as MART-1 and MiTF to help differentiate lentigo maligna from benign melanocytic lesions.
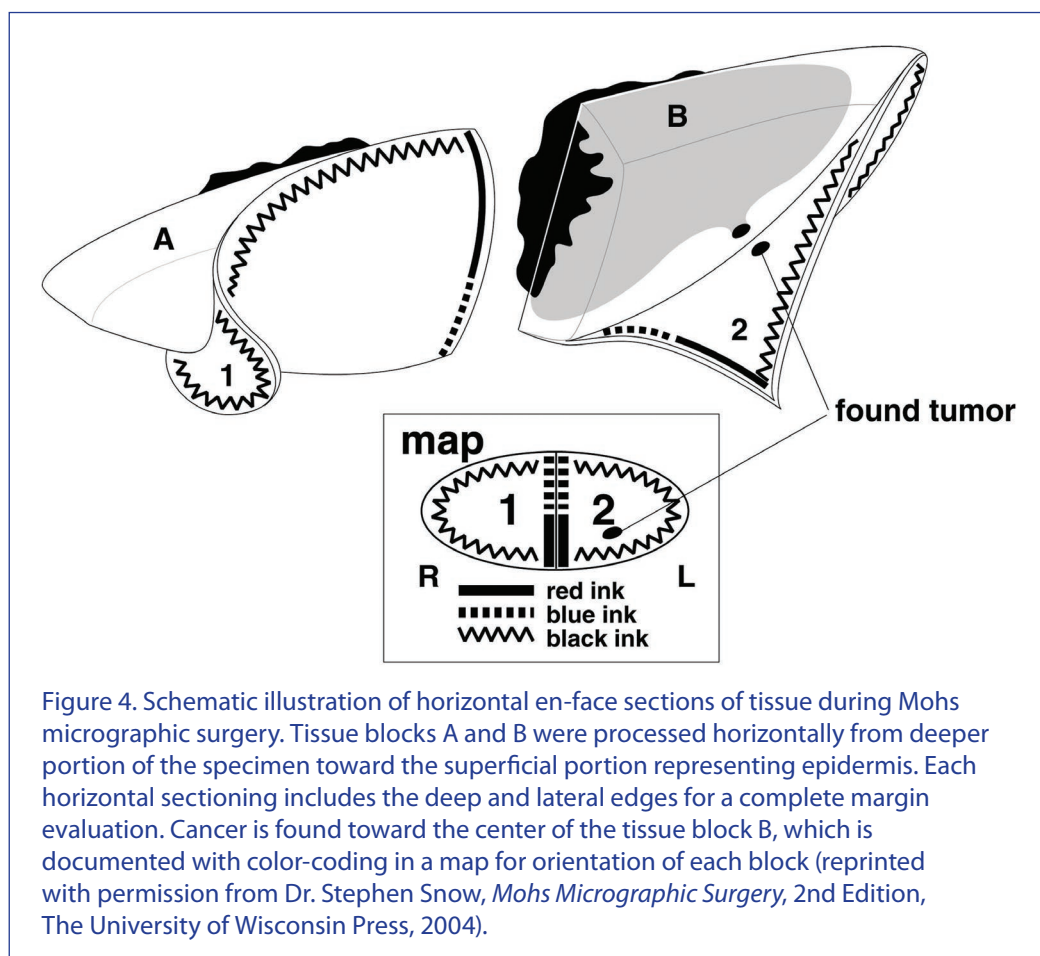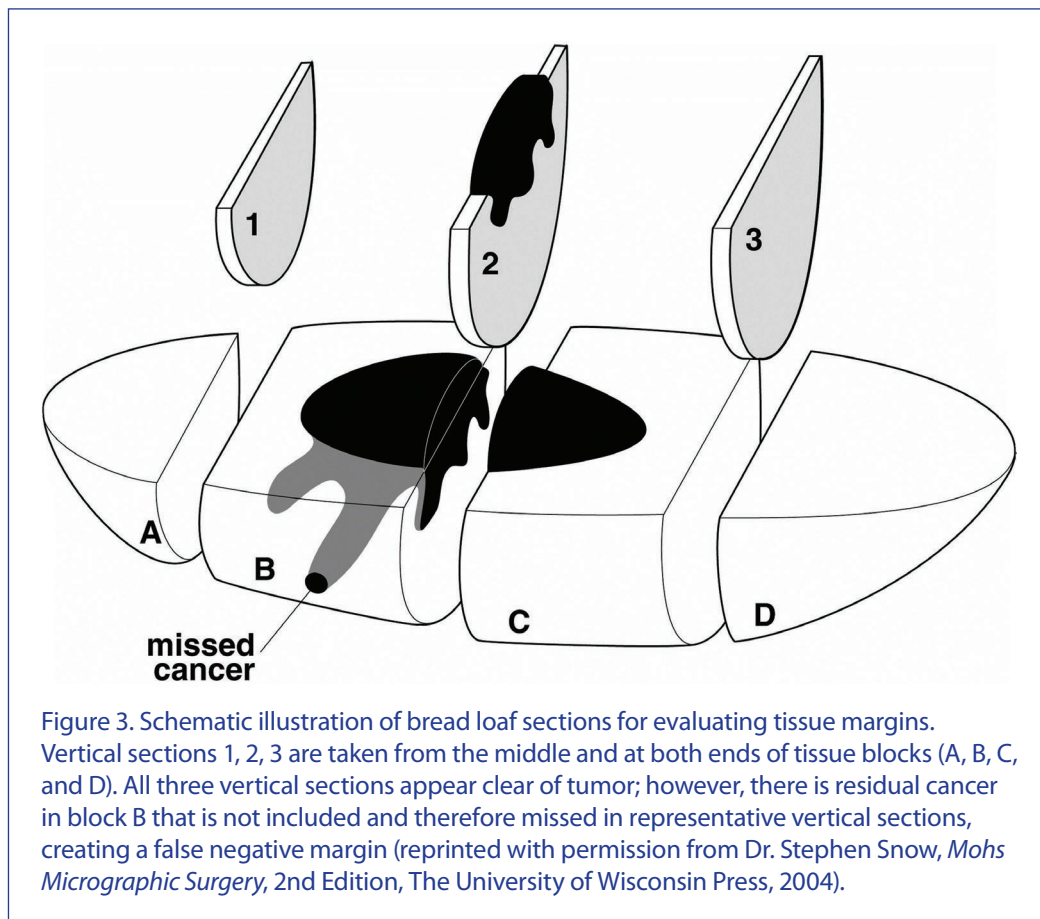
Some authors have discussed the use of melanocyte count to help determine histological margins and predict risk of recurrence. Gorman et al. [50] showed that melanocyte count is a strong predictor of lentigo maligna recurrence; patients were divided into low, intermediate, and high-risk groups based on the melanocyte count.

Treatment of lentigo maligna

Surgical excision is the mainstay of treatment. National Comprehensive Cancer Network, a consensus group that develops evidence-based practice guidelines (http://www.nccn.org), has recognized that wide local excision with 0.5–1 cm margins is insufficient for lentigo maligna, as opposed to other types of melanoma *in situ*. Traditional wide local excision specimens are processed by the bread loaf technique (Figure 3). Standard bread loaf techniques result in vertical sections at 2–4 mm intervals, which allow examination of less than 0.01% of the specimen surface area [51]. In order to examine 100 percent of the margin, vertical sections would have to be performed every 0.1 mm, which would be technically difficult [52]. Therefore, wide local excision processed by bread loaf technique is not ideal for complete margin control of lentigo maligna, in which the background of melanocytic hyperplasia often obscures the true borders of the lesion both clinically and histologically. In studies that include treatment of lentigo maligna with MMS and staged excision, it is not uncommon to find that greater than 1 cm margin is required to achieve histologically negative margins. In addition, 5–52% of lesions diagnosed initially as melanoma *in situ* had a dermal invasive component discovered at re-excision [53], further indicating the inadequacy of pre-determined excision margins. For these reasons, surgical excisions followed by more complete histological assessment of margins are preferred in the management of lentigo maligna, examples of which include traditional frozen-section MMS and staged excision aided by paraffin-embedded, permanent sections.

Mohs micrographic surgery

MMS is a well-developed surgical technique ideal for treatment of different types of skin cancers that grow in a contiguous fashion [54]. It is a tissue-sparing technique that allows for complete and immediate examination of the entire peripheral margin around the skin cancer (Figure 4). Dr. Frederic Mohs at the University of Wisconsin–Madison first developed the idea in the 1930s when he discovered that 20% zinc chloride solution injected into tumors of rats

Figure 3. Schematic illustration of bread loaf sections for evaluating tissue margins. Vertical sections 1, 2, 3 are taken from the middle and at both ends of tissue blocks (A, B, C, and D). All three vertical sections appear clear of tumor; however, there is residual cancer in block B that is not included and therefore missed in representative vertical sections, creating a false negative margin (reprinted with permission from Dr. Stephen Snow, *Mohs Micrographic Surgery*, 2nd Edition, The University of Wisconsin Press, 2004).

Figure 4. Schematic illustration of horizontal en-face sections of tissue during Mohs micrographic surgery. Tissue blocks A and B were processed horizontally from deeper portion of the specimen toward the superficial portion representing epidermis. Each horizontal sectioning includes the deep and lateral edges for a complete margin evaluation. Cancer is found toward the center of the tissue block B, which is documented with color-coding in a map for orientation of each block (reprinted with permission from Dr. Stephen Snow, *Mohs Micrographic Surgery*, 2nd Edition, The University of Wisconsin Press, 2004).

showed well-preserved cell histology. He used a fixed-tissue technique for over a decade to excise tumors under complete microscopic margin control. The technique then evolved to the use of horizontal frozen sections in the 1950s and 60s, which then widely replaced the fixed-tissue technique [55]. Dermatological surgeons are the primary practitioners of MMS, in which they play a dual role of surgeon and pathologist. MMS is widely used and accepted for excision of nonmelanoma skin cancers, including basal cell carcinoma and squamous cell carcinoma in cosmetically sensitive areas, but is also used by some dermatological surgeons for excision of lentigo maligna and lentigo maligna melanoma. Although the use of MMS for lentigo maligna is controversial, it is included in the AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for MMS [56].

The excision of lentigo maligna with MMS usually occurs during one working day. The clinically apparent lesion is outlined and then excised; this debulk section is sent for paraffin-embedded, permanent sections to examine for possible invasion. Then, a margin of tissue is excised around this debulk area with a scalpel positioned at a 45-degree angle. The 45-degree inward bevel allows the tissue to lie down in a way that facilitates en-face processing (parallel to the surgical margin). Scores are made on the skin edge with the scalpel and correspond to the orientation of the tissue. The tissue is then divided into sections and inked for frozen-section en-face processing. The orientation and inking pattern of individual sections are recorded on a map. The processing and evaluation of the tissue takes a variable amount of time, usually 0.5–2 hours. This also may take longer depending on the need for special stains. The surgeon then analyzes the slides and carefully documents areas on the peripheral or deep margin that show tumor. Tissue is excised only around the positive margin, thereby sparing excision of normal tissue. This process is repeated until the margins are clear of tumor [54,57]. When histologically negative margins are achieved, the patient can have reconstruction either on the same day or within the following few days.

Published rates of recurrence for lentigo maligna and lentigo maligna melanoma treated with MMS range from 0 to 6.25% [57–69], except for one study that reported a recurrence rate as high as 33% with MMS (6/18), as compared with 7.3% (3/41) with staged excision during a mean follow-up time of almost 10 years [59]. The authors admitted that the small amount of MMS cases performed and ascertainment technique likely contribute to the high recurrence rate. In contrast, Bricca et al. [62] reported a 5-year recurrence rate of 0.2% in a prospective study of 625 patients who underwent MMS for lentigo maligna and lentigo maligna melanoma. This study included updated data from previous studies, in which the authors had extensive experience with MMS for lentigo maligna [57,68–70]. This discrepancy in cure rates highlights why the use of MMS for lentigo maligna remains controversial. The key limiting factor is the accuracy of interpretation of melanocytic lesions on frozen-section histology. Certain cytoplasmic features that may help distinguish lentigo maligna such as perinuclear

retraction are lost under frozen-section processing [71]. Frozen-section processing also alters the morphology of keratinocytes and produces halos that mimic melanocytes, adding to the error in recognizing tumor cells. As early as 1991, Zitelli's group reported 100% sensitivity and 90% specificity in detecting atypical melanocytes at the margins of melanoma with frozen sections, using permanent sections as a gold standard [72]. However, other investigators have reported lower accuracy; Barlow et al. report a sensitivity of 59% and specificity of 81% [71]. Inevitably, the validity of using frozen sections to assess melanoma margins has been challenged because interpretation of melanoma excision margins on frozen sections depends heavily on the level of experience of the individual surgeon. Therefore, frozen-section histology is generally disputed and discouraged by an overwhelming majority of physicians involved in the treatment of melanoma.

To aid in intra-operative margin control during MMS excision for melanoma, a variety of IHC stains have been studied that highlight melanocytes, including S-100, HMB-45, MART-1, Mel-5, and MiTF. Among all tested markers, MART-1 and MiTF are proving more useful than others. In contrast to their established value in permanent sections, their use in frozen sections during MMS has remained restricted to a limited number of Mohs surgeons. A survey of 378 fellowship-trained Mohs surgeons revealed that approximately 90% responders felt that IHC on frozen sections were helpful while only about 22% were using it in practice [73]. Extra time involved with tissue processing, along with the lack of education and cost, are the main deterrents for a wider adoption of immunostain during MMS. The time needed to perform immunostain protocols has improved over the past decade from over 2 hours to less than 1 hour [74]. Few rapid protocols are available for MART-1 with the reported duration as short as 16 minutes [75–77]. A 35-minute protocol is reported for MiTF [78]. It raised another concern as to whether an inappropriately shortened duration may lead to an inflated, false negative rate in margin assessment.

Staged excision

Staged excision relies on paraffin-embedded, permanent sections rather than frozen sections for histological evaluation of surgical margins. Various staged excision techniques have been proposed in an attempt to identify a valid and reliable method in excising lentigo maligna and lentigo maligna melanoma with clear margins: 'square method' [22,79,80], 'perimeter technique' or 'spaghetti technique' [15,21,81], 'slow Mohs' [66], staged radial sections [24,53] and staged 'mapped' excisions [23,25,26,59]. Favorable recurrence rates of 0–12% have been reported in several case series with follow-up duration ranging from 4 months to 5 years (Table 1) [14,15, 18–26,80–84]. The highest recurrence rates were found in the two studies with the longest follow-up of 5 years: 4.8% [24] and 12% [83]. Staged excision offers greater margin control than standard surgical excision and avoids some of the pitfalls related to MMS with frozen sections.

Table 1. Staged excisions for lentigo maligna and lentigo maligna melanoma: technique, margin evaluation, follow-up, and recurrence rate.

Reference	Technique	Margin evaluation (complete or partial)	Average follow-up months (years)	Recurrence rate (%)
Patel et al. 2014	Square procedure	En-face sections (complete)	60 (5)	0/21 (0)
Lawrence et al. 2014	Slow Mohs	En-face sections (complete)	60 (5)	7.74 (12)
Abdelmalek et al. 2012	Geometric staged excision	En-face sections (complete)	32.3 (2.7)	4/239 (1.7)
Gaudy-Marqueste et al. 2011	Spaghetti technique	En-face sections (complete)	25.36 (2.1)	1/21 (4.7)
Bosbous et al. 2009	Slow Mohs	En-face sections (complete)	27 (2.25)	1/59 (1.7)
Moller et al. 2009	Staged marginal and central excision	En-face sections (complete)	14 (1.2)	0/49 (0)
Hazan et al. 2008	Staged excision	Serial sections at 2 mm intervals (partial)	Not reported	117 lesions, recurrence not reported
Jejurikar et al. 2007	Square procedure	Vertical sectioning (partial)	31 (2.6)	0/51 (0)
Mahoney et al. 2005	Perimeter technique	En-face sections (complete)	4.7 (0.4)	0/11 (0)
Huilgol et al. 2004	Staged excision	Vertical, radial sections (partial)	38 (3.2)	4/161 (2.5)
Bub et al. 2004	Staged excision	Vertical, radial sections (partial)	57 (4.75)	3/62 (4.8)
Malhotra et al. 2003	Staged excision	Vertical sections	32 (2.6)	4/141 (2.8)
Agarwal-Antal et al. 2002	Polygonal staged excision	Serial sections from true margin inward (complete)	48 (4)	0/92 (0)
Clayton et al. 2000	Slow Mohs	En-face sections (complete)	22 (1.8)	3/106 (2.8)
Hill and Gramp 1999	Staged excision	Vertical sections (partial)	25 (2)	1/66 (1.5)
Johnson et al. 1997	Square procedure	Vertical sections (partial)	Not reported	0/35 (0)

Staged marginal and central excision, square procedure, perimeter technique, and spaghetti technique – excision of peripheral margins to obtain complete margin control before resection of tumor.

At our institution, staged excision with en-face permanent sections is the treatment of choice for lentigo maligna, also known as 'slow Mohs' excision. The first stage involves taking a 6 mm margin around the clinical lesion (Figure 1C), which has been described by Zitelli et al. with frozen sections [68,69]. First, the clinical margin of the lentigo maligna is outlined taking into account the clinical appearance with natural light, Wood's lamp examination, and the histopathologic diagnosis of previous scouting biopsies. Second, a central debulk specimen is excised by taking 3 mm of clinically normal skin around the outlined lesion to the depth of superficial subcutaneous fat. This debulk specimen is submitted separately for paraffin-embedded, permanent sections and is vertically sectioned using bread loaf technique to assess Breslow depth. Third, an extra 3 mm margin is marked lateral to the debulk defect; this is excised with a scalpel angled at 45 degrees as a single piece down to deep subcutaneous fat or fascia (Figure 1D). The 12 o'clock position is scored on the specimen and sutured on the patient to preserve orientation. In the same way as with MMS, the excised specimen is then divided in a way that facilitates accurate processing by the histotechnicians. Each subsection is

inked, placed in a separate tissue cassette, and processed with en-face paraffin-embedded, permanent sections for complete margin evaluation. A map is drawn that specifically outlines orientation and color-coding of the individual subsections of the specimen. If warranted, a partial closure is performed to obtain hemostasis and simplify wound care for the patient while awaiting histological evaluation of the margin status (Figure 1E). In addition, a narrow strip of normal appearing, sun-damaged skin is often taken as a control, usually from the contralateral side of the face (Figure 1F).

The permanent vertical sections of the central debulk specimen and en-face sections of the 'slow Mohs' specimens are examined by experienced dermatopathologists. Results are usually available in 24–48 hours. If indicated, MART-1 and MiTF are used at our institution to aid in diagnosis, which add another 2 to 3 days to the histological analysis of the tissue. If the debulk specimen confirms the presence of lentigo maligna or reveals no remaining cancer but scar tissue, there is no change in the diagnosis of lentigo maligna. However, if the debulk specimen demonstrates an invasive component, the Breslow depth and

Figure 5A. Subtotal shave biopsy of an ill-defined brown patch on the left cheek confirmed the diagnosis of lentigo maligna in this elderly woman.
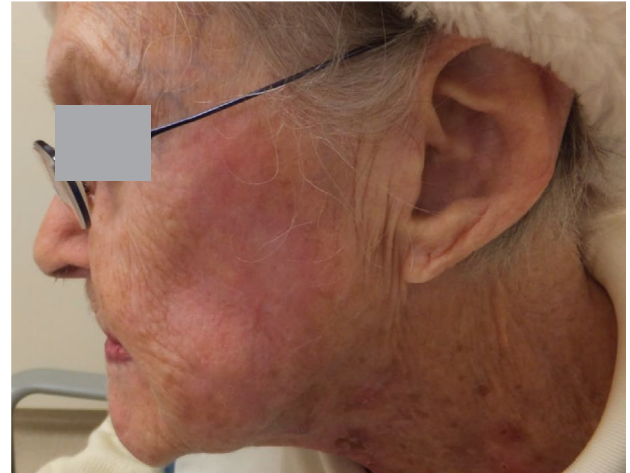

Figure 5B. The patient was treated with imiquimod 5% cream five times weekly for approximately two months. At her three-month post-treatment follow-up, she had mild hypopigmentation and erythema on the left cheek.

other pertinent histological features will be reported and the lesion will be upgraded to lentigo maligna melanoma and staged per AJCC guidelines. At our institution, stage 1A invasive lentigo maligna melanoma is still managed with 'slow Mohs' excision, while 1B and beyond will be referred to surgical oncology services for consultation for possible sentinel lymph node biopsy and additional wide local excision. It is worth noting that when treating lentigo maligna, or potentially upgraded lentigo maligna melanoma, 'slow Mohs' excision reaches a depth of deep subcutaneous fat or fascia. The authors have never encountered any positive tumor involving deep margins. If lateral surgical margins are positive, the patient returns for a second stage 'slow Mohs' excision. Another 3 mm margin is taken laterally around the positive area (Figure 1G). The specimen is again color-coded with ink, mapped, and sent to dermatopathology for en-face tissue processing and histopathologic analysis. If special stains are needed, this may prolong the time between stages or before repair. The process is repeated until clear peripheral margins are achieved. The final defects are often large and complicated due to subclinical spread of lentigo maligna and require coordinated reconstruction by plastic surgery or oculoplastic services (Figure 1H).

Different techniques of staged excision have been reported in the literature as mentioned. One main difference among various techniques is how the marginal tissue is processed. Some authors report serial vertical sectioning [53], while others use en-face permanent sections. The major advantage of en-face processing is that it allows for examination of 100 percent of the peripheral margin and minimizes the risk of missing radial extension of lentigo maligna. It also allows the surgeon to take additional excision stages only around involved margins, thereby sparing excision of normal tissue. One caveat is that en-face processing of tissue for permanent section can be difficult.

Therefore, it requires skilled staff, which may not be present at all institutions. Another challenge of en-face evaluation is that it does not allow assessment of the change in melanocyte density from the center of the lesion to the periphery, a feature that is helpful to differentiate between sun-damaged skin and lentigo maligna [85].

Nonsurgical interventions

Imiquimod

Imiquimod is a member of a class of immune response modifiers called imidazoquinolines. It is an immune response stimulator that enhances both the innate and acquired immune pathways (particularly T helper cell type 1-mediated immune responses). Imiquimod causes cytokine induction in the skin through induction of Toll-like receptors. This then triggers an inflammatory cascade that causes the host's immune system to recognize and subsequently destroy tumor cells. An indirect effect of imiquimod is stimulation of interferon-gamma production from Th-1 cells, which thereby stimulates cytotoxic T lymphocytes [86]. Cytotoxic T cells are responsible for destruction of tumor and establishment of immunological memory for future protection [87].

Imiquimod is licensed in the United States and United Kingdom for treatment of genital warts, actinic keratoses, and superficial basal cell carcinoma. It is used off-label for lentigo maligna. Collected data suggest possible benefit but its efficacy in lentigo maligna has been evaluated only in limited, uncontrolled studies, case reports, and case series with relatively limited short follow-up of less than 5 years [88–101].

Although there is no evidence that imiquimod 5% cream is better than observation alone in patients who are elderly and/or cannot have a large surgical excision, it is often presented

as a treatment option given its beneficial outcome in certain cases. Nevertheless, it is important to discuss the risks and benefits of imiqiumod with patients, including the lack of evidence, the risk of undertreating or masking a possible invasive melanoma, the risk of recurrence, and side effects such as inflammation. Some authors suggest that treatment course should be followed up by repeat biopsies [92]. Figures 5A and 5B represent a patient who had exuberant inflammatory response with imiquimod and disappearance of the clinical lesion after 2 months of treatment. Close follow-up is suggested for patients who use imiquimod, and biopsy should be strongly considered if there is ever recurrence of pigment or any development of induration.

Radiation therapy

Radiotherapy, like imiquimod, is a noninvasive treatment option that has been used as a primary treatment for lentigo maligna in patients who are poor surgical candidates. Studies have used Grenz ray therapy for treatment of lentigo maligna [102–104]. Data are limited regarding the use of radiotherapy, and long-term follow-up outcomes are lacking. Fogarty performed a retrospective analysis of all studies from 1941 to 2009 with a mean follow-up of 3 years; 18/349 (5%) lesions recurred [105]. Radiotherapy may be a promising option for the treatment of lentigo maligna; however, it is not widely utilized and prospective trials are needed.

Miscellaneous treatments

A recent Cochrane review discussed other treatments that have been used for lentigo maligna, including azelaic acid, lasers, electrodessication and curettage, cryosurgery, and 5-fluorouracil 5% cream [106]. Currently, these methods are not recommended because they are only used anecdotally in limited studies, they don't offer microscopic margin control, and they would likely not treat any periadnexal extension of lentigo maligna or lentigo maligna melanoma [107].

Conclusion

Lentigo maligna is a slow-growing melanoma *in situ* on the head and neck region. Clinical and histopathologic diagnosis of this entity is sometimes difficult. Clinically, the lesion may appear similar to benign diagnoses, such as a solar lentigo,

seborrheic keratosis, pigmented actinic keratosis, lichen planus-like keratosis, or benign nevus. Histologically, atypical melanocytic hyperplasia present on normal, sun-damaged skin can sometimes appear very similar to lentigo maligna. Tools such as dermoscopy, Wood's light examination, RCM, scouting biopsies for histopathologic, and IHC stains can help exclude benign findings and aid in the diagnosis of lentigo maligna.

High-quality evidence is lacking for the treatment of lentigo maligna. Surgical interventions with complete margin control remain the gold standard, which include staged excision with rush permanent sections and MMS. Although these are considered the first-line therapy for this condition, there are no randomized controlled trials validating their use and showing long-term effects on morbidity and mortality. The use of nonsurgical interventions in selected patients who are not surgical candidates may be preferable. The nonsurgical intervention that has been most studied is topical imiquimod, although it also lacks high-quality evidence. It can be used by experienced providers with close patient follow-up. Sometimes repeat biopsies are needed to confirm clearance or monitor for recurrence. Radiation is a promising therapy for treatment of lentigo maligna, but more studies are needed to support its use.

When approaching patients with a new diagnosis of lentigo maligna, it is preferable to give them consultation before any procedure takes place. It is important to discuss the slow-growing nature of lentigo maligna and the risk of invasive disease. One must take the age and comorbidities of each individual patient into account when creating a treatment plan. Subclinical spread of lentigo maligna may create a large surgical defect with the need for extensive reconstruction to maintain acceptable cosmesis. Some patients may choose not to have surgery or are poor surgical candidates due to advanced age and comorbidities. If this is the case, second-line therapy with imiquimod, radiation, or close observation alone are acceptable alternatives to surgical management, as long as the patient understands all risks and benefits of each treatment option.

Acknowledgments

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