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Managing Melanoma In Situ

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Melanoma is a highly aggressive skin cancer with an increasing incidence. Melanoma in situ is an early, non-invasive form in which the tumor is confined to the epidermis. Treatment of melanoma in situ is challenging due to the frequent subclinical microscopic spread and to the presentation on the head and neck in cosmetically sensitive areas with chronic sun damage. Optimizing tumor eradication is imperative to reduce the potential progression into invasive disease and metastasis, all while maintaining cosmesis. Multiple treatment regimens have been implemented for managing difficult melanoma in situ tumors. We provide a thorough review of surgical, and non-surgical, management of melanoma in situ which can pose therapeutic dilemmas due to size, anatomic location, and subclinical spread.

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Melanoma is a highly aggressive form of skin cancer with an increasing incidence.[1] Melanoma in situ (MIS) is an early form of melanoma in which the malignancy is confined to the epidermis. According to the American Cancer Society, an estimated 68,720 new cases of malignant melanoma were reported in 2009, and 53,120 new cases of melanoma in situ. Lentigo maligna is a subtype of MIS found on sun-exposed areas and accounts for approximately 80% of all MIS tumors.[2] With its increasing incidence and being a precursor to invasive melanoma, the treatment of MIS, in particular lentigo maligna, is a topic of increasingly significant interest. The ideal management of MIS is openly debated.

Etiology and Epidemiology

Melanoma is a malignant tumor arising from melanocytes. Melanoma is an aggressive, heterogeneous cancer with both host and environmental risk factors for development.[1] Both rare high-risk susceptibility genes and common polymorphic genes have been linked to an increased risk.[1] Exposure to ultraviolet radiation remains the predominant environmental risk factor for melanoma. However, the history of significant sunburns rather than chronic ultraviolet exposure seems to more greatly increase the risk for development of melanoma.[1,3] The use of tanning beds has also contributed to the increased incidence of melanoma, especially in the younger population. The presence of multiple nevi (greater than 50) is associated with a greater risk of melanoma, with the exception of lentigo maligna. Lentigo maligna, unlike other melanomas, has a greater association with nonmelanoma skin cancers.[3]

Diagnostic Criteria

Melanoma in situ can have a highly variable presentation, from a well-demarcated, small brown macule on healthy-appearing skin to an asymmetric, variably pigmented large patch on grossly actinically damaged skin (Fig. 1). It can even present as a nondescript pink patch, especially on fair skin. Clinical appearance along with history of change, new onset, or any symptoms, such as itch or pain may prompt a biopsy.

Histologic examination of the entire lesion is critical to diagnosis of melanoma in situ. Even when the clinically darkest or "most suspicious" part of a pigmented lesion is biopsied, there is a risk of missing the histologically most significant area. Partial biopsy may show only MIS while there is an unidentified invasive component elsewhere. Melanoma in situ presents with atypical melanocytes confined to the epidermis. Features consistent with a diagnosis of MIS include a predominance of single atypical melanocytes; multiple single melanocytes greater in the epidermis instead of in the basal layer; and confluent, broad, irregularly sized, and distributed nests of melanocytes. The epidermal component is often poorly demarcated with single melanocytes that tend to trail off. Although many view lentigo maligna as a form of in situ melanoma, it remains somewhat controversial whether lentigo maligna should be regarded as a melanocytic dysplasia as opposed to in situ melanoma.[4] Histopathologically, lentigo maligna is characterized by atypical melanocytes, singly and in nests, usually confined to the basal layer and with little pagetoid invasion of the epidermis as opposed to other mel-

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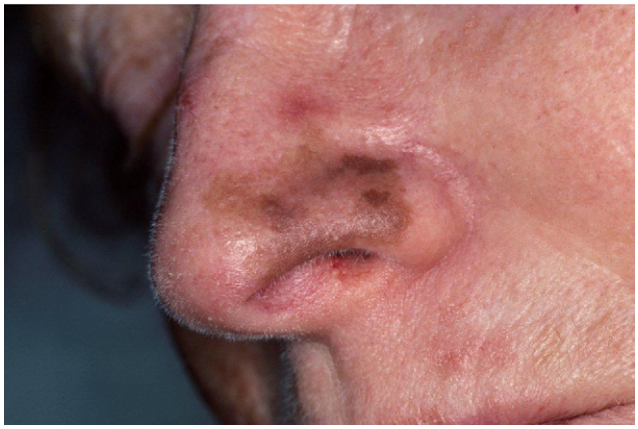

Figure 1 Classic clinical appearance of lentigo maligna in sun-exposed area. Photo courtesy of H.L. Parlette, III, MD.

anoma in situs.[4] Occasionally, multinucleate melanocytes with prominent dendritic processes are present in the basal layer.[4] Biopsies of lentigo maligna also typically reveal evidence of chronic actinic damage, such as solar elastosis.

Multiple stains may be implemented to facilitate the diagnosis of MIS, including S-100, HMB-45, Mel-5, and MART-1/Melan-A. S-100 is an acidic Ca^{2+}- and Zn^{2+}-binding protein that stains melanomas as well as benign melanocytic lesions, dendritic cells, histiocytes, Schwann cells, muscle, chondrocytes, and eccrine and apocrine cells.[5] S-100 is useful in identifying the dermal component of melanomas as well as desmoplastic melanomas.[5] HMB-45 is a mouse monoclonal antibody that recognizes melanosome-associated sialated glycoprotein seen in malignant melanocytes.[5] Mel-5 recognizes gp75, a glycoprotein abundantly present in melanocytes.[5] It briskly stains melanomas but also many other nonmelanocytic lesions.[5] MART-1/Melan-A is a cytoplasmic melanosome-associated melanocyte differentiation antigen present in 80-100 percent of melanomas.[5] Most recently, fluorescence in situ hybridization test has been used to distinguish between benign nevi and malignant melanoma in histologically ambiguous melanocytic neoplasms. The fluorescence in situ hybridization (FISH) test is an assay that uses DNA probes hybridized to the melanocytic lesion and identifies multiple recurrent chromosomal copy number changes seen in more than 95% of melanomas. The fluorescence in situ hybridization test may be used as an ancillary tool with difficult histology.[6]

Management of Melanoma In-Situ

Management of melanoma in situ can often pose a therapeutic dilemma. Ill-defined clinical margins, especially with lentigo maligna, frequently yields unsatisfactory cure rates with standard excision. The frequent occurrence of MIS, especially lentigo maligna, on the head and neck in cosmetically sensitive areas warrants optimal margin control. Furthermore, the presentation of MIS in nonsurgical candidates raises management questions. Multiple treatment modalities are employed for managing melanoma in situ, each with their individual strengths and weaknesses. We will provide an overview of the various treatment options to delineate the preferred regimens.

Excisional Surgery

Surgical excision of melanoma in situ has long been the treatment of choice. Excision ensures removal of periadnexal melanocytes and allows for thorough histologic assessment identifying any potentially previously undetected invasive component. The standard 5-mm margin for melanoma in situ was established at the 1992 National Institutes Health consensus conference and supported by the American Academy of Dermatology's 2001 guidelines for treatment of melanoma.[7,8] Unfortunately, the 5-mm margin is inadequate for many MIS lesions, especially those on the head and neck and sun-damaged skin.[4,9-15] Recurrence rates after excision with 5 mm margins range from 6% to 20%.[16-19] Multiple studies have confirmed the unsatisfactory clearance of MIS tumor with routine 5 mm margin excisions.[11,12,14,15,20-30] The need for larger margins and/or better margin control has been recognized.[13]

Various staged excisional techniques with better margin control have been devised and revised to optimize tissue analysis and reduce recurrence rates. In 1990, Dhawan et al[31] first described a modified staged surgery allowing for margin control in the treatment of lentigo maligna. The technique consists of excision and mapping of the tumor similar to standard Mohs micrographic surgery. Rushed permanent sections are then examined by a dermatopathologist and subsequent stages taken as necessary to clear the tumor.[31] This technique is now referred to as the "slow Mohs" procedure. Arguments against "slow Mohs" include a potentially prolonged opened wound, leading to a greater infection risk and the formation of granulation tissue during the wait time (Fig. 2) .[13] Rush permanent sections reduce wait time while maintaining high-quality histology.[23] Prophylactic oral antibiotics are used to reduce infection risks with delayed closures. Wound granulation may actually benefit and accelerate heal-

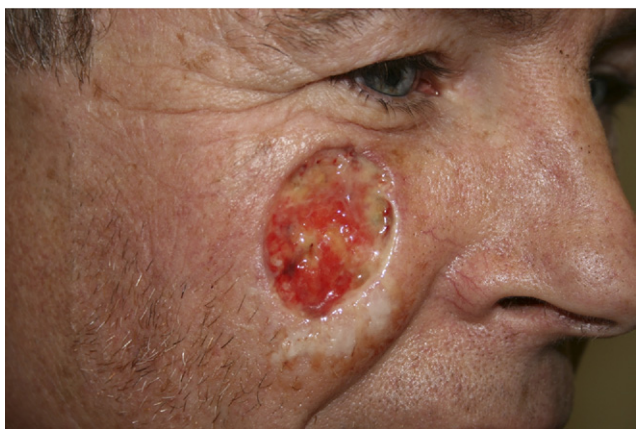

Figure 2 Two days status post completion of slow Mohs excision for melanoma in situ, clear margins after second stage. Early granulation tissue formation evident.

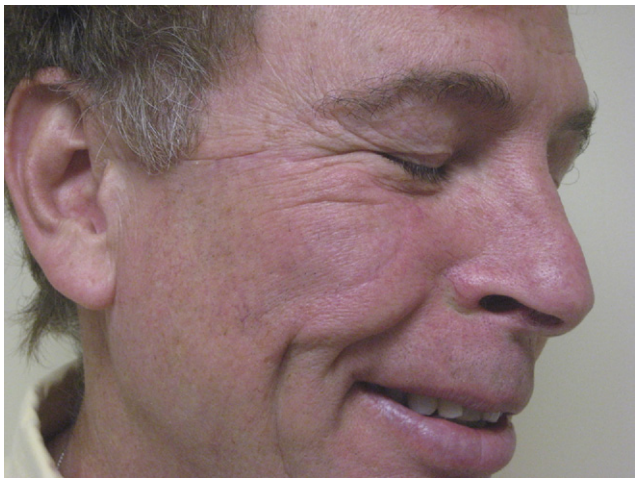

Figure 3 Good cosmetic result 6 months status post rotation flap closure following a staged slow Mohs excision.

ing of the final closure as the wound healing process has already started (Fig. 3).

Alternative staged excision methods have been developed, including analyzing small strip, 2-mm peripheral margins, 1 week before primary tumor excision to guide margin control.[12,15,20,23,26,29,32,33] The reported benefit of the peripheral rim preanalysis is to avoid prolonged open wounds. Disadvantages with this technique include delay in tumor excision and an unsuspected invasive component may not be identified until after closure of the defect.[13]

Recurrence rates for the staged excisions range from 0% to 5% with variable follow-up.[11,12,15,21-23,26-28,30,32-39] Total margin control by the use of staged excisions with permanent sections offers a simple, effective treatment for MIS tumors with indistinct margins, eliminating the concerns of inadequate margins and higher recurrence rates. A good working relationship with the dermatopathologist is imperative for success. Long-term follow-up with prospective studies is still needed to more thoroughly evaluate the efficacy of staged excisions with permanent sections.

Mohs Micrographic Surgery

Compared with standard excision, Mohs micrographic surgery (MMS), like staged excisions, provides the advantages of complete margin evaluation, tissue conservation, and greater cure rates for MIS and lentigo maligna.[9,40] The main advantage over the staged excision techniques is immediate reconstruction. MMS involves tangential excision of the tumor allowing for examination of 100% of the peripheral margins.[9,41] Despite the aforementioned advantages, controversy exists regarding the use of MMS for the treatment of MIS because of significant difficulties in recognizing malignant melanocytic cells on frozen sections.[9,24,28,39,41,42] Zitelli et al[42] reported 100% sensitivity and 90% specificity of frozen section in the detection of atypical melanocytes at the margins of melanoma based on comparison with paraffin-embedded specimens. Subsequent investigations have reported lower accuracy. Barlow et al report a sensitivity of only 59% and specificity of 81%.[43] Bene et al found that only 95.1% of MIS lesions considered clear on frozen section analysis were truly clear when analyzed with subsequent permanent sections.[39] Interpretation of melanocytic lesions with frozen sections can be very challenging. Vacuolated keratinocytes can be difficult to differentiate from melanocytes and dermal inflammatory cells may obscure melanocytes.[9,41]

Malignant melanocytes must also be differentiated from benign melanocytic hyperplasia, frequently found in sun-damaged skin. Weyers et al[44] identified criteria indicative of malignant melanoma compared with benign melanocytes. The greatest diagnostic value is the presence of melanocytic nests. Irregular distribution of pigment and melanocytes, adnexal extension, and pagetoid spread are additional findings suggestive of malignancy.[44]

Immunostaining of frozen sections has been studied to determine its utility in better identifying atypical melanocytes. Several stains have been used in frozen section processing, including S-100, HMB-45, Mel-5, and MART-1/Melan-A. Comparative studies have found MART-1/Melan-A to be the most sensitive and specific immunostain for identifying melanoma in frozen section.[24,25,28,45] Protocols for MART-1 staining techniques with frozen sections provide high efficacy detection of MIS.[46] Many advocate the use of immunostains in preparation of frozen sections for MIS. Limitations include additional processing time, skill level of the histotechnician, and the possibility of false-positive margins caused by the staining of pigmented actinic keratoses and actinically damaged skin.[47]

Topical Imiquimod

Topical imiquimod has reported efficacy for melanoma in situ and lentigo maligna. Imiquimod is a synthetic imidazoquinoline amine that stimulates immune activity. The innate immune system is activated, binding toll-like receptors 7 and 8, leading to synthesis and release of multiple cytokines, including interferon-α and tumor necrosis factor-α. The result is apoptosis and suppression of tumor genesis.[9,48]

Imiquimod is currently approved by the Food and Drug Administration for the treatment of external genital warts, actinic keratoses, and superficial basal cell carcinomas. The use for lentigo maligna was first reported in 2000 for a large scalp lesion on an elderly male. He remained clear at 9-months follow-up.[49] Subsequent reports and studies have shared protocols for clearance of MIS with response rates ranging from 66% to 100%.[9,49-68,69,70,61]

Despite a positive response to imiquimod, the optimal treatment regimen has yet to be defined. Furthermore, response to therapy and tumor clearance are difficult to assess post treatment, leading to the concern for recurrence or, even more worrisome, invasive disease. One large case series showed only 30 of 33 cases to be histologically clear of tumor when judged clinically clear after 3 months of therapy.[68] The use of topical imiquimod for a superficial, but potentially very aggressive malignancy is risky when there is potential of an incorrect initial diagnosis as melanoma in situ due to failure to detect an invasive component on initial biopsy. As many as 22% of pigmented lesions believed to be MIS or

lentigo maligna on initial biopsy have invasive components identified histologically after complete excision.[9] Patients have developed invasive melanoma after treatment with imiquimod for lentigo maligna.[50,51] Imiquimod represents an alternative treatment option for MIS and lentigo maligna that are particularly large and/or are on cosmetically sensitive areas in elderly and/or poor surgical candidates.

Radiation Therapy

Radiation therapy (XRT) is a noninvasive, destructive treatment option for MIS and lentigo maligna. Treatment with radiation is appealing for elderly patients and for poor surgical candidates with large MIS lesions on the head and neck. A 95% clearance is reported with the Miescher technique, delivering high-dose Grenz ray or soft x-rays (12-50 kV) with surface doses of 20 Gy once weekly for 4 to 5 weeks.[71] Conventional radiotherapy is reportedly effective as a treatment modality with an 86% clearance rate at 5 years.[18,72-74]

Radiation therapy is a good second-line treatment best suited for nonsurgical candidates. The nonselective tissue destruction is a significant side effect. XRT may yield a poor cosmetic outcome with skin pallor, atrophy and telangiectasias involving the entire treatment field.[72]

Laser Treatment

Multiple lasers, to include the argon, carbon dioxide, Q-switched ruby, Q-switched alexandrite, and Q-switched neodymium-doped yttrium-aluminum-garnet, have been used for management of MIS.[75-80] Although reports proclaiming short treatment duration, minimal postoperative care, and excellent cosmesis exist, the use of lasers for management of melanoma in situ is associated with high recurrence rates and is still below the standard of care for most tumors. Both inadequate margin control and inadequate laser targeting of the tumor lead to high recurrence rates. Atypical cells may extend down appendageal structures or may be amelanotic and, thus, elude laser destruction.[80] Laser therapy may offer an excellent option in the future, but is currently not a recommended therapy for MIS.

Conclusions

The incidence of melanoma in situ, and particularly lentigo maligna, continues to increase. It is imperative to understand the multiple treatment options, as well as the associated risks and benefits, to best guide our patients' therapy. Excision of melanoma in situ remains the treatment of choice. Given the location, tumor characteristics, surgical candidacy, and provider capabilities, treatment may vary. Routine surgical excision with standard 5-mm margins may be sufficient for small, well-demarcated tumors on less actinically damaged skin. "Slow-Mohs" with permanent section tissue analysis is preferred for less discrete lesions, especially lentigo malignas, on actinically damaged skin. Mohs micrographic surgery could be the treatment of choice for MIS provided a there is a Mohs surgeon skilled in reading melanocytic neoplasms on frozen-tissue sections, a highly skilled histotechnician, and a laboratory able to adequately perform the necessary special immunostains. The limitations of Mohs for MIS are the limited number of Mohs surgeons capable and/or comfortable performing Mohs for melanoma in situ. This is due to the difficulty in reading melanocytic histology on frozen sections, the lack of skilled technicians, and the high liability associated with recurrence.

Alternative treatments for melanoma in situ include radiation therapy and topical imiquimod. Radiation therapy has a longer history of use and follow-up but with greater tissue destruction and scarring. Topical imiquimod has variable predictability in responsiveness and clearance but with excellent cosmetic results. Both treatments may be considered for nonsurgical candidates or large, inoperable tumors. Additionally, imiquimod may be considered for unique scenarios in cosmetically sensitive areas.

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