
Melanoma on chronically sun-damaged skin: Lentigo maligna and desmoplastic melanoma



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There are multiple, genetically distinct pathways that give rise to melanoma. Melanomas on sun-damaged skin (MSDS), including lentigo maligna and desmoplastic melanoma, have distinct genetic profiles and are uniquely linked to chronic ultraviolet exposure. In this article, we discuss the etiologies of lentigo maligna and desmoplastic melanoma, emerging diagnostic adjuncts that might be helpful for accurately identifying these lesions, and the clinical relevance of their frequent co-occurrence. We present unique and overlapping features of these entities and discuss challenges in MSDS management, including margin assessment, excision, and the potential role of nonsurgical therapy. Last, we address the role of immunotherapy in invasive disease. Understanding MSDS as distinct from melanoma arising on intermittently sun-exposed or sun-protected skin will ultimately help optimize patient outcomes. (*J Am Acad Dermatol* 2019;81:823-33.)

Key words: dermoscopy; desmoplastic melanoma; lentigo maligna melanoma; melanoma; reflectance confocal microscopy; sun-damaged skin.

Primary cutaneous melanoma is usually categorized as superficial spreading, lentigo maligna (LM), nodular, or acral lentiginous on the basis of histologic morphology and the belief that all melanomas arise from a common pathway.^{1,2} However, since the divergent pathways model was described in 2003,^{3,4} genomic studies have supported the hypothesis that melanomas associated with chronic sun damage are genetically distinct from those arising on intermittently sun-exposed parts of the body.⁵⁻⁹ Current frameworks now divide melanomas on the basis of their genetic profile and ultraviolet (UV) association, with chronic sun-induced damage melanoma and desmoplastic melanoma (DM) representing distinct entities linked by their association with extensive UV exposure.¹⁰

Although LM and DM have differing genetic profiles, their frequent co-occurrence and shared relationship with UV exposure have significant clinical implications. With an aging population, the incidence of melanoma on sun-damaged skin

(MSDS) is increasing. Early diagnosis and an understanding of how MSDS differs from melanoma arising on intermittently sun-exposed or sun-protected skin is important to optimize patient outcomes.

MORPHOLOGY

The melanoma morphology typically associated with chronic sun exposure is lentigo maligna melanoma (LMM). The in situ form, LM, has been referred to as an infective senile freckle¹¹ or Hutchinson melanotic freckle¹² and can resemble a solar lentigo, pigmented actinic keratosis, or lichen planus-like keratosis.¹³ LM exhibits a long radial growth pattern^{14,15} and represents 79%-83% of all melanoma in situ (MIS) cases.¹⁶ Estimated rates of progression from LM to LMM vary widely; in a 1987 epidemiologic analysis, a 5% lifetime risk for invasion was estimated for a person given an LM diagnosis at age 45 years.¹⁷ Once dermal involvement occurs, LMM has the same prognosis as other

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invasive melanomas when adjusted for Breslow thickness.¹⁸

While rare, DM, a variant characterized by spindled melanocytes and dense collagenous stroma, is also linked to sun exposure. DM is commonly identified on chronically sun-exposed areas of the body, including the head, neck, and extremities. DM is often reported in association with overlying LM and LMM.¹⁹⁻²¹ In a 2013 study, 89% of DM lesions occurred on sun-exposed areas, and 83% were associated with MIS, most commonly LM.²² DM tends to be thick when definitively identified, possibly because of delayed diagnosis.¹⁹ It has a high local recurrence rate, is associated with neurotropism, and is less likely to metastasize to local lymph nodes despite its depth.²³ Prognosis for DM is controversial, even when adjusting for tumor thickness.²⁴⁻²⁷

EPIDEMIOLOGY

The incidence of MSDS is difficult to estimate. Registry data on MIS might be incomplete, thus underestimating LM incidence.²⁸ In a 2014 study, LM occurred at an estimated rate of 13.7 cases/100,000 person-years.²⁹ Evidence suggests that rates of LM and LMM are steadily increasing, with the incidence of LMM increasing faster than any other melanoma subtype.^{16,29,30} DM occurs in 2 per 1,000,000 individuals but is estimated to be increasing by 4.6% per year.²⁰ As the US population ages, it can be expected that variants of MSDS will continue to become more prevalent.³¹

PATHOGENESIS

Melanoma has one of the highest mutation rates of all human cancers,³² and mutation rates are especially high in MSDS due to chronic UV exposure.³³⁻³⁷ UV radiation (UVR) stimulates melanin production, drives melanocytes to enter the cell cycle, and induces oxidative damage, leading to the production of signature C>T and CC>TT photoproducts.^{38,39} UVR can cause mutations in hair follicle stem cells, contributing to LM development.⁴⁰ Cellular changes induced by UVR are potentiated by the immunosuppressive effects of UV light, resulting in decreased immune surveillance.⁴¹

On the basis of recent genomic analyses, the Cancer Genome Atlas Network categorized cutaneous melanomas into 4 genomic subtypes: mutant

BRAF, mutant *NRAS*, mutant *NF1*, and triple wild-type.⁴² Each mutation involves the mitogen-activated protein kinase pathway,^{10,43} a series of receptor tyrosine kinases that respond to growth factor stimulation and, when constitutively activated, promotes cellular proliferation and inhibition of apoptosis.⁴⁴ Although the Cancer Genome Atlas

Network subtypes represent the most common mutations in melanoma overall, their roles in MSDS are poorly understood. *BRAF* mutations, for example, occur in 50%-81% of primary cutaneous melanomas^{5,43,45} but are significantly less common in MSDS (11%-21%).^{5,7,46} Similarly, *NF1* mutations occur in 14% of all melanomas, but in a 2015 analysis, 93% of DMs analyzed were found to harbor *NF1*

mutations.⁴⁷ MSDS are also more likely to be associated with mutations in *KIT*, a tyrosine kinase involved in the mitogen-activated protein kinase, phosphoinositide 3-kinase, and signal transducer and activator of transcription 3 pathways.⁴⁸ *KIT* mutations occur in <2% of all melanomas⁴⁹ but are found in 25%-28% of MSDS.^{6,50} Multiple gain- or loss-of-function mutations have also been implicated in MSDS, including *CCND1*, a cyclin involved in cell cycle regulation, *MITE*, a transcription regulator of cellular proliferation, and *TP53*, a tumor suppressor gene.¹⁰ The genetic profile of MSDS has important implications for selecting targeted therapies.

CLINICAL PRESENTATION

The presentation of MSDS is variable, and LM, LMM, and DM might appear similar to benign lesions. Classically, LM and LMM occur on the face of older, male patients (Fig 1).^{11,12,28,51} A history of chronic solar damage and other UV-associated neoplasms is frequently present.^{5,12,52,53}

DM presents a clinical challenge as well (Fig 2).^{10,19,54} DM might be misdiagnosed as a benign entity and treated with cryotherapy, steroids, or laser therapy before diagnosis is confirmed. In one 2013 retrospective study, 27% of DM cases analyzed had been treated as benign lesions before biopsy and definitive diagnosis.²²

DERMOSCOPY

Dermoscopic characteristics of LM are well described in the literature and include asymmetric pigmented follicular openings, dark rhomboidal

CAPSULE SUMMARY

- Melanoma on sun-damaged skin is a unique entity that includes lentigo maligna, lentigo maligna melanoma, and desmoplastic melanoma.
- These melanomas often present subtly and can behave aggressively; thus, they require clinical acumen, the use of all available diagnostic tools, and appropriately aggressive treatment.

Abbreviations used:

AAD:	American Academy of Dermatology
DM:	desmoplastic melanoma
LM:	lentigo maligna
LMM:	lentigo maligna melanoma
MIS:	melanoma in situ
MMS:	Mohs micrographic surgery
MSDS:	melanoma on sun-damaged skin
NCCN:	National Comprehensive Cancer Network
RCM:	reflectance confocal microscopy
UV:	ultraviolet
UVR:	ultraviolet radiation

structures (angulated lines), and gray dot granules (peppering).⁵⁴⁻⁶⁰ Additional notable features include a follicular circle within a circle pattern, indicative of atypical melanocytes extending down adnexa,⁵⁷ and angulated lines. Gray pigmentation might be the most common finding in early LM and, in one 2015 analysis, was found in 88.6% of LM cases (Fig 3, A).^{59,60}

The dermoscopic features of DM are less well described. Typical melanocytic structures, such as globules or a pigment network, are observed in 43%-60% of DMs. However, in 2 recent studies, ≥ 1 melanoma-specific structure was present on dermoscopic exam in 100% of DMs analyzed. These included atypical or polymorphous vascular structures (81%-87%), crystalline structures (shiny white lines, 80%), an annular-granular pattern (24%-40%), and scar-like areas (8%-67%).^{23,54} Evidence of regression, such as gray dot granules, is also common in DM (Fig 3, B).²²

REFLECTANCE CONFOCAL MICROSCOPY (RCM)

RCM is a noninvasive tool that can be helpful for identifying MSDS. RCM can be used to image skin to a depth of 250 μm (superficial dermis), and its utility for the diagnosis of melanocytic lesions is well established (Fig 4).⁶¹⁻⁶⁵ The RCM criteria for LM and LMM diagnosis (sensitivity 85%, specificity 76%) have been previously described.⁶⁶

The use of RCM to identify DM has been studied, but unique features remain elusive. Cellular atypia and pagetoid spread are usually visible.⁶⁷ Dermal inflammation, spindle cells in the superficial dermis, and nucleated cells in the dermis can help distinguish DM from non-DM MIS, but these features are not present in all cases and might be seen in other lesions.²³

The limitations of RCM include the equipment cost, training requirement, and inability to visualize deeper than 250-300 μm , which is particularly disadvantageous in identifying dermal entities, such as DM.²⁸ In addition, pagetoid melanocytes

might be difficult to distinguish from dendritic Langerhans cells.⁶⁸

HISTOLOGY

Despite the fact that MSDS tends to appear on cosmetically sensitive sites, excisional biopsy with narrow margins, incisional biopsy of the most concerning or thickest part of the lesion, or excisional broad shave biopsy below the anticipated plane of the lesion are the gold standard for diagnosis.^{15,69} Because DM is associated with LM and LMM, site selection for a partial biopsy should be carefully considered to avoid missing a dermal component. The use of RCM to determine biopsy site has been used successfully in cases of facial LM and LMM,⁷⁰ and using RCM to determine the type and size of the biopsy required for proper sampling is recommended.

Both LM and DM present histopathologic challenges. LM is often subtle and might only show increased numbers of atypical melanocytes at the dermoepidermal junction, a finding also attributable to chronic sun damage.^{52,71} Margins might be difficult to delineate because lesion edges can blend with background melanocytic hyperplasia, prompting the recommendation that a control biopsy be taken from a clinically unaffected area.¹⁵ The most reproducible feature of LM is proliferation of atypical melanocytes at the dermoepidermal junction with underlying solar elastosis (Fig 5).^{11,13,51,71-73}

DM is defined by desmoplasia, but the diagnostic requirements are controversial. DM may be classified as pure or mixed, with pure DM defined by prominent desmoplasia throughout the tumor and mixed DM having a higher cellular density (Fig 5).⁷³ DM presents without an obvious associated MIS up to 30% of the time,¹⁹ and when it is paucicellular, it can be confused with a scar. There should be an increased index of suspicion and evaluation for DM in the biopsy specimen when LM and LMM has been excised.

Immunohistochemistry can be useful in both LM and DM. Staining patterns for LM are identical to those described for other types of cutaneous melanomas,^{11-13,72} but nuclear stains (microphthalmia transcription factor, SOX-10, soluble adenylyl cyclase) could play a larger role in defining margins.⁷⁴ For DM, staining patterns are variable and might be negative with standard melanocytic markers (human melanoma black 45 and melanoma antigen recognized by T cells 1).⁷⁵ As a result, S-100 is commonly used, although it might be positive in multiple types of dermal tumors. Wilms tumor 1, SOX-10, nestin, and p75 have all been proposed as equally sensitive to and much more specific than S-100.⁷⁶

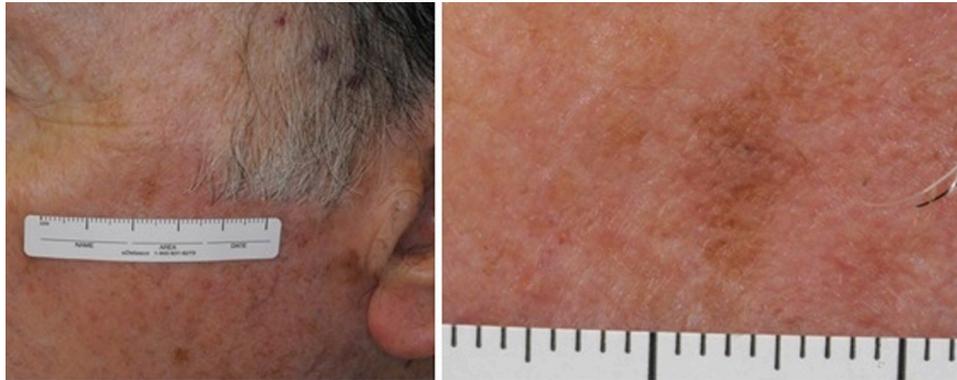


Fig 1. Lentigo maligna in 76-year-old man with history of multiple melanomas. On his follow-up exam, an irregular 5-mm pigmented macule on the left cheek was noted. Lentigo maligna and lentigo maligna melanoma are typically slow growing and present as flat, irregularly pigmented, brown-to-black macules with asymmetric borders. The edges might be obscured by other manifestations of chronic sun damage^{11,28,51}; regression is common.¹²



Fig 2. Desmoplastic melanoma appearing as a scar-like lesion. These lesions tend to arise on sun-damaged skin of the head and neck and are often hypopigmented or amelanotic.^{10,54} Desmoplastic melanoma might appear as a nodule, plaque, or scar-like lesion or be identified as a palpable component within a pigmented lesion.¹⁹

EXCISION

The primary goal in treating MSDS is surgical excision with histologically negative margins to eliminate the risks of residual tumor and recurrence.⁶⁷ This is challenging for multiple reasons. LM, LMM, and DM tend to occur in cosmetically sensitive areas, particularly the head and neck. In addition, because it is often difficult to determine the clinical margins of LM and skip areas have been described, surgical margins might be equivocal.⁷⁷ LM notoriously extends beyond the clinically apparent lesion; a Wood's lamp,⁶⁷ dermoscopy,⁷⁸ and RCM have all been utilized as tools in surgical planning.^{28,77,79-83} Last, nerve involvement in DM is common and, if extensive, can make surgical excision technically challenging.

A significant proportion (16%-32.5%) of tumors classified as LM on biopsy are upstaged to invasive

disease after definitive surgical excision and leveling of the specimen.⁸⁴⁻⁸⁶ In many studies, the 5-mm margin accepted in a 1992 National Institutes of Health consensus statement⁸⁷ was found to be too narrow for LM and LMM,^{78,84,88-91} and newer guidelines acknowledge that clinically measured surgical margins might need to be >5 mm.^{69,92} A variety of staged surgical techniques to ensure adequate margins have been studied,^{78,82,93-97} and Mohs micrographic surgery (MMS) currently shows the most promise.^{88,98-101} In a 2017 retrospective analysis of MIS patients, no difference was found between MMS and excision with respect to local recurrence and survival.¹⁰¹ Other studies have demonstrated improved outcomes with MMS for MIS of the head and neck.^{88,102,103} Determining the extent of margin clearance and reading melanocytic lesions on frozen section can be challenging,¹⁰⁴ but Mohs surgeons often now use immunohistochemistry stains to accurately identify melanocytes.¹⁰⁵ Slow Mohs (in which the tumor is embedded in paraffin, sectioned en-face, and reviewed by a dermatopathologist) results in similar rates of margin clearance and recurrence.^{106,107} Last, although time-consuming, RCM can be used intraoperatively to help determine lateral free margins and unexpected asymmetric extensions of the melanoma.⁸³ The recent American Association of Dermatology (AAD) guidelines suggests considering MMS for LM of the face, ears, or scalp, with the stipulation that if invasive disease is identified, complete excision and a formal pathology review should be performed.¹⁰⁸

NONSURGICAL TREATMENT MODALITIES

Although surgical modalities offer the best chance of cure for local disease, there is a limited role for

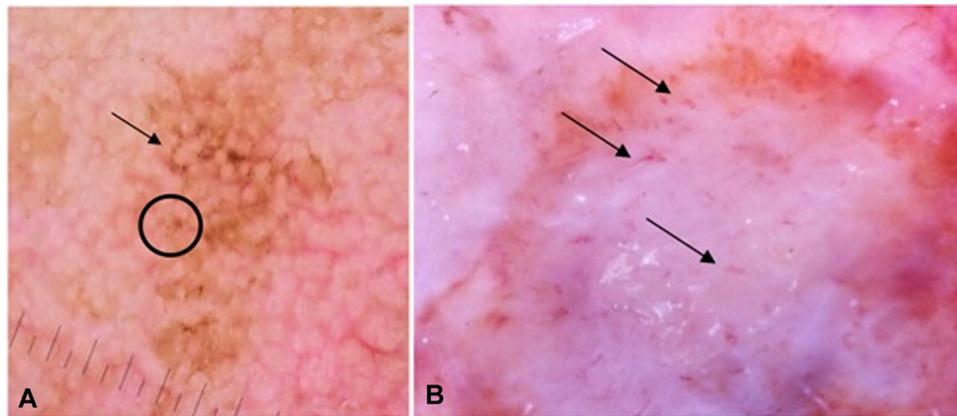


Fig 3. **A**, Dermoscopy of lentigo maligna demonstrating angulated lines (*arrow*) and gray dot granules (*circle*). **B**, Dermoscopy of desmoplastic melanoma revealing polymorphous blood vessels (*arrows*).

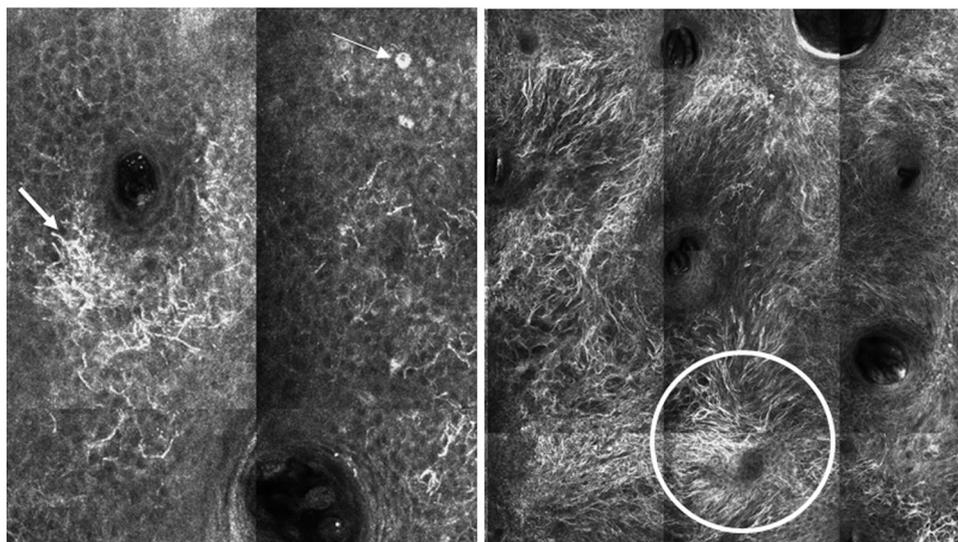


Fig 4. Reflectance confocal microscopy of lentigo maligna. Reflectance confocal microscopy images often demonstrate disrupted architecture or a honeycomb pattern of the epidermis and disruption of the dermoepidermal junction by atypical melanocytes. Extension of refractile dendritic cells down hair follicles might also be seen.⁶⁵ Our patient's lesion demonstrated at the spinous granular level bright pagetoid cells that are dendritic (*thick arrow*) and rounded (*thin arrow*) focally infiltrating the epidermis. At the dermoepidermal junction, there are sheets of dendritic cells in the pattern of tangled lines and around follicles (*circle*).

nonsurgical therapy in MSDS, especially for lesions in cosmetically sensitive areas or patients with comorbidities. Disadvantages of nonsurgical treatment include the risk of missing or undertreating invasive melanoma, higher local recurrence rates, the risk of subclinically positive margins, and the absence of long-term randomized clinical trial data.⁶⁹ When LM is treated nonsurgically, the possibility of an underlying DM should always be considered and ruled out. Imiquimod, a synthetic imidazoquinoline amine with inflammatory and antitumor effects, currently shows the most promise for topical

treatment of LM.¹⁰⁹ Published histologic clearance rates range 59%-75%,¹¹⁰⁻¹¹⁴ but protocols vary and follow-up periods are short.¹¹⁰⁻¹¹⁵ National Comprehensive Cancer Network (NCCN) recommendations reserve imiquimod for MIS patients with positive margins after optimal surgery.⁹² Cryotherapy,^{116,117} laser,¹¹⁸⁻¹²⁰ curettage and electrodesiccation,^{121,122} fluorouracil,¹²¹⁻¹²³ and photodynamic therapy¹²⁴ have also been studied.

Radiotherapy might play a role in the treatment of MSDS as primary therapy for in situ lesions when surgery is not an option or as adjuvant treatment after

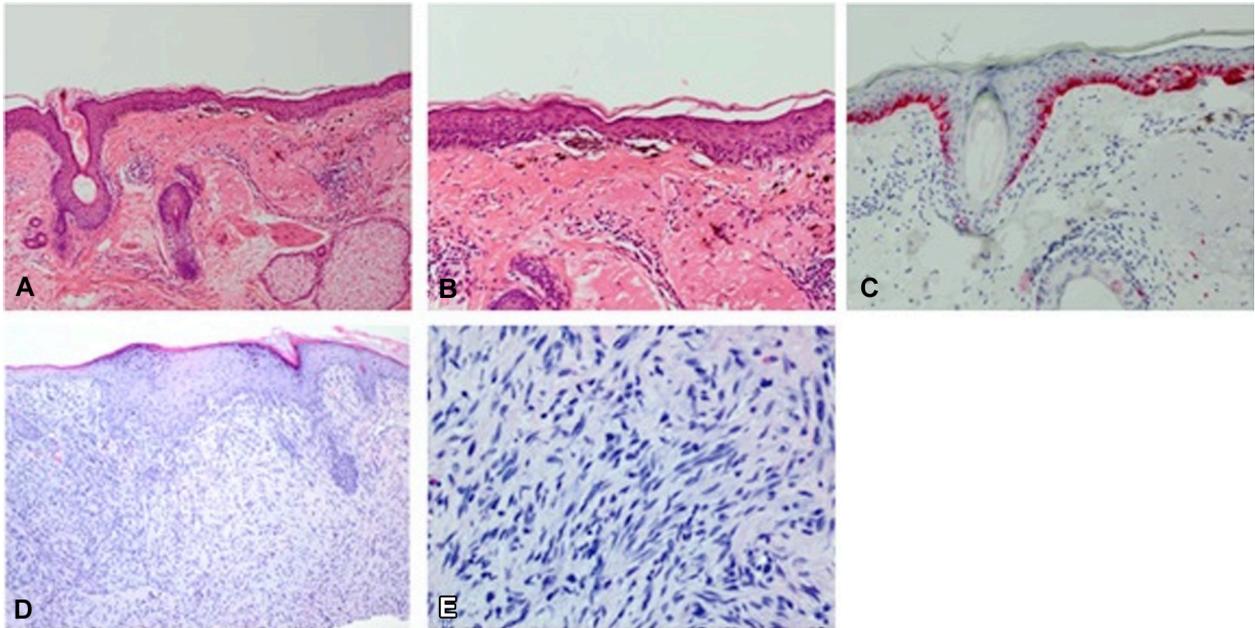


Fig 5. Histochemical characterization of lentigo maligna (A-C) and desmoplastic melanoma (D and E). A-C, There is no minimum number of melanocytes for diagnosis of lentigo maligna, but the presence of junctional nests (rather than single cells) has been suggested as a defining feature.¹⁵ Descent of melanocytes along adnexal structures and pagetoid spread are also highly concerning features.^{13,71,72} Our case demonstrated atypical single and nested melanocytic hyperplasia predominantly at the dermoepidermal junction and extending down adnexa, which is highlighted in C. D and E, Clusters of hyperchromatic spindle cells with elongated nuclei and lymphocytic aggregates are characteristic of desmoplastic melanoma and should raise suspicion and prompt the use of immunostaining.⁷³ (A, B, D, and E, Hematoxylin-eosin stain; C, S-100 immunostain: A and D, $\times 100$; B and C, $\times 200$; E, $\times 400$.) (Images courtesy of Dr Katalin Ferenczi, UCONN Dermatopathology Lab.)

excision.¹²⁵⁻¹³³ When used as primary treatment for LM, recurrence rates for radiotherapy can be as high as 14%, and there is little data on histologic clearance.⁶⁹ NCCN suggests that radiotherapy should be considered for patients who are not good candidates for surgery or who have positive margins after surgical resection. Adjuvant radiotherapy might also be appropriate for DM when there is extensive neurotropism limiting surgical options.⁹²

INVASIVE DISEASE

Once MSDS is invasive, workup and staging are largely the same as for other cutaneous melanomas. Current clinical guidelines do not distinguish between MSDS and other types of melanoma in terms of treatment, including surgical options.¹³⁰

The recommended margins for excision of invasive disease are based on high-level, randomized control trial data, although the 2019 AAD guidelines do acknowledge that many studies excluded head and neck sites.¹⁰⁸ Retrospective studies suggest that MMS might be used in the treatment of invasive melanoma,^{99,102,105,134} but follow-up periods are

short and prospective data are needed. Currently, both the NCCN and AAD caution against sub-1-cm margins, regardless of anatomic site or surgical technique.^{92,108}

The NCCN does acknowledge uncertainty regarding the probability and prognostic significance of a positive sentinel lymph node biopsy in DM.⁹² In a 2017 systematic review, rates of positive sentinel lymph node biopsy were found to be lower in DM than other types of melanoma, and nodal status was concluded to be an important predictor of survival. This is especially true for mixed DM, which has higher rates of micrometastases to regional lymph nodes.¹³⁵

KIT mutations are more common in MSDS, suggesting that tyrosine kinase inhibitors might play a larger therapeutic role. Early studies of tyrosine kinase inhibitors failed to show improvement in patients with metastatic disease, but these trials enrolled patients with all forms of melanoma and might have been skewed toward non-MSDS disease.¹³⁶ More recent trials of imatinib and second generation tyrosine kinase inhibitors that have

selected patients with MSDS or known *KIT* mutations are more promising.¹³⁷⁻¹⁴⁰ For DM, there is little data on effective immunotherapy because of its unique genetic profile and relative rarity. There has been minimal research to date on immunotherapy for *NFI*-associated tumors.¹⁴¹ However, DM demonstrates increased programmed cell death ligand 1 expression compared with other melanoma subtypes,¹⁴² and initial studies of programmed cell death 1 or programmed cell death ligand 1 blockade have shown promising results.

CONCLUSION

MSDS is a unique entity clinically, genetically, and therapeutically. Although LM and DM are genetically distinct, they are linked by their relationship to UV exposure and often co-occur. Their unique and overlapping features in the context of MSDS warrant additional study to improve patient outcomes.

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