Improved Diagnostic and Prognostic Strategies For Desmoplastic Melanoma

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Diagnosis of desmoplastic melanoma (DM) has long been a challenge for clinicians and pathologists alike. However, new clues and strategies are emerging to aid in early detection and diagnosis and to better determine prognosis.

DM is an uncommon variant of spindle cell melanoma, believed by some to represent a sarcomatoid variant of melanoma. It accounts for less than 4 percent of primary cutaneous melanomas, and the overall incidence rate has been reported to be 2.0 per million US persons, with an annual 4.6 percent increase.\(^1,2\)

The definition and classification of DM has evolved through the years. It was first used in 1971 by Conley, et al\(^3\) to refer to the association of invasive tumor cells with abundant stromal collagen. Eight years later, Reed and Leonard\(^4\) introduced the term neurotropic melanoma to describe a variant of DM with prominent neural involvement (neurotropism). Subsequently, in 2004, Busam, et al\(^5\) further classified DMs into pure DM (pDM) and mixed DM (mDM), based on the degree of desmoplasia (growth of dense connective tissue or stroma) present in the tumor; pDMs have more and mDMs less than 90 percent desmoplasia. The distinction between pDM and mDM appears to have clinical, therapeutic, and prognostic significance; pDM is associated with better overall survival (OS) and less frequent metastasis to regional lymph nodes than mDM. In contrast, improved diagnostic and prognostic strategies

From the Editors

In this issue of The Melanoma Letter, my co-editor, Dr. Marghoob, and my very close colleague, Dr. Jaimes, provide an excellent review of our current state of knowledge of the relatively rare and clinically challenging entity ‘desmoplastic’ melanoma. The phenomenon of desmoplasia can be superimposed on all four commonly considered ‘histogenic subtypes’ of melanoma (superficial spreading, lentigo maligna, acral/mucosal, and nodular), but as the authors note, is most frequently associated with lentigo maligna melanoma (LMM) and to a lesser extent with superficial spreading melanoma. The association of desmoplasia with LMM, chronic sun exposure, and advanced age is quite important, because it suggests that the incidence of desmoplastic melanoma can be anticipated to increase significantly with the aging of the population.

These melanomas are challenging to clinician and pathologist alike because they typically lack a melanoma-like appearance either clinically or histologically. Accordingly, a high index of suspicion is critical to their early detection. Even once correctly diagnosed, desmoplastic melanoma presents unique challenges in clinical management, given its propensity to involve nerves and recur locally. The authors explore these issues in detail along with the relatively recent observation that desmoplastic melanoma may differ in its biologic behavior based on the histologic extent and homogeneity of the desmoplasia. This distinction between ‘pure’ and ‘mixed’ desmoplastic melanoma is only recently becoming more widely appreciated, more consistently reported by pathologists, and more seriously considered in the management of these patients.

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mDM appears to display similar biologic behavior to other, non-desmoplastic melanoma subtypes, such as superficial spreading melanoma.

**Risk Factors**

DM has been associated with risk factors such as male gender, older age, chronic ultraviolet radiation exposure, and sun-damaged skin. In general, men have about twice the risk of developing DM as women, and this disparity grows even higher in the older population.

**Diagnosis**

Diagnosis of DM can be difficult, not only clinically but histologically. Clinically, early diagnosis of DM is challenging, since it often presents with a non-specific or non-descriptive morphology. While it may manifest a morphology commonly associated with malignant tumors (e.g., basal cell carcinoma, squamous cell carcinoma, and amelanotic melanoma), it is often mistaken for a benign lesion (e.g., scar, dermatofibroma, neurofibroma, cyst, sclerosing melanocytic nevus). In a recent study at eight dermatology clinics for high-risk patients, at least 27 percent of DM cases were initially diagnosed as benign lesions and treated with cryotherapy, lasers, or intralesional steroids before the definitive diagnosis of DM was confirmed by biopsy.

Efforts to enhance clinical recognition of suspected DM are ongoing. Improved knowledge of its risk factors as well as its clinical and dermoscopic characteristics may provide clues, leading to earlier biopsy.

### 1. Clinical and Dermoscopic Characteristics

DM often manifests features commonly associated with banal lesions, and frequently presents as amelanotic, firm, palpable, or indurated lesions with ill-defined borders. Since it most often appears on sun-damaged skin, especially on the head and neck, it is not uncommon for patients to present with a history of a non-specific or scar-like lesion located on chronically sun-damaged skin that developed without any antecedent trauma.

The primary clinical morphology of DM alone provides insufficient criteria for recognition. However, two case series have shown that dermoscopy may provide additional information indiscernible to the unaided eye; it thus can prompt clinical concern and further testing. Dermoscopically, DMs may appear as featureless lesions or may reveal one or more melanoma-specific structures, in particular atypical vascular structures, granularity, blue-white veils, atypical globules, and crystalline structures or atypical networks. In addition, dermoscopic features of lentigo maligna melanoma (LMM), such as annular granular pattern and polygonal lines, can be seen in up to one third of DM cases (Table 2). Jaimes, Chen, Dusza, et al. recently described the clinical and dermoscopic features of DM as a function of the histopathological subtypes. Their research demonstrated that pDM and mDM cannot be clinically distinguished from one another; however, with dermoscopy some differences were noted: pDMs more often reveal a monomorphic vessel pattern, with dotted vessels being the most common. In contrast, mDMs tend to present with a polymorphous vascular pattern and a vascular blush.

Since DMs have a prominent dermal stromal component, palpation remains an important part of the clinical examination. Accordingly, DM should be considered in the differential diagnosis of any firm lesion encountered on chronically sun-damaged skin, even if under dermoscopy it appears to be featureless. In addition, since DMs can be associated with LMM, all clinically suspect LMMs should also be palpated to ensure there are no subcutaneous firm nodules within. For any such firm areas discovered, if a benign diagnosis cannot be assured, a biopsy should be performed. Furthermore, if a firm lesion also reveals any of the dermoscopic structures described in Table 2, a biopsy should be strongly contemplated.

### 2. Histopathology of DM

On routine hematoxylin and eosin-stained sections, DMs are characterized by the presence of an invasive melanoma with abundant collagenous matrix. Usually, pDMs are pauci-cellular with a prominent component of desmoplasia throughout the majority of the tumor (>90 percent). In contrast, mDMs have a higher cell density, which may be observed throughout the tumor, or

<table>
<thead>
<tr>
<th>Gender (male:female)</th>
<th>DM:7 LMM:35,36</th>
<th>SSM:35-37</th>
<th>Nodular:36,37</th>
<th>Acral:36,38</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>66</td>
<td>60.7 - 67.5</td>
<td>44.8 - 53.3</td>
<td>56.4 - 62.3</td>
</tr>
<tr>
<td>Sun exposure link</td>
<td>Chronic</td>
<td>Chronic</td>
<td>Intermittent</td>
<td>Minimal to none</td>
</tr>
<tr>
<td>Location</td>
<td>Sun-damaged skin, in particular head and neck, followed by extremities and trunk</td>
<td>Sun-damaged skin, in particular head and neck, followed by upper extremities</td>
<td>Intermittently sun-damaged skin, such as back, followed by shoulders and lower extremities</td>
<td>Any site</td>
</tr>
<tr>
<td></td>
<td>Volar skin of palms and soles, nails</td>
<td></td>
<td></td>
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Table 1. Risk Factors for Desmoplastic Melanoma and Non-desmoplastic Melanomas

DM: desmoplastic melanoma; LMM: lentigo maligna melanoma; SSM: superficial spreading melanoma
may manifest as nodules of solid spindle and/or epithelioid melanocytes against a background of classic pauci-cellular DM.

In approximately one third of DMs, there is no identifiable in situ melanoma, and histopathologic recognition of the malignant dermal spindle cells may be challenging. DMs associated with an in situ melanoma in the epidermis and/or follicular epithelium are easier to recognize histopathologically. LM is the most common type of melanoma associated with DM, followed by superficial spreading melanoma (SSM). It has been suggested that mDMs may be easier to recognize clinically, based on the presence of a superficial component consisting of either an LM or an SSM. In contrast, early pDMs may be relatively inconspicuous, since these tumors usually appear as dermal nodules or plaques and generally lack epidermal clues such as pigmentation.

Immunohistochemical studies are often needed for optimal assessment of tumor thickness and to distinguish DMs from non-melanocytic mimickers. S-100 is one of the most valuable diagnostic markers for the disease. However, caution is warranted when evaluating scars for possible residual DM. Scars can contain S-100-positive cells, which may be confused with DM; however, these S-100 positive cells tend to be scattered and isolated in scars, whereas they are strongly positive in DMs. Tumors of Schwann cells, such as Schwannoma, neurofibroma, or malignant peripheral nerve sheath tumors, cannot be distinguished from DM by S-100. Other immunohistochemical studies that can be useful in select cases include antibodies, nerve growth factor receptor, and Sox 10. Other melanocyte differentiation antigens, such as gp100, Melan-A/Mart-1, tyrosinase, and microphthalmia transcription factor are usually negative in DM.

### Table 2. Dermoscopic Structures Seen in Desmoplastic Melanomas

<table>
<thead>
<tr>
<th>Dermoscopic structure</th>
<th>Definition</th>
<th>Schematic illustration</th>
</tr>
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<tbody>
<tr>
<td>Atypical vascular structures</td>
<td>Serpentine vessels, dotted vessels, polymorphous vessels (2 or more vessel morphologies), vascular blush and/or red globules</td>
<td>![Schematic illustration of atypical vascular structures]</td>
</tr>
<tr>
<td>Granularity, also known as peppering</td>
<td>Tiny, blue-gray granules</td>
<td>![Schematic illustration of granularity]</td>
</tr>
<tr>
<td>Blue-white veil</td>
<td>Confluent blue pigmentation with an overlying white “ground glass” haze</td>
<td>![Schematic illustration of blue-white veil]</td>
</tr>
<tr>
<td>Atypical globules</td>
<td>Multiple dots and/or globules of different size, shape and color, asymmetrically and/or focally distributed within the lesion</td>
<td>![Schematic illustration of atypical globules]</td>
</tr>
<tr>
<td>Crystalline structures, also known as shiny white lines or streaks</td>
<td>Shiny, white linear streaks that are often oriented parallel or orthogonal to each other. This structure is more conspicuous with polarized light dermoscopy.</td>
<td>![Schematic illustration of crystalline structures]</td>
</tr>
<tr>
<td>Atypical network</td>
<td>Increased variability in the width of the network lines, their color and distribution. The hole sizes also have increased variability. The network lines may end abruptly at the periphery.</td>
<td>![Schematic illustration of atypical network]</td>
</tr>
<tr>
<td>Annular granular pattern</td>
<td>Blue-gray or black granules and dots situated around follicular openings. The pigment around the adnexal openings often appears to be asymmetrically distributed, creating asymmetric follicular openings.</td>
<td>![Schematic illustration of annular granular pattern]</td>
</tr>
<tr>
<td>Polygonal lines</td>
<td>Dark brown to blue-gray interfollicular pigment that manifests as lines oriented in a zig-zag pattern. These lines eventually form rhomboidal structures, which are commonly seen in LMM.</td>
<td>![Schematic illustration of polygonal lines]</td>
</tr>
<tr>
<td>Featureless</td>
<td>No structures or vessels are observed.</td>
<td>![Schematic illustration of featureless]</td>
</tr>
</tbody>
</table>
DMs, especially deeply infiltrating tumors located in the head and neck region, can infiltrate and extend along nerves (neurotropism). Neurotropic DMs (NDM) have been associated with deeper tumors, greater mitotic activity, local infiltration, multiple recurrences, and more metastases than DMs without neurotropism. When NDM involves the head and neck region, it may give rise to trigeminal and facial nerve neuropathies, and may result in higher rates of CNS metastases due to direct tumor extension. As a result, some have advocated adjuvant radiation therapy to improve local control.

3. Molecular findings

There is a paucity of information regarding the molecular profile of DM. Some studies have demonstrated a decrease in the expression of genes involved in melanin synthesis and increased expression of the glycoprotein clusterin, which is involved in physiological processes such as cell adhesion and tissue and fibrous remodeling. Unfortunately, fluorescence in situ hybridization has had limited diagnostic value in differentiating DM from benign melanocytic lesions. However, array-comparative genomic hybridization may prove helpful in select cases – for example, in distinguishing DM from sclerosing Spitz nevus through detection of a copy number gain of chromosome 11p in the absence of any other chromosomal changes. Such a finding would support the diagnosis of a benign nevus and, for all practical purposes, exclude the diagnosis of DM.

Prognosis

Five-year and 10-year DM-specific survival have been reported to be 84.8 and 79.2 percent respectively, with five-year OS between 67 percent and 89 percent. Factors associated with an increased risk for DM-specific death include male gender, advancing age, and location on the head or neck.

Whether the prognosis of DM is more or less favorable than for non-DMs remains unclear. Some studies have reported no significant difference in patient survival rates. Other studies have shown a poorer prognosis for DM while still others have demonstrated a more favorable prognosis for DM compared to non-DMs of similar thickness. Some studies have even suggested that desmoplasia may confer better survival for patients with tumors greater than 4 mm.

The classification of DMs into the two histologic subtypes (pDM and mDM) has demonstrated prognostic differences in disease-free survival. Patients with mDM have shown a 3.5-fold greater risk for metastasis or death, and a shorter time to recurrence, while pDMs have a lower frequency of regional lymph node involvement (1 percent) as compared with mDM (10 percent) or other melanoma subtypes (6 percent; P < 0.05, pDM vs. other types).

The impact of neurotropism on survival continues to be studied. Some researchers have shown that NDM is associated with a 30 percent decrease in 8-year survival, while others have reported no association of neurotropism with a worse OS, despite the observation of a higher local recurrence rate in patients with NDM.

**Sentinel Lymph Node Biopsy (SLNB)**

The impact of regional lymph node status on the survival of patients with DM remains uncertain and somewhat controversial. Regional lymph node involvement is reported in 0 to 18.8 percent of cases, which is less frequent than observed for other cutaneous melanomas. Unlike non-DMs, the nodal status of patients with DMs does not appear to predict prognosis, with the 5-year OS being virtually the same for node-positive and node-negative patients (65 percent for node-negative, 64 percent for node-positive, p = 0.86). Nevertheless, some studies show that the risk of death is higher for patients with DM-positive lymph nodes (95 percent CI: 1.94-4.65). These inconsistencies may be due to differences in definitions used for selecting DM cases for inclusion in studies, or to the use of data acquired prior to our understanding of the differences between pDM and mDM.

Overall, the consensus of experts in the field is that the risk of developing nodal involvement in DM is in fact lower than for patients with non-DM melanoma. Given this lower risk and the questionable prognostic value of knowing the patient’s SLNB status, the utility of SLNB in management of DM patients has been brought into question, with some authors now recommending against routine SLNB. This is particularly true for patients with pDMs, since significant differences in lymph node positivity have been observed between patients with pDM and those with mDM (1.4 percent in pDM patients compared to 18.5 percent in mDM patients). In fact, Mohabati, et al recently reported that staging pDMs of the head and neck by SLNB may not be necessary, given the preponderance of negative SLNBs and the low incidence of both lymphovascular invasion and recurrence.

Weighing all the facts, many have suggested that rather than eliminating SLNB altogether, selective SLNB should still be considered and encouraged in patients with mDM, as well as in pDM patients with additional high-risk factors, such as younger age, presence of neurotropism, high mitotic rate, and tumor ulceration.  

**Distant Metastases**

Systemic metastasis occurs in 7-44 percent of DM cases, with lung, liver, and bone the most commonly involved.
areas. Risk for distant metastasis can vary depending on histopathological type, the risk higher for patients with mDM than for those with pDM.

Management

Wide Local Excision (WLE) remains the main line of treatment for DM. The extent of surgical resection, independent of tumor thickness, has been shown to be a predictor for survival. Patients undergoing WLE with margins greater than 1 cm have a better OS than those undergoing excisions of less than 1 cm (67 percent vs. 60 percent; p=0.029). In addition, wide margins can reduce the rate of local recurrence resulting from persistent disease present focally near the excision margin and/or along nerves (neurotropism). The recurrence rate is as high as 20 percent in neurotropic DM cases vs. only 6.8 percent in non-neurotropic DM cases. It has also been shown that DMs excised with margins <1 cm have a higher rate of local recurrence than those excised with margins >2 cm. Maurichi, et al compared outcomes with different surgical margins based on histologic type, in both thin (<2 mm) and thick (>2 mm) pDMs and mDMs. Thin pDMs excised with 1 cm margins had a higher rate of recurrence and worse 5-year OS (60 percent versus 85.2 percent, P=0.014) than those treated with 2 cm margins. Patients whose thick pDMs were excised with 2 cm margins had similar survival to patients whose thin pDMs were excised with 2 cm margins (86.6 percent versus 85.2 percent). Finally, the mortality risk in patients with mDM increased according to their stage but was independent of width of excision margins, suggesting that the behavior of mDM is similar to that of non-desmoplastic melanomas. Hence, to minimize the risk of local recurrence and metastasis, WLE with clear margins is recommended for both subtypes of DM, and whenever feasible, a 2 cm margin appears to offer the highest cure rates.

However, there are cases where wide margins and deep excisions are not feasible, for example with DMs that are deeply infiltrating or located in cosmetically, structurally, or functionally sensitive areas such as the periorbital or periocular regions of the face. In these circumstances, adjuvant radiation therapy may improve local control of the disease. There is some evidence that adjuvant radiotherapy may provide added value for DMs at high risk for local recurrence, including tumors excised with narrow margins, those removed with positive excision margins, or those with neurotropism. However, given the limited data about adjuvant radiation therapy’s role in DM, the available evidence remains somewhat controversial, and the most appropriate dose, fractionation, and target volume of radiation remain to be elucidated. Ongoing prospective studies on adjuvant radiation therapy for DM will likely clarify its role in management of the disease.

Finally, since there are scarce follow-up data pertaining to the management of patients with distant metastatic DM, the role for systemic therapies with medications such as ipilimumab remains to be determined.
Conclusion
Although DM can be a diagnostic challenge for clinicians and pathologists, certain clues may improve detection and aid in diagnosis of these tumors. For instance, diagnosis of DM should be considered when evaluating non-specific, scar-like lesions displaying irregular vessels under dermoscopy, or when a dermal firm nodule is noted during palpation of a suspected LMM. Once a DM is diagnosed, the pathologic distinction between pDM and mDM should be documented, since this information enhances management decisions and provides prognostic information. While routine SLNB may not be necessary for pDMs, it should be discussed with patients and considered for those with additional high-risk features. To reduce local recurrence, WLE with clear margins is recommended, and whenever feasible, 2 cm margins are ideal. Adjuvant radiotherapy should be considered for tumors at high risk for local recurrence. We remain optimistic that future studies will improve our current knowledge and understanding of the biology of DMs. This in turn will likely lead to more accurate diagnosis and help to target therapies for this malignancy.

References