J Cutan Pathol 2009: 36: 425–432
doi: 10.1111/j.1600-0560.2008.01058.x
Blackwell Munksgaard. Printed in Singapore

Journal of
Cutaneous Pathology

Continuing Medical Education Article

Subclassification of desmoplastic melanoma: pure and mixed variants have significantly different capacities for lymph node metastasis

Background: There is disagreement about the behavior and optimal management of desmoplastic melanoma (DM), particularly regarding the incidence of lymph node (LN) involvement. Recently, investigators have noted the frequently heterogenous histologic composition of DM and have found significant differences between pure desmoplastic melanoma (PDM) (≥90% comprised of histologically typical DM) and mixed desmoplastic melanoma (MDM) [≥10% DM and >10% conventional melanoma (CM)].
Method: We reviewed 87 cases of DM comparing the histologic and clinical features of PDM (n = 44) to MDM (n = 43).
Results: At surgical staging, there were LN metastases in 5 of 23 (22%) MDM patients, whereas all 17 PDM patients had negative LN biopsies (0%) (p = 0.04). PDM was less often clinically pigmented (36% vs. 67%) and had a lower mean mitotic index (1.3 vs. 3.0).
Conclusions: There are differences between PDM and MDM, the most important of which is the incidence of LN involvement. Our findings support the clinical utility of classifying DM into pure and mixed subtypes because the negligible rate of nodal involvement in PDM does not support the routine performance of sentinel LN biopsy in this subgroup of melanoma patients. In contrast, the incidence of LN involvement in MDM is comparable to that of CM.

George E, McClain SE, Slingluff CL, Polissar NL, Patterson JW. Subclassification of desmoplastic melanoma: pure and mixed variants have significantly different capacities for lymph node metastasis. J Cutan Pathol 2009; 36: 425–432. © 2008 Blackwell Munksgaard.

Evan George[1], Susannah E. McClain[2], Craig L. Slingluff[3], Nayak L. Polissar[4] and James W. Patterson[5,6]

[1]Department of Pathology, University of Washington, Seattle, WA, USA,
[2]Department of Dermatology, University of Maryland, Baltimore, MD, USA,
[3]Department of Surgical Oncology, University of Virginia Medical Center, Charlottesville, VA, USA,
[4]The Mountain-Whisper-Light Statistical Consulting, Seattle, WA, USA,
[5]Department of Pathology and
[6]Department of Dermatology, University of Virginia Medical Center, Charlottesville, VA, USA

Evan George, MD, Department of Anatomic Pathology, University of Washington Medical Center, PO Box 356100, 1959 NE Pacific Street, Seattle, WA 98195, USA
Tel: 206 598 6400
Fax: 480 247 5798
e-mail: evang9@u.washington.edu

Accepted for publication April 14, 2008

Desmoplastic melanoma (DM) has challenged both pathologists and clinicians since it was first recognized as a distinct entity by Conley et al. [1] in 1977. This report of seven patients and subsequent publications by other investigators emphasized adverse features of DM including delayed diagnosis, deep invasion, propensity for neural invasion, frequent local recurrence and eventually distant metastases.[1–3] More recently, studies that analyzed prognostic variables in a multivariate manner suggest that DM may have a more favorable prognosis than conventional melanoma (CM) when controlling for established prognostically significant variables.[4–7]

The literature reveals substantial variation in the frequency of lymph node (LN) involvement in DM, with reports ranging from 0% to 15%.[8–13] Since the

This study was presented in part at the Annual Scientific Meeting of the American Society of Dermatopathology in Baltimore, MD, USA, October 20, 2007.

1990s, the sentinel lymph node (SLN) biopsy procedure has been widely incorporated into the initial management of melanoma patients; hence, an accurate estimation of the likelihood of LN metastasis in DM patients has become relevant to clinical management.

Recently, Busam and colleagues have emphasized that DM specimens frequently show histologic heterogeneity, and individual neoplasms often have areas with the histologic features of CM (e.g. epithelioid cell or spindle cell) combined with areas showing the classic histologic features of DM.[7,14] The latter category of tumors has been referred to as 'mixed desmoplastic melanoma' (MDM) or 'combined desmoplastic melanoma'. These investigators postulated that differences in clinical behavior between 'pure desmoplastic melanoma' (PDM) and 'MDM' might account for the wide variation in the reported incidence of LN involvement as well as disagreement regarding the overall prognosis for DM relative to that of CM. Well-defined, qualitative and quantitative criteria were proposed: for PDM, classic DM histology had to constitute at least 90% of an individual neoplasm. Neoplasms with greater than 10% but less than 90% classic DM histology in combination with greater than 10% CM histology were classified as MDM.[7,14] Utilizing these criteria, investigators of two large institutions have found a higher incidence of LN metastasis in MDM. Both also found a higher survival rate for PDM compared with MDM.[14–16]

Whether the clinical behavior of so-called 'neurotropic melanoma' (NM) differs significantly from that of ordinary DM has also generated some debate. This form of melanoma is comprised entirely or predominantly of neuromatous-appearing elements and currently is considered a variant of DM by most authorities.

The objectives of this study were to review our institution's experience with DM, to apply strict histologic criteria for subclassification into PDM or MDM and to compare the clinical presentation, incidence of LN metastasis, histopathologic composition of metastases, and survival in the two groups. A secondary objective was to identify cases of NM and calculate the incidence of LN involvement.

Materials and methods

Selection of subjects

This study was approved and granted a waiver of patient consent by the Investigational Review Board of the University of Virginia Health System (Charlottesville, VA, USA). Patients with a diagnosis of DM or NM who received care or consultation services from the University of Virginia Health System between 1980 and 2005 were identified from the surgical pathology archives and the surgical oncology database maintained by one of the authors (C. L. S.). Cases of melanoma in which desmoplastic features or neurotropic features were mentioned in the histopathologic diagnosis were also reviewed.

Histopathologic criteria and prognostic variables

To be included in this study, representative histologic sections from the patient's primary melanoma had to be available for review by the authors. At least 10% of the tumor had to exhibit classic histology of DM. **The histology of classic DM was defined as follows: a dermal-based, paucicellular proliferation of atypical spindle cells in a sclerotic or neuromatous stroma with evidence of melanocytic differentiation (either immunohistochemical evidence or histologic evidence of an associated conventional-appearing intraepidermal melanocytic neoplasm)** (Fig. 1). Areas with histologic features similar to those of peripheral nerve sheath neoplasms were accepted as part of the morphologic spectrum of classic DM histology for purposes of this study (Fig. 2). **Nests of epithelioid melanocytes or compactly arranged groups of atypical spindle cells were interpreted as CM histology** (Fig. 3). Areas with cellular density intermediate between that of CM and that of typical DM were categorized as 'borderline cellularity' (BC). Cases with predominance of BC histology were excluded. Initially, histologic sections from a representative sample of cases were reviewed together by two authors (E. G. and J. W. P.) to validate reproducibility of the previously published criteria for PDM and MDM.[14–17] Thereafter, all available slides pertinent to each melanoma patient were reviewed by one author (E. G.).

For neoplasms exhibiting more than one histologic pattern (Fig. 4), the relative proportion of classic DM, NM, BC and CM were determined semiquantitatively for each case based on histologic examination of slides from the primary neoplasm. For tabulation purposes, areas of NM were considered equivalent to areas of classic DM. Based on this estimate, cases were initially segregated into three groups: PDM with at least 90% DM; mixed desmoplastic melanoma, desmoplastic melanoma predominant (MDM-DMP) with DM at least 50% but less than 90%; mixed desmoplastic melanoma, conventional melanoma predominant (MDM-CMP) with DM constituting greater than 10% but less than 50% of the primary neoplasm. After initial evaluation of data showed no significant differences between MDM-DMP and MDM-CMP, cases from these two groups were consolidated into a single group designated 'MDM'.

Additional histologic variables that were evaluated include Breslow thickness, Clark's level of invasion, mitotic index (the number of mitotic figures per square millimeter expressed in single digit whole numbers and derived by counting mitoses in five

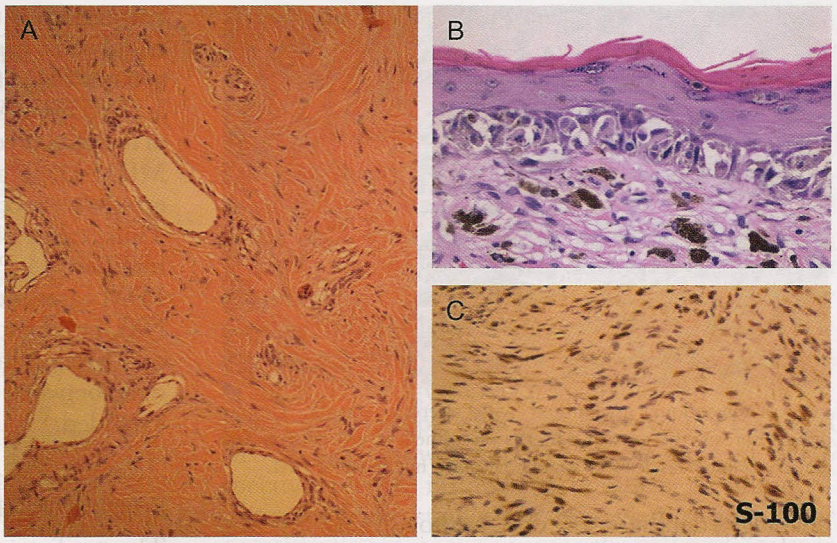

Fig. 1. Classic desmoplastic melanoma. A) Mildly atypical spindle cells in a dense, fibrous matrix. B) Overlying epidermis showing melanoma *in situ*. C) S-100 immunoreactivity in the dermal spindle cells.

consecutive high power fields in the most mitotically active area), vascular invasion (including either lymphatic vessels or blood vessels), ulceration, neural or perineural invasion, regression and final margin status. A positive margin was defined as invasive melanoma present at the inked margin. If invasive melanoma did not extend to the inked margin but was within two millimeters, this was considered a close margin. The presence of perineural or intraneural invasion was noted. If three or more nerve bundles were involved, this was considered 'extensive neural invasion'.

LN evaluation

If available, sections of LNs, regional metastases and distant metastases were also reviewed. Most SLNs were examined according to the following protocol. Each node was subsectioned into thin slices and entirely submitted for histologic processing. From each paraffin block, at least one hematoxylin and eosin-stained section and two immunohistochemically stained sections were prepared from a total of at least three histologic levels. The immunohistochemical evaluation of SLNs included antibodies detecting S-100 protein and at least one additional antibody-recognizing moieties commonly expressed by melanocytes (melan-A/Mart-1, HMB-45 and tyrosinase). A SLN was considered positive if melanoma cells were shown in either hematoxylin and eosin-stained slides or immunohistochemically stained slides.

Staging and clinical follow up

Staging results and clinical follow-up data were obtained from the patients' medical records including clinical notes and pathology reports, the surgical

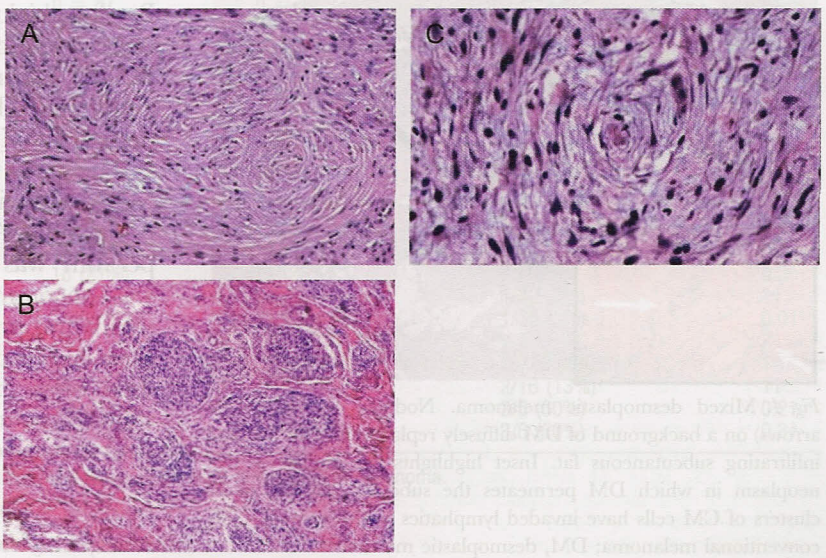

Fig. 2. Various neuromatous patterns. A) Concentrically arranged spindle cells in a fibrous matrix vaguely resembling neural structures. B) Neoplastic spindle cells within peripheral nerve bundles. C) Wavy nuclei in a loose fibrillar matrix resembling peripheral nerve sheath tumor.

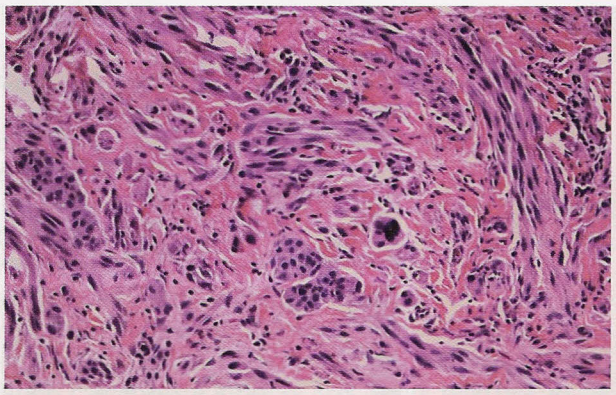

Fig. 3. Conventional melanoma with sclerotic stroma. Despite diffuse fibrosis, the growth patterns of epithelioid cell clusters and densely cellular fascicles of spindle cells are not those of DM.

oncology database of one author (C. L. S.), the University of Virginia Health System cancer registry and the Virginia State Department of Health cancer registry.

Statistical analysis

For statistical comparisons, the chi-squared test or Fisher's exact test were used for testing the association between two categorical variables. The two-sample *t*-test, assuming unequal variances, was used to compare continuous variables between two groups, and the one-factor ANOVA or the Kruskal-Wallis test was used to compare continuous variables among more than two groups.

Results

Histopathologic review of primary lesions

After review of the histologic sections, 87 cases fulfilled criteria for inclusion. Based on semiquantitative estimation of the histologic composition of primary neoplasms, cases were initially segregated into three groups: PDM (44 patients), MDM-DMP (21 patients) and MDM-CMP (22 patients). After initial evaluation of the data revealed no significant differences between MDM-DMP and MDM-CMP, cases from these two groups were consolidated into a single group, 'MDM'. Thus, cases of PDM and MDM were balanced in number: 44 PDM and 43 MDM patients. The 44 PDM cases included eight neoplasms with features of NM, i.e. predominantly neuromatous histology. One case predominantly showed cellular density intermediate between CM and typical DM, and this case was excluded.

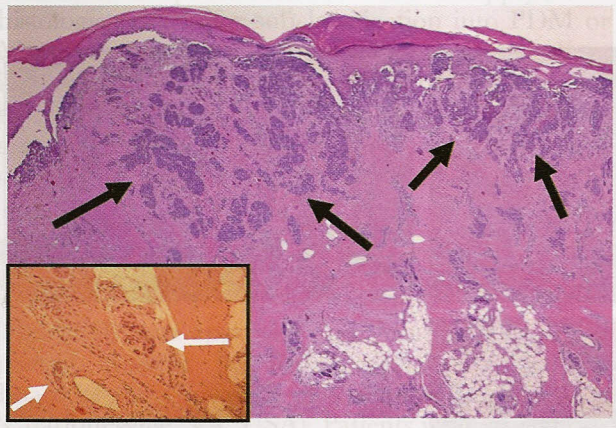

Fig. 4. Mixed desmoplastic melanoma. Nodules of CM (black arrows) on a background of DM diffusely replacing the dermis and infiltrating subcutaneous fat. Inset highlights the duality of this neoplasm in which DM permeates the subcutaneous fat, while clusters of CM cells have invaded lymphatics (white arrows). CM, conventional melanoma; DM, desmoplastic melanoma.

Demographics and clinical features

The median age was higher in PDM than in MDM (67 years vs. 60 years) (Table 1). There was a male predilection in all groups, which was most pronounced in PDM (M : F = 1.75). Anatomically, 61% of PDM arose on the head and neck compared with 44% in MDM. Clinical presentation as a pigmented lesion was nearly twice as frequent in MDM as in PDM (67% vs. 36%).

Pathology results

Histopathologic variables of established prognostic significance were evaluated by an E.G. as an integral part of the study's retrospective slide review (Table 2). In a significant number of cases, the neoplasm involved the full thickness of the biopsy sections available for review; therefore, the recorded Breslow thickness measurements and Clark's levels represent minimum values for a substantial portion of cases. In both PDM and MDM, the neoplasms were deeply invasive at the time of diagnosis, and most were either Clark's level IV or V. The minimum mean and median Breslow thickness were 3.4 mm and 2.5 mm in PDM, respectively, compared with 5.0 mm and 3.0 mm in MDM. Ulceration was not a common finding in either group but was seen more frequently in MDM than in PDM (12% vs. 7%).

The mean mitotic index was significantly higher in MDM than in PDM (3.0 vs. 1.3 mitoses per mm^2, $p = 0.002$). A mitotic index of two or more mitoses per mm^2 was frequently observed in MDM (37%) but was uncommon in PDM (7%). The incidence of perineural or intraneural invasion was high in both groups, but neural invasion was most frequent and most often extensive in PDM: 41% of PDM cases showed neural invasion and 25% had extensive neural invasion, defined as involvement of three or more nerve bundles in the reviewed histologic sections. MDM exhibited neural invasion in 28% of cases, which was extensive in 16%.

Table 1. Demographics and clinical characteristics*

	All patients	PDM (≥90% DM)	MDM (DM < 90%)	p Value
Total number of patients (n)	87	44	43	
Age	n = 86	n = 43	n = 43	0.02
Range (years)	29–95	37–95	29–81	
Median (years)	68	69	66	
Mean (years)	64	67	60	
Gender	n = 87	n = 44	n = 43	0.5
Female	35 (40%)	16 (36%)	19 (44%)	
Male	52 (60%)	28 (64%)	24 (56%)	
Anatomic region	n = 87	n = 44	n = 43	0.2
Head/neck	46 (53%)	27 (61%)	19 (44%)	0.11
Extremities	26 (30%)	10 (23%)	16 (37%)	0.14
Trunk	15 (17%)	7 (16%)	8 (19%)	0.7
Clinical appearance	n = 37	n = 22	n = 15	
Pigmented	18 (49%)	8/22 (36%)	10/15 (67%)	0.07
Primary treatment	n = 59	n = 27	n = 22	
WLE	57 (97%)	25/27 (93%)	32/32 (100%)	
Amputation	1 (2%)	1/27 (4%)	0/32	
WLE and radiation	1 (2%)	1/27 (4%)	0/32	

DM, desmoplastic melanoma; MDM, mixed desmoplastic melanoma; PDM, pure desmoplastic melanoma; WLE, wide local excision.
*For variables with more than two categories, such as anatomic site, the statistical significance is shown for a) a global comparisons among all categories and b) a comparison of each category (vs. all other categories combined).

The incidence of histologically identifiable invasion of lymphatic or blood vascular spaces was very low in PDM (2%) and more frequent in MDM (12%). Fully developed areas of regression were only rarely discernible (PDM – 0% and MDM – 2%). The presence of neoplastic cells at or in close proximity to the final surgical margins (either recorded in the initial pathology report or observed during this study) was more common in PDM than in MDM (21% vs. 3%, p = 0.01).

Immunohistochemistry

Immunoperoxidase studies had been performed in a significant number of cases as part of the initial diagnostic examination (Table 2). When available, these were reviewed by E.G. and immunoreactivity in the neoplastic cell population was scored as either positive or negative. If slides were unavailable for retrospective review, results were derived from the original pathology report if available. No significant immunophenotypic differences between PDM and MDM were shown; however, at the time of retrospective review, insufficient numbers of immunohistochemically stained sections were available for a systematic comparison among the various histologic patterns.

LN examination

Histopathologic evaluation of regional LNs was performed in 40 patients (Tables 3 and 4). The most common procedure was SLN biopsy. LN metastases were documented in 5/23 MDM patients (22%). In contrast, no LN metastases were identified in 17 PDM patients (0%). This difference was statistically significant (p = 0.04). Of the eight cases of PDM with predominantly neuromatous histology, five had been surgically staged by SLN biopsies, all of which were negative for metastases.

Table 2. Summary of pathologic findings

	All patients	PDM (≥90% DM)	MDM (DM < 90%)	p Value
Minimum Breslow thickness (mm)	n = 87	n = 44	n = 43	
Range	0.45–44.0	0.45–12	0.60–44	
Median	2.6	2.5	3.0	
Mean	4.2	3.4	5.0	0.2
Minimum Clark's level	n = 87	n = 44	n = 43	
Range	3–5	3–5	3–5	
Mean	4.4	4.5	4.2	0.3*
Ulceration	8 (9%)	3 (7%)	5 (12%)	0.3
Mitotic index (mitoses/mm^2)‡	n = 87	n = 44	n = 43	0.002*
≤1	68 (78%)	41 (93%)	27 (63%)	
≥2	19 (22%)	3 (7%)	16 (37%)	
Range	<1–25	<1–7	<1–25	
Mean	2.1	1.3	3.0	
Neural and vascular invasion	n = 87	n = 44	n = 43	
Vascular invasion	6 (7%)	1 (2%)	5 (12%)	0.11
Neural/perineural invasion	30 (34%)	18 (41%)	12 (28%)	0.2
Extensive neural/perineural invasion (≥3 foci)	18 (21%)	11 (25%)	7 (16%)	0.3
Regression	1 (1%)	0/44	1/43 (2%)	1†
Positive or close (≤2 mm) final surgical margin	7/59 (12%)	6/29 (21%)	1/30 (3%)	0.01*
Immunohistochemical reactivity				
S-100 protein	54/55 (98%)	29/30 (97%)	25/25 (100%)	1†
HMB-45	4/34 (12%)	2/18 (11%)	2/16 (13%)	1†
Mart-1/Melan A	3/8 (38%)	0/3 (0%)	3/5 (60%)	0.2†
Tyrosinase	5/16 (31%)	2/10 (20%)	3/6 (50%)	0.3†

DM, desmoplastic melanoma; MDM, mixed desmoplastic melanoma; PDM, pure desmoplastic melanoma.
*Kruskal-Wallis test.
†Fisher's exact test.
‡Mitotic index for individual cases expressed in single-digit whole numbers.

Table 3. Pathologic staging of nodal status: surgical procedure and results

	PDM, n = 44	MDM, n = 43
Procedure		
Any surgical LN staging	17 (39%)	23 (53%)
SLN biopsy	13 (77%)	16 (70%)
SLN biopsy and LN dissection	1 (6%)	4 (17%)
Procedure not specified	3 (18%)	3 (13%)
Results		
Average number of SLNs	2.8	2.5
Patients with positive LN	0 (0%)	5 (22%)*

LN, lymph node; MDM, mixed desmoplastic melanoma; PDM, pure desmoplastic melanoma; SLN, sentinel lymph node.
*p = 0.04 (PDM vs. MDM) (chi-squared test).

Histologic sections of involved LNs were available for the authors' review in three of the five MDM patients with positive nodes (Table 4). In all three cases, LN metastases exhibited CM histology and areas of classic DM histology were not observed. In one of the node-positive MDM cases for whom slides were not available for the authors' review, the original surgical pathology report indicated that rare clusters of atypical melanocytes were identified only in immunohistochemically stained slides from an SLN.

Pathologic examination of distant metastases

Histologic specimens from distant metastases were available for the authors' review in four patients (Table 4). This included one PDM patient with bone and lung metastases, and a needle core biopsy from the sacrum of this patient showed histologic features of classic DM. For three patients with MDM, histologic sections from metastases (adrenal, lung and brain) were available for review. In all three biopsy specimens, only CM histology was observed, unaccompanied by areas of classic DM.

Discussion

Since the initial description of DM by Conley in 1971,[1] this distinctive form of melanoma has generated both interest and consternation for pathologists as well as clinicians. The features most consistently emphasized in prior reports are the deceptively bland histologic appearance of DM frequently leading to misdiagnosis and the propensity for locally aggressive behavior manifested by a high local recurrence rate as well as frequent neural invasion. Although less frequently emphasized, DM also has a well-documented capacity for distant metastasis.[1–3,11,13,18]

The incidence of regional LN involvement at the time of initial management ranges from 0–15% in published clinical series, leading to disagreement regarding DM's ability to metastasize to LNs.[9–13,19–21] Addressing this is relevant to the management of patients with DM.

Recently, Busam, Hawkins and colleagues have called attention to the frequent coexistence of histologically conventional-appearing melanoma (CM) and DM within individual neoplasms.[7,14,15] Although this observation had been noted by previous authors, its clinical significance had not been systematically addressed.[5]

These authors hypothesized that the presence and relative quantity of CM might influence the clinical behavior of DM, accounting for the discrepant findings among previously reported clinicopathologic series.[7,14,15] Applying strict criteria to distinguish PDM from MDM, only 1 of 92 (1%) PDM patients had histopathologically documented nodal involvement at the time of initial management compared with 18% of MDM patients.[7,15] With longer clinical follow

Table 4. Summary of metastases and comparison of the histologic composition of primary neoplasms vs. metastases

Histology of primary					Metastatic sites				
Summary type	% DM	% SC	% EC	% BC	Location	SLN (+/total)	LND (+/total)	Path rereview by authors	Histology of metastases
MDM-DM	50	25	0	25	RLN	*	*	Yes	SC
MDM-CM	10	90±		0	RLN	2/2	0/2	Yes	SC/EC
MDM-CM	30	0	70	0	RLN	1/4	0/46	Yes	EC
MDM-DM	50	40	10	0	RLN	4/4	1/26	No	Not available
MDM-CM	20	80	0	0	RLN	1/1	0/10	No	Focal node involvement by IHC, described as rare clusters and single atypical melanocytes.
Summary type	% DM	% SC	% EC	% BC	Location	Location biopsied	Type of biopsy	Path rereview by authors	Histology of metastases
PDM	98	0	2	0	Lung, bone	Bone (sacrum)	Core needle	Yes	DM
MDM-DM	70	0	30	0	Brain, adrenal	Adrenal	Core needle	Yes	EC
MDM-DM	50	25	0	25	Lung	Lung	Core needle	Yes	SC
MDM-CM	40	0	60	0	Brain	Brain	Resection	Yes	EC

BC, borderline cellularity (between DM and conventional spindle cell melanoma); DM, desmoplastic melanoma histology; EC, epithelioid cell; LND, lymph node dissection; MDM-CM, mixed desmoplastic melanoma, predominantly conventional; MDM-DM, mixed desmoplastic melanoma, predominantly desmoplastic; PDM, pure desmoplastic melanoma; RLN, regional lymph node; SC, spindle cell; SLN, sentinel lymph node.
*Number of nodes not specified.
±90% Spindle and epithelioid cells.

up, the total incidence of regional LN metastasis increased to 2% for PDM and 44% for MDM.[15] Similarly, Pawlik et al. found positive SLN biopsies in 2% of PDM patients vs. 16% of patients with MDM.[16]

In this study, none of 17 PDM patients (0%) had positive LN biopsies, whereas 5 of 23 (22%) MDM patients had LN metastases at initial management ($p = 0.04$). We applied strict histologic criteria (at least 90% classic DM histology for PDM), similar to those utilized by Busam and others,[7,14,16,17] except that our study included cases with predominantly neuromatous stroma in the PDM group as this group of neoplasms, usually designated neurotropic melanoma (NM), is generally regarded as a variant of DM.[22] However, Busam et al. excluded such cases because some studies suggest that they may behave more aggressively than ordinary DM.[14,23] In this study, eight patients in the PDM group had predominantly NM histology (≥70% of primary neoplasm). Five of them had been staged using SLN biopsies, all of which were negative for metastatic melanoma. Although limited by the small number of NM cases, these findings support the view that NM and PDM have a comparably low risk for regional LN metastasis. Additional studies with larger numbers of NM cases are necessary for validation.

Compilation of data from this study and the above two previous reports [15,16], reveals a 1.3% (2 of 151 patients) incidence of LN involvement at the time of initial diagnosis for PDM compared with 18.5% (15 of 81 patients) for MDM if strict histologic criteria are applied (Table 5). Thus, histologic subclassification into pure and mixed variants appears to have clinical utility in the management of patients with DM. The significant incidence of LN involvement in MDM is comparable to that of CM, and the yield from SLN biopsy would probably be substantial. However, the very low incidence of LN metastasis in PDM suggests that SLN biopsies probably will have a very low yield in this group of patients.

Although criteria for recommending SLN biopsy vary slightly at different institutions, currently, the usual practice is not to perform SLN biopsy in thin melanoma of the conventional type because of the low incidence of LN metastasis, typically estimated in the range of 2–4%. This is slightly higher than the apparent incidence of nodal involvement in PDM (1–2%) according to the compiled data in Table 5. Thus, it would be logical for clinicians not to recommend SLN biopsy for PDM.

Regarding the metastatic potential of DM and its proposed subtypes, we also compared the morphologic composition of nodal and visceral metastases to that of the primary neoplasm. Based on individual experience, some authors have indicated that local recurrences of DM generally show typical DM histologic features, whereas LN metastases are usually comprised of CM with only rare examples of nodal metastases exhibiting the histologic features of DM.[14,24] Descriptions of the histology of distant visceral metastases are more variable; DM, CM or mixtures of both have been described. In this study (Table 4), histologic sections were available from three of five MDM cases with LN metastases, and CM histology unaccompanied by DM histology was observed in all three cases. Although limited by the small number of cases, these findings lend additional support to the view that PDM has minimal capacity for regional LN metastasis.

For one patient with PDM and distant metastases to lung and bone, a histologic specimen (needle core biopsy of the sacrum) was available for review and showed typical DM histology. Tissue specimens were also available from three MDM patients with distant metastases, all of which had CM histology. These findings suggest that both PDM and MDM have a capacity for distant metastasis, though the numbers are too small to compare their relative risks.

This study also compared various clinical and histopathologic features in PDM and MDM patients, summarized in Tables 1 and 2. One finding that may be of practical utility to dermatopathologists is a significant difference in mitotic rate. A mitotic index of two or more mitoses per mm^2 was uncommon in PDM (7%) but frequent in MDM (37%, $p = 0.002$). Thus, if frequent mitotic figures are observed, pathologists should be hesitant to make a diagnosis of PDM.

Initially, the objectives of this study included comparison of survival between PDM and MDM.

Table 5. Compiled regional LN surgical staging data for clinically node-negative PDM and MDM patients

Author	Number of PDM patients	Number and percentage of PDM patients with +RLN	Number of MDM patients	Number and percentage of MDM patients with +RLN
*Hawkins et al. (MSK)[15]	92	1 (1%)	39	7 (18%)
†Pawlik et al. (MDA)[16]	46	1 (2%)	19	3 (16%)
‡George et al. (UVA) (this study)	17	0	23	5 (22%)
Total	155	2 (1.4%)	81	15 (18.5%)

MDA, M. D. Anderson Cancer Center; MDM, mixed desmoplastic melanoma; MSK, New York Memorial Sloan-Kettering Cancer Center; PDM, pure desmoplastic melanoma; +RLN, regional lymph nodes positive for metastatic melanoma at the time of initial surgical staging; SLN, sentinel lymph node; UVA, University of Virginia Health System.
*The number of patients who were staged by SLN biopsy is not indicated.
†All patients in this study were staged by SLN biopsy.
‡SLN biopsy was the initial surgical staging procedure in greater than 80% of surgically staged patients.

However, clinical follow-up information was not available for many of our patients, precluding a statistically meaningful comparison of melanoma-specific mortality.

Conclusions

1. Pure desmoplastic melanoma (PDM) has minimal capacity for LN metastasis.
2. Subclassification of desmoplastic melanoma (DM) into pure and mixed variants has clinical utility: clinicians may be dissuaded from routinely recommending sentirel LN biopsies in patients with PDM. Nevertheless, several caveats should be recognized:
   (a) The interobserver reproducibility of this subclassification should be validated formally.
   (b) Given the frequently heterogenous histologic composition of DM, an unequivocal diagnosis of PDM should not be rendered on superficial biopsies or small partial biopsies.
   (c) Despite the presence of desmoplasia, pathologists should be reluctant to make a diagnosis of PDM if cellularity is dense or if mitotic activity is brisk (two or more mitoses/mm^2).
   (d) We and other investigators have occasionally encountered neoplasms with desmoplastic features but with cellular density intermediate between that of typical DM and that of conventional spindle cell melanoma.[25] Such neoplasms should not be placed in the PDM category until their clinical behavior is better delineated and histologic criteria are validated.
3. The scope of this study was limited to histologic observations and their correlation with clinical behavior so that subclassification of DM can be readily integrated into routine pathology practice. Nevertheless, the authors acknowledge that much remains to be learned about this intriguing form of melanoma and that future investigations, particularly at the molecular level, will probably advance our understanding.[26]

References

1. Conley J, Lattes R, Orr W. Desmoplastic malignant melanoma (a rare variant of spindle cell melanoma). Cancer 1971; 28: 914.
2. Reed RJ, Leonard DD. Neurotropic melanoma. A variant of desmoplastic melanoma. Am J Surg Pathol 1979; 3: 301.
3. Egbert B, Kempson R, Sagebiel R. Desmoplastic malignant melanoma. A clinicohistopathologic study of 25 cases. Cancer 1988; 62: 2033.
4. Carlson JA, Dickersin GR, Sober AJ, et al. Desmoplastic neurotropic melanoma. A clinicopathologic analysis of 28 cases. Cancer 1995; 75: 478.
5. Skelton HG, Smith KJ, Laskin WB, et al. Desmoplastic malignant melanoma. J Am Acad Dermatol 1995; 32: 717.
6. Spatz A, Shaw HM, Crotty KA, et al. Analysis of histopathological factors associated with prolonged survival of 10 years or more for patients with thick melanomas (>5 mm). Histopathology 1998; 33: 406.
7. Busam KJ, Mujumdar U, Hummer AJ, et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. Am J Surg Pathol 2004; 28: 1518.
8. Reiman HM, Goellner JR, Woods JE, et al. Desmoplastic melanoma of the head and neck. Cancer 1987; 60: 2269.
9. Jain S, Allen PW. Desmoplastic malignant melanoma and its variants. A study of 45 cases. Am J Surg Pathol 1989; 13: 358.
10. Su LD, Fullen DR, Lowe L, et al. Desmoplastic and neurotropic melanoma. Cancer 2004; 100: 598.
11. Livestro DP, Muzikansky A, Kaine EM, et al. Biology of desmoplastic melanoma: a case-control comparison with other melanomas. J Clin Oncol 2005; 23: 6739.
12. Posther KE, Selim MA, Mosca PJ, et al. Histopathologic characteristics, recurrence patterns, and survival of 129 patients with desmoplastic melanoma. Ann Surg Oncol 2006; 13: 728.
13. Cummins DL, Esche C, Barrett TL, et al. Lymph node biopsy results for desmoplastic malignant melanoma. Cutis 2007; 79: 390.
14. Busam KJ. Cutaneous desmoplastic melanoma. Adv Anat Pathol 2005; 12: 92.
15. Hawkins WG, Busam KJ, Ben-Porat L, et al. Desmoplastic melanoma: a pathologically and clinically distinct form of cutaneous melanoma. Ann Surg Oncol 2005; 12: 207.
16. Pawlik TM, Ross MI, Prieto VG, et al. Assessment of the role of sentinel lymph node biopsy for primary cutaneous desmoplastic melanoma. Cancer 2006; 106: 900.
17. Gyorki DE, Busam K, Panageas K, et al. Sentinel lymph node biopsy for patients with cutaneous desmoplastic melanoma. Ann Surg Oncol 2003; 10: 403.
18. Beenken S, Byers R, Smith JL, et al. Desmoplastic melanoma. Histologic correlation with behavior and treatment. Arch Otolaryngol Head Neck Surg 1989; 115: 374.
19. Jaroszewski DE, Pockaj BA, DiCaudo DJ, et al. The clinical behavior of desmoplastic melanoma. Am J Surg 2001; 182: 590.
20. Thelmo MC, Sagebiel RW, Treseler PA, et al. Evaluation of sentinel lymph node status in spindle cell melanomas. J Am Acad Dermatol 2001; 44: 451.
21. Berk DR, Johnson DL, Uzieblo A, et al. Sentinel lymph node biopsy for cutaneous melanoma: the Stanford experience, 1997–2004. Arch Dermatol 2005; 141: 1016.
22. Kossard S, Doherty E, Murray E. Neurotropic melanoma. A variant of desmoplastic melanoma. Arch Dermatol 1987; 123: 907.
23. Baer SC, Schultz D, Synnestvedt M, et al. Desmoplasia and neurotropism. Prognostic variables in patients with stage I melanoma. Cancer 1995; 76: 2242.
24. Bruijn JA, Mihm MC Jr, Barnhill RL. Desmoplastic melanoma. Histopathology 1992; 20: 197.
25. Skelton HG, Maceira J, Smith KJ, et al. HMB45 negative spindle cell malignant melanoma. Am J Dermatopathol 1997; 19: 580.
26. Busam KJ, Zhao H, Coit DG, et al. Distinction of desmoplastic melanoma from non-desmoplastic melanoma by gene expression profiling. J Invest Dermatol 2005; 124: 412.