Differing biologic behaviors of desmoplastic melanoma subtypes: Insights based on histopathologic, immunohistochemical, and genetic analyses

Kevin Yang, BS,[a] and Meera Mahalingam, MD, PhD, FRCPath[a,b]
Boston and West Roxbury, Massachusetts

Desmoplastic melanoma (DM) is an uncommon variant of melanoma that can be challenging to diagnose. Phenotypic variations in terms of the proportion of spindled cells and fibromucinous stroma have led to the subclassification of pure (>90% spindled cells) and mixed (<90% spindled cells admixed with epithelioid cells) histopathologic DM subtypes. This subclassification is not just semantic; several studies have underscored differences in clinical and prognostic behaviors of the subtypes. In this review, we parse the literature on DM subtypes with an emphasis on histopathologic, immunohistochemical, and genetic data to ascertain whether these factors influence and/or affect their differing biological behaviors. Demographics regarding age, location, and clinical behavior of the subtypes are detailed, as is the impact of dermoscopy as a diagnostic adjunct. Despite the plethora of markers used, our findings suggest that few differentiate between the DM subtypes. Differential expression of PD-L1 suggests that patients with the mixed subtype are likely better candidates for anti-PD/PD-L1 therapy. Significant differences between the subtypes in terms of neurofibromin expression and the frequency of *TERT* promoter mutations suggest that the subtypes have distinct genetic drivers. Thus, immunohistochemical and genetic analyses imply that these likely affect the biological behaviors of the DM subtypes. (J Am Acad Dermatol 2020;83:523-31.)

Key words: genetics; immunohistochemistry; mixed desmoplastic melanoma; pure desmoplastic melanoma.

CLINICAL BEHAVIOR

In 2004, Busam et al[1] underscored that "phenotypic heterogeneity of desmoplastic melanoma (DM) is underrecognized." These histopathologic differences in DM appear to influence clinical behavior, although a recent study indicates otherwise.[2]

Hawkins et al[3] were the first to compare the clinical behavior and patient outcomes of the DM subtypes. They observed that mDM had a significantly higher 2- and 5-year melanoma-specific mortality than pDM.[3] In comparing patients with DM and conventional melanoma (CM) with localized primary disease, they found no significant difference in melanoma-specific mortality despite a mean tumor depth of 4.5 mm for pDM and 2.1 mm for CM.[3] In contrast, a recent study on a cohort of patients with pDM and superficial spreading melanomas found an improved melanoma-specific survival (MSS) for pDM versus superficial spreading melanomas.[4]

Comparing patients with pDM and mDM, Hawkins et al[3] found less regional node metastasis, less involvement/recurrence in the regional node basin, and less local recurrence in the former. Pawlik

From the Tufts University School of Medicine, Boston[a]; and Dermatopathology Section, Department of Pathology and Laboratory Medicine, Veterans Adminstration Consolidated Laboratories, West Roxbury.[b]
Funding sources: None.
Conflicts of interest: None disclosed.
IRB approval status: Not applicable.
Accepted for publication February 6, 2020.
Reprint requests: Meera Mahalingam, MD, PhD, FRCPath, Dermatopathology Section, VA-Integrated-Service-Network-1 (VISN1), Department of Pathology and Laboratory Medicine (113), 1400 VFW Pkwy, West Roxbury, MA 02132. E-mail: me@meeramahalingam.com.
Published online February 14, 2020.
0190-9622
Published by Elsevier on behalf of the American Academy of Dermatology, Inc.
https://doi.org/10.1016/j.jaad.2020.02.014

et al[5] corroborated this and found that the incidence of positive sentinel lymph nodes between mDM and non-DM were comparable. George et al[6] found no lymph node metastasis in patients with pDM but observed nodal metastases in patients with mDM, arguing against sentinel lymph node biopsies for pDM.

Han et al[7] found a 27% nodal metastatic rate in patients with mDM, significantly higher than the 17% for patients with pDM. Despite this, the number of patients with pDM with nodal disease was still substantial.[7] They also noted that although the histopathologic subtype can predict nodal status, it does not necessarily predict MSS.[7] They suggested that even though mDMs can have an increased nodal metastasis rate, once the tumors spread lymphatically, they follow a similar disease course regardless of the subtype, arguing in favor of sentinel lymph node biopsies being performed on both subtypes.[7]

Regarding local recurrence, Pawlik et al[5] observed no cases of local recurrence after resection of pDM. They attributed this to their aggressive resection approach (wide excision with at least 2-cm margins).[5] Despite this, they observed recurrences in 21% of mDMs, providing further evidence of the clinical relevance of histopathologic subtyping of DM.[5]

CAPSULE SUMMARY

- Immunohistochemical and genetic analyses of the DM) subtypes suggest that these likely affect their different biological behaviors.
- The clinical differences between the DM subtypes, with mixed DM being the more aggressive subtype, help guide management of the disease.

DEMOGRAPHICS

Regarding age, our summary indicates that the median age is similar between patients with pDM and mDM but surpasses that of patients with non-DM[3,5] (Table I).

Regarding sex predilection, our synopsis shows that male patients are affected more commonly with similar frequencies in mDM and pDM. In contrast, some studies found that pDM was more frequent in male patients.[5,6,8] Notably, Howard et al[4] found the male incidence to be 67% vs 49% in pDM vs non-DM.

Regarding location, our summary shows that mDM and pDM seem to occur in the head and neck region with similar frequencies (Table I). Notably, Hawkins et al[3] found that both mDM and pDM occurred here significantly more than non-DM. Although both subtypes occur in the trunk with similar frequency, mDM is more frequent in the extremities (Table I).

ANCILLARY STUDIES

Dermoscopy

Emerging evidence suggests that dermoscopy can be a clinically useful supplementary tool to identify DM.[9-11] Debarbieux et al,[9] the first to describe dermoscopic characteristics of DM retrospectively, found an absence of classic criteria in half and attributed this to the fact that these were clinically hypopigmented. Abnormal vascular patterns/regression were clinically useful features in identifying DM.[9]

Jaimes et al[10] looked at the DM subtypes from 8 different melanoma centers to analyze their common phenotypic traits. They noted that in 16 of 37 cases (8 mDM and 8 pDM), a malignant neoplasm diagnosis was not even considered, and the patients were inefficiently given unsuccessful treatments before biopsies were performed.[10] They found that 57% of all DMs lacked melanocytic structures (pigment networks/aggregated globules/streaks/negative networks).[10] Despite this, they noted that all DMs showed at least 1 melanoma-specific structure (81% atypical vascular structures, 32% peppering/crystalline structures, 24% annular granular pattern, 19% blue-white veils/atypical globules, 14% atypical networks, 8% scar-like areas/off-center blotches, and 3% peripheral tan/structureless areas).[10] Both subtypes contained atypical vascular structures (81%).[10] Of note, peppering was more common in pDM than mDM (44% vs 24%).[10] For mDM, there was more variety in melanoma-specific structures not found in pDM (negative networks, follicular obliteration, off-center blotches, peripheral tan/structureless areas).[10] Lentigo maligna was the most frequently associated epidermal component (60% of pDM, 50% mDM).[10]

HISTOPATHOLOGY

Cytomorphology

The pDM subtype exhibits more than 90% spindled cells, whereas mDM exhibits less than 90% spindled cells with admixed epithelioid cells (Fig 1). These cutoffs have been used in several studies with and without modifications.[3-5,7,10,12-15] For example, Howard et al[4] classified cases as pDM if they contained at least 80% desmoplastic features, and Hawkins et al[3] classified cases as pDM if they exhibited 80% to 90% desmoplastic features. **[F1-4/C]**

Abbreviations used:

CM:	conventional melanoma
DM:	desmoplastic melanoma
mDM:	mixed desmoplastic melanoma
MDM-CMP:	mixed desmoplastic melanoma, conventional melanoma predominant
MDM-DMP:	mixed desmoplastic melanoma, desmoplastic melanoma predominant
MSS:	melanoma-specific survival
pDM:	pure desmoplastic melanoma

Lawrence et al[14] and Kraft et al[15] classified cases as mDM only if the desmoplastic component was at least 50% but less than 90%.

Borderline cellularity was a term used for regions of cellular density between that of CM cytomorphology and classic DM, and *neurotropic melanoma* was a term used for cases composed predominantly of neuromatous-appearing elements.[6] In cases that showed more than 1 histopathologic pattern, the investigators determined the proportions of classic DM, CM, neurotropic melanoma, and borderline cellularity.[6] Notably, areas with neurotropic cytomorphology were placed in the classic DM category.[6] Using these guidelines, the investigators divided DM into 3 subtypes: pDM (at least 90% classic DM); mixed DM, DM predominant (MDM-DMP) (50%-90% classic DM); and mixed DM, CM predominant (MDM-CMP) (10%-50% classic DM).[6] In the current literature, few studies use this detailed subclassification.[6,16,17] Using these cutoffs, we previously found that, of the total DMs, 39% were MDM-DMP and 61% were MDM-CMP.[16,17] George et al[6] claimed that they found no significant differences in the data between MDM-DMP and MDM-CMP, and subsequently combined them into 1 mDM group.[6] Our own experience suggests that this conclusion may not be valid because we have shown differences in PD-L1 expression between MDM-CMP, MDM-DMP, and pDM.[17]

Looking specifically at pDM, Stowman et al[18] noted scattered lymphocytic aggregates (termed *tertiary lymph lymphoid structures*) within the lesion or in the periphery in 91% cases, leading them to suggest that lymphoid aggregates may be helpful in recognizing pDM.

In a study detailing fine-needle biopsy characteristics, Murali et al[19] noted that pDMs were composed of spindled and epithelioid cells (40%) or predominantly spindled cells (60%), whereas mDMs were composed of epithelioid cells (60%), a combination of spindled and epithelioid (27%), or just spindled cells (13%).[19] Compared with CM, pDM showed significantly lower cellularity and less intranuclear cytoplasmic invaginations, whereas mDM showed significantly less prominent nuclei and more intracellular cytoplasmic invaginations.[19] They also found that the mDM subtype was composed of significantly fewer bizarre/giant tumor cells and contained epithelioid cells more often than pDM.[19]

Prognosticators

We found that perineural invasion is less commonly associated with mDM compared with pDM (34% vs 44%) (Table I). In contrast, Conic et al[2] found no difference in perineural invasion between mDM and pDM (42% vs 40% respectively).

We found a smaller median depth for mDM compared with pDM (3 vs 3.6 mm) (Table I). Pawlik et al[5] corroborated this and noted that pDM is more invasive than CM (3.5 vs 1.5 mm). Although several studies confirm this, there are others contradicting it (Table I). Hawkins et al[3] found the depth of pDM to be significantly less than that of mDM and significantly more than that of CM (mean: 4.8 mm, 6.5 mm, and, 2.1 mm, respectively). Maurichi et al[20] found no significant difference between the thickness of pDM and mDM. Despite the greater depth, pDM has a lower rate of recurrence and less regional node involvement compared with mDM.

We found that ulceration occurs more frequently in mDM versus pDM (Table I). In contrast, Busam et al[1] found higher rates of ulceration in pDM compared with mDM.[1] Although we corroborated this previously, our rates were overall lower in both.[21] Howard et al[4] found that ulceration occurred more often in pDM than CM. Of note, Pawlik et al[5] found that ulceration occurred less frequently in pDM compared with both mDM and CM.

We found that regression and histopathologic pigmentation were more frequent in mDM than in pDM (Table I).

Regarding an overlying in situ component, de Almeida et al[12] found that mDM and pDM had a similar frequency, a finding different from ours of a slightly higher incidence in mDM compared with pDM (78% vs 61%, respectively).[12,21]

IMMUNOHISTOCHEMISTRY

S100 protein

Regarding S100P immunoreactivity, to date, there does not appear to be any significant difference between the subtypes (99% pDM and 100% mDM) (Table II[22-25]). Using an intensity-based scoring criterion (0-2), Ramos-Herberth et al[26] found that in pDM, the average staining scores were 1.8 and 2

Table I. Chronological review of published studies regarding histopathologic and demographic information of desmoplastic melanoma subtypes

References	Sample size	Thickness, mm	Ulceration, %	PNI	Regression, %	Pigmentation, %	Median age, y	Male, %	Head and neck, %	Trunk, %	Extremity, %	Conclusions
2004[1]	mDM: n = 37 pDM: n = 55	mDM: 5.0* pDM: 3.6*	mDM: 76 pDM: 84	mDM: 54 pDM: 58	NP NP	NP NP	mDM: 61 pDM: 65	mDM: 70 pDM: 58	mDM: 65 pDM: 53	mDM: 14 pDM: 22	mDM: 22 pDM: 26	Classifying DM into subtypes may allow for more consistency in future analysis.
2005[3]	mDM: n = 39 pDM: n = 92	mDM: 5.5* pDM: 3.6*	NP NP	NP NP	NP NP	mDM: 38 pDM: 43	mDM: 64 pDM: 63	mDM: 90* pDM: 61*	mDM: 49 pDM: 51	mDM: 23 pDM: 23	mDM: 28 pDM: 26	pDM is associated with more favorable outcomes compared with mDM and CM.
2006[5]	mDM: n = 19 pDM: n = 46	mDM: 1.7* pDM: 3.5*	mDM: 28* pDM: 7*	NP NP	NP NP	NP NP	mDM: 64 pDM: 61	mDM: 53 pDM: 59	mDM: 28 pDM: 21	mDM: 39 pDM: 34	mDM: 33 pDM: 45	pDM has a lower incidence of positive SLN compared to mDM, thus SLNB is not recommended for pDM.
2008[12]	mDM: n = 62 pDM: n = 51	mDM: 3.0 pDM: 4.0	mDM: 15 pDM: 10	mDM: 34 pDM: 37	mDM: 10 pDM: 6	mDM: 37* pDM: 20*	mDM: 70 pDM: 72	mDM: 44 pDM: 53	mDM: 73 pDM: 74	mDM: 15 pDM: 14	mDM: 8 pDM: 2	Clinicians should be more wary of DM because it can be commonly misdiagnosed.
2009[6]	mDM: n = 43 pDM: n = 44	mDM: 3.0 pDM: 2.5	mDM: 12 pDM: 7	mDM: 28 pDM: 41	mDM: 2 pDM: 0	mDM: 67 pDM: 36	mDM: 66 pDM: 69	mDM: 56 pDM: 64	mDM: 44 pDM: 61	mDM: 19 pDM: 16	mDM: 37 pDM: 23	pDM has less nodal involvement than mDM and does not support routine SLNB.
2010[8]	mDM: n = 129 pDM: n = 123	mDM: 2.2* pDM: 2.9*	mDM: 25 pDM: 19	mDM: 27* pDM: 44*	NP NP	NP NP	mDM: 59 pDM: 62	mDM: 61 pDM: 72	mDM: 19* pDM: 33*	mDM: 29 pDM: 29	mDM: 53 pDM: 38	SLN involvement was lower in DM compared with CM. DM should be evaluated routinely in patients with primary cutaneous melanomas.
2010[20]	mDM: n = 124 pDM: n = 118	mDM: 1.9 pDM: 2.1	mDM: 23 pDM: 22	mDM: 26 pDM: 36	NP NP	mDM: 48 pDM: 39	mDM: 63* pDM: 65*	mDM: 71 pDM: 68	mDM: 55 pDM: 56	mDM: 27 pDM: 25	mDM: 19 pDM: 19	Limited excision width is associated with significantly higher local recurrence rate and mortality in pDM.
2012[21]	mDM: n = 19 pDM: n = 24	mDM: 5.5 pDM: 3.7	NP NP	mDM: 78 pDM: 61	NP NP	mDM: 50 pDM: 52	mDM: 75 pDM: 70	mDM: 44 pDM: 61	NP NP	NP NP	NP NP	Significant differences in expression of Ki-67 and CD117 were found between pDM and mDM in the cohort.
2013[10]	mDM: n = 21 pDM: n = 16	mDM: 2.8 pDM: 4.10	mDM: 5 pDM: 0	mDM: 19 pDM: 31	mDM: 21 pDM: 6	NP NP	mDM: 70 pDM: 67	mDM: 62 pDM: 56	mDM: 48 pDM: 50	mDM: 19 pDM: 31	mDM: 14 pDM: 19	Dermoscopy can help in evaluating DM in the clinic. Common clues include peppering, atypical vascular structures, and melanoma-specific structures.

REV 5.6.0 DTD ■ YMJD14230_proof ■ 21 June 2020 ■ 1:11 pm

2016[16]	mDM: n = 34	mDM: 3*	mDM: 6	mDM: 53	NP	NP	mDM: 62	mDM: 71*	NP	NP			Neurofibromin may play a significant role in DM. Association of *RETp*, neurofibromin loss, and perineural involvement may suggest neurotrophic involvement in DM.
	pDM: n = 44	pDM: 3.7*	pDM: 9	pDM: 59	NP	NP	pDM: 66	pDM: 46*	NP	NP			
2018[2]	mDM: n = 43	mDM: 3.5	mDM: 30	mDM: 42	mDM: 2	NP	mDM: 64	mDM: 67	mDM: 51	mDM: 16	mDM: 33		pDM and mDM seem to have similar clinical characteristics and outcomes.
	pDM: n = 15	pDM: 3.4	pDM: 13	pDM: 40	pDM: 0	NP	pDM: 60	pDM: 47	pDM: 73	pDM: 20	pDM: 7		
2019[4]	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP		pDM has lower risk of melanoma-specific death compared with superficial spreading melanomas.
	pDM: n = 119	pDM: 4.2	pDM: 20	NP	NP	NP	pDM: 74	pDM: 67	NP	NP	NP		

CM, Conventional melanoma; *DM*, desmoplastic melanoma; *mDM*, mixed desmoplastic melanoma; *NP*, not performed; *pDM*, pure desmoplastic melanoma; *PNI*, perineural invasion; *SLN*, sentinel lymph node.
*Indicates statistical significance between the subtypes.

(intraepidermal vs invasive component), whereas in mDM, the average staining score was 2 (intraepidermal and invasive component). Examining pDM alone, Plaza et al[27] found that all cases showed a strong and diffuse cytoplasmic/nuclear staining pattern. Thus, S100P does not appear to be a valuable discriminatory tool.

p75NGFR

Although our summary shows a higher p75NGFR immunoreactivity in pDM compared with mDM (75% vs 59%) (Table II), individual studies indicate no significant difference between the subtypes, even using different scoring criteria.[21,28,29] Thus, p75NGFR does not appear to discriminate between the subtypes, with the caveat that Plaza et al[27] looked at only pDM, which might have skewed the data.

SOX10

Our summary shows similar SOX10 immunopositivity in the subtypes (96% pDM, 95% mDM) (Table II). Using a scoring criterion based on expression intensity alone, Ramos-Herberth et al[26] corroborated this and demonstrated the utility of SOX10 in staining both epidermal and dermal components. Thus, SOX10 immunoreactivity appears to be of limited value as a discriminatory tool.

Microphthalmia transcription factor

Only select studies have specifically looked at microphthalmia transcription factor (MITF) immunostaining in the subtypes. Looking only at pDM, while using a scoring criterion based on proportion alone, Plaza et al[27] found that 5% of pDMs were $MITF^{+}$. Using a scoring criterion based on the intensity alone, Ramos-Herberth et al[26] observed that the intraepidermal component stained more strongly than the dermal component in both subtypes. There are insufficient data to determine the utility of MITF as a discriminatory tool.

HMB45

Data regarding HMB45 immunostaining in the subtypes is sparse (Table II). Comparing pDM to mDM, our summary shows 16% versus 36% HMB45 immunopositivity, respectively (Table II). Comparing pDM to mDM and using criteria that included intensity and proportion, Lazova et al[28] found 0% pDM versus 60% mDM. Notably, in mDM, only the CM component was immunopositive.[28] Similarly, Pagès et al[30] found no expression of HMB45 in pDM compared with 100% expression in mDM. Looking at pDM alone, Plaza et al[27] found that 23% showed HMB45 immunoreactivity. Ramos-Herberth et al[26] found that there was strong staining

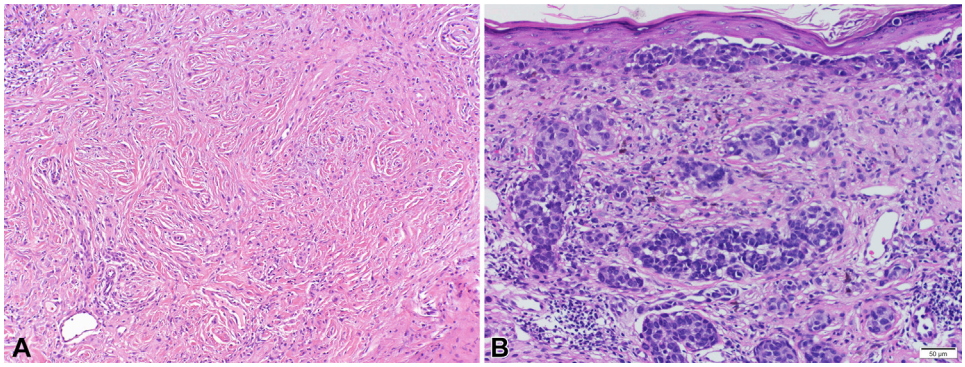

Fig 1. Representative examples of desmoplastic melanoma subtypes. (Hematoxylin-eosin stain.) **A**, Pure subtype. **B**, Mixed subtype.

within the intraepidermal component but no staining within the dermal component in both subtypes. Thus, HMB45 appears limited as an immunodiscriminatory tool.

Ki-67

We found a significantly higher Ki-67 immunopositivity in mDM versus pDM (28% vs 5%, respectively).[17] In contrast, Lazova et al[28] found 100% Ki-67 expression in pDM compared with 75% in mDM, although statistical significance was not ascertained. Notably, in pDM, the Ki-67 expression was weak (<10% positivity), whereas in mDM, it was strong (10%-50% immunopositivity).[28] Thus, the value of Ki-67 in the subtypes is still unclear.

PD-L1

We and others have found that mDM was more likely to express PD-L1 compared with pDM after controlling for confounding factors, suggesting that patients with mDM are likely better candidates for anti-PD/PD-L1 therapy.[17,31] In contrast, Eroglu et al[32] found no significant difference in PD-L1 expression between the subtypes. We have also previously shown that all PD-L1 immunopositive mDM cases were of the MDM-CMP category and that PD-L1 expression was more prone to occur in the CM component.[17] These findings suggest that PD-L1 expression may be an indicator of an aggressive immunophenotype. Using a much higher cutoff (≥25% to denote positivity), Kraft et al[15] showed that tumoral PD-L1 expression significantly correlated with mDM histopathology, tumor thickness, mitoses, recurrence, and metastases. They also observed that PD-L1 immunoexpression correlated with poor progression-free survival and poor MSS, and they showed that mDM also predicts poor progression-free survival.[15] Regarding treatment, Eroglu et al[32] evaluated unresectable pDM and mDM cases that were treated with pembrolizumab/nivolumab/anti-PD-L1 antibody BMS-936559, or a combination. After a median follow-up of 22 months, they showed that 70% of patients showed objective responses to treatment.[32] Notably, the study found no statistical difference between pDM and mDM in their objective response rates or overall survival.[32]

CD117

We previously found a significantly higher CD117 expression in mDM (78%) compared with pDM (26%).[21] Examining pDM alone, Plaza et al[27] found that none of the pDM cases expressed CD117. Given this, CD117 immunoexpression does appear to be of discriminatory value.

GENETICS

RET

Narita et al[33] showed a significantly higher incidence of *RETp* in DM (61%) compared with non-DM (31%). Looking at the subtypes, our summary of 4 studies showed similar expression of *RETp* in both pDM and mDM (30% vs 27%, respectively) (Table III). Notably, Jahn et al[34] found a higher expression of *RETp* in mDM compared with pDM (38% vs 25%).

NF1

Wiesner et al[24] found no difference in *NF1* mutations in the subtypes (86% pDM vs 100% mDM). Looking for the neurofibromin protein as an alternative to screening for *NF1* mutations, we found that neurofibromin loss was significantly more common in pDM versus mDM (80% vs 56%).[16]

TERT

We observed significantly higher *TERT* promoter mutation frequencies in mDM versus pDM (54% vs 23%), suggesting that the subtypes have distinct genetic drivers.[35] Conversely, albeit in a smaller

Table II. Overview of studies on immunohistochemical markers for desmoplastic melanoma subtypes

	S100		p75NGFR		SOX10		MITF		HMB45		CD117		Ki-67		KBA.62		Tyrosinase		Nestin	
References	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM	pDM	mDM
Ramos-Herbert et al[26]	7/7	2/2	NP	NP	7/7	2/2	1.7 in IE, .25 in ID	2 in IE, 1 in ID	1.5 in E, 0 in ID	1 in E, 0 in ID	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
Lazova et al[28]	5/5	5/5	5/5	5/5	NP	NP	NP	NP	0/5	3/5	NP	NP	3/3	3/4	NP	NP	NP	NP	NP	NP
Plaza et al[27]	40/40	NP	38/40	NP	40/40	NP	2/40	NP	9/40	NP	0/40	NP	NP	NP	13/40	NP	NP	NP	40/40	NP
Miller et al[21]	NP	NP	14/23	12/18	20/23	17/18	NP	NP	NP	NP	6/23*	14/18*	5%*	28%*	NP	NP	NP	NP	19/23	16/18
Frydenlund et al[29]	NP	NP	15/24	13/19	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP	NP
Pagès et al[30]	3/3	4/4	NP	NP	NP	NP	NP	NP	0/4	4/4	NP	NP	NP	NP	3/3	4/4	NP	NP	NP	NP
George et al[6]	29/30	25/25	NP	NP	NP	NP	NP	NP	2/18	2/16	NP	NP	NP	NP	NP	NP	2/10	3/6	NP	NP

E, Epidermal component; *ID*, intradermal component; *IE*, intraepidermal component; *mDM*, mixed desmoplastic melanoma; *MITF*, microphthalmia transcription factor; *NP*, not performed; *pDM*, pure desmoplastic melanoma.
*Indicates statistical significance between the subtypes.

Table III. Summary of genetic studies involving *RETp*, *NF1*, and *TERT* for desmoplastic melanoma subtypes

	RETp			*NF1*			*TERT*		
References	Total DM	pDM	mDM	Total DM	pDM	mDM	Total DM	pDM	mDM
Narita et al[33]	43/70	NP	NP	NP	NP	NP	NP	NP	NP
Barr et al[22]	9/30	NP	NP	NP	NP	NP	NP	NP	NP
Miller et al[21]	12/41	8/24	4/17	NP	NP	NP	NP	NP	NP
Frydenlund et al[17]	12/43	7/23	5/19	NP	NP	NP	NP	NP	NP
Jahn et al[34]	6/20	3/12	3/8	NP	NP	NP	NP	NP	NP
Kadokura et al[16]	22/77	13/43	9/34	54/78 showed neurofibromin loss	35/44*	19/34*	NP	NP	NP
Lawrence et al[14]	10/46	NP	NP	NP	NP	NP	NP	NP	NP
Gutzmer et al[23]	NP	NP	NP	10/15	NP	NP	NP	NP	NP
Wiesner et al[24]	NP	NP	NP	14/15	6/7	8/8	NP	NP	NP
Shain et al[36]	NP	NP	NP	9/20	NP	NP	17/20	NP	NP
Jour et al[25]	NP	NP	NP	18/27	NP	NP	NP	NP	NP
Eroglu et al[32]	NP	NP	NP	14/17	NP	NP	NP	NP	NP
Yang et al[35]	NP	NP	NP	NP	NP	NP	26/76	11/48*	15/28*

DM, Desmoplastic melanoma; *mDM*, mixed desmoplastic melanoma; *NP*, not performed; *pDM*, pure desmoplastic melanoma.
*Indicates statistical significance.

REV 5.6.0 DTD ■ YMJD14230_proof ■ 21 June 2020 ■ 1:11 pm

study by Shain et al,[36] the genetic profiles in pDM and mDM were similar.

CONCLUSIONS

In terms of biologic behavior, mDM exhibits more regional node metastases, a higher recurrence rate, and a higher mortality rate. Compared with the pDM subtype, tumors of the mDM subtype are more often clinically pigmented, are less likely to show perineural invasion, and are thinner.

Dermoscopy appears to have some utility in recognizing DM and in differentiating between the subtypes.

Despite the plethora of immunohistochemical markers used for diagnosing DM, few differentiate between the subtypes. Overall, our experience suggests that PD-L1 immunoexpression appears to be associated with the host response, as ascertained by the presence of $CD8^+$ lymphocytes and the mDM subtype. Enhanced PD-L1 expression in the mDM subtype suggests that these patients are likely better candidates for anti-PD/PD-L1 therapy. The immunohistochemical stain CD117, although of limited utility as a histopathologic adjunct in DM, does appear to discriminate between the DM subtypes.

Significant differences between the subtypes in terms of neurofibromin expression and the frequency of *TERT* promoter mutations suggest that the subtypes have distinct genetic drivers.

Immunohistochemical and genetic analyses of larger sample sizes of the DM subtypes are required to confirm the clinical relevance and biological significance of these conclusions.

REFERENCES

1. Busam KJ, Mujumdar U, Hummer AJ, et al. Cutaneous desmoplastic melanoma: reappraisal of morphologic heterogeneity and prognostic factors. *Am J Surg Pathol*. 2004;28:1518-1525.
2. Conic RZ, Ko J, Allam SH, et al. Mixed versus pure variants of desmoplastic melanoma: the Cleveland clinic experience. *Ann Plast Surg*. 2018;80:277-281.
3. Hawkins WG, Busam KJ, Ben-Porat L, et al. Desmoplastic melanoma: a pathologically and clinically distinct form of cutaneous melanoma. *Ann Surg Oncol*. 2005;12:207-213.
4. Howard MD, Wee E, Wolfe R, et al. Differences between pure desmoplastic melanoma and superficial spreading melanoma in terms of survival, distribution and other clinicopathologic features. *J Eur Acad Dermatol Venereol*. 2019;33:1899-1906.
5. Pawlik TM, Ross MI, Prieto VG, et al. Assessment of the role of sentinel lymph node biopsy for primary cutaneous desmoplastic melanoma. *Cancer*. 2006;106:900-906.
6. George E, McClain SE, Slingluff CL, et al. Subclassification of desmoplastic melanoma: pure and mixed variants have significantly different capacities for lymph node metastasis. *J Cutan Pathol*. 2009;36(4):425-432.
7. Han D, Han G, Zhao X, et al. Clinicopathologic predictors of survival in patients with desmoplastic melanoma. *PLoS One*. 2015;10:119716.
8. Murali R, Shaw HM, Lai K, et al. Prognostic factors in cutaneous desmoplastic melanoma: a study of 252 patients. *Cancer*. 2010;116:4130-4138.
9. Debarbieux S, Ronger-Salve S, Dalle S, et al. Dermoscopy of desmoplastic melanoma: report of six cases. *Br J Dermatol*. 2008;159:360-363.
10. Jaimes N, Chen L, Dusza SW, et al. Clinical and dermoscopic characteristics of desmoplastic melanomas. *JAMA Dermatol*. 2013;149:413-421.
11. Maher NG, Solinas A, Scolyer RA, et al. Detection of desmoplastic melanoma with dermoscopy and reflectance confocal microscopy. *J Eur Acad Dermatol Venereol*. 2017;31:2016-2024.
12. de Almeida LS, Requena L, Rutten A, et al. Desmoplastic malignant melanoma: a clinicopathologic analysis of 113 cases. *Am J Dermatopathol*. 2008;30(3):207-215.
13. Mohebati A, Ganly I, Busam KJ, et al. The role of sentinel lymph node biopsy in the management of head and neck desmoplastic melanoma. *Ann Surg Oncol*. 2012;19:4307-4313.
14. Lawrence NF, Hammond MR, Frederick DT, et al. Ki-67, p53, and p16 expression, and G691S RET polymorphism in desmoplastic melanoma (DM): a clinicopathologic analysis of predictors of outcome. *J Am Acad Dermatol*. 2016;75:595-602.
15. Kraft S, Fernandez-Figueras MT, Richarz NA, et al. PDL1 expression in desmoplastic melanoma is associated with tumor aggressiveness and progression. *J Am Acad Dermatol*. 2017;77:534-542.
16. Kadokura A, Frydenlund N, Leone DA, et al. Neurofibromin protein loss in desmoplastic melanoma subtypes: implicating NF1 allelic loss as a distinct genetic driver? *Hum Pathol*. 2016;53:82-90.
17. Frydenlund N, Leone D, Yang S, et al. Tumoral PD-L1 expression in desmoplastic melanoma is associated with depth of invasion, tumor-infiltrating CD8 cytotoxic lymphocytes and the mixed cytomorphological variant. *Mod Pathol*. 2017;30:357-369.
18. Stowman AM, Hickman AW, Mauldin IS, et al. Lymphoid aggregates in desmoplastic melanoma have features of tertiary lymphoid structures. *Melanoma Res*. 2018;28(3):237-245.
19. Murali R, Loughman NT, McKenzie PR, et al. Cytologic features of metastatic and recurrent melanoma in patients with primary cutaneous desmoplastic melanoma. *Am J Clin Pathol*. 2008;130:715-723.
20. Maurichi A, Miceli R, Camerini T, et al. Pure desmoplastic melanoma: a melanoma with distinctive clinical behavior. *Ann Surg*. 2010;252:1052-1057.
21. Miller DD, Emley A, Yang S, et al. Mixed versus pure variants of desmoplastic melanoma: a genetic and immunohistochemical appraisal. *Mod Pathol*. 2012;25:505-515.
22. Barr J, Amato CM, Robinson SE, et al. The ret g691s polymorphism is a germline variant in desmoplastic malignant melanoma. *Melanoma Res*. 2012;22:92-95.
23. Gutzmer R, Herbst RA, Mommert S, et al. Allelic loss at the neurofibromatosis type 1 (NF1) gene locus is frequent in desmoplastic neurotropic melanoma. *Hum Genet*. 2000;107(4):357-361.
24. Wiesner T, Kiuru M, Scott SN, et al. NF1 mutations are common in desmoplastic melanoma. *Am J Surg Pathol*. 2015;39:1357-1362.
25. Jour G, Andeen NK, Al-Rohil R, et al. Novel enriched pathways in superficial malignant peripheral nerve sheath tumors and spindle/desmoplastic melanomas. *J Pathol*. 2018;244(1):97-106.
26. Ramos-Herberth FI, Karamchandani J, Kim J, et al. SOX10 immunostaining distinguishes desmoplastic melanoma from excision scar. *J Cutan Pathol*. 2010;37:944-952.

27. Plaza JA, Bonneau P, Prieto V, et al. Desmoplastic melanoma: an updated immunohistochemical analysis of 40 cases with a proposal for an additional panel of stains for diagnosis. *J Cutan Pathol*. 2016;43:313-323.
28. Lazova R, Tantcheva-Poor I, Sigal AC. P75 nerve growth factor receptor staining is superior to S100 in identifying spindle cell and desmoplastic melanoma. *J Am Acad Dermatol*. 2010;63(5): 852-858.
29. Frydenlund N, Leone DA, Mitchell B, et al. Neurotrophin receptors and perineural invasion in desmoplastic melanoma. *J Am Acad Dermatol*. 2015;72(5):851-858.
30. Pagès C, Rochaix P, al Saati T, et al. KBA.62: a useful marker for primary and metastatic melanomas. *Hum Pathol*. 2008;39: 1136-1142.
31. Kaunitz GJ, Cottrell TR, Lilo M, et al. Melanoma subtypes demonstrate distinct PD-L1 expression profiles. *Lab Invest*. 2017;97:1063-1071.
32. Eroglu Z, Zaretsky JM, Hu-Lieskovan S, et al. High response rate to PD-1 blockade in desmoplastic melanomas. *Nature*. 2018;553:347-350.
33. Narita N, Tanemura A, Murali R, et al. Functional RET G691S polymorphism in cutaneous malignant melanoma. *Oncogene*. 2009;28:3058-3068.
34. Jahn SW, Kashofer K, Halbwedl I, et al. Mutational dichotomy in desmoplastic malignant melanoma corroborated by multigene panel analysis. *Mod Pathol*. 2015;28: 895-903.
35. Yang S, Leone D, Frydenlund N, et al. Frequency of telomerase reverse transcripter promoter mutations in desmoplastic melanoma subtypes: analyses of 76 cases. *Melanoma Res*. 2016;26:361-366.
36. Shain AH, Garrido M, Botton T, et al. The genetic evolution of melanoma from precursor lesions. *N Engl J Med*. 2015;373: 1926-1936.