Desmoplastic and Neurotropic Melanoma

Analysis of 33 Patients with Lymphatic Mapping and Sentinel Lymph Node Biopsy

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BACKGROUND. Desmoplastic and neurotropic melanoma (DNMM) occasionally metastasizes to regional lymph nodes and extranodal sites. The value of sentinel lymph node biopsy (SLNB) has not been demonstrated clearly for patients with DNMM. The authors report on the utility of SLNB in the management of patients with DNMM.

METHODS. The authors identified 33 patients with DNMM who were seen during a 5-year period in their institution who underwent lymphatic mapping and SLNB. Clinical and histopathologic data were reviewed.

RESULTS. Thirty-three patients with DNMM underwent SLNB (mean Breslow depth, 4.0 mm; median, 2.8 mm). There were 25 male patients and 8 female patients with a median age of 61 years (range, 31–86 years). Fifty-two percent of tumors presented in the head and neck region, and 24% were associated with lentigo maligna. Four of 33 patients (12%) without clinical evidence of metastatic disease who underwent SLNB had at least 1 positive sentinel lymph node. No additional positive lymph nodes were found in subsequent therapeutic regional lymphadenectomy in any of these four patients.

CONCLUSIONS. SLNB detected subclinical metastases of DNMM to regional lymph nodes. SLNB at the time of resection can provide useful information to guide early treatment and, coupled with lymphadenectomy in positive patients, may limit tumor spread and prevent recurrence at the draining lymph node basin. ***Cancer* 2004;100:598–604.** © *2003 American Cancer Society.*

KEYWORDS: desmoplastic, neurotropic, melanoma, sentinel lymph node biopsy, metastasis.

In 1971, Conley et al. described an uncommon and distinct variant of melanoma that often presented as a hard, subcutaneous tumor of fibrous appearance deep to a primary, superficial, melanotic lesion.[1] These bulky tumors generally were located in the head and neck region, often beneath lentigo maligna. The tumors were highly malignant, stubbornly recurring, and often metastasizing neoplasms. In their seminal study, those authors observed regional lymph node metastases in 3 of 7 patients (42%), pulmonary metastases in 4 of 7 patients (57%), and death related to disseminated disease in 4 of 7 patients (57%). The authors proposed the term *desmoplastic malignant melanoma* for this unusual variant of spindle cell melanoma accompanied by dense fibrosis. Eight years later, Reed and Leonard observed that spindle cell melanomas with a dominant neuroid appearance and neurotropism often also manifested desmoplasia, and those authors suggested that *neurotropic melanoma* is best considered a variant of desmoplastic melanoma.[2] In their study of desmoplastic and neurotropic malignant melanoma (DNMM), Reed and Leonard noted regional lymph node metastases in 2 of 16 patients (12.5%), pulmonary metastases in 1 of 16 patients (6%), and death

related to disease in 9 of 16 patients (56%). Other investigators have observed similar behavior and metastatic rates for DNMM.[3–10]

In patients with DNMM without clinical evidence of regional lymph node involvement, there is general consensus that combined lymphatic mapping and sentinel lymph node biopsy (SLNB) is the most appropriate strategy for obtaining staging information.[3,4,11–13] SLNB detects early metastases to regional lymph nodes in a variety of malignancies.[14–23] Given the low rate of associated morbidity and complications,[24] SLNB seems an ideal staging tool for these tumors. However, to our knowledge to date, the results reported in the literature have suggested that the use of SLNB may not be reliable for DNMM. Indeed, in 4 recent studies involving a total of 62 patients with DNMM who underwent SLNB, only 1 patient was diagnosed with a positive sentinel lymph node (SLN).[4,11–13] Given the infrequent involvement of SLNs by DNMM, could SLNB lack sensitivity in detecting lymph node metastasis for this tumor type? Or is SLNB a sensitive technique with a low yield because DNMM does not spread preferentially to lymph nodes? Should a staging SLNB be performed at all for patients with DNMM? To address these important questions, we reviewed our experience with DNMM and the results of SLNB for this tumor type.

MATERIALS AND METHODS

We searched the clinical data base of the University of Michigan Multidisciplinary Melanoma Clinic for all patients with DNMM who underwent SLNB from October, 1997 to October, 2002. Clinical data and histopathologic material were reviewed on all patients. At our institution, indications for SLNB are clinically localized melanoma $\geq$ 1.0 mm Breslow depth or clinically localized melanoma $\leq$ 1.0 mm with other potentially adverse features, such as ulceration and extensive vertical regression to at least 1.0 mm in depth. Young patients with tumors exhibiting a high mitotic rate ($>$ 1 per mm) also are counseled regarding SLNB. Contraindications for SLNB include poor health/high surgical risk and the presence of suspected palpable lymph node and/or distant metastatic disease.

The procedures for lymphatic mapping and SLNB used in our institution are similar to those described previously.[14–16,23] Briefly, 1 mCi of unfiltered Tc^{99m}-sulfur colloid is injected intradermally at 4 points around the primary tumor site 2–4 hours prior to surgery. Dynamic imaging is performed on the neck, axillary, and groin regions to localize the SLN(s). The patient is then brought to the operating room, where 1–2 cc of Lymphazurin blue dye (isosulfan blue) are injected intradermally around the primary tumor site. After induction of general anesthesia, the surgical sites are prepared, sterilized, and draped. In vivo tracer counts of the primary tumor site and lymph node basins are measured with a hand-held γ probe. An incision is made in the lymph node basin(s) showing increased radioactivity, within the confines of a putative radical lymphadenectomy incision. All blue-stained, *hot* lymph nodes (defined as in vivo tracer counts $>$ 100 cpm above background or 10% of the cpm of the hottest detected lymph node, whichever was less) are identified and removed. After harvesting SLNs, the primary tumor site is excised with 1–2-cm margins. All tissues are submitted in 10% buffered formalin for histopathologic evaluation.

Primary tumor specimens were processed routinely in the histology laboratory. SLNs were sectioned serially into 2–3-mm-thick sections and embedded in paraffin. Two serial, 5-μm sections of each SLN tissue block were stained with hematoxylin and eosin (H&E) for routine histologic examination. To confirm metastatic disease identified on H&E-stained sections or detect occult metastases, a 5-μm section of each SLN block was immunostained for S-100 protein (1:500 dilution; Dako Corporation, Carpinteria, CA) and for melan-A (1:12.5 dilution; Dako Corporation).

Patients with at least one positive sentinel lymph node were offered regional lymphadenectomy. All lymph nodes retrieved from the lymphadenectomy specimen were sectioned serially into 2–3-mm-thick sections and were processed routinely in the histology laboratory. H&E sections of the lymph nodes were evaluated for metastatic tumor. Immunohistochemical stains (S-100 protein and melan-A) were not obtained routinely on lymph nodes from the complete lymph node dissection.

Clinicopathologic data from each patient were tabulated (Table 1). For statistical comparisons of continuous variables (Breslow depth with or without SLN metastasis or mitotic rate with or without SLN metastasis), we used a Student two-sample t test, assuming unequal variance, with all P values two-tailed. Data were analyzed with Microsoft Excel Software (Microsoft Corp., Bellevue, WA). To test for a nonrandom association between categoric variables (site on head and neck or ulceration or neurotropism) and SLN metastasis, we used a 2-sided Fisher exact test because of the small number in 50–75% of statistical cells. Data were analyzed with MedCalc Statistic Software (MedCalc, Mariakerke, Belgium). This study was conducted under an exemption granted by the University of Michigan Institutional Review Board for Human Subject Research.

RESULTS

We identified 33 patients (4%) with DNMM from our data base of 836 patients with melanoma who under-

TABLE 1
Clinical and Histopathologic Data on Patients with Desmoplastic-Neurotropic Melanoma with Sentinel Lymph Node Biopsies

Patient	Gender	Age (yrs)	Site of primary tumor	Coexisting in situ melanoma	Breslow depth (mm)	Clark level	Dermal mitotic rate (per mm^2)	Ulceration	Neutropism	SLNs		Follow-up and duration (mos after diagnosis)
										Site	No. positive	
1	Male	70	Scalp	LM	6.0	V	3	Present	Present	Left neck	2/6	0/27 LNs in LAD AWOD (4)
2	Male	66	Left neck	LM	3.7	IV	2	Present	None identified	Left neck	1/1	0/19 LNs in LAD AWOD (6)
3	Female	47	Midback	None identified	4.8	IV	1	None identified	Present	Left axilla	1/3	0/31 LNs in LAD AWOD (8)
4	Male	31	Right foot	AL	2.8	V	1	None identified	Present	Right groin	2/2	0/20 LNs in LAD AWOD (17)
5	Male	68	Left shoulder	None identified	2.6	IV	< 1	None identified	None identified	Back + neck	0/3	AWOD (66)
6	Female	37	Left chin	None identified	5.3	IV	1	None identified	Present	Left neck	0/1	AWOD (37)
7	Male	53	Right arm	None identified	0.8	IV	< 1	None identified	None identified	Right axilla	0/1	AWOD (22)
8	Male	65	Left neck	LM	2.4	IV	< 1	None identified	None identified	Left parotid	0/1	LTFU
9	Male	69	Scalp	LM	1.8	IV	6	None identified	None identified	Left neck	0/2	AWOD (4)
10	Female	68	Back	SSM	2.5	IV	1	None identified	None identified	Right axilla	0/2	AWOD (17)
11	Male	60	Left shoulder	SSM	7.8	IV	< 1	None identified	None identified	Left axilla	0/2	AWOD (12)
12	Male	81	Right arm	None identified	9.0	V	1	Present	Present	Right axilla	0/1	AWOD (25)
13	Male	80	Left lower lip	None identified	5.0	IV	< 1	None identified	Present	Left submental	0/4	LTFU
14	Female	50	Left arm	None identified	1.9	IV	< 1	None identified	None identified	Left axilla	0/4	AWOD (4)
15	Female	55	Left arm	None identified	1.5	IV	< 1	Present	None identified	Left axilla	0/2	Developed lung nodules; LTFU
16	Male	86	Left cheek	None identified	4.7	V	1	None identified	Present	Left neck	0/2	AWOD (7)
17	Male	56	Right temple	None identified	9.0	V	< 1	None identified	Present	Right neck	0/2	Mets to lung and to 1 right neck LN: DOD (20)
18	Female	42	Posterior neck	None identified	6.0	V	< 1	Present	Present	Bilateral neck	0/6	AWOD (53)
19	Male	74	Left ear	None identified	1.9	IV	< 1	None identified	None identified	Left cervical	0/2	AWOD (37)
20	Male	37	Scalp	None identified	8.2	V	< 1	None identified	Present	Right neck	0/2	AWOD (5)
21	Male	78	Right leg	SSM	1.1	V	1	None identified	None identified	Right groin	0/2	AWOD (3)
22	Male	58	Midback	None identified	3.4	IV	1	None identified	None identified	Right axilla	0/4	AWOD (14)
23	Male	49	Right arm	SSM	1.9	IV	< 1	None identified	None identified	Right axilla	0/1	AWOD (38)
24	Male	59	Left cheek	LM	1.9	IV	< 1	None identified	Present	Left cervical	0/1	AWOD (39)
25	Male	78	Scalp	None identified	8.5	V	1	None identified	None identified	Left neck	0/1	AWOD (2)
26	Male	73	Left shoulder	None identified	1.0	IV	1	None identified	None identified	Left supraclav	0/1	AWOD (9)
27	Male	79	Scalp	LM	2.6	V	1	None identified	Present	Left neck	0/3	AWOD (10)
28	Male	40	Scalp	LM	5.5	V	< 1	None identified	Present	Left neck	0/4	AWOD (39)
29	Male	64	Chest wall	SSM	7.8	IV	< 1	None identified	None identified	Bilateral axilla	0/5	AWOD (24)
30	Male	47	Right back	SSM	7.0	IV	4	Present	Present	Bilateral groin	0/2	AWOD (7)
31	Male	60	Scalp	None identified	1.7	IV	10	None identified	None identified	Bilateral neck	0/2	AWOD (13)
32	Female	63	Right arm	None identified	1.6	IV	< 1	None identified	None identified	Right axilla	0/1	AWOD (45)
33	Female	61	Right neck	LM	0.9	IV	< 1	None identified	None identified	Right cervical	0/1	AWOD (2)

SLN: sentinel lymph node; LM: lentigo maligna type; LNs: lymph nodes; LAD: lymphadenectomy; AWOD: alive and well without disease; AL: acral lentiginous type; LTFU: lost to follow-up; SSM: superficial spreading type; Mets: metastases; DOD: died of disease; supraclav: supraclavicular.

went wide local excision and SLNB between October, 1997 and October, 2002 (Table 1). There were 25 male patients and 8 female patients with a median age of 61 years (range, 31–86 years). Tumors measured 4.0 mm in mean Breslow thickness (median, 2.8 mm; range, 0.8–9.0 mm). Tumors were located in the head and neck region (n = 17 patients), back and trunk (n = 7 patients), and limbs (n = 9 patients). A preexisting in situ melanoma was identified in 15 of 33 patients (45%), including lentigo maligna (n = 8 patients), superficial spreading (n = 6 patients), and acral lentiginous (n = 1 patient) types. Nearly all were deeply invasive into reticular dermis and subcutis (Clark level IV and V). In the primary tumors, neurotropism was observed in 14 tumors, 3 of which metastasized to SLNs. Six tumors were ulcerated, two of which metastasized to SLNs. None of the primary tumors demonstrated angiolymphatic spread or satellitosis in histologic sections. The dermal mitotic rate ranged from < 1 mm^2 to 10/mm^2.

Of 33 patients with DNMM who underwent SLNB, 30 patients underwent tumor resection and SLNB at our institution. Four of 33 patients (12%) had 1 or more positive SLNs. In one patient with DNMM arising in the scalp (Fig. 1), tumor metastasized to two of six SLNs in the left neck (Fig. 2). In another patient with DNMM from the neck (Fig. 3), tumor spread to an SLN in the neck (Fig. 4). In both patients, metastatic tumor retained a spindled appearance and elicited a fibrosing reaction that obliterated the subcapsular si-

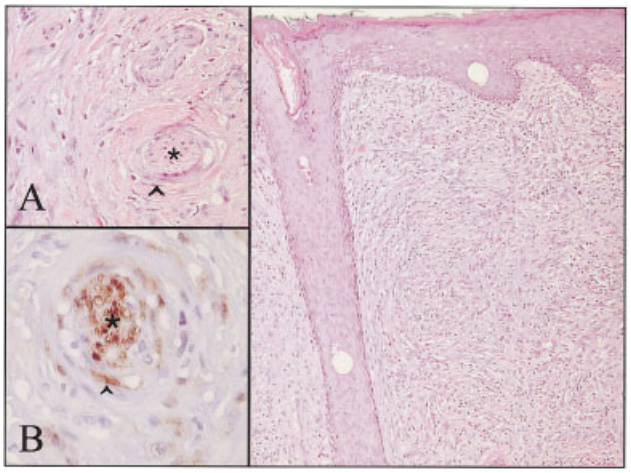

FIGURE 1. Atypical spindle cells of desmoplastic and neurotropic melanoma from Patient 1 invading the superficial and deep dermis. Tumor cells in the sclerotic dermis (arrowhead in inset A) surrounded and grew around nerve bundles (asterisk in inset A). In immunostained sections, nerve bundles (asterisk in inset B) and surrounding melanoma cells (arrowhead in inset B) were found to express S-100 protein.

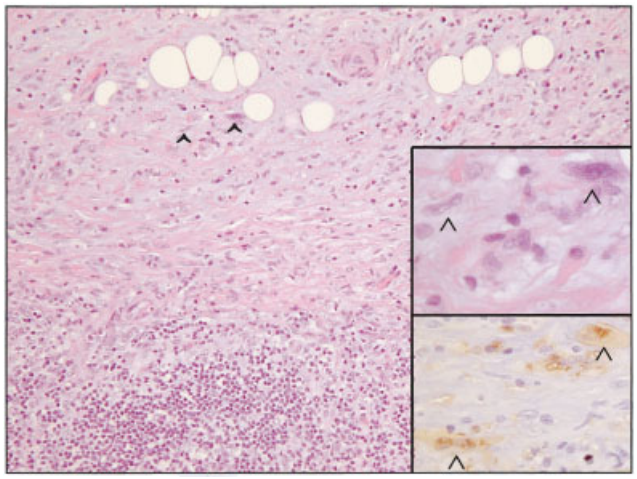

FIGURE 2. A sentinel lymph node from Patient 1 demonstrated obliteration of the subcapsular sinus and thickening of the lymph node capsule. Highly atypical, S-100 positive spindle cells of desmoplastic and neurotropic melanoma (arrowheads and *insets*) infiltrated the lymph node capsule and elicited a fibrosing reaction.

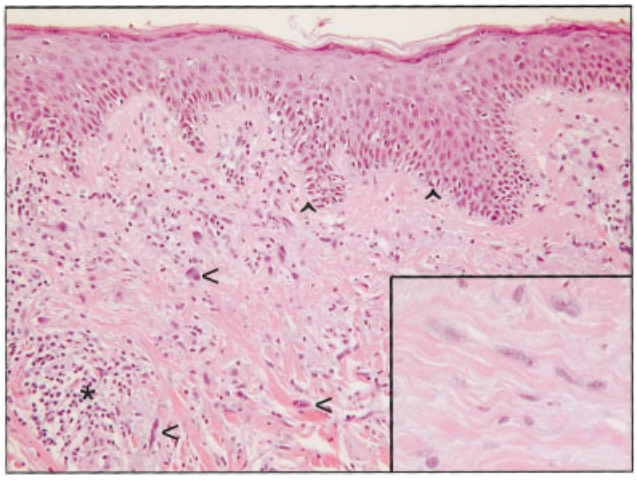

FIGURE 3. From Patient 2, desmoplastic and neurotropic melanoma (DNMM) (leftward arrowheads) arose on sun-damaged skin beneath in situ melanoma, lentigo maligna type (upward arrowheads). Often observed in DNMM, nodular lymphoid aggregates (asterisk) were present within and peripheral to the tumor. Again, tumor cells characteristically elicited a fibrosing reaction in the dermis (*inset*).

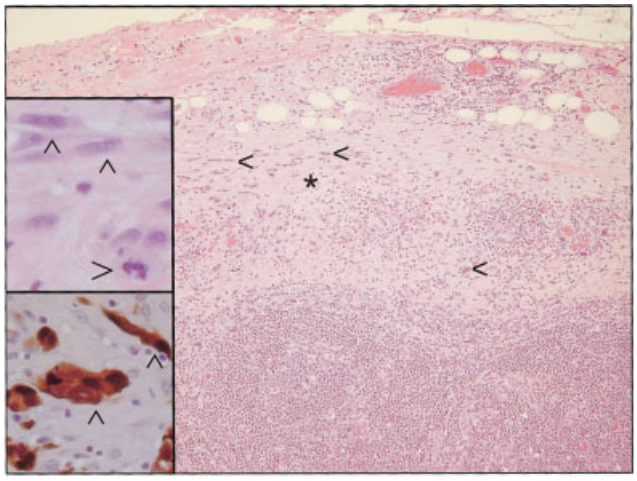

FIGURE 4. A sentinel lymph node from Patient 2 showed a pattern of tumor spread to the lymph node similar to that in Patient 1. There was obliteration of the subcapsular sinus accompanied by infiltration of the lymph node capsule (asterisk) by highly atypical, S-100 positive spindle cells of desmoplastic and neurotropic melanoma (arrowheads and *insets*).

nus and expanded the lymph node capsule (Figs. 2, 4). In two patients with DNMM from the midback region (Fig. 5) and right foot (Fig. 6), tumor metastasized to one of three left axillary SLNs and to two of two right groin SLNs, respectively. In both patients, a few clusters of tumor cells displayed an epithelioid morphology (Figs. 7, 8). No additional involved lymph nodes were identified in subsequent regional lymphadenectomy.

No statistically significant association was noted between several clinicopathologic factors and SLN metastasis. The mean Breslow depth of tumors that metastasized to SLNs was not significantly different from the mean Breslow depth of tumors that did not metastasize to SLNs (4.33 mm vs. 3.98 mm; $P = 0.70$). The mean mitotic rate of tumors that metastasized to SLNs (1.75/mm^2) was not significantly different from the mean mitotic rate of tumors that did not metastasize to SLNs (1.00/mm^2; $P = 0.27$). There was no

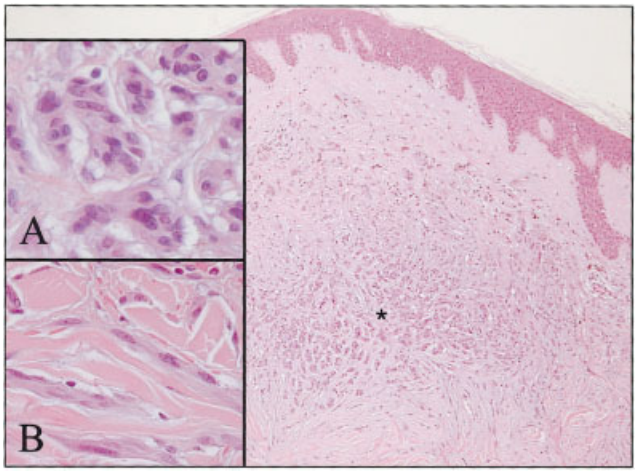

FIGURE 5. Desmoplastic and neurotropic melanoma from Patient 3 showed a small population of conventional epithelioid melanoma cells (asterisk and *inset A*) in the upper part of the tumor and atypical spindle cells invading the deep dermis accompanied by prominent desmoplasia (*inset B*).

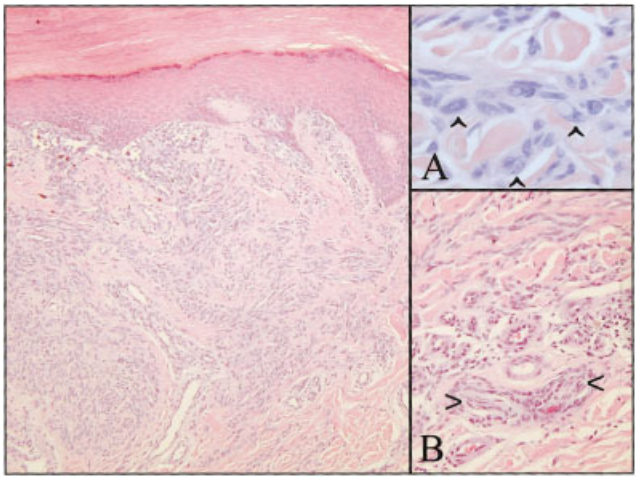

FIGURE 6. Desmoplastic and neurotropic melanoma arising in acral lentiginous melanoma from the foot of Patient 4 showed highly atypical spindle melanocytes infiltrating the dermis (arrowheads in inset A). Tumor cells displayed neurotropism surrounding and invading nerve twigs in deep dermis (arrowheads in inset B).

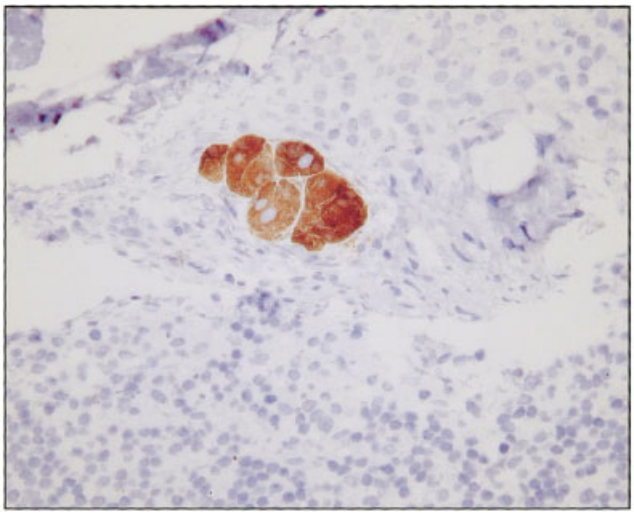

FIGURE 7. One of a few clusters of metastatic epithelioid melanoma in the lymph node parenchyma from Patient 3 was found to express melan-A.

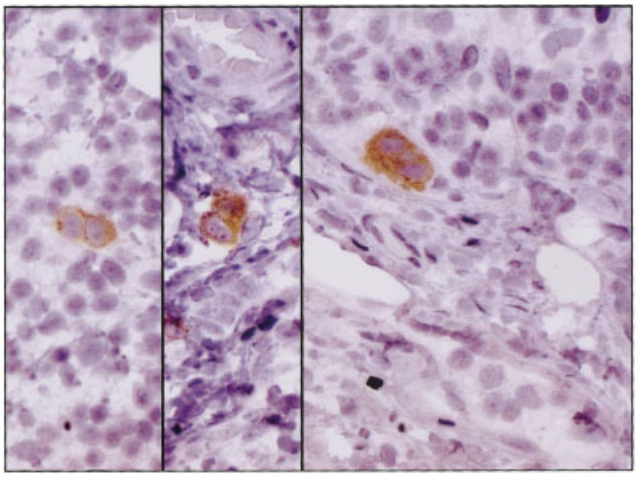

FIGURE 8. In the sentinel lymph node from Patient 4, a few clusters of melan-A positive, atypical epithelioid cells were identified in the parenchyma and peritrabecular areas, consistent with metastatic melanoma.

significant association between SLN metastasis and site on the head and neck ($P = 1.00$), tumor ulceration ($P = 0.14$), or neurotropism ($P = 0.29$).

Clinical follow-up was available on 30 of 33 patients (91%) who underwent SLNB, ranging in duration from 2 months to 66 months (median, 13.5 months; mean, 20 months). All four patients with positive lymph node status were alive and well without clinically apparent disease at the time of this report. Of the remaining 29 patients with negative SLNs, the tumor recurred in a regional lymph node and metastasized to the lungs of one patient (Patient 17) 9 months and 13 months after SLNB, respectively. The patient died of disseminated disease 20 months after the initial diagnosis of DNMM. One patient (Patient 15) developed lung nodules that were suspicious for metastatic disease but was lost to follow-up. Two patients with negative SLNs were lost to follow-up. The remaining 25 patients with negative SLNs were alive and well without evidence of disease at the time of last follow-up.

DISCUSSION

An analysis of the experience with DNMM at the University of Michigan Cancer Center confirms many of the observations in the literature regarding the pre-

TABLE 2
Reported Patients with Desmoplastic Melanoma without Sentinel Lymph Node Biopsy

Investigators	Average age (yr)	Average Breslow depth (mm)	No. of patients (%)			
			Regional lymph node metastases	Pulmonary metastases	Mortality rate	Follow-up (mos)
Devaraj et al.[6]	67	5.78	4/13 (31.0)	4/13 (31.0)	3/13 (23.0)	Mean, 40.0
Quinn et al.[3]	61	2.5	26/280 (9.0)	NR	27.8%	60.0
Smithers et al.[7,8]	61	4.5	6/45 (13.0)	2/45 (4.0)	5/45 (11.0)	1–108
Beenken et al.[9]	63	5.75	2/13 (15.4)	5/13 (38.0)	4/13 (30.0)	Mean, 55.0
Payne et al.[4]	63	2.6	3/30 (10.0)	2/30 (6.0)	1/30 (3.0)	Mean, 18.0
Reed and Leonard[2]	59	NR	2/16 (12.5)	1/16 (6.0)	9/16 (56.0)	24–108
Egbert et al.[10]	61	NR	3/25 (12.0)	NR	3/25 (12.0)	Mean, 32.4
Carlson et al.[5]	59	4.1	4/28 (14.0)	3/28 (11.0)	3/26 (11.5)	Mean, 36.0
Conley et al.[1]	53	NR	3/7 (42.0)	4/7 (57.0)	4/7 (57.0)	NR

NR: not reported.

sentation and natural history of this uncommon melanoma. DNMM typically presents in the head and neck region of elderly males.[3] The tumor most often occurs in lentigo maligna (42%) and, in the majority of patients, is deeply invasive at the time of diagnosis.[3] In our study, DNMM presented predominantly in the head and neck region (52%) of males (76%) with a mean age of 61 years. Tumors were deeply invasive (mean Breslow depth, 4.0 mm; median Breslow depth, 2.8 mm), and many were associated with lentigo maligna (24%).

Findings from this study also offer new insights into the clinical significance of SLNB for this tumor. Specifically, we document the utility of SLNB in detecting early metastases of DNMM to regional lymph nodes. The incidence of lymph node metastasis has been estimated to range from 8% to 15% for DNMM,[11] although a few studies have observed higher rates (Table 2). Of 33 patients with DNMM who underwent SLNB, positive SLNs were identified in 4 of 33 patients (12%), which is consistent with the incidence of lymph node metastasis reported in the literature.[3–11]

Cumulative data in the literature suggest that, compared with non-DNMM melanomas of the same depth, DNMM metastasizes less commonly to regional lymph nodes.[3,11–13] The reported incidence of lymph node metastasis in non-DNMM melanomas with a Breslow thickness of 1.5–4.0 mm ranges from 19% to 28.7%.[25,26] In our institutional data base, 22% of non-DNMM melanomas with a mean Breslow thickness of 2.9 mm had positive SLNB results. In contrast, only 12% of DNMM with an mean Breslow thickness of 4.0 mm had positive SLNB results, supporting the observation that, although DNMM is often deeply invasive, the tumor metastasizes to lymph nodes less frequently than conventional melanoma.

Despite the lower incidence of lymph node involvement in DNMM compared with non-DNMM melanoma, an argument can be made for performing SLNB in DNMM. It has been proposed that SLNB should be considered when a primary melanoma measures thicker than 1 mm and should be applied selectively for tumors that measure $\leq$ 1.0 mm, if ulceration is present, and perhaps if the lesion is invasive to Clark level IV or higher.[27] If SLNB should be considered for melanomas 1 mm thick, with an expected SLN positivity of about 8%,[26] then the higher observed SLN positivity rate of 12% for DNMM offers a reason to perform the procedure.

It is important for the histopathologist to recognize several possible pitfalls in the interpretation of SLNs for DNMM. First, the microscopic features of metastatic DNMM can vary and may not resemble the primary tumor.[1,2] In lymph nodes, their histology can manifest as that of classic malignant melanoma, that of a desmoplastic spindle cell tumor, or both.[1,2] In two patients in the current study, melanoma cells in SLNs displayed an epithelioid morphology, even though the primary tumor consisted predominantly of spindle cells (Figs. 5–8). In two other patients, metastatic DNMM exhibited a spindle cell morphology with associated desmoplastic stroma resembling the primary tumor (Figs. 1–4). Second, interpretation may be complicated by the presence of only a few tumor cells in the SLNs. In two patients in the current study, only a few clusters of melanoma cells were identified in SLN sections (Figs. 7, 8). Immunohistochemical stains for melan-A were pivotal in identifying microscopic metastases in both patients. Third, although DNMM usually expresses S-100 protein, the tumor often does not mark for more specific melanocyte markers, such as HMB-45, and inconsistently expresses melan-A.[28,29]

We encountered two such patients who were negative for melan-A (Figs. 1–4). However, a positive diagnosis was made on each case based on the combined histopathologic and immunophenotypical features (highly atypical, S-100 positive spindle cells obliterating the lymph node sinuses and abnormally expanding the capsule).

The use of SLNB for DNMM has been reported in 4 studies involving a total of 62 patients with only 1 SLNB (1.6%) that produced positive results.[4,11–13] In contrast, in the current study, we present a group of 33 patients in which SLNB detected occult lymph node disease in 4 patients (12%). SLNB allowed early detection of occult, metastatic DNMM, which, coupled with lymphadenectomy, may have limited tumor spread and prevented tumor recurrence at the draining lymph node basin in these four patients. Whether early detection and treatment of lymph node metastasis improves overall survival is not clear at this time, and long-term follow-up of these patients will be required to make this determination.

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