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Solitary Dermal Melanoma: Beginning or End of the Metastatic Process?

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Abstract

Background—Solitary dermal melanoma (SDM) is confined to the dermal and/or subcutaneous tissue without an epidermal component. It is unclear whether this lesion is a subtype of primary melanoma or distant cutaneous metastasis from an unknown primary. We evaluated our large experience to determine the prognosis and optimal management of SDM.

Methods—Our melanoma referral center's database of prospectively acquired records was used for identification and clinicopathologic analysis of patients presenting with SDM between 1971 and 2005.

Results—Of 12,817 database patients during a 34-year period, 101 (0.8%) presented with SDM. Of 92 patients free of distant metastasis on initial presentation, 55 (60%) were observed and 37 (40%) underwent nodal staging by elective or sentinel lymphadenectomy: regional metastases were identified in 7 (19%). Nodal recurrence occurred in 1 (3.3%) of 30 patients with histopathology-negative nodes, as compared with 13 (24%) of 55 patients who underwent nodal observation instead of nodal staging. Thus, 21 (23%) of 92 patients had nodal metastasis identified during surgical nodal staging or postoperative nodal observation. At a median follow-up of 68 months, estimated 5-year overall survival rate was 73% for 71 patients with localized disease versus 67% for 21 patients with regional disease ($P=0.25$) versus 22% for 9 patients with distant disease ($P=0.009$, regional versus distant disease).

Conclusions—SDM resembles intermediate-thickness primary cutaneous melanoma with respect to prognostic characteristics and clinical evolution, but its rate of distant metastasis justifies radiographic staging and its high rate of regional node metastasis justifies wide excision and sentinel lymphadenectomy.

Keywords

Solitary dermal melanoma; Prognosis; Management; Primary melanoma

Synopsis

Solitary dermal melanoma (SDM) is an infrequent entity with an uncertain etiology and unclear prognosis. We evaluated the incidence and prognosis of SDM and provide management recommendations.

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INTRODUCTION

Melanoma without a known epidermal primary may present clinically in various forms including metastatic melanoma with palpable lymphadenopathy involving single or multiple sites or a solitary dermal lesion. Solitary dermal melanoma (SDM) is confined to the dermis and/or subcutaneous tissue without an epidermal component and is without other physical evidence of melanoma. SDM is infrequently reported in literature with incidences between 0.4% and 0.9% (Table 1).¹⁻⁶ Because of this infrequency, the prognostic significance of SDM remains unclear. Some have found this entity to be similar to stage IV metastatic disease (M1a) or in transit metastases (N2c) from an unknown primary, portending a poor overall prognosis,^{1, 5} whereas others report survival rates exceeding 80%,^{2-4, 7} pointing to either a regressed primary melanoma or a distinct entity called a primary dermal melanoma.

The rarity, uncertain etiology, and unclear prognostic implications of SDM have discouraged a standardized approach to its evaluation and management. Although sentinel lymphadenectomy (SL) and radiographic studies are routine for evaluation of localized melanoma and distant melanoma, respectively, their role for evaluation of SDM is less certain. Sentinel lymph node (SLN) procedure is a standard staging and management technique for primary cutaneous melanoma and is also useful for isolated local and in-transit recurrent melanoma from a known primary.⁸⁻¹⁰ If SDM represents a form of localized/early stage melanoma or in-transit disease, then sentinel lymphadenectomy may prove to be useful in detecting microscopic nodal metastasis. However, if the prognostic outcome of SDM represents a later stage melanoma, then radiographic evaluation would be essential to detect distant disease not evident on physical examination. We reviewed our large experience with melanoma to evaluate the incidence and prognosis of SDM and define management recommendations for these patients.

PATIENTS AND METHODS

The prospectively collected melanoma database at the John Wayne Cancer Institute was reviewed to identify all patients presenting with SDM between January 1971 and December 2005. SDM was defined by clinical and histologic evidence of a single focus of melanoma limited to dermal and/or subcutaneous tissue without an epidermal component, and with no known primary. Melanoma was diagnosed by either excision or fine-needle aspiration (FNA).

Patients underwent a thorough examination including cutaneous evaluation to search for a potential primary source. Staging evaluation and further surgical treatment were performed within a 3 month period from the initial diagnosis of SDM. Sentinel lymphadenectomy (SL) or elective lymphadenectomy (EL) was undertaken to evaluate for regional disease. Patients underwent radiographic studies, including brain and body imaging available at the time of diagnosis, to evaluate for distant metastases.

Treatment involved excision of SDM with or without nodal evaluation which occurred concurrently or separately from SDM excision but within 3 months of initial diagnosis. Wider excision of the SDM was performed if deemed necessary to achieve adequate margins. Histopathology-positive sentinel lymph nodes were subsequently managed with completion regional lymphadenectomy (CRL).

Patient clinical information including age, sex, site of melanoma, treatment, nodal assessment, and clinical outcomes were noted from our prospectively-acquired database and chart review. Results of lymphadenectomy including site, nodal positivity, and type of nodal procedure were recorded.

Follow-up period was defined as the interval between the date of diagnosis of SDM and death due to any cause or last follow-up. Time to nodal progression was defined as the interval between surgical treatment (wide excision and/or lymphadenectomy) of SDM and diagnosis of a subsequent nodal recurrence. Overall survival was defined as the interval between surgical treatment of SDM and death due to any cause or censored at last follow-up. Survival rates and median survival times were derived from the Kaplan-Meier method and compared by log-rank test. Significant covariates ($P < 0.05$) on survival were identified by multivariate analysis using Cox regression. Statistical analysis was performed using SAS software (SAS Institute Inc, Cary, NC).

Approval for this retrospective study was obtained from the John Wayne Cancer Institute-Saint John's Health Center (JWCI-SJHC) joint institutional review board.

RESULTS

The clinical information for 12,817 melanoma patients was prospectively registered during the study period. Among the more than 900 patients with an unknown primary melanoma, 101 presented with SDM (Table 2). Most patients were younger than 60 years of age (69%) and male (62%). Both the mean age and median age were 52 years (range, 21 to 84 years). The most frequent site for SDM was the extremity (42%). Mean and median follow-up periods were 7.3 years and 5.6 years, respectively (range, 0.4 to 34.5 years).

Staging evaluation of 101 SDM patients revealed localized melanoma in 85 (84%) patients, regional melanoma in 7 (7%) patients, and distant melanoma in 9 (9%) patients. Of 92 (91%) patients with local or regional disease, 37 (40%) underwent nodal staging by SL or EL, and 55 (60%) underwent nodal observation without nodal staging (Figure 1).

Of 37 patients assessed by nodal staging, 20 (54%) underwent SL (3 with positive SLNs and 17 with negative SLNs) while 17 (46%) were managed by EL (4 with positive nodes and 13 with negative nodes). Thus, seven patients had histopathology-positive nodes (4 in axilla, 1 in neck, 2 in groin). The mean number of tumor-positive nodes was 1.4 (median, 1; range, 1 to 3). All seven patients with a tumor-positive SLN underwent CRL. Nodal recurrence occurred in 1 (3.3%) of 30 patients with histopathology-negative nodes.

Of 55 patients who underwent nodal observation, 13 (24%) developed nodal recurrence. All 13 patients had palpable nodal metastases in the drainage basin predicted by the anatomic site of the SDM and as would be expected for a known primary melanoma in the same site. Mean time to nodal progression was 21.5 months (median, 15.2 months; range, 4.3 to 72.2 months). Sites of nodal involvement included three in the neck, four in the axilla, five in the groin, and one in the interpectoral region. The number of nodes removed ranged from 1 to 44, and three patients had only a single node removed. In 12 patients with nodal metastasis, the mean number of positive nodes was 2 (median, 1; range, 1 to 6). Complete nodal data was not available for the remaining patient, who was treated with CRL and subsequent radiation therapy.

In summary, 21 (23%) of 92 patients with local/regional disease had nodal metastasis at the time of nodal staging or developed nodal metastasis during nodal observation.

Of the 101 patients, the nine with distant disease had metastases in the brain (2 patients), lung (2 patients), or multiple sites (5 patients). Initial treatment for metastatic disease included single therapy with interleukin (1 patient), radiation (1 patient), vaccine (1 patient), chemotherapy (1 patient), biochemotherapy (1 patient), or a combination of immunotherapy and cytokines (2 patients). Treatment information was not available for two patients.

Respective median and 5-year overall survivals for the 101 patients were 8.3 years and 66%. Since 14 of 92 patients developed nodal progression that might have been due to missed nodal disease, survival was analyzed by combining this group with the seven node-positive patients. Overall survival comparison for 71 patients with localized disease versus 21 patients with regional disease was not statistically significant ($P=0.25$), but comparison for 21 patients with regional disease versus 9 patients with distant disease was statistically significant ($P=0.009$, Figure 2). Of the 71 patients with localized disease (71), those younger than 60 years had significantly better survival (Table 3). Sex, site of SDM, and decade of diagnosis were not significant. Age was the only variable that was prognostically significant by multivariate analysis ($P=0.029$; hazard ratio, 2.201; 95% CI, 1.086 to 4.461).

DISCUSSION

Our study, the largest yet reported on solitary dermal melanoma, confirms the low (<1%) incidence of SDM in the melanoma population and the generally favorable survival after wide excision of SDM in patients without distant metastasis. Because our experience represents the largest single-institution review of SDM thus far reported, its demographic data are not subject to the variations of smaller studies.^{2, 3} Most of our patients were younger than 60 years and most were male, consistent with prior studies of unknown primary melanoma and population-based studies.¹¹⁻¹⁴ Because younger patients with melanoma tend to show a more favorable prognosis than older patients,^{14, 15} the age distribution of our population and of other reported SDM populations^{2-4, 7} might have improved overall survival. Scoggins et al¹⁶ reported that male sex was independently associated with thicker primary cutaneous melanomas and worse prognosis, although male patients did not have a higher rate of nodal metastases. This trend was not evident in our patients with SDM, possibly due to a durable immune response that stops tumor progression.

Similar to demographic data, reports of site distribution are either inconsistent or not available in prior studies.^{1-7, 17} Most of our patients had SDM on an extremity. Reasons for the preferential location of SDM in the extremity remain unclear, since there was an insignificant difference in comparison to other sites. However, larger studies on primary cutaneous melanoma have shown a more favorable outcome with the extremity site compared to trunk and head/neck sites.^{14, 18}

Explanations for SDM include 1) distant subcutaneous metastasis (M1a) or regional intransit metastasis (N2c) from a primary that underwent complete regression, 2) a primary dermal melanoma (PDM), or 3) a primary melanoma with regressed epidermal component. The first explanation portends the poorest outcome with reported 5-year OS rates of 19% for an M1a lesion¹⁹ and 12-42% for an N2c lesion^{20, 21} in patients with a known primary melanoma. Similarly, some have reported a 5-year survival rate of 25% and median survival of 28 months for solitary subcutaneous lesions in patients without a known primary.^{1, 5} These survival rates are too low to support metastasis from an unknown primary as an explanation for SDM in our study group.

A more feasible explanation for SDM is either a PDM or a primary melanoma with regressed epidermal component. Contrary to the poorer outcomes expected for M1a and N2c lesions, reported 5-year survival rates for localized primary melanoma with an epidermal component are 45% to 95% depending on the thickness and presence of ulceration.¹⁹ Several small studies evaluated the thickness in resected nonulcerated SDM lesions; mean Breslow thickness was approximately 6 to 7 mm, a depth characteristic of a thick primary melanoma,^{2, 3} but the lower range of thickness included 1 to 2 mm, a depth characteristic of intermediate-thickness melanoma. Although these studies and others^{4, 7} were too small for statistically meaningful analysis of survival, their reported outcomes were more similar to those for nonulcerated

intermediate and thick primary melanomas (5-year OS rates of 67 to 89%)¹⁹ than to those for metastatic disease (Table 1).

It is less clear if SDM represents PDM or an epidermally regressed primary. Swetter et al² described PDM as a unique subtype of melanoma, which may be biologically less aggressive than primary melanoma of similar Breslow thickness and associated with prolonged survival. In their follow-up immunohistochemical study, Cassarino et al¹⁷ reported that PDM could be distinguished from primary nodular melanoma and cutaneous metastatic melanoma by significant differences in the IHC staining of several antigens. Some have speculated that a primary dermal melanoma may arise from nonepidermal melanocytes or intradermal nevi.³ If so, then one would expect evidence of a preexisting residual nevus, but none were evident in the specimens of the aforementioned studies. Also, the introduction of selection bias for this specific entity may have affected the results in such studies.^{2, 3} Others have demonstrated a regression phenomenon of the epidermal component evidenced by a lymphocytic infiltrate.²² An immune-mediated process may confine the tumor locally, and the passage of time might eliminate detectable evidence of regression with a lymphocytic infiltrate.

In our study, the staging of SDM yielded three prognostic groups based on extent of disease. The prognosis for patients with localized disease (5-year survival of 73%) was similar to that described in other studies of SDM^{2-4, 7} and similar to that associated with intermediate or thick primary melanomas. Prognosis for patients with nodal involvement (5-year survival of 67%) matched or exceeded that for patients presenting with regional node metastasis from a known primary melanoma. Importantly, 23% of patients presenting with an SDM had evidence of nodal involvement or later developed nodal disease. Of those not staged by nodal evaluation, 24% had disease that progressed to regional nodes. Hence, microscopic nodal disease may have been detected if nodal evaluation had been performed on original diagnosis of SDM. Such a high percentage of nodal involvement is not unexpected since the predicted occurrence of microscopic nodal metastasis correlates directly with tumor Breslow thickness.^{23, 24} Hence, this is a strong indication for routine use of sentinel node biopsy as a staging and management tool.⁸⁻¹⁰ As expected, prognosis was least favorable (5-year survival of 22%) when the staging work-up revealed distant metastasis (9%). Staging evaluation was essential to identify this cohort of patients for appropriate stage-related treatment.

Like the smaller studies of SDM,^{2, 3} our study is subject to the selection bias inherent in a retrospective search. However, even if a future prospective analysis lowers the estimated survival rates, our findings allow specific recommendations for staging and management of patients presenting with clinical and histologic evidence of a solitary subcutaneous melanoma without an epidermal component. These patients require thorough evaluation with attention to the history and dermatologic exam, and a full metastatic survey including imaging studies. If there is no clinical or radiographic evidence of metastatic disease, the regional nodes should be assessed with sentinel lymphadenectomy because approximately 23% of SDM patients will harbor nodal metastasis.

In conclusion, patients with SDM have survival characteristics not unlike those associated with intermediate or thick primary melanoma. Because patients with regional nodal metastasis from SDM have a prognosis similar to that for patients with regional nodal metastasis from a known primary melanoma, they should be managed for regional rather than distant disease.

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FIG 1.
Study results from 1971 to 2005.

FIG 2.
Overall survival comparison of solitary dermal melanoma involved locally, regionally, and distant.

Reported rates of incidence and survival of resected dermal melanoma

TABLE 1

Reference ^a (year)	Solitary Dermal Melanoma No.	Total Melanoma No.	Incidence (%)	Survival rate (%)	Median (months)
Lee et al (current)	85 ^b 71 ^c	12817	0.7 0.6	71 (5yr) 73 (5yr)	103.2 158.4
Katz et al ¹ (2005)	12 ^d	2485	0.48	25 (5yr)	NR
Swetter et al ² (2004)	7	1800	0.39	100 (5yr)	NR
Bowen et al ³ (2000)	11	1800	0.61	83 (8yr)	NR
Anbari et al ⁷ (1997)	3	NR	NR	100 (4yr)	NR
Schlagenhauff et al ⁴ (1997)	30 ^e	3258	0.92	83 (5yr)	NR
Reintgen et al ⁵ (1983)	18	2612	0.69	NR	28
Giuliano et al ⁶ (1980)	9 ^f	980	0.92	NR	NR

NR, not reported.

^aAll appeared to have localized disease.
^bTotal number prior to nodal recurrence.
^cSolitary dermal melanoma after accounting for nodal recurrence.
^dType of treatment not mentioned; unclear if all patients had solitary lesions.
^eUnclear if all patients had solitary lesions.
^fType of treatment was highly variable; 4 of 5 resected were alive more than 5 years after diagnosis; unclear if all patients had solitary lesions.

TABLE 2
Characteristics of patients with solitary dermal melanoma

Variable	All Patients (N=101)		Patients After Staging ^a (N=71)	
	No	(%)	No	(%)
Age				
<60	70	(69)	50	(70)
≥60	31	(31)	21	(30)
Sex				
Male	63	(62)	43	(61)
Female	38	(38)	28	(39)
Dermal Site				
Head/Neck	19	(19)	13	(18)
Trunk	39	(39)	27	(38)
Extremity	43	(42)	31	(44)
Decade of Diagnosis				
1970-79	7	(7)	5	(7)
1980-89	22	(22)	12	(17)
1990-99	49	(48)	38	(53)
2000-05	23	(23)	16	(23)
Solitary dermal nodule	85		NA	
LN progression	14			
Axilla	4			
Neck	3			
Groin	6			
Other	1			
No progression	71			
Nodal disease	7		NA	
Axilla	4			
Neck	1			
Groin	2			
Distant disease	9		NA	
Brain	2			
Lung	2			
Multiple	5			

NA, not applicable.

^a After nodal and radiographic staging, factoring in patients with nodal progression.

TABLE 3

Overall survival comparison of variables

Variable	N	Median Survival (Years)	5-yr OS (%)	10-yr OS (%)	P-value
Age					
<60	50	17.8	81	64	0.025
≥60	21	5.4	60	30	
Sex					
Female	28	8.9	79	49	0.91
Male	43	17.2	67	58	
Site of SDM					
Head/Neck	13	NR	83	55	0.065
Trunk	27	6.8	69	37	
Extremities	31	23.7	76	68	
Decade of diagnosis					
1970-79	5	23.7	100	80	0.78
1980-89	12	7.6	75	42	
1990-99	38	NR	71	53	
2000-05	16	NR	53	NR	

NR, not reached.