Primary Dermal Melanoma

Distinct Immunohistochemical Findings and Clinical Outcome Compared With Nodular and Metastatic Melanoma

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Objective: To provide an updated and expanded analysis of clinical outcome and immunohistochemical (IHC) findings unique to primary dermal melanoma (PDM) that may be used to differentiate this entity from primary nodular melanoma (PNM) and cutaneous metastatic melanoma (MM).

Design: Cohort analysis and extensive IHC panel comparing PDM with PNM and cutaneous MM.

Setting: Melanoma clinics and pathology departments of academic and VA medical centers.

Patients: Thirteen patients with a solitary dermal or subcutaneous nodule of histologically proven melanoma, prospectively followed through April 30, 2007.

Interventions: Clinical, pathologic, and IHC assessment of patients diagnosed as having PDM.

Main Outcome Measures: Long-term clinical outcome and determination of unique clinical and IHC features in the study cohort compared with other melanoma subtypes.

Results: Histologically, there was no evidence of an overlying in situ component, ulceration, or regression, and there was no associated nevus in any cases. Clinical history and findings from workup, including imaging studies, skin examination, and sentinel lymph node biopsy, were negative for evidence of melanoma elsewhere. The mean Breslow depth was 9.6 mm. Two patients developed satellite or in-transit recurrences, 1 developed pulmonary metastasis, and another died of liver metastases. Overall, the cohort showed a 92% melanoma-specific survival rate at a mean duration of follow-up of 44 months. The IHC findings showed that PDM exhibited lower levels of staining for the antigens p53 (P = .02), Ki-67 (Mib-1) (P = .002), cyclin D1 (P = .001), and podoplanin (recognized by D2-40 antibody) lymphovascular staining (P < .001) compared with MM and PNM. All other markers were comparable.

Conclusions: Patients with PDM have remarkably prolonged survival compared with patients with MM or PNM of similar thickness. Preliminary results suggest that PDM may be characterized by lower levels of p53, Ki-67, cyclin D1, and D2-40 compared with histologically similar MM and PNM.

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Primary Dermal Melanoma (PDM) is a newly described variant of melanoma that is confined to the dermis and/or subcutis and histologically simulates a cutaneous metastasis. Only 2 case series in the literature have specifically identified PDM, although previous studies have reported rare cases of apparent solitary metastatic melanoma (MM) to the skin of unknown primary origin with unexpectedly prolonged survival. It is likely that at least some of these previously reported cases represent what would now be identified as PDM. Compared with cases of MM to distant skin, subcutaneous, and nodal sites (stage IV M1a disease based on current AJCC staging criteria), the estimated 5-year survival rate of patients with PDM has been surprisingly favorable (5%-19% vs 80%-100%, respectively). We previously reported a cohort of 7 patients with PDM from Stanford University Medical Center (SUMC), Stanford, California, and VA Palo Alto Health Care System (VAPAHCS), Palo Alto, California, who demonstrated 100% survival at mean follow-up of 41 months (range, 10-64 months). Herein, we extend that study with long-term follow-up (mean duration of follow-up, 44 months; range, 6-94 months) of a larger cohort of 13 patients. None had a history or evidence of primary melanoma, regressed primary melanoma, or MM after extensive clinical and radiologic workup. Histologically, all cases were characterized by a deep dermal and/or subcutaneous tumor nodule, which was often well circumscribed and showed classic cytologic features of malignant melanoma. The initial diagnosis favored MM in nearly all of the cases. In addition,
we examined an extensive panel of immunohistochemical (IHC) stains to identify any potential differences in the expression of various melanocytic, oncogenic, and proliferation-related markers between those with PDM (hereinafter, PDM group) vs those with primary nodular melanoma (PNM) and MM (hereinafter, PNM and MM groups) to the skin.

The study was approved by the SUMC and VAPAHCS institutional review boards. Patients with PDM were identified from the files of the Department of Pathology at SUMC and the Pathology Service at the VAPAHCS. Initial cases were identified by both institutions based on a search of all cases histologically reviewed by the pathologist, but clinical and imaging studies failed to reveal any evidence of another primary or metastatic site involved by melanoma. Clinical outcome and recurrence were assessed through April 30, 2007, or until death from disease.

Abbreviations: DOD, died of disease; FU, follow-up; NA, not applicable; ND, not done; NED, no evidence of disease; neg, negative; NV, not available; SLN, sentinel lymph node.

Follow-up through April 30, 2007, including disease-free survival, time to local recurrence or distant metastasis, or death from melanoma or other disease.

Patient died of unrelated causes.

Patient relocated and was lost to FU.

An SLN biopsy performed at the time of excision of in-transit metastasis at month 12 of FU was negative for disease. Additional in-transit metastasis excised at month 14.

Local, persistent-disease recurrence within the melanoma scar at month 4 of FU owing to incomplete surgical excision at time of diagnosis. Tumor was excised, and findings from metastatic workup were negative; NED as of month 6 of FU.
RESULTS

Thirteen cases of PDM were identified, including 8 men and 5 women, with a median age at diagnosis of 74 years (mean, 70 years; range, 21-85 years) (Table 1). No other cases in the SUMC melanoma clinics (since 1995) or VAPAHCS melanoma database (since 1990) had similar clinical presentation (ie, presumed solitary cutaneous metastasis of unknown primary site and lack of nodal or visceral involvement). Clinically, most lesions were described as cysts or subcutaneous nodules, and the clinical differential diagnosis typically included cyst vs basal cell carcinoma, squamous cell carcinoma, dermatofibroma, adnexal tumor, and neurofibroma. In a few cases, the lesion appeared blue-gray or slightly violaceous, but in only 1 case was the diagnosis of amelanotic melanoma specifically mentioned in the clinical differential diagnosis (Figure 1). There did not seem to be any definite site predilection for PDM because most lesions were found both in the head and neck region (cheek and scalp) as well as the upper and lower extremities (Table 1). One truncal PDM near the left axillary fold was identified.

Complete clinical workup, including skin examinations and thorough imaging studies (computed tomography [CT] and positron electron tomography [PET], as well as brain magnetic resonance imaging [MRI]), was performed on most patients and failed to reveal evidence of another primary melanoma or MM. In addition, none of the patients had a clinical history or evidence suggestive of a completely regressed primary melanoma at another site. Wide local excision of 9 of the 13 cases from SUMC and VAPAHCS was performed with 2-cm margins, as is our standard procedure for primary melanoma thicker than 2 mm. Sentinel lymph node (SLN) biopsies were performed in 11 of the 13 patients at diagnosis, findings in 10 of which were negative for MM, and 1 of which was lost in processing (Table 1). Patients were followed up for a mean duration of 44 months (range, 6-94 months; median, 36 months). Three elderly patients in our initial PDM cohort died from unrelated causes (small cell lung cancer, myocardial infarction, and chronic lymphocytic leukemia) after 70 to 94 months of follow-up, and 2 moved to other states, with 1 lost to follow-up at 20 months and the other disease-free 57 months after diagnosis.

Four patients developed recurrent disease, 1 of which consisted of a solitary satellite metastasis adjacent to the melanoma scar 7 months after initial diagnosis and treatment, which was excised. No further recurrence was detected in this patient, who expired from other causes after 7 years of follow-up. Another patient, who also happened to be the youngest in our study (21 years old at diagnosis of disease), developed asymptomatic liver metastasis, which was detected on surveillance PET 3.5 years later, and subsequently died from complications related to her disease. A third patient, in whom SLN biopsy was not performed at diagnosis, developed an in-transit metastasis between the PDM scar on the arm and the axillary nodal basin 12 months after undergoing wide local excision alone. An SLN biopsy was performed at the time of excision of the in-transit metastasis, and findings were negative for regional nodal disease. Imaging with combined PET/CT and brain MRI scans were negative for visceral metastasis. A subsequent in-transit metastasis in this patient at month 14 of follow-up prompted additional wide local excision and treatment with adjuvant high-dose interferon. Finally, a fourth patient was diagnosed as having an asymptomatic pulmonary metastasis at month 23 of follow-up, initially detected on surveillance chest radiograph, followed by staging with PET/CT, findings of which were otherwise negative for disease.

Histologically, cases of PDM were typically characterized by a solitary, well-circumscribed but unencapsulated, deep dermal and/or subcutaneous melanoma (Figure 2A and B). Some of the lesions showed areas of extensive hemorrhage (Figure 2C) and cystic degeneration. The Breslow depth ranged from 2.5 to 30.0 mm (mean, 9.64 mm; median, 7.0 mm; Table 1). The tumor cells showed a variety of morphologic patterns, including epithelioid, spindled, and occasionally rhabdoid features, and were frankly cytologically malignant with pleomorphism, hyperchromatic nuclei, prominent nucleoli, and frequent mitoses (Figure 2D, arrows). Necrosis was also present in many of the cases in the centers of large nests (Figure 2D, center top). There were no surface or follicular connections on examination of multiple sections, and no cases exhibited any overlying ulceration or evidence of regression, as would be expected in a PNM with loss of the overlying junctional component. In addition, there were no findings suggestive of a preexisting nevus such as a congenital or blue nevus. No association with a peripheral nerve, as may be seen in a malignant peripheral nerve sheath tumor (MPNST), was identified in any case.

IHC RESULTS

Extensive IHC analysis of the 13 PDM cases was performed and compared with 24 cases of MM and PNM, including 15 cases of MM (13 of which were documented cutaneous metastases with concomitant visceral disease and 9 of which were classic PMNs). The panel
included antibodies directed against BCL-2, p53, p16, cyclin D1 (bcl-1), KIT, Ki-67, podoplanin (D2-40), c-ERBB2, MEL-CAM, E-cadherin, nestin, CD166, and KBA-62. We found statistically significant differences between PDM vs MM and PNM (which were grouped together for the initial statistical analysis) in the oncogenic and proliferation-related markers p53, cyclin D1, and Ki-67 (see Table 2 for \( P \) values). Cyclin D1 was typically strongly positive in a nuclear pattern in the MM and PNM group (Figure 3A) (mean percentage of positive cells, 37.7%) vs the PDM group (mean, 7.0%; \( P = .001 \)), in which the pattern was often weak and focal (Figure 3B). Immunohistochemical staining for p53 was also more strongly and diffusely positive in the MM (Figure 4A) and PNM groups (19.5%) vs the PDM cases (3.0%; \( P = .02 \)), which showed focal, often weak, nuclear staining (Figure 4B). In addition, Ki-67 was typically high in the MM (Figure 5A) and PNM groups (29.4%) vs the PDM group (7.9%; \( P = .002 \)) (Figure 5B). In addition, we found a significant difference in lymphangiogenesis as measured by D2-40 staining in the PDM (mean [SD] LVD, 12.8 [7.7]/mm²) vs the MM and PNM groups (mean LVD, 21.7 [6.0]/mm²; \( P < .001 \)).

The statistically significant IHC results are also summarized graphically in Figure 6 and Table 2. The other markers, including stem cell markers nestin and CD166,
did not show any significant differences between the groups (see Table 2 for P values). Interestingly, KIT expression was negative in only about half of our MM cases, despite reportedly being lost in most MMs. In the PDM group, only 5 of 13 patients were completely negative for KIT by IHC staining, which includes 2 of the cases with recurrence or metastasis. None of our cases showed any IHC staining with c-ERBB2, which has only been reported in rare cases of melanoma.

**Primary dermal melanoma** is a distinct subtype of melanoma characterized by improved patient survival and unique IHC findings (lower p53, Ki-67, cyclin D1, and D2-40 expression) compared with both cutaneous MM and PNM, which it may simulate histologically. Since our initial report of PDM in 2004, we have continued to prospectively identify, treat, and follow the largest cohort of patients with presumed PDM. Improved ability to diagnosis PDM via IHC markers will help to avoid potential misdiagnosis as stage IV cutaneous metastasis and result in optimal patient management and counseling regarding prognosis.

Metastatic melanoma involving distant skin and/or subcutaneous or lymph node sites is regarded as stage IV disease (anyTanyN1a), according to current AJCC melanoma staging guidelines and carries a dismal prognosis.
with an estimated 5-year survival rate of 19% and median survival of only 7 to 15 months. In contrast, patients with solitary deep dermal or subcutaneous melanomas with no history of melanoma elsewhere have a much better prognosis.1-5 To date, our PDM cohort currently shows a 92% survival rate at a mean follow-up of 44 months. Only 1 patient has died of disease in our series, secondary to complications arising from liver metastasis detected 3.5 years after her primary lesion was discovered. Interestingly, this patient was also the youngest (21 years old at the time of diagnosis of PDM) in our series. A second patient developed solitary pulmonary metastasis at the end of our follow-up period, and it is possible that the overall survival rate will decrease with continued surveillance of this patient. To date, only 2 other patients have developed local satellite or in-transit recurrences, including a 75-year-old man who presented with a primary lesion on his cheek and experienced a satellite metastasis 6 months later. This was completely excised, and the patient was without disease at the time of his death from other causes 7 years later. Another patient treated at an outside facility developed 2 in-transit metastases 12 and 14 months after diagnosis of PDM and was treated with adjuvant high-dose interferon following complete excision and was disease free at 16 months' follow-up.

Although it is conceivable that our entire cohort may represent the estimated 19% who survive 5 years with stage IV M1a disease, we find this probability unlikely and would counter that potential inclusion of PDM cases misclassified as solitary cutaneous metastasis in the AJCC worldwide database (anyTanyNM1a)6 may contribute to falsely elevated survival rates for this subgroup of patients. Furthermore, the observed occurrence of satellite or in-transit metastasis in 2 of our patients argues more strongly for a diagnosis of primary melanoma with subsequent local intralymphatic metastasis rather than the original diagnosis of cutaneous metastasis, which should arise via hematogenous dissemination and would be extremely unlikely to then spread through dermal lymphatics.

Histologically, all of our specimens showed large, usually well-circumscribed, dermal-based tumors with no epidermal or follicular connections. By definition, none showed evidence of ulceration, regression, or a preexisting nevus. The initial histologic impression was almost uniformly that of MM, which was confirmed by positive IHC staining for melanocytic markers. Given the obviously malignant cytological features present in all of our specimens, with frequent mitoses and necrosis, the diagnosis of a nevoid or so-called minimal deviation melanoma, which is characterized by deceptively low-grade cytologic atypia, would not be seriously considered in the differential. In addition, the diagnosis of PNM was excluded owing to the lack of any overlying epidermal involvement, ulceration (which could mask an epidermal component), or evidence of regression. None of our specimens showed any association with a preexisting benign dermal-based nevus, such as a blue nevus. Therefore, although findings in 2 cases showed some heavily pigmented (nondendritic) tumor cells, the interpretation of a malignant blue nevus, which typically requires the presence of a benign preexisting blue nevus component,10-12 would also be inappropriate. In addition, the reported cases of malignant blue nevus have shown an aggressive course with poor prognosis,10-12 in contrast to our study cohort.
Although other differential diagnostic considerations could also include an MPNST and clear cell sarcoma or malignant melanoma of soft parts (MMSP), the clinical and histologic findings of both of these tumors are distinct from melanoma.13,14 The MPNSTs are typically associated with large peripheral nerves, occur in patients with neurofibromatosis, may be partially encapsulated, and show areas with neural differentiation and myxoid stroma,13 which were lacking in our patients. In addition, the presence of frequent nesting and occasional melanin pigment were observed in our cases, which would be unexpected, although the latter may rarely be seen, in MPNSTs. Immunohistochemically, MPNSTs are typically only focally and weakly positive for S100 and are negative for all other melanocytic markers,13,15 whereas the IHC findings in all of our cases were strongly positive for S100 and 1 or more other melanocytic markers. Although MMSP shares much histologic and IHC overlap with melanoma, the clinical presentation is much different because these typically occur on the distal, often lower, extremities of children and young adults (age range, 10-40 years).13 Only 1 of our patients was younger than 40 years, and her tumor presented on the temple. In addition, these are deep-seated soft tissue tumors, typically attached to aponeuroses or tendons.14 Histologically, although the tumors show nesting, they are typically composed of spindled cells with clear cytoplasm, and prominent fibrous septae course between the nests.13 Our cases showed typical cytologic features of melanoma, with nests composed of epitheloid, round-to-oval, and occasionally rhabdoid-appearing, cosinophilic-staining cells, lacking the spindling or cytoplasmic clearing of MMSP. In addition, consistent with their slow growth and indolent behavior, MMSP typically has a low mitotic rate and lack necrosis, in contrast to the findings in our cases, which showed frequent mitoses and necrosis.

In a recent publication, Deyrup et al16 described a small series of rare tumors referred to as paraganglioma-like dermal melanocytic tumors.10 These tumors were exclusively dermal-based and composed of nested, clear-to-amphophilic cells, often separated by fibrous strands, features reminiscent of a paraganglioma. The tumors stained positive for melanocytic markers including S100, HMB-45, and microphthalmia transcription factor. Although these authors16 mentioned that PDM was considered in the histologic differential, their tumors were cytologically bland, lacking frequent mitotic activity or necrosis, in contrast to PDM. In addition, none of their patients experienced a recurrence or metastasis.10 In short, paraganglioma-like dermal melanocytic tumor seems to represent a benign dermal-based melanocytic tumor. Although it is intriguing to speculate whether these tumors could be related to (or be a benign precursor of) PDM, tumors that show frankly malignant cytologic features should not be confused with this entity and should be diagnosed as melanoma.

Although IHC analysis alone cannot be used to make the diagnosis of PDM, it is useful for confirming the melanocytic nature of these tumors if there is any histologic uncertainty. In addition, the findings of statistically significant differences in p53, Ki-67, cyclin D1, and D2-40 staining between the PDM group and the PNM and MM groups suggest that these markers may be useful in confirming suspected cases of PDM (see Table 2 for P values). The lower levels of oncogenesis-related (defective nuclear p53) and cell-cycle and proliferation-related (cyclin D1 and Ki-67) proteins likely correlate with the less aggressive behavior of PDM vs MM and PNM. In addition, tumor lymphangiogenesis (measured by D2-40) is frequently seen in invasive melanoma and MM and correlates with lymph node metastasis and reduced survival.17,18 Therefore, the lower level of D2-40 staining in the PDM group vs the MM and PNM groups is also consistent with these tumors having a lower metastatic potential. However, in practical terms, positivity for 1 or more of these markers certainly cannot exclude the diagnosis of MM, and metastatic evaluation should still be performed with complete clinical, surgical, and radiologic studies as indicated. Likewise, taking a careful medical history is necessary to exclude a primary melanoma (including regressed) or MM at another site. Based on our assumption that PDM represents a primary and not metastatic process, we performed an SLN biopsy on all internal cases for additional staging purposes. Interestingly, no positive SLNs or nodal recurrence were detected in any patients.

The etiology of PDM remains unknown. It may be postulated that these tumors arise from a dermal-based melanocytic stem cell that may either be normally present or the result of aberrant migration of neural crest cells during embryogenesis. However, our stem cell analysis showed no statistically significant differences in expression of stem cell markers in the PDM group vs the PNM and MM groups (see Table 2 for P values). Although this provides no conclusive evidence that PDM arises from a dermal melanocytic stem cell, it also may merely indicate that all malignant melanocytic neoplasms have a high proportion of pluripotent progenitor cells, which are responsible for tumor growth. These results are similar to those of Klein et al19 who found similarly high levels of nestin and CD166 in both invasive and MM (as well as lower levels in nevi and in situ lesions), indicating that these markers are widely expressed and cannot reliably separate primary melanoma from MM. Alternatively, these tumors may arise from a preexisting dermal nevus that is subsequently completely overrun by the melanoma. Although none of our cases showed any evidence of a preexisting nevus, there is no way to completely exclude this possibility. In either case, for unclear reasons, these tumors seem to behave in a comparatively indolent fashion, with only 1 of 13 patients dying from disease in our cohort and another diagnosed with visceral metastasis 2 years after diagnosis. Although our follow-up is limited, with a median duration of 36 months, patients with nodular melanoma of comparable depth, and certainly patients with stage IV MM, would be expected to have much lower survival over a similar time period.

Dermatologists and pathologists should consider PDM in the differential diagnosis of patients with solitary cutaneous MM of unknown origin. Immunohistochemical analysis may help to differentiate this distinct clinicopathologic variant of melanoma from cutaneous metastasis, with which it is most commonly confused.
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