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Primary dermal melanoma

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Abstract Primary dermal melanoma (PDM) is a rare subtype of melanoma with an estimated incidence of <1%. PDM manifests entirely in the dermis or subcutis and histopathologically mimics cutaneous melanoma metastasis due to its lack of connection to the overlying epidermis. A thorough history and examination, including imaging evaluation for metastatic disease, reveals no prior history or concurrent primary cutaneous or metastatic melanoma lesion. Despite its histopathologic similarities to melanoma metastasis, PDM is associated with an unexpectedly favorable prognosis. This review discusses the clinical and histopathologic features of PDM as a distinct subtype of melanoma, as well as the current approach to clinical staging and management.

Primary dermal melanoma (PDM), also called solitary dermal melanoma, is a rare subtype of cutaneous melanoma (CM) confined to the dermis and/or subcutis. Unlike CM, which typically arises from epidermal melanocytes at the dermal-epidermal junction, PDM is thought to originate from nonepidermal melanocyte populations, such as melanocytic remnants from embryologic migration of neural crest cells or preexisting dermal nevi that have been completely replaced by a melanoma.[1,2] PDMs thus lack any association with the overlying epidermis and are frequently mistaken for cutaneous metastasis (in-transit or distant disease), from which they are often histopathologically indistinguishable. Multiple studies of PDM have revealed an unexpectedly excellent prognosis, even when compared with primary invasive melanomas of a similar clinical stage.[4–6] Accurate diagnosis of PDM is essential for appropriate management and patient counseling.

PDM as a unique melanoma subtype

Dermal and subcutaneous melanoma lesions manifesting in the absence of a known primary tumor were historically assumed to represent distant cutaneous metastases and were classified as stage IV disease in the former American Joint Committee on Cancer staging criteria.[3] Some studies of melanoma of unknown primary site observed that solitary cutaneous metastasis confined to the dermis or subcutaneous tissue (in the absence of documented nodal or visceral disease) demonstrated markedly improved overall survival compared with that for typical stage IV disease. In one series of 40 patients with melanoma with an unknown primary tumor, three patients who presented with subcutaneous nodules were alive at the time of study completion, representing a 100% four-year survival rate, compared with a four-year survival rate of 55% for the entire cohort that included nodal and visceral lesions.[4] A larger study demonstrated an 83% five-year survival rate for 30 patients with metastases limited to the skin and subcutaneous tissues on initial presentation, which was higher than the expected five-year survival rate of 50% for patients with known primary CM and subsequent in-transit metastasis.[5] A similar five-year survival rate of 80% was noted in five patients with subcutaneous-only disease in another study.[6] In the three studies mentioned above, the patients with skin-confined metastases were treated with surgical excision only.

Given the discrepant survival rates for patients with these presumed cutaneous-only metastases, the concept of PDM

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was proposed after a retrospective study[1] of 1800 melanoma patients at an academic medical center. Of these 1800 patients, eleven had solitary lesions of melanoma confined to the dermis and/or subcutaneous tissue that histologically mimicked a cutaneous metastasis with unknown primary site. All 11 patients lacked evidence of a concurrent primary melanoma, prior history of melanoma, or evidence of visceral or nodal disease at the time of presentation, and all were treated with wide local excision with 1 to 2 cm margins, with only one receiving adjuvant interferon. After a median follow-up period of 46 months, the estimated eight-year survival rate was 83%, in agreement with previous studies of solitary cutaneous metastatic melanoma of unknown primary site. A similar study[7] in 2004 identified an additional seven patients with dermal-based melanomas, no prior melanoma history, and negative metastatic staging evaluation, including sentinel lymph node biopsy (SLNB) and cross-sectional imaging studies. Histopathologic and immunohistochemical assessment of these melanomas revealed them to be identical to lesions of bona fide cutaneous metastases. The five-year survival rate for these seven patients was 100%, in stark contrast to the expected five-year survival rate of 19% for stage IV melanoma at the time of publication. The remarkably favorable prognosis demonstrated in these studies supported the notion of PDM as a distinct entity from true stage IV disease or in-transit stage III disease.

Clinical presentation

PDM is rare, with incidence rates of 0.4% to 0.9% reported in the literature.[8] Data regarding its clinical and histopathologic presentation and prognosis are thus limited to a few case series (Table 1).[9-12] Some series report a slight predominance in men,[1,7-10] though there is no clear sex predisposition in other series.[11] Similar to other types of melanoma, PDM is more common in the elderly, with reported mean ages of diagnosis in the sixth to eighth decades,[1,2,8-11] although there have been occasional presentations in young adults.[2,11,13] Lesions may appear as a solitary dermal skin-colored nodule or as a pink or violaceous papule (Figure 1) and are frequently not recognized as concerning for melanoma by the clinician. Common clinical differential diagnoses include nonmelanoma skin cancer, nevus, folliculitis, cyst, dermatofibroma, or other adnexal tumors.[2,11] PDM may occur on the trunk, head and neck region, and upper and lower extremities, without clear predilection for any particular anatomic site. An important consideration is a history of a prior or concurrent primary melanoma, including a regressed skin lesion. These may be excluded based on a thorough patient interview, physical examination, and medical record review. Given the histopathologic similarity to cutaneous metastasis, cross-sectional imaging is often recommended to exclude the potential of underlying visceral melanoma with true cutaneous metastasis.

Histopathologic and molecular features

On a purely histopathologic basis, PDM is indistinguishable from CM metastases. Clinical correlation is critical to differentiate between these possibilities, and PDM should only be diagnosed after evidence of another primary melanoma (cutaneous, mucosal, or uveal) or history of a possible precursor lesion has been excluded by a work-up to exclude metastatic visceral disease.

Although there are no consensus criteria for the histopathologic diagnosis of PDM, many studies use the criteria set forth in a previous contribution (Table 2).[7] PDM appears as a well-circumscribed tumor confined to the dermis or subcutis with no associated epidermal connection or *in situ* lesion (Figure 2). A distinct Grenz zone may separate the dermally based tumor from the overlying epidermis. Similar to primary invasive melanomas, PDMs may demonstrate a variety of cytomorphologic characteristics, including spindled, epithelioid, or rhabdoid features, as well as typical features of malignant neoplasia such as increased mitotic activity, nuclear atypia, and cellular pleomorphism. Immunohistochemistry for PDM is expected to be similar to that for conventional melanomas, demonstrating positive expression of S100, SOX10, HMB-45, and other proteins.

PDM should be distinguished from a primary invasive melanoma with loss of the intraepidermal component. This may appear to be the case if a biopsy did not adequately sample the epidermal component, and evaluation of multiple histopathologic sections may be needed to confirm the absence of epidermal involvement. Rare atypical melanocytes in the overlying epidermis or papillary dermal changes suggestive of regression may indicate a regressed epidermal component of the primary melanoma (particularly nodular subtype), although histopathologic assessment of regression features may sometimes be challenging. Overlying ulceration may obscure an effaced epidermal component of a primary invasive melanoma, and thus a diagnosis of PDM cannot confidently be made in this scenario; overlying ulceration typically implies the presence of an epidermal component.

Although the presence of a preexisting melanocytic nevus has been considered an exclusion criterion for the diagnosis of PDM by some investigators, others have classified lesions associated with an intradermal nevus as PDM.[11] Cases that do not strictly meet the histopathologic criteria[7] may still be compatible with PDM on clinical grounds if there is an unequivocal intradermal lesion on clinical examination and no other history of concurrent or prior cutaneous or metastatic melanoma.[12]

The histopathologic differential diagnosis of PDM includes cellular blue nevus, malignant blue nevus, and other dermal-based melanocytic tumors, such as intradermal Spitz tumors or intermediate-grade melanocytic tumors

Table 1 Published case series of primary dermal melanoma (PDM) or solitary dermal melanoma.

Study	No. of cases	Inclusion criteria	Median or mean age in y (range)	Sex, n (%)	Median or mean BD in mm (range)	Followup (median, range)	Staging and/or treatment	Survival	Recurrences
Bowen et al[1], 2000	11	- Histologically confirmed solitary lesion of presumed CM metastasis - No clinical evidence of primary melanoma - Histopathologic absence of epidermal component or regression.	Mean 55.7 (28-90)	Men 6 (55%) and Women 5 (45%)	Mean 6.98 mm (1.0-23.0)	46 mo (17-104 mo)	All patients: WLE with 1-2 cm margins One patient: adjuvant IFN	Estimated 8-y OS of 83%	Recurrence rate 2/11 (18%) - 1 local recurrence - 1 distant metastasis (lung), died of disease
Swetter et al[7], 2004*	7	See Table 2	Median 75 (22-85)	Men 5 (71%) and Women 2 (29%)	Mean 7.0 (2.5-11.7)	34 mo (10-64 mo)	All patients: WLE with SLNB 2/7 patients: adjuvant high-dose IFN	100%	One local recurrence
Cassarino et al[2], 2008	13	Same as Swetter et al[7], 2004	Median 74 (21-85)	Men 8 (62%) and Women 5 (38%)	Mean 9.6 (2.5-30.0)	36 mo (6-94 mo)	9/13 patients: WLE with 2 cm margins 11/13 patients: SLNB	92% MSS at the time of study completion	Recurrence rate 4/13 (31%): - one local scar recurrence - one in-transit metastasis - two distant metastases
Lee et al[8], 2009	101	- Clinical and histologic evidence of a single focus of melanoma limited to dermis/subcutis without epidermal component or known primary. - Other histopathologic criteria not specified	Median 52 (21-84)	Men 63 (62%) and Women 38 (38%)	NR	5.6 y (0.4-34.5 y)	All patients: WLE 37/101 patients: nodal staging (sentinel or elective lymphadenectomy) - positive SLNB: 7/37 9/101 patients with evidence of distant disease at the time of staging	Of 71 patients with localized disease only, 5-y OS: 72.7%	Of 92 patients without distant disease at staging: - seven patients with positive nodes during nodal staging - 14 patients with nodal recurrence

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Table 1 (*continued*)

Study	No. of cases	Inclusion criteria	Median or mean age in y (range)	Sex, n (%)	Median or mean BD in mm (range)	Followup (median, range)	Staging and/or treatment	Survival	Recurrences
Sidiropoulos et al[9], 2014	49	- Histopathology compatible with PDM - No evidence of separate primary melanoma - No evidence of ulceration or regression	Median 55 (8-83)	Men 25 (51%) and Women 24 (49%)	Median 1.9 (0.5-10.05)	Mean 26 mo (2-108 mo)	All patients: WLE 34/49 patients: SLNB - positive SLNB: 6/34	47/48 (97.9%) patients were alive at the time of the study; data not available for one case	Recurrence rate 9/48 (19%): - five in-transit metastases - one regional lymph node disease - three distant metastases
Teow et al[10], 2015	9	- Histologically confirmed dermal or sub-CM - No evidence of epidermal involvement, overlying ulceration, scarring, regression, associated nevus - No history of melanoma elsewhere or regional/distant metastases at presentation	Median 67 (48-80)	Men 7 (78%) and Women 2 (22%)	Median 3.4 (1.7-11.5)	68 mo (NR)	All patients: WLE No patients with SLNB	8/9 patients with available followup; 5-y OS: 87.5%	Recurrence rate 3/8 (37.5%) - four disease-free at followup - three with melanoma recurrence - one died of unknown cause

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Table 1 (*continued*)

Study	No. of cases	Inclusion criteria	Median or mean age in y (range)	Sex, n (%)	Median or mean BD in mm (range)	Followup (median, range)	Staging and/or treatment	Survival	Recurrences
Harris et al[11], 2020	62	- Histopathology compatible with PDM - No evidence of concurrent primary melanoma or history of previous melanoma - No evidence of microsatellitosis, ulceration, epidermal component, or regression.H9WO	Mean 64.1 (±SD 14.0)	Men 35 (56%) and Women 27 (44%)	Median 3.5 (0.35-50)	6.3 y (NR)	All patients: WLE 32/62 patients: SLNB -positive SLNB: 0	5-y OS: 87.1% 5-y MSS: 91.5%	5-y recurrence rate: 19/62 (30.6%) - six local recurrences - nine regional metastases - two in-transit metastases - six distant metastases
Zamir et al[12], 2020	26	- Strict histologic criteria of Swetter et al[7] - For lesions not meeting above strict histopathologic criteria, clinically unequivocal intradermal lesion of melanoma	Median 69 (3.5-85)	Men 11 (42%) and Women 15 (58%)	Median 5.8 (1.8-25.0)	62 mo (8-132)	25/26 patients: WLE (1 patient declined) 20/26 patients: SLNB - positive SLNB: 5/20 2/26 patients: radical dissection (clinical stage III disease at presentation) three patients: adjuvant therapy - One local radiation therapy - One high-dose IFN - One combination of IL-2, cisplatin, darcarbazine, and radiation therapy	20/26 patients alive at completion of study; 5-y MSS: 76.9%	NR

BD, Breslow depth; CM, cutaneous melanoma; IFN, interferon; IL, interleukin; MSS, melanoma-specific survival; NR, not reported; OS, overall survival; SLNB, sentinel lymph node biopsy; WLE, wide local excision.

* Cases were also included in the Cassarino et al[2], 2008 series.

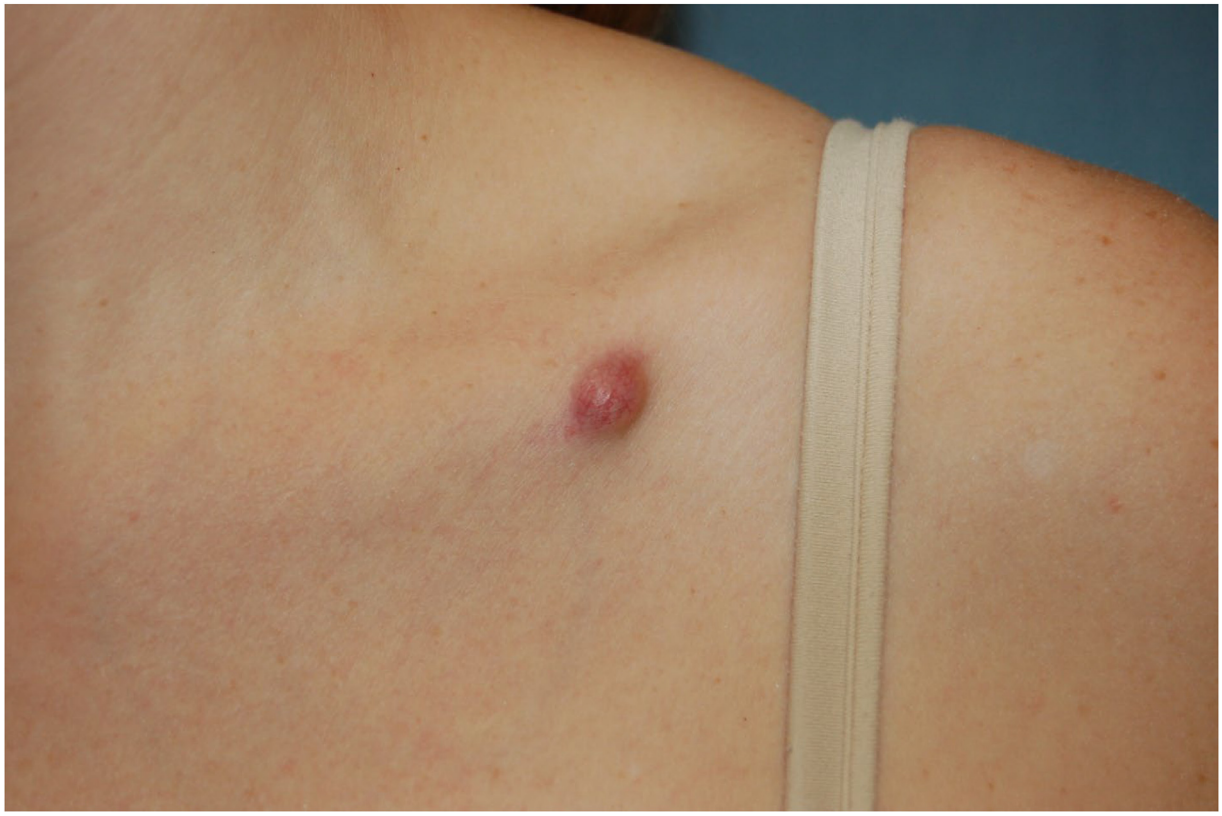

Fig. 1 Clinical presentation of PDM. A solitary smooth pink-brown nodule with overlying telangiectasias is noted over the left clavicle. PDM typically appears as a solitary dermal nodule or violaceous papule and may not be recognized as melanoma by the clinician.

Table 2 Proposed histopathologic criteria for primary dermal melanoma.

- Dermal-based melanocytic neoplasm
- Histopathologic features of malignancy (eg, cytologic atypia, nuclear pleomorphism, and increased mitoses)
- Absence of an intraepidermal/in situ component
- Absence of ulceration
- Absence of regression
- Absence of a preexisting melanocytic nevus
- Positive S100 immunohistochemical staining
- Absence of continuity with large peripheral nerves

Concurrent primary melanoma or history of melanoma must be excluded clinically.

As described by Swetter et al, 2004.

(ie, melanocytoma).[14] Clear cell sarcoma ("melanoma of soft parts"), malignant peripheral nerve sheath tumor, and other S100-positive dermal-based neoplasms are additional diagnostic considerations.[2] These can often be distinguished from melanoma on the basis of additional immunohistochemical and/or molecular studies. For example, blue nevi typically demonstrate *GNAQ/GNA11* mutations, and clear cell sarcoma demonstrates a characteristic *EWSR1* gene rearrangement.[14]

Given the histomorphologic similarities between PDM and CM metastases, one study attempted to differentiate PDM from metastatic disease on the basis of immunohistochemistry. In an analysis of a panel of 13 immunohistochemical markers in PDMs,[2] CM metastases, and cutaneous nodular melanomas, expression patterns of p53 and cyclin D1 in PDM were significantly weaker and more focal than those in metastatic melanoma and primary nodular melanoma. Proliferation index Ki-67 and angiogenesis, as measured using D2-40 staining, were also significantly lower in PDM. The authors hypothesized that the lower expression of oncogenesis-related (p53), cell cycle-related (Ki-67 and cyclin D1), and lymphangiogenesis-related (D2-40) proteins could correlate

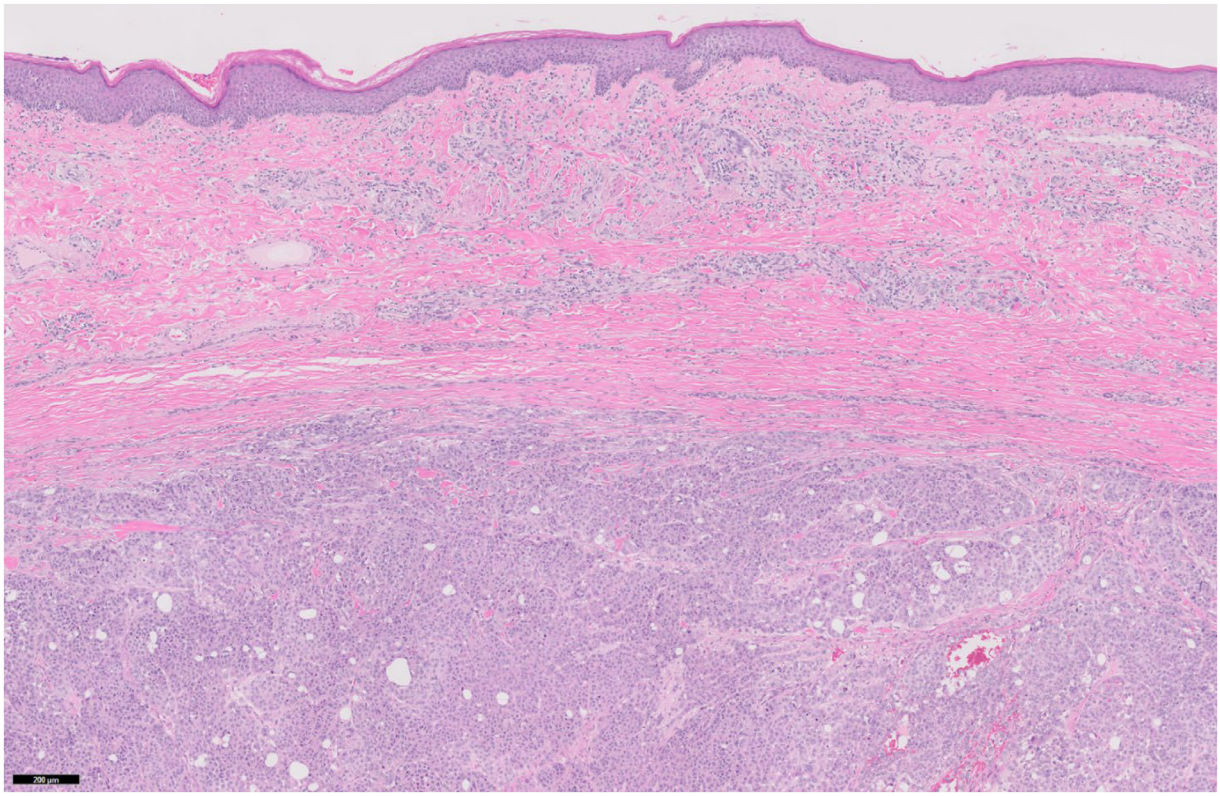

Fig. 2 Histopathologic presentation of PDM. A large, well-circumscribed tumor is present in the deep dermis without any connection to the overlying epidermis, simulating a cutaneous metastasis. Scale bar, 200 μm; original magnification × 50.

with the less aggressive clinical behavior of PDM, with their patient cohort demonstrating 92% melanoma-specific survival at a mean follow-up period of 44 months. They emphasized that immunohistochemistry alone cannot entirely exclude the possibility of metastatic melanoma and that complete metastatic work-up in the setting of PDM is generally advisable.

A limited number of studies have evaluated the genetic basis of PDM, with current available data suggesting that PDM does not demonstrate a genetic profile distinct from that of conventional CM or correlate with the BRCA1–associated protein 1 (BAP-1) cancer predisposition syndrome. One group[15] has performed exon sequencing of 1,000 cancer-related genes in three cases of PDMs. This has revealed similar genetic mutations as conventional melanomas, including *BRAF, EPHA1, DAPK3*, and *CLP1*, as well as loss of *p16/CKDN2A*. These three PDM cases also lacked the *GNAQ* and *GNA11* mutations typical of blue nevi or other melanocytic neoplasms seen in the setting of a germline *BAP-1* mutation. In another study,[11] 28 of 35 tumors analyzed using fluorescent in situ hybridization demonstrated copy number alterations commonly seen in conventional melanoma, including gains of 6p25 (58%), gains of 11q13 (24%), deletions of 6q23 (12%), homozygous deletions of 9q21 (*CDKN2A* locus, 26%), and gains of 8q24 (64%). A smaller, more recent study[16] demonstrated similar findings in five PDMs, with *NRAS* hotspot mutations noted in two tumors and *MAP2K1* deletion in another tumor. Copy number variations were also noted in their cohort, including loss of 9p21 in one tumor.

Prognosis

As noted in the initial small case series describing PDM, several larger studies have shown the prognosis for PDM to be favorable, with overall survival rates ranging from 80% to 100%. Unlike in conventional CM, PDM outcome does not appear to strongly correlate with Breslow depth, with PDMs often demonstrating less aggressive behavior than primary invasive melanomas of similar Breslow depth (measured from the overlying epidermis) or with largest dermal tumor diameter (measured apart from the epidermis).

An Australian study[9] of 62 PDMs found that PDMs had significantly greater overall survival and melanoma-specific survival than matched stages I to II and stage IV, M1a (ie, distant skin, soft tissue, and/or nonregional lymph node metastasis) controls with similar demographic and histopathologic characteristics. Disease-free survival in patients with PDMs was similar to that in stages I to II controls but superior to that in stage IV controls, suggesting that PDMs behave more similarly to primary CMs than metastatic deposits from

an occult or regressed primary site. In another series of 49 PDMs,[11] a significantly higher proportion of PDMs involved deeper Clarks levels compared with a cohort of conventional melanomas, yet there was no significant correlation between disease recurrence and any demographic or histopathologic feature. When evaluated by gene expression profiling with the DecisionDx-Melanoma assay (Castle Biosciences, Inc), 11 of 13 analyzed PDMs (85%) demonstrated a low-risk (class I) profile, compared with only 6 of 15 conventional melanomas (40%), in line with observations supporting the generally excellent prognosis of PDM.

Staging and management

With the increasing acceptance of PDM as a distinct subtype of primary melanoma, staging and management practices have shifted away from the original stage IV classification. The 2009 American Joint Committee on Cancer seventh edition melanoma staging guidelines[17] make the first allusion to PDM, noting that in patients with a "presumed single skin metastasis from an unknown primary site," the possibility of a regressed primary melanoma should be excluded; once a primary lesion was excluded, however, no further guidance is provided on how to stage these cases, if not stage IV. The most recent American Joint Committee on Cancer eighth edition guidelines for CM[18] do not elaborate further on specific staging considerations for PDM.

Given the tendency of PDM to follow a clinical course akin to that of primary CM, the accepted convention has been to apply the same staging criteria as primary invasive melanoma, with T stage based on the Breslow depth as measured from the granular layer to the deepest aspect of the dermal tumor and recommendations for pathologic staging with SLNB based on tumor thickness.

Although no PDM-specific treatment guidelines exist, management of PDM is generally approached in the same manner as that for primary invasive melanomas of the same clinical stage. Wide local excision of the primary lesion, with 1 to 2 cm margins depending on the Breslow depth, remains the mainstay of treatment, with the majority of PDMs in prior case series demonstrating excellent outcomes with only surgical excision. Prior studies of PDM used SLNB inconsistently, possibly due to different SLNB practices at the time of publication.

A series of 101 solitary dermal melanoma cases (which included a subset of PDMs based on the above histopathologic criteria)[8] demonstrated nodal metastasis in 23% of patients, suggesting that SLNB staging is of value. Because PDMs typically demonstrate a greater Breslow depth than primary invasive melanomas by nature of their dermal placement, most lesions will likely qualify for SLNB based on current National Comprehensive Cancer Network guidelines,[19] and the risks and benefits of the SLNB procedure should be discussed with the patient.

In contrast to primary invasive melanomas, for which baseline imaging studies are generally not recommended in asymptomatic patients, baseline imaging with positron emission tomography and/or computed tomography or contrast-enhanced computed tomography of the chest, abdomen, and pelvis should be considered in potential cases of PDM to exclude the possibility of an occult primary or other nodal/visceral metastases suggestive of stage III or IV disease at the outset.[19] In addition, after the US Food and Drug Administration approved systemic adjuvant anti-PD-1 monotherapy for stage IIB and IIC melanomas, referral to medical oncology is often warranted to discuss the risks and benefits of this option. Given the rarity of PDM, the rationale for cross-sectional imaging to exclude true metastatic disease, and considerations for SLNB and adjuvant immunotherapy in most patients, a multidisciplinary approach is generally recommended for these patients.

Conclusions

PDM represents a rare variant of CM with a generally favorable prognosis, despite its clinical and histopathologic presentation mimicking metastatic melanoma. Recognition of this melanoma subtype will facilitate appropriate patient counseling, treatment, and surveillance strategies.

Declaration of competing interest

The authors declare no conflicts of interest.

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