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Primary dermal melanoma: a West Australian cohort

James Teow,*¶ Olivia Chin,*¶ Mark Hanikeri*† and Benjamin A. Wood*‡§

*Western Australian Melanoma Advisory Service, St John of God Subiaco Hospital, Perth, Western Australia, Australia
†Plastic and Reconstructive Surgery, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia
‡Anatomical Pathology, PathWest Laboratory Medicine, QEII Medical Centre, Perth, Western Australia, Australia
§School of Pathology and Laboratory Medicine, The University of Western Australia, Perth, Western Australia, Australia

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Correspondence
Associate Professor Benjamin A. Wood, PathWest Laboratory Medicine, QEII Medical Centre, J Block, Monash Avenue, Nedlands, Perth, WA 6009, Australia.
Email: benjamin.wood@health.wa.gov.au

J. Teow MBBS; **O. Chin** MBBS; **M. Hanikeri** MBBS, FRACS; **B. A. Wood** BMed, FRCPA.

¶These authors contributed equally to this work.

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Abstract

Background: The objectives of this study were to identify a subgroup of patients with putative primary dermal melanoma after thorough multidisciplinary clinical and histological evaluation, and to describe the clinical, histological and selected molecular features of these lesions.

Methods: The records of the Western Australian Melanoma Advisory Service were searched for potential cases of primary dermal melanoma. The clinical and histological features were reviewed, immunohistochemical assessment was performed and clinical outcomes recorded.

Results: Eighteen cases of putative primary dermal melanoma with available clinical data were identified. Two of 12 cases in which further histological sections could be obtained were excluded because of the presence of findings suggesting an epidermal origin on these further sections. In one additional case, such origin could not be histologically excluded. Median follow-up period for the remaining cases was 68 months. Confirmed primary dermal melanoma accounts for 0.87% of cases of melanoma referred to a subspecialist melanoma advisory service. These cases show significant histological overlap with dermal/subcutaneous metastases of melanoma, but display a relatively good prognosis, with a 5-year survival of 87.5%.

Conclusion: Our results support the recognition of a distinct group of melanoma that mimics metastatic melanoma, but is associated with a relatively favourable outcome. The group of putative primary dermal melanoma is likely to be heterogenous, including cases of primary nodular melanoma in which epidermal connection has not been identified, metastatic melanoma with an occult primary lesion and true primary dermal melanoma.

Introduction

The large majority of melanomas arise from melanocytes at the dermo-epidermal junction. Rarely, melanomas are suggested to arise from melanocytes within hair follicles[1] or within the intradermal component of a congenital melanocytic naevus.[2] There have been reports, however, of a small subgroup of patients with primary dermal melanoma (PDM).[3,4] This somewhat controversial group of lesions constitutes <1% of patients with melanoma.[3,4] PDM is defined by the presence of an isolated dermal/subcutaneous melanoma without evidence of origin from a melanocytic naevus or features of 'malignant blue naevus'. By definition, there is an absence of an in situ component, surface ulceration or evidence of overlying regression/scarring. In addition, dermal clear cell sarcoma should be excluded by histological assessment, and if appropriate, fluorescence *in situ* hybridization testing. Such lesions are typically interpreted histologically as likely metastatic melanoma. To meet the criteria for PDM, the possibility of metastasis from cutaneous or occult extracutaneous sites must be excluded by thorough clinical history, examination, review of medical records and review of pathological samples, ideally in the setting of a multidisciplinary melanoma management team.[3–6]

Despite absence of an identifiable primary lesion, tumours that meet these criteria have widely been considered to represent cutaneous/subcutaneous metastasis and were identified as stage IV M1a disease in older American Joint Committee on Cancer (AJCC) staging systems.[7] The AJCC has recently updated the TNM staging guidelines for cutaneous melanoma.[7,8] A key change is that 'metastatic melanoma from an unknown site' is now categorized as stage III, rather than as stage IV, as per previous guidelines, reflecting the

better prognosis of this group of lesions and raising the possibility that some cases might indeed represent a distinct form of primary lesion.

The current study was designed to identify cases of PDM from the files of the Western Australian Melanoma Advisory Service (WAMAS) to further our understanding of the clinical and histological features of this uncommon potential subgroup of patients with melanoma.

Methods

Ethics approval

Ethics approval was granted by the St John of God Health Care Ethics Committee (reference number: 601).

WAMAS database

WAMAS was established in 2000 to provide comprehensive advice regarding the management of complex, advanced and metastatic malignant melanoma. The WAMAS database collects prospective data for all patients who are referred to the service. On referral, all patients are asked to complete a survey. A clinic appointment is then scheduled with members of the WAMAS panel, comprising a surgeon, a pathologist, a dermatologist and an oncologist. Histopathology slides are obtained and reviewed by the WAMAS pathologist. Examination and staging information is entered into the WAMAS database.

Data collection

We performed a retrospective database search based on WAMAS data from 2000 to 2012. Initial selection included all melanomas staged as $TxN0M_{1a}$. The WAMAS clinic records were requested for these patients, and the files independently reviewed by two of the authors (JT, OC) to recruit suitable patients based on strict inclusion and exclusion criteria.

Selection criteria

Inclusion criteria were the presence of biopsy-proven dermal or subcutaneous melanoma on review of the WAMAS pathology report. Patients were excluded if these lesions were reported as showing any epidermal or junctional involvement, if there was overlying ulceration, scarring or features of regression, or if the lesion arose in association with a melanocytic naevus according to the original WAMAS pathology review. Other exclusion criteria included any history of melanoma elsewhere and evidence of regional or distant metastasis at presentation.

Follow-up

In order to obtain an updated consent, patients who met the inclusion criteria were contacted by the WAMAS Clinical Nurse Coordinator for their willingness to participate in ongoing research. Consenting patients were interviewed by telephone by one of the authors (JT, OC) using a standard questionnaire. Further information was obtained by contact with general practitioners and from hospital records.

Histopathology review

Available haematoxylin and eosin sections were re-reviewed by one of the authors (BAW) to ensure that the pathological criteria for PDM were met. A range of histopathological attributes were recorded including tumour location, size, solar elastosis, Breslow thickness, mitotic activity, necrosis, presence of lymphatic/vascular space invasion and lymphocytic reaction. Immunohistochemical testing was performed using antibodies to BAP1 and V600E mutant BRAF protein by standard techniques using a Ventana BenchMark XT immunostainer (Ventana Medical Systems, Tucson, AZ, USA). Briefly, after deparaffinization of tissue sections and retrieval using CC1 solution, the sections were incubated with BAP1 antibody (clone C-4, 1/50 dilution, Santa Cruz Biotechnology, Dallas, TX, USA) or VE1 antibody (1/400 dilution, Spring Bioscience, Pleasanton, CA, USA) and standard washing applied. Detection was performed using Ventana UltaView DAB for BAP1 and Ventana OptiView DAB for VE1 (Ventana Medical Systems) and haematoxylin counterstain was employed. Positive and negative controls were included for each immunostaining run and showed appropriate staining.

Statistical analysis

Relationship between tumour thickness using the Breslow methodology and maximum tumour dimension was calculated using Pearson correlation coefficient. Survival rates were compared with data from the AJCC Cancer Staging System for Cutaneous Melanoma Seventh Edition.[8] Analysis of variance was performed to assess the relationship between Breslow thickness and tumour size using StatPlusLE 2009 (AnalystSoft Inc., Walnut, CA, USA).

Results

Sixty-three patients with $TxN0M_{1a}$ disease were identified in the WAMAS database from January 2000 to December 2012, of whom 18 met the selection criteria. Histological sections were available for 12 patients. Three patients were excluded after this further histological review and obtaining additional sections from the paraffin blocks. One patient's histology demonstrated ulceration overlying the tumour and another patient was found to have a junctional component. In both cases, these findings were not apparent on the initial slides and were only discovered upon obtaining further sections for immunohistochemical study. A third patient was excluded as the initial biopsy did not include overlying skin surface, precluding exclusion of potential epidermal origin.

Seven of the nine remaining patients were men, with age at diagnosis ranging from 48 to 80 years (median 67 years). An overview of the clinical and pathological features is presented in Table 1.

The majority of the lesions were purely dermal tumours, composed of large epithelioid cells. Seven of the nine cases occurred on skin that displayed solar elastosis. Cytoplasmic melanin pigmentation was only present in two cases, and areas of necrosis were seen in four cases. In all cases, the melanocytic character of the tumour had been confirmed in the original diagnostic workup by the performance of an appropriate immunohistochemical panel. Tumour giant cells were identified in small numbers in two cases, but other features of clear cell sarcoma were not seen. The majority of lesions were associated with a mild to moderate peripheral lymphocytic reaction, with tumour infiltrating lymphocytes present in two cases. Mitotic figures were identified in all but one case and, in most lesions, were abundant (median 6/mm^2). The case with no identifiable mitotic activity showed extensive necrosis and more focal

Table 1 Clinical and histological features

Study number	Gender/ age	Location	Mitoses (mm^2)	Breslow thickness (mm)	Maximum dimension (mm)	Clark level	T staging AJCC 2010
1	M/67	Left elbow	8	10.00	12.50	V	T4a
2	M/73	Back	8	3.40	5.50	IV	T3a
3	M/68	Back	6	2.00	3.25	IV	T2a
4	M/80	Back	2	4.65	6.00	IV	T4a
5	M/48	Left scapula	2	4.85	4.50	IV	T4a
6	M/70	Left scapula	6	1.70	2.50	IV	T2a
7	F/57	Right neck	5	11.50	11.00	V	T4a
8	F/62	Right neck	0	2.90	4.50	IV	T3a
9	M/63	Right arm	12	3.40	4.00	IV	T3a

AJCC, American Joint Committee on Cancer; F, female; M, male.

necrosis was identified in a further three cases. All nine cases had technically satisfactory immunohistochemical staining with BAP1 antibody, while eight showed satisfactory reactivity with VE1 antibody. One case showed artefactual background staining and was excluded from analysis of VE1 stain. There was no evidence of a V600E BRAF mutation in any of the cases and none showed immunohistochemical evidence of BAP1 abnormality.

When calculated by the Breslow method, the median thickness was 3.4 mm, with a range from 1.7 to 11.5 mm. The maximum tumour diameter ranged from 2.5 to 12.5 mm, with a median of 4.5 mm. Breslow thickness and maximum tumour dimension were closely correlated (Pearson correlation coefficient 0.96).

All patients were treated by wide local excision and achieved histologically clear margins. Sentinel node biopsy was not performed for any patient, although one patient underwent fine needle aspiration of a regional node with negative findings. Staging computed tomography and/or positron emission tomography scanning was recommended for all patients, but declined by one patient. By definition, cases included in this study had negative findings.

Eight patients had available follow-up, with a median duration of 68 months. Three patients were alive at the time of the study with a follow-up of less than 5 years. Five patients had a follow-up of 5 or more years. The overall 5-year survival was 87.5%. Of the eight patients, four were free of disease at the most recent follow-up and three developed further melanoma. One patient died of unknown causes at 63 months. There was no statistically significant difference in Breslow thickness or maximum tumour dimension between patients who developed recurrence when compared with those free of disease at 5 years ($P = 0.209$ and 0.298, respectively).

Discussion

The term 'primary dermal or subcutaneously derived melanoma' (PDM) was coined by Bowen *et al*. in the first of a small number of case series that describe and characterize a subgroup of solitary lesions confined to the dermal and/or subcutaneous tissues without evidence of nodal metastasis.[3–6]

The prevalence of PDM has been found to be less than 1% of patients with melanoma.[3,4] They have previously been assumed to be dermal or subcutaneous metastasis and identified as stage IV (M1a) disease according to the previous AJCC classification.[7]

Several reports have suggested that this group may behave differently to other stage IV melanomas and it has been proposed that this better survival suggests that at least a proportion of these cases do not represent subcutaneous or in-transit metastases from regressed or otherwise occult primary lesions.[3] More recently, a study by Sidiropoulos *et al*. identified a higher incidence of a favourable gene expression profile in PDM when compared with cutaneous metasases.[9]

The largest review of PDM by Lee *et al*. found those with localized disease alone had a 5-year survival rate of 73%.[10] Further studies have provided supporting data, with prognosis comparable to junctional derived melanomas with a similar depth of invasion determined by their Breslow thickness.[11] Similarly, Swetter *et al*. described a cohort of seven individuals who developed melanoma without junctional or epidermal involvement.[12] They initially found that these patients had a more favourable prognosis (100% survival after a mean follow-up of 41 months) than epidermally involved melanoma with similar Breslow thickness. They proposed that traditional Breslow depth measurement might overestimate the clinical aggressiveness in these patients and a surrogate measure of maximum tumour diameter in the vertical plane might better reflect the outcome.[12] A subsequent study from the same databases was performed on a cohort of 13 patients with a mean follow-up of 44 months demonstrating a 92% melanoma-specific survival.[11] Immunohistochemical analysis revealed unique immunohistochemistry profiles, with lower levels of p53 expression, cell cycle and proliferation-related proteins, and tumour lymphangiogenesis potential (measured by D2-40 staining).[11]

In our series, we found an 87.5% 5-year survival after a median follow-up of 68 months, consistent with findings from previous studies.[3] AJCC Stage IIA T3aN0M0 disease represents non-ulcerated melanoma with Breslow thickness between 2.01 and 4.00 mm. This group bears closest resemblance to our cohort's median thickness of 3.4 mm, with a 5-year survival of 79%,[8] similar to that of our group of patients with PDM, lending support to the contention that these lesions may represent a distinct form of primary melanoma, though of course the number of cases with follow-up in our series is too small for definitive assessment. In our cases, there was a strong relationship between Breslow thickness and maximum tumour dimension, with these measurements being within 2.5 mm for all cases. When compared with Breslow thickness, measurement of the maximum tumour dimension provided a slightly higher median size, speaking against the possibility that measurement of Breslow thickness significantly overestimated the tumour volume in these cases. Of course there are some specific configurations of tumour for which these measurements would be

significantly different, but the prognostic implications in such cases have not been established. Given the small number of cases and paucity of adverse outcomes, we were not able to demonstrate a statistically significant relationship between clinical behaviour and either parameter.

It is important to note that of the 12 patients in whom further histological review was possible, three cases were eliminated, in two cases because of the identification of findings on additional sections, which were not apparent on the initial diagnostic material. This finding emphasizes the significant possibility of sampling error in distinguishing PDM from cases of nodular melanoma, particularly in cases in which the lesion lies close to the epidermis on initial sections. Cases of putative PDM represent a heterogenous group of tumours, including primary nodular melanoma with an occult intraepidermal component, metastatic melanoma with an initially occult primary origin, possibly very rare examples of melanoma arising within and obliterating a pre-existing melanocytic naevus, and a group of true PDM. The potential cell of origin of true PDM is unclear, although origins from dermal melanocytes, embryologic-melanocytic migration remnants or aberrations, or melanocytes associated with deeper appendageal structures in the dermal or subcutaneous tissues have been proposed.

Immunohistochemical study of our cases did not reveal evidence of V600E BRAF mutation, which is found in 31% of cases of melanoma in our population.[13] Further investigation of larger numbers of cases is required to determine whether PDM represents a group of melanoma with low rates of BRAF abnormality. BAP1 abnormalities are associated with predominantly intradermal melanocytic proliferations composed of large epithelioid cells.[14] BAP1 abnormalities are found in approximately 5% of primary cutaneous melanomas and immunohistochemical staining represents an accurate method of screening for loss of protein expression.[15] We have previously encountered examples of primary melanocytic lesions with BAP1 abnormalities initially misinterpreted as metastatic melanoma on the basis of an absent intraepidermal component and atypical epithelioid cytomorphology. We sought to determine whether BAP1 abnormalities might be present in PDM. In our cases no evidence of loss of BAP1 expression was detected.

Our results support the contention that with strict inclusion criteria, it is possible to recognize a distinct group of PDM, with better clinical outcomes than might be expected for metastatic disease, representing 0.87% of cases of melanoma in the WAMAS registry. These cases show similar outcomes to primary melanomas of equivalent Breslow thickness. In our material, Breslow thickness and maximum tumour dimension were closely correlated and in such cases, it seems likely that either measurement would provide appropriate prognostic data, although the small number of cases in our series limits this assessment. Our data raise the possibility that PDM may have a lower rate of BRAF V600E mutation, although once again, study of larger numbers of cases is required to test this hypothesis. PDM may be difficult to identify clinically,[16] resembling non-melanocytic lesions such as subcutaneous cystic or vascular processes or non-melanoma skin cancer.[12] Similarly, separating these rare lesions from more common histological differential diagnoses and dermal clear cell sarcoma requires careful pathological evaluation. There is a clear need for further evaluation of PDM, predicated upon thorough clinical and pathological assessment to allow the biological and clinical attributes of this rare potential subgroup of cutaneous melanoma to be further studied.

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