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Animal-type melanoma: a clinical and histopathological study of 22 cases from a single institution

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Summary

Background Animal-type melanoma is a rare distinct melanoma subtype, characterized by proliferation of heavily pigmented epithelioid and spindled melanocytes that resembles the heavily pigmented melanomas seen in grey horses. While animal-type melanoma is generally considered to be more indolent than conventional melanoma, only a limited number of cases have been reported and, as such, the clinical characteristics of animal-type melanoma are incompletely understood.
Objectives To characterize the clinical and histopathological features of animal-type melanoma, and determine any features that may predict outcome.
Patients/Methods Data was extracted from a prospectively collected melanoma database (1994–2008), and a retrospective pathology database (1991–2008) for all patients with a diagnosis of both equivocal (8) and unequivocal (14) malignant animal-type melanoma. We reviewed the clinical and histopathological features, including the sentinel lymph node biopsy (SLNB) status.
Results A total of 22 patients were identified, with a median age of 35 years. The median Breslow depth was 2·22 mm. A SLNB was performed in 17 patients, eight (47%) were positive. Younger age was associated with: (i) animal-type melanoma with features equivocal for malignancy (median age of 7 vs. 48 years, $P = 0{\cdot}01$), and (ii) a negative SLNB (median age 12 vs. 53 years, $P = 0{\cdot}03$). Four patients with unequivocal animal-type melanoma developed recurrent metastatic disease, with one patient death. No patient with an equivocal animal-type melanoma or negative SLNB developed recurrent disease; however, this did not reach statistical significance ($P = 0{\cdot}13$ and $P = 0{\cdot}09$, respectively).
Conclusions Animal-type melanoma has a propensity for regional lymphatic metastasis and is rarely capable of disseminated metastatic disease and death. Animal-type melanoma appears to exhibit a spectrum of biological behaviour, with young patient age associated with more indolent disease.

Animal-type melanoma is a rare subtype of melanoma with distinct clinicohistopathological features that closely resemble the heavily pigmented melanocytic tumours found in grey horses.[1,2] In horses, these tumours are known as equine melanotic disease and occur in up to 80% of grey horses older than 15 years of age.[3,4] The tumours found in equine melanotic disease are characterized by indolent behaviour, although they are capable of metastasis.[5] The lesions are often multiple, and frequently involve the undersurface of the tail, perianal skin, lips and the eyelids.[4] A similarity between heavily pigmented equine and human melanocytic tumours was first proposed by Darier, who introduced the term melanosarcoma.[6] Subsequently, these human tumours have been described as animal-type melanoma, equine-type melanoma, pigment synthesizing melanoma, melanoma with prominent pigment synthesis and pigmented epithelioid melanocytoma.[7–10]

Histologically, animal-type melanoma is a heavily pigmented compound or dermal melanocytic tumour comprised of epithelioid and spindled melanocytes. While malignant cytology can be seen, there is often a bland cytological appearance, low mitotic activity, and infrequent ulceration or regression.[7–9] The appearance of animal-type melanoma closely resembles epithelioid blue naevi (EBN), which are associated with the Carney complex, but also occur sporadically.[11–13] In one case series, the presence of ulceration was the only histological factor which differentiated animal-type melanoma from EBN.[9] As ulceration is uncommon in animal-type melanoma, it is frequently indistinguishable from EBN.[9] Given the

histological overlap, the term pigmented epithelioid melanocytoma has been suggested to encompass the full spectrum of tumours ranging from EBN to animal-type melanoma.[9] To date, only a small number of animal-type melanoma cases have been reported and as such the biological behaviour of animal-type melanoma remains uncertain. Some reports suggest that animal-type melanoma may be more indolent than conventional melanoma and may have a better prognosis, as most patients reported in the literature have done well.[8,9] However, poor outcomes with distant metastatic disease and death have occurred.[7,14] It has been suggested that animal-type melanoma with an overtly malignant cytological appearance may have a poorer prognosis than animal-type melanoma with less atypical features; however, these findings were not statistically significant.[15]

Herein, we report our experience with animal-type melanoma including clinical and histopathological features. Our objective was to further characterize the behaviour and other features of animal-type melanoma, and to determine any factors that may correlate with outcome.

Methods

Study approval was obtained from the Institutional Review Board of the University of Michigan Medical School. We searched our prospectively collected melanoma database from 1994 to 2008 and the Department of Pathology retrospective database from 1991 to 2008, for all cases with a diagnosis of animal-type melanoma, equine-type melanoma, pigment synthesizing melanoma, and pigmented epithelioid melanocytoma. Clinical parameters were extracted from the medical record including: age, sex, eye/hair colour, Fitzpatrick skin type, prior severe sunburns, history or presence of dysplastic naevi, presence of blue naevi, presence of multiple lentigines, lesion location, lesion colour and shape, sentinel lymph node biopsy (SLNB) status if performed, and complete lymph node dissection (CLND) status if performed. The histopathological parameters extracted included Breslow depth, Clark level, growth phase (radial or vertical), mitotic rate and the presence or absence of ulceration, regression, angiolymphatic invasion, adventitial extension and neurotropism. We recorded whether the pathologist interpreted the lesion as equivocal or borderline for animal-type melanoma with an uncertain biological potential, or as unequivocal malignant animal-type melanoma. The equivocal lesions were characterized as symmetrical, well circumscribed, and having a less atypical cytological appearance. The lesions determined to be unequivocal malignant animal-type melanoma were asymmetrical, with poor circumscription, an aberrant growth pattern, and a malignant cytological appearance.

In patients who had a SLNB, the location, number of positive and negative nodes, status of haematoxylin and eosin (H&E), S-100 and melan-A staining on the SLN, and the presence and morphology of any capsular nodal naevi were recorded. For positive SLNs, the surface area of the lymph node involved, and the location of the tumour deposit within the SLN was recorded. The SLNB technique and the method of SLN evaluation have been described previously.[16,17] Follow-up data was obtained from the medical record and from the University of Michigan Cancer Registry. For patients with recurrent disease, the date and location of each episode of recurrence was recorded.

Statistical analysis

The Wilcoxon rank-sum test was used to assess the association between a continuous variable (such as age at diagnosis and Breslow depth) and a two-level malignancy characteristic variable. The χ^2 and Fishers exact tests were used to assess the association between categorical variables, as appropriate. The association between lymph node metastasis and biological potential adjusting for age was assessed through logistic regression. Survival estimates were calculated using the Kaplan–Meier method and compared through the log-rank test. A P-value of 0·05 or less was considered to be statistically significant, and all of the tests were two-sided.

Results

We identified 22 patients with a diagnosis of animal-type melanoma (Figs 1 and 2). The median patient age was 35 years (5–71 years). The majority of patients had brown or blond hair (17 patients, 77%), and blue, green or hazel eye colour (13 patients, 59%). Most patients were Fitzpatrick skin type I–III (16 of 22, 73%), with 15 patients (68%) reporting a history of a severe sunburn. On examination nine patients (41%) had clinically dysplastic naevi, two (9%) had clinical blue naevi, none had multiple lentigines, and none had Carney

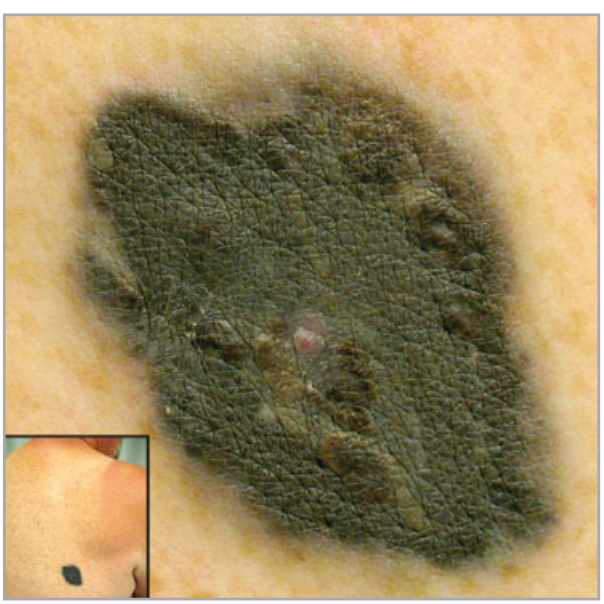

Fig 1. A 5 × 3·3 cm heavily pigmented animal-type melanoma on the back of a 71-year-old man, Breslow depth 11 mm with a positive sentinel lymph node biopsy.

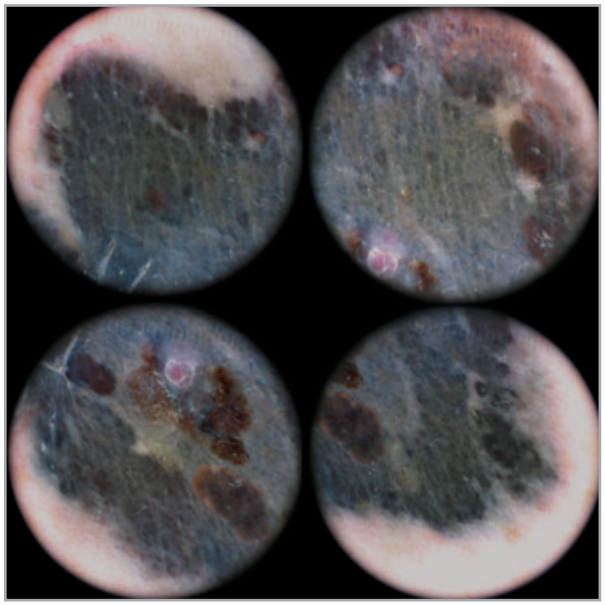

Fig 2. Dermoscopic appearance of the animal-type melanoma in Figure 1. There is an extensive blue-white structure with irregular brown blotches, and a focal amelanotic area with central dotted vessels.

complex. The Breslow depth ranged from 0·32 mm to 11 mm, with a median depth of 2·22 mm. Two (9%) lesions had evidence of histological regression and no lesions had features of angiolymphatic invasion, neurotropism or adventitial extension. The other main clinical and histopathological features are summarized in Table 1.

Of the 22 lesions with a primary diagnosis of animal-type melanoma, 14 (64%) were reported as unequivocal malignant animal-type melanoma, while eight (36%) were reported as animal-type melanoma with equivocal or borderline features (Figs 3–6). Five (36%) of 14 with unequivocal malignant animal-type melanoma were female; and four (50%) of eight equivocal animal-type melanoma cases were female ($P = 0{\cdot}66$). The Breslow depth of unequivocal malignant animal-type melanoma ranged from 0·4 mm to 11 mm, median 2·3 mm. The Breslow depth of equivocal animal-type melanoma ranged from 0·32 mm to 3·85 mm, median 2·1 mm ($P = 0{\cdot}66$). There were no significant differences in the presence of ulceration and regression, or the mitotic rate between the two groups. Patient age was significantly different between equivocal and unequivocal malignant animal-type melanoma cases. The median age was 7 years (range 5–64 years) for equivocal animal-type melanoma compared with 48 years (range 11–71 years) for unequivocal malignant animal-type melanoma ($P = 0{\cdot}01$).

SLNB was performed in 17 patients, with eight (47%) positive. The microscopic metastatic deposits in the SLN were detected on H&E in all eight positive SLNBs, with tumour deposits most frequently found in both the subcapsular space and parenchyma (63%) (Fig. 7). Immunostaining with S100 and Melan-A was positive in four patients with a positive SLNB (50%) and was not reported in the remaining four patients. The majority of tumour deposits involved > 1% of the SLN surface area (75%), ranging from 2% to 90% surface area involved. Of the 17 patients who underwent SLNB, six had an equivocal animal-type melanoma, and 11 had an unequivocal malignant animal-type melanoma. A SLNB was not performed in five patients; two had a Breslow depth of less than 0·75 mm, one had a SLNB attempted but due to technical issues it was not performed, one was a 4-year-old with an equivocal animal-type melanoma whose parents decided against SLNB and one was treated in 1991 prior to the adoption of SLNB at our institution. A CLND was performed in seven of eight patients with a positive SLNB. One (14%) of these seven had additional positive non-SLNs.

The differences between SLNB positive and negative cases are summarized in Table 2. The Breslow depth of the positive SLNB group ranged from 0·98 to 11 mm (median 3·83 mm)

Table 1 Clinical and histopathological features of patients with unequivocal malignant and equivocal animal-type melanoma (ATM)

	Total	Unequivocally malignant ATM	Equivocal ATM
Sex			
Female	9	5	4
Male	13	9	4
Lesion colour			
Brown/Black	15	10	5
Unknown	7	4	3
Lesion shape			
Raised	15	9	6
Flat	3	3	0
Unknown	4	2	2
Lesion size (Diameter)			
Less than 6 mm	1	1	0
Greater than 6 mm	12	7	5
Unknown	9	6	3
Location			
Head and neck	6	3	3
Trunk	6	5	1
Upper limbs	7	4	3
Lower limbs	2	2	0
Genitalia	1	0	1
Breslow depth (median)	2·22	2·30	2·10
Clark level			
II	1	1	0
III	2	1	1
IV	16	9	7
V	3	3	0
Ulceration			
Present	2	2	0
Absent	20	12	8
Mitotic rate			
≤ 1	13	4	5
> 1	9	10	3
Growth phase			
Radial	1	1	0
Vertical	19	12	7
Unknown	2	1	1

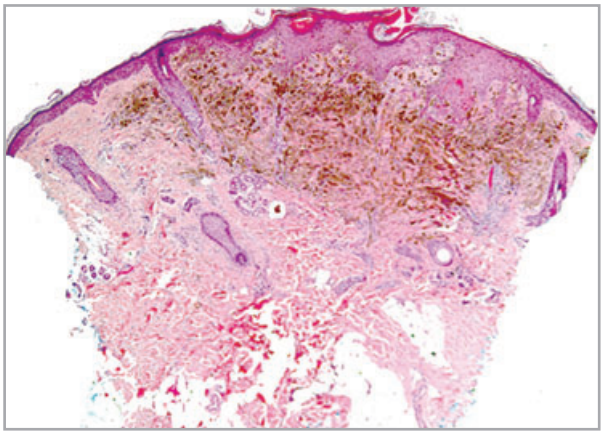

Fig 3. An animal-type melanoma from a 6-year-old boy, Breslow depth 2·55 mm. There is a well-circumscribed, symmetrical proliferation of heavily pigmented melanocytes with epidermal hyperplasia. This lesion was considered to have equivocal features and the patient is alive and disease free 42 months after his diagnosis.

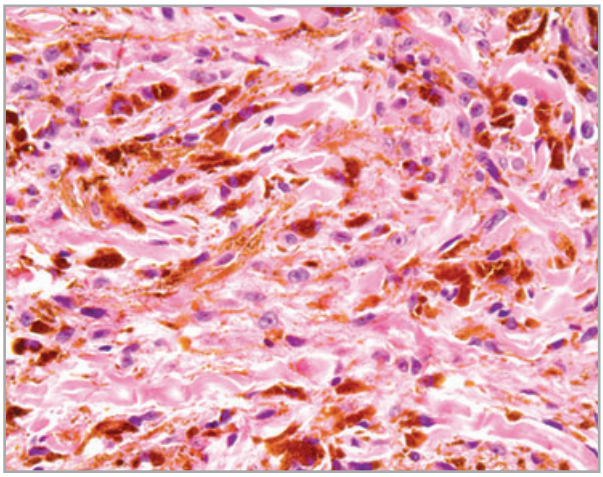

Fig 4. High-power view of the animal-type melanoma in Figure 2. There are heavily pigmented epithelioid and spindle melanocytes with prominent nucleoli. There is only a mildly atypical cytological appearance and no visible mitotic figures.

compared with 0·75–3·75 mm (median 2·55 mm, P = 0·37) in the negative SLNB group. Patient age was significantly different between the two groups. SLNB positive cases had a median age of 53 years (range 6–71 years), compared with 12 years (range 5–50 years) (P = 0·03) in the SLNB negative group. Microscopic or macroscopic lymph node metastases were present in nine (64%) patients with an unequivocal malignant animal-type melanoma, compared with one (12·5%) equivocal animal-type melanoma (P = 0·03); however, when controlled for age this association was not significant (P = 0·17). No other histopathological features significantly predicted regional lymph node involvement.

The Kaplan–Meier estimated median follow-up was 16·1 months (6·7–35·4 months). The Kaplan–Meier disease-

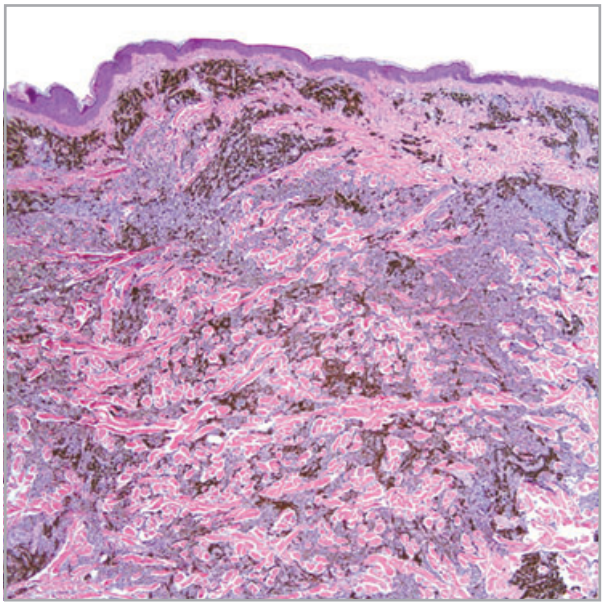

Fig 5. A low-power view of the animal-type melanoma shown in Figure 1. There is a poorly circumscribed, asymmetrical dermal proliferation of heavily pigmented atypical melanocytes, with an aberrant growth pattern.

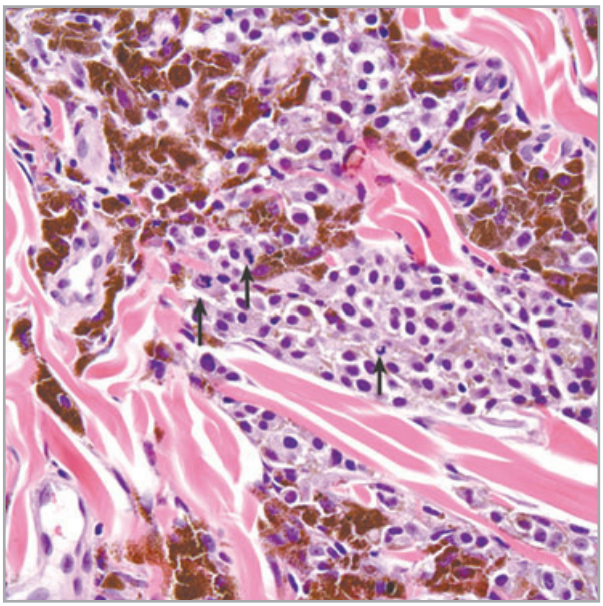

Fig 6. A high-power view of the animal-type melanoma shown in Figure 4. There are heavily pigmented epithelioid melanocytes with a number of mitoses (arrows). This lesion was considered to be an unequivocally malignant animal-type melanoma, and has subsequently recurred with dermal and lymphatic metastases.

free survival curves are illustrated in Figure 8. A total of four patients (18%) developed recurrent disease, with one death from disease (5%). No patient with a negative SLNB (median follow-up 10·5 months, 6·7–42·3 months) or an equivocal animal-type melanoma (median follow-up 12·8 months,

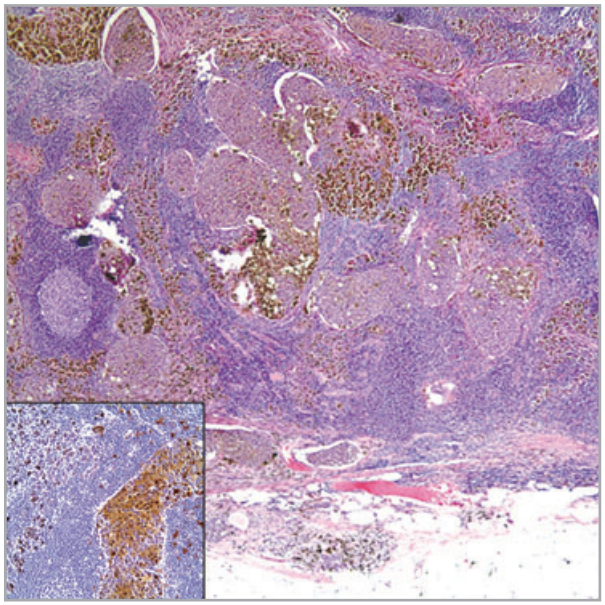

Fig 7. Metastatic animal-type melanoma within a sentinel lymph node (SLN) from the patient in Figure 4. There are heavily pigmented melanocytes within the SLN parenchyma. Immunostaining with S-100 (inset) shows metastatic melanoma cells staining a rich brown, compared with light brown melanin-laden histiocytes.

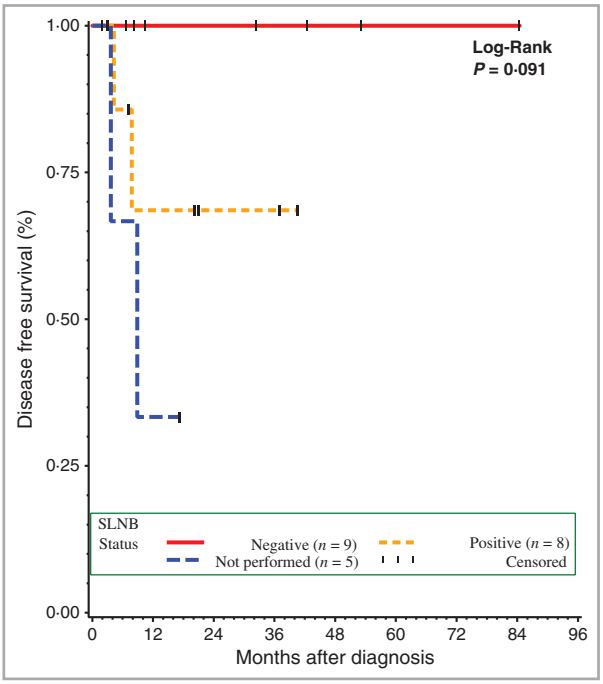

Fig 8. Kaplan–Meier disease-free survival curves for animal-type melanoma according to sentinel lymph node biopsy status; positive, negative and not performed.

3·1–42·3 months) developed recurrent disease; however, this did not reach statistical significance (P = 0·09 and P = 0·13, respectively). The clinical and histopathological features of the patients with recurrent disease are shown in Table 3. Of the patients with recurrent disease, two patients did not undergo SLNB (40% of total patients and 67% of unequivocal animal-type melanoma who did not have SLNB performed). One of these developed regional lymph node metastases 10 and 35 months after diagnosis, and the other developed regional lymph node disease followed by visceral metastases, which resulted in death 2·5 years following the initial diagnosis. In the two patients with recurrent disease who had a positive SLNB, one developed in-transit metastases and hepatic metastases 9 months after diagnosis. The other patient had a positive SLNB in the right axilla involving 90% of the lymph node surface area. An axillary CLND was performed which revealed

Table 2 Analysis of differences between sentinel lymph node (SLN) biopsy status

	Total	SLN+	SLN−	SLN not performed	P-value[a]
Number	22	8	9	5	
Sex					0·15
Female	9	2	6	1	
Male	13	6	3	4	
Age (median)	35·4	53·3	12·4	46·3	0·03[b]
Breslow depth (median)	2·22	3·83	2·55	1·26	0·37[b]
Clarks level					0·36
II	1	0	0	1	
III	2	1	0	1	
IV	16	5	8	3	
V	3	2	1	0	
Biological potential					0·13
Unequivocally malignant animal-type melanoma	14	7	4	3	
Equivocal animal-type melanoma	8	1	5	2	
Clinical recurrence	4	2	0	2	

SLN, sentinel lymph node. [a]Fisher's exact test unless noted otherwise. [b]Calculated using Wilcoxon rank-sum test.

Table 3 Clinical and histopathological features of patients with recurrent animal-type melanoma

Age at diagnosis	Breslow depth (mm)	Ulceration	Mitotic rate (mitoses/mm^2)	SLNB status (% SLN involved)	Site of recurrence	Disease status (at last follow-up)	Follow-up from diagnosis (months)
46	1·9	No	4	Not performed	Regional lymph nodes	AWD	35
53	8·5	No	8	Positive 40%	In transit & distant	AWD	15
71	11	No	5	Positive 90%	In transit & regional lymph nodes	AWD	4
44	1·26	No	0	Not performed	Regional lymph nodes & distant	DOD	30

SLNB, sentinel lymph node biopsy; SLN, sentinel lymph node; AWD, alive with disease; DOD, died of disease.

a further 35 of 37 lymph nodes positive for melanoma with extranodal extension. Two months after the axillary CLND, he developed in-transit metastases and further lymph node metastases in the right supra-clavicular basin. A right posterior neck dissection was performed, with 13 of 20 lymph nodes positive for melanoma with extranodal extension.

Discussion

In our series of 22 animal-type melanomas, a high rate of regional lymphatic involvement (47%) was observed, and two (9%) cases of distant metastatic disease were noted. Younger age was associated with an equivocal animal-type melanoma and a lower probability of a positive SLNB. Our results suggest that animal-type melanoma exhibits a spectrum of malignant potential, with younger patients more likely to have indolent disease.

We identified two categories of animal-type melanoma, those with identifiable characteristics designated by the reporting pathologist as unequivocal malignant animal-type melanoma, and those with identifiable features designated as equivocal animal-type melanoma or borderline lesions. Patients with equivocal animal-type melanoma were significantly younger than those with unequivocal animal-type melanoma. This may, in part, be due to a reluctance of the reporting pathologist to label a young patient with a definite diagnosis of melanoma. However, it is also possible that the animal-type melanoma lesions seen in younger patients demonstrate a different underlying biological process. Interestingly, a positive SLNB was significantly associated with increasing age in patients with animal-type melanoma. Conversely, in patients with conventional melanoma, decreasing age is associated with a positive SLNB, and paradoxically a better prognosis.[17–19] This may be due to younger patients possessing a more effective immune system which is capable of eliminating micrometastatic deposits and preventing further metastasis from occurring.[19] Our finding that older patients with animal-type melanoma had a higher incidence of positive SLNs further supports that animal-type melanoma may behave differently and exhibit a different biological nature in younger patients.

Previous reports have found that animal-type melanoma has the ability to metastasize to regional lymph nodes, but despite this, has a low likelihood of distant metastatic spread and an overall good prognosis.[9] In their series, Zembowicz *et al.*[9] reported 41 patients with a diagnosis of a pigmented epithelioid melanocytoma. Of the 24 cases that underwent regional lymph node sampling, 46% had evidence of regional lymph node metastases. Despite this high rate of regional lymph node involvement, only one patient developed distant disease and none died from disease.[9] In our study, we also found a high rate of regional lymph node involvement with 47% of patients who underwent sentinel lymph node sampling having nodal metastatic disease. Furthermore, of our 14 patients with an unequivocal malignant animal-type melanoma, 64% had evidence of either microscopic (7) or macroscopic (2) regional lymph node metastases. This rate of regional nodal involvement is higher than that found in conventional melanoma, which has an average SLN positive rate of 20% for melanomas > 1 mm in depth.[20–22] The higher rate in our series may be in part due to the deeper average Breslow depth (3·45 mm for the unequivocal malignant animal-type melanomas), as conventional melanomas > 3 mm in depth have been reported to have a positive SLN in up to 55% of cases in at least one study.[23] However, animal-type melanoma may have an inherent propensity for regional lymphatic spread that is greater than conventional melanoma.

In contrast to our findings, others have reported a low incidence of lymph node involvement in animal-type melanoma, including Orlandi *et al.*[24] and Scolyer *et al.*[25] who reported no positive SLNs in seven patients and five patients with animal-type melanoma, respectively. We note that the variation in the reported rates of nodal involvement in animal-type melanoma may be due to the small numbers involved. However, the studies that have reported a low rate of nodal involvement and a good prognosis may have included more animal-type melanomas at the benign EBN-like end of the animal-type melanoma spectrum, which may be more similar to the lesions that we classified as equivocal or borderline animal-type melanoma. For example, the study by Orlandi *et al.*[24] only included cases with a low mitotic rate, and an absence of ulceration and marked cytological atypia. According to our findings, animal-type melanoma with these features may have more indolent biological behaviour and these criteria would exclude many of the cases that we classified as unequivocal malignant animal-type melanomas.

Despite the propensity for regional lymph node involvement, we only observed two animal-type melanomas with dis-

tant metastases. In our series there were no deaths in SLNB positive animal-type melanoma with a median follow-up of 17·6 months (4·1–37·1 months). In comparison, SLNB positive conventional melanoma has an 82–88% melanoma specific survival at 2 years.[20,26] Our results suggest that animal-type melanoma may be less biologically aggressive than conventional melanoma with an overall better prognosis; however, this needs to be confirmed in future studies involving larger patient numbers and longer follow-up. It is possible that animal-type melanoma may behave similarly to equine melanotic disease, with long periods of relative indolent disease, which may be followed by a late more aggressive transformation. Of note, the animal-type melanoma that developed distant metastatic disease in our study did not have any predictive features, and the one animal-type melanoma that resulted in death was a relatively thin lesion (Breslow depth 1·26 mm), with a low mitotic rate.

The possible indolent behaviour of animal-type melanoma has led some investigators to suggest that animal-type melanoma may not need to be managed as aggressively as conventional melanoma, and that SLNB and adjuvant therapy may be unnecessary.[27] Based on our interpretation of the available evidence, we currently recommend that all cases of animal-type melanoma be excised with appropriate margins. At our institution we recommend performing a SLNB in both equivocal and unequivocal malignant animal-type melanomas that are greater than 1 mm in Breslow depth or 0·75–1 mm with other adverse features such as ulceration or a high mitotic rate.[17,18] While we are able to provide reassurance to younger patients that they appear to have more indolent disease with a better prognosis; we believe a role for SLNB exists in these patients. Although SLNB did not significantly predict outcome ($P = 0{\cdot}09$), no patient with a negative SLNB developed recurrent disease. In addition, the SLNB may have therapeutic value as 67% of patients who were candidates for but did not have a SLNB performed developed macroscopic lymph node metastases. If the SLNB shows metastatic disease, at the current time we recommend consideration of CLND and we discuss the option of adjuvant interferon-α2b therapy.

In conclusion, our results suggest that animal-type melanoma exhibits a propensity to regional lymph node involvement, but despite this may be less aggressive than conventional melanoma with a better prognosis. Animal-type melanoma appears to exist in a spectrum ranging from indolent to aggressive biological behaviour and, as a result, some lesions labelled as animal-type melanoma may have a more favourable outcome. While young age may be associated with a more benign histological appearance and behaviour, further research is required to fully delineate the true biological nature of animal-type melanoma.

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