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Histological type and biological behavior of primary cutaneous malignant melanoma

2. An analysis of 86 cases located on so-called acral regions as plantar, palmar, and sub-/parungual areas

Knud Søndergaard

Department of Pathology, The Finsen Institute, Rigshospitalet, Strandboulevarden 49, DK-2100 Copenhagen, Denmark

Summary. Primary cutaneous malignant melanomas are generally divided into 3 separate clinico-pathological variants, lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM), and nodular melanoma (NM). Recently an additional variant, acral lentiginous melanoma (ALM), has been defined, occurring on acral regions, defined as plantar, palmar, and sub-/parungual areas. Histological examination of 86 primary melanomas on acral regions revealed 24 (28%) acral lentiginous melanomas (ALM), 23 (27%) superficial spreading melanomas (SSM), 18 (21%) nodular melanomas (NM), and 21 (24%) unclassifiable melanomas. No LMM was seen. The prognosis was found to be the same in patients with SSM and ALM. However, by correlating histological type with frequency of antecedent nevus, duration of melanoma and dominant invasive tumor cell, it was demonstrated that histologically typical ALM differed from histologically typical SSM by their infrequent origin from antecedent nevi, their lower local growth rate, and their more frequent content of spindle cells. These findings support ALM as a valid melanoma subtype only when clearly defined histologically.

Key words: Malignant melanoma – Acral – Planta, palma, sub-/parungual – Histological types

Primary cutaneous melanomas are commonly divided into 3 separate clinico-pathological entities, i.e. lentigo maligna melanoma (LMM), superficial spreading melanoma (SSM), and nodular melanoma (NM) (Clark et al. 1969; McGovern et al. 1973).

Recently, Reed stated that volar and subungual melanomas represented a distinct clinico-pathological type of melanoma different from the above mentioned types (Clark et al. 1975; Reed 1976). The new type was named acral lentiginous melanoma (ALM). However, other authors stressed that

Offprint requests to: K. Søndergaard at the above address

a substantial proportion of volar and subungual melanomas were not ALM, but SSM or NM (Søndergaard and Olsen 1980; Feibleman et al. 1980).

In the present study the results of a retrospective histological classification of primary volar and sub-/parungual melanomas in 86 patients were correlated with currently recorded historical data in order to clarify the following problems concerning ALM:

1. Can ALM be classified along the histological lines described by Reed (1976)?

2. Is there evidence that ALM is a distinct entity within cutaneous melanoma?

Material and methods

By reviewing 2,012 patients with primary cutaneous melanoma, 86 patients were found with melanomas located on *acral regions,* defined as plantar, palmar, and sub-/parungual areas. In 79 out of the 86 patients (92%) the primary lesion was excised at the Finsen Institute, whereas 7 patients (8%) were admitted for extended excision after primary total excision elsewhere. For the microscopic examination the original sections were used as well as 4 new haematoxylin-eosin stained sections. If the primary melanoma or parts of it were excised elsewhere the original sections or newly made sections were borrowed.

The clinical reporting included the following points as previously described by Søndergaard (1983)

1. *Site of tumor*
2. *Sex and age of patient*
3. *Presence and duration of antecedent nevus*
4. *Duration of symptoms of melanoma*
5. *Clinical stage*

The histological evaluation of the melanoma included

1. *Histological type of melanoma*

Histological type of melanoma according to Clark et al. (1969) and McGovern et al. (1973) as previously described by Søndergaard (1983):

a) *Lentigo maligna melanoma (LMM)*

b) *Superficial spreading melanoma (SSM)* (Fig. 1).

c) *Nodular melanoma (NM)* (Fig. 2).

In the present study a further 2 types were defined:

d) *Acral lentiginous melanoma (ALM)* as described by Reed (1976) (Fig. 3): Melanomas characterized by linear proliferation of tumor cells in the basal layer of the epidermis extending more than 3 rete ridges from areas of dermal invasion. Acanthosis and elongation of rete ridges was present. In areas without dermal invasion, epidermal tumor invasion was slight and junctional nesting of tumor cells occasional.

e) *Melanomas of unclassifiable type (UM)* designated melanomas not included in the above mentioned groups.

2. *Type of dominant invasive tumor cells, recorded as follows*

a) Nevoid

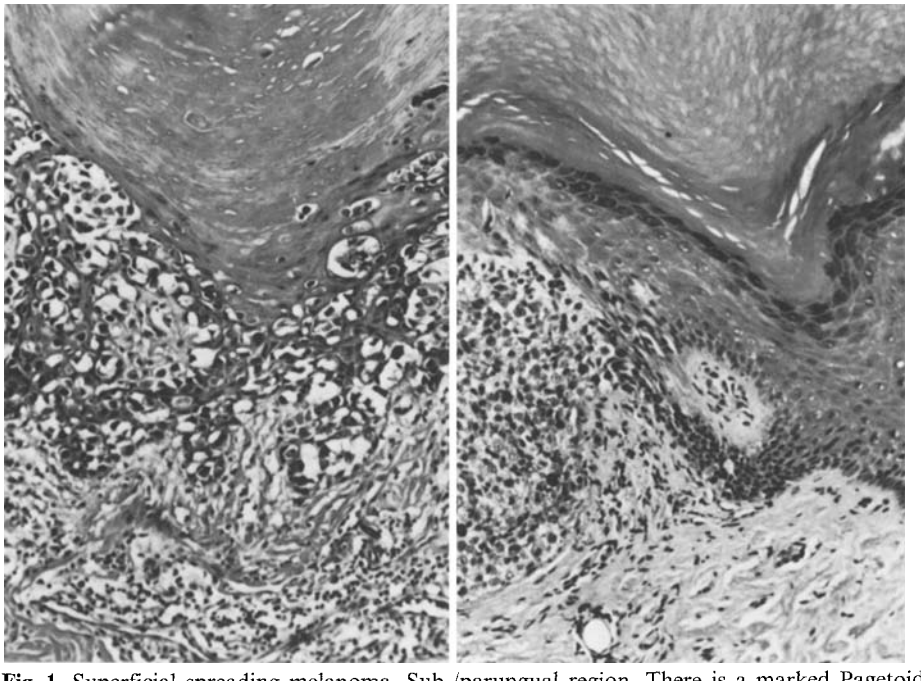

Fig. 1. Superficial spreading melanoma. Sub-/parungual region. There is a marked Pagetoid spread of tumor cells in the hyperplastic epidermis. No dermal invasion is found in this area. Haematoxylin and eosin. × 130

Fig. 2. Nodular melanoma. Planta. There is no intra-epidermal spread of tumor cells surrounding the invasive part of melanoma. Haematoxylin and eosin. × 130

b) Epithelioid
c) Spindle
d) Balloon
e) Equal mixture of two or more cell types

3. *Presence of obviously benign nevus cells*

4. *Maximal tumor thickness*

Maximal tumor thickness in mm according to Breslow (1970), as previously described (Søndergaard 1980).

Statistical analysis

The cumulative survival rates were calculated by the life table method and compared by the logrank test (Peto et al. 1977). Where appropriate Chi square test and Student's *t*-test were used. Significance was assessed at $p < 0.05$.

Results

In 82 out of 86 melanomas (95%) at least one cross-section included the surrounding epidermis from two opposite sides of tumor. In 4 cases (5%) it was only possible to investigate the epidermis to one side of the tumor. As shown in Table 1 two or more cross-sections were available from 72% of the tumors (62/86).

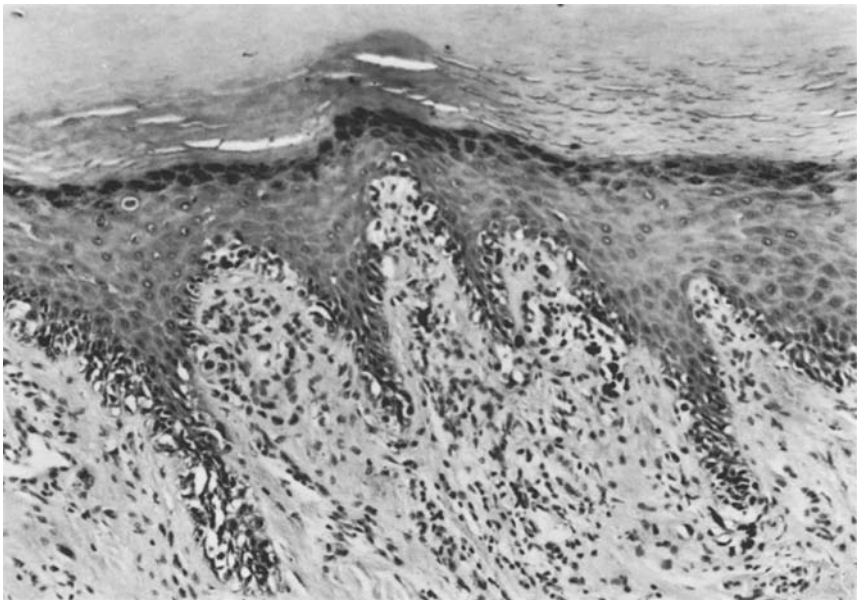

Fig. 3. Acral lentiginous melanoma adjacent to an area of dermal invasion. Planta. There is a lentiginous proliferation of tumor cells in the hyperplastic epidermis. Haematoxylin and eosin. ×130

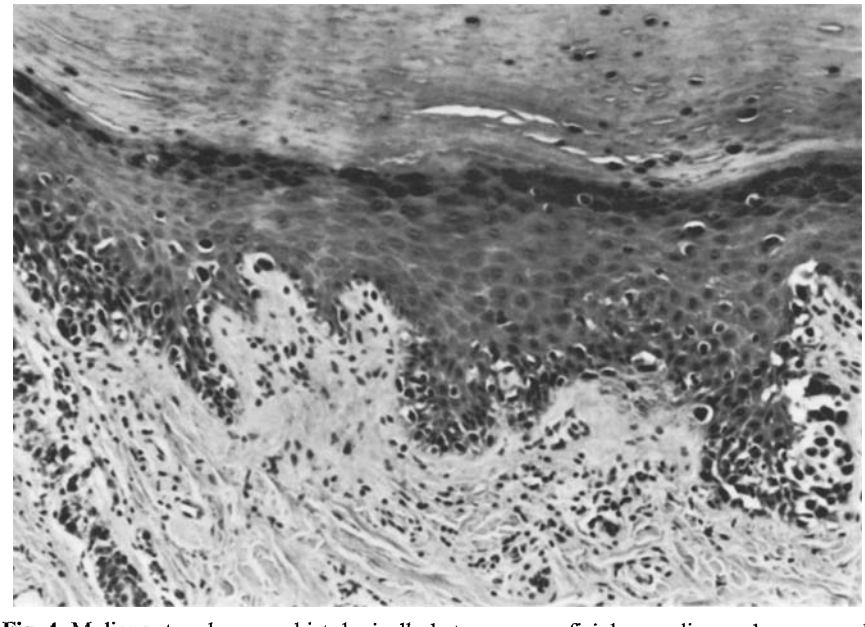

Fig. 4. Malignant melanoma, histologically between superficial spreading melanoma and acral lentiginous melanoma (SSM-ALM). Planta. Lentiginous proliferation of tumor cells is found (*left*) as well as moderate Pagetoid extension and junctional nesting of tumor cells (*right*). There is no dermal invasion in this area. Haematoxylin and eosin. ×130

Table 1. Number of cross-sections per lesion available for the histological classification of 86 primary acral melanomas

Number of cross-sections per melanoma	Number of melanomas
1	24
2	26
3	16
4	5
5 or more	15
Total	86

Table 2. Histological type correlated with sex and age of 86 patients with primary acral melanoma

Age of patient (years)	Histological type of melanoma										Total	
	ALM		SSM-ALM		SSM		NM		NM-ACM			
	M	F	M	F	M	F	M	F	M	F	M	F
0–14	0	0	0	0	0	0	0	0	0	0	0	0
15–24	0	0	0	0	0	0	0	0	0	0	0	0
25–34	0	0	0	0	0	1	0	0	0	0	0	1
35–44	0	1	0	2	1	1	1	2	0	0	2	6
45–54	3	2	1	2	0	4	1	2	0	1	5	11
55–64	5	4	3	1	1	4	0	2	1	0	10	11
65–74	1	3	0	6	4	2	4	2	0	1	9	14
75–84	2	3	1	2	1	3	0	4	0	0	4	12
85 or more	0	0	0	0	0	1	0	0	0	0	0	1
Total	11	13	5	13	7	16	6	12	1	2	30	56

Table 3. Histological type correlated with site of primary acral melanoma in 30 males and 56 females

Site of primary melanoma	Histological type of melanoma										Total	
	ALM		SSM-ALM		SSM		NM		NM-ACM			
	M	F	M	F	M	F	M	F	M	F	M	F
Planta	7	7	4	9	5	13	2	7	1	2	19	38
Sub-/parungual area of toe	2	5	0	2	1	2	4	1	0	0	7	10
Palma	1	0	0	0	1	0	0	1	0	0	2	1
Sub-/parungual area of finger	1	1	1	2	0	1	0	3	0	0	2	7
Total	11	13	5	13	7	16	6	12	1	2	30	56

Table 4. Various clinical and histological features correlated with histological type of melanoma

Histological type of melanoma	Duration of antecedent nevus					Duration of history of melanoma			
	0–2 years	2–5 years	> 5 years	life long	uncer-tain	< 1 years	1–3 years	> 3 years	uncer-tain
ALM	20	1	2	0	1	15	7	1	1
SSM-ALM	15	0	1	1	1	12	5	0	1
SSM	12	1	6	2	2	17	3	0	3
NM	16	1	0	0	1	13	4	0	1
NM-ACM	2	0	1	0	0	3	0	0	0
Total	65	3	10	3	5	60	19	1	6

30 patients were males (35%) and 56 females (65%). 64 patients were in clinical stage I, 18 in stage II, and 4 in stage III. Table 2 and 3 show the sex- and age-distribution and the sites of the various types of melanoma. 3 melanomas were located on the palm, 57 on the sole, and 26 on sub-/parungual areas (finger 9 and toe 17).

As shown in Table 4 there were 24 ALM, 23 SSM, and 18 NM. No LMM was found. Eighteen melanomas (*SSM-ALM*) histologically were in a position intermediate between SSM and ALM (Fig. 4): In the adjacent intra-epidermal area of the melanomas a lentiginous proliferation of tumor cells was found as well as areas with moderate Pagetoid extension of tumor cells. In 3 cases (*NM-ACM*) it was uncertain whether or not the lateral intra-epidermal proliferation of tumor cells extended more than 3 rete ridges beyond areas of clear dermal invasion, i.e. whether the melanomas were NM or melanomas with adjacent intra-epidermal component (ACM).

Significantly more SSM (8/21, 38%) than ALM and SSM-ALM (4/40, 10%) arose from a nevus that had been present for many years, i.e. more than 5 years, or as long the patients could recall ($p < 0.01$) (Table 4).

Microscopic examination showed obviously benign nevus cells in none of the 86 melanomas.

For the different types the frequency of melanomas with a history of more than one year's duration was as follows:

ALM 8/23 (35%), SSM-ALM 5/17 (29%), SSM 3/20 (15%), and NM 4/17 (24%). The differences were not statistically significant (Table 4).

The average tumor thickness was significantly greater for NM (5.59 mm) than for SSM (3.25 mm) and ALM (3.68) ($p < 0.01$) (Table 4). The difference between SSM and ALM was not significant ($p > 0.4$).

In significant more ALM (9/24, 38%) than SSM and SSM-ALM (6/42, 14%) the dominant invasive tumor cell was of spindle cell type ($p < 0.05$) (Table 4).

As shown in Fig. 5 the 5-year survival (10-year survival) for the different types was: ALM 43% (23%), SSM 46% (22%), NM 38% (28%), SSM-ALM 68% (61%), and NM-ACM 33% (33%). The differences were not statistically significant ($p > 0.3$).

in 86 patients with primary acral melanoma

Type of dominant invasive tumor cells					Tumor thickness in mm (average)	Total
Nevoid	Epithel.	Spindle	Balloon	Mixture		
0	10	9	0	5	3.68	24
0	12	2	0	4	2.33	18
1	15	4	0	3	3.25	23
0	10	5	0	3	5.59	18
0	3	0	0	0	2.51	3
1	50	20	0	15	3.68	86

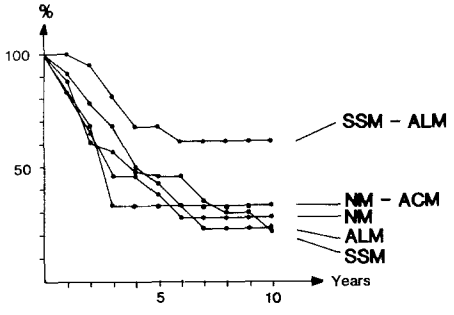

Fig. 5. Cumulative survival rates corresponding to histological types of melanoma

Discussion

The histological material was considered suitable for the reclassification of the histological type, as at least one cross-section from 95% (82/86), of the melanomas included the normal epidermis from 2 opposite sides of the lesion. Furthermore at least 2 cross-sections were available from 72% (62/86) of the tumors. In 92% (79/86) of the cases the melanoma was sectioned at the same laboratory, securing a uniform procedure.

The 86 patients were 4% of 2,012 consecutive cases of primary cutaneous melanoma for which histological material was available. Similar, Clark et al. (1979) and Feibleman et al. (1980) found that 4–6% of their cutaneous melanomas showed acral distribution.

Out of 86 acral melanomas, 57 (66%) were located on the planta, 26 (31%) on sub-/parungual areas, and only 3 (3%) on the palma. Also in other studies it was found that plantar melanomas were much more frequent than palmar melanomas (Wanebo et al. 1975; Coleman et al. 1980; Feibleman et al. 1980), and that subungual melanomas took up an intermediate position (Wanebo et al. 1975; Feibleman et al. 1980).

Only 16% of the patients (13/81) with acrally located melanoma stated that the melanoma arose from an antecedent nevus which had been present for many years or as long as the patient could recall. It was significantly less frequent than other cutaneous melanomas, of which 63% (1,117/1,769) arose from agelong or lifelong pre-existing nevi (Søndergaard 1983)

($p < 0.0005$). This is in accordance with the histological demonstration of clearly benign nevus cells in none of the 86 acral melanomas in contrast to 9% (177/1,916) of other cutaneous melanomas (Søndergaard 1983). The infrequent occurrence of antecedent nevi in acral melanomas also corresponds with the finding of Coleman et al. (1980) that most of their patients denied a pre-existing lesion at the site of the tumor.

The duration of symptoms was the same for acral melanomas and for other cutaneous melanomas, as it was less than one year for 75% (60/80) for the acral melanomas compared to 76% (1,324/1,740) for other cutaneous melanomas (Søndergaard 1983). This does not conflict with the finding of Coleman et al. (1980), that the duration prior to treatment varied from a few months to several years for acral melanomas.

Reed (Clark et al. 1975; Reed 1976) stated that volar and subungual malignant melanomas represented a clinico-histological subtype different from LMM, SSM, and NM. Because of the acral distribution of tumor and the radial lentiginous proliferation of tumor cells the lesions were named acral lentiginous melanomas (ALM). Absent solar changes excluded LMM.

In recent papers Arrington et al. (1977); Clark et al. (1979); Coleman et al. (1980); and Feibleman et al. (1980) also considered ALM as a distinct clinico-pathological entity of cutaneous melanoma different from LMM, SSM, and NM. However, the relative proportion of ALM among the acrally located melanomas varied considerably in various studies.

Arrington et al. (1977) found that 27 out of 33 plantar melanomas showed an adjacent intra-epidermal component characteristic for ALM. No SSM was found. In the remaining 6 cases the histological material was inadequate to permit determination of whether or not an adjacent intra-epidermal component was present. However, on the basis of clinical photographs, some of the 6 lesions were presumably NM.

In 1980 Coleman et al. published 47 plantar and palmar melanomas of which 35 were ALM. In the remaining 12 cases the material was inadequate for determination of whether or not an adjacent intra-epidermal component was present.

Patterson and Helwig (1980) found that out of 63 subungual melanomas with sufficient histological material 35 (55%) were ALM, 25 (40%) NM, and 3 (5%) SSM.

However, Feibleman et al. (1980) found that a substantial proportion of the acral melanomas with adjacent intra-epidermal component were SSM. Out of 51 melanomas with sufficient histological material, 31 (61%) were ALM, 18 (35%) SSM, and 2 (4%) NM. Beyond this, "a few cases" had an adjacent intra-epidermal component in which a differentiation between SSM and ALM could not be made.

Wanebo et al. (1975) found that out of 26 plantar and subungual melanomas 4 (15%) were ALM, 13 (50%) SSM, and 9 (35%) NM.

The pronounced variation in the relative proportions of ALM and SSM was most likely due to the histological criteria being inadequately defined to permit differentiation between SSM and ALM in a great number of acrally located melanomas. Presumably such melanomas (SSM-ALM) were

classified as SSM in some studies and as ALM in others. The reason for the variation of NM from 4% to 40% in the above mentioned studies is obscure.

In the present study of 86 acral melanomas 24 (28%) were ALM, 23 (27%) SSM, and 18 (21%) NM. In accordance with other studies no LMM was found (Wanebo et al. 1975; Arrington et al. 1977; Clark et al. 1979; Coleman et al. 1980; Feibleman et al. 1980; Søndergaard and Olsen 1980). There was good histological differentiation between melanomas with adjacent intra-epidermal component (ACM) and melanomas without (NM), as only 3 melanomas (3%) were classified as NM-ACM. On the contrary, the differentitaion between SSM and ALM was uncertain in many cases, as 18 melanomas (SSM-ALM) (21%) had an adjacent intra-epidermal component which histologically lay between that of SSM and that of ALM.

It has been stated that in ALM the intra-epidermal tumor cells are characterized by prominent dendrites (Arrington et al. 1977, Feibleman et al. 1980). This feature was found to be of little importance in the differentiation between SSM and ALM, as pigmented dendrites could not be demonstrated in many ALM and were sometimes found in SSM.

In the present study, the subtypes ALM, SSM, and SSM-ALM were correlated with various clinical and histological variables in order to investigate further whether ALM and SSM might represent 2 separate entities of melanoma, and if so, to what group SSM-ALM belonged.

The prognosis was independent of the histological type of melanoma (Fig. 5). However, as shown in Table 4, ALM, SSM, and SSM-ALM differed from one another in the following respects:

1. ALM arose from an antecedent nevus as infrequently as did SSM-ALM. In contrast, significantly more patients with SSM than with ALM and SSM-ALM stated that their melanomas arose from antecedent nevi which had been present for many years or always ($p < 0.01$).

2. In 35% of ALM, 29% of SSM-ALM, and 15% of SSM the duration of symptoms was more than 1 year. The differences were not statistically significant. However, as the same tumor thickness was found in ALM and SSM, it indicated that ALM had a lower growth rate than SSM. This is in accordance with the statement of Ackerman and Su (1979), that the in-situ phase is of longer duration in ALM than in SSM.

3. The same low frequency of spindle cells as the predominant invasive tumor cell was found in SSM and SSM-ALM. On the contrary, significantly more ALM than SSM and SSM-ALM showed predominantly spindle cells in the invasive part of the tumor ($p < 0.05$).

The present findings supported the assumption that histologically typical cases of ALM and SSM represented 2 different entities of cutaneous melanomas. ALM differed from SSM by its lentiginous adjacent intraepidermal tumor spread, its infrequent origin from an antecedent nevus, its lower growth rate, and its frequent composition of spindle cells. An attempt should therefore be made to classify histologically typical cases of SSM and ALM.

The subgroup classified as SSM-ALM was not related more to SSM than to ALM, as histologically and clinically it lay between SSM and ALM.

Conclusions

1. Acrally located melanomas accounted for 4% of primary cutaneous melanomas.

2. Acrally located melanomas arose less frequently from antecedent nevi than did other cutaneous melanomas.

3. For patients with acrally located melanomas the prognosis was not correlated with histological type of melanoma.

4. The histological classification was usable, as typical cases of NM, SSM, and ALM were found. No LMM was seen. However, a number of melanomas (21%) were unclassifiable by having an adjacent intra-epidermal tumor spread which lay between that of SSM and ALM.

5. It is recommended that acrally located melanomas with adjacent intra-epidermal tumor spread be classified by histological examination as SSM, ALM or unclassifiable melanomas, as histologically typical ALM differed from histologically typical SSM by its infrequent origin from antecedent nevus, its lower growth rate, and its frequent content of spindle cells.

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