Melanoma Research, 1, pp. 245–249

Spatial association of melanocytic naevus and melanoma

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A series of 233 consecutive primary cutaneous melanomas was histologically and clinically studied. Histologically, 53 melanomas (22.7%) were associated with naevus cells. Such a high degree of association suggests that melanocytic naevus may be a precursor of a large number of melanomas. Analysing the cases according to Clark's levels and Breslow's index, a decrease in the naevus–melanoma association was seen with tumour progression, suggesting that advanced tumours may overgrow pre-existing nevus cells, appearing as *de novo* melanomas. The comparison between histological and clinical data suggest some interpretations of the natural history of melanoma.

Key words: Melanocyte, melanocytic naevus, melanoma.

Introduction

Many clinical observations have suggested the existence of a close link between melanocytic naevi and melanoma. The number of naevi is related to the risk of melanoma: subjects with a high number of naevi have a more than threefold increase in melanoma risk,[1] and those with more than 120 naevi have a relative risk for melanoma nine times higher than individuals with 0–10 naevi.[2] Moreover, some melanocytic lesions, described in the recent past and known as dysplastic naevi, have been reported to be associated with a high risk for melanoma.[3–5] In patients with familial melanoma, a relatively high number of naevi is often associated with non-familial melanoma (dysplastic naevus syndrome).[4]

The clearest evidence of the relationship between naevi and melanoma, however, is their well established spatial association. A clinical history of a pre-existing naevus at the site of a melanoma is recorded for 19–85% of cases; naevus cells in contiguity with a melanoma have been observed histologically in 4–72% of melanomas.[6]

Since data from the literature on this subject vary, we decided to study clinically and histologically a series of primary cutaneous melanomas.

Patients, materials and methods

Two hundred and thirty-three consecutive primary cutaneous malignant melanomas were excised from 224 patients at the II Dermatologic Clinic and at the Department of Plastic Surgery of Florence University between 1 January 1985 and 30 April 1989. All cases were histologically examined at the Institute of Pathological Anatomy and Histology, University of Florence, and included in the Italian Melanoma Registry of the National Operative Force against Cutaneous Melanoma (FONMeC). Four melanomas were excised from a single patient affected by the dysplastic naevus syndrome, and three tumours were excised from one other patient; each of four other patients had two melanomas excised.

Each lesion was entirely embedded in paraffin. In each case, the mean number of paraffin blocks examined was six (range 2–15); the total number was about 1400. About 2500 hematoxylin–eosin stained sections were reviewed by two pathologists (CU, RB). Breslow's index was calculated by one pathologist (CU).

Histologically, three categories were identified: I, positive for naevus cells; II, doubtful for naevus cells; III, negative for naevus cells.

Criteria used to distinguish naevus cells from melanoma cells were those used by Elder *et al.*[7] adopted by Friedman *et al.*[8] and recently used by Stolz *et al.*.[9] Positive cases required the presence of nests, sheets or cords of cytologically benign naevus

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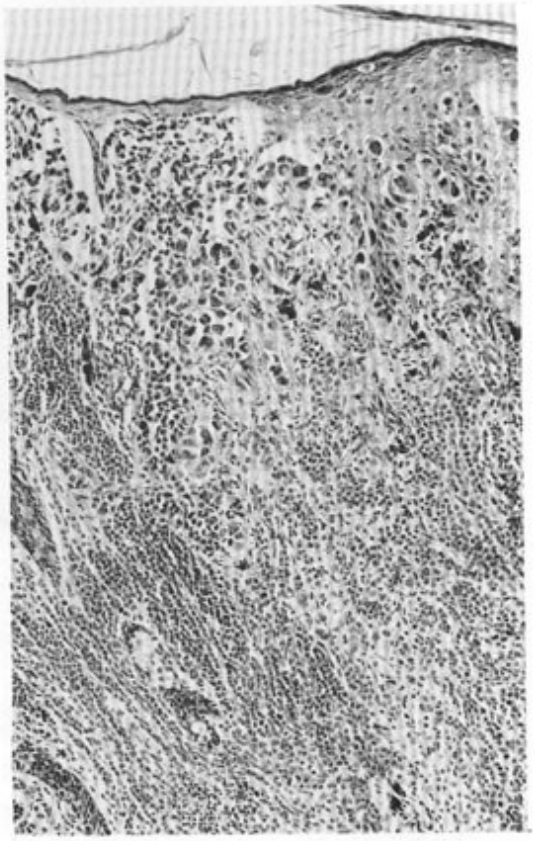

Figure 1. Melanoma associated with a melanocytic naevus: abrupt transition between melanoma cells and naevus cells, arranged in cords and sheets (H & E, ×120).

Table 1. Histological differentiation between small melanoma cells and dermal naevus cells[a]

Feature	Small melanoma cells	Dermal naevus cells
Melanin	Generally present	Generally absent
Pattern	Nested	Cell separated from neighbouring cell by eosinophilic material
Relationship between superficial and deep cells	Continuity	Abrupt dissociation
Nuclear pleomorphism and hyperchromatism	Present	Absent
Mitoses	Rare	Absent

[a]Adapted from Elder *et al.*[7] Friedman *et al.*[8] and Stolz *et al.*[9]

cells, generally devoid of melanin, without atypias or mitoses, in contiguity with melanoma or in sections adjacent to the tumour. The presence of an abrupt transition between naevus cells and melanoma cells was particularly emphasized (Table 1) (Figures 1 and 2).

Patients were divided into three groups on the basis of clinical history, evaluated by two of us (VG, BG): (A) existence of a pigmented lesion since birth or childhood, or present lesion lasting for >10 years; (B) present lesion lasting for 5–10 years; (C) present lesion lasting for <5 years.

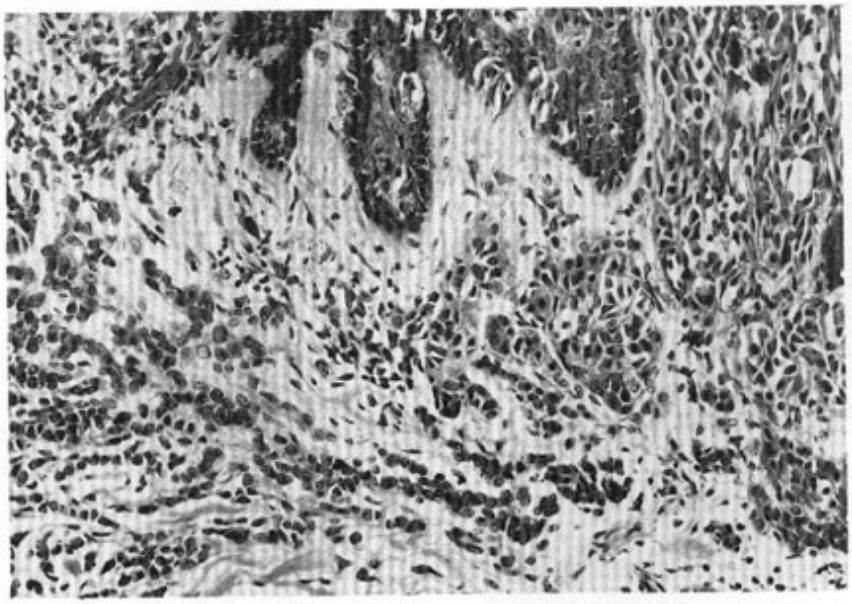

Figure 2. Melanoma associated with a melanocytic naevus: alveolar pattern of melanoma cells and cords of cytologically benign naevus cells (H & E, ×320).

Table 2. Histological and clinical analysis of 233 melanomas

	Clinical stage				
	>10 years (A)	5–10 years (B)	<5 years (C)	Unknown	
Histology					
Positive (I)	22	16	15		53 (22.7%)
Doubtful (II)	1	1			2 (0.9%)
Negative (III)	62	38	74	4	178 (76.4%)
Total	85 (36.5%)	55 (23.6%)	89 (38.2%)	4	233

Results

Histopathologically, 53 melanomas were associated with naevus cells (group I, 22.7%); two were classified as doubtful (group II, 0.9%), and 178 as negative (group III, 76.4%) (Table 2).

Clinically, the 233 melanomas were classified as follows: group A = 85 cases (36.5%); group B = 55 (23.6%); group C = 89 (38.2%); 4 unknown.

Comparison of clinical data with histology showed that 24.7% of the 85 patients in group A were histologically positive, while 83.1% of the 89 patients of group C were histologically negative (Table 2).

Of patients with histological evidence of a melanocytic naevus associated with melanoma (group I, 53 cases) 71.6% had had a lesion for more than 5 years' duration (Table 2). Of patients without histological evidence of a melanocytic naevus (Group III, 178 cases) 41.5% had had a lesion for less than 5 years' duration (Table 2).

Histological analysis revealed that 27.7% of 166 superficial spreading melanomas (46 cases) and 50.0% of 10 acral lentiginous melanomas (5 cases) were associated with melanocytic naevus. Nodular melanomas (23) were found associated in one case and lentigo maligna/lentigo maligna melanomas (30) in one case (Table 3). Of the 53 melanomas associated with a melanocytic naevus 86.8% were SSM and 9.4% ALM.

Table 3. Histological analysis of 233 melanomas

Type	No. cases	No. positive cases	%
SSM	166	46	27.7
ALM	10	5	50.0
NM	23	1	
LM/LMM	30	1	
Unclassified	4	–	
Total	233	53	22.7

No. of positive cases = number of melanomas histologically associated with a melanocytic naevus.
SSM=Superficial spreading melanomas; ALM=acral lentiginous melanomas; NM=nodular melanomas; LM/LMM=lentigo maligna/lentigo melanomas.

Table 4. Distribution of 233 melanomas according to Clark's levels

Level	No. cases	No. positive cases	%
I	40	5	12.5
II	48	16	33.3
III	67	19	28.3
IV	71	13	18.3
V	6	–	
Unknown	1	–	
Total	233	53	22.7

No. of positive cases = number of melanomas histologically associated with a melanocytic naevus.

Table 5. Distribution of 233 melanomas according to Breslow's index

Thickness (mm)	No. cases	No. positive cases	%
≤0.76	88	20	22.7
0.76–1.50	49	16	32.6
1.51–3.00	47	7	14.9
>3.00	45	9	20.0
Unknown	4	1	
Total	233	53	22.7

No. of positive cases = number of melanomas histologically associated with a melanocytic naevus.

The distribution of all melanomas and positive cases according to Clark's levels and to Breslow's index are shown in Tables 4 and 5, respectively.

In 44 cases (83%) naevus cells were found beneath the melanoma; in eight cases (15.1%) they were adjacent to the tumour, in one case they were both beneath and adjacent to the melanoma. Congenital features (naevus cells within the collagen of the lower two-thirds of the reticular dermis and in periadnexial sites) were noted in five cases (9.4%).

Discussion

Our results showed histological association of melanocytic naevus and melanoma in 22.7% of patients which is in agreement with other recent studies: Rhodes *et al.*[10] found 27.4%, Friedman *et al.*[8] 23.3%, Black[11] 23%, Stolz *et al.*[9] 22%. When two lesions are histologically (spatially) associated, their association may be coincidental or causal. Coincidental associations are rare, and since the incidence is relatively high, the association between naevus and melanoma must be considered as causal.[12] This suggests that melanocytic naevus may be a precursor of an important proportion of melanomas (27.7% of SSM). Of course, only a very small fraction of naevi play such a role, and this type of naevus should therefore be identified. It should be determined whether it is histologically recognizable and whether it is identifiable with lesions that have been considered to be precursors of melanoma (dysplastic naevi).

It is interesting that six patients presented with multiple melanomas: one patient had four neoplasms (three associated with a naevus) and a family history of melanoma; one patient had three melanomas; four patients each had two melanomas (in two patients both tumours were associated with a naevus). Seven of the 15 multiple melanomas of our study were associated with a naevus (46.7%), compared to the 22.7% association in the rest of the patients. These data indicate a closer relationship between multiple melanoma and melanocytic naevus.

In this study, congenital naevus was associated with melanoma in five of 233 cases (2.1%); such a rate is lower than that reported by Rhodes *et al.*[10] (19/234 cases; 8.1%).

The distribution of melanomas according to Clark's levels showed a rate of association of 33.3% in level II melanomas and 28.3% in level III lesions. In level IV lesions, it decreased to 18.3% (Table 4). An analogous trend was observed in the distribution of lesions according to Breslow's index: 32.6% of 0.76–1.50 mm melanomas were associated with a melanocytic naevus, compared with 14.9% of 1.51–3.00 mm melanomas (Table 5). These data may be interpreted as evidence that tumours in advanced stages overgrow pre-existing naevus cells, and thus may appear as *de novo* melanomas.

However, our results showed that in melanoma *in situ* (level I) the rate of association (12.5%) is lower than in levels II and III (33.3% and 28.3%, respectively). If the hypothesis of the destruction of nevus by melanoma cells is correct, melanoma *in situ* should have an association incidence similar that of level II lesions. However, an explanation of this finding could be that melanomas *in situ* arising in a pre-existing naevus probably offer less evident clinical features than more advanced tumours or than *de novo* intra-epidermal melanomas, so that the correct clinical diagnosis and consequent excision of the lesion are delayed until the melanoma reaches level II or more.

In this study, the rate of apparent disagreement between histological and clinical data ranged from 20 to 75%. This may be due to erroneous answers from patients or to technical factors (i.e. an insufficient number of sections). In analysing our data, however, other possibilities have to be considered.

Of 178 melanoma patients without a histologically demonstrated naevus (group III), 62 (34%) belonged to group A (suggestive of a pre-existing naevus) (Table 2). Moreover, 62 (73%) of 85 patients in group A were histologically negative for a naevus (Table 2). These data suggest that a fraction of melanomas may have a life history longer than is currently thought. In some cases, it is also possible that a pre-existing naevus was obliterated by melanoma cells. In fact, melanomas of patients with lesions of >5 years' duration (groups A and B) showed a mean thickness of 1.9 mm; whereas those of patients with lesions of <5 years' duration (group C) had a mean thickness of only 1.64 mm.

Moreover, 15 of 53 (28%) melanomas associated with a naevus of group I were observed in patients belonging to group C (not suggestive of a pre-existing naevus). Although these 15 cases represent only 16% of group C, this fact may suggest that a naevus may appear and a melanoma may arise within it in a relatively short period of time (<5 years). Further studies need to clarify the type of naevus which can progress so rapidly to melanoma and whether it may coincide with the so-called dysplastic naevus.

Such suggestions may be useful for the understanding of the natural history of melanomas, while awaiting future studies that will throw light on the enigmatic relationship between melanocytic naevus and melanoma.

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(Received 16 May 1991; accepted 26 July 1991)