Arch Dermatol Res (1985) 277:362–369

Archives of Dermatological Research

Nevoid Malignant Melanoma

C. Schmoeckel, C. E. Castro, and O. Braun-Falco

Dermatologische Klinik und Poliklinik der Universität München, Frauenlobstr. 9, D-8000 München 2, Federal Republic of Germany

Summary. Primary cutaneous malignant melanomas with histological features suggestive of benign nevocytic nevi were studied. From a total of about 3,500 cases, 33 patients with sufficient records, histological slides, and follow-up (at least 5 years for disease-free cases) were found; 15 of them had developed metastases, and 8 had died of disseminated melanoma. Some of the following histological characteristics were always observed: cellular atypia, mitoses, infiltration of adnexa, and in the deeper dermis, infiltrative growth, pigmented tumor cells, sharply demarcated tumor nests, and the absence of maturation. Tumor thickness was the most important prognostic criterion. Clinically, the tumors corresponded to nodular and superficial spreading melanomas. It is concluded that, in rare instances, malignant melanomas strongly resemble benign melanocytic/nevocytic nevi. Such cases do not appear to have a lower degree of malignancy and should be treated as normal malignant melanomas.

Key words: Melanoma – Nevi, nevocytic

Introduction

Cutaneous malignant melanomas are currently classified according to the histogenetic types characterized by Clark et al. [3]. In addition, two rare variants – desmoplastic [4] and neurotropic [8] melanomas – are known.

Occasionally, malignant melanomas may have histological features suggestive of benign melanocytic/nevocytic nevi, and some of them are likely to be wrongly diagnosed as benign nevi. Several such cases, in which the correct diagnosis was made only when metastases occurred, prompted us to look for similar cases in our records. The purpose was to analyze their biologic behavior and to determine clinical and histological diagnostic criteria. While studying these cases, it became obvious that they were definitely malignant melanomas rather than atypical nevi or unusual melanomas with uncertain prognoses (minimal deviation melanoma [5, 7, 9, 10]).

Offprint requests to: Prof. Dr. C. Schmoeckel (address see above)

Materials and Methods

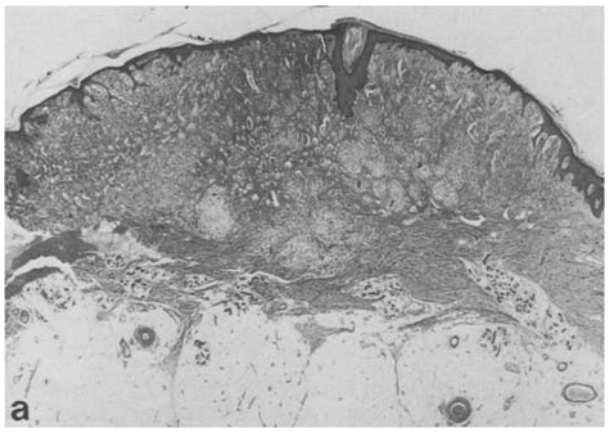
The histological slides of approximately 2,000 cases of primary cutaneous malignant melanoma collected by the German Melanoma Study Group (conducted by Prof. Dr. Heite, Freiburg) and of about 1,500 cases seen in our own department were re-evaluated. Cases with markedly nevoid features were selected. The following nevoid characteristics (not always simultaneously present) distinguished these cases from common malignant melanomas:

1. Lack of considerable junctional activity and absence of scattered tumor cells within the epidermis.
2. Presence of monomorphous nevocytic tumor cells.
3. Nevoid architectural pattern, i.e., poorly demarcated tumor base with little or no inflammatory reaction, sharp lateral demarcation, and symmetry of the whole lesion.

There was extensive documentation (including black-and-white photographs) for all these cases, which was correlated with the histological appearance of the tumors.

The following cases were discarded:

1. Cases which, when revaluated, appeared to be benign nevi (including Spitz's nevi and spindle-cell nevi).
2. Cases with a follow-up of less than 5 years (unless metastases had occurred).
3. Since serial sections were usually unavailable, special care was taken to ensure that the histological sections were representative of the main tumor.
4. Cases with histological sections not meeting standard requirements.
5. Cases in which the clinical course and/or the histological sections of the tumor were suggestive of metastases.



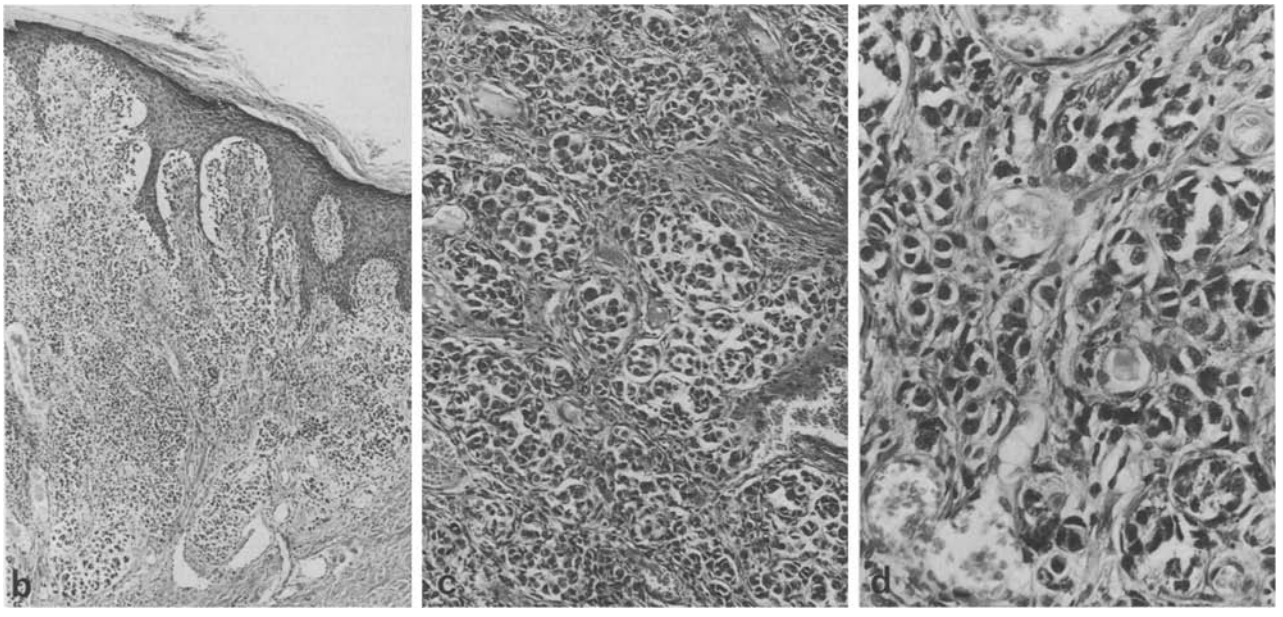


Fig. 1. a Case 1. Tumor at the periphery of a congenital nevus with atypical tumor cells and without maturation in depth; metastases after 12 months. **b** Margin revealing few individual tumor cells within the epidermis and absence of inflammatory reaction at the tumor base. **c** Medium magnification showing demarcated nests of atypical tumor cells at the lower tumor base. **d** Higher magnification of cells depicted in c reveals atypical nuclei, and dusty and granular pigment within the cytoplasm of the tumor cells

Table 1a. Clinical and histological findings in patients with nevoid malignant melanoma without later metastases

Case	Clinical characteristics			Histological findings			
	Sex	Age (years)	Location	Horizontal diameter (mm)	Tumor thickness (mm)	Mitotic index (mitoses/mm^2)	Prognostic index
1	F	36	Foot	12	0.70	1.0	0
2	F	47	Foot	5	1.50	2.7	4
3	M	49	Trunk	29	1.30	0	0
4	F	45	Lower extremity	6	0.70	3.3	2
5	F	49	Lower extremity	12	3.80	6.7	25
6	F	39	Lower extremity	13	2.60	0	0
7	F	70	Upper extremity	26	0.86	2.0	2
8	F	46	Lower extremity	8	2.10	0	0
9	F	56	Lower extremity	9	0.77	0	0
10	M	52	Lower extremity	9	0.55	0.7	<1
11	M	45	Trunk	13	4.60	0	0
12	M	22	Lower extremity	12	9.80	0	0
13	F	28	Foot	9	0.86	0	0
14	F	40	Lower extremity	9	1.30	0	0
15	F	40	Upper extremity	5	2.00	0	0
16	M	44	Lower extremity	17	4.20	0	0
17	F	44	Lower extremity	9	0.90	0	0
18	F	16	Lower extremity	9	1.70	1.4	2

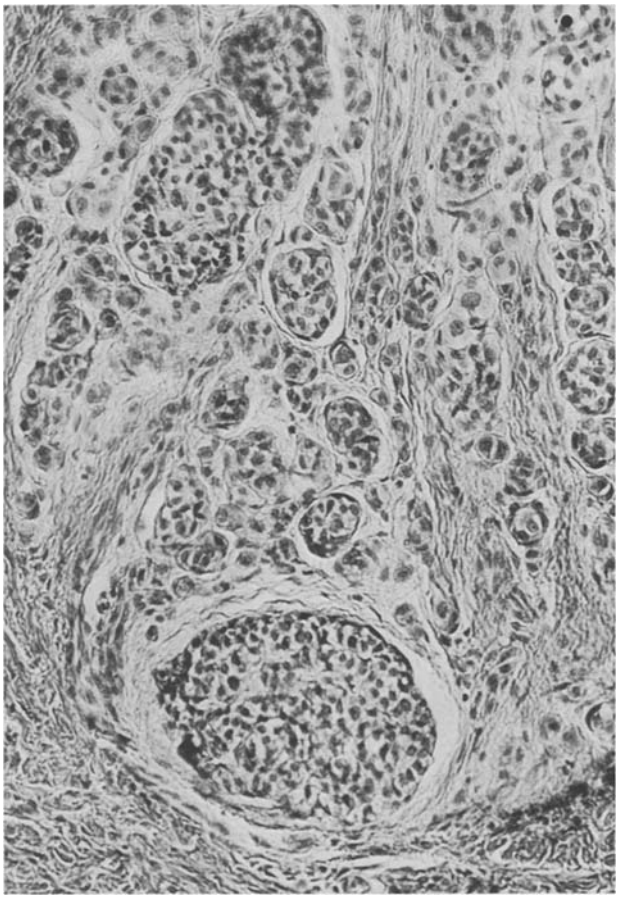


Fig. 2. Case 4. Plantar melanoma with nevoid appearance histologically showing sharply demarcated nests of tumor cells in depth; metastases after 96 months

In all of these cases, the following histological indicators were determined:

1. Tumor thickness according to Breslow [2].
2. Mitotic index, defined as the maximum number of mitoses per square millimeter (11), as well as the prognostic index, defined as the product of tumor thickness and the mitotic index (11).
3. Ulceration.
4. Vascular invasion.

Results

Thirty-three cases were selected for further evaluation. Eighteen cases had been disease free for at least 5 years, whereas 15 had later developed metastases. Eight patients were known to have died because of disseminated malignant melanoma; the others had been lost from follow-up or had only recently been seen.

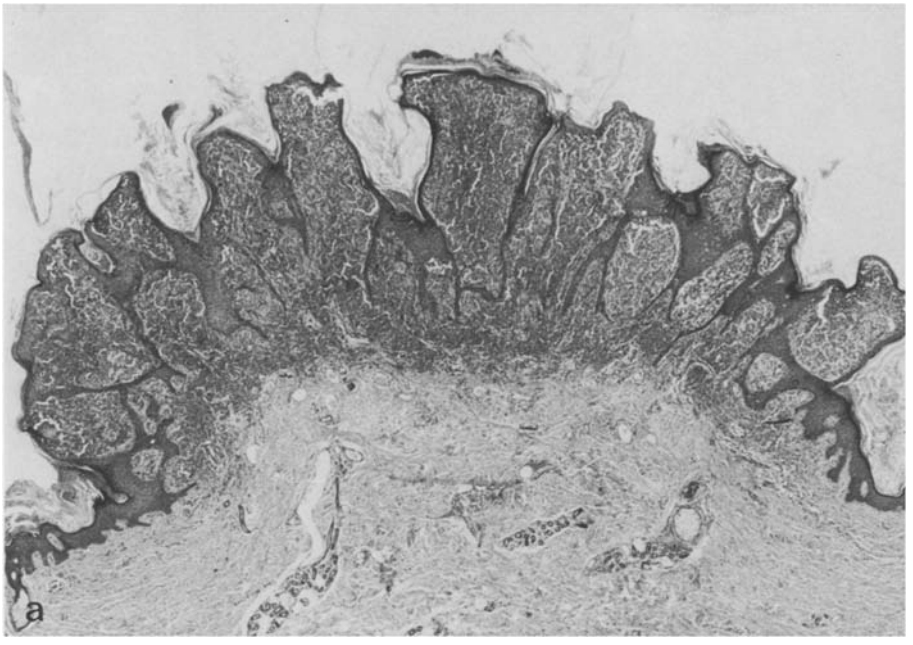
The clinical and histological findings for these patients are listed in Table 1. In general, the tumors were not clinically different from normal melanomas, and characteristic features could not be found.

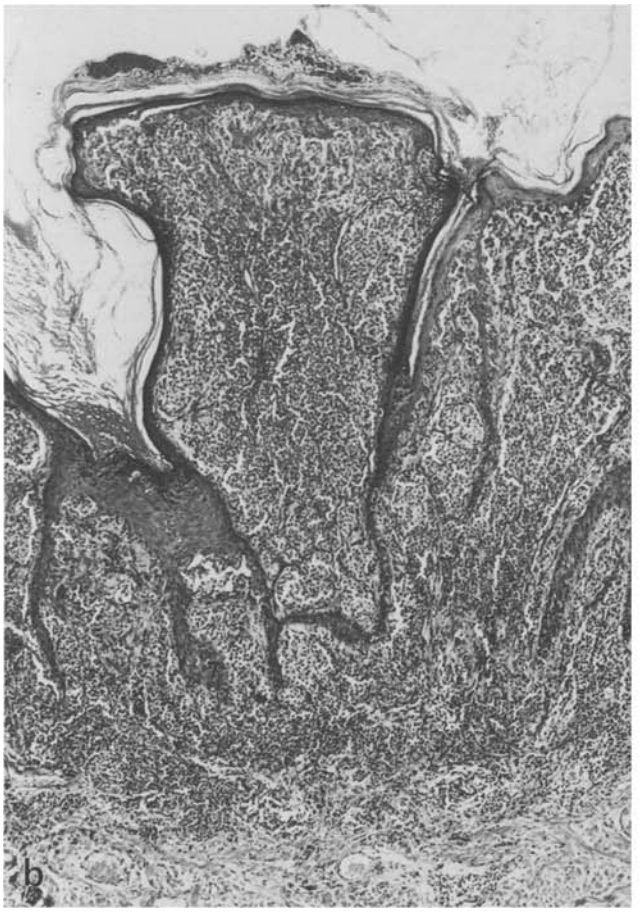
The cases were divided (Table 2) into risk groups according to tumor thickness [2] as well as a combination of prognostic criteria [11]. The most important prognostic criterion appeared to be tumor thickness; due to the small number of cases, the value of the mitotic index [11] as well as that of the prognostic index [11] could not be assessed statistically.

Histological evaluation of these cases revealed several criteria suggestive of malignant melanoma, thus

Table 1b. Clinical and histological findings in patients with nevoid malignant melanoma with later metastases

Case	Clinical characteristics			Histological findings				
	Sex	Age (years)	Location	Horizonal diameter (mm)	Tumor thickness (mm)	Mitotic index (mitoses/mm^2)	Prognostic index	Metastases (months)
1	F	50	Lower extremity	12	3.6	0	0	12
2	M	46	Lower extremity	5	1.5	0	0	77
3	F	39	Trunk	16	1.7	18.8	31	5
4	F	76	Plantar	11	1.7	2.0	3	96
5	F	69	Plantar	12	1.7	1.3	2	50
6	F	49	Lower extremity	7	1.7	2.0	3	97
7	F	51	Upper extremity	9	1.7	6.7	11	7
8	F	60	Lower extremity	10	3.4	0.7	2	2
9	M	45	Head	16	2.1	0	0	9
10	F	60	Lower extremity	7	2.6	6.8	18	35
11	F	59	Foot	10	1.4	0	0	63
12	M	39	Head	10	1.4	0	0	37
13	F	35	Upper extremity	6	0.9	0.7	<1	21
14	F	69	Trunk	9	1.4	3.4	5	60
15	F	43	Lower extremity	7	0.5	2.0	1	9





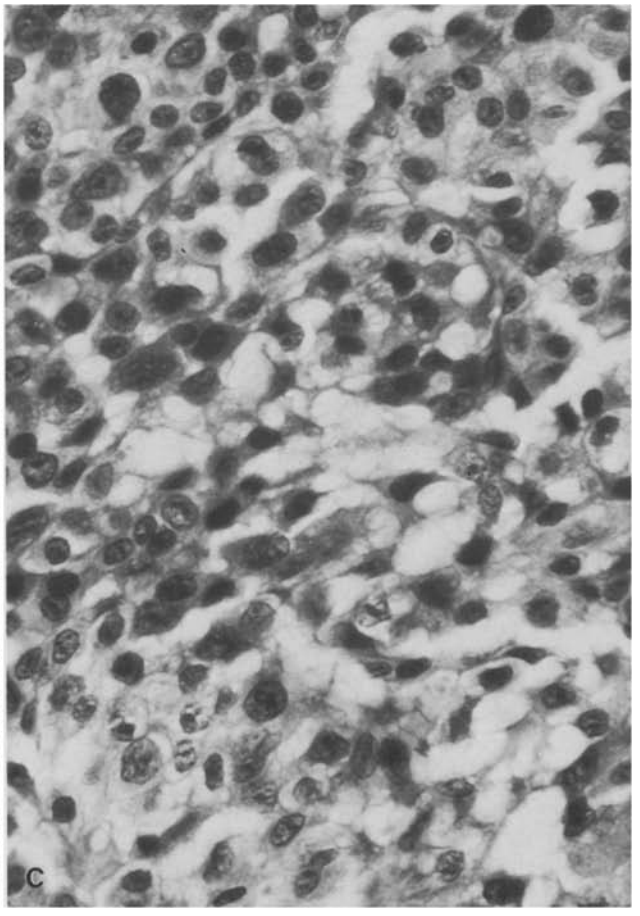


Fig. 3. a Case 7. Papillomatous tumor; metastases after 7 months, and death due to dissemination after 4 additional months. **b** Medium magnification. **c** High magnification revealing polymorphous tumor cell

allowing them to be distinguished from benign melanocytic/nevocytic nevi (Table 3); these criteria were not always simultaneously present. Vascular invasion was never observed.

Discussion

Minimal deviation melanoma has been mentioned and described by Reed and co-workers in several articles

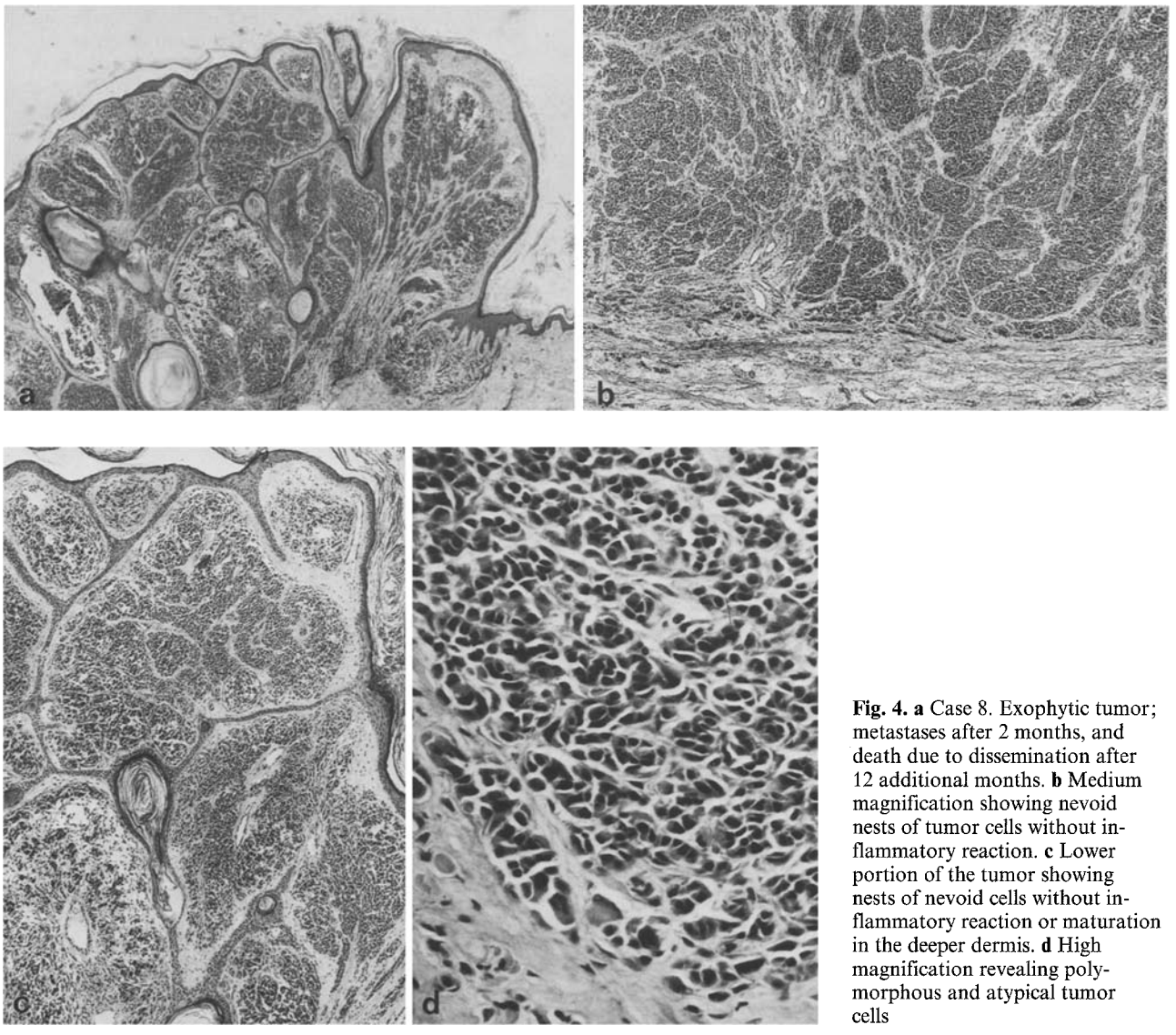


Fig. 4. a Case 8. Exophytic tumor; metastases after 2 months, and death due to dissemination after 12 additional months. **b** Medium magnification showing nevoid nests of tumor cells without inflammatory reaction. **c** Lower portion of the tumor showing nests of nevoid cells without inflammatory reaction or maturation in the deeper dermis. **d** High magnification revealing polymorphous and atypical tumor cells

[5, 7, 9, 10]. It is thought to be a nevocytic/melanocytic tumor of indeterminate risk which may recur or metastasize [5]. It is characterized by vertical growth extending into the reticular dermis; when it fills only the papillary layer, it has been termed borderline melanoma by these authors [10]. A follow-up in 21 cases disclosed recurrent disease in only 3 patients [5]. Two other case reports – both with later metastases – can be found in the literature [1, 13].

It is not quite certain whether the cases observed by Reed and co-workers correspond to the cases presented in the present study. The follow-up of our cases gave a different impression: in rare instances, malignant melanomas may resemble melanocytic/nevocytic nevi, Spitz's nevi, or spindle-cell nevi, and they are therefore likely to be wrongly diagnosed as benign tumors. The cases analyzed in the present study did not behave differently from normal melanomas. Therefore, we believe that such tumors are definitely malignant melanomas, and their malignant potential should not be underestimated. Since typical histological features of melanomas (such as intraepidermal spread of tumor cells, ulceration, and an increased mitotic index) may be absent, their diagnosis must be based on other criteria not normally seen in benign nevi (Table 3). Furthermore, prognostic criteria [11] may falsely indicate a favorable prognosis. Tumor thickness [2] appeared to be the most important indicator. It is well known that certain similarities to benign nevocytic nevi can be found in many malignant melanomas. From our findings, we conclude that these various nevoid features may be pronounced in some rare cases.

Histopathologists should be aware of this histological variant of malignant melanoma. In this way, a too-small resection margin may be avoided when treating

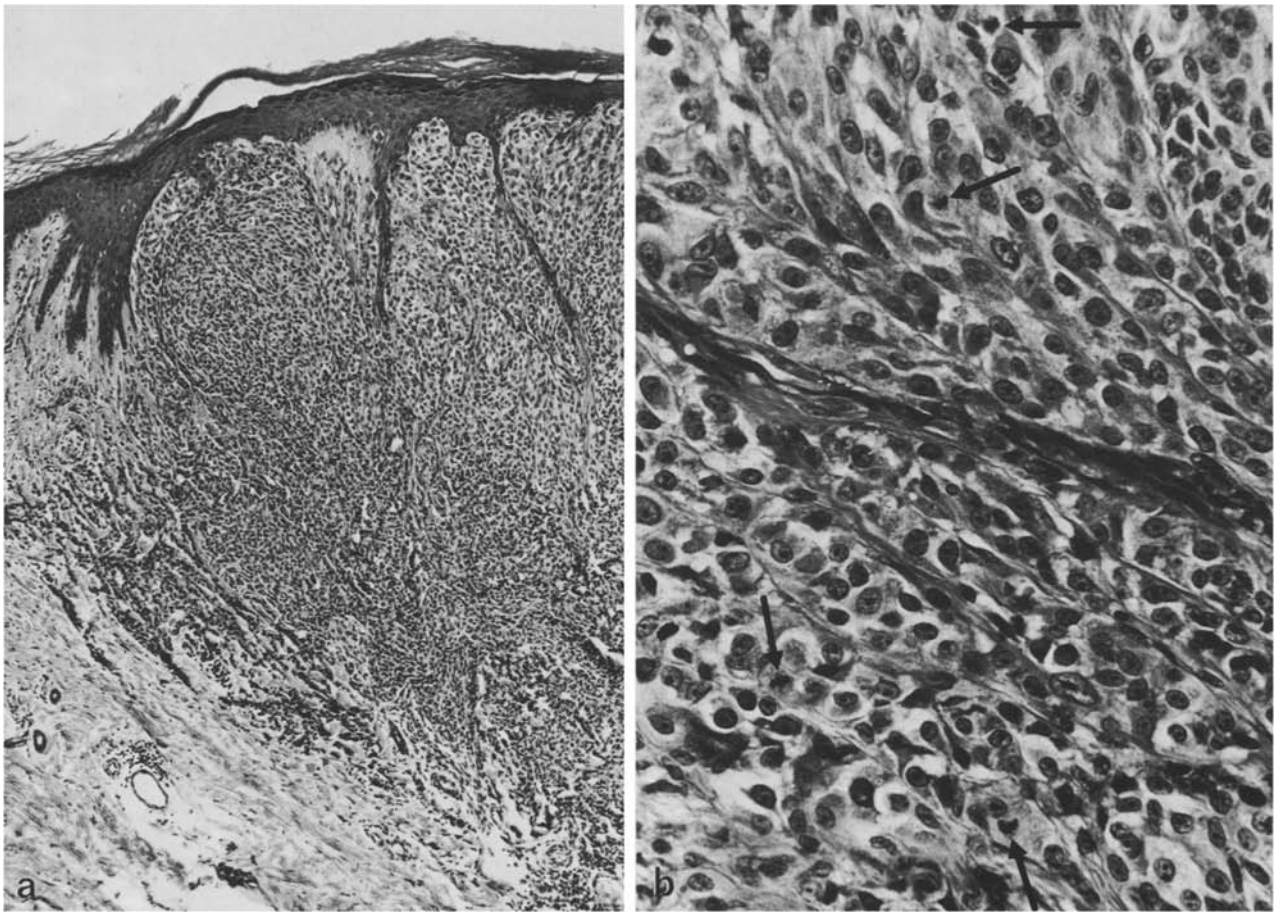


Fig. 5. a Case 10. Margin of a nodular tumor with little junctional activity. Metastases after 35 months, and death due to dissemination after 3 additional months. **b** Higher magnification revealing medium-sized nuclei with prominent nucleoli as well as numerous mitoses (*arrows*)

Table 2. Patients with nevoid malignant melanoma classified according to risk groups

	Tumor thickness [2]	Combined prognostic criteria [11]
Low-risk group	Tumor thickness $\leqslant 0.75$ mm $n = 4$ Disease free, 3 (75%)	Tumor thickness $\leqslant$ 0,75 mm and Mitotic index $\leqslant$ 10 mit/mm^2 $n = 4$ Disease free, 3 (75%)
Intermediate risk group	Tumor thickness 0.76–2.9 mm $n = 23$ Disease free, 11 (48%)	All other cases $n = 26$ Disease free, 14 (54%)
High-risk group	Tumor thickness $\geqslant$ 3.0 mm $n = 6$ Disease free, 4 (56%)	Prognostic index (tumor thickness $\times$ mitotic index) $\geqslant$ 13 $n = 3$ Disease free, 1 (33%)

such tumors; small resection margins appear to be associated with a higher rate of local recurrences [12], and thus, the induction of distant metastases in individual cases cannot be excluded.

Several factors may account for the nevoid appearance of some melanomas or of parts of some melanomas. (Step sections may disclose areas with a morphology more typical of melanomas.) In our view, melanomas are basically malignant melanocytic/nevocytic nevi (C. Schmoeckel and O. Braun-Falco, in preparation), i.e., melanocytic nevi with disorderly growth, in which a malignant transformation occurs

Table 3a. Patients without later metastases

Case	Nevus-like criteria					Criteria indicative of malignant melanoma						
	Nevoid pattern	Symmetric	"Buckshot" absent	Nevoid tumor cell	Monomorphous tumor cells	Tumor nests sharply demarcated	Pigmented tumor cells in deep dermis	Cellular atypia	Mitoses	Infiltration of adnexa	No maturation in deep dermis	Infiltrative growth in deep dermis
1	+	+	+	+	+	+	+	+	−	−	+	+
2	+	−	+	+	+	+	+	+	+	−	+	+
3	+	−	+	+	+	+	+	+	+	+	−	+
4	+	−	+	+	+	+	+	+	+	+	+	+
5	−	−	+	+	+	+	+	+	+	−	+	+
6	+	+	+	+	+	+	+	+	−	−	+	+
7	−	−	+	+	+	+	+	+	+	+	+	+
8	+	−	+	+	−	−	+	+	−	−	+	+
9	+	−	+	+	+	+	+	+	−	−	+	+
10	+	−	+	+	+	+	+	+	+	−	+	+
11	+	+	+	+	+	+	+	+	−	+	+	+
12	+	+	+	+	+	+	+	+	−	+	+	+
13	+	−	+	+	+	+	+	+	−	+	+	+
14	+	−	+	+	+	+	+	+	−	−	+	+
15	+	+	+	+	+	+	+	+	−	+	+	+
16	+	−	+	+	+	+	+	+	−	+	+	+
17	+	−	+	+	+	+	+	+	+	−	+	+
18	+	−	+	+	+	+	+	+	−	−	+	+

Table 3b. Patients with later metastases

Case	Nevus-like criteria					Criteria indicative of malignant melanoma						
	Nevoid pattern	Symmetric	"Buckshot" absent	Nevoid tumor cell	Monomorphous tumor cells	Tumor nests sharply demarcated	Pigmented tumor cells in deep dermis	Cellular atypia	Mitoses	Infiltration of adnexa	No maturation in deep dermis	Infiltrative growth in deep dermis
1	+	+	+	+	+	+	+	+	−	+	+	+
2	+	−	+	+	+	+	+	+	−	+	+	+
3	−	−	+	+	+	+	+	+	+	−	+	+
4	+	+	+	+	+	+	+	+	+	+	+	+
5	+	+	+	+	+	+	+	+	+	−	+	+
6	+	+	+	+	+	+	−	+	+	−	−	+
7	+	+	+	+	+	+	+	+	+	−	+	+
8	+	−	+	+	+	+	+	+	+	+	+	+
9	+	−	+	+	+	−	−	+	−	+	+	+
10	+	+	+	+	+	+	+	+	+	+	+	+
11	+	−	+	+	+	+	+	+	−	+	+	−
12	+	−	+	+	+	−	+	+	−	+	+	+
13	+	+	+	+	+	+	+	+	+	−	+	+
14	+	+	+	+	+	+	+	+	+	−	+	+
15	+	+	+	+	+	+	−	+	+	−	+	+

at a very early or later stage of development. There are many similarities between melanocytic nevi and malignant melanomas; in this respect, nevoid melanomas, which have the closest resemblance to nevi, constitute the end of a spectrum. In tumor pathology, there are other examples where the distinction between benign and malignant variants are difficult to assess by histopathological criteria alone, e.g., endocrine and neuroendocrine tumors.

Three other factors could account for the nevus-like appearance of some malignant melanomas. While studying initial melanomas (C. Schmoeckel and O. Braun-Falco, in preparation), it became apparent that the invasion of malignant melanocytes into the dermis occasionally occurs with little or no simultaneous spread throughout the epidermis. Furthermore, as with dermal nevi, the proliferation of these tumor cells within the epidermis may subside at a later stage. The origin of malignant melanomas in dermal nevi also appears to be a possibility [6].

References

1. Becker DW Jr, Miller CJ, Keller HB (1980) Metastatic minimal-deviation melanoma. Ann Plast Surg 4:230–237
2. Breslow A (1975) Tumor thickness, level of invasion, and node dissection in stage-I cutaneous melanoma. Ann Surg 182:572–575
3. Clark WH Jr, From L, Bernardino EA, Mihm MC (1969) The histogenesis and biologic behavior of primary human malignant melanoma of the skin. Cancer Res 29:705–726
4. From L, Hanna W, Kahn HJ, Gruss J, Marks A, Baumal R (1983) Origin of desmoplastic malignant melanoma. Hum Pathol 14:1072–1080
5. Muhlbauer JE, Margolis RJ, Mihm MC Jr, Reed RJ (1983) Minimal deviation melanoma: a histologic variant of cutaneous malignant melanoma in its vertical growth phase. J Invest Dermatol 80:3s–5s
6. Okun M, Dimattia A, Thompson J, Pearson SH (1974) Malignant melanoma developing from intradermal nevi. Arch Dermatol 110:599–601
7. Reed RJ (1978) Minimal deviation melanoma (consultation case). Am J Surg Pathol 2:215–220
8. Reed RJ, Leonard DD (1979) Neurotropic melanoma: a variant of desmoplastic melanoma. Am J Surg Pathol 3:301–311
9. Reed RJ, Ichinose H, Clark WH, Mihm MC Jr (1975) Common and uncommon melanocytic nevi and borderline melanomas. Semin Oncol 2:119–147
10. Reed RJ, Clark WH, Mihm MC Jr. (1981) Premalignant melanocytic dysplasia. In: Ackerman AB (ed) Pathology of malignant melanoma. Masson, New York, pp 159–183
11. Schmoeckel C, Bockelbrink A, Bockelbrink H, Braun-Falco O (1983) Low- and high-risk malignant melanoma. II. Multivariate analyses for a prognostic classification. Eur J Cancer Clin Oncol 19:237–243
12. Schmoeckel C, Bockelbrink A, Bockelbrink H, Kistler H, Braun-Falco O (1984) Low- and high-risk malignant melanoma. III. Prognostic significance of the resection margin. Eur J Cancer Clin Oncol 19:245–249
13. Warner TF, Sook Seo J, Bennett JE (1980) Minimal deviation melanoma with epidermotropic metastases arising in a congenital nevus. Am J Surg Pathol 4:175–183

Received September 20, 1984