Classification of Cutaneous Malignant Melanoma

A Reassessment of Histopathologic Criteria for the Distinction of Different Types

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BACKGROUND. Human cutaneous malignant melanoma currently is classified into four principle types: nodular, superficial spreading, lentigo maligna, and acral lentiginous. The criteria for the histopathologic diagnosis of these types are not applied consistently. Nevertheless, the classification has become the foundation of many clinical, histopathologic, epidemiologic, and molecular studies. The results of those studies can have validity only if the classification itself is valid. For this reason, the authors reassessed histopathologic criteria advocated for the distinction of the different types of melanoma and searched for other repeatable constellations of findings that may serve to define distinct subsets of the neoplasm.

METHODS. Nine hundred fifteen melanomas were examined with regard to 72 parameters that are considered to be important for histopathologic diagnosis. The results were analyzed statistically with special attention to findings that have been reported to be characteristic of the four principle types of melanoma.

RESULTS. The histopathologic criteria advocated for the distinction of different types of melanoma were found not to correlate with one another. A logistic regression analysis did not detect any other repeatable constellation of morphologic findings that may reflect a distinct biologic subgroup.

CONCLUSIONS. The validity of the current classification of cutaneous malignant melanoma into four principle types could not be substantiated. Malignant melanoma may present with many different forms, but these forms appear to be part of a continuous spectrum rather than examples of distinct biologic entities. ***Cancer* 1999;86:288–99.** © *1999 American Cancer Society.*

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Primary cutaneous malignant melanoma is currently classified into four principle types: nodular melanoma (NM), superficial spreading melanoma (SSM), lentigo maligna melanoma (LMM), and acral-lentiginous melanoma (ALM). These four types are considered by some authors to be distinct clinicopathologic entities that differ from one another with regard to etiology, biologic properties, and prognosis. For example, LMM has been claimed to originate from spindle-shaped junctional melanocytes, thus representing "melanocytic malignant melanoma," and SSM has been claimed to originate from round junctional nevus cells, representing "nevocytic malignant melanoma."[1] The risk for developing LMM has been said to be determined mostly by skin type, whereas the major risk factor for the development of SSM has been said to be the total number of melanocytic nevi.[2] LMM is thought to differ from SSM, in that it is related to chronic cumulative solar damage, has a longer period of intraepidermal growth, has slower growth of nodules, has migration of the neoplasm ("as the lesion spreads into one area, it seems to leave a

previously involved area"), and has a more favorable prognosis.[3] SSM has been claimed to differ from NM etiologically by a stronger association with the number of vacations in sunny climates. Whereas SSM is said to be associated with a history of sunburns in childhood, a "significant protective effect of sunburn" has been claimed to exist for NM.[4] In contrast to the other types of melanoma, ALM has been related pathogenetically to factors like pressure and friction.[5] LMM, SSM, and ALM occur with a female preponderance, whereas NM has been reported to occur more commonly in males. Neoplastic cells of NM are said to differ from those of the other types by their inherent "capacity to invade into, survive, and replicate in the dermis."[3,6] Those properties have been claimed to result in a worse prognosis. However, numerous studies have failed to reveal differences in prognosis of the four major types if the thickness of lesions is taken into account.[7–11] Some authors have denied the existence of principal differences between the subtypes and have suggested discarding the current classification of malignant melanoma.[12,13]

The main point of criticism is the lack of agreed upon criteria for recognition of the four major types: Different criteria have been employed by different authors and even by the same authors at different times. The only type of melanoma that is defined clearly is NM. According to the original description of the subtypes by Clark and coworkers in 1969, "the demonstration of dermal invasion throughout the lesion, where ever there is intraepidermal growth, is nodular melanoma by definition. If this growth extends beyond the width of three rete ridges in any section, the tumor is classified as a superficial spreading melanoma."[14] This definition aside, however, there is little agreement about NM. Some authors attribute NM to "vertical growth" of neoplastic cells from the outset,[3] whereas others emphasize signs of regression in the periphery of the nodule.[15] Cytologically, NM is said to be composed chiefly of epithelioid melanocytes,[16,17] but spindle-shaped and nevus-like cells also are said to occur.[17]

According to Clark's original article, SSM differs from LMM clinically, in that it has an arciform outline instead of a wholly irregular outline, an elevated surface instead of a flat surface, and shows less variation in color. Histopathologically, SSM was said to be composed chiefly of epithelioid melanocytes and characterized by prominent pagetoid growth and only slight pleomorphism. In contrast, LMM was said to be composed chiefly of spindled melanocytes and to show minimal pagetoid growth and prominent pleomorphism.[14] Subsequently, criteria were changed: Some were added, and others were diminished. LMM was said to be associated with prominent growth of neoplastic cells in adnexal epithelial structures, solar elastosis, and atrophy of the epidermis.[16–18] The epidermis, however, also could be normal,[16] and involvement of skin appendages was not found to be helpful in discriminating between LMM and SSM.[19] The inflammatory cell infiltrate of LMM was said to be either sparse[16] or pronounced,[18] and, instead of being spindle shaped, neoplastic cells in the superficial dermis were said to be round or cuboidal with prominent nucleoli and eosinophilic cytoplasm.[17] In SSM, mitotic figures were said to be present regularly[14] or rarely,[16] and the epidermis was described as normal or hyperplastic[18] but also as atrophic.[17] In one report, Clark averred that "the single histologic feature of greatest value in distinguishing between the radial-growth phase of SSM and LMM is the presence of invasion in SSM and the absence of invasion in LMM,"[3] but this criterion was not used by other authors or by Clark himself in subsequent articles.

ALM was described by Richard Reed in 1976 as a variant of melanoma "that with rare exceptions originates on palmar and plantar surfaces." Histopathologically, it was said to be characterized by "marked acanthosis, elongation of rete ridges, and lentiginous proliferation of atypical melanocytes in the epidermis" and by spindle-shaped and "nevus cell"-like cells in the dermis.[20] Subsequently, Reed and other authors reaffirmed the existence of ALM as a "distinct clinicopathologic entity,"[20] referring to additional histopathologic features of it: the absence of pronounced pagetoid growth, the rarity of nests, the predominance of markedly atypical melanocytes as solitary units, and the frequent presence of dendritic melanocytes in the epidermis, desmoplasia in the dermis, and a pronounced inflammatory cell infiltrate. However, those criteria were not applied consistently in different papers.[20–23] According to some authors, ALM may occur in nonglabrous skin, and other types of melanoma may be seen on palms and soles. In one study, ALM was said to account for only 8–12% of acral melanomas, the most common types being SSM and NM.[24] In contrast, other authors use the term ALM as a synonym for melanomas on palms, soles, digits, and nail beds[25] and aver that "knowledge of the site alone should indicate the nature of the lesion without resort to the cumbersome acral-lentiginous description."[15]

Because of these conflicting statements, the interobserver reliability in subclassifying malignant melanoma is low,[26] and the reported incidence of the different types varies markedly, from 1.4% to 14.2% for LMM, from 39% to 73.7% for SSM, and from 13.3% to 50% for NM.[27] Despite these findings and the agreement about the irrelevance of subclassification with

regard to prognosis, a statement about the type of melanoma generally is demanded as part of a histopathology report.[28,29] Moreover, some authors continue to base therapeutic decisions on the reported histopathologic type of melanoma,[30] and the current classification remains the basis for experimental studies that try to relate the different types of melanoma to certain immunohistochemical and molecular findings.[31–33] The results obtained in those studies, however, can be valid only if the premises on which they are built have legitimacy. For this reason, we reassessed the criteria for classification of malignant melanoma by evaluating the degree of correlation between histopathologic findings that are said to be typical of the four principle types and by searching for other repeatable constellations of findings that may serve to define distinct subsets of malignant melanoma.

MATERIALS AND METHODS

We examined sections from 987 lesions diagnosed as malignant melanoma from the files of the Center of Dermatology and Andrology of the Justus-Liebig University of Giessen. All sections were evaluated independently by two observers (M.E., W.W.); in cases of divergent judgments, lesions were reexamined together. In 72 cases (7.3%), the diagnosis of melanoma was found to be incorrect: Most of those lesions were Spitz's nevi, Halo nevi, recurrent nevi, or Clark's nevi that had been irritated. Every change in diagnosis was discussed with a third dermatopathologist.

The remaining 915 melanomas had been collected from 550 female patients and 329 male patients. In 23 patients, two primary melanomas had been excised; in 4 patients, three primary melanomas had been excised; and in 1 patient, six primary melanomas had been excised. The age of the patients ranged between 9 years and 92 years, with a median age of 56 years. Ninety-five percent of patients were between the ages of 21 years and 87 years. In 389 cases, clinical pictures were available that allowed to measure the greatest dimension of the lesions. By dividing the mean of the two greatest lesion dimensions through the thickness measured according to Breslow, an index was calculated for these melanomas that reflected the correlation of horizontal and vertical extension.

Histopathologic sections from the 915 melanomas were analyzed with regard to Clark level, thickness of the lesions according to Breslow, and 70 additional histopathologic parameters pertaining to the architecture of the lesions, nests of melanocytes, cytologic features of melanocytes, and associated findings (Tables 1–4). Because of incomplete excision of some melanomas, not all criteria could be assessed in all of the cases. In eight instances, both peripheral edges of the lesion were missing, preventing assessment of circumscription and presence of a "shoulder." In 13 instances, absence of one peripheral edge prevented the assessment of symmetry; and, in 25 instances, the biopsy specimens failed to reveal the entire thickness of the lesion.

The results obtained were analyzed statistically with regard to findings that have been said to be characteristic of the four principle types of melanoma. Because invasive melanomas without a "shoulder" (NM) and melanomas on glabrous skin (ALM) were significantly thicker than the other melanomas, an additional analysis was made for lesions in which the thickness was within the range of standard deviation. Furthermore, a configuration analysis was performed to determine possible correlations between criteria that may reflect distinct biologic subgroups.

TABLE 1
Architectural Features

Feature	Percent
Symmetry with regard to	
Distribution of melanocytes	3
Distribution of pigment	2
Distribution of inflammatory cells	3
Circumscription	
Sharp (by nests of melanocytes)	15
Relatively sharp (single melanocytes extending beyond the last nest ≤ 3 rete ridges)	13
Poor (single melanocytes extending beyond the last nest > 3 rete ridges)	72
Shoulder (intraepidermal melanocytes extending beyond dermal component > 3 rete ridges)	81
Presence of melanocytes in	
Epidermis	100
Adnexal epithelium	99
Papillary dermis	87
Reticular dermis	36
Subcutis	3
Blood vessels	5
Predominance of single melanocytes over nests	
Wide (> 50% of greatest dimension)	73
Focal (< 50% of greatest dimension)	25
None	2
Presence of suprabasilar melanocytes in mid epidermis only (lower half of spinous zone)	
Wide (> 10% of greatest dimension)	55
Focal (< 10% of greatest dimension)	40
None	5
Presence of suprabasilar melanocytes throughout the entire epidermis	
Wide (> 10% of greatest dimension)	20
Focal (< 10% of greatest dimension)	51
None	29

TABLE 2
Nests of Melanocytes

Feature	Percent
Presence of nests of melanocytes	99
Nests differing markedly in	
Size	93
Shape	92
Distance from one another	98
Presence of nests above the junction	
Wide (> 10% of greatest dimension)	10
Focal (< 10% of greatest dimension)	35
None	55
Confluence of nests	
Wide (> 50% of nests)	80
Focal (10–50% of nests)	17
Sporadic (< 10% of nests)	3

TABLE 3
Cytologic Features of Melanocytes

Feature	Percent
Predominance in the epidermis of	
Oval melanocytes	77
Polygonal melanocytes	6
Spindled melanocytes	13
Pagetoid melanocytes	4
Dendritic melanocytes	0
Predominance in the dermis of	
Oval melanocytes	66
Polygonal melanocytes	18
Spindled melanocytes	13
Pagetoid melanocytes	1
Dendritic melanocytes	0
Atypical nuclei (larger than those of keratinocytes, hyperchromatic, with prominent nucleoli)	
Wide (> 10% of melanocytes)	29
Focal (< 10% of melanocytes)	67
None	4
Mitotic figures per high powerfield	
>4	4
1–4	25
<1	71
Maturation of melanocytes with progressive decent to the dermis	5
≥2 circumscribed areas with distinct populations of cells	8

TABLE 4
Associated Findings

Feature	Percent
Presence on glabrous skin	4
Epidermis	
Hyperplastic	19
Atrophic	13
Not different from surrounding skin	68
Solar elastosis	
None	34
Slight (few and delicate elastotic fibers)	31
Moderate (many thick elastotic fibers)	21
Severe (nodular solar elastosis)	14
Regression	
Fibrosis of papillary dermis	24
Perpendicular blood vessels with prominent endothelia	22
Skip areas	13
Melanophages more numerous than melanocytes in foci	13
Two or more of these four criteria fulfilled	24
Inflammatory cell infiltrate	
Lichenoid	33
Perivascular only	66
Not stronger than in surrounding skin	1
Lamellar/concentric fibroplasia	15
Angiectases in papillary dermis	45
Ulceration	19
Associated melanocytic nevus	5
Metastasis in loco	3

RESULTS

The results are summarized in Tables 1–4. The mean thickness of the melanomas according to Breslow was 1.68 mm, the median was 0.9 mm, and the standard deviation was 2.14. One hundred twenty melanomas were confined to the epithelium (in situ melanomas).

NM

Of 795 "invasive" melanomas (i.e., melanomas with a dermal component), 741 exhibited a "shoulder," that is, the intraepidermal portion of the neoplasm extended for >3 rete ridges beyond the dermal portion. Forty-six invasive melanomas had no shoulder and, thus, fulfilled Clark's criteria for NM. Invasive melanomas without a shoulder were significantly thicker (mean, 4.01 mm; standard deviation, 2.42 mm) than those that had a shoulder (mean, 1.51 mm; standard deviation, 1.19 mm). When comparing invasive melanomas with and without a shoulder, the most striking differences were found with regard to circumscription (100% sharply or relatively sharply defined vs. 27.7% with and without a shoulder, respectively), regression (defined as the presence of two or more of the four criteria shown in Table 4; 84.8% vs. 24.6% with and without a shoulder, respectively), ulceration (60.9% vs. 18.4% with and without a shoulder, respectively), atypical nuclei in >10% of melanocytes (67.4% vs. 31.1% with and without a shoulder, respectively) predominance of polygonal ("epithelioid") melanocytes in the dermis (41.3% vs. 17% with and without a shoulder, respectively), >4 mitotic figures per high power field (HPF; 13% vs. 3.4% with and without a shoulder, respectively). presence of melanocytes in the upper half of the epidermis (30.4% vs. 75.1% with and without a shoulder, respectively), and predominance of single melanocytes over nests in >50% of the greatest

dimension of the lesion (41.3% vs. 70.9% with and without a shoulder, respectively).

To assess the influence of thickness, we compared 32 melanomas without a shoulder in which the thickness was within the range of standard deviation (1.59–6.43 mm) with 210 melanomas of the same thickness that possessed a shoulder. Although the range of thickness of the lesions was still rather broad, differences between both groups were less evident (e.g., 40.6% vs. 31% with and without a shoulder, respectively, for predominance of polygonal melanocytes in the dermis; 67.4% vs. 57.6% with and without a shoulder, respectively, for atypical nuclei in >10% of melanocytes; 8.1% vs. 3.4% with and without a shoulder, respectively, for >4 mitotic figures per HPF; and 25% vs. 60% with and without a shoulder, respectively, for the presence of single melanocytes in the upper half of the epidermis).

The histopathologic features mentioned most commonly in the literature as typical for NM are 1) epithelioid melanocytes in the dermis, 2) no distinct populations of cells (as a consequence of primarily "vertical growth"), 3) ulceration, and 4) regression. In combination, these criteria were fulfilled by 5 of 46 invasive melanomas (10.9%) without a shoulder and in 23 of 740 invasive melanomas (3.1%) with a shoulder. This difference was significant statistically ($P = 0.006$). However, for lesions of a thickness within the range of standard deviation, the corresponding numbers were 5 of 32 melanomas (15.6%) without a shoulder and 6 of 210 melanomas (7.6%) with a shoulder. In the chi-square test, this difference was insignificant ($P = 0.133$).

According to Clark, NM may undergo early "intralesional transformation," resulting in the presence of more than one distinct population of cells.[3] If the number of populations of cells was not considered, then the remaining three criteria for NM were fulfilled by 7 of 46 melanomas (15%) without a shoulder and by 38 of 740 melanomas (5.1%) with a shoulder. The most decisive variables for distinction of both groups of melanoma were found to be sharp or relatively sharp circumscription, regression, and ulceration. In combination, these three parameters were encountered in 10 of 46 melanomas (21.7%) without a shoulder and in only 4 of 740 melanomas (0.5%) with a shoulder.

ALM

Although some authors contend that ALM may occur on nonglabrous skin and other types of melanoma occur on palms and soles, there is general agreement that presence on glabrous skin is the single most important criterion for recognition of ALM. To test the validity of the concept of ALM as a distinct entity, we compared histopathologic findings from 39 melanomas on glabrous skin (4.3%) with those of 876 melanomas on nonglabrous skin (95.7%) and found the most striking differences with regard to the presence of at least slight solar elastosis (5.1% vs. 68.% of melanomas on glabrous and nonglabrous skin, respectively), atrophy of the epidermis (0% vs. 13% of melanomas on glabrous and nonglabrous skin, respectively), predominance of spindle-shaped melanocytes in the epidermis (2.6% vs. 13.7% of melanomas on glabrous and nonglabrous skin, respectively), ulceration (30.8% vs. 18% of melanomas on glabrous and nonglabrous skin, respectively), presence of a perivascular inflammatory cell infiltrate (92.3% vs. 65.3% of melanomas on glabrous and nonglabrous skin, respectively), predominance of oval melanocytes in the dermis (71.8% vs. 58.1% of melanomas on glabrous and nonglabrous skin, respectively), and metastases in loco (10.3% vs. 2.7% of melanomas on glabrous and nonglabrous skin, respectively).

Because melanomas on glabrous skin were significantly thicker (mean, 2.78 mm; standard deviation; 2.08 mm) than those on nonglabrous skin (mean, 1.4 mm; standard deviation, 1.25 mm), we investigated the possible influence of thickness by comparing 20 of 39 melanomas (51.3%) on glabrous skin with a thickness that was within the range of standard deviation (0.7–4.86 mm) with 404 of 876 melanomas (46.1%) of the same thickness on nonglabrous skin. Again, differences became less evident, e.g., with regard to atrophy of the epidermis (0% vs. 10.4% of melanomas on glabrous and nonglabrous skin, respectively), predominance of spindle-shaped melanocytes in the epidermis (5% vs. 11.6% of melanomas on glabrous and nonglabrous skin, respectively), and predominance of oval melanocytes in the dermis (70% vs. 60.4% of melanomas on glabrous and nonglabrous skin, respectively).

The histopathologic features mentioned most commonly in the literature as characteristic of ALM are 1) absence of epidermal atrophy, 2) absence of melanocytes in the upper reaches of the epidermis, 3) predominance of single melanocytes over nests within the epidermis, 4) predominance of spindle-shaped melanocytes in the dermis, and 5) evidences of regression. This combination of criteria was fulfilled by 2 of 39 melanomas (5.1%) on glabrous skin and by 6 of 876 melanomas (0.7%) on nonglabrous skin. This difference was highly significant ($P < 0.005$), although the number of cases was too small to permit reliable judgments. The three single features for which the greatest differences were found (absence of solar elastosis, presence of a perivascular inflammatory cell infiltrate, and predominance of oval melanocytes in the dermis)

were present in combination in only 2 of 39 melanomas (5.1%) on glabrous skin and in 27 of 876 melanomas (3.1%) on nonglabrous skin. This difference did not reach statistical significance ($P = 0.95$).

SSM and LMM

Neither SSM nor LMM is defined clearly. The criteria for the differentiation of both types of melanoma mentioned most commonly in the literature are 1) normal or hyperplastic (SSM) versus atrophic epidermis (LMM); 2) absence (SSM) versus presence of solar elastosis (LMM); 3) presence (SSM) versus absence of single melanocytes in the upper reaches of the epidermis (LMM); 4) predominance of epithelioid or pagetoid melanocytes (SSM) versus predominance of spindle-shaped melanocytes (LMM); 5) relatively sharp (SSM) versus poor circumscription (LMM); 6) only slight (SSM) versus pronounced nuclear atypia (LMM); and 7) absence (SSM) versus presence of regression (LMM). We evaluated those criteria for all melanomas, excluding invasive melanomas without a shoulder (NM) and melanomas on glabrous skin (ALM).

Of the remaining 830 melanomas, only 3 (0.4%) fulfilled all seven criteria for SSM. The first four criteria are considered to be most important for distinguishing SSM from LMM. They were seen in combination in 26 of 830 melanomas (3.1%). If only three criteria for SSM were taken into account, then the most common constellation of findings was absence of epidermal atrophy, no solar elastosis, and presence of single melanocytes in the upper half of the epidermis (181 cases; 21%). All other combinations of three criteria were seen in $<10\%$ of the cases.

None of the 830 melanomas fulfilled all seven criteria for LMM. The first four criteria that are considered to be most important for distinguishing LMM from SSM were seen together in 7 of 830 melanomas (0.7%). If only three criteria for LMM were considered, then the most common constellation of findings (epidermal atrophy, solar elastosis, and absence of single melanocytes in the upper half of the epidermis) was seen in 46 cases (5.5%).

The combination of all seven criteria for either SSM or LMM was seen with approximately the same frequency in invasive melanomas without a shoulder (NM) and in melanomas on glabrous skin (ALM). Altogether, the most common combination of those criteria was 1) normal or hyperplastic epidermis, 2) poor circumscription, 3) presence of single melanocytes in the upper reaches of the epidermis, 4) solar elastosis, and 5) no signs of regression. This constellation of findings was noted in 235 of 830 melanomas (28.3%).

The histopathologic findings most commonly associated with solar elastosis were poor circumscription (89% for melanomas with severe solar elastosis vs. 74% for melanomas with slight or moderate solar elastosis vs. 61% for melanomas without solar elastosis), epidermal atrophy (33% vs. 12% vs. 6%, respectively, compared with the epidermis adjacent to the neoplasm), <1 mitotic figure per HPF (77% vs. 76% vs. 62%, respectively), and absence of nuclear atypia (11% vs. 2% vs. 2%, respectively). A combination of these four parameters was seen in none of 312 melanomas without solar elastosis, in 2 of 477 melanomas (0.4%) with slight or moderate solar elastosis, and in 4 of 124 melanomas (3%) with severe solar elastosis. No significant differences with regard to solar elastosis were found for other variables, such as the predominating type of cell, the presence of melanocytes in the upper reaches of the epidermis, signs of regression, and density of the inflammatory cell infiltrate.

Because melanomas in sun-damaged skin are said by some authors to be characterized by a long period of intraepidermal growth and late invasion into the dermis,[3] we assessed the index of greatest lesion dimension and thickness in melanomas with and without solar elastosis. The index was calculated by dividing the mean of the two greatest lesion dimensions through the thickness; a high index, therefore, signified a thin melanoma with a large greatest dimension. For an index ≤ 10, solar elastosis was noted in 108 of 176 cases (61%); for an index >10 and ≤ 20, solar elastosis was seen in 51 of 86 cases (59%); and, for melanomas with an index >20, solar elastosis was found in 96 of 127 cases (75%). The difference with regard to solar elastosis between melanomas with an index ≤ 10 and melanomas with an index >20 was statistically significant ($P < 0.001$).

DISCUSSION

At the beginning of the 20th century, melanomas were recognized only in far advanced stages and were described as multinodular fungating tumors. In 1892, Jonathan Hutchinson described the flat stage of melanoma but considered it to be a benign freckle. In 1916, William Dubreuilh described those freckles in patients of all ages and on sun-exposed and protected sites. He did not consider them to be malignant and referred to them as "circumscribed precancerous melanosis," but he recognized them as early stages in the development of melanoma. Dubreuilh distinguished melanomas arising on a circumscribed precancerous melanosis from those arising in association with a nevus and from "melanome d'emblée," i.e., a nodular lesion arising in seemingly normal skin. The reasons for this classification were presumed differences in biologic behavior: "Melanome d'emblée" was thought

to be highly malignant, whereas melanomas arising in a circumscribed precancerous melanomis were regarded as relatively benign.[34]

When Clark developed his classification of malignant melanoma in the 1960s, he built on that of Dubreuilh. In contrast to his predecessor, Clark recognized that only few melanomas arise in association with a nevus and, therefore, skipped this category. He retained "melanome d'emblée" as a distinct type of melanoma and referred to it as "nodular melanoma." The other melanomas, i.e., those with a recognizable flat component, were divided into LMM and SSM. Although Clark considered LMM to be a distinct entity, he thought of NM initially as "a quite malignant neoplasm from the outset, but . . . probably not a different biologic entity when compared with superficial spreading melanoma."[14] However, he soon changed his mind and described NM as a distinct biologic type of melanoma characterized by "direct tumor progression."[3]

The consequences of Clark's classification of malignant melanoma were profound. With regard to the management of patients, treatment was adjusted to the type of melanoma, because NM and ALM were thought to have a more grim prognosis than SSM and LMM. Whereas complete excision was considered to be adequate for LMM, excisions with wide margins and elective lymph node dissections were recommended for the other types of melanoma.[35] It took almost 20 years to appreciate that the subtypes do not differ from one another prognostically if the thickness is taken into account.[7–11] With regard to research, numerous studies were conducted in search of evidence for fundamental biologic differences between the types of melanoma. The cells of invasive nodules of LMM were said differ ultrastructurally from those of SSM and NM.[1,3,36] Differences between the three types also were claimed to exist with regard to the synthesis of melanosomes,[37] the biology of the "epidermal melanin unit,"[37] the activities of certain enzymes (such as tyrosinase, glucose-6-phosphate-dehydrogenase, and succinate dehydrogenase[38,39]), and the expression of receptors for estrogen and progesterone.[40] SSM was said to differ from LMM and NM by being related to human lymphocyte antigen-DR5,[41] and, more recently, differences were described for the expression of bFGF,[42] p53 protein,[31,43] and mutations of the *ras* gene.[32,33]

However, establishing the differences between neoplasms requires well-defined study groups that are not provided for by the current use of criteria for classification of melanoma. For this reason, we tried to define the types of melanoma better by reassessing the value of criteria for differentiation. In part, data from the literature could be confirmed. This was especially the case for NM, which was found to differ from nonnodular melanomas especially by sharp circumscription, regression, and ulceration. Those differences, however, are related directly to the definition of NM. When all melanomas that show an extension of intraepidermal melanocytes beyond a dermal component are excluded, it is not surprising that the remaining melanomas are found to be circumscribed relatively sharply. Likewise, an exophytic nodule is more likely to become traumatized and ulcerated than a broad plaque. Also, if the peripheral portion of a melanoma is wiped out by regression, then the remaining nodule is likely to fulfill the definition of NM.

Nonnodular melanomas were found to differ from NM by the more common presence of melanocytes in the upper reaches of the epidermis and by predominance of single melanocytes over nests in >50% of the greatest dimension of the lesion. Those findings were encountered chiefly in the peripheral portion of nonnodular melanomas that, by definition, is absent in NM. In short, these two criteria also are related directly to the definition of NM and are not independent variables that might support the concept that NM is a distinct entity. The other differences between NM and nonnodular melanoma, such as higher numbers of mitotic figures and atypical nuclei, seem to be related to size. When neoplasms with a thickness beyond the range of standard deviation were excluded from consideration, differences between both groups were far less pronounced.

The histopathologic features mentioned most commonly in the literature as typical for NM were seen in combination in only 5 of 915 melanomas (0.5%), a number too low to qualify as the basis for a meaningful classification. The definition of NM was fulfilled by 46 of 915 melanomas (5%). This number is lower than anticipated from data in the literature. In Clark's original article, for example, NM was said to account for 31.6% of melanomas.[14] The discrepancy may be explained partially by the fact that, in the 1960s, melanomas usually were recognized at a later stage than in the 1980s and 1990s, when most of the melanomas in our study were excised. The later a melanoma is excised, the more likely are neoplastic melanocytes in the dermis to "overgrow" those within the epidermis, thus creating a lesion that fulfills the definition of NM. Another mechanism that may be responsible for NM is complete regression of the intraepidermal component of the neoplasm, which also is more common in advanced lesions. Indubitable signs of regression were encountered in 39 of our 46 cases of NM (84.8%) (Fig. 1). The high frequency of regression supports the observation by McGovern,

who recognized in 1982 that, "as a result of spontaneous regression occurring in the intraepidermal component of an SSM, the surviving nodule may be classified as having no intraepidermal component."[15] A third mechanism that may contribute to the "formation" of NM is an artifact during sectioning of a biopsy specimen. Some thick melanomas have only a tiny macular component that may be overlooked easily and may not be contained in histopathologic sections, turning a nonnodular melanoma into an apparent NM. In sum, the differences between NM and nonnodular melanomas found in our study are either related directly to the definition of NM or reflect changes in advanced melanomas. The absence of independent variables distinguishing NM from nonnodular melanomas supports McGovern's conclusion that "it would seem reasonable to cease using the terms superficial spreading and nodular melanoma," because their main differences are not due to "any inherent attribute of the histogenetic pattern."[15]

Also, with regard to ALM, data from the literature could be confirmed partially. Melanomas on glabrous skin were found to differ from melanomas on nonglabrous skin, especially by the absence of solar elastosis and epidermal atrophy. Those differences are related directly to the definition of ALM as a type of melanoma occurring on glabrous skin that is relatively sun protected and covered by a thick epidermis. Other findings said to be typical of ALM were found with approximately the same frequency in melanomas on both glabrous and nonglabrous skin, e.g., the presence of melanocytes in the upper reaches of the epidermis (74.4% glabrous vs. 70.5% nonglabrous) and the predominance of single melanocytes over nests in >50% of the greatest dimension of the lesions (79.5% glabrous vs. 72.4% nonglabrous). The histopathologic features mentioned most commonly in the literature as typical for ALM were seen in combination in only 2 of 915 melanomas (0.2%), disqualifying this constellation of findings as a basis for classification.

The constellation of findings said to distinguish SSM from LMM was seen in 3 of 915 melanomas (0.4%), whereas the constellation of findings said to be characteristic of LMM was not seen in a single case. Even if only the three or four criteria said to be most important for differentiation were considered, they were not fulfilled by the vast majority of lesions. These results are in accordance with those of previous studies. Clark himself found in 1984 that "agreement among pathologists is least for LMM" and that strict application of criteria for LMM results in reclassification of most cases to the effect that "LMM is a rarity."[4] In sum, classification of melanomas as SSM or LMM usually is based on only a small fraction of the purported criteria and, thus, is highly subjective (Figs. 2–4).

For some authors, the decisive criterion for distinguishing LMM from SSM is the presence of marked solar elastosis. According to Barnhill and Mihm, "it is generally accepted that the diagnosis of lentigo maligna requires the presence of severe solar changes in both the epidermis and dermis."[17] The tendency to equate LMM with melanomas in severely sun-damaged skin explains some of the ostensibly unique biologic properties of LMM, i.e., development especially in sun-exposed skin of elderly patients. Arthur Sober wrote in 1988: "Melanoma subtypes should be examined separately when looking for etiologic factors. Clearly, chronic cumulative solar damage plays a strong role in lentigo maligna melanoma, not seen with the other subtypes."[44] It is equally clear, however, that evidence of chronic cumulative solar damage will be found inevitably in melanomas classified as LMM as long as severe sun damage is a requirement for diagnosis. Similar to NM and ALM, the allegedly unique characteristics of LMM are related directly to its definition and are not independent variables that might support the classification of LMM as a distinct biologic entity.

According to our study, the criteria advocated for the distinction of SSM and LMM do not separate two morphologic groups of melanoma from one another. If only solar elastosis was considered, then there were significant correlations between solar elastosis on the one hand and poor circumscription, epidermal atrophy, sparseness of mitotic figures, absence of atypical nuclei, and a high ratio of greatest lesion dimension and thickness on the other hand. A combination of these parameters, however, was extremely rare. Furthermore, the correlation of single parameters with solar elastosis was too weak to allow for recognition of distinct morphologic types of melanoma. For example, poor circumscription was most common in melanomas with severe solar elastosis (89%), but most melanomas without evidence of solar elastosis (61%) also were circumscribed poorly. The ratio of diameter and thickness tended to be higher in melanomas with solar elastosis, but it was >20 (e.g., a greatest lesion dimension of at least 20 mm for melanomas measuring 1 mm in thickness) in 31 of 134 melanomas (23%) without solar elastosis and ≤10 in 108 of 255 melanomas (42%) with solar elastosis. The latter finding is in accordance with reports in the literature on melanomas in severely sun-damaged skin that were deeply invasive despite short duration and small size.[45]

In sum, the weak correlation of solar elastosis with independent morphologic variables militates against the suitability of solar elastosis as a basis for classifi-

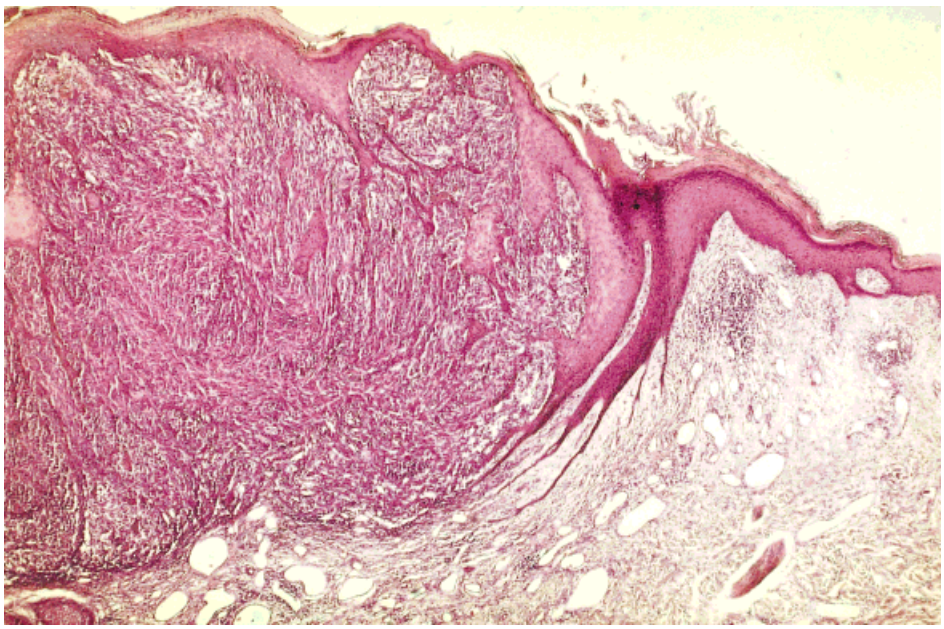

FIGURE 1. Superficial spreading melanoma or nodular melanoma (NM)? This melanoma shows no extension of intraepidermal melanocytes beyond dermal melanocytes; therefore, it fulfills the definition of NM. It is not a "primary NM," however, as evidenced by signs of regression (perpendicular blood vessels and fibrosis in a thickened papillary dermis) adjacent to the nodule.

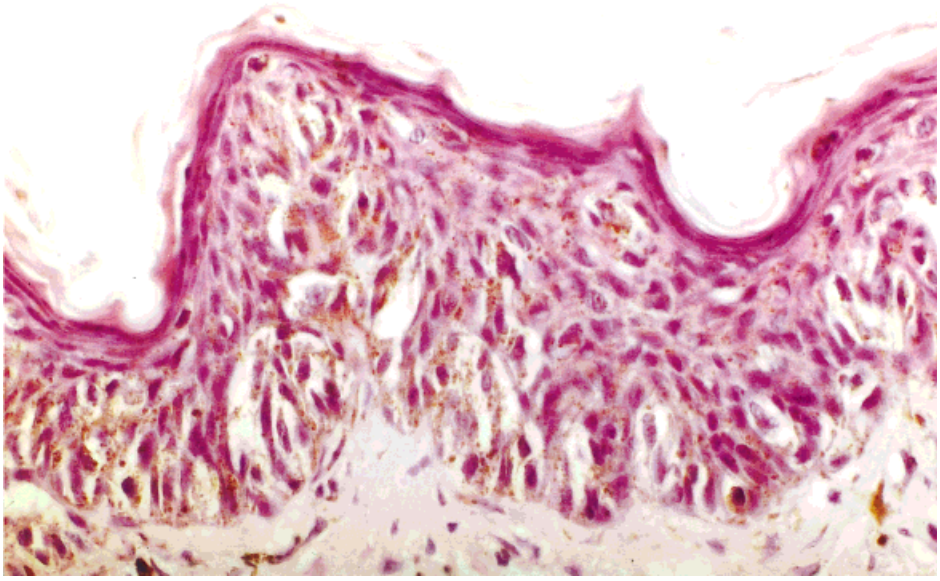

FIGURE 2. Lentigo maligna melanoma (LMM) or superficial spreading melanoma (SSM)? This melanoma shows a combination of features claimed to be typical of LMM (predominance of spindled melanocytes, predominance of single melanocytes over nests) and SSM (many melanocytes in the upper part of the epidermis).

cation. If different diseases are to be distinguished from one another morphologically, then repeatable constellations of findings are mandatory. If there really are distinct biologic types of melanoma, then such constellations have to be expected. Our study did not reveal evidence for the existence of unique constellations of findings for melanoma with or without solar elastosis, for melanoma with or without a shoulder, or for melanoma that occurred in glabrous or nonglabrous skin.

Are there repeatable constellations of findings other than those currently used for classification of

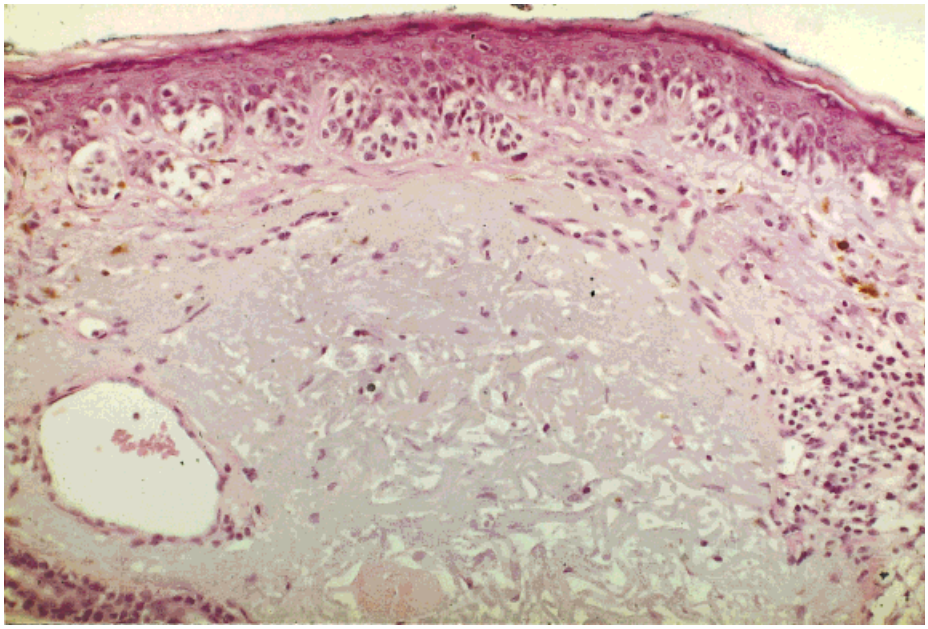

FIGURE 3. Lentigo maligna melanoma (LMM) or superficial spreading melanoma (SSM)? This melanoma shows a combination of features claimed to be typical of LMM (severe solar elastosis, only few melanocytes above the dermoepidermal junction) and SSM (predominance of nests over single melanocytes, absence of atypical nuclei).

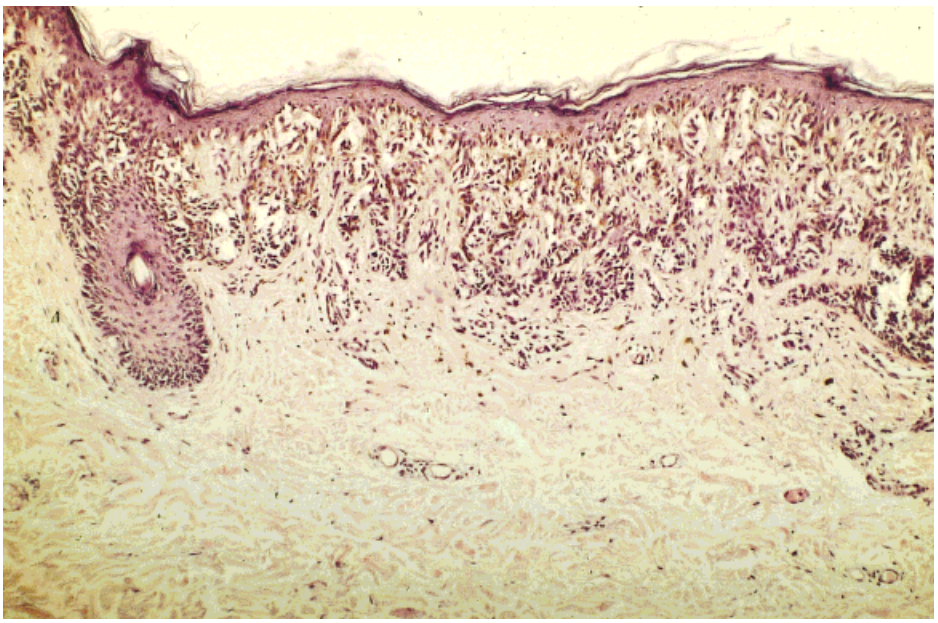

FIGURE 4. Lentigo maligna melanoma (LMM) or superficial spreading melanoma (SSM)? This melanoma seems to be typical of LMM (predominance of spindled melanocytes, no melanocytes above the dermoepidermal junction, prominent involvement of adnexal epithelial structures), but there is no solar elastosis. The lesion was broad, asymmetrical, and poorly circumscribed, ruling out the possibility of a melanocytic nevus.

melanoma? Indeed, out of the criteria advocated for the distinction of SSM and LMM, we found a constellation of five variables that was seen in almost one-third of our cases: 1) normal or hyperplastic epidermis, 2) poor circumscription, 3) the presence of single melanocytes in the upper reaches of the epidermis, 4) solar elastosis, and 5) no signs of regression. Could this constellation of findings serve as a basis for a new classification of melanoma? It cannot, because the combination of the corresponding opposite criteria

(atrophic epidermis, relatively sharp circumscription, the absence of single melanocytes in the upper reaches of the epidermis, no solar elastosis, and signs of regression) was not seen in a single case. The criteria mentioned above are simply variables that describe melanoma "per se," and some of them belong to the most important findings that distinguish melanoma from other melanocytic neoplasms.

In conclusion, our study of more than 70 histopathologic parameters in 915 melanomas failed to substantiate the current classification of melanoma. No evidence was found for any other repeatable constellation of morphologic findings that may allow to separate distinct types of melanoma from one another. Malignant melanoma may present with many different forms, but these forms seem to be part of a continuous spectrum. Lesions that fulfill the criteria for NM, ALM, SSM, and LMM belong to that spectrum but represent only four of hundreds of constellations of findings. According to our data, classifying malignant melanoma into distinct histopathologic groups is arbitrary and should be omitted. This conclusion is supported by the lack of compelling evidence that certain histopathologic parameters, other than those related to the size of melanoma, are associated with distinct types of biologic behavior. Differences in biologic behavior among individual melanomas seem to be caused by a complex interplay of factors that remain unknown.

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